Evaluation of Controlled IL-12 in Combination with a PD-1 Inhibitor in Subjects with Recurrent Glioblastoma

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Abstract

Background: Ad-RTS-hIL-12 (Ad) is a novel gene therapy candidate conditionally expressing IL-12 under the control of veledimex (V) acting via the proprietary RheoSwitch Therapeutic System (RTS) gene switch with a therapeutic window. Intratumoral Ad + oral V monotherapy (Phase 1 study, NCT02026271) resulted in a new sustained intra-tumor influx of activated cytotoxic T cells, consistent with an immune-mediated anti-tumor effect improving median overall survival (mOS) of subjects with recurrent glioblastoma (rGBM). This correlated with an increased circulating $CD8^+/FoxP3^+$ T cell ratio ("cytoindex"), an emerging biomarker for mOS. PD-1 expression on infiltrating T cells at biopsy after Ad+V, supports combining controlled IL-12 with a PD-1 inhibitor to further augment T-cell-mediated anti-tumor effects. The rationale is also supported by increased OS (100% combo vs 63% for Ad+V vs 40% for anti-PD-1) in mice bearing GL-261 glioma.

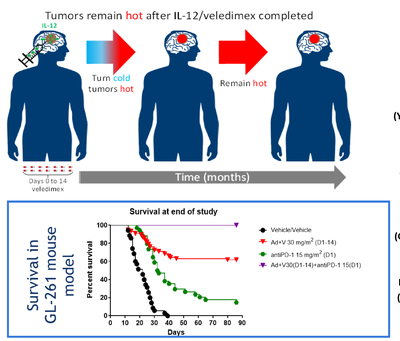
Methods: An ongoing open label, dose-escalation Phase 1 trial (NCT03636477) is evaluating safety and tolerability of local, controlled IL-12 with nivolumab (nivo) in adult subjects with rGBM. Ad was administered by single intratumoral injection (2 x 10^{11} viral particles, Day 0) plus V (10-20 mg) PO QD x 15 with nivo (1-3mg/kg) IV on Days -7, 15, then Q2W.

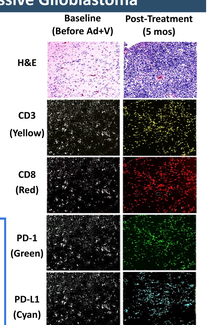
Results: Safety data revealed a similar profile as Ad+V monotherapy. Adverse reactions (ARs) during follow-on nivo dosing were consistent with anti-PD-1 reports. ARs were manageable and reversible with no synergistic toxicities. Nivo alone did not alter peripheral IL-12 levels (median baseline (before anti-PD-1) 0.9 pg/mL; Day 0 1 pg/mL) increasing to 5.5 pg/mL on Day 3. Nivo alone increased peripheral T cells ($CD3^+CD8^+$ median baseline 23%; Day 0 26%) and Ad+V elevated peripheral $CD3^+CD8^+$ to 31% at Day 14. Nivo alone decreased regulatory T cells (FoxP3 baseline 1.5% vs Day 0 0.8%). Ad+V decreased these to 0.3% (Day 14). Combination therapy improved the cytoindex (baseline 15; Day 0 29; Day 14 80).

Conclusions: Controlled IL-12 production using Ad+V with nivo is a rational combination with initial data consistent with immune-mediated anti-tumor effects with a favorable safety profile, warranting continued investigation in rGBM.

(Submitted February 2019)

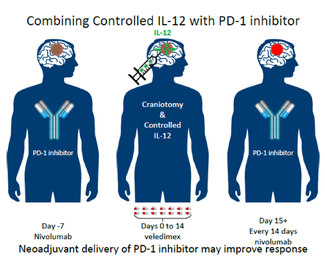
Background: Monotherapy in Recurrent or Progressive Glioblastoma





Subject 037: 5 months after single cycle of treatment of Ad-RTS-hIL-12 + V (modified from SNO 2017)

Ad-RTS-hIL-12 Intratumoral Injection Regulated by Veledimex Drives Cytotoxic Immune Response



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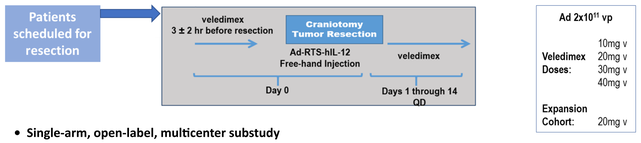
Recurrent or progressive glioblastoma subjects eligible for ATI001-102 scheduled for SOC resection who have not previously been treated with inhibitors of immuno-checkpoint pathways

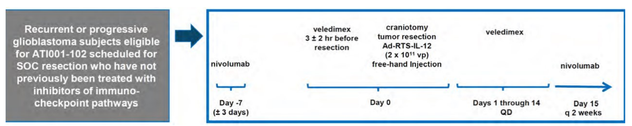
Study Designs

A. ATI001-102 Controlled IL-12 Main Study Schema — Recurrent or Progressive Glioblastoma



- **Single-arm, open-label, multicenter substudy**
- **N=31 in craniotomy group**
- **N=15 in 20 mg veledimex (V) dosing level**
- **Overall survival in the 20-mg V cohort was 12.7 months (mean follow-up time of 13.1 months) Subjects who received low-dose (≤ 20-mg) steroid during active treatment (Days 0-14) had an mOS of 17.8 months**
- **Biopsy-confirmed pseudoprogression (3/3)**
- **20 mg V dose to be taken forward as Phase 3 dose**

B. ATI001-102 Immune Checkpoint Inhibitor (iCPI) Substudy Schema



- **Single-arm, open-label, dose-escalation, multicenter substudy (NCT03636477) of ATI001-102**
- **3 dosing cohorts (10mg V, 1mg/kg nivolumab; 10mg V 3mg/kg nivolumab; 20mg V, 3mg/kg nivolumab**
- **N = 8 (enrolled as of 06 May 2019)**
- **Enrollment is ongoing (up to 18 subjects)**

Subject Characteristics (updated as of 06May2019)

	Cohort 1: Ad+V (10 mg) Nivolumab (1 mg/kg) N=3	Cohort 2: Ad+V (10 mg) Nivolumab (3 mg/kg) N=3	Cohort 3: Ad+V (20 mg) Nivolumab (3 mg/kg) N=2
Gender (M:F)	1:2	1:2	1:1
Age (mean, range)	43.0 (30, 63)	59.4 (52, 66)	61.4 (47, 76)
Performance (KPS, screening) 70-80 90-100	 0 3	 0 3	 1 1
Recurrences (mean, range)	1.7 (1, 3)	1 (1, 1)	1.5 (1, 2)
Lines of Therapy (mean, range)	1.3 (1, 2)	1 (1, 1)	2 (1, 3)
IDH Mutation Status Mutated:Wild-Type	 1:2	 0:3	 1:1
V dosing compliance (%) (mean)	97.8	100	TBD
Cumulative Steroid Use Days 0-14 (mg) (mean, range) % receiving ≤20mg steroids during active dosing	 64.7 (0, 116) 33%	 3.3 (0, 10) 100%	TBD

Note: Data Collection and Cleaning Ongoing

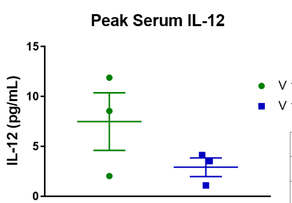
Safety Results

Adverse Event + / Dose cohort / Relatedness	Cohort 1: Ad+V (10 mg) Nivolumab (1 mg/kg) N=3		Cohort 2: Ad+V (10 mg) Nivolumab (3 mg/kg) N=3		Cohort 3: Ad+V (20 mg) Nivolumab (3 mg/kg) N=2		ATI001-102 Main Study Ad+V 10 and 20mg with Craniotomy N=21
	Ad+V	Nivo	Ad+V	Nivo	Ad+V	Nivo	Ad+V
Related ≥ Grade 3 AEs							
Lymphocyte count decreased	1 (33%)	0	1 (33%)*	1 (33%)*	1 (50%)	0	3 (20%)
ALT increased	0	0	1 (33%)	0	0	0	3 (20%)
Edema cerebral	0	1 (33%)	0	0	0	0	0
Lipase increased	0	0	0	1 (33%)	0	0	0
Cytokine Release Syndrome (ZIOPHARM CRS Working Definition)							
Grade 3	0		0		0		2 (10%)

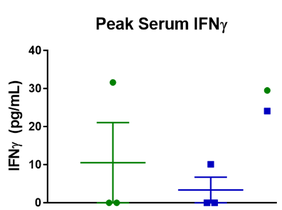
+CTCAE v5.0 as applicable; *One ≥ Grade 3 AE (Lymphocyte count decreased) was considered related to both Ad+V and nivo

- **No DLTs**
- **One SAE of cerebral edema was considered related to nivolumab alone**
- **No SAEs were considered related to Ad+V or in the combination with nivo**
- **No related Grade 4 or fatal AEs**
- **No clinically significant overlapping toxicities**

Serum Cytokine Concentrations

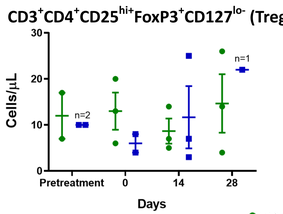


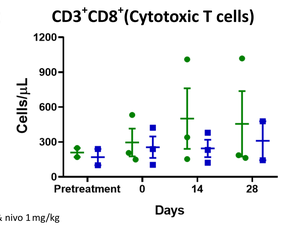
	Baseline	Pre - Ad+V	Peak		
IL-12 (pg/mL)	Mean ± SD	Mean ± SD	Mean ± SD	Min	Max
V 10mg & nivo 1mg/kg	1.2 ± 0.7	0.9 ± 0.3	7.5 ± 5.0	2.1	11.9
V 10mg & nivo 3mg/kg	0.7 ± 0.2	1.1 ± 0.7	2.9 ± 1.6	1.1	4.1

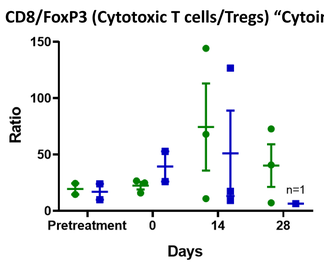


	Baseline	Pre - Ad+V	Peak		
IFNγ (pg/mL)	Mean ± SD	Mean ± SD	Mean ± SD	Min	Max
V 10mg & nivo 1mg/kg	3.6 ± 6.2	2.8 ± 4.8	10.5 ± 18.2	0	31.6
V 10mg & nivo 3mg/kg	0.0 ± 0.0	0.0 ± 0.0	3.4 ± 5.8	0	10.1

Peripheral Blood Flow Cytometry







Cytoindex	V 10mg & Nivo 1mg/kg			V 10mg & Nivo 3mg/kg		
	Mean	SD	N	Mean	SD	N
Pre-treatment	19.5	7.0	2	17.0	9.9	2
Day 0	22.4	5.8	3	39.4	19.0	2
Day 14	74.4	66.9	3	51.1	65.5	3
Day 28	40.2	32.8	3	6.5	NA	1

Conclusions

The encouraging safety and efficacy data previously observed in monotherapy may be enhanced with immune checkpoint inhibitors:

- **Enrollment is ongoing in the 3+3 dose escalation study, with regulatory pauses required between patients and cohorts. Mean follow-up is 4.5 months (min 0.4 months for most recently enrolled patient, max 10.1 months for the first enrolled patient)**
- **66% received low-dose concurrent steroids (≤20 mg dexamethasone total, Days 0-14)**
- **Pre-dosing with nivolumab did not have impact on cytokine levels prior to Ad+V**
- **Increased measurement of recombinant IL-12 and endogenous IFNγ in the serum following initiation of Ad+V (Controlled IL-12), which is consistent with previously reported data of Ad+V monotherapy**
- **Cytoindex, an emerging biomarker for effects of IL-12, showed activation of the immune system**
- **Adverse reactions were predictable based on the safety profile of each drug as a monotherapy; no significant overlapping toxicities were identified**

Controlled IL-12 production using Ad+V with nivolumab is a rational combination with initial data consistent with immune-mediated anti-tumor effects with a favorable safety profile, warranting continued investigation in rGBM and initiation of a Phase 2 trial of Ad+V in combination with cemiplimab-rwlc is planned to open Q2 2019