A Phase 1 Study of Ad-RTS-hIL-12 + Veledimex in Adult Recurrent Glioblastoma: Dose determination with updated overall survival

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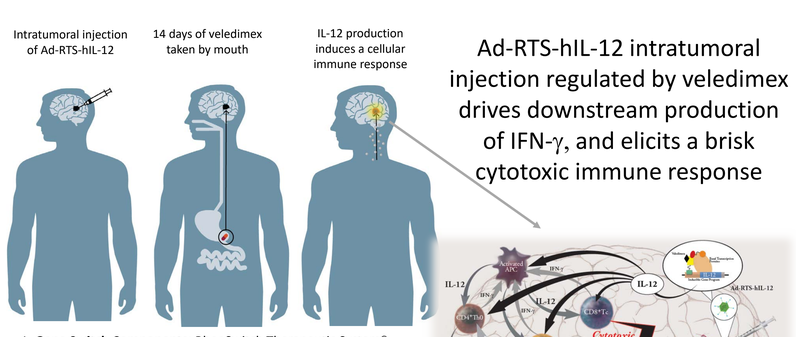
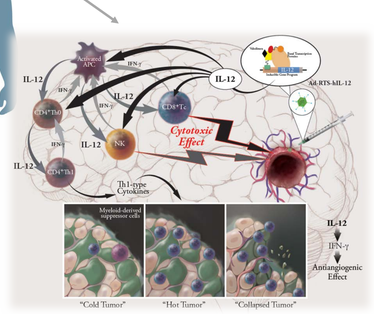
Abstract

Ad-RTS-hIL-12 (Ad) is a novel gene therapy expressing IL-12 via the RheoSwitch Therapeutic System® gene switch under control of an oral activator ligand, veledimex (V). We previously reported on an open label Phase I trial describing biological activity of recombinant IL-12 with downstream IFN-γ and activation of the immune system. We provide an update on the intratumoral injections of Ad ($2x10^{11}$ virus particles [vp]) + V for patients with recurrent GBM (rGBM) in Group 1 (G1) (craniotomy, n=31) and initial results for Group 2 (G2) (stereotactic administration n=7). In G1, the V 20-mg cohort mOS increased to 12. 7 months with mean follow-up of 12. 9 months. 20-mg V in G1 showed fewer toxicities and higher V compliance (84%) compared with higher-doses of V (30 and 40-mg) with 75% and 67%, respectively. These data are encouraging compared to historical data that predict mOS of 5 to 8 months. An additional cohort at V 10-mg (n=6) was well tolerated, but subtherapeutic, with a mOS of 7. 6 months (mean follow-up 6. 7 months). There was an association between V dose level, blood-brain-barrier penetration, and drug-related adverse events (AEs) with increased TEAEs observed above V 20-mg. Subgroup analyses across all cohorts did not detect statistically significant differences including extent of resection or IDH mutation status. Subjects (20-mg V) who received a cumulative dose of ≤10mg of dexamethasone during the first 15 days of treatment showed improved OS versus >100mg of dexamethasone, suggesting corticosteroid-mediated blunting of the IL-12 dependent immune-mediated therapeutic effect. In the G2 20-mg V cohort, similar cytokine levels and reversible AEs were observed compared to G1; follow up is ongoing and mOS will be presented. Based on these results and the best risk-benefit profile, the 20-mg V dose level was chosen for further investigation. Combination with an immune checkpoint inhibitor in rGBM is underway.

Background on Controllable hIL-12



Ad-RTS-hIL-12 intratumoral injection regulated by veledimex drives downstream production of IFN-γ, and elicits a brisk cytotoxic immune response



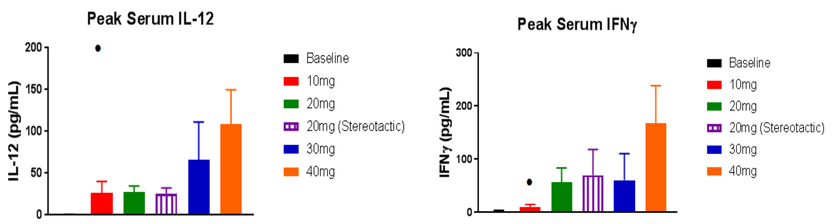
1. **Gene Switch Components:** RheoSwitch Therapeutic System® (RTS®) technology includes VP16-RXR (co-activation partner, CAP) and Gal4-EcR (ligand-inducible transcription factor, LTF. Without ligand, LTF binds to the inducible promoter and does not form a stable complex with CAP.
2. **Inducible Promoter:** Customizable (RTS®) promoter to which basal transcription proteins are recruited and the target gene (IL-12) is transcribed.
3. **Activator Ligand (veledimex):** After oral administration, this ligand, an ecdysone analog, stabilizes a conformational change in the LTF leads to a stable, high-affinity interaction with CAP.

Subject Characteristics

Characteristic	Ad-RTS-hIL-12 (2X10[11] vp)				
	Craniotomy 10 mg V (N=6)	Craniotomy 20 mg V (N=15)	Stereotactic 20 mg V (N=7)	Craniotomy 30 mg V (N=4)	Craniotomy 40 mg V (N=6)
Age in years Mean (Min, Max)	49 (29, 61)	46 (26, 68)	51 (28, 73)	59.75 (43, 74)	47.67 (36, 58)
Gender Male : Female	3 : 3	10 : 5	5 : 2	2: 2	4: 2
Recurrence (n)					
1st	2	4	4	1	2
2nd	4	5	2	2	2
3rd or more	0	6	1	1	2
Prior Lines of Treatment (mean)	2.0	2.2	2.3	3.0	2.5
Prior Bevacizumab					
Yes	1	4	2	4	1
No	5	11	5	0	5
Prior Surgeries Mean (Min, Max)	1 (0, 2)	1.53 (0, 3)	1.86 (1, 3)	1.5 (1, 3)	1.67 (1, 3)
Grade at Study Entry					
HGG, Gr III	1	2	0	0	0
Glioblastoma, Gr IV	5	13	7	4	6
IDH Status					
Wild-Type	5	8	2	3	5
Mutated	1	5	1	0	1
Unknown	0	2	4	1	0
KPS at Screening					
≥ 90	3	9	3	3	2
≥ 70 and < 90	3	6	4	1	4
Steroids in prior 4wks					
Yes	3	8	2	2	4
No	3	7	5	1	2
Unknown	0	0	0	1	0
Total Steroid Use in mg Days 0-14 (mg) Mean (Min, Max)	61 (0, 102)	60 (0, 140)	51 (0, 163)	87 (0-136)	45 (10-102)
Veledimex Dosing Compliance	79%	84%	90%	63%	58%

Group 1: Craniotomy with Ad+V Dose Escalation 10-40 mg (N=31). Group 2: Stereotactic Ad + V 20 mg (N=7). Data cut-off (12 Oct 2018). Data collection and follow-up is ongoing.

Serum Cytokine Levels Demonstrating that RTS Controls IL-12



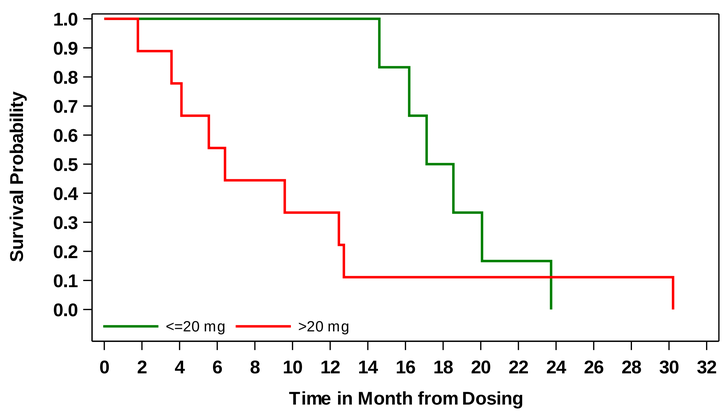
Mean± SEM. (•) One outlier subject removed (Grubb's test) due to prohibited CYP3A4 interacting concomitant medications.

Safety Results

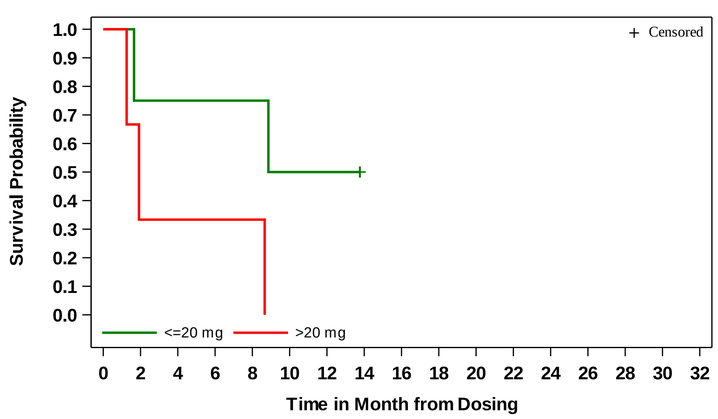
Adverse Event (AE)	Craniotomy 10 mg V (N=6)	Craniotomy 20 mg V (N=15)	Stereotactic 20 mg V (N=7)	Craniotomy 30 mg V (N=4)	Craniotomy 40 mg V (N=6)
Related ≥ Grade 3 AEs That Occurred in ≥ 5% of Subjects (TEAE)					
Lymphopenia	1 (17%)	3 (20%)	1 (14%)	2 (50%)	2 (33%)
AST/ALT Increased	2 (33%)	1 (7%)	0	0	2 (33%)
Leukopenia	1 (17%)	1 (7%)	1 (14%)	0	0
Neutropenia	1 (17%)	1 (7%)	1 (14%)	0	0
Hyponatremia	0	2 (13%)	0	0	1 (17%)
Headache	0	3 (20%)	0	0	0
Thrombocytopenia	0	2 (13%)	0	0	0
Confusional State	0	0	1 (14%)	0	1 (17%)
Related ≥ Grade 3 Neurological AEs					
Headache	0	3 (20%)	0	0	0
Confusional State	0	0	1 (14%)	0	1 (17%)
Delirium	0	0	1 (14%)	0	0
Brain Edema	0	0	0	1 (25%)	0
Aseptic Meningitis	0	1 (7%)	0	0	0
Cytokine Release Syndrome (ZIOPHARM CRS Working Definition)					
Grade 2	2 (33%)	4 (27%)	0	2 (50%)	2 (33%)
Grade 3	0	2 (13%)	1 (14%)	1 (25%)	3 (50%)

Dexamethasone Impact on Overall Survival (20mg veledimex)

Veledimex 20mg Cohort Craniotomy Group



Veledimex 20mg Cohort Stereotactic Group

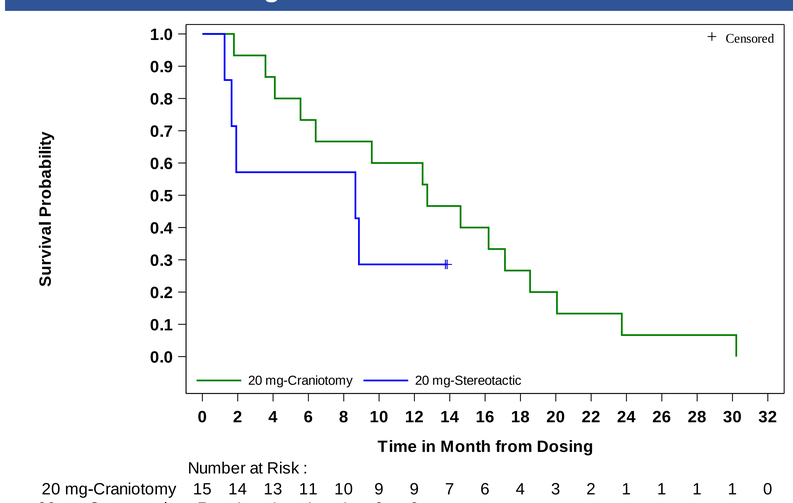


20 mg V Cohort	Dexamethasone Use (Days 0-14)	mOS (months)	Lower bound	Upper bound	Mean F/U	No. Events	No. Censored
Craniotomy	≤20 mg	17.8	14.6	23.7	18.4	6	0
	>20 mg	6.4	1.8	12.7	9.6	9	0
Stereotactic	≤20 mg	Not reached	1.7	Not reached	9.5	2	2
	>20 mg	1.9	1.3	8.7	3.9	3	0

Survival by Cohorts

Adverse Event	Craniotomy 10 mg V (N=6)	Craniotomy 20 mg V (N=15)	Stereotactic 20 mg V (N=7)	Craniotomy 30 mg V (N=4)	Craniotomy 40 mg V (N=6)
Median OS	**7.6**	**12.7**	**8.7**	**3.4**	**8.3**
95% CI (Lower, Upper)	1.8, 9.8	4.1, 17.1	1.3, -	0.5, 5.2	3.9, -
Mean Follow-up (mos)	6.7	13.1	7.1	3.1	13.1
6 month survival rate	66.7	73.3	57.1	0	83.3
12 month survival rate	0	60	28.6	0	33.3
18 month survival rate	0	26.7	Not reached	0	33.3
# of Events	6	15	5	4	5

Overall Survival: 20 mg Cohorts

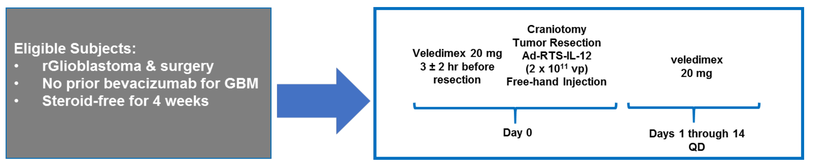


Conclusions

- **Median overall survival of 12.7 months is maintained with a mean follow-up time of 13.1 months in the 20 mg V craniotomy cohort which compares favorably to historical controls, with 4 subjects (26.7%) alive at 18 months**
- **mOS of 17.8 months in 20 mg V craniotomy cohort when steroids were ≤ 20 mg total over 14 days**
- **The 20 mg V dose was selected as the Phase III dose based on risk-benefit analysis**
- **Stereotactic 20 mg V dose was administered safely supratentorially**
- **Concurrent elevated steroid use (>20 mg total over 14 days) remains a negative contributing factor on overall survival**
- **Related AEs remain predictable and reversible across cohorts upon discontinuance of V. There were no drug-related deaths**
- **An expansion substudy of Ad+V 20 mg is ongoing in non-steroid-dependent subjects at entry and who were not previously treated with bevacizumab**
- **Enrollment is ongoing in a combination substudy of Ad+V with nivolumab**

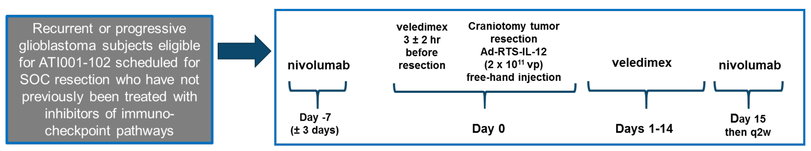
Next Steps Include: Ongoing Expansion and Combination Substudies

Expansion Substudy Schema



- Single-arm, open-label, multicenter substudy (NCT03679754) of the ATI001-102 Main study
- N=25
- Enrollment is ongoing

CPI Combination Substudy Schema



- Single-arm, open-label, dose-escalation, multicenter substudy (NCT03636477) of the ATI001-102 Main study
- N= up to 18
- Enrollment is ongoing
- Dosing cohorts
  - 10mg V, 1mg/kg nivolumab (completed)
  - 10mg V, 3mg/kg nivolumab (SRC and DSMB have authorized escalation)
  - 20mg V, 3mg/kg nivolumab (planned)