Final Results of Controlled IL-12 Monotherapy and in Combination with PD-1 Inhibitor in Adult Subjects with Recurrent Glioblastoma

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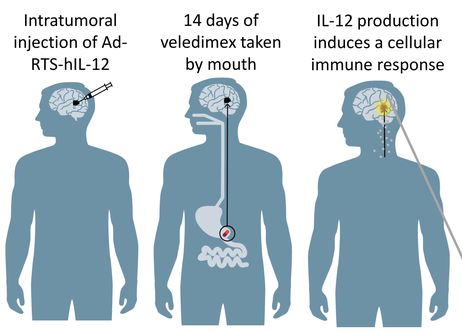
Submitted Abstract

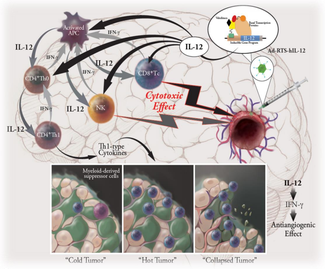
Ad-RTS-hIL-12(Ad) is a gene therapy candidate conditionally expressing IL-12 under the transcriptional control of veledimex(V) acting via the RheoSwitch Therapeutic System® gene switch. Veledimex plasma and tumor PK demonstrated a dose-response relationship and crossing the BBB. PD-1+ T-cells were increased in tumor biopsy samples after treatment with Controlled-IL-12 in a phase-I study. This finding was the rationale for conducting 2 trials of Controlled-IL-12 in combination with PD-1-inhibitor to enhance T-cell-mediated anti-tumor effects. Data from two completed phase-I studies (presented in SNO2020), and an ongoing phase-II study of Controlled-IL-12 with cemiplimab study for treatment of recurrent glioblastoma (rGBM) will be discussed.
Ziopharm has conducted 3 phase-I (NCT02026271/NCT03679754 (monotherapy), NCT03636477 (combination with nivolumab)) and one phase-II (NCT04006119) multicenter, open-label, single-arm trial in subjects with rGBM is evaluating Ad (single intratumoral injection, 2 x 10^{11}-viral-particles, Day 0) with oral V dosing (20mg, Days 0-14) with cemiplimab infusions (350 mg IV) on Days -7, 15, then Q3W. Systemic biomarkers (serum cytokines, and immune-activation-markers), local effects (tumor cytokines, T-cell immunobiology, pathology), neoepitope, and imaging will be assessed.
Subject characteristics (Controlled IL-12 monotherapy (n=75); combination (Controlled IL-12 with anti-PD-1s, n=61)) were consistent across all 3 studies. Safety profiles were comparable between monotherapy and in combination with anti-PD-1s. Adverse reactions (ARs) after nivolumab or cemiplimab were consistent with labeling of anti-PD-1s. ARs related to Controlled IL-12 were all manageable and reversible with no synergistic toxicities in combination with anti-PD-1s. Increases in serum cytokine levels and pathology findings consistent with immune-mediated anti-tumor effect were observed in subjects who received Controlled-IL-12 monotherapy and in combination with anti-PD-1s. Final survival data and results from neoepitope analysis will be presented. Further investigation is warranted to understand the impact of monotherapy vs. combination, concurrent steroids use and unifocal vs. multifocal disease on overall survival in subjects with rGBM receiving Controlled-IL-12.

Background on Controlled IL-12



- Ad-RTS-hIL-12 intratumoral injection regulated by veledimex drives downstream production of endogenous IFN-γ, and elicits a brisk cytotoxic immune response
- Systemic corticosteroids are routinely used to treat edema in patients with intracranial tumors. However, it is not well studied if or when corticosteroids can be administered without abrogating the benefits of immunotherapy.

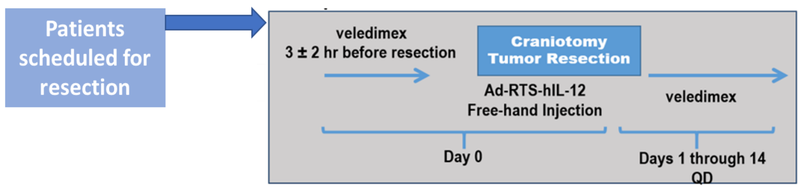
1. **Gene Switch Components:** RheoSwitch Therapeutic System® (RTS®) technology includes VP16-RXR (co-activation partner, CAP) and Gal4-EcR (ligand-inducible transcription factor, LTF. Without ligand, LTF binds to the inducible promoter and does not form a stable complex with CAP.
2. **Inducible Promoter: C**ustomizable (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.



As previously presented at SNO 2019

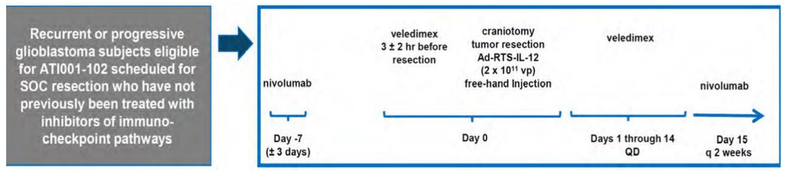
Study Designs

Main Study Schema: ATI001-102 Controlled IL-12 (monotherapy)



- NCT02026271: Phase 1, single-arm, open-label, dose-escalation, multicenter study
- N=15 in 20 mg veledimex (V) dosing level
- Study is completed

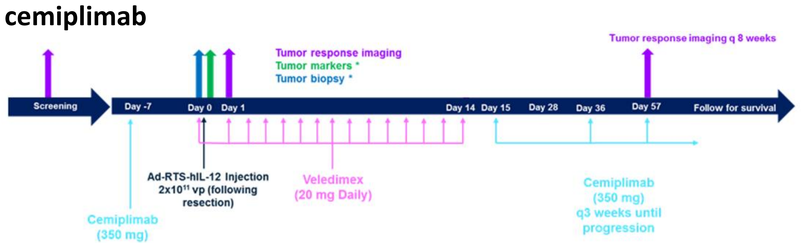
Substudy Schema: ATI001-102 in Combination with nivolumab



- NCT03636477: Phase 1, single-arm, open-label, dose-escalation, multicenter substudy
- 3 dosing cohorts: 10mg V, 1mg/kg nivolumab (n=3); 10mg V, 3mg/kg nivolumab (n=3); and 20mg V, 3mg/kg nivolumab (n=15)
- Neoadjuvant dose of nivolumab on Day -7, q 2 weeks after V dosing
- Study is completed

Study Design Cont.

Study Schema: ATI001-204 Controlled IL-12 in Combination with cemiplimab



- NCT04006119: Phase 2, single-arm, open-label, multicenter substudy
- Ad-RTS-hIL-12: intratumoral 2 x 10^{11} vp administered on Day 0
- Veledimex: 20 mg PO QD on Days 0 to 14
- Cemiplimab: 350 mg IV on Day -7, Day 15, and approximately every 3 weeks (Q3W) until confirmed progression (iRANO), unacceptable toxicity or subject withdrawal

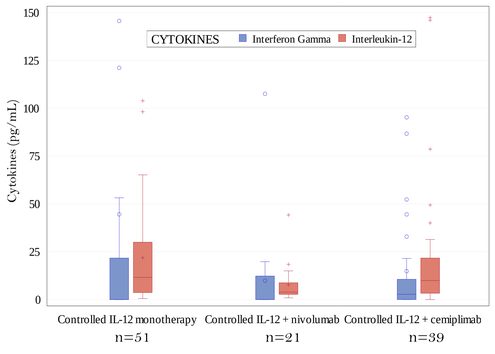
Subject Characteristics by Study

Characteristics	Controlled IL-12 Monotherapy N=52	Controlled IL-12 + nivolumab N=21	Controlled IL-12 + cemiplimab N=40
Age in years, Mean (SD)	50.1 (13.5)	57.3 (14.1)	55.5 (13.4)
Gender			
Female	19 (36.5%)	9 (42.9%)	15 (37.5%)
Male	33 (63.5%)	12 (57.1%)	25 (62.5%)
Disease Status at Entry[2]			
Unifocal	37 (71.2%)	15 (71.4%)	33 (82.5%)
Multifocal	15 (28.8%)	6 (28.6%)	7 (17.5%)
Number of Lesions at Entry[3]			
1	25 (48.1%)	10 (47.6%)	28 (70.0%)
2	18 (34.6%)	7 (33.3%)	7 (17.5%)
3+	9 (33%)	4 (19.0%)	5 (12.5%)
Number of recurrences			
1st recurrence	29 (55.8%)	15 (71.4%)	30 (75.0%)
≥2 recurrence	21 (40.4%)	5 (23.8%)	10 (25.0%)
Missing	2 (3.8%)	1 (0.8 %)	0 (0%)
IDH Status, N (%)			
Mutated	9 (17.3%)	2 (9.5%)	1 (2.5%)
Wild-Type	37 (71.2%)	19 (90.5%)	37 (92.5%)
Missing	6 (11.5%)	0 (0%)	2 (5.0%)
Methylation Status, N (%)			
Methylated	19 (36.5%)	8 (38.1%)	10 (25.0%)
Unmethylated	23 (44.2%)	11 (52.4%)	28 (70.0%)
Missing	10 (19.2%)	2 (9.5%)	2 (5.0%)
KPS at Screening, N (%)			
≥70 - 90	19 (36.5%)	4 (19.0%)	25 (62.5%)
≥ 90	33 (63.5%)	17 (81.0%)	15 (37.5%)
Concurrent Steroids Use			
Dexamethasone (total, Days 0-14)			n=39[1]
≤20 mg	32 (61.5%)	17 (81.0%)	31 (79.5%)
>20 mg	20 (38.5%)	4 (19.0)	8 (20.5%)
Veledimex Dosing Compliance (%)			n=39[1]
100%	28 (53.8%)	16 (76.2%)	23 (59.0%)
< 100%	24 (46.2%)	5 (23.8%)	16 (41.0%)

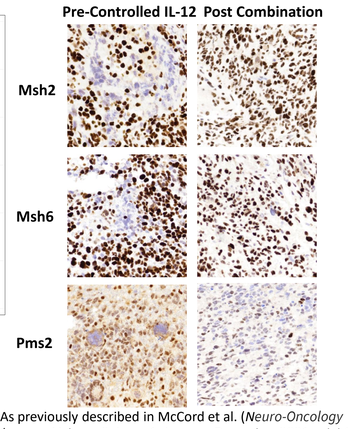
[1]One subject only received cemiplimab (Ad-RTS-hIL-12 + veledimex were not administered). [2]Based on number of reported enhancing lesions. [3]Based on number of enhancing and non-enhancing lesions.

Serum Cytokines and Pathology Findings

Peak Serum IL-12 and IFNγ by Study



Subject* who entered the ATI001-204 study with a hypermutated glioma. Following treatment with Controlled IL-12 and cemiplimab had disappearance of alterations in MSH2, MSH6 and PMS2 suggests that this combination therapy activated the immune system to target the glioma cells with the mismatch repair deficiency.

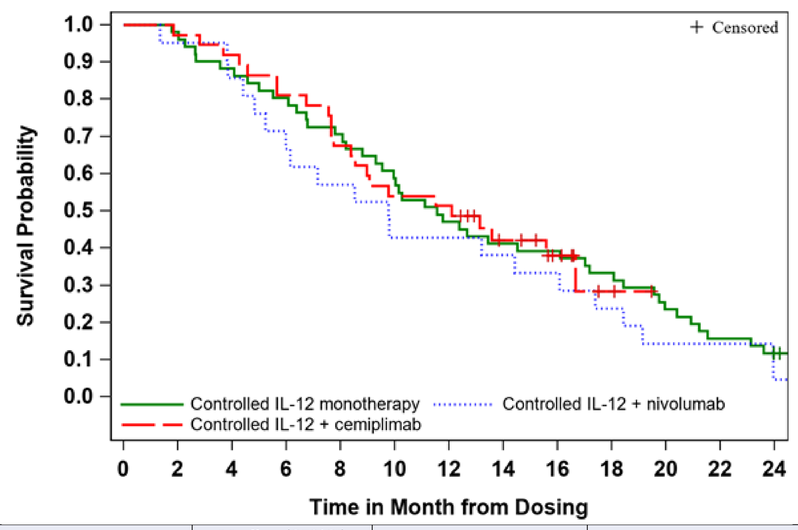


* As previously described in McCord et al. (*Neuro-Oncology Advances*, Volume 3, Issue 1, January-December 2021, vdab045)

Safety Profile

Safety	Controlled IL-12 Monotherapy (n=52, 20 mg V)	Controlled IL-12 + nivolumab (n=21)	Controlled IL-12 + cemiplimab (n=40)
Any Drug-Related TEAEs Leading to Treatment Discontinuations	3 (5.8 %) (Ad+V)	3 (14.3 %)	3 (7.5 %)
Hemoglobin Decreased	1 (1.9%) (Ad+V)	0	0
Leukopenia	1 (1.9%) (Ad+V)	0	0
Thrombocytopenia	1 (1.9%) (Ad+V)	0	0
AST Increased	3 (5.8%) (Ad+V)	0	0
ALT Increased	3 (5.8%) (Ad+V)	0	0
LDH Increased	1 (1.9%) (Ad+V)	0	0
Liver Function Test Increased	1 (1.9%) (Ad+V)	0	0
Pyrexia	1 (1.9%) (Ad+V)	0	1 (2.5%) (Ad+V and cemi)
Arthralgia	0	1 (4.8%) (nivo)	0
Immune Reconstitution Inflammatory Syndrome	0	1 (4.8%) (nivo)	0
Cold Type Haemolytic Anaemia	0	1 (4.8%) (Ad+V and nivo)	0
Headache	0	1 (4.8%) (Ad+V and nivo)	0
Mental Disorder	0	0	1 (2.5%) (Ad+V)
Cytokine Release Syndrome	0	0	1 (2.5%) (Ad+V)
Encephelopathy	0	0	1 (2.5%) (Ad+V)
Transaminases Increased	0	0	1 (2.5%) (cemi)
Any Drug-Related Serious TEAEs	11 (21.2 %)	5 (23.8 %)	10 (25.0 %)
Aseptic Meningitis	1 (1.9%) (Ad+V)	0	0
Brain Oedema	0	3 (14.3%)(Ad+V (n=1), nivo (n=2))	2 (5%) (Ad+V and cemi)
Cytokine Release Syndrome	2 (3.8%) (Ad+V)	0	1 (2.5%) (Ad+V and cemi)
Encephelopathy	0	0	4 (10%) (Ad+V (n=3) Ad+V and cemi (n=1))
Enterocolitis	0	0	1 (2.5%) (cemi)
Headache	1 (1.9%) (Ad+V)	0	0
Hemiparesis	0	0	1 (2.5%) (Ad+V)
Leukopenia	1 (1.9%) (Ad+V)	0	0
Live Function Test Increased	1 (1.9%) (Ad+V)	0	0
Mental Disorder	0	0	1 (2.5%) (Ad+V)
Mental Status Change	1 (1.9%) (Ad+V)	0	0
Nausea	2	0	0
Neutropenia	1 (1.9%) (Ad+V)	0	0
Neutrophil Count Decreased	1 (1.9%) (Ad+V)	0	1 (2.5%) (Ad+V)
Pyrexia	2 (3.8%) (Ad+V)	0	1 (2.5%) (Ad+V and cemi)
Seizure	1 (1.9%) (Ad+V)	0	0
Thrombocytopenia	2 (3.8%) (Ad+V)	0	0
Arthralgia	0	1 (4.8%) (nivo)	0
Cold Type Haemolytic Anaemia	0	1 (4.8%) (Ad+V and nivo)	0
Cytokine Release Syndrome	0	1 (4.8%) (Ad+V and nivo)	0
Immune Reconstitution Inflammatory Syndrome	0	1 (4.8%) (nivo)	0

Overall Survival



Study	Median (95%CI) (Months)	Number of Events (%)	Number of Censored (%)
Controlled IL-12 monotherapy	11.6 (8.8 , 17.0)	47 (92.2)	4 (7.8)
Controlled IL-12 + nivolumab	9.8 (5.2 , 16.1)	20 (95.2)	1 (4.8)
Controlled IL-12 + cemiplimab	12.1 (8.4 , 16.7)	23 (62.2)	14 (37.8)

Discussion and Conclusion

- Controlled IL-12 monotherapy and in combination with checkpoint inhibitors demonstrated immune activation by increases in serum IL-12 with associated downstream production of IFNγ
- The safety profiles were comparable between Controlled IL-12 monotherapy and in combination with anti-PD-1 therapies
  - Adverse Reactions (ARs) related to Controlled IL-12 were all manageable and reversible
  - Frequency of ARs leading to study discontinuation and serious ARs were similar across studies
  - There have been no drug-related deaths in either monotherapy or in combination with anti-PD-1s
- Median overall survival for Controlled IL-12 monotherapy (n=51) was 11.6 (8.8, 17.0) months, Controlled IL-12 with nivolumab (n=21) was 9.8 (5.2, 16.1) months and Controlled IL-12 with cemiplimab (n=37) was 12.1 (8.4, 16.7) months
- Future studies should investigate the schedule of Controlled IL-12 and anti-PD-1 administration and whether neoadjuvant dosing should be reconsidered