PD-1 Inhibition can be Combined with IL-12 in Subjects with Recurrent Glioblastoma

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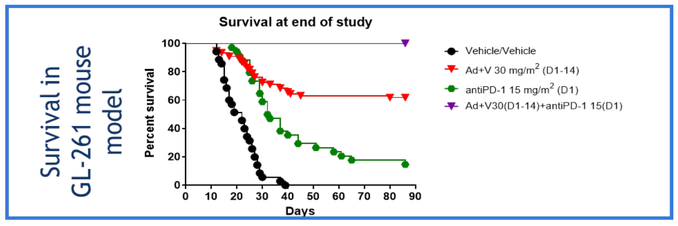
Submitted Abstract

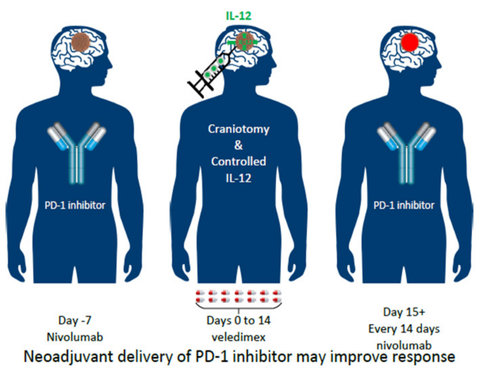
Monotherapy with intratumoral Ad-RTS-hIL-12 (Ad), a novel gene therapeutic conditionally expressing IL-12 under the transcriptional control of oral veledimex (V, 20 mg) acting via the proprietary RheoSwitch Therapeutic System® (RTS®), was shown in a phase 1 Main study (NCT02026271) to elicit a sustained intra-tumoral activated cytotoxic T-cell response with co-expression of PD-1. Additionally, the Main study showed improved median overall survival (mOS), compared to historical controls, in subjects with recurrent glioblastoma (rGBM) receiving Ad + V. Herein, we report updated findings from on an ongoing open label, dose-escalation Phase 1 substudy (NCT03636477) evaluating safety and tolerability of local, controlled IL-12 plus nivolumab in adult subjects with rGBM. Ad was administered by single intratumoral injection (2 x 10^{11} viral particles) on Day 0 plus V (10 and 20 mg) PO QD x 15 with nivolumab (1 and 3mg/kg) IV on Days -7, 15, then Q2W. Subjects have been accrued into three cohorts and follow-up is ongoing. Data from all three cohorts regarding dose escalation of V and nivolumab will be presented. The initial safety profile during V dosing period was similar to Ad+V monotherapy with adverse reactions being dose-related and rapidly reversible upon discontinuation of V. And those adverse reactions during the follow on nivolumab dosing were tolerable and manageable and consistent with nivolumab labeling, with no synergistic toxicities, and drug-related deaths. In the first two cohorts (where data is available), combination therapy improved the biomarker "cytoindex" (ratio of circulating $CD8^+$ T cells to $FoxP3^+$ regulatory T cells). (In the Main study, cytoindex correlated with overall survival). 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. Further phase 2 investigation of Ad+V plus a checkpoint inhibitor in rGBM is planned.

Background on Combining Controlled IL-12 with PD-1 Inhibitor

Preclinical Study:



- Ad-RTS-hIL-12 (Ad) intratumoral injection regulated by veledimex (Ad+V) drives downstream production of endogenous IFN-γ, and elicits a cytotoxic immune response
- Controlled IL-12 production was able to stimulate the immune system in the tumor microenvironment
- PD-1 inhibitor therapy resulted in a partial reduction in tumor
- The combination of both therapies resulted in a substantial increase in survival versus control and the monotherapies
- A clinical study initiated to assess the combination of Ad+V with an immune checkpoint inhibitor in subjects with recurrent GBM



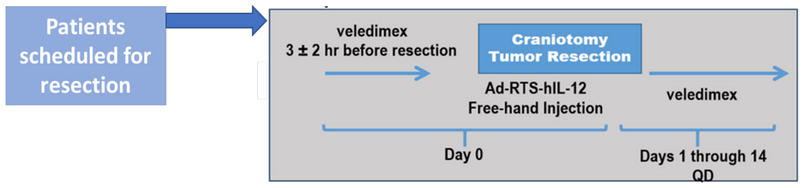
Neoadjuvant delivery of PD-1 inhibitor may improve response

Adapted from Nat Med 2019 Mar, 25(3):477-486

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

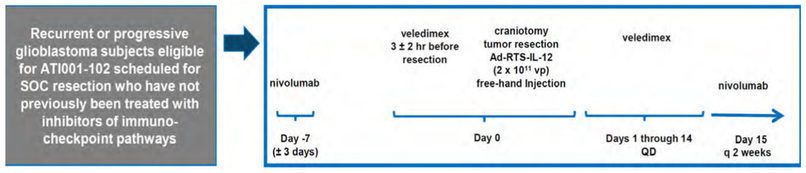
Study Design

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



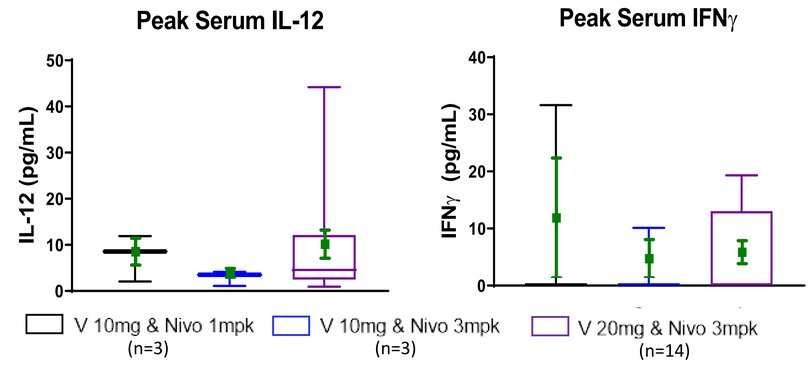
- NCT02026271: Phase 1, single-arm, open-label, dose-escalation, multicenter study
- N=15 in 20 mg veledimex (V) dosing level
- Study enrollment and follow-up have been completed
- Overall survival in the 20-mg V cohort was 12.7 mons (mean follow-up time of 13.1 mons). Subjects (n=6, unifocal) who received low-dose (≤ 20-mg) steroid during active dosing (Days 0-14, coinciding with administration of V) had an mOS of 17.8 mons

Substudy Schema: ATI001-102 Immune Checkpoint Inhibitor (iCPI)



- 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
- Subject treatment is currently ongoing

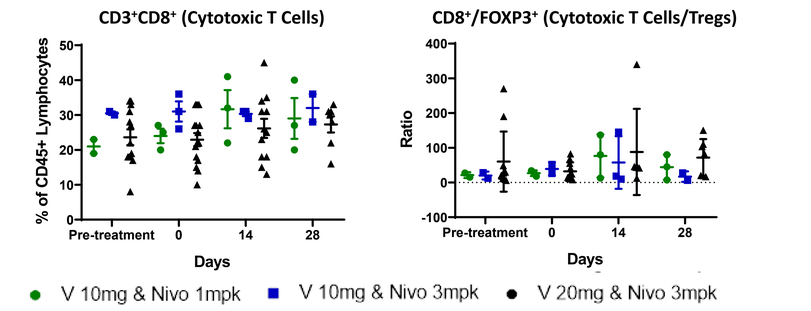
Serum Cytokine Levels Demonstrate that V Controls IL-12 via RTS



IL-12 (pg/mL)	Baseline	Pre - Ad+V	Peak		
	Mean ± SEM	Mean ± SEM	Mean ± SEM	Min	Max
V 10mg & Nivo 1mpk	1.2 ± 0.4	0.9 ± 0.2	7.5 ± 2.9	2.1	11.9
V 10mg & Nivo 3mpk	0.7 ± 0.1	1.1 ± 0.4	2.9 ± 0.9	1.1	4.1
V 20mg & Nivo 3mpk	0.4 ± 0.1	0.6 ± 0.1	9.1 ± 3.0	0.9	44.2

IFNγ (pg/mL)	Baseline	Pre - Ad+V	Peak		
	Mean ± SEM	Mean ± SEM	Mean ± SEM	Min	Max
V 10mg & Nivo 1mpk	3.6 ± 3.6	2.8 ± 2.8	10.5 ± 10.5	0	31.6
V 10mg & Nivo 3mpk	0 ± 0	0 ± 0	3.4 ± 3.4	0	10.1
V 20mg & Nivo 3mpk	0 ± 0	0 ± 0	4.5 ± 2.0	0	19.3

Peripheral Blood Flow Cytometry and Cytoindex



Cytoindex was measured as the ratio of $CD8^+/FoxP3^+$ (cytotoxic/suppressor to regulatory) T cells

Evidence of Immune-Mediated Anti-Tumor Response by Serial MRI

In the Main Study 3/3 subjects underwent biopsy at suspected progression which confirmed extensive immune (T-cell) infiltrate per Sci Transl Med. 2019 Aug 14;11(505). Below are serial MRI scans from a CPI Substudy subject showing progression at Week 12 consistent with pseudoprogression, followed by a partial response by iRANO (64% reduction) measured through Week 36. Subject remains on treatment and monitoring is ongoing.

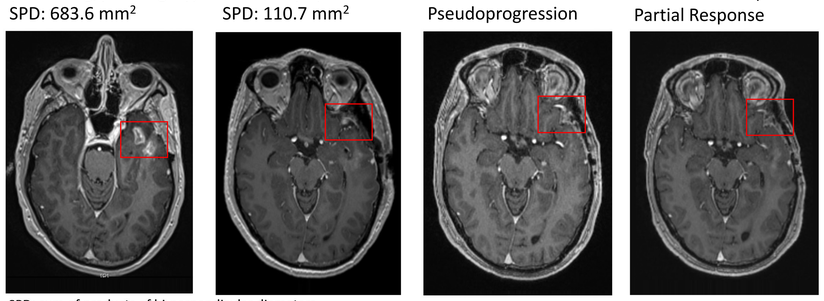
- Subject 106, 59 year old male with 1 prior line of therapy
- Unifocal disease at study entry, with 1 enhancing and 1 non-enhancing lesion
- Received 15 doses of 10 mg of veledimex and 3 mg/kg of nivolumab (21 doses)
- Received 10 mg of dexamethasone during active dosing
- Experienced Grade 2 CRS

Pre-Baseline (Screening/pre-surgery) SPD: 683.6 mm^2

Baseline (at time of Ad+V, Day 0) SPD: 110.7 mm^2

12 Weeks after Ad+V SPD: 185.3 mm^2 Pseudoprogression

36 Weeks after Ad+V SPD: 39.9 mm^2 (64% reduction) Partial Response



SPD: sum of products of bi-perpendicular diameters

Safety Results[1]

Adverse Event [2]	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=3		Expansion Cohort: Ad+V (20 mg) Nivolumab (3 mg/kg) N=12	
Relationship	Ad+V	Nivo	Ad+V	Nivo	Ad+V	Nivo	Ad+V	Nivo
Related ≥ Grade 3 AEs								
Lymphocyte count decreased[3]	0	1 (33%)	2 (67%)	1 (33%)	1 (33%)	0	2 (17%)	0
ALT increased	1 (33%)	0	0	0	2 (67%)	0	0	0
Edema, cerebral	0	1 (33%)	0	0	0	0	0	0
Lipase increased	0	0	0	1 (33%)	0	0	0	0
Related SAEs								
Cerebral Edema	0	1 (33%)	0	0	0	0	0	0
Cytokine Release Syndrome	0	0	0	0	0	0	1 (33%)	0
Cytokine Release Syndrome[4]								
Grade 2	3 (100%)		3 (100%)		2 (67%)		5 (42%)	
Grade 3	0		0		0		1	

[1]Data collection and cleaning are ongoing; [2]CTCAE v5.0 as applicable; [3]One ≥ Grade 3 AE (Lymphocyte count decreased) was considered related to both Ad+V and nivolumab; [4]Ziopharm Cytokine Release Syndrome, Working Definition.

Recurrent GBM Subject Characteristics

Characteristics[1]	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=3	Follow-on Cohort Ad+V (20 mg) Nivolumab (3 mg/kg) N=12
Age in years, Mean (Min, Max)	43.0 (30, 63)	59.4 (52, 66)	60.1 (47, 76)	59.7 (24, 78)
Gender				
Male	1 (33%)	1 (33%)	1 (33%)	6 (50%)
Female	2 (67%)	2 (67%)	2 (67%)	6 (50%)
Disease Status at Entry[2]				
Unifocal	2 (67%)	3 (100%)	3 (100%)	2 (17%)
Multifocal	1 (33%)	0	0	3 (25%)
TBD	0	0	0	7 (58%)
Number of Lesions at Entry[3]				
1	1 (33%)	2 (67%)	2 (67%)	0
2	1 (33%)	1 (33%)	1 (33%)	2 (17%)
3+	1 (33%)	0	0	3 (25%)
TBD	0	0	0	7 (58%)
Number of recurrences				
1st recurrence	2 (67%)	3 (100%)	2 (67%)	8 (67%)
≥2 recurrence	1 (33%)	0	1 (33%)	3 (25%)
TBD	0	0	0	1 (8%)
Prior Lines of Treatment (Mean)	1 (1, 1)	1 (1, 1)	1.7 (1,3)	1.6 (1,4)
IDH Status, N (%)				
Mutated	1 (33%)	0	1 (33%)	0
Wild-Type	2 (67%)	3 (100%)	2 (67%)	12 (100%)
Methylation Status, N (%)				
Methylated	2 (67%)	1 (33%)	0	5 (42%)
Unmethylated	1 (33%)	2 (67%)	3 (100%)	5 (42%)
TBD	0	0	0	2 (17%)
KPS at Screening, N (%)				
≥70 - 90	0	0	2 (67%)	2 (17%)
≥ 90	3 (100%)	3 (100%)	1 (33%)	10 (83%)
Cumulative Steroid Use				
Days 0-14 (mg) (Mean, Range)	64.7 (0, 116)	3.3 (0, 10)	0 (0, 0)	25.5 (0, 280)
Concurrent Steroids Use				
Dexamethasone (total, Days 0-14)				
≤20 mg	1 (33%)	3 (100%)	3 (100%)	10 (83%)
>20 mg	2 (67%)	0	0	1 (8%)
TBD	0	0	0	1 (8%)
Veledimex Dosing Compliance (%) V qd (for 15 days)	97.8%	100%	95.5%	93.3%

[1]Data collection and cleaning are ongoing: Data as of 14Nov19 [2]Based on number of reported enhancing lesions. [3]Based on number of enhancing and non-enhancing lesions.

Discussion and Conclusion

- The interim data for the combination with an immune checkpoint inhibitor are comparable to the encouraging data observed in monotherapy using Controlled IL-12
  - In monotherapy, (Main ATI001-102 + Expansion Substudy) 20 mg subjects with unifocal disease at entry, receiving low-dose steroids (N=20) concurrent with V dosing show a trend towards longer median overall survival (16.2 mons) – SNO 2019, poster ATIM-18
  - Median overall survival has not been reached in this combination substudy: Mean follow up is 4.8 mons (min 0.9, max 16.9); Subject treatment is currently ongoing
  - Drug-related toxicities in the iCPI substudy were comparable to the Main Study, being predictable, dose-related, and promptly reversible upon discontinuation of veledimex and with no drug-related deaths
  - Moreover, in the iCPI Substudy there were no DLTs, no SAEs were considered related to the combination with nivo, and no clinically significant overlapping toxicities were observed
- Data shows activity of Ad+V in combination with iCPI
  - Serum IL-12 was detected in all subjects following initiation of Ad+V, which is consistent with previously reported data on Ad+V monotherapy
  - Cytoindex findings support activation of the cellular immune system by Controlled IL-12
  - MRI findings of pseudoprogression followed by partial response
- The findings of this substudy suggest that Controlled IL-12 production using Ad+V and nivolumab is a rational combination with a favorable safety profile and initial data consistent with immune-mediated anti-tumor effects
- To further investigate Ad+V in combination with an iCPI in rGBM subjects, a phase 2 trial of Ad+V in combination with cemiplimab-rwlc is currently ongoing (NCT04006119)