Phase 2 Trial of Controlled IL-12 in Combination with PD-1 Inhibitor in Adult Subjects with Recurrent Glioblastoma

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Presented by: Rimas V. Lukas, MD

Disclosure Statement

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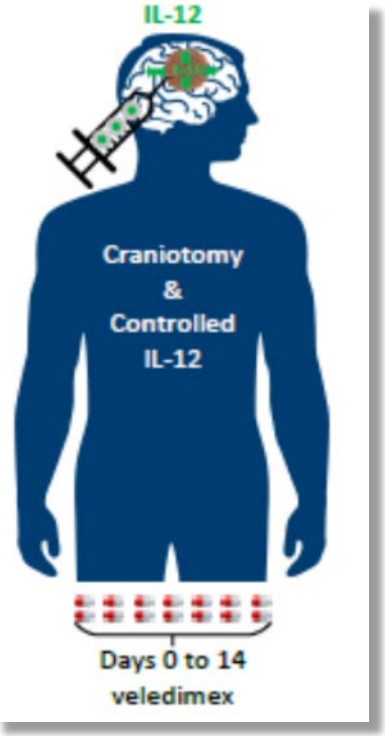
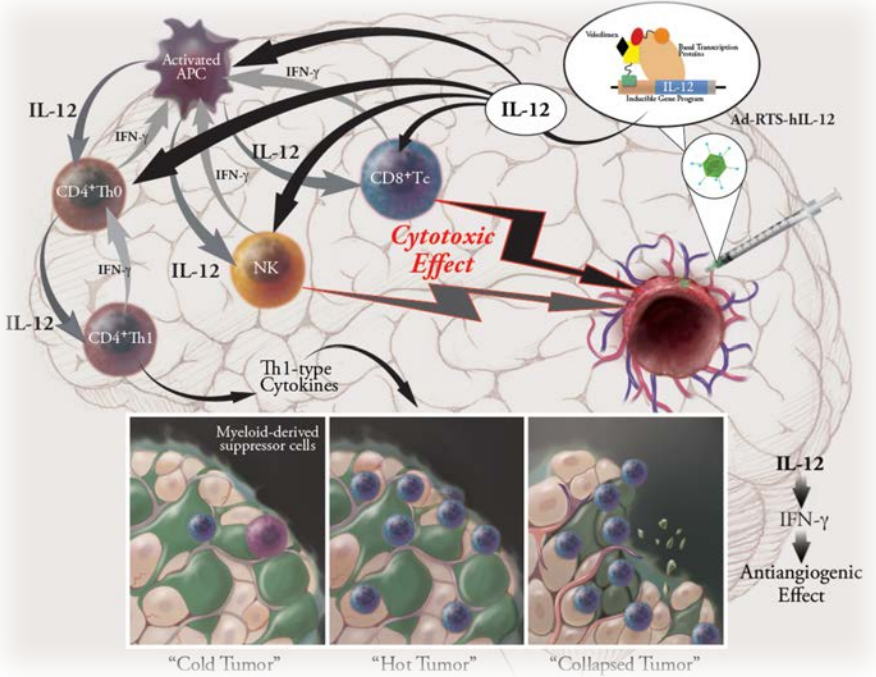
Controlled IL-12 is a Gene Therapy Vector in which IL-12 Expression is under Control of a Regulatable Promoter, Switched on by the Small Molecule Ligand, Veledimex (V)





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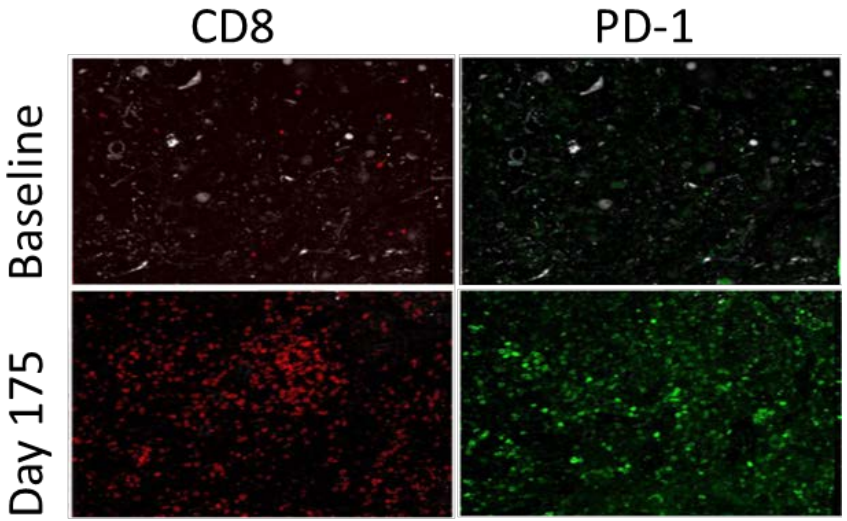
Rationale for Combining Controlled IL-12 with a PD-1 Inhibitor

In a phase 1 trial of IL-12 gene monotherapy for rGBM Controlled IL-12 was well tolerated, showed encouraging survival benefits and evidence of increased $CD8^+$ immune infiltrates in post-treatment biopsies (Chiocca et al., *Sci Trans Med*, 2019)

- Ad-RTS-hIL-12 (Ad) intratumoral injection regulated by veledimex (V) drives downstream production of endogenous IFNγ, which then elicits a brisk cytotoxic immune response
- In a preclinical model PD-1 inhibitor therapy resulted in a partial reduction in tumor
- A phase 2 clinical study was initiated to assess the combination of Ad+V with an anti-PD-1 in subjects with recurrent GBM

However, there was evidence of a suppressive tumor microenvironment with increased expression of PD-1



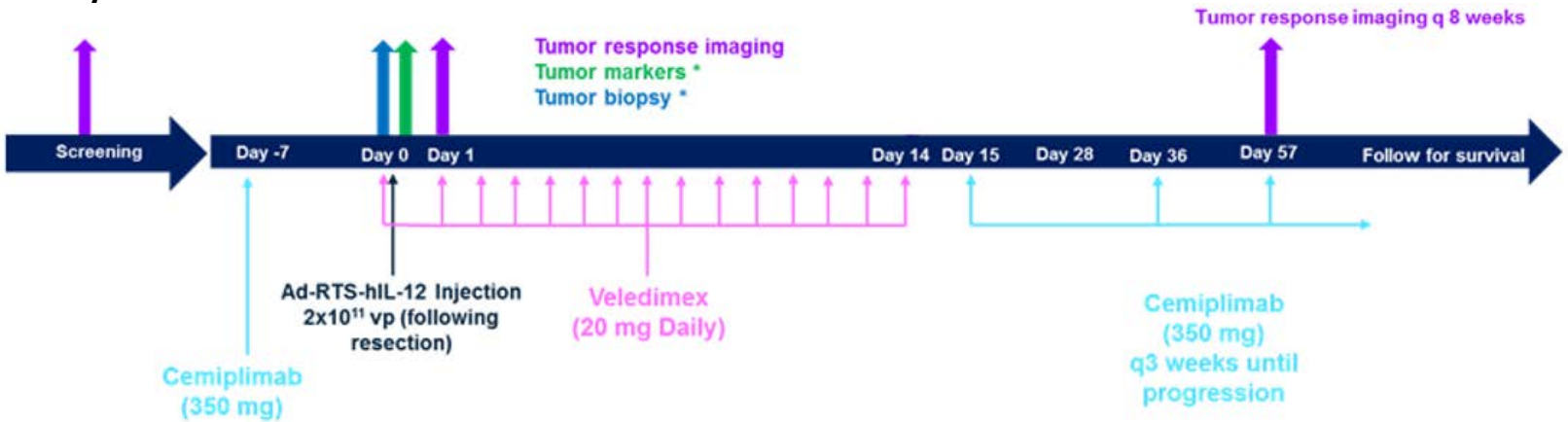
Study Design (NCT04006119)

Study dose:

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

Study Schema: ATI001-204



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*Approved as a monotherapy for the treatment of patients with metastatic CSCC or locally advanced CSCC who are not candidates for curative surgery or curative radiation

Subject Characteristics

Subjects with recurrent glioblastoma who were I/O naïve* had characteristics consistent with previously presented data and published studies

- Not previously treated with iCPIs (e.g., anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-CTLA4) or agents specifically targeting T cells
- Cemiplimab dosing is ongoing for 8 subjects

Characteristics[1]	Ad+V (20 mg) Cemiplimab-rwlc (350 mg/kg) N=40
Age in years, Mean (Min, Max)	55 (26, 75)
Gender	
Male	15 (37.5%)
Female	25 (62.5%)
Disease Status at Entry[2]	
Unifocal	33 (82.5%)
Multifocal	7 (7.5%)
Number of Lesions at Entry[3]	
1	27 (67.5%)
2	7 (17.5%)
3+	6 (15.0%)
Number of recurrences	
1st recurrence	26 (65.0%)
≥2 recurrence	14 (35.0%)
Prior Lines of Treatment, Mean (Min, Max)	1.5 (1, 3)
IDH Status, N (%)	
Mutated	2 (5.0%)
Wild-Type	37 (92.5%)
TBD	1 (2.5%)
Methylation Status, N (%)	
Methylated	11 (27.5%)
Unmethylated	28 (70.0%)
TBD	1 (2.5%)
KPS at Screening, N (%)	
≥70 - 90	14 (35.0%)
≥ 90	26 (65.0%)
Cumulative Steroid Use (N=25)	
Days 0-14 (mg) (Mean, Range)	9.2 (0, 84.0)
Concurrent Steroids Use Dexamethasone (total, Days 0-14)	
≤20 mg	22 (55.0%)
>20 mg	4 (10.0%)
TBD	14 (35.0%)
Veledimex Dosing Compliance (%)	
100%	20 (51.3%)
<100%	12 (30.8%)
TBD	7 (17.9%)
Cemiplimab Doses (Mean, Range)	5.5 (1, 15)

[1]Data as of 16Oct2020. Data collection and cleaning ongoing, [2]Based on number of reported enhancing lesions, [3]Based on number of enhancing and non-enhancing lesions

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Safety Results Were Similar to Monotherapy

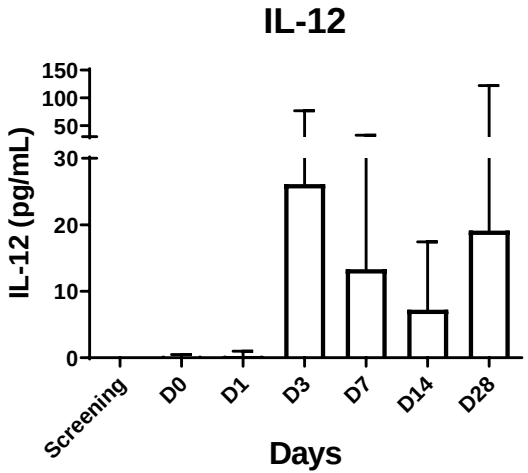
- Initial safety data (189 unique adverse reactions in 40 subjects) appeared similar to Ad+V monotherapy and the cemiplimab label, respectively, being manageable without synergistic toxicities and generally reversible
- Of 65 SAEs reported in 27 subjects, 11 SAEs in 9 subjects were related to Ad+V, of which 6 were also related to cemiplimab. None were related to cemiplimab alone
- There were 3 SUSARs in 2 subjects
  - Hemiparesis, Encephalopathy, Acute Cholecystitis
- There were no related fatal events

Totals[1]	Ad+V (20 mg) + Cemiplimab-rwlc (350 mg/kg) (Frequency, N=40)
# of SAEs	65 (67.5)
# of SUSARs	3 (7.5)
Related SAEs (related to A+V, Cemi or Both)	
Brain oedema	2 (5.0)
Cytokine release syndrome	1 (2.5)
Encephalopathy	4 (10.0)
Hemiparesis	1 (2.5)
Mental disorder	1 (2.5)
Neutrophil count decreased	1 (2.5)
Pyrexia	1 (2.5)
Cytokine Release Syndrome[4]	
Grade 2	12 (30.0)
Grade 3	3 (7.5)

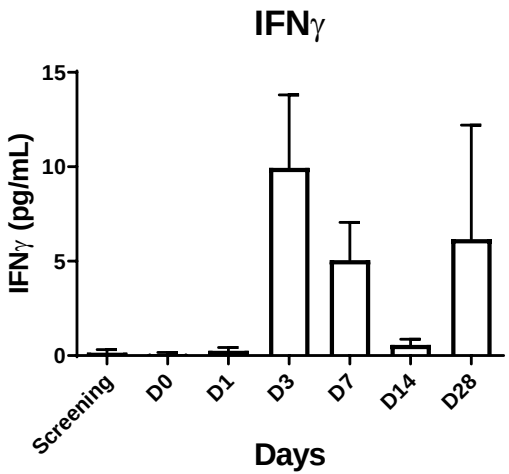
Treatment Emergent Adverse Events (>10%)						
Preferred Term[1]	Related to Ad + V alone (N=34)		Related to Cemi alone (N=34)		Related to both (N=34)	
	Any Grade	>= Grade 3	Any Grade	>= Grade 3	Any Grade	>= Grade 3
Any related AE	28 (70.0)	9 (22.5)	25 (62.5)	4 (10.0)	26 (65.0)	15 (37.5)
ALT increased	3 (7.5)	0	0	0	4 (10.0)	1 (2.5)
Headache	4 (10.0)	0	0	0	2 (5.0)	0
Lymphocyte decreased	6 (15.0)	3 (7.5)	1 (2.5)	0	5 (12.5)	3 (7.5)
Lymphopenia	1 (2.5)	1 (2.5)	0	0	4 (10.0)	3 (7.5)
Nausea	5 (12.5)	0	1 (2.5)	1 (2.5)	3 (7.5)	0
Pyrexia	18 (45.0)	0	0	0	6 (15.0)	1 (2.5)
Rash maculo-papular	0	0	5 (12.5)	0	0	0
Vomiting	6 (15.0)	0	2 (5.0)	0	1 (2.5)	0
WBC count decreased	0	0	1 (2.5)	0	4 (10.0)	2 (5.0)

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

Serum Cytokine Levels then Cytotoxic T Cells Increased Following Ad + V Administration



Visit	Scrn	D0	D1	D3	D7	D14	D28
N	36	36	30	36	31	34	31



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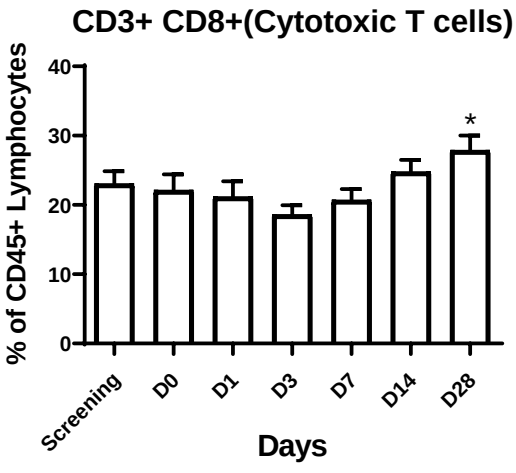

Visit	Scrn	D0	D1	D3	D7	D14	D28
N	35	32	25	35	31	34	31

- Serum IL-12 levels which were 0 ± 0 pg/mL (screening) and 0.1 ± 0.1 pg/mL (Day 0) pretreatment (Ad+V), increased following Ad+V to 26.1 ± 8.5 pg/mL (Day 3). (mean ± SEM)
- Serum IFNγ levels did not increase after neoadjuvant cemiplimab dose (screening), 0.2 ± 0.2 pg/mL; Day 0, 0.1 ± 0.1 pg/mL, but increased after Ad+V to 9.9 ± 3.9 pg/mL on Day 3. (mean ± SEM)
- CD3+CD8+ cytotoxic T cells increased between Day 0 and Day 28.

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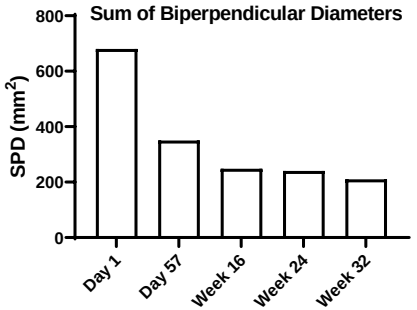
Evidence of Immune-Mediated Anti-Tumor Response from MRIs

Subject 009, 69-year-old female status post 1 prior line of therapy

- Recurrent GBM at study entry, with 1 enhancing and 1 non-enhancing lesion
- Received 14/15 doses of veledimex (20 mg)
- Administered no dexamethasone during active dosing
- AE of Grade 2 CRS



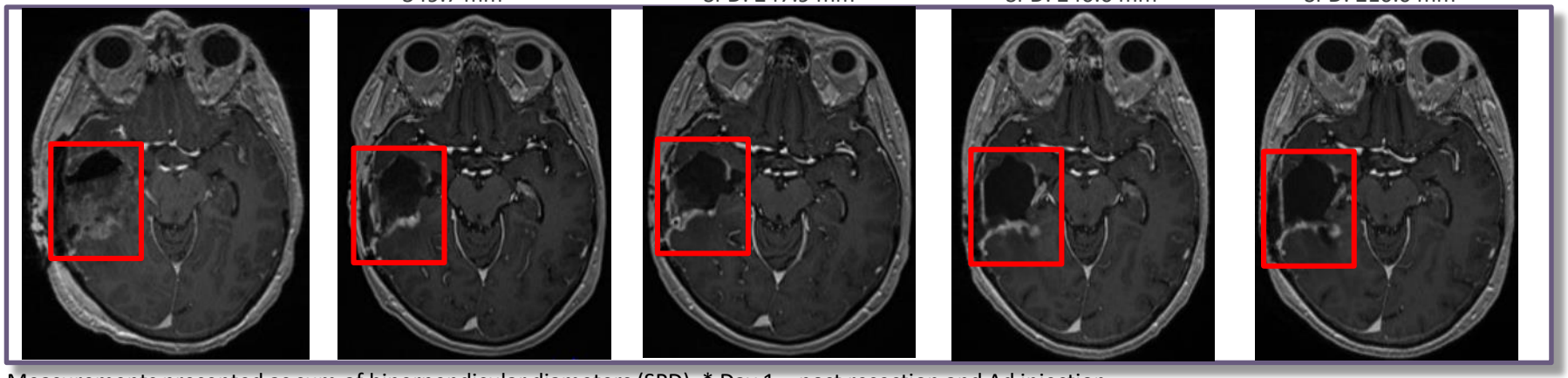
Baseline*
SPD: 680.6 mm²

Day 57 – SD
349.7 mm²

Week 16 – PR
SPD: 247.9 mm²

Week 24 – PR
SPD: 240.0 mm²

Week 32 – PR
SPD: 210.0 mm²



Measurements presented as sum of biperpendicular diameters (SPD), * Day 1 – post resection and Ad injection

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Discussion and Conclusion

Results for Ad+V in combination with the cemiplimab are comparable to Controlled IL-12 monotherapy

- The increase in serum cytokine levels provide evidence that V controls IL-12 transcription via the RTS® gene switch
  - Consistent with previously reported data of Ad+V monotherapy, increases in serum IL-12 and downstream IFNγ were detected following initiation of Ad+V
  - Peak serum IL-12 levels for AD+V and cemiplimab were higher than either for monotherapy V 20 mg (ASCO 2020) or the Ad+V combination with nivolumab (SNO 2020)
- Controlled IL-12 resulted in activation of the immune system
  - Circulating cytotoxic T cells slightly but significantly increased (Day 28) although the clinical significance is undetermined
- Controlled IL-12 with cemiplimab was well tolerated
- Serial MRIs showed evidence of an immune-mediated anti-tumor response
- Median overall survival has not been reached in this combination study
- Mean follow-up time was 6.5 months (1.9 min, 14.5 max)
- Enrollment is complete
- Cemiplimab dosing and follow-up are ongoing