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 therapy conditionally expressing IL-12 under the transcriptional control of viral vcl (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 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 1011 viral particles) on Day 0 plus V (10 and 20 mg) PO QD x 15 days with nivolumab (1 and 3 mg/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 the 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 by Ad+V with a combination of IL-12 with a nivolumab was a rapidly reversible and manageable adverse reaction 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 cytokine release syndrome (CRS), a potentially fatal systemic inflammatory 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 burden.
• 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.

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 mos (mean follow-up time of 13.1 mos).
  - Subjects (n=6, unifocal) who received low-dose (≤ 20 mg) steroid during active dying (Days 0-14), coinciding with administration of V, had an mOS of 17.8 mos.

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

- Nivolumab (1 mg/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 the 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 by Ad+V with a combination of IL-12 with a nivolumab was a rapidly reversible and manageable adverse reaction with a favorable safety profile. Further phase 2 investigation of Ad+V plus a checkpoint inhibitor in rGBM is planned.

Safety Results1

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Cohort 1: Ad+V (10 mg)</th>
<th>Cohort 2: Ad+V (10 mg)</th>
<th>Cohort 3: Ad+V (3 mg/kg)</th>
<th>Expansion Cohort</th>
<th>Cohort 4: Ad+V (20 mg)</th>
<th>Cohort 5: Ad+V (3 mg/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymphocyte count decreased</td>
<td>0 (133%)</td>
<td>2 (67%)</td>
<td>1 (33%)</td>
<td>0 (133%)</td>
<td>2 (67%)</td>
<td>0 (133%)</td>
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<tr>
<td>ALT increased</td>
<td>0 (133%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
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<tr>
<td>Hemoglobin decreased</td>
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<td>0 (0%)</td>
<td>0 (0%)</td>
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</tr>
<tr>
<td>Cerebral Edema</td>
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<td>0 (0%)</td>
<td>0 (0%)</td>
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<tr>
<td>Cytokine Release Syndrome</td>
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<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
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</tbody>
</table>

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 AT1001-102 + 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 mos) – SNV 2019, poster AM-18.
- Median overall survival has not been reached in this combination substudy: Mean follow up is 4.8 mos (min 0.9, max 16.9); Subject treatment is currently ongoing.
- Drug-related toxicities in the ICI 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 ICI 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 ICI:
  - 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 with 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 ICI in rGBM subjects, a phase 2 trial of Ad+V in combination with cemiplimab-rwlc is currently ongoing (NCT040006119).

1 Data collection and cleaning are ongoing; *CTCAE v5.0 as applicable; **One subject at Grade 2 (lymphocyte count decreased) was considered related to both Ad+V and nivolumab; *Ziopharm Cytokine Release Syndrome, Working Definition.