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 1 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 (GBM) in Group 1 (G1) [cerebellar, n=33] 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 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.

**Safety Results**

**Adverse Event (AE)**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Craniotomy 10 mg V (N=6)</th>
<th>Craniotomy 20 mg V (N=15)</th>
<th>Stereotactic 20 mg V (N=7)</th>
<th>Craniotomy 30 mg V (N=4)</th>
<th>Craniotomy 40 mg V (N=6)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Adverse Event</strong></td>
<td>20 mg</td>
<td>20 mg</td>
<td>20 mg</td>
<td>20 mg</td>
<td>20 mg</td>
</tr>
<tr>
<td><strong>Hematologic (5% of Subjects)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>20 mg</td>
<td>20 mg</td>
<td>20 mg</td>
<td>20 mg</td>
<td>20 mg</td>
</tr>
<tr>
<td><strong>Hypotension</strong></td>
<td>20 mg</td>
<td>20 mg</td>
<td>20 mg</td>
<td>20 mg</td>
<td>20 mg</td>
</tr>
<tr>
<td><strong>Pertinent Effects</strong></td>
<td>20 mg</td>
<td>20 mg</td>
<td>20 mg</td>
<td>20 mg</td>
<td>20 mg</td>
</tr>
<tr>
<td><strong>Thrombocytopenia</strong></td>
<td>20 mg</td>
<td>20 mg</td>
<td>20 mg</td>
<td>20 mg</td>
<td>20 mg</td>
</tr>
<tr>
<td><strong>Confusional State</strong></td>
<td>20 mg</td>
<td>20 mg</td>
<td>20 mg</td>
<td>20 mg</td>
<td>20 mg</td>
</tr>
</tbody>
</table>

**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 craniotherapy 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 craniotherapy 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 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 discontinuation 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 AT001-102 Main study
- N≥25
- Enrollment is ongoing

**CPI Combination Substudies Schema**

- Single-arm, open-label, dose-escalation, multicenter substudy (NCT03684677) of the AT001-102 Main study
- N=up to 18
- Enrollment is ongoing
- Dosing cohorts: 10 mg V, 1mg/kg nivolumab (completed)
- 10mg V, 3mg/kg nivolumab (SRC and DSBM have authorized escalation)
- 20mg V, 3mg/kg nivolumab (planned)