Phase 1 Safety and Pharmacokinetics of ADU-1604, an Anti-CTLA-4 Antibody, in Adults with Metastatic Melanoma

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Presented at the 2018 European Society for Medical Oncology/Immunotherany Congress, December 13 - 16, 2018, Geneva, Switzerland

Introduction
ADU-1604 is a humanized IgG4-κ monoclonal antibody targeting a novel epitope on CTLA-4, a negative regulator of T-cell activation, also known as an immune checkpoint. ADU-1604 is currently in clinical development for use as monotherapy.

ADU-1604 was characterized in vitro and shown to bind to human CTLA-4, block recruitment of CD80 and CD86 to CTLA-4, and stimulate IL-2 production by activated T-cells.

ADU-1604 enhanced T-cell dependent hepatitis B surface antigen-vaccine-induced antibody responses in cynomolgus monkeys and demonstrated anti-tumor activity in a mouse small cell lung cancer patient-derived xenograft model.

ADU-1604 toxicity program, which included 3 studies in cynomolgus monkeys, demonstrated weakly irritant (IV) administration of ADU-1604 was well tolerated at doses up to 30 mg/kg.

Background
ADU-1604 binds to unique epitope on hCTLA-1604

Figure 1. ADU-1604 Structure

Figure 2. ADU-1604 Stools Tumor Growth in NSCLC Patient-Derived Xenograft Humanized Mouse Model

Figure 3. hCTLA-4 Binding and Enhancement of IL-2 Production by ADU-1604 in vitro

Table 1. Summary of ADU-1604 in vitro Characterization

<table>
<thead>
<tr>
<th>Species cross-reactivity</th>
<th>EC50 (EC02: 2.4 μM)</th>
<th>T cell cross-reactivity</th>
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<tbody>
<tr>
<td>AS/HCD induction</td>
<td>Capable/AS/HCD</td>
<td>Unique (compared to dimers/monomers)</td>
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Figure 4. ADU-1604 Enhances HBsAg Antibody Response in Cynomolgus Monkeys

Table 2. Key Inclusion and Exclusion Criteria

<table>
<thead>
<tr>
<th>Key Inclusion Criteria</th>
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<tbody>
<tr>
<td>1. No prior treatment with anti-CTLA-4 antibodies</td>
<td>1. Previous treatment with anti-CTLA-4 antibodies and/or agents that block immune checkpoint pathways</td>
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<tr>
<td>2. Adequate organ and marrow function at screening, as defined by the following laboratory parameters:</td>
<td>2. Prior treatment with another investigational anti-CTLA-4 antibody or an immune checkpoint inhibitor in the metastatic setting</td>
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<tr>
<td>3. Active untreated brain metastases</td>
<td>3. Prior line of targeted therapy in the metastatic setting</td>
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<td>4. Administration of chemotherapy, targeted therapy, or biological agents, including interferon, within 28 days of first dose</td>
<td>4. Administration of corticosteroids at a dose exceeding 10 mg/day during the 28 days prior to first dose</td>
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<td>5. Prior treatment with radiolabeled antibodies</td>
<td>5. Active immune-mediated inflammatory disease</td>
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<td>6. Prior treatment with monoclonal antibodies or vaccines</td>
<td>6. Prior anti-CTLA-4 therapy within 10 days of first dose</td>
</tr>
<tr>
<td>7. Administration of biologic agents, including monoclonal antibodies, within 30 days of first dose</td>
<td>7. Administration of nonbiologic agents, including antibiotics, antivirals, or antifungals, in the 28 days prior to first dose</td>
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Figure 5. Study Site Locations

Figure 6. First-In-Human, Open-Label, Multicenter, Dose-Escalation Study of ADU-1604 (IV)

CONCLUSIONS

- ADU-1604 has the potential to address the need for improved efficacy in treatment-resistant patients.
- ADU-1604’s phase 1 studies will inform future development of phase 2 clinical studies.

References:

Acknowledgments:
We would like to thank all of our investigators and their teams for their dedication and commitment to this important trial. We thank all trial participants and their families. We acknowledge the support of the ADU-1604 investigators at all institutions and their patients.

Phase 1 Study Design
- This first-in-human, open-label, multi-site, dose-escalation study is conducted in adults with metastatic melanoma without further establishment treatments.

- All patients are assessable.

- Dose Escalation: Start with 0.3 mg/kg of ADU-1604 IV infusion in 3 subjects using a 3+3 design until the recommended phase 3 dose (RPD) is defined (represented by the dose tolerated while not exceeding the maximum tolerated dose or maximum dose (10 mg/kg)).

- Dose Confirmation: 7 additional subjects receive ADU-1604 at the RPD until the maximum number of planned doses are administered (4 treatment cycles), disease progression is confirmed, or consent is withdrawn, whichever occurs first.

- All sites are to be designated as a study site at the data cut-off.

- All patients are assessable.

- 5 of 10 study sites are active and open to recruitment.

- As of December 4, 2019:
  - The study has started enrollment with three patients consented
  - Cohort 1 has been filed (3 patients dosed)

- PRELIMINARY RESULTS

- Primary objectives of the first-in-human study are to determine the RPD by evaluating the safety, pharmacokinetics, and PCMs (pharmacodynamics) of ADU-1604 administered by IV infusion.

- Secondary objectives to:
  - Characterize the safety of ADU-1604 at the RPD
  - Characterize the PK of ADU-1604 administered by IV infusion following a single dose and repeat dosing
  - Assess the immunogenicity of ADU-1604

ENDPOINTS
- Primary: Incidence of dose limiting toxicity
  - Treatment-emergent adverse events
  - Treatment-related adverse events

- Secondary:
  - Incidence and severity of TEAEs, serious adverse events, changes from baseline in safety parameters
  - Pharmacodynamic analysis of PBMCs (ex vivo incubation) and in vitro-induced cytokines

- Patient disposition of TEAEs
  - Tumor response induction
  - Tumor response duration
  - Disease control
  - Duration of disease control
  - Disease control rate
  - Safety of ADU-1604
  - Safety of ADU-1604 in combination with other anti-CTLA-4 antibodies

- Exploratory endpoints:
  - Characterize the PK of ADU-1604 by examining changes from baseline in selected blood and tumor biomarkers (immunological monitoring as well as potential prognostic and/or predictive biomarkers)
  - Determine the metastatic activity of ADU-1604 by monitoring overall survival, duration of response, disease control, and duration of disease control; and assess progression-free survival and overall survival
  - Investigate the mechanism of action of ADU-1604 using tumor tissue and peripheral blood biomarkers

- ADU-1604 is an Anti-CTLA-4 Antibody that binds to unique epitope on hCTLA-1604

- ADU-1604 is currently being developed for use as monotherapy.

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