Background

ADG116 is a fully human anti-CTLA-4 IgG1 monoclonal antibody that binds to a unique and highly conserved epitope of CTLA-4 using the NEBODY™ technology platform. Targeting this unique epitope enables a novel MoA for CTLA-4 mediated T cell activation in comparison to ipilimumab, resulting in a potential improved safety and tolerability profile compared to CTLA-4 antibodies currently in clinical development.

Methodology

To assess the safety and tolerability of ADG116 at escalating dose levels, in combination with pembrolizumab, a Phase 1b/2, open-label, dose escalation and expansion study was conducted. The primary objectives of the study were to determine the maximum tolerated dose (MTD) and recommend Phase 2 dose (RPD) for ADG116 in combination with pembrolizumab.

Secondary Objectives

To assess the PD, dose proportionality, immunogenicity of both agents, and the effect of long-term administration on safety and tolerability profile

Previously, in a Phase 1 dose escalation study (NCT04501276), ADG116 monotherapy (100, 300, 500 mg/kg) showed improved safety and tolerability profile up to 500 mg/kg with only one grade 3 anti-DAC116 antibodies detected. Here we report the preliminary safety, PK, biomarker change and anti-tumor activity from a Phase Ib/2 study, where ADG116 is combined with pembrolizumab (KEYTUMRAD) in patients with advanced/metastatic solid tumors (ADG116-001, NCT05274742). (KEYNOTE-C57).

Targeting a Distinct Epitope of CTLA-4 with Unique MOA

ADG116 NEBODY® vs. Ipilimumab and Tremelimumab

Figure 1: Binding Epitopes and Activities of different Anti-CTLA-4 Molecules. A. Overlay of binding epitopes for ADG116 and tremelimumab with a lack of overlap for ipilimumab. B. T-cell proliferation assay activity for Tremelimumab or Ipilimumab in T-cell proliferation assay. C. ADG116 and tremelimumab have high activity in T-cell proliferation assay (T-cell proliferation assay activity for Tremelimumab or Ipilimumab in T-cell proliferation assay). D. ADG116 and tremelimumab have high activity in T-cell proliferation assay (T-cell proliferation assay activity for Tremelimumab or Ipilimumab in T-cell proliferation assay).

Clinical Study Key Objectives and Methods

Primary Objectives

To assess the safety and tolerability of ADG116 at escalating dose levels, in combination with pembrolizumab.

Secondary Objectives

To determine the maximum tolerated dose (MTD) and recommended Phase 2 dose (RPD) for ADG116 in combination with pembrolizumab.

Patient Baseline Characteristics

Adverse Events

No DLT was observed, although late enrollment, G3 of ADG116 alone, a mouse cross reactive antibodies to the ADG116 epitope were not present, and the ADG116 MTD was not reached.

Clinical Activity Assesments

Frequencies of Proliferating CD8

As of September 1, 2022, 6 patients had been treated with ADG116 (3 mg/kg, Q3W) + Pembrolizumab (200 mg, Q3W) combination therapy.

Case #1: CEA reduction in a MSS CRC patient with lung metastasis

Figure 4: Survival plot for patients treated with ADG116 (3 mg/kg) + pembrolizumab compared with pembrolizumab alone.

Figure 3: TRAEs at 3 mg/kg ADG116 (200mg) combination therapy.

Figure 5: Barplot for patients treated with ADG116 (3 mg/kg) + pembrolizumab compared with pembrolizumab alone.

Clinical Safety Assessments

ADG116 (3 mg/kg, Q3W) + Pembrolizumab (200mg, q12W), n=6

Table 2: Frequencies of TRAEs with different Grades

Table 2: Base line Characteristics of Patients

Clinical Case Studies (MSS CRC patients with lung or liver metastases)

Case #1: CEA reduction in a MSS CRC patient with lung metastasis

Case #2: CEA reduction in a MSS CRC patient with liver metastasis

Results

ADG116 has shown a manageable safety and tolerability profile.

No DLT was observed, although late onset grade 3 toxicity was noted after repeat Q3W dosing in one patient.

Changes in tumor burden related biomarker, i.e., a 43% and 27% reduction from baseline in CEA levels were noted for two metastatic MSS CRC patients (both were SD at their last tumor assessments).

Immune activation was observed in the periphery, as manifested by enhanced T cell proliferation and increased proinflammatory cytokine release following treatment.

ADG116 PK when combined with pembrolizumab did not alter ADG116 serum PK when compared with ADG116 monotherapy.

The mean terminal half-life of ADG116 is estimated to be >10 days for Cycle 1 PK, consistent with minimal accumulation after Q3W repeat dosing in this study.

Conclusions

This study has established a safety and potential active dose level for ADG116 in combination with pembrolizumab.

ADG116 (3 mg/kg, Q3W) in combination with pembrolizumab (200 mg) has shown a manageable safety and tolerability profile.

No DLT was observed, although late onset grade 3 toxicity was noted after repeat Q3W dosing in one patient.

Changes in tumor burden related biomarker, i.e., a 43% and 27% reduction from baseline in CEA levels were noted for two metastatic MSS CRC patients (both were SD at their last tumor assessments).

Immune activation was observed in the periphery, as manifested by enhanced T cell proliferation and increased proinflammatory cytokine release following treatment.

ADG116 PK when combined with pembrolizumab is similar to that of ADG116 monotherapy.

This study has established a safety and potential active dose level for ADG116 in combination with pembrolizumab. This dosing regimen warrants further clinical evaluation.

Clinical Pharmacokinetics

ADG116 (3 mg/kg) in combination with pembrolizumab has shown a manageable safety and tolerability profile.

No DLT was observed, although late onset grade 3 toxicity was noted after repeat Q3W dosing in one patient.

Changes in tumor burden related biomarker, i.e., a 43% and 27% reduction from baseline in CEA levels were noted for two metastatic MSS CRC patients (both were SD at their last tumor assessments).

Immune activation was observed in the periphery, as manifested by enhanced T cell proliferation and increased proinflammatory cytokine release following treatment.

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