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A Phase 1b/2, Open-Label, Dose Escalation and Expansion Study of an Anti-CTLA-4 NEOBody™ ADG116 in Combination with Pembrolizumab (Anti-PD-1 Antibody) in Patients with Advanced/Metastatic Solid Tumors: A Preliminary Update

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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 NEObody™ technology platform. Targeting this unique epitope enables a novel MOA for CTLA-4 mediated T cell activation in comparison with ipilimumab (**Figure 1**), resulting in a partial CD80/86 ligand blockade for safer T cell activation and stronger ADCC that enhance the Treg depletion in the TME. The nature of the highly conserved epitope affords the cross-species characterization of ADG116 in preclinical species and a seamless translation to the clinic. Nonclinical studies demonstrated robust single agent efficacy of ADG116 and synergistic anti-tumor effects when combined with anti-PD-1 in syngeneic tumor models (**Figure 2**).

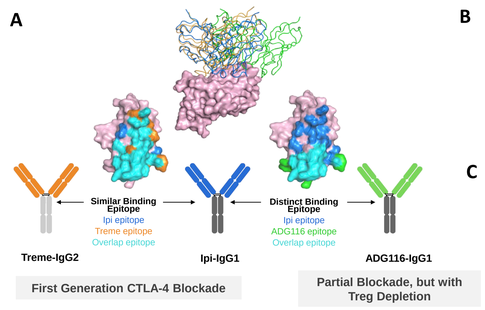
Previously, in a Phase 1 dose escalation study (NCT04501276), ADG116 monotherapy (iv, Q3W) showed improved safety and tolerability profile up to 15 mg/kg over the approved anti-CTLA-4 therapy; the MTD was not reached. As much as 100% reduction in tumor target lesion(s) and long-lasting stable diseases were observed in multiple heavily pre-treated patients including those bearing “immune cold” tumors[1].

Here we report the preliminary safety, PK, biomarker change and anti-tumor activity from a Phase1b/2 study, where ADG116 is combined with pembrolizumab (KEYTRUDA®) in patients with advanced/metastatic solid tumors (ADG116-P001, NCT05277402 (KEYNOTE-C97)).

MOA: Mechanism of action; TME tumor microenvironment; Iv: intravenous administration; Q3W: once every 3 weeks. MTD: maximum tolerated dose 1. Richardson, Tolcher et al, Phase 1 dose-finding study of a novel anti–CTLA-4 antibody ADG116 as monotherapy in patients with advanced solid tumors, ESMO-IO 2021, Poster # 137P

Targeting a Distinct Epitope of CTLA-4 with Unique MOA

ADG116 NEObody™ vs. Ipilimumab and Tremelimumab



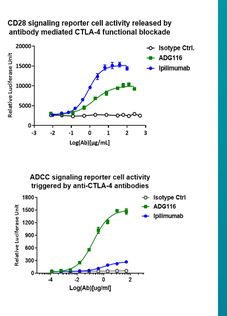


Figure 1. Binding Epitopes and Activities of different Anti-CTLA-4 Molecules. **A.** Overlay of binding epitopes of ADG116 (green), ipilimumab (blue) and/or Tremelimumab (orange) on CTLA-4 structure. **B.** The unique binding epitope of ADG116 results in a softer CTLA-4 checkpoint blockade compared with ipi and treme; **C.** ADG116 shows a stronger ADCC/ADCP activity for Treg depletion in TME.

Anti-tumor Efficacy of ADG116 in Combination with Anti-PD-1 Antibody in Non-clinical Tumor Models

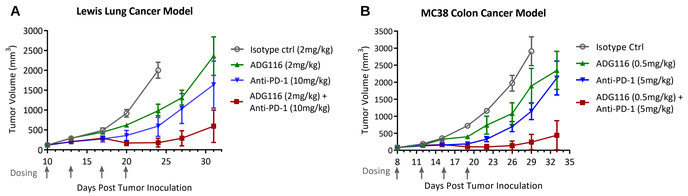


Figure 2. The TGI of ADG116 in combination with anti-PD-1 was evaluated in syngeneic murine tumor models of Lewis lung carcinoma (A) and MC38 colon adenocarcinoma (B). ADG116 alone, a mouse cross-reactive anti-PD-1 alone, or their combination, was administered intraperitoneally twice a week for 4 doses in mice with subcutaneous tumors (average tumor volume around 80~120 mm³ at the start of dosing). Tumor growth was measured twice a week during the studies. The combination of ADG116 and anti-PD-1 induced synergistic antitumor efficacy in both models.

Clinical Study Key Objectives and Methods

Primary Objectives

- To assess the safety and tolerability of ADG116 at escalating dose levels, in combination with pembrolizumab
- To determine the maximum tolerated dose (MTD) and recommended Phase 2 dose (RP2D) for ADG116 in combination with pembrolizumab

Secondary Objectives

- To assess the PK, dose proportionality, immunogenicity of both agents and relationship between immunogenicity and PK, safety, and efficacy parameters, as well as early sign of antitumor activity associated with the ADG116 + pembrolizumab combination regimen

Patient Baseline Characteristics

- As of September 5, 2022, 6 patients had been treated with ADG116 (3mg/kg, Q3W) + Pembrolizumab (200mg, Q3W) combination therapy
- Patients were generally heavily pre-treated (Table 1)
- Tumor types consist of the breast, colon and pancreatic cancer, etc., and are generally considered as “cold” tumors

Table 1. Baseline Characteristics of Patients

Characteristics	N = 6
Age (years), median (range)	61.5 (47, 74)
Female, n (%)	3 (50%)
Race, n (%)	
Caucasian, n (%)	5 (83%)
Black or African American, n (%)	1 (17%)
ECOG, n(%)	
0	2 (33%)
1	4 (67%)
Number of regimens prior to enrollment, n (%)	
≥3	3 (50%)
Prior immunotherapy, n (%)	2 (33%)

Clinical Safety Assessments

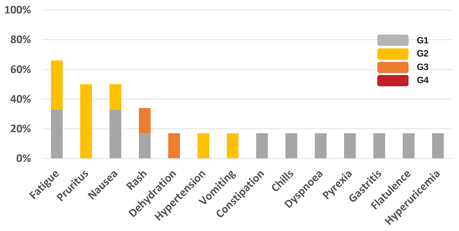
ADG116 (3 mg/kg, iv Q3W) + Pembrolizumab (200mg, iv, Q3W), n=6

- Manageable safety and tolerability profile with no dose-limiting toxicities
- Most frequent TRAEs observed: fatigue (4/6, 67%), pruritus (3/6, 50%) and nausea (3/6, 50%)
- Two patients had Grade 3 TRAEs: one Grade 3 dehydration (Cycle 3) and one Grade 3 rash (Cycle 1) (Table 2 and Figure 3)

Table 2. Frequencies of TRAEs with different Grades

Grade	G1	G2	G3	G4/5
TRAE n (%)	1 (17%)	3 (50%)	2 (33%)	0

Figure 3. TRAEs at 3 mg/kg ADG116 + Pembrolizumab (200mg)



Clinical Activity Assessments

Figure 4. Swimmer plot for patients treated with ADG116 (3 mg/kg) + pembrolizumab combination therapy

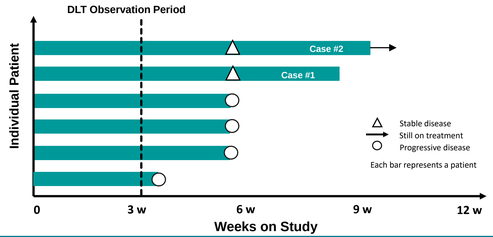
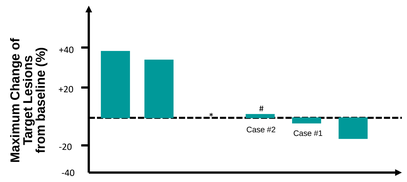


Figure 5. Waterfall plot for patients treated with ADG116 (3 mg/kg) + pembrolizumab combinational therapy

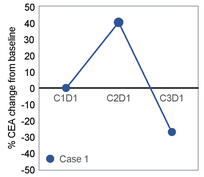


* One patient showed disease progression before first scan, and is excluded from this analysis.
\# Patient still on treatment.

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

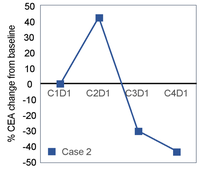
Case #1: CEA reduction in a MSS CRC patient with lung metastasis

- 47 yrs old female patient with target lesions of pulmonary nodule of 19 and 33 mm at baseline
- Previously received 5 lines of systemic therapies:
  - FOLFOX/Avastin, FOLFIRI/Avastin, APN401 (T-cell based therapy), FOLFIRI/Vectibix, IPH5201 (CD39 mAb)
- Showed SD with 4% reduction in sum target lesions at the end of C2



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

- 46 yrs old male patient with target lesions in the liver, lymph node and lung of 74, 22 and 20 mm at baseline, respectively
- Previously received 5 lines of systemic therapies:
  - FOLFOX, FOLFIRI/Avastin, Erbitux, Lonsurf, and IO-202 (LILRB4 mAb)
- Showed SD with 3% increase in sum target lesions at the end of C2



CEA: Carcinoembryonic antigen

Pharmacodynamic Analysis in the Periphery

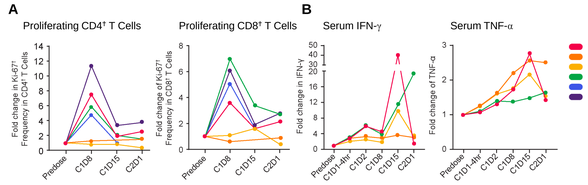
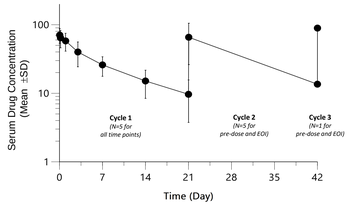


Figure 6. Modulation of immune biomarkers by combination treatments Treatment by ADG116 + pembrolizumab increased peripheral levels of CD4+ and CD8+ T cell proliferation (Ki-67+) shown by flow cytometry analysis (A, data available for all 6 patients), and increased serum levels of proinflammatory cytokines including IFN-γ and TNF-α (B, data available for 4 of 6 patients). All data are compared to that of pre-dose baseline.

Clinical Pharmacokinetics

Figure 7. ADG116 serum PK when dosed at 3 mg/kg Q3W in combination with pembrolizumab



SD: standard deviation
EOI: end of infusion

Protocol specified PK sampling time points were used for PK graphing, noncompartmental analysis (NCA) and summary statistics

PK data cut-off: 10/07/2022

- Combination treatment 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
- Combination treatment has no apparent ADA impact on ADG116 PK

Conclusions

- 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 are similar to that of ADG116 monotherapy
- This study has established a safe and potentially active dose level for ADG116 in combination with pembrolizumab. This dosing regimen warrants further clinical evaluation

This study is in collaboration with Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.

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