Abstract 3105: Phase 1, dose-escalation study of ADG106, a fully human anti-CD137 agonistic antibody, in subjects with advanced solid tumors or relapsed/refractory non-Hodgkin lymphoma

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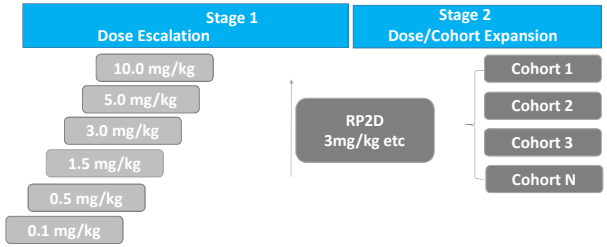
Background

- Ligation of CD137 induces a co-stimulatory signal on activated CD8⁺ T cells and natural killer (NK) cells, resulting in proliferation, increased pro-inflammatory cytokine secretion and cytolytic function.
- ADG106 is a fully human agonistic anti-CD137 monoclonal IgG4 antibody; ADG106 targets the evolutionally conserved epitope of CD137 with cross-species reactivity across mouse, rat, monkey, and human CD137 and exhibits novel mechanism of actions for CD137 agonism, CD137 ligand antagonism and potent cross-linking via FcγRIIb.
- Preclinical studies demonstrated the anti-tumor activities of ADG106 for both single agent and combination therapy in multiple syngeneic mouse models including liver, breast, and colon cancers. ADG 106 also shows synergistic effect in combination with PD-1/PD-L1, CTLA4, chemo, and targeted agents.
- There were no observable adverse findings in GLP toxicity studies at doses up to 100 mg/kg in rats and 200 mg/kg in monkey with a weekly repeat-dosing for one month.

Methods

- This phase 1 study was initiated to evaluate the safety and tolerability of ADG106, as well as the pharmacokinetics, immunogenicity and preliminary clinical activities.
- The dose escalation includes accelerated titration (0.1 mg/kg) and conventional dose escalation (0.5, 1.5, 3.0, 5.0 and 10 mg/kg). Dose-expansion cohorts started at dose levels proven to be tolerable and with evidence of clinical and biological activities.
- ADG106 was administered once every 3 weeks (Q3W) by intravenous infusion. Patients with advanced solid tumors or non-Hodgkin lymphoma, who are refractory or relapsed after exhausting all available therapies, were enrolled for ADG106 treatment, until disease progression, intolerable toxicity, withdrawal of consent, or a maximum of 24 months.

Figure 1: Study Design



RP2D: recommended phase 2 dose

Demographics

- As of Apr 24, 2020, 23 patients at 6 cohorts were enrolled, 18 patients were in the dose escalation cohort and 5 patients were in the dose expansion cohort at 3mg/kg etc.
- Patients with wide spectrum of solid tumors and Non-Hodgkin's lymphoma were enrolled.

Safety and Tolerability

- Among 23 patients, median treatment duration was 18.35 weeks (min/max: 12.1/33.1 weeks).
- 1 patient at 10mg/kg experienced the DLT (grade 4 neutrophil count decreased).
- A total of 52.2% of drug-related treatment-emergent adverse events (TEAEs) were observed

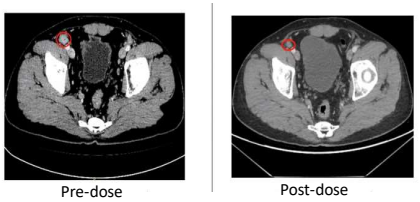
Table 1: Drug-Related TEAEs Occurring in >1 Patients (as of Apr/24/2020)

Patients with TEAEs, n(%)	0.1mg/kg (n=1)	0.5mg/kg (n=3)	1.5mg/kg (n=5)	3.0mg/kg (n=6)	5.0mg/kg (n=5)	10.0mg/kg (n=3)	Overall (n=23)
Neutrophil count decreased	0	0	0	1(16.7)	0	2(66.7)	3(13.0)
White blood cell count decreased	0	0	0	1(16.7)	0	2(66.7)	3(13.0)
Vomiting	0	0	1(20.0)	0	1(20.0)	1(33.3)	3(13.0)
Nausea	0	0	1(20.0)	0	0	1(33.3)	2(8.7)
Asthenia	0	0	0	1(16.7)	0	1(33.3)	2(8.7)
Pruritus	0	0	1(20.0)	1(16.7)	0	0	2(8.7)
Rash	1(100)	0	0	1(16.7)	0	0	2(8.7)

Anti-tumor Efficacy

- 12 of 20 evaluable patients were evaluated as SD (DCR 60%), with 5 patients showing tumor shrinkage.

Figure 2: Patient CT Scans



Pre-dose Post-dose

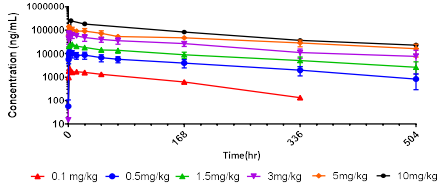
Target lesion of the Non-Hodgkin Lymphoma

- 46 years old male with stage III non-Hodgkin lymphoma.
- Prior therapies included chemotherapy, folate analog metabolic inhibitor, and autologous hematopoietic stem cell transplantation.
- CT scans indicated >50% tumor reduction in one of the targeted lesions while receiving ADG106 treatment. See Figure 5 for PD marker responses.

Pharmacokinetics and Immunogenicity

- The kinetics of ADG106 concentrations in cycle 1 at different dose levels demonstrate dose proportional increases of exposure, with a half-life around 7 days when doses ≥ 0.5 mg/kg.
- ADG106 treatment emergent or boosted anti-drug-antibody (ADA) occurred in 5 of 23 patients tested so far.

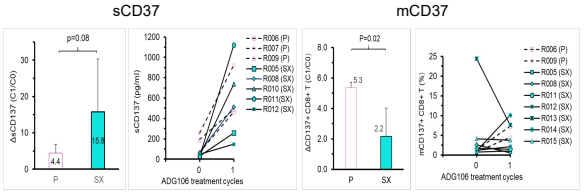
Figure 3: Mean Serum Concentrations of ADG106 in Cycle 1



Pharmacodynamics

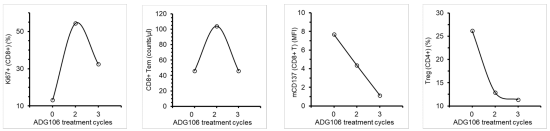
- There is a trend that sCD137 in plasma increases more but mCD137 on CD8⁺ T-cell increases less in patients with stable diseases than those in patients with progression diseases after one cycle of ADG106 treatment. The increase of CD137 expression upon ADG106 treatment indicates that ADG106 engages the activation of the CD137 signaling pathway in CD8⁺ T-cells.
- Proliferative (Ki67⁺) CD8⁺ and effector memory T-cell tends to increase after one cycle of ADG106 treatment in patients with stable vs progressive disease.

Figure 4: Increased CD137 Expression on CD8⁺ T-cells by ADG106 Treatment



P: progression of diseases; SX: stable disease; sCD137: soluble CD37; mCD137: membrane CD137
R006-R012: patient ID; C0: before treatment; C1: completion of one cycle of treatment

Figure 5: The Effect of ADG106 Treatment on non-Hodgkin lymphoma



Non-Hodgkin Lymphoma patient, who achieved >30% overall tumor reduction in targeted lesions, showed increased proliferation (Ki67⁺) of CD8⁺ T and effector memory cells, decreased mCD137 (membrane CD137) of CD8⁺ T-cells, and decreased Treg cells, upon ADG106 treatment.

Conclusions

- ADG106 demonstrated favorable safety and tolerability profiles at doses up to 5 mg/kg, and dose expansion at 3mg/kg etc is being explored.
- Potential biological activity (saturation of target based on receptor occupancy) and pharmacodynamics biomarker response were observed.
- Preliminary clinical activity was seen in patients with non-Hodgkin's lymphoma and certain solid tumors with strong pharmacologic PD biomarkers, which warrants further evaluation.
- Clinical trial information: NCT03802955.

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