A Phase 1b/2 Study of a Novel Anti-CTLA-4 NEObody™ ADG116 Monotherapy and in Combination with Toripalimab (TORI; Anti-PD-1 Antibody) in Patients with Advanced / Metastatic Solid Tumors

ADAGENE

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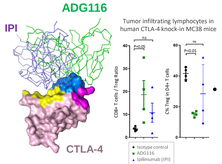
Background

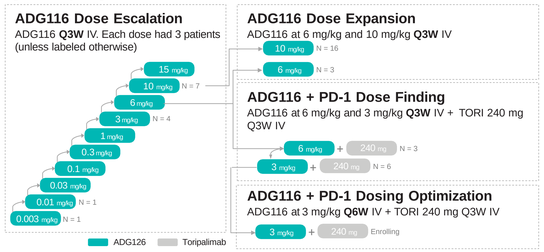


- ADG116 is a differentiated anti-CTLA-4 fully human IgG1 NEObody®, targeting a unique and evolutionally conserved epitope of CTLA-4 for seamless translational studies with species cross-reactivity from mouse, monkey to human
- ADG116 is designed to differentiate from ipilimumab and tremelimumab with novel MOA to enable partial ligand blocking, stronger ADCC and enhanced T regulatory cell (Treg) depletion in the tumor microenvironment (TME)
- ADG116 demonstrates potent anti-tumor activity in multiple syngeneic murine tumor models, with 5 to 10-fold higher efficacy than ipilimumab as a single agent, and in combination with anti-PD-1 therapy

Method

We present interim data from a phase 1b/2, open-label, non-randomized study in patients with advanced / metastatic solid tumors (ADG116-1003, NCT04501276)

Figure 1. Study Design*



Data cutoff: September 19, 2022
*N indicate number of patients by data cutoff date; IV = intravenous, Q3W = Every 3 weeks; Q6W = Every 6 weeks

Primary Endpoints: Safety and tolerability; determine MTDs and RP2Ds

Secondary Endpoints: PK, ADA, objective response, DoR, PFS, and OS

Key Inclusion Criteria: ECOG ≤ 1. Prior treatment by anti-PD-1 and/or anti-CTLA-4 therapy are allowed

Imaging was performed every 6 weeks for the first 4 cycles, then every 9 weeks afterwards. Tumor response was investigator-determined using RECIST v1.1

Result

Baseline Characteristics

- Across all dose levels, 50 patients received ADG116 monotherapy. Among the 36 patients who received ≥ 3 mg/kg, the most common tumor types include epithelial ovarian cancer (n = 8) and pancreatic adenocarcinoma (n = 4)
- Nine patients received ADG116 (3 or 6 mg/kg) in combination with TORI 240mg Q3W
- Patients were heavily pre-treated

Table 1. Patient demographics and baseline characteristics

Characteristics	ADG116 (N = 50)	ADG116 + TORI (N = 9)
Age (years), median (range)	62 (35, 92)	59 (32, 69)
Female, n (%)	25 (50)	6 (67)
Race, n (%)		
Caucasian, n (%)	33 (66)	5 (56)
Asian, n (%)	16 (32)	4 (44)
Native American, n (%)	1 (2)	0
ECOG PS, n (%)		
0	26 (52)	3 (33)
1	24 (48)	6 (67)
Number of prior lines of treatment, n (%)*		
1	6 (12)	2 (22)
2	12 (24)	2 (22)
≥3	32 (64)	4 (44)
Prior immunotherapy, n (%)	18 (36)	0
ADG116 dose administered		
Median (range)	2 (1, 5)	3 (1, 5)

* Prior treatment information of one patient who received ADG116 + TORI was missing

Safety: ADG116 Monotherapy

- G1/2 and G3/4 treatment-related adverse events (TRAEs) were reported in 28 (56%) and 3 (6%) out of 50 patients, respectively. No G5 TRAEs were reported
- Treatment-related serious adverse events (SAEs) were reported in 4 (8%) patients across all groups, including one G4 hyperglycemia, one G2 immune-related enterocolitis, one G2 pneumonitis and one G2 asthenia
- A DLT event (G4 hyperglycemia) occurred in the 10 mg/kg cohort
- 2 patients (4%) discontinued due to TRAEs (including one G2 and another G3 immune-related enterocolitis)
- TRAE incidence and severity appeared to be dose-dependent (Table 2)

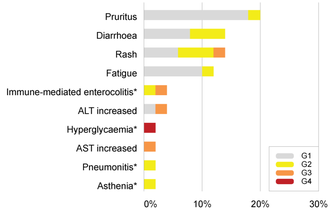


Table 2. TRAEs reported at any dose level of ADG116 monotherapy

Dose levels (mg/kg)	N	All G n (%)	G1 n (%)	G2 n (%)	G3 n (%)	G4 n (%)	G5 n (%)
All	50	31 (62)	17 (34)	11 (22)	2 (4)	1 (2)	0
≤ 0.3	11	3 (27)	3 (27)	0	0	0	0
1	3	2 (67)	2 (67)	0	0	0	0
3	4	3 (75)	1 (25)	2 (50)	0	0	0
6	6	5 (83)	3 (50)	2 (33)	0	0	0
10	23	15 (65)	8 (35)	4 (17)	2 (9)	1 (4)	0
15	3	3 (100)	0	3 (100)	0	0	0

Figure 2. TRAEs reported in > 10% of patients (any grade) or in ≥ 1 patient (grade 3/4 or treatment-related SAE) at any dose level of ADG116 monotherapy. *Treatment-related SAE included one G4 hyperglycemia, one G2 immune-related enterocolitis, one G2 pneumonitis and one G2 asthenia. AST=Aspartate aminotransferase; ALT=Alanine aminotransferase.

Efficacy: ADG116 Monotherapy

- Across all dose levels, disease control rate (DCR) = 33% in 36 evaluable patients*
- Among the three patients treated by ADG116 at 15 mg/kg, initial partial response was observed in one patient with Kaposi's sarcoma

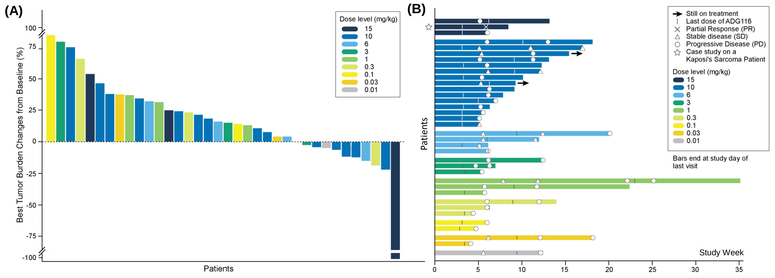


Figure 3. Response to ADG116 monotherapy in 36 evaluable patients* (A) Waterfall plot of response. Maximum tumor burden reduction was assessed according to RECIST 1.1 (B) Swimmer plot. *Evaluable patients: Patients with at least one valid post treatment tumor assessment

Case study: Initial Partial Response to ADG116 Monotherapy in a Patient with Kaposi's Sarcoma

- Male, 69 years, ECOG PS 0
- Previously received multiple surgeries for both left and right feet and 1 line of systemic therapy (etoposide)
- Dosed by ADG116 at 15 mg/kg Q3W, and developed Grade 2 asthenia after 2 cycles
- Partial response observed at the first tumor assessment before patient withdrew consent

Table 4.Tumor burden in a patient with Kaposi's sarcoma who received ADG116 at 15 mg/kg Q3W

		Baseline	End of C2
Target Lesion	TL1- Left foot	10 mm	0 mm
	Sum	10 mm	0 mm (-100%)
Non-Target Lesion	Multiple nodules at left medial and plantar	Present	Reduced
New Lesion		NA	No
Overall Response		NA	PR

Pharmacodynamics

ADG116 monotherapy induces peripheral immune activation, as manifested by increases of serum proinflammatory cytokines including IFN-γ and TNF-α

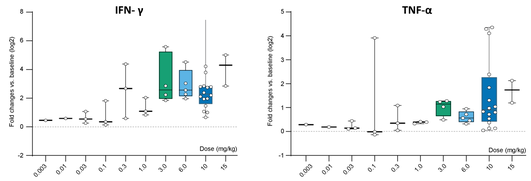


Figure 7. Pharmacodynamics of peripheral serum cytokine levels of IFN- γ and TNF-α before and after treatment by ADG116 monotherapy

Safety: ADG116 + Toripalimab

- TRAE incidence and severity appeared to be dose-dependent (Table 5)

ADG116 6 mg/kg Q3W + Toripalimab 240 mg Q3W (N = 3)

- DLTs were reported in 2 patients (G3 diarrhea and G3 immune-related myocarditis). G3 TRAEs were reported in 3 (100%) out of 3 patients
- This dose level was not tolerated for this combination. Dose of ADG116 was de-escalated to 3 mg/kg Q3W

ADG116 3 mg/kg Q3W + Toripalimab 240 mg Q3W (N = 6)

- G1/2 and G3 TRAEs were reported in 3 (50%) and 3 (50%) out of 6 patients, respectively. No G4/5 TRAEs were reported. No patient discontinued due to TRAEs
- G3 TRAEs were observed in one patient in cycle 1 and two patients in ≥ cycle 3
- Treatment-related SAEs were reported in 2 (33%) patients (G3 diarrhea & G3 nausea)
- DLTs were reported in 1 patient (G3 diarrhea)

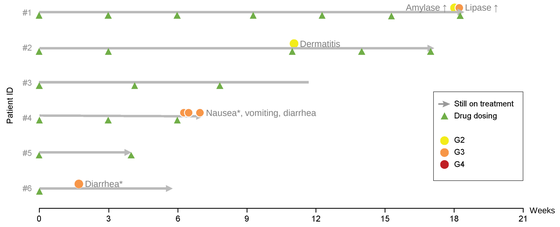


Figure 4. TRAEs (≥ G2) reported in patients administered ADG116 (at 3 mg/kg) in combination with toripalimab (N = 6) Grade 1 TRAEs in ≥ 2 patient included rash (3 pts), diarrhea (2 pts) and pruritis (2 pts).* Treatment-related SAEs were reported in 2 patients

Table 5. TRAEs reported at ADG116 (3 or 6 mg/kg, Q3W) in combination with toripalimab (240 mg, Q3W)

TRAE, n (%)	N	All G n (%)	G1 n (%)	G2 n (%)	G3 n (%)	G4/ G5 n (%)
ADG116 (3 mg/kg, Q3W) + TORI	6	6 (100)	2 (33)	1 (17)	3 (50)	0
ADG116 (6 mg/kg, Q3W) + TORI	3	3 (100)	0	0	3 (100)	0

Efficacy: ADG116 + Toripalimab

- Objective response rate (ORR) = 14%, and disease control rate (DCR) = 86% among 7 evaluable patients* who were treated with ADG116 (3 or 6mg/kg Q3W) + TORI (240 mg, Q3W)
  - Among the 5 evaluable patients* who received ADG116 3 mg/kg Q3W + TORI 240 mg Q3W, ORR = 20% and DCR = 100%
- One CR observed in an HNSCC patient at ADG116 (3 mg/kg) + TORI

	ADG116 (3 mg/kg, Q3W) + TORI (N* = 5)
ORR (%)	20%
DCR (%)	100%
CR, n (%)	1 (20%)
PR, n (%)	0
SD, n (%)	4 (80%)
PD, n (%)	0

Table 6. Summary of response rate in 5 evaluable patients* treated by ADG116 (3 mg/kg, Q3W) + TORI (240 mg, Q3W)

* Evaluable patients: Patients with at least one valid post treatment tumor assessment

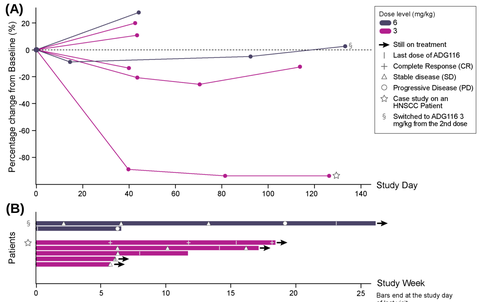


Figure 5. Response to ADG116 in combination with toripalimab in 7 evaluable patients* with at least one valid post treatment tumor assessment (A) Spider plot (B) Swimmer plot
* Evaluable patients: Patients with at least one valid post treatment tumor assessment. § This patient only received one dose of ADG116 6 mg/kg in combination with toripalimab and subsequently reduced to ADG116 3 mg/kg in combination with toripalimab

Case study: Durable Complete Response to ADG116 3 mg/kg Q3W + TORI 240 mg Q3W in a Recurrent HNSCC Patient

- Male, 64 years, ECOG PS 1, HPV negative recurrent head and neck squamous cell carcinoma (HNSCC)
- Previously received
  - For locally advanced HNSCC: Right modified cervical lymph node dissection followed by adjuvant radiotherapy
  - For recurrent HNSCC: Concurrent chemoradiotherapy (which included weekly cisplatin that was poorly tolerated)
- Durable complete response observed (ongoing beyond Cycle 6)

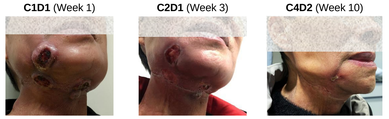


Figure 6. Photos of external lesions (right mandibular and right submandibular) at C1D1, C2D1 and C4D2

Table 7. Tumor burden in a recurrent HNSCC patient administered ADG116 3 mg/kg Q3W + TORI 240 mg Q3W

		Baseline	End of C2	End of C4	End of C6
Target Lesion	TL1 - Right mandibular	32 mm	Disappeared	Disappeared	Disappeared
	TL2 - Right submandibular	18 mm	Disappeared	Disappeared	Disappeared
	TL3 – Lymph node (left submandibular)	15 mm	8 mm	8 mm	5 mm
	Sum	65 mm	8 mm	8 mm	5 mm
Non-Target Lesions	3	Present	Disappeared	Disappeared	Disappeared
New Lesion		NA	No	No	No
Overall		NA	CR	CR	CR

Pharmacokinetics

- Serum PK of ADG116 monotherapy was approximately linear with dose. Average terminal half-life was estimated to be ~10 days. This is consistent with limited drug accumulation (< 2-fold) after Q3W repeat dosing
- No apparent sign of ADA impact on the PK of ADG116 across studied dose levels
- Combination of ADG116 with toripalimab did not appear to change the PK of ADG116 when compared with PK profile of ADG116 monotherapy

Conclusion

- ADG116 monotherapy shows improved safety and tolerability profile up to 15 mg/kg over the approved anti-CTLA-4 therapy, with no MTD. DCR = 33% including an initial partial response in the Kaposi's sarcoma patient
- ADG116 at 3 mg/kg shows a manageable safety profile in combination with TORI, with encouraging efficacy, including durable CR observed in 1 patient with HNSCC (ongoing beyond cycle 6)
  - ORR = 20% and DCR = 100% among the 5 evaluable patients who received ADG116 3 mg/kg Q3W + TORI 240 mg Q3W
- Further dose optimization such as extended dosing interval for ADG116 in combination with anti-PD-1 therapy is being evaluated

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