# Assessment of Biomarker Kinetics for ADG106 (anti-CD137 Agonist) as Monotherapy or Combined with Toripalimab

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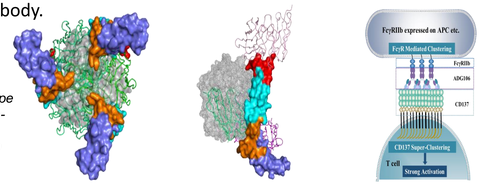
2021 ESMO IO Conference, Abstract Number #463

## Background

- ADG106, a human anti-CD137 IgG4 agonist antibody engineered using Adagene's NEObody™ technology, binds specifically and with high affinity to a unique and conserved epitope of CD137 on activated human T cells. ADG106 blocks CD137 ligand binding and stimulates CD4+ and CD8+ T cell proliferation and proinflammatory interferon-gamma (IFN-γ) release while displaying a low risk for adverse immune responses. We present here studies of changes in immune activation associated pharmacodynamic (PD) markers, including soluble CD137 (sCD137) following treatment in >100 patients in the US and China with ADG106 alone or combined with toripalimab, an anti-PD-1 antibody.

**Figure 1: Mechanism of Action of ADG106**

- ✓ *Targeting CD137/4-1BB conserved epitope with novel MOA and broad species cross-reactivity*
- ✓ *CD137 stimulates the immune system to fight cancer cells and is a key driver for long-lasting T-cell proliferation*




Natural Ligand-like Activation | Competitive with CD137L | Cross-linking

## Methods

- Specimens were collected from ADG106 clinical trials shown below:
  - ✓ *ADG106-1008: NCT04775680 (ADG106 Q3W + toripalimab 240mg Q3W IV dosing)*
  - ✓ *ADG106-1001: NCT03707093 (ADG106 Q3W IV dosing)*
  - ✓ *ADG106-1002: NCT03802955 (ADG106 Q3W IV dosing)*
- Peripheral blood immune cell subpopulations were profiled by flow cytometry and serum drug, cytokine, and total sCD137 levels were quantified using validated assays.
- Mathematical modeling was performed.

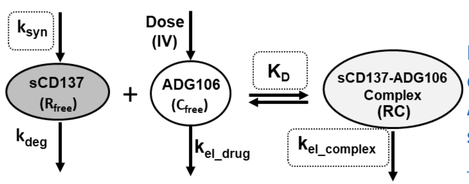



**Figure 2: schematic representation of the model structure describing ADG106 PK and its interaction with sCD137**

Total sCD137= sCD137-ADG106 complex + free sCD137

The kinetics of the total target (sCD137) concentration ($R_{tot}$) can be described by:

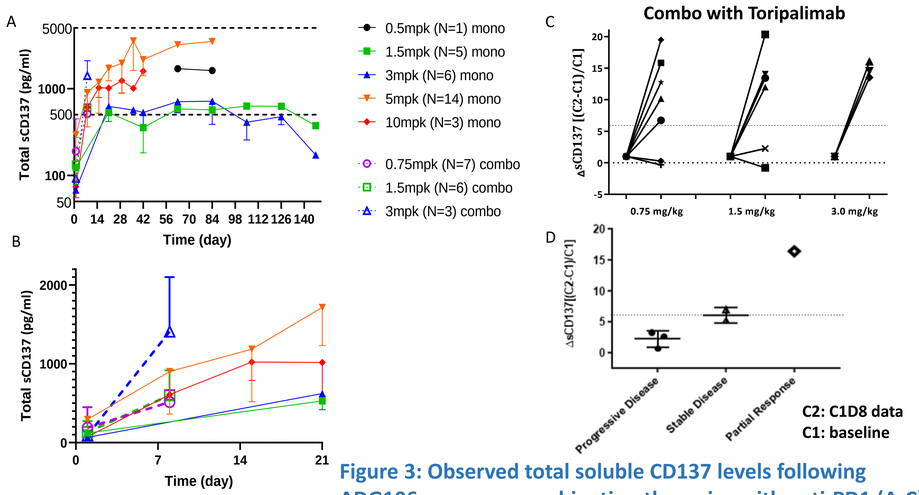
$$\frac{dR_{tot}}{dt} = k_{syn} - k_{deg} \times R_{free} - k_{el\_complex} \times RC \quad (1)$$

The target synthesis rate constant ($k_{syn}$) of sCD137 was estimated from the initial rising slope of the total target profiles based on individually available data. When $R_{tot}$ reaches steady state (plateau), $dR_{tot}/dt = 0$, i.e., the right side of **Equation 1** equals zero. The highest ADG106-sCD137 complex concentration (RC) can be reached when $k_{deg} \times R_{free}$ approaches 0, i.e., $R_{free}$ becomes infinitely low when the antibody dose is very high. In this situation, $k_{syn} - k_{el\_complex} \times C_{ss\_complex} = 0$, and therefore $C_{ss\_complex} = k_{syn}/k_{el\_complex}$.

***References:*** *Zheng, S. et al.,(2020) mAbs, 12:1,*
*Zheng, S. et al., (2015) J. Clin. Pharmacol., 55(Suppl. 3), S75–S84.*

## Results: Observed Pharmacodynamic (PD) Biomarkers

- Following ADG106 mono- or combination therapies, dose-dependent increases in sCD137 were observed in both scenarios (**Fig 3A-C**) and were associated with clinical activities in monotherapy (**Fig 3D**).




Mean±SEM is shown.

**Figure 3: Observed total soluble CD137 levels following ADG106 mono- or combination therapies with anti-PD1 (A-C); sCD137 induction ratio correlates with tumor shrinkage in monotherapy in nasopharyngeal carcinoma (D)**

- Increase in serum IFN-γ, IL-6, natural killer (NK) cells (**Fig 4A-D**), and T cell subsets were seen with ADG106 therapies.

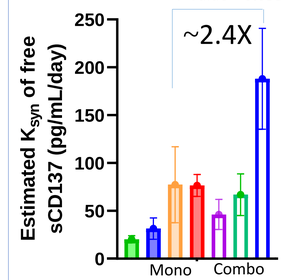



**Figure 4: ADG106 plus toripalimab increased serum IFN-γ levels (A) and serum IL-6 levels (B, showing solid tumor patients only) as early as 4 hours post treatment. Increased NK cell proliferation after monotherapy (C) and combination therapy with Toripalimab (D) was also observed.**

## Results: >2-Fold Synergistic Combination Effect

- The estimated mean (±SEM) synthesis rate constant ($K_{syn}$) of free sCD137 after the 1st dose (cycle 1) was comparable for ADG106 (5–10mg/kg) alone versus ADG106 (0.75mg/kg) + toripalimab. Furthermore, ADG106 (3mg/kg) with toripalimab resulted in >2-fold higher $K_{syn}$ than the maximum for ADG106 monotherapy (**Fig 5**).
- The computed ADG106-sCD137 complex elimination half-life after monotherapy was **>5–10 days**, mimicking ADG106 population elimination kinetics, the PK of which was not altered by toripalimab.
- Modeling suggested continuous free sCD137 production throughout the dosing cycles, potentially through CD137-expressing immune cell activation after repeat dosing.

*P value =0.055 (3mpk combo vs. 5 and 10mpk mono combined, 1-sided T test)*




Mean ± SEM is shown

1.5mpk mono
3mpk mono
5mpk mono
10mpk mono
0.75mpk combo
1.5mpk combo
3mpk combo

**Figure 5: Estimated mean (±SEM) synthesis rate constant of free sCD137 ADG106 monotherapy or combination treatment with toripalimab**

- ✓ *1.5 and 3mpk mono $K_{syn}$ likely slightly under-estimated due to lack of C1D8 data*

## Conclusions

- ADG106 treatments alone and in combination with anti-PD1 therapy increased serum IFN-γ, IL-6, natural killer cells, and T cell subsets. Soluble CD137 levels increased with immune activation, suggesting sCD137 as a sensitive dose-responsive PD biomarker for ADG106 therapy. ADG106 in combination with anti-PD-1 Ab toripalimab led to >2-fold greater immune activation than ADG106 alone, including patients who failed prior anti-PD-1 and/or CTLA-4 therapies, thereby supporting ADG106 combination therapies. Recommended phase 2 dose (RP2D) and optimal dosing regimens of ADG106 in combination with a number of anti-PD1 mAbs are aided by the PD biomarker findings (e.g., ~ optimal at 3mg/kg) and are explored further.

## Acknowledgements & Disclosure

- The authors would like to thank all patients and their families and caregivers for participating in our study; all clinical investigators, clinical study teams and ADG106 project team for their contributions to this study.
- Dr. Li Zhang has received clinical research institution funding from Adagene for the role of site principal investigator; for questions, contact Zhangli6@mail.sysu.edu.cn .
- This study is funded by Adagene, Inc.; for questions, contact ir@adagene.com .