AGEN2034, a novel anti-PD-1 antibody that combines effectively with CTLA-4 pathway blockade to enhance T cell activity

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ABSTRACT

AGEN2034, a novel anti-PD-1 antibody that combines effectively with CTLA-4 pathway blockade to enhance T cell activity

PD-1 (or CD279) is a co-inhibitory receptor that suppresses T cell function upon binding to its ligands, PD-L1 or PD-L2. PD-1 signaling functions cooperatively with CTLA-4 to limit T cell activation during priming by antigen-presenting cells, leading to reduced proliferation, cytokine and chemokine production and cell survival. Anti-PD-1 antibody therapies that block the interaction between PD-1 and its ligands have shown durable clinical responses in several agents, but particularly in combination with antibodies that antagonize CTLA-4.

AGEN2034, a novel human IgG4 anti-PD-1 antibody, potently inhibits PD-1 liging to PD-1 and PD-L2, resulting in enhanced T cell responsiveness in vitro as well as in a non-human primate model. AGEN2034 combined effectively with AGEN1884, a human IgG1 anti-CTLA-4 antibody, anti-TIGIT or anti-LAG-3 to further enhance T cell responsiveness. Furthermore, the combination of AGEN2034 and anti-TIGIT blocked a pharmacodynamic response in cynomolgus monkeys, including a transient increase in proliferation and IFN-γ (interferon-gamma) secretion in a subset of central memory and effector T cell subsets.

AGEN2034 was well tolerated, and a no-observed-adverse-effect level (NOAEL) could be established up to 40 mg/kg in non-human primates. AGEN2034 is currently under evaluation in a Phase 1/2 study in subjects with advanced melanoma and other cancers (NCT03101399) and studies to evaluate AGEN2034 in combination with AGEN1884 are planned.

RATIONAL BEHIND ANTI-PD-1 AND ANTI-CTLA-4 COMBINATION THERAPY

Anti-PD-1 Blockade

Ligands: PD-L1 is expressed on the surface of activated macrophages and tumor cells; PD-L2 is expressed on dendritic cells and macrophages

T cell expression: T cells commonly express elevated levels of PD-1 during chronic tumor antigen stimulation

Anti-PD-1 blockade functions to restore antigen-specific T cell effector function mainly in the tumor microenvironment

Anti-PD-1 and anti-CTLA-4 combination therapy have demonstrated robust antitumor efficacy in preclinical mouse tumor models and improved response rates in the clinic, such as in patients with metastatic melanoma, advanced small cell lung cancer (SCLC), and metastatic renal cell carcinoma (RCC).

AGENUS THERAPEUTIC ANTIBODIES IN PHASE I / II CLINICAL TRIALS

AGEN2034

AGEN1884

Target

PD-1

PD-1

PD-L1

PD-L1

Characterization

Fully human IgG4-229P

Fully human IgG1

Discovery Platform

Retrospective Display

Retrospective Display

Mechanism of Action

Antagonist

Antagonist

Clinical Trial #

NCT03104699

NCT02844822

‘Clinical activity of AGEN2034 in subjects with metastatic or locally advanced solid tumors, with a consecutive Phase 2 expansion to evaluate efficacy in subjects with recurrent, unresectable, or metastatic (advanced) central cancer that has progressed after a platinum doublet.’

AGEN3207

AGEN1202

Target

AGF

PD-L1

Characterization

Fully human IgG4

Fully human IgG1

Discovery Platform

Retrospective Display

Retrospective Display

Mechanism of Action

Antagonist

Antagonist

Clinical Trial #

NCT03104699

NCT03104699

Anti-PD-1

Anti-PD-1

AGEN2034 DOES NOT ACTIVATE FCγR RECEPTOR IIa SIGNALING, CONSISTENT WITH AN IgG4 FC REGIONS

Legend: A) Antagonist antibody was stimulated with Staphylococcal enterotoxin A peptide in the presence of dose titration of AGEN2034 or IgG4 isotype antibody for 5 days. Cytokine production (example: IL-2) was measured in the culture supernatant at day 5.

AGEN2034 EFFECTIVELY COMBINES WITH AGEN1884 TO FURTHER ENHANCE CYTOKINE SECRETION

Legend: A) Human PBMCs from two healthy donors were stimulated with Staphylococcal enterotoxin A peptide in the presence of AGEN2034 or IgG4 isotype antibody (10µg/ml) alone or in combination with anti-CTLA-4, AGEN1884, (10µg/ml) for 5 days. Cytokine expression (example: IL-2) was measured in the culture supernatant at day 5.

AGEN2034 COOPERATES WITH OTHER IMMUNOMODULATORY ANTIBODIES TO ENHANCE T CELL RESPONSIVENESS

Legend: A) Human PBMCs were stimulated with Staphylococcal enterotoxin A peptide in the presence of AGEN2034 or IgG4 isotype antibody (10µg/ml) alone or in combination with anti-LAG-3 (A) or anti-TIGIT (B) antibodies for 5 days. Cytokine production in example (A-Lag-3) was measured in the culture supernatant at day 5.

AGEN2034 IS SAFE AND WELL-TOLERATED

Legend: A) A K B C

AGEN2034 was well-tolerated up to the NOAEL of 40 mg/kg

TK analysis showed dose proportionality with some accumulation no gender differences.

Estimated AGEN2034 half-life of 12 days

SUMMARY

• AGEN2034 (anti-PD-1, IgG4) and AGEN1884 (anti-CTLA-4, IgG1) antibodies were discovered in a humanized mouse minimal display antibody format (Retrospective Display™)

• AGEN2034 potently blocks ligand binding to enhance T cell activation and rescue T cell responsiveness in peptide stimulation and T cell suppression assays

• AGEN2034 cooperates with other anti-PD-1 and anti-CTLA-4-based immuno-modulatory pathways to further enhance T cell responsiveness.

• In cynomolgus monkeys, AGEN2034 in combination with AGEN1884, also promoted a pharmacodynamic response of CD8+ T cell expansion in vivo

• Clinical trials (NCT03104699) evaluating AGEN2034 in patients with advanced solid tumors (Phase 1) with expansion to second-line cervical cancer (Phase 2) is ongoing.

Acknowledgments

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Active Disclosures

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