Poster # 366

A Phase 1 Study of AGEN2373, a Novel CD137 Agonist Antibody Designed to Avoid Hepatoxicity, in Patients with Advanced Solid Tumors

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Background

AGEN2373 is a high-affinity CD137 agonist antibody dependent on Fc gamma receptor binding for CD137 receptor clustering resulting in the selective enhancement of innate and adaptive immune cells

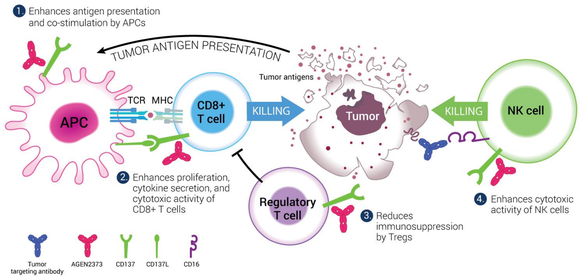

Figure 1. AGEN2373 mechanism of action. AGEN2373 (fully human, IgG1λ) is designed to enhance antitumor immunity through multiple mechanisms-of-action. Antibody-mediated CD137 agonist activity is anticipated to enhance antigen-presenting cell (APC), T cell, and natural killer (NK) cell function.[1,2] AGEN2373 may also target intratumoral T-regulatory (Tregs) for antibody-dependent cell cytotoxicity or phagocytosis (ADCC/ADCP)-mediated destruction.[3]

Dose Dependent Induction of CD137 (4-1BB) With AGEN2373

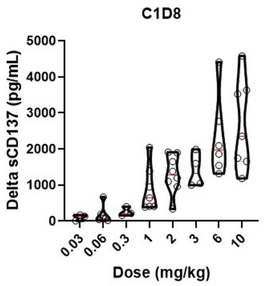

Figure 2. Soluble CD137 induction as a function of AGEN2373 dose in patients receiving AGEN2373 monotherapy (N=45, 0.03 mg/kg n=3, 0.06 mg/kg n=6, 0.3 mg/kg n=3, 1 mg/kg n=7, 2 mg/kg n=8, 3 mg/kg n=4, 6 mg/kg n=7, 10 mg/kg n=7). Induction of soluble CD137 was dose dependent with 2 mg/kg as the lowest saturating dose, suggesting this is the minimum predicted efficacious dose. Confirmatory analyses are being conducted. Violin plots show all data points with medians in red and quartiles in blue.

Phase I Study Overview (NCT04121676)

Objective

Evaluate the safety, tolerability, and dose-limiting toxicity of AGEN2373 as monotherapy in patients with advanced solid tumors.

Treatment schedule

AGEN2373 was administered intravenously every 2 weeks (Q2W), Q3W, or Q4W at doses between 0.03 and 10 mg/kg using a standard 3+3 dose-escalation design.

Results

Baseline Demographics

Demographic	All Patients N=46
Age	
Median (range)	64 (33-82)
Sex, n (%)	
Male	30 (65)
Female	16 (35)
ECOG PS, n (%)	
0	8 (17)
1	38 (83)
Prior Lines of Therapy, n (%)	
Median (range)	4 (1-14)
0	1 (2)
1	2 (4)
2	6 (13)
≥3	37 (80)

Table 1. Baseline demographics and patient characteristics (N=46). ECOG PS, Eastern Cooperative Oncology Group performance status.

Efficacy

Efficacy	Patients n=20
ORR, % (95% CI)	10 (1-32)
BOR, n (%)	
CR	0
PR	2 (10)
SD	7 (35)
PD	11 (55)
DCR (CR + PR + SD), % (95% CI)	45 (23-69)
12-month OS, % (95% CI)	39 (14-63)
Median OS, months	7.2 (5.1-NR)
Median PFS, months	1.9 (1.6-5.8)

Table 2. Efficacy in patients treated with 2 mg/kg or higher (n=20). BOR, best overall response; CR, confirmed response; DCR, disease control rate; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease.

Clinical Activity: Maximum Change in Target Lesion Size From Baseline (%)

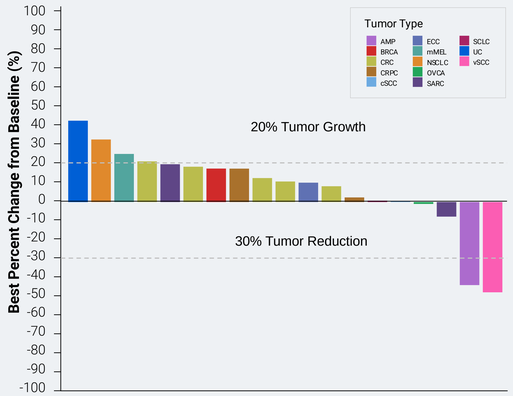

Figure 3A. Waterfall plot showing best percentage change in target lesion size from baseline (n=20).

Tumor type is indicated by color coding of bars. Data are presented for patients treated at 2 mg/kg or higher. Notable responses included: a patient with vSCC with a confirmed PR (cPR) while remaining on AGEN2373 (2 mg/kg Q2W for ~40 wks); a patient with ampullary carcinoma with four prior regimens who had a cPR on (6 mg/kg Q3W) with complete resolution of the pancreatic lesion; and a patient with CRPC with a confirmed 38% tumor reduction in liver target lesions (10 mg/kg Q3W) who was non-evaluable due to palliative radiation to bone metastases.

Clinical Activity: Percent Changes in Target Lesions Over Time

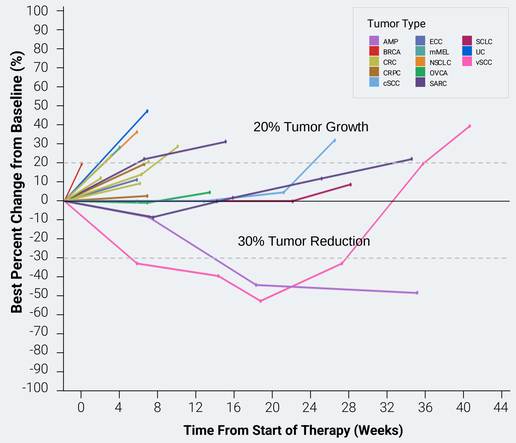

Figure 3B. Spider plot showing changes in target lesions as a function of time (n=20).

AMP, ampullary cancer; BRCA, breast cancer; cPR, confirmed partial response; CRC, colorectal cancer; CRPC, castrate resistant prostate cancer; cSCC, cutaneous squamous cell carcinoma; ECC, eccrine carcinoma; mMEL, mucosal melanoma; NSCLC, non-small cell lung cancer; OVCA, ovarian; Q2W, every 2 weeks; Q3W, every 3 weeks; SARC, sarcoma; SCLC, small cell lung cancer; UC, urothelial cancer; vSCC, vulvar squamous cell carcinoma.

Safety and Tolerability

Treatment-Related Adverse Events of All Grades

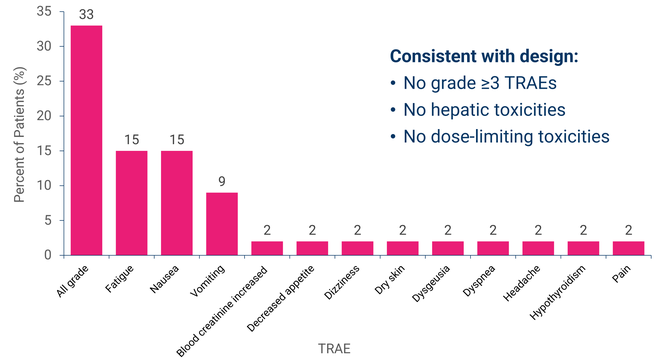

Figure 4. Treatment-related adverse events of all grades (N=46).

Conclusions

- ✓ AGEN2373 is a CD137 agonist antibody designed to selectively enhance tumor immunity, while mitigating off-target effects associated with systemic activation of CD137
- ✓ Bioanalytic data suggest that induction of soluble CD137 (soluble 4-1BB) is a dose-dependent biomarker of AGEN2373 treatment
- ✓ AGEN2373 monotherapy showed objective responses, clinical benefit, and a tolerable safety profile in heavily pretreated patients with solid tumors
- ✓ No high-grade treatment-related toxicities or evidence of hepatotoxicity, as designed
  - Differentiated from previous CD137-targeted agents that reported dose-limiting toxicities
- ✓ The combination of AGEN2373 + botensilimab, a novel multifunctional and Fc-enhanced CTLA-4 antibody, is currently being evaluated in patients with PD-(L)1 refractory melanoma at a dose of 10 mg/kg every 3 weeks

References:

1. Bartkowiak and Curran, *Front Oncol* 2015
2. Masu et al., *PLOS One* 2018
3. Freeman et al., *J Clin Invest* 2020

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