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Phase 1/2 Study of CTLA-4 Inhibitor AGEN1884 + PD-1 Inhibitor AGEN2034 in Patients With Advanced/Refractory Solid Tumors, With Expansion Into Second-Line Cervical Cancer and Solid Tumors

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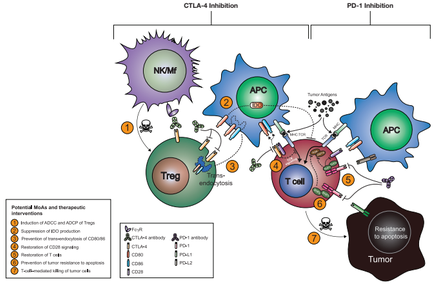
BACKGROUND

- Antigen-specific T-cell activation is regulated by a balance of co-stimulatory and co-inhibitory signals, such as those mediated by inhibitory receptors cytotoxic T-lymphocyte–associated antigen 4 (CTLA-4) and programmed cell death protein-1 (PD-1) (**Figure 1**).[1]
- Binding of these receptors to their ligands results in impaired T-cell function. For these reasons, antibody blockade of PD-1 and CTLA-4 has been identified as a therapeutic modality to reinvigorate or induce tumor-specific T-cell immunity.[1]

Figure 1. Overview of Pathways Affected by CTLA-4 and PD-1



- In clinical trials, the combined inhibition of PD-1 and CTLA-4 pathways by blocking receptor-ligand interactions has resulted in objective clinical response and increased survival in several solid tumor indications, including melanoma and non-small cell lung carcinoma. As a result, ipilimumab (anti–CTLA-4) in combination with nivolumab (anti–PD-1) has been approved as a first line of treatment in patients with metastatic melanoma and is currently being tested in multiple other indications.[2-4]
- Agenus' proprietary antibodies, AGEN2034 (anti–PD-1 human IgG4 monoclonal antibody) and AGEN1884 (anti–CTLA-4 human IgG1 monoclonal antibody) are currently under evaluation as monotherapy in phase 1/2 studies in subjects with advanced tumors (NCT03104699 and NCT02694822, respectively).
- A phase 1/2, open-label, multi-arm trial to investigate the safety, tolerability, pharmacokinetics, and biological and clinical activity of AGEN1884 in combination with AGEN2034 in patients with metastatic or locally advanced solid tumors is currently ongoing (C550-01; ACTRN12618000003279; NCT03495882).

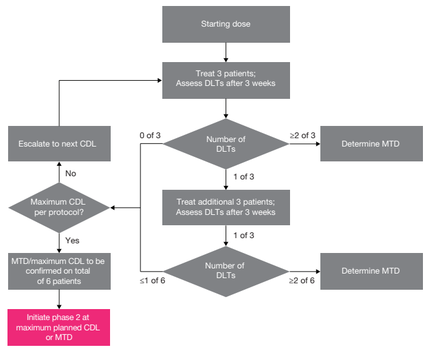
OBJECTIVE

- The objective of this study is to assess safety and tolerability of AGEN1884 in combination with AGEN2034 in patients with advanced/refractory solid tumors, with expansion into select solid tumors.

METHODS

- This is an ongoing phase 1/2, open-label, study of AGEN1884 in combination with AGEN2034 in subjects with advanced solid tumors, including cervical cancer.
- The study consists of 2 phases:
  - Phase 1: Dose escalation (focus of this poster)
  - Phase 2: Expansion in select tumors (ongoing)
- Phase 1 consisted of a standard 3+3 dose escalation with the following escalating dose levels and schedules:
  - AGEN2034 1 mg/kg administered every 2 weeks (q2w) in combination with AGEN1884 1 mg/kg administered every 6 weeks (q6w)
  - AGEN2034 3 mg/kg administered every 2 weeks (q2w) in combination with AGEN1884 1 mg/kg administered every 6 weeks (q6w)
- AGEN2034 was administered IV over 60 min and AGEN1884 IV over 90 mins. AGEN1884 was to be administered on the same day as AGEN2034 ≥30 min after the completion of AGEN2034 administration.
- Dose escalation will continue until AGEN2034 3 mg/kg + AGEN1884 1 mg/kg (maximum combination dose level) is shown to be safe or the maximum tolerated dose (defined as the combination below which ≥33% of subjects develop dose-limiting toxicities [DLTs]) is reached.
- A schematic of the phase 1 dose-escalation design is presented in **Figure 2**.

Figure 2. Dose-Escalation Study Flow



CDL, combination dose level; DLT, dose-limiting toxicity; MTD, maximum tolerated dose.

- Each subject will receive the combination treatment for a maximum of 24 months or until confirmed disease progression, unacceptable toxicity, or any criterion for withdrawal from the trial or the investigational medicinal products occurs.
  - Patients who do not complete the DLT observation period of 21 days after the first dose, for reasons other than a DLT, will be replaced.
  - Cohorts will be backfilled to 10 subjects once they have reached DLT or MTD.
- Eligible patients include adults (aged ≥18 years) with a histologically or cytologically confirmed diagnosis of a metastatic or locally advanced solid tumor for which no standard therapy is available or standard therapy has failed.
- The treatment phase was divided into 6-week cycles, each beginning with the combined administration of AGEN2034 and AGEN1884 on day 1. Thereafter, AGEN2034 will be administrated q2w, completing the 6-week cycle.
  - Tumor assessments are to be conducted at 6, 12, and 18 weeks from first dose, and every 9 weeks thereafter until disease progression is confirmed or a new line of therapy is initiated.
- Phase 1 endpoints:
  - Primary: Occurrence of DLTs in patients in dose escalation during the first 21 days of treatment
  - Secondary:
    - Confirmed best overall response per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1, as determined by the investigator
    - Frequency and nature of treatment-emergent adverse events (TEAEs)
    - Pharmacokinetic profile and immunogenicity of AGEN1884 and AGEN2034

RESULTS

- As of July 16, 2018, the study was ongoing, though total enrollment was achieved in the phase 1 portion (ie, 10 patients in each dose cohort). Data are preliminary as it is being cleaned and/or collected at this time.
- Five patients had discontinued from the study treatment prior to data extract:
  - AGEN2034 1 mg/kg q2w + AGEN1884 1 mg/kg q6w: Progressive disease, n=1; investigator decision, n=1
  - AGEN2034 3 mg/kg q2w + AGEN1884 1 mg/kg q6w: Progressive disease, n=3
- There was 1 death not related to the study (66-year-old female with lung cancer treated with AGEN2034 1 mg/kg q2w + AGEN1884 1 mg/kg q6w died due to disease progression).
- Patients were Caucasian (100%) and primarily female (75%), with a median of 2.3 months from the most recent recurrence/progression to the administration of the first combination dose (**Table 1**).
- The cancer types for the 20 patients were as follows: breast cancer (triple negative, n=2; with lung metastases, n=1; with dermal lymphatics, n=1), ovarian cancer (n=2), mesothelioma (pleural, n=1; peritoneal, n=1), squamous carcinoma of head and neck (tongue; n=1), anal squamous carcinoma (n=1), pleomorphic soft tissue sarcoma (n=1), lung cancer (n=1), metastatic leiomyosarcoma (n=1), advanced gastrointestinal stromal tumor (n=1), rhabdomyosarcoma (n=1), alveolar rhabdomyosarcoma (n=1), recurrent chordoma of the thoracic spine (n=1), chordoma (n=1), colorectal-rectal (n=1), esophageal adenocarcinoma (n=1).

Table 1. Demographics and Baseline Characteristics (Safety Set)

	AGEN2034 1 mg/kg + AGEN1884 1 mg/kg (N=10)	AGEN2034 3 mg/kg + AGEN1884 1 mg/kg (N=10)	Total *Patients* (N=20)
Age (years)			
Mean (SD)	58.4 (8.13)	47.6 (19.68)	53.0 (15.66)
Min, Max	43, 69	21, 79	21, 79
Female, n (%)	8 (80%)	7 (70%)	15 (75%)
BMI (kg/m^2)			
Mean (SD)	28.71 (8.227)	27.48 (7.006)	28.10 (7.464)
Min, Max	18.8, 40.9	20.9, 45.5	18.8, 45.5
ECOG performance status, n (%)			
0	5 (50%)	7 (70%)	12 (60%)
1	5 (50%)	3 (30%)	8 (40%)
Time between most recent progression and first dose date (months)			
n	6	6	12
Mean (SD)	2.26 (1.665)	2.34 (1.002)	2.30 (1.311)

BMI, body mass index; ECOG, Eastern Cooperative Oncology Group.

- An overview of safety and tolerability is presented in **Table 2**.

Table 2. Overview of Treatment-Emergent Adverse Event (Safety Set)

Patients, n (%)	AGEN2034 1 mg/kg + AGEN1884 1 mg/kg (N=10)	AGEN2034 3 mg/kg + AGEN1884 1 mg/kg (N=10)	Total *Patients* (N=20)
Any TEAE	10 (100%)	9 (90%)	19 (95%)
Any serious TEAE	3 (30%)	2 (20%)	5 (25%)
Any grade ≥3 TEAE	3 (30%)	2 (20%)	5 (25%)
Any immune-related TEAE	5 (50%)	4 (40%)	9 (45%)
Any treatment-related TEAE	8 (80%)	7 (70%)	15 (75%)
Any treatment-related serious TEAE	1 (10%)	2 (20%)	3 (15%)
Any treatment-related grade ≥3 TEAE	0	2 (20%)	2 (10%)

TEAE, treatment-emergent adverse event.

- As of July 16, 2018, no DLTs have been observed, and none of the TEAEs led to discontinuation or death.
- TEAEs were reported in 19 of 20 patients (95%), with the most common MedDRA version 18.1 preferred terms listed in (**Table 3**).
- Most TEAEs were mild to moderate in severity (grade 1 or 2); 5 patients experienced TEAEs of grade ≥3.
  - AGEN2034 1 mg/kg q2w + AGEN1884 1 mg/kg q6w: Vomiting, n=1; wound and cancer pain, n=1; hypotension, n=1
  - AGEN2034 3 mg/kg q2w + AGEN1884 1 mg/kg q6w: Lower respiratory tract infection and pneumonia, n=1; pulmonary embolism, n=1
  - Of these, the events of lower respiratory tract infection and pulmonary embolism were considered related to study treatment by the investigator.

Table 3. Most Common* Treatment-Emergent Adverse Event (Safety Set)

Patients, n (%)	AGEN2034 1 mg/kg + AGEN1884 1 mg/kg (N=10)	AGEN2034 3 mg/kg + AGEN1884 1 mg/kg (N=10)	Total *Patients* (N=20)
Fatigue	5 (50%)	5 (50%)	10 (50%)
Nausea	3 (30%)	4 (40%)	7 (35%)
Pruritus	2 (20%)	3 (30%)	5 (25%)
Chills	3 (30%)	1 (10%)	4 (20%)
Vomiting	2 (20%)	2 (20%)	4 (20%)
Back pain	4 (40%)	0	4 (20%)

*Occurring in ≥20% of patients.

- Serious TEAEs occurred in 5 patients: 3 receiving AGEN2034 1 mg/kg q2w + AGEN1884 1 mg/kg q6w and 2 receiving AGEN2034 3 mg/kg q2w + AGEN1884 1 mg/kg q6w
- 3 patients experienced serious TEAEs considered related to study treatment.
  - AGEN2034 1 mg/kg q2w + AGEN1884 1 mg/kg q6w: Diarrhea, n=1
  - AGEN2034 3 mg/kg q2w + AGEN1884 1 mg/kg q6w: Lower respiratory tract infection, n=1; pulmonary embolism, n=1
- The summary of best overall response is listed in **Table 4**.
- The partial response was ongoing in one of the women with metastatic ovarian cancer. For patients with >90 days of treatment, stable disease was ongoing for 1 female with breast cancer (with lung metastases), 1 female with metastatic ovarian cancer, and 1 male with pleomorphic soft tissue sarcoma (with lung metastases).

Table 4. Summary of Best Overall Response at Time of Data Cut-off

Patients, n (%)	AGEN2034 1 mg/kg + AGEN1884 1 mg/kg (N=10)	AGEN2034 3 mg/kg + AGEN1884 1 mg/kg (N=10)	Total *Patients* (N=20)
Complete response	0	0	0
Partial response	1	0	1
Stable disease	5	1	6
Progressive disease	3	6	9
Not evaluable	1	0	1
Pending	0	3	3

Overall response determined by Response Evaluation Criteria in Solid Tumors (RECIST) v1.1.

DISCUSSION

- In the phase 1 portion, which is still ongoing, preliminary results demonstrate that AGEN1884 (1 mg/kg q6w) + AGEN2034 (3 mg/kg q2w) is generally safe, well tolerated, and active in adults with select advanced/refractory solid tumors.
- The phase 2 portion of this study evaluating AGEN1884 in combination with AGEN2034 in adults with second-line cervical cancer and other solid tumors is ongoing.
  - The phase 2 recommended dosing was determined as AGEN2034 3 mg/kg q2w + AGEN1884 1 mg/kg q6w.

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Disclosures

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