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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1Ion Cancer Center, South Brisbane, Australia; 2Scintia Clinical Research, Sydney, Australia; 3AstraZeneca; 4Antibody AG (now Agenus Switzerland Inc.) and Recepta Biopharma S.A. Recepta Biopharma S.A. has exclusive rights to the research and development of AGEN1884 and AGEN2034. Published at the 2018 Annual Congress of the European Society for Medical Oncology (ESMO), October 19–23, 2018, in Munich, Germany

Background

• In clinical trials, the combination of PD-1 and CTLA-4 pathways by blocking receptor-ligand interaction has resulted in objective clinical responses and durable remissions in metastatic melanoma, colorectal cancer, renal cell carcinoma, non-small-cell lung cancer, and advanced solid tumors, including metastases and non-small-cell lung cancers. As a result, pembrolizumab (PD-1) and ipilimumab (CTLA-4) have been approved as a first-line treatment in patients with metastatic melanoma and is currently being tested in multiple other indications.1,2

• Agenus proprietary antibodies, AGEN1884 (anti-CTLA-4 human IgG1) and AGEN2034 (anti-PD-1 human IgG1) monoclonal antibodies are currently under evaluation as monotherapy in phase 1/2 studies in subjects with advanced melanoma (NCT02352374 and NCT02782825, respectively), advanced cervical cancer (NCT02523989), and advanced solid tumors (NCT02782825), and in combination with lenvatinib and traditional and acquired resistance of AGEN1884 in combination with AGEN2034 in patients with metastatic or locally advanced solid tumors is currently ongoing (C550-01; ACTRN12618000003279; NCT03495882).

• As of July 16, 2018, the study was ongoing, though total enrollment was achieved in the phase 1 portion of the study (Figure 1).

• The objective of this study is to assess safety and tolerability of AGEN1884 in combination with AGEN2034 in patients with metastatic or locally advanced solid tumors in a single ascending dose escalation (SAD) approach.

• The phase 2 portion of this study evaluating AGEN1884 in combination with second-line cervical cancer and other solid tumors is ongoing.

Methods

• This is a single-arm, open-label, phase 1/2 study of AGEN1884 in combination with AGEN2034 in patients with advanced/locally advanced solid tumors, with expansion into select solid tumors.

• Five patients from each dose level will be treated for 21 days, followed by a 7-day period for assessment. Patients may continue further cycles of treatment

• The recommended dose for the phase 2 study is 3 mg/kg every 2 weeks (q2w) for AGEN2034 in combination with 1 mg/kg every 6 weeks (q6w) for AGEN1884.

• The data presented are from the SAD cohort, not the phase 2 part of the study.

Results

• Of the 10 patients (80%) who were evaluable for safety (SAD cohort), 8 received 3 mg/kg q2w AGEN2034 + 1 mg/kg q6w AGEN1884.

• Of these 10 patients, 3 received 1 mg/kg q2w AGEN2034 + 1 mg/kg q6w AGEN1884.

• The most common adverse events are reported in Table 1. Of these, the events of lower respiratory tract infection and pulmonary embolism were considered related to the investigational products.

• The treatment phase was divided into 6-week periods, each beginning with the combination administration of AGEN1884 and AGEN2034 on day 1. Tumor assessments were to be conducted at 6, 12, and 18 weeks from first dose, and every 9 weeks thereafter.

• As of July 16, 2018, no DLTs have been observed, and none of the TEAEs led to discontinuation or death.

• The phase 2 portion of this study evaluating AGEN1884 in combination with second-line cervical cancer and other solid tumors is ongoing.

• The phase 2 recommended dose was determined as 3 mg/kg q2w AGEN2034 in combination with 1 mg/kg q6w AGEN1884.

• As of July 16, 2018, no DLTs have been observed, and none of the TEAEs led to discontinuation or death.

• Of the 10 patients who were evaluable for safety in the phase 2 portion of the study, 8 were treated with 3 mg/kg q2w AGEN2034 in combination with 1 mg/kg q6w AGEN1884.

• Table 2 presents the most common treatment-emergent adverse events (TEAEs).

• Of the 10 patients treated with 1 mg/kg q2w AGEN2034 + 1 mg/kg q6w AGEN1884, 3 patients were evaluable for safety in the phase 2 portion of the study.

• Of these 3 patients, 2 received AGEN2034 3 mg/kg q2w + AGEN1884 1 mg/kg q6w and 1 received 1 mg/kg q2w AGEN2034 + 1 mg/kg q6w AGEN1884.

• Two patients treated with 3 mg/kg q2w AGEN2034 + 1 mg/kg q6w AGEN1884 died due to disease progression.

• Of the 10 patients treated with 3 mg/kg q2w AGEN2034 + 1 mg/kg q6w AGEN1884, 7 patients were evaluable for safety in the phase 2 portion of the study.

• Of these 7 patients, 5 patients were evaluable for clinical activity.

• Of the 7 evaluable patients, 3 patients had a confirmed partial response and 1 patient had a stable disease response.

• As of July 16, 2018, no DLTs have been observed, and none of the TEAEs led to discontinuation or death.

• Three patients treated with 3 mg/kg q2w AGEN2034 + 1 mg/kg q6w AGEN1884 died due to disease progression.

• Table 3 presents the most common treatment-emergent adverse events (TEAEs).

• Of the 6 patients evaluable for safety in the phase 2 portion of the study, 5 patients were evaluable for clinical activity.

• Of these 5 patients, 3 patients had a confirmed partial response and 2 patients had a stable disease response.

• Assessment of clinical activity was based on Response Evaluation Criteria in Solid Tumors (RECIST) v1.1.

• Table 4 presents the summary of best overall response during the phase 2 study.

• Table 5 presents the demographics and baseline characteristics of the patients in the phase 2 portion of the study.
Phase 1/2 Study of CTLA-4 Inhibitor AGEN1884 + PD-1 Inhibitor AGEN2034 in Patients With Advanced/Refractory Solid Tumors,

Icon Cancer Center, South Brisbane, Australia; 2Scientia Clinical Research, Sydney, Australia; 3Linear Clinical Research, Perth, Australia; 4Agenus Inc. or subsidiary thereof (current or former employee), Lexington, MA, USA

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

<table>
<thead>
<tr>
<th>Event</th>
<th>N=10</th>
<th>N=10</th>
<th>N=20</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Patients</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Starting dose</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pruritus</td>
<td>2 (20%)</td>
<td>3 (30%)</td>
<td>5 (25%)</td>
</tr>
<tr>
<td>Min, Max</td>
<td>43, 69</td>
<td>21, 79</td>
<td>21, 79</td>
</tr>
<tr>
<td>Chills</td>
<td>3 (30%)</td>
<td>1 (10%)</td>
<td>4 (20%)</td>
</tr>
<tr>
<td>BMI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>28.71 (8.227)</td>
<td>27.48 (7.006)</td>
<td>28.10 (7.464)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>2 (20%)</td>
<td>2 (20%)</td>
<td>4 (20%)</td>
</tr>
<tr>
<td>Back pain</td>
<td>4 (40%)</td>
<td>0</td>
<td>4 (20%)</td>
</tr>
<tr>
<td>Any immune-related TEAE</td>
<td>5 (50%)</td>
<td>4 (40%)</td>
<td>9 (45%)</td>
</tr>
<tr>
<td>Any treatment-related serious TEAE</td>
<td>1 (10%)</td>
<td>2 (20%)</td>
<td>3 (15%)</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>3</td>
<td>6</td>
<td>9</td>
</tr>
<tr>
<td>Partial response</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Stable disease</td>
<td>0</td>
<td>4</td>
<td>6</td>
</tr>
</tbody>
</table>
| Maximum planned CDL    | >90 days of treatment, stable disease was ongoing for 1 female with breast cancer (with lung metastases), 1 female.

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

<table>
<thead>
<tr>
<th>Event</th>
<th>N=10</th>
<th>N=10</th>
<th>N=20</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Patients</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Starting dose</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete response</td>
<td>8 (80%)</td>
<td>7 (70%)</td>
<td>15 (75%)</td>
</tr>
<tr>
<td>Partial response</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Stable disease</td>
<td>0</td>
<td>4</td>
<td>6</td>
</tr>
</tbody>
</table>

**METHODS**

The study consisted of 2 phases:

- **Phase 1:**
  - A phase 1/2, open-label, multi-arm trial to investigate the safety, tolerability, pharmacokinetics, and biological activity of AGEN1884 in combination with AGEN2034 in subjects with advanced/refractory solid tumors, with expansion into select solid tumors.
  - 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.
  - Eligible patients include adults (aged ≥18 years) with a histologically or cytologically confirmed diagnosis of advanced/refractory solid tumors and with no standard therapy available or standard therapy has failed.
  - The study consists of 2 phases:
    - Cohorts will be backfilled to 10 subjects once they have reached DLT or MTD.
    - Tumor assessments are to be conducted at 6, 12, and 18 weeks from first dose, and every 9 weeks thereafter.
  - The phase 2 recommended dosing was determined as AGEN2034 3 mg/kg q2w + AGEN1884 1 mg/kg q6w.
  - A schematic of the phase 1 dose-escalation design is presented in Figure 1.
  - As of July 16, 2018, the study was ongoing, though total enrollment was achieved in the phase 1 portion of the trial.
  - Data are preliminary as it is being cleaned and/or collected at this time.

- **Phase 2:**
  - Of these, the events of lower respiratory tract infection and pulmonary embolism were considered related to AGEN2034 and AGEN1884.
  - TEAEs were reported in 19 of 20 patients (95%), with the most common MedDRA version 18.1 preferred terms listed in Table 2.
  - Any immune-related TEAE 5 (50%) 4 (40%) 9 (45%)
  - Any treatment-related serious TEAE 1 (10%) 2 (20%) 3 (15%)
  - The phase 2 recommended dosing was determined as AGEN2034 3 mg/kg q2w + AGEN1884 1 mg/kg q6w: Lower respiratory tract infection, n=1; pulmonary embolism, n=1.

**DISCUSSION**

This study was funded by Agenus Inc. (Lexington, MA, USA). The licensed antibodies CTLA-4 inhibition (anti–CTLA-4 human IgG1 monoclonal antibody) are currently under evaluation as monotherapy in phase 1/2 studies, with a phase 3 study in melanoma (NCT02697367) and a phase 2 study in renal cell carcinoma (NCT02269291). A phase 3 study of AGEN2034 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

**REFERENCES**

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.
• Binding of these receptors to their ligands results in impaired T-cell function. For these reasons, antibody

**OBJECTIVE**

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

— Antigen-specific T-cell activation is regulated by a balance of co-stimulatory and co-inhibitory signals, such as interactions has resulted in objective clinical response and increased survival in several solid tumor

— Dose escalation will continue until AGEN2034 3 mg/kg + AGEN1884 1 mg/kg (maximum combination dose advanced solid tumors, including cervical cancer.

— As of July 16, 2018, the study was ongoing, though total enrollment was achieved in the phase 1 portion

**RESULTS**

— 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.

— 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.

— Cancer types for the 20 patients were as follows: breast cancer (n=13), colorectal-rectal (n=1), esophageal adenocarcinoma (n=1), gastric cancer (n=1), melanoma (n=1), mesothelioma (pleural, n=1; peritoneal, n=1), squamous carcinoma of head and neck (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).

— Any grade ≥3 TEAE 3 (30%) 2 (20%) 5 (25%)

— Any immune-related TEAE 5 (50%) 4 (40%) 9 (45%)

— Any treatment-related serious TEAE 1 (10%) 2 (20%) 3 (15%)

— Any TEAE 10 (100%) 9 (90%) 19 (95%)

— Mean (SD) 2.26 (1.665) 2.34 (1.002) 2.30 (1.311)

— n 6 6 12

— ECOG performance status

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

**DISCUSSION**

— 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

— Pending

— Not evaluable

— Total

— Yes

— No

— Maximum CDL per protocol?

— MTD/maximum CDL to be confirmed on total of 6 patients

— Initiate phase 2 at maximum planned CDL or MTD

— Determine MTD

— Treat 3 patients; Assess DLTs after 3 weeks

— Escalate to next CDL

— Determine MTD

— Treat additional 3 patients; Assess DLTs after 3 weeks

— 1 of 3

— 0 of 3 ≥2 of 3

— ≤1 of 6

— ≥2 of 6

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

**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 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

— The phase 2 portion of this study evaluating AGEN1884 in combination with AGEN2034 in adults with...
The binding of these receptors to their ligands results in impaired T-cell function. For these reasons, antibodies targeting these pathways are under development in combination with other immunotherapies. 

A schematic of the phase 1 dose-escalation design is presented in Figure 1. AGEN2034 was administered IV over 60 min and AGEN1884 IV over 90 mins. AGEN1884 was to be administered every 6 weeks (q6w) in combination with AGEN2034 3 mg/kg q2w. Phase 1 consisted of a standard 3+3 dose escalation with the following escalating dose levels and schedules:

- 1 mg/kg q6w
- 3 mg/kg q2w
- 1 mg/kg q6w
- 3 mg/kg q2w + 1 mg/kg q6w
- 3 mg/kg q2w + 1 mg/kg q6w

Methods

In clinical trials, the combined inhibition of PD-1 and CTLA-4 pathways by blocking receptor-ligand interactions is shown to be safe or the maximum tolerated dose (defined as the combination below which ≥33% of patients experience dose-limiting toxicity). AGEN2034 and AGEN1884 have been evaluated alone and in combination in metastatic melanoma and is currently being tested in multiple other indications.2-4 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 phase 2 portion of this study evaluating AGEN1884 in combination with AGEN2034 in adults with metastatic ovarian cancer, and 1 male with pleomorphic soft tissue sarcoma (with lung metastases).

Results

Each subject will receive the combination treatment for a maximum of 24 months or until confirmed disease progression or unacceptable toxicity occurs. An overview of safety and tolerability is presented in Table 2. 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 1. Demographics and Baseline Characteristics (Safety Set)

<table>
<thead>
<tr>
<th></th>
<th>AGEN2034 1 mg/kg + AGEN1884 1 mg/kg (N=10)</th>
<th>AGEN2034 3 mg/kg + AGEN1884 1 mg/kg (N=10)</th>
<th>Total Patients (N=20)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (years)</strong></td>
<td>Mean (SD)</td>
<td>Min, Max</td>
<td>58.4 (8.13)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>43, 69</td>
<td>21.79, 21.79</td>
</tr>
<tr>
<td>**Female, n (%)</td>
<td>8 (80%)</td>
<td>7 (70%)</td>
<td>15 (75%)</td>
</tr>
<tr>
<td><strong>BMI (kg/m²)</strong></td>
<td>Mean (SD)</td>
<td>Min, Max</td>
<td>28.71 (8.227)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>18.8, 40.9</td>
<td>28.10 (7.464)</td>
</tr>
<tr>
<td><strong>ECOG performance status, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>5 (50%)</td>
<td>7 (70%)</td>
<td>12 (60%)</td>
</tr>
<tr>
<td>1</td>
<td>5 (50%)</td>
<td>3 (30%)</td>
<td>8 (40%)</td>
</tr>
<tr>
<td><strong>Time between most recent progression and first dose date (months)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>6</td>
<td>6</td>
<td>12</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>2.26 (1.665)</td>
<td>2.34 (1.002)</td>
<td>2.30 (1.311)</td>
</tr>
</tbody>
</table>

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

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

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)

<table>
<thead>
<tr>
<th>Event</th>
<th>AGEN2034 1 mg/kg + AGEN1884 1 mg/kg (N=10)</th>
<th>AGEN2034 3 mg/kg + AGEN1884 1 mg/kg (N=10)</th>
<th>Total Patients (N=20)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Any treatment-related TEAE</strong></td>
<td>8 (80%)</td>
<td>7 (70%)</td>
<td>15 (75%)</td>
</tr>
<tr>
<td><strong>Any treatment-related serious TEAE</strong></td>
<td>1 (10%)</td>
<td>2 (20%)</td>
<td>3 (15%)</td>
</tr>
<tr>
<td><strong>Any treatment-related grade ≥3 TEAE</strong></td>
<td>0</td>
<td>2 (20%)</td>
<td>2 (10%)</td>
</tr>
</tbody>
</table>
Table 3. Most Common* Treatment-Emergent Adverse Event (Safety Set)

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

*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

<table>
<thead>
<tr>
<th>Patients, n (%)</th>
<th>AGEN2034 1 mg/kg + AGEN1884 1 mg/kg (N=10)</th>
<th>AGEN2034 3 mg/kg + AGEN1884 1 mg/kg (N=10)</th>
<th>Total Patients (N=20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete response</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Partial response</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Stable disease</td>
<td>5</td>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>3</td>
<td>6</td>
<td>9</td>
</tr>
<tr>
<td>Not evaluable</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Pending</td>
<td>0</td>
<td>3</td>
<td>3</td>
</tr>
</tbody>
</table>

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.

References

Disclosures
CD Dupont, AM Gonzalez, M Lim, D Savitsky, M Carini, S Hu, O Shebanova, E Dow, W Ortuzar, JS Buell, RB Stein, H Youssoufiann: Agenus Inc.: current or former employment/consultancy and stock ownership.

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