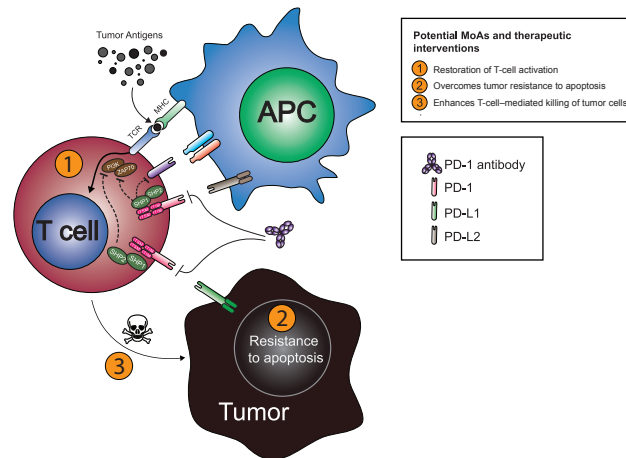


BACKGROUND

- Inhibition of the programmed cell death protein-1 (PD-1) pathways by blockade of receptor-ligand interactions has been demonstrated in numerous clinical trials to result in objective clinical response and increased survival in solid tumor indications (**Figure 1**).¹⁻⁴
- PD-1 signaling is mediated by 2 ligands: PD-1 ligand 1 (PD-L1, or CD274) and PD-1 ligand 2 (PD-L2, or CD273).⁵
- Upon binding to PD-L1 or PD-L2, PD-1 signaling in T cells can potentially attenuate TCR signaling, resulting in diminished cytokine and proliferative responses, reduced T-effector cell cytolytic activity, and impaired central memory T-cell differentiation.⁶

Figure 1. Pathways Affected by PD-1



- AGEN2034 is a novel, fully human monoclonal immunoglobulin G4 (IgG4) designed to block PD-1 from interacting with its ligands PD-L1 and PD-L2.
- AGEN2034 blocks interaction with PD-L1 and PD-L2, mediates human T-cell activation in vitro, and activates T cells in vivo in non-human primates.⁷
- The current study (NCT03104699) evaluates AGEN2034 in patients with advanced, refractory malignancies, including cervical cancer. Here, we present an interim analysis of the data collected, cleaned, and analyzed as of July 26, 2018.

OBJECTIVE

- *Phase 1:* To assess the safety and tolerability of different AGEN2034 dose levels in patients with metastatic and/or locally advanced solid tumors in order to determine recommended phase 2 dosing
- *Phase 2:* To assess the efficacy and safety of AGEN2034 in patients with recurrent, unresectable, or metastatic cervical cancer

METHODS

- This is a phase 1, open-label, dose-escalation trial of AGEN2034 with a phase 2 expansion in patients with select solid tumors currently ongoing.
- Primary outcome measures were to assess:
 - Phase 1: Occurrence of dose-limiting toxicities (DLTs) in subjects in dose escalation during the first 21 days of treatment
 - Phase 2: Best overall response (BOR), according to Response Evaluation Criteria in Solid Tumors, version 1.1 (RECIST 1.1), as determined by an independent endpoint review committee (IERC), in patients with advanced cervical cancer
- Secondary outcome measures were to assess:
 - Safety and tolerability, PK profile, and immunogenicity
 - BOR, duration of response, progression-free survival, and overall survival (with a 1-year time frame; phase 2 only), per RECIST 1.1, as determined by the IERC (phase 2 only) and investigator (both phases).

- Exploratory outcome measures were to:
 - Evaluate biological responses to AGEN2034 in blood/serum
 - Association of PD-L1 expression with clinical responses (phase 2)

Phase 1: Dose Escalation for Recommended Phase 2 Dosing

- Phase 1 consisted of a standard 3+3 dose-escalation design with the following escalating dose levels and schedules:
 - Part A: 1, 3, and 10 mg/kg administered intravenously q2w
 - Part B: 6 and 10 mg/kg administered intravenously q3w
- AGEN2034 was administered for up to 2 years or until confirmed progression, unacceptable toxicity, or any criterion for stopping the study drug or withdrawal from the trial occurred.
- Eligible patients included male and female patients (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.

Phase 2: Expansion in Patients With Recurrent, Unresectable, or Metastatic Cervical Cancer

- The recommended phase 2 dosing of AGEN2034, established in phase 1, is to be administered for a maximum of 2 years or until confirmed progression, unacceptable toxicity, or any criterion for stopping the study drug or withdrawal from the trial occurs.
- For the phase 2 portion of the study, an Independent Data Management Committee was established to evaluate safety and efficacy, and an IERC was established to adjudicate tumor response.
- Inclusion and exclusion criteria were the same as phase 1, except for the following:
 - Patients were female (aged ≥18 years) and must have a histologically or cytologically confirmed diagnosis of a metastatic or locally advanced, unresectable squamous-cell carcinoma, adenosquamous carcinoma, or adenocarcinoma of the cervix.
 - Patients must have relapsed after a platinum-containing doublet administered for treatment of advanced disease.
 - Patients must have measurable disease on imaging based on RECIST 1.1.
- The null hypothesis to be tested is that the objective response rate (ORR) does not exceed 10% (H0: ORR 10%), and the alternative hypothesis is that the ORR is greater than 10% (H1: ORR >10%). ORR was defined as the proportion of patients with confirmed BOR of partial or complete response.

PHASE 1 RESULTS

Patient Disposition and Demographics

- As of July 26, 2018, a total of 50 patients had been recruited, enrolled, and treated in the phase 1 dose-escalation portion of the study, with each dosage group comprising 10 patients.
 - Dosages: 1 mg/kg q2w, 3 mg/kg q2w, 10 mg/kg q2w, 6 mg/kg q3w, 10 mg/kg q3w
- Demographics and baseline characteristics of the phase 1 cohorts are detailed in **Table 1**, with patient disposition detailed in **Table 2**.
 - Median (range) time since the most recent recurrence/progression to the administration of the first dose was 1.7 (0.2, 11.2) months.
 - 70% of the subjects had a ECOG Performance Status of 1.

Table 1. Phase 1 Demographics and Baseline Characteristics

	1 mg/kg q2w n=10	3 mg/kg q2w n=10	10 mg/kg q2w n=10	6 mg/kg q3w n=10	10 mg/kg q3w n=10	All Patients N=50
Age (years)						
Median	58.5	58.5	53.0	63.0	60.5	58.5
Min, max	23, 77	31, 76	39, 73	40, 72	50, 79	23, 79
Females, n (%)	8 (80%)	8 (80%)	9 (90%)	9 (90%)	8 (80%)	42 (84%)

Table 2. Phase 1 Patient Disposition

	1 mg/kg q2w n=10	3 mg/kg q2w n=10	10 mg/kg q2w n=10	6 mg/kg q3w n=10	10 mg/kg q3w n=10	All Patients N=50
Discontinued study, n (%)	4 (40%)	3 (30%)	1 (10%)	1 (10%)	2 (20%)	11 (22%)
Death	3 (30%)	2 (20%)	0	1 (10%)	0	6 (12%)
Withdrawal of consent	1 (10%)	0	1 (10%)	0	1 (10%)	3 (6%)
Continuing in study at time of data extract, n (%)	6 (60%)	7 (70%)	9 (90%)	9 (90%)	8 (80%)	39 (78%)
Follow-up time (days)						
Median	314.5	257.5	245.5	178.5	118.5	191.0
Min, max	49, 464	48, 368	45, 312	57, 200	50, 157	45, 464

Safety and Tolerability

- No DLTs were observed in the phase 1 dose-escalation phase.
- A summary of the treatment-emergent adverse event (TEAE) profile is provided in **Table 3**.
- The most common TEAEs were fatigue (n=22), nausea (n=17), decreased appetite (n=15), diarrhea (n=14), and vomiting (n=13).

Table 3. Phase 1 Treatment-Emergent Adverse Events

Patients, n (%)	1 mg/kg q2w n=10	3 mg/kg q2w n=10	10 mg/kg q2w n=10	6 mg/kg q3w n=10	10 mg/kg q3w n=10	All Patients N=50
TEAEs	10 (100%)	10 (100%)	10 (100%)	10 (100%)	9 (90%)	49 (98%)
Grade ≥3	7 (70%)	5 (50%)	6 (60%)	5 (50%)	3 (30%)	26 (52%)
Serious	5 (50%)	4 (40%)	2 (20%)	5 (50%)	1 (10%)	17 (34%)
Led to discontinuation	2 (20%)	2 (20%)	0	1 (10%)	0	5 (10%)
Led to death	1 (10%)	2 (20%)	0	0	0	3 (6%)
TRAEs	8 (80%)	8 (80%)	10 (100%)	6 (60%)	4 (40%)	36 (72%)
Grade ≥3	1 (10%)	2 (20%)	2 (20%)	1 (10%)	2 (20%)	7 (14%)
Serious	2 (20%)	4 (40%)	0	1 (10%)	0	7 (14%)
Led to discontinuation	0	2 (20%)	0	0	0	2 (4%)
Led to death	0	1 (10%)	0	0	0	1 (2%)

TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event.

- 36 patients experienced a TEAE that was considered related to treatment (TRAE), with only 2 patients experiencing a TRAE that resulted in treatment discontinuation (3 mg/kg q2w: hepatitis, n=1; pneumonitis, n=1).
 - The TRAE of hepatitis was fatal in a 76-year-old Asian female.
- 7 patients reported a TEAE of grade ≥3 considered related to treatment:
 - 1 mg/kg q2w: 1 patient (pneumonitis)
 - 3 mg/kg q2w: 2 patients (1 hepatitis, blood alkaline phosphatase increased, blood bilirubin increased, aspartate aminotransferase increased, alanine aminotransferase increased; 1 dyspnea)
 - 10 mg/kg q2w: 2 patients (1 rash; 1 diarrhea)
 - 6 mg/kg q3w: 1 patient (nausea, vomiting, hyperglycemia)
 - 10 mg/kg q3w: 1 patient (colitis)
- 17 patients reported serious TEAEs, with gastrointestinal disorders being the most common system organ class (n=5 patients).
 - The most common preferred term was pneumonitis (1 mg/kg q2w, n=1; 3 mg/kg q2w, n=1). All other serious TEAEs occurred in <2 patients.
- 8 patients reported serious TRAEs:
 - 1 mg/kg q2w: 2 patients (1 pneumonitis; 1 diarrhea)
 - 3 mg/kg q2w: 4 patients (1 pneumonitis; 1 adrenal insufficiency; 1 hepatitis; 1 confusional state)
 - 6 mg/kg q3w: 2 patients (1 nausea and vomiting; rash)

Clinical Response

- Of the 38 evaluable patients, 3 partial responses (all confirmed) were noted in patients with cervical, ovarian, and breast cancers in the 1-mg/kg and 3-mg/kg cohorts (**Table 4**).

Table 4. Phase 1 Summary of Best Overall Response by Treatment

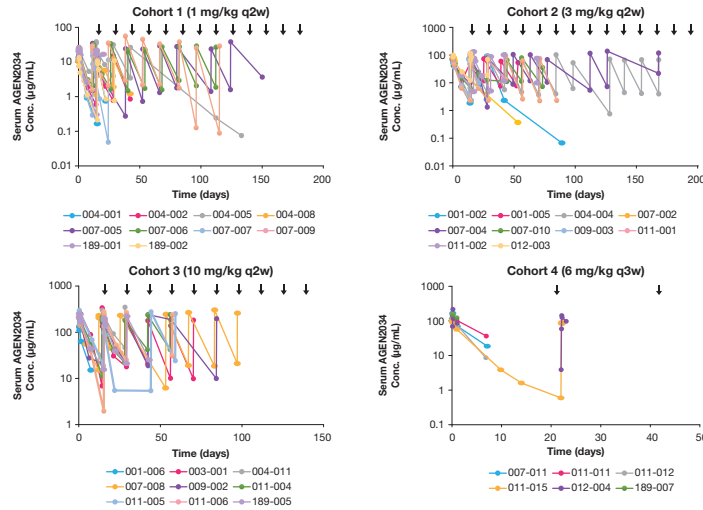
	1 mg/kg q2w n=7	3 mg/kg q2w n=8	10 mg/kg q2w n=10	6 mg/kg q3w n=7	10 mg/kg q3w n=6	All Patients N=38
Complete response	0	0	0	0	0	0
Partial response	1 (5.46)	2 (1.38 and 9.97)	0	0	0	3
Stable disease	3	4	6	6	4	23
Progressive disease	3	2	4	1	2	12

Overall response determined by Response Evaluation Criteria in Solid Tumors (RECIST) v1.1. Numbers in parentheses represent the duration of best overall response for each patient in months. Tumor type where responses were seen: ovarian cancer, cervical cancer, and breast cancer.

Pharmacokinetic Profile

- Serum concentrations of AGEN2034 collected and analyzed to date are displayed in **Figure 2**.

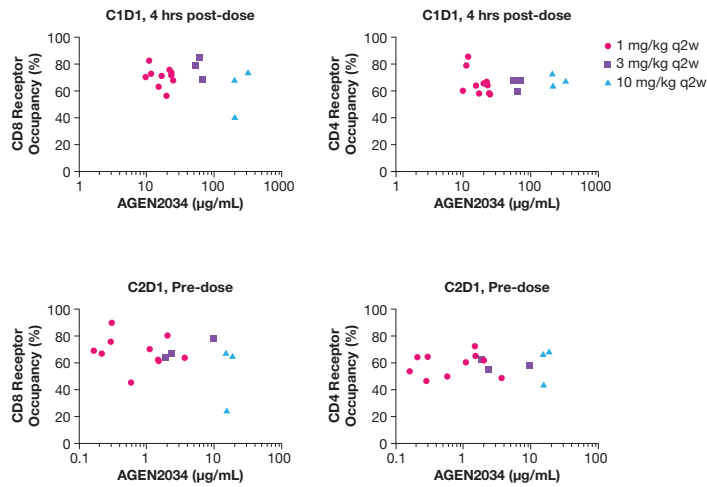
Figure 2. Pharmacokinetic Profile of AGEN2034



Serum concentrations plotted on a log₁₀ scale. Arrows indicate estimated treatment day (q2w or q3w).

- Receptor occupancy on circulating effector CD4⁺ and CD8⁺ T cells was quantified by flow cytometry (**Figure 3**). Receptor occupancy values were similar 4 hours post-dosing to those observed 2 weeks later. Furthermore, receptor occupancy levels were consistent over all doses tested and all exposures measured. These results suggest that the maximum possible receptor occupancy was obtained.

Figure 3. Receptor Occupancy (RO) on CD4⁺ and CD8⁺ T Effector Memory Cells Following Treatment With AGEN2034



For each subject in each dose cohort, receptor occupancy is plotted as a function of the concentration of AGEN2034 in the serum measured at the same timepoint. Receptor occupancy and AGEN2034 concentrations were measured 4 hours after the initial dosing, and 2 weeks later (prior to the administration of the second dose). For each graph, cohorts are indicated by the color and the shape. Concentrations of AGEN2034 are indicated on the x-axis, and receptor occupancy is indicated on the y-axis.

PHASE 2 RESULTS

- The recommended phase 2 dosing established in phase 1 was AGEN2034 3 mg/kg q2w.
- As of July 26, 2018, a total of 6 females with cervical cancer had been recruited, enrolled, and treated in the phase 2 portion of the study (Table 5).

Table 5. Phase 2 Demographics and Baseline Characteristics

	3 mg/kg q2w N=6
Age (years)	
Median (min, max)	60.5 (36, 67)
ECOG performance status, n (%)	
0	1 (16.7%)
1	5 (83.3%)
Time since progression (months)	
Median (min, max)	1.69 (0.8, 8.1)
Current cancer status, n (%)	
Localized	1 (16.7%)
Metastatic	5 (83.3%)

ECOG, Eastern Cooperative Oncology Group.

- 1 patient discontinued from the study treatment due to disease progression (Table 6).

Table 6. Phase 2 Patient Disposition

	3 mg/kg q2w N=6
Discontinued from study treatment, n (%)	1 (16.7%)
Disease progression	1 (16.7%)
Continuing on study at time of data extract, n (%)	5 (83.3%)
Follow-up time (days)	
Median (min, max)	138.5 (74, 177)

Clinical Response

- At time of data cut-off, a total of 9 patients (3 from phase 1 and 6 from phase 2) with cervical cancer had been treated with AGEN2034.
- The summary of BOR is listed in Table 7.

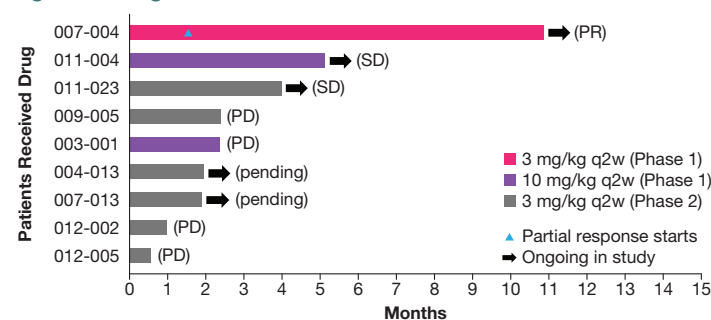
Table 7. Summary of Best Overall Response in Cervical Cancer Patients

	Phase 1 3 mg/kg q2w n=1	Phase 1 10 mg/kg q2w n=2	Phase 2 3 mg/kg q2w n=6	Total Cervical Cancer Population N=9
Complete response	0	0	0	0
Partial response	1 (10)	0	0	1*
Stable disease	0	1 (2.8)	1 (1.6)	2
Progressive disease	0	1	3	4
Not evaluable	0	0	2	2

Overall response determined by Response Evaluation Criteria in Solid Tumors (RECIST) v1.1. Numbers in parentheses represent the duration of best overall response for each patient in months.

- **Figure 4** depicts the duration of progression-free survival at the time of data cut-off.
 - Posterior data cut of September 18, 2018, showed there is a new confirmed PR out of the 6 patients in the cervical cancer expansion cohort; therefore, there are 2 PRs in the overall cervical cancer group.

Figure 4. Progression-Free Survival in Cervical Cancer Patients



Progression-free survival determined by Response Evaluation Criteria in Solid Tumors (RECIST) v1.1. Best overall response indicated in parentheses. PD, progressive disease; PR, partial response; SD, stable disease.

Safety and Tolerability

- At time of data cut-off, no DLTs were reported for any of the patients, and 5 of the 6 patients reported a TEAE (Table 8).
- TEAEs occurring in >1 patient included abdominal pain (n=3) and pyrexia (n=2).
- 3 patients experienced a TEAE of grade ≥ 3 , including anemia, international normalized ratio increased, back pain, diarrhea, and abdominal pain.
- Serious TEAEs occurred in 3 patients, including colitis, abdominal pain, back pain, diarrhea, and pyrexia (n=1 each).
 - The events of diarrhea and colitis were considered related to treatment.
- 1 patient had a TRAE of grade ≥ 3 , which was serious (diarrhea).
- No TEAEs led to treatment discontinuation or study withdrawal.

Table 8. Phase 2 Summary of Treatment-Emergent Adverse Events

Patients, n (%)	3 mg/kg q2w N=6
TEAEs	5 (83.3%)
Grade ≥ 3	3 (50.0%)
Serious	3 (50.0%)
TRAEs	3 (50.0%)
Grade ≥ 3	1 (16.7%)
Serious	1 (16.7%)

TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event.

DISCUSSION

- AGEN2034 is a pharmacologically active, well-tolerated PD-1 antagonist antibody, demonstrating early signs of clinical activity in the phase 1 and 2 portions of the study in patients with advanced refractory malignancies including cervical cancer.
- No DLT were observed in the Phase I portion of the study.
- PK determinations are under ongoing analysis as more information is gathered.
- Receptor occupancy results from the current study are comparable to data available for commercially available PD-1 antagonists.
- The phase 2 expansion in patients with relapsed/refractory cervical cancer is continuing to recruit (NCT03104699).

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Disclosures

G Yuan, CD Dupont, M Lim, AM Gonzalez, D Savitsky, S Coulter, O Shebanova, E Dow, W Ortuzar, J Buell, RB Stein, H Youssoufian: *Agenus Inc.*: current or former employment/consultancy and stock ownership.

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