Phase 1, Open-Label, Multiple-Ascending-Dose Trial of AGEN1884, an Anti–CTLA-4 Monoclonal Antibody, in Advanced Solid Malignancies

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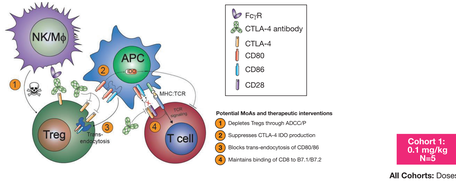
BACKGROUND

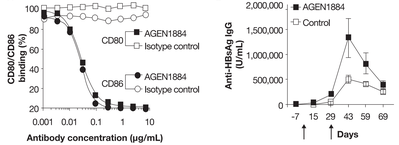
- Cytotoxic T-lymphocyte–associated protein 4 (CTLA-4) is an immune checkpoint that is expressed by activated T cells. A member of the immunoglobulin superfamily, CTLA-4 plays a key role in the down-regulation of the immune system through the transmission of an inhibitory signal to T cells.
- The therapeutic blockade of CTLA-4 has been demonstrated to enhance T-cell reactivity to tumor-specific antigens, translating to significant improvement in overall survival in certain patients.

Figure 1: Overview of pathways affected by CTLA-4



- AGEN1884 is a human IgG1 monoclonal antibody targeting the co-inhibitory protein CTLA-4.
- This inhibition results in enhanced T-cell responsiveness *in vitro* and in a nonhuman primate vaccination model. AGEN1884 binds to CTLA-4 expressed on T cells and inhibits the CTLA-4–mediated down-regulation of T-cell activation. This inhibition leads to a cytotoxic T-lymphocyte–mediated immune response against cancer cells.

Figure 2: AGEN1884 blocks binding of CTLA-4 to CD80/CD86 and is pharmacologically active *in vivo*



Panel A: Binding of fluorescently-labeled CD80-Fc or CD86-Fc (1 nM) to CTLA-4 in the presence of increasing concentrations of AGEN1884 or an IgG1 isotype control. Binding to CTLA-4-linked microspheres was assessed using Luminex. Representative data indicate the mean ± SEM in each treatment group (n≥2). **Panel B:** Cynomolgus macaques (n=6 per group) were given 10 mg/kg of AGEN1884 via IV administration with a HepB (ENGERIX-B®) vaccine SC and KLH vaccine IM on days 1 and 29. Duplicate samples were analyzed for anti-HBsAg-specific IgG serum titers.

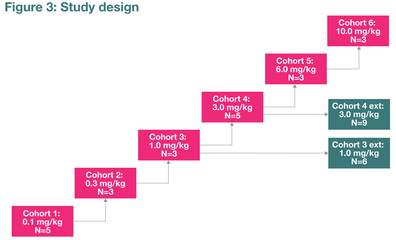
Clinical Trial

- Purpose: To evaluate the safety, pharmacokinetic (PK), and pharmacodynamics of an anti–CTLA-4 human monoclonal antibody (AGEN1884), and to estimate the maximum tolerated dose (MTD) in subjects with advanced or refractory cancer
- Clinical Trials Registry Number: NCT02694822

METHODS

- The C-500-01 study is an open-label, phase 1, multicenter study. This presentation is an interim analysis of data that was collected as of May 16, 2017.
- The study consists of a 3+3 dose-escalation design starting at a near minimally anticipated biologic effect level (MABEL) dose, with expansion cohorts at 1.0 mg/kg and 3.0 mg/kg.

Figure 3: Study design



All Cohorts: Doses 1-3: Q3W dosing; Doses 4 and beyond: Q3W, Q6W, or Q12W dosing.

- Key inclusion criteria
  - Male and female subjects (aged ≥18 years) with advanced or treatment-refractory solid tumors and an anticipated life expectancy of ≥12 weeks at screening were recruited.
  - Subjects were required to have Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 or 1.
- Primary outcome measures were to:
  - Identify any dose-limiting toxicities (DLTs)
  - Establish the MTD
  - Determine plasma concentrations on day 1 (at 2, 6, and 24 hours), day 8, day 15, and day 22
- Secondary outcome measures included objective response rate, duration of response, progression-free survival, and overall survival.
- An exploratory assessment of biomarkers was undertaken to identify biomarkers that may predict pharmacologic activity or response to AGEN1884.

Dosing and Administration

- AGEN1884 was administered intravenously every 3 weeks for the first 4 doses and continuation after 4 doses may be every 3, 6 or 12 weeks.

RESULTS

- As of May 16, 2017, 16 subjects had been recruited, enrolled, and treated:
  - Cohort 1 (0.1 mg/kg): n=5
  - Cohort 2 (0.3 mg/kg): n=3
  - Cohort 3 (1.0 mg/kg): n=3
  - Cohort 4 (3.0 mg/kg): n=5
- The median follow-up time for these subjects is 8.3 weeks (range, 0–35 weeks).
- The mean treatment duration with AGEN1884 was 6 weeks (range, 0–28 weeks).

Patient Disposition

- The median age of the 16 subjects was 61 years (range, 26–88 years), and ECOG status ranged from 0 to 2 (a protocol deviation was written to include the subject with ECOG status of 2).
- Patient demographics are presented in Table 1.

Table 1: Patient demographics

		0.1 mg/kg N=5*	0.3 mg/kg N=3	1.0 mg/kg N=3	3.0 mg/kg N=5*	All Subjects N=16
Age, years	Mean	49.8	58.0	53.0	71.6	58.8
	Min–Max	26–62	46–65	39–70	50–88	26–88
Gender, n	Male	3	1	1	3	8
	Female	2	2	2	2	8
Race, n	White	4	3	2	2	11
	African American	0	0	1	1	2
	Other	1	0	0	2	3
Ethnicity, n	Hispanic/ Latino	1	1	1	1	4
	Not Hispanic or Latino	4	2	2	4	12
ECOG Performance Status, n	0	1	0	1	0	2
	1	3	3	2	5	13
	2†	1	0	0	0	1
Primary Diagnosis, n	Localized	3	0	0	0	3
	Metastatic	2	3	3	5	13

ECOG, Eastern Cooperative Oncology Group. *Patients were substituted for reasons other than DLTs. †A protocol deviation was written to include this subject.

Safety and Tolerability

- Overall, AGEN1884 was well tolerated. The majority of observed adverse events (AEs) were consistent with the subjects' underlying cancer disease (Table 2).

Table 2: Summary of treatment-emergent adverse events (TEAEs)

	0.1 mg/kg N=5	0.3 mg/kg N=3	1.0 mg/kg N=3	3.0 mg/kg N=5	All Subjects N=16
Any TEAEs	5	3	3	5	16
Grade ≥3	3	2	0	2	7
SAEs	2	2	0	2	6
TRAEs	3	2	3	1	9
Grade ≥3	0	2	0	0	2
Serious	0	0	0	0	0
Deaths*	0	0	0	1	1
TEAEs Leading to Discontinuation	2	0	0	1	3
Any Dose-Limiting Toxicity	0	0	0	0	0

*Not related to study drug. SAE, serious adverse event; TRAE, treatment-related adverse event.

Dose-Limiting Toxicities

- No DLTs or related significant AEs were reported by the subjects treated to date.

Treatment-Emergent Adverse Events

- TEAEs were observed in all subjects.
- The most common TEAEs were fatigue and vomiting (n=5 each), followed by diarrhea and abdominal pain (n=4 each). TEAEs of anemia, decreased appetite, nausea, constipation, dyspnea, increased blood creatinine, back pain, respiratory failure, and headache occurred in 3 subjects each.

TEAEs of Grade ≥3

- TEAEs of grade ≥3 (severe or higher) were experienced by a total of 5 subjects: 3 receiving 0.1 mg/kg, 2 receiving 0.3 mg/kg, and 2 receiving 3.0 mg/kg.
- Of the grade ≥3 TEAEs, respiratory failure was reported in 3 subjects each (2 with 0.1 mg/kg and 1 with 3.0 mg/kg) and anemia, fatigue, and hyponatremia were reported in 2 subjects each. All other grade ≥3 TEAEs occurred in 1 subject each.
- No Grade ≥3 TEAEs were observed with 1.0 mg/kg.
- No dose response for the occurrence of grade ≥3 TEAEs was observed.

Treatment-Related AEs and Treatment-Related AEs of Grade ≥3

- A total of 9 subjects experienced TEAEs assessed as being at least possibly related to AGEN1884 by the investigator (ie, treatment-related AEs [TRAEs]).
- The most common TRAEs were fatigue and diarrhea (n=3 each), followed by nausea, vomiting, abdominal pain, and headache (n=2 each). All other TRAEs were reported in 1 subject each.
- Two TRAEs were of grade ≥3: fatigue (0.1 mg/kg) and pancytopenia (0.3 mg/kg).

Serious Adverse Events

- As of May 16, 2017, 6 of the 16 subjects experienced serious TEAEs (SAEs):
  - 2 subjects in the 0.1 mg/kg cohort (asthenia, n=1; hyperbilirubinemia, n=1)
  - 2 subjects in the 0.3 mg/kg cohort (febrile neutropenia and dyspnea, n=1; gastroenteritis, n=1)
  - 2 subjects in the 3.0 mg/kg cohort (hyponatremia, n=1; pleural effusion, n=1)
- No SAE for any subject was considered related to the study treatment. One death occurred in the 3.0 mg/kg cohort: the subject experienced a Grade 5 event of hyponatremia secondary to disease progression (refractory pancreatic cancer), which led to the death of this subject. The investigator assessed the event as not related to study drug.

TEAEs Leading to Permanent Discontinuation of Treatment

- 3 subjects (2 receiving 0.1 mg/kg, 1 receiving 3.0 mg/kg) were discontinued permanently from study treatment due to TEAEs.
  - None were considered related to the study drug.

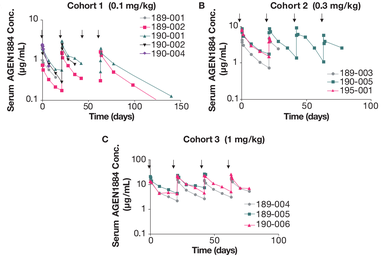
Laboratory Evaluations

- No clinically significant changes in blood pressure, heart rate, or other vital signs were observed during the treatment period.
- No infusion-related reactions/hypersensitivities were reported.
- With the exception of the clinically relevant hematology laboratory results associated with the SAE febrile neutropenia, no clinically significant hematology abnormalities were evident. No dose-dependent changes in hematology parameters were observed.

Pharmacokinetic Profile

- Preliminary PK analysis of AGEN1884 can be seen in Figure 4.

Figure 4: Semi-log plot of PK profile of AGEN1884 for 0.1, 0.3, and 1.0 mg/kg dose cohorts



Downward arrows indicate each of the 4 treatment cycles administered per the protocol. Serum samples were not collected for 3rd cycle of AGEN1884 administration, per amendment 1 of the protocol (**Panel A**). Subsequent amendment instructed for serum sample collection for PK testing during 3rd cycle of treatment.

- The observed average half-life of AGEN1884, calculated for 3 patients observed for a full DLT period at 0.1, 0.3, and 1.0 mg/kg dose levels, is 9.6, 8.8, and 11.0 days, respectively.
- The average area under the curve increased with each increasing dose level, from 333 to 1295 to 3247 µg*hr/mL.
- Average C_{max} of the first dosing cycle is also increased with increasing dose level, as observed in Figure 4, from 1.6 to 7.1 to 17.0 to 170.7 µg/mL at 3.0 mg/kg (not pictured).
- This preliminary PK data demonstrates that AGEN1884 is increasing in distribution with increasing dose levels.

Clinical Response

- Of the 16 subjects enrolled and treated, 6 discontinued participation because of disease progression.
- 4 subjects remain in the study, and enrollment for additional cohorts is ongoing.

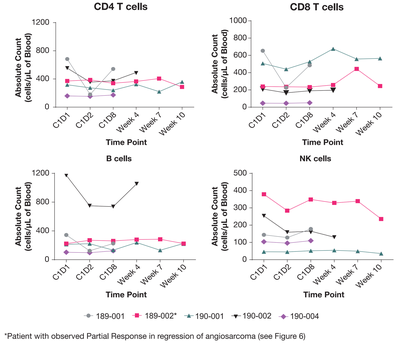
Table 3: Summary of overall response by treatment

	0.1 mg/kg N=5	0.3 mg/kg N=3	1.0 mg/kg N=3	3.0 mg/kg N=5	All Subjects N=16
Partial Response	1	0	0	0	1
Stable Disease	1	1	0	0	2
Progressive Disease	0	0	2	0	2

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

- Preclinical studies demonstrated CTLA-4^{high} expressing cells (eg, regulatory CD4+ T cells) undergo ADCC in the presence of AGEN1884.
- At Week 7, there was an increase in the levels of both CD4 and CD8 T cells for patient 189-002, with no change in B cells and an overall reduction in NK cells.
- No significant changes in ALC have been observed to date.

Figure 5: Absolute cell counts of patients in cohort 1 treated with AGEN1884 at 0.1 mg/kg

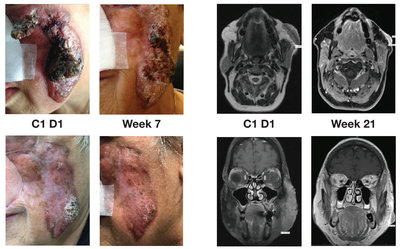


*Patient with observed Partial Response in regression of angiosarcoma (see Figure 6)

Partial Response

- 1 confirmed partial response by Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 criteria.
  - Patient 189-002 was a 62-year-old female being treated for angiosarcoma in Cohort 1 (0.1 mg/kg).
  - At Week 33, a 92% reduction of target lesion was observed.

Figure 6: Partial response of angiosarcoma of nose and cheeks after treatment with AGEN1884



DISCUSSION

- This interim analysis of a phase 1 study demonstrated an acceptable safety profile for AGEN1884 in subjects with advanced solid tumors at the 0.1, 0.3, 1.0, and 3.0 mg/kg dose levels.
- Dose escalation is ongoing, and updated safety and PK data are forthcoming.
- Based on data for the 16 treated subjects and for the cohorts that have cleared the DLT observation period, the dosage of 1.0 mg/kg every 3 weeks is considered safe and well tolerated.
- Although symptoms associated with immune-related adverse events have been reported (diarrhea, rash, and pruritus), none have required treatment with corticosteroids and none that were possibly related prompted delays in treatment.

Sources

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Acknowledgments

AGEN1884 was developed under a Collaborative Research and Development Agreement between Ludwig Cancer Research, 4-Antibody AG and Recepta Biopharma S.A. AGEN1884 is partnered with Recepta Biopharma S.A. for certain South American rights. We wish to thank the subjects, as well as the investigators and their teams, who participated in this study. Writing and poster development support was provided by The Medicine Group and funded by Agenus Inc.

Presented at the 53rd Annual Meeting of the American Society of Clinical Oncology; Chicago, Illinois; June 2–6, 2017.