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Clinical Trial Registration
- This trial is registered with ClinicalTrials.gov, NCT03104699.

Single-agent activity of a novel PD-1 inhibitor, AGEN2034, in recurrent ovarian cancer

Subset analysis of phase 1 dose-escalation NCT03104699 study

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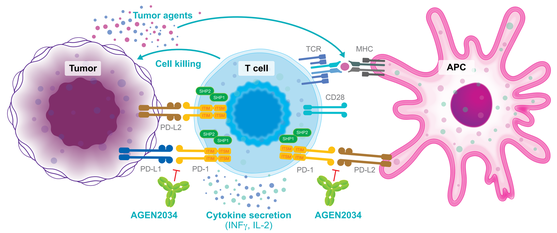
Background

AGEN2034 (balstilimab) is a novel, fully human monoclonal immunoglobulin G4 (IgG4) antibody, designed to block PD-1 from interacting with its ligands PD-L1 and PD-L2 with high affinity. The overall objective of the study was to assess safety, MTD, pharmacokinetic (PK) and pharmacodynamic (PD) characteristics of AGEN2034 monotherapy in patients with advanced, refractory malignancies **(Figure 1).**

Figure 1. Mechanism of Action of AGEN2034



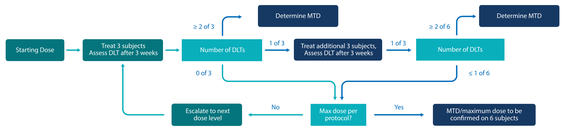
Objective

The purpose of this subset analysis is to investigate safety, maximum tolerated dose (MTD), pharmacokinetic (PK) and pharmacodynamic (PD) characteristics of AGEN2034 monotherapy in patients with advanced ovarian cancer enrolled in the Solid Tumor phase I study

Methods

- Between April 2017 – April 2019 50 patients with advanced solid tumors were enrolled in a phase 1 dose escalation study treated with every 2 weeks infusion of AGEN2034 at the dose range of 1–10 mg/kg. Within the study population a subset of patients with heavily pretreated recurrent epithelial ovarian cancer was identified
- Twelve patients with recurrent epithelial ovarian cancer were enrolled in the Phase I dose escalation. Median age was 58 years (range 41–77) with ECOG 0–1 and a median of 4 prior lines of systemic treatment (ranging from 1 to 8)
- All 12 patients received platinum-based treatment prior to study entry. No DLTs were observed

Figure 2. Study design – dose escalation



Eligibility criteria

- Patients with any histologically or cytologically confirmed metastatic or locally advanced solid tumor for whom no standard therapy is available, or the patient has failed the standard therapy (the current analysis represents subset of patients with ovarian cancer)
- Have objective evidence of disease diagnosed by local site investigator Must have received prior platinum-based treatment and failed previous systemic therapy, with progression following the most recent therapy within 6 months of study enrollment. No prior treatment with of PD-1, PD-L1 or CTLA-4 antagonist
- Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 and life expectancy ≥3 months.
- Have adequate organ function as indicated by pre-specified laboratory values

Analysis

The primary safety endpoint was dose limiting toxicity (DLT).
Secondary endpoints included PK profiling, Immunogenicity and Best overall response rate per RECIST 1.1 assessed by the investigator. Exploratory end points included biomarkers assessment, in blood/serum association with clinical outcomes.

Results

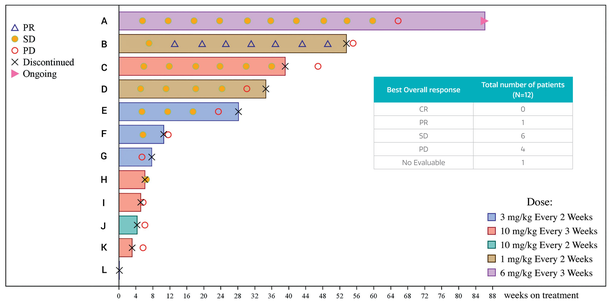
Table 1. Baseline characteristics

	Statistics	Total (N = 12)
Age (years)	n	12
	Mean (STD)	58.5 (8.11)
	Median	58.0
	Min, Max	41, 77
Race		
White	n (%)	9 (75.0)
Black or African American	n (%)	1(8.3)
Asian	n (%)	2 (16.7)
ECOG PS*		
0	n (%)	5 (41.7)
1	n (%)	7 (58.3)
Prior lines of systemic therapy*		
1	n (%)	1(8.3)
2	n (%)	1(8.3)
3	n (%)	3 (25.0)
> 3	n (%)	7 (58.3)

** Platinum resistance defined as any relapse within 6 months of completion of platinum-based chemotherapy*
** Platinum resistant YES: 7 NO: 5*
** 5 out of 7 were platinum resistant after first line*

- In this subset of recurrent ovarian cancer patients, 1 of 12 patients developed a durable partial response (42 wks) at the lowest dose level (1 mg/kg), 7 patients demonstrated at least stable disease lasting 8.7 – 65.7 weeks, with 5 of them meeting the DCR criteria of at least 12 weeks of duration. Four patients demonstrated progressive disease at the first on treatment tumor evaluation

Figure 3. Objective response rate (ORR) determined by investigator per RECIST v.1.1



Best Overall response	Total number of patients (N=12)
CR	0
PR	1
SD	6
PD	4
No Evaluable	1

Abbreviations: CR, complete response; SD, stable disease; PR, partial response, PD, progressive disease.

- In this subset of 12 patients with recurrent ovarian cancer
- 1 patient developed a durable partial response (PR) (42wks) at the lowest dose level (1 mg/kg),
- 6 patients demonstrated at least stable disease (SD) lasting 8.7 to 65.7 weeks,
- 5 patients met the DCR criteria of at least 12 weeks of duration, and
- 4 patients demonstrated progressive disease at the first on-treatment tumor evaluation

Figure 4. Spider plot of percent change in target lesion, ovarian cancer patients in dose escalation phase

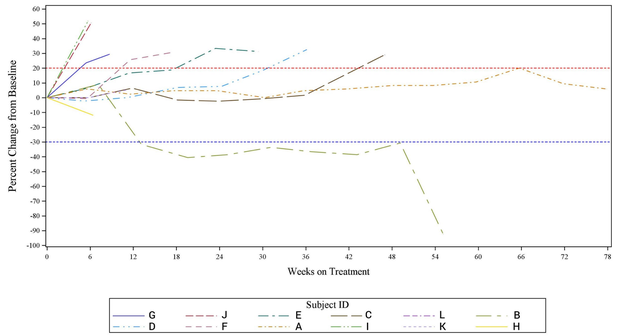
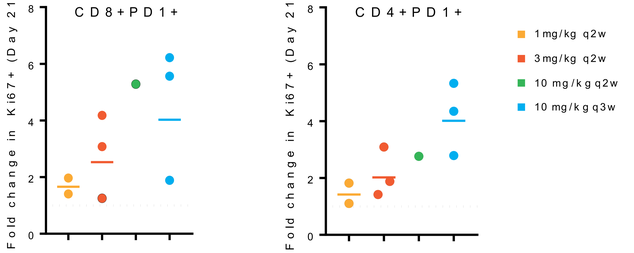


Figure 5. Pharmacodynamic immune response to AGEN2034 in ovarian cancer subset

- The frequency of Ki67+CD8+ and Ki67+CD4+ T-cells was increased at 3 weeks after AGEN2034 treatment in most subjects from the C-700 Phase 1
- In the ovarian cancer subset, biologically meaningful increase in Ki67 was most prominent in PD1+ CD8+ and PD1+CD4+ T-cells

Fold change in the frequency of CD8+PD1+Ki67+ or CD4+PD1+Ki67+ T-cells at the peak of immunologic response (Day 21) in the ovarian cancer subset (N=9).



Fold change in Ki67 expression was calculated as a ratio of % of PD1+CD4+ or PD1+CD8+ T- cells positive for Ki67 at Day 21 to the baseline. CD8, CD4, Ki67 expression was measured by flow cytometry.

Safety and Tolerability

Table 2. Drug-related treatment-emergent adverse events reported by investigator

	Total (N = 12)	
Preferred Term	Any Grade	Grade 3/4
Any TEAE	10 (83.3)	1 (8.3)
Fatigue	5 (41.7)	0
Rash maculo-papular	3 (25.0)	0
Pain	3 (25.0)	0
Diarrhoea	2 (16.7)	1 (8.3)
Headache	2 (16.7)	0

- The most common AE's were fatigue and nausea (83.3%) mainly grade 1or 2. Grade 3 or 4 AE's occurred only in 1 patient overall with the highest dose of AGEN2034
- Grade 3 or 4 AE's occurred in one patient receiving the highest dose and frequency (10mg/kg/2w) of AGEN2034

Table 3. Immune-related adverse event reported by the investigator

	Total (N = 12)	
Preferred Term	Any Grade	Grade 3/4
Any TEAE	7 (58.3)	1 (8.3)
Diarrhoea	2 (16.7)	1 (8.3)
Hyperthyroidism	2 (16.7)	0
Hypothyroidism	2 (16.7)	0
Blood creatinine increased	1 (8.3)	0
Cystitis	1 (8.3)	0

Table 4. Treatment overview-emergent adverse events

	Total (N = 12)
Any TEAE	12 (100.0)
Any trial drug related TEAE	10 (83.3)
Any serious TEAE	2 (16.7)
Any trial drug related serious TEAE	1 (8.3)
Any grade >= 3 TEAE	7 (58.3)
Any grade 3/4 TEAE	5 (41.7)
Any trial drug related grade >= 3 TEAE	4 (33.3)
Any TEAE leading to death	0 (0.0)
Any trial drug related TEAE leading to death	0 (0.0)
Any TEAE leading to permanent treatment discontinuation	1 (8.3)

Conclusions

- AGEN2034 is generally well-tolerated PD-1 antagonist antibody, indicative of early signals of clinical activity, including in recurrent ovarian cancer, there were no DLT's observed at all dose levels
- Ovarian cancer patients demonstrated an on-target immunological effect of PD-1 blockade on CD8 and CD4 + T-cells detected at the periphery indicative of the pharmacodynamic response to AGEN2034
- The activity noted in ovarian cancer warrants additional investigation, given the lack of effective therapy and low survival rates for patients with recurrent ovarian cancer, results reported here accentuate the role of the immune checkpoint inhibitors in this patient population.
- In total efficacy and safety, PK and PD data suggest that 3mg/kg Q2W is the recommended phase II dose for AGEN2034
- AGEN2034 is in a trial designed for BLA filing in 2L cervical cancer. Interim data is planned for presentation later this year

References

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Acknowledgments

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Disclosures

CD Dupont, W Ortuzar, A Wijatyk, H Youssoufian, R Kaleta, I Sapir, I Shapiro
H Youssoufian – an Agenus Inc. current or former employment/consultancy and stock ownership

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