agenus

Poster # 479

AGEN1181, an Fc-enhanced anti-CTLA-4 antibody, alone and in combination with balstilimab (anti-PD-1) in patients with advanced solid tumors: Phase I results

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Background

AGEN1181 is an Fc-enhanced anti-CTLA-4 mAb

Fc optimization allows coverage of all FcγRIIIA (CD16) polymorphic variants and broadens the therapeutic benefit to potentially 40% additional patients by targeting those who express the low-affinity allele while enhancing benefit for those with the high affinity allele.

The observed benefits include:

- T cell priming – expanding responses in poorly immunogenic tumor types
- Treg depletion – eliminate key contributors to immunotherapy resistance
- T cell memory formation – durable antitumor immunity and disease control
- Improved safety: Fc-engineered to avoid complement mediated toxicity associated with many current immune checkpoint inhibitors

Phase I/Ib Study Overview (NCT03860272)

Dose escalation - Monotherapy
AGEN1181 IV
Q3W: 0.1, 0.3, 1, 2, 3 mg/kg
Q6W: 1, 2 mg/kg

Dose escalation – Combination
AGEN1181 IV Q6W: 0.1, 0.3, 1, 2 mg/kg
+ balstilimab IV Q2W 3 mg/kg

Dose expansion - Combination
AGEN1181 IV Q6W: 1, 2 mg/kg
+ balstilimab IV Q2W 3 mg/kg

Key points

1. Prior anti-PD-1 therapy allowed
2. Imaging performed every six weeks
3. Cross-over to combination allowed

Baseline Demographics

Characteristic	N =116
Age	
Median (range)	62 (28-82)
ECOG PS, n (%)	
0	41 (35.3)
1	75 (64.7)
Tumor indication, n (%)	
Colorectal	33 (28.4)
Ovarian	15 (12.9)
Hepatocellular	7 (6.0)
Angiosarcoma	7 (6.0)
Pancreatic	6 (5.2)
Other	48 (41.4)
Prior lines of therapy, n (%)	
1-2	48 (41.4)
3+	68 (58.6)
Prior anti-PD-1/PD-L1 therapy, n (%)	
Yes	36 (31.0)
No	80 (69.0)

Clinical Pharmacology

- Serum AGEN1181 terminal elimination half-life (t½) is 13.4 days
- AGEN1181 clearance appears to be independent of dose, duration of treatment, dosing frequency, or co-administration with balstilimab
- AGEN11811 and balstilimab ADA frequency is low (total 3%) and without evidence of effect on drug exposure

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Clinical Activity

Summary of objective responses

Tumor Type	BOR	Duration (weeks)	FcγRIII allele
MSS CRC	cPR	60	V/F
MSS CRC*	cPR	48 +	V/F
MSS CRC	cPR	24 +	V/F
MSS CRC	uPR	6	V/F
Ovarian	cPR	12 +	Unk
Ovarian*	cPR	18	F/F
Ovarian	cPR	18	V/F
MSS Endometrial*	cCR	36	F/F
MSS Endometrial	cPR	60	V/F
MSS Endometrial	uPR	12	F/F
Angiosarcoma	cPR	24 +	Unk
Angiosarcoma	cPR	24 +	Unk
Pancreatic	cPR	24 +	F/F
Cervical*	cPR	12 +	V/F
NSCLC*	cPR	12 +	Unk
Leiomyosarcoma	uPR	12 +	Unk
Melanoma*	cPR	12	F/F

MSS, microsatellite stable; Unk, unknown. Asterisk, PD-1 relapsed/refractory patients; "+" symbol indicates response ongoing (data cutoff, Sept 17th 2021)

- DCR for AGEN1181 as monotherapy is 44.8% and 64.4% in combination.
- [Disease control rate defined as BOR of CR, PR, or SD ≥6 weeks for patients treated with AGEN1181 ≥1 mg/kg and completed ≥1 on-treatment scan]

AGEN1181 has broad and durable activity as monotherapy

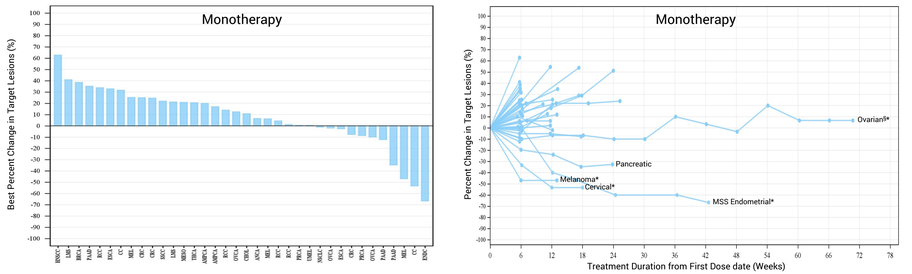

Figure 1. Waterfall plots show best percentage change in target lesion size from baseline. Spider plot shows changes in target lesions as a function of time. *PD-1 relapsed/refractory pts, §Cross-over pts.

AGEN1181 has broad and durable activity in combination with anti-PD-1 inhibition

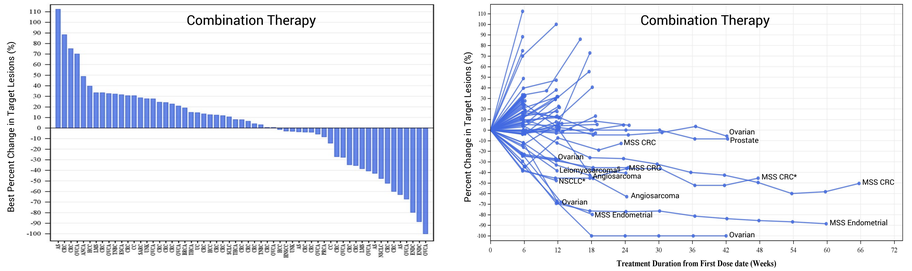

Figure 2. Waterfall plot shows best percentage change in target lesion size from baseline (includes cross-over patients). Spider plot shows changes in target lesions as a function of time. *PD-1 relapsed/refractory pts, §Cross-over pts.

Responses in select indications

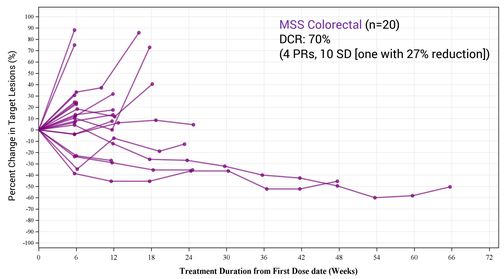

Figure 3. MSS CRC patients treated with ≥1 mg/kg AGEN1181 plus balstilimab.

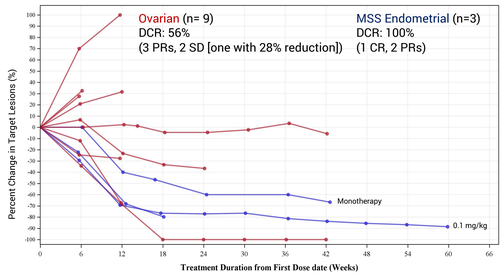

Figure 4. Gynecologic malignancies: patients with ovarian cancer treated with ≥1 mg/kg AGEN1181 plus balstilimab; MSS endometrial patients treated with monotherapy or lower combination dosing as indicated.

Safety and Tolerability

Adverse event summary

	All Patients N = 116		Monotherapy N = 44		Combination N = 85*	
	Any Grade	Grade 3-5	Any Grade	Grade 3-5	Any Grade	Grade 3-5
Any TEAE	113 (97.4)	71 (61.2)	43 (97.7)	26 (59.1)	69 (81.2)	42 (49.4)
Serious AE	64 (55.2)	56 (48.3)	21 (47.7)	19 (43.2)	38 (44.7)	33 (38.8)
Treatment-related AE	93 (80.2)	24 (20.7)	32 (72.7)	12 (27.3)	57 (67.1)	11 (12.9)

* Includes cross-over patients

- AGEN1181 monotherapy included Q3W and Q6W dosing, combination (+ balstilimab) Q6W only
- MTD not reached with either monotherapy or combination dosing
- Treatment-related discontinuation rate was 16%, primarily due to diarrhea/colitis (12%)
- Thirty-six patients (31%) received ≥40 mg/kg prednisone equivalent daily treatment, with the majority of these cases (92%) due to diarrhea

Summary of select irAEs

All Patients ≥1 mg/kg AGEN1181 (mono + combo)	N = 102	
	Any Grade	Grade 3-5
GI		
Diarrhea/colitis	43 (42.2)	11 (10.8)
Liver		
ALT increased	4 (3.9)	0
AST increased	4 (3.9)	0
Skin		
Rash	24 (23.5)	2 (2.0)
Endocrine		
Hypophysitis	0	0
Adrenal insufficiency	2 (2.0)	0
Hypothyroidism	5 (4.9)	0
Hyperthyroidism	3 (2.9)	0
Lung		
Pneumonitis	0	0

- No immune-related hypophysitis, pneumonitis, or high-grade hepatitis
- Two grade 5 events deemed related to treatment occurred: 1. intestinal perforation, not surgically treated; 2. chronic colitis, elected hospice

All other TRAEs ≥Grade 3

All Patients ≥1 mg/kg	N = 102
Fatigue	3 (2.9)
Acute kidney injury	1 (1.0)
Anemia	1 (1.0)
Bicytopenia	1 (1.0)
Confusional state	1 (1.0)
Decreased appetite	1 (1.0)
Dehydration	1 (1.0)
Eczema	1 (1.0)
Enterocolitis infectious	1 (1.0)
Hypotension	1 (1.0)
Infusion related reaction	1 (1.0)
Large intestinal perforation	1 (1.0)
Lymphocyte count decreased	1 (1.0)
Nausea	1 (1.0)
Stomatitis	1 (1.0)
Vomiting	1 (1.0)

Conclusions

- AGEN1181 is a next generation CTLA-4 inhibitor that exhibits clinical activity, both as monotherapy and in combination with balstilimab, in heavily pretreated patients across 9 treatment-resistant, poorly immunogenic tumor types.
- Clinical benefit is durable with both objective responses and prolonged stable disease.
- AGEN1181 is well tolerated with an improved safety profile compared to first generation CTLA-4 inhibitors: notably no hypophysitis, pneumonitis, or clinically meaningful hepatitis.
- Pivotal Phase II programs are in development for MSS CRC, GYN malignancies, and Melanoma.

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