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Poster # 734

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AGEN1181, an Fc engineered anti-CTLA-4 antibody, demonstrates clinical activity, alone or in combination with balstilimab (anti-PD-1), and broadens the therapeutic potential of CTLA-4 therapy

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Background

AGEN1181 leverages a novel Fc-mechanism of action to promote:

- ✓ Superior efficacy: enhanced T cell priming, Treg depletion and T cell memory formation for durable anti-tumor immune response
- ✓ Improved safety: avoid complement mediated toxicity associated with many current immune checkpoint inhibitors
- ✓ Expand therapeutic reach: broaden potential benefit to an additional ~40% of patients expressing the low-affinity FcγRIIIA (CD16) allele, while enhancing benefit for those with the high affinity allele

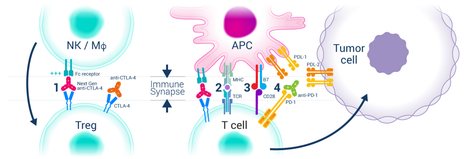


Figure 1: Mechanism of action of AGEN1181

1. Optimized Fc to enhance Treg depletion
2. Optimized Fc to enhance immune synapse quality and T cell priming & activation
3. Reverse T cell dysfunction and restore tumor targeting T cell responses
4. Superior T cell memory responses & improve durability of response

AGEN1181 outperforms conventional IgG1 CTLA-4 mAbs

FcγR co-engagement is critical for activity: AGEN1181 expands T cell responsiveness to donors that express the low affinity FcγRIIIA 158F allele

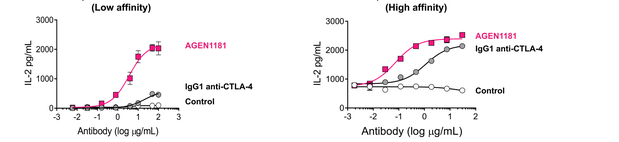


Figure 2: Evaluation of IL-2 production by human PBMCs donors that are homozygous for the low affinity hFcγRIIIA F/F haplotype, or heterozygous for the high affinity hFcγRIIIA V/F haplotype and stimulated with staphylococcal enterotoxin A (SEA) peptide together with increasing concentrations of AGEN1181, anti-CTLA-4 hIgG1, or an hIgG1 Fc-enhanced (FcE) isotype control antibody. Polymorphism in Fcγ receptor was determined by PCR followed by Sanger sequencing.

AGEN1181^{ms} expands therapeutic benefit against PD-1 refractory tumors

Robust tumor control in combination with anti-PD-1 and focal radiation

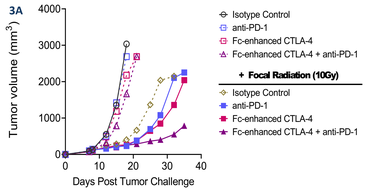


Figure 3A: C57BL6 mice, were challenged subcutaneously (s.c.) with B16F10 cells. Tumor bearing mice received no radiation or a single-dose 10 Gy radiation treatment administered using a Small Animal Radiation Research Platform. Mice were subsequently treated intraperitoneally (i.p) with anti-CTLA-4 Fc enhanced (AGEN1181ms-surrogate) and anti-PD-1 or the corresponding isotype control. Tumor volume was measured by electronic caliper. Individual tumor volumes by group are shown.

Curative responses in combination with chemotherapy in treatment resistant pancreatic cancer

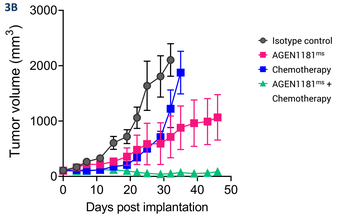


Figure 3B: C57BL/6 mice were implanted s.c with KPC (KrasG12D, P53-/- Pdx1-Cre) tumor chunks with an approximate size of 100mm^3 isolated from KPC-tumor bearing mice. Mice were treated with a triple chemotherapy regimen, Fc-enhanced anti-CTLA-4 (AGEN1181ms-surrogate), isotype control antibodies or the combination of chemotherapy and Fc-enhanced anti-CTLA-4. Chemotherapy-treated mice received Gemcitabine (70 mg/kg) and Cisplatin (4 mg/kg) administered i.p and nab-paclitaxel (25 mg/kg) administered intravenously on days 1 and 4. Fc-enhanced anti-CTLA-4 or isotype control antibodies were administered i.p twice a week for three weeks at 100 μg/dose. Tumor volume was measured by electronic caliper. Individual tumor volumes by group are shown.

Phase 1 study of AGEN1181 as monotherapy or in combination with balstilimab (NCT03860272)

Primary: Safety and tolerability

Secondary: Pharmacokinetics profile, ORR per RECIST 1.1

Exploratory: Pharmacodynamic, polymorphism of (FcγR) expression

Key Inclusion Criteria

1. ≥ 18 years of age
2. Histologically or cytologically confirmed diagnosis of metastatic or locally advanced solid tumor for which no standard therapy is available or standard therapy has failed
3. Measurable disease on imaging based on Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1)

Dose escalation (3+3 design)
AGEN1181 monotherapy IV
Q3W & Q6W
Doses evaluated: 0.1, 0.3, 1, 2 mg/kg

Dose escalation (Accelerated titration and (3+3 design)
AGEN1181 IV Q6W + balstilimab IV Q2W
Doses evaluated: 0.1, 0.3, 1 mg/kg

Selected Indications

- PD1 Refractory NSCLC
- PD1 Refractory Metastatic Melanoma
- Endometrial Cancer
- Hepatocellular Carcinoma
- Angiosarcoma
- Colorectal Cancer
- Other

AGEN1181 therapy was well tolerated in patients across multiple tumor types

	MONO	COMBO	MONO	COMBO	MONO	COMBO	MONO	COMBO	MONO	MONO
	Overall*	Overall**	0.1 mg/kg Q3W	0.1 mg/kg Q6W	0.3 mg/kg Q3W	0.3mg/kg Q6W	1.0 mg/kg Q3W	1.0 mg/kg Q6W	1.0 mg/kg Q6W	2.0 mg/kg Q3W
System Organ Class	(N=23)	(N=18)	(N=4)	(N=3)	(N=5)	(N=3)	(N=7)	(N=8)	(N=3)	(N=3)
Preferred Term	n(%)	n(%)	n(%)	n(%)	n(%)	n(%)	n(%)	n(%)	n(%)	n(%)
Any immune-related TEAE	**11 (47.83)**	**6 (33.33)**	**2 (50.00)**	**1 (33.33)**	**2 (40.00)**	**0**	**5 (71.43)**	**5 (62.50)**	**1 (33.33)**	**1 (33.33)**
Skin and subcutaneous tissue disorders	**6 (26.09)**	**3 (16.67)**	**1 (25.00)**	**0**	**1 (20.00)**	**--**	**3 (42.86)**	**3 (37.50)**	**0**	**1 (33.33)**
Gastrointestinal disorders	**6 (26.09)**	**1 (5.56)**	**1 (25.00)**	**0**	**2 (40.00)**	**0**	**2 (28.57)**	**1 (12.50)**	**0**	**1 (33.33)**
Endocrine disorders	**1 (4.35)**	**1 (5.56)**	**0**	**1 (33.33)**	**0**	**0**	**0**	**0**	**1 (33.33)**	**0**
Blood and lymphatic system disorders	**0**	**1 (5.56)**	**0**	**0**	**0**	**0**	**0**	**1 (12.50)**	**0**	**0**

Table 1: Summary of investigator reported treatment emergent immune-mediated adverse events by system organ class in patients treated with AGEN1181 alone or in combination with balstilimab.
*Overall number of patients exposed to monotherapy includes 1 patient in the 2 mg/kg Q6W with no irAEs reported as of data cut-off (October 6th, 2020).
** 4 patients from monotherapy cohorts were treated past progression in a rescue cohort with AGEN1181 + balstilimab combination. None of the patients from the rescue cohort experienced immune-mediated adverse events.

Immune mediated adverse events by grade

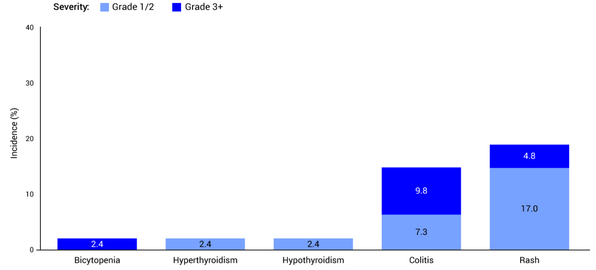


Figure 4: Investigator reported adverse events by grade in the monotherapy, combination and rescue cohorts combined. Skin toxicities and colitis were the most common immune-mediated toxicities. Immune mediated adverse events observed were consistent with similar agents in class. There is no evidence of hepatic toxicity or neurohypophysitis observed to date. Data cut-off October 6th , 2020.

AGEN1181 promotes clinical benefit in majority of treated patients

Responders with both low and high affinity FcγRIIIA

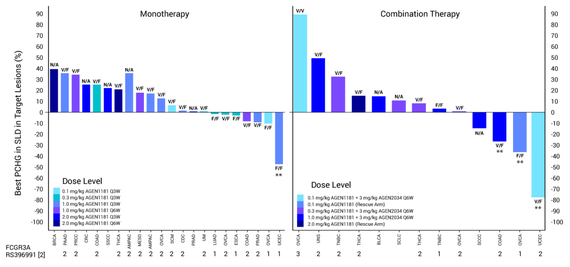
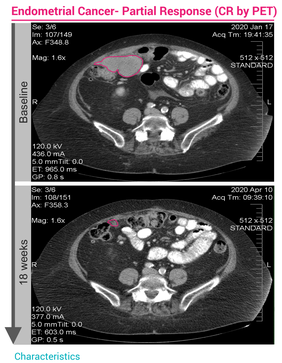


Figure 5: Best percentage change in sum of largest diameter (SLD) in target lesion stratified by FcγRIIIA expression in the monotherapy and combination arms

AGEN1181 promoted durable responses in patients that progressed on prior anti-PD-1 or chemoradiation

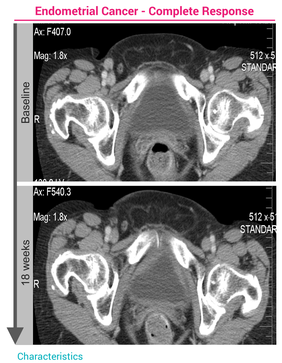
Durable responses achieved in patients that were BRCA-, microsatellite stable (MSS) and PD-L1 negative

Endometrial Cancer- Partial Response (CR by PET)



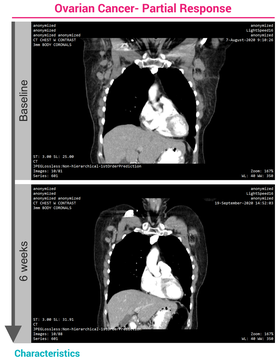
Characteristics
- 72y.o, White female
- BRCA 1/2 (-), PDL1 (-), TP53, PI3K-WT, MSS
- **Heterozygous FcγRIIIA (V/F)**
- AGEN1181 0.1mg/kg Q6W + balstilimab 3 mg/kg Q2W
- **Durable response (ongoing >36 wks)**

Endometrial Cancer - Complete Response



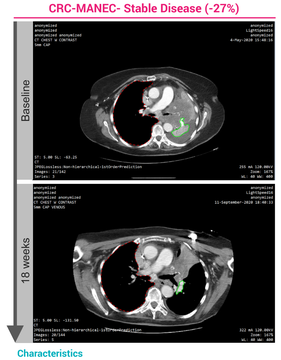
Characteristics
- 74y.o, White female
- PDL1 (-), PIK3CA, FBXW7, TP53, MSS
- **Homozygous FcγRIIIA (F/F)**
- AGEN1181 1mg/kg Q3W
- **Durable response (30 wks)**

Ovarian Cancer- Partial Response



Characteristics
- 75y.o, White female,
- PDL1 (-), BRCA 1-2 inconclusive, PAX8 (+), ER/PR (-), HER2 (-)
- **Low-affinity FcγRIIIA (F/F)**
- AGEN1181 0.1mg/kg: **Durable SD (72 wks)**
- AGEN1181 1mg/kg Q6W + bal 3 mg/kg Q2W: **PR**

CRC-MANEC- Stable Disease (-27%)



Characteristics
- 81y.o, White female,
- MSS, TMB = 5, KRAS (-), BRAF (-)
- **Heterozygous FcγRIIIA (V/F)**
- AGEN1181 1mg/kg Q6W + balstilimab 3mg/kg Q2W

Figure 6: Tumor assessment for patients treated with AGEN1181 monotherapy or in combination with balstilimab.

Complete responder to AGEN1181 therapy had low TMB but a high density of high affinity neo-antigens

Endometrial cancer patient with complete response to AGEN1181

Figure 7: Distribution of high affinity (<300 nM) neo-antigens predicted with NETMHCPanII using WES and RNASeq data from 12 tumor FPE samples (3 PD, 7 SD, 1 CR, 1 N/A) arising from singe nucleotide variants (SNVs) and indels **A)** and fusion events **B)** categorized by response status (complete response [CR], stable disease [SD] and progressive disease [PD]).

Pharmacodynamic analyses: AGEN1181, alone or in combination with balstilimab, enhances peripheral T cell activation

Dose-dependent increase in ICOS$^+$, HLADR$^+$, or Ki67$^+$ CD4 T cells

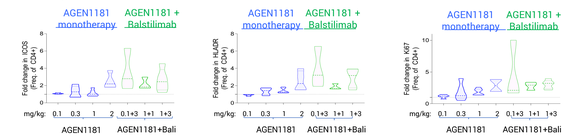
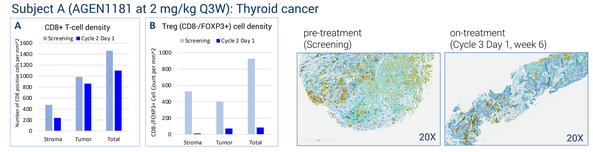


Figure 8: Peripheral flow cytometry analysis using PBMCs from patients treated with AGEN1181 collected at Day 8 after the first dose. Data is represented as a fold change over baseline (pre-treatment, Day 1) of frequency of activated CD4+ T-cells out of total CD4+ cells.

AGEN1181 promotes selective depletion of intratumoral Tregs

Subject A (AGEN1181 at 2 mg/kg Q3W): Thyroid cancer



AGEN1181 enhances intratumoral CD8+ T cell infiltration

CD68 CD8 FoxP3

Subject B (AGEN1181 at 2 mg/kg Q6W): Sinonasal SCC

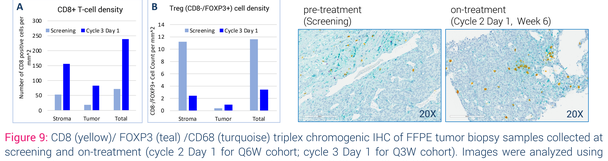


Figure 9: CD8 (yellow)/ FOXP3 (teal) /CD68 (turquoise) triplex chromogenic IHC of FFPE tumor biopsy samples collected at screening and on-treatment (cycle 2 Day 1 for Q6W cohort; cycle 3 Day 1 for Q3W cohort). Images were analyzed using Flagship Biosciences image analysis software for quantification of CD8+, FoxP3+, CD68+ cells as positive or negative. Tregs were defined as FoxP3+/CD8- cells. Machine learning algorithms were implemented to separate out lymphocyte-like cells and to stratify all cells as belonging to the 'tumor' or 'stromal' compartments. The markups were reviewed by Flagship pathologist for accuracy. Outputs of the digital analysis included CD8+, FoxP3+, CD68+ cell density (cells per mm^2) depicted in the corresponding graphs **A)** and **B)**.

Conclusions

AGEN1181:

- ✓ Demonstrates clinical activity in heavily pretreated patients as monotherapy or in combination with balstilimab
- ✓ Clinical responses in patients with both the low and high affinity FcγRIIIA alleles, unlike first generation anti-CTLA-4 molecules that generally benefit only those patients who express the high affinity allele.
- ✓ Promotes durable responses in patients that progressed on prior anti-PD-1 or chemoradiation therapy
- ✓ Avoid complement mediated toxicities – no evidence of hypophysitis to date
- ✓ First anti-CTLA-4 mAb to demonstrate intratumoral Treg depletion in patients with advanced solid tumors

References: Waight et al., Cancer Cell 2018; Arce-Vargas et al., Cancer Cell 2018

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