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 avoiding complement-mediated toxicity associated with many current immune checkpoint inhibitors
- Expanded therapeutic reach: broadens potential benefit to an additional ~40% of patients expressing the low-affinity FcγRIIIA (158F) allele, while enhancing benefit for those with the high-affinity allele

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, polymeric (of Fcγ) expression

Key Inclusion Criteria
- ≥18 years of age
- Histologically or cytologically confirmed diagnosis of metastatic or locally advanced solid tumor for which no standard therapy is available or on study
- Measurable disease in imaging based on Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1)

Dose escalation (3rd design)
AGEN1181 Monotherapy
Doses eval: 0.1, 0.3, 1.2 mg/kg

Selected Indications
- PD1 Refractory Melanoma (N=7)
- Endometrial Cancer (N=7)
- Non-Small Cell Lung Cancer (N=11)
- Thyroid Cancer

AGEN1181 promotes clinic benefit in majority of treated patients
Responders with both low and high affinity FcγRIIIA

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

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

Dose-dependent increase in ICOS+, HLADR+, or CD4+ T cell frequencies

AGEN1181 promotes selective depletions of intratumoral Tregs

Subject to AGEN1181 (0.3 mg/kg) OTG-1

Conclusions
- 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 chemotherapy
- First anti-CTLA-4/anti-PD1 to demonstrate intratumoral Treg depletion in patients with advanced solid tumors

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Figure 1: Mechanism of action of AGEN1181

Figure 2: Evaluation of ICOS+ and HLADR+ cells by FACS analysis for the low-affinity FcγRIIIA (158F) Fab, or high-affinity FcγRIIIA (158V) Fab antibody and stimulated with PD1 and sIL2-4Rα.

Figure 3: AGEN1181 therapy was well tolerated in patients across multiple tumor types

Figure 4: AGEN1181 therapy was effective in patients across multiple tumor types

Figure 5: Best percentage change in sum of largest diameter (SDI) in target lesions caused by FcγRIIIA in the monotherapy and combination arms

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

Table 1: Summary of pivotal reported treatment emergent immune-mediated adverse events by system organ class in patients treated with AGEN1181 alone or in combination with balstilimab

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Event</th>
<th>N (%)</th>
<th>Monotherapy</th>
<th>Combination</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal</td>
<td>Diarrhea</td>
<td>5 (62.5%)</td>
<td>2 (25%)</td>
<td>3 (30%)</td>
</tr>
<tr>
<td>Blood and lymphatic</td>
<td>Hematological</td>
<td>5 (62.5%)</td>
<td>2 (25%)</td>
<td>3 (30%)</td>
</tr>
<tr>
<td>Endocrine</td>
<td>Diabetes</td>
<td>2 (25%)</td>
<td>0 (0%)</td>
<td>2 (20%)</td>
</tr>
<tr>
<td>Skin and subcutaneous</td>
<td>Pruritus</td>
<td>2 (25%)</td>
<td>0 (0%)</td>
<td>2 (20%)</td>
</tr>
</tbody>
</table>

Figure 7: Distribution of high affinity (330 MD) neo-antigens predicted with NeTmRNA platform using APL and VEGF as target tumor antigens, along with the low-affinity (158F) Fab antibody

Figure 8: Peripheral T cell phenotype analysis using FACS from patients treated with AGEN1181 (N=7) or balstilimab (N=7) in the first 3 cycles. Data is shown as a box and whisker plot of median (IQR) at day 1 at 10X frequency

Figure 9: Percentage of PD1+ and HLADR+ cells in the total T cell population in patients treated with AGEN1181 0.3 mg/kg Q6W

Figure 10: Flow cytometry measures analysis using FACS from patients treated with AGEN1181 (N=7) or balstilimab (N=7) in the first 3 cycles. Data is shown as a box and whisker plot of median (IQR) at day 1 at 20X frequency

Figure 11: Flow cytometry measures analysis using FACS from patients treated with AGEN1181 (N=7) or balstilimab (N=7) in the first 3 cycles. Data is shown as a box and whisker plot of median (IQR) at day 1 at 20X frequency