Characterization of the Pharmacodynamic Activity of AGEN1181, an Fc-enhanced CTLA-4 Antibody, Alone and in Combination With the PD-1 Antibody Balstilimab

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AGEN1181 leverages a novel Fc-mechanism of action to promote:
1. Superior efficacy: Enhanced T cell priming, T cell depletion and T cell memory formation for durable anti-tumor immune response
2. Improved safety: Avoid complement mediated toxicity associated with many current immune checkpoint antibodies
3. Expand therapeutic reach: by improved binding to CD16 (FcγRIIIA) in patients with advanced solid tumors

Primary: AGEN1181 mechanism of action
Secondary: AGEN1181 in combination with balstilimab
Explanatory: Pharmacodynamics, CD16/FcγRIIIA polymorphism expression

Study Design
Phase I study assessing the safety and efficacy of AGEN1181 (anti-CTLA-4), both as monotherapy and in combination with balstilimab (anti-PD-1), in patients with advanced solid tumors (NCT03860272)

End Points
Primary: Safety and tolerability
Secondary: Pharmacokinetics profile (PK) per RECIST 1.1

AGEN1181 Exhibits Single-Agent and Combination Clinical Activity in Patients With Advanced Solid Tumors

Table 1. Responses observed in Phase I trial of AGEN1181 as monotherapy and in combination with balstilimab

<table>
<thead>
<tr>
<th>Subject</th>
<th>Tumor Type</th>
<th>Dose Schedule</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Colorectal cancer</td>
<td>AGEN1181 0.1 mg.kg Q2W then AGEN1181 1 mg/kg Q2W</td>
<td>PR</td>
</tr>
<tr>
<td>B</td>
<td>Endometrial (MSS, V/V high affinity)</td>
<td>AGEN1181 0.1 mg.kg Q2W then AGEN1181 1 mg/kg Q2W</td>
<td>CR (by PET)</td>
</tr>
<tr>
<td>C</td>
<td>Ovarian cancer</td>
<td>AGEN1181 0.1 mg.kg Q2W then AGEN1181 1 mg/kg Q2W</td>
<td>PR</td>
</tr>
<tr>
<td>D</td>
<td>Sinonasal SCC</td>
<td>AGEN1181 0.1 mg.kg Q2W then AGEN1181 1 mg/kg Q2W</td>
<td>CR</td>
</tr>
</tbody>
</table>

Pharmacodynamic Analysis at the Periphery
Enhanced Peripheral T Cell Activation With AGEN1181 as Monotherapy and in Combination With Balstilimab

Dose-dependent increase in Ki67+ CD4+ and CD8+ T-cells and ICOS+, HLA-DR+ CD4+ T-cells 7 days post first dose

Sustained CD4+ T cell activation by AGEN1181 monotherapy and in combination with balstilimab

AGEN1181 in Combination With Balstilimab Promotes Intra-tumoral Recruitment and Activation of CD8 T Cells

Increased TCR diversity in the TME and increased tumor-specific TCR diversity in the blood

Tumor-specific TCR clone frequency expansion at the periphery and in the TME

Conclusions
AGEN1181:
• Demonstrates clinical activity in heavily pretreated patients as monotherapy or in combination with balstilimab
• Induces sustained T cell activation at the periphery
• Causes selective Treg depletion in the tumor microenvironment (TME)
• Promotes intra-tumoral recruitment of activated TILs in combination with balstilimab
• Expands clinical responses to patients with low affinity or heterozygous FCγRIIIA SNP genotype

References: [Provide references here]

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