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

Steven O'Day1, Anthony E-Khoueiry2, Chethan Ramamurthy3, Andrea Bulullock3, Irina Shapiro3, Serina Ng1, Hayong Han1, Lennik Ohanjanian5, Remigiusz Kalaeta3, Anna Wiatry3, Oliva Wiatry5, Waldor Ortuzu Felu4, Marek Ancwickicz4, Jennifer S. Bueli3, Dhan Chand1, Michael Gordon4

1 City-of-Lanarkshire Health and Social Care Partnership, 2 University of California, 3Flagship Biosciences and Precision for Medicine, 4Genus Inc., 5Translational Genomics Research Institute (TGen), Phoenix, AZ

Background

AGEN1181 leverages a novel Fc mechanism of action to promote:
- Superior efficacy enhanced T cell priming/presentation 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: increase potential benefits to an additional 40% of patients expressing the low-affinity FcγRIIA (30%) allele, while enhancing benefits for those with the high affinity allele

Phase 1 study of AGEN1181 as monotherapy or in combination with basilistimab (NCT03862072)

Primary: Safety and tolerability
Secondary: Pharmacodynamics profile, ORR in RECIST 1.1

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

ODEs in AGEN1181

- Dose escalation (3+3 design)
- AGEN1181 monotherapy 1 mg/kg Q3W
- Doses evaluated: 0.1, 0.3, 1.2 mg/kg

Dose escalation (Accelerated ration and (3+3 design)
AGEN1181 + basilistimab: IV Q6W
Doses evaluated: 0.1, 0.3, 1.2 mg/kg

 WIFI

AGEN1181 promotes clinical benefit in majority of treated patients

- Responders with both low and high affinity FcγRIIA

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

Durable responses achieved in patients that were BRCA-Au5652, 57 haplotype bearing and were treated with AGEN1181 therapy was well tolerated in patients across multiple tumor types

Dosing: Dose-dependent increase in KOIS: HLA-DR, or Ki67 CD4 T cells

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

AGEN1181 promotes selective depletion of intratumoral Tregs

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

AGEN1181 enhances intratumoral CD8+ T cell infiltration

Subject B (AGEN1181 at 2 mg/kg QM) Severe SEC

Conclusions

AGEN1181:
- Demonstrates clinical activity in heavily pretreated patients as monotherapy in combination with basilistimab
- Clinical responses in patients with both the low and high affinity FcγRIIA alleles, unlike first generation anti-CTLA-4 mAbs 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 chemotherapeutic therapy
- Avoid complement mediated toxicity

For further reading, please see the references provided at the end of the document.