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AACR 2020 Presentation

Fc-Enhanced CTLA-4 (AGEN1181) and Fc-Enhanced TIGIT (AGEN1327) Combinations Show Curative Benefit

CTLA-4 + PD-1 therapy is the most validated and most frequently tested I-O plus I-O combination to date. As of this publication, this combination has been approved in 6 different settings with an additional ~20 in clinical development. Despite the groundbreaking improvements this combination treatment provides, the majority of patients still do not respond to either 1st generation CTLA-4 (Yervoy®) monotherapy or to treatments in combination with PD-1. One of the reasons for this is a genetic polymorphism which substantially limits the number of patients who benefit from CTLA-4 therapy. In 2018, Agenus scientists specifically engineered the Fc region of our antibodies targeting both CTLA-4 and TIGIT to address these limitations.

THE RESULT: The functionality and antitumor immunity of our Fc-enhanced CTLA-4 and TIGIT antibodies were significantly improved compared to every reference and competitive antibody we tested.

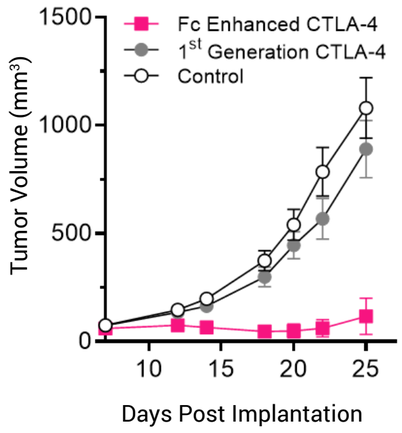
FIRST: AGEN1181 Monotherapy Achieved A Complete Response In Early Clinical Development

The enhanced design of AGEN1181 provides the following major advantages over other approaches:

- Improved T cell responses
- Superior intratumoral Treg depletion
- Better expansion of memory T cells for improved durability of response
- A much broader target patient population (3X more than 1st gen CTLA-4)
- Better safety profile by avoiding complement-dependent adverse events

At AACR 2020, we demonstrated the ability of our Fc-engineered CTLA-4 antibody to produce curative responses as monotherapy against immunogenic tumors by enhancing intratumoral Treg depletion and T cell priming in mouse tumor models. This is in contrast with 1st generation CTLA-4 antibodies, which do not provide this benefit. These data support our strategy to develop AGEN1181 as both monotherapy and in combination with our PD-1 antibody, balstilimab.

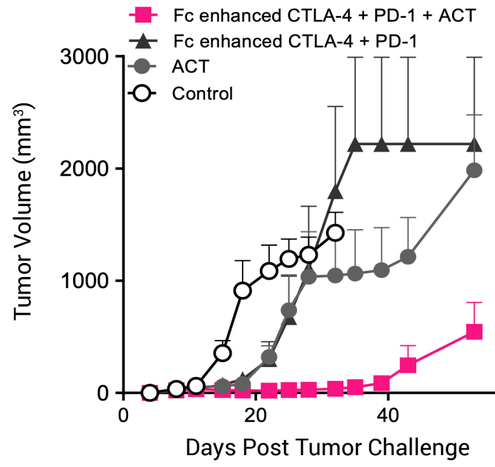
The data below show the profound advantage of our Fc-enhanced CTLA-4 antibody.

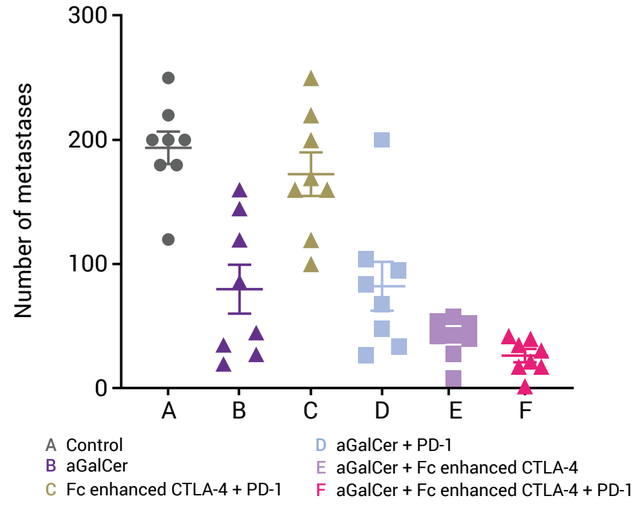


NEXT: AGEN1181 Combinations Across Our Pipeline Provide Curative Preclinical Responses In Tumors Unresponsive To Other I-O Treatments

Agenus' advantage includes a unique pipeline of checkpoint antibodies plus adoptive cell therapies (ACT) together with our vaccines. The power and versatility of our pipeline gives us the flexibility to develop what could potentially be the best and most effective combination therapies for cancer patients. Our AACR presentation highlighted AGEN1181 as an ideal combination partner with each of the modalities in our pipeline. These combinations are ideal for promoting curative responses in aggressive cancers that do not respond to other I-O therapies, including PD-1 antibodies, the hallmarks of I-O.

The data below show the profound responses when our Fc-enhanced CTLA-4 antibody is combined with other I-O agents in our pipeline.





AGEN1181 and AGEN1327 data presented in mouse tumor models were generated using murine surrogates

CELL THERAPY: In a murine tumor model resistant to existing immune therapies, our Fc-enhanced anti-CTLA-4 + our anti-PD-1 + our cell therapy significantly improved the tumor control achieved by cell therapy alone. More importantly, the addition of AGEN1181 and anti-PD-1 made these responses long lasting, suggesting curative responses.

This experiment demonstrated that none of the mice treated with cell therapy alone were alive two months post treatment while more than 80% of mice treated with AGEN1181 combination therapy survived. Our data demonstrate the potential of AGEN1181 in extending the benefit of cell therapy to cancers that do not respond to current immunotherapies.

ACTIVATED iNKT CELLS AND ALPHA-GalCer:

We have shown the ability to enhance iNKT mediated tumor killing with the use of Alpha-GalCer (an iNKT activating agent) in various experiments. When we use our Fc-enhanced CTLA-4 antibody in combination with Alpha-GalCer and anti-PD-1 in our experiments, we see robust tumor clearance in a difficult-to-treat lung metastases model. These experiments show a strong infiltration of iNKT cells to the lungs with the addition of Alpha-GalCer, and this anti-tumor effect is further potentiated by the addition of our Fc-enhanced anti-CTLA-4 antibody in combination with our anti-PD-1 antibody. It is worth noting that we have recently acquired a significant amount of the scarce clinical supplies of Alpha-GalCer for our anticipated combination clinical trials with iNKTs.

TIGIT: AGEN1181 + our Fc-enhanced TIGIT monospecific promises to be yet another potent combination. At AACR, we saw data indicating that 1st generation anti-TIGIT is inactive as monotherapy. **We have previously released data showing that our Fc-enhanced TIGIT monospecific (AGEN1327) demonstrates** superior immune activation **and** preclinical tumor killing **as monotherapy compared to competitor 1st generation agents.** The superiority of our Fc-enhanced TIGIT over the Fc-silent and Fc-competent TIGITs in development suggests its potential as the best-in-class option when combined with a PD-1. We demonstrated at AACR that combining AGEN1181 with our TIGIT antibody also boosts T cell responses seen with TIGIT monotherapy alone. This further demonstrates the potential of differentiated combinations with our agents, such as with our Fc-enhanced CTLA-4 and TIGIT antibodies.

STANDARD OF CARE: In today's quickly-evolving I-O landscape, it is beneficial to consider combinations involving standard of care (SoC) approaches such as chemotherapy and radiation therapy for rapid clinical development. To that end, we revealed at AACR that the addition of AGEN1181 nearly doubled the tumor control achieved with PD-1 + radiation in tumors resistant to checkpoint blockade. We also illustrated the impact of combining AGEN1181 with our **heat shock protein-based vaccine** and our **QS21 adjuvant.** While vaccination alone was unable to drive a curative response in mice, the combination with AGEN1181 and PD-1 was able to do so, with curative outcomes in ~75% of mice treated.

SUMMARY: Taken together, data from an exhaustive set of experiments and well-designed clinical trials indicate:

- The advantages of our Fc enhancement technology
- The unprecedented advantages of AGEN1181 based on clinical and preclinical data
- Our ability to facilitate effective combinations based on our possession of a substantial number of I-O agents/modalities
- A preview of what can be expected from our Fc-enhanced TIGIT antibodies

Early clinical data for AGEN1181, presented at ASCO by Dr. Steven O'Day, has shown responses in cancers with poor prognosis (MSS-endometrial), including those that failed to respond to PD-1 therapy. Responses were noted in patients who have a genetic polymorphism that makes them unlikely respond to 1st generation CTLA-4. Therefore, AGEN1181 has blockbuster potential as monotherapy and in combination with our deep I-O portfolio. We believe that our Fc-enhanced TIGIT antibodies have similar potential, particularly when combined with anti-PD-1s.

AGEN1181 and AGEN1327 data presented in mouse tumor models were generated using murine surrogates