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TIGIT: The 3rd Validated I-O Target

Agenus Fc-enhanced TIGITs to Maximize Benefit

After several years of slow progress, the field of immuno-oncology (I-O) is starting to register another wave of advances. At the start of 2020, anti CTLA-4 + PD-1 therapy was the only validated combination regimen. This past May, new clinical data was published demonstrating that combining TIGIT and PD-(L)1 can nearly double efficacy in patients compared to PD-(L)1 monotherapy. This makes TIGIT the second validated I-O pathway that combines effectively with PD-(L)1 blockade. Thus, TIGIT is shaping up as the next breakthrough target for I-O. This conviction is supported by the launch of multiple late-stage clinical trials by biopharma companies such as Roche and Merck. In addition, TIGIT has been the subject of several recent strategic collaborations.

Agenus' portfolio of TIGIT targeting antibodies includes a **monospecific candidate (AGEN1327)** and a **bispecific candidate (AGEN1777)**. The design of both antibodies has been enhanced to maximize therapeutic benefit. We discuss the nature and rationale of these enhancements in today's newsletter.

Dhan Chand, Head of Drug Discovery at Agenus, will join a panel of experts at the TIGIT Therapies Digital Summit to discuss the benefits of TIGIT blockade in I-O and key molecular design considerations for the optimal antibody performance.

"Following the successes of CTLA-4 and PD-1 blockade, TIGIT has demonstrated its potential to be the 3rd effective therapeutic target in I-O. At Agenus, we are advancing a rationally designed TIGIT portfolio designed for optimal performance in order to benefit more patients and deliver superior efficacy as compared to other TIGIT molecules"

What is TIGIT?

TIGIT is a central inhibitor of immune response to cancer. In the tumor microenvironment, it is overexpressed on T cells and NK cells, which are two immune cell types that our body leverages to kill cancers. The mechanism by which TIGIT overexpression interferes with T cell and NK cell killing is known. TIGIT binds to PVR, a protein expressed on cancer cells; and through this binding, the ability of T and NK cells to fight cancer is weakened[1]. TIGIT is also overexpressed on regulatory T cells (Tregs), which create an immune-suppressive environment. Although the mechanism by which TIGIT expression enhances the immune suppressive nature and stability of Tregs remains to be fully understood, its function in impacting Treg activity has been shown to be significant[2].

Since TIGIT/PVR binding helps cancer grow, blocking TIGIT is an attractive therapeutic option. Anti-TIGIT antibodies are designed to accomplish this by helping restore the cancer killing abilities of T and NK cells. Moreover, one negative consequence of treatment with PD-1 antibodies is an increase in TIGIT expression[3], underscoring the potential benefit of combining TIGIT with PD-1 therapies.

Why is Fc enhancement key to optimizing TIGIT antibody performance?

There are currently two classes of TIGIT antibodies in Phase 2/3 clinical trials. The differences between these two classes are mainly related to the structure of their Fc region. The first class of antibodies has an Fc-competent backbone that allows them to engage Fc receptors on immune cells. This interaction facilitates the ability of immune cells, such as NK cells or macrophages, to destroy cancers. The second class of antibodies was designed with a "silent" Fc-region, so they do not engage with Fc receptors on immune cells. It is believed that this may prevent the potential depletion of critical immune cells in the tumor. However, the importance of the Fc region in antibody design has been well described. In a number of preclinical experiments, silencing the Fc region has been shown to blunt an antibody's ability to kill tumors. Hence, Fc silent antibodies lack the advantage offered by Fc-competent antibodies.

Further, we were the first to show that **"enhancing" the Fc-region of TIGIT antibodies improves their tumor fighting abilities**. Fc-enhancement has been shown to increase the ability of TIGIT antibodies to activate T cells versus Fc-competent antibodies **(see Figure 1)**[4,5]. Agenus is advancing two Fc enhanced anti-TIGIT antibodies: a TIGIT monospecific **(AGEN1327)** and a bispecific (AGEN1777) – the second arm targets an undisclosed receptor. This same Fc design feature was used by Agenus to improve the activity of our next-generation CTLA-4 agent (AGEN1181); this agent has already shown pronounced clinical benefit in early clinical trials.

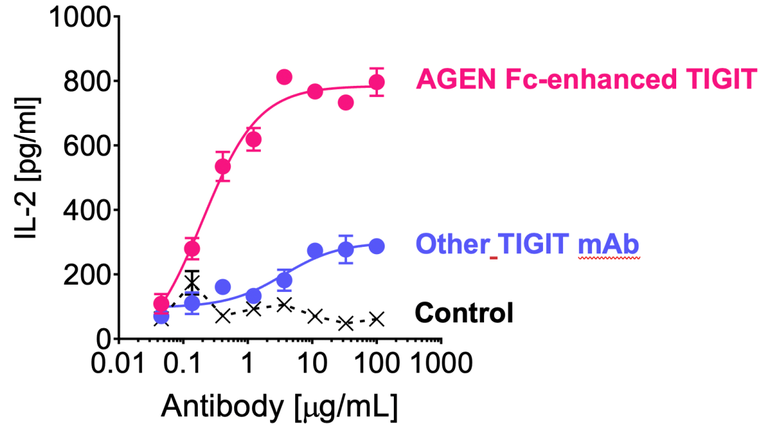

Figure 1: *Fc-enhancement increases the ability of TIGIT antibodies to activate T cells*

Forward-Looking Statements: This Agenus Newsletter includes forward-looking statements that are made pursuant to the safe harbor provisions of the federal securities laws, including statements regarding TIGIT being the next breakthrough I-O target, the anticipated therapeutic benefit and potential of Agenus' TIGIT antibodies, and anticipated timing for initiating clinical trials. These statements are subject to risks and uncertainties, including those described in our SEC filings.

Agenus' Fc-enhanced TIGIT antibodies demonstrate improved tumor killing versus other TIGIT antibodies

In addition to improving T cell activation, our Fc-enhanced TIGIT antibodies enable significant tumor control. In preclinical experiments, **our Fc-enhanced TIGIT monospecific has outperformed all other TIGIT antibodies tested (see Figure 2). It is designed to be used as an optimal combination partner to PD-1 therapy.** To this end, we have already shown that our Fc-enhanced TIGIT monospecific leads to superior T cell activation when combined with other I-O antibodies such as anti-PD-1 or anti-LAG-3 agents, versus combinations involving its Fc-competent counterpart[5].

Thus, Fc-competent TIGIT antibodies in development have limitations. Recent clinical data from two Fc-competent TIGITs indicates that they have limited activity as monotherapy and in patients who are unresponsive to PD-1 therapy. On the other hand, **our Fc-enhanced bispecific TIGIT antibody has demonstrated dramatic tumor killing activity as monotherapy in a difficult to treat colon cancer model where PD-1 blockade is ineffective (see Figure 3). AGEN1777 is designed to be used as monotherapy in tumors that don't respond to PD-1 therapy, potentially offering significant differentiation vs. TIGIT antibodies in late-stage development.** Thus, Fc enhancement leads to a clear superior performance benefit as measured by anti-tumor activity.

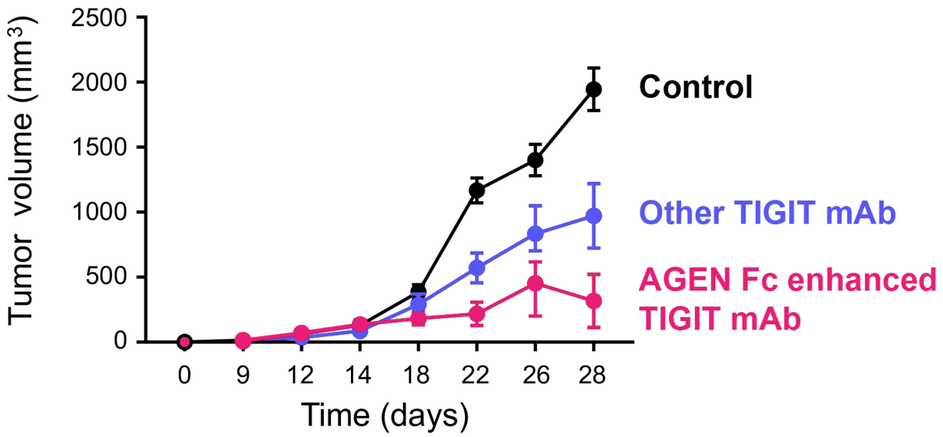

Figure 2: *Tumor control: Agenus' Fc-enhanced TIGIT monospecific offers superior benefit*

In summary

To support the advantages of our Fc-enhanced TIGIT antibodies, we have generated robust preclinical data to indicate:

1. The Fc-enhanced design of our TIGIT antibodies enables them to deliver superior T cell activation and tumor killing vs. other TIGIT antibodies.
2. Our Fc-enhanced TIGIT monospecific has the potential to combine more effectively with other immunotherapies such as PD-1 and LAG-3 antibodies versus Fc-competent TIGIT antibodies.
3. Our Fc-enhanced TIGIT bispecific is a potential first-in-class agent that could be used as monotherapy in patients unresponsive to PD-1 therapy. These are settings in which Fc-competent counterparts have shown limited clinical activity.
4. In addition to the aforementioned benefits, the Fc-enhanced nature of our TIGIT antibodies also positions them to target an additional 40% of patients who are less likely to respond to TIGIT antibodies in late-stage development due to a genetic polymorphism.

At the upcoming Society for Immunotherapy of Cancer (SITC) Annual Meeting in November, we will be presenting additional data on the benefits of Fc-enhancement for TIGIT antibodies. Thus, we believe that we are uniquely positioned to maximize benefit from blocking the TIGIT pathway with two distinct molecules on track to enter the clinic in 2021.

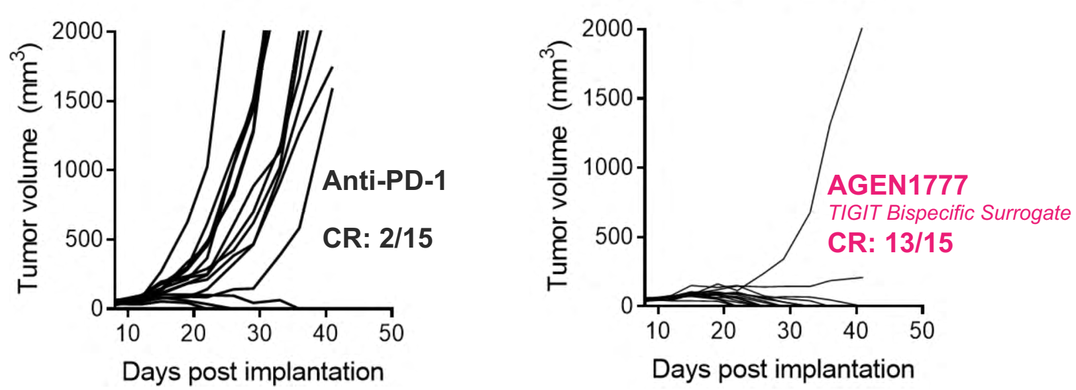

Figure 3: *Tumor control: Agenus' Fc-enhanced TIGIT bispecific shows significant potential as monotherapy in PD-1 refractory colon cancer mouse model*

References

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