agenusnews

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Perspectives on Seven Agenus Programs Presented at SITC

Agenus Strategy to defeat cancer - New clinical responses - Novel platform for response prediction – Unique MOAs

The Society for Immunotherapy of Cancer's (SITC) Annual Meeting is one of the most prestigious medical conferences in immuno-oncology (I-O). An estimated 5,000 medical and scientific professionals attended the conference this year. **Agenus presented updates from a record seven programs, with all its abstract submissions having been accepted. Presentations included data from four clinical programs** and a novel Agenus platform designed for treatment optimization by predicting which patients are likely to respond to specific treatments or combinations.

Agenus I-O Strategy

Agenus' mission is to develop cancer cures by mobilizing synergistic components of the immune system and optimizing their use based on disease and patient specific considerations. As a first step, we are developing **balstilimab** and **zalifrelimab**, antibodies which block I-O targets (PD-1 and CTLA-4). Our next generation antibody targeting CTLA-4 **(AGEN1181)** was designed (via Fc engineering) to deliver superior performance vs. first-generation antibodies. We have applied these design advantages embedded in AGEN1181 to the development of antibodies against other novel targets such as our TIGIT monospecific and bispecific molecules **(AGEN1327, AGEN1777).** In addition, we are developing antibodies and cell therapies to drive other important components of the immune system. These include agents that are designed to 1) block the immune-suppressive effects of myeloid cells (**AGEN1531**), 2) enhance memory T and NK cell immune response (**AGEN2373**, **AGEN1777**), 3) weaken suppressive activity of regulatory T cells (**AGEN1181**, **AGEN1223**) and also importantly, 4) a universal allogeneic (off-the-shelf) cell therapy (**AgenT-797 iNKT cells**), which has the capacity to treat solid tumors (~90% of all cancers) as well as serious viral infections such as COVID-19.

Many of these agents from Agenus' arsenal of immune system enhancers are currently in clinical development as monotherapies or combinations. We believe that one of the key drivers of success in developing cancer cures is the ability to use what is needed, when it is needed. We believe that having a comprehensive portfolio of agents and predictive platforms under one roof is crucial for the speed and success of bringing effective treatments to patients with cancer.

Our first two T cell targeting antibodies (balstilimab/zalifrelimab) are important drivers of adaptive immune response. CTLA-4/PD-1 combinations have been gaining ground, having now been approved in seven cancer settings. Today, we are witnessing the benefits of our strategic decision to develop our own first-generation antibodies; balstilimab +/- zalifrelimab is showing clinical benefit in several cancers, including in PD-L1 negative cervical cancer patients, for whom there are no approved therapies. In addition, important benefits of having these antibodies in our portfolio include: 1) freedom to combine them with our other portfolio agents, 2) business development opportunities which we have started monetizing, and 3) our ability to responsibly price treatment protocols comprised of several novel agents.

In September of this year, we announced initiation of a rolling BLA filing for balstilimab; FDA review is currently underway for the modules submitted thus far.

Agenus Fc Enhancement and Agenus VISION Platforms

In a breakthrough publication in Cancer Cell, our scientists discovered that modifying the "Fc region" of certain antibodies, significantly improves their functionality and anti-tumor immunity. We first applied this science in developing a next-generation CTLA-4 antibody **(AGEN1181)** and subsequently identified that TIGIT antibodies **(AGEN1327, AGEN1777)** benefit from similar engineering. Our pipeline has since expanded to include molecules that activate innate immunity with the addition of TIGIT, CD137 and iNKT cell programs. As our pipeline has grown, it has become increasingly clear that we need to better understand which drugs work as optimal combinations. To effectively design these combination strategies, we need to understand how the immune system reacts to these therapies over time. It is also important to identify which patients may best benefit from each regimen. These needs gave rise to our VISION platform. We presented updates on all these efforts last week at SITC. In today's newsletter, we summarize these presentations and contextualize their significance. All poster presentations can be accessed through our website.

AGEN1181 Shows Additional Clinical Responses in Phase 1

At SITC, we reported new data on 41 patients: 23 patients treated with AGEN1181 monotherapy and 18 patients treated with the combination of AGEN1181 and balstilimab. AGEN1181 is Fc-enhanced to deliver improved performance versus first-generation IgG1 CTLA-4 agents such as Yervoy, the only approved CTLA-4 antibody. Our novel design seeks to improve the immune attack on cancer through various mechanisms. These include increased T cell activation and depletion of immune-suppressive intra-tumoral regulatory T cells (T regs). At SITC, we reported that these design elements have been validated in the clinic thus far. **AGEN1181 is the first anti-CTLA-4 antibody to clinically demonstrate selective depletion of intra-tumoral Tregs.**

AGEN1181 is also designed to optimally combine with various therapies such as checkpoint inhibitors, radiation, and chemotherapy. Prior to SITC, at another prominent scientific conference, AACR (American Association of Cancer Research), we presented preclinical data demonstrating that these combinations promote robust tumor control and curative responses. At SITC, we reported that this combination potential was validated in a Phase 1 trial. We observed multiple responses in patients treated with AGEN1181 and balstilimab **(see Table 1). This includes a previously unreported partial response (PR) in an ovarian cancer patient and major tumor reduction of 27% in a metastatic colorectal cancer (CRC) patient.** All responses

have been durable **(see Table 1)** – responding patients had at least one characteristic associated with poor prognosis: PD-L1 negativity, BRAF negativity and/or microsatellite stable disease status.

Further, the Fc-enhanced design of AGEN1181 is critical in extending the benefit of CTLA-4 blockade to patients who express BOTH the low and high affinity FcγRIIIA allele. Yervoy does not typically benefit patients expressing the low affinity allele (F/F); these patients constitute ~40% of the population. On the other hand, **all AGEN1181 responders to date carried less favorable genetic characteristics; that is, these patients are homozygous or heterozygous for the F/F or V/F FcγRIIIA allele (see Table 1).**

We are excited that these data support prospects of AGEN1181 development as monotherapy and in combination with balstilimab as well as with other agents in our portfolio. We will specifically target cancers where limited immunotherapy options are currently available. **The Phase 2 trial is underway in MSS-endometrial and colorectal cancers as well as in PD-1 refractory melanoma and NSCLC.**

In addition, treatment with AGEN1181 has been well-tolerated to date, with patients showing no evidence of neuroendocrine toxicities, which are typically seen with first-generation CTLA-4 agents.

Agenus' Fc-enhanced TIGIT – Superior anti-tumor Activity

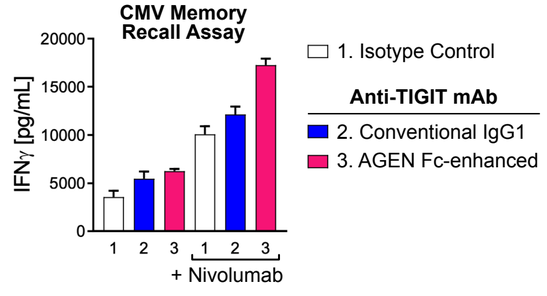
Agenus was the first to show that "enhancing" the Fc-region of TIGIT antibodies improves their tumor-fighting abilities. This is in contrast to two other classes of TIGIT antibodies (Fc-competent or Fc-silent). Anti-TIGIT antibodies help restore the cancer-killing abilities of T and NK immune cells. We have previously demonstrated in pre-clinical models that Fc-enhanced TIGIT antibodies improve T cell activation when compared to their Fc-competent counterparts, which achieve this effect sub-optimally. At SITC, we presented data demonstrating that **Agenus' Fc-enhanced TIGIT, additionally, improves NK cell activation and function versus an Fc-competent antibody, in pre-clinical models. We also demonstrated that Fc-enhanced TIGIT antibodies demonstrate superior activity in combination with PD-1 antibodies, compared to less optimal performance of Fc-competent antibodies (See Figure 1).**

Table 1. Summary of clinical results - AGEN1181 +/- balstilimab

Tumor Type	Response	Dose	FcγRIIIA Status	Durability
Endometrial MSS, PD-L1 (-)	CR	AGEN1181: 1mg/kg Q3W	F/F Low affinity	30 weeks
Endometrial MSS, PD-L1 (-)	CR (PET scan)	AGEN1181: 0.1mg/kg Q6W Balstilimab: 3mg/kg Q2W	V/F Heterozygous	Ongoing, >36 weeks
Ovarian ER/PR (-), HER2 (-), PD-L1 (-)	PR	AGEN1181: 1mg/kg Q6W Balstilimab: 3mg/kg Q2W	F/F Low affinity	72 weeks SD (0.1mg/kg AGEN1181); PR upon combo crossover
CRC-MANEC MSS, KRAS (-), BRAF (-)	27% tumor reduction	AGEN1181: 1mg/kg Q6W Balstilimab: 3mg/kg Q2W	V/F Heterozygous	Ongoing - recent patient

Similar to the advantages demonstrated with Fc-enhanced AGEN1181, we showed that Fc-enhanced TIGIT antibodies have the potential to expand the population of patients who benefit from treatment. This is achieved by providing benefit to patients who express a polymorphism in FcγRIIIA alleles. These patients are also less likely to respond to the TIGIT antibodies currently in late-stage clinical development. **Thus, our Fc-enhanced TIGIT approach enables us to potentially achieve monotherapy benefit, deepen benefit compared to other TIGIT antibodies, and extend this benefit to a broader patient population.** Our Fc-enhanced monospecific / bispecific programs are anticipated to enter the clinic in 2021.

Figure 1. Fc-enhanced TIGIT demonstrates superior T cell activation and priming when used in combination with PD-1 antibodies (IL-2 levels correlate with these attributes) .



AGEN2373, our CD137 Agonist, Shows Clinical Benefit Without Liver Toxicity in Ongoing Phase 1 Trial

CD137 is yet another important target for cancer immunotherapy because it represents a potent pathway that regulates cancer-fighting T and NK cell responses. Experts agree that finding a way to target CD137 without liver toxicity would be a major advancement in cancer treatment. AGEN2373 may just be such a CD137 agonist antibody.

The first CD137 agonist antibody to enter the clinic, Urelumab (BMS), showed promising signals of efficacy in early trials but was not advanced due to severe liver toxicity. We specifically designed AGEN2373, our CD137 agonist, to deliver optimal clinical activity while overcoming this limitation of liver toxicity. Our antibody is designed to activate T and NK cells in the presence of certain receptors, which is also expected to minimize other potential toxicities. **Our SITC presentation elucidated that AGEN2373 monotherapy has shown a favorable safety profile with no evidence of liver toxicity in 16 patients dosed up to 1 mg/kg.** In contrast, urelumab treatment at the same dose has led to significant liver toxicity. **Further, AGEN2373 treatment led to increased trafficking of T and NK cells in the tumor microenvironment, while promoting robust depletion of intra-tumoral Tregs in pre-clinical models; all important to achieve a successful immune response**.

Four patients achieved long terms disease stabilization and demonstrated no evidence of cancer growth at week 16 when treated with AGEN2373 monotherapy. Our SITC data also highlighted that **AGEN2373 combines with PD-1 and Fc-enhanced CTLA-4 antibodies to improve responses in a cold tumor mouse model.** Combination studies with balstilimab are expected to commence shortly in the clinic.

Agenus' VISION Platform Can Predict Which Patients Will Respond to Therapy With High (86%) Accuracy

Our proprietary - Virtual Systems for Immuno-Oncology (VISION) - platform interrogates how cancer cells interact with antibodies and

small molecules in the tumor microenvironment. We analyze data generated in our experimental models in concert with patient data using proprietary models and algorithms, with the use of AI. Our VISION platform is designed to enable us to predict how immunotherapies and other anti-cancer agents will perform in patients, and to discover and optimize a new generation of immunotherapies.

At SITC, we presented data indicating that **VISION can accurately predict certain clinical outcomes.** Response rates to anti-PD-1 in cervical cancer are as low as 13%; this creates an imperative need to predict which patients will benefit from PD-1 therapy. While the PD-L1 IHC is currently the default standard biomarker for anti PD-1 therapy, **our VISION platform outperformed IHC PD-1 responses with more accuracy (see Figure 2).**

The AGENUS VISION PLATFORM was also designed to enable us to predict rational drug combinations. For example, while the co-blockade of TIGIT and PD-1 significantly enhanced tumor killing, dual targeting of TIM-3 and PD-1 did not improve activity versus PD-1 alone. These findings may explain why the combination of anti-PD-1 and anti-TIGIT antibodies in clinical development has been effective. With its portfolio of novel molecules and cell therapies, Agenus is leveraging the power of VISION to develop cures for patients with cancer.

***Figure 2**. VISION outperforms standard IHC in predicting PD-1 responders*

60%	87%	86%
PD-L1* IHC Accuracy Solid Tumors	Agenus Model Melanoma Accuracy	Agenus Model Cervical Accuracy

*Commercially available test

AgenT-797, the AgenTus Clinical Stage Allogeneic iNKT Cell Therapy, Demonstrates Potent Tumor Killing

Invariant natural killer T cells (iNKT cells) are a unique cell type that combine features of two critical arms of the immune system, T cells (adaptive immunity) and NK cells (innate immunity). They promote an immune response through various mechanisms, such as the production of both cytotoxic and regulatory cytokines. This makes them invaluable in combating diseases like COVID-19 and cancer. In fact, when combined with several of Agenus' checkpoint antibodies, iNKT triggering cell therapy shows curative potential in refractory cancer models.

AgenT-797 is our allogenic iNKT cell therapy that can be used "off-the-shelf". It does not require any genetic manipulation. We have manufactured these cells with >99% purity, as demonstrated at SITC, producing up to 100 patient doses from a single batch. Unlike approved cell therapies, these properties of our iNKTs enable a reduction in the time and cost it takes to treat patients.

At SITC, we presented data demonstrating that activated iNKT cells promote direct tumor killing and tumor microenvironment conditioning. We have also demonstrated iNKTs can be engineered to express CARs for more targeted tumor killing. AgenT-797 is advancing in the clinic to treat patients with COVID-19. We expect to begin dosing cancer patients this year.

Agenus Presents FIRST Report of Radiologic Pseudoprogression and its Importance In Cervical Cancer Trials

Dr. David O'Malley presented the first ever report of pseudoprogression occurrence in cervical cancer following treatment with immunotherapies. These data were generated from two clinical trials evaluating balstilimab +/- zalifrelimab (anti CTLA-4) in >300 patients combined. Detailed clinical results from these studies were recently presented at ESMO.

Pseudoprogression (PsP) is a phenomenon in which an initial radiologic increase in tumor size is observed. This increase is often mediated by an inflammatory immune response. When inflammation subsides, a radiologic shrinkage in tumor size is observed, reflecting an immunologic tumor response. PsP is an early sign of benefit to patients receiving immunotherapy but if it is misdiagnosed as tumor progression, it can lead to premature discontinuation of treatment.

If PsP is misdiagnosed as progression, immunotherapy may be discontinued prematurely and replaced with a potentially toxic or ineffective subsequent therapy. Across our two clinical trials in cervical cancer, 21 patients demonstrated evidence of PsP. Why is this identification of PsP important? PsP in our trials was accompanied with clinical benefit, including weight stabilization, improvement in performance status, and decreased pain. We presented a few of these case studies at SITC, including a case in which a patient demonstrated disease progression until week 30 before showing delayed response. These findings underscore the importance of diagnosing PsP to avoid premature termination of treatment and to ensure optimal patient care.

Zalifrelimab is Active in PD-1 Refractory Cancers, Including Rare Tumors

While anti-PD-1 antibodies are widely used, they don't generally provide curative benefit to patients. In addition, a growing group of patients fail anti-PD-1 therapy. Recent studies have shown that one mechanism of PD-1 resistance is through the upregulation of the CTLA-4 receptor on T cells. At SITC, we reported data showing that zalifrelimab, an anti-CTLA-4 antibody, is active in patients who have failed anti-PD-1 therapy.

Out of 28 such patients evaluated, 3 had ongoing responses(1 CR, 2 PRs). The confirmed objective response rate in these refractory patients was 11.1% with a disease control rate of 51.9%. Patients benefiting from zalifrelimab included those with durable responses in rare tumors such as locally advanced angiosarcoma, where no effective treatment options exist. We recently launched a Phase 2 study with Dr. Breelyn Wilky, the Director of Sarcoma Medical Oncology at University of Colorado Anschutz Medical Campus, to explore the combination of zalifrelimab and balstilimab with standard of care (doxorubicin) in soft tissue sarcomas. There are 5,000 deaths annually in the US from soft tissue sarcomas, highlighting the large unmet need that our therapies could potentially fulfill.

As these SITC presentations demonstrate, we are constantly striving to expand our reach to more cancer patients by advancing innovative drug candidates designed to deliver curative benefit. Our science along with our broad portfolio of immuno-oncology agents give us the ability to match patients to therapies using optimal combinations. We look forward to sharing additional updates in the future.