agenusnews

Vol. 3 · Issue 20 · October 06, 2020

Did You Know? *Facts about Agenus*

Agenus' pipeline addresses all three validated immuno-oncology (I-O) targets (CTLA-4, PD-1 and TIGIT). In addition, it includes therapeutic modalities that target a broad range of additional novel I-O pathways. We believe that we have built ALL the capabilities required to advance projects from a therapeutic concept to a viable drug candidate. In other words, we can discover a new target, develop antibodies against that target, engineer antibodies to deliver optimal immune responses and manufacture antibodies at high speed with minimal reliance on external contract organizations. Did you know the following facts about Agenus? Read on to find out!

Agenus discovered MK-4830 (anti-ILT-4) has generated exciting clinical data for Merck

In April 2014, Agenus entered into a collaboration with Merck to discover and develop therapeutic antibodies against ILT-4 and another (undisclosed) cancer target. ILT-4 is expressed by myeloid cells, which are recruited to the tumor microenvironment (TME) to induce cancer growth and suppress the body's immune response. Targeting ILT-4 reverses immune suppressive effects in the tumor micro environment and enhances cancer killing.

At the ESMO Medical Congress last month, Merck presented positive data from its Phase 1 study evaluating MK-4830. Patients were treated with MK-4830 as monotherapy (n=50) or in combination with Keytruda (n=34). ***MK-4830 was active both as a single agent and in combination with Keytruda***, demonstrating an ORR of 24% (n=8/34) in patients who received the combination. All responses occurred in heavily pretreated patients, including five who had progressed on prior anti-PD-1 therapy.

These clinical data not only validate our discovery platform but also reinforce the significance of targeting myeloid cell biology – a critical next step in combating cancer. The activity we see in patients who have progressed on PD-1 therapy is particularly important, as this growing population currently has limited treatment options. Through our collaboration, we are eligible for additional $85M in milestone payments as well as royalties on worldwide product sales.

Also to note – we have unencumbered myeloid cell and TME modifying agents which are currently in development.

AGEN1181 has demonstrated the only known complete response (CR) to CTLA-4 monotherapy in endometrial cancer

Agenus was the first to discover and report on the importance of Fc engineering in optimizing CTLA-4 antibodies. Fc engineering allows an antibody to perform important functions beyond those that can be achieved with conventional antibodies. For example: it can improve the communication between other immune cells and T cells to enable optimal T cell activation, signaling, proliferation and durable memory formation. Hence, our Fc engineered AGEN1181 is a multifunctional anti-CTLA-4 antibody capable of doing just that. It is uniquely designed to improve on the tumor fighting abilities of first-generation CTLA-4 agents. Consistent with its design, we have already observed eradication of tumor (complete response; CR) at a low therapeutic dose of AGEN1181 (1mg/kg) in a patient who had a very poor prognosis. This patient had all the odds against her for an immunologic response; her cancer was microsatellite stable (MSS), did not express PD-L1 protein and she had failed prior PD-1 therapy.

In addition, this patient had a genetic polymorphism. This polymorphism typically precludes response to a first generation CTLA-4 inhibitor such as Yervoy. With its multifunctional characteristics, we believe that AGEN1181 can triple the population of patients who currently respond to Yervoy by also benefiting patients who express this genetic polymorphism. In >1000 non-melanoma patients treated with Yervoy across 10+ tumor types, only four CRs have been reported to date. In contrast, we have already observed a CR in our early Phase 1 trial with AGEN1181 monotherapy.

What's next? To develop this molecule in large indications where no active treatments exist. These include PD-1 relapsed / refractory melanoma, non-small cell lung cancer (NSCLC) and MSS cancers such as endometrial and colorectal cancers. We are currently enrolling expansion cohorts in each of these settings in contemplation of next steps in our efforts to accelerate our path to potential BLA filings.

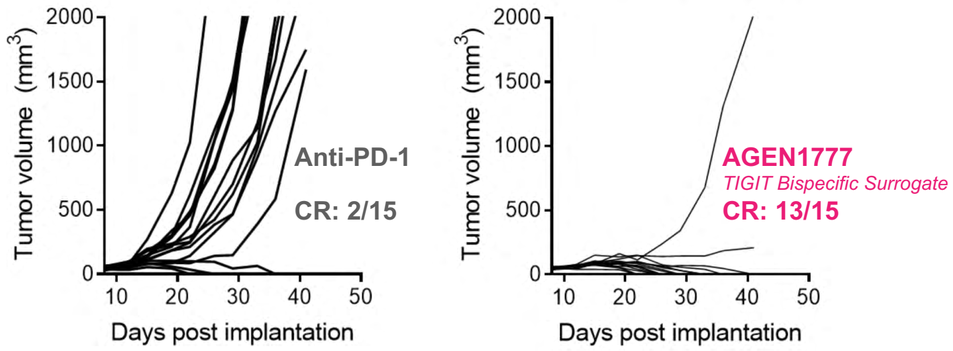
Agenus' TIGIT bispecific could be a first-in-class agent designed to be used as MONOTHERAPY in PD-1 unresponsive cancers

At AACR this year, data from a ***first-generation TIGIT*** antibody program was clear – it was inactive as monotherapy despite having a competent Fc backbone. First generation TIGIT antibodies have also shown limited activity in patients who have progressed on anti PD-1 therapy. There is a second group of TIGIT antibodies in development where the Fc backbone has been modified to be "silent" ***(Fc-silent TIGIT)***. We are yet to see clinical data from these programs, however, preclinical evidence suggests that silencing the Fc region leads blunts the antibody's ability to kill tumors. As a third alternative, the Fc region of TIGIT antibodies can be enhanced. Agenus was the first to discover and report that ***Fc enhanced TIGIT*** antibodies could improve activity against tumors dramatically.

TIGIT is overexpressed in multiple tumors and is implicated in driving resistance to anti-PD-1. Our TIGIT bispecific, AGEN1777, is Fc-enhanced and designed to be used as monotherapy against tumors that are unresponsive to PD-1 antibodies. It is a potential first-in-class molecule that co-targets another inhibitory receptor - not yet disclosed- which is also expressed on T cells and NK cells. We discovered that this co-targeting using our bispecific provides superior immune activation in preclinical models. Further, the Fc-enhanced design of AGEN1777 is also expected to confer superior tumor killing properties for reasons that relate to Fc engineering discussed above.

To this point, AGEN1777 has demonstrated dramatic tumor killing activity in a colon cancer model where PD-1 monotherapy is ineffective. This could be a significant advantage vs. other types of TIGIT antibodies that are currently in development. AGEN1777 is expected to enter the clinic in 2021.

AGEN1777 shows effective tumor control as monotherapy in a PD-1 refractory colon cancer mouse model



Agenus' QS-21 Stimulon™ adjuvant is key for the high activity of the world's most successful recent vaccine

QS-21 StimulonTM is a proven adjuvant which has been safely dosed in over 10 million individuals. It is a key component of GSK's shingles vaccine, Shingrix, which has >90% efficacy. Shingrix is one of the most successful vaccine launches in recent years, whose sales topped $2.3 billion in its second year of launch. Its benefit is durable, with sustained efficacy of more than 85% for the first four years after vaccination. Importantly, this high efficacy is maintained in the elderly, who are at higher risk of morbidity and mortality from shingles.

QS-21's advantages versus other vaccine adjuvants include: i) superior antibody responses, ii) stimulation of T cell immune response, iii) a reduction of the antigen dose required to achieve optimal immune response and iv) enhancement of immune responses to notoriously weak antigens.

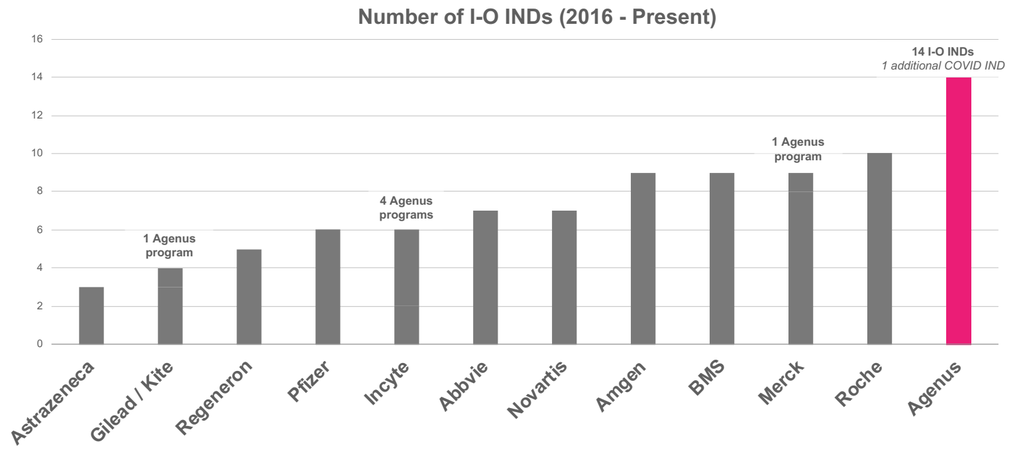
Agenus is pursuing a plant cell culture based method of QS-21 production to make this adjuvant available in much higher quantities and at a significantly reduced cost. This proprietary process is expected to reduce manufacturing costs by more than 90% relative to the current method of QS-21 production, while enabling scale-up to produce quantities that can be used in vaccines to fight COVID-19 and future pandemics.

Agenus has capabilities to rapidly progress from target discovery to manufacturing

At Agenus, we believe that having end-to-end capabilities that we control in-house is critical for our success and competitiveness. Minimizing reliance on external parties/vendors, is critical to advancing our programs rapidly from concept to the clinic. Agenus' ***VISION platform*** enables us to replicate the tumor micro environment in vitro (in our laboratory). This allows us to identify and discover ***NEW*** T cell, myeloid cell, TME conditioning and cancer cell targets. Once we identify a target for development, we have two proprietary antibody display platforms and an automated high throughput screening platform to enable rapid, high quality antibody discovery. Our Fc-engineering capabilities provide additional advantages by helping us design antibody candidates which are capable of optimally enhancing innate and adaptive anti-tumor immunity; the innate immune system is our body's first line of defense comprising of NK cells, macrophages which fight common invaders immediately while our adaptive immune system is a sophisticated and complex system comprising of B and T cells that are custom-made to protect us against every possible invader. We are then able to manufacture clinical-grade antibodies three to four times faster than industry standards at our Berkeley manufacturing facility. Thanks to these capabilities, we have delivered 14 INDs in I-O (as well as one IND in COVID-19) in the last 4 years, outpacing every large pharma in the field.

Once in the clinic, we often manage our own clinical development and operations to expedite our trials. Due to our robust clinical development capabilities, we have progressed from IND clearance to site activation and patient dosing 2.5 times faster than industry standards.

Agenus has delivered more INDs in I-O vs. big pharma



More did you knows:

- Agenus' balstilimab is the first known anti PD-1 to benefit cervical cancer patients independent of PD-L1 biomarker or histology status
- Agenus has initiated rolling BLA submission for balstilimab monotherapy in second-line cervical cancer
- The two independent studies evaluating balstilimab +/- zalifrelimab (anti CTLA-4) are the largest trials of immunotherapies published to date in relapsed cervical cancer
- The 6% CR rate reported with balstilimab + zalifrelimab could be a big and potentially curative benefit for cervical cancer patients

We have captured additional details in our prior newsletter issue, where we summarize the significance of the data presented at ESMO Virtual Congress 2020 from balstilimab +/- zalifrelimab trials in recurrent/metastatic cervical cancer.