agenus news

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Excerpts from KOL presentations during AGENUS R&D Day in NYC on Nov 15

Full R&D day recording and presentation available

Agenus R&D Day held in NYC on Nov 15 was our first in the last 4 years, and included presentations from 3 top clinical experts in I-O, Dr. Steven O'Day, Dr. Bradley Monk, and Dr. Manuel Hidalgo. In addition, Agenus clinical scientists presented the latest data and BLA filing plans for our CTLA-4 and PD-1 programs as well as an overview of our next generation CTLA-4 molecule – a potentially important and transformative breakthrough as monotherapy that can further drive the commercial differentiation of our PD-1 antibody by enabling a superior combination therapy. There were also presentations on our discovery engine and capabilities, partnership plans, expected 2019 cash and corporate milestones, and the status of AgenTus programs and plans. Full presentations are available.

In today's issue, you will find highlights from the talks of our KOLs.

Why is the mechanism of both CTLA-4 and PD-1 blockade critically important?

Why is CTLA-4 critical for delivering durable responses alone or in combinations with other agents? Can we demonstrate benefit in rapid, single arm studies?

Dr. Steven O'Day

Executive Director of the John Wayne Cancer Institute and Cancer Clinic
Director of Providence Los Angeles Regional Research
Professor of Medical Oncology and Director of Immuno-Oncology
Co-Director of Melanoma and Cutaneous Oncology Research Program

I have been at the forefront of immunotherapy and treated the first patient with a CTLA-4 inhibitor 19 years ago. Prior to immunotherapy, responses were difficult to achieve. While heterogeneity of tumors allows for rapid responses in some, aggressive clones become resistant and shorten survival. The FDA got a little worried about how one may demonstrate real benefit, and that is why they required big randomized Phase III studies with long follow-up survival data; which is difficult to achieve. I think the world is different now because responses are so durable with I-O drugs that disease control after about a year to 18 months is highly predictive of survival. It allows for benefit to be shown quicker with single-arm studies where there is significant added improvement than historic precedence.

NOW, I want to discuss CTLA-4 and PD-1 as important and complimentary pathways: these agents work through two distinctly different mechanisms. What they have in common is that they both target T-cells. However, it is important to note that blocking CTLA-4 activates T-cells early, while PD-1 activates them at a later phase of the cancer immunity cycle. This fact explains the durability we see with the combination of these agents versus monotherapy with PD-1. When you are building a battle of troops, it takes time; it takes 3 to 6 months to know whether somebody is responding to combination CTLA-4 and PD-1 therapy. While with PD-1 alone, responses take only 2 to 3 months. That is because in such patients, the T-cells are already where they need to be, and hence, they are resurrected with PD-1 monotherapy. However, in these patients you may be resurrecting exhausted T-cells, and therefore responses may not be as durable. **When you have fresh troops in the battle, such as with CTLA-4 drugs, responses are likely to be more durable, and importantly they have memory. It is for these reasons that I am a strong believer in the benefit of this combination. Agenus has a first generation CTLA-4 agent, zalifrelimab, but it also has a next generation agent, AGEN1181. This molecule has shown improved T cell priming and activation as well as depletion of suppressive regulatory T cells in preclinical models, with potential to be a best in class therapy. I am excited to be treating eligible patients with this promising NexGen CTLA-4 therapy in the clinic.**

Melanoma, for example, was considered a dismal cancer a few years ago. Now, we have 60-month outcome data for patients treated with the combination, showing 50% of patients remaining alive as long-term survivors. This is amazing data that is significant and a major improvement for these patients.

Agenus' zalifrelimab targets CTLA-4 and is advancing in combination trials with balstilimab, a PD-1 inhibitor. Then there is AGEN1181, a novel, next generation CTLA-4 agent.

In cervical cancer, there is response to PD-1 inhibitors, but the response is not as impressive as in melanoma. However, when CTLA-4 is added we are seeing increased responses which can provide significant benefit to patients with this disease. There are around 12,500 new cases of cervical cancer in the US and patients with recurrent disease, often young women, have poor prognosis. Cervical cancer is attractive for immunotherapy because it is a virally induced disease, where CTLA-4 combination has shown to increase response rates to exceed 20%. **Agenus' CTLA-4 and PD-1 inhibitors are advancing rapidly for a potential BLA filing to address this debilitating disease.**

Now on the opposite spectrum, there are tumors that are just not responsive to immunotherapy. The role of combinations in these tumors, also known as cold tumors, is very, very important, and **the pipeline that Agenus offers addresses the possibility to individualize combinations to elicit responses in these patients. This includes drug candidates like Agenus' CD137 agonist and bispecific molecules.**

Highlighting the criticality of I-O therapies and Agenus' robust portfolio to achieve optimal benefit with combinations for cancer patients

Dr. Manuel Hidalgo

Chief of the Division of Hematology and Medical Oncology
Weill Cornell Medicine and New York Presbyterian/Weill Cornell Medical Center

Immuno-oncology and precision therapy are two of the new pillars of cancer treatment. PD-1 is an important I-O target. PD-1 inhibitors have achieved a significant number of approvals in many tumor types. However, there is much room for improvement, which can be achieved by evaluating combination therapies. CTLA-4 is a foundational I-O target, and the combination of CTLA-4 and PD-1 is more effective than PD-1 alone in treating many types of cancers. Melanoma, renal cell carcinoma and non-small cell lung cancer are three major examples – we have discovered that these cancers are among many in being sensitive to immune therapy.

Highlighting the advantage of Agenus in driving higher responses with its CTLA-4 + PD-1 combinations in patients with cervical cancer

Dr. Bradley J. Monk

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Cervical cancer is the fourth leading cause of cancer in women and the fourth leading cause of death. It is a very difficult disease to treat. There will be 4,250 deaths this year in our country from cervical cancer. In 2006, topotecan was approved, and 8 years later, in 2014, Avastin was approved to treat this devastating disease. Ultimately, last June, pembrolizumab was approved with a single arm trial with 14% overall response rates in a small trial of 77-patients – so as you can see because of this large unmet need, a small single arm trial led to an approval. I believe that Agenus can do even better because the addition of CTLA-4 blockade makes warm tumors hot, and we are already seeing important trends of higher benefit in several trials with such combinations.

Agenus' CTLA-4 + PD-1 combination trial is moving rapidly in the clinic, having achieved target enrollment, and is ahead of the competition. The company expects to file a BLA in 2020 in the setting of recurrent, metastatic cervical cancer, where there is a need for transformative therapies. In fact, Agenus' combination could represent a best in class therapeutic option for these patients. We are excited to bring this combination to our patients.