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Frequently Asked Questions and Answers

Thirteen Agenus I-O discoveries are currently advancing in Agenus-sponsored as well as collaborator-sponsored clinical trials. On August 6, 2020, our internal and external experts convened to share updates from our portfolio programs. Today's Agenusnews provides highlights of these discussions and answers frequently asked questions.

Highlights From Agenus' R&D Call

We plan to initiate our rolling BLA filing for balstilimab (PD-1) monotherapy in second-line cervical cancer this quarter. Our combination trial with zalifrelimab (1st generation CTLA-4) in the same indication has completed accrual; BLA plans for the combination are underway. Data from our clinical trials in other cancers show that balstilimab (bali) and zalifrelimab (zali) are active in other tumor types as well. Dr. Bree Wilky presented new responses to zali monotherapy in PD-1 refractory cancers (3 partial responses). She also discussed zali's potential in treating angiosarcoma, an aggressive cancer, based on responses which have been achieved. We recently announced a partnership with Betta Pharmaceuticals, who will be developing bali and zali in Greater China. This partnership has netted Agenus $35M in upfront payment and equity investment; with up to $100M in milestones plus royalties on net sales.

We are advancing several additional novel antibodies. They include our next-generation CTLA-4 antibody, AGEN1181, as monotherapy and in combination with bali. Dr. Chuck Drake highlighted a new complete response (CR) by PET to AGEN1181. This is the second complete response to AGEN1181, which he indicated was highly noteworthy for an early clinical trial that is generally designed to evaluate safety. These data on bali/zali and 1181/bali were discussed in more detail in the last issue of our newsletter.

On our call, we also noted evidence of durable stable disease in patients treated with another one of our novel antibodies, AGEN2373, a differentiated CD137 agonist. It is noteworthy that no evidence of liver toxicity was reported at 1mg/kg dose, which has hampered the development of a competitor antibody. Next, AGEN2373 is on track to advance into combination studies with bali this Fall.

Outside of our I-O portfolio, we are also advancing various therapeutic programs against COVID-19. A trial for AgenTus's iNKT cells in COVID is expected to commence this Fall. We are also establishing a proprietary method of producing our highly potent QS-21 adjuvant, which enhances antibody titers in SARS-CoV-2 models. Key advantages of this method include a renewable raw material source, which is expected to support scalable production of QS-21 and yield as much as 90% reduction in costs. This has the potential to generate billions of doses of QS-21 for application in pandemic vaccines such as one against COVID-19.

Agenus Answers Questions From The Field

Balstilimab (PD-1) / Zalifrelimab (first-gen CTLA-4)

1. **How many responses, including CRs, have been reported to date in bali and zali trials?**

   In bali/zali trials, we have reported 28 responses to date among 236 patients who were treated as of previous reports. These 236 patients encompass multiple solid tumor types and were enrolled across zali monotherapy, bali monotherapy and bali + zali trials. Subsequently our trials have enrolled a total of more than 450 patients; we will be disclosing data on these additional patients at upcoming medical conferences.

   Below is the breakdown of the 28 responders that we have disclosed to date across 6 different cancers:

- **Bali +/- zali trials of 2L cervical cancer**
  - 6 responses including one **1 CR** with bali monotherapy in the first 42 patients reported. Responders include patients with PD-L1 negative status. To put this into perspective, Keytruda, the only approved PD-1 agent in this setting, has achieved 14% response rate but in a subset of patients who are PD-L1 positive. We expect to present updated data from this trial at a major medical conference this year.
  - 14 responses including **4 CRs** with bali + zali in the first 55 patients reported. Responders here also include patients with PD-L1 negative status. We expect to present updated data from this trial at a major medical conference this year.
- **Zali monotherapy**
  - 3 responses (angiosarcoma, SCCHN and neuroendocrine cancer) among 43 patients in our Phase 2 study which is enrolling patients who are PD-1 refractory.
  - 1 CR in an angiosarcoma patient out of 38 patients enrolled in our first Phase 1 trial. As reported by Dr. Wilky during our R&D call, this patient has been in remission for 4 years with no sign of cancer recurrence.
- **Bali monotherapy in other cancers**
  - 3 responses (one each in cervical, ovarian, breast cancer) in the Phase 1 dose escalation study among 38 patients, as reported during ESMO 2018.
- **Bali + zali in other cancers**
  - 1 response (ovarian cancer) among 20 patients treated in our first Phase 1 dose escalation study of bali + zali. This data was also reported during ESMO 2018.

2. **Will Agenus be filing BLAs for bali +/- zali in 2L cervical cancer solely based on data presented so far?**

   Our full data set for BLA submission is **substantially** larger than what we have previously presented. For reference, accelerated approval of Keytruda in cervical cancer was based on data collected from a cohort of 98 patients, 77 of whom were PD-L1 positive. Our fully-enrolled bali monotherapy and bali + zali trials include approximately double the patient population that yielded accelerated approval for Keytruda in cervical cancer. Our trial includes patients regardless of their PD-L1 expression status and encompasses all major cervical cancer histologies.

3. **What are the anticipated BLA filing timelines for bali monotherapy and bali + zali? When will Agenus present updated data from these trials?**

   We are on track to initiate a rolling BLA submission for bali monotherapy this quarter (Q3 2020) with our CMC module. We plan to conclude submission this year.

   Our bali + zali trial is also fully enrolled. We have cleared the expected median patient follow-up time to present mature observations of clinical activity. We plan to have a completed data packet for submission by year end and will define our filing plans based on continued dialogue with the FDA. Thus, our teams plan to have both filings ready for submission this year. We will keep our stakeholders informed of our progress. We plan to present data from both studies at a major medical conference this year.

4. **Will Agenus' BLA filings be directed towards PD-L1+ cervical patients, similar to Keytruda?**

   We have reported ~14% overall response rate (ORR) across all cervical cancer patients treated with bali monotherapy, inclusive of PD-L1 negative patients. On the other hand, ~14% ORR noted with Keytruda treatment is restricted to a population of patients expressing PD-L1. In this sub-population, we observe improved response rates with bali monotherapy over Keytruda (data to be reported at an upcoming conference).

   With bali + zali, we previously reported ~26% ORR among the first 55 evaluable patients, regardless of their PD-L1 expression status. In contrast, currently-available therapies have a response rate of ~10-14%.

   Thus, our agents could represent potential best-in-class treatment options for ALL metastatic cervical cancer patients who have stopped responding to previous treatments. Given this important differentiation vs. Keytruda, we expect to engage with the FDA to advance our therapies to all eligible patients.

5. **Is there a minimum response rate that needs to be met with bali / zali to have a viable path for accelerated approval?**

   The FDA's regulations do not define a minimum response rate to qualify for accelerated approval. However, an important reference is the accelerated approval granted to Keytruda for 14% response rate in patients with PD-L1 positive cervical cancer. As mentioned earlier, both bali monotherapy and bali + zali have demonstrated improved therapeutic benefit over this precedent and available chemotherapies. Despite Keytruda's accelerated approval, there is no standard of care in second-line cervical cancer because its clinical benefit is pending validation from a larger confirmatory trial. Thus, there remains a large unmet need for effective therapies in this setting. For these reasons, we anticipate that leveraging the accelerated approval pathway will remain viable for bali +/- zali.

6. **How does Agenus intend to expand development of bali and zali beyond cervical cancer?**

   CTLA-4 + PD-1 is the most validated I-O + I-O regimen with 6 approvals in indications including cancers of the skin, lung, kidney, liver, and colon. Further, PD-(L)1 agents have been approved as monotherapy or in chemotherapy combinations in >15 cancers. The number of approvals is expected to grow, particular in early stage disease (adjuvant/neo-adjuvant setting). This is expected to double the market opportunity, which exceeded $20B in 2019. Combined sales of CTLA-4 and PD-1 antibodies are projected to exceed $50B by 2025.

   We plan to expand the use of bali +/- zali to other large indications where CTLA-4 + PD-1 antibodies have approval, such as melanoma, NSCLC and RCC. We are evaluating opportunities to drive broader use of our agents via inclusion in NCCN guidelines. By deploying this strategy, securing a 5-10% share in these cancers alone could translate into a $1B+ annual revenue opportunity for Agenus.

AGEN1181 (Next-Generation, Multipurpose CTLA-4)

7. **How many patients have been treated with AGEN1181? How many responses, including CRs, have been reported to date?**

   As of our R&D update call on August 6, 2020, 36 patients have been treated with AGEN1181 as monotherapy or in combination with bali. Twenty-six of these patients are considered "evaluable" in that they have completed scans to assess their disease status. Nine of these patients have yet to undergo tumor assessment scans and in one case we are awaiting results of the completed scan. Among evaluable patients, we have previously reported **1 CR** and **1 CR by PET** - both in aggressive cancers with poor prognosis (endometrial). Both patients were treated with low doses of AGEN1181 (1mg/kg or lower). Importantly, they both expressed a genetic polymorphism that would make them less likely to respond to a first-generation CTLA-4 therapy such as Yervoy. Taken together, AGEN1181 demonstrates potential to expand the therapeutic reach of the CTLA-4 drug class. It is designed to provide benefit to 3X more patients vs. Yervoy.

8. **How does Agenus intend to position AGEN1181 in the I-O market? What indications will be pursued for development?**

   We plan to develop AGEN1181 as monotherapy and in combinations. Based on our observations, AGEN1181 is active in tumors that are not responding to first-generation I-O therapy. This gives us an important development advantage. We plan to pursue accelerated approval strategies in highly prevalent cancers where no active treatments exist. These include PD-1 refractory NSCLC, melanoma, and MSS tumors such as endometrial and colorectal cancers. There are >40,000 eligible patients in the US for these initial indications alone. We may also

incorporate patient enrichment strategies based on biomarkers that could enable a more rapid development path.

9. Has Agenus launched expansion cohorts to evaluate AGEN1181 in these indications? Could data from these cohorts support approval?

We have launched expansion cohorts to evaluate the clinical benefit of AGEN1181 in these indications. We will be evaluating AGEN1181 as monotherapy and in combination with bali at active doses that have been cleared by the safety monitoring committee to date (0.3-1mg/kg). This positions us to build a robust data package to accelerate our path to potential BLA filings. Upon confirmation of clinical benefit in these cohorts, we intend to rapidly and nimbly expand the development program at the recommended dose level to support potential accelerated approval strategies.

10. Is Agenus continuing to dose escalate AGEN1181 despite launching expansion cohorts?

In parallel to dosing patients in our expansion cohorts, we will continue to dose escalate AGEN1181 since we have yet to reach the maximum tolerated dose. Our aim is to identify the optimal dose at which we can safely deliver maximal therapeutic benefit to patients.

11. When is Agenus expected to present updated data from its AGEN1181 trial?

We anticipate presenting updated data at a major medical conference this year.

COVID-19 Programs

12. When is the first COVID-19 patient expected to be dosed with AgenTus's iNKT cell therapy?

The FDA has already cleared the IND to dose patients with our iNKT cell therapy. This trial will be conducted at New York Presbyterian Hospital. We are working with our collaborators to address a final set of protocol amendments and anticipate dosing the first patient in the very near term.

13. How does Agenus expect its plant cell culture derived QS-21 to support pandemic vaccines? How soon can Agenus supply QS-21 at scale using this process?

QS-21 stimulon™ 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 offers >90% efficacy and durable benefit. Importantly, this high efficacy is maintained in the elderly, who are at higher risk of morbidity and mortality arising from pandemic infections such as COVID-19. However, the current source of QS-21 is from bark extracts and this raw material has multiple disadvantages: limited supply, variable quality depending on environmental conditions and high cost of purification. These disadvantages make it prohibitive for inclusion in high-volume, low-margin vaccines against pandemic pathogens.

Agenus is pursuing a plant cell culture based method of QS-21 production. This is a renewable raw material source. Upon application of our proprietary manufacturing process, this method could yield high quantities of QS-21, potentially enough for billions of doses of vaccines. At the same time, this process is expected to reduce manufacturing costs by more than 90% relative to the bark extract process. The program is currently advancing to GMP scale-up, which we anticipate will be completed in as early as 18 months. This would enable much broader use of this adjuvant, including for vaccines against future pandemics. Another important application could be flu vaccines, a multi-billion dollar market where current approaches only demonstrate 40-60% efficacy.

The WHO has noted that a COVID-19 vaccine would need to be ~70% efficacious to stop spread of the virus. Current vaccines in development will likely need help to meet these standards and be safe across different age groups. These are challenges for which QS-21 is well suited. It is compatible with all known COVID-19 vaccine formats being pursued.

Financial Operations

14. How does Agenus intend to manage its cash runway beyond Q3 2021?

We ended the second quarter of 2020 with a cash balance of $79 million. Since then, we have already received $35 million from closing our recent partnership with Betta Pharmaceuticals. We also anticipate cash inflows from meeting milestones in our existing partnerships. Based on these projections and our current plans, we anticipate our cash runway to extend to Q3 2021.

We expect to launch our first commercial product in 2021, which would transform us into a revenue-generating company. We are also exploring partnership opportunities that would accelerate the development of our portfolio while partially monetizing its value. We expect these developments to support our cash position substantially beyond Q3 2021.

15. Is Agenus working on formalizing additional partnerships? Is a new partnership expected to be larger in scale than those announced in the past year?

We are in active discussions with a number of companies encompassing several assets in our portfolio that could unlock significant value in the I-O market. Our business strategy is to out-license a portion of our portfolio to generate meaningful upfront and long-term financial value, while bringing these discoveries to patients as efficiently as possible. We intend to retain U.S. rights to the majority of our pipeline to build our future commercial business. We will share further updates at an appropriate time.