BIG DATA – How does Agenus use this exciting new advance for delivering cures to patients?

Two recent peer-reviewed Agenus publications provide early glimpses

Data released from recent trials are providing unequivocal evidence of the benefits of combining CTLA-4 with PD-1. These two antibodies have distinctly different mechanisms of action, each critically important in unleashing immune attack against cancer. Combinations of these agents have delivered remarkable and more sustainable benefit to patients across multiple tumor types. In fact, some of these responses have been curative in previously untreatable cancers. We have seen complete responses with our pivotal stage CTLA-4 candidate, Zalifrelimab (AGEN1884). One such patient with angiosarcoma has had a complete remission which is now beyond 3 years. This response is the only one of its kind to anti CTLA-4 monotherapy in this disease, a debilitating and fatal cancer with no effective treatments.

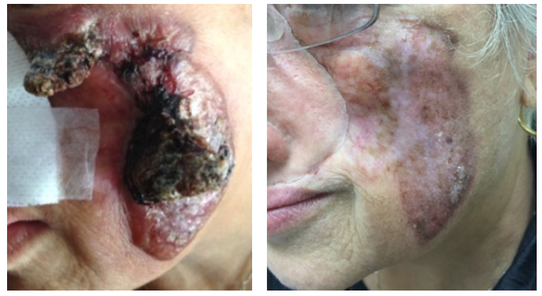
The question of why this patient has had a complete response is being studied by our bioinformatics, genomic, and computational teams. They set out to investigate this case to uncover the clues that would enable us to help more patients in a targeted manner, using the broad range of I-O agents in our portfolio. In our quest to perfect the application of big data, we have used our genomics platform to examine thousands of tumors and identify drivers of response to immunotherapy across different cancer types. We published our findings in two separate peer-reviewed journals this August.

Our CTLA-4 antibody, Zalifrelimab, has produced the only known complete response to CTLA-4 monotherapy in angiosarcoma

Angiosarcoma is an uncommon and a highly aggressive soft tissue cancer. Responses to chemotherapy tend to be short-lived and patients eventually succumb to their disease. Hence, effective therapies are badly needed to treat angiosarcoma patients. Drs. Wilky and Trent have been exploring the benefit of checkpoint inhibitors for angiosarcoma patients. In their Phase 1 trial they used Zalifrelimab to treat a patient who had a recurrent and disfiguring angiosarcoma. At three years out, this patient remains cured and has returned to her normal life. The observations were recently published in a manuscript 'Angiosarcoma patients treated with immune checkpoint inhibitors: a case series of seven patients from a single institution' by the *Journal for ImmunoTherapy of Cancer*.

In this study, seven angiosarcoma patients were treated with checkpoint inhibitors, including anti-PD-1 (pembrolizumab), anti-PD-1 (pembrolizumab) plus axitinib and our anti-CTLA-4 (Zalifrelimab). Five patients exhibited response to therapy, highlighting the benefit of immunotherapy in this cancer, but only one patient had a complete response (CR); she was treated with monotherapy Zalifrelimab. In fact, she responded to the lowest dose, 0.1mg/kg, despite being heavily pretreated, including prior radiation.

Figure 1 Angiosarcoma of the cheek treated with Agenus' zalifrelimab



Before After

How does Agenus' bioinformatics group use BIG DATA to determine who is likely to respond?

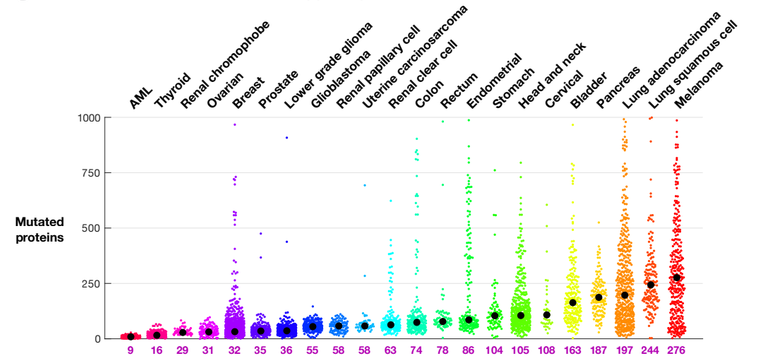
Our expert bioinformaticians and clinicians have been studying this question. In the case of this patient, they examined the DNA and RNA from the tumor to identify a fingerprint capturing key drivers of response. The intent is to use our finding in order to identify more patients who may benefit from this therapy. ***We found evidence that 31 fusion genes predicted to generate aberrant proteins, or neoantigens, existed in this tumor. The immune system generally directs its army of cells to the tumor environment to promote killing when proper triggers of recognition are activated. The number of fusions in a tumor may represent one fingerprint of response: those tumors with many fusions may be more likely to respond to Zalifrelimab treatment. We believe, findings of this nature will play a key role in helping us determine the right patient populations for the right treatment or the right combination treatment.***

Our state-of-the-art genomics platform and knowledge predict tumors that are responsive to immunotherapies

As described above, our genomics platform can be leveraged to suggest responders to treatment, such anti-CTLA-4/anti-PD-1 antibodies. To this end, we published a few findings in Frontiers in Immunology titled Mutation-Derived Neoantigens for Cancer Immunotherapy.

We applied our computational platform to the thousands of tumors that have been profiled by The Cancer Genome Atlas (TCGA). While other researchers have calculated overall mutation rates in various cancers, we ***enhanced the relevance of this metric by focusing on mutations that are recognized by the immune system***. Using our platform, we identified and cataloged mutations from over 10,000 tumors. In fact, melanoma and lung cancers responding to anti-CTLA-4 and anti-PD-1 treatment, have the most mutated proteins. By grouping lung cancers by patient's smoking history, we find that tumors from smokers have on average four times as many mutated proteins as from non-smokers. While anti-PD-1 therapy is increasingly adopted in lung cancer, extrapolating from our results, lung tumor response to therapy may be higher in smokers than in non-smokers.

Figure 2 TMB across tumor types profiled from TCGA data



Immunotherapies are also approved in colon, endometrial and bladder tumors; these tumors have many mutated proteins as well. Microsatellite-instability-high (MSI-H) tumors, a class of tumors with many mutations, occur in these organs. Like the angiosarcoma patient with many fusion mutations, we found that MSI-H tumors frequently respond to immunotherapy more frequently, particularly to CTLA-4 + PD-1 combination therapy.

Our lead CTLA-4 and PD-1 programs are advancing in BLA path studies in recurrent, metastatic cervical cancer. As seen in **Figure 2**, this is a tumor type with a relatively high mutation burden, where CTLA-4 + PD-1 combination therapy is demonstrating better responses. **Such insights, combining our understanding of the landscape of tumor antigens with knowledge of how the immune system recognizes tumors, together with our broad I-O portfolio empowers us to design high impact trials for rapid approval. These capabilities along with our ability to use findings from our own analysis of BIG DATA is allowing us to identify resistance mechanisms and novel, druggable targets to achieve ultimate cures with our first and best-in-class therapies.**

Figure 3 Correlation between TMB and smoking status in lung cancer