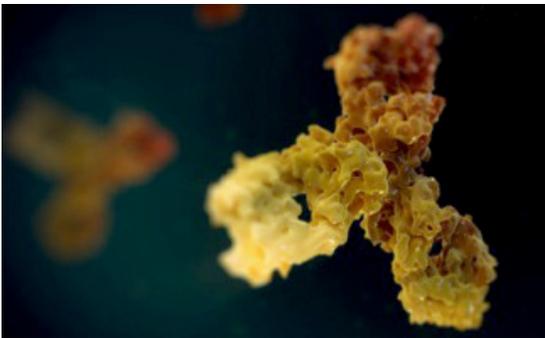


## Targeting Cancers with Agenus' Proprietary Combinations

### How CTLA-4 and PD-1 Combination Cures Patients

*CTLA-4 and PD-1 are the first and only I-O antibodies to be approved as combination agents. The available data so far suggest that this combination improves both response rates and durability of response—akin to potential cure for cancer patients.*



In aggressive cancers, like Melanoma, Microsatellite Instability-High Metastatic Colorectal Cancer (MSI-H CRC), Small Cell Lung Cancer and Renal Cell Carcinoma, the addition of CTLA-4 to PD-1 improves overall response rates compared to PD-1 treatment alone.

In some of these tumors, the addition of CTLA-4 to PD-1 has doubled response rates (see [link](#)) compared to patients who receive PD-1 monotherapy. Very importantly, the addition of CTLA-4 to PD-1 results in improving the duration of response in some of these cancers. In patients with metastatic melanoma ~78% of patients are alive and treatment free at 3 years, a significant improvement over either PD-1 (54%) or CTLA-4 (32%) alone ([SITC 2017](#)).

*Agenus' strategy in cervical cancers is to pursue both PD-1 monotherapy and combination therapy for potential rapid approval. For the monotherapy approach, we have an opportunity for accelerated approval in the 2L+ setting, where PD-1 has been approved, but response rates remain low at only ~14%. The addition of CTLA-4 provides an opportunity to improve both response rates and durability of responses for cervical cancer patients in this setting.*

## Second-line (2L) Cervical Cancer: A Compelling BLA Strategy for Agenus

---



Cervical cancer represents a tumor type where combination of CTLA-4 and PD-1 could improve response rates meaningfully.

Almost all cervical cancer results from infection with the sexually-transmitted virus, HPV. HPV encodes oncogenes which not only drive cancerous growth but also can be recognized by the patient's T lymphocytes as "non-self". As a result of this immune recognition, cancer cells up-regulate PD-L1 to defend against immune attack.

Over 80% of cervical cancers express high levels of PD-L1 when the patient is first seen. The use of antibodies that bind to PD-1 and prevent PD-L1-mediated T cell inhibition, such as AGEN2034, enables killer T cells to more effectively attack and eliminate cancer cells in this setting. When these killer cells destroy the cancer cells, they release other non-self-antigens that result from mutations within the cancer cells. Adding CTLA-4 to PD-1 is expected to increase the variety of killer T cells against a broad spectrum of features of each patient's cancer. This is expected to lead to more effective tumor destruction, increased response rates, and importantly, durable responses. Combination CTLA-4 and PD-1 is expected to result in better near-term responses and help achieve a greater percentage of lasting responses as measured by 3-year survival curves and beyond.

Cervical cancer is most frequently diagnosed among women aged 35-44. There are 13,000 new cases of cervical cancer annually and 4,000 deaths in the US alone.<sup>1</sup>

These cancers impact patients and oftentimes very young families. While the very recent approval of PD-1 monotherapy for 2L cervical cancer has offered hope, substantial opportunity exists to improve current response rates of 14% and PFS of ~2 months with PD-1 monotherapy.

---

<sup>1</sup> Reference: American Cancer Society, Cervical Cancer US Statistics 2018  
<https://www.cancer.org/cancer/cervical-cancer/about/key-statistics.html>

## Agenus' path for rapid approval

---



CTLA-4 and PD-1 therapies have been approved in relatively small trials, including single arm trials evaluating benefit in a few dozen patients using surrogate endpoints. Approvals have been achieved in as little as 4 years following first in human studies. With this precedence, our AGEN1884 (CTLA-4) and AGEN2034 (PD-1) regimen represents the most clinically advanced combination with registrational potential.

- Earlier this year, PD-1 monotherapy was approved in 2L cervical cancer via the accelerated approval pathway in a small trial, with <100 patients, and response rates ~ 14%. Based on early signals from our clinical trial, we are pursuing a similar path with AGEN2034 monotherapy in this indication. This Agenus [trial](#) is actively accruing patients with an anticipated BLA filing of 2020.
- Given the immunogenicity of cervical cancer, our strategy for pursuing the combination of AGEN1884 and AGEN2034 for potential approval is designed to improve response rates and durability of response vs. PD-1 alone. This represents a second path to accelerated approval, also with an anticipated BLA filing in 2020.

On a very positive note, the regulatory landscape is quickly changing to keep pace with rapidly advancing science. Very recently, the FDA commissioner outlined a [plan](#) to modernize drug development by seeking partners to deliver effective drugs with innovation and speed for patient access. Agenus' mission is very much aligned with speedy innovation.

**We are also building on our first-generation PD-1 and CTLA-4 therapies with our next generation monospecific and bispecific antibodies designed to address tumor resistance pathways and improve effector T cell function.**