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CTLA-4 + PD-1 Inhibitors Demonstrate Remarkable Efficacy and Durability of Response at ESMO 2019

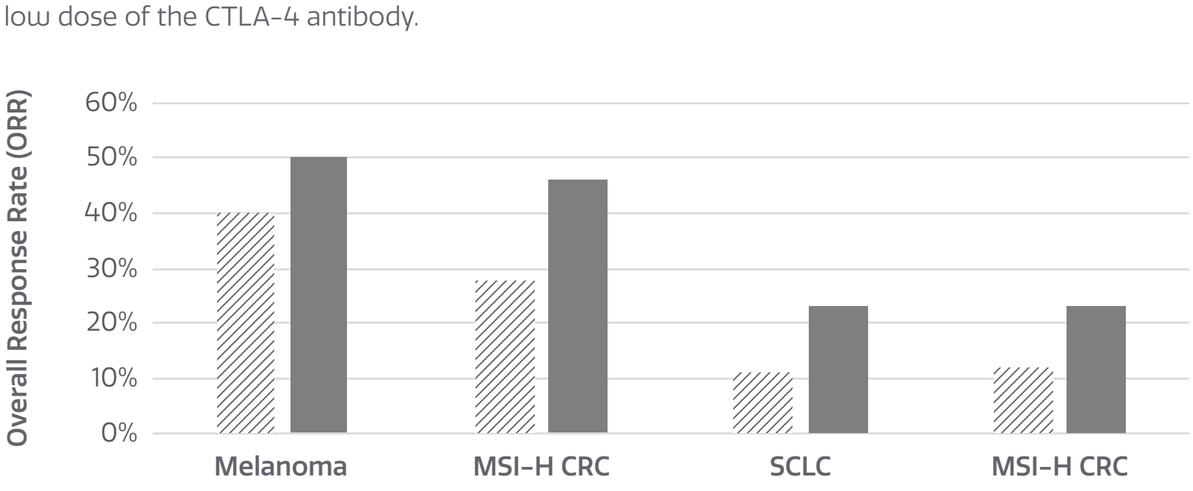
AGEN's Lead Assets Inhibit CTLA-4 and PD-1 and Are Advancing in BLA Path Cervical Cancer Trials

One of the most significant benefits of combining anti-CTLA-4 and anti-PD-1 therapy is the nearly doubling in response rates that has now been demonstrated across multiple tumor types. In addition, CTLA-4 + PD-1 combinations have produced deep, durable and potentially curative responses in some patients with difficult to treat tumors. To this end, in 2018, the Nobel Prize in Medicine was awarded to Dr. James Allison and Dr. Tasuku Honjo for the establishment of CTLA-4 and PD-1 as cancer immunotherapy targets.

Agenus is advancing two lead assets targeting CTLA-4 (AGEN1884) and PD-1 (AGEN2034) in pivotal trials targeting recurrent or metastatic cervical cancer. We presented data at ESMO last year demonstrating clinical activity with both of these assets. Specifically, with AGEN1884, we have seen a complete and durable response in a patient with refractory angiosarcoma. We also reported positive early clinical data from our combination study of AGEN1884 and AGEN2034 (anti PD-1). As of the data cut-off of July 2018, 44% of the 16 evaluable patients experienced clinical benefit[1], including a partial responder and 6 patients with stable disease. We have already seen signs of durable response from our combination therapy in these patients who presented with difficult to treat cancers. For example, we observed the partial response as early as 2 months from treatment initiation, which continued at the time of data cut-off. Disease stabilization was observed as early as 6 weeks and maintained for some patients through 18 weeks of follow-up. We expect to present interim analysis data for the combination from our pivotal study by the end of this year as well as file our first BLA in 2020.

CTLA-4 + PD-1 Therapy Produces High Response Rate and Durability in Cervical Cancer

We expect our CTLA-4 + PD-1 combination to improve response rates compared to PD-1 monotherapy, and more importantly, enhance the durability of response. Currently, there is only one approved immunotherapy to treat second line cervical cancer, offering a response rate of ~14% in PD-L1+ patients. At ESMO this year, we saw new data emerge highlighting how a CTLA-4 + PD-1 combination regimen can produce a response rate of ~23% in this setting, even using a low dose of the CTLA-4 antibody.



Source:
Melanoma (1L): Opdivo® package insert; MSI-H CRC (Previously treated): Opdivo® package insert; SCLC (2L): Checkmate-032; Cervical (2L): Keynote-158 and Checkmate-358 (all comers, regardless of PD-L1 expression)

The response rate was even higher in treatment naïve patients or those receiving a higher dose of the CTLA-4 antibody. More importantly, the combination was well tolerated and at a median follow up of >10 months, the responses were durable. Additionally, responses were seen in low PD-L1 negative expressers, who currently do not benefit from approved PD-1 monotherapy. These data reinforce the potential of our lead programs and we are excited to advance these therapies to patients in need.

CTLA-4 + PD-1 Combination Significantly Enhances Longevity of Response in Multiple Malignancies

At ESMO 2019, five-year survival data following CTLA-4 + PD-1 targeting treatment was presented in the first line melanoma setting. This is the longest follow up for any Phase 3 immunotherapy combination study. In total, 945 patients were treated with the combination or either agent as monotherapy. Once thought to be an incurable disease, more than half of melanoma patients treated with the combination were alive at 5 years. This significantly exceeded the benefit seen when either asset was administered as a single agent. Importantly, the number of complete responses also increased at analyses performed at the 3-, 4- and 5-year mark. Patients who received the combination continued to benefit from it for a long duration of time even after going off study treatment (see table below) – with no loss in quality of life.

	Anti CTLA-4	Anti PD-1	Anti CTLA-4 + PD-1
Treatment-Free Interval in Patients Who Discontinued Study Therapy	1.9 months	1.8 months	**18.1 months**
Proportion of Patients Alive and Treatment-Free at 5 Years	45%	58%	**74%**

Source: J.M. Larkin et al.; Checkmate-067 ESMO 2019 presentation

Importantly, we have seen remarkable durability with CTLA-4 combinations in more than one tumor type. In a Phase 3 lung cancer study presented at ESMO this year, the combination was the first and only dual immunotherapy to demonstrate improved overall survival versus chemotherapy in this setting. With a minimum follow-up of 29.3 months, patients treated with the combination experienced a nearly four times longer duration of response compared to patients treated with chemotherapy, regardless of PD-L1 expression level. In fact, CTLA-4 combinations also improved outcomes compared to PD-1 + chemotherapy. CTLA-4 combination therapy was well tolerated and now offers an option to patients who cannot tolerate chemotherapy.

	Chemotherapy	Anti CTLA-4 + PD-1
Overall Survival	13.9 months	**17.1 months**
Duration of response (≥1% PD-L1)	6.2 months	**23.2 months**
Duration of response (<1% PD-L1)	4.8 months	**18 months**

Source: S. Peters et al.; Checkmate-227 ESMO 2019 presentation

Given these data, we are not only enthusiastic to advance AGEN1884 in combination studies, but also our next-generation CTLA-4 antibody, AGEN1181, in the clinic. We believe this antibody has the potential to expand the benefit of CTLA-4 inhibition to a wider patient population, including an estimated 40% of patients who are unlikely to fully benefit from first generation CTLA-4 therapies due to a genetic predisposition. We anticipate commencing combinations studies of AGEN1181 with our PD-1 agent by the end of this year.

[1] Clinical benefit is defined as complete responses, partial responses or disease stabilization.