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Balstilimab Monotherapy and Balstilimab plus Zalifrelimab Trials Presented at ESMO

Largest Reported Studies of Immunotherapies in Recurrent/Metastatic (R/M) Cervical Cancer Show Clinical Activity Beyond Currently Available Therapies

The European Society for Medical Oncology (ESMO) Congress is Europe's most notable platform for presenting clinical data. Dr. David O'Malley, Professor of Obstetrics and Gynecology at The Ohio State University College of Medicine and the Director of the Division of Gynecologic Oncology, The Ohio State University Comprehensive Cancer Center, presented late-breaking preliminary data from two independent studies evaluating balstilimab alone as well as balstilimab in combination with zalifrelimab in relapsed / metastatic cervical cancer. *In today's newsletter, we summarize this presentation and highlight the significance of these data.*

Cervical cancer patients have a substantial need for more effective treatments. The American Cancer Society estimates there will be nearly **14,000 new cases and 4,300 cervical cancer deaths in the United States in 2020.** There are no effective treatment options for a broad population of patients with this cancer **(see Table 2)**. Keytruda, the only approved immunotherapy for cervical cancer patients, has demonstrated an ORR of 14%, but its benefit is restricted to patients whose cancers express a specific biomarker (PD-L1). Thus, there is a need for new therapies that reach a broader population of patients who can benefit. **Based on our data presented at ESMO, balstilimab +/- zalifrelimab have shown activity in all cervical cancer subtypes, independent of histology and PD-L1 status, and may represent important options for the treatment of second-line cervical cancers. In our efforts to make our therapies available to patients with second-line cervical cancer, we have initiated our rolling BLA submission for balstilimab.**

Balstilimab is the first known PD-1 inhibitor with broad activity in all cervical cancer subtypes

In two separate trials which have completed enrollment of over 300 patients in total, balstilimab and balstilimab plus zalifrelimab have shown benefit regardless of the patient's tumor histology or PD-L1 biomarker status. To be more specific, **balstilimab demonstrated a 14% objective response rate (ORR) across all patients with no restrictions based on histology and PD-L1 status.**

Importantly, in PD-L1 positive tumors, balstilimab demonstrates an ORR of 19%, which is a ~40% increase over Keytruda (14%). Further, in peer-reviewed publications, Keytruda reported no responses in patients whose tumors are PD-L1 negative. On the other hand, in our trial, balstilimab benefited PD-L1 negative patients with an ORR of 10% **(see Table 1).** These results are significant because studies suggest that as many as 60% of cervical cancer patients could be PD-L1 negative.

In the most prevalent cervical cancer histology (squamous cell carcinoma), balstilimab demonstrated an ORR of 18%. Furthermore, balstilimab also benefited patients with adenocarcinoma and adenosquamous carcinoma, populations not frequently represented in clinical trials. These data highlight the ability of our therapies to demonstrate responses across a broad population of patients.

Table 1: Tumor Response with balstilimab +/- zalifrelimab

	Balstilimab n=160*	Balstilimab + Zalifrelimab n=143*
Response rates (ORR)	**14%**	**22%**
PD-L1 (+)	19%	27%
PD-L1(-)	10%	11%
Complete Response	2%	6%
Partial Response	12%	16%
Median duration of response (months)	15.4 months	Not Reached
ORR by tumor histology		
Squamous cell carcinoma	18%	27%

** mITT population; treatment related discontinuation was measured in the safety population: n=161 for bali and n=155 for bali + zali. Data cut-off: July 31, 2020*

Zalifrelimab plus Balstilimab increases response rates and complete responses

The addition of CTLA-4 inhibitor to anti-PD-1 therapy has been shown to substantially increase response rates across numerous cancers. Consistent with these observations, the combination of zalifrelimab and balstilimab demonstrates substantial expansion of benefit to patients. **The combination demonstrates an ORR of 22% in all patients regardless of PD-L1 status or histology and an ORR of 27% in patients with PD-L1 positive tumors or in patients with squamous cell histology (Keytruda demonstrates an ORR of 14% in PD-L1 positive**

patients). Responses to the combination are also seen in PD-L1 negative patients, who are excluded from the Keytruda label **(see Table 1). Further, the combination also produces durable responses (median is not yet reached, with some responses exceeding 16.6 months).**

Our combination also increased rates of complete **tumor elimination (complete response rate of 6%), which is at least 2 times higher than what has been reported with PD-1 monotherapies (see Tables 2 & 3). This increase in proportion of patients whose cancers disappear is potentially significant, since cervical cancer often returns and progresses quickly (~2-3 months) with currently available therapies.**

Table 2: Tumor response with balstilimab +/- zalifrelimab vs. currently marketed products

	Chemotherapy Topotecan[1] n=40	Roche Bevacizumab[2] n=46	Merck PD-1 Pembrolizumab[3] n=98	AGEN PD-1 Balstilimab n=160*	AGEN PD-1+ CTLA-4 Bali/Zali n=143*
Response rate	**12.5%**	**10.9%**	**12%** 14% (PD-L1+); 0% (PD-L1-)	**14%** 19% (PD-L1+); 10% (PD-L1-)	**22%** 27% (PD-L1+); 11% (PD-L1-)
Complete response	2.5%	0%	3%	2%	6%
Partial response	10%	10.9%	9%	12%	16%
Median duration of response	N/A	6.21 months	Not reached (Median follow-up: 10.2 months)	15.4 months (Median follow-up: ~12 months)	Not reached (Median follow-up: ~12 months)
Treatment related discontinuation (%)	N/A	8.7%	4.1%	3.7%	6.5%

**Assessed on safety population – 161 patients treated with balstilimab and 155 patients treated with balstilimab + zalifrelimab*

Table 2 references:

1. Bookman et al., Gynecol Oncol. 2000 Jun;77(3):446-9

2. Monk et al., J Clin Oncol. 2009 Mar 1;27(7):1069-74

3. Chung HC et al., J Clin Oncol. 2019 Jun 10;37(17):1470-1478

Table 3: Tumor response with balstilimab +/- zalifrelimab vs. other products in development

	Seattle Genetics ADC Tisotumab vedotin[1] n=101	Regeneron PD-1 Cemiplimab[2] n=10	AGEN PD-1 Balstilimab n=160*	AGEN PD-1+ CTLA-4 Bali/Zali n=143*
Response rate	**24%**	**10%**	**14%** 19% (PD-L1+); 10% (PD-L1-)	**22%** 27% (PD-L1+); 11% (PD-L1-)
Complete response	7%	0%	2%	6%
Partial response	17%	10%	12%	16%
Median duration of response	8.3 months	N/A (3.7 months +)	15.4 months (Median follow-up: ~12 months)	Not reached (Median follow-up: ~12 months)
Treatment related discontinuation (%)	13%	0%**	3.7%	6.5%

**Assessed on safety population – 161 patients treated with balstilimab and 155 patients treated with balstilimab + zalifrelimab*

Table 3 references:

1. Coleman et al. ESMO 2020

*2. Rischin et al. Annals of Oncology (2018); ** Discontinuation due to TEAEs*

Balstilimab +/- Zalifrelimab provide durable clinical benefit and are well-tolerated

Balstilimab monotherapy and balstilimab in combination with zalifrelimab have the potential to provide longer term clinical benefit in all patients with no exclusions. **The median duration of response for balstilimab monotherapy was over 15 months and it has not yet been reached for our combination trial.** Durable responses are important because even patients who respond to chemotherapy relapse in as early as 2-3 months. Even therapies currently in development have reported only a median duration of response lasting ~8 months **(see Table 3)**.

Our therapies have demonstrated responses while remaining well-tolerated in patients. The discontinuation rates in our monotherapy trial was a modest 3.7% due to TRAEs. With Keytruda, 4.1% of patients have been reported to discontinue treatment due to TRAEs. Even our combination is well tolerated, with only 6.5% of patients discontinuing treatment due to TRAEs. For reference, another CTLA-4 + PD-1 regimen (ipilimumab + nivolumab) demonstrated a 13.3% discontinuation rate in a study of second-line cervical cancer.

Our trials represent the largest studies executed to date for evaluating immunotherapies in cervical cancer, underscoring the robustness of the data presented at ESMO. With durable and well-tolerated responses across all patient populations, our therapies appear to represent a highly effective and clinically advanced treatment option with significant potential in second-line cervical cancer.

Dr. David O'Malley, an expert in gynecologic oncology, joined members of Agenus' management team in a webcast hosted by Dr. Matt Phipps of William Blair on Monday September 21, 2020 at 2:30 p.m. ET. You can access a replay of the webcast here.

In the webcast, Dr. O'Malley discussed the data he presented at ESMO and provided his perspective on the data, noting:

There are limited treatment options for cervical cancer patients progressing on first-line therapy. With balstilimab monotherapy and in combination with zalifrelimab, we see compelling response rates, including in PD-L1 negative patients. Currently, the response rates in PD-L1 negative patients to pembrolizumab is 0%. The 6% complete response rate with the combination of zalifrelimab and balstilimab is particularly exciting. This is almost unheard of in cervical cancer. Importantly, we see durable responses with balstilimab as monotherapy and in combination with zalifrelimab, including in PD-L1 negative patients, which is a differentiator. I am excited to have these as potential treatment options for discussion with my patients.