agenus

Agenus Inc. or subsidiary thereof (current or former employee), Lexington, MA 02421, USA.

Poster # 245

# Single-agent Zalifrelimab (anti-CTLA-4) Shows Clinical Benefit in Rare Tumors – Case Reports from a Phase 2 Study (NCT02694822)

Cesar A. Perez[1]; Robert Wesolowski[2]; Breelyn Wilky[1]; Waldo Ortuzar Feliu[3]; Hong Zhang[3]; Irina Shapiro[3]; Anna Wijatyk[3]; Remigiusz Kaleta[3]; Jonathan Trent[1]

[1]Division of Oncology, Sylvester Comprehensive Cancer Center at University of Miami Miller School of Medicine; [2]Division of Medical Oncology, The Ohio State University Comprehensive Caner Center; [3]Agenus Inc.

## Background

Zalifrelimab is a fully human monoclonal antibody that selectively binds cytotoxic T lymphocyte-associated protein 4 (CTLA-4) with high affinity. In this manner, zalifrelimab is designed to enhance T-cell immunity by antagonizing the inhibitory checkpoints of immune cell activation regulated by CTLA-4 signaling.

Previously, a durable and complete response was reported in a patient with recurrent cutaneous angiosarcoma as part of the Phase 1 evaluation of zalifrelimab (1). This was the first demonstration of a complete response in an individual treated with CTLA-4 inhibition as monotherapy in this rare malignancy.

Here we report additional findings of clinical benefit seen in rare tumor types from an ongoing phase 2 evaluation of single-agent zalifrelimab in patients with solid tumors who had progressed on prior programmed death 1 (PD-1)/programmed death ligand 1 (PD-L1) inhibitor treatment.

## Study Design

The open label Phase 2 study (NCT02694822) is evaluating the safety, clinical activity, pharmacokinetics, and pharmacodynamics of single-agent zalifrelimab in patients with advanced or metastatic solid tumors. Patients are required to have progressed on a prior PD-1/PD-L1 inhibitor and have exhausted available standard treatment options. Patients were administered zalifrelimab at 1mg/kg by intravenous infusion, once every 3 weeks.

## Results

At the time of data cutoff, 45 patients were enrolled and are included in the safety analyses. Zalifrelimab monotherapy is well tolerated. The most frequent treatment-related adverse events included fatigue, anemia, nausea, and vomiting (Table 1); the majority of cases were mild (grades 1 or 2) and readily managed with appropriate supportive care.

Twenty-eight patients had evaluable disease; maximum changes in target lesions from baseline are shown in Figure 1. One patient was excluded from efficacy analyses because the patient did not meet the criteria for response evaluable disease. The confirmed objective response rate seen in the efficacy evaluable population was 11.1% (1 complete response [CR] and 2 partial responses [PRs]) and the disease control rate (CR, PR, SD) was 51.9%. The CR was achieved in a PD-1/PD-L1 refractory patient with head and neck squamous cell carcinoma (HNSCC).

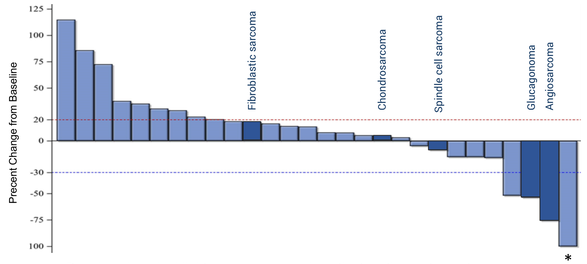
To date, the study has enrolled 5 patients with solid tumors considered rare (per NIH definition of fewer than 15 new cases per 100,000 people per year). This subset included individual cases of cutaneous angiosarcoma, metastatic glucagonoma, chondrosarcoma, spindle cell sarcoma, and fibroblastic sarcoma (Figure 2). Two of these patients, one with cutaneous angiosarcoma and another with glucagonoma, achieved confirmed PRs, both with short times to response. Moreover, each of these PRs are durable and ongoing (> 45 and > 30 weeks, respectively). In a third rare tumor patient with spindle cell sarcoma, stable disease was seen as best response prior to progression.

Case reports of the two patients experiencing PRs are presented in Figures 3-6.

### Table 1. Treatment-Related Adverse Events

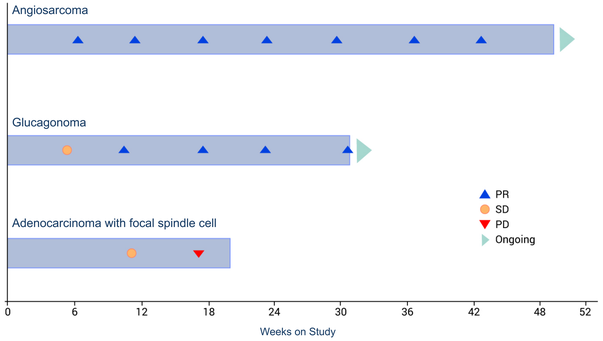
| Preferred Term | Safety Population N=45 | |
|---|---|---|
| | All Grade N (%) | Grade ≥3 N (%) |
| **Any TEAE** | **39 (86.7)** | **24 (53.3)** |
| Fatigue | 12 (26.7) | 2 (4.4) |
| Anemia | 11 (24.4) | 1 (2.2) |
| Nausea | 11(24.4) | 0 |
| Vomiting | 10 (22.2) | 1 (2.2) |
| Diarrhea | 9 (20.0) | 0 |
| Dyspnea | 7 (15.6) | 2 (4.4) |
| Pruritus | 5 (11.1) | 0 |
| Rash | 4 (8.9) | 1 (2.2) |
| Rash maculo-papular | 3 (6.7) | 0 |
| Blood creatinine increased | 3 (6.7) | 0 |
| Pyrexia | 2 (4.4) | 0 |
| Aspartate aminotransferase increased | 2 (4.4) | 0 |
| Hypothyroidism | 2 (4.4) | 0 |
| Flush | 2 (4.4) | 0 |
| Adrenal insufficiency | 1 (2.2) | 0 |
| Colitis | 1 (2.2) | 1 (2.2) |
| Pneumonia | 1 (2.2) | 1 (2.2) |
| Hypophysitis | 1 (2.2) | 0 |

### Figure 1. Maximum Change in Target Lesions (%) from Baseline




Dark blue bars highlight responses seen in patients with rare tumor types
Asterisk denotes HNSCC patient with a confirmed CR to zalifrelimab monotherapy

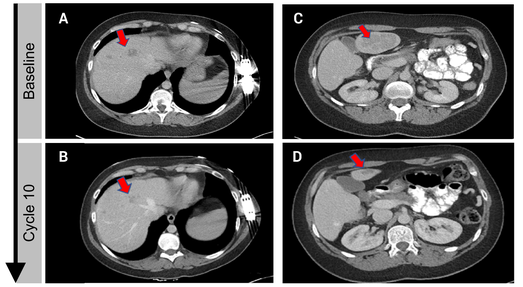
### Figure 2. Time to Response and Treatment Duration in Patients with Rare Tumors




## Case 1: Metastatic Glucagonoma

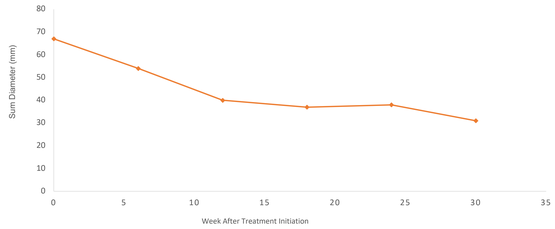
- **Primary Diagnosis**
  - Stage IV glucagonoma with low grade glucagonoma syndrome (generalized rash) in 29-year old white female diagnosed in 2014
- **Prior anti-cancer treatments**
  - Mar 2014 - ongoing. - Octreotide
  - July 2014 - Trans-arterial chemoembolization (TACE)
  - Mar 2015 – Feb 2016 - everolimus
  - Mar 2016 – Feb 2018 - chemotherapy (capecitabine/temozolomide)
  - Feb 2018 - Dec 2019 - pembrolizumab
- **Baseline condition**
  - ECOG PS: 1
  - Target lesions: metastatic lesions in liver
  - Non-target lesions: metastatic lesions in liver and pancreas
- **Current treatment**
  - Dec 2019 – ongoing. - Zalifrelimab 1mg q3w iv
  - Partial Response Week 12
  - Safety: Treatment-emergent adverse events (TEAEs) include Grade 1 diarrhea, fatigue, nausea, vomiting, dysuria, PTT, hypocalcemia, and Grade 2 anemia and hypothyroidism

### Figure 3. CT Scan of Liver Lesions in Patient with Metastatic Glucagonoma




Target lesions in liver: right lobe at screening (A) and (B) at Day 1 Cycle 10. Left lobe at screening (C) and (D) at Day 1 Cycle 10

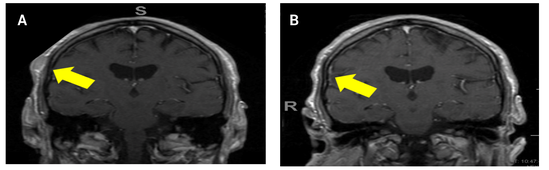
### Figure 4. Target Lesion in Patient with Metastatic Glucagonoma During Treatment




## Case 2: Locally Advanced Cutaneous Angiosarcoma

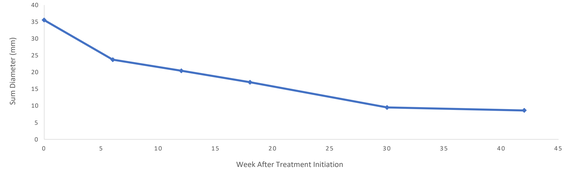
- **Primary Diagnosis**
  - Recurrent cutaneous angiosarcoma of the scalp in a 66-year old white male diagnosed in 2018
- **Prior anti-cancer treatments**
  - Aug 2018 - Jan 2019 - paclitaxel
  - Feb 2019 – Sept 2019 - pembrolizumab
- **Baseline condition**
  - ECOG PS: 0
  - Target lesions: 2 ulcerative skin lesions
  - Non-target lesions: none
- **Current treatment**
  - Oct 2019 – ongoing - zalifrelimab 1mg q3w iv
  - PR at Week 6 (confirmed at Week 12)
  - Safety: TEAEs include Grade 1 macular rash, hyperglycemia, cough, sinus pain, and Grade 2 intermittent leukopenia, APTT elevation, PT/INR elevation

### Figure 5. MRI Imaging of Scalp in Patient with Recurrent Angiosarcoma




Images A) target lesion of scalp at screening B) target lesion of scalp at Day 1 Cycle 6

### Figure 6. Target Lesion in Patient with Recurrent Angiosarcoma During Treatment




## Conclusions

- Responses on single agent zalifrelimab were identified in patients who had exhausted standard treatment options and progressed on PD-1/PD-L1 inhibiting therapy.
- Durable responses were observed in 2 rare tumors – cutaneous angiosarcoma and low-grade glucagonoma and disease stabilization was observed in a rare spindle cell carcinoma. This may support previous data that CTLA-4 inhibition following anti-PD-1 treatment may impart a meaningful treatment benefit for patients with rare tumor types [1; 2]. Follow-up studies are in preparation.
- Single-agent zalifrelimab was well tolerated with a manageable safety profiles.

References

1. Vaia Florou, et.al Journal for Immunotherapy of Cancer 2019 7:213
2. Sandip P. Patel, et.al Clinical Cancer Research May 2020 volume 26, issue 10