A Phase 1/2 Study of REGN5678 (Anti-PSMAxCD28, A Costimulatory Bispecific Antibody with Cemiplimab (Anti-PD-1) in Patients with Metastatic Castration-Resistant Prostate Cancer

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Background

Prostate cancer

- Prostate cancer is the second leading cause of cancer death in men in the US.
- In 2018, there were approximately 1.3 million new cases of prostate cancer, leading to est. 308,895 deaths worldwide. 1 Androgen deprivation therapy (ADT), in the form of surgical or chemical castration, is the standard for metastatic prostate cancer. 1, 2
- AST provides disease remission, suppressing prostate-specific antigen (PSA) by 80-90% of patients with metastatic prostate cancer. 2 However, after a mean time of 3-5 years, patients may experience disease progression, and the median overall survival is 3 years. 3
- Metastatic Castration-Resistant PC (mCRPC) have a poor prognosis and a median survival time of 9-13 months. 3

REGN5678

- Bispecific antibodies (bsAbs) are emerging as a protein-based therapeutic strategy for directing T-cell-mediated cytotoxicity in a tumor antigen specific manner, typically by binding to both tumor antigen and the cluster of differentiation 3 (CD3) receptor on T-cells. 4
- REGN5678 is a human IgG4-based, first-in-class, costimulatory bisoval designed to target prostate tumors by bridging prostate-specific antigens (PSA) expressing tumor cells with the T-cell receptor and cluster of differentiation 28 (CD28)-expressing T-cells, and provides an amplified T-cell receptor (CD3)-complex-mediated T-cell activation within the tumor through the activation of CD28 signaling. 5
- By engaging previously activated T-cells that express CD28, REGN5678 may exhibit less toxicity than CD28-directed bispecifics.

Figure 1. REGN5678 mechanism of action

Study design

- This Phase 1/2, open-label, multicenter, part-two study is investigating the safety, and preliminary efficacy of REGN5678 monotherapy in combination with cemiplimab in patients with mCRPC who have experienced disease progression after prior therapies (NCT02773875). 6
- Dose escalation: A 3-week safety lead-in of REGN5678 monotherapy of the assigned dose level will be administered intravenously biweekly and continued for combination therapy of REGN5678 at the assigned dose level every 3 weeks and cemiplimab 350 mg every 3 weeks (Q3W). 7
- A modified 3+3 design is (n=4) is utilized.

Dose escalation: Initial doses are followed by observation in a monitored setting.

- Dose escalation of REGN5678 will proceed until a maximum tolerated dose is attained or is dose or dose recommendations (e.g. recommended Phase 2 dose) is selected for expansion on the basis of tolerability and evidence of antitumor activity.

Dose expansion: Following selection of dose level in the dose escalation phase, patients will receive combination therapy of REGN5678 at the assigned dose level of REGN5678 and cemiplimab 350 mg Q3W without a 3-week lead-in of REGN5678 monotherapy.

- Prior to enrollment of an expansion cohort, three to six additional patients are enrolled in a further lead-in. The first cohort of six patients is enrolled in order to further evaluate safety and biologic activity.

- The duration of study for each patient will vary based on the occurrence of dose-limiting adverse events, withdrawal of consent, if study withdrawal is made clear, or completion of study (Figure 2).

Figure 2. Study design flow diagram

patient eligibility

- Key inclusion and exclusion criteria are provided in Table 2 and Table 3.

Statistical analysis

- The actual sample size of the dose escalation cohorts will depend on estimation of 350-365 deaths worldwide. 1
- The null hypothesis will be rejected if ≥4 responders are observed in the 27 patients.

regulatory considerations

- This study is currently open to enrolling patients.

Clinical Relevance

- REGN5678 as combination therapy with cemiplimab is >5%.
- The ORR of the modified PCWG3 criteria of patients treated with REGN5678 in combination with cemiplimab is 15%.
- There is an unmet need to develop novel therapies for mCRPC that has progressed through prior therapies.
- REGN5678 is a PSMAxCD28 human IgG4-based costimulatory bsAb being investigated in combination with cemiplimab in a Phase 1/2, open-label, multicenter study of patients with mCRPC.
- This study will provide valuable insight into the potential of REGN5678 as combination therapy with cemiplimab to improve outcomes for patients with mCRPC.
- This study is currently open to enrolling patients.

Methods

Study objectives

- Study objectives are provided in Table 1.

Table 1. Primary and secondary objectives

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<td>To assess safety, tolerability, and PK of REGN5678 on monotherapy and in combination with cemiplimab.</td>
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<tr>
<td>Secondary objectives</td>
<td>To determine the dose of REGN5678 in monotherapy and in combination with cemiplimab.</td>
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Dose escalation

- To determine the optimal dose of REGN5678 in monotherapy and in combination with cemiplimab.

Dose expansion

- To determine the optimal dose of REGN5678 in combination with cemiplimab.

Evaluating objectives

- To assess exploratory efficacy of REGN5678 monotherapy and in combination with cemiplimab.
- To evaluate biomarkers that may correlate with response to therapy and secondarily be predictive of drug efficacy.

Table 2. Key inclusion and exclusion criteria

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Statistical hypothesis

- There is no formal statistical hypothesis for the dose escalation phase of the study. Analyses will be descriptive and exploratory in nature.

- For each dose expansion cohort, the primary endpoint will be tested according to the following null (H0) and alternative hypotheses. 7

- The ORR per modified PCWG3 criteria of patients treated with REGN5678 in combination with cemiplimab is >5%.
- The ORR of the modified PCWG3 criteria of patients treated with REGN5678 in combination with cemiplimab is 15%.

Summary

- Cemiplimab is currently approved for the treatment of metastatic melanoma with a primary endpoint of progression-free survival and overall survival. 7
- This study is currently open to enrolling patients.

References


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