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

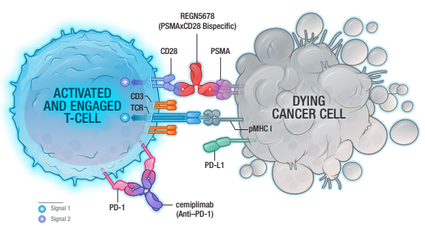
Prostate cancer

- Prostate cancer is the second leading cause of cancer death in men in the US.[1]
- In 2018, there were approximately 1.3 million new cases of prostate cancer, causing an estimated 358,989 deaths worldwide.[2]
- Androgen deprivation therapy (ADT), in the form of surgical or chemical castration, is a standard treatment for recurrent prostate cancer.[3]
- ADT provides disease remission, suppressing prostate-specific antigen (PSA) in 80–90% of patients with metastatic prostate cancer.[4] However, after a mean time of 2–3 years, patients may experience disease progression, and develop castration-resistant prostate cancer (CRPC).[5]
- Patients with metastatic CRPC (mCRPC) have a poor prognosis and a median survival time of 9–13 months.[6]

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.[7]
- REGN5678 is a human IgG4-based, first-in-class, costimulatory bsAb designed to target prostate tumors by bridging prostate specific membrane antigen (PSMA)-expressing tumor cells with the costimulatory receptor, cluster of differentiation 28 (CD28), on T-cells, and providing amplified T-cell receptor-CD3 complex-mediated T-cell activation within the tumor through the activation of CD28 signaling (**Figure 1**).
- By engaging previously activated T-cells that express CD28, REGN5678 may exhibit less toxicity than CD3 directed bi-specifics.

Figure 1. REGN5678 mechanism of action



PD-1, programmed cell death-1; PD-L1, programmed death-ligand 1; pMHC I, peptide (antigen)-bound major histocompatibility complex class I; TCR, T-cell receptor.

- At the tumor site, REGN5678 may synergize with anti–PD-1 inhibitors, similar to cemiplimab.
- In mouse models, REGN5678 in combination with PD-1 antibody improved anti-tumor activity compared with either therapy alone.[8]
- Here, we describe the ongoing Phase 1/2 study of REGN5678 in combination with cemiplimab for the treatment of mCRPC.

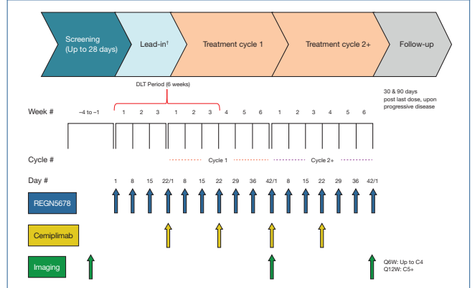
Methods

Study design

This Phase 1/2, open-label, multicenter, two-part study is investigating the safety, tolerability, pharmacokinetics (PK), and anti-tumor activity of REGN5678 alone and in combination with cemiplimab in patients with mCRPC who progressed after prior therapies (NCT03972657).

- **Dose escalation**: A 3-week safety lead-in of REGN5678 monotherapy at the assigned dose level will be administered intravenously (IV) once weekly (QW), followed by combination therapy of REGN5678 at the assigned dose level IV QW and cemiplimab 350 mg IV every 3 weeks (Q3W).
  - A modified 3+3 design (4+3) is utilized.
  - During 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 a dose or doses (e.g. recommended Phase 2 dose) is/are selected for expansion based on tolerability and evidence of anti-tumor activity.
- **Dose expansion**: Following selection of dose level(s) in the dose escalation phase, patients will receive combination therapy of REGN5678 at the assigned dose level IV QW and cemiplimab 350 mg IV Q3W without a 3-week lead-in of REGN5678 monotherapy.
  - Prior to enrollment of an expansion cohort, three to six additional patients will be enrolled at the given dose level without a 3-week REGN5678 monotherapy lead-in in order to further evaluate safety and biologic activity.
- The duration of study for each patient will vary based on the occurrence of intolerable treatment-emergent adverse events, withdrawal of consent, or if study withdrawal criterion is met, or confirmed progressive disease (**Figure 2**).

Figure 2. Study flow diagram



†Dose escalation cohorts will receive a 3-week monotherapy lead-in.
Dose expansion cohorts are not expected to receive the 3-week monotherapy lead-in of REGN5678.
C, cycle; DLT, dose-limiting toxicity; Q6W, every 6 weeks, Q12W, every 12 weeks.

Study objectives

- Study objectives are provided in **Table 1**.

Table 1. Primary and secondary objectives

Primary objectives
Dose escalation: • To evaluate safety, tolerability, and PK of REGN5678 as monotherapy and in combination with cemiplimab
Dose expansion: • To determine the composite ORR per modified PCWG3 criteria of REGN5678 in combination with cemiplimab
Secondary objectives
Dose escalation: • To determine the composite ORR per modified PCWG3 criteria of REGN5678 in combination with cemiplimab • To assess efficacy of REGN5678 in combination with cemiplimab, as measured by additional criteria • To assess immunogenicity of REGN5678 in combination with cemiplimab
Dose expansion: • To characterize the safety profile in each expansion cohort • To characterize the PK of REGN5678 in combination with cemiplimab • To assess efficacy of REGN5678 in combination with cemiplimab, as measured by additional criteria • To assess immunogenicity of REGN5678 in combination with cemiplimab
Exploratory objectives
• To assess exploratory efficacy of REGN5678 monotherapy and in combination with cemiplimab, as measured by additional criteria • To evaluate biomarkers that may correlate with mechanism of action and/or activity to increase understanding of disease/target or observed toxicity • To characterize tumor gene variants including homologous DNA repair gene mutations and tumor mutational burden in available tumor tissue biopsies • To develop a molecular understanding of mCRPC and other cancers

DNA, deoxyribonucleic acid; ORR, objective response rate; PCWG3, Prostate Cancer Working Group 3.

Patient eligibility

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

Statistical analysis

Sample size

- In the dose escalation phase, the planned sample size is approximately 42 patients.
  - The actual sample size of the dose escalation cohorts will depend on DLTs observed, resultant cohort sizes, and the number of dose levels explored.
- In the dose expansion phase, up to three cohorts with a maximum of 27 patients per cohort are planned.
  - The sample size is determined using Simon 2-stage Minimax design with 1-sided significant level of 5% and power of 80% when the true ORR is 20%.
  - The null hypothesis will be rejected if ≥4 responders are observed in the 27 patients.

Table 2. Key inclusion criteria

- Men ≥18 years old
- Histologically or cytologically confirmed adenocarcinoma of the prostate without pure small cell carcinoma
- mCRPC that has progressed within 6 months prior to screening, determined by one of the following:
  - PSA progression defined by a minimum of two rising PSA levels with a ≥1-week interval between each assessment, where the PSA value at screening should be ≥4 ng/mL
  - Radiographic disease progression in soft tissue per Response Evaluation Criteria in Solid Tumors version 1.1[9] criteria with or without PSA progression
  - Radiographic disease progression in bone defined as the appearance of ≥2 new bone lesions on bone scan with or without PSA progression
- Received ≥2 lines of approved systemic therapy for mCRPC, including a second-generation hormonal agent
- Available tumor tissue (archival or newly obtained)
- Either had an orchiectomy OR is on LHRH agonist or antagonist therapy with serum testosterone <50 ng/dL AND agrees to stay on LHRH agonist or antagonist therapy during the study
- Eastern Cooperative Oncology Group performance status of ≤1
- Adequate organ and bone marrow function as documented by:
  - Hemoglobin ≥9 g/dL
  - Absolute neutrophil count ≥1.0 x 10^9/L
  - Platelet count ≥100 x 10^9/L
- Adequate hepatic and renal function

LHRH, luteinizing hormone-releasing hormone.

Table 3. Key exclusion criteria

- Receiving treatment in another therapeutic study, or has participated in a study of an investigational agent/device within 4 weeks of first dose of study therapy
- Prior treatment with an approved systemic therapy within 3 weeks of dosing
- Prior radiotherapy or major surgery within 14 days of first dose of study therapy
- Prior systemic biologic therapy within five half-lives of first dose of study therapy
- Prior treatment with PSMA-targeting therapy
- Dose escalation:
  - Prior anti-cancer immunotherapy within five half-lives prior to study therapy
  - Prior treatment with sipuleucel-T is permitted
  - History of CNS metastases, including previously treated metastases
- Dose expansion:
  - Prior anti-cancer immunotherapy
  - Prior treatment with sipuleucel-T is permitted
  - Untreated or active primary brain tumor, CNS metastases, leptomeningeal disease, or spinal cord compression
- Patients who have not recovered from immune-mediated adverse events 3 months prior to initiation of study drug therapy except for endocrinopathies adequately managed with hormone replacement
- Any condition that requires ongoing/continuous corticosteroid therapy (>10 mg prednisone/day) or anti-inflammatory equivalent within 1 week prior to the first dose of study therapy
- Ongoing or recent (≤5 years) evidence of significant autoimmune disease that required treatment with systemic immunosuppressive treatments, excluding vitiligo, childhood asthma that has resolved, endocrinopathies that require only hormone replacement, or psoriasis that does not require systemic treatment
- Known history of, or any evidence of interstitial lung disease, or active, non-infectious pneumonitis in the past 5 years
- Uncontrolled infection with human immunodeficiency virus, hepatitis B or hepatitis C infection; or diagnosis of immunodeficiency

CNS, central nervous system.

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 efficacy endpoint will be tested according to the following null (H_0) and alternative hypotheses (H_a):
  - H_0: The ORR per modified PCWG3 criteria of patients treated with REGN5678 in combination with cemiplimab is ≤5%
  - H_a: The ORR per modified PCWG3 criteria of patients treated with REGN5678 in combination with cemiplimab is >5%.

Summary

- 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.

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