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A Study of REGN3767, an Anti-LAG-3 Antibody, Alone and in Combination with Cemiplimab (REGN2810), an Anti-PD1 Antibody, in Advanced Cancers

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Background

Target Biology

- Lymphocyte activation gene 3 (LAG-3) is an immune checkpoint receptor that binds major histocompatibility complex (MHC) class II.[1] LAG-3 is expressed on antigen-experienced (memory) CD4+ and CD8+ T-cells, γδ T-cells, regulatory T-cells, B-cells, NK cells, NK T-cells, and dendritic cells.[2,3] Upon activation of antigen experienced T-cells, surface expression of LAG-3 is increased,[4] and engagement of LAG-3 by MHC class II results in T-cell inhibition, negatively regulating T-cell proliferation, activation, cytolytic function, and proinflammatory cytokine production.[5] Analysis of immune-cell infiltrates from human tumors show that a subset of CD4+ and/or CD8+ cells co-express LAG-3 and programmed death-1 (PD-1) and may be associated with decreased T-cell effector function and tumor escape.[6,7]

REGN3767, an anti-LAG-3 VelocImmune® antibody

- REGN3767 is a fully human, hinge-stabilized IgG4 monoclonal antibody (mAb) that binds with high affinity to LAG-3 and blocks this pathway of inhibitory T-cell signaling (**Figure 1**). Nonclinical studies have shown that REGN3767 has the ability to block LAG-3/MHC Class II inhibitory T-cell signaling in cell-based *in vitro* assays. In double humanized LAG-3$^{hum/hum}$ PD-1$^{hum/hum}$ mice, REGN2810 (cemiplimab; a human monoclonal PD-1 antibody) monotherapy and the combination of cemiplimab plus REGN3767 reduced average tumor volumes compared to control treated groups.[8]

Rationale and Hypothesis

- Based on preclinical and clinical data, dual inhibition of LAG-3 and PD-1 blockade appear to offer synergistic anti-tumor effects and suggest a promising immunotherapy combination that warrants clinical investigation.[6–9]

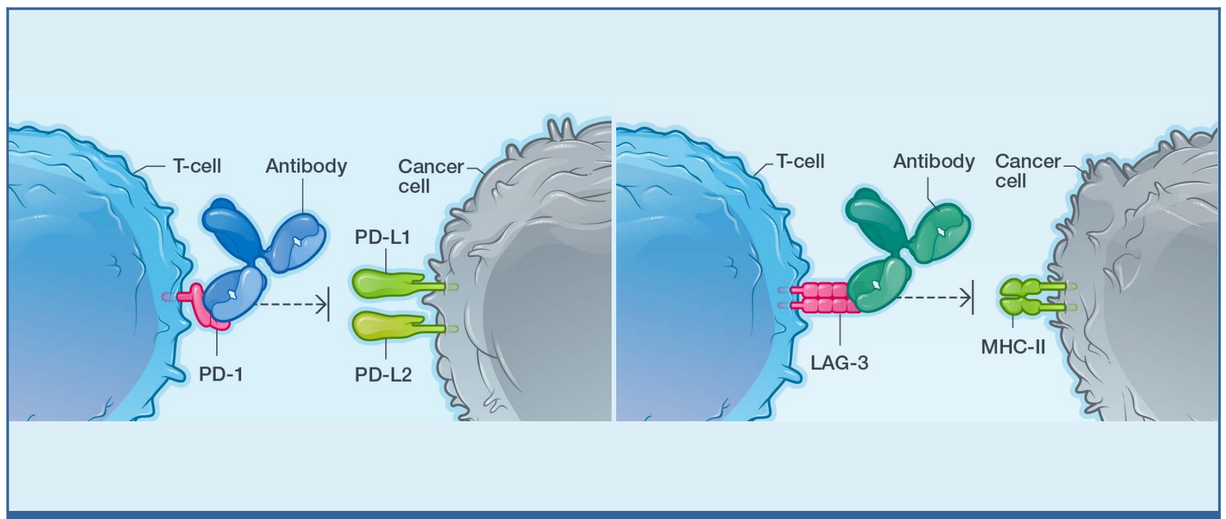


Figure 1. The role of LAG-3 in cancer immunotherapy

Study Design

First-in-Human Study R3767-ONC-1613 (NCT03005782)

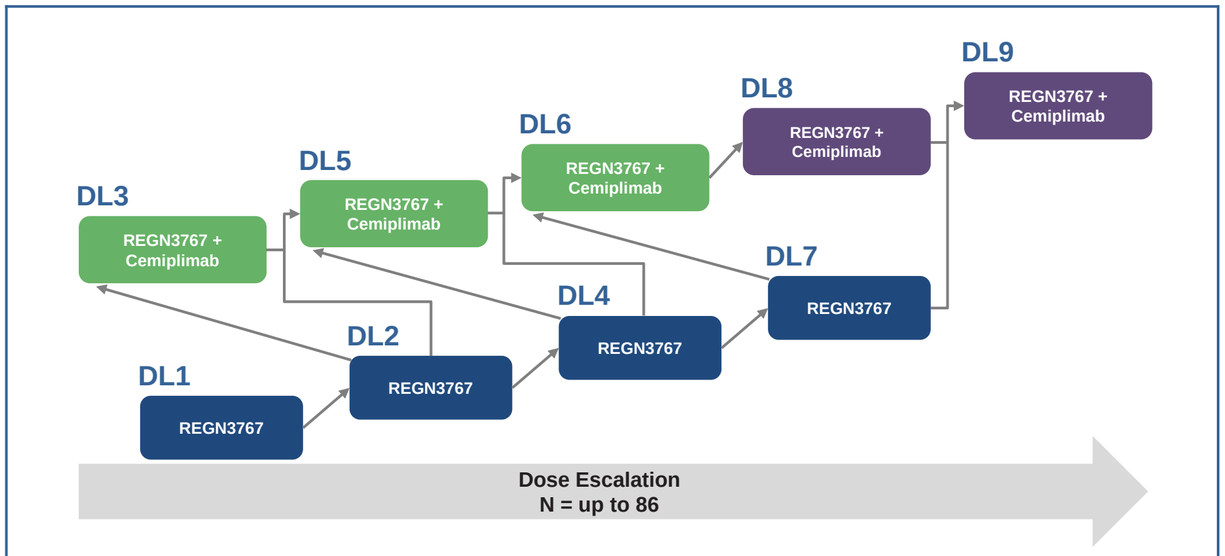
- This first-in-human study is designed to assess the safety, tolerability, pharmacokinetics (PK), and preliminary anti-tumor activity of REGN3767 as monotherapy and in combination with cemiplimab in patients with advanced malignancies.

Dose Escalation (Figure 2)

- Monotherapy is exploring 4 escalating REGN3767 dose levels in a modified 3+3 (4+3) design.
- Combination therapy of REGN3767 with cemiplimab is exploring 5 escalating dose levels, concurrently after dose level 1. For each escalation step, the dose of at least one of the two antibodies is increased.

Dose Expansion

- Once a dose level(s) is selected in the dose escalation, tumor specific cohorts will be opened for expansion. Solid tumor expansion cohorts will enroll per Simon's two-stage design to evaluate safety and preliminary efficacy:
  - REGN3767 monotherapy will be tested in a lymphoma cohort
  - REGN3767 in combination with cemiplimab will be tested in multiple solid tumor cohorts.



DL, dose level.

Figure 2. Dose Escalation

Objectives

Primary objectives

- Dose escalation: safety and pharmacokinetics, to determine dose level(s) for expansion cohorts.
- Dose expansion: overall response rate (ORR) by RECIST 1.1[10] or Lugano criteria[11] as applicable.

Secondary objectives

- Dose escalation: immunogenicity, ORR.
- Dose expansion: safety and PK.

Exploratory objectives

- To assess the predictive potential and correlation to clinical response for biomarkers of interest:
  - Circulating tumor nucleic acids
  - Peripheral blood mononuclear cell subset distribution, T-cell activation status and expression of immune checkpoint molecules
  - Tumor RNA expression
  - Number and distribution of tumor infiltrating lymphocytes
  - Expression levels of PD-1, PD-L1, LAG-3, MHC class II and possibly other immune modulators or their ligands
  - Mutations in known oncogenes and potential tumor neoantigens
  - Tumor mutational burden.

Selected Key Eligibility Criteria

Key Inclusion:

- Adults with advanced malignancy
- Patients with controlled human immunodeficiency virus infections, hepatitis B, and hepatitis C are allowed
- Prior anti-PD-1/PD-L1 treatment is allowed for several cohorts.

Key Exclusion:

- Prior therapy with LAG-3 inhibitor
- Corticosteroid therapy (>10 mg prednisone/day or equivalent) within 1 week prior to the first dose of study drug.

This trial is actively enrolling patients in the US and UK. Additional enrollment is being planned for Ireland and South Korea.

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