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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 cell 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, cemiplimab (a human monoclonal PD-1 antibody) monotherapy and the combination of cemiplimab with 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]

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.

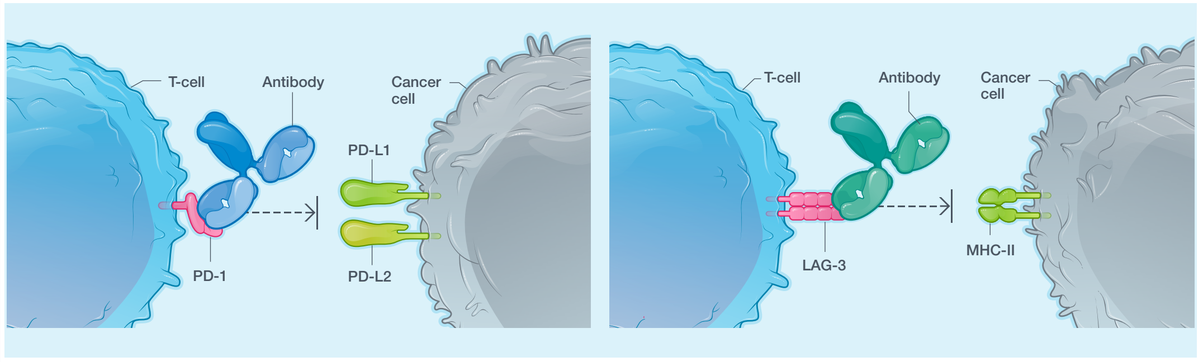
Dose Escalation (Figure 2)

- 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

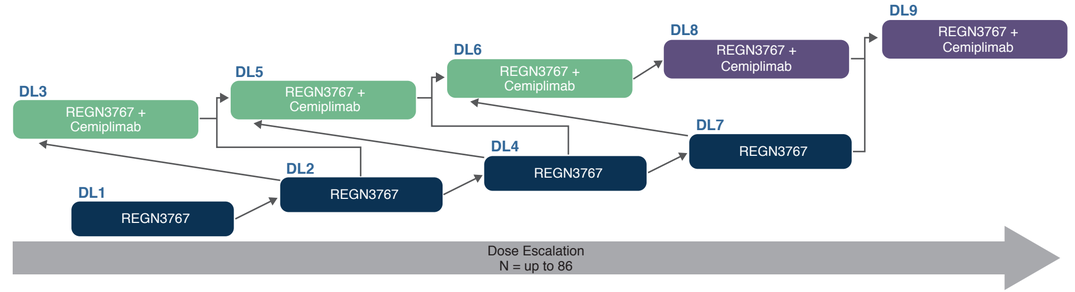
- Once a dose level(s) is selected in the dose escalation, tumor specific cohorts will be opened for expansion. Solid tumor expansion cohorts will enroll per Simon's two-stage design to evaluate safety and preliminary efficacy:
  - REGN3767 monotherapy will be tested in a lymphoma cohort
  - REGN3767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

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



PD-L1, programmed cell death-ligand 1; PD-L2, programmed cell death-ligand 2.

Figure 2. Dose escalation



DL, dose level.

Table 1. Objectives

Primary objectives

- Dose escalation: safety and PK, to determine dose level(s) for expansion cohorts.
- Dose expansion: overall response rate (ORR) by Response Evaluation Criteria In Solid Tumors Version 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 planned for Ireland and South Korea.

References

1. Huard B et al. *PNAS*. 1997;94:5744–5749.
2. Huard B et al. *Immunogenetics*. 1994;39:213–217.
3. Miyazaki T et al. *Int Immunol*. 1996;8:725–729.
4. Macon-Lemaitre L et al. *Immunology*. 2005;115:170–178.
5. Goldberg MV, Drake CG. *Curr Top Microbiol Immunol*. 2011;344:269–278.
6. Baitsch L et al. *J Clin Investig*. 2011;121:2350–2360.
7. Jie HB et al. *Br J Cancer*. 2013;109:2629–2635.
8. Burova E et al. *Cancer Res*. 2016;76:14(suppl:1158/1538–7445).
9. Ascierto PA et al. *J Clin Oncol*. 2017;35:15(suppl: 9520–9520).
10. Eisenhauer EA et al. *Eur J Cancer*. 2009;45:228–247.
11. Cheson BD et al. *J Clin Oncol*. 2014;32:3059–3068.

Acknowledgments

The authors would like to thank the patients, their families, all other investigators, and all investigational site members involved in this study. The study was funded by Regeneron Pharmaceuticals, Inc. Medical writing and typesetting support was provided by Prime, Knutsford, UK, funded by Regeneron Pharmaceuticals, Inc.

For any questions regarding this poster presentation, please contact Kyri.Papadopoulos@startsa.com.

Poster presented at the 2019 ASCO-SITC Clinical Immuno-Oncology Symposium, February 28 – March 2, 2019, San Francisco, California (encore of ASCO 2018 poster presentation).