A Phase I/II, Open-label, Two Part Study of GSK3359609 in Combination With Tremelimumab in Patients With Selected, Advanced Solid Tumors

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Background

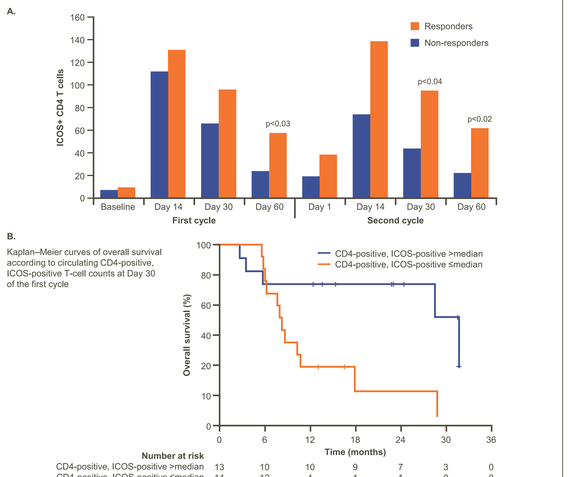
- GSK3359609 is an inducible T cell co-stimulator (ICOS) agonist antibody selected for its potent binding, agonist activity against human ICOS, and low/no depleting effects.[1]
- Tremelimumab is a cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) antagonist antibody.
- It is hypothesized that the combination of these two agents will provide greater anti-tumoral response than either agent alone.
  - Upregulation of ICOS+ T cells with anti-CTLA-4 antibody treatment was demonstrated in blood, lymph nodes and in tumors in various syngeneic mouse tumor models with surrogate CTLA-4 antibodies. Additionally, the anti-tumor activity with anti-CTLA-4 antibodies was much diminished in the absence of ICOS.[2-4]
  - Increases in ICOS+ CD4 T cells in blood was shown to have a positive association with response in tremelimumab-treated chemotherapy-resistant patients with malignant mesothelioma.[4,5]
  - Combination treatment of anti-CTLA-4 and ICOS resulted in improved anti-tumor activity over each single agent alone in two independent mouse tumor models in studies GSK conducted in collaboration with IGR.[6]
  - In vitro stimulation of peripheral blood mononuclear cells (PBMCs) from ipilimumab-treated patients with anti-CD3 and non-depleting agonist ICOS monoclonal antibody (mAb) GSK3359609 was able to rescue the low T cell activation observed in patients that had poor response to anti-CTLA-4 treatment alone.[6]
- Symptoms of colitis were not observed in mice treated with anti-CTLA-4 in combination with agonistic anti-ICOS mAbs.[6]

Methods

Rationale for ICOS/CTLA-4 study

- ICOS expression on T cells has been shown to be upregulated after anti-CTLA-4 treatment.
- ICOS+ CD4+ T cells, positive association with response in tremelimumab-treated chemotherapy-resistant patients with malignant mesothelioma (**Figure 1a and 1b**).[5] Similar data with ipilimumab and tremelimumab in melanoma.

Figure 1. Association with Response



Kaplan–Meier curves of overall survival according to circulating CD4-positive, ICOS-positive T-cell counts at Day 30 of the first cycle

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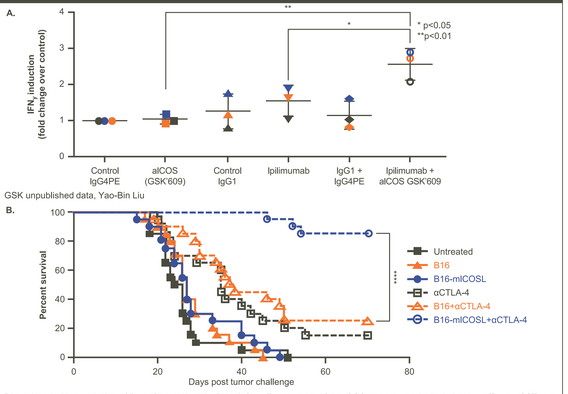
- Enhanced T cell function (**Figure 2a**) and anti-tumor activity (**Figure 2b**)[2] with engagement of the ICOS pathway along with anti-CTLA-4 antibody combination in non-clinical models.

Figure 2. Engagement of ICOS pathway



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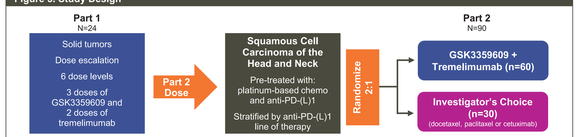
Study Overview (Figure 3)

Study Duration

- Treatment until disease progression, unacceptable toxicity or death or completion of 2 years of treatment.

Figure 3. Study Design



Study Objectives

Part 1

- Primary
  - Determine safety, tolerability of GSK3359609 in combination with tremelimumab (G+T).
  - Determine the recommended phase 2 dose.
- Secondary
  - Evaluate clinical activity of G+T (overall response rate and disease control rate – modified Response Evaluation Criteria in Solid Tumors [iRECIST]).
  - Characterize the pharmacokinetic (PK) properties of G+T when administered in combination.
  - Determine immunogenicity of G+T when administered in combination.
- Exploratory
  - Pharmacodynamic (PD) changes in markers of target engagement, immune cell profiles, immune activation/function and/or changes in tumor biology post treatment relative to baseline.

Part 2

- Primary
  - Evaluate the clinical activity of G+T compared with standard of care (SoC) in patients.
- Secondary
  - Evaluate PK, immunogenicity, safety and tolerability of G+T compared with SoC.

Study Population

- 114 adult patients with relapsed/refractory solid tumors.

Part 1

- Melanoma.
- Squamous cell carcinoma of the head and neck (SCCHN; oral cavity, larynx, oropharynx, hypopharynx, nasal cavity/paranasal sinuses).
- Non-small cell carcinoma lung cancer.
- Urothelial carcinoma of the upper and lower urinary tract.
- Clear cell renal cell carcinoma.
- Castrate-resistant prostate cancer.

Part 2

- SCCHN (oral cavity, larynx, oropharynx, hypopharynx, nasal cavity/paranasal sinuses).

Key Eligibility Criteria – Inclusion

Part 1

- Relapsed/refractory solid tumors (see Study Population).
- Disease that has progressed after standard therapy for the specific tumor type, or for which standard therapy has proven to be ineffective, intolerable, or is considered inappropriate, or if no further standard therapy exists, or where standard therapy is refused.
- May or may not have had prior programmed death-ligand 1 (PD1-L1) treatment.

Part 2

- SCCHN.
- Failed at least 1 platinum-based chemo and at least 1 anti-PD-1/PD-L1 (as combo or separate).

Both Part 1 and 2

- Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) score of 0 or 1.
- Measurable disease using RECIST 1.1 criteria.
- Adequate organ function.

Key Eligibility Criteria – Exclusion

Both Part 1 and 2

- ≥4 lines of prior therapy.
- ≥Grade 3 toxicity considered related to prior immunotherapy and that led to treatment discontinuation.
- Toxicity related to prior treatment that has not resolved to ≤Grade 1 (except alopecia, vitiligo, hearing loss, endocrinopathy managed with replacement therapy, and peripheral neuropathy which must be ≤Grade 2).
- Central nervous system (CNS) metastases, with the following exception: Participants with previously treated CNS metastases who are clinically stable and had no requirement for steroids during at least 14 days prior to first dose of study intervention or SoC.
- Autoimmune disease (current or history) or syndrome that required systemic treatment within the past 2 years.
- No prior CTLA-4 (including tremelimumab) or ICOS-directed therapies at any time.

Study Design

Part 1

- Escalating doses of GSK3359609 and tremelimumab.
- GSK3359606 administered as an intravenous (IV) infusion every 3 weeks.
- Tremelimumab administered as an IV infusion every 3 weeks for 16 weeks then every 12 weeks.

Part 2

- Doses of GSK3359609 and tremelimumab determined based on results of Part 1.
- Patients randomized to either GSK3359609/tremelimumab or SoC.
  - SoC = Investigator's choice of single-agent docetaxel, paclitaxel, or cetuximab.
- Same administration schedule as Part 1.

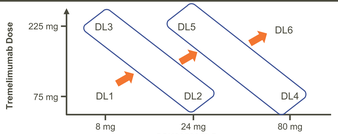
Both Part 1 and 2

- Treatment for up to 2 years.
- Patients may continue treatment after progression of disease if they meet criteria (eg, documented clinical benefit, absence of clinically significant disease progression, no decline in ECOG PS).

Part 1 – Dose Escalation Process

Zone-based dose escalation **(Figure 4)**

Figure 4. Dose Escalation



- Dose limiting toxicity (DLT) observation period is 28 days.
- Accelerated titration design is planned for the first 2 dose levels in Part 1, with 1 patient enrolled at each dose level.
- Bivariate Continuous Reassessment Method (CRM) will inform subsequent dose escalation decisions in Part 1.
- Doses within the same zone may be enrolled at the same time.
- Additional patients will be enrolled in PK/PD cohort(s).

Dose-Limiting Toxicity (DLT)

- Defined as an adverse event (AE) that meets one of the criteria listed below and considered by the Investigator to be clinically relevant and attributed (probably, or possibly) to the study intervention during the 28-day DLT observation period.

Table 1. Dose-Limiting Toxicity Definition

Toxicity	Dose-Limiting Toxicity Definition
Hematologic	• Febrile neutropenia • Grade 4 neutropenia of >7 days in duration or requiring granulocyte-colony stimulating factor • Grade 4 anemia • Grade 3 thrombocytopenia with bleeding or Grade 4 thrombocytopenia
Non-hematologic	• Grade 4 toxicity • Grade 3 pneumonitis • Any ≥Grade 2 pneumonitis that does not resolve to ≤ Grade 1 within 3 days of the initiation of maximal supportive care • Grade 3 toxicity that does not resolve to ≤ Grade 1 or baseline within 3 days despite optimal supportive care • Any Grade 2 ocular toxicity requiring systemic steroids, or any ≥ Grade 3 ocular toxicity
Other	• Any other toxicity considered to be dose-limiting which in the judgment of the Investigator and Medical Monitor that occurs within or beyond four weeks will be considered in the selection of the dose to recommend for expansion cohorts

Key Study Assessments

- Safety
  - AEs, labs, electrocardiograms, immunogenicity.
- Clinical Activity
  - RECIST 1.1 for Immune-based Therapeutics (iRECIST for tumor progression).
- PK
  - Pre-infusion and at various time points post infusion.
- PD
  - Immune cell phenotyping, assessment of PBMCs and cytokines.
  - Tumor biopsies (before and on-treatment) in PK/PD cohort(s) and a subset in Part 2.

Study Status

- Recruitment in Part 1 started in December 2018.
- Study sites in Australia, Canada, United States for Part 1.
- Additional countries/sites to be added for Part 2.
- ClinicalTrials.gov identifier: NCT03693612.
- Study is funded by GlaxoSmithKline (GSK) and is run in collaboration with AstraZeneca/MedImmune.

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