Pharmacokinetic/pharmacodynamic (PK/PD) exposure-response characterisation of the ICOS agonist monoclonal antibody, GSK3359609, from INDUCE-1, a Phase I open-label study

Poster No: 1971P

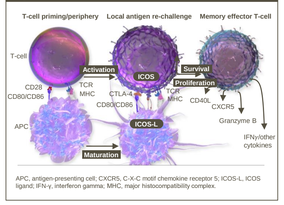
Maio M[1], Groenland SL[2], Bauer T[3], Rischin D[4], Gardeazabal I[5], Moreno V[6], Trigo J[7], Chisamore M[8], Shaik JS[9], Rigat F[10], Ellis C[9], Chen H[9], Gagnon R[9], Scherer SJ[9], Turner D[9], Yadavilli S[9], Ballas M[9], Hoos A[9], Angevin E[11]

[1]University Hospital of Siena, Siena, Italy; [2]Netherlands Cancer Institute – Antoni van Leeuwenhoek, Amsterdam, the Netherlands; [3]Sarah Cannon Research Institute/Tennessee Oncology, PLLC, Nashville, TN, USA; [4]Peter MacCallum Cancer Centre and the University of Melbourne, Melbourne, Australia; [5]Institut Català d'Oncologia, Spain; [6]START Madrid-FJD, University Hospital "Fundacion Jimenez Diaz", Madrid, Spain; [7]Hospital Ramón y Cajal, Madrid, Spain; [8]Merck & Co., Inc., North Wales, PA, USA; [9]GSK, Collegeville, PA, USA; [10]GSK, Stevenage, UK; [11]Gustave Roussy Institut de Cancérologie, Villejuif, France

Background

- Inducible T-cell co-stimulator (ICOS), a member of the CD28 immunoglobulin (Ig) receptor superfamily that includes cytotoxic T-lymphocyte associated protein-4 (CTL4) and programmed cell death protein 1 (PD-1), has a pivotal role in proliferation, differentiation, survival and function of T-cells.[1]
- ICOS is highly upregulated upon T-cell receptor (TCR) stimulation[1] and is expressed on tumour infiltrating lymphocytes (TIL) (CD4$^+$ T helper cells, CD8$^+$ cytotoxic T-cells and regulatory T [T reg] cells) in many tumours (**Figure 1**).[2]
- An increase in ICOS$^+$ T-cells on-treatment was found to be correlated with response and survival in patients with metastatic melanoma treated with ipilimumab or metastatic mesothelioma treated with tremelimumab (CTLA-4 blockade).[3,4]

Figure 1. ICOS mechanism of action



APC, antigen-presenting cell; CXCR5, C-X-C motif chemokine receptor 5; ICOS-L, ICOS ligand; IFN-γ, interferon gamma; MHC, major histocompatibility complex.

- Consistent with CTLA-4 and PD-1 blockade, ICOS agonism is anticipated to modulate T-cell dynamics resulting in prolonged control of tumour growth kinetics and survival in patients.
- GSK3359609 is a humanised IgG4 antibody selected for its potent binding, agonist activity through the human ICOS receptor and low/no T-cell depleting effects via antibody-dependent cellular toxicity in non-clinical models.[5]
- Preclinical data have shown that ICOS agonism reduces tumour growth and provides a rationale for targeting ICOS with GSK3359609 as a monotherapy and in combination with pembrolizumab.[5,6]
- INDUCE-1 (204691; NCT02723955) is an open-label, first-in-human study evaluating the safety, tolerability, pharmacokinetics (PK), pharmacodynamics (PD) and anti-tumour activity of GSK3359609 alone and in combination with other regimens, including pembrolizumab, in selected solid tumours such as head and neck squamous cell carcinoma (HNSCC; primary, secondary and further exploratory endpoint analyses are reported separately in Poster 1119PD).[7]

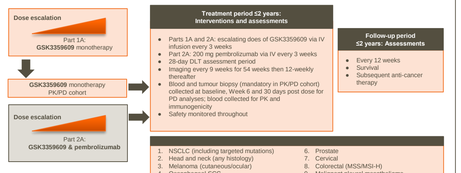
Study objectives

- Key exploratory and interim PK/PD analyses of the INDUCE-1 study are presented here, updated from prior data, presented at the European Society of Medical Oncology (ESMO) 2018 Congress, to include additional patients and analyses.[8]
  - Characterisation of GSK3359609 PK disposition across all patients with at least one evaluable GSK3359609 concentration (N=464).
  - Assessment of the exposure-response relationships for patients with HNSCC from the dose escalation expansion cohorts.
  - Evaluation of the PD effects of GSK3359609 in blood and tumour based on ICOS receptor expression/occupancy and immune phenotyping, as well as evaluation of gene expression changes in the tumour microenvironment.

Methods

Study design

Figure 2. Study design



Treatment period ≤2 years: Interventions and assessments

- Parts 1A and 2A: escalating does of GSK3359609 via IV infusion every 3 weeks
- Part 2A: 200 mg pembrolizumab via IV every 3 weeks
- 28-day DLT assessment period
- Imaging every 9 weeks for 54 weeks then 12-weekly thereafter
- Blood and tumour biopsy (mandatory in PK/PD cohort) collected at baseline, Week 6 and 30 days post dose for PD analyses; blood collected for PK and immunogenicity
- Safety monitored throughout

Follow-up period ≤2 years: Assessments

- Every 12 weeks
- Survival
- Subsequent anti-cancer therapy

1. NSCLC (including targeted mutations)
2. Head and neck (any histology)
3. Melanoma (cutaneous/ocular)
4. Oesophageal SCC
5. Bladder/urothelial
6. Prostate
7. Cervical
8. Colorectal (MSS/MSI-H)
9. Malignant pleural mesothelioma

- Accelerated titration design for first 3 dose levels in Part 1A; 1 patient enrolled at each dose level.
- Modified toxicity probability interval method informed subsequent dose escalation decisions in Parts 1A/2A (minimum 3 patients per dose level).
- Starting dose of 0.001 mg/kg: the projected human dose based on the minimally anticipated biologic effect observed in preclinical studies.

DLT, dose-limiting toxicity; IV, intravenous; MSI-H, high microsatellite instability; MSS, microsatellite stability; NSCLC, non-small-cell lung carcinoma.

- This first-in-human, open-label, multicentre study includes patients with advanced/metastatic or recurrent malignancy that have progressed after standard therapy (more detailed inclusion and exclusion criteria are presented in Poster 1119PD).[7]
- INDUCE-1 consists of two parts (Part 1 GSK3359609 monotherapy and Part 2 GSK3359609 combination therapy) whereby each part consists of a dose escalation phase (Parts 1A and 2A) followed by a cohort expansion phase (Parts 1B and 2B) (**Figure 2**).

PK analysis

- A preliminary population PK data set was constructed with all pooled concentration–time data.
- Serial plasma samples were collected throughout; PK samples were assayed by validated enzyme-linked immunosorbent assay and concentration–time data was modelled using nonlinear mixed effects, as implemented in NONMEM.

HNSCC exposure-response analysis

- Exposure-efficacy analysis was carried out on participants with HNSCC naïve to prior anti-PD-1/programmed death ligand 1 (PD-L1) therapy who had received the study drug in either the Part 2A dose escalation or Part 2B HNSCC cohort.
- Exploratory regression analysis was performed to evaluate potential associations between GSK3359609 exposure and change in tumour sum of longest diameters (SLD).
- The exposure measure for exposure-response analyses was defined as first dose area under the curve (AUC) or individual predicted Week 6 trough concentration, derived from population PK model. Because of linear PK and lack of time-dependency in GSK3359609 clearance, C_{trough} is highly correlated to AUC. Hence, the two exposure metrics are essentially interchangeable.
- Investigator assessed overall response rate (ORR) and disease control rate (DCR; defined as percentage of patients with a best overall response of immune-related complete response or immune-related partial response at any time, plus an immune-related stable disease ≥9 weeks) per immune-related response evaluation criteria in solid tumours, was summarised by binned exposure estimates and described using a conventional logistic regression model.

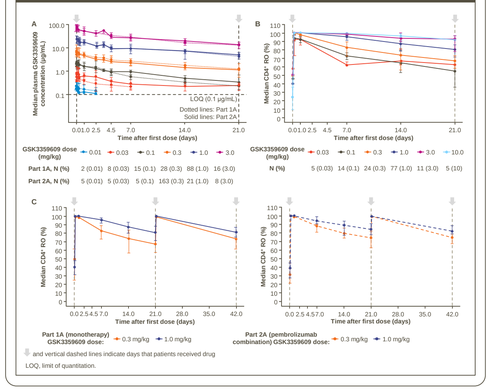
PD analysis

- Flow cytometry was performed instream throughout the study to evaluate ICOS receptor occupancy (RO) with GSK3359609.
- For PK/PD and expansion cohorts, tumour tissue was collected at pre-dose and at Week 6 for evaluation of overall TIL, changes in activation, proliferation and gene expression changes.
- The exposure measure for PK/PD analyses was defined as Week 6 pre-dose trough concentration derived from the population PK model.
- Evaluation of gene expression changes in the tumour microenvironment were performed using the Nanostring nCounter platform.
- MultiOmyx multiplexed immunofluorescence was used to characterise the immune phenotype of the TIL.
- The relationship between intention-to-treat dose and changes in MultiOmyx™ or Nanostring data (dose–PD response curves) was assessed by maximum likelihood fit of quadratic LOESS models in R. Markers showing any change in dose significant at the 99% confidence level were highlighted as strongly dose-dependent. A high confidence level was selected to protect this exploratory dose-response analysis from false positive errors.

Results

Pharmacokinetics and target engagement

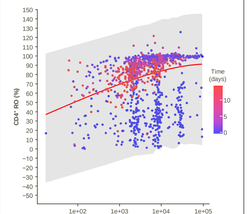
Figure 3. (A) Dose-proportional PK from 0.01 to 3.0 mg/kg, (B) Peak CD4$^+$ RO corresponding to maximum plasma concentration and (C) CD4$^+$ RO with GSK3359609 0.3 and 1.0 mg/kg monotherapy versus combination with pembrolizumab



LOQ, limit of quantitation.

- PK and target engagement characteristics of GSK3359609 are similar to those of prior reports,[8] with a population clearance estimate of ~0.27 L/day and central volume estimate of ~3.6 L, and limited impact of bodyweight on systemic exposure.
- Plasma concentrations of GSK3359609 increase in a dose-proportional manner with no apparent pembrolizumab interaction (**Figure 3A**), while ICOS RO is maintained above ~70% with GSK3359609 doses of 0.1 mg/kg and higher (**Figure 3B**). Minimal differences in RO are observed for CD4+ with GSK3359609 doses of 0.3 mg/kg and 1.0 mg/kg (**Figure 3C**), with similar results for CD8+ (data not shown). However, there are large variability in RO for doses <1.0 mg/kg (**Figure 4**).

Figure 4. RO with GSK3359609 concentration



Exposure-response characterisation

- Evidence of target engagement and tumour size reduction is observed in the recurrent/relapsed (R/R) HNSCC expansion cohort with GSK3359609 0.3 mg/kg and 200 mg pembrolizumab. Full results of this HNSCC expansion are reported separately[8] (poster number: 1119PD).
- A potential association between exposure (AUC) and unconfirmed Best Overall Response, DCR, and percent change in SLD at Week 9 is observed in HNSCC. None of the slope estimates from these three regression analyses are statistically significant (p>0.05; **Figure 5**).
- Further, since the HNSCC exposure-response data were collected primarily at a single dose level of 0.3 mg/kg, interpretation may be confounded by an underlying association of catabolic clearance and disease status, as previously reported for other similar oncology biologics.[9] Hence, randomised dose-ranging cohorts are currently enrolling to enable deconvolution of GSK3359609 PK and other latent confounders to delineate the role of exposure, and thus impact of dose selection, on patient outcome in this setting. These data will be reported separately.

Figure 5. Regression of (A) best overall response, (B) disease control rate, and (C) observed percentage change from baseline in tumour SLD at Week 9 by GSK3359609 exposure in HNSCC dose escalation and expansion cohorts illustrates a weak association that is not statistically significant (all regression p>0.05)

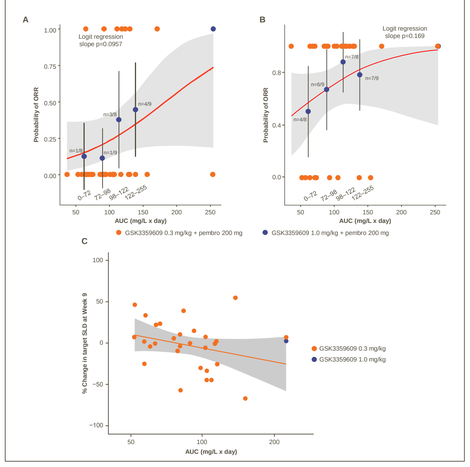
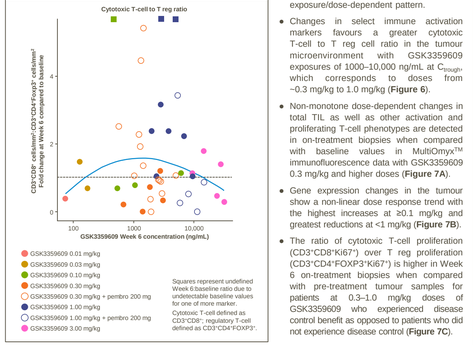


Figure 6. A potentially favourable CD8:T reg ratio at Week 6 on-treatment compared to pre-treatment samples was observed at GSK3359609 exposure of 1000–10,000 ng/mL and GSK3359609 ~0.3–1.0 mg/kg



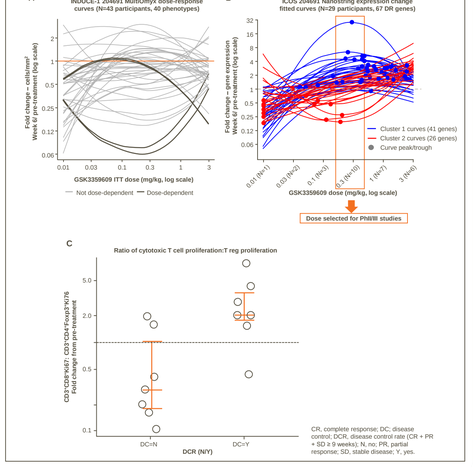
Squares represent undefined Week 6 baseline ratio due to undetectable baseline values for one of more marker.

Cytotoxic T-cell defined as CD3$^+$CD8$^+$; regulatory T-cell defined as CD3$^+$CD4$^+$FOXP3$^+$.

MultiOmyx and gene expression data

- Quantitative evaluation of TILs in paired tumour biopsies demonstrates on-study changes in TILs follow a non-linear, exposure/dose-dependent pattern.
- Changes in select immune activation markers favours a greater cytotoxic T-cell to T reg cell ratio in the tumour microenvironment with GSK3359609 exposures of 1000–10,000 ng/mL at C_{trough}, which corresponds to doses from ~0.3 mg/kg to 1.0 mg/kg (**Figure 6**).
- Non-monotone dose-dependent changes in total TIL as well as other activation and proliferating T-cell phenotypes are detected in on-treatment biopsies when compared with baseline values in MultiOmyx™ immunofluorescence data with GSK3359609 0.3 mg/kg and higher doses (**Figure 7A**).
- Gene expression changes in the tumour show a non-linear dose response trend with the highest increases at ≥0.1 mg/kg and greatest reductions at <1 mg/kg (**Figure 7B**).
- The ratio of cytotoxic T-cell proliferation (CD3$^+$CD8$^+$Ki67$^+$) over T reg proliferation (CD3$^+$CD4$^+$FOXP3$^+$Ki67$^+$) is higher in Week 6 on-treatment biopsies when compared with pre-treatment tumour samples for patients at 0.3–1.0 mg/kg doses of GSK3359609 who experienced disease control benefit as opposed to patients who did not experience disease control (**Figure 7C**).

Figure 7. (A) MultiOmyx dose-response curves, (B) Nanostring gene expression curves and (C) Ratio of cytotoxic T-cell to T reg cell proliferation



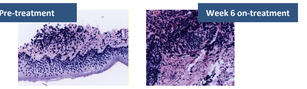
CR, complete response; DC; disease control; DCR, disease control rate (CR + PR + SD ≥ 9 weeks); N, no; PR, partial response; SD, stable disease; Y, yes.

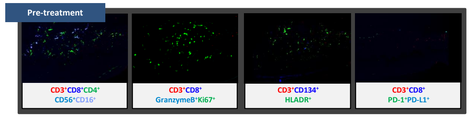
Patient case study

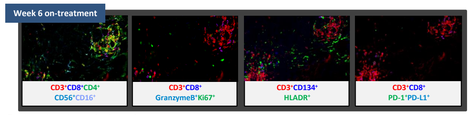
GSK3359609 monotherapy

History

- Initial diagnosis: March 2013, BRAF negative, N/KRAS mutation positive Stage Ib superficial spreading melanoma.
- Diagnosed with metastasis: January 2017.
- Prior regimens:
  - Nivolumab (advanced/metastatic, 22 August 2017–12 June 2018)
  - Electrochemotherapy (March 2018).
- Study treatment
  - Cycle 1 Day 1 (24 July 2018); GSK3359609 monotherapy at 1.0 mg/kg.







Post-treatment sample showed:

- Higher TIL including cytotoxic, helper T-cells and NK cells
- More Granzyme B$^+$ T-cells and less proliferating tumour cells
- Increase in activated T-cells as observed with greater OX40 and HLADR expression
- Upregulation of PD-1 and PD-L1 upon GSK3359609 treatment.

- Immune phenotyping of the tumours using multiplexed immunofluorescence exhibits increase in functional markers representing TIL activation, cytotoxic function and proliferation in on-treatment tumour biopsy for subject number compared to their pre-treatment samples.

Conclusions

- GSK3359609 PK disposition is consistent with other humanised monoclonal antibodies, with low clearance and limited central volume of distribution. GSK3359609 PK was not affected by pembrolizumab.
- Evidence of target engagement and tumour size reductions is demonstrated in patients with R/R HNSCC and melanoma treated with 0.3–1.0 mg/kg doses of GSK3359609.
- A GSK3359609 dose range of 0.3–1.0 mg/kg is associated with a cytotoxic T-cell favourable anti-tumour microenvironment as demonstrated by increases in CD8:T reg ratio and their proliferation changes. The data provide further pharmacological evidence of agonist stimulation of the ICOS receptor at these doses, which could translate to clinical benefit.
- Overall, the current PK and non-monotone PD data provide evidence of GSK3359609 target engagement and biological activity and support continued exploration of GSK3359609 at 0.3–1.0 mg/kg, corresponding to a fixed dose range of ~24–80 mg.

References

1. Hutloff A, et al. *Nature* 1999; 397: 263-6.
2. Mayes PA, et al. *Nat Rev Drug Discov.* 2018; 17: 509-27.
3. Di Giacomo AM, et al. *Cancer Immunol Immunother.* 2013; 62:1021–1028.
4. Calabrò L, et al. *Lancet Oncol.* 2013; 14:1104–1111.
5. Brett S, et al. *ESMO* 2018 poster presentation: Abstract 1840P.
6. Yadavilli S, et al. *Abstract* 1637, Cancer Research 2017; 77: 1637.
7. Rischin D, et al. *ESMO* 2019 poster presentation: Abstract 1119PD.
8. Hansen AR, et al. *ESMO* 2018 poster presentation: Abstract 1138PD.
9. Turner DC, et al. *Clin Cancer Res.* 2019; 24(23): 5841-5849.

Presenting author email address: mmaiocro@gmail.com

Presented at
The European Society for Medical Oncology (ESMO) Congress, Barcelona, Spain, 27 September – 1 October 2019

Acknowledgements
We thank the patients and their families, the participating site co-investigators, research nurses, coordinators, supportive staff, and the GSK 204691 study and the ICOS biomarker team with special thanks to Qing Xia for data analysis support. The human biological samples were sourced ethically, and their research use was in accord with the terms of the informed consents under an IRB/EC approved protocol. Funding for this study 204691, NCT02723955, was provided by GlaxoSmithKline (GSK) in collaboration with Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA. Editorial support was provided by Chloe Stevenson of Fishawack Indicia Ltd, UK, and was funded by GSK.

EudraCT number: 2016-000148-32. ClinicalTrials.gov identifier:NCT02723955.