Updated Analysis of the Inducible T-Cell Co-Stimulatory Receptor (ICOS) Agonist, GSK3359609, in Combination With Pembrolizumab in Patients With Anti–PD-1/L1 Treatment-Naïve Head and Neck Squamous Cell Carcinoma (HNSCC)

Poster No. 178

Angevin E[1], Groenland SL[2], Lim AM[3], Martin-Liberal J[4], Moreno V[5], Trigo J[6], Le Tourneau C[7], Mathew M[8], Cho D[9], Hansen A[10], Vincente Baz D[11], Maio M[12], Italiano A[13], Bauman J[14], Chisamore M[15], Zhou H[16], Ellis C[16], Ballas M[16], Hoos A[16], Rischin D[17]

[1]Gustave Roussy Drug Development Department, Villejuif, France; [2]Netherlands Cancer Institute – Antoni van Leeuwenhoek, Amsterdam, the Netherlands; [3]Linear Clinical Research and Sir Charles Gairdner Hospital, Nedlands, Western Australia; [4]Vall d'Hebron Institute of Oncology (VHIO)-Cellex Center, Barcelona, Spain; [5]START Madrid-FJD, University Hospital "Fundacion Jimenez Diaz", Madrid, Spain; [6]Hospital Universitario Virgen de la Victoria, Málaga, Spain; [7]Department of Drug Development and Innovation (D3i), Institut Curie, Paris, France; [8]Columbia University Medical Center, New York, NY, USA; [9]New York University Langone Medical Center, New York, NY, USA; [10]Princess Margaret Cancer Centre, Toronto, ON, Canada; [11]Hospital Universitario Virgen Macarena, Seville, Spain; [12]University Hospital of Siena, Siena, Italy; [13]Institut Bergonié, Bordeaux, France;[14]Fox Chase Cancer Center, Philadelphia, PA, USA; [15]Merck & Co., Inc., Kenilworth, NJ, USA; [16]GSK, Collegeville, PA, USA; [17]Peter MacCallum Cancer Centre and the University of Melbourne, Melbourne, Australia

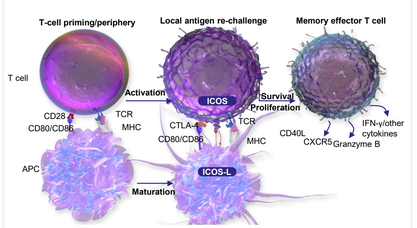
Background

ICOS is a member of the CD28 immunoglobulin receptor superfamily[1] that includes programmed cell death protein 1 (PD-1) and cytotoxic T-lymphocyte–associated protein 4 (CTLA-4)[2] and has a pivotal role in proliferation, differentiation, survival, and function of T cells (**Figure 1**).[3–6]

GSK3359609 is a humanized immunoglobulin G4 antibody selected for its agonist activity through the human ICOS receptor and low/no T-cell–depleting effects via antibody-dependent cellular toxicity in nonclinical models.[7]

Consistent with CTLA-4 and PD-1 blockade, ICOS agonism is anticipated to modulate T-cell dynamics to result in prolonged control of tumor growth kinetics and survival in patients with solid tumors.

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; TCR, T-cell receptor.

Rationale for combination of GSK3359609 with pembrolizumab in HNSCC

Nonclinical data support the rationale for targeting ICOS with GSK3359609 in combination with pembrolizumab (anti–PD-1) in HNSCC:

- Analysis of The Cancer Genome Atlas (TCGA) RNA-sequencing data showed strong correlation of ICOS and programmed death ligand 1 (PD-L1) in solid tumors such as HNSCC.[8]
- HNSCC is highly immunogenic, with tumors harboring high levels of both natural killer cells and CD8$^+$ T cells in addition to elevated expression of immune checkpoint modulators including PD-1 and ICOS.[9,10]
- ICOS agonist treatment led to upregulation of PD-1/L1 expression,[7] and an ICOS agonist in combination with PD-1 blockade resulted in enhanced antitumor activity when compared with either treatment alone.[7,8]

Promising initial results for GSK3359609 in HNSCC

INDUCE-1 (204691; NCT02723955) is an open-label, first-in-human study evaluating the safety, tolerability, pharmacokinetics (PK), pharmacodynamics (PD), and antitumor activity of GSK3359609 alone and in combination with other regimens, including pembrolizumab, in selected solid tumors including HNSCC.

- The study consists of dose escalation (DE) and cohort expansion (CE) phases.

Preliminary data from the INDUCE-1 CE phase demonstrated that GSK3359609 in combination with pembrolizumab had a promising signal for antitumor activity, with durable responses observed in 34 evaluable patients with PD-1/L1–naïve HNSCC[11]; as of July 26, 2019, the overall response rate (ORR) was 24%, median progression-free survival (mPFS) was 5.6 months, and median overall survival (mOS) was not reached.[11]

- In addition to activity in combination with pembrolizumab, GSK3359609 also showed single-agent activity in PD-1/L1–experienced patients with HNSCC.[11]

Objective

Here we report updated efficacy and safety data from the INDUCE-1 CE phase of GSK3359609 in combination with pembrolizumab in patients with anti–PD-1/L1 treatment-naïve HNSCC.

Methods

Study objectives

Study objectives and eligibility criteria have been described previously.[12]

The objectives of the updated analyses presented here are:

- **Primary:** Determine the safety and tolerability of GSK3359609 in combination with pembrolizumab in patients with HNSCC.
- **Secondary:** Further evaluate the antitumor activity of GSK3359609 in combination with pembrolizumab in patients with HNSCC.
- **Exploratory:** Evaluate the PD effects of GSK3359609 monotherapy in the blood and tumor, which include, but are not limited to, receptor occupancy, immune phenotyping, changes in tumor-infiltrating lymphocyte, and gene expression; these effects have also been evaluated in separate analyses.[13]

Study design

INDUCE-1 consists of two parts (Part 1: GSK3359609 monotherapy and Part 2: GSK3359609 combination therapy), whereby each part consists of a DE phase followed by a CE phase (**Figure 2**).

- Results from the DE cohorts[12] and CE PK/PD cohort[13] have previously been reported.

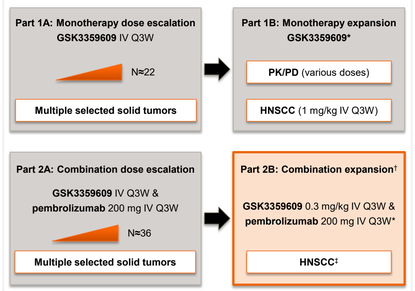
Within the HNSCC combination cohort, the recommended doses from Part 2A were selected for further investigation of safety, PK/PD activity, and preliminary clinical activity in Part 2B (CE).

Disease assessments were performed every 9 weeks through Week 54, then every 12 weeks.

ORR, disease control rate (DCR; defined as the percentage of patients with a complete response, partial response, or stable disease [SD] for ≥9 weeks or ≥18 weeks), PFS, and OS were assessed.

PD-L1 immunohistochemistry (IHC) testing was performed using an investigational version of the PD-L1 IHC 22C3 pharmDx assay (Agilent, Carpinteria, CA, USA).

Figure 2. Study Design



*For ≤2 years or until disease progression/unacceptable toxicity; †patients enrolled in Part 2B cohorts (GSK3359609/pembrolizumab combination) may be stratified by PD-L1 IHC status and prior PD-1/L1 treatment; ‡a subset of patients with HNSCC was randomized to one of three doses of GSK3359609 in combination with pembrolizumab 200 mg (data analysis ongoing, not part of the data set shown).
IV, intravenous; Q3W, every 3 weeks.

Key inclusion criteria

- Histological/cytological diagnosis of HNSCC with disease that is metastatic or locally/regionally recurrent.
- Anti–PD-1/L1 treatment naïve.
- ≤5 prior lines of therapy for advanced disease including both standard-of-care and investigational therapies.

Key exclusion criteria

- Prior anticancer or investigational therapy within 30 days or five half-lives, whichever is shorter.
- Grade ≥3 toxicity related to prior immunotherapy and led to treatment discontinuation.

Results

Demographics

As of March 30, 2020, 34 PD-1/L1–naïve patients in the combination HNSCC EC (Part 2B) were enrolled and received GSK3359609 0.3 mg/kg in combination with pembrolizumab 200 mg (**Table 1**); 34 patients were evaluable for efficacy analyses (evaluable population comprises all participants who received ≥1 dose of GSK3359609 and had ≥1 post-baseline disease assessment, or had progressed, died, or permanently discontinued treatment).

The median age was 62 years (range: 37–77), and 85% of patients were male.

Overall, 53% of patients received ≥1 prior line of systemic therapy in the metastatic setting, and 6% received ≥3 prior lines of therapy.

Table 1. Patient Demographics and Disease Characteristics

	Combination EC (N=34)
Sex, n (%), female/male	5 (15)/29 (85)
Median age, years (min, max)	62 (37, 77)
Primary site, n (%)	
Oropharynx	9 (26)*
Non-oropharynx	24 (71)
Oral cavity	11 (46)
Larynx	5 (21)
Hypopharynx	4 (17)
Nasosinus	3 (13)
Nasopharynx	1 (4)
Unknown	1 (3)
Disease setting, n (%)	
Data available	32 (94)
Metastatic	31 (97)
Local/regional recurrent only	1 (3)
Data not available	2 (6)
Number of prior systemic regimens in advanced/metastatic setting, n (%)	
0	16 (47)
1	11 (32)
2	5 (15)
≥3	2 (6)
Immunotherapy naïve, n (%)	34 (100)
PD-L1 status, n (%)	29 (85)
Data available	2 (7)
CPS <1	20 (69)
CPS ≥1 and <20	7 (24)
CPS ≥20	5 (15)
Data not available	

*33% of these patients were HPV positive and 66% were HPV negative.
CPS, combined positive score; HPV, human papilloma virus.

Clinical activity

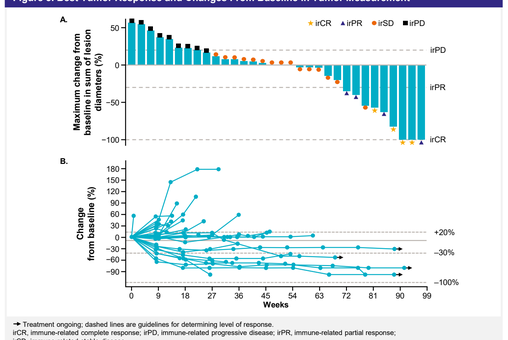
ORR for the 34 evaluable patients was 24% (95% CI: 10.7, 41.2; n=8).

- There were 4 complete responses and 4 partial responses.

DCR ≥9 weeks was 68% (95% CI: 49.5, 82.6; n=23) and DCR ≥18 weeks was 47% (95% CI: 29.8, 64.9; n=16) (**Figure 3A**).

Responses were durable, with all responding patients maintaining benefit for ≥6 months (**Figure 3B**).

Figure 3. Best Tumor Response and Changes From Baseline in Tumor Measurement



→ Treatment ongoing; dashed lines are guidelines for determining level of response.
iCR, immune-related complete response; iPD, immune-related progressive disease; iPR, immune-related partial response; iSD, immune-related stable disease.

Among patients with known PD-L1 IHC data (85%; n=29/34) (**Table 1**), the 2 patients with a CPS <1 had SD, 12/20 (60%) patients with CPS ≥1 and <20 had a response (complete response or partial response) or SD, and 5/7 (71%) patients with CPS ≥20 had a response or SD; CPS is determined by the number of staining tumor and immune cells relative to total tumor cells.

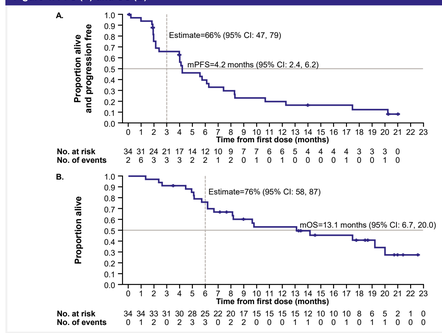
mPFS was 4.2 months (95% CI: 2.4, 6.2) (**Figure 4A**).

- The PFS rate at 3 months was estimated as 66% (95% CI: 47, 79).

mOS was 13.1 months (95% CI: 6.7, 20.0) (**Figure 4B**).

- The OS rate at 6 months was estimated as 76% (95% CI: 58, 87).

Figure 4. PFS (A) and OS (B)



Safety

Adverse events (AEs) and serious AEs in patients are described in **Table 2**.

- Overall, GSK3359609 in combination with pembrolizumab had a manageable safety profile.

Treatment-related AEs were reported in 66% of patients (**Figure 5**).

- The majority of the treatment-related AEs were Grade 1 or 2, with 6% of patients experiencing Grade ≥3 events.

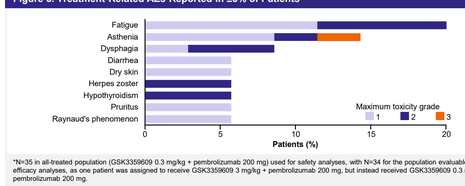
Immune-related AEs were not formally evaluated, but AEs with potential immune-mediated etiology were all Grade 1 or Grade 2.

Table 2. AE Profile

	Combination EC (N=35*)
Any AE	34 (97)
AE related to study treatment	23 (66)
AE leading to permanent discontinuation of study treatment	2 (6)
AE leading to dose interruption/delay	5 (14)
Any Grade ≥3 AE	14 (40)
Grade ≥3 AE related to study treatment	2 (6)
Grade 5 AE	1 (3)
Grade 5 AE related to study treatment	0

*N=35 in all-treated population (GSK3359609 0.3 mg/kg + pembrolizumab 200 mg) used for safety analyses, with N=34 for the population evaluable for efficacy analyses, as one patient was assigned to receive GSK3359609 3 mg/kg + pembrolizumab 200 mg, but instead received GSK3359609 0.3 mg/kg + pembrolizumab 200 mg.

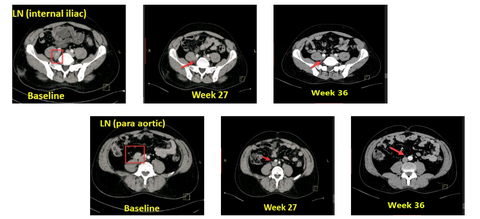
Figure 5. Treatment-Related AEs Reported in ≥5% of Patients*



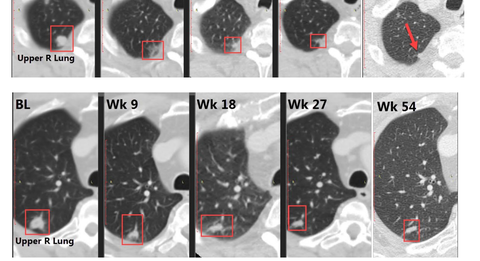
*N=35 in all-treated population (GSK3359609 0.3 mg/kg + pembrolizumab 200 mg) used for safety analyses, with N=34 for the population evaluable for efficacy analyses, as one patient was assigned to receive GSK3359609 3 mg/kg + pembrolizumab 200 mg, but instead received GSK3359609 0.3 mg/kg + pembrolizumab 200 mg.

	Case study 1: 44-year-old man	Case study 2: 72-year-old man
Disease	• R/M oral cavity SCC with distal nodal metastases • PD-L1 CPS: 6 • Disease burden: 39 mm (two target lesions: para aortic LN and internal iliac LN)	• R/M laryngeal SCC with lung metastases • PD-L1 CPS: 2 • Disease burden: 28 mm (two target lesions: lung)
Prior treatment	• Local excision/LN dissection • Cisplatin/radiotherapy (radiosensitizer) • Radiotherapy • Paclitaxel/carboplatin	• Laryngectomy/thyroidectomy • Methotrexate
Study treatment status	• Treatment ongoing at Week 96	• Treatment ongoing at Week 93
Best overall response	• Complete response (confirmed)	• Partial response (confirmed)

Case study 1



Case study 2



BL, baseline; LN, lymph node; R, right; R/M, recurrent/metastatic; SCC, squamous cell carcinoma; Wk, Week.

Conclusions

GSK3359609 in combination with pembrolizumab continues to show durable responses in patients with R/M HNSCC.

GSK3359609 in combination with pembrolizumab has a manageable safety profile.

The PFS and OS results show promising activity and support randomized clinical trials evaluating PFS and OS of GSK3359609 in combination with pembrolizumab in HNSCC.

- INDUCE-3 (NCT04128696) is a randomized, adaptive Phase II/III trial evaluating GSK3359609 in combination with pembrolizumab, versus pembrolizumab plus placebo, as a first-line treatment for PD-L1–positive R/M HNSCC[14]; the INDUCE-3 trial design is presented separately in Poster No. 252.[14]

Disclosures

This study was funded by GlaxoSmithKline (GSK) (204691, clinicaltrials.gov ID NCT02723955, EudraCT number 2016-000148-32) in collaboration with Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA. The presenting author (**EA**) declares the following real or perceived conflicts of interest during the last 3 years in relation to this presentation: had advisory/consultancy roles for MedImmune, Celgene, GSK, Merck Sharp and Dohme, and Roche; has received research funding from AbbVie, Pfizer, GSK, Sanofi, MedImmune, and Octimet; and reports travel/accommodations/expenses from Innate Pharma, Celgene, GSK, AbbVie, Bristol-Myers Squibb (BMS), and AstraZeneca (AZ). **SLG** has no conflicts of interest to declare. **AML** reports travel/accommodations/expenses from Merck Sharpe and Dohme. **JML** has had advisory/consultancy roles for Novartis, Roche, BMS, and Pierre Fabre; has held speakers' bureau roles for Novartis, Roche, MSD, Pfizer, BMS, Astellas Pharma, and Pierre Fabre; and reports travel/accommodations/expenses from Novartis, Roche, MSD, Pfizer, BMS, Ipsen, and Pierre Fabre. **VM** is an employee of START; had has advisory/consultancy roles for Merck, BMS, Bayer, and Janssen Oncology; has held a speaker bureau role for Bayer; reports travel/accommodations/expenses from Sanofi/Regeneron; has provided expert testimony for Medscape/Bayer and Nanobiotix; reports a relationship of other nature with BMS; and reports research funding from AbbVie, ACEA Biosciences, AdaptImmune, Amgen, AZ, Bayer, BeiGene, BMS, Boehringer Ingelheim, Celgene, Eisai, E-therapeutics, GSK, Janssen, Menarini, Merck, Nanobiotix, Novartis, Pfizer, PharmaMar, PsiOxus Therapeutics, Puma Biotechnology, Regeneron, Rigon TEC, Roche, Sanofi, Sierra Oncology, Synthon, Taiho Pharmaceutical, Takeda, Tesaro, and Transgene. **JT** has held advisory/consultancy roles for BMS, MSD, Takeda, and EISAI; held speakers' bureau roles for AZ, Bayer, MSD, and EISAI; and reports travel/accommodations/expenses from MSD and BMS. **CLT** has held advisory/consultancy roles for Amgen, MSD, BMS, Merck Serono, AZ, Nanobiotix, GSK, and Roche; reports travel/accommodations/expenses from MSD, BMS, and AZ; and has received honoraria from Novartis, BMS, MSD, Merck Serono, Roche, and Nanobiotix. **MMathew's** immediate family member holds stocks/shares in Navinita LLC and CorMedix. **DC** has had advisory/consultancy roles at HUYA BioScience International, Nektar, Torque, PureTech, and Pfizer and provided expert testimony for Genentech and Abbott/AbbVie. **AHa** has had advisory/consultancy roles for Genentech/Roche, Merck, GSK, BMS, Novartis, Boston Biomedical, and Boehringer Ingelheim; reports honoraria from Merck, AZ/MedImmune, Pfizer, GSK/Novartis, and BMS; and reports research funding from Karyopharm Therapeutics, Merck, BMS, Boehringer Ingelheim, GSK, Novartis, Roche/Genentech, and Janssen. **DVB** reports honoraria from AZ, Merck, BMS, Roche, MSD, and Pfizer; has had advisory/consultancy roles for AZ, Merck, BMS, Roche, MSD, and Pfizer; has provided expert testimony for MSD; and reports travel/accommodations/expenses from AZ. **MMaio** reports advisory/consultancy roles and travel/accommodations/expenses from BMS, Roche, AZ, MSD, Merck, Pierre Fabre, and Alfasigma; reports travel/accommodations/expenses from Amgen; holds patents/royalties/intellectual property (IP) in DNA Hypomethylating agents for cancer therapy; and holds stocks/shares in Theravance. **AI** has held advisory/consultancy roles for, received honoraria from, and received research funding from Roche and Bayer; has had an advisory/consultancy role for and received honoraria from Daiichi Sankyo, Epizyme, and Lilly; has had a consultancy/advisory role for Immune Design; received honoraria from Novartis and IPSEN; reports research funding from AZ/MedImmune, PharmaMar, MSD Oncology, and Merck Serono; and holds patents/royalties/IP in BMS. **JB** has had advisory/consultancy roles at Pfizer, Bayer, and AZ, and reports travel/accommodations/expenses from Trident Therapeutics. **MC** is an employee of and holds stocks/shares in Merck. **HZ** and **CE** are employees of and hold stocks/shares in GSK. **MB** is an employee of, reports stocks/shares in, received research funding from, holds patents/royalties/IP in, has received travel/accommodations/expenses from, and has held leadership roles at GSK; holds stocks/shares in BMS; and holds patents/royalties/IP in AZ. **AHo** is an employee of, holds stocks/shares and patents/royalties/IP in GSK, has had leadership roles at and owns stocks/shares in Imugene, and is a board member at Sabin Institute and Cancer Research Institute. **DR** reports travel/accommodations/expenses from Merck and reports research funding from Genentech/Roche, Merck, Regeneron, BMS, and GSK.

Acknowledgments

We thank the patients and their families, the participating site co-investigators, research nurses, coordinators, supportive staff, and INDUCE-1 study team including Sapna Yadavilli (biomarker lead), Courtney Henry (statistical support), Ruby Sung (statistical support), and Nancy Haeusser (programming 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. Editorial support (in the form of writing assistance, assembling tables and figures, collating author comments, grammatical editing, and referencing) was provided by Becky Salisbury, PhD, and Victoria Hunter, MSc, at Fishawack Indicia Ltd, UK, and was funded by GSK.

References

1. Hutloff A, et al. *Nature* 1999;397:263–6; 2. Sharpe AH, et al. *Nat Rev Immunol* 2002;2:116–26; 3. Burmeister Y, et al. *J Immunol* 2008;180:774–82; 4. Fazilleau N, et al. *Nat Immunol* 2007;8:753–61; 5. Guedan S, et al. *Blood* 2014;124:1070–80; 6. Simpson TR, et al. *Curr Opin Immunol* 2010;22:326–32; 7. Brett S, et al. ESMO 2018 poster presentation: Abstract 1840P; 8. Yadavilli S, et al. AACR 2017 poster presentation: Abstract 1637/15; 9. Cavalieri S, et al. *Cancer Treat Rev* 2018;65:78–86; 10. Mandal R, et al. *JCI Insight* 2016;117:e89829; 11. Rischin D, et al. ESMO 2019 poster presentation: Abstract 1119PD; 12. Hansen A, et al. ESMO 2018 poster presentation: Abstract 1138PD; 13. Maio M, et al. ESMO 2019 poster presentation: Abstract 1971P; 14. Hansen A, et al. ASCO 2020 poster presentation: Abstract TPS6591.

Please find the online version of this poster by scanning the quick response (QR) code or via http://tago.ca/ASCO_12.
Copies of this poster obtained through QR Code are for personal use only and may not be reproduced without permission from ASCO® and the author of this poster.

For questions, please contact presenting author Eric Angevin at Eric.ANGEVIN@gustaveroussy.fr

Presented at the American Society for Clinical Oncology (ASCO) Congress, Virtual Scientific Program, May 29–31, 2020