Inducible T-cell co-stimulatory (ICOS) receptor agonist, GSK3359609, alone and in combination with pembrolizumab: preliminary results from INDUCE-1 expansion cohorts in head and neck squamous cell carcinoma (HNSCC)

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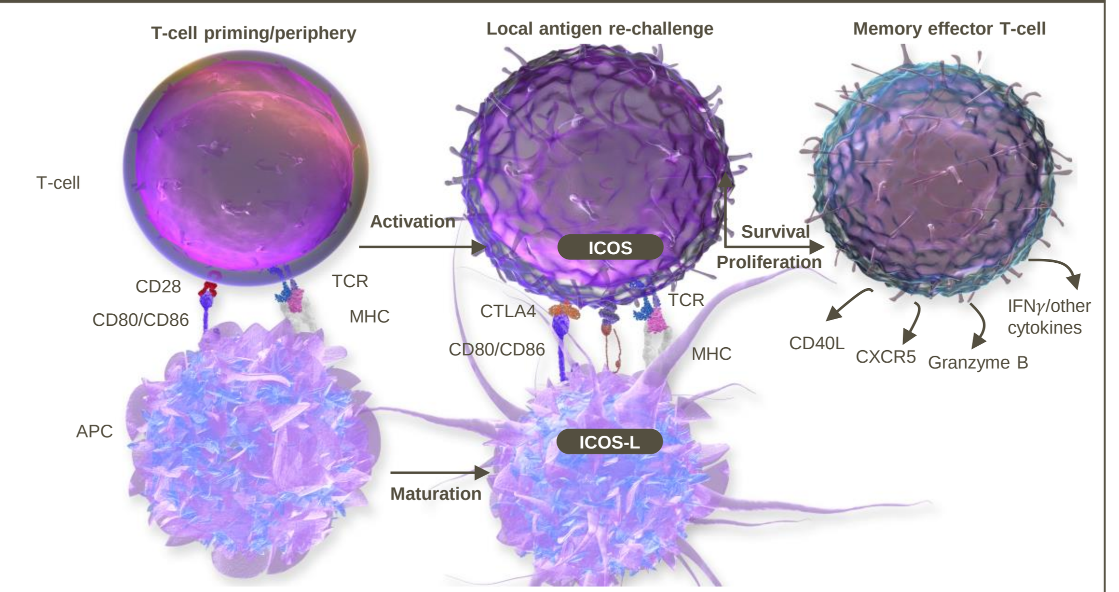
Background

- Inducible T-cell co-stimulator (ICOS), a member of the CD28 immunoglobulin (Ig) receptor superfamily that includes cytotoxic T-lymphocyte associated protein-4 (CTLA-4) 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]
- 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.

Figure 1. ICOS mechanism of action



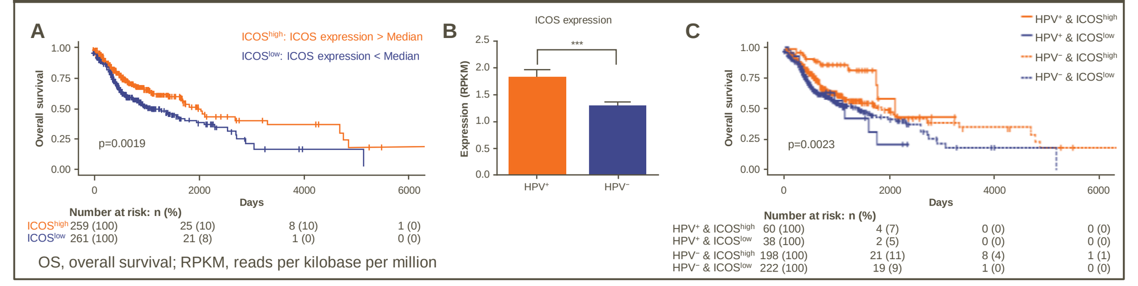
APC, antigen-presenting cell; CXCR5, C-X-C motif chemokine receptor 5; ICOS-L, ICOS ligand; IFN-γ, interferon gamma; MHC, major histocompatibility complex.

- 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]
- Anti-tumour activity observed with an ICOS agonist is further enhanced in combination with CTLA-4 and PD-1 blockade in non-clinical models.[5,6] ICOS agonist treatment led to upregulation of PD-1/programmed death-ligand 1 (PD-L1) expression in these models.[5] Furthermore, analysis of The Cancer Genome Atlas (TCGA) RNA-sequencing data shows strong correlation of ICOS and PD-L1 in solid tumours, further supporting clinical evaluation of this combination.[6]
- The unique mechanistic profile of GSK3359609 as an ICOS agonist allows investigation of the anti-tumour potential of targeting a T-cell co-stimulator alone and in combination with pembrolizumab.
- 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.
  - The study consists of dose escalation (DE) and cohort expansion (CE) phases.
  - Findings from DE and the PK/PD monotherapy cohort demonstrated a range of GSK3359609 doses (≥0.1–1 mg/kg) have biological and clinical activity, supporting the mechanism of action of GSK3359609 and ICOS as a clinical target.[7-9]
  - Here we report preliminary efficacy and safety findings of GSK3359609 used alone and in combination with pembrolizumab in head and neck squamous cell carcinoma (HNSCC), in PD-1/L1-experienced and PD-1/L1-naïve patients, respectively.

Rationale for exploration of GSK3359609 in HNSCC

- HNSCC is highly immunogenic with tumours harbouring 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.[10-12]
- Analysis of RNA data obtained from TCGA showed ICOS expression is highest (36.9%; 157/426) in head and neck (H&N) tumours when compared with a number of other solid tumours; further analysis of ICOS expression and OS effect in HPV+/HPV− HNSCC from TCGA data is shown in **Figure 2**.

Figure 2. A) OS rates are higher in patients with high ICOS-expressing (ICOS^high) HNSCC tumours when compared with patients with low ICOS expressing (ICOS^low) HNSCC tumours; B) ICOS expression is higher in HPV+ H&N tumours than those that are HPV−; and C) OS rates are higher in patients with HPV+/ICOS^high HNSCC tumours, when compared with patients with HPV+ICOS^low HNSCC tumours



OS, overall survival; RPKM, reads per kilobase per million

Study objectives

- Study objectives and eligibility criteria have been described previously.[8]
- The objectives of the analyses presented here are:
  - Primary: Determine the safety and tolerability of GSK3359609 as monotherapy and in combination with pembrolizumab in patients with HNSCC.
  - Secondary: Evaluate the anti-tumour activity of GSK3359609 as monotherapy and in combination with pembrolizumab in patients with HNSCC.
- Exploratory: The PD effects of GSK3359609 monotherapy in the blood and tumour, which include, but are not limited to, receptor occupancy, immune phenotyping, changes in TIL and gene expression, have been evaluated in separate analyses.[9]

Methods

Key inclusion criteria

- Histological/cytological diagnosis of HNSCC with disease that is metastatic or locally/regionally recurrent.
- Disease that has progressed after standard HNSCC therapy, or for which standard therapy has proven ineffective, intolerable or is considered inappropriate, or if no further standard therapy exists, with the exception that prior treatment with pembrolizumab was not required for the GSK3359609/pembrolizumab expansion cohorts (EC).
- ≤5 prior lines of therapy for advanced disease including both standard of care and investigational therapies.

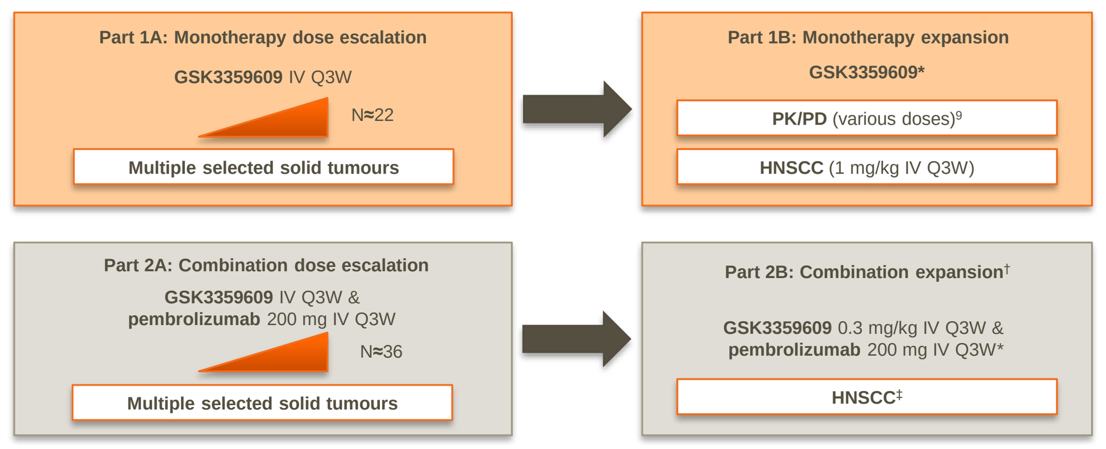
Key exclusion criteria

- Prior anticancer or investigational therapy within 30 days or five half-lives, whichever is shorter.
- Prior pembrolizumab washout is not required in patients receiving GSK3359609 in combination with pembrolizumab.
- ≥Grade 3 toxicity related to prior immunotherapy and led to treatment discontinuation.

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 3**).
  - The DE phases (Parts 1A and 2A) were previously reported.[8]
  - Within the HNSCC cohorts, the recommended doses from Parts 1A and 2A were selected for further investigation of safety, PK/PD activity, and preliminary clinical activity in Part 1B and 2B (CE).
- Disease assessments were performed every 9 weeks through Week 54, then every 12 weeks.
- Overall response rate (ORR), disease control rate (DCR), progression-free survival (PFS) and overall survival (OS) were assessed.

Figure 3. 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 HNSCC patients were randomised 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.

Results

Demographics

- As of 26 July 2019, 17 PD-1/L1-experienced patients in the monotherapy and 34 PD-1/L1-naïve patients in the combination HNSCC ECs were enrolled (**Table 1**); 16 and 34 patients, respectively, were evaluable for efficacy analysis (evaluable population comprises all participants who received ≥1 dose of GSK3359609 and had ≥1post-baseline disease assessment, or had progressed, died or permanently discontinued treatment).
- In the monotherapy EC, 82% of patients in the all-treated population (patients who received ≥1 dose of GSK3359609) received ≥1 prior line in the metastatic setting; in the combination EC, 53% received ≥1 prior line in the metastatic setting.

Efficacy

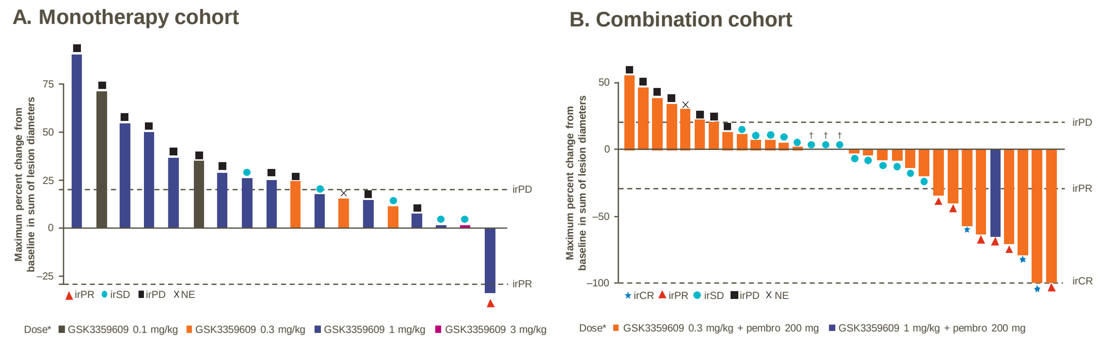
- Of the 16 evaluable patients in the monotherapy cohort, the ORR was 6% (n=1; 95% confidence interval [CI]: 0.2, 30.2) and the DCR, defined as the percentage of patients with a complete response, partial response or stable disease for ≥9 weeks, was 31% (n=5; 95% CI: 11, 58.7) (**Figure 4A**). In the combination cohort ORR was 24% (n=8; 95% CI: 10.7, 41.2) (**Figure 4B**) and the DCR was 65% (n=22; 95% CI: 46.5, 80.3) from 34 evaluable patients.

Table 1. Patient demographics and disease characteristics

	Monotherapy EC N=17	Combination EC N=34
Sex, n (%), female / male	3 (18) / 14 (82)	5 (15) / 29 (85)
Median age, years (min, max)	56 (41-73)	62 (37-77)
Primary site, n (%)		
Oropharynx*	5 (29)	10 (29)
Non-oropharynx†	12 (71)	24 (71)
Disease setting, n (%)		
Metastatic	16 (94)	31 (91)
Local/regional recurrent only	1 (6)	3 (9)
≥2 target & non-target lesion locations, n (%)	16 (94)	27 (79)
≥3 prior systemic regimens in advanced/metastatic setting, n (%)	6 (36)‡	2 (6)

*HPV positive: 80% in monotherapy EC and 30% in combination EC; †majority were oral cavity or hypopharynx (>50%); included the primary sites such as: nasopharynx, sinonasal cavity, and HNSCC of unknown primary; ‡50% (n=3) of these patients had ≥4 prior systemic regimens in advanced/metastatic setting.

Figure 4. Best tumour response



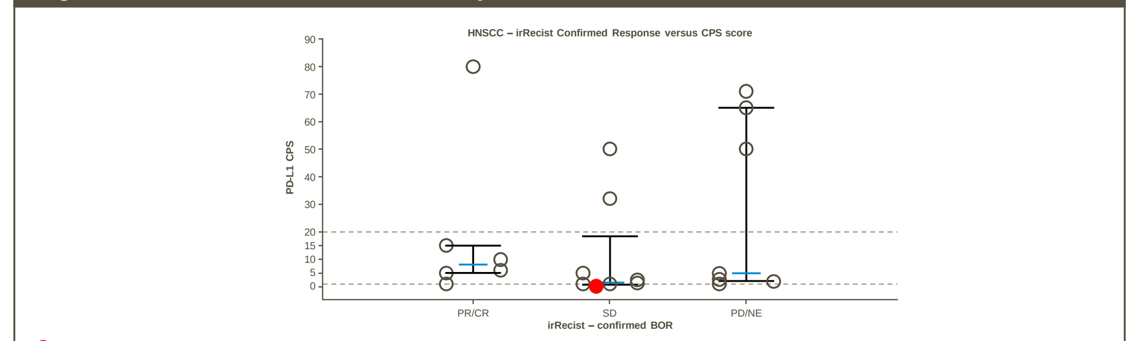
*Patients from both DE and CE phases included.

*Patients (non-randomised) from both DE and CE phases included; †patients received GSK3359609 0.3 mg + pembro 200 mg.

irCR, immune-related complete response; irPD, immune-related progressive disease; irPR, immune-related partial response; irSD, immune-related stable disease; NE, not evaluable; pembro, pembrolizumab

- PD-L1 immunohistochemistry (IHC) testing was performed using an investigational version of the PD-L1 IHC 22C3 pharmDx assay (Agilent, Carpinteria, CA, USA). Among patients with known PD-L1 IHC data (n=21/34), a majority of responders and patients with stable disease have PD-L1 status <20 (10/14 patients with combined positive score [CPS] ≥1 and <20, and 1 patient with CPS <1; CPS is the number of staining tumour and immune cells relative to total tumour cells) (**Figure 5**).

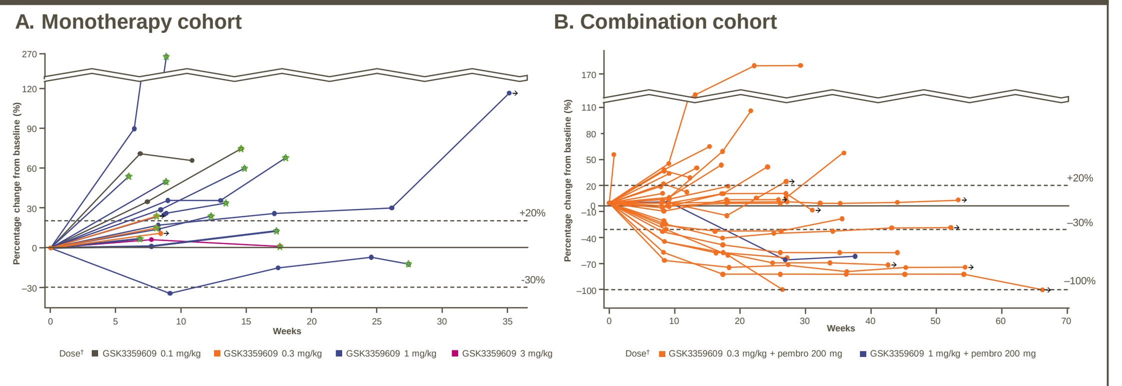
Figure 5. PD-L1 immunohistochemistry



● denotes CPS <1 was imputed to 0.5 to enable graphing; area between the dashed lines indicates 1 ≤ CPS <20; the median is indicated by a blue line. BOR, best overall response; CPS, combined positive score; CR, complete response; irRECIST, immune-related Response Evaluation Criteria In Solid Tumours; PD, progressive disease; PR, partial response; SD, stable disease

- Further accrual in the monotherapy cohort was halted due to protocol defined futility rules.
- Responses in the combination cohort were durable with all responding patients maintaining benefit for ≥6 months (median not reached [NR]; 95% CI: 4.2 months, NR) (**Figure 6B**).

Figure 6. Change from baseline in tumour measurement



★PD-1/L1 experienced patients; → treatment ongoing; †patients from both DE and CE phases included.
Dashed lines are guidelines for determining level of response. Breaks in y-axes inserted to facilitate data interpretation.

- Median PFS in the combination cohort was 5.6 months (95% CI: 2.4, 7.4) (**Figure 7**).
- For the combination cohort, median OS was not reached at time of analysis (95% CI: 8.2, NR) (**Figure 8**); further analyses of OS are ongoing.

Figure 7. PFS for combination therapy

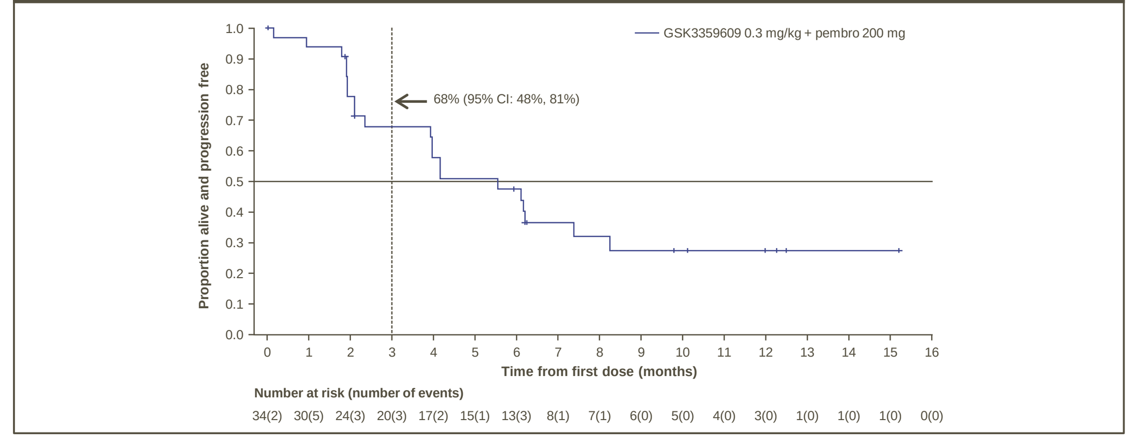
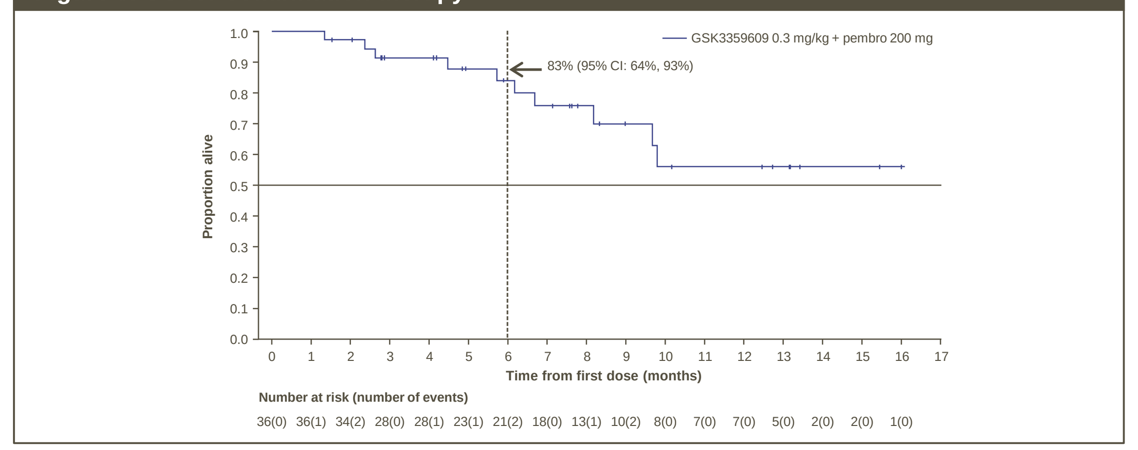


Figure 8. OS for combination therapy



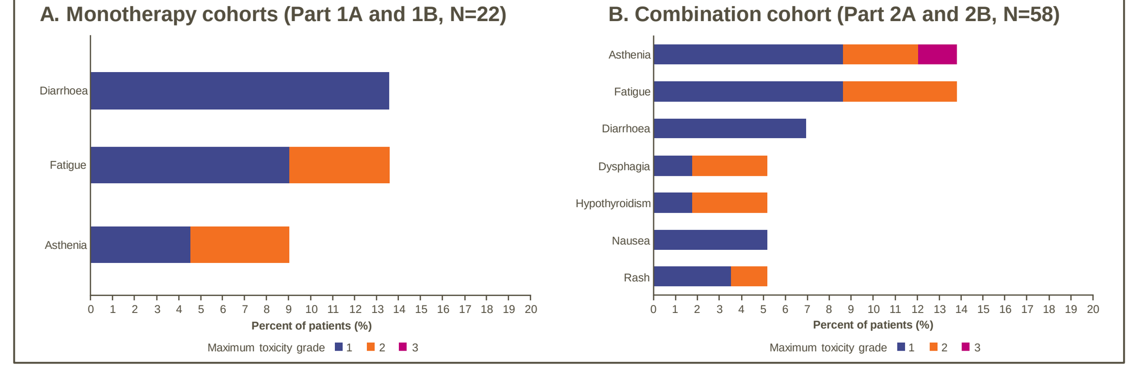
Safety

- Adverse events (AEs) and serious AEs (SAEs) in patients with HNSCC (all study cohorts) are described in **Table 2**.
  - Overall, both GSK3359609 alone and in combination with pembrolizumab were well tolerated in HNSCC populations.
- Treatment-related AEs in patients with HNSCC across all study cohorts in the monotherapy (n=22) and combination populations (n=58) (**Figure 9**) were consistent with that previously reported.[8]

Table 2. AEs and SAEs in the HNSCC cohorts

n, (%)	Monotherapy GSK3359609 all doses (N=22)	Combination GSK3359609 all doses & pembrolizumab 200 mg (N=58)
Any AE	22 (100)	52 (90)
AE related to study treatment	9 (41)	37 (64)
AEs leading to permanent discontinuation of study treatment	0	3 (5)
AEs leading to dose interruption/delay	3 (14)	5 (9)
Any Grade ≥3 AE	15 (68)	19 (33)
Grade ≥3 AE related to study treatment	2 (9)	4 (7)
Grade 5 AEs	0	2 (3)
Grade 5 AE related to study treatment	0	0

Figure 9. Treatment-related AEs reported in ≥5% of patients

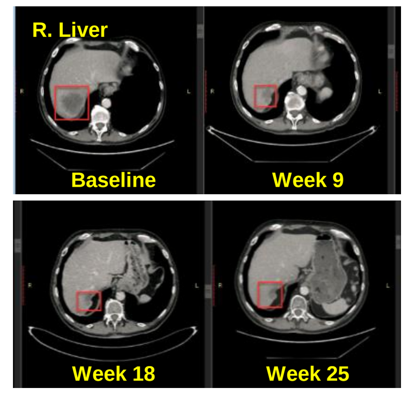


Case study 1

GSK3359609 monotherapy:
HNSCC Patient – 64 year old male

History:

- Diagnosis:
  - Initial diagnosis: April 2013; Stage IVa HNSCC (oral cavity)
- Prior regimens:
  - Cisplatin/radiotherapy (adjuvant, July–Sept 2013, complete response)
  - Carboplatin (Dec 2016–Mar 2017; progressive disease) → cetuximab maintenance (Mar–May 2017; progressive disease)
  - Methotrexate (June–Aug 2017; progressive disease)
  - Nivolumab (Oct–Dec 2017; progressive disease)
- Study treatment
  - Cycle 1 Day 1: 15 Jan 2018
  - GSK3359609 monotherapy at 1 mg/kg to Week 30, then receiving GSK3359609 + pembrolizumab 200 mg (crossover) from Week 33 to Week 51

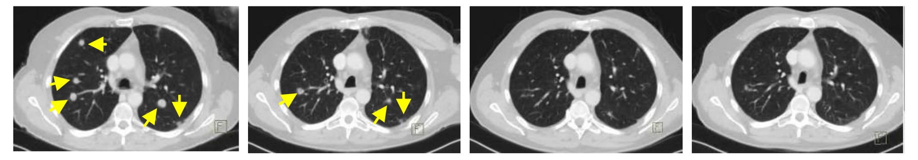


Case study 2

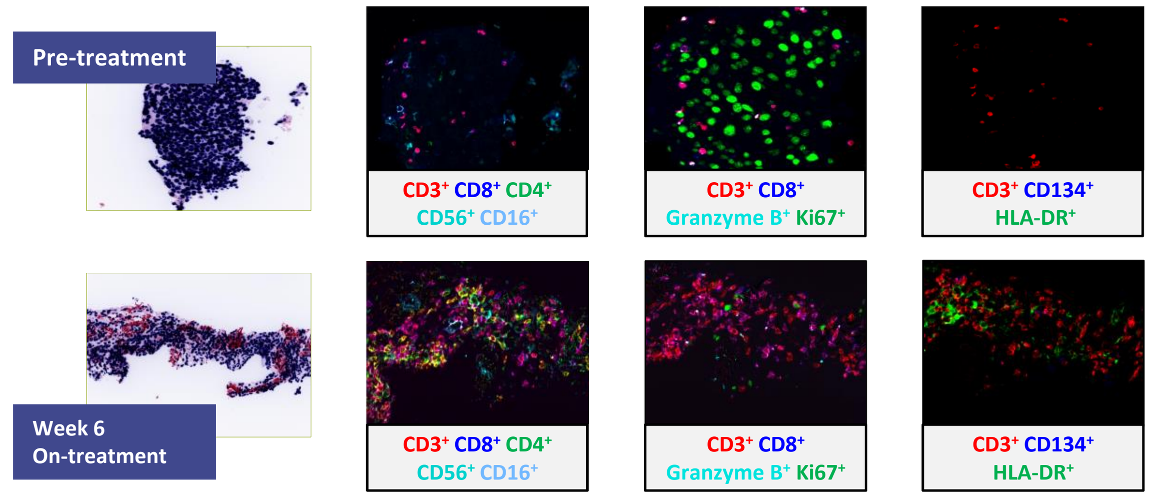
GSK3359609/pembrolizumab combination therapy:
HNSCC Patient – 61 year old male

History:

- Diagnosis:
  - Initial diagnosis: 20 Nov 2017, Stage III, HPV+ oropharyngeal squamous cell carcinoma)
  - Diagnosis with metastasis: 13 Dec 2017
- Prior regimens:
  - Radiotherapy (8 Jan–23 Feb 2018, progressive disease) with cisplatin (radio-sensitiser, 9 Jan–30 Jan 2018) and carboplatin/paclitaxel (radio-sensitiser, 20 Feb 2018)
- Study treatment
  - Cycle 1 Day 1: 6 Aug 2018; discontinued after Week 30 due to progressive disease
  - GSK3359609 at 0.3 mg/kg + pembrolizumab 200 mg
  - PD-L1 CPS 15



Baseline Week 9 Week 18 Week 27



Post-treatment sample showed

- More TILs including cytotoxic, helper T-cells and natural killer cells.
- More proliferating T-cells, granzyme B+ cells and less proliferating tumour cells.
- More activated T-cells as observed with greater OX40 and human leukocyte antigen D (HLA-DR) expression.

Conclusions

- GSK3359609 monotherapy and in combination with pembrolizumab shows a manageable safety profile in patients with previously treated HNSCC.
- GSK3359609 has single-agent activity in PD-1/L1-experienced HNSCC with a promising signal in combination with pembrolizumab in PD-1/L1 naïve HNSCC. Further follow-up, including survival, is ongoing in this study (204691).
- Randomised trials are ongoing to investigate the potential survival benefit of GSK3359609 ICOS agonist.

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Disclosures

SLG has no conflicts of interest to declare. MMathew holds equity in Navinta LLC. DR has had an advisory/consultancy role for Merck Sharp & Dohme (MSD), Regeneron, GSK and Bristol-Myers Squibb (BMS); received institutional grant/research support from Regeneron, Roche, MSD, GSK, BMS and travel/accommodation/expenses from MSD. AML has received advisory board support (uncompensated) from MSD and BMS with travel and accommodation expenses. JML has received lecture fees, advisory fees and travel grants from BMS, MSD, Novartis, Roche and Pierre Fabre; lecture fees from Astellas and Ipsen and travel grants from Pfizer and Ipsen. VM has had an advisory/consultancy role for Merck and BMS; received travel/accommodation/expenses from Regeneron/Sanofi and BMS; given presentations for Nanobiotix, BMS and received research grant/funding support from Medscape/Bayer. JT has had an advisory/consultancy and speakers bureau role for and received travel expenses from Roche, AstraZeneca, Boehringer-Ingelheim, BMS and MSD. CLT has financial interests in MSD, BMS, GSK, Astra Zeneca, Nanobiotix, Rakuten, Roche, Merck Serono and Celgene. DC has had an advisory/consultancy role for Nektar Therapeutics, PureTech, HUYA Pharmaceuticals and Torque Pharmaceuticals. AHansen has had an advisory/consultancy role for and research grant/funding support from Genentech/Roche, Merck, GSK, BMS, Novartis, Boston Biomedical, Boehringer-Ingelheim, AstraZeneca and Medimmune. DVB has had an advisory/consultancy role for AstraZeneca, Roche, Pfizer, Boehringer-Ingelheim and MSD. MMaio has had an advisory board role for and travel expenses from GSK, BMS, AstraZeneca, Roche, MSD, Incyte and patient's fee for subjects enrolled in clinical trials from BMS, GSK, AZ, Roche, Merck, MSD, Incyte and Novartis. AI has had an advisory/consultancy role for Bayer, Epizyme, ImmuneDesign, Lilly, Merck, MSD, Novartis and Roche and received institutional grant/research support from AstraZeneca, Bayer, Merck, MSD, Pharmamar and Roche. JB has had an advisory/consultancy role from Pfizer and Bayer. MC is an employee of and holds stocks/shares in Merck. HZ is an employee of GSK. MB is an employee of GSK and holds stock in GSK, BMS, Abbott and Novartis. CE, DRogan and AHoos are employees of and hold stocks/shares in GSK. EA has an advisory/consultancy role for MSD, GSK, Celgene Research and MedImmune; received travel/accommodation/expenses from AbbVie, Roche, Sanofi, Pfizer, MedImmune, Innate Pharma, Celgene and BMS and is a principal/sub-investigator of clinical trials for AbbVie, Aduro, Agios, Amgen, Argen-x, Astex, AstraZeneca, Aveo pharmaceuticals, Bayer, Beigene, Blueprint, BMS, Boehringer-Ingelheim, Celgene, Chugai, Clovis, Daiichi Sankyo, Debiopharm, Eisai, Eos, Exelixis, Forma, Gamamabs, Genentech, Gortec, GSK, H3 Biomedicine, Incyte, Innate Pharma, Janssen, Kura Oncology, Kyowa, Lilly, Loxo, Lysarc, Lytix Biopharma, Medimmune, Menarini, Merus, MSD, Nanobiotix, Nektar Therapeutics, Novartis, Octimet, Oncoethix, Oncopeptides AB, Orion, Pfizer, Pharmamar, Pierre Fabre, Roche, Sanofi, Servier, Sierra Oncology, Taiho, Takeda, Tesaro and Xencor.

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