INDUCE-1: Report on Safety Run-in Cohorts Combining Inducible T-cell Co-stimulatory Receptor Agonist GSK3359609 With 5-Fluorouracil/Platinum Chemotherapy, With or Without Pembrolizumab, for the Treatment of Advanced Solid Tumors

Poster No. 205

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Background

The programmed cell death protein 1 (PD-1) inhibitor pembrolizumab was approved as first-line treatment for recurrent or metastatic (R/M) head and neck squamous cell carcinoma (HNSCC) alone or in combination with the chemotherapy regimen 5-fluorouracil plus platinum agent (5-FU/platinum) based on results from the KEYNOTE-048 study.[1]

In some patients, inhibition of suppressive immune checkpoint pathways alone may not elicit an effective tumor response; therefore, combining agents with immunomodulatory properties (including chemotherapies) that target different aspects of the cancer immunity cycle may generate more effective immune responses and overcome possible escape mechanisms.[2,3]

Co-stimulators such as inducible T-cell co-stimulatory (ICOS) receptor agonists may enhance the adaptive immune response and potentiate the antitumor activity of immunomodulatory and other anticancer therapies.[4]

GSK3359609 is a humanized immunoglobulin 4 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. It has demonstrated antitumor activity in combination with cytotoxic T-lymphocyte–associated protein-4 (CTLA-4) and PD-1 blockade in nonclinical models.[4]

Results from the Phase I INDUCE-1 study, the first-in-human study of GSK3359609, demonstrated that GSK3359609 with or without pembrolizumab has a manageable safety profile in patients with advanced solid tumors[5] and promising antitumor activity in patients with anti–PD-1/programmed death ligand 1 (PD-L1) therapy-naive HNSCC.[6]

Objective

Here we report safety and pharmacokinetic (PK) data from the INDUCE-1 safety cohort of GSK3359609 in combination with 5-FU/platinum chemotherapy plus pembrolizumab in patients with recurrent or metastatic HNSCC, and without pembrolizumab in patients with advanced solid tumors.

Methods

Study design

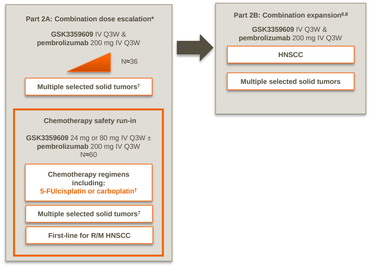
INDUCE-1 (NCT02723955) is a Phase I study with two parts: Part 1: GSK3359609 monotherapy and Part 2: GSK3359609 combination therapy, with each part consisting of a dose escalation phase followed by a cohort expansion phase (**Figure 1**).

- The dose escalation phases (Parts 1A and 2A)[3] and expansion cohort results for patients with HNSCC[4] were previously reported.
- Part 2A also includes safety run-in cohorts evaluating GSK3359609 combinations with chemotherapy with or without pembrolizumab. Preliminary results of combinations including 5-FU/platinum chemotherapy are reported in this poster:
  - GSK3359609 plus 5-FU/platinum was evaluated in advanced solid tumors.
  - GSK3359609 plus 5-FU/platinum plus pembrolizumab was evaluated as a first-line treatment for R/M HNSCC.

5-FU (1000 mg/m^2/platinum (cisplatin 100 mg/m^2 or carboplatin area under the curve [AUC] 4–6 mg/mL/min) was administered every 3 weeks (Q3W) for 4–6 cycles, and GSK3359609 (24 or 80 mg) with or without pembrolizumab (200 mg) was administered Q3W for up to 2 years/35 cycles or until disease progression or unacceptable toxicity.

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

Figure 1. Study design for INDUCE-1 Part 2



*GSK3359609 may also be evaluated in combination with other immunotherapies; †data from this regimen only are presented in this poster.
IV, intravenous

Key inclusion criteria

Diagnosis of selected solid tumors that are metastatic or recurrent/regional, and measurable according to Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 guidelines.

Eastern Cooperative Oncology Group (ECOG) Performance Status of 0–1.

Adequate organ function.

Disease that had progressed following standard therapy (or for which standard therapy had proven ineffective or intolerable or was considered inappropriate, or if no further standard therapy exists), with the exception that prior treatment with pembrolizumab was not required for patients with HNSCC.

≤5 prior lines of systemic therapy, including both standard of care and investigational therapies if receiving GSK3359609 plus 5-FU/platinum.

Disease deemed incurable by local therapies if receiving first-line treatment of GSK3359609 plus 5-FU/platinum plus pembrolizumab for R/M HNSCC.

Outcome assessments

Safety (adverse events [AEs], serious AEs [SAEs]) and PK were assessed.

Results

Patient characteristics

As of data cut-off of March 30, 2020, a total of 33 patients were enrolled in these 5-FU/platinum safety cohorts:

- 14 patients in the GSK3359609 plus 5-FU/platinum cohort and 19 in the GSK3359609 plus 5-FU/platinum plus pembrolizumab cohort (**Table 1**).
- All patients received at least one dose of study treatment and were evaluated for safety (safety data cut-off March 16, 2020).

Table 1. Patient baseline characteristics

Characteristic	GSK3359609 plus 5-FU/platinum (advanced solid tumors) (n=14)	GSK3359609 plus 5-FU/platinum plus pembrolizumab (HNSCC) (n=19)
Tumor type, n (%)		
Head and neck	5 (36)	19 (100)
HNSCC	4 (80)	19 (100)
Other	1 (20)	0
Colorectal cancer	3 (21)	-
Malignant pleural mesothelioma	2 (14)	-
Melanoma	1 (7)	-
Bladder/urothelial	1 (7)	-
Cervical cancer	1 (7)	-
Other	1 (7)*	-
Primary site (HNSCC), n (%)		
Oropharynx	1 (25)	9 (47)†
Non-oropharynx	3 (75)	8 (42)
Hypopharynx	-	3 (38)
Oral cavity	-	4 (50)‡
Larynx	-	1 (13)
Unknown primary	-	2 (11)
Age, median (range), years	57.5 (45–80)	61.0 (46–74)
Sex, n (%)		
Female	4 (29)	2 (11)
Male	10 (71)	17 (89)
Disease setting, n (%)‡		
Metastatic only	-	4 (21)
Local/regional recurrent only	-	6 (32)
Metastatic and local/regional recurrent	-	9 (47)
Chemotherapy regimen received, n (%)		
5-FU + cisplatin	5 (36)	8 (42)
5-FU + carboplatin	9 (64)	11 (58)
Prior lines of systemic anticancer therapy in advanced/metastatic setting, n (%)		
0	3 (21)	-
1	4 (29)	-
2	3 (21)	-
≥3	4 (29)	-
PD-L1 expression (CPS score), n (%)§		
Known CPS score	-	11 (58)
CPS <1	-	1 (9)
CPS ≥1	-	10 (91)
CPS ≥20	-	8 (73)
Unknown	-	8 (42)

*Salivary gland; †human papillomavirus status was positive in 1 patient, negative in 4 patients, and unknown in 4 patients; ‡data based on screening documents; §data pending formal transfer into official database.
CPS, combined positive score

Pharmacokinetics

No difference in GSK3359609 exposure was observed in combination treatment compared with GSK3359609 monotherapy; preliminary plasma PK parameters of chemotherapy agents are shown in **Table 2**.

Table 2. Preliminary plasma PK parameters*

Chemotherapy	Dose	N	PK parameter, median (range)	
			C_{max} (μg/mL)	$AUC_{(0-t)}$ (h*μg/μL)
Carboplatin	AUC 4–6 mg/mL/min	38	27.9 (1.96, 48)	54.6 (4.32, 81.4)
Cisplatin	100 mg/m^2	10	4.12 (2.43, 5.96)	11.9 (7.52, 16.7)
5-FU	1000 mg/m^2/day	17	0.51 (0.03, 10.1)	24.5 (1.28, 488)

*Day 1, first dosing interval.
Note: PK parameters are computed with nominal times; data are from patients in any study cohort who received these agents and are not limited to cohorts described in this poster.
C_{max}, maximum concentration

Safety

As of safety data cut-off of March 16, 2020, all patients in both cohorts had experienced at least one AE and at least one treatment-related AE (**Table 3**).

The most common AEs of any grade (occurring in ≥40% patients) for the following subgroups were:

- GSK3359609 plus 5-FU/cisplatin (advanced solid tumors): asthenia, alopecia, diarrhea, nausea, and neutropenia.
- GSK3359609 plus 5-FU/carboplatin (advanced solid tumors): nausea and neutropenia.
- GSK3359609 plus 5-FU/cisplatin plus pembrolizumab (first-line for HNSCC): diarrhea, nausea, anemia, and fatigue.
- GSK3359609 plus 5-FU/carboplatin plus pembrolizumab (first-line for HNSCC): mucosal inflammation and neutropenia.

Treatment-related AEs were mostly Grade 1 or 2, with the most common being the same as the AEs reported above with the exception of anemia in patients treated first-line for HNSCC who received cisplatin (reported in 38%).

Grades 3–4 treatment-related AEs are shown in **Figure 2**.

SAEs were more frequent among patients who received cisplatin compared with carboplatin in both cohorts (**Table 3**).

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

Clinical activity

At data cut-off of March 30, 2020, 23 (70%) patients remained on study treatment (**Figure 3**); these include 8 (57%) patients with advanced solid tumors and 15 (79%) patients receiving first-line treatment for HNSCC. Patients are being followed for clinical activity.

Table 3. Safety summary

	GSK3359609 plus 5-FU/cisplatin (advanced solid tumors) (n=5)	GSK3359609 plus 5-FU/carboplatin (advanced solid tumors) (n=9)	GSK3359609 plus 5-FU/cisplatin plus pembrolizumab (HNSCC) (n=8)	GSK3359609 plus 5-FU/carboplatin plus pembrolizumab (HNSCC) (n=11)
AE of any grade, n (%)	5 (100)	9 (100)	8 (100)	11 (100)
Treatment related	5 (100)	9 (100)	8 (100)	11 (100)
Leading to treatment discontinuation*	0	0	3 (38)	2 (18)
Leading to dose reduction†	1 (20)	2 (22)	1 (13)	4 (36)
Leading to dose delay/interruption†	1 (20)	2 (22)	2 (25)	4 (36)
Any SAE, n (%)	3 (60)	0	7 (88)	4 (36)
Treatment related	3 (60)	0	4 (50)	2 (18)
Fatal	0	0	1 (13)‡	0
Treatment related, fatal	0	0	0	0

*5 patients discontinued 5-FU and/or platinum due to associated toxicities (vomiting, diarrhea/colitis, chest pain/atrial fibrillation, cytopenias, and worsening of asthenia); †most common causes of treatment delay or dose reduction were cytopenias, such as neutropenia and thrombocytopenia, and mucositis; ‡mouth hemorrhage, not treatment related.

Figure 2. Grade ≥3 treatment-related AEs by preferred term and maximum grade

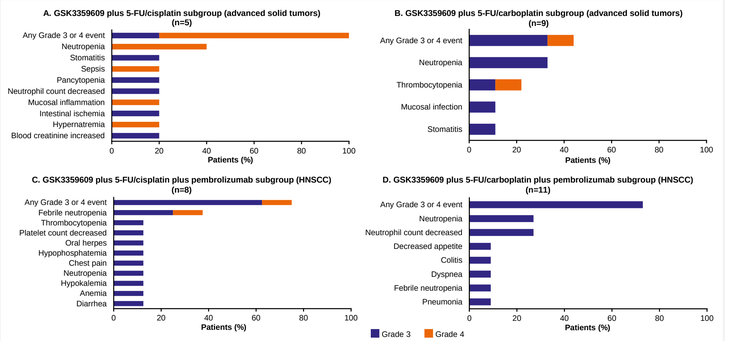
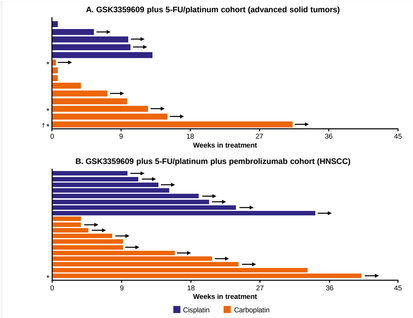


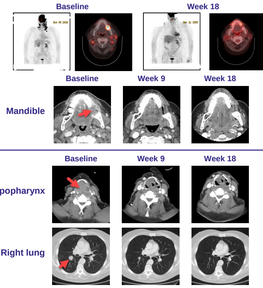
Figure 3. Duration of treatment



Note: duration of treatment in weeks is defined as (last dosing date−first dosing date)/7
→Treatment ongoing; *indicates anti–PD-(L1)–experienced patients; †indicates anti–CTLA-4–experienced patients.

	Case study 1: 62-year-old female	Case study 2: 70-year-old male
Disease	• SCC of the oral cavity • PD-L1 CPS: 100 • Disease burden: 63 mm (three target lesions: left mandibular mass, left neck I LN, left supraclavicular LN)	• SCC of the hypopharynx • PD-L1 CPS: 50 • Disease burden: 79 mm (three target lesions: right hypopharyngeal mass and two lung masses)
Prior treatment	• No prior treatment	• No prior treatment
Study treatment and status	• GSK3359609 plus 5-FU/cisplatin plus pembrolizumab • Treatment ongoing at Week 24	• GSK3359609 plus 5-FU/carboplatin plus pembrolizumab • Treatment ongoing at Week 24
Best overall response	• Partial response	• Partial response

Case study 1



LN, lymph node; SCC, squamous cell carcinoma

Summary

GSK3359609 combined with standard doses of chemotherapy ± pembrolizumab has a manageable safety profile. The majority of treatment-related AEs reported were Grade 1 or Grade 2 and consistent with the known chemotherapy ± pembrolizumab toxicities.

- These data support continued follow-up to further investigate long-term clinical activity and safety of these regimens.

Disclosures

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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. **RA** has had advisory/consultancy roles at Regeneron and AZ; has received travel/accommodation/expenses from Sarah Cannon Research Institute; and has received research funding from Array BioPharma, BMS, Huntsman Cancer Institute, Merck Co., AZ, AbbVie Inc., Regeneron, G1 Therapeutics, Inc., Eli Lily, Genentech, Inc., MedImmune, LLC, GSK, Novartis, Peloton Therapeutics, Inc., Baxalta, Eli Lilly and Company, EMD Serono Inc., Boehringer Ingelheim, TESARO, Inc., Pfizer Inc., and Checkpoint Therapeutics, Inc. **MC** is an employee of Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA and holds stocks/shares in Merck & Co., Inc., Kenilworth, NJ, USA. **DRogan** is an employee of, holds stocks/shares in, and received institutional research funding and travel/accommodation/expenses from GSK. **RS** and **CH** are employees of GSK. **DT** and **CE** are employees of and hold stocks/shares in GSK.

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