Protocol Amendment 03

Study ID: 209229

Official Title of Study: A Randomized, Double-blind, Adaptive, Phase II/III Study of GSK3359609 or Placebo in Combination with Pembrolizumab for First-Line Treatment of PD-L1 Positive Recurrent/Metastatic Head and Neck Squamous Cell Carcinoma

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TITLE PAGE

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Protocol Number: 209229

Compound Number: GSK3359609

Study Phase: Phase III

Short Title: A Phase II/III study of GSK3359609 in combination with pembrolizumab compared with pembrolizumab plus placebo in participants with PD-L1 positive recurrent or metastatic HNSCC

INDUCE-3

Sponsor Name and Legal Registered Address:

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SPONSOR SIGNATORY:

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Sumita Roy-Ghanta, MD Clinical Development Lead, Oncology Research & Development GlaxoSmithKline	**Date**

The signed page is a separate document.

Medical Monitor Name and Contact Information [will be provided separately OR can be found in the Study Reference Manual]

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY		
Document	**Date**	**Document Number**
Amendment 3	*29-JUN-2021*	*TMF-13842230*
Amendment 2	*19-MAY-2020*	*2019N403389_03*
Amendment 1-UK1	*10-FEB-2020*	*2019N403389_02*
Amendment 1	*24-OCT-2019*	*2019N403389_01*
Original Protocol	*20-AUG-2019*	*2019N403389_00*

Amendment 3: 29-JUN-2021

Overall Rationale for the Amendment: A Dear Investigator Letter (DIL) dated 13-April-2021 was issued requiring the stopping of further screening and the discontinuation of the administration of GSK3359609 (feladilimab) or placebo for all participants on INDUCE-3, effective immediately. Further to the DIL, since all participants have the option to remain on pembrolizumab alone as study therapy, GSK issued a Protocol Clarification Letter (PCL) dated 28-April-2021 to reduce any unnecessary burden of on treatment and follow up assessments (the PCL did not alter any screening assessments). This protocol amendment is a follow up to the PCL, with a primary intent to only update the SoA; other impacted, relevant sections were also updated accordingly. Additionally, updates were made to management guidelines to align with pembrolizumab IB update.

Section # and Name	Description of Change	Brief Rationale
1.4 Schedule of Activities (SoA)	Assessments related to GSK3359609 (feladilimab) were removed. These include feladilimab/placebo infusions; feladilimab PK collections, immunogenicity, IRR lab panel, plasma collections, PBMC collections, optional biopsy, Patient Reported Outcomes (PROs), Healthcare Resource Utilization (HCRU), prior protocol required disease assessments, follow-up subsequent anticancer therapy and disease assessments, and pembrolizumab second course.	Since there will be no further screening into the study and no further dosing of GSK3359609 or placebo, there is no need to collect samples, PROs or efficacy assessments to determine the effect of GSK3359609.
6 Study Intervention	Line added to refer to SoA	Alignment with updated SoA
6.1.1 Duration of Second Course	Section deleted	2nd Course will not be administered as subsequent anti-cancer therapy will not be followed and PFS2 will not be analysed as the study is terminated with no further screening.
6.6.1. General Guidelines for Immune-Related Adverse Events	Table 5 was updated for irAEs including neurological toxicities and exfoliative dermatologic conditions	To align with pembrolizumab IB update (Edition 20-Mar-2021)

Section # and Name	Description of Change	Brief Rationale
7.1 Discontinuation of Study Intervention	Removed wording around 2nd Course. Added timeframe for completion of survival follow-up.	2nd Course will not be administered as subsequent anti-cancer therapy will not be followed and PFS2 will not be analysed as the study is terminated with no further screening. A timeframe for completion of survival follow-up is added as study is terminated.
8.1. Efficacy Assessments	Removed requirement for confirmatory scan per iRECIST	iRECIST may be followed at Investigator discretion once progression is determined by RECIST 1.1 up to a maximum of 35 cycles
8.1.1. Disease Assessments	Removed wording around 2nd Course	2nd Course will not be administered as subsequent anti-cancer therapy will not be followed and PFS2 will not be analysed as the study is terminated with no further screening
9.4 Statistical Analyses	Added that primary and secondary endpoints would be included in main CSR. A separate final CSR will report updated key safety analyses at end of study.	Clarifies reporting as the study is terminated with no further screening
10.14. Appendix 14: Second Treatment Course	Removed wording around 2nd Course	2nd Course will not be administered as subsequent anti-cancer therapy will not be followed and PFS2 will not be analysed as the study is terminated with no further screening
10.3.5. Reporting of SAE to GSK	Removed requirement for investigator to show evidence of SAE causality in the eCRF within 72 hours	Change to GSK standard procedure

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1. PROTOCOL SUMMARY

1.1. Background

1.1.1. Inducible T Cell Costimulatory Receptor and GSK3359609

Inducible T cell co-stimulatory receptor (ICOS) is a co-stimulatory receptor belonging to the CD28/B7immunoglobulin (Ig) super family with expression restricted to T cells [Hutloff, 1999]. ICOS differentiates from first generation immunomodulatory antibodies directed against Cytotoxic T-Lymphocyte-Associated Protein 4 (CTLA-4) and PD-1/PD-L1 by targeting a different axis in the antitumor T cell response cascade and promoting activation. ICOS is weakly expressed on resting T cells yet is highly induced on CD4+ and CD8+ T cells upon T cell receptor (TCR) engagement with cognate antigen and activation. The effect of ICOS agonist activity is to promote activation of cytotoxic CD8+ and conventional CD4+ cells, augmenting the expansion, function and survival of these populations thereby resulting in an increased antitumor immune response that is durable [Fan, 2014; Paulos, 2010; Wakamatsu, 2013, Sharpe, 2002].

GSK3359609 is a humanized anti-ICOS mAb selected for its nanomolar (nM) binding to and agonist activity in ICOS-expressing CD4+ and CD8+ effector T cells. GSK3359609 is specifically engineered as an IgG4 hinge-stabilized isotype, IgG4PE, to markedly decrease binding affinity of the Fc (Fragment crystallizable) region of the mAb to activating Fcγ receptors and C1q, and thereby diminish the cytotoxic potential of GSK3359609 that would result in depletion of ICOS-positive T cells through antibody-dependent or complement-dependent cell mediated mechanisms, respectively. Moreover, the IgG4PE isotype retains functional binding to the Fcγ inhibitor receptor, FcγRIIb, a feature described as critical for modulating antibody agonist activity [Li, 2011], which also may be essential for optimal ICOS agonist activity and its associated antitumor effects in humans.

The T cell activating potential of GSK3359609 was evaluated in multiple in vitro assay formats as a single agent and in combination with other immune checkpoint inhibitors. GSK3359609 in combination with pembrolizumab demonstrated a more robust pro-inflammatory cytokine response, including increases in interferon gamma (IFNγ) secretion, than either single agent alone. In vivo experiments in different mouse models either using GSK3359609/pembrolizumab or anti-mouse ICOS in combination with PD-1 surrogate antibodies demonstrated enhanced growth inhibition and increased survivability of mice compared to either agent alone. The upregulation of ICOS with the mouse anti-PD-1 antibodies and the converse whereby ICOS mouse surrogate antibodies increased tumor PD-L1 expression in these in-vivo experiments further support evaluating this combination. Furthermore, analysis of The Cancer Genome Atlas gene expression data demonstrates that tumors with higher ICOS expression also tend to have higher PD-L1 expression, with head and neck squamous cell carcinomas observed as having the highest ICOS expression suggesting that targeting both axes may result in greater anti-tumor immune response.

Refer to the GSK3359609 IB for details on the non-clinical experiments and findings [GlaxoSmithKline Document Number 2017N319717_03, 2020].

1.1.1.1. GSK3359609 Clinical Experience

INDUCE-1 (Study 204691; NCT02723955) is an ongoing, first in-human, dose escalation and expansion study of GSK3359609, alone and in combination with other agents including pembrolizumab, in participants with advanced solid tumors. Analysis from the dose escalation phases of GSK3359609 monotherapy (Part 1A, n=22) and GSK3359609 combination with pembrolizumab (Part 2A, n=36), and GSK3359609 monotherapy pharmacokinetic (PK)/pharmacodynamic cohort (n=47) demonstrated GSK3359609 alone and in combination with pembrolizumab was well tolerated across the 0.001–3 mg/kg dose range. Maximum tolerated dose (MTD) was not reached in Part 1A and Part 2A; maximum administered dose of GSK3359609 as a monotherapy and in combination with pembrolizumab was 3 mg/kg. A range of GSK3359609 doses (≥0.1-1 mg/kg) demonstrated biological and clinical activity supporting the mechanism of action of a non-depleting ICOS agonist as a clinical target [Hansen, 2018].

A summary safety analyses from a later clinical data cut-off date of 16 March 2020 that included all participants dosed with GSK3359609 monotherapy (n=249), which included participants dosed at GSK3359609 10 mg/kg (MAD), or GSK3359609 in combination with pembrolizumab (n= 340) showed that 42% (n=104) and 58% (n=197) of participants, respectively, experienced at least 1 treatment-related adverse events (TR-AE). In the overall Part 1 population, TR-AEs occurring in ≥5% of participants were fatigue (10%, n=26), asthenia (9%, n=23), diarrhea (6%, n=16), pruritis (6%, n=14), nausea (5%, n=13) and arthralgia (5%, n=12). Eleven participants (4%) experienced at least 1 ≥Grade 3 TR-AE; none of which were Grade 5 in severity. In the overall Part 2 population (GSK3359609 combination with pembrolizumab), TR-AEs occurring in ≥5% of participants were diarrhea (9%, n=32), asthenia (9%, n=32), fatigue (9%, n=29), pruritus (7%, n=23), aspartate aminotransferase elevations (6%, n=22), alanine aminotransferase elevations (6%, n=19), nausea (5%, n=17), hypothyroidism (5%, n=16) and rash (5%, n=16). Twenty-one participants (6%) experienced at least 1 ≥Grade 3 TR-AE, 3 of whom experienced at least 1 treatment-related Grade 5 event (<1%). Refer to GSK3359609 IB for further details [GlaxoSmithKline Document Number 2017N319717_03, 2020].

1.1.2. Pembrolizumab

Pembrolizumab is a potent humanized IgG4 mAb with high specificity of binding to the PD-1 receptor, thus inhibiting its interaction with PD-L1 and PD-ligand 2 (PD-L2). Based on preclinical in vitro data, pembrolizumab has high affinity and potent receptor blocking activity for PD-1. Pembrolizumab has an acceptable preclinical safety profile and is in clinical development as an intravenous (IV) immunotherapy for advanced malignancies. Keytruda (pembrolizumab) is indicated for the treatment of patients across a number of indications, which includes first-line treatment of metastatic or unresectable recurrent HNSCC. Pembrolizumab and nivolumab, another PD-1 inhibitor, is also considered a second-line/subsequent-line standard of care for patients with R/M HNSCC.

Refer to the pembrolizumab IB [Merck, 2021] and approved labeling for detailed background information on MK-3475.

The most common reported AEs (≥20% of patients) with pembrolizumab single agent include fatigue, musculoskeletal pain, decreased appetite, pruritus, diarrhea, nausea, rash, pyrexia, cough, dyspnea, constipation, pain and abdominal pain [KEYTRUDA, 2019]. Serious and fatal AEs associated with treatment include immune-mediated adverse reactions, which consisted of pneumonitis, colitis, endocrinopathies (i.e., hypophysitis, thyroid disorders, and Type1 diabetes mellitus), hepatitis, nephritis, infusion reactions, and skin reactions including Stevens-Johnson syndrome and toxic epidermal necrolysis.

1.1.2.1. Pharmaceutical and Therapeutic Background

The PD-1 receptor-ligand interaction is a major pathway hijacked by tumors to suppress immune control. The normal function of PD-1, expressed on the cell surface of activated T cells under healthy conditions, is to down-modulate unwanted or excessive immune responses, including autoimmune reactions. PD-1 (encoded by the gene Pdcd1) is an Ig superfamily member related to CD28 and CTLA-4 that has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (PD L1 and/or PD-L2) [Greenwald, 2005; Okazaki, 2001].

The structure of murine PD-1 has been resolved [Zhang, 2004]. PD-1 and its family members are type I transmembrane glycoproteins containing an Ig-variable–type (IgV type) domain responsible for ligand binding and a cytoplasmic tail responsible for the binding of signaling molecules. The cytoplasmic tail of PD-1 contains 2 tyrosine-based signaling motifs, an immunoreceptor tyrosine-based inhibition motif, and an immunoreceptor tyrosine-based switch motif. Following T cell stimulation, PD-1 recruits the tyrosine phosphatases, SHP-1 and SHP-2, to the immunoreceptor tyrosine-based switch motif within its cytoplasmic tail, leading to the dephosphorylation of effector molecules such as CD3 zeta (CD3ζ), protein kinase C-theta (PKCθ**),** and zeta-chain-associated protein kinase (ZAP70), which are involved in the CD3 T cell signaling cascade [Okazaki, 2001; Chemnitz, 2004; Shepard, 2004; Riley, 2009]. The mechanism by which PD-1 down-modulates T cell responses is similar to, but distinct from, that of CTLA-4, because both molecules regulate an overlapping set of signaling proteins [Parry, 2005; Francisco, 2010]. As a consequence, the PD 1/PD-L1 pathway is an attractive target for therapeutic intervention.

1.1.2.2. Non-clinical and Clinical Studies

Therapeutic studies in mouse models have shown that administration of antibodies blocking PD-1/PD-L1 interaction enhances infiltration of tumor-specific CD8+ T cells and ultimately leads to tumor rejection, either as a monotherapy or in combination with other treatment modalities [Hirano, 2005; Blank, 2004; Weber, 2010; Strome, 2003; Spranger, 2014; Curran, 2010; Pilon-Thomas, 2010]. Anti-mouse PD-1 or anti-mouse PD-L1 antibodies have demonstrated antitumor responses in models of squamous cell carcinoma, pancreatic carcinoma, melanoma, acute myeloid leukemia and colorectal carcinoma [Strome, 2003; Curran, 2010; Pilon-Thomas, 2010; Nomi, 2007; Zhang, 2004]. In such studies, tumor infiltration by CD8+ T cells and increased IFNγ, granzyme B and perforin expression were observed, indicating that the mechanism underlying the antitumor activity of PD-1 checkpoint inhibition involved local infiltration and activation of effector T cell function *in vivo* [Curran, 2010]. Experiments have confirmed the *in vivo* efficacy of anti-mouse PD-1 antibody as a monotherapy, as well as in combination with

chemotherapy, in syngeneic mouse tumor models (for detail refer to pembrolizumab IB; Merck, 2021).

1.1.3. GSK3359609 Monotherapy and in Combination with Pembrolizumab in HNSCC

The ongoing INDUCE-1 expansion phase is investigating GSK3359609 as a monotherapy (Part 1B) and GSK3359609 in combination with pembrolizumab (Part 2B) in participants with HNSCC. At the clinical data cut-off date of 26 July 2019, 17 participants with anti-PD-1/L1 treatment experienced HNSCC received at least 1 dose of 1 mg/kg GSK3359609 in Part 1B cohort. In the treated population (n=17), the median age was 56 years (range: 41-73 years); 82% were male and 82% received ≥1 prior line of systemic therapy in the advanced/metastatic setting. Sixteen of the 17 dosed participants were considered evaluable for efficacy analysis; the overall response rate (ORR) in the evaluable population was 6% with 1 of the 16 participants achieving a partial response (PR).

In the Part 2B cohort, 34 participants with anti-PD-1/L1 naïve HNSCC received at least one cycle of 0.3 mg/kg GSK3359609 in combination with 200 mg pembrolizumab. In the treated population (n=34), the median age was 62 years (range 37-77 years); 85% were male and 53% received ≥1 prior line of systemic therapy in the advanced/metastatic setting. All 34 dosed participants were considered evaluable for efficacy analyses. The ORR in the evaluable population (n=34) was 24% (95% CI: 10.7%, 41.2%) with 8 of the 34 participants achieving a complete response (n=3) or PR (n=5); disease control rate (DCR) was 65% (n=22; 95% CI: 46.5, 80.3). In addition, the majority of participants that achieved a response or stable disease had PD-L1 CPS status <20 (10/14 participants with CPS≥1 and <20, and 1 participants with CPS <1). The median progression-free survival (PFS) was 5.6 months (95% CI: 2.4, 7.4) [Rischin, 2019].

1.2. Synopsis

Protocol Title: A Randomized, Double-blind, Adaptive, Phase II/III Study of GSK3359609 or Placebo in Combination with Pembrolizumab for First-Line Treatment of PD-L1 Positive Recurrent/Metastatic Head and Neck Squamous Cell Carcinoma

Short Title: INDUCE-3: A Phase II/III study of GSK3359609 in combination with pembrolizumab compared with pembrolizumab plus placebo in participants with PD-L1 positive recurrent or metastatic HNSCC

Rationale:

KEYNOTE-048 (KN-048; NCT02358031) is a randomized, three arm study in patients with recurrent or metastatic (R/M) HNSCC who had not received prior systemic therapy in the R/M setting. In the standard first-line treatment arm patients received chemotherapy (platinum and fluorouracil) in combination with cetuximab based on the EXTREME protocol [Vermorken, 2008]. In the two experimental arms patients either receive pembrolizumab in combination with platinum plus fluorouracil (5FU) or alone. Pembrolizumab was given at a dose of 200 mg every 3 weeks (Q3W), for up to 35 cycles.

Pembrolizumab alone and in combination with chemotherapy compared with the EXTREME regimen as first-line treatment improved the survival of patients with R/M HNSCC. However, the degree of overall survival (OS) improvement for pembrolizumab alone or in combination with 5FU/platinum chemotherapy depended on the programmed cell death receptor 1-ligand 1 (PD-L1) combined positive score (CPS) status [Burtness, 2018; Rischin, 2019], with OS improvement in the total PD-L1 population requiring pembrolizumab in combination with 5FU-platinum regimen. Although pembrolizumab alone did not reach statistical significance for superiority in the final OS analysis in the total population (HR: 0.83 [95% CI: 0.70-0.99; p-value: 0.0199), the interim analysis declared pembrolizumab alone as delivering non-inferior OS effect in this population. More importantly, the frequency of all treatment related toxicities (58.3% versus 96.9%) and ≥ Grade 3 events (16.7% versus 69.0%) were much less with pembrolizumab alone as compared with the EXTREME regimen. The results from KN48 supported the Food and Drug Administration (FDA) approval of pembrolizumab alone and in combination with 5FU platinum chemotherapy as first-line treatment of patients with R/M HNSCC in the PD-L1 CPS ≥1 and total populations, respectively [KEYTRUDA, 2019]. In the European Union (EU), the European Commission approved pembrolizumab alone or in combination with 5FU platinum chemotherapy in the PD-L1-positive (CPS ≥1) populations [KEYTRUDA, 2019].

Despite the treatment advancements pembrolizumab has afforded patients with R/M HNSCC, there remains an unmet need due to the limited population of benefit with the aim to further improve disease control, a feature that if not addressed adversely impacts patient quality of life in the disease setting, and to improve survival across all HNSCC populations.

The non-clinical data demonstrate that the activity of targeting ICOS with an agonist antibody is further enhanced with PD-1 blockade and that the mechanisms of action for each antibody are complementary with one another as evidenced by the non-clinical findings that treatment with a mouse anti-PD-1 antibody resulted in upregulation of ICOS+ cluster of differentiation (CD)4+ and CD8+ T cells in tumors and lymph nodes; conversely, treatment with anti-mouse ICOS antibodies increased PD-L1 levels in the tumor. Furthermore, when combined, the two agents resulted in a greater survival effect than either agent alone in syngeneic mouse tumor models (refer to Section 1.1.1). The preliminary clinical data from INDUCE-1 demonstrate that the combination of GSK3359609 with pembrolizumab exhibits promising antitumor activity in participants with HNSCC (refer to Section 1.1.3).

Combining immunomodulatory agents targeting different components of the cancer immunity cycle [Chen, 2013] may be able to overcome the multiple mechanisms of immune suppression which prohibit an effective antitumor immune response. Thus, targeting both the ICOS and PD-1 axes may translate into enhanced clinical activity and expand the population that benefits with the combination of GSK3359609 (ICOS agonist antibody) and pembrolizumab (PD-1 blocking antibody) which is supported by the available non-clinical and clinical evidence. The clinical data from INDUCE-1 has validated the non-clinical findings whereby the 24% ORR observed with the combination of GSK3359609 and pembrolizumab was higher than that observed with GSK3359609 monotherapy as described in Section 1.1.3, and higher than that reported for

pembrolizumab alone as first-line therapy [Burtness, 2018] or subsequent-line therapy [Cohen, 2019] in R/M HNSCC. The purpose of Study 209229 is to evaluate if the addition of GSK3359609 to pembrolizumab improves the efficacy of pembrolizumab in participants with PD-L1 CPS ≥1 R/M HNSCC.

Objectives and Endpoints:

Objectives	Endpoints
Primary[1]	
• Compare the efficacy of GSK3359609 in combination with pembrolizumab to pembrolizumab plus placebo in the Programmed Death Ligand 1 (PD-L1) expression positive (CPS ≥1) population and in the PD-L1 expression high (CPS≥20) population	• OS in the PD-L1 CPS ≥1 and PD-L1 CPS ≥20 populations, defined as the time from the date of randomization to the date of death due to any cause • PFS per RECIST v1.1 by investigator assessment the PD-L1 CPS ≥1 population, defined as the time from the date of randomization to the date of first documented disease progression or death due to any cause, whichever comes first
Secondary[1]	
• Further compare the efficacy of GSK3359609 in combination with pembrolizumab compared with pembrolizumab plus placebo	• PFS per iRECIST (iPFS) by investigator assessment in the PD-L1 CPS ≥1 population • PFS per RECIST v1.1 and iPFS by investigator assessment in the PD-L1 CPS ≥20 population • Milestone OS rate at 12 and 24 months in the PD-L1 CPS ≥1 and CPS ≥20 populations • ORR per RECIST v1.1 by investigator assessment in PD-L1 CPS ≥1 and CPS ≥20 populations • DCR per RECIST v1.1by investigator assessment in PD-L1 CPS ≥1 and CPS ≥20 populations • DoR per RECIST v1.1 by investigator assessment in PD-L1 CPS ≥1 and CPS ≥20 populations
• Evaluate the safety and tolerability of GSK3359609 in combination with pembrolizumab compared with pembrolizumab plus placebo	• Frequency and severity of AEs, AESI, SAEs • Dose modifications (i.e., interruptions, discontinuations)
• Evaluate and compare disease related symptoms and impact on function and health-related quality of life (HRQoL) of GSK3359609/pembrolizumab versus pembrolizumab plus placebo	• The time to deterioration in pain measured by the EORTC QLQ-H&N35 pain domain in the PD-L1 CPS ≥1 and CPS ≥20 populations • The time to deterioration in physical function measured by the PROMIS PF 8c in the PD-L1 CPS ≥1 and CPS ≥20 populations

Abbreviations: AE=adverse events; AESI=adverse events of special interest; DCR=disease control rate; DoR=duration of response; EORTC H&N35= European Organisation for Research and Treatment of Cancer Head and Neck 35 Item Module; HRQoL= health-related quality of life; iPFS=immune-based PFS; iRECIST=immune-based Response Evaluation Criteria in Solid Tumors;

ORR=overall response rate; OS=overall survival; ; PFS=progression-free survival; PROMIS-PF-8c= Patient-Reported Outcomes Measurement Information System-Physical Function-Short Form

1. Refer to Section 9.4.1.2 for definitions of efficacy endpoints, Section 9.1 for key endpoints/hypotheses and Section 9.8 or multiplicity control.

Overall Design:

This is a randomized, double-blind, Phase II/III study comparing a combination of GSK3359609 (ICOS agonist) and pembrolizumab to pembrolizumab plus placebo in participants with PD-L1 CPS ≥1 recurrent or metastatic HNSCC of the oral cavity, oropharynx, hypopharynx or larynx.

The study will evaluate the efficacy of GSK3359609 in combination with pembrolizumab compared with pembrolizumab plus placebo as a standard first-line chemotherapy-free regimen in HNSCC. All participants will be stratified by 2 factors i) PD-L1 CPS status (CPS ≥20 vs. 1≤ CPS <20); ii) HPV status in oropharyngeal cancers (positive vs. negative/unknown) vs non-oropharyngeal cancers then randomly assigned in a 1:1 ratio to the GSK3359609/ pembrolizumab arm or pembrolizumab/placebo arm.

A 2-in-1 adaptive Phase II/III design [Chen, 2018] is considered, with the option to expand the Phase II study seamlessly into Phase III confirmatory study, without changing the eligibility criteria, endpoints or randomization scheme.

ORR per RECIST v1.1 will be used for the adaptive decision. This analysis will be conducted in the approximately first 100 participants (PD-L1 CPS ≥1 population) with a minimum follow-up of 6 months. If at this interim analysis, the outcome meets the defined ORR positive criterion, the study will expand from a Phase II to a Phase III design with 600 participants randomized. If the outcome does not meet the defined criteria, then the study will remain as Phase II with 374 participants randomized.

All participants randomized are included for inference at the end of Phase II or Phase III regardless of the interim adaptive decision. In addition, all primary endpoints and key secondary endpoints are formally tested for statistical significance at the end of Phase II or Phase III.

Disclosure Statement: This is a parallel group treatment study with 2 arms that is double-blinded. Crossover between study treatment arms is not permitted.

Number of Participants:

Overall, the Phase II study will randomize approximately 374 participants with a 1:1 ratio between the GSK3359609 in combination with pembrolizumab (Arm 1) and pembrolizumab and placebo (Arm 2). Based on the prevalence of PD-L1 CPS status reported in KN-048 [Burtness, 2018], in a target sample size of 374 participants with PD-L1 CPS ≥1 (PD-L1 positive expression), the study will enroll approximately 198 participants with PD-L1 CPS ≥20 (PD-L1 high expression).

Should the decision be made to expand the Phase II study into Phase III study an additional 226 participants will be randomly assigned to treatment in a 1:1 ratio between

the GSK3359609/pembrolizumab combination treatment arm and the pembrolizumab/placebo treatment arm.

The participants randomized prior to the adaptive decision which consists of those participants included in the analysis for the adaptive decision will be included in Phase III analyses. The Phase III study will have an overall sample size of 600 participants in the PD-L1 CPS ≥1 population and 318 participants in the PD-L1 CPS ≥20 population. The overall proportion of participants by PD-L1 CPS status will be capped such that the maximum proportion of participants in PD-L1 CPS ≥20 or 1≤ CPS <20 will not exceed the planned proportion by 5% for either subgroup.

Intervention Groups and Duration:

The study is comprised of three periods: screening, treatment, and follow-up. The total duration of study participation begins with the signing of the informed consent form (ICF). After a screening period of up to 28 days, eligible participants will be randomly assigned to 1 of the 2 treatment arms.

For participants who meet all eligibility criteria and are randomized within the study, the maximum duration of treatment with pembrolizumab, GSK3359609 and placebo is expected to be approximately 2 years, up to 35 cycles. A decision to permanently discontinue treatment due to disease progression may be based upon immune-based RECIST [iRECIST]) as disease progression per RECIST v1.1 is further evaluated for confirmation by imaging/clinical assessments ≥4 weeks later and is critical to the analysis of immune-based PFS (iPFS) [Seymour, 2017].

The follow-up period begins when study treatment is permanently discontinued; participants will undergo follow-up assessments for safety, PFS on first subsequent anti-cancer therapy (PFS2) and survival as indicated in the Schedule of Activities (SoA); refer to Section 1.4. The total duration of study participation begins with the signing of the ICF through the final protocol-defined follow-up assessment for survival.

Participants will be randomly assigned to either receive the combination of GSK3359609 24 mg plus pembrolizumab 200 mg or placebo plus pembrolizumab 200 mg. GSK3359609, placebo, and 200 pembrolizumab are administered each as a 30-minute IV infusion once Q3W. GSK3359609 or placebo will be administered first followed by pembrolizumab.

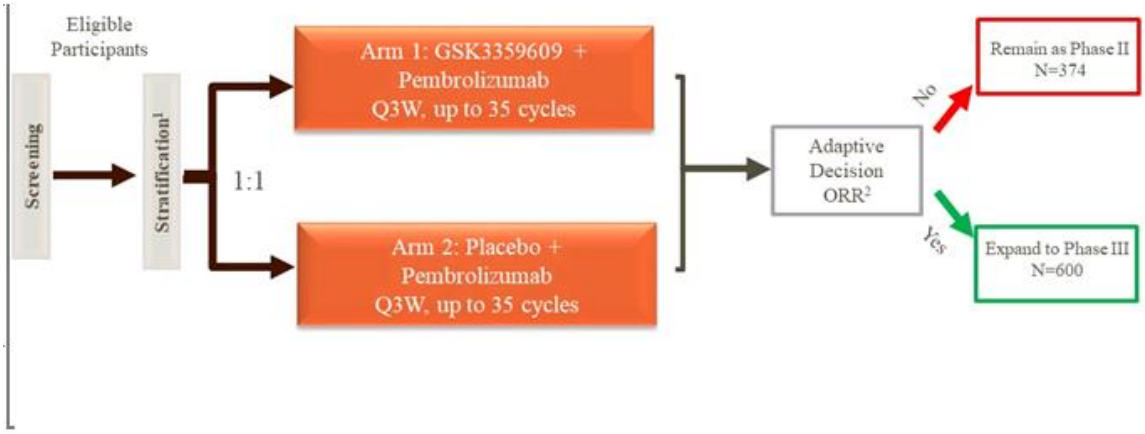
Independent Data Monitoring Committee:

The study will use an Independent Data Monitoring Committee (IDMC). The IDMC membership and governance will be outlined in a separate charter.

The IDMC will make recommendations for discontinuation or modification of the study based on ongoing reviews of safety data according to the Charter. In addition, the IDMC will also evaluate all interim efficacy data, including the adaptive decision as well as interim analyses of PFS and OS, and make a recommendation based on observed results of the study.

In this double-blind study, all GSK and site personnel will be restricted from access to interim analysis results provided to the IDMC until the conclusion of the study, unless the IDMC recommends significant changes to study conduct that require a protocol amendment. In this scenario, after receiving the IDMC recommendation and a decision by Chief Medical Officer (CMO), a review of the data may be required. A select group from GSK, as determined by the CMO will be unblinded to review the data to agree on future study conduct. Depending on the recommendation of the IDMC, the Sponsor may prepare a regulatory submission. More details will be provided in the IDMC Charter.

1.3. Schema



Abbreviations: CPS=combined positive score; GSK609=GSK3359609; HPV=human papilloma virus; ORR=overall response rate; PD-L1=programmed death ligand-1; Q3W=every three weeks; vs=versus

1. Stratification Factors:
   - PD-L1 Status (CPS ≥20 vs. 1≤ CPS <20)
   - HPV status in oropharynx sites only (positive vs. negative/unknown) vs non-oropharynx
2. ORR assessed by RECIST v1.1; refer to Section 9.5 for further details on adaptive decision analysis

1.4. Schedule of Activities (SoA)

Table 1 Schedule of Activities

Procedure	Screening (up to 28 Days Before Randomization)	Treatment Period[1, 4]									TDV[2].	Follow-up[3] (±14 Days)	Notes TDV = Treatment Discontinuation Visit
		Day 1	Weeks (± 3 Days) 3	6	9	12	15	18	21	>21			
Screening Only, Safety and Disease Assessments													
Informed Consent	X												ICF can be signed up to 45 days before randomization.
Inclusion and Exclusion Criteria	X												Review eligibility prior to randomization.
Demography	X												
Disease History, Medical History (Past and Current Conditions; Includes Tobacco, Alcohol and Drug Substance Usage), Prior Anticancer Therapies; HPV status by p16 IHC in oropharyngeal cancers*	X												*HPV status assessed by p16 IHC testing using CINtec p16 Histology assay. If local p16 testing results are not available, or cannot be assessed by the specified method, a tumor tissue sample may be submitted for p16 testing at the designated central laboratory.

Procedure	Screening (up to 28 Days Before Randomization)	Treatment Period[1, 4]									TDV[2].	Follow-up[3] (±14 Days)	Notes TDV = Treatment Discontinuation Visit
			Weeks (± 3 Days)										
		Day 1	3	6	9	12	15	18	21	>21			
Physical Examination	X	X	X	X	X	X	X	X	X	Q3W	X		Full physical exam at Screening; Not required to be performed on Day 1 if Screening exam was performed within 72 hours from time of the scheduled first dose. After Screening, brief physical exam. Must be assessed within 3 days prior to dosing.
ECOG PS	X	X	X	X	X	X	X	X	X	Q3W	X		Must be assessed within 3 days prior to dosing.

Procedure	Screening (up to 28 Days Before Randomization)	Treatment Period[1, 4]									TDV[2].	Follow-up[3] (±14 Days)	Notes TDV = Treatment Discontinuation Visit
			Weeks (± 3 Days)										
		Day 1	3	6	9	12	15	18	21	>21			
Serum Pregnancy Test (WOCBP only)	X												Required within 72 hours prior to randomization. Monthly urine/serum (preference) pregnancy testing may also be performed as consistent with local standards however if a urine test is positive or borderline, or in the event of a missed menstrual period or suspicion of pregnancy, a serum β-hCG test will be required.
Hepatitis B and C	X												If test otherwise performed within 3 months prior to randomization, testing at screening is not required (refer to Table 15)

Procedure	**Screening (up to 28 Days Before Randomization)**	**Treatment Period[1, 4]**									**TDV[2].**	**Follow-up[3] (±14 Days)**	**Notes** **TDV = Treatment Discontinuation Visit**
		Weeks (± 3 Days)											
		Day 1	**3**	**6**	**9**	**12**	**15**	**18**	**21**	**>21**			
Hematology, Coagulation, Clinical Chemistry, Urinalysis Laboratory Assessments (Refer to Table 15)	X	X	X	X	X	X	X	X	X	Q3W	X		Required within 7 days of randomization day Not required to be tested on Day 1 if Screening labs are within 72 hours from time of scheduled first dose. Must be drawn within 3 days prior to dosing
Thyroid Function Testing	X			X		X		X		Q6W	X		Must be drawn within 3 days prior to dosing
ECHO or MUGA/12-lead ECG/ Cardiac Troponin I or T	X												After Screening, perform as clinically indicated. QT interval/duration will be corrected using Fridericia's formula

Procedure	**Screening (up to 28 Days Before Randomization)**	**Treatment Period[1, 4]**									**TDV[2].**	**Follow-up[3] (±14 Days)**	**Notes** **TDV = Treatment Discontinuation Visit**
			Weeks (± 3 Days)										
		Day 1	**3**	**6**	**9**	**12**	**15**	**18**	**21**	**>21**			
Vital Signs	X	X	X	X	X	X	X	X	X	Q3W	X		Must be assessed within 3 days prior to dosing. Height will be recorded at Screening only. Refer to Protocol Section 8.2.3.

Tumor Tissue Collection for 22C3 PharmDx PD-L1 IHC Assay^ Testing by Central Laboratory	X*												*Assessment(s) can commence after signed ICF within 45 days prior to randomization. Refer to Section 5.1, inclusion 12. for tumor tissue requirements (i.e., whether archival tumor tissue is acceptable or fresh biopsy is required). PD-L1 IHC by central lab testing; evaluable result required prior to randomization. ^The PD-L1 IHC 22C3 pharmDx assay is US FDA approved and CE marked in the EU p16 IHC testing by central lab if local results not available (refer to Section 8; [oropharyngeal only]) *This tissue will be used for exploratory biomarkers
AE/AESI/SAE Review	X	←==========									X	X	All AEs are to be graded according to NCI-CTCAE (Version 5.0)

Procedure	**Screening (up to 28 Days Before Randomization)**	**Treatment Period[1, 4]**									**TDV[2].**	**Follow-up[3] (±14 Days)**	**Notes** **TDV = Treatment Discontinuation Visit**
			Weeks (± 3 Days)										
		Day 1	**3**	**6**	**9**	**12**	**15**	**18**	**21**	**>21**			
													Refer to Section 8.3.1 for time period of collection
Concomitant Medication Review	X	←==========								→	X	X*	*Concomitant medications used to treat AEs/AESI/SAEs during the follow-up period are to be reported.
Disease Assessments	X				X*		X*						*For participants who received at least 1 dose of GSK3359609 (feladilimab) or placebo scans should be completed at W9, W15 and then move to standard practice. For participants who received only pembrolizumab or who received GSK3359609 (feladilimab) and are past W15, scans should be completed according to standard practice.

Procedure	**Screening (up to 28 Days Before Randomization)**	**Treatment Period[1, 4]**									**TDV[2].**	**Follow-up[3] (±14 Days)**	**Notes TDV = Treatment Discontinuation Visit**
			Weeks (± 3 Days)										
		Day 1	**3**	**6**	**9**	**12**	**15**	**18**	**21**	**>21**			
Study Treatment													
Randomization		X											Randomization may occur up to 3 days before Day 1; the preference is to randomize within 24 hours before Day 1.

Procedure	Screening (up to 28 Days Before Randomization)	Treatment Period[1, 4]									TDV[2].	Follow-up[3] (±14 Days)	Notes TDV = Treatment Discontinuation Visit
			Weeks (± 3 Days)										
		Day 1	3	6	9	12	15	18	21	>21			
Pembrolizumab		X	X	X	X	X	X	X	X	Q3W			Day 1: study administration window is within 3 days of randomization Participants will receive study treatment up to the maximum duration of 35 cycles unless one of the following events occurs earlier: •Disease progression •Death •Unacceptable toxicity (refer to Protocol Section 6.6 and subsections) •Pregnancy (refer to Protocol Section 8.3.5 for details)

Procedure	Screening (up to 28 Days Before Randomization)	Treatment Period[1, 4]									TDV[2].	Follow-up[3] (±14 Days)	Notes TDV = Treatment Discontinuation Visit
		Day 1	Weeks (± 3 Days) 3	6	9	12	15	18	21	>21			
Patient Reported Outcome Assessments[5]													
Genetics Research													
Genetics Research Blood Sample		X											Optional, collected if genetics research optional consent signed; consent must be signed before sample is drawn Sample will be collected on Day 1 predose. NOTE: sample may be collected beyond predose/Day 1 with signed consent
Fresh Tumor Biopsy*													*Optional biopsy at: • Screening in those participants who provide archival tumor tissue (refer to Section 5.1 for archival tissue requirements)

Procedure	Screening (up to 28 Days Before Randomization)	Treatment Period[1, 4]									TDV[2].	Follow-up[3] (±14 Days)	Notes TDV = Treatment Discontinuation Visit
		Day 1	Weeks (± 3 Days) 3	6	9	12	15	18	21	>21			
Follow-up Assessments													
Survival												Q12W	Participants will be contacted via telephone contact every 12 weeks until death or participant's withdrawal from further contact or until the last patient discontinues treatment and has had their last follow up for safety.

Abbreviations: AE = Adverse Events; AESI = Adverse Events of Special Interest;; ECG = electrocardiogram; ECHO = echocardiogram; ECOG PS= Eastern Cooperative Oncology Group Performance Status; EOI= end of infusion; HPV = human papilloma virus; ICF = Informed Consent Form; MUGA = Multigated Acquisition Scan; Q3W = every 3 weeks; Q6W = every 6 weeks; Q12W = every 12 weeks; Q24W = every 24 weeks; SAE = Serious Adverse Events; TDV = Treatment Discontinuation visit; US = United States; WOCBP = woman of childbearing potential

1. If administration of study treatment is delayed ≤7 days due to adverse events, assessments indicated to occur at the dosing visit can be scheduled to occur when dosing occurs. If administration of study treatment is delayed > 7 days due to adverse events, assessments indicated at the dosing visit are to be performed at the expected scheduled visit (±window) with the exception of the following: PK sample collection; immunogenicity sample collection, and the PRO assessments. If the dosing Week visit that is delayed > 7 days occurs at a visit when disease assessments are required, then PRO assessments are required to be administered to the participant.
2. Do not repeat tests that have already been performed within 3 days or scans within 6 weeks of the TDV. The assessments required at the study treatment discontinuation visit (permanent discontinuation) must be completed within 30 days from the date study treatment was discontinued and must occur prior to the start of subsequent anti-cancer therapy; the window for this visit is +10 days.
3. The follow-up visits will commence after decision to permanently discontinue study treatment for any reason is made including completion of 35 cycles. .

2. INTRODUCTION

Head and neck squamous cell carcinoma (HNSCC) is one of the most common malignancies worldwide, accounting for more than 550,000 new cases and 380,000 deaths per year [Vos, 2017; Naghavi, 2017]. HNSCC is a heterogeneous disease, encompassing a variety of tumors that originate from different anatomic subsites in the head and neck region, and include carcinomas of the oral cavity, oropharynx, hypopharynx, nasopharynx, larynx, and nasal cavity/sinuses.

The etiology of HNSCC is well-established as being multifactorial with risk factors that include tobacco smoking and alcohol consumption; human papilloma virus (HPV) infection is also an important factor in the pathophysiology and prognosis of HNSCC which includes playing an immunosuppressive role, mainly in the oropharyngeal region [Gillison, 2015; Ang, 2010; Fung, 2017]. Most patients are diagnosed with locally advanced disease and are usually treated with multimodal therapy including surgery, radiotherapy/±chemotherapy and systemic therapy.

Despite advances in surgical and radiation techniques, as well as the addition of chemotherapy and epidermal growth factor receptor-targeting monoclonal antibodies (mAbs) in the treatment of locally advanced HNSCC, more than half of patients eventually experience relapse or distant metastases. Most of these patients are no longer suitable for curative treatment approaches. For locally recurrent disease, local treatment options such as surgery and radiotherapy play an important role in this setting. For recurrent disease no longer amenable to local therapy or metastatic HNSCC, platinum-based chemotherapy ± cetuximab was the standard treatment option in the United States (US) before the US FDA approval of pembrolizumab in this setting. Even with current multi-agent chemotherapy that now includes pembrolizumab, the expected median survival for a patient in the incurable or metastatic relapse setting remains under 15 months [KEYTRUDA, 2019].

2.1. Study Rationale

KEYNOTE-048 (KN-048; NCT02358031) was a randomized, three arm study in patients with recurrent or metastatic (R/M) HNSCC who had not received prior systemic therapy in the R/M setting. In the standard first-line treatment arm patients received chemotherapy (platinum and fluorouracil) in combination with cetuximab based on the EXTREME protocol [Vermorken, 2008]. In the 2 experimental arms patients either receive pembrolizumab in combination with platinum plus fluorouracil (5FU) or pembrolizumab alone. Pembrolizumab was given at a dose of 200 mg every 3 weeks (Q3W), for up to 35 cycles.

Pembrolizumab alone and in combination with chemotherapy compared with the EXTREME regimen as first-line treatment improved the survival of patients with R/M HNSCC. However, the degree of overall survival (OS) improvement for pembrolizumab alone or in combination with 5FU/platinum chemotherapy depended on the programmed cell death receptor 1-ligand 1 (PD-L1) combined positive score (CPS) status.[Burtness, 2018; Rischin, 2019], with OS improvement in the total PD-L1 population requiring pembrolizumab in combination with 5FU-platinum regimen. Although pembrolizumab

alone compared to the EXTREME regimen did not reach statistical significance for superiority at the final OS analysis in the total population (HR: 0.83 [95% CI: 0.70-0.99; p-value: 0.0199), the analysis declared pembrolizumab alone as delivering a non-inferior OS effect in this population. More importantly, the frequency of all treatment related toxicities (58.3% versus 96.9%) and ≥ Grade 3 events (16.7% versus 69.0%) were much less with pembrolizumab alone as compared with the EXTREME regimen.

The KN-048 results supported the Food and Drug Administration (FDA) approval of pembrolizumab alone and in combination with 5FU platinum chemotherapy as first-line treatment of patients with R/M HNSCC in the PD-L1 CPS ≥1 and total populations, respectively [KEYTRUDA, 2019]. In the EU, the European Commission approved pembrolizumab alone or with 5FU platinum chemotherapy in the PD-L1-positive (CPS ≥1) population [KEYTRUDA, 2019]. In addition pembrolizumab alone and in combination with 5FU-platinum chemotherapy were incorporated into the National Comprehensive Cancer Network (NCCN) and the Society for Immunotherapy of Cancer guidelines as an option for the first-line treatment in patients with non-nasopharyngeal HNSCC; the choice of which pembrolizumab-based regimen may consider PD-L1 expression status as well as other patient and disease characteristics [National Comprehensive Cancer Network (NCCN), 2021; Cohen, 2019].

However, there was a lack of improvement in PFS with pembrolizumab alone and in combination with chemotherapy compared with the EXTREME regimen in the overall population and in the PD-L1 CPS populations analyzed. Moreover, the ORR reported for pembrolizumab alone was 23.3 % in PD-L1 CPS ≥20 population, 19.1% in PD-L1 CPS ≥1 population and 16.9% in the total population; which was lower than the ORR observed with the EXTREME regimen [Burtness, 2018; Rischin, 2019]. Despite the treatment advancements pembrolizumab has afforded patients with R/M HNSCC, there remains an unmet need due to the limited population of benefit with the aim to further improve disease control, a feature that if not addressed, adversely impacts patient quality of life in this disease setting, and to improve survival across all HNSCC populations.

The non-clinical data demonstrate that the activity of targeting ICOS with an agonist antibody is further enhanced with PD-1 blockade. Further rationale for targeting the ICOS and PD-1 axes is supported by the non-clinical finding that treatment with a mouse anti-PD-1 antibody resulted in upregulation of ICOS+ cluster of differentiation (CD)4+ and CD8+ T cells in tumors and lymph nodes; conversely, treatment with anti-mouse ICOS antibodies increased PD-L1 levels in the tumor. Furthermore, when combined, the 2 agents resulted in a greater survival effect than either agent alone in syngeneic mouse tumor models (refer to Section 1.1.1). The preliminary clinical data from INDUCE-1 demonstrate that the combination of GSK3359609 with pembrolizumab exhibits promising antitumor activity in participants with HNSCC (refer to Section 1.1.3).

Combining immunomodulatory agents targeting different components of the cancer immunity cycle [Chen, 2013] may be able to overcome the multiple mechanisms of immune suppression which prohibit an effective antitumor immune response and contribute to the progression of HNSCC [Ferris, 2015]. Thus, targeting both the ICOS and PD-1 axes may translate into enhanced clinical activity and expand the population that benefits with the combination of GSK3359609 (ICOS agonist antibody) and

pembrolizumab (PD-1 blocking antibody) which is supported by the available non-clinical and clinical evidence. The clinical data from INDUCE-1 has validated the non-clinical findings whereby the 28% ORR observed with the combination of GSK3359609 and pembrolizumab was higher than GSK3359609 monotherapy as described in Section 1.1.3, and higher than that reported for pembrolizumab alone as first-line therapy [Burtness, 2018; Rischin, 2019] or subsequent-line therapy [Cohen, 2019] in R/M HNSCC. The purpose of Study 209229 is to evaluate if the addition of GSK3359609 to pembrolizumab as first-line treatment improves the efficacy of pembrolizumab in participants with R/M HNSCC.

2.2. Benefit/Risk Assessment

Summaries of findings from both clinical and non-clinical studies conducted with GSK3359609 [GSK3359609 IB, GlaxoSmithKline Document Number 2017N319717_03, 2020] and pembrolizumab [Merck, 2021] can be found in the respective IBs.

The following sub sections outline the risk assessment and mitigation strategy for GSK3359609 in combination with pembrolizumab in this protocol.

2.2.1. Risk Assessment

Of 260 participants treated with the combination of GSK3359609 (at various doses) and pembrolizumab in various tumor types across the dose escalation and expansion phases of the INDUCE-1 study, 94% experienced at least 1 adverse event regardless of causality; with 41% experiencing at least 1 ≥Grade 3 event and 41% experiencing at least 1 serious event. The events reported with the highest frequency (≥10%) regardless of causality were anemia, fatigue, nausea, diarrhea, asthenia, pyrexia, deceased appetite, dyspnea, constipation, cough and vomiting; these most common all-cause AEs are consistent with the those reported for pembrolizumab alone [KEYTRUDA, 2019]. Regarding immune related events (irAEs) most have been low grade and were treated successfully; few high grade irAEs were considered significant or required hospitalization (i.e., hyperglycemia and pneumonitis). Refer to the GSK3359609 IB for further details [GlaxoSmithKline Document Number 2017N319717_03, 2020].

Table 2 outlines the risk assessment and mitigation strategy for this protocol.

Table 2 Risk Assessment and Mitigation Strategy

Potential Risk of Clinical Significance	Summary of Data/ Rationale for Risk	Mitigation Strategy
Immune-related AEs	• Inflammatory AEs such as diarrhea/colitis, pneumonitis, nephritis, and hepatotoxicity are well established as treatment emergent AEs with immune-modulating agents and are consistent with the immune stimulatory mechanism of action of these agents.	Participants with the following medical history are ineligible for this study • Toxicity (≥Grade 3) related to prior immunotherapy leading to study treatment discontinuation • Active autoimmune disease (refer to Section 5.2 exclusion criterion 8) • Severe hypersensitivity to another mAb • Established management guidelines for irAEs/treatment related AEs (refer to Section 6.6) • Further details on the identification, evaluation, and management of toxicities with a potential immune etiology (refer to Section 6.6); refer to pembrolizumab prescribing information for further details
Hypersensitivity reaction	• Risk for infusion reactions and hypersensitivity is inherent to many mAbs [Brennan, 2010]	• Participants with history of severe hypersensitivity to another mAb are ineligible for this study • Details on management of infusion reactions are included in Section 6.6.2.

Potential Risk of Clinical Significance	Summary of Data/ Rationale for Risk	Mitigation Strategy
Severe cytokine release syndrome (sCRS)	• ICOS is a costimulatory receptor that can stimulate proliferation and activation of T cells • GSK3359609 is an ICOS agonist that can co-stimulate T cell activation in the context of TCR signal • No CRS events have been reported in clinical programs investigating GSK3359609 (refer to GSK3359609 IB; GlaxoSmithKline Document Number 2017N319717_03, 2020)	• Management of CRS events is provided in the Section 6.6.2.
Immune complex disease	Immune complex formation and deposition findings in non-clinical safety studies (refer to GSK3359609 IB; GlaxoSmithKline Document Number 2017N319717_03, 2020)	• Clinical laboratory safety assessments and immunogenicity testing is included in the study (refer to Table 1)

Abbreviations: AE= adverse event; CRS=cytokine release syndrome; ICOS=inducible T cell co-stimulatory receptor; IB=Investigator's brochure; mAb=monoclonal antibody; SoA=schedule of activities; TCR=T cell receptor

2.2.2. Overall Benefit: Risk Conclusion

This is a randomized, double-blinded, adaptive design, Phase II/III study of pembrolizumab (a standard of care) plus placebo or in combination with GSK3359609 for first line treatment of R/M HNSCC. Regarding benefit, the focus should be on the following key points: first, the KN-048 results support pembrolizumab as a backbone agent as a standard of care for the first-line treatment of R/M HNSCC in which OS for pembrolizumab alone was superior to the EXTREME regimen in the PD-L1 CPS ≥1 population (refer to Section 2.1); second, GSK3359609 in combination with pembrolizumab was shown to have a positive ORR and median PFS in a small cohort (n=29) of participants with PD-1/L1 treatment naïve HNSCC (refer to Section 1.1.3). The risks seen in participants exposed to GSK3359609 (at various doses) in combination with pembrolizumab are summarized in Table 2 and are consistent with those observed with pembrolizumab alone. Of 260 participants treated with the combination of GSK3359609 and pembrolizumab in the INDUCE-1 study, most had at least 1 adverse event, the majority of which were low grade in severity. The evidence to date for the combination of GSK3359609 with pembrolizumab favor an acceptable safety profile and an expected clinical benefit in participants with HNSCC within the context of the anti-tumor effects observed in the small cohort of participants with HNSCC enrolled in INDUCE-1. Additionally, the safety profile of pembrolizumab alone is more favorable than the EXTREME regimen as the frequency of ≥Grade 3 events and AEs leading to treatment discontinuation were markedly lower in comparison with the EXTREME regimen. Therefore, within the context of the significant survival effect and the favorable safety profile of pembrolizumab monotherapy in the first-line R/M HNSCC PD-L1 CPS ≥1 population, pembrolizumab plus placebo as the control arm is supported. Moreover, initiating a Phase II/III adaptive design study to investigate pembrolizumab in combination with GSK3359609 provides participants with first-line R/M HNSCC a potentially favorable risk/benefit profile.

3. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary[1]	
• Compare the efficacy of GSK3359609 in combination with pembrolizumab to pembrolizumab plus placebo in the Programmed Death Ligand 1 (PD L1) expression positive (CPS ≥1) population and in the PD-L1 expression high (CPS ≥20) population	• OS in PD-L1 CPS ≥1 and CPS ≥20 populations defined as the time from the date of randomization to the date of death due to any cause • PFS per RECIST v1.1 by investigator assessment in PD-L1 CPS ≥1 population, defined as the time from the date of randomization to the date of first documented disease progression or death due to any cause, whichever comes first
Secondary[1]	
• Further compare the efficacy of GSK3359609 in combination with pembrolizumab compared with pembrolizumab plus placebo	• PFS per iRECIST (iPFS) by investigator assessment in the PD-L1 CPS ≥1 population • PFS per RECIST v1.1 and iPFS by investigator assessment in PD-L1 CPS ≥20 population

Objectives	Endpoints
	• Milestone OS rate at 12 and 24 months in the PD-L1 CPS ≥1 and CPS ≥20 populations • ORR per RECIST v1.1 by investigator assessment in the PD-L1 CPS ≥1 and CPS≥20 populations • DCR per RECIST v1.1 by investigator assessment in the PD-L1 CPS ≥1 and CPS ≥20 populations • DoR per RECIST v1.1 by investigator assessment in the PD-L1 CPS ≥1 and CPS ≥20 populations
• Evaluate the safety and tolerability of GSK3359609 in combination with pembrolizumab compared with pembrolizumab plus placebo	• Frequency and severity of AEs, AESI, SAEs • Dose modifications (i.e., interruptions, discontinuations)
• Evaluate and compare disease related symptoms and impact on function and health-related quality of life (HRQoL) of GSK3359609/pembrolizumab versus pembrolizumab plus placebo	• The time to deterioration in pain measured by the EORTC QLQ-H&N35 pain domain in the PD-L1 CPS ≥1 and CPS ≥20 populations • The time to deterioration in physical function measured by the PROMIS PF 8c in the PD-L1 CPS ≥1 and CPS ≥20 populations
Exploratory	
• Compare the efficacy of GSK3359609 in combination with pembrolizumab to pembrolizumab plus placebo	• ORR, DoR, DCR per iRECIST • PFS2, defined as the time from the date of randomization to the date of second objective disease progression per RECIST v1.1, or death due to any cause, whichever first
• Evaluate and compare disease-related symptoms, overall bother of treatment side effects, and impact on function and HRQoL of GSK3359609/pembrolizumab versus pembrolizumab plus placebo	• Symptomatic AEs as measured by the FACT GP5 • Changes in other domains of quality of life as measured by the selected EORTC IL50/51 (subset of domains of the EORTC QLQ-C30 and EORTC QLQ-H&N35), BPI-I3 and EQ-5D-3L
• Evaluate healthcare resource utilization of participants in the GSK3359609 combination with pembrolizumab arm versus participants in the placebo combination with pembrolizumab arm	• Non-protocol healthcare encounters, such as provider visits, emergency room visits, hospitalizations, medications, tests, or procedures
• Evaluate GSK3359609 PK properties	• Summary of GSK3359609 concentrations and Cmax, Cmin, AUC (0-τ) as data permit
• Determine immunogenicity of GSK3359609	• Anti-drug antibody incidence
• Explore relationship between biomarkers in tumor and blood, such as immune response biomarkers, target expression and efficacy endpoints	• Tumor and blood-based analysis of DNA, RNA, and protein analytes/profiles[2]; OS, PFS, ORR, other efficacy parameters
• Genetics Research: Investigate the relationship between host genetic variations and response to therapy	• Germline genetic evaluations may be conducted for:

Objectives	Endpoints
	• Clinical response, including GSK3359609/pembrolizumab or any concomitant medicines • Disease susceptibility, severity, and progression and related conditions

Abbreviations: AE=adverse events; AESI=adverse events of special interest; Brief Pain Inventory-Item 3= BPI-I3; DCR=disease control rate; DNA=deoxyribonucleic acid; DoR=duration of response; EORTC IL50=European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Item Library 50; EORTC IL51=EORTC Item Library 51; EQ-5D-3L=EuroQoL 5 Dimensions; FACT-GP5 = Functional Assessment of Cancer Therapy – General (Item GP5); HRQoL=health-related quality of life; iPFS = immune-based progression-free survival; iRECIST=immune-based Response Evaluation Criteria in Solid Tumors; ORR=overall response rate; OS=overall survival; PFS=progression-free survival; PROMIS-PF-8c= Patient-Reported Outcomes Measurement Information System-Physical Function-Short Form; RECIST= Response Evaluation Criteria in Solid Tumors; RNA=ribonucleic acid

1. Refer to Section 9.4.1.2 for definitions of efficacy endpoints, Section 9.1 for key endpoints/hypotheses and Section 9.8 for multiplicity control
2. Refer to Section 8.8 for details on biomarkers

4. STUDY DESIGN

4.1. Overall Design

This is a randomized, double-blind, adaptive Phase II/III study comparing a combination of GSK3359609 (ICOS agonist) and pembrolizumab to pembrolizumab plus placebo in participants with PD-L1 CPS ≥1 recurrent or metastatic HNSCC of the oral cavity, oropharynx, hypopharynx or larynx.

The study will evaluate the efficacy of GSK3359609 (ICOS agonist) in combination with pembrolizumab compared with pembrolizumab as a first-line chemotherapy-free regimen in HNSCC. All participants will be stratified by the following factors i) PD-L1 CPS status (CPS ≥20 vs. 1≤ CPS <20); ii) HPV status (oropharyngeal cancers [positive vs. negative/unknown] vs. non-oropharyngeal cancers) then randomly assigned in a 1:1 ratio to the GSK3359609/pembrolizumab arm or pembrolizumab/placebo arm.

A 2-in-1 adaptive Phase II/III design [Chen, 2018] is considered, with the option to expand the Phase II study seamlessly into Phase III confirmatory study, without changing the eligibility criteria, endpoints or randomization scheme.The study schematic is provided in Section 1.3. The study does not permit crossover between study treatment arms as one of the primary endpoints is overall survival and the study is double blinded.

The adaptive decision will be guided by the analysis of ORR/DCR per RECIST v1.1 in the approximate first 100 participants (PD-L1 CPS ≥1 population) with a minimum follow-up of 6 months. If at this interim analysis, the outcome meets the defined ORR positive criterion (refer to Section 9.5), the study will expand from a Phase II to a Phase III design with 600 participants randomized. If the outcome does not meet the defined criteria, then the study will remain as Phase II with 374 participants randomized. The overall proportion of participants by PD-L1 CPS status will be capped such that the maximum proportion of participants in PD-L1 CPS≥20 or 1≤CPS <20 will not exceed the

planned proportion by 5% for either subgroup; refer to Section 9.2 for expected prevalence and planned sample size estimates.

All participants randomized are included for inference at the end of Phase II or Phase III regardless of the interim adaptive decision. In addition, all primary endpoints and key secondary endpoints are formally tested for statistical significance at the end of Phase II or Phase III.

The detailed interim analysis plan including making the adaptive decision is pre-specified in Section 9.5.

4.2. Scientific Rationale for Study Design

A 2-in-1 adaptive Phase II/III design [Chen, 2018] is considered as an efficient approach to either expand a Phase II study seamlessly into a Phase III study with pre-specified adaptive decision rules, by randomizing additional participants without changing the inclusion and exclusion criteria for enrollment, endpoints and randomization scheme. This approach supports the Phase III design by properly balancing the risk and benefit of the expansion decision. If the decision is not to expand, the study remains as a Phase II design and the primary analysis is conducted at the end of Phase II.

The selection of ORR as the endpoint for the adaptive decision is supported by a meta-analysis of data from published HNSCC studies.

Randomization will be stratified by the following factors associated as prognostic, and selective of clinical benefit from pembrolizumab:

1. PD-L1 CPS (degree of benefit from pembrolizumab alone depended on PD-L1 status [Burtness, 2018])
2. HPV status (established as a prognostic factor in the oropharynx region and oropharyngeal cancers are staged according by HPV status [Fung, 2017; AJCC, 2017])

The selection of pembrolizumab monotherapy as the control arm is supported by the data from KN-048; the evidence of which supported the FDA approval of pembrolizumab monotherapy in the first-line disease setting for patients with PD-L1 CPS ≥1 R/M HNSCC [Burtness, 2018; Rischin, 2019].

The primary endpoints are appropriate for this population as overall survival is the gold standard measure of clinical benefit and PFS by RECISTv1.1 as a direct measure of disease control in a randomized Phase III study setting.

The double-blinded design will mitigate the intentional or inadvertent bias inherent to an open-label study.

4.3. Justification for Dose

4.3.1. GSK3359609 Dose Justification

The dose of GSK3359609 planned for registration studies in HNSCC is 24-mg administered Q3W. The 24 mg dose of GSK3359609 was selected based upon the cumulative clinical evidence to date from the first-time in human (FTIH) Study 204691/INDUCE-1 that included preliminary efficacy data from the GSK3359609/pembrolizumab combination HNSCC expansion cohort, pooled preliminary population PK and exposure-response assessments, as well as peripheral target engagement and preliminary tumor biomarker assessments. Overall, GSK3359609 clinical data demonstrate a lack of dose-dependent differences in efficacy or safety outcomes. A flat GSK3359609 exposure-response relationship for efficacy and safety was found in participants across the range of dose levels evaluated (0.001mg/kg to 3 mg/kg). Exposures for 24-mg Q3W are expected to lie within this dose level range and will be close to those obtained with 0.3 mg/kg Q3W, the dose level where in the HNSCC cohort durable objective responses were observed in combination with 200-mg pembrolizumab.

The PK disposition of GSK3359609 was evaluated after 30 minutes of IV infusion at the aforementioned dose level range in Study 204691. A preliminary population PK model (n = 251; October 2018), which characterized the influence of body weight, age, and other participant covariates on exposure, has been developed. Results indicate the PK disposition of GSK3359609 is consistent with that of other humanized mAbs, which typically have a low clearance (CL) and a limited central volume of distribution (Vc). Plasma concentration-time profiles of GSK3359609 exhibit a bi-exponential decline with dose-proportional increases in exposure, e.g. Cmax and Cmin. The preliminary comparisons of the FTIH data from Part 1 (monotherapy) versus Part 2 (pembrolizumab combination) demonstrate no differences in GSK3359609 exposure with concomitant administration of pembrolizumab; no drug-drug interaction affecting PK for the combination of GSK3359609 and pembrolizumab would be anticipated given that both are mAb catabolized via high capacity, non-specific pathways.

The preliminary FTIH population PK analysis dataset encompassed a wide distribution of bodyweight, with a median of 73 kg and a range of 40.8–133 kg. Estimates (90% confidence intervals [CI]) of the relationship between clearance and body weight based on the population PK model revealed an allometric exponent (α) of 0.056 (95% CI, -0.364– 0.475) for the CL and 0.314 (95% CI, -0.009 – 0.637) for Vc. In theory, body-weight–based dosing would be considered most appropriate where CL scales linearly with patient bodyweight (α equals to 1), whereas fixed dosing would be more appropriate when CL is unaffected by body weight (α = 0). Given that α estimates were closer to 0 for both CL and Vc, no advantage of weight-based dosing over fixed dosing is expected for GSK3359609. Distributions of GSK3359609 exposures from potential fixed doses administered Q3W were simulated with the preliminary FTIH population PK model and compared with the distributions expected from weight-based dosing regimens, using bodyweight distributions resampled from the Centers for Disease Control National Health and Nutrition Examination Survey database. These simulations reveal that a GSK3359609 bodyweight-based dose results in slightly higher exposure in heavier

weight participants, with a GSK3359609 fixed dose expected to provide more consistent control of PK variability across the entire bodyweight spectrum.

As previously indicated, no MTD was established and no dose limiting toxicities were observed in the dose escalation cohorts over the range of GSK3359609 dose levels (0.001 mg/kg [~0.08 mg] to 3 mg/kg [~240 mg]) evaluated in Study 204691. An exposure-response, time-to-event analysis of all reported ≥Grade 2 AEs supports the conclusion of similar safety outcomes across the exposure/dose range evaluated, both in pooled monotherapy cohorts and pembrolizumab combination cohorts. Evidence of target engagement and objective evidence of tumor size reduction were observed in the HNSCC expansion cohort at the 0.3 mg/kg dose level. Doses of 0.3 mg/kg (~24-mg) showed high ICOS receptor occupancy (RO) levels on CD4 and CD8 T cells over the 21-day dosing cycle. Concentration-ICOS RO analyses suggest bodyweight-based doses of approximately >0.1 mg/kg maintained approximately >~70% CD4/CD8 RO over the entire dosing interval. Preliminary exposure-response assessments of tumor size reduction at Week 9 (stratified by tumor type) demonstrate little difference in efficacy outcomes across the exposure/ dose range evaluated.

Hence, the integrated body of evidence supports a 24-mg Q3W dose for evaluation in the pivotal studies of HNSCC in combination with pembrolizumab. The distribution of exposures from the 24-mg fixed dose are predicted to considerably overlap those obtained with the 0.3 mg/kg dose, and importantly, will maintain individual patient exposures within the exposure range established in the FTIH study.

4.3.2. Pembrolizumab Dose Justification

The planned dose of pembrolizumab for this study is 200 mg Q3W. This pembrolizumab dose and schedule is consistent with that administered in the KN-048 study and which is administered in combination with GSK3359609 in the ongoing INDUCE-1 study.

Based on the totality of data generated in the Keytruda development program, 200 mg Q3W is the appropriate dose of pembrolizumab for adults across all indications, regardless of tumor type. As outlined below, this dose is justified by:

- Clinical data from 8 randomized studies demonstrating flat dose- and exposure-efficacy relationships from 2 mg/kg Q3W to 10 mg/kg every 2 weeks (Q2W),
- Clinical data showing meaningful improvement in benefit-risk including overall survival at 200 mg Q3W across multiple indications, and
- Pharmacology data showing full target saturation in both systemic circulation (inferred from PK data) and tumor (inferred from physiologically-based PK [PBPK] analysis) at 200 mg Q3W.

Among the 8 randomized dose-comparison studies, a total of 2262 participants were enrolled with melanoma and non-small cell lung cancer, covering different disease settings (treatment naïve, previously treated, PD-L1 enriched, and all-comers) and different treatment settings (monotherapy and in combination with chemotherapy). Five studies compared 2 mg/kg Q3W versus 10 mg/kg Q2W (KN001 Cohort B2, KN001

Cohort D, KN002, KN010, and KN021), and 3 studies compared 10 mg/kg Q3W versus 10 mg/kg Q2W (KN001 Cohort B3, KN001 Cohort F2 and KN006). All of these studies demonstrated flat dose- and exposure-response relationships across the doses studied representing an approximate 5- to 7.5-fold difference in exposure. The 2 mg/kg (or 200 mg fixed-dose) Q3W provided similar responses to the highest doses studied. Subsequently, flat dose-exposure-response relationships were also observed in other tumor types including head and neck cancer, bladder cancer, gastric cancer and classical Hodgkin's Lymphoma, confirming 200 mg Q3W as the appropriate dose independent of the tumor type. These findings are consistent with the mechanism of action of pembrolizumab, which acts by interaction with immune cells, and not via direct binding to cancer cells.

Additionally, pharmacology data clearly show target saturation at 200 mg Q3W. First, PK data in KN001 evaluating target-mediated drug disposition conclusively demonstrated saturation of PD-1 in systemic circulation at doses much lower than 200 mg Q3W. Second, a PBPK analysis was conducted to predict tumor PD-1 saturation over a wide range of tumor penetration and PD-1 expression. This evaluation concluded that pembrolizumab at 200 mg Q3W achieves full PD-1 saturation in both blood and tumor.

Finally, population PK analysis of pembrolizumab, which characterized the influence of body weight and other participant covariates on exposure, has shown that the fixed-dosing provides similar control of PK variability as weight-based dosing, with considerable overlap in the distribution of exposures from the 200 mg Q3W fixed dose and 2 mg/kg Q3W dose. Supported by these PK characteristics and given that fixed-dose has advantages of reduced dosing complexity and reduced potential of dosing errors, the 200 mg Q3W fixed-dose was selected for evaluation across all pembrolizumab protocols.

4.4. End of Study Definition

A participant is considered to have completed the study if he/she has completed all phases of the study including follow-up for survival or until follow-up for survival is no longer required (refer to Section 7.1).

The end of the study is defined as the date of the last visit of the last participant in the study.

5. STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1. Inclusion Criteria

Participants are eligible to be included in the study if all of the following criteria apply:

1. Capable of giving signed informed consent/assent which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol

2. Male or female, age ≥18 years at the time consent is obtained (minimum age requirement per local regulatory requirements)

3. Histological or cytological documentation of HNSCC that was diagnosed as recurrent or metastatic and considered incurable by local therapies

4. Primary tumor location of the oral cavity, oropharynx, hypopharynx or larynx.

5. No prior systemic therapy administered in the recurrent or metastatic setting (with the exception of systemic therapy completed >6 months prior if given as part of multimodal treatment for locally advanced disease, and no disease progression/recurrence within 6 months of the completion of systemic treatment with curative intent)

6. Measurable disease per RECIST version 1.1 guidelines
    a. **Note**: if a participant has a solitary measurable lesion which was previously irradiated, that lesion must have progressed per RECIST v1.1 definition, following completion of radiation
7. ECOG Performance PS score of 0 or 1

8. Adequate organ function as defined in Table 3

Table 3 Definitions of Adequate Organ Function

System	Laboratory Values
Hematologic[a]	
ANC	≥1.5x10^9/L
Hemoglobin	≥9 g/dL
Platelets	≥100x10^9/L
Hepatic	
Albumin	≥2.5 g/dL
ALT	≤2.5xULN or ≤5xULN for participants with documented liver metastases
Total bilirubin	Bilirubin ≤1.5xULN (isolated bilirubin > 1.5xULN is acceptable if bilirubin is fractionated and direct bilirubin <35%)
Coagulation	
INR OR PT aPTT	≤1.5 × ULN unless participant is receiving anticoagulant therapy as long as PT or aPTT is within therapeutic range of intended use of anticoagulants
Renal	
Calculated CrCl[b]	≥30 mL/min
Cardiac	
Ejection fraction[c]	≥50%

Abbreviations: aPTT = activated partial thromboplastin time ANC = Absolute neutrophil count; ALT = alanine aminotransferase; CrCl = creatinine clearance; ECHO=echocardiogram; eGFR=estimated glomerular filtration rate; INR = international normalization ratio; MUGA= multigated acquisition scan; PT = prothrombin time; TSH = thyroid-stimulating hormone; ULN = upper limit of normal; WNL = within normal limits

a. Participants may be transfused or receive growth factor treatment to meet minimum hematologic values up to 7 days prior to determining eligibility
b. Estimated CrCl/eGFR is required to be calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) or Cockcroft-Gault formula; either formula is acceptable and must be consistently used for each participant throughout the study (refer Appendix 6).
c. MUGA is acceptable if ECHO is not available; for each participant the same modality must be used for all subsequent evaluations

9. Life expectancy of at least 12 weeks

10. Female participants: must not be pregnant (as confirmed by a negative serum beta-human chorionic gonadotrophin [β-hCG] test in females of reproductive potential; for further details refer to Section 10.4), not breastfeeding, and at least one of the following conditions apply:

    a. Not a woman of childbearing potential (WOCBP) as defined in Section 10.4.1.

   b. A WOCBP who agrees to use a method of birth control from 30 days prior to randomization and for at least 120 days after the last dose of study treatment. Refer to Section 10.4.2 for permitted contraceptive methods; contraceptive use should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

   c. The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy

11. Male participants with female partners of child-bearing potential: must agree to use a highly effective contraception while receiving study treatment and for at least 120 days after the last dose of study treatment and refrain from donating sperm during this period. Refer to Section 10.4.2 for permitted contraceptive methods; contraceptive use should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

12. Provide tumor tissue from excisional or core biopsy (fine needle aspirates and bone biopsies are not acceptable) acquired within 2 years prior to date of PD-L1 immunohistochemistry (IHC) testing by central laboratory. A fresh tumor biopsy, using a procedure that is safe for the participant on a lesion not previously irradiated (unless lesion progressed) will be required if previously acquired tumor tissue (i.e., archival tumor tissue) was acquired > 2 years or is unavailable//unsuitable for PD-L1 testing.

13. Have PD-L1 IHC CPS ≥1 status by central laboratory testing (refer to Section 5.4 for definition of screen failure based on PD-L1 CPS restrictions)

   a. A specific PD-L1 CPS status may be required to fulfill eligibility (refer to Section 9.2 for details on estimated number of participants by PD-L1 CPS status) if a PD-L1 CPS status cap is implemented (study population proportion by PD-L1 CPS status will not exceed 5% of the planned proportions of the PD-L1 CPS subgroups (CPS ≥20 and 1≤ CPS <20)

14. Have results from testing of HPV status for oropharyngeal cancer (refer to Section 8 and Table 1 for details on testing requirements)

5.2. Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

1. Prior therapy with an anti-PD-1/L1/L2 and/or anti-ICOS directed agent

2. Systemic approved or investigational anticancer therapy within 30 days or 5 half-lives of the drug, whichever is shorter. At least 14 days must have elapsed between the last dose of prior anticancer agent and the date of randomization

3. Has high risk of bleeding (examples include but not limited to tumors encasing or infiltrating a major vessel [i.e. carotid, jugular, bronchial artery] and/or exhibits other high-risk features such as an arteriovenous fistula)

   NOTE: Principal investigator should consult the GSK Medical Monitors to confirm eligibility of patients with disease features that may confer a high risk of tumor associated hemorrhage.

4. Active tumor bleeding

5. Grade 3 or Grade 4 hypercalcemia

6. Major surgery ≤ 28 days prior to randomization. Participants must have also fully recovered from any surgery (major or minor) and/or its complications before randomization

7. Toxicity from previous anticancer treatment that includes:

   a. Grade 3/Grade 4 toxicity considered related to prior immunotherapy and that led to treatment discontinuation
   b. Toxicity related to prior treatment that has not resolved to ≤Grade 1 (except alopecia, hearing loss, endocrinopathy managed with replacement therapy, and peripheral neuropathy which must be ≤Grade 2)

8. Received transfusion of blood products (including platelets or red blood cells) or administration of colony stimulating factors (including granulocyte colony-stimulating factor, granulocyte-macrophage colony-stimulating factor, recombinant erythropoietin) within 14 days prior to randomization

9. Central nervous system (CNS) metastases, with the following exception: Participants with asymptomatic CNS metastases who are clinically stable and have no requirement for steroids for at least 14 days prior to randomization

   Note: Participants with carcinomatous meningitis or leptomeningeal spread are excluded regardless of clinical stability

10. Invasive malignancy or history of invasive malignancy other than disease under study within the last 3 years, except as noted below:

a. Any other invasive malignancy for which the participant was definitively treated, has been disease-free for ≤3 years and in the opinion of the principal investigator and GSK Medical Monitor will not affect the evaluation of the effects of the study treatment on the currently targeted malignancy, may be included in this clinical study

b. Curatively treated non-melanoma skin cancer or successfully treated in situ carcinoma

c. Low-risk early stage prostate cancer defined as follows: Stage T1c or T2a with a Gleason score ≤ 6 and prostatic-specific antigen <10 ng/mL either treated with definitive intent or untreated in active surveillance that has been stable for the past year prior to randomization

11. Autoimmune disease (current or history; refer to Table 19) or syndrome that required systemic treatment within the past 2 years

    Note: Replacement therapies which include physiological doses of corticosteroids for treatment of endocrinopathies (for example, adrenal insufficiency) are not considered systemic treatments

12. Has a diagnosis of immunodeficiency or is receiving systemic steroids (>10 mg oral prednisone per day or equivalent) or other immunosuppressive agents within 7 days prior to randomization

    Note:
    a) Physiologic doses of corticosteroids for treatment of endocrinopathies or steroids with minimal systemic absorption, including topical, inhaled, or intranasal corticosteroids may be continued if the participant is on a stable dose, up to a maximum of 10 mg prednisone per day or equivalent
    b) Steroids as premedication for hypersensitivity reactions (e.g., computed tomography [CT] scan premedication) are permitted.

13. Receipt of any live vaccine within 30 days prior randomization

14. Prior allogeneic/autologous bone marrow or solid organ transplantation

15. Has current pneumonitis or history of non-infectious pneumonitis that required steroids or other immunosuppressive agents

    Note: post-radiation changes in the lung related to prior radiotherapy and/or asymptomatic radiation-induced pneumonitis not requiring treatment (Grade 1) may be permitted if agreed upon by the investigator and Medical Monitor.

16. Recent history (within the past 6 months) of uncontrolled symptomatic ascites, pleural or pericardial effusions

17. Recent history (within the past 6 months) of gastrointestinal obstruction that required surgery, acute diverticulitis, inflammatory bowel disease, or intra-abdominal abscess

18. Recent history of allergen desensitization therapy within 4 weeks of randomization

19. History or evidence of cardiac abnormalities within the 6 months prior to randomization which include:

    a. Serious, uncontrolled cardiac arrhythmia or clinically significant electrocardiogram abnormalities including second degree (Type II) or third-degree atrioventricular block

    b. Cardiomyopathy, myocardial infarction, acute coronary syndromes (including unstable angina pectoris), coronary angioplasty, stenting or bypass grafting

    c. Congestive heart failure (Class II, III, or IV) as defined by the New York Heart Association functional classification system

    d. Symptomatic pericarditis

20. Cirrhosis or current unstable liver or biliary disease per investigator assessment defined by the presence of ascites, encephalopathy, coagulopathy, hypoalbuminemia, esophageal or gastric varices, or persistent jaundice.

    Note: Stable non-cirrhotic, chronic liver disease (including Gilbert's syndrome or asymptomatic gallstones) or hepatobiliary involvement of malignancy is acceptable if participant otherwise meets entry criteria

21. Active infection requiring systemic therapy

22. Known HIV infection, or positive test for hepatitis B active infection (presence of hepatitis B surface antigen), or hepatitis C active infection (refer to Table 15)

23. History of severe hypersensitivity to monoclonal antibodies or any ingredient used in the study treatment formulations (refer to Table 4)

24. Known history of active tuberculosis

25. Any serious (≥Grade 3) and/or unstable pre-existing medical condition (aside from malignancy)

26. Any psychiatric disorder, or other condition that could interfere with participant's safety, obtaining informed consent, or compliance to the study procedures in the opinion of the investigator

27. Pregnant, breastfeeding, or expecting to conceive or father children within the projected duration of the study, starting with the screening visit through 120 days after the last dose of study treatment

28. Is currently participating in (unless in follow-up phase and 4 weeks have elapsed from last dose of prior investigational agent), or has participated in a study of an investigational agent or has used an investigational device within 4 weeks prior to date of randomization

Note: Participants who have entered the follow-up phase of an investigational study may participate provided it has been 4 weeks after the last dose of the previous investigational agent.

5.3. Lifestyle Considerations

There are no dietary restrictions nor lifestyle restrictions other than the contraceptive requirements defined in Section 10.4.

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but do not meet 1 or more eligibility criteria and therefore are not subsequently randomized. If participants are required to have a specific positive PD-L1 CPS status based on Competent Authority and/or IRB/Ethics Committee restrictions, or an Investigator's decision, then a participant who is not otherwise randomized due to a PD-L1 CPS result will be considered a screen failure.

A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse events (SAEs).

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened; rescreened participants will be assigned a new participant number.

6. STUDY INTERVENTION

Refer to the Schedule of Activities for administration of study interventions.

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol. The term study intervention or study treatment may be used in the protocol and study supportive documents (e.g., study reference manual) interchangeable and apply to an individual study drug or the combination of study drugs.

6.1. Study Intervention(s) Administered

For participants who meet all eligibility criteria and are randomized within the study, the maximum duration of treatment with pembrolizumab, GSK3359609 and placebo is

expected to be approximately 2 years up to 35 cycles. A decision to permanently discontinue treatment due to disease progression may be based upon immune-based RECIST (iRECIST) as disease progression per RECIST v1.1 guideline is further evaluated per iRECIST for confirmation by imaging/clinical assessments ≥4 weeks later and is critical to the analysis of immune-based PFS (iPFS) [Seymour, 2017].

Participants will be randomly assigned to either receive the combination of GSK3359609 24 mg plus pembrolizumab 200 mg or placebo plus pembrolizumab 200 mg. GSK3359609, placebo, and pembrolizumab are each administered as a 30-minute IV infusion once Q3W. GSK3359609 or placebo will be administered first followed by pembrolizumab.

GSK3359609, pembrolizumab, and placebo (refer to Table 4) will be administered intravenously to participants at each study site under medical supervision of an investigator or designee. GSK3359609/Placebo will be administered first followed by the infusion of pembrolizumab. The date and time of administration will be documented in the source documents and reported in the electronic case report form (eCRF). Participants should remain under observation at the study site post-study treatment infusion per the judgement of the investigator or as per institutional guidelines or regulatory requirements.

The study reference manual (SRM) contains details on product administration and specific instructions for the preparation of both GSK3359609 and pembrolizumab infusions, and administration of these infusions. The description, preparation and administration of placebo is provided in the SRM.

Table 4 Study Intervention Description and Administration

	Study Agent[1]		
Product Name:	GSK3359609	Pembrolizumab	Placebo
Product Description	Humanized anti-ICOS IgG4 mAb	Humanized anti-PD-1 IgG4 mAb	Sterile normal saline
Dosage form /strength:	10 mg/mL solution	100 mg/4 mL solution/25 mg/mL	0.9% Sodium Chloride for Injection
Planned dosage level(s):	24 mg	200 mg	N/A
Route of Administration	IV infusion	IV infusion	IV infusion
Dosing instructions/ Frequency:	Administer diluted product /once Q3W (refer to SRM for infusion time)	Administer diluted product /once Q3W (refer to SRM for infusion time)	Administer product /once Q3W (refer to SRM for infusion time)
Packaging and Labelling	Provided in vials labelled as required per country requirement.	Provided in vials labelled as required per country requirement.	Provided by the site unless required by the Sponsor as per country requirement
Study Arm	1	1 and 2	2
Manufacturer	GSK	Merck	N/A

Abbreviations: GSK=GlaxoSmithKline; IgG4=immunoglobulin G4; IV-intravenous; mAb=monoclonal antibody; mg=milligram; ml=millilitre; N/A=not applicable; PD-1=programmed cell death receptor1; Q3W=every three weeks; SRM=study reference manual

1. Refer to GSK3359609 [GlaxoSmithKline Document Number 2017N319717_03, 2020] and Pembrolizumab IB [Merck, 2021] for formulation description

6.2. Preparation/Handling/Storage/Accountability

1. The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.
2. Only participants enrolled in the study may receive study intervention and only authorized site staff may supply or administer study intervention. All study interventions must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.
3. The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).
4. Further guidance and information for the final disposition of unused study intervention are provided in the SRM.
5. Under normal conditions of handling and administration, study intervention is not expected to pose significant safety risks to site staff. Take adequate precautions to avoid direct eye or skin contact and the generation of aerosols or mists. In the case of unintentional occupational exposure notify the monitor, Medical Monitor and/or GSK study contact.
    - A Material Safety Data Sheet (MSDS)/equivalent document describing occupational hazards and recommended handling precautions either will be provided to the investigator, where this is required by local laws, or is available upon request from GSK.

6.3. Measures to Minimize Bias: Randomization and Blinding

Randomization will occur centrally using an Interactive Response Technology (IRT); refer to the SRM for detail on randomization process. Participants will be randomly assigned to a study treatment arm in a 1:1 ratio to either receive the combination of GSK3359609 24 mg plus pembrolizumab 200 mg or placebo plus pembrolizumab 200 mg.

Randomization will be stratified according to the following factors:

1. PD-L1 CPS status (CPS ≥20 vs. 1≤ CPS <20)
2. HPV status (oropharyngeal cancers [positive vs. negative/unknown] vs. non-oropharyngeal cancers).

The overall proportion of participants by PD-L1 CPS status will be capped by the IRT such that the maximum proportion of participants in PD-L1 CPS ≥20 or 1≤ CPS <20 will not exceed the planned proportion by 5% for either subgroup.

This is a double-blind study. The participant, the investigator and site staff involved in the treatment administration or clinical management of the participants will remain

blinded to each participant's assigned study treatment throughout the course of the study. Site unblinded staff will provide the investigative blinded staff with prepared blinded GSK3359609 or placebo infusion solutions, packaged identically in order to maintain the blinding, for administration at scheduled infusion visits. Refer to the SRM for information on labelling and dispensing procedures to mitigate unblinding. In the event a participant's study treatment assignment is unblinded to the blinded site staff and/or the participant, the participant is permitted to continue/remain in the study; the site must notify the GSK's clinical research associate (CRA) within 24 hours.

GSK personnel or delegates, except GSK staff involved in the review/monitoring of site pharmacy records and GSK clinical supplies group, will remain blinded to each participant's assigned study treatment throughout the course of the study.

GSK's Global Clinical Safety and Pharmacovigilance staff may unblind the intervention assignment for any participant with an SAE. If the SAE requires that an expedited regulatory report be sent to one or more regulatory agencies, a copy of the report, identifying the participant's intervention assignment, may be sent to investigators in accordance with local regulations and/or GSK policy.

In the event of a medical emergency, Investigators may unblind a participant's treatment assignment immediately through the IRT system by accessing a participant's home screen using the Subjects tab and clicking the Unblind button. Further details may be found in the SRM and the IRT manual.

6.4. Study Intervention Compliance

- All study agents will be intravenously administered to participants at the site. Administration will be documented in the source documents and reported in the eCRF. Refer to the SRM for further details.

6.5. Concomitant Therapy

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the participant is receiving at the time of enrollment or receives during the study must be recorded along with:

- reason for use
- dates of administration including start and end dates
- dosage information including dose and frequency

The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

6.5.1. Permitted Medications and Non-drug Therapies

All participants should receive full supportive care during the treatment course of the study, including transfusion of blood and blood products, growth factors and treatment with antibiotics, antiemetics, antidiarrheals, and analgesics, bisphosphonates or other medications as appropriate. Seasonal flu vaccine is permitted as an injection only, that is,

intra-nasal flu vaccine is not permitted. Elective palliative surgery or radiation may be permitted on a case-by-case basis in consultation with GSK Medical Monitor.

The following medications are permitted as indicated:

a. Bisphosphonates and receptor activator of nuclear factor-kappaB ligand (RANKL) inhibitors (e.g., denosumab): permitted for treatment of bone metastasis or other indicated conditions such as hypercalcemia provided participants have been on a stable dose for at least 4 weeks prior to randomization date. **Note**: prophylactic use in participants without evidence or history of bone metastasis is not permitted, except for the treatment of osteoporosis.

b. Steroids: refer to Section 6.6 and the associated sub-sections for acceptable use while participant is receiving study treatment. Participants with pre-existing conditions requiring steroids are permitted to continue taking up to a maximum of 10 mg of prednisone per day or equivalent provided the participant has been on a stable dose for at least 28 days before date of randomization; refer to exclusion criterion 9 in Section 5.2 for further requirements.

6.5.2. Prohibited Medications and Non-drug Therapies

The following medications are prohibited before the date of randomization (refer to Section 5.2 for specific time requirements) and while on treatment in this study:

a. Anticancer therapies other than those referred to as Study Intervention/Treatment that include but are not limited to chemotherapy, immunotherapy, biologic therapy, hormonal therapy (other than physiologic replacement), surgery, and radiation therapy (other than palliative intervention as described in Section 6.5.1)
b. Any investigational drug (s) other than those referred to as Study Intervention/Treatment
c. Live vaccines such as intra-nasal flu vaccine
d. Steroids at >10 mg of prednisone per day or equivalent; refer to Section 6.5.1 for permitted use of steroids in cases where prescribed for the treatment of immune related adverse events.

6.5.2.1. Anti-cancer Therapy After Study Intervention Discontinuation

Treatment with ICOS or ICOS ligand directed/targeted agents as post study anti-cancer therapy are prohibited for participants who permanently discontinue study treatment.

6.6. Dose Modification

Distinct safety management guidelines, including dose modification algorithms, are provided in this section for:

- GSK3359609
- Pembrolizumab

Please note: In instances where the investigator is directed to permanently discontinue study treatment, the instructions are mandatory as described in Section 7.1.

All AEs are to be graded according to NCI-CTCAE (version 5.0) [NCI, 2017]. All dose modifications and the reason(s) for the dose modification must be documented in the eCRF.

Refer to pembrolizumab prescribing information [KEYTRUDA, 2019] for additional information regarding the background and the management of other AEs or potential safety-related issues. The investigator may consult the GSK Medical Monitor on study treatment modifications (i.e., holds or discontinuation) or on the management of AEs.

6.6.1. General Guidelines for Immune-Related Adverse Events

AEs associated with immunotherapy treatment may be immune-mediated. These immune-related AEs (irAEs) may occur shortly after the first dose or several months after the last dose of treatment, or during the treatment course, and may affect more than one body system simultaneously. Therefore, early recognition of and initiation of treatment for these events is critical to reduce potential complications. Based on existing data from the study 204691, most treatment-related AEs were Grade 1 or 2, managed with supportive care and if appropriate the administration of corticosteroids.

For suspected irAEs, ensure adequate evaluation to confirm the etiology or exclude other causes. Additional procedures or tests such as, but not limited to, bronchoscopy, endoscopy, or skin biopsy may be included as part of the evaluation. Based on the severity of irAEs, withhold or permanently discontinue treatment and administer corticosteroids. Dose modification and toxicity management guidelines for irAEs associated with immunotherapies are provided in Table 5.

Before administration of study treatment, investigators are to review a participant's AEs, concomitant medications, and clinical evaluation results, e.g., vital signs, laboratory results, ECOG PS, physical examination findings, responses, etc. as outlined in the Schedule of Activities (Table 1) to monitor for new or worsening irAEs and ensure continues dosing is appropriate.

Adverse Events of Special Interest (AESI)

AESI are defined as events of potential immunologic etiology, including irAEs. Such events recently reported after treatment with other immune modulatory therapy include colitis, uveitis, hepatitis, pneumonitis, diarrhea, endocrine disorders, and specific cutaneous toxicities, as well as other events that may be immune mediated.

Table 5 Dose Modification and Toxicity Management Guidelines for Immune-Related AEs

General instructions:

- Corticosteroid taper should be initiated upon irAE improving to ≤Grade 1 and continue to taper over at least 4 weeks.
- For situations where immunotherapy treatment has been withheld, treatment can be resumed after irAE has been reduced to ≤Grade 1 and corticosteroid has been

tapered. Immunotherapy treatment should be permanently discontinued if irAE does not resolve or corticosteroids cannot be reduced to ≤10 mg prednisone or equivalent per day within 12 weeks of last dose of study treatment.

- For severe and life-threatening irAEs, IV corticosteroid should be initiated first followed by oral steroid. Other immunosuppressive treatment should be initiated if irAEs cannot be controlled by corticosteroids.

Immune-related AEs	Severity Grade or Condition (CTCAEv5.0)	Action Taken to: GSK3359609[a]/ Pembrolizumab	Management: Corticosteroid and/or Other Therapies	Monitoring and Follow-up
Respiratory				
Pneumonitis	Grade 2	Withhold	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper • Add prophylactic antibiotics for opportunistic infections	• Monitor participants for signs and symptoms of pneumonitis. • Evaluate participants with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment.
	Grade 3 or Grade 4, or recurrent Grade 2	Permanently discontinue		
Gastrointestinal				
Diarrhea / Colitis	Grade 2 or Grade 3	Withhold	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	• Monitor participants for signs and symptoms of enterocolitis (i.e., diarrhea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (i.e., peritoneal signs and ileus). • Participants with ≥ Grade 2 diarrhea suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis. • Participants with diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid
	Grade 4 or recurrent Grade 3	Permanently discontinue		

Immune-related AEs	Severity Grade or Condition (CTCAEv5.0)	Action Taken to: GSK3359609[a]/ Pembrolizumab	Management: Corticosteroid and/or Other Therapies	Monitoring and Follow-up
				and electrolytes should be substituted via IV infusion.
Hepatobiliary				
AST / ALT elevation or increased bilirubin	Grade 2	Withhold	• Administer corticosteroids (initial dose of 0.5-1 mg/kg prednisone or equivalent) followed by taper	• Monitor with liver function tests (consider weekly or more frequently until liver enzyme value returned to baseline or is stable. • Refer to Appendix 8 for liver safety required actions and follow-up assessments and study treatment guidelines.
	Grade 3 or Grade 4	Permanently discontinue	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	
Endocrine				
Type 1 diabetes mellitus (T1DM) or Hyperglycemia	New onset T1DM or Grade 3 or Grade 4 hyperglycemia associated with evidence of β-cell failure	Withhold[b]	• Initiate insulin replacement therapy for participants with T1DM • Administer an anti-hyperglycemic in participants with hyperglycemia	• Monitor participants for hyperglycemia or other signs and symptoms of diabetes.
Hypophysitis	Grade 2	Withhold	• Administer corticosteroids and initiate hormonal replacements as clinically indicated.	• Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency).
	Grade 3 or Grade 4	Withhold or permanently discontinue[b]		
Hyperthyroidism	Grade 2	Continue	• Treat with non-selective beta-blockers (e.g., propranolol) or thionamides as appropriate	• Monitor for signs and symptoms of thyroid disorders.
	Grade 3 or Grade 4	Withhold or Permanently discontinue[b]		
Hypothyroidism	Grade 2, Grade 3, or Grade 4	Continue	• Initiate thyroid replacement hormones (e.g., levothyroxine	• Monitor for signs and symptoms of thyroid disorders

Immune-related AEs	Severity Grade or Condition (CTCAEv5.0)	Action Taken to: GSK3359609[a]/ Pembrolizumab	Management: Corticosteroid and/or Other Therapies	Monitoring and Follow-up
			or liothyronine) per standard of care	
Renal				
Nephritis: Grade according to increased creatinine or acute kidney injury	Grade 2	Withhold	• Administer corticosteroids (prednisone 1-2 mg/kg or equivalent) followed by taper	• Monitor changes of renal function
	Grade 3 or Grade 4	Permanently discontinue		
Cardiovascular				
Myocarditis	Grade 2, Grade 3 or Grade 4	Permanently discontinue	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes.
Neurological				
Neurological Toxicities	Grade 2	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes.
	Grade 3 or Grade 4	Permanently discontinue		
Skin				
Exfoliative Dermatologic Conditions	Suspected SJS, TEN, or DRESS	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes.
	Confirmed SJS, TEN, or DRESS	Permanently discontinue		
Other				
All other immune-related AEs	Grade 3, or intolerable/ persistent Grade 2	Withhold or discontinue based on the type of event	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology or exclude other causes
	Grade 4 or recurrent Grade 3	Permanently discontinue		

Abbreviations: AE=adverse events; ALT=alanine aminotransferase; AST= aspartate aminotransferase; CTCAE=common terminology criteria for adverse events; DRESS=Drug Rash with Eosinophilia and Systemic Symptom; GI=gastrointestinal irAE=immune-related AE; IV=intravenous; kg=kilogram; mg=milligram; SJS=Stevens-Johnson Syndrome; T1DM=Type 1 diabetes mellitus; TEN=toxic epidermal necrolysis

a. The actions taken for GSK3359609 infer an action required for placebo due to the blinded design.
b. The decision to withhold or permanently discontinue study treatment is at the discretion of the investigator or treating physician. If control is achieved or ≤Grade 2, study treatment may be resumed.
c. The events that require discontinuation include but are not limited to encephalitis, and other clinically important irAEs (e.g., vasculitis and sclerosing cholangitis).

6.6.2. Dose Modification and Toxicity Management of Infusion-Reactions Related to Immunotherapy Treatment

Infusion reactions are a well-documented AE associated with the administration of mAb. Infusion reactions typically develop within 30 minutes to 2 hours after initiation of drug infusion, although symptoms may be delayed for up to 48 hours. The incidence of infusion reactions varies by mAb agent, and there are multiple mechanisms known to lead to infusion-related reactions including both IgE-dependent anaphylactic and non-IgE dependent anaphylactoid hypersensitivities. Cytokine release syndrome, and when severe, cytokine "storm", has been identified as a sequela of the immune system activation associated with infusion reactions.

Infusion reactions may affect any organ system in the body; most are mild in severity, although severe and even fatal reactions occur. As a group, infusion reactions (including both cytokine-mediated and allergic) usually occur during or within a few hours of drug infusion. Occasionally, a reaction may occur 1 to 2 days after administration. The NCI-CTCAE (version 5.0) for grading adverse reactions during chemotherapy administration has a scale for grading the severity of infusion reactions and separate grading scales for allergic reactions and anaphylaxis. While use of these separate grading scales may be useful for classifying the nature of an infusion reaction for research purposes, they are less useful for clinical care, since it may not be obvious if the participant is having an allergic infusion reaction or a non-allergic infusion reaction.

Clinically, an infusion reaction may present with flushing, itching, urticaria, and/or angioedema, repetitive cough, sudden nasal congestion, shortness of breath, chest tightness, wheeze, sensation of throat closure or choking, and/or change in voice quality, faintness, tachycardia (or less often bradycardia), hypotension, hypertension and/or loss of consciousness, nausea, vomiting, abdominal cramping, and/or diarrhea, sense of impending doom, tunnel vision, dizziness, and/or seizure, severe back, chest, and pelvic pain. Refer to Table 7 for dose modification and treatment guidance for immunotherapy infusion reactions.

To better understand the underlying etiology of these events, serum tryptase, C-reactive protein (CRP), ferritin, and a cytokine panel should be drawn during the occurrence of an infusion reaction/CRS of any grade as outlined in Table 6. The serum tryptase, CRP and ferritin panels should be performed at the investigator's designated local laboratory. The serum cytokine panel will be performed at a GSK designated laboratory. These data will aid in the classifying (albeit retrospectively) the etiology of the AE.

Table 6 Infusion-Related Reaction Laboratory Panel

Analyte	Relationship to Adverse Event
Serum tryptase[a]	IgE-related infusion reaction (Allergic/anaphylaxis) [Schwartz, 2006]
Serum CRP[a]	Elevated in CRS [Lee, 2014]
Serum ferritin[a]	Elevated in CRS [Lee, 2014]
Serum cytokine panel[b] (***IFNγ****^, ***TNFα****^, ***IL1β,*** IL2*, IL4, ***I-6****^, ***IL8****, IL10*, ***IL12p70***, and IL13)	* Reported to be elevated in CRS [Lee, 2014] ^ Consistently reported as elevated in CRS [Lee, 2014]

Abbreviations: CRP = C-reactive protein; CRS = Cytokine release syndrome; IFNγ = Interferon gamma; TNFα =Tumor necrosis factor alpha; IL = Interleukin.

a. Performed by investigator designated local laboratory if available; otherwise performed by GSK designated laboratory

b. Performed by a GSK designated laboratory; note: in participants enrolled from China sites, only the analytes **bolded** and *italicized* will be tested.

The guidelines provided in Table 7 are suggestions. Investigators and site staff may also follow their site standard operating procedures for the treatment of these events.

Table 7 Infusion Reaction Dose Modification and Treatment Guidelines

NCI CTCAE Grade	Treatment	Premedication at Subsequent Dosing
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	• Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator.	• None

Grade 2
Requires therapy or infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤24 hrs.
	• **Stop Infusion**
	• Additional appropriate medical therapy may include but is not limited to:
	  ○ IV fluids
	  ○ Antihistamines
	  ○ NSAIDs
	  ○ Acetaminophen
	  ○ Narcotics
	• Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator
	• If symptoms resolve within 1 hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g. from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the participant should be premedicated for the next scheduled dose
	Participants who develop Grade 2 toxicity despite adequate
		• Participant may be premedicated 1.5hr (± 30 minutes) prior to infusion of study drugs with:
		  ○ Diphenhydramine 50 mg po (or equivalent dose of antihistamine).
		  ○ Acetaminophen 500-1000 mg po (or equivalent dose of analgesic).

NCI CTCAE Grade	Treatment	Premedication at Subsequent Dosing
	premedication should be permanently discontinued from further study treatment	
Grades 3 or Grade 4 **Grade 3:** Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates) Grade 4: Life-threatening; pressor or ventilatory support indicated	• **Stop Infusion** • Additional appropriate medical therapy may include but is not limited to: o Epinephrine** o IV fluids o Antihistamines o NSAIDs o Acetaminophen o Narcotics o Oxygen o Pressors o Corticosteroids • Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator • Hospitalization may be indicated. **In cases of anaphylaxis, epinephrine should be used immediately. **Participant is permanently discontinued from further study treatment.**	• No subsequent dosing
Note: Appropriate resuscitation equipment should be available at the bedside and a physician readily available during the period of drug administration. For further information, please refer to the Common Terminology Criteria for Adverse Events v5.0 (CTCAE) at http://ctep.cancer.gov		

Abbreviations: CTCAE=common terminology criteria for adverse events; hr=hour; IV=intravenous; mg=milligram; ml=millilitres; NSAID=nonsteroidal anti-inflammatory drug; po=per os [by mouth]

6.7. Intervention after the End of the Study

Participants receiving study treatment at the time of the final analysis may continue to receive study treatment until treatment is discontinued as indicated in Section 7.1. At the time of the interim analysis for the adaptive decision or at other interim/final analyses (refer to Section 9.5), the IDMC may make a recommendation regarding the continuation of study treatment based on the outcome; this decision will be communicated to Investigators whereby subsequent communication to participants may be required.

Participants who permanently discontinue study treatment will not receive any additional treatment from GSK. The investigator is responsible for ensuring that consideration has been given to the post-study care based on the participant's medical condition. Refer to SoA (Table 1) and Section 7.1 for details on the follow-up assessments required for participants who permanently discontinued study treatment. Refer to Section 6.5.2.1 on prohibited post-study therapies.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

Participants will receive study treatment for the duration indicated in Section 6.1 as applicable, unless one of the following events occurs earlier:

- Disease progression
- Death
- Unacceptable toxicity (refer to Section 6.6 and subsections)
- Pregnancy (refer to Section 8.3.5 for details)

In addition, study treatment may be permanently discontinued for any of the following reasons:

- Deviation(s) from the protocol or non-compliance with study requirements
- Request of the participant or proxy (withdrawal of consent by participant or proxy)
- Discretion of the investigator
- Participant is lost to follow-up
- Closure or termination of the study

Participants who have disease progression by RECIST v1.1 may continue study treatment up to the protocol specified 35 cycles at the discretion of the Investigator to confirm progression as per iRECIST guidelines. Nevertheless, the consideration to continue study treatment should be balanced by clinical judgment as to whether the participant is clinically stable. Continuation on study treatment is contingent upon the following conditions:

- Absence of clinical signs or symptoms indicating clinically significant disease progression
- ECOG PS has not worsened, or worsening by no more than 1 point from baseline
- Absence of rapid disease progression or threat to vital organs or critical anatomical sites (e.g., CNS metastasis, respiratory failure due to tumor compression, or spinal cord compression) requiring urgent alternative medical intervention.
- No significant, unacceptable, or irreversible toxicities related to study treatment.

All participants who permanently discontinue study treatment for any reason (except consent withdrawn) will have safety assessments at the time of discontinuation and during follow-up as specified in the SoA.

The primary reason study treatment was permanently discontinued must be documented in the participant's medical records and eCRF. If the participant voluntarily discontinues from treatment due to toxicity, 'adverse event (AE)' will be recorded as the primary reason for permanent discontinuation on the eCRF.

Once a participant has permanently discontinued from study treatment, the participant will not be allowed to be retreated. Refer to the SoA for assessments to be performed at the time study treatment is permanently discontinued and for evaluations that need to be completed.

All participants who permanently discontinue study treatment without disease progression will be followed for progression according to the protocol-defined on-treatment disease assessment schedule in the SoA until one or more of the following occur:

- a new anticancer therapy is initiated
- disease progression
- death

All participants who permanently discontinue study treatment for any reason, except withdrawal of consent (refer to Section 7.2), will be followed for survival every 12 weeks until death or until last patient discontinues treatment and has had their last follow up for safety.

The every 12-week schedule (refer to Table 1 SoA for details of frequency of all assessments during follow-up period) should begin once study treatment has been permanently discontinued. If participants are unable or unwilling to attend clinic visits during follow-up, contact to assess survival, may be made via another form of communication (e.g., telephone, email, etc.).

7.1.1. Liver Chemistry Stopping Criteria

Liver chemistry stopping, and increased monitoring criteria have been designed to assure participant safety and evaluate liver event etiology.

Discontinuation of study intervention for abnormal liver tests is required when:

- a participant meets one of the conditions outlined in Appendix 8 and Section 6.6.1 or
- when in the presence of abnormal liver chemistries not meeting protocol-specified stopping rules, the investigator believes study intervention discontinuation is in the best interest of the participant.

7.1.1.1. Study Intervention Restart or Rechallenge after liver stopping criteria met

If participant meets liver chemistry stopping criteria do not restart/rechallenge participant with study intervention unless:

- GSK Medical Governance approval **is granted**
- Ethics and/or IRB approval is obtained, if required, and
- Separate consent for intervention restart/rechallenge is signed by the participant

Refer to Appendix 8 and Section 10.8.1 for details.

If GSK Medical Governance approval to restart/rechallenge participant with study intervention **is not granted**, then participant must permanently discontinue study intervention
and may continue in the study for protocol-specified follow up assessments.

7.2. Participant Discontinuation/Withdrawal from the Study

- A participant may withdraw from the study at any time at his/her own request or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance or administrative reasons. This is expected to be uncommon.
- At the time of withdrawing from the study, if possible, an early treatment discontinuation visit should be conducted. Refer to SoA (Table 1) for the assessments at the time of study discontinuation.
- The participant will be permanently discontinued both from the study intervention and from the study at that time.
- If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- A participant will be considered to have withdrawn from the study if the participant has not died and is lost to follow-up.

7.3. Lost to Follow Up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.

- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

8. STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA.
- Protocol waivers or exemptions are not allowed
- Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log or equivalent to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (e.g., blood count) and obtained before signing of ICF may be utilized for screening or baseline purposes provided the procedure met the protocol-specified criteria and was performed within the time frame defined in the SoA.
- The maximum volume of blood collected from each participant from Screening through Week 21 of the study treatment phase is estimated not to exceed 180 mL
    - **Note:** Repeat or unscheduled blood samples may be taken for safety reasons or for technical issues with the samples; these estimates are not included in the calculated maximum

Screening

All screening assessments must be performed within 28 days prior to randomization unless otherwise specified. The ICF may be signed within 45 days prior to randomization; archival tumor tissue collection or tumor tissue biopsy procedure can be performed as of 45 days prior to randomization after participant ICF obtained.

The term 'baseline' refers to the assessment performed during the screening period prior to first dose of study treatment that serves as a comparison or control. For example, the baseline laboratory assessment is the laboratory assessment performed prior to first dose.

Refer to SoA (Table 1) for additional details on assessments required at Screening and prior to start of study treatment.

The following assessments are required during screening:

- Demographic parameters such as year of birth and sex will be captured
- Medical history including cardiovascular medical history, tobacco use, and other risk factors will be assessed as related to the inclusion/exclusion criteria

- Disease characteristics including medical, surgical, and treatment history (best response to prior therapy [radiotherapy and systemic] will be recorded), date of initial diagnosis, primary tumor location, stage at initial diagnosis, histology, HPV status (if available, by the CINtec p16 histology assay; required in oropharyngeal cancers, refer to Table 1), tumor genetic/genomic features and current sites of disease will be taken as part of the disease history/status.
- Tumor tissue sent to central laboratory (refer to Section 5.1, inclusion criterion 12 for tissue requirements) for the following required screening assessments:
  - PD-L1 protein expression using the PD-L1 IHC 22C3 pharmDx assay by central laboratory testing; an CPS ≥1 result is required for eligibility
    - **NOTE**: the PD-L1 IHC 22C3 pharmDx is US FDA approved and CE marked in the EU
  - p16 IHC using the CINtec p16 histology assay for the assessment of HPV status (only required in oropharyngeal cancers and if results not available by local laboratory testing)

Baseline lesion assessments per RECIST v1.1 guideline [Eisenhauer, 2009] are required within 28 days randomization and include:

- Computed tomography (CT) scan with contrast of the chest and abdomen (must include complete imaging of the liver
  - **Note:** Although a CT scan is preferred, magnetic resonance imaging (MRI) may be used as an alternative method of baseline disease assessment, especially for those participants where a CT scan is contraindicated due to allergy to contrast. The method used to document baseline status must be used consistently throughout disease assessment visits to facilitate direct comparison. Refer to RECIST 1.1 guidelines for use of fluorodeoxyglucose-positron emission tomography (FDG-PET)/CT; this modality is permitted provided the CT portion is with contrast and is of diagnostic quality [Eisenhauer, 2009; Seymour, 2017].
- MRI/CT scan of head and neck region with IV gadolinium/contrast, respectively
- MRI of brain with and without IV gadolinium (if clinically indicated)
- Bone scan (if clinically indicated)
- Clinical disease assessment for palpable/visible lesions
- Other areas as indicated by the participant's underlying disease present prior to screening

Refer to Section 8.1 for baseline documentation of target and non-target lesions.

Safety and laboratory assessments (refer to Section 8.2 and Section 8.2.6) required at baseline include:

- Physical examination (refer to Section 8.2.1)
- ECOG Performance Status (refer to Section 8.2.2)
- Vital Signs (refer to Section 8.2.3)

- Concomitant medication
  - Recorded starting from screening through post-study treatment follow-up.
  - Record all medications the participant is taking including prescription medications, over-the-counter drugs or preparations, and herbal preparations including any cannabinoids and/or recreational drugs used.
  - At a minimum, the drug name, route of administration, dose, and frequency of dosing, along with start and stop dates must be recorded.
- Electrocardiogram (ECG; refer to Section 8.2.4)
- Echocardiogram (ECHO; refer to Section 8.2.5)
- Laboratory assessments (refer to Section 10.2).

Follow-up assessments

Participants who permanently discontinue study treatment for any reason, except withdrawal of consent (refer to Section 7.2), will be followed for survival every 12 weeks (±14 days) until death.

8.1. Efficacy Assessments

RECIST version 1.1 guidelines will be used to determine the overall tumor burden at screening, select target and non-target lesions, and in the disease assessments through the duration of the study [Eisenhauer, 2009]. The primary measure of response-based efficacy endpoints is according to RECIST v1.1 definitions as assessed by the Investigator. Scans will be collected centrally; refer to Section 9.7 for details on response assessment by BICR.

Additionally, iRECIST guidelines may used in the assessment of response/progression to account for the unique tumor kinetics observed with immunotherapeutic agents which may manifest as an increase in tumor burden then later is followed by regression suggesting the apparent observed neoplastic growth representing transient lymphocyte infiltration. Thus, participants with disease progression by RECIST version 1.1 guidelines may have a confirmatory disease assessment no sooner than 4 weeks after the date disease progression was declared in order to confirm disease progression by iRECIST guidelines. Confirmatory scans may be done as per clinical standard of care and at the discretion of the Investigator up to the protocol specified 35 cycles. The visit level responses and treatment-based decisions will incorporate iRECIST guidelines [Seymour, 2017].

Refer to the SoA (Table 1) for the frequency of disease assessments post Screening. Imaging of the head/neck, chest and abdomen is required at each disease assessment visit and at confirmation of disease progression; the same modality used at Screening must remain consistent throughout the study duration. Other imaging modalities and regions assessed at Screening and required to measure/evaluate the target and nontarget lesions are required at each visit and for confirmation of disease progression.

A random BICR audit will be performed at the time of the primary PFS analysis. Participant BICR randomization designation will not be known to the investigators; refer to Section 9.7 for details.

All imaging scans and clinical assessments (i.e., photographs) performed at Screening and at each disease assessment visit, including unscheduled assessment visits, are required to be uploaded at each visit occurrence for BICR. Refer to the imaging manual for details on imaging/clinical assessment requirements and submission guidelines.

8.1.1. Disease Assessments

- RECIST version 1.1 guidelines will be used to determine the overall tumor burden at screening, select target and non-target lesions, and in the disease assessments through the duration of the study [Eisenhauer, 2009].
- As indicated in RECIST version 1.1 guidelines:
  - Lymph nodes that have a short axis of <10 mm are considered non-pathological and must not be recorded or followed.
  - Pathological lymph nodes with <15 mm but ≥10 mm short axis are considered non-measurable.
  - Pathological lymph nodes with ≥15 mm short axis are considered measurable and can be selected as target lesions; however, lymph nodes should not be selected as target lesions when other suitable target lesions are available.
  - Measurable lesions up to a maximum of two lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as target lesions, and recorded and measured at baseline. These lesions should be selected based on their size (lesions with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinically).

Note: Cystic lesions thought to represent cystic metastases must not be selected as target lesions when other suitable target lesions are available.

Note: Measurable lesions that have been previously irradiated and have not been shown to be progressing following irradiation must not be considered as target lesions.

  - Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by CT or MRI can be considered measurable. Bone scans, FDG-PET scans or X-rays are not considered adequate imaging techniques to measure bone lesions.
  - All other lesions (or sites of disease) must be identified as non-target and must also be recorded at baseline. Non-target lesions will be grouped by organ. Measurements of these lesions are not required, but the presence or absence of each must be noted throughout follow-up.
- Disease assessment modalities may include imaging (e.g., CT scan, MRI, bone scan) and physical examination (as indicated for palpable/superficial lesions).
- At each post-baseline assessment, evaluation of the sites of disease (all target and non-target lesions) identified by the baseline scans is required. CT scans with contrast of the chest, and abdomen, or if contra-indicated, MRI, is required at each post-baseline assessment. To ensure comparability between the baseline and

subsequent assessments, the same method of assessment and the same technique will be used when assessing response.

- Refer to the SoA for the frequency of disease assessment. Assessments must be performed on a calendar schedule and should not be affected by dose interruptions/delays.
- Participants whose disease responds (either CR or PR) may have a confirmatory disease assessment performed at least 4 weeks after the date of assessment during which the response was demonstrated. More frequent disease assessments may be performed at the discretion of the investigator.

8.2. Safety Assessments

Planned time points for all safety assessments are provided in the SoA.

8.2.1. Physical Examinations

- A complete physical examination performed at Screening will include, at a minimum, assessment of the cardiovascular, respiratory, gastrointestinal, and neurological systems.
- A brief physical examination performed at each subsequent visit will include, at a minimum, assessments of the skin, lungs, cardiovascular system, and abdomen (liver and spleen).
- Investigators should pay special attention to clinical signs related to previous serious illnesses.

8.2.2. Performance Status

Performance status will be assessed using the ECOG scale at each visit; refer to Appendix 5.

8.2.3. Vital Signs

- Vital signs will be measured after 5 minutes of rest and will include temperature, systolic and diastolic blood pressure, pulse rate, respiratory rate, and oxygen saturation (measured by pulse oximetry). Blood pressure should be taken in the same position throughout the study and captured in the eCRF.
- Vital signs will be measured more frequently if warranted by clinical condition of the participant.
- If a participant develops fever and infusion related reaction or cytokine release syndrome is suspected, refer to management guidelines (Section 6.6.2).
- Height will be recorded at Screening only.
- Weight will be measured and recorded (in kilograms) at baseline and at every treatment visit.

8.2.4. Electrocardiograms

A 12-lead ECG will be performed at Screening as indicated in the SoA using an ECG machine that calculates the heart rate and measures PR, QRS, and QT intervals. The QT interval corrected for heart rate or RR interval using Fridericia's formula may be by machine or manual calculation. ECG after Screening will be performed as clinically indicated.

8.2.5. Echocardiograms

Echocardiogram will be performed at Screening to assess cardiac ejection fraction for the purpose of study eligibility, as specified in the SoA and Section 5.1. Additional ECHO assessments may be performed if clinically warranted. MUGA can be used in lieu of ECHO (if not available) in the assessment of LVEF; the same modality should be used in any subsequent assessments.

8.2.6. Clinical Safety Laboratory Assessments

- Refer to Appendix 2 for the list of clinical laboratory tests to be performed and to the SoA for the timing and frequency. The clinical laboratory tests will be performed by local laboratory unless otherwise indicated.
- The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
- All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 30 days after the last dose of study intervention should be repeated until the values return to normal or baseline or are no longer considered significantly abnormal by the investigator or medical monitor.
- If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified and the sponsor notified.
- All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the SoA.

8.3. Adverse Events and Serious Adverse Events

The definitions of an AE or SAE can be found in Appendix 3.

The investigator and any qualified designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study intervention or the study, or that caused the participant to discontinue the study intervention (Refer to Section 7).

All AEs are to be graded according to NCI-CTCAE (version 5.0) [NCI, 2017].

8.3.1. Time Period and Frequency for Collecting AE and SAE Information

- All AESIs and SAEs will be collected from the start of treatment until 90 days after the last dose of study treatment at the time points specified in the SoA (refer to Appendix 3 for details on SAEs). However, any SAEs assessed as related to study participation (e.g., study treatment, protocol-mandated procedures, invasive tests, or change in existing therapy) will be recorded from the time a participant consents to participate in the study. If subsequent anti-cancer treatment is initiated during the 90-day follow-up period yet <30 days after the date study treatment was discontinued, AESI ad SAEs must continue to be collected until 30 days after last dose of study treatment.
- All AEs will be collected from the start of study treatment until 30 days after the last dose of study treatment at the time points specified in the SoA (Table 1).
- Medical occurrences that begin before the start of study treatment but after obtaining informed consent will be recorded in the Medical History/Current Medical Conditions section of the CRF and not in the AE section.
- All SAEs will be recorded and reported to the Sponsor or designee immediately and under no circumstance should this exceed 24 hours. The investigator will submit any updated SAE data to the Sponsor within 24 hours of learning of the event.
- Investigators are not obligated to actively seek AEs or SAEs in former study participants. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study treatment or study participation, the investigator must promptly notify the Sponsor.

8.3.2. Method of Detecting AEs and SAEs

- The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 3.
- Care will be taken not to introduce bias when detecting AE and/or SAE. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrence.

8.3.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs and non-serious AESIs will be followed until events are resolved, stabilized, otherwise explained, or the participant is lost to follow-up as defined in Section 7.3. Further information on follow-up procedures is given in Appendix 3.

8.3.4. Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.
- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and investigators.
- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.
- An investigator who receives an investigator safety report describing a SAE or other specific safety information e.g., summary or listing of SAE) from the sponsor will review and then file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

8.3.5. Pregnancy

- If a participant becomes pregnant while on study treatment, study treatment must be immediately discontinued.
- Details of all pregnancies in female participants and female partners of male participants will be collected after the start of study treatment and until 120 days after the last dose of study treatment.
- If a pregnancy is reported, the investigator should inform GSK within 24 hours of learning of the pregnancy.
- Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAE.

8.3.6. Cardiovascular and Death Events

For any cardiovascular events detailed in Section 10.3.3 and all deaths, whether or not they are considered SAEs, specific Cardiovascular (CV) and Death sections of the CRF will be required to be completed. These sections include questions regarding cardiovascular (including sudden cardiac death) and non-cardiovascular death.

The CV CRFs are presented as queries in response to reporting of certain CV MedDRA terms. The CV information should be recorded in the specific cardiovascular section of the CRF within one week of receipt of a CV Event data query prompting its completion.

The Death CRF is provided immediately after the occurrence or outcome of death is reported. Initial and follow-up reports regarding death must be completed within one week of when the death is reported.

8.3.7. Events of Clinical Interest

Selected events that may be non-serious or serious adverse events and are considered as Events of Clinical Interest (ECI) in this study protocol and must be reported to the Sponsor.

Events of clinical interest include:

1. An overdose of Study Treatment (GSK3359609/Pembrolizumab), as defined in Section 8.4, that is not associated with clinical symptoms or abnormal laboratory results.
2. An elevated AST (aspartate aminotransferase) or ALT (alanine aminotransferase) lab value that is greater than or equal to 3X the upper limit of normal and an elevated total bilirubin lab value that is greater than or equal to 2X the upper limit of normal and, at the same time, an alkaline phosphatase lab value that is less than 2X the upper limit of normal, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.*

*Note: These criteria are based upon available regulatory guidance documents. The purpose of the criteria is to specify a threshold of abnormal hepatic tests that may require an additional evaluation for an underlying etiology. The study site guidance for assessment and follow up of these criteria can be made available. It may also be appropriate to conduct additional evaluation for an underlying etiology in the setting of abnormalities of liver blood tests including AST, ALT, bilirubin, and alkaline phosphatase that do not meet the criteria noted above. In these cases, the decision to proceed with additional evaluation will be made through consultation between the study investigators and the GSK Medical Monitor. However, abnormalities of liver blood tests that do not meet the criteria noted above are not ECIs for this study.

8.4. Treatment of Overdose

In the event there is an overdose of GSK3359609 and/or pembrolizumab the investigator must:

1. Contact the Medical Monitor immediately.
2. Closely monitor the participant for AEs/SAEs and laboratory abnormalities for at least 130 days.
3. Obtain a PK analysis within 28 days from the date of the last dose of study treatment if requested by the Medical Monitor (determined on a case-by-case basis)
4. Document the quantity of the excess dose as well as the duration of the overdosing in the eCRF.

An overdose event that is not associated with clinical symptoms or abnormal laboratory results is defined as an ECI; refer to Section 8.3.7 for details on the expedited reporting requirements for ECI.

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the Medical Monitor based on the clinical evaluation of the participant.

8.4.1. GSK3359609

An overdose of GSK3359609 is defined as administration of a dose that is >240 mg (>10 times the 24 mg intended dose). There is no specific antidote for overdose with GSK3359609. In the event of a suspected overdose, it is recommended that the appropriate supportive clinical care be instituted as dictated by the participant's clinical status.

8.4.2. Pembrolizumab

An overdose of pembrolizumab is defined as ≥1000 mg (5 times the dose) of pembrolizumab. In the event of a suspected overdose, it is recommended that the appropriate supportive clinical care be instituted as dictated by the participant's clinical status.

8.5. Pharmacokinetics

- Plasma samples will be collected for measurement of GSK3359609 concentrations at the timepoints specified in the SoA. Refer to the Q2 laboratory manual for instructions on the collection and handling of the plasma samples. The actual date and time (24-hour clock time) of each sample will be recorded.
- Samples will be used to evaluate the PK of GSK3359609. Samples collected for analyses of GSK3359609 plasma concentration may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study.

Drug concentration information that would unblind the study will not be reported to investigative sites or blinded personnel until the study has been unblinded. If appropriate, de-identified drug concentration information may be analysed prior to study unblinding. In that case, GSK Clinical Pharmacology Modelling Simulation analysts will have access to a blinded population PK dataset (including, but not limited to, concentration, actual dosing information, demographics, and some vital sign and laboratory information, but excluding adverse event and efficacy information) at several time points (e.g., prior to each interim analysis) throughout the trial for population PK model development/refinement.

8.6. Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

8.7. Genetics

Refer to Appendix 7 for information regarding genetics research.

A blood sample for deoxyribonucleic acid (DNA) isolation will be collected from participants who have consented to participate in the genetics analysis component of the study. Participation is optional. Participants who do not wish to participate in the genetic research may still participate in the study.

In the event of DNA extraction failure, a replacement genetic blood sample may be requested from the participant. Signed informed consent will be required to obtain a replacement sample unless it was included in the original consent.

Details on blood volume collected, the processes for collection, shipment and destruction of these samples can be found in Q2 laboratory manual.

8.8. Biomarkers

- Collection of samples for biomarker research is also part of this study. The following samples for biomarker research are required and will be collected from all participants in this study as specified in the SoA:
    - Whole blood for peripheral blood mononuclear cell (PBMC) isolation. The PBMC may be used for biomarker assays including but not limited to TCR diversity, functional assays and immune cell phenotyping etc.
    - Plasma at baseline and on-treatment timepoints specified in the SoA. The sample may be used to extract and analyze cell-free DNA (cfDNA) and/or cell-free ribonucleic acid (cfRNA) as well as other soluble factors and proteins.
    - Archival tumor tissue (refer to Section 8.8.3): tumor tissue acquired within 2 years prior to randomization is required otherwise fresh tumor biopsy performed at Screening will be required.
- Optional samples for biomarker research to be obtained from participants at the following timepoints:
    - Tumor biopsy at Screening in those participants providing archival tissue (i.e., archival tumor tissue meets the protocol defined time requirements)
    - Tumor tissue biopsy during the treatment period in participants with a mixed tumor response and/or disease progression.
    - Tumor tissue biopsy at the completion of 35 cycles of study treatment
- Samples may be tested for ICOS expression, germline and/or somatic mutations including and tumor mutation burden, gene expression, TCR sequences and/ or any other DNA, RNA or protein-based biomarker that may emerge from other studies using the test drugs, to evaluate their association with the efficacy endpoints to the study treatments.
- In addition, with the participant's consent, samples will be stored, and analysis may be performed on biomarker variants thought to play a role in the mechanism of action, sensitivity or resistance or could support future combinations. Analyses may include associations of biomarker variants with efficacy endpoints.

Furthermore, the samples and any biomarker data generated may be used to support the development and filing of a diagnostic.

Samples may be stored for a maximum of 15 years (or according to local regulations) following the last participant's last visit for the study at a facility selected by the sponsor to enable further analysis of biomarker responses to study intervention.

8.8.1. RNA Research

Transcriptome studies will be conducted using either next generation sequencing (NGS) based technologies, targeted probe set and/or alternative equivalent technologies, which facilitates the simultaneous measurement of the relative abundances of thousands of ribonucleic acid (RNA) species resulting in a transcriptome profile for each blood and/ or tumor sample. This will enable the evaluation of baseline transcriptome profiles or any changes upon treatment with the study drugs that may correlate with response to the combination of GSK3359609 and Pembrolizumab. This may include tumor and/or immune cells from blood as well as from tumor tissues.

RNA expression studies may be conducted using quantitative reverse transcriptase polymerase chain reaction (RT-qPCR), and/or alternative equivalent technologies, which can facilitate the simultaneous measurement of the relative abundances of RNA species resulting in an RNA expression profile for each blood and/or tumor tissue samples. The RNAs assayed may be those involved with the pathogenesis of HNSCC; the biology of ICOS-ICOSL or PD-1-PD-L1 signaling pathways and may help identify responder populations to the combination of GSK3359609 and pembrolizumab or pembrolizumab and placebo. The RNAs that code for these proteins and/or regulatory RNAs may also be studied.

The same samples may also be used to confirm findings by application of alternative technologies.

8.8.2. DNA Research

DNA analysis using either whole exome and/or targeted sequencing of circulating tumor DNA from plasma and/or tumor will be performed. T cell repertoire analysis for clonality and diversity of TCRs at baseline and on treatment may also be evaluated.

8.8.3. Tumor Tissue

All participants will provide archival tumor tissue or if not available or evaluable for screening assessments (refer to Section 5.1 inclusion 12 and SoA [Table 1]) then a fresh pre-treatment biopsy. Fresh biopsy will be optional at Screening for those participants providing archival tissue. The tumor tissue collected (archival or fresh biopsy material) will be evaluated by methods that include PD-L1 IHC testing (using the US FDA approved and CE-marked EU PD-L1 IHC 22C3 pharmDx assay), other IHC tests and may include multiplex immunofluorescence technologies or other methods for evaluating the expression of phenotypic and functional immune cell markers on tumor infiltrating lymphocytes (TIL) and other immune cells as well as markers on tumor cells. Additionally, tumor tissue may undergo DNA/RNA-based genetic/genomic profiling (i.e., tumor mutation burden, T cell receptor diversity) which may include sequencing technologies that provide DNA/RNA sequence information. In addition, when possible, similar analyses will be performed on tumor tissue obtained upon progression. These

samples may also be evaluated for predictive measures of efficacy; if a predictive biomarker is identified, these tissues may be used for the development of a diagnostic test. Details for the sample collection, processing, storage and shipment will be provided in the SRM and Q2 laboratory manual.

8.8.4. Blood Samples

Plasma and/or serum samples are collected at baseline, during treatment and at disease progression to evaluate soluble factors such as cytokines, chemokines and other secreted proteins as well as cfDNA/cfRNA.

PBMC samples will be collected at baseline, during treatment and at disease progression and may be used for evaluating the expression of phenotypic and functional immune cell markers as well as for evaluating the polyfunctionality of immune cells and to test any novel biology emerging from other ICOS studies.

Other biomarkers may be evaluated as determined by additional data. Details for the samples collection, processing, storage and shipment will be provided in the SRM and Q2 laboratory manual.

8.9. Immunogenicity

Antibodies to GSK3359609 will be evaluated in serum samples collected from all participants according to the SoA. Additionally, serum samples should also be collected at the final visit from participants who discontinued study intervention or were withdrawn from the study. These samples will be tested by the sponsor or sponsor's designee.

Serum samples will be screened for antibodies binding to GSK3359609 and the titer of confirmed positive samples will be reported. Other analyses may be performed to verify the stability of antibodies to GSK3359609 and/or further characterize the immunogenicity of GSK3359609.

The detection and characterization of antibodies to GSK3359609 will be performed using a validated assay method by or under the supervision of the sponsor. All samples collected for detection of antibodies to study intervention will also be evaluated for GSK3359609 concentration to enable interpretation of the antibody data. Antibodies may be further characterized and/or evaluated for their ability to neutralize the activity of GSK3359609.

8.10. Medical Resource Utilization and Health Economics

Healthcare resource utilization (HCRU) will be collected for all participants randomized to study treatment and may be used to conduct exploratory economic analyses. HCRU includes non-protocol healthcare encounters, such as provider visits, emergency room visits, hospitalizations (including ward, admission and discharge dates, and primary discharge diagnosis), medications, tests, or procedures.

8.11. Patient Reported Outcomes

The below questionnaires to assess patient-reported symptoms, functioning, and treatment tolerability during the study will be administered at the time-points indicated in SoA (Table 1). The questionnaires will be administered to participants in different regions based on the availability of translated versions; further details on the participant questionnaires can be found in the SRM.

PRO	Concepts
EORTC IL50	Select domains of the EORTC-QLQ-C30 general cancer module
EORTC IL51	Select domains of the EORTC QLQ-H&N35 cancer specific symptom module
BPI- I3	Pain severity
PROMIS-SF PF 8c	Physical function
PGIS/PGIC	Patient global impression of severity/change
EQ-5D-3L	HRQoL, for utility assessments
FACT-GP5	Overall toxicity burden

8.11.1. EORTC Item Library 50 and 51: Select Domains from the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire 30-item Core module (EORTC QLQ-C30) and 35-Item Head and Neck Module (EORTC QLQ-H&N35)

The EORTC QLQ-C30 is the core module designed to cover a broad range of cancer patients and is intended to be supplemented with disease-specific sub-scales as necessary to assess QoL aspects particular to a given type of cancer and to improve the specificity and sensitivity of measurement [Sprangers, 1993; Aaronson, 1993]. Select domains from the EORTC QLQ-C30 will be administered and will be referred to as the EORTC IL50.

The EORTC QLQ-H&N35 is a head and neck specific module with multi-item scales [Bjordal, 1994]. The mouth pain, swallowing, speech problems, opening mouth, coughing, feeding tube, and trouble with social eating domains will be administered and will be referred to as the EORTC IL51.

8.11.2. Brief Pain Inventory Short-Form- Item 3 (BPI-I3)

The Brief Pain Inventory Short Form was designed to assess pain and its impact in cancer. Item 3 measures 'pain at its worst' in the last 24 hours using a numerical rating scale of 0 [redacted] to 10 [redacted] scale [Cleeland, 1994].

8.11.3. The Patient-Reported Outcomes Measurement Information System- Short Form Physical Function- 8 item (PROMIS SF PF 8c)

The Patient-Reported Outcomes Measurement Information System (PROMIS) is a universally applicable set of instruments measuring patient-reported health across

different patient populations developed by the US National Institutes for Health (NIH) [Cella, 2007). The PROMIS-SF PF assesses physical function and measures self-reported capability rather than actual performance of physical activities. This includes the functioning of one's upper extremities (dexterity), lower extremities (walking or mobility), and central regions (neck, back), as well as instrumental activities of daily living, such as running errands.

8.11.4. Patient Global Impression Items (PGIS and PGIC)

The Patient Global Impression of Severity (PGIS) assesses global impression of symptoms severity at baseline and subsequent timepoints. The second question, the Patient Global Impression of Change (PGIC) serves to rate the global change in symptoms at subsequent time points. In addition to evaluating symptom severity and change, these questions serve as anchors to establish thresholds of clinically meaningful change for the questionnaires in the study [Guy, 1976].

8.11.5. Europol Questionnaire (EQ-5D-3L)

The EQ-5D-3L is a standardized instrument for use as a measure of health utility. It is designed for self-completion or interview administration and is cognitively simple, taking only a few minutes to complete.

The EQ-5D-3L self-assessment questionnaire has 2 parts. The first part consists of 5 items covering 5 dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression). Each dimension is measured by a 3-point Likert scale (no problems, some or moderate problems, and unable or extreme problems). Respondents are asked to choose one level that reflects their "own health state today" for each of the 5 dimensions. Respondents can be then classified into one of 243 distinct health states. The second part is a 20-cm visual analogue scale (EQ-VAS) that has endpoints labelled "best imaginable health state" and "worst imaginable health state" anchored at 100 and 0, respectively. Respondents are asked to indicate how they rate their own health by drawing a line from an anchor box to that point on the EQ-VAS which best represents their own health on that day. EQ-5D-3L health states are converted to a single summary index by applying a formula that essentially attaches weights to each of the levels in each dimension. The formula is based on the valuation of EQ-5D-3L health states from general population samples.

8.11.6. Functional Assessment of Cancer Therapy – General Population (FACT-GP5)

The FACT-G (now in Version 4) is a 27-item compilation of general questions divided into 4 primary QoL domains: Physical Well-Being, Social/Family Well-Being, Emotional Well-Being, and Functional Well-Being [Cella, 1993]. It is considered appropriate for use with participants with any form of cancer and has also been used and validated in other chronic illness condition (e.g., HIV/AIDS and multiple sclerosis) and in the general population (using a slightly modified version).

The FACT-G scale has been developed and validated [Cella, 1993] and is widely used to measure HRQoL in patients with a broad range of cancer diagnoses [Lee, 2004]. The FACT GP5 item is a single item from the FACT-G, which assesses how bothersome the side effects of treatment are for cancer patients. The recall period is the past 7 days, and the item has a 5-category response scale ranging from "0=[redacted]" to "4=[redacted]". This item is being included to assess the overall tolerability of treatment from the participant's perspective.

9. STATISTICAL CONSIDERATIONS

9.1. Statistical Hypotheses

9.1.1. Primary Hypotheses

The following primary hypotheses will be tested:

Overall Survival (OS)

- Hypothesis (H1): GSK3359609 in combination with pembrolizumab prolongs OS compared with pembrolizumab/placebo in participants with PD-L1 CPS≥1 R/M HNSCC.

- Hypothesis (H2): GSK3359609 in combination with pembrolizumab prolongs OS compared with pembrolizumab/placebo in participants with PD-L1 CPS≥20 R/M HNSCC.

Progression-free Survival (PFS)

- Hypothesis (H3): GSK3359609 in combination with pembrolizumab prolongs PFS by investigator assessment compared with pembrolizumab/placebo in participants with PD-L1 CPS≥1 R/M HNSCC.

9.1.2. Key Secondary Hypotheses

The following key secondary hypotheses will be tested:

Immune-based progression-free Survival (iPFS)

- Hypothesis (H4): GSK3359609 in combination with pembrolizumab prolongs iPFS by investigator assessment compared with pembrolizumab/placebo in participants with PD-L1 CPS≥1 R/M HNSCC.

Time to Deterioration (TTD) in Pain

- Hypothesis (H5): GSK3359609 in combination with pembrolizumab prolongs TTD in Pain (measured by EORTC QLQ H&N 35 pain domain) compared with pembrolizumab/placebo in participants with PD-L1 CPS≥1 R/M HNSCC.

- Hypothesis (H6): GSK3359609 in combination with pembrolizumab prolongs TTD in Pain (measured by EORTC QLQ H&N 35 pain domain) compared with pembrolizumab/placebo in participants with PD-L1 CPS≥20 R/M HNSCC.

TTD in Physical Functioning

- Hypothesis (H7): GSK3359609 in combination with pembrolizumab prolongs TTD in Physical Functioning (measured by PROMIS PF 8c) compared with pembrolizumab/placebo in participants with PD-L1 CPS≥1 R/M HNSCC.

- Hypothesis (H8): GSK3359609 in combination with pembrolizumab prolongs TTD in Physical Functioning (measured by PROMIS PF 8c) compared with pembrolizumab/placebo in participants with PD-L1 CPS≥20 R/M HNSCC.

9.2. Sample Size Determination

The 2-in-1 adaptive Phase II/III study design [Chen, 2018] allows expanding the Phase II study seamlessly into a Phase III confirmatory study; refer to Section 4 for details of the study design.

The Phase II study will randomize approximately 374 participants with a 1:1 ratio between the GSK3359609 in combination with pembrolizumab arm and the pembrolizumab/placebo arm. Assuming the prevalence rate of PD-L1 CPS ≥20 among the PD-L1 CPS ≥1 population is 53%, a sample size of 374 PD-L1 CPS ≥1 participants will provide approximately 198 PD-L1 CPS ≥20 participants.

Should expanding the Phase II study into a Phase III be decided, a total of 600 participants with PD-L1 CPS ≥1 will be randomized in a 1:1 ratio between the GSK3359609 in combination with pembrolizumab arm and the pembrolizumab/placebo arm, including those participants already enrolled. Participants already used for the decision making in the ongoing study will be included in Phase III analyses. The Phase III study will have an overall sample size of 600 participants. Assuming the aforementioned prevalence rate of PD-L1 CPS status, a sample size of 600 participants with PD-L1 CPS ≥1 status will provide 318 PD-L1 CPS ≥20 participants.

The study is event-driven, and the sample size calculation is driven by overall survival events. The assumptions for the sample size and power calculation apply to the study whether it remains as a Phase II study (i.e. without expansion) or expands to a Phase III study (i.e. with expansion).

Overall Survival (OS)

A long-term survival benefit, observed as a long-lasting plateau towards the tail of the survival curve, and a delayed treatment effect, observed as a late separation in survival curves between the experimental and control arms, have been reported in randomized clinical trials among participants treated with immuno-oncology drugs.

Given the OS data reported in the KN-048 clinical trial, a long-term survival benefit in the pembrolizumab/placebo arm and potential non-proportional hazards with a delayed treatment effect are anticipated. Therefore, the sample size and power calculation of OS in PD-L1 CPS ≥1 participants and PD-L1 CPS ≥20 participants are based on the following assumptions:

1. Overall survival in the pembrolizumab/placebo arm follows a piecewise exponential distribution with the milestone OS rates in the

pembrolizumab/placebo arm the same as the rates in the pembrolizumab arm reported in the KN-048 trial.

That is, the survival rates at 6, 12, 24 and 36 months are approximately 71%, 50.4%, 28.9% and 22.1%, respectively, with a median survival of 12.3 months for PD-L1 CPS≥1 participants in the pembrolizumab/placebo arm; the survival rates at 6, 12, 24 and 36 months are approximately 74%, 56.4%, 35.3% and 29.3%, respectively, with a median survival of 14.9 months for PD-L1 CPS≥20 participants in the pembrolizumab/placebo arm

2. True hazard ratio between GSK3359609 in combination with pembrolizumab and the pembrolizumab/placebo arm is time varying leading to a delayed treatment effect with a lag-time of 6 months. For the first 6 months from randomization, a hazard ratio of 1 is assumed in PD-L1 CPS ≥1 and CPS ≥20 participants. For the time beyond 6 months from randomization, a hazard ratio of ~0.512 and ~0.446 is assumed in PD-L1 CPS ≥1 and CPS ≥20 participants, respectively
3. An enrollment period of ~15 months if the study remains as a Phase II study, and an enrollment period of ~19 months if the study expands to a Phase III study
4. Yearly drop-out rate of 5%.

Progression-free Survival (PFS)/Immune-based Progression-free Survival (iPFS)

The power calculation of PFS/iPFS in PD-L1 CPS ≥1 participants is based on the following assumptions:

1. PFS/iPFS in the pembrolizumab/placebo arm follows a piecewise exponential distribution with the milestone PFS/iPFS rates in the pembrolizumab/placebo arm the same as the rates in the pembrolizumab arm reported in the KN-048 trial.

   That is, the PFS/iPFS rates at 6 and 12 months are approximately 28.7% and 20.6%, respectively, with a median PFS/iPFS of 3.2 months for PD-L1 CPS ≥1 participants in the pembrolizumab/placebo arm
2. True hazard ratio for PFS/iPFS between the GSK3359609 in combination with pembrolizumab arm and the pembrolizumab/placebo arm of 0.61 for PD-L1 CPS ≥1 participants
3. If the study remains as a Phase II study, an enrollment period of 15 months and a minimum of 14-month follow-up after enrollment completion

   If the study expands to a Phase III study, an enrollment period of 19 months and a minimum of 9-month follow-up after enrollment completion
4. Yearly dropout rate of 10%.

9.2.1. Remain as a Phase II Study

Overall Survival

The final OS analysis in the PD-L1 CPS≥1 and CPS≥20 participants for a Phase II study (i.e. without expansion) will be carried out after approximately 244 deaths in PD-L1

CPS≥1 participants have occurred between the GSK3359609 in combination with pembrolizumab arm and the pembrolizumab/placebo arm, barring early stopping for futility or efficacy. It is expected that approximately 113 deaths in PD-L1 CPS≥20 participants have occurred between the GSK3359609 in combination with pembrolizumab arm and the pembrolizumab/placebo arm.

With the above numbers of OS events and before any alpha re-allocation, the study provides, a 79.8% power in the PD-L1 CPS≥1 participants and a 60% power in the PD-L1 CPS≥20 participants to demonstrate superiority of OS of GSK3359609 in combination with pembrolizumab relative to pembrolizumab plus placebo at the pre-specified initial alpha (one-sided) level of 2.49%. Please refer to Section 9.8 for details in the alpha spending.

Progression-free Survival/Immune-based progression-free Survival

The estimated numbers of PFS/iPFS events for a Phase II study (i.e. without expansion) at the final PFS evaluation are estimated to be 281 in the PD-L1 CPS≥1 participants.

The estimated number of PFS/iPFS events in the PD-L1 CPS≥1 participants provides a 67.6% power for detecting a HR of 0.61 in PFS/iPFS in the PD-L1 CPS≥1 participants at the alpha level of 0.01% (one-sided).

9.2.2. Expand to a Phase III Study

Overall Survival

The final OS analysis in the PD-L1 CPS≥1 and CPS≥20 participants for a Phase III study (i.e. with expansion) will be carried out after approximately 367 deaths in the PD-L1 CPS≥1 participants have occurred between the GSK3359609 in combination with pembrolizumab arm and the pembrolizumab/placebo arm, barring early stopping for futility or efficacy. It is expected that approximately 171 deaths in PD-L1 CPS≥20 participants have occurred between the GSK3359609 in combination with pembrolizumab arm and the pembrolizumab/placebo arm.

With the above numbers of OS events and before any alpha re-allocation, the study provides a 90.1% power in the PD-L1 CPS≥1 participants and a 73.5% power in the PD-L1 CPS≥20 participants to demonstrate superiority of OS of GSK3359609 in combination with pembrolizumab relative to pembrolizumab plus placebo at the pre-specified initial alpha (one-sided) level of 2.49%.

Progression-free Survival/Immune-based Progression-free Survival

The estimated numbers of PFS/iPFS events for a Phase III study (i.e. with expansion) at the final PFS evaluation are estimated to be 432 in the PD-L1 CPS≥1 participants.

The estimated number of PFS/iPFS events in the PD-L1 CPS≥1 participants provides a 92.5% power for detecting a HR of 0.61 in PFS/iPFS in the PD-L1 CPS≥1 participants at the alpha level of 0.01% (one-sided).

The family-wise type I error rate for the primary hypotheses on PFS and OS as well as the key secondary hypotheses on iPFS, TTD in pain and TTD in PF is strongly controlled at the alpha level of 2.5% (one-sided). The strategy to address multiplicity issues with regards to multiple efficacy endpoints, multiple populations and interim analyses are described in Section 9.5 and Section 9.8.

The study is considered to have met the study primary objective if GSK3359609 in combination with pembrolizumab is superior to pembrolizumab administered with placebo on either PFS OR OS in PD-L1 CPS≥1 participants.

9.2.3. Sample Size Sensitivity

In the case that there is no violation of the proportional hazards in OS between GSK3359609 in combination with pembrolizumab and the pembrolizumab/placebo arm throughout the entire course of the study, the powers in OS for PD-L1 CPS ≥1 participants and PD-L1 CPS ≥20 participants are estimated below.

Specifically, a constant OS hazard ratio of 0.71 in PD-L1 CPS ≥1 participants and 0.67 in PD-L1 CPS ≥20 participants is assumed, in addition to the assumptions in the distribution of the survival curve, the enrollment duration and the drop-out rate as described in the OS sample size calculation in Section 9.2. It is assumed that the sample size and the number of OS events at each look in the proportional hazard case follow the expected number in the non-proportional hazards case (details in Section 9.5).

If the study remains as a Phase II trial, the study provides a 75.3% power to detect a hazard ratio of 0.71 in OS for PD-L1 CPS ≥1 participants, and a 55.6% power to detect a hazard ratio of 0.67 in OS for PD-L1 CPS ≥20 participants, respectively, under the proportional hazards assumption at the one-sided alpha level of 2.49%.

If the study expands to a Phase III trial, the study provides a 90.1% power to detect a hazard ratio of 0.71 in OS for PD-L1 CPS ≥1 participants, and a 73.5% power to detect a hazard ratio of 0.67 in OS for PD-L1 CPS ≥20 participants, respectively, under the proportional hazards assumption at the one-sided alpha level of 2.49%.

The sample size, power calculations, and simulations were performed in the software EAST 6 and R (package “gsDesign”).

9.3. Populations for Analyses

For purposes of analysis, the following populations are defined:

Population	Description
All Screened	All participants who sign the ICF.
Intent-to-treat	All randomized participants whether or not randomized intervention was administered.

Population	Description
	This population will be based on the study intervention to which the participant was randomized and will be the primary population for the analysis of efficacy data.
Safety	All randomized participants who take at least 1 dose of study intervention. Participants will be analysed according to the intervention received.
Pharmacokinetic	The Pharmacokinetic Population will consist of those participants in the Safety Population from whom at least 1 PK sample has been obtained and analysed. This population will be the primary population for PK analyses.

Details on the populations for analyses will be included in the statistical analysis plan.

9.4. Statistical Analyses

This section summarizes key analysis elements; complete details of the planned analysis methodologies will be included in the statistical analysis plan. If, after the study has begun, but prior to any unblinding, changes made to primary and/or key secondary hypotheses, then the protocol will be amended (consistent with ICH Guideline E9). Changes to exploratory or other non-confirmatory analyses made after the protocol has been finalized, but prior to unblinding, will be documented in the statistical analysis plan and referenced in the Clinical Study Report (CSR) for the study. Post hoc exploratory analyses will be clearly identified in the CSR.

Primary and secondary endpoints will be included in the main CSR. A separate final CSR will report updated key safety analyses at the end of study. Further details will be outlined in the statistical analysis plan.

9.4.1. Efficacy Analyses

The intention-to-treat (ITT) population that includes all randomized participants will serve as the primary population for the efficacy analyses.

Stratified statistical analyses will be based on the following stratification factors, PD-L1 expression (CPS ≥20 vs. 1≤ CPS <20), and HPV status (positive vs. negative). Participants with oropharynx HPV negative/unknown and non-oropharyngeal tumors will be combined as the HPV negative group in the stratified analyses. Details will be documented in the statistical analysis plan.

An outline of the analysis strategy for efficacy endpoints is presented in Table 8. Details are outlined in Section 9.4.1.1 and Section 9.4.1.2 and will be further delineated in the statistical analysis plan.

Table 8 Analysis Strategy for Key Efficacy Endpoints

Endpoint	Statistical Method[1]	Analysis Population	Missing Data Approach
OS	Test: Stratified log-rank test to assess the treatment difference Estimation: Stratified Cox model with Efron's tie handling method to assess the magnitude of treatment difference	ITT	Model based • Censoring rule(s)
PFS/iPFS	Test: Stratified log-rank test to assess the treatment difference Estimation: Stratified Cox model with Efron's tie handling method to assess the magnitude of treatment difference	ITT	Model based • Censoring rule(s)
ORR/DCR per RECIST v1.1	Stratified Miettinen and Nurminen's method with sample size weights	ITT	Participants with missing data are considered non-responders and conservatively included in denominator
Duration of Response per RECIST v1.1	Summary statistics using Kaplan-Meier method	All Responders in ITT	Non-responders are excluded from analysis

Abbreviations: DCR=disease control rate; iPFS=immune based progression-free survival; iRECIST=immune-based response evaluation criteria in solid tumors; ITT=intent-to-treat; ORR=overall response rate; OS=overall survival; PFS=progression-free survival

1. Statistical models are described in further detail in the statistical analysis plan. Statistical analyses of PFS, ORR, DCR, and duration of response per RECIST v1.1 and iRECIST follow similarly.

9.4.1.1. Primary Analyses

Overall Survival

OS is defined as the interval of time from the date of randomization to the date of death due to any cause. Participants without documented death will be censored at last known alive date.

The non-parametric Kaplan-Meier method will be used to estimate the survival curves. The treatment difference in survival will be assessed by the stratified log-rank test. A stratified Cox proportional hazard model with Efron's method of tie handling will be used to assess the magnitude of the treatment difference (i.e., the hazard ratio). The hazard ratio and its 95% confidence interval from the stratified Cox model with a single treatment covariate will be reported.

The max-combo test, Restricted Mean Survival Time (RMST) method, or piecewise HR method may be conducted as appropriate to account for the possible non-proportional hazards effect. Additional analyses of OS adjusting for the effect of subsequent treatment may be performed based on recognized methods, if a sufficient proportion of participants switch. The choice of the method will be based on an examination of the appropriateness of the data to the assumptions required by the method. To further account for the possible confounding effect, a supplementary analysis of OS censoring participants at the time of initiation of new therapy will be performed.

Progression-Free-Survival per RECIST 1.1

Progression-free-survival (PFS) per RECIST 1.1 is defined as the time from the date of randomization to the date of the first documented disease progression per RECIST 1.1 based on investigator assessment, or death due to any cause, whichever occurs first.

A summary of the assignments for progression and censoring dates for the primary analysis of PFS per RECIST v1.1 is specified in Table 9. Supplementary analyses of PFS per RECIST v1.1 with different censoring rules will be delineated in the statistical analysis plan.

Table 9 Censoring Rules for Primary Analysis of PFS per RECIST 1.1

Situation	Primary Analysis
No or incomplete baseline disease assessments and the participant has not died	Censored at the date of randomization
No post-baseline disease assessments and the participant has not died	Censored at the date of randomization
With post-baseline disease assessments, new anticancer treatment is not initiated and no documented PD or death	Censored at the date of last adequate[1] radiological disease assessment
With post-baseline disease assessments and new anticancer treatment is initiated (prior to documented PD or death)[2]	Censored at the date of last adequate radiological disease assessment on or prior to the initiation of new anticancer treatment
PD or death documented after ≤1 missed disease assessment	Progressed at the date of documented PD[3] or death
PD or death documented after ≥2 missed disease assessments	Censored at the date of last adequate radiological disease assessment prior to the ≥2 missed disease assessment

Abbreviations: CR=complete response; PD=progressive disease; PFS=progression-free survival; PR=partial response; RECIST=response evaluation criteria in solid tumors; SD=stable disease

1. An adequate assessment is defined as an assessment where the investigator assessed response is CR, PR, or SD.
2. If PD and new anti-cancer therapy occur on the same day, it is assumed that the progression was documented first (i.e. outcome is progression; the date is the date of the assessment for progression).
3. The earliest of (i) Date of radiological assessment showing new lesion (if progression is based on new lesion); or (ii) Date of radiological assessment showing unequivocal progression in non-target lesions, or (iii) Date of last radiological assessment of measured lesions (if progression is based on increase in sum of measured lesions).

The non-parametric Kaplan-Meier method will be used to estimate the PFS curves. The treatment difference in PFS will be assessed by the stratified log-rank test. A stratified Cox proportional hazard model with Efron's method of tie handling will be used to assess the magnitude of the treatment difference (i.e., hazard ratio) between the treatment arms. The hazard ratio and its 95% confidence interval from the stratified Cox model with Efron's method of tie handling and with a single treatment covariate will be reported.

In case the proportional hazards assumption is not valid in PFS, the max-combo test, RMST method or piecewise HR as appropriate may be performed for PFS to account for the possible non-proportional hazards effect.

9.4.1.2. Secondary Analyses

Progression-Free Survival per iRECIST (iPFS)

Progression-free survival per iRECIST (iPFS) is one of the key secondary endpoints of this study. It is defined as the interval of time from the date of randomization to the date of the first documented disease progression confirmed consecutively per iRECIST based on investigator assessment, or death due to any cause, whichever occurs first.

Unlike RECIST 1.1, iRECIST requires the confirmation of progression and uses the terms unconfirmed progressive disease (iUPD) and confirmed progressive disease (iCPD).

The progression event date (iPD date) to be used in the calculation of PFS per iRECIST should be the first date of documented iUPD provided that iCPD is confirmed at the next assessment. If iUPD occurs, but is disregarded because of later iSD, iPR, or iCR, that iUPD date should not be used as the progression event date.

If progression is not confirmed and there is no subsequent iSD, iPR, or iCR, then the iUPD date will be used as iPD date in the following scenarios:

- Participant discontinues study treatment because the participant was judged not to be clinically stable
- Participant does not undergo further response assessments due to any reason (i.e., participant refusal, protocol non-compliance, or participant death)
- Next timepoint response of iUPD, and iCPD never occurs

Determination of dates of iPFS events and dates for censoring in the secondary analysis of iPFS are summarized in Table 10.

Table 10 Censoring Rules for Analysis of iPFS

Situation	Primary Analysis
No or incomplete baseline disease assessments and the participant has not died	Censored at the date of randomization
No post-baseline disease assessments and the participant has not died	Censored at the date of randomization
With post-baseline disease assessments, new anticancer treatment is not initiated, and no iPD date or death	Censored at the date of last radiological disease assessment
With post-baseline disease assessments, new anticancer treatment is initiated (prior to iPD date or death)[1]	Censored at the date of last radiological disease assessment on or prior to the initiation of new anticancer treatment
iPD date or death after ≤1 missed disease assessment	Progressed at the iPD date[2] or death
iPD date or death documented after ≥2 missed disease assessments	Censored at the date of last radiological disease assessment prior to the ≥2 missed disease assessment

Abbreviations: iPD=immune-based progressive disease; iPFS=progression-free survival per iRECIST

1. If the iPD date and new anti-cancer therapy occur on the same day, it is assumed that the progression was documented first (i.e. outcome is progression; the date is the date of the assessment for progression).
2. The earliest date of radiological assessments of lesion in which progression criteria are met for the iPD date.

The non-parametric Kaplan-Meier method will be used to estimate the iPFS curves. The treatment difference in iPFS will be assessed by the stratified log-rank test. A stratified Cox proportional hazard model with Efron's method of tie handling will be used to assess the magnitude of the treatment difference (i.e., hazard ratio) between the treatment arms. The hazard ratio and its 95% confidence interval from the stratified Cox model with Efron's method of tie handling and with a single treatment covariate will be reported.

In case the proportional hazards assumption is not valid for iPFS, the RMST method or piecewise HR as appropriate may be conducted for iPFS to account for the possible non-proportional hazards effect.

OS rate at 12 and 24 months

The non-parametric Kaplan-Meier method will be used to estimate the survival curves. OS rate at 12 months and 24 months and the corresponding 95% CI will be estimated from the Kaplan-Meier analysis.

Objective Response Rate/Disease Control Rate

ORR per RECIST v1.1 is defined as the proportion of the participants who have a complete response (CR) or partial response (PR) as the best overall response per RECIST v1.1 based upon investigator assessment.

DCR per RECIST v1.1 is defined as the percentage of participants with a best overall response of CR or PR at any time plus SD meeting the minimum time of 15 weeks per RECIST v1.1 based upon investigator assessment.

Stratified Miettinen and Nurminen's method will be used for comparison of the ORR/DCR between two treatment groups. The difference in ORR/DCR and its 95% confidence interval from the stratified Miettinen and Nurminen's method with strata weighting by sample size with a single treatment covariate will be reported. Participants with unknown or missing response will be treated as non-responders, that is, these participants will be included in the denominator when calculating the percentage of ORR and DCR.

Duration of Response

Duration of response (DoR) per RECIST v1.1 is defined as the time from first documented evidence of CR or PR until first documented disease progression per RECIST v1.1 based upon investigator assessment or death due to any cause, whichever occurs first, among participants who demonstrated CR or PR as the best overall response per RECIST v1.1. If sample size permits, DoR per RECIST v1.1 will be summarized descriptively using Kaplan-Meier medians and quartiles.

9.4.1.3. Exploratory Analyses

An exploratory analysis of ORR per iRECIST will be performed using the stratified Miettinen and Nurminen's method. The corresponding 95% CI for ORR will also be provided. Participants with unknown or missing responses will be treated as non-responders, i.e., these participants will be included in the denominator when calculating percentages of response.

If sample size permits, DoR per iRECIST will be summarized descriptively using Kaplan-Meier medians and quartiles.

An exploratory analysis of PFS2, defined as the time from randomization to subsequent disease progression per RECIST 1.1 based on investigator assessment after initiation of first new anti-cancer therapy, or death from any cause, whichever first, will be carried out. Participants alive and for whom a second objective disease progression has not been observed will be censored at the last time known to be alive and without second objective disease progression.

Further details of efficacy analyses will be described in the statistical analysis plan.

9.4.2. Safety Analyses

The safety population will serve as the primary population for the analyses of safety data in this study. Safety analyses will follow a tiered approach [Crowe, 2009] as shown in Table 11. The tiers differ with respect to the analyses that will be performed. Tier 1 safety endpoints that will be critical to inferential testing for statistical significance will be provided with p-values and 95% confidence intervals for between-group comparisons.

For this protocol, there are no Tier 1 events. All safety parameters will be considered Tier 2 or Tier 3. Tier 2 parameters will be assessed via point estimates with 95% CI provided for between-group comparisons; only point estimates by treatment group are

provided for Tier 3 safety parameters. The between-treatment difference will be analyzed using the Miettinen and Nurminen method.

Based on emerging external data, the analysis strategy for safety endpoints may be modified to improve the integrity and efficiency of the design. Should this happen, the change will be documented elsewhere, if not in a protocol amendment, at the earliest time before any unblinding of the data. Refer to the statistical analysis plan for further details.

Table 11 Analysis Strategy for Safety Parameters

Safety Tier	Safety Endpoint	95% CI for Treatment Comparison	Descriptive Statistics
Tier 2	Any AE	X	X
	Any Serious AE	X	X
	Any Grade 3-5 AE	X	X
	Any Treatment-Related AE	X	X
	Any Treatment-Related Serious AE	X	X
	Any Grade 3-5 and Treatment-Related AE	X	X
	Dose Modification due to AE	X	X
	Discontinuation due to AE	X	X
	Death	X	X
	Specific AEs, SOCs (incidence ≥ 4 of participants in 1 of the treatment groups)	X	X
Tier 3	Specific AEs, SOCs (incidence < 4 of participants in both treatment groups)		X
	Change from Baseline Results (Labs, ECGs, Vital Signs)		X

Abbreviations: AE=adverse event; CI=confidence intervals; ECG=electrocardiogram; SOC=system organ class

9.4.3. Patient Reported Outcomes

EORTC IL50 and IL51(subset of domains from the EORTC QLQ-C30 and H&N35 respectively) are not pure efficacy or safety endpoints because they are affected by both disease symptoms and treatment tolerability in addition to HRQoL domains.

The time to deterioration (TTD) curves in Pain measured by the EORTC QLQ-H&N35 pain domain (included in the EORTC IL51) and the TTD in Physical Function (PF) measured by the PROMIS PF 8c will be analysed in the ITT population using the non-parametric Kaplan-Meier method.

The treatment effect in TTD in Pain and PF will be assessed separately by the stratified log-rank test. A stratified Cox proportional hazard model with Efron's method of tie handling will be used to assess the magnitude of the treatment difference (i.e., hazard ratio) between the treatment arms. The hazard ratio and its 95% confidence interval from the stratified Cox model with Efron's method of tie handling and with a single treatment covariate will be reported.

For both Pain and PF, TTD will be defined as the time from the date of randomization to the date of first definitive meaningful deterioration in score compared to baseline. The deterioration has to be:

- Meaningful, i.e. greater than a clinically meaningful within-individual change in score, as defined below;

- Definitive, i.e. all subsequent assessment of the score are also showing a clinically meaningful deterioration compared to baseline, or no further score is available for the patients for any reason (including disease progression or death)

Patients who don't show meaningful deterioration will be censored at the time of the last available PRO assessment.

As no threshold for meaningful within-individual change is established for the EORTC QLQ-H&N35 pain domain score or PROMIS PF 8c score, the value for use in the TTD analyses will be determined using blinded interim data. These analyses will be performed before study unblinding and the value will be set-up before database lock. The full procedure for determination of meaningful within-person change in EORTC QLQ-H&N35 pain domain score and PROMIS PF 8c score will be fully described in the clinical statistical analysis plan or in a standalone analysis plan as appropriate. It will include anchor-based approach using the patient global impression of severity and change as an anchor, and possibly other clinical anchors (e.g. ECOG status). Supportive distribution-based methods may be applied as sensitivity analyses.

The selected domains from the EORTC IL50, EORTC IL51, BPI-I3 and EQ-5D-3L changes will be summarized as part of the exploratory analysis. Longitudinal and descriptive data analysis can be used to evaluate patient reported outcomes. The detailed PRO analysis plan will be included in and the statistical analysis plan.

9.4.4. Other Exploratory Analyses

PK, pharmacodynamic, biomarker exploratory analyses, and health economic assessment will be described in the statistical analysis plan. Theses exploratory analyses may be presented separately from the main CSR.

9.5. Interim Analyses

Adaptive Decision Making

The analysis for adaptive decision will be conducted using ORR/DCR per RECIST v1.1 based on investigator assessment when approximately the first 100 PD-L1 CPS ≥1 participants have a minimum follow-up of 6 months.

The adaptive decision criteria will be positive if there is at least 8% improvement of ORR in the GSK3359609 in combination with pembrolizumab arm comparing with the pembrolizumab/placebo arm in PD-L1 CPS ≥1 population. Table 12 presents the operating characteristics of the adaptive decision criteria based on the improvement of ORR. Confirmation of CR and PR is not required in the adaptive decision making.

1) If the ORR outcome per RECIST v1.1 is positive with ΔORR≥8% in PD-L1 CPS ≥1 population, the study continues to an originally planned Phase III sample size for a definitive Phase III evaluation.

2) If the ORR/DCR outcome per RECIST v1.1 is negative with ΔORR<0% and ΔDCR<0% in PD-L1 CPS ≥1 population, the study may stop for futility depending on the recommendation of IDMC based on the totality of the data; refer to the IDMC charter for details.
3) Otherwise, the study will continue as planned Phase II sample size for a definitive Phase II evaluation.

Table 12 Operating Characteristics of the Adaptive Decision Based on the PD-L1 CPS ≥1 Population

IA Probability	**ΔORR = (ORR.GSK3359609/Pembrolizumab – ORR.Pembrolizumab/Placebo)**				
True ΔORR[1]	**0%**	**4%**	**8%**	**16%**	**20%**
Stopping for futility[2] ΔORR<0%	45%	27%	14%	2%	1%
Continuation with Phase II ΔORR≥0% and ΔORR<8%	40%	42%	35%	15%	7%
Expansion to Phase III ΔORR≥8%	15%	31%	51%	83%	92%

Abbreviations: CPS=combine positive score; IA=interim analysis; PD-L1=programmed death ligand-1; ORR=overall response rate

1. The probability is estimated based on 50,000 simulations and it is assumed that the ORR of the Pembrolizumab/Placebo arm is 19% in the simulations.
2. The final futility decision is based on both ORR and DCR; the probability of futility will be lower.

A meta-analysis was performed using published PD-1/L1 treated studies in HNSCC; the analysis only included data from PD-1/L1 regimens that did contain chemotherapy. The selection of ORR as the endpoint for the adaptive decision is supported by results of the meta-analysis which showed that median OS is significantly positively correlated with ORR (refer to Section 10.11 for details). There is no penalty in alpha spending for the option to expand Phase II to Phase III, given that neither OS nor PFS are negatively correlated with ORR per RECIST v1.1 based on this meta-analysis (Section 10.11).

All participants from the study are used for statistical inference at the end of Phase II or Phase III regardless of the interim expansion decision. In addition, all the primary and key secondary endpoints are formally tested for statistical significance at the end of Phase II or Phase III.

PFS/iPFS Analysis and Interim Analyses of OS

The study is designed to have 1 PFS/iPFS analysis and 2 OS analyses in PD-L1 CPS ≥1 participants. Two OS analyses will be performed in PD-L1 CPS ≥20 participants. The safety of the treatment will also be assessed at the interim analysis.

The timing of PFS/iPFS analysis and the OS interim analysis is triggered by the pre-specified number of PFS events in the PD-L1 CPS ≥1 population.

At the time of PFS/iPFS analysis, the OS interim analysis will be conducted in PD-L1 CPS ≥1 participants to allow for early stopping of the study due to efficacy or allow for

non-binding futility analysis. PD-L1 CPS ≥20 participants will be tested sequentially if OS is significant in PD-L1 CPS ≥1 participants.

The timing of the final OS analysis in the PD-L1 CPS ≥1 and CPS ≥20 participants will be triggered by the pre-specified number of OS events in the PD-L1 CPS ≥1 population.

The nominal significance levels for the interim and final analyses of OS will be determined by the Lan-DeMets spending function based upon the O'Brien-Fleming boundary. The futility bounds of this study are non-binding and the bounds are considered guidance rather than strict bounds.

Table 13 summarizes the information fraction, sample size and decision guidance for the planned PFS/iPFS and OS analyses as a Phase II study. Table 14 summarizes the information fraction, sample size and decision guidance for the planned PFS/iPFS and OS analyses as a Phase III study.

Efficacy boundaries and non-binding futility boundaries are based on initially assigned type I error rate before any alpha re-allocation and projected number of events at study milestones. The actual boundaries will be determined from the actual number of events at the time of the specified interim analysis using the alpha- and beta- spending functions. Actual futility bounds will be updated if overall beta is changed with respect to alpha re-allocation.

Results of all interim analyses, including the adaptive decision, PFS/iPFS analysis, and OS interim analysis, will be reviewed by an independent data monitoring committee (IDMC). Further details of interim analyses will be provided in the IDMC Charter. Any change to the planned event size will be described in the statistical analysis plan before any unblinding of the data.

Table 13 Summary of Timing, Sample Size and Decision Guidance at the Planned PFS and OS Analyses as a Phase II Study

Analysis	Key Endpt	Population	Expected Number of Events (Information Fraction)	Efficacy Boundary[1]		Non-Binding Futility Boundary[1]	
				p-value	Cumulative alpha	p-value	Cumulative beta
PFS FA, OS IA (H1-H4)	PFS/ iPFS	CPS≥1	~281 (100%)	0.0001	0.0001	NA	NA
	OS	CPS≥1	~205 (84%)	0.0144	0.0144	0.4483	0.0101
		CPS≥20[2]	~95 (84.1%)	0.0144	0.0144	0.5546	0.0184
OS FA (H1, H2)	OS	CPS≥1	~244 (100%)	0.0208	0.0249	0.0208	0.2474
		CPS≥20[2]	~113 (100%)	0.0208	0.0249	0.0208	0.4440

Abbreviations: CPS=combined positive score; Endpt=endpoint; FA=final analysis; H=hypothesis; HR=hazard ratio; IA=interim analysis; NA=not applicable

1. Efficacy boundaries and non-binding futility boundaries are based on initially assigned type I error rate (one-sided) before any alpha re-allocation and projected number of events at study milestones. Actual efficacy boundaries will be based on actual numbers of events available at study milestones and actual futility bounds will be updated if overall beta is changed with respect to re-allocation.
2. The descendant OS hypothesis in PD-L1 CPS≥20 participants will be tested only if the parent OS hypothesis in PD-L1 CPS≥1 participants is significant.

Table 14 Summary of Timing, Sample Size and Decision Guidance at the Planned PFS and OS analyses as a Phase III Study

Analysis	Key Endpt	Population	Expected Number of Events (Information Fraction)	Efficacy Boundary[1]		Non-Binding Futility Boundary[1]	
				p-value	Cumulative alpha	p-value	Cumulative beta
PFS FA, OS IA (H1-H4)	PFS/ iPFS	CPS≥1	~432 (100%)	0.0001	0.0001	NA	NA
	OS	CPS≥1	~295 (80.4%)	0.0124	0.0124	0.4775	0.0020
		CPS≥20[2]	~137 (80.1%)	0.0122	0.0122	0.5927	0.005
OS FA (H1, H2)	OS	CPS≥1	~367 (100%)	0.0213	0.0249	0.0213	0.0991
		CPS≥20[2]	~171 (100%)	0.0213	0.0249	0.0213	0.2648

Abbreviations: CPS=combined positive score; Endpt=endpoint; FA=final analysis; H=hypothesis; HR=hazard ratio; IA=interim analysis; NA=not applicable

1. Efficacy boundaries and non-binding futility boundaries are based on initially assigned type I error rate (one-sided) before any alpha re-allocation and projected number of events at study milestones. Actual efficacy boundaries will be based on actual numbers of events available at study milestones and actual futility bounds will be updated if overall beta is changed with respect to re-allocation.
2. The descendant OS hypothesis in PD-L1 CPS≥20 participants will be tested only if the parent OS hypothesis in PD-L1 CPS≥1 participants is significant.

9.6. Independent Data Monitoring Committee

The study will use an IDMC. The IDMC membership and governance will be outlined in a separate charter.

The IDMC will make recommendations for discontinuation or modification of the study based on ongoing reviews of safety data according to the Charter. In addition, the IDMC will also evaluate all interim efficacy data, including the adaptive decision, PFS/iPFS analysis and OS interim analysis, and make a recommendation based on observed results of the study.

In this double-blind study, all GSK and site personnel will be restricted from access to interim analysis results provided to the IDMC until the conclusion of the study, unless the IDMC recommends significant changes to study conduct that require a protocol amendment. In this scenario, after receiving the IDMC recommendation and a decision by Chief Medical Officer (CMO), a review of the data may be required. A select group from GSK, as determined by the CMO will be unblinded to review the data to agree on future study conduct. Depending on the recommendation of the IDMC, the Sponsor may prepare a regulatory submission. More details will be provided in the IDMC Charter.

9.7. Blinded Independent Central Review Auditing

A random sample-based BICR auditing approach will be used to assess whether bias exists in estimation of PFS hazard ratio between investigator assessments and BICR assessments [Stone, 2015] if the study expands to a Phase III trial. The study is currently designed as a randomized, double-blind study. The risk of investigator bias can be mitigated in a properly double-blinded randomized study [Dodd, 2008].

The objective of the sample-based BICR approach is to corroborate the analysis results of the investigator-assessed PFS and to assist in the evaluation of potential bias in investigator-assessed PFS in PD-L1 CPS ≥1 participants if the study expands to a Phase III trial. The BICR audit approach is not intended to provide an alternative means of definitive analysis.

Evaluation bias will be assessed through the use of measure proposed by Stone et al [Stone, 2015]. The hazard ratio (HRR), where HRR is defined as the ratio of the hazard ratio (HR) for the treatment effect estimated from the BICR to the corresponding HR for the investigator assessments. Larger values of HRR are suggestive of a less acceptable bias. The maximum acceptable HRR will be derived based on the graded approach [Stone, 2015]. For example, in order to preserve two-thirds of the observed HR based on investigator assessment, the maximum acceptable HRR is 1.213 if the full study HR based on investigator assessment for PFS in PD-L1 CPS ≥1 participants is 0.61.

If the sample HRR is within the range specified by the maximum acceptable HRR, it is concluded that the sample is sufficient to rule out meaningful levels of bias, and no further scans will be assessed by the BICR; otherwise the BICR will be performed in all PD-L1 CPS ≥1 participants.

The audit size of the sample-based BICR will be 45% of all PD-L1 CPS ≥1 participants if the study expands to a Phase III trial. Assuming the correlation in the logarithm of HRs between investigator assessment and BICR is 0.8, with the maximum acceptable HRR of 1.213 and the testing of evaluation of bias is conducted at the 10% alpha level, and 72% of participants have an event according to investigator assessment and 67% according to BICR, the audit size of 45% will ensure that the specificity is ~93.7% in PD-L1 CPS ≥1 participants.

Further details on the BICR auditing approach will be included in the statistical analysis plan.

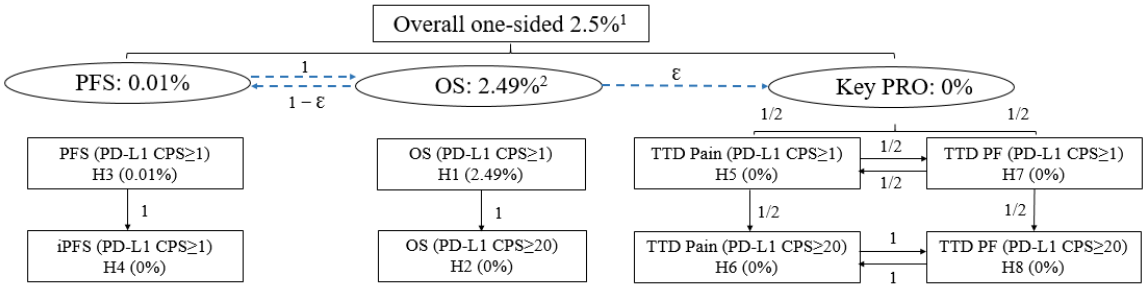
9.8. Multiplicity

The trial uses the graphical method [Maurer, 2013] to provide strong multiplicity control for multiple hypotheses as well as interim analyses.

The family-wise type I error for this study is strongly controlled at 2.5% (one-sided).

Figure 1 shows the initial one-sided alpha-allocation for PFS/iPFS, OS, and key PRO endpoints. Hypotheses presented as nodes in squares are divided into three subfamilies presented in ellipsoids. The weights for re-allocation from each subfamily/hypothesis to the others are represented on the lines connecting hypotheses. The multiplicity control strategy applies whether the study remains as a Phase II trial or expands to a Phase III trial.

Figure 1 Multiplicity Testing Strategy for Comparisons Between GSK3359609 in Combination with Pembrolizumab and Pembrolizumab Administered with Placebo



Abbreviations: CPS = combined positive score; H = hypothesis; I = GSK3359609; iPFS = progression-free survival per iRECIST; OS = overall survival; P = pembrolizumab; PF=physical function; PFS = progression-free survival per RECIST v1.1; PD-L1 = programmed cell death receptor 1-ligand 1; TTD=time to deterioration

1. The alpha level assigned to a subfamily will be rolled over only if the hypotheses within the subfamily are all significant based on the weight for re-allocation presented on the dashed lines connecting subfamilies. Within each subfamily, the weights for re-allocation from each hypothesis to the others are represented on the solid lines connecting hypotheses.
2. ε = 5/6 if both hypotheses in the OS subfamily (i.e. PD-L1 CPS≥1 and PD-L1 CPS≥20 participants) are significant at the time of PFS/iPFS analyses; if the OS hypothesis is not significant in either population at the time of PFS/iPFS analyses, then ε = 1 at the final OS analysis.

The alpha re-allocation for PFS/iPFS, OS and key PRO endpoints is further explained below:

Overall Survival

- An initial alpha level of 2.49% is allocated to the OS hypothesis in the PD-L1 CPS≥1 participants.
- If PFS and iPFS tests are both significant in PD-L1 CPS≥1 participants, the OS hypothesis in the PD-L1 CPS≥1 participants will be tested at 2.5% (re-allocated alpha).
- OS in the PD-L1 CPS≥20 participants is tested sequentially at the same overall alpha level as that of OS in PD-L1 CPS≥1 participants if GSK3359609 in combination with pembrolizumab demonstrates superiority to pembrolizumab plus placebo in OS in PD-L1 CPS≥1 participants. If OS is not significant in PD-L1 CPS≥1 participants, the formal conclusion of statistical significance on OS in PD-L1 CPS≥20 participants will not be drawn.

The following alpha- and beta-spending functions are used in the OS hypothesis of PD-L1 CPS≥1 participants and PD-L1 CPS≥20 participants.

- For the OS hypothesis, the alpha-spending function based on Lan-DeMets O'Brien-Fleming approximation spending function and the beta-spending function based on the Hwang-Shih-DeCani boundary method with a gamma parameter of -20 are constructed to implement group sequential boundaries that control the type I error rate as well as allow for non-binding futility analysis.

Section 9.5 demonstrates the planned analyses as well as bounds and boundary properties for OS hypothesis testing. Efficacy boundaries and non-binding futility boundaries are based on initially assigned type I error rate before any alpha re-allocation and projected number of events at study milestones. The actual boundaries will be determined from the actual number of events at the time of the specified interim analysis using the alpha- and beta- spending functions. Actual futility bounds will be updated if overall beta is changed with respect to alpha re-allocation.

Progression-free Survival/Immune-based Progression-free Survival

- An initial alpha level of 0.01% is allocated to the PFS hypothesis in PD-L1 CPS≥1 participants.
- If the OS hypotheses in both PD-L1 CPS≥1 participants and PD-L1 CPS≥20 participants are significant at the time of the OS interim analysis, the PFS hypothesis in PD-L1 CPS≥1 participants will be tested at 0.425% (re-allocated alpha).
- If the PFS hypothesis in PD-L1 CPS≥1 is significant, the hypothesis of iPFS in PD-L1 CPS≥1 will be tested sequentially at the same alpha level.

Key Patient Reported Outcomes (TTD in Pain, TTD in PF)

- Only if GSK3359609 in combination with pembrolizumab demonstrates superiority to pembrolizumab plus placebo in OS in both populations (PD-L1 CPS≥1 participants and PD-L1 CPS≥20 participants), will key secondary PRO endpoints be tested. The alpha level from OS hypothesis will be propagated to key PRO hypotheses.

- If OS meets superiority in both populations at the time of the OS interim analysis, a total of 2.075% alpha level will be propagated to key PRO hypotheses.

- If OS meets superiority in both populations at the time of the final OS analysis but PFS or iPFS fails to demonstrate superiority in PD-L1 CPS≥1 participants, a total of 2.49% alpha level will be propagated to key PRO hypotheses.

- If OS meets superiority in both populations at the time of the final OS analysis and PFS and iPFS both demonstrate superiority in PD-L1 CPS≥1 participants, a total of 2.5% alpha level will be propagated to key PRO hypotheses.

- The alpha level propagated from OS will be equally split between TTD in Pain and TTD in PF in PD-L1 CPS ≥1 participants, with the possibility to further propagate the levels between each other.

- If 1 of 2 key PRO hypotheses in PD-L1 CPS ≥1 participants is rejected based on the re-allocated alpha level, the key PRO hypotheses in PD-L1 CPS ≥20 participants can be tested based on the (updated) weight, with the possibility to further propagate the levels between each other.

- Based on the re-allocated cumulative alpha level, the nominal significance level for each key PRO endpoint will be calculated based on the Lan-DeMets O'Brien-Fleming approximation alpha-spending function.

Details on multiplicity will be provided in the statistical analysis plan.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1. Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
  - Applicable ICH Good Clinical Practice Guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents (e.g., advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IEC/IRB approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- The investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC
  - Notifying the IRB/IEC of SAE or other significant safety findings as required by IRB/IEC procedures
  - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations.

10.1.2. Informed Consent Process

- The investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorized representative and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary. Participants or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.

- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative.

10.1.3. Data Protection

- Participants will be assigned a unique identifier by the sponsor. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

10.1.4. Dissemination of Clinical Study Data

- Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the clinical study report.
- GSK will also provide the investigator with the full summary of the study results. The investigator is encouraged to share the summary results with the study participants, as appropriate.
- GSK will provide the investigator with the randomization codes for their site only after completion of the full statistical analysis.
- The procedures and timing for public disclosure of the protocol and results summary and for development of a manuscript for publication for this study will be in accordance with GSK Policy.
- GSK intends to make anonymized patient-level data from this trial available to external researchers for scientific analyses or to conduct further research that can help advance medical science or improve patient care. This helps ensure the data provided by trial participants are used to maximum effect in the creation of knowledge and understanding

10.1.5. Data Quality Assurance

- All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (e.g., laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

- The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing strategy (e.g., risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Monitoring Plan.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The sponsor assumes accountability for actions delegated to other individuals (e.g., Contract Research Organizations).
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICF, pertaining to the conduct of this study must be retained by the investigator for 25 years from the issue of the final Clinical Study Report (CSR)/ equivalent summary unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

10.1.6. Source Data

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Definition of what constitutes source data can be found in SRM and Monitoring Plan

10.1.7. Study and Site Closure

GSK or its designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of GSK. Study sites will be closed upon study

completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the investigator
- Discontinuation of further study intervention development

10.2. Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 15 will be performed by local laboratory.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.
- Pregnancy Testing Refer to Section 5.1 Inclusion Criteria for screening pregnancy criteria.
- Additional serum or urine pregnancy tests may be performed, as determined necessary by the investigator or required by local regulation, to establish the absence of pregnancy at any time during the participant's participation in the study.

Table 15 Protocol-Required Safety Laboratory Assessments

Laboratory Assessments	**Parameters**			
Hematology	RBC Indices	WBC count with Differential		Platelets
	Hemoglobin	Neutrophils		
	Hematocrit	Lymphocytes		
	RBC count	Monocytes		
		Eosinophils		
		Basophils		
Clinical Chemistry	BUN[a]	Potassium	Bilirubin	AST (SGOT)
	Creatinine[b]	Sodium	Total protein	ALT (SGPT)
	Glucose	Calcium	Albumin	Alkaline phosphatase
Coagulation	INR or PT			
	aPTT			
Cardiac Function	Troponin I or Troponin T			
Thyroid Function	Thyroid stimulating hormone Free T4 Free T3			
Routine Urinalysis	Specific gravity pH, glucose, protein, blood and ketones			
Other Screening Tests[c]	Hepatitis B (HBsAg)[d] Hepatitis C (Hep C antibody)[d] Serum β-hCG Pregnancy test (as needed for women of child bearing potential)			

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; β-hCG = beta-human chorionic gonadotropin; BUN = blood urea nitrogen; eGFR=estimated glomerular filtration rate; HBsAg = Hepatitis B surface antigen; RBC = red blood cells; SGOT = serum glutamic oxaloacetic transaminase; SGPT = serum glutamic pyruvic transaminase; T3 = triiodothyronine; T4 = thyroxine; WBC = white blood cells; INR = International Normalized Ratio; PT = Prothrombin Time; aPTT = Activated Partial Thromboplastin Time

a. Required if local laboratory testing is available
b. Creatinine clearance/eGFR is also required to be calculated using one of the formulas provided in Section 10.6
c. HIV testing for eligibility is not required unless mandated by local health authority. Tuberculosis testing is not required unless mandated by local health authorities.
d. Central laboratory testing will be performed if local laboratory testing not available. Participants with positive Hepatitis C antibody due to prior resolved disease can be enrolled, only if a confirmatory negative Hepatitis C RNA test is obtained. Hepatitis C RNA Test is optional with negative Hepatitis C antibody test.

10.3. Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1. Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of a study intervention, whether or not considered related to the study intervention. • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a study intervention.

Events <u>Meeting</u> the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (i.e., not related to progression of underlying disease). • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae. • "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE.

Events <u>NOT</u> Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.

- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition.
- Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2. Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (e.g., hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

A SAE is defined as any untoward medical occurrence that, at any dose:
Results in death
Is life-threatening The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
Requires inpatient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AE. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
Results in persistent disability/incapacity • The term disability means a substantial disruption of a person's ability to conduct normal life functions. • This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

Is a congenital anomaly/birth defect
Other situations: • Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious. Examples of such events include invasive or malignant cancers other than the cancer under study, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

10.3.3. Definition of Cardiovascular Events

Cardiovascular Events (CV) Definition:
Investigators will be required to fill out the specific CV event page of the CRF for the following AEs and SAEs: • Myocardial infarction/unstable angina • Congestive heart failure • Arrhythmias • Valvulopathy • Pulmonary hypertension • Cerebrovascular events/stroke and transient ischemic attack • Peripheral arterial thromboembolism • Deep venous thrombosis/pulmonary embolism • Revascularization

10.3.4. Recording and Follow-Up of AE and SAE

AE and SAE Recording
• When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory, and diagnostics reports) related to the event. • The investigator will then record all relevant AE/SAE information in the CRF. • It is **not** acceptable for the investigator to send photocopies of the participant's medical records to GSK in lieu of completion of the GSK /AE/SAE CRF page.

- There may be instances when copies of medical records for certain cases are requested by GSK. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to GSK.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The investigator will make an assessment of severity for each AE and SAE reported during the study and will assign a grade according to the NCI-CTCAE v5.0 [NCI, 2017].

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The investigator will also consult the Investigator's Brochure (IB) and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred, and the investigator has minimal information to include in the initial report to GSK. However, **it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to** GSK**.**
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AE and SAE
• The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by GSK to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals. • New or updated information will be recorded in the originally completed CRF. • The investigator will submit any updated SAE data to GSK within 24 hours of receipt of the information.

10.3.5. Reporting of SAE to GSK

SAE Reporting to GSK via Electronic Data Collection Tool
• The primary mechanism for reporting SAE to GSK will be the electronic data collection tool. • If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) in order to report the event within 24 hours. • The site will enter the SAE data into the electronic system as soon as it becomes available. • After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data. • If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to the Medical Monitor by telephone. • Contacts for SAE reporting can be found in SRM.

SAE Reporting to GSK via Paper CRF
• Facsimile transmission of the SAE paper CRF is the preferred method to transmit this information to the **X/medical monitor or the SAE coordinator**. • In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service. • Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE CRF pages within the designated reporting time frames. • Contacts for SAE reporting can be found in SRM.

10.4. Appendix 4: Contraceptive Guidance and Collection of Pregnancy Information

GSK3359609 and pembrolizumab may have adverse effects on a fetus in utero. Furthermore, it is not known if pembrolizumab has transient adverse effects on the composition of sperm. In order to participate in the study, participants of childbearing potential must adhere to the contraception requirement as indicated in Section 5.1 and Section 10.4.2. If there is any question that a participant of childbearing potential will not reliably comply with the requirements for contraception, that participant should not be entered into the study

10.4.1. Definitions:

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile (see below).

If fertility is unclear (e.g., amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study intervention, additional evaluation should be considered.

Women in the following categories are not considered WOCBP

1. Premenarchal
2. Premenopausal female with 1 of the following:
   - Documented hysterectomy
   - Documented bilateral salpingectomy
   - Documented bilateral oophorectomy

   For individuals with permanent infertility due to an alternate medical cause other than the above, (e.g., mullerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry.

   Note: Documentation can come from the site personnel's: review of the participant's medical records, medical examination, or medical history interview.
3. Postmenopausal female
   - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
     - A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with more than one FSH measurement is required.

- Females on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

10.4.2. Contraception Guidance:

Male participants

- Male participants with female partners of child-bearing potential are eligible to participate if they agree to ONE of the following during the protocol-defined time frame in Section 5.1:
  - Are abstinent from penile-vaginal intercourse as their usual and preferred lifestyle (abstinent on a long term and persistent basis) and agree to remain abstinent
  - Agree to use a male condom plus an additional method of contraception with a failure rate of <1% per year as described in Table 16 when having penile-vaginal intercourse with a woman of childbearing potential
- Men with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile penetration for the duration of the study and for at least 120 days after the last dose of study treatment.

Female participants

Table 16 Highly Effective Contraceptive Methods

CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE:
• **Highly Effective Methods[b] That Have Low User Dependency** *Failure rate of <1% per year when used consistently and correctly.*
• Implantable progestogen-only hormone contraception associated with inhibition of ovulation[c]
• Intrauterine device (IUD)
• Intrauterine hormone-releasing system (IUS)[c]
• Bilateral tubal occlusion
• Vasectomized partner   • *Note: Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 90 days.*
• **Highly Effective Methods[b] That Are User Dependent** *Failure rate of <1% per year when used consistently and correctly.*

• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[c]
  • oral
  • intravaginal
  • transdermal
  • injectable

• Progestogen-only hormone contraception associated with inhibition of ovulation[c]
  • oral
  • injectable

• Sexual abstinence   • *Note: Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.*
a. Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for those participating in clinical studies. b. Failure rate of <1% per year when used consistently and correctly. Typical use failure rates differ from those when used consistently and correctly. c. If locally required, in accordance with Clinical Trial Facilitation Group (CTFG) guidelines, acceptable contraceptive methods are limited to those which inhibit ovulation as the primary mode of action. Note: Periodic abstinence (calendar, sympto-thermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea method (LAM) are not acceptable methods of contraception. Male condom and female condom should not be used together (due to risk of failure with friction)

10.4.3. Collection of Pregnancy Information:

Male participants with partners who become pregnant

- Investigator will attempt to collect pregnancy information on any male participant's female partner of a male study participant who becomes pregnant while participating in this study.
- After obtaining the necessary signed informed consent from the pregnant female partner directly, the investigator will record pregnancy information on the appropriate form and submit it to GSK within 24 hours of learning of the partner's pregnancy.
- The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to GSK.
- Generally, follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for procedure.

Female Participants who become pregnant

- Investigator will collect pregnancy information on any female participant, who becomes pregnant while participating in this study.
- Information will be recorded on the appropriate form and submitted to GSK within 24 hours of learning of a participant's pregnancy.
- Participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow up information on participant and neonate, which will be forwarded to GSK Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date.
- Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.
- A spontaneous abortion (occurring at < 22 weeks gestational age) or still birth (occurring at > 22 weeks gestational age) is always considered to be an SAE and will be reported as such.
- Any SAE occurring as a result of a post-study pregnancy which is considered reasonably related to the study intervention by the investigator, will be reported to GSK as described in Appendix 3. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.

Any female participant who becomes pregnant while participating

- will discontinue study intervention.

10.5. Appendix 5: ECOG Performance Status

Grade	Descriptions
	CCI - This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by third party copyright laws and therefore have been excluded.

[Oken, 1982]

10.6. Appendix 6: Renal Function Measures

CKD-EPI Formula

Chronic Kidney Disease (CKD) stage: Kidney Disease Outcomes Quality Initiative (KDOQI) CKD stages 3/4/5 defined by estimated glomerular filtration rate (eGFR) using the CKD Epidemiology Collaboration (CKD-EPI) formula [Levey, 2009].

$GFR = 141 \times \min(S_{cr}/\kappa, 1)^{\alpha} \times \max(S_{cr}/\kappa, 1)^{-1.209} \times 0.993^{Age} \times 1.018$ [if female] $\times$ 1.159 [if black]

where:
S_{cr} is serum creatinine in mg/dL,
κ is 0.7 for females and 0.9 for males,
α is -0.329 for females and -0.411 for males,
min indicates the minimum of S_{cr}/κ or 1, and
max indicates the maximum of S_{cr}/κ or 1.

Cockcroft-Gault Formula

The Cockcroft-Gault formula is a commonly-used surrogate marker for actual creatinine clearance (CrCl) and employs creatinine measurements and a participant's weight (kg) to predict the clearance.

If the participant is obese *(>30% over ideal body weight*), use ideal body weight in calculation of estimated CrCl.

If the participant is *below ideal body weight*, use actual body weight in calculation of estimated CrCl.

Cockcroft-Gault Formula for serum creatinine in mmol/L

CrCl (mL/min)=	Q X (140-age [years]) X actual body weight (kg)[a] / 814 X serum creatinine (mmol/L)
Q=0.85 for females Q=1.0 for males	
OR	
a. Calculation of Ideal Body Weight Using the Devine Formula [Devine, 1974]	
Male participants:	
	50.0 kg + (2.3 kg X each inch over 5 feet) or 50.0 kg + (0.906 kg X each cm over 152.4 cm)
Female participants:	
	45.5 kg + (2.3 kg X each inch over 5 feet) or 45.5 kg + (0.906 kg X each cm over 152.4 cm) c

Cockcroft-Gault Formula for serum creatinine in mg/dL

CrCl (mL/min)=	Q X (140-age [years]) X actual body weight (kg)[a] / 72 X serum creatinine (mg/dL)
Q=0.85 for females Q=1.0 for males	

For example:

For a male participant with actual body weight = 90.0 kg and height = 68 inches, the calculation would be as follows:

Ideal body weight= 50.0 + (2.3) (68-60) = 68.4 kg

This participants's actual body weight is >30% over ideal body weight. In this case, the participant's ideal body weight of 68.4 kg should be used in calculating estimated creatinine clearance

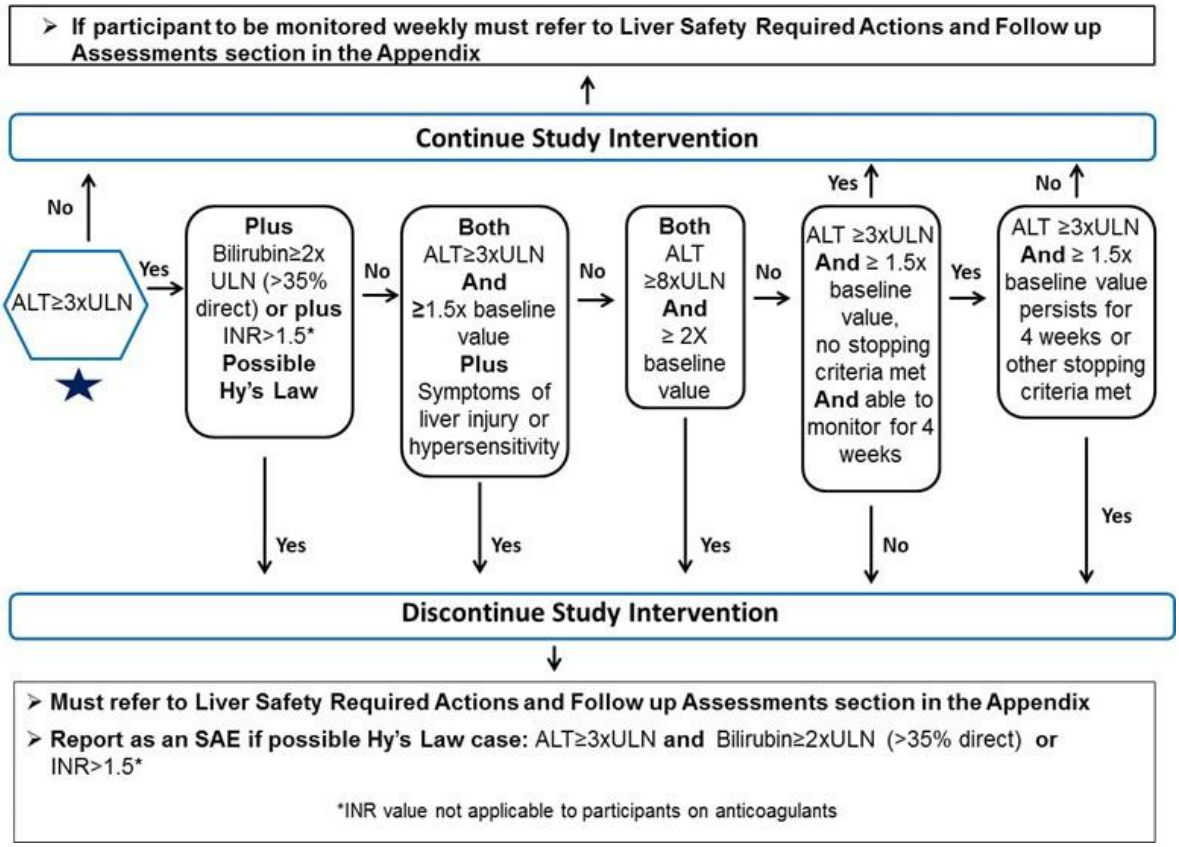
10.7. Appendix 7: Genetics

USE/ANALYSIS OF DNA

- Genetic variation may impact a participant's response to study intervention, susceptibility, severity and progression of disease. Variable response to study intervention may be due to genetic determinants that impact drug absorption, distribution, metabolism, and excretion; mechanism of action of the drug; disease etiology; and/or molecular subtype of the disease being treated. Therefore, where local regulations and IRB/IEC allow, a blood sample will be collected for DNA analysis
- DNA samples will be used for research related to study intervention or HNSCC and related diseases. They may also be used to develop tests/assays including diagnostic tests related to study intervention or study interventions of this drug class, and HNSCC. Genetic research may consist of the analysis of one or more candidate genes or the analysis of genetic markers throughout the genome or analysis of the entire genome (as appropriate)
- DNA samples will be analyzed as described in exploratory study objectives/endpoints (refer to Section 3). A detailed description of analyses will be documented in a statistical analysis plan prior to initiation of analyses. Planned analyses and results of genetic investigations will be reported either as part of the clinical statistical analysis plan and clinical study report (CSR), or in a separate genetics statistical analysis plan and report, as appropriate. Additional analyses may be conducted if it is hypothesized that this may help further understand the clinical data.
- The samples may be analyzed as part of a multi-study assessment of genetic factors involved in the response to study intervention or study treatments of this class. The results of genetic analyses may be reported in the clinical study report or in a separate study summary.
- The sponsor will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.
- The samples will be retained while research on study intervention (or study interventions of this class) or HNSCC continues but no longer than 15 years after the last participant last visit or other period as per local requirements.

10.8. Appendix 8: Liver Safety: Required Actions, Follow-up Assessments and Study Intervention Rechallenge Guidelines

Figure 2 Liver Stopping Algorithm and Monitoring Event Algorithm[1]



[1] Study intervention refers to study drugs that comprise a study treatment arm. The algorithm/guideline applies to all study drugs.

Table 17 Liver Chemistry Stopping Criteria –Liver Stopping Event

Event	Criteria
ALT-absolute	**Both** ALT ≥ 8xULN **and** ≥2X baseline value
ALT Increase	**Both** ALT ≥ 3xULN **and** ≥1.5 X baseline value that persists for ≥4 weeks
Bilirubin[1, 2]	ALT ≥ 3xULN **and** bilirubin ≥ 2xULN (>35% direct bilirubin)
INR[2]	ALT ≥ 3xULN **and** INR>1.5
Cannot Monitor	**Both** ALT ≥ 3xULN **and** ≥ 1.5x baseline value **and** cannot be monitored weekly for ≥4 weeks

Symptomatic[3]	**Both** ALT ≥ 3xULN **and** ≥ 1.5x baseline value associated with symptoms (new or worsening) believed to be related to liver injury or hypersensitivity

Required Actions and Follow up Assessments following ANY Liver Stopping Event[4]	
Actions	**Follow Up Assessments**
• **Immediately** discontinue study drug(s) • Report the event to GSK **within 24 hours** • Complete the liver event CRF and complete SAE data collection tool if the event also meets the criteria for an SAE[2] • Perform liver event follow up assessments • Monitor the participant until liver chemistries resolve, stabilize, or return to within baseline (see **MONITORING** below) • **Do not restart/rechallenge** participant with study drug(s) unless allowed per protocol and GSK Medical Governance approval **is granted**(refer to Section 7.1.1.1) • If restart/rechallenge **not allowed or not granted**, permanently discontinue study drug(s) and may continue participant in the study for any protocol specified follow up assessments **MONITORING:** **<u>For bilirubin or INR criteria:</u>** • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin and INR) and perform liver event follow up assessments within **24 hours**	• Viral hepatitis serology[5] • Obtain INR and recheck with each liver chemistry assessment until the transaminases values show downward trend • Blood samples for pharmacokinetic (PK) analysis of each study drug, obtained within 48 hours after last dose[6] • Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH) • Fractionate bilirubin, if total bilirubin≥2xULN • Obtain complete blood count with differential to assess eosinophilia • Record the appearance or worsening of clinical symptoms of liver injury, or hypersensitivity, on the AE report form • Record use of concomitant medications on the concomitant medications report form including acetaminophen, herbal remedies, other over the counter medications • Record alcohol use on the liver event alcohol intake case report form **<u>For bilirubin or INR criteria:</u>** • Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total immunoglobulin G (IgG or gamma globulins)

• Monitor participant twice weekly until liver chemistries resolve, stabilize or return to within baseline • A specialist or hepatology consultation is recommended **For All other criteria:** • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin and INR) and perform liver event follow up assessments within **24-72 hours** • Monitor participant weekly until liver chemistries resolve, stabilize or return to within baseline	• Serum acetaminophen adduct HPLC assay (quantifies potential acetaminophen contribution to liver injury in participants with definite or likely acetaminophen use in the preceding week [James, 2009]). **NOTE: not required in China** • Liver imaging (ultrasound, magnetic resonance, or computerized tomography) and /or liver biopsy to evaluate liver disease; complete Liver Imaging and/or Liver Biopsy CRF forms

1. Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation is not immediately available, discontinue study drug(s) for that participant if ALT ≥ 3xULN **and** bilirubin ≥ 2xULN. Additionally, if serum bilirubin fractionation testing is unavailable, **record presence of detectable urinary bilirubin on dipstick**, indicating direct bilirubin elevations and suggesting liver injury
2. All events of ALT ≥ 3xULN **and** bilirubin ≥ 2xULN (>35% direct bilirubin) or ALT ≥ 3xULN **and** INR>1.5, which may indicate severe liver injury (possible 'Hy's Law'), **must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis)**; the INR threshold value stated will not apply to participants receiving anticoagulants
3. New or worsening symptoms believed to be related to liver injury (such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, or jaundice) or believed to be related to hypersensitivity (such as fever, rash or eosinophilia)
4. Study drugs refer to all drugs that comprise a study treatment arm. Refer to the central laboratory manual for instructions on sample requirements for follow-up tests performed at central laboratory.
5. Includes: Hepatitis A IgM antibody; Hepatitis B surface antigen and Hepatitis B Core Antibody (IgM); Hepatitis C RNA; Cytomegalovirus IgM antibody; Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing); Hepatitis E IgM antibody.
6. Record the date/time of the PK blood sample draw and the date/time of the last dose of study drug prior to blood sample draw on the CRF. If the date or time of the last dose is unclear, provide the participant's best approximation. If the date/time of the last dose cannot be approximated OR a PK sample cannot be collected in the time period indicated above, do not obtain a PK sample. Instructions for sample handling and shipping are in the SRM.

Table 18 Liver Chemistry Increased Monitoring Criteria – Liver Monitoring Event

Criteria	Actions
ALT ≥3xULN and ≥ 1.5x baseline value and not meeting any stopping criteria **without** symptoms believed to be related to liver injury or hypersensitivity, **and** who can be monitored weekly for 4 weeks.	• Notify the GSK medical monitor **within 24 hours** of learning of the abnormality to discuss participant safety. • Participant can continue study drug(s) • Participant must return weekly for repeat liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) until they resolve, stabilize or return to within baseline • If at any time participant meets the liver chemistry stopping criteria, proceed as described above • If, after 4 weeks of monitoring, ALT <3xULN and <1.5 X baseline value, and bilirubin <2xULN, monitor participants twice monthly until liver chemistries normalize or return to within baseline

10.8.1. Study Intervention Rechallenge Guidelines

10.8.1.1. Rechallenge Following Liver Stopping Events that are Possibly Related to Study Treatment

Following drug-induced liver injury, **drug rechallenge is associated with a 13% mortality across all drugs in prospective studies** [Andrade, 2009]. Clinical outcomes vary by drug, with nearly 50% fatality with halothane readministered within one month of initial injury. However, some drugs seldom result in recurrent liver injury or fatality.

Risk factors for a fatal drug rechallenge outcome include:

- Hypersensitivity [Andrade, 2009] with initial liver injury (e.g. fever, rash, eosinophilia)
- Jaundice or bilirubin >2xULN with initial liver injury (direct bilirubin >35% of total)
- Participant currently exhibits severe liver injury defined by: ALT ≥3xULN, bilirubin ≥2xULN (direct bilirubin >35% of total), or INR≥1.5
- Serious adverse event or fatality has earlier been observed with drug rechallenges [Hunt, 2010; Papay, 2009]

- Evidence of drug-related preclinical liability (e.g. reactive metabolites; mitochondrial impairment [Hunt, 2010])

Rechallenge refers to resuming study treatment following drug induced liver injury (DILI). Because of the risks associated with rechallenge after DILI this should only be considered for a participant for whom there is compelling evidence of benefit from a critical or life-saving medicine, there is no alternative approved medicine available, and a benefit:risk assessment of rechallenge is considered to be favorable.

Approval by GSK for rechallenge with study treatment can be considered where:

- Investigator requests consideration of rechallenge with study treatment for a participant who is receiving compelling benefit with study treatment that exceeds risk, and no effective alternative therapy is available.
- Ethics Committee or Institutional Review Board approval for rechallenge with study treatment must be obtained, as required.
- If the rechallenge is approved by GSK Medical Governance in writing, the participant must be provided with a clear description of the possible benefits and risks of study treatment administration, including the possibility of recurrent, more severe liver injury or death.
- The participant must also provide signed informed consent specifically for the rechallenge with study treatment. Documentation of informed consent must be recorded in the study chart.
- Study treatment must be administered at the dose specified by GSK.
- Participants approved by GSK Medical Governance for rechallenge with study treatment must return to the clinic twice a week for liver chemistry tests until stable liver chemistries have been demonstrated and then standard laboratory monitoring may resume as per protocol.
- If after study treatment rechallenge, participant meets protocol-defined liver chemistry stopping criteria, study treatment should be permanently discontinued.
- GSK Medical Monitor, and the Ethics Committee or Institutional Review Board as required, must be informed of the participant's outcome following study treatment rechallenge.
- GSK to be notified of any adverse events, as per Section 10.3.

10.8.1.2. Restart Following Transient Resolving Liver Stopping Events NOT Related to Study Treatment

Restart refers to resuming study intervention following liver stopping events in which there is a clear underlying cause (other than DILI) of the liver event (e.g. biliary obstruction, pancreatic events, hypotension, acute viral hepatitis). Furthermore, restart is not permitted following liver stopping event when the underlying cause was alcohol-related hepatitis.

Approval by GSK for study treatment restart can be considered where:

- Investigator requests consideration for study treatment restart if liver chemistries have a clear underlying cause (e.g., biliary obstruction, hypotension and liver chemistries have improved to normal or are within 1.5 x baseline and ALT <3xULN).
- Possible study intervention-induced liver injury has been excluded by the investigator and the study team. This includes the absence of markers of hypersensitivity (otherwise unexplained fever, rash, eosinophilia). If study intervention-related liver injury cannot be excluded, the guidance on rechallenge in Section 10.8.1.1 will apply.
- There is no evidence of alcohol-related hepatitis
- Ethics Committee or Institutional Review Board approval of study treatment restart must be obtained, as required.
- If restart of study treatment is approved by GSK Medical Governance in writing, the participant must be provided with a clear description of the possible benefits and risks of study treatment administration, including the possibility of recurrent, more severe liver injury or death.
- The participant must also provide signed informed consent specifically for the study treatment restart. Documentation of informed consent must be recorded in the study chart.
- Study treatment must be administered at the dose specified by GSK.
- Participants approved by GSK Medical Governance for restarting study treatment must return to the clinic once a week for liver chemistry tests until stable liver chemistries have been demonstrated and then laboratory monitoring may resume as per protocol.
- If after study treatment re-start, participant meets protocol-defined liver chemistry stopping criteria, follow usual stopping criteria instructions.
- GSK Medical Monitor, and the Ethics Committee or Institutional Review Board as required, must be informed of the participant's outcome following study treatment restart.
- GSK to be notified of any adverse events, as per Section 10.3.

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10.9. Appendix 9: Country-specific Requirements

Not Applicable.

10.10. Appendix 10: Abbreviations and Trademarks

Abbreviations

ADA	Anti-drug antibodies
AE	Adverse Event
AESI	Adverse Events of Special Interest
ALT	Alanine Aminotransferase
ANC	Absolute Neutrophil Count
AST	Aspartate Aminotransferase
AUC(0-t)	Area under the plasma concentration-time curve from time 0 to the time of the last quantifiable concentration)
AUC(0-τ)	Area under the concentration-time curve over the dosing interval
β-hCG	Beta-human chorionic gonadotropin
BPI-I3	Brief Pain Inventory- Item 3
cfDNA	cell-free DNA
CI	Confidence Interval
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
Cmax	Maximum observed concentration
Cmin	Minimum Observed Concentration;
CNS	Central Nervous System
CPD	Confirmed Progressive Disease
CR	Complete Response
CrCl	Creatinine Clearance
CRP	C Reactive Protein
CRS	Cytokine Release Syndrome
CSR	Clinical Study Report
CT	Computed Tomography
CTLA-4	Cytotoxic T-Lymphocyte-Associated Protein 4
CV	Cardiovascular
DCR	Disease Control Rate
DILI	Drug-induced Liver Injury
DNA	Deoxyribonucleic Acid
DoR	Duration of Response
ECHO	Echocardiogram
ECI	Events of Clinical Interest
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
EORTC IL50	European Organization for Research and Treatment of Cancer Item Library 50 (a subset of domains from the EORTC QLQ-C30)
EORTC IL51	European Organization for Research and Treatment of Cancer Item Library 51 (a subset of domains from the EORTC QLQ-HN35)

EORTC QLQ C30	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire – 30 item Core Module
EU	European Union
FACT-G	Functional Assessment of Cancer Therapy - General
Fc	Fragment Crystallizable
FcγR	FC-gamma Receptor
FDA	Food and Drug Administration
FDG-PET	Fluorodeoxyglucose Positron Emission Tomography
FTIH	First-time-in-human
GSK	GlaxoSmithKline
H	Hypothesis
HNSCC	Head and Neck Squamous Cell Carcinoma/Cancer
HPV	Human Papilloma Virus
HRQoL	Health-related Quality of Life
HRT	Hormone Replacement Therapy
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICOS	Inducible T Cell Co-Stimulatory Receptor
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committees
IFNγ	Interferon, gamma
Ig	Immunoglobulin
IHC	Immunohistochemistry
IL	Interleukin
INR	International Normalized Ratio
irAE	Immune-related Adverse Event
IRB	Institutional Review Board
iRECIST	Immune-based RECIST
IRR	Infusion-related Reactions
IRT	Interactive Response Technology
IV	Intravenous
kg	Kilogram(s)
KN	KEYNOTE
LVEF	Left Ventricular Ejection Fraction
mAb	Monoclonal Antibody
MedDRA	Medical Dictionary for Regulatory Activities
µg	Microgram(s)
mg	Milligram(s)
mmHg	Millimeters of Mercury
mL	Milliliter(s)
MRI	Magnetic Resonance Imaging
MSDS	Material Safety Data Sheet

MSEC	Millisecond(s)
MTD	Maximum Tolerated Dose
MUGA	Multigated Acquisition Scan
NCI-CTCAE	National Cancer Institute - Common Toxicity Criteria for Adverse Events
NK	Natural Killer
nM	Nanomolar(s)
NOAEL	No Observed Adverse Effect Level
ORR	Overall Response Rate
OS	Overall Survival
PBMC	Peripheral Blood Mononuclear Cell
PD	Progressive Disease
PD-1	Programmed Death Receptor Protein 1
PD-L	PD Ligand
PFS	Progression-free Survival
PK	Pharmacokinetics
PR	Partial Response
PS	Performance Status
Q2W	Every 2 Weeks
Q3W	Every 3 Weeks
Q6W	Every 6 Weeks
Q12W	Every 12 Weeks
QTc	QT interval duration corrected
R/M	Recurrent/Metastatic
RANKL	Receptor Activator of Nuclear Factor-kappa B Ligand
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	Ribonucleic Acid
RO	Receptor Occupancy
SAE	Serious Adverse Event
SD	Stable Disease
SRM	Study Reference Manual
TCR	T Cell Receptor
TDV	Treatment Discontinuation Visit
TIL	Tumor Infiltrating Lymphocytes
TNFα	Tumor Necrosis Factor, alpha
Treg	T Regulatory Cells
TSH	Thyroid Stimulating Hormone
TTD	Time to Deterioration
ULN	Upper Limit of Normal
UPD	Unconfirmed Progressive Disease
UPM	Unit Probability Mass
US	United States
WOCBP	Woman of Childbearing Potential

Trademark Information

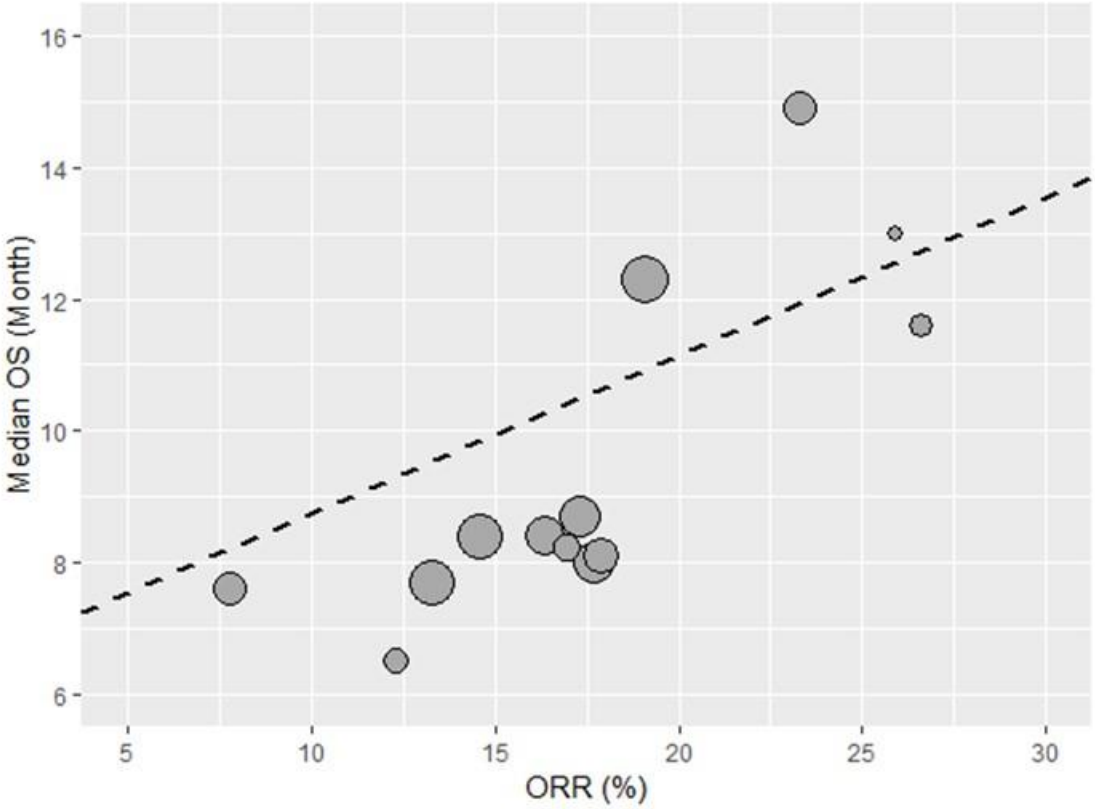
Trademarks of the GlaxoSmithKline group of companies
NONE

Trademarks not owned by the GlaxoSmithKline group of companies
Keytruda

10.11. Appendix 11: Meta-Analysis of HNSCC Studies

The meta-analysis includes the following HNSCC studies in the first-line and subsequent line disease setting: KN-012, KN-055, KN-040, KN-048, Checkmate-141, and Condor.

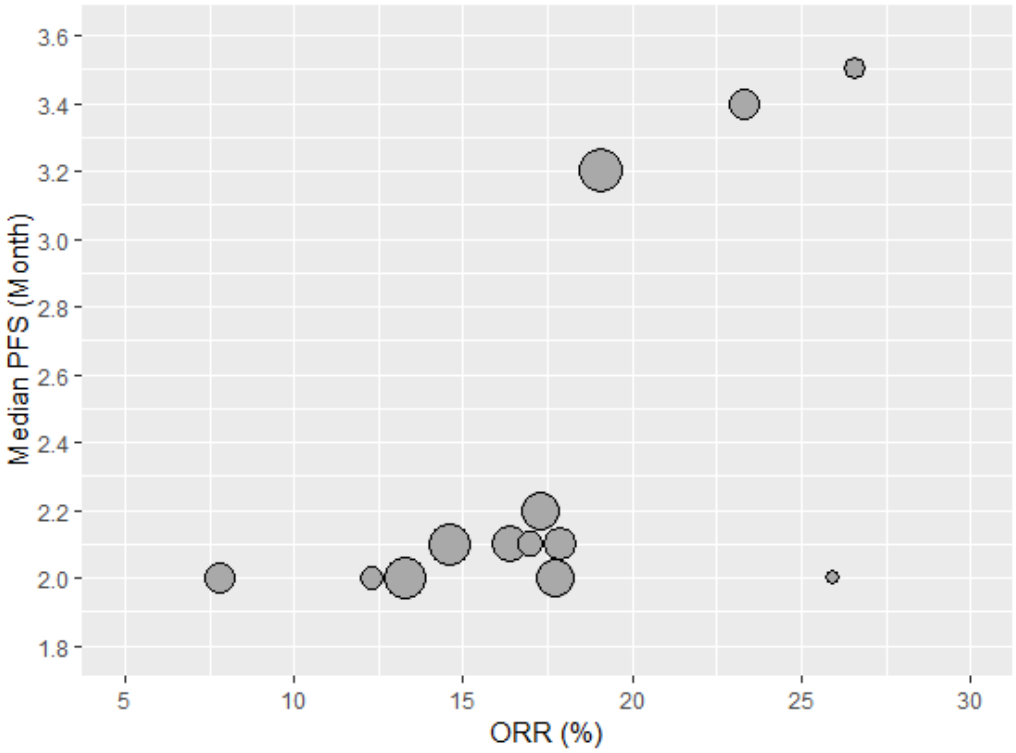
Figure 3 Median OS versus ORR in PD-1/L1 Arms Without Chemotherapy



Abbreviations: ORR=overall response rate; OS=overall survival; PD-1/L1=programmed cell death receptor 1/ligand-1

1. Note: The size of the circle indicates the relative sample size

Figure 4 Median PFS versus ORR in PD-1/L1 Arms Without Chemotherapy



Abbreviations: ORR=overall response rate; PFS=progression-free survival; PD-1/L1=programmed cell death receptor 1/ligand-1

Note: The size of the circle indicates the relative sample size

10.12. Appendix 12: Immune-related Diseases

Table 19 Potential Immune-mediated Diseases

Neuroinflammatory Disorders	**Musculoskeletal Disorders**	**Skin Disorders**
• Cranial nerve disorders, including paralyses/paresis (e.g. Bell's palsy) • Optic neuritis • Multiple sclerosis • Transverse myelitis • Guillain-Barré syndrome, including Miller Fisher syndrome and other variants • Acute disseminated encephalomyelitis, including site specific variants: e.g. non-infectious encephalitis, encephalomyelitis, myelitis, myeloradiculoneuritis • Myasthenia gravis, including Lambert-Eaton myasthenic syndrome • Immune-mediated peripheral neuropathies and plexopathies, (including chronic inflammatory demyelinating polyneuropathy, multifocal motor neuropathy and polyneuropathies associated with monoclonal gammopathy). • Narcolepsy	• Systemic lupus erythematosus and *associated conditions* • *Systemic* Scleroderma *(Systemic sclerosis)*, including diffuse systemic form and CREST syndrome • *Idiopathic inflammatory myopathies, including* Dermatomyositis, Polymyositis, • Antisynthetase syndrome • Rheumatoid arthritis *and associated conditions including* Juvenile chronic arthritis and Still's disease) • Polymyalgia *rheumatica* • Spondyloarthritis, including ankylosing spondylitis, reactive arthritis (Reiter's Syndrome) and undifferentiated spondyloarthritis • Psoriatic arthropathy • Relapsing polychondritis • Mixed connective tissue disorder	• Psoriasis • Vitiligo • Erythema nodosum • Autoimmune bullous skin diseases (including pemphigus, pemphigoid and dermatitis herpetiformis) • Alopecia areata • Lichen planus • Sweet's syndrome • *Localized Scleroderma* (Morphoea)
Liver disorders	**Gastrointestinal disorders**	***Endocrine disorders***
• Autoimmune hepatitis • Primary biliary cirrhosis • Primary sclerosing cholangitis • Autoimmune cholangitis.	• *Inflammatory Bowel disease, including* Crohn's disease, ulcerative colitis, *microscopic colitis, ulcerative* proctitis • Celiac disease • *Autoimmune pancreatitis*	• Autoimmune thyroiditis (including Hashimoto thyroiditis) • Grave's or Basedow's disease • Diabetes mellitus type I • Addison's disease • *Polyglandular autoimmune syndrome* • *Autoimmune hypophysitis*

Vasculitides	***Blood disorders***	**Others**
• Large vessels vasculitis including: giant cell arteritis such as Takayasu's arteritis and temporal arteritis. • Medium sized and/or small vessels vasculitis including: polyarteritis nodosa, Kawasaki's disease, microscopic polyangiitis, Wegener's granulomatosis, Churg–Strauss syndrome (allergic granulomatous angiitis), Buerger's disease (thromboangiitis obliterans), necrotizing vasculitis and anti-neutrophil cytoplasmic antibody (ANCA) positive vasculitis (type unspecified), Henoch-Schonlein purpura, Behcet's syndrome, leukocytoclastic vasculitis.	• *Autoimmune hemolytic anemia* • *Autoimmune thrombocytopenia* • *Antiphospholipid syndrome* • *Pernicious anemia* • *Autoimmune aplastic anemia* • *Autoimmune neutropenia* • *Autoimmune pancytopenia*	• Autoimmune glomerulonephritis (including IgA nephropathy, glomerulonephritis rapidly progressive, membranous glomerulonephritis, membranoproliferative glomerulonephritis, and mesangioproliferative glomerulonephritis) • *Ocular autoimmune diseases (including autoimmune uveitis and autoimmune retinopathy)* • Autoimmune myocarditis/cardiomyopathy • Sarcoidosis • Stevens-Johnson syndrome • Sjögren's syndrome • Idiopathic pulmonary fibrosis • Goodpasture syndrome • Raynaud's phenomenon

10.13. Appendix 13: Protocol Amendment History

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents (TOC).

DOCUMENT HISTORY		
Document	**Date**	**Document Number**
Amendment 2	*19-MAY-2020*	*2019N403389_03*
Amendment 1-UK1	*10-FEB-2020*	*2019N403389_02*
Amendment 1	*24-OCT-2019*	*2019N403389_01*
Original Protocol	*20-AUG-2019*	*2019N403389_00*

Amendment 2 [19-MAY-2020]

Overall Rationale for the Amendment: The rationale for the amendment was to include eligibility criteria to restrict the population to have recurrence > 6 months from completion of chemo-radiation therapy, to address complications of rapid disease progression such as increased risk of tumor associated bleeding that is inherent to the underlying disease of HNSCC and clarification regarding unstable medical condition. Additional updates included accounting for the possibility of a non-proportional hazard effect and tail effect in the statistical plan; definition of second course of study treatment that was expanded to include participants who complete 35 cycles of study treatment.

Section # and Name	Description of Change	Brief Rationale
Section 1.1.3 – GSK3359609 Monotherapy and in Combination with Pembrolizumab in HNSCC	Updated the clinical data	Clinical data changed based on later data-cut
Section 1.2 – Synopsis; Section 2.1 –Study Rationale	Updated the background on pembrolizumab marketing application status in Europe	Pembrolizumab ± chemotherapy were approved by EC for the first-line treatment of PD-L1 CPS ≥1 recurrent/metastatic HNSCC
Section 1.4 – Schedule of Activities	Added a window for Physical Examinations, added Coagulation assessments, added notes for immunogenicity, blood sample for genetics research; fresh tumor and patient reported outcomes (PRO) collections	To provide clarity for assessments
Section 3 – Objectives and Endpoints	Added objective and endpoint to support the healthcare resource utilization assessment	Exploratory objective was inadvertently omitted
Section 5.1– Inclusion Criteria	Revised criterion 4 to restrict the population to have recurrence > 6 months from completion of chemo-radiation therapy. Revised the reference date for age of archival tumor tissue to thePD-L1 testing date.	Updated to address population with rapid progression. .Reference date for PD-L1 testing would be used to determine age of archival tissue not randomization date.

Section # and Name	Description of Change	Brief Rationale
Section 5.2– Exclusion Criteria	Added criteria for exclusion of patients with high risk of bleeding and clarification for the definition of severe/unstable medical conditions	In response to high risk of bleeds that are an inherent feature in HNSCC; provided clarification to eligibility requiring definition which included Grade 3/Grade 4 hypercalcemia
Section 6.1 – Study Intervention(s) Administered	Added that participants should remain under observation at the study site post-study treatment infusion per the judgement of the investigator Clarified maximum 35 cycles of study treatment is approximately 2 years	In response to request from an EC to provide guidance on observation period post infusions Clarification that maximum duration of study treatment is defined by cycles not time.
Section 7.1 – Discontinuation of Study Intervention	Added language to address retreatment defined as Second Course	To allow participants to have the option for retreatment upon progression after achieving a response/stable disease
Section 8.8 – Biomarkers and Section 8.8.3 – Tumor Tissue	Added additional information on timepoints for optional tumor tissue biopsy collections	To clarify timepoints of tissue collections
Section 9.2 – Sample Size Determination	Updated OS scenarios to account for the possibility of non-proportional hazards and long term benefit/tail effect. Updated PFS based on revised assumptions.	In KEYNOTE-48 a delayed treatment effect and tail effect were observed in OS. Additionally, PFS assumption rates in the pembrolizumab arm are based on those reported in the KN-048 trial.

Section # and Name	Description of Change	Brief Rationale
Section 9.2.1 – Remain as a Phase II Study; Section 9.2.2 – Expand to a Phase III Study	Updated alpha spend based on revised allocation of alpha for OS and PFS; also updated associated power.	To allocate less to PFS to require higher threshold to declare statistical significance. Power is updated based on non-proportional assumptions and tail effect for OS
Section 9.2.3 – Sample Size Sensitivity	Created sample size determination and power	Power is updated based on proportional assumptions and tail effect for OS as a sensitivity analysis
Section 9.5 – Interim Analysis	Updated the number of OS analysis in the CPS ≥20 population from 3 to 2	Under the non-proportional hazard assumption for OS, the 1 interim analysis for the CPS ≥20 population retains acceptable power
Section 9.7– Blinded Independent Central Review	Updated BICR auditing size strategy and the maximum acceptable HRR,	To align with revised HR assumptions for PFS
Section 9.8 – Multiplicity	Updated alpha spend based on revised allocation of alpha for OS and PFS. Other updates based on revised assumptions	To allocate less to PFS to require higher threshold to declare statistical significance
Section 10.14 – Second Treatment Course	Created SoA table for Treatment Phase	To present the assessments required

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