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

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.

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:

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

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,

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		

- 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)

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.

8.3.7. 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.

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.

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.

- 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.

- 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.

- 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.

- 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.*

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

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)

- 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.

.

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

   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)

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.

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.

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.

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)

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

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

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

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

- 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.

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.

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.

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.

- 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

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

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.

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.

• 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.

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.

• 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.

10.9. Appendix 9: Country-specific Requirements

Not Applicable.

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

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:

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.

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.