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Pembrolizumab (MK-3475) plus platinum and gemcitabine as first-line treatment of recurrent/metastatic head and neck squamous cell carcinoma (PIPER): a phase 2, multicentre, single-arm protocol study in Malaysia

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ABSTRACT

Introduction Treatment combination of pembrolizumab plus platinum and 5-fluorouracil (PF) has increased the survival of recurrent or metastatic (R/M) head and neck squamous cell carcinoma (HNSCC). The combination of platinum and gemcitabine (PG) has been shown to be superior to PF in the treatment of R/M nasopharyngeal carcinoma patients. Therefore, we hypothesise that the combination of pembrolizumab with PG would be comparable to pembrolizumab with PF as a first-line treatment in R/M HNSCC.

Methods and analysis This is an open-label, multicentre, single-arm, phase 2 study of pembrolizumab plus PG for first-line treatment in subjects with R/M HNSCC in Malaysia. The study is conducted using the Optional Simon optimal 2-stage design. At the initial stage, 26 subjects will be enrolled and if seven or more patients achieve an objective response rate (ORR), then 63 patients will be enrolled. Subjects will be given pembrolizumab 200 mg[3] every 3 weeks up to 35 cycles in combination with chemotherapy for up to six cycles of platinum (either cisplatin at 35 mg/m^2 intravenous on day 1 and day 8 or carboplatin at area under the curve 5 intravenous on day 1 of each 3-week cycle) and gemcitabine at 1250 mg/m^2 intravenous on days 1 and 8 of a 3-week cycle. The primary end point is the ORR as per Response Evaluation Criteria in Solid Tumors 1.1. Secondary end points include the overall survival, progression free survival, response duration and safety. The exploratory objectives include relationships of microbiome profiles, prognostic and predictive biomarkers with the clinical responses.

Ethics and dissemination The study was approved by the ethics committee of the University Malaya Medical Centre (202213–10884). Findings will be disseminated through conference presentations and peer review publications.

Trial registration number ClinicalTrials.gov (www.clinicaltrial.gov); NCT05286619.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This study will inform on the efficacy and safety of the combination of pembrolizumab and platinum with a novel agent gemcitabine in patients with recurrent or metastatic head and neck squamous cell carcinoma.
⇒ We are also exploring the relationship of microbiomes, prognostic and predictive biomarkers in relation to clinical response for patients who are on pembrolizumab and platinum and gemcitabine.
⇒ This is a phase 2 single-arm study with a limited number of participants, so there is no standard arm comparison.

INTRODUCTION

Background

Head and neck squamous cell carcinoma (HNSCC) is the fourth most common cancer in Malaysia with 3842 cases diagnosed in 2020.[1] Malaysia is a multiethnicity country consisting of Malay, Chinese, Indian and the minority Indigenous people. HNSCC with the exclusion of nasopharyngeal carcinoma is diagnosed across all ethnic groups with the highest propensity among the Indians.[2]

Patients with recurrent or metastatic (R/M) HNSCC generally have poor survival, with a median survival of 6 to 15 months depending on patient- and disease-related factors. Chemotherapy is indicated for most of these patients, and the regimen of choice is influenced by multiple clinical factors, including patient comorbidities, performance status (PS), previous therapy and pathologic features. Often, the regimen of choice is also governed by practical considerations relating

to infrastructure and resources within the healthcare system.[3]

Following the KEYNOTE-048 trial (KN048), pembrolizumab (MK-3475) with or without chemotherapy has been approved as a first-line treatment of R/M HNSCC. In the combination group, MK-3475 was combined with platinum and 5-fluorouracil (5-FU) (PF) resulting in an objective response rate (ORR) of 35.6%, and an improved overall survival (OS) compared with the EXTREME regimen.[4] While effective, the PF combination approved for use with MK-3475 is not a commonly used regimen in the Asian setting. The 4 days continuous infusion of 5-FU that necessitates hospitalisation and the toxicity profile of 5-FU have made other more practical combinations such as platinum and gemcitabine (PG) a treatment of choice,[5] where patients are able to receive treatment in an outpatient setting. However, the efficacy and safety of this novel combination of MK-3475 with PG have not been formally assessed in Asians nor in the non-Asian setting.

The PG regimen has previously demonstrated to be superior to PF in the treatment of R/M nasopharyngeal carcinoma patients by increasing the objective response rate and survival with fewer severe adverse events (SAE).[6] Notably, comparing Asians and non-Asians, a meta-analysis demonstrated that the 6 months progression free survival (PFS) of patients treated with PG was better among Asians.[7] Gemcitabine treatment could be advantageous when considering a combination with anti-PD1 as it induces a proinflammatory tumour microenvironment that is favourable for immunotherapy.[8] The combination treatment of gemcitabine and anti-PD1 also shifted resting macrophages to an M1 phenotype, increasing tumour immunity that resulted in significantly better survival in animal models.[9] Furthermore, a phase III trial comparing the overall survival of patients treated with nivolumab (another anti-PD-1) in combination with chemotherapy (platinum and gemcitabine) versus chemotherapy has recently started (NCT04458909).

In the treatment of R/M HNSCC, the combination of platinum with other chemotherapeutic agents including taxanes is used.[10] Indeed, KEYNOTE-B10 evaluated the safety and efficacy of combining MK-3475 with carboplatin and paclitaxel (PT).[11] Although PT has also been used in the Asian setting, twice as many Asian patients suffered from severe neutropenia when treated with carboplatin plus PT compared with non-Asians (70.9% in Asian, 33.7% in non-Asian) in a subanalyses of non-small cell lung cancer (NSCLC) patients, and toxicity was significantly less when a combination of cisplatin and gemcitabine (PG) was used (PT vs PG; 70.9% vs 53.9% in Asians, 33.7% vs 25.3% in non-Asians).[12] As PG might be better tolerated among Asians, this suggests that the tolerability of the PG regimen could be better compared with PT when combined with MK-3475, among Asian patients. We believe that the novel combination of MK-3475 with platinum and gemcitabine, a regime which is commonly used in Asia, would be comparable, if not better than MK-3475 with platinum and 5-FU, in terms of its efficacy and safety as first-line treatment in R/M HNSCC, particularly in an Asian cohort. We also believe that split dose cisplatin is well tolerated and as effective in combination with gemcitabine and pembrolizumab compared with pembrolizumab in combination with 5-fluorouracil and platinum as reported in KEYNOTE-048 for the treatment of R/M HNSCC.[13]

Our clinical trial represents a novel study where the impact of combining the anti-PD1 antibody pembrolizumab with a commonly used chemotherapy regimen PG in the R/M HNSCC will be evaluated (NCT05286619). Alongside this clinical trial, a translational research project will provide a deep understanding of the dynamic changes in the immune and microbiome states that are associated with responses to treatment and patient outcome. These results will have important implications for the treatment of R/M HNSCC patients and the identification of potential biomarkers of response.

METHODS

Objectives

The outcome measures are the following: the primary objective is to determine the ORR per Response Evaluation Criteria in Solid Tumors (RECIST) 1.1. The secondary objectives are to evaluate the OS, PFS, duration of response (DOR), survival in relation to programmed cell death ligand 1 (PD-L1) status and to evaluate safety. In addition, the correlation between ORR and OS with PD-L1 combined positive score (CPS) and the number of participants with treatment-related adverse events as assessed by Common Terminology Criteria for Adverse Events (CTCAE) will be evaluated. Other outcome measures (exploratory objectives) are to explore the correlation between: (1) genetic variation with clinical outcome; (2) microbiome profiling with clinical outcome; and (3) changes in the circulatory immune cells throughout the treatment of patients. All outcome measures will be determined at 24 months. The trial design is depicted in figure 1.

Study design

This is an investigator-initiated open-label, single-arm, phase 2 study of pembrolizumab plus PG in subjects with R/M HNSCC to be conducted in conformance with Good Clinical Practices, and all participants are required to provide written informed consent prior to enrolment. The study is registered with ClinicalTrials.gov registration number NCT05286619, the Malaysian National Medical Research Register (NMRR) with NMRR ID-22–00597 U2F and University Malaya Medical Centre Medical Ethics Committee MREC ID NO 202213–10884.

Inclusion criteria

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

1. Male/female participants who are at least 18 years of age on the day of signing informed consent with

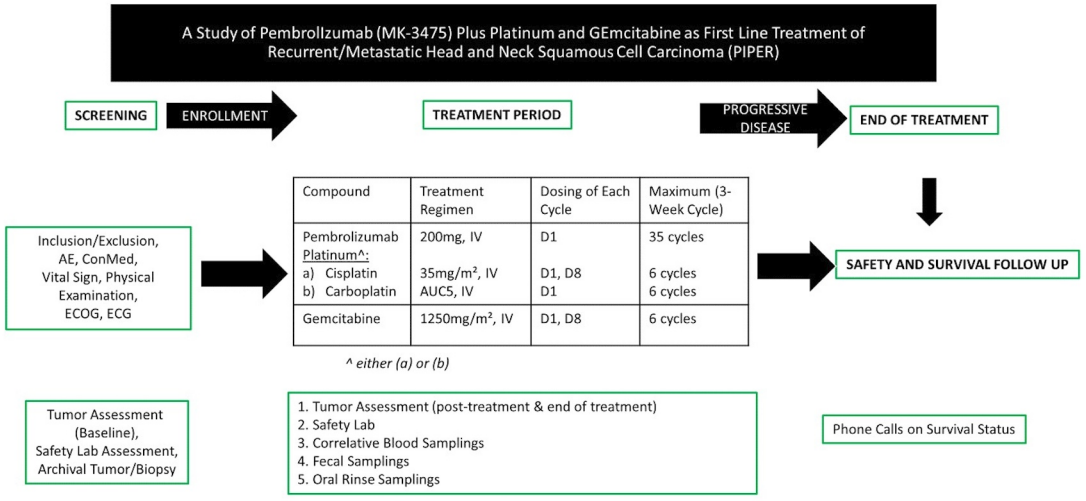

Figure 1 The trial design. AE, adverse event; AUC, area under the curve; ConMed, concomitent medication; ECOG, Eastern Cooperative Oncology Group; IV, intravenous.

histologically confirmed diagnosis of R/M HNSCC that is considered incurable by local therapies will be enrolled in this study:
   - Subject may not have had prior systemic therapy administered in the recurrent or metastatic setting. Systemic therapy which was completed more than 6 months prior to signing consent if given as part of multimodal treatment for locally advanced disease is allowed.
   - The eligible primary tumour locations are oropharynx, oral cavity, hypopharynx and larynx.
   - Subject may not have a primary tumour location site of nasopharynx (any histology).
2. A male participant must agree to use a contraception as detailed in online supplemental appendix 1: contraceptive guidance and pregnancy testing of this protocol starting with the first dose of study treatment through the treatment period and for at least 180 days after the last dose of study treatment and refrain from donating sperm during this period.
3. A female participant is eligible to participate if she is not pregnant (see online supplemental appendix 1: contraceptive guidance and pregnancy testing), not breastfeeding and at least one of the following conditions applies:
   a. Not a woman of childbearing potential (WOCBP) as defined in online supplemental appendix 1: contraceptive guidance and pregnancy testing.
   b. A WOCBP who agrees to follow the contraceptive guidance in online supplemental appendix 1: contraceptive guidance and pregnancy testing during the treatment period and for at least 180 days after the last dose of study treatment.
4. The participant (or legally acceptable representative if applicable) willing and able to provide a written informed consent for the trial. The participant may also provide consent for Future Biomedical Research. However, the subject may participate in the main trial without participating in Future Biomedical Research.
5. Have measurable disease based on RECIST 1.1. Lesions situated in a previously irradiated area are considered measurable if progression has been demonstrated in such lesions.
6. Archival or fresh tumour tissues must be available for evaluating relevant biomarkers. Newly obtained core needle or excisional biopsy of a tumour lesion not previously irradiated is preferred to archived tissue. If newly obtained samples cannot be obtained due to inaccessibility or patient safety concern, submission of paraffin block or formalin-fixed, paraffin embedded slides of up to 3 years prior to trial enrolment are acceptable (15 unstained slides of 5 microns in thickness).
7. Have an Eastern Cooperative Oncology Group (ECOG) PS of 0 to 1. Evaluation of ECOG is to be performed within 7 days prior to the first dose of study intervention.
8. Have adequate organ function as defined below. Specimens must be collected within 10 days prior to the start of study intervention.
   a. Absolute neutrophil count ≥1500 /µL.
   b. Platelets ≥1 00 000 /µL.
   c. Haemoglobin ≥9.0 g/dL or ≥5.6 mmol/L.
   d. Creatinine ≤1.5 × upper limit normal (ULN).
   e. Total bilirubin ≤1.5 ×ULN OR direct bilirubin ≤ULN for participants with total bilirubin levels >1.5 × ULN.
   f. Aspartate transaminase and alanine transaminase ≤2.5 × ULN (≤5 × ULN for participants with liver metastases).
   g. International normalised ratio OR prothrombin time (PT). Activated partial thromboplastin time (aPTT) ≤1.5 × ULN unless the participant is receiving anticoagulant therapy as long as PT or aPTT is within therapeutic range of intended use of anticoagulants.

Exclusion criteria

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

1. Has disease that is suitable for local therapy administered with curative intent.
2. Has progressive disease within 6 months of completion of curatively intended treatment for locoregionally advanced HNSCC.
3. Patient with an expected life expectancy of less than 3 months.
4. A WOCBP who has a positive urine pregnancy test within 72 hours prior to treatment allocation (see Appendix 4). If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.
5. Has received prior therapy with an anti-PD-1, anti-PD-L1 or antiPDL2 agent or with an agent directed to another stimulatory or co-inhibitory T-cell receptor (eg, CTLA-4, OX40, CD137).
6. Has received prior systemic anti-cancer therapy including investigational agents within 4 weeks (could consider shorter interval for kinase inhibitors or other short half-life drugs) prior to start of study treatment.
   Note: Participants must have recovered from all AEs due to previous therapies to ≤grade 1 or baseline. Participants with ≤grade 2 neuropathy may be eligible. Participants with endocrine-related AEs grade ≤2 requiring treatment or hormone replacement may be eligible.
   Note: If the participant had major surgery, the participant must have recovered adequately from the procedure and/or any complications from the surgery prior to starting study intervention.
7. Has received prior radiotherapy within 2 weeks of start of study intervention. Participants must have recovered from all radiation-related toxicities, not require corticosteroids and not have had radiation pneumonitis. A 1-week washout is permitted for palliative radiation (≤2 weeks of radiotherapy) to non-CNS disease.
8. Has received a live vaccine or live-attenuated vaccine within 30 days prior to the first dose of study drug. Administration of killed vaccines is allowed.
9. Is currently participating in or has participated in a study of an investigational agent or has used an investigational device within 4 weeks prior to the first dose of study intervention.
   Note: Participants who have entered the follow-up phase of an investigational study may participate as long as it has been 4 weeks after the last dose of the previous investigational agent.
10. Has a diagnosis of immunodeficiency or is receiving chronic systemic steroid therapy (in dosing exceeding 10 mg daily of prednisone equivalent) or any other form of immunosuppressive therapy within 7 days prior to the first dose of study drug.
11. Has a known additional malignancy that is progressing or has required active treatment within the past 5 years. Participants with basal cell carcinoma of the skin, squamous cell carcinoma of the skin or carcinoma in situ (eg, breast carcinoma, cervical cancer in situ) that have undergone potentially curative therapy are not excluded.
12. Has known active CNS metastases and/or carcinomatous meningitis. Participants with previously treated brain metastases may participate provided they are radiologically stable, that is, without evidence of progression for at least 4 weeks by repeat imaging (note that the repeat imaging should be performed during study screening), clinically stable and without requirement of steroid treatment for at least 14 days prior to first dose of study intervention. This exception does not include carcinomatous meningitis which is excluded regardless of clinical stability.
13. Has severe hypersensitivity (≥grade 3) to pembrolizumab and/or any of its excipients.
14. Has active autoimmune disease that has required systemic treatment in the past 2 years (ie, with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (eg, thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency) is not considered a form of systemic treatment and is allowed.
15. Has a history of (non-infectious) pneumonitis/interstitial lung disease that required steroids or has current pneumonitis/interstitial lung disease.
16. Has an active infection requiring systemic therapy.
17. Has a known history of HIV infection.
18. Has a known history of hepatitis B (defined as hepatitis B surface antigen reactive) or known active hepatitis C virus (defined as HCV RNA (qualitative) is detected) infection.
    Note: no testing for hepatitis B and hepatitis C is required unless mandated by local health authority.
19. Has a history or current evidence of any condition, therapy or laboratory abnormality that might confound the results of the study, interfere with the participant's participation for the full duration of the study or is not in the best interest of the participant to participate in the opinion of the treating investigator.
20. Has known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial.
21. Is pregnant or breastfeeding or expecting to conceive or father children within the projected duration of the study, starting with the screening visit through 120 days after the last dose of trial treatment.
22. Has had an allogenic tissue/solid organ transplant.

Eligible participants and enrolment

Eligible participants can be from any oncological clinics, oral and maxillofacial surgery clinics as well as otorhinolaryngology surgery clinics throughout Malaysia who are referred to participating centres of University Malaya Medical Centre (UMMC), National Cancer Institute

(IKN) and Kuala Lumpur General Hospital (HKL). A written informed consent will be obtained from all participants before participation. On consented, participants will be screened for eligibility. Data will be captured in the electronic medical record and entered as well as kept in the electronic capture database hosted by REDCap.

Intervention

The study will be conducted using the Optional Simon optimal 2-stage design. Based on the sample size calculations, 26 evaluable patients will be accrued in stage 1. An interim analysis will be performed and if six or fewer patients out of the 26 evaluable patients achieve complete response (CR) or partial response (PR), the study will be stopped early for futility. If the study has passed the first stage with seven or more patients who achieved CR/PR, then the study will move on to the second stage where a total of 63 subjects with R/M HNSCC will be enrolled for examination of the efficacy and safety of the combination of pembrolizumab with PG as first-line treatment. The study started recruitment on 22 September 2022 and expected to be completed in September 2027. All subjects will be given pembrolizumab (200 mg intravenous on day 1 of each 3-week cycle up to 35 cycles) in combination with platinum (either cisplatin at 35 mg/m^2 intravenous using a split dose regimen on day 1 and day 8 or carboplatin at area under the curve (AUC) 5 intravenous on Day 1 of each 3 week cycle, up to six cycles) and gemcitabine at 1250 mg/m^2 intravenous on days 1 and 8 of each 3-week cycle for up to six cycles. The cisplatin dose of 35 mg/m^2 day 1 and day 8 was chosen based on the local practice. Study activities are depicted in online supplemental S2.

Adverse events (AEs) associated with pembrolizumab exposure, including coadministration with additional compounds, may represent an immunologic aetiology. These immune-related AEs (irAEs) may occur shortly after the first dose or several months after the last dose of pembrolizumab/combination treatment. For suspected irAEs, ensure adequate evaluation to confirm aetiology or exclude other causes. Dose modification and toxicity management guidelines for irAEs associated with pembrolizumab/combination treatment are provided in online supplemental table S3.

If one or all the chemotherapy components are discontinued, subjects can continue with pembrolizumab up to the full 35 cycles. Dose modifications or dose interruptions should not be used to resolve grade 2 or grade 3 AEs of anaemia or leucopenia that are related to chemotherapy. To ensure that subjects can receive adequate chemotherapy dosing, standard supportive care measures (eg, erythrocyte infusion, thrombocyte infusion, granulocyte colony-stimulating factor and erythropoietin) should be used first before dose modification if there are no other reasons to modify dosing for chemotherapy agents at the discretion of the treating physician.

Disease status will be followed by imaging studies at six weekly intervals (±7 days) during the first year and every 9 weeks (±7 days) after the first year, until disease progression, withdrawal of consent, death or end of study. RECIST 1.1 will be used as the primary efficacy endpoint of response rate. Safety will be monitored according to the National Cancer Institute CTCAE V.5.0.

The intervention(s) to be used in this trial is outlined in table 1.

Justification for dose

The planned dose of pembrolizumab for this study is 200 mg every 3 weeks (Q3W). Based on the totality of data generated in the Keytruda development programme, 200 mg Q3W is the appropriate dose of pembrolizumab for adults across all indications and regardless of tumour type. As outlined below, this dose is justified by:

a. Clinical data from nine randomised studies in melanoma, NSCLC including KN480 indications demonstrating flat dose- and exposure-efficacy relationships from 2 mg/kg Q3W to 10 mg/kg every 2 weeks.
b. Population pharmacokinetic (PK) analysis showing that both fixed dosing and weight-based dosing provides similar control of PK variability with considerable overlap in the distributions of exposures, supporting suitability of 200 mg Q3W.
c. Clinical data showing meaningful improvement in benefit-risk including OS at 200 mg Q3W across multiple indications.
d. Pharmacology data showing full target saturation in both systemic circulation (inferred from PK data) and

Table 1 Trial Intervention(s)

Drug	Dose/potency	Dose frequency	Route of administration	Regimen/treatment period	Use
Pembrolizumab	200 mg	Every 3 weeks	Intravenous infusion	Day 1 of each cycle (3-week cycle)	Experimental regimen
Cisplatin*	35 mg/m^2	Every 3 weeks	Intravenous infusion	Day 1 and day 8 of each cycle (3-week cycle) for six cycles	
Carboplatin*	AUC 5	Every 3 weeks	Intravenous infusion	Day 1 of each cycle (3-week cycle)	
Gemcitabine	1250 mg/m^2	Every 3 weeks	Intravenous infusion	Day 1 and day 8 of each cycle (3-week cycle) for six cycles	

*either cisplatin or carboplatin
AUC, area under the curve.

tumour (inferred from physiologically based PK analysis) at 200 mg Q3W.

The doses and schedules of chemotherapy treatment with pembrolizumab for this trial have been based on previous trials such as KN021 (NCT02039674), KN048 (NCT02358031) and KN059 (NCT02335411) which investigated the addition of pembrolizumab to chemotherapy in lung cancer, head and neck cancer, and gastric cancer, respectively, since February 2014. In KN021, these combinations included cisplatin, carboplatin and gemcitabine, each combined with pembrolizumab. The proposed doses and schedules for the chemotherapy are as follows: cisplatin 35 mg/m^2 on days 1 and 8 or carboplatin AUC 5 on day 1 and gemcitabine on days 1 and 8 of a 3-week cycle. The dose of cisplatin 35 mg/m^2 on day 1 and day 8 with a cumulative dose of 70 mg/m^2 per cycle is chosen based on the local experience on the tolerability and efficacy as compared with cumulative dose 80 mg/m^2 per cycle as per many of the nasopharyngeal carcinoma study. Split-dosing of cisplatin has shown good activity in combination with gemcitabine with favourable toxicity profiles in patients with other advanced malignancy including non-small lung cancer (13).

Concomitant medications/vaccinations (allowed and prohibited)

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the ongoing trial. If there is a clinical indication for one of these or other medications or vaccinations specifically prohibited during the trial, discontinuation from trial therapy or vaccination may be required. The final decision on any supportive therapy or vaccination rests with the investigator and/or the participant's primary physician. However, the decision to continue the participant on study intervention requires the mutual agreement of the investigator, the sponsor and the participant.

Acceptable concomitant medications

All treatments that the investigator considers necessary for a participant's welfare may be administered at the discretion of the investigator in keeping with the community standards of medical care. All concomitant medication will be recorded on the case report form including all prescription, over the counter, herbal supplements and intravenous medications and fluids. If changes occur during the trial period, documentation of drug dosage, frequency, route and date may also be included on the case report form. All concomitant medications received within 28 days prior to the first dose of trial intervention and up to 30 days after the last dose of trial intervention should be recorded. If participants experience an SAE or event of clinical interest (ECI), concomitant medications administered 30 days after the last dose of trial intervention are to be recorded.

Prohibited concomitant medications

Participants are prohibited from receiving the following therapies during the screening and treatment phase (including retreatment for post-CR relapse) of this trial:

- Anti-neoplastic systemic chemotherapy or biological therapy.
- Immunotherapy not specified in this protocol.
- Chemotherapy not specified in this protocol.
- Investigational agents other than pembrolizumab.
- Radiation therapy.
  Note: Radiation therapy to a symptomatic solitary lesion or to the brain may be allowed at the investigator's discretion. The subject must have clear measurable disease outside the radiated field. Administration of palliative radiation therapy will be considered clinical progression for the purposes of determining PFS.
- Live vaccines within 30 days prior to the first dose of study treatment and while participating in the study. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster, yellow fever, rabies, BCG and typhoid vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (eg, FluMist) are live attenuated vaccines and are not allowed.
- Systemic glucocorticoids for any purpose other than to modulate symptoms from an event of clinical interest of suspected immunologic aetiology. The use of physiologic doses of corticosteroids may be approved after consultation with the sponsor. Additionally, a short, limited course of steroids may be used to treat medical conditions and/or AEs during the study after sponsor notification and consultation.
  Note: Inhaled steroids are allowed for management of asthma/COPD.
  Note: Use of prophylactic corticosteroids to avoid allergic reactions (eg, to intravenous contract dye) or use of corticosteroids as premedication for chemotherapeutic agents specified in the protocol is permitted.

Participants who, in the assessment by the investigator, require the use of any of the aforementioned treatments for clinical management should be removed from the study. All treatments that the investigator considers necessary for a participant's welfare may be administered at the discretion of the investigator in keeping with the community standards of medical care. Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the ongoing study. If there is a clinical indication for any medication or vaccination specifically prohibited during the study, discontinuation from study therapy or vaccination may be required. The final decision on any supportive therapy or vaccination rests with the investigator and/or the participant's primary physician. However, the decision to continue the participant on study treatment requires the mutual agreement of the investigator, the sponsor and the participant. However, the decision to continue the participant on

study intervention requires the mutual agreement of the investigator, the sponsor and the participant.

There are no prohibited therapies during the post-treatment follow-up phase.

Primary, secondary and exploratory endpoints

ORR will be evaluated as the primary efficacy endpoint, while OS, PFS and DOR will be evaluated as the secondary efficacy endpoints. Efficacy will be determined by imaging at baseline and every 6 weeks during the first year and every 9 weeks thereafter (or earlier as clinically indicated per principal investigator (PI) discretion) until disease progression (PD) or treatment discontinuation. Response will be determined by RECIST 1.1 and Immune-RECIST (iRECIST).

ORR is defined as the proportion of subjects who achieve a CR or PR per RECIST 1.1 criteria. PFS at 6 months and at 12 months is defined as the proportion of patients who have not progressed at 6 months and 12 months with PFS calculated from the start of treatment to the date of progression or death from any cause. OS is defined as time from the start of treatment to the date of death from any cause, whichever comes first. Subjects without documented death at the time of the final analysis will be censored at the date of the last follow-up. For subjects who demonstrate a confirmed CR or PR, DOR is defined as the time from first documented evidence of CR or PR until disease progression or death due to any cause, whichever comes first. Response duration for subjects who have not progressed or died at the time of analysis will be censored at the date of their last tumour assessment.

PD-L1 expression status is evaluated based on the number of PD-L1–staining cells (tumour cells, lymphocytes and macrophages) relative to all viable tumour cells using an immunohistochemistry assay. The assay uses a CPS as a measure of PD-L1 positivity, in which a CPS of <1 = negative; ≥1 = positive; and ≥20 = strongly positive. The correlation of ORR and OS to the subject's PD-L1 expression as CPS <1, CPS ≥1 or CPS ≥20 will be evaluated.

For the exploratory endpoints, the study includes translational analyses of potential factors predictive of clinical response including immune repertoire, genetic variations, microbiome profiling and changes in circulatory immune cells throughout the treatment period.

Safety

All participants enrolled will be evaluated for safety. Participants will be assessed at every visit while they are on treatment for AEs and laboratory values. Physical examinations will be conducted as per institutional standard. National Cancer Institute CTCAE V.5.0 will be used to grade the AEs and laboratory values. Any abnormal biochemical laboratory values will be monitored during the follow-up phase until all study drug-related toxicities are resolved or otherwise. Non-study-related additional measures will be performed as indicated. A Safety Review Committee will perform a safety data review to ensure the trial is safe to be continued. The annual safety report will be provided during the study period.

Baseline and follow-up evaluation

Full history and physical examinations will be done on screening visit, first visit and at the end of treatment visit. For cycles that do not require a full physical exam, directed physical examination will be performed by investigators, and new clinical findings will be recorded as AEs. Vital signs including the ECOG PS will be recorded at screening, prior to the administration of each dose of trial treatment and at treatment discontinuation. All participants must have initial staging with a CT scan of the brain, neck, thorax, abdomen and pelvis; ECG; laboratory assessment for haematological, biochemistry urinalysis; and thyroid and coagulation profile at screening. At every visit, AE assessment, vital signs and laboratory assessment are also done, and directed physical examinations are performed as described in the schedule of activities (online supplemental table S2). Tumour assessment by CT scan will be done after +/-9 weeks of treatment initiation and +/-6 weeks thereafter or more frequently if indicated for the first 1 year and +/-9 weekly after 1 year. Imaging should be done until disease progression. Objective response should be confirmed by a repeat imaging assessment. Tumour imaging to confirm PR or CR should be performed at least 4 weeks after the first indication of a response is observed. Participants will then return to regular scheduled imaging every 6 weeks, starting with the next scheduled imaging time point.

Pembrolizumab may produce antitumour effects by potentiating endogenous cancer-specific immune responses. Standard RECIST may not provide an accurate response assessment of immunotherapeutic agents such as pembrolizumab. In such case, iRECIST will be used, using RECIST 1.1 with the following adaptations:

If radiologic imaging by a central imaging vendor verifies initial PD, tumour assessment should be repeated ≥4 weeks later to confirm PD with the option of continuing treatment per below while awaiting radiologic confirmation of progression. If repeat imaging shows a reduction in the tumour burden compared with the initial scan demonstrating PD, treatment may be continued/resumed. If repeat imaging confirms progressive disease, subjects will be discontinued from study therapy.

In subjects who have initial evidence of radiological PD verified by a central imaging vendor, it is at the discretion of the treating physician whether to continue a subject on study treatment until repeat imaging is obtained. When feasible, subjects should not be discontinued until progression is confirmed.

In participants who discontinue study treatment, tumour imaging should be performed at the time of treatment discontinuation (±4-week window). If previous imaging was obtained within 4 weeks prior to the date of discontinuation, then imaging at treatment discontinuation is not mandatory. In participants who discontinue study treatment due to documented disease progression

and the investigator elects not to implement iRECIST, this is the final required tumour imaging.

All participants who stop study intervention with stable disease or better may be eligible for up to an additional 17 cycles (approximately 1 year) of pembrolizumab treatment if they progress after stopping study treatment from the initial treatment phase. This retreatment is termed the second course Phase of this study and is only available if the study remains open.

The mandatory safety follow-up visit should be conducted approximately 30 days after the last dose of study intervention or before the initiation of a new anticancer treatment, whichever comes first. Participants who are eligible for retreatment with pembrolizumab may have up to two safety follow-up visits, one after the initial treatment period and one after the second course treatment.

Sampling for translational study

Tumour tissue collection

Archival tumour tissues will also be collected in addition to blood, oral rinse and faecal samples.

Sample size, the two-staged procedures

The study will be conducted using the Optional Simon optimal 2-stage design.[14] We hypothesised that the response rate to pembrolizumab in combination with platinum and gemcitabine in R/M HNSCC patients will be 36%. The null hypothesis and alternative hypothesis of the Simon 2-stage design is 23% and 36%, respectively. Assuming power of 0.80 and Type 1 error rate (α, one-sided) of 0.10, 26 evaluable patients will be accrued in stage 1. An interim analysis will be performed and if six or fewer patients out of the 26 evaluable patients achieve CR/PR, the study will be stopped early for futility. Otherwise, 37 additional patients will be accrued for a total of 63 patients. Considering an estimated 10% attrition rate, we plan to enrol up to 69 patients to have 63 patients with evaluable response. The null hypothesis will be rejected if there are 19 or more responses observed in 63 evaluable patients, which would be sufficiently interesting to warrant further investigation in later trials.

Statistical methods

All patients screened and enrolled will be accounted for. All enrolled discontinuations will be summarised by reason for discontinuation. The number of patients screened and enrolled will be presented. The Full Analysis Set (FAS) population will serve as the primary population for the analysis of efficacy data in this study. The FAS population consists of all subjects who (1) receive at least one dose of study treatment and (2) have a baseline scan with measurable disease per RECIST 1.1. For the primary efficacy endpoint, investigators assessed RECIST 1.1 ORR, the point estimate of ORR, and its 95% will be provided. For secondary efficacy endpoints (PFS, OS and DOR), summary statistics using Kaplan-Meier method will be provided as appropriate. All possible effort will be done to contact patients and relatives as well as contacting National Registry Department for patients latest survival status and AEs' missing data.

Monitoring

Monitoring will be done centrally by Cancer Research Malaysia (CRMY). Data monitors from CRMY will review and manage data entry centrally and compile the data/reports required for statistical analysis (eg, interim analysis), reporting to sponsor (PI) and Merck Sharp & Dohme on quarterly basis or whenever required. Questra Clinical Research Co. Ltd will perform onsite visits for source data review and verification. An independent data monitoring will review safety data should any serious AE occur.

Ethics and dissemination

The study will be conducted in accordance with legal and regulatory requirements, as well as the general principles set forth in the International Ethical Guidelines for Biomedical Research Involving Human Patients (Council for International Organizations of Medical Sciences 2002), Guidelines for GCP (ICH 1996) and the Declaration of Helsinki (World Medical Association 2008).

The study was approved by the ethics committee of the University Malaya Medical Centre (202213–10884) and National Medical Research Register (NMRR ID-22–00597U2F). Findings will be disseminated through conference presentations and peer review publications.

Patient and public involvement

During planning the trial, patients and the public were not involved in any part including opinion, design, drafting and data collection.

Accrual and amendment

Patients are initially recruited from University Malaya Medical Centre, General Hospital Kuala Lumpur and National Cancer Institute Putrajaya. On discussions among the primary investigators from the three centres, there were suggestions to revise some parts of the protocol with justifications, and there was a need to add additional centres to increase recruitments. The suggestions for protocol amendment were then shared with the sponsor for comments and approval, and then the protocol amendment was submitted to the medical research ethics committee and regulators. Two protocol amendments were done:

1. To change the primary investigator in National Cancer Institute and addition of collection of oral rinse for future biomarker studies.
2. Additional two new sites of Hospital Wanita dan Kanak-Kanak Sabah Likas and Hospital Pulau Pinang.

Both amendments were reviewed by University Malaya Medical Centre Medical Ethics Committee and National Medical Research Registry. Both certified bodies also reviewed the change in informed consent materials that will be provided to the patients. The amendment was approved.

Protocol version: Pembrolizumab MISP Protocol V.3.0 Dated 27 January 2022.

Discussion

Pembrolizumab is proven to be effective as first-line treatment of R/M HNSCC as monotherapy or in combination with platinum and 5-FU for patients expressing PD-L1 positive with superior overall survival benefit compared with the EXTREME regime. The effectiveness of pembrolizumab combination with platinum and PT is also proven in the Keynote B10 trial. However, the superiority of the combination of pembrolizumab with other novel chemotherapy is unknown. To our knowledge, this is the first study to test the activity, potential efficacy and tolerability of pembrolizumab in combination with platinum and gemcitabine, and hopefully this will provide efficacy data for such a combination. Depending on the success of this trial, it will potentially be an option for this combination in the future especially for those patients who cannot tolerate 5-FU or PT combinations with pembrolizumab.

Trial status

The trial began in September 2022 and successfully completed stage 1 enrolment and allowed to proceed to stage 2. Lead site, all three sites (UMMC,[9] HKL[7] and IKN[3]) were initiated earlier and actively recruiting.

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Contributors WZWI contributed to the main ideas, writing, reviewing and correcting the protocol and manuscript. WZWI is also the study sponsor, lead investigator, corresponding author and guarantor. SCC contributed to the main ideas, writing, reviewing and correcting the protocol and manuscript. BS was involved in reviewing and contributing ideas and correcting the protocol and manuscript. GFH, IMN, CKT, YFW, SHT, KPL and AWYC reviewed and approved the protocol and manuscript. AY contributed to the statistical ideas and reviewed the protocol and manuscript. Role of study sponsor: the project will be supervised and coordinated by the lead investigator on behalf of Lead Site (Universiti Malaya Medical Centre).

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Competing interests WZWI received research grants, travel grants and speaker honorarium from Merck Sharp & Dohme Inc., BeiGene Inc., Novartis Inc., AstraZeneca Inc. and National Cancer Centre (NCC) Japan. GFH received research grants, travel grants and speaker honorarium from Eli Lilly Inc., Regeneron Pharmaceuticals, Merck Sharp & Dohme Inc., AB Science, Astellas Pharma Inc., Tessa Therapeutics, Roche Holding AG, Arcus Biosciences, AstraZeneca, Pfizer Inc., Janssen Research and Development, Mirati Therapeutics Inc., Novartis AG, Amgen Inc. and Boehringer Ingelheim AG. IMN received travel grants and speaker honorarium from Merck Sharp & Dohme Inc., Novartis Inc., AstraZeneca Inc., Pfizer Inc., Mirati Therapeutics Inc., MYXMO and ESMO. YFW received speaker honorarium from Merck Sharp & Dohme Inc., Bristol-Myers Squibb (Malaysia) Sdn Bhd, Novartis Inc., Pfizer Inc. and F. Hoffmann-La Roche Ltd. (Roche) and received research grants from Merck Sharp & Dohme Inc., Novartis Inc., F. Hoffmann-La Roche Ltd. (Roche), AstraZeneca, Eli Lilly and Company, Prestige Biopharma Ltd., Incyte Corporation, Janssen Pharmaceuticals, ZymeWorks Pharmaceuticals and National Cancer Centre (NCC) Japan. SCC, CKT, BS, SHT, KPL, AWYC and AY have no conflict of interest to declare pertaining to this study.

Patient and public involvement Patients and/or the public were not involved in the design, conduct, reporting or dissemination plans of this research.

Patient consent for publication Consent obtained directly from patient(s).

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Online supplementary 1

Appendix 1: Contraceptive Guidance and Pregnancy Testing

Woman of Childbearing Potential (WOCBP)
A woman is considered fertile following menarche and until becoming post-menopausal unlesspermanently sterile (see below)

Women in the following categories are not considered WOCBP:
- Premenarchal
- Premenopausal female with 1 of the following:
    - Documented hysterectomy
    - Documented bilateral salpingectomy
    - Documented bilateral oophorectomy

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

Contraception Requirements

Male Participants:

Male participants with female partners of childbearing potential are eligible to participate if they agree to one of the following during the protocol defined time frame:
- Be abstinent from penile-vaginal intercourse as their usual and preferred lifestyle (abstinent on a long term and persistent basis) and agree to remain abstinent

- Use a male condom plus partner use of a contraceptive method with a failure rate of <1% per year as described in **Table 1** when having penile-vaginal intercourse with a woman of childbearing potential who is not currently pregnant.

○ Note: 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.

Female Participants:

Female participants of childbearing potential are eligible to participate if they agree to use a highly effective method of contraception consistently and correctly as described in **Table 1** during the protocol-defined time frame.

Table 1 Highly Effective Contraception Methods

Highly Effective Contraceptive Methods That Are User Dependent a *Failure rate of <1% per year when used consistently and correctly.*
● Combined (estrogen- and progestogen- containing) hormonal contraception b, c ○ Oral ○ Intravaginal ○ Transdermal ○ Injectable
● Progestogen-only hormonal contraception b, c ○ Oral ○ Injectable
Highly Effective Methods That Have Low User Dependency *Failure rate of <1% per year when used consistently and correctly.* ● Progestogen- only contraceptive implant b, c ● Intrauterine hormone-releasing system (IUS) b ● Intrauterine device (IUD) ● Bilateral tubal occlusion

● Vasectomized partner A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.
● Sexual abstinence 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 treatment. 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.)
Notes: Use should be consistent with local regulations regarding the use of contraceptive methods for participants of clinical studies. a) Typical use failure rates are lower than perfect-use failure rates (i.e. when used consistently and correctly). b) If hormonal contraception efficacy is potentially decreased due to interaction with study treatment, condoms must be used in addition to the hormonal contraception during the treatment period and for at least 108 days after the last dose of study treatment. c) If locally required, in accordance with Clinical Trial Facilitation Group (CTFG) guidelines, acceptable hormonal contraceptives are limited to those which inhibit ovulation.

Pregnancy Testing

WOCBP should only be included after a negative highly sensitive urine or serum pregnancy test. Following initiation of treatment, pregnancy testing will be performed whenever an expected menstrual cycle is missed or when pregnancy is otherwise suspected; at the time points specified in the Schedule of Activities (online supplement 2 Table 2), and as required locally. Pregnancy testing will be performed whenever an expected menstrual cycle is missed or when pregnancy is otherwise suspected.

Online supplementary S2

Study Activities

Table 2. Study Schedule of Activities (Initial Treatment with Pembrolizumab, Gemcitabine and Cisplatin or Carboplatin)

Study Period:	Screening	Treatment Cycles (3-Week Cycles)[a]												End of Treatment	Post-Treatment		
Treatment Cycle/Title:	Screening	1		2		3		4		To be repeated beyond 6 cycles[a]				Discon-tinuation	Safety Follow-up	Follow-Up Visits[b]	Survival Follow-up[c]
										5		6					
Treatment Day		1	8	1	8	1	8	1	8	1	8	1	8	At time of discon	30 days post discon	Every 6 weeks post discon	Every 12 weeks
Scheduled Window (Days)[d]	-28 to -1		±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3				
Administrative Procedures																	
Informed Consent	X[e]																
Informed Consent for Future Biomedical Research	X[f]																
Inclusion/Exclusion Criteria	X																
Participant Identification Card	X																
Demographics and Medical History	X																
Prior/Concomitant Medication Review[g]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Prior Treatment for Head and Neck Cancer	X																
Trial Treatment Administration		X	X	X	X	X	X	X	X	X	X	X	X				
Post-study Anticancer Therapy Status																X	X
Survival Status																	X
Clinical & Safety Procedures																	
Disease Details	X																
Adverse Event/Serious Adverse Event Review[h]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[i]	X[i]	
Vital Signs (heart rate, blood pressure), Weight, and Height[k]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		

Study Period:	Screening	Treatment Cycles (3-Week Cycles)[a]												End of Treatment	Post-Treatment		
Treatment Cycle/Title:	Screening	1		2		3		4		To be repeated beyond 6 cycles[a] 5		To be repeated beyond 6 cycles[a] 6		Discon-tinuation	Safety Follow-up	Follow-Up Visits[b]	Survival Follow-up[c]
Treatment Day		1	8	1	8	1	8	1	8	1	8	1	8	At time of discon	30 days post discon	Every 6 weeks post discon	Every 12 weeks
Scheduled Window (Days)[d]	-28 to -1		±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3				
Full physical examination including height and weight	X													X			
Directed Physical Examination		X		X		X		X		X		X		X			
ECOG Performance Status[n]	X	X		X		X		X		X		X					
12-lead ECG	X																
Laboratory Procedures/ Assessments: Analysis Performed by LOCAL Laboratory																	
Pregnancy Test – Serum or Urine[l]	X																
PT/INR and aPTT[m]	X[n]																
Hematology[o]	X[n]			X		X		X		X		X		X	X[p]		
Chemistry[o]	X[n]			X		X		X		X		X		X	X[p]		
Urinalysis[o]	X[n]			X				X				X[j]		X	X[p]		
T3, FT4 and TSH[o]	X[n]			X				X				X[j]		X	X[p]		
Laboratory Procedures/ Assessments: Analysis Performed by CENTRAL Laboratory																	
Correlative Blood Samples[q]		X[q]		X[q]		X[q]		X[q]				X[q]		X[q]		X[q]	
Correlative Faecal Samples[q]		X[q]		X[q]		X[q]		X[q]				X[q]		X[q]		X[q]	
Correlative Oral Rinse Samples[q]		X[q]		X[q]		X[q]		X[q]				X[q]		X[q]		X[q]	
Efficacy Procedures																	
Tumour imaging and RECIST assessment	X[r]							X[S]				X[S]		X[t]		X[b,t]	
Tumour Tissue Collection																	

Study Period:	Screening	Treatment Cycles (3-Week Cycles)[a]												End of Treatment	Post-Treatment		
Treatment Cycle/Title:	Screening	1		2		3		4		To be repeated beyond 6 cycles[a]				Discon-tinuation	Safety Follow-up	Follow-Up Visits[b]	Survival Follow-up[c]
										5		6					
Treatment Day		1	8	1	8	1	8	1	8	1	8	1	8	At time of discon	30 days post discon	Every 6 weeks post discon	Every 12 weeks
Scheduled Window (Days)[d]	-28 to -1		±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3				
Archival or Newly Obtained Tissue Collection for PD-L1 biomarker analysis[U]	X[u]													X[v]			
Archival Tissue Collection for Future Biomarker Research[v,w]	X[w]													X[v,w]			

Online supplements S3

Table 3.

Table 3. Dose modification and toxicity management guidelines for immune-related AEs associated with pembrolizumab monotherapy and IO Combinations

General instructions:

1. Severe and life-threatening irAEs should be treated with IV corticosteroids followed by oral steroids. Other immunosuppressive treatment should begin if the irAEs are not controlled by corticosteroids.
2. Study intervention must be permanently discontinued if the irAE does not resolve or the corticosteroid dose is not ≤ 10mg/day within 12 weeks of the last study intervention treatment.
3. The corticosteroid taper should begin when the irAE is ≤ Grade 1 and continue at least 4 weeks.
4. If study intervention has been withheld, study intervention may resume after the irAE decreased to ≤ Grade 1 after corticosteroid taper.

irAEs	Toxicity Grade (CTCAE v5.0)	Action With Pembrolizumab	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
Pneumonitis	Grade 2	Withhold	· Administer corticosteroids (initial dose of 1 to 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
	Recurrent Grade 2, Grade 3 or 4	Permanently discontinue		
Diarrhea/ Colitis	Grade 2 or 3	Withhold	· Administer corticosteroids (initial dose of 1 to 2 mg/kg prednisone or equivalent) followed by taper	· Monitor participants for signs and symptoms of enterocolitis (ie, diarrhea, abdominal pain, blood or mucus in stool with or without fever) and of

	Recurrent Grade 3 or Grade 4	Permanently discontinue		bowel perforation (ie, 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 and electrolytes should be substituted via IV infusion
AST or ALT Elevation or Increased Bilirubin	Grade 2 [a]	Withhold	· Administer corticosteroids (initial dose of 0.5 to 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)

	Grade 3 [b] or 4 [c]	Permanently discontinue	· Administer corticosteroids (initial dose of 1 to 2 mg/kg prednisone or equivalent) followed by taper	
T1DM or Hyperglycemia	New onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of b-cell failure	Withhold [d]	· Initiate insulin replacement therapy for participants with T1DM · Administer antihyperglycemic 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 4	Withhold or permanently discontinue [d]		
Hyperthyroidism	Grade 2	Continue	· Treat with nonselective beta-blockers	· Monitor for signs and symptoms of thyroid disorders

	Grade 3 or 4	Withhold or permanently discontinue[d]	(eg, propranolol) or thionamides as appropriate	
Hypothyroidism	Grade 2, 3 or 4	Continue	· Initiate thyroid replacement hormones (eg, levothyroxine or liothyronine) per standard of care	· Monitor for signs and symptoms of thyroid disorders
Nephritis: grading according to increased creatinine or acute kidney injury	Grade 2	Withhold	· Administer corticosteroids (prednisone 1 to 2 mg/kg or equivalent) followed by taper	· Monitor changes of renal function
	Grade 3 or 4	Permanently discontinue		
Neurological Toxicities	Grade 2	Withhold	· Based on severity of AE administer corticosteroids	· Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3 or 4	Permanently discontinue		
Myocarditis	Grade 1	Withhold		· Ensure adequate evaluation to confirm

	Grade 2, 3 or 4	Permanently discontinue	· Based on severity of AE administer corticosteroids	etiology and/or exclude other causes
Exfoliative Dermatologic Conditions	Suspected SJS, TEN, or DRESS	Withhold	· Based on severity of AE administer corticosteroids	· Ensure adequate evaluation to confirm etiology or exclude other causes
	Confirmed SJS, TEN, or DRESS	Permanently discontinue		
All Other irAEs	Persistent Grade 2	Withhold	· Based on severity of AE administer corticosteroids	· Ensure adequate evaluation to confirm etiology or exclude other causes
	Grade 3	Withhold or discontinue based on the event [e]		
	Recurrent Grade 3 or Grade 4	Permanently discontinue		

AE(s)=adverse event(s); ALT= alanine aminotransferase; AST=aspartate aminotransferase; CTCAE=Common Terminology Criteria for Adverse Events; DRESS=Drug Rash with Eosinophilia and Systemic Symptom; GI=gastrointestinal; IO=immuno-oncology; ir=immune related; IV=intravenous; SJS=Stevens-Johnson Syndrome; T1DM=type 1 diabetes mellitus; TEN=Toxic Epidermal Necrolysis; ULN=upper limit of normal.

Note: Non-irAE will be managed as appropriate, following clinical practice recommendations.

[a] AST/ALT: >3.0 to5.0 x ULN if baseline normal; >3.0 to 5.0 x baseline, if baseline abnormal;
bilirubin:>1.5 to 3.0 x ULN if baseline normal; >1.5 to 3.0 x baseline if baseline abnormal

[b] AST/ALT: >5.0 to 20.0 x ULN, if baseline normal; >5.0 to 20.0 x baseline, if baseline abnormal; bilirubin:>3.0 to 10.0 x ULN if baseline normal; >3.0 to 10.0 x baseline if baseline abnormal

[c] AST/ALT: >20.0 x ULN, if baseline normal; >20.0 x baseline, if baseline abnormal;
bilirubin: >10.0 x ULN if baseline normal; >10.0 x baseline if baseline abnormal

[d] The decision to withhold or permanently discontinue pembrolizumab is at the discretion of the investigator or treating physician. If control achieved or ≤ Grade 2, pembrolizumab may be resumed.

[e] Events that require discontinuation include, but are not limited to: encephalitis and other clinically important irAEs (eg, vasculitis and sclerosing cholangitis).