Taiwan CDE (Health Authority)
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**TITLE:**

A post-licensure prospective observational registry study in real-world Taiwanese cancer patients with microsatellite instability-high (MSI-H) or deficient mismatch repair (dMMR) genes

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# PROTOCOL SUMMARY

| | |
|---|---|
| Title | A post-licensure prospective observational registry study in real-world Taiwanese cancer patients with microsatellite instability-high (MSI-H) or deficient mismatch repair (dMMR) genes |
| Vendor/Collaborator | To be determined |
| Rationale | Pembrolizumab has demonstrated significant efficacy in clinical trials (protocol numbers KN158 and KN164) among MSI-H/dMMR patients with a diagnosis of advanced unresectable or metastatic solid tumors. The proposed study is to provide complimentary real-world data in a similar patient population after the approval of the pan-tumor indication for MSI-H/dMMR. |
| Primary Objective(s) | In an observational study in advanced MSI-H/dMMR cancer patients treated with pembrolizumab and followed prospectively,<br>1) describe demographic and clinicopathological characteristics; and<br>2) describe clinical outcomes of interest (objective response rate and duration of response). |
| Study Design | In major cancer centers in Taiwan, patients with a diagnosis of advanced unresectable or metastatic solid tumors who had progressed on prior standard therapy following index diagnosis will be screened for MSI/MMR status. Patients tested MSI-H (including deficient mismatch repair, dMMR), and have received at least one dose of pembrolizumab will be enrolled following consent and prospectively followed through a registry. Pre-specified clinical outcomes will be determined by qualified medical professionals in a standardized fashion and recorded. |
| Study Population | A total of 20 patients with a diagnosis of advanced unresectable or metastatic, non-colorectal (CRC) solid tumors, who tested MSI-H, and had progressed after receiving prior standard therapy following the index diagnosis and then received at least one dose of pembrolizumab, will be included into the proposed study. |
| Study Duration | The recruitment period is estimated to take at least 2 years, depending on the speed of uptake of pembrolizumab; and all patients who respond to the treatment of pembrolizumab will be followed through the registry for a minimum of 1 year following response to measure duration of response. |
| Exposure and Outcome | The exposure of interest in the proposed study is treatment with pembrolizumab. The primary outcome is patient's response to pembrolizumab treatment (complete response, partial response, stable disease, or progression). Response to treatment will be assessed using Response Evaluation Criteria in Solid Tumors (RECIST) 1.1. Duration of response will also be described among those who respond to the treatment of pembrolizumab. |
| Statistical Methods | Descriptive analyses will be performed to report the patients' characteristics, and objective response rate among patients received pembrolizumab. Specifically, frequencies with corresponding 95% confidence intervals will be used to describe the patients' characteristics. For clinical outcomes, proportion of the objective response rate and corresponding 95% confidence interval will be reported. Kaplan-Meier survival curves will be used to report the duration of response. If median |

| | |
|---|---|
| | duration of response is reached within the study follow-up period, then it will also be reported. |
| Sample Size and Power Calculations | The study sample size was mandated by the Taiwanese regulatory agency. The proposed study will include 20 patients meeting the study inclusion/exclusion criteria. The 20-patient sample size produces a two-sided 95% confidence interval with a precision (half-width) equal to 19% for the response rate, assuming a 20% objective response rate. |
| Limitations | Because of the non-interventional nature of this study in a real-world setting, clinical visit schedules and tumor response assessment visits will be dependent on individual treating physicians with no pre-specified standards. Introduction of some variation in the measurement of clinical outcomes is possible. In addition, funneling and selection biases can potentially exist in this study, as inherent limitations in observational studies. However, the objective of this study is aimed to provide much needed information regarding pembrolizumab use in Taiwanese MSI-H cancer patients in the real world and is not meant to be compared directly to the clinical trial results. |

# 1 Background and Rationale

## 1.1 Background

### 1.1.1 PD-1/PD-L1 pathway in cancers and pembrolizumab

The PD-1 receptor-ligand interaction is a major pathway hijacked by tumors to suppress immune control. The normal function of PD-1, which is expressed on the cell surface of activated T-cells under healthy conditions, is to downregulate excessive immune responses, including autoimmune reactions. PD-1 (encoded by the gene *Pdcd1*) is a member of the Ig superfamily related to CD28 and CTLA-4, which has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (PD-L1 and/or PD-L2). [1,2]

Pembrolizumab is a highly selective humanized mAb that binds to the human PD-1 receptor and blocks the interaction between PD-1 and its 2 ligands: PD-L1 and PD-L2. The PD-1 pathway represents a major immune control switch that may be engaged by ligands expressed in the tumor microenvironment. High expression of PD-L1 on tumor cells has been found to correlate with poor prognosis and survival in various cancers. This PD-1/PD-1 ligand axis can be exploited to re-activate T cells and promote tumor cell destruction. By inhibiting the PD-1 receptor from binding to its ligands, pembrolizumab activates tumor-specific cytotoxic T lymphocytes in the tumor microenvironment and stimulates antitumor immunity.

### 1.1.2 Mismatch Repair Deficiency and Microsatellite Instability

#### *1.1.2.1 Microsatellite Instability*

Microsatellites are tracts of repetitive DNA in which certain DNA motifs (ranging in length from 1–6 or more base pairs) are repeated, typically 5–50 times [3]. These repetitive DNA sequences are more frequently copied incorrectly when DNA polymerases cannot bind efficiently to repair sequence errors that occur during DNA replication. Microsatellite instability (MSI) is the condition of genetic hypermutability that results from impaired DNA mismatch repair (MMR), or deficient (defective) MMR (dMMR). The presence of MSI represents phenotypic evidence that MMR is not functioning normally. MMR proteins include MLH1, MSH2, MSH6 and PMS2. They are responsible for recognizing and correcting errors in mismatched nucleotides and insertions/deletions. MSI usually arises from germline mutation in components of the MMR machinery; or somatic hypermethylation of the MLH1 promoter [4].

#### *1.1.2.2 Detection of MSI/dMMR and relevant Guidelines*

In 1993, MSI was first linked to a subgroup of colorectal cancer (CRC) patients (hereditary nonpolyposis CRC, HNPCC; or Lynch syndrome), as well as a portion of nonhereditary (sporadic) colorectal tumors. The presence of MSI in tumor tissue was associated with unique clinical features and prognosis. Therefore, the need to develop uniform criteria for MSI or dMMR detection was growing [5].

In 1997, a U.S. National Cancer Institute workshop on MSI for cancer detection and familial predisposition, developed guidelines for international criteria for determination of MSI in CRC (the Bethesda guidelines) [5]. To ensure reproducibility and standardization, the guidelines recommended a reference panel of 5 microsatellites (the Bethesda panel), including two mononucleotide loci ((BAT 25 and BAT 26)) and three dinucleotide loci (D2S123, D5S346, D17S250), for detection of MSI. This testing is polymerase chain reaction (PCR)-based, and a shift in the size of at least two of the 5 microsatellite loci is defined as MSI-high (MSI-H); and a shift in the size of only one microsatellite locus is considered MSI-low (MSI-L) [5]. Subsequently, the Promega corporation has developed a now widely used alternative to the Bethesda panel (the MSI Analysis System), which has improved sensitivity over the Bethesda panel, especially for endometrial cancer [6]. Immunohistochemistry (IHC) is another approach by detecting MMR proteins (MLH1, MSH2, MSH6 and PMS2) to determine which MMR gene is likely mutated. If all MMR proteins present, it is unlikely that any of MMR gene is mutated. A loss of expression in ≥1 mismatch repair proteins was defined as dMMR. The IHC-based assay performance characteristics are comparable to those of MSI testing with a high concordance rate [7].

Genetic sequencing is an approach that is mostly used for research purposes. The massively parallel DNA sequencing technologies enable interrogation of MSI at more loci than the typically 5-7 genes included in the PCR- or IHC-based assays. However, these sequencing methods are not standardized and require substantially more resources, and thus are mostly used academically [8,9].

In clinical oncology practice, current MMR/MSI testing with either an MMR protein IHC-based assay or PCR-based MSI loci testing is used mainly in the management of CRC patients, as recommended by the, European Society for Medical Oncology, National Comprehensive Cancer Network (NCCN), and American Society of Clinical Oncology [10-12]. Per the ESMO guidelines (2016) MSI testing is recommended in the metastatic disease setting that can assist clinicians in genetic counselling [13]. The most recent NCCN guidelines recommend that MMR or MSI loci testing be performed for all patients with metastatic colorectal, gastric, and esophageal cancers. It should also be noted that this guideline recommends either IHC-based testing or PCR-based testing in clinical decision making, and that "IHC for MMR and PCR for MSI are different assays measuring the same biological effect" because "patients determined to have defective MMR status are biologically the same population as those with MSI-H status." As such, both tests are widely and readily available in the EU and the US for routine clinical testing of tumor samples for any cancer, CRC or non-CRC.

### *1.1.2.3 Epidemiology of MSI-H/dMMR in cancers*

Several recent publications that investigated the prevalence of MSI-H across different tumors showed that the prevalence varied widely by tumor type and by disease stage [8,9, 14, 15]. By examining genetic sequencing data across different cancers of all stages, several tumor types, including endometrial, colorectal, and gastric cancers, were consistently found with the highest prevalence of MSI-H, generally above 10% [8,9,14,15]. MSI-H is present in about 15% of all CRC (mostly sporadic) [5, 16-18]. For most other cancers, the prevalence of MSI was well below 5% [8,9,14,15]. A review article on the literature of MSI in different cancers also reported corroborative results showing higher MSI-H prevalence in the aforementioned three cancers [4].

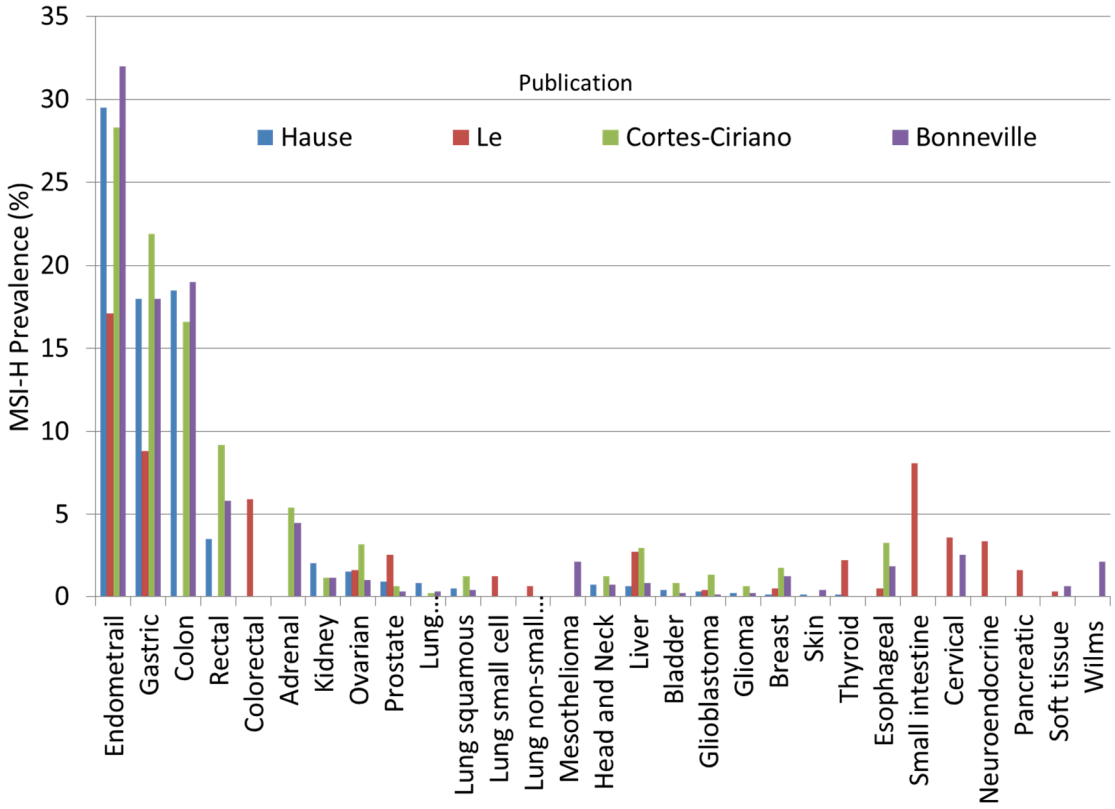


Figure 1. MSI-H prevalence in recent publications testing MSI across different cancer types Data extracted from [8,9, 14,15].

A general pattern of lower prevalence of MSI-H in more advanced stage of cancer was observed in a study among more than 12,000 cancer samples representing 32 distinct tumor types [14]. In that study, the overall MSI-H prevalence in stages I-III cancers was 8%; and the prevalence in stage IV cancers was 4% [14]. Other studies also demonstrated the same patterns in various cancers. For CRC, a systematic review also suggested that MSI is more

common among stage II (~20%) than stage III (~12%) CRC and is even less frequent among stage IV (~4%) disease {[18]. In sporadic endometrial cancer that accounts for the vast majority of endometrial cancer, MSI-H is observed in 11-32% of the patients [8,9, 15, 19-22]. Studies that reported MSI-H specifically in patients with advanced stage endometrial cancer tended to report a lower MSI-H prevalence between 11-22% [19, 22-24]. Differential MSI prevalence by stage of cancer was also reported in gastric cancer. In a study with 1,990 Korean gastric cancer patients, the prevalence of MSI-H in stages I-III, and IV patients was 13.7% and 5.3%, respectively [24]. Similar findings were reported in a study with 250 Italian gastric cancer patients [15]. Another large study also reported 11% MSI-H prevalence in stages I-III gastric cancer patients, compared to 6% in stage IV patients [14].

One of these 4 papers further examined MSI prevalence in early vs. late stage within each cancer type, as shown in Figure 2 [14]. Virtually all late stage cancers reported a lower-than-5% MSI prevalence, except for endometrial and gastric cancers.

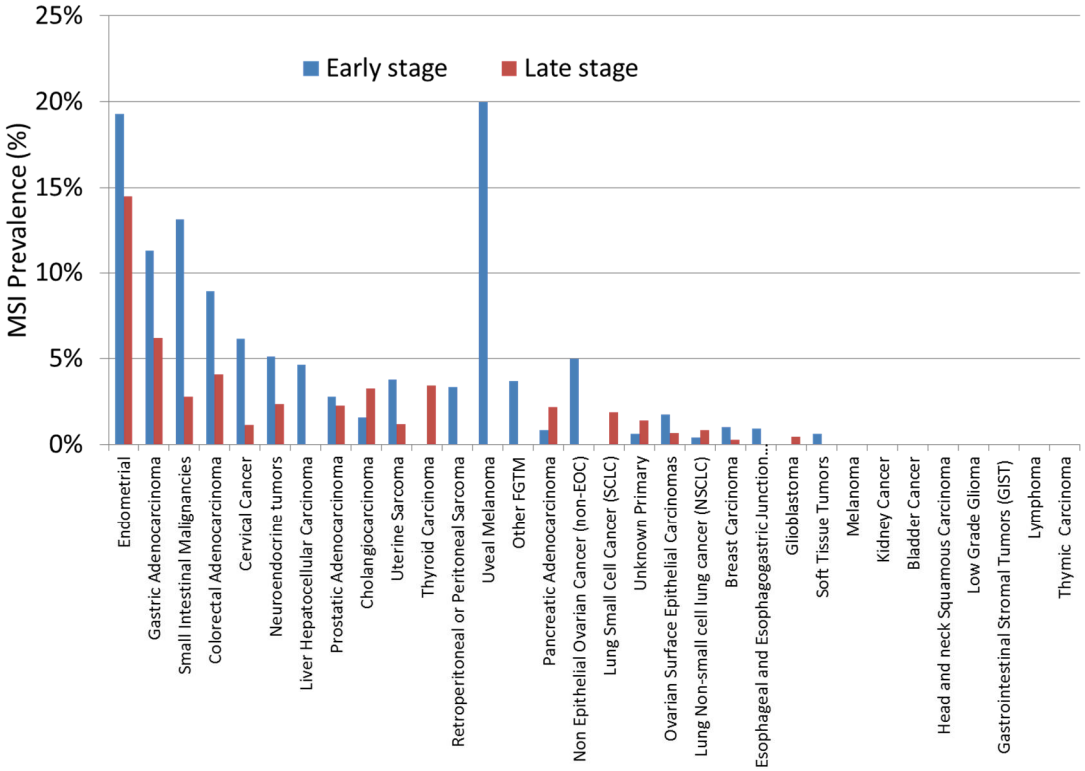


Figure 2. MSI-H prevalence by stage of disease and cancer type
Data extracted from [14].

In summary, it is well recognized that the highest MSI-H prevalence is observed in colorectal, endometrial, and gastric cancers. In contrast, the prevalence of MSI-H in other cancer types is generally low, below 5%. In addition, the pattern of a lower MSI-H

prevalence in advanced stage (IV) of cancer, compared to that in the earlier stage (I-III) of the disease is observed unequivocally across different cancer types.

#### *1.1.2.4 Pembrolizumab MSI-H regulatory submission in Taiwan*

The MSI-H application provides results from 2 clinical studies supporting the use of pembrolizumab for the treatment of patients with advanced MSI-H cancer in the 2L and higher settings.

Pooled efficacy and safety results from KEYNOTE-164 (subjects from Cohort A with MSI-H CRC) and KEYNOTE-158 (subjects with MSI-H non-CRC), referred to as the MSI-H population in this document, demonstrate that pembrolizumab treatment provides substantial clinical benefit with durable responses in subjects with MSI-H cancer across multiple tumor types, and that pembrolizumab treatment is safe and well tolerated in this patient population. Treatment with pembrolizumab therefore provides a meaningful improvement compared with available therapies. The aforementioned submission included 61 CRC and 94 non-CRC patients. The combined ORR was 33.5% (95% CI 26.2%-41.6%). Stratified analyses by CRC vs non-CRC reported an objective response rate of 27.9% (95% CI 17.1%-40.8%) and 37.2% (95% CI 27.5%-47.8%), respectively.

The approved indication for pembrolizumab in this application is for the treatment of patients with the following unresectable or metastatic MSI-H/dMMR cancers.

- colorectal cancer that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan, or
- solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options [see Clinical Studies (12.8)].

This indication is approved under accelerated approval based on tumor response rate and durability of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials

## 1.2 Rationale

[redacted]

[redacted].

The purpose of this proposed multi-center, prospective, observational study is to complement the clinical trial data included in the submission by describing the effectiveness and safety of pembrolizumab use among advanced MSI-H patients with prior therapy history under real-world clinical practice conditions in Taiwan.

# 2 Objectives and Hypotheses

## 2.1 Primary Objective(s) & Hypothesis(es)

In an observational study in advanced MSI-H cancer patients treated with pembrolizumab and followed prospectively,

1) describe demographic and clinicopathological characteristics; and
2) describe clinical objective response rate and duration of response

## 2.2 Secondary Objective(s) & Hypothesis(es)

In an observational study in advanced MSI-H cancer patients treated with pembrolizumab and followed prospectively,

1) describe the treatment-emergent adverse events for pembrolizumab as reported during routine clinical care; and
2) if data allow, describe progression-free survival and overall survival as observed within the study period

# 3 METHODOLOGY

## 3.1 Summary of Study Design

In major cancer centers in Taiwan (number to be determined), patients with a diagnosis of advanced unresectable or metastatic non-CRC solid tumor (primarily focused on gastric and gynecological cancers), who have progressed after prior standard therapy following the index diagnosis, tested MSI-H (including dMMR), and received at least one dose of pembrolizumab will be identified. Patients with already determined MSI-H/dMMR status via IHC/PCR/NGS testing prior to study initiation will also be identified. These patients will then be enrolled and prospectively followed through a registry. Pre-specified clinical outcomes will be determined by qualified medical professionals in a standardized fashion and recorded. Figure 3 depicts the high-level overall study design. The recruitment/enrollment period is estimated to take at least 2 years, and all enrolled

patients who respond to the treatment of pembrolizumab will be followed for at least 1 year following the date of response or at the time of death, whichever occurs first, after enrollment. Based on the data submitted to Taiwanese regulatory agency, for CRC, the median PFS was 2.3 months, and median OS was not reached for up to 12+ months of follow-up; for non-CRC, the median PFS was 5.4 months, and the median OS was 13.4 months. Therefore, the 1-year minimum of follow-up following response date should be appropriate to capture the main clinical endpoints of interest.

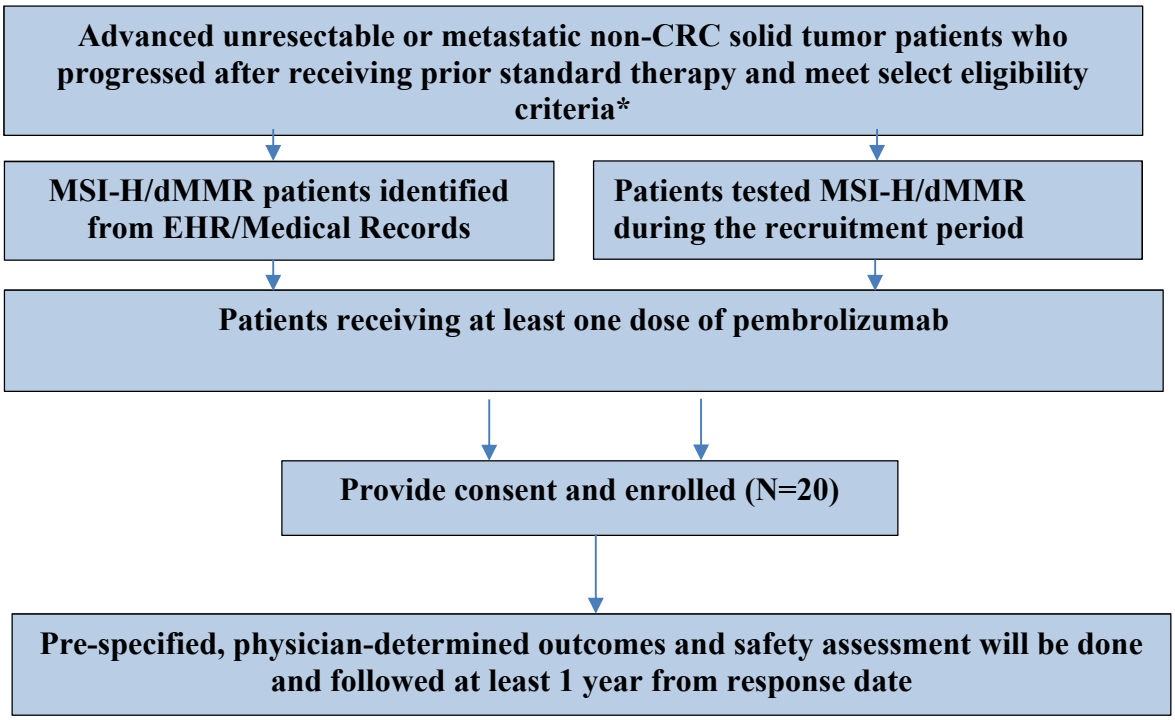


Figure 3. Study design flow chart

*Not deceased, have measurable tumor at baseline, do not have hematologic or other primary malignancies, did not receive checkpoint inhibitors

## 3.2 Study Population

A total of 20 MSI-H/dMMR, non-CRC patients with an advanced solid cancer (primary focus will be gastric and gynecological cancers) diagnosis and a history of previous treatment will be included in this study. In the recruitment phase, we will work with investigators at major cancer centers in Taiwan to proactively identify eligible patients. MSI-H/dMMR status can be determined by any specific assays (IHC- or PCR-based) that are used in routine clinical practice. In addition, patients tested with next-generation sequencing (NGS) with a derived MSI-H status across all solid tumor types will also be considered to enrich the study population. The recruitment phase will be closed once 20 non-CRC patients are consented and included in the registry. It is estimated that at least

2 years are needed for the patient identification, recruitment, and registration. The study is expected to commence in Q1 or Q2, 2020 and continue till Q4, 2025. However, the actual length of time needed will be dependent on the uptake of pembrolizumab in MSI-H/dMMR patients and actual recruitment rate.
Among the MSI-H cancer patient is identified to be potentially eligible, electronic health records (EHR) and medical charts may be used to further determine the eligibility of the patients, particularly regarding medical and treatment histories. Patients who already had an MSI-H/dMMR status determined via prior testing will be identified via EHR and medical records and patients who tests MSI-H/dMMR during the recruitment period will also be identified prospectively. These patients will be consented to be enrolled in the registry once they have received at least one dose of pembrolizumab as part of their clinical management and met other eligibility criteria. Patient selection for MSI/MMR tests will be up to the physician's discretion and clinical relevance. Clinical outcomes of interest as specified in the Objectives will be recorded according to pre-specified and standardized format, along with treatment emergent adverse events (TEAEs) as reported by either the patient or the treating physician. The follow-up of the patients will be at least 1 year from the response date of the patients who respond to pembrolizumab treatment.

### 3.3 Inclusion Criteria

- Adult (≥20years) patients who met the approved MSI-H indication conditions
    - Had a diagnosis of advanced solid cancer
    - Had a history of prior standard treatment(s)
    - Had progressed on prior standard treatment(s) based on RECIST 1.1 or disease-specific tumor response measurement that are commonly used and accepted
- Were confirmed to be MSI-H through either specific MSI/MMR testing or NGS testing
- Received at least one dose of pembrolizumab
- Provided informed consent to participate in the study

### 3.4 Exclusion Criteria

- Had a diagnosis of hematologic cancer
- Had a diagnosis of CRC
- Already deceased at the time of identification
- Had received checkpoint inhibitors prior to the index diagnosis
- Have or had other primary malignancies

# 4 Variables and Epidemiological Measurements

Data collection in this study will be based a combination of primary and secondary data. Briefly, leveraging the existing EHR systems in each of the cancer centers, if available, information on MSI/MMR testing results and previous medical history and selective baseline clinicopathological characteristics of the study population at enrollment will be extracted. Information that cannot be collected from the EHR system will be extracted from medical charts by trained medical chart extractors. Treatment history, clinical outcomes, and TEAEs following the administration of pembrolizumab will be collected by study staff prospectively.

## 4.1 Exposure

The primary "exposure" variable in this study is the use of pembrolizumab. Information on pembrolizumab use will be collected primarily through prospective registry via a pre-specified, standardized case report form (CRF), supplemented with EHR if needed and appropriate. Start and stop dates, number of cycles, total dose, and any dose modification and reason(s) for the modification will also be collected.

## 4.2 Outcomes

This study will capture both clinical and safety outcomes for each participating patient. All investigators will be requested to use Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 and/or a disease-specific tumor response measurement that are commonly used and accepted for determining tumor responses. The primary clinical outcome is tumor response, which will be categorized into complete response (CR), partial response (PR), progressive disease (PD), and stable disease (SD). The tumor responses will be determined by the investigators who treat the cancer patient, subsequent to an investigators' meeting to reiterate the essential elements to standardize the diagnostic criteria. Date of assessment and the basis of assessment will be captured. The assessment of tumor response will be performed as in routine clinical setting without a study-specified visit schedule. Death is also a clinical outcome and will be captured during the study period. With the collected tumor response and death information, objective response rate (ORR) can be derived. Duration of response (DoR) will also be captured among the responders. Specific definitions of these endpoints are provided in the Statistical Analysis Plan section (section 9). Survival information for both responders and non-responders will be collected periodically from medical records, contact through site investigators or from Taiwan death registry for up to two years from end of follow up.

Safety information regarding TEAEs will be recorded as reported by the patients and/or the treating physicians in course of routine clinical care, without further prompting. TEAEs are AEs that occur sequent to the first administration of the first dose of pembrolizumab. Definitions for AE and SAE are provided in section 7. The severity of

the TEAEs will be assessed and determined according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 5 severity grading.

### 4.3 Covariates

- Baseline demographic characteristics, such as
  - Age
  - Gender
  - Smoking
- Baseline clinicopathological characteristics, such as
  - Eastern Cooperative Oncology Group (ECOG) status
  - Laboratory test results, including MSI/MMR status
  - Cancer-related medical history prior to enrollment into the study
    - Diagnosis of cancer
    - Histology
    - Treatment history
    - Stage of cancer
    - Any disease specific categorizations (e.g. Child-Pugh classification, castrate resistance, etc.)
    - Comorbidities
  - Vital signs
    - Height
    - Weight
    - Blood pressure
    - Heart rate
- Concomitant medications during study period

# 5 Study Flow Chart

Table 1. Study flow chart

| Study Period | Screening/identification | Observation/Follow-up | | |
|---|---|---|---|---|
| | | Baseline (at enrollment) | Treatment visit(s)[a] | Assessment of clinical outcomes[b] |
| Potential patients identified through medical records | X | | | |
| Inclusion/Exclusion Criteria | X | X | | |
| Informed Consent | X | | | |
| MSI/MMR status determination | X | | | |
| Demographic characteristics as described in section 4 | | X | | |
| Clinicopathological characteristics as described in section 4 | | X | | X |
| Vital signs as described in section 4 | | X | X | X |
| Concomitant medications | | X | X | |
| Tumor response as described in section 4 | | | | X |
| TEAEs | | | X | X |

[a] Visits are according to real-world routine clinical practice. There are no protocol-specified schedules for these visits. The "study visits" indicate time points at which data is being collected from the patient or the physician.

[b] Typically, the assessment visit (with imaging, etc.) occurs approximately 2-3 months after the initial treatment in Taiwan

# 6 STUDY PROCEDURES

## 6.1 Study Procedures

The study design (Figure 3 in section 3) and study flow chart (Table 1 in section 5) summarize the study procedures to be performed at each visit. Individual study procedures are described in detail below. It may be necessary to perform additional evaluations/testing by the Sponsor for reasons related to subject safety.

### 6.1.1 Administrative Procedures

#### 6.1.1.1 MSI-H or dMMR identification

In collaboration with investigators at selective major cancer centers in Taiwan, we will identify eligible patients to be enrolled into the study through a combination of proactive identification and review of EHR and medical records. Medical records of identified patients will be reviewed to confirm prior specific MSI/MMR testing or NGS testing and MSI-H/dMMR status. Patients who did not have prior testing will be included if they have confirmed MSI-H status through MSI/MMR tests during the study period as advised by their physician. Patient selection for MSI/MMR tests will be up to the physician's discretion and clinical relevance. Patients will likely receive PCR-based tests performed by the hospital pathology department or as per other standard institutional processes (third party). Once a patient is confirmed to have MSI-H, and prescribed by the treating physician to receive pembrolizumab, the patient's EHR and/or medical charts will be further reviewed to ensure that the patient meets all inclusion and exclusion criteria. Once the eligibility is confirmed, the patient will then be enrolled in the study.

#### 6.1.1.2 General Informed Consent

Consent must be documented by the subject's dated signature or by the subject's legally acceptable representative's dated signature on a consent form along with the dated signature of the person conducting the consent discussion.

A copy of the signed and dated consent form should be given to the subject before participation in the study.

The informed consent form and any written information provided to the subject must receive the IRB/ERC's approval/favorable opinion in advance of use. The subject or his/her legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the subject's willingness to continue participation in the study. The communication of this information will be provided and documented via a revised consent form or addendum to the original consent form that captures the subject's dated signature or by the subject's legally acceptable representative's dated signature.

Specifics about a study and the study population will be added to the consent form template.

The informed consent will adhere to IRB/ERC requirements, applicable laws and regulations and Sponsor requirements.

The ICF for the study will be finalized upon receiving agreement on the final protocol from Taiwan CDE.

#### 6.1.1.3 Baseline data collection

A CRF will be developed by a qualified vendor (TBD) and used to collect information at baseline, the time at enrollment. Each patient is assigned a unique identification number, which is exclusively used for study purpose. For the study duration and afterwards, only the investigators or authorized site study personnel will have access to the key linking the study unique identification number back to the patient's identity to identify the patient.

Demographic characteristics, vital signs, and ECOG physical performance score will be assessed and recorded by investigators or other study staff at the baseline visit. MSI/MMR test method and results, laboratory test results, the diagnosis, histology, staging, and treatment history of cancer, along with any disease-specific categorization information and comorbidity will be extracted from the medical records/EHR if available. The investigators will attempt to collect the information that is not available in the medical records/EHR during the baseline visit if feasible.

#### 6.1.1.4 Treatment information

Information on treatment with pembrolizumab per the treating physician's discretion in routine clinical practice will be collected and recorded by the study investigators/staff during the study period. The start and stop dates for the administration of pembrolizumab and number of cycles given to the patient will be recorded. If dose modification is made during the course of treatment, the date will be recorded, along with the reason(s) for the modification. In addition, during the study period, use of cancer-related concomitant medications will also be recorded by the investigator of study staff.

Spontaneous, patient and/or investigator-reported TEAEs within the study follow up period will be recorded by the study investigator/staff per the specifications in section 7. The study investigators will determine the severity of the TEAEs based on the NSCI CTCAE v5 severity grading.

### 6.1.4 Clinical outcomes

The timing of clinical outcome assessments will take place per routine clinical schedules. The typical clinical practice in Taiwan for the assessment of tumor responses takes place approximately 2-3 months after the initiation of the treatment. Prior to the beginning of this study, an investigators' meeting will take place to review study design, procedures, and standards. It will be emphasized to all investigators that, it is important to keep the assessment visit schedule as close to 2-3 months as much. In addition, it will be re-

iterated that RECIST version 1.1 should be used for the assessment. Tumor response will be categorized as CR, PR, PD, and SD per RECIST. The basis (clinical, pathologic, radiologic, combination, etc.) for the response assessment, and the date the assessment is performed will also be recorded.

Survival information will be collected periodically from medical records, contact through site investigators or from Taiwan death registry for up to two years from end of follow up for all participants. This information will be used for PFS and DoR assessments among responders.

#### 6.1.4.1 Withdrawal/Discontinuation

When a subject discontinues/withdraws prior to trial completion, all applicable activities scheduled for the final trial visit should be performed at the time of discontinuation.

# 7 Safety Reporting and Related Procedures

**Introduction**

This is a primary data collection non-interventional study being conducted within routine medical practice. All direction for medication usage is at the discretion of a physician in accordance with usual medical practice. No administration of any therapeutic or prophylactic agent is required in this protocol, and there are no procedures required as part of this protocol.

## 7.1 Adverse Event Reporting

### 7.1.1 INVESTIGATOR RESPONSIBILITY:

If the investigator becomes aware of any serious adverse event (SAE), including death due to any cause, or non-serious adverse reaction (NSAR) following the use of pembrolizumab, or any other Merck product, the event must be reported according to Table 2. The investigator must evaluate each SAE for causality and record causality on the AE form for each event reported.

Similarly, pre-specified Health Outcomes of Interest (HOIs) that meet criteria for SAE/NSAR, special situations, and any spontaneously reported AEs must be reported according to Table 2.

**Table 2: AE Reporting Timeframes and Process for Investigators and Vendors**

| EVENT TYPE | INVESTIGATOR TIMEFRAME | VENDOR TIMEFRAME |
|---|---|---|
| | **Investigator to Vendor [1], [2]** | **Vendor to Merck [3]** |
| SAE, regardless of causality (primary data collection)<br>Serious pre-specified HOI<br>Serious Special Situation, regardless of causality | 24 hours from receipt | 2 BD/3 CD from time of receipt from investigator |
| NSAR<br>Non-Serious pre-specified HOI if NSAR<br>Non-serious Special Situation, regardless of causality | 10 CD from receipt | 10 CD from time of receipt from investigator |
| Spontaneously reported adverse events for Merck products-submit using above timeframes | | |
| If the investigator elects to submit AEs for **non-Merck products**, they should be reported to the market authorization holder (MAH) for that product or to the health authority according to the institution's policy or local laws and regulations. Note: Per **[2],** below, AEs for comparators must be entered in study database. | | |
| Follow-up to any event-submit using above timeframes | | |
| BD-Business Day; CD-Calendar Day | | |
| **[1]** AE reports from investigators must be transmitted via fax, secure email (if available), or entered directly into vendor's electronic data collection (EDC) platform, if utilized.<br>**[2] Investigator to Vendor**: Applies to events for **Merck study product**, **non-Merck comparators**, and ***other*** **Merck products** when a VENDOR is managing AE reporting from investigator to Merck. Events for **Merck study product** and **non-Merck comparators** are entered in study database for tabulation in study report. Events for ***other*** **Merck products** are *not entered in study database* but must be forwarded to Merck for regulatory reporting.<br>**[3] Vendor to Merck:** Applies to events for **Merck study product** and ***other*** **Merck products** if the vendor is managing AE reporting between investigator and Merck. Not applicable for studies not using a vendor for AE reporting. | | |

**Submitting AE reports to Merck : All AEs must be submitted to Local PV Taiwan: FAX:** PPD **, in English using an AE form (attached) for reporting to worldwide regulatory agencies as appropriate.**

### 7.1.2 STUDY REPORT:

The final study report, and any planned interim analysis, will include aggregate listings of all events collected for pembrolizumab and will be provided to regulatory agencies by the sponsor as required.

### 7.1.3 PERIODIC SAFETY UPDATE REPORTS:

Any relevant safety information will be summarized in the appropriate Periodic Safety Update Report (PSUR)/Periodic Benefit Risk Evaluation Report (PBRER) and/or Development Safety Update Reports (DSUR) if required.

## 7.2 DEFINITIONS

### 7.2.1 Adverse Event (AE)

Any untoward medical occurrence in a patient or clinical investigation subject administered sponsor's product and which does not necessarily have to have a causal relationship with this product. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of the product, whether or not considered related to the product. Any worsening (i.e., any clinically significant adverse change in frequency and/or intensity) of a preexisting condition that is temporally associated with the use of the product, is also an adverse event.

### 7.2.2 Adverse Reaction (AR); also referred to as Adverse Drug Reaction (ADR)

An AE which has a causal relationship with the product, that is, a causal relationship between the product and the adverse event is at least a reasonable possibility.

### 7.2.3 Serious Adverse Event (SAE)/Serious Adverse Reaction (SAR)

An adverse event or adverse reaction that results in death, is life threatening, results in persistent or significant disability/incapacity, requires inpatient hospitalization, prolongation of existing inpatient hospitalization, is a congenital anomaly/birth defect, or is another important medical event. Other important medical events that may not result in death, may not be life-threatening, or may not require hospitalization may be considered an SAE/SAR when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the other outcomes listed previously. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home and blood dyscrasias or convulsions that do not result in inpatient hospitalization.

### 7.2.4 Non-serious Adverse Reaction (NSAR)

An adverse reaction that does not meet any of the serious criteria in 7.2.3.

### 7.2.5 Special Situations

The following special situations are considered important safety information and must be reported, regardless of seriousness or causality, if the investigator becomes aware of them:

- Overdose
- Exposure to product during pregnancy or lactation
- Lack of therapeutic effect
- Off-label use, medication error, misuse, abuse, or occupational exposure
- Suspected transmission via a medicinal product of an infectious agent
- Unexpected Therapeutic Benefit/Effect

### 7.2.6 Health Outcome of Interest (HOI)

Health Outcomes of Interest (HOIs) are pre-specified clinical events or outcomes that are collected according to the protocol. HOIs may be represented as diagnosis, treatment or procedures. Examples of HOIs include syncope or hypoglycaemia collected as study endpoints. HOIs must be assessed as part of AE collection and may meet criteria for AE reporting. Specifically, the investigator must assess each HOI for serious criteria and causality. If the HOI meets criteria specified in the protocol for AE reporting, then it must be reported as such.

### 7.2.7 Sponsor's product

Sponsor’s product includes any pharmaceutical product, biological product, device, diagnostic agent or protocol-specified procedure, whether investigational (including placebo or active comparator product) or marketed, manufactured by, licensed by, provided by or distributed by the Sponsor for human use.

### 7.2.8 Causality Assessment

A causality assessment is the determination of whether or not there is at least a reasonable possibility that a product caused the adverse event. Causality must be recorded on the AE form by the investigator for each reported event in relationship to a Sponsor's product.

**Primary Data Collection**

The assessment of causality is to be determined by an investigator who is a qualified healthcare professional according to his/her best clinical judgment. Use the following criteria as guidance (not all criteria must be present to be indicative of causality to a Sponsor's product): There is evidence of exposure to the Sponsor's product; the temporal sequence of the AE onset relative to the administration of the Sponsor's product is reasonable; the AE is more likely explained by the Sponsor's product than by another cause.

### 7.3 Adverse Event Reconciliation

AE reconciliation will be performed between the safety database and study data to ensure all reportable events were reported and received. Starting from when the first patient is enrolled through the end of data collection, all reportable events will be reconciled on a periodic basis.

# 8 Product Quality Complaint Reporting

## 8.1 INVESTIGATOR RESPONSIBILITY:

Any occurrence of a product quality complaint for a Merck product identified during the conduct of the study, must be reported by the study investigator or qualified designee using the Product Quality Complaint (PQC) Reporting Form following the directions in Table 3. The PQC Reporting Form must be fully completed in English. Once the PQC Reporting Form is submitted, the investigator or designee may be contacted for further information.

If both an AE and a PQC occur, the AE should be reported according to the AE reporting requirements in the protocol and the PQC should be reported per Table 3.

**Table 3: PQC Reporting Timeframes and Process for Investigators**

| **EVENT TYPE** | **INVESTIGATOR TIMEFRAME** |
|---|---|
| | **Investigator to Merck** |
| **PQC** | 24 hours from receipt |
| PQC reports must be submitted via e-mail by the investigator to the local designated point of contact (DPOC) using a PQC form. | |
| **Submitting PQC reports to Merck: All PQCs must be submitted to the local DPOC in English using a PQC form** (attached)**. The following e-mail addresses should be used by country:** PPD | |

## 8.2 DEFINITIONS

### 8.2.1 Product Quality Complaint (PQC).

Any communication that describes a potential defect related to the identity, strength, quality, purity or performance of a product identified by an external customer. This includes potential device or device component malfunctions.

### 8.2.2 Malfunction

The failure of a device (including the device component of a combination product) to meet its performance specifications or otherwise perform as intended. Performance specifications include all claims made in the labeling for the device.

# 9 Statistical Analysis Plan

## 9.1 Statistical Methods

The analyses will be of descriptive nature in this study. The study is not aimed to test any pre-specified hypothesis. All analyses will be performed by the sponsor or designee after the completion of the study and the study data files are locked and released.

### 9.1.1 Primary Objective(s): Calculation of Epidemiological Measure(s) of Interest (e.g. descriptive statistics, hazard ratios, incidence rates, test/retest reliability)

Descriptive analysis, including univariate analyses and cross tabulations, will be used for presenting baseline demographic and clinicopathological characteristics of the MSI-H/dMMR patients included in this study. Frequencies or mean and/or median will presented for discrete and continuous variables, respectively, with corresponding 95% confidence intervals (CIs). In addition, frequency of MSI/MMR testing method will also be presented to provide additional context.

ORR is defined as the combined proportion of patients with a CR or PR tumor response per the investigator's assessment, presented as a percentage with corresponding 95% CI. The primary analysis will be on combined ORR with all patients included in the study.

DoR is measured from the time of initial response until the time at which it is determined that tumor progression occurs. Kaplan-Meier plots will be generated to describe DoR with median DoR estimated along with the corresponding 95% CI.

Subgroup analyses in individual caner types for ORR and DoR will be performed only if adequate number (>5) of patients have the specific cancer.

### 9.1.2 Secondary Objective(s): Calculation of Epidemiological Measure(s) of Interest (e.g. hazard ratios, incidence rates, test/retest reliability)

TEAEs will be summarized for the study population using the NCI CTAE version 5. Frequencies with corresponding 95% CIs will be calculated by MedDRA system organ class (SOC), and worst

CTCAE grade. These analyses will be performed for TEAEs, drug-related TEAEs, treatment-emergent SAEs, drug-related treatment-emergent SAEs, and TEAEs leading to dose modification, interruption, or permanent dose discontinuation.
PFS is defined as the length of time between the day on which the first dose of pembrolizumab is given to the day on which PD is determined by the study investigator, or the day of death, whichever happens first. Kaplan-Meier plot will be generated to describe the PFS in the study population. Univariate analysis of PFS will be performed and the median PFS along with inter-quartile range will be reported with 95% CIs.

OS in this study is the length of time measured from the day on which the first dose of pembrolizumab is given to the day of death (of any cause). Similar analyses as performed for PFS will be performed for OS.

For PFS and OS, for patients with no events, the censoring date will be the last date of tumor response assessment performed and the last date the patient is seen alive during the study period. Subgroup analyses in individual caner types may be performed for PFS and OS, if there are at least >5 cancer patients in the subgroup.

## 9.2 Bias

### 9.2.1 Methods to Minimize Bias

The characteristics of the study population will be heavily dependent on the uptake of MSI/MMR testing among cancer patients, as well as the uptake of pembrolizumab for the pan-tumor MSI-H indication. It is possible that there will be a funneling bias in recruiting patients who are sicker and more willing to consider a new indication and the MSI/MMR test. The descriptive analyses on baseline demographic and clinicopathological characteristics of the study population, particularly ECOG performance status and caner staging information, may help shed lights of such potential bias. Since this study is not intended to generate information to be directly compared to the results of the MSI-H clinical trials, but rather, to supplement clinical outcomes and safety data in Taiwanese patients in a real-world setting, the occurrence of funneling bias should be taken into consideration when interpreting the study results, which should not be directly compared to those in the clinical trials.

Selection bias may also occur since all study sites will be major cancer centers in Taiwan. Typically, these tertiary centers may attract sicker patients than the overall indicated patient population. However, the baseline patient characteristics will provide critical information in recognizing the occurrence of selection bias.

### 9.2.2 Limitations

This study is an observational study in a real-world setting, so there are some inherent limitations. All study visits are accordingly to real-world clinical practices with no standardized, pre-specified visit schedules. Therefore, time-related clinical outcomes that

are dependent on the time when the tumor response, which is not pre-specified and can vary widely, is assessed will be impacted. Similarly, tumor responses, as well as many clinicopathologic findings, are assessed by individual treating physician/institute per their routine clinical practice, there may be more variations regarding the clinical outcomes and safety assessment, compared to a clinical trial with standardized clinical procedures and outcome assessments. However, the objective of this study is aimed to provide much needed information regarding pembrolizumab use in MSI-H Taiwanese cancer patients in the real world and is not meant to be compared directly to the clinical trial results.

### 9.3 Sample Size and Power Calculations

Based on the consideration of feasibility and timeliness for study results reporting, as well as the mandate from Taiwanese CDE, the proposed study will include approximately 20 patients meeting the study inclusion/exclusion criteria. We assumed lower ORRs than reported in the regulatory submission, taking into consideration of the real-world setting. As mentioned earlier, in clinical trials KN164 and KN158, the combined ORR was 33.5% (95% CI 26.2%-41.6%). Stratified analyses by CRC vs non-CRC reported an objective response rate of 27.9% (95% CI 17.1%-40.8%) and 37.2% (95% CI 27.5%-47.8%), respectively.

Table 4 summarized the precisions yielded by varying sample size and ORR assumptions. The 20-patient sample size produces a two-sided 95% CI with a precision (half-width) equal to 19%, assuming a 20% ORR.

Table 4. Precision of ORR estimates with varying sample size and ORR assumption

| Sample size | ORR (%) | Precision (half-width of CI, %) | Lower limit (%) | Upper limit (%) |
|---|---|---|---|---|
| 20 | 10 | 15 | 0 | 25 |
| 20 | 20 | 19 | 1 | 39 |
| 20 | 30 | 21 | 9 | 51 |
| 20 | 40 | 22 | 18 | 62 |
| 20 | 50 | 23 | 27 | 73 |

# 10 ADMINISTRATIVE AND REGULATORY DETAILS

## 10.1 Confidentiality

### 10.1.1 Confidentiality of Data

By signing this protocol, the investigator affirms to the Sponsor that information furnished to the investigator by the Sponsor will be maintained in confidence, and such information will be divulged to the Institutional Review Board, Ethics Review Committee or similar or expert

committee; affiliated institution and employees, only under an appropriate understanding of confidentiality with such board or committee, affiliated institution and employees. Data generated by this study will be considered confidential by the investigator, except to the extent that it is included in a publication as provided in the Publications section of this protocol.

### 10.1.2 Confidentiality of Subject Records

By signing this protocol, the investigator agrees that the Sponsor (or Sponsor representative) or Institutional Review Board/Independent Ethics Committee (IRB/IEC), may consult and/or copy study documents to verify worksheet/case report form data. By signing the consent form, the subject agrees to this process. If study documents will be photocopied during the process of verifying worksheet/case report form information, the subject will be identified by unique code only; full names/initials will be masked prior to transmission to the Sponsor.

By signing this protocol, the investigator agrees to treat all subject data used and disclosed in connection with this study in accordance with all applicable privacy laws, rules and regulations.

### 10.1.3 Confidentiality of Investigator Information

By signing this protocol, the investigator recognizes that certain personal identifying information with respect to the investigator, and all subinvestigators and study site personnel, may be used and disclosed for study management purposes, as part of a regulatory submissions, and as required by law. This information may include:

- name, address, telephone number and e-mail address;
- hospital or clinic address and telephone number;
- curriculum vitae or other summary of qualifications and credentials; and
- other professional documentation.

Consistent with the purposes described above, this information may be transmitted to the Sponsor, and subsidiaries, affiliates and agents of the Sponsor, in your country and other countries, including countries that do not have laws protecting such information. Additionally, the investigator's name and business contact information may be included when reporting certain serious adverse events to regulatory agencies or to other investigators. By signing this protocol, the investigator expressly consents to these uses and disclosures.

If this is a multicenter study, in order to facilitate contact between investigators, the Sponsor may share an investigator's name and contact information with other participating investigators upon request.

## 10.2 Compliance with Financial Disclosure Requirements

Financial Disclosure requirements are outlined in the US Food and Drug Administration Regulations, Financial Disclosure by Clinical Investigators (21 CFR Part 54). It is the Sponsor's responsibility to determine, based on these regulations, whether a request for Financial Disclosure

information is required. It is the investigator's/subinvestigator's responsibility to comply with any such request.

The investigator/subinvestigator(s) agree, if requested by the Sponsor in accordance with 21 CFR Part 54, to provide his/her financial interests in and/or arrangements with the Sponsor to allow for the submission of complete and accurate certification and disclosure statements. The investigator/subinvestigator(s) further agree to provide this information on a Certification/Disclosure Form, commonly known as a financial disclosure form, provided by the Sponsor or through a secure password-protected electronic portal provided by the Sponsor. The investigator/subinvestigator(s) also consent to the transmission of this information to the Sponsor in the United States for these purposes. This may involve the transmission of information to countries that do not have laws protecting personal data.

## 10.3 Compliance with Law, Audit and Debarment

By signing this protocol, the investigator agrees to conduct the study in an efficient and diligent manner and in conformance with this protocol; generally accepted standards of Good Pharmacoepidemiology Practice; and all applicable local laws, rules and regulations relating to the conduct of the clinical study.

The investigator also agrees to allow monitoring, audits, Institutional Review Board/Independent Ethics Committee review and regulatory agency inspection of study-related documents and procedures and provide for direct access to all study-related source data and documents.

The investigator agrees not to seek reimbursement from subjects, their insurance providers or from government programs for procedures included as part of the study reimbursed to the investigator by the Sponsor.

The Investigator shall prepare and maintain complete and accurate study documentation in compliance with Good Pharmacoepidemiology Practice, standards and applicable local laws, rules and regulations; and, for each subject participating in the study, provide all data, and, upon completion or termination of the study, submit any other reports to the Sponsor as required by this protocol or as otherwise required pursuant to any agreement with the Sponsor.

Study documentation will be promptly and fully disclosed to the Sponsor by the investigator upon request and also shall be made available at the investigator’s site upon request for inspection, copying, review and audit at reasonable times by representatives of the Sponsor or any regulatory agencies. The investigator agrees to promptly take any reasonable steps that are requested by the Sponsor as a result of an audit to cure deficiencies in the study documentation and worksheets/case report forms.

The investigator must maintain copies of all documentation and records relating to the conduct of the study in accordance with their institution’s records retention schedule which is compliant with all applicable regional and national laws and regulatory requirements. If an institution does not have a records retention schedule to manage its records long-term, the investigator must maintain all documentation and records relating to the conduct of the study for 5 years after final report or first publication of study results, whichever comes later, per GPP guidelines. This documentation includes, but is not limited to, the protocol, worksheets/case report forms, advertising for subject

participation, adverse event reports, subject source data, correspondence with regulatory authorities and IRBs/ERCs, consent forms, investigator's curricula vitae, monitor visit logs, laboratory reference ranges, laboratory certification or quality control procedures and laboratory director curriculum vitae. All study documents shall be made available if required by relevant regulatory authorities. The investigator must consult with the Sponsor prior to discarding study and/or subject files.

The investigator will promptly inform the Sponsor of any regulatory agency inspection conducted for this study.

Persons debarred from conducting or working on studies by any court or regulatory agency will not be allowed to conduct or work on this Sponsor's studies. The investigator will immediately disclose in writing to the Sponsor if any person who is involved in conducting the study is debarred or if any proceeding for debarment is pending or, to the best of the investigator's knowledge, threatened.

In the event the Sponsor prematurely terminates a particular study site, the Sponsor will promptly notify that site's IRB/IEC.

According to European legislation, a Sponsor must designate an overall coordinating investigator for a multi-center study (including multinational). When more than one study site is open in an EU country, Merck, as the Sponsor, will designate, per country, a national principal coordinator (Protocol CI), responsible for coordinating the work of the principal investigators at the different sites in that Member State, according to national regulations. For a single-center study, the Protocol CI is the principal investigator. In addition, the Sponsor must designate a principal or coordinating investigator to review the study report that summarizes the study results and confirm that, to the best of his/her knowledge, the report accurately describes the conduct and results of the study in the study's final report. The Sponsor may consider one or more factors in the selection of the individual to serve as the Protocol CI and or CSR CI (e.g., availability of the CI during the anticipated review process, thorough understanding of study methods, appropriate enrollment of subject cohort, timely achievement of study milestones). The Protocol CI must be a participating study investigator.

## 10.5 Quality Management System

By signing this protocol, the Sponsor agrees to be responsible for implementing and maintaining a quality management system with written development procedures and functional area standard operating procedures (SOPs) to ensure that studies are conducted and data are generated, documented, and reported in compliance with the protocol, accepted standards of Good Pharmacoepidemiology Practice, and all applicable federal, state, and local laws, rules and regulations relating to the conduct of the study.

## 10.6 Data Management

The investigator or qualified designee is responsible for recording and verifying the accuracy of subject data. By signing this protocol, the investigator acknowledges that his/her electronic signature is the legally binding equivalent of a written signature. By entering his/her electronic signature, the investigator confirms that all recorded data have been verified as accurate.

For an outsourced study the institutional policies of the vendor should be followed for development of data management plans. However, the vendor should ensure compliance with Good Pharmacoepidemiology Practice, and all applicable federal, state, and local laws, rules and regulations relating to the conduct of the study.

# 11 Publications

Publication plans, and restrictions will be according to the study agreement with the investigators' sites. Any publication authorship will follow the International Committee of Medical Journal Editors (ICMJE) guidelines.

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**No table of figures entries found.**

# 13 Appendices

PV-GLB-01-ER04+Global+Safety+Intake+

# 14 Attachments

# 2 15 SIGNATURES

### Sponsor's Representative

| TYPED NAME | SIGNATURE | DATE |
|---|---|---|
| _____ | _____ | _____ |

### Investigator

I agree to conduct this study in accordance with the design outlined in this protocol and to abide by all provisions of this protocol (including other manuals and documents referenced from this protocol); deviations from the protocol are acceptable only with a mutually agreed upon protocol amendment. I agree to conduct the study in accordance with generally accepted standards of Good Pharmacoepidemiology Practice. I also agree to report all information or data in accordance with the protocol and, in particular, I agree to report any serious adverse experiences as defined in Section 7 – Safety Reporting and Related Procedures. I understand that information that identifies me will be used and disclosed as described in the protocol, and that such information may be transferred to countries that do not have laws protecting such information. Since the information in this protocol and the referenced Investigator's brochure is confidential, I understand that its disclosure to any third parties, other than those involved in approval, supervision, or conduct of the study is prohibited. I will ensure that the necessary precautions are taken to protect such information from loss, inadvertent disclosure, or access by third parties.