DRUP – Drug specific study manual for PEMBROLIZUMAB (Keytruda)

1. Drug specific in- and exclusion criteria

Pembrolizumab specific criteria are highlighted in light grey.

Inclusion criteria	Yes	No	n.a.
1. Patients must be ≥18 years of age.			
2. Histologically-proven locally advanced or metastatic solid tumor, multiple myeloma or non-Hodgkin lymphoma, with symptomatic disease progression or progression according to RECIST-criteria after standard anti-cancer therapy, or for whom no such treatment is available or indicated.			
a. *For patients with a primary brain tumor: histologically confirmed recurrent or de novo primary brain tumor, with unequivocal progression after prior therapy, at least 3 months after radiotherapy (either first line chemo-radiotherapy or re-irradiation), and with stable or decreasing dosage of steroids for at least 7 days prior to the baseline MRI scan.*			
3. High mutational load tumor, defined as missense mutational burden of >140 (with a pre-planned subset analysis for patients with a missense mutational burden of >290), as determined by whole exome sequencing. A complete sequencing report, confirming this tumor profile, has to be submitted for patient enrollment.			
4. ECOG performance status 0-1			
5. For patients with central nervous system (CNS) metastasis: lesions must be stable on imaging for ≥4 weeks, patients must be stable symptom-wise, and off steroids for ≥1 week prior to start of study treatment.			
a. *For patients with a primary brain tumor: (I) Patients who require anti-convulsant therapy must be taking non-enzyme inducing antiepileptic drugs (non-EIAED). EIAED are prohibited. Patients previously on EIAED must be switched to non-EIAED at least 2 weeks prior to randomization. (II) No radiotherapy within the three months prior to the diagnosis of progression. (III) No radiotherapy with a dose over 65 Gy, stereotactic radiosurgery or brachytherapy unless the recurrence is histologically proven.*			
6. Patients must have normal organ and bone marrow function measured within 10 days prior to administration of study treatment as defined below:			
a. Absolute neutrophil count (ANC) ≥ 1.5 x 10^9/L			
b. Hemoglobin > 5.6 mmol/l without EPO or transfusion dependency (within 7 days of assessment)			
c. Platelet count > 100 x 10^9/L			
d. Total bilirubin < 1.5 x ULN or direct bilirubin ≤ ULN for subjects with total bilirubin levels > 1.5 ULN			
e. AST (SGOT) and ALT (SGPT) < 2.5 x institutional ULN (or < 5 x ULN in patients with known hepatic metastases)			
f. Serum creatinine ≤ 1.5 × ULN or calculated or measured creatinine clearance (GFR can also be used in place of creatinine or CrCl) ≥ 60 mL/min for subject with creatinine levels > 1.5 X institutional ULN (Creatinine clearance should be calculated per institutional standard.)			
g. Albumin >2.5 mg/dL			

Inclusion criteria	Yes	No	n.a.
h. International Normalized Ratio (INR) or Prothrombin Time (PT) ≤1.5 X ULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants			
i. Activated Partial Thromboplastin Time (aPTT) ≤1.5 X ULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants			
7. Objectively measurable disease (by physical or radiographic examination, according to RECIST v1.1 for patients with solid tumors, or according to IMWG, Lugano, RANO or GCIG criteria, resp., for patients with multiple myeloma, non-Hodgkin lymphoma, glioblastoma or ovarian cancer in case of CA125-based evaluation).			
8. A new (obtained ≤2 months before inclusion, and without any type of anti-cancer therapy within those ≤2 months) fresh frozen tumor biopsy specimen for extensive biomarker testing is mandatory before the start of treatment with a targeted agent included in the protocol. Alternatively, fresh frozen tumor tissue acquired in the context of a standard care procedure may be used, provided that no systemic anti-cancer treatment was given between the procedure and start of study treatment within DRUP. The following exceptions are made: a) An exception is made for patients with a primary brain tumor, only if the mandatory DRUP pre-treatment biopsy for biomarker analysis cannot safely be obtained: i. The fresh frozen tumor biopsy sample may be replaced by fresh frozen tumor tissue, obtained earlier from recurrent disease, as part of standard of care surgical procedure (i.e., performed at progression) ii. If no fresh frozen tumor tissue is available for NGS, and the risk of obtaining a new tumor biopsy is considered too high, no biopsy will be required. In this case, the study coordinators must be informed in advance, and there will be no reimbursement for the biopsy procedure. b) In case WGS is performed on tumor tissue outside the context of a clinical trial before inclusion, and without any type of anti-cancer therapy between the collection of tissue and inclusion in DRUP, this can replace the DRUP pre-treatment biopsy, provided that the patient gives consent to use his/her WGS data for biomarker analysis in DRUP. c) An exception is made for patients that underwent an allogenic hematopoietic stem cell transplantation prior to study enrollment, since this will prevent a correct WGS analysis due to a mismatch between the biopsy specimen and the required blood sample.			
9. Ability to understand and the willingness to sign a written informed consent document.			
10. For orally administered drugs, the patient must be able to swallow and tolerate oral medication and must have no known malabsorption syndrome.			
11. Women of child-bearing potential and men must agree to use adequate contraception for the duration of study participation, and for four months following completion of study therapy.			

Inclusion criteria	Yes	No	n.a.
12. Female subject of childbearing potential should have a negative urine or serum pregnancy within 72 hours prior to receiving the first dose of study medication. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.			

Exclusion criteria	Yes	No	n.a.
1. Patients that are eligible for on-label treatment with pembrolizumab or for ongoing phase 2 / 3 trials with pembrolizumab are excluded from treatment with pembrolizumab within the DRUP trial.			
2. Prior treatment with an anti PD-1, anti PD-L1, or anti PD-L2 agent.			
3. Is currently participating and receiving study therapy or has participated in a study of an investigational agent and received study therapy or used an investigational device within 4 weeks of the first dose of treatment.			
4. Hypersensitivity to pembrolizumab or any of its excipients.			
5. Has a diagnosis of immunodeficiency or is receiving systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to the first dose of trial treatment. *Exception: The use of low dose corticosteroids (prednisone ≤10 mg daily or equivalent) is allowed.*			
6. Has a known history of active TB (Bacillus Tuberculosis)			
7. Has an active infection requiring systemic therapy.			
8. Has a known history of Human Immunodeficiency Virus (HIV) (HIV 1/2 antibodies).			
9. Has known active Hepatitis B (e.g., HBsAg reactive) or Hepatitis C (e.g., HCV RNA [qualitative] is detected).			
10. Has active autoimmune disease that has required systemic treatment in the past 2 years (i.e. 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, etc.) is not considered a form of systemic treatment.			
11. Has had a prior anti-cancer monoclonal antibody (mAb) within 4 weeks prior to study Day 1 or who has not recovered (i.e., ≤ Grade 1 or at baseline) from adverse events due to agents administered more than 4 weeks earlier.			
12. Has had prior chemotherapy, targeted small molecule therapy, or radiation therapy within 2 weeks prior to study Day 1 or who has not recovered (i.e., ≤ Grade 1 or at baseline) from adverse events due to a previously administered agent. - Note: Subjects with ≤ Grade 2 neuropathy are an exception to this criterion and may qualify for the study. - Note: If subject received major surgery, they must have recovered adequately from the toxicity and/or complications from the intervention prior to starting therapy.			
13. Has a known additional malignancy that is progressing or requires active treatment. Exceptions include basal cell carcinoma of the skin or squamous cell carcinoma of the skin that has undergone potentially curative therapy or in situ cervical cancer.			

Exclusion criteria	Yes	No	n.a.
14. Has received a live vaccine within 30 days of planned start of study therapy. Note: Seasonal influenza vaccines for injection are generally inactivated flu vaccines and are allowed; however intranasal influenza vaccines (e.g., Flu-Mist®) are live attenuated vaccines, and are not allowed.			
15. Patients with meningitis carcinomatosa			
16. Has a history of (non-infectious) pneumonitis that required steroids or current pneumonitis.			
17. Ongoing toxicity > grade 2, other than alopecia.			
18. Patient is receiving any other anti-cancer therapy (cytotoxic, biologic, radiation, or hormonal other than for replacement). Required wash out period prior to starting study treatment is at least two weeks. An exception is made for patients suffering from CRPC, who are allowed to continue androgen deprivation therapy.			
19. Patient is pregnant or nursing, or expecting to conceive or father children within the projected duration of the trial, starting with the pre-screening or screening visit through 120 days after the last dose of trial treatment.			
20. Patients with clinically significant preexisting cardiac conditions, including uncontrolled or symptomatic angina, uncontrolled atrial or ventricular arrhythmias, or symptomatic congestive heart failure are not eligible.			
21. Patients with known left ventricular ejection fraction (LVEF) < 40% are not eligible.			
22. Patients with stroke (including TIA) or acute myocardial infarction within 3 months before the first dose of study treatment are not eligible.			
23. Patients with any other clinically significant medical condition which, in the opinion of the treating physician, makes it undesirable for the patient to participate in the study or which could jeopardize compliance with study requirements including, but not limited to: ongoing or active infection, significant uncontrolled hypertension, or severe psychiatric illness/social situations.			

NB Please note that official prescription instructions, as outlined in the Summary of Product Characteristics (SPC, most recent version can be downloaded from https://www.ema.europa.eu/en/medicines) and / or any other official documents concerning this drug, will always take precedence over this manual. This manual is provided for practical support; treatment can be performed according to local standard-of-care protocols.

2. Treatment schedule

	Screening (≤28 days before start)	After screening, before start	1 treatment cycle = 21 days D1 of every treatment cycle	At the end of every 3rd treatment cycle	After end of treatment (≤30 days after stop)
Concurrent meds	x		x		
Adverse events			x		
Physical exam	x		x[1]		
Vital signs	x		x[1]		
Performance Status	x		x		
CBC w/diff, platelets	x		x		
Serum chemistry	x[2]		x[2]		
Serum pregnancy test	x[6]				
Tumor biopsy		x[5]			x[5]
Pembrolizumab (Keytruda)			x[3]		
Response evaluation	x[4]			x[4]	

1. According to local standard clinical practice, or as clinically indicated.
2. Patients should be monitored for signs and symptoms of immune-related hepatitis, renal dysfunction and endocrinopathies. Regular monitoring of the laboratory tests listed below is recommended.
3. Pembrolizumab is administered intravenously once every 3 weeks.
4. A baseline scan should be performed <28 days before start of treatment. Tumor assessments will initially be repeated every 9 weeks after treatment initiation. If the patient continues study treatment beyond 4 response evaluations (i.e., 36 weeks), response evaluation will thereafter be performed at the end of every 4th treatment cycle (i.e., every 12 weeks).
5. If screening is positive, a mandatory DRUP pre-treatment biopsy will be performed. After end of treatment a post-treatment biopsy can be obtained. The post-treatment biopsy is optional.
6. During screening, a serum test should be performed within 7 days before the first dose of pembrolizumab for all female participants of childbearing potential.

Laboratory tests:

Hematology	Chemistry	Urinalysis	Other
Hematocrit	Albumin	Blood	Serum β-human chorionic gonadotropin†
Hemoglobin	Alkaline phosphatase	Glucose	(β-hCG)†
Platelet count	Alanine aminotransferase (ALT)	Protein	PT (INR)
WBC (total and differential)	Aspartate aminotransferase (AST)	Specific gravity	aPTT
Red Blood Cell Count	Lactate dehydrogenase (LDH)	Microscopic exam *(If abnormal)*	Total thriiodothyronine (T3)
Absolute Neutrophil Count	Carbon Dioxide ‡	results are noted	Free tyroxine (T4)
Absolute Lymphocyte Count	*(CO_2 or biocarbonate)*	Urine pregnancy test †	Thyroid stimulating hormone (TSH)
	Uric Acid		

Hematology	Chemistry	Urinalysis	Other
	Calcium		
	Chloride		
	Glucose		
	Phosphorus		
	Potassium		
	Sodium		
	Magnesium		
	Total Bilirubin		
	Direct Bilirubin *(If total bilirubin is elevated above the upper limit of normal)*		
	Total protein		
	Blood Urea Nitrogen		

† Perform on women of childbearing potential only. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test will be required.

‡ If considered standard of care in your region.

3. Administration and starting dosage

Drug	Dose/Potency	Dose Frequency	Route of Administration	Regimen/Treatment Period	Use
Pembrolizumab	200 mg	Q3W	IV infusion	Day 1 of each 3 week cycle	Experimental

Trial treatment should be administered on Day 1 of each cycle after all procedures/assessments have been completed. Trial treatment may be administered up to 3 days before or after the scheduled Day 1 of each cycle due to administrative reasons. All trial treatments will be administered on an outpatient basis.

Pembrolizumab 200 mg will be administered as a 30 minute IV infusion every 3 weeks. Sites should make every effort to target infusion timing to be as close to 30 minutes as possible. However, given the variability of infusion pumps from site to site, a window of -5 minutes and +10 minutes is permitted (i.e., infusion time is 30 minutes: -5 min/+10 min).

From a microbiological point of view, the reconstituted or diluted solution should be used immediately. The reconstituted or diluted solution must not be frozen. If not used immediately, chemical and physical in-use stability of pembrolizumab has been demonstrated for 96 hours at 2°C to 8°C. This 24-hour hold from reconstitution may include up to 6 hours at room temperature (at or below 25°C). If refrigerated, the vials and/or intravenous bags must be allowed to come to room temperature prior to use.

Patients should be treated with pembrolizumab until disease progression or unacceptable toxicity. Atypical responses (i.e., an initial transient increase in tumor size or small new lesions within the first few months followed by tumor shrinkage) have been observed. It is recommended to continue treatment for clinically stable patients with initial evidence of disease progression until disease progression is confirmed.

Subjects may withdraw consent at any time for any reason or be dropped from the trial at the discretion of the investigator should any untoward effect occur. In addition, a subject may be withdrawn by the investigator or the Sponsor if enrollment into the trial is inappropriate, the trial plan is violated, or for administrative and/or other safety reasons. A subject must be discontinued from the trial for any of the following reasons:

- The subject or legal representative (such as a parent or legal guardian) withdraws consent.
- Confirmed radiographic disease progression. Note: A subject may be granted an exception to continue on treatment with confirmed radiographic progression if clinically stable or clinically improved.
- Unacceptable adverse experiences.
- Intercurrent illness that prevents further administration of treatment
- Investigator's decision to withdraw the subject
- The subject has a confirmed positive serum pregnancy test
- Noncompliance with trial treatment or procedure requirements
- The subject is lost to follow-up

4. How supplied

Pembrolizumab will be supplied as 25 mg/mL concentrate for solution for infusion.

Drugs can be (re-)ordered by filling in the required fields in the eCRF. Drugs will be shipped to the site's pharmacy. Per shipment, sufficient drug can be ordered to treat the patient until the next response evaluation (and 1 cycle beyond for the first order, to cover the period in between response evaluation and re-supply).

The investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution and usage of investigational product in accordance with the protocol and any applicable laws and regulations.

- Packaging and Labeling Information: clinical supplies will be affixed with a clinical label in accordance with regulatory requirements.
- Storage and Handling Requirements: clinical supplies must be stored in a secure, limited-access location under the storage conditions specified on the label. Receipt and dispensing of trial medication must be recorded by an authorized person at the trial site. Clinical supplies may not be used for any purpose other than that stated in the protocol.

5. Dose modifications for toxicity

Adverse events (both non-serious and serious) associated with pembrolizumab exposure may represent an immunologic etiology. These adverse events may occur shortly after the first dose or several months after the last dose of treatment. Pembrolizumab must be withheld for drug-related toxicities and severe or life-threatening AEs as per 3 below. See Section 5.6 for supportive care guidelines, including use of corticosteroids.

Recommended treatment modifications for pembrolizumab:

Immune-related adverse reactions	**Severity**	**Treatment modification**
Pneumonitits	Grade 2	Withhold until adverse reactions recover to Grades 0-1*
	Grade 3 or 4, or recurrent Grade 2	Permanently discontinue
Colitis	Grades 2 or 3	Withhold until adverse reactions recover to Grades 0-1*
	Grade 4 or recurrent Grade 3	Permanently discontinue
Nephritis	Grade 2 with creatinine > 1.5 to ≤ 3 times upper limit of normal (ULN)	Withhold until adverse reactions recover to Grades 0-1*
	Grade ≥ 3 with creatinine > 3 times ULN	Permanently discontinue
Endocrinopathies	Grade 2 adrenal insufficiency and hypophysitis	Withhold treatment until controlled by hormone replacement
	Grades 3 or 4 adrenal insufficiency or symptomatic hypophysitis Type 1 diabetes associated with Grade ≥ 3 hyperglycaemia (glucose > 250 mg/dL or > 13.9 mmol/L) or associated with ketoacidosis Hyperthyroidism Grade ≥ 3	Withhold until adverse reactions recover to Grades 0-1* For patients with Grade 3 or Grade 4 endocrinopathies that improved to Grade 2 or lower and are controlled with hormone replacement, if indicated, continuation of pembrolizumab may be considered after corticosteroid taper, if needed. Otherwise treatment should be discontinued.
	Hypothyroidism	Hypothyroidism may be managed with replacement

		therapy without treatment interruption.
Hepatitis	Grade 2 with aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 3 to 5 times ULN or total bilirubin > 1.5 to 3 times ULN	Withhold until adverse reactions recover to Grades 0-1*
	Grade ≥ 3 with AST or ALT > 5 times ULN or total bilirubin > 3 times ULN	Permanently discontinue
	In case of liver metastasis with baseline Grade 2 elevation of AST or ALT, hepatitis with AST or ALT increases ≥ 50% and lasts ≥ 1 week	Permanently discontinue
Skin reactions	Grade 3 or suspected Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN)	Withhold until adverse reactions recover to Grades 0-1*
	Grade 4 or confirmed SJS or TEN	Permanently discontinue
Other immune-related adverse reactions	Based on severity and type of reaction (Grade 2 or Grade 3)	Withhold until adverse reactions recover to Grades 0-1*
	Grades 3 or 4 myocarditis Grades 3 or 4 encephalitis Grades 3 or 4 Guillain-Barré Syndrome	Permanently discontinue
	Grade 4 or recurrent Grade 3	Permanently discontinue

Note: toxicity grades are in accordance with National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.03 (NCI-CTCAE v.4.03).

* If treatment-related toxicity does not resolve to Grades 0-1 within 12 weeks after last dose of KEYTRUDA, or if corticosteroid dosing cannot be reduced to ≤ 10 mg prednisone or equivalent per day within 12 weeks, KEYTRUDA should be permanently discontinued.

Pembrolizumab should be permanently discontinued for Grade 4 or recurrent Grade 3 immune-related adverse reactions, unless otherwise specified in Table above.

Dosing interruptions are permitted in the case of medical / surgical events or logistical reasons not related to study therapy (e.g., elective surgery, unrelated medical events, patient vacation, and/or holidays). Subjects should be placed back on study therapy within 3 weeks of the scheduled interruption, unless otherwise discussed with the Sponsor. The reason for interruption should be documented in the patient's study record.

6. Treatment interruption

Discontinuation of treatment may be considered for participants who have attained a confirmed complete response (CR) and have been treated for at least 8 cycles (at least 24 weeks), receiving at least 2 doses of pembrolizumab beyond the date when the initial CR was declared. These participants may be eligible for second course treatment, as described in section 7.Patients who have ongoing clinical benefit (SD, PR or CR) and who have completed 35 treatments (approximately 2 years) of pembrolizumab should stop treatment. These patients may be eligible for second course treatment, as described in section 7.

After treatment discontinuation, response evaluations need to be performed:

1. First year after treatment interruption: every 3 months
2. Second and third year after treatment interruption: every 4 months
3. Fourth and fifth year after treatment interruption: every 6 months
4. Thereafter: once a year

Treatment can only be interrupted after consultation with the central DRUP study team.

	Before interruption of pembrolizumab	During interruption	At clinical/radiological progression
Consult DRUP study team	X		X
Response evaluation		X	X
Re-screening			X
Biopsy			X (optional)

7. Second course treatment

All participants who stop study treatment with SD 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 and the participant meets the following conditions:

Either

- Stopped initial treatment with study treatment after attaining an investigator-determined confirmed CR based on RECIST 1.1, and
    - Was treated with at least 8 cycles of study treatment before discontinuing treatment, and
    - Received at least 2 treatments with pembrolizumab beyond the date when the initial CR was declared

OR

- Had SD, PR, or CR and stopped study treatment after completion of 35 administrations (approximately 2 years) of study treatment for reasons other than disease progression or intolerability.

AND

- Experienced an investigator-determined radiographic disease progression by RECIST 1.1 after stopping initial treatment, and
    - No new anticancer treatment was administered after the last dose of trial treatment, and
    - The subject meets all of the safety parameters listerd in the inclusion criteria and none of the safety parameters listed in the exclusion criteria, and the trial is ongoing.

An objective response or progression of disease that occurs during the Second Course Phase for a subject will not be counted as an event for the primary analysis of either endpoint in this trial.

Furthermore, the following criteria apply for the second course phase treatment:

1. After the Second Course Phase, subjects should be followed for up to two years, with no option for retreatment with pembrolizumab on study.
2. Subjects who are eligible per the requirements in Section 7 for treatment with pembrolizumab during the Second Course Phase (retreatment) may have up to two safety follow- up visits, one after the Initial Treatment Phase and the second after the Second Course Phase.
3. Subjects who are eligible to receive retreatment with pembrolizumab according to the criteria in Section 7 will move from the Follow-Up Phase to the Second Course Phase when they experience disease progression. Details are provided in the Trial Flow Chart (Section 7) for retreatment with pembrolizumab.
4. Concomitant medications: The investigator or qualified designee will record medication, if any, taken by the subject during the trial through the Safety Follow-up Visit. In addition, new medications started during the Second Course Phase through to the Second Course Phase Safety Follow-up Visit, respectively, should be recorded. All medications related to reportable SAEs and ECIs should be recorded.

5. Prohibited Concomitant Medications

a. Subjects are prohibited from receiving the following therapies during the Second Course Phases of this trial
b. Antineoplastic systemic chemotherapy or biological therapy not specified in this protocol.
c. Immunotherapy not specified in this protocol.
d. Chemotherapy not specified in this protocol.
e. Investigational agents other than pembrolizumab.
f. Radiation therapy; radiotherapy for symptom management is allowed.
g. Note: Radiation therapy to a symptomatic solitary lesion of to the brain may be allowed at the Investigator’s discretion

h. Live vaccines within 30 days prior to the first dose of trial treatment and while participating in the trial. 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.

i. Prolonged therapy with systemic glucocorticoids (>7 days) for any purpose other than to modulate symptoms from an immune-related Adverse Event (as listed in section 5.6.1) or for use as a pre-medication for chemotherapeutic agents specified in the protocol. Brief, limited use of systemic corticosteroids (≤7 days) are permitted where such use is considered standard of care (e.g. as pre-medication for contrast allergy or for COPD exacerbation). Replacement doses of steroids (for example, prednisone 10 mg daily) are permitted while on study. The use of physiologic doses of corticosteroids may be approved after consultation with the Sponsor.

j. Subjects who, in the assessment by the investigator, require the use of any of the aforementioned treatments for clinical management should be removed from the trial. Subjects may receive other medications that the investigator deems to be medically necessary.

k. The Exclusion Criteria describes other medications which are prohibited in this trial.

6. There are no prohibited therapies during the Post-Treatment Follow-up Phase.

Second Course (Retreatment) Tumor Imaging:

A scan must be performed within 30 days prior to starting/restarting treatment with pembrolizumab. Local reading (investigator assessment with site radiology reading) will be used to determine eligibility. The first on study imaging assessment should be performed at 12 weeks (84 days ± 7 days) after the start/restart of treatment. Subsequent tumor imaging should be performed every 12 weeks or more frequently if clinically indicated.

Per RECIST 1.1, partial or complete response should be confirmed by a repeat tumor imaging assessment not less than 4 weeks from the date the response was first documented. The tumor imaging for confirmation of response may be performed at the earliest 4 weeks after the first indication of response, or at the next scheduled scan, whichever is clinically indicated. Subjects will then return to regular scheduled imaging every 12 weeks, starting with the next scheduled imaging time point. Subjects who obtain a confirmation scan do not need to undergo scheduled tumor imaging if it is < 4 weeks later and may wait until the next scheduled imaging time point.

Imaging should continue to be performed until disease progression, the start of new anti-cancer treatment, withdrawal of consent, death, or notification by the Sponsor, whichever occurs first. Disease progression may be confirmed at least 4 weeks after the first tumor imaging indicating progressive disease in clinically stable subjects.

In subjects who discontinue trial treatment, tumor imaging should be performed at the time of treatment discontinuation (± 4 week window). If a previous scan was obtained within 4 weeks

prior to the date of discontinuation, then a scan at treatment discontinuation is not mandatory. In subjects who discontinue trial treatment due to documented disease progression, this is the final required tumor imaging.

In subjects who discontinue trial treatment without documented disease progression, every effort should be made to continue monitoring their disease status by radiologic imaging every 12 weeks (84 days ± 7 days) until (1) the start of new anti-cancer treatment, (2) disease progression, (3) death, or (4) the end of the study, whichever occurs first.

8. Warnings and precautions

Subjects should receive appropriate supportive care measures as deemed necessary by the treating investigator. Suggested supportive care measures for the management of adverse events with potential immunologic etiology are outlined below. Where appropriate, these guidelines include the use of oral or intravenous treatment with corticosteroids as well as additional anti-inflammatory agents if symptoms do not improve with administration of corticosteroids. Note that several courses of steroid tapering may be necessary as symptoms may worsen when the steroid dose is decreased. For each disorder, attempts should be made to rule out other causes such as metastatic disease or bacterial or viral infection, which might require additional supportive care. The treatment guidelines are intended to be applied when the investigator determines the events to be related to pembrolizumab.

Note: if after the evaluation the event is determined not to be related, the investigator does not need to follow the treatment guidance (as outlined below).

It may be necessary to perform conditional procedures such as bronchoscopy, endoscopy, or skin photography as part of evaluation of the event.

Pembrolizumab may be restarted within 12 weeks after last dose of pembrolizumab if the adverse reaction recovers to Grade ≤ 1 and corticosteroid dose has been reduced to ≤ 10 mg prednisone or equivalent per day.

Pembrolizumab must be permanently discontinued for any Grade 3 immune-related adverse reaction that recurs and for any Grade 4 immune-related adverse reaction toxicity, except for endocrinopathies that are controlled with replacement hormones

<u>Immune-related pneumonitis</u>

Pneumonitis has been reported in patients receiving pembrolizumab. Patients should be monitored for signs and symptoms of pneumonitis. Suspected pneumonitis should be confirmed with radiographic imaging and other causes excluded. Corticosteroids should be administered for Grade ≥ 2 events (initial dose of 1-2 mg/kg/day prednisone or equivalent followed by a taper); pembrolizumab should be withheld for Grade 2 pneumonitis, and permanently discontinued for Grade 3, Grade 4 or recurrent Grade 2 pneumonitis

<u>Immune-related colitis</u>

Colitis has been reported in patients receiving pembrolizumab. Patients should be monitored for signs and symptoms of colitis, and other causes excluded. Corticosteroids should be administered for Grade ≥ 2 events (initial dose of 1-2 mg/kg/day prednisone or equivalent followed by a taper); pembrolizumab should be withheld for Grade 2 or Grade 3 colitis, and permanently discontinued for Grade 4 or recurrent Grade 3 colitis. The potential risk of gastrointestinal perforation should be taken into consideration.

Immune-related hepatitis

Hepatitis has been reported in patients receiving pembrolizumab. Patients should be monitored for changes in liver function (at the start of treatment, periodically during treatment and as indicated based on clinical evaluation) and symptoms of hepatitis, and other causes excluded. Corticosteroids should be administered (initial dose of 0.5-1 mg/kg/day (for Grade 2 events) and 1-2 mg/kg/day (for Grade ≥ 3 events) prednisone or equivalent followed by a taper) and, based on severity of liver enzyme elevations, pembrolizumab should be withheld or discontinued.

Immune-related nephritis

Nephritis has been reported in patients receiving pembrolizumab. Patients should be monitored for changes in renal function, and other causes of renal dysfunction excluded. Corticosteroids should be administered for Grade ≥ 2 events (initial dose of 1-2 mg/kg/day prednisone or equivalent followed by a taper) and, based on severity of creatinine elevations, pembrolizumab should be withheld for Grade 2, and permanently discontinued for Grade 3 or Grade 4 nephritis.

Immune-related endocrinopathies

Severe endocrinopathies, including adrenal insufficiency, hypophysitis, type 1 diabetes mellitus, diabetic ketoacidosis, hypothyroidism, and hyperthyroidism have been observed with pembrolizumab treatment.

Long-term hormone replacement therapy may be necessary in cases of immune-related endocrinopathies.

Adrenal insufficiency (primary and secondary) has been reported in patients receiving pembrolizumab. Hypophysitis has also been reported in patients receiving pembrolizumab. Patients should be monitored for signs and symptoms of adrenal insufficiency and hypophysitis (including hypopituitarism) and other causes excluded. Corticosteroids to treat adrenal insufficiency and other hormone replacement should be administered as clinically indicated. Pembrolizumab should be withheld for Grade 2 adrenal insufficiency or hypophysitis until the event is controlled with hormone replacement. Pembrolizumab should be withheld or discontinued for Grades 3 or 4 adrenal insufficiency or symptomatic hypophysitis. Continuation of pembrolizumab may be considered, after corticosteroid taper, if needed. Pituitary function and hormone levels should be monitored to ensure appropriate hormone replacement.

Type 1 diabetes mellitus, including diabetic ketoacidosis, has been reported in patients receiving pembrolizumab. Patients should be monitored for hyperglycaemia or other signs and symptoms of diabetes. Insulin should be administered for type 1 diabetes, and pembrolizumab should be withheld

in cases of type 1 diabetes associated with Grade ≥ 3 hyperglycaemia or ketoacidosis until metabolic control is achieved.

Thyroid disorders, including hypothyroidism, hyperthyroidism and thyroiditis, have been reported in patients receiving pembrolizumab and can occur at any time during treatment. Hypothyroidism is more frequently reported in patients with HNSCC with prior radiation therapy. Patients should be monitored for changes in thyroid function (at the start of treatment, periodically during treatment and as indicated based on clinical evaluation) and clinical signs and symptoms of thyroid disorders. Hypothyroidism may be managed with replacement therapy without treatment interruption and without corticosteroids. Hyperthyroidism may be managed symptomatically. Pembrolizumab should be withheld for Grade ≥ 3 until recovery to Grade ≤ 1 hyperthyroidism. Thyroid function and hormone levels should be monitored to ensure appropriate hormone replacement.

For patients with Grade 3 or Grade 4 endocrinopathies that improved to Grade 2 or lower and are controlled with hormone replacement, if indicated, continuation of pembrolizumab may be considered after corticosteroid taper, if needed. Otherwise treatment should be discontinued.

Immune-related skin adverse reactions

Immune-related severe skin reactions have been reported in patients receiving pembrolizumab. Patients should be monitored for suspected severe skin reactions and other causes should be excluded. Based on the severity of the adverse reaction, pembrolizumab should be withheld for Grade 3 skin reactions until recovery to Grade ≤ 1 or permanently discontinued for Grade 4 skin reactions, and corticosteroids should be administered.

Cases of Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) have been reported in patients receiving pembrolizumab. For suspected SJS or TEN, pembrolizumab should be withheld and the patient should be referred to a specialised unit for assessment and treatment. If SJS or TEN is confirmed, pembrolizumab should be permanently discontinued.

Caution should be used when considering the use of pembrolizumab in a patient who has previously experienced a severe or life-threatening skin adverse reaction on prior treatment with other immune-stimulatory anti-cancer agents.

Other immune-related adverse reactions

The following additional clinically significant, immune-related adverse reactions have been reported in clinical studies or in post-marketing experience: uveitis, arthritis, myositis, myocarditis, pancreatitis, Guillain-Barré syndrome, myasthenic syndrome, haemolytic anaemia, sarcoidosis, encephalitis, myelitis, vasculitis, cholangitis sclerosing, gastritis and cystitis noninfective.

Based on the severity and type of the adverse reaction, pembrolizumab should be withheld for Grade 2 or Grade 3 events and corticosteroids administered.

Pembrolizumab may be restarted within 12 weeks after last dose of pembrolizumab if the adverse reaction recovers to Grade ≤ 1 and corticosteroid dose has been reduced to ≤ 10 mg prednisone or equivalent per day.

Pembrolizumab must be permanently discontinued for any Grade 3 immune-related adverse reaction that recurs and for any Grade 4 immune-related adverse reaction.

For Grades 3 or 4 myocarditis, encephalitis or Guillain-Barré syndrome, pembrolizumab should be permanently discontinued.

Severe infusion-related reactions, including hypersensitivity and anaphylaxis, have been reported in patients receiving pembrolizumab. For Grades 3 or 4 infusion reactions, infusion should be stopped and pembrolizumab permanently discontinued. Patients with Grades 1 or 2 infusion reaction may continue to receive pembrolizumab with close monitoring; premedication with antipyretic and antihistamine may be considered.

Interaction with other medicinal products and other forms of interaction

No formal pharmacokinetic drug interaction studies have been conducted with pembrolizumab. Since pembrolizumab is cleared from the circulation through catabolism, no metabolic drug-drug interactions are expected.

The use of systemic corticosteroids or immunosuppressants before starting pembrolizumab should be avoided because of their potential interference with the pharmacodynamic activity and efficacy of pembrolizumab. However, systemic corticosteroids or other immunosuppressants can be used after starting pembrolizumab to treat immune-related adverse reactions. Corticosteroids can also be used as premedication, when pembrolizumab is used in combination with chemotherapy, as antiemetic prophylaxis and/or to alleviate chemotherapy-related adverse reactions.

Fertility, pregnancy and lactation

Women of childbearing potential

Women of childbearing potential should use effective contraception during treatment with pembrolizumab and for at least 4 months after the last dose of pembrolizumab. Pregnancy There are no data on the use of pembrolizumab in pregnant women. Animal reproduction studies have not been conducted with pembrolizumab; however, in murine models of pregnancy blockade of PD-L1 12 signalling has been shown to disrupt tolerance to the foetus and to result in an increased foetal loss. These results indicate a potential risk, based on its mechanism of action, that administration of pembrolizumab during pregnancy could cause foetal harm, including increased rates of abortion or stillbirth. Human immunoglobulins G4 (IgG4) are known to cross the placental barrier; therefore, being an IgG4, pembrolizumab has the potential to be transmitted from the mother to the developing foetus. Pembrolizumab should not be used during pregnancy unless the clinical condition of the woman requires treatment with pembrolizumab.

Breast-feeding

It is unknown whether pembrolizumab is secreted in human milk. Since it is known that antibodies can be secreted in human milk, a risk to the newborns/infants cannot be excluded. A decision should be made whether to discontinue breast-feeding or to discontinue pembrolizumab, taking into

account the benefit of breast-feeding for the child and the benefit of pembrolizumab therapy for the woman.

Fertility

No clinical data are available on the possible effects of pembrolizumab on fertility. There were no notable effects in the male and female reproductive organs in monkeys based on 1-month and 6-month repeat-dose toxicity studies.

Concomitant medications / vaccinations: 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 investigator should discuss any questions regarding this with the Merck Clinical team. The final decision on any supportive therapy or vaccination rests with the investigator and/or the subject's primary physician.

- Acceptable concomitant medications: All treatments that the investigator considers necessary for a subject's welfare may be administered at the discretion of the investigator in keeping with the community standards of medical care.
- Prohibited concomitant medications: subjects are prohibited from receiving the following therapies during the Screening and Treatment Phase (including retreatment for post-complete response relapse) of this trial:
    - Antineoplastic 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.
    - Live vaccines within 30 days prior to the first dose of trial treatment and while participating in the trial. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster, yellow fever, rabies, BCG, and typhoid vaccine.
    - Systemic glucocorticoids for any purpose other than to modulate symptoms from an event of clinical interest of suspected immunologic etiology. The use of physiologic doses of corticosteroids may be approved after consultation with the Sponsor.
- Subjects who, in the assessment by the investigator, require the use of any of the aforementioned treatments for clinical management should be removed from the trial. Subjects may receive other medications that the investigator deems to be medically necessary. The Exclusion Criteria describes other medications which are prohibited in this trial. There are no prohibited therapies during the Post-Treatment Follow-up Phase.

9. Events of Clinical Interest

Selected non-serious and serious adverse events are also known as Events of Clinical Interest (ECI) and must be reported within 24 hours to the Sponsor and within 2 working days to Merck Global Safety. (Attn: Worldwide Product Safety; FAX 215-661-6229).

For the time period beginning when the consent form is signed until treatment allocation, any ECI, or follow up to an ECI, that occurs to any subject must be reported within 24 hours to the Sponsor and within 2 working days to Merck Global Safety if it causes the subject to be excluded from the trial, or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

For the time period beginning at treatment allocation through 90 days following cessation of treatment, or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier, any ECI, or follow up to an ECI, whether or not related to Merck product, must be reported within 24 hours to the Sponsor and within 24 hours to Merck Global Safety.

Events of clinical interest for this trial include:

1. An overdose of pembrolizumab (defined as any dose of 1,000 mg or greater (≥5 times the indicated dose)), that is not associated with clinical symptoms or abnormal laboratory results.

2. An elevated AST or ALT lab value that is greater than or equal to 3X the upper limit of normal and an elevated total bilirubin lab value that is greater than or equal to 2X the upper limit of normal and, at the same time, an alkaline phosphatase lab value that is less than 2X the upper limit of normal, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.*

*Note: These criteria are based upon available regulatory guidance documents. The purpose of the criteria is to specify a threshold of abnormal hepatic tests that may require an additional evaluation for an underlying etiology.