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TITLE: Immunomodulation of pembrolizumab plus docetaxel for the treatment of r/m SCCHN after platinum failure

NCT02718820
EudraCT NUMBER (Studies in Europe only): 2015-002325-18

PRINCIPAL INVESTIGATOR:

[redacted]

Monitor:

[redacted]

TRIAL SUMMARY

Abbreviated Title	PemDoc
Trial Phase	I/II
Clinical Indication	Recurrent and metastatic head and neck cancer after platinum failure
Trial Type	Interventional prospective, single-arm, phase II
Route of administration	Intravenous
Trial Blinding	Unblinded open label
Treatment Groups	1
Number of trial subjects	22
Estimated enrollment period	24 months
Objectives	**Primary objective** • To evaluate the Overall Response Rate (CR/PR) rate in patients treated with pembrolizumab plus docetaxel for recurrent or metastatic (R/M) HNSCC after platinum-based first-line therapy • To evaluate the safety of pembrolizumab in combination with docetaxel in subjects diagnosed with R/M HNSCC **Secondary objectives** • To describe Best Overall Response categories (CR, PR, SD, PD) in patients treated with pembrolizumab in combination with docetaxel in subjects diagnosed with R/M HNSCC after platinum-based first-line therapy • To describe individual duration of response over time • To evaluate changes in health-related quality-of-life assessments from baseline in subjects with R/M HNSCC using the EORTC QLQ C-30 and EORTC QLQ-H&N35. • To assess median Overall Survival (OS) and Progression Free Survival (PFS) in this patient population **Exploratory objectives** • To assess PD-L1 as a predictive marker for response to pembrolizumab – Examination of PD-L1 expression in blood and tumor tissue, including infiltrating immune cells, obtained during biopsy of primary tumor (and recurrent tumor if available)

	• To investigate molecular genetic pattern in tumor tissue obtained during biopsy of the primary tumor (and recurrent tumor if available) via next generation sequencing (NGS) using the Qiagen Comprehensive Cancer GeneRead DNAseq Targeted Panel in order to predict response to docetaxel/pembrolizumab.
Selection criteria	**Inclusion criteria:** • The patient has provided written informed consent prior to any study-related procedure. • The patient is at least 18 years of age • Histologically proven locally advanced unresectable, recurrent and/or metastatic squamous cell carcinoma of the oropharynx, hypopharynx, larynx or oral cavity not amenable for salvage surgery • P16 mutation status has to be determined • Documented progressive disease based on investigator assessment according to RECIST 1.1, following receipt of a cisplatin and/or carboplatin based regimen independent of whether patient progressed during or after platinum based therapy. Platinum therapy might have been administered either as part of induction chemotherapy (12 months), chemoradiation (6 months) or as first line systemic palliative chemotherapy (6 months). • Measurable disease according to RECIST 1.1. • The patient has a life expectancy of at least 3 months. • Has a performance status of 0 or 1 on the ECOG Performance Scale • Female subject of childbearing potential should have a negative urine or serum pregnancy prior to study registration and re-tested 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. • Female subjects of childbearing potential should be willing to use 2 methods of birth control or be surgically sterile, or abstain from heterosexual activity for the course of the study through 120 days after the last dose of study medication. Subjects of childbearing potential are those who have not been surgically sterilized or have not been free from menses for > 1 year.

	• Male subjects should agree to use an adequate method of contraception starting with the first dose of study therapy through 120 days after the last dose of study therapy. • Demonstrate adequate organ function as defined in Table 1, all screening labs should be performed within 10 days of treatment initiation. **Exclusion criteria:** • Prior taxane therapy is not allowed except as part of induction therapy (at least 6 months before study entry) • Nasopharyngeal carcinomas or salivary glands cancers are not eligible • 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. • 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. • Has a known history of active TB (Bacillus Tuberculosis) • Hypersensitivity to pembrolizumab or any of its excipients. • 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. • 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: If subject received major surgery, they must have recovered adequately from the toxicity and/or complications from the intervention prior to starting therapy. • 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.

	• Has known active central nervous system (CNS) metastases and/or carcinomatous meningitis. Subjects with previously treated brain metastases may participate provided they are stable (without evidence of progression by imaging for at least four weeks prior to the first dose of trial treatment and any neurologic symptoms have returned to baseline), have no evidence of new or enlarging brain metastases, and are not using steroids for at least 7 days prior to trial treatment. This exception does not include carcinomatous meningitis which is excluded regardless of clinical stability. • 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 (e.g. thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment. • Has known history of, or any evidence of active, non-infectious pneumonitis. • Has an active infection requiring systemic therapy. • Has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the trial, interfere with the subject's participation for the full duration of the trial, or is not in the best interest of the subject to participate, in the opinion of the treating investigator. • Has known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial. • Is pregnant or breastfeeding, 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. • Has received prior therapy with an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent. • Has a known history of Human Immunodeficiency Virus (HIV) (HIV 1/2 antibodies). • Has known active Hepatitis B (e.g., HBsAg reactive) or Hepatitis C (e.g., HCV RNA [qualitative] is detected). • Has received a live vaccine within 30 days of planned start of study therapy.
Duration of Participation	Each subject will participate in the trial until death, drop out, or loss-to-follow-up from the time the subject signs the Informed Consent Form

	(ICF) through the final contact. Treatment on trial will continue until disease progression is confirmed.

GLOSSARY OF ABBREVIATIONS

AE adverse event

ALT alanine aminotransferase

aPTT activated partial thromboplastin time

ASCT autologous stem cell transplantation

AST aspartate aminotransferase

BRAF v-Raf murine sarcoma viral oncogene homolog B1

beta-HCG beta human chorionic gonadotrophin

CHF congestive heart failure

CNS central nervous system

CT computed tomography

CTLA4 cytotoxic T-lymphocyte-associated protein 4

CR complete remission

CRF case report form

CrCl creatinine clearance

CTCAE Common Terminology Criteria for Adverse Events

ECG electrocardiogram

ECOG Eastern Cooperative Oncology Group

EDTA ethylenediaminetetraacetic acid

ELISA Enzyme-linked Immunoabsorbent Assay

EORTC European Organization for Research and Treatment of Cancer

FAS Full analysis set

GCP Good Clinical Practice

HBV sAg hepatitis B virus surface antigen

HCV RNA hepatitis C virus ribonucleic acid

HIV human immunodeficiency virus

HNSCC head and neck squamous cell carcinoma

HPV human papilloma virus

ICH International Conference on Harmonisation

IEC Independent Ethics Committee

INR International Normalized Ratio

IPCG International Primary Central Nervous System Lymphoma Collaborative Group

IRB Institutional Review Board

ITIM immunoreceptor tyrosine inhibitory motif

ITSM immunoreceptor tyrosine-based switch motif

mAbs monoclonal antibodies

MRI magnetic resonance imaging

MSD Merck Sharp & Dohme

MTX methotrexate

NaCl natrium chloride

NCI National Cancer Institute

NGS Next generation sequencing

NSCLC and non-small cell lung carcinoma

NYHA New York Heart Association

PD progressive disease

PD-1 programmed death 1

PD-L1 programmed death ligand 1

PR partial remission

PT prothrombin time

RCC renal cell carcinoma

SAE Serious adverse event

SD stable disease

SmPC Summary of product characteristics ULN upper limit of normal

SOP standard operating procedure

sGOT serum glutamic oxaloacetic transaminase

sGPT serum glutamic-pyruvic transaminase

TAM tumor-associated macrophages

TILs tumor-infiltrating lymphocytes

WBC white blood cells

WHO World Health Organization

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1. INTRODUCTION AND STUDY RATIONALE

1.1. Introduction

Squamous cell carcinoma of the head and neck (HNSCC), which accounts for 90% of head and neck cancers, is the tenth most common cancer worldwide with over 650000 new cases per year[1-3]. The major risk factors for HNSCC development comprise alcohol and tobacco consumption[4]. During the last decades human papilloma virus infection (HPV) has been identified to contribute to the development of oropharyngeal HNSCC in a subgroup of patients[5]. These population show a more favourable prognosis compared to HPV negative disease[5]. A multidisciplinary approach involving radiation oncologists, medical oncologist and head and neck surgeons is necessary for the optimal management of these patients. Standard treatment options include surgery, (chemo)radiation and chemotherapy. Despite improvements of treatment regimens the recurrence rate of stage III/IV disease after curative therapy is about 30-40% in the first 2 years of follow up and a constant rate of 2-3% per year of second primaries is observed[6,7]. In locoregionally unresectable recurrent or metastatic (R/M) disease palliative poly-chemotherapy is the mainstay of therapy. Although novel targeted therapies such as cetuximab in the past decade have been implemented in these regimens, the prognosis of patients with locoregionally advanced R/M disease remains poor. The median survival time of these patients is 6-8 months [8]. Based on the results of the EXTREME study a combination regimen containing a platinum drug, 5-FU and weekly cetuximab has become standard of care in this setting[9]. For patients, who progressed after platinum based therapy, treatment options are scarce. Besides platinum drugs, MTX or taxanes such as paclitaxel or docetaxel were shown to be of particular use at this stage of disease[10-14]. Thus, it is obvious that novel treatment strategies are desperately needed.

1.2. Programmed death receptor-1 (PD-1, CD279) background

The importance of intact immune surveillance in controlling outgrowth of neoplastic transformation has been known for decades. Accumulating evidence shows a correlation between tumor-infiltrating lymphocytes (TILs) in cancer tissue and favorable prognosis in various malignancies. In particular, the presence of CD8+ T-cells and the ratio of CD8+ effector T-cells / FoxP3+ regulatory T-cells seems to correlate with improved prognosis and long-term survival in many solid tumors.

The PD-1 receptor-ligand interaction is a major pathway hijacked by tumors to suppress immune control. The normal function of PD-1, expressed on the cell surface of activated T-cells under healthy conditions, is to down-modulate unwanted or excessive immune responses, including autoimmune reactions. PD-1 (encoded by the gene Pdcd1) is an Ig superfamily member related to CD28 and CTLA-4 which has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (PD-L1 and/or PD-L2). The structure of murine PD-1 has been resolved. PD-1 and family members are type I transmembrane glycoproteins containing an Ig Variable-type (V-type) domain responsible for ligand binding and a cytoplasmic tail which is responsible for the binding of signaling molecules. The cytoplasmic tail of PD-1 contains 2 tyrosine-based signaling motifs, an immunoreceptor tyrosine-based inhibition motif (ITIM) and an immunoreceptor

tyrosine-based switch motif (ITSM). Following T-cell stimulation, PD-1 recruits the tyrosine phosphatases SHP-1 and SHP-2 to the ITSM motif within its cytoplasmic tail, leading to the dephosphorylation of effector molecules such as CD3ζ, PKCθ and ZAP70 which are involved in the CD3 T-cell signaling cascade. The mechanism by which PD-1 down modulates T-cell responses is similar to, but distinct from that of CTLA-4 as both molecules regulate an overlapping set of signaling proteins. PD-1 was shown to be expressed on activated lymphocytes including peripheral CD4+ and CD8+ T-cells, B-cells, T regs and Natural Killer cells. Expression has also been shown during thymic development on CD4-CD8- (double negative) T-cells as well as subsets of macrophages and dendritic cells. The ligands for PD-1 (PD-L1 and PD-L2) are constitutively expressed or can be induced in a variety of cell types, including non-hematopoietic tissues as well as in various tumors. Both ligands are type I transmembrane receptors containing both IgV- and IgC-like domains in the extracellular region and contain short cytoplasmic regions with no known signaling motifs. Binding of either PD-1 ligand to PD-1 inhibits T-cell activation triggered through the T-cell receptor. PD-L1 is expressed at low levels on various non-hematopoietic tissues, most notably on vascular endothelium, whereas PD-L2 protein is only detectably expressed on antigen-presenting cells found in lymphoid tissue or chronic inflammatory environments. PD-L2 is thought to control immune T-cell activation in lymphoid organs, whereas PD-L1 serves to dampen unwarranted T-cell function in peripheral tissues. Although healthy organs express little (if any) PD-L1, a variety of cancers were demonstrated to express abundant levels of this T-cell inhibitor. PD-1 has been suggested to regulate tumor-specific T-cell expansion in subjects with melanoma. This suggests that the PD-1/PD-L1 pathway plays a critical role in tumor immune evasion and should be considered as an attractive target for therapeutic intervention.

1.3. Study rationale

During the last years there has been increasing preclinical and clinical evidence that immune-checkpoint inhibitors might play a role in HNSCC: It has been shown that PD-L1 expression is very common in tonsillar crypt epithelium in the presence of HPV infection[15]. In the R/M setting it has been demonstrated that PD-L1 is highly expressed [15]. Apart from that PD-L1 expression seems to correlate with the HPV status [16]. Trials evaluating pembrolizumab in head and neck cancer have demonstrated clinical activity in patients with recurrent and/or metastatic disease. KEYNOTE 012 is a phase Ib study of pembrolizumab in patients with HPV-negative and HPV-positive head and neck cancer. This trial enrolled an initial 60 patient cohort with R/M HNSCC for treatment with single agent pembrolizumab. Preliminary results of this cohort were reported at the Annual Meeting of the American Society of Clinical Oncology (ASCO) in 2014, showing an overall response rate (confirmed and unconfirmed) of 19.6% (10 partial responses [PRs], 1 complete response [CR] out of 56 patients evaluable for response) at the time of the meeting. An additional 16/56 patients (28.6%) experienced stable disease (SD), with 51% of patients experiencing some numerical decrease in tumor burden from baseline. Seventeen total patients with CR, PR, or SD remain on therapy at the time of the reporting for > 6 months. There were no new or unexpected toxicity signals in this patient cohort, with infrequent grade 3-4 drug-related (DR) adverse events (AEs).

Although these data are promising, conventional chemotherapy is still the mainstay of treatment of R/M HNSCC patients. Besides platinum drugs, taxanes such as paclitaxel or docetaxel were shown to be of particular use in this setting[10-13]. Apart from their cytotoxic effects there is profound evidence that these chemotherapeutics interact with the immune system as well: A very recent preclinical study demonstrated that chemoradiation and taxane containing induction chemotherapy in stage III/IV SCCHN patients results in PD-1 up-regulation[17]. On the other hand it is generally known that single agent taxane treatment exerts immunomodulatory effects: In preclinical models it has been shown that docetaxel therapy enhances immune response in combination with cancer vaccines[18]. Clinically it has been demonstrated very recently in prostate cancer patients that there is a major effect on regulatory T cells after docetaxel exposure providing further scientific rationale for the combination of taxanes either with cancer vaccines or immune checkpoint inhibitors[19].

In summary the combination of docetaxel and pembrolizumab after platinum failure seems to be an interesting approach as a salvage therapy in R/M HNSCC patients, might boost the immune response and exert superior anti-tumor activity.

1.4. Pembrolizumab Background

Refer to the Investigator's Brochure (IB)/approved labeling for detailed background information on MK-3475.

1.4.1. Pharmaceutical Background of Pembrolizumab

Pembrolizumab is a potent and highly selective humanized monoclonal antibody (mAb) of the IgG4/kappa isotype designed to directly block the interaction between PD-1 and its ligands, PD-L1 and PD-L2. Keytruda™ (pembrolizumab) has recently been approved in the United Stated for the treatment of patients with unresectable or metastatic melanoma and disease progression following ipilumumab and, if BRAF V600 mutation positive, a BRAF inhibitor.

1.4.2. Preclinical and Clinical Trial Data

Refer to the Investigator's Brochure for Preclinical and Clinical data.

1.4.3. Rationale for Dose Selection/Regimen/Modification

An open-label Phase I trial (Protocol 001) is being conducted to evaluate the safety and clinical activity of single agent MK-3475. The dose escalation portion of this trial evaluated three dose levels, 1 mg/kg, 3 mg/kg, and 10 mg/kg, administered every 2 weeks (Q2W) in subjects with advanced solid tumors. All three dose levels were well tolerated and no dose-limiting toxicities were observed. This first in human study of MK-3475 showed evidence of target engagement and objective evidence of tumor size reduction at all dose levels (1 mg/kg, 3 mg/kg and 10 mg/kg

Q2W). No MTD has been identified to date. 10.0 mg/kg Q2W, the highest dose tested in PN001, will be the dose and schedule utilized in Cohorts A, B, C and D of this protocol to test for initial tumor activity. Recent data from other clinical studies within the MK-3475 program has shown that a lower dose of MK-3475 and a less frequent schedule may be sufficient for target engagement and clinical activity.

PK data analysis of MK-3475 administered Q2W and Q3W showed slow systemic clearance, limited volume of distribution, and a long half-life (refer to IB). Pharmacodynamic data (IL-2 release assay) suggested that peripheral target engagement is durable (>21 days). This early PK and pharmacodynamic data provides scientific rationale for testing a Q2W and Q3W dosing schedule.

A population pharmacokinetic analysis has been performed using serum concentration time data from 476 patients. Within the resulting population PK model, clearance and volume parameters of MK-3475 were found to be dependent on body weight. The relationship between clearance and body weight, with an allometric exponent of 0.59, is within the range observed for other antibodies and would support both body weight normalized dosing or a fixed dose across all body weights. MK-3475 has been found to have a wide therapeutic range based on the melanoma indication. The differences in exposure for a 200 mg fixed dose regimen relative to a 2 mg/kg Q3W body weight based regimen are anticipated to remain well within the established exposure margins of 0.5 – 5.0 for MK-3475 in the melanoma indication. The exposure margins are based on the notion of similar efficacy and safety in melanoma at 10 mg/kg Q3W vs. the proposed dose regimen of 2 mg/kg Q3W (i.e. 5-fold higher dose and exposure). The population PK evaluation revealed that there was no significant impact of tumor burden on exposure. In addition, exposure was similar between the NSCLC and melanoma indications. Therefore, there are no anticipated changes in exposure between different indication settings.

The rationale for further exploration of 2 mg/kg and comparable doses of pembrolizumab in solid tumors is based on: 1) similar efficacy and safety of pembrolizumab when dosed at either 2 mg/kg or 10 mg/kg Q3W in melanoma patients, 2) the flat exposure-response relationships of pembrolizumab for both efficacy and safety in the dose ranges of 2 mg/kg Q3W to 10 mg/kg Q3W, 3) the lack of effect of tumor burden or indication on distribution behavior of pembrolizumab (as assessed by the population PK model) and 4) the assumption that the dynamics of pembrolizumab target engagement will not vary meaningfully with tumor type.

The choice of the 200 mg Q3W as an appropriate dose for the switch to fixed dosing is based on simulations performed using the population PK model of pembrolizumab showing that the fixed dose of 200 mg every 3 weeks will provide exposures that 1) are optimally consistent with those obtained with the 2 mg/kg dose every 3 weeks, 2) will maintain individual patient exposures in the exposure range established in melanoma as associated with maximal efficacy response and 3) will maintain individual patients exposure in the exposure range established in melanoma that are well tolerated and safe.

A fixed dose regimen will simplify the dosing regimen to be more convenient for physicians and to reduce potential for dosing errors. A fixed dosing scheme will also reduce complexity in the logistical chain at treatment facilities and reduce wastage.

1.4.4. Docetaxel dose selection

Docetaxel is a semisynthetic taxane derived from a precursor extracted from the needles of the European yew, Taxus baccata. It has a mechanism of action which is similar to (or may be identical to) paclitaxel. Docetaxel enhances microtubule assembly and inhibits the depolymerization of tubulin. As with paclitaxel, this can lead to bundles of microtubules in the cell, which by blocking cells in the M phase of the cell cycle results in the inability of the cells to divide. This contrasts with the action of other spindle poisons in clinical use such as colchicine or vinca-alkaloids which inhibit tubulin assembly in microtubules. Comparing paclitaxel and docetaxel using the "tubulin *in vitro* assay", the concentration required to provide 50% inhibition of microtubule disassembly (or IC50) for Docetaxel is 0.2 µm and for paclitaxel is 0.4 µm.

Docetaxel will be administered at 75mg/m2 every three weeks, which is a well established and approved regimen in various malignancies including HNSCC[20]. This regimen has been tested in numerous clinical trials both as a monotherapy and in combination with other cytotoxic drugs and monoclonal antibodies, which did not result in unacceptable toxicity. Additionally, docetaxel 75mg/m2 every three weeks is part of the currently used induction chemotherapy regimens in HNSCC, where it is combined with cisplatin and 5-FU[21]. Thus the choice of Docetaxel 75mg/m2 Q3W seems to be an appropriate dose in combination with pembrolizumab 200mg Q3W.

For further details please refer to the attached product information.

2. STUDY OBJECTIVES

2.1 Primary Objectives

- To evaluate the Overall Response Rate (CR/PR) rate in patients treated with pembrolizumab plus docetaxel for R/M HNSCC after platinum-based first-line therapy. If there are 7 or more successes (CR or PR) out of the 22 patients the study is considered to be a success and the null hypothesis (Clinical Benefit Rate is ≤15 %) will be rejected in favour of the alternative hypothesis of a higher Overall Response Rate.

- To evaluate the safety of pembrolizumab in combination with docetaxel in subjects diagnosed with R/M HNSCC

2.2 Secondary Objectives

- To describe Best Overall Response categories (CR, PR, SD, PD) in patients treated with pembrolizumab in combination with docetaxel in subjects diagnosed with R/M HNSCC after platinum-based first-line therapy.
- To describe individual duration of response over time
- To evaluate changes in health-related quality-of-life assessments from baseline in subjects with R/M HNSCC using the EORTC QLQ C-30 and EORTC QLQ-H&N35.
- To assess median Overall Survival (OS) and Progression Free Survival (PFS) in this patient population

2.3 Exploratory Objectives

- To assess PD-L1 as a predictive marker for response to pembrolizumab
  - Examination of PD-L1 expression in blood and tumor tissue, including infiltrating immune cells, obtained during biopsy of primary tumor (and recurrent tumor if available)
- To investigate molecular genetic pattern in tumor tissue obtained during biopsy of the primary tumor (and recurrent tumor if available) via next generation sequencing (NGS) using the Qiagen Comprehensive Cancer GeneRead DNAseq Targeted Panel in order to predict response to docetaxel/pembrolizumab.

3. TOTAL NUMBER OF PATIENTS

22 evaluable patients.

4. SELECTION CRITERIA

4.1. Inclusion Criteria

- The patient has provided written informed consent prior to any study-related procedure.

- The patient is at least 18 years of age
- Histologically proven locally advanced unresectable, recurrent and/or metastatic squamous cell carcinoma of the oropharynx, hypopharynx, larynx or oral cavity not amenable for salvage surgery
- P16 mutation status has to be determined
- Documented progressive disease based on investigator assessment according to RECIST 1.1, following receipt of a cisplatin and/or carboplatin based regimen independent of whether patient progressed during or after platinum based therapy. Platinum therapy might have been administered either as part of induction chemotherapy (12 months), chemoradiation (6 months) or as first line systemic palliative chemotherapy (6 months).
- Measurable disease according to RECIST 1.1.
- The patient has a life expectancy of at least 3 months.
- Has a performance status of 0 or 1 on the ECOG Performance Scale
- Female subject of childbearing potential should have a negative urine or serum pregnancy prior to study registration and re-tested 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.
- Female subjects of childbearing potential should be willing to use 2 methods of birth control or be surgically sterile, or abstain from heterosexual activity for the course of the study through 120 days after the last dose of study medication. Subjects of childbearing potential are those who have not been surgically sterilized or have not been free from menses for > 1 year.
- Male subjects should agree to use an adequate method of contraception starting with the first dose of study therapy through 120 days after the last dose of study therapy.
- Demonstrate adequate organ function as defined in Table 1, all screening labs should be performed within 10 days of treatment initiation.

System	Laboratory Value
Hematological	
Absolute neutrophil count (ANC) Platelets	≥1,500 /mcL ≥100,000 / mcL

Hemoglobin	≥9 g/dL or ≥5.6 mmol/L
Renal Creatinine	≤2xULN
Hepatic Total bilirubin	≤1.5xULN **OR** Direct bilirubin ≤ULN for subjects with total bilirubin levels >1.5xULN
AST (SGOT) and ALT (SGPT)	≤2.5xULN **OR** ≤5xULN for subjects with liver metastases
Coagulation International Normalized Ratio (INR) or Prothrombin Time (PT) Activated Partial Thromboplastin Time (aPTT)	≤1.5xULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants ≤1.5xULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants

4.2. Exclusion Criteria

The subject must be excluded from participating in the trial if the subject:

- Prior taxane therapy is not allowed except as part of induction therapy (at least 6 months before study entry)
- Nasopharyngeal carcinomas or salivary glands cancers are not eligible
- 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.
- 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.
- Has a known history of active TB (Bacillus Tuberculosis)
- Hypersensitivity to pembrolizumab or any of its excipients.
- 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.

- 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: If subject received major surgery, they must have recovered adequately from the toxicity and/or complications from the intervention prior to starting therapy.

- 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.

- Has known active central nervous system (CNS) metastases and/or carcinomatous meningitis. Subjects with previously treated brain metastases may participate provided they are stable (without evidence of progression by imaging for at least four weeks prior to the first dose of trial treatment and any neurologic symptoms have returned to baseline), have no evidence of new or enlarging brain metastases, and are not using steroids for at least 7 days prior to trial treatment. This exception does not include carcinomatous meningitis which is excluded regardless of clinical stability.

- 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 (e.g. thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment.

- Has known history of, or any evidence of active, non-infectious pneumonitis.

- Has an active infection requiring systemic therapy.

- Has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the trial, interfere with the subject's participation for the full duration of the trial, or is not in the best interest of the subject to participate, in the opinion of the treating investigator.

- Has known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial.

- Is pregnant or breastfeeding, 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.

- Has received prior therapy with an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent.

- Has a known history of Human Immunodeficiency Virus (HIV) (HIV 1/2 antibodies).

- Has known active Hepatitis B (e.g., HBsAg reactive) or Hepatitis C (e.g., HCV RNA [qualitative] is detected).

- 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.

5. ENDPOINT ASSESSMENT

5.1. Safety

Safety analyses will be performed in all treated subjects. Descriptive analysis of safety will be presented using National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 (See Appendix II). All on-study AEs, treatment-related AEs, SAEs, and treatment-related SAEs will be tabulated using worst grade per NCI CTCAE v 4.0 criteria by system organ class and preferred term. On-study laboratory parameters including haematology, chemistry, liver function, and renal function will be summarized using worst grade NCI CTCAE v 4.0 criteria.

5.2. Response assessment

Response will be measured according to the RECIST 1.1 criteria using a CT scan or MRI every 12 weeks. However, RECIST 1.1 will be adapted to account for the unique tumor response characteristics seen with treatment of pembrolizumab. Immunotherapeutic agents such as pembrolizumab may produce antitumor effects by potentiating endogenous cancer-specific immune responses. The response patterns seen with such an approach may extend beyond the typical time course of responses seen with cytotoxic agents, and can manifest a clinical response after an initial increase in tumor burden or even the appearance of new lesions. Standard RECIST may not provide an accurate response assessment of immunotherapeutic agents such as pembrolizumab. Therefore, RECIST 1.1 will be used with the following adaptations:

If radiologic imaging shows initial PD, tumor assessment should be repeated ≥4 weeks later in order to confirm PD with the option of continuing treatment per below while awaiting radiologic confirmation of progression. If repeat imaging shows a reduction in the tumor burden compared to the initial scan demonstrating PD, treatment may be continued / resumed. If repeat imaging

confirms progressive disease, subjects will be discontinued from study therapy. In subjects who have initial evidence of radiological PD, it is at the discretion of the treating physician whether to continue a subject on study treatment until repeat imaging is obtained. This clinical judgment decision should be based on the subject's overall clinical condition, including performance status, clinical symptoms, and laboratory data. Subjects may receive pembrolizumab treatment while waiting for confirmation of PD if they are clinically stable as defined by the following criteria:

• Absence of signs and symptoms indicating disease progression
• No decline in ECOG performance status
• Absence of rapid progression of disease
• Absence of progressive tumor at critical anatomical sites (e.g., cord compression) requiring urgent alternative medical intervention

When feasible, subjects should not be discontinued until progression is confirmed. This allowance to continue treatment despite initial radiologic progression takes into account the observation that some subjects can have a transient tumor flare in the first few months after the start of immunotherapy, but with subsequent disease response. Subjects that are deemed clinically unstable are not required to have repeat imaging for confirmation of progressive disease.

5.3. Response duration

Response duration (CR, PR, or SD) will be measured from the time measurement criteria for CR or PR are first met. Patients without evidence of progression will be censored at the last follow-up visit date. If a patient received a subsequent anti-tumoral therapy without prior documentation of disease progression, the patient will be censored at the date of starting new anti-tumoral therapy.

5.4. EEORTC QLQ-C30 and eEORTC QLQ-H&N35 questionnaire

The EORTC-QLQC30 is the most widely used cancer specific HRQoL instrument, which contains 30 items and measures five functional dimensions (physical, role, emotional, cognitive and social), three symptom items (fatigue, nausea/vomiting, and pain), six single items (dyspnea, sleep disturbance, appetite loss, constipation, diarrhea, and financial impact), and a global health and quality of life scale [22].

The EORTC QLQ-H&N35 is in use worldwide as one of the standard instruments for measuring quality of life in head and neck cancer subjects and consists of 7 multi-item scales measuring pain in the mouth, problems with swallowing, senses, speech, social eating and social contact, and 11 single-item scales assessing problems with teeth, mouth opening, dry mouth, sticky saliva, coughing, feeling ill, use of analgesics, use of nutritional supplements, use of feeding tube, weight gain, and weight loss[23]. The EORTC QLQ-C30 and EORTC QLQ-H&N35 are psychometrically

and clinically validated instruments appropriate for assessing quality of life in subjects with head and neck cancer. These instruments were used in the EXTREME registration trial comparing platin-5-fluorouracil alone versus combined with cetuximab as first-line treatment in R/M HNSCC which led to the FDA approval of cetuximab monotherapy in subjects with R/M HNSCC refractory to cisplatin.

5.5. Exploratory analyses

Tumor tissue assessment

Formalin-fixed and paraffin embedded tumor tissue from the initial diagnosis or recurrent tumors will be collected where available. We will perform immunohistochemistry for PD-L1 and PD1 as described previously [24]. Expression of PD-L1 (positive versus negative using a 1% cut-off) and the frequency of PD1+ tumor-infiltrating lymphocytes (low versus high as determined semiquantitatively) will be described (frequencies, percentages). Additionally circulating PD-L1 expression will be measured in patients' blood samples.

Next generation sequencing

On the molecular level HNSCC shows a wide spectrum of genetic aberrations: Mutations such as in the oncogenic EGFR-MEK, PI3K-AKT, NOTCH, PTEN, JAK-STAT or cMET pathways or in tumor suppressor genes have been frequently described for SCHNN[25,26]. However, just a few serve as oncogenic drivers as recently described for PI3K mutations in SCHNN[25,27]. While it is well known that PD-L1 is regulated by interferon gamma and cytokine release, the association between oncogenic pathways and PD-L1 expression is still under investigation. A recent publication demonstrated the link between PD-L1 expression and oncogenic pathways in melanoma cell lines[28]. For HNSCC this question has not been addressed so far. Thus, next generation sequencing (NGS) of tumor tissues will be performed and a panel of 160 genes that are most commonly mutated in cancers will be investigated (Qiagen Comprehensive Cancer GeneRead DNAseq Targeted Panel). Tissue will be collected before treatment with pembrolizumab/docetaxel, stored and at the end of the study bioinformatics will be done.

6. INVESTIGATIONAL PLAN

6.1. Screening and Enrolment

The Investigator is responsible for keeping a record of all subjects who sign an Informed Consent Form for entry into the study. All subjects will be screened for eligibility. Study assessments must take place within 28 days prior to initiation of therapy unless otherwise specified. Screening pregnancy tests for women of child-bearing potential must occur ≤24 hours from initiation of therapy. All eligible patients will be informed about alternative treatment options outside the trial although no standard is defined.

6.2. Treatment

All patients will receive pembrolizumab intravenously 200mg every 3 weeks in combination with docetaxel 75mg/m2 every three weeks for 6 cycles followed by pembrolizumab maintenance 200mg every 3 weeks until tumor progression, unacceptable toxicity or withdrawal of consent.

6.3. Monitoring and Inspection by authorities

Study initiation visit, monitoring visits, remote monitoring and close-out visit will be performed at specified time points by sponsor personnel. The investigator also agrees to allow audits, IRB/ERC review and regulatory authority inspection of trial-related documents and procedures and provide for direct access to all trial-related source data and documents.

6.4. Follow-up

During the treatment period all patients will attend their regular treatment visits every three weeks before the next application of pembrolizumab plus docetaxel. Treatment visits include clinical examination and blood work-up. Furthermore, all patients will be assessed for response by CT or MRI scans: the first one (baseline) within 4 weeks before start of therapy, then every 12 weeks or if clinically indicated.

Patients who have discontinued study drug for any reason (e.g. clinical progression, withdrawal of consent) will perform an End of Treatment Visit after stop of therapy. The patient will then enter the Post-Treatment Follow-up period, which lasts either until death, loss to follow-up, or end of trial, whatever comes first. Post-Treatment Follow-Up Visits should be performed every 3 months.

6.5. Withdrawal of consent

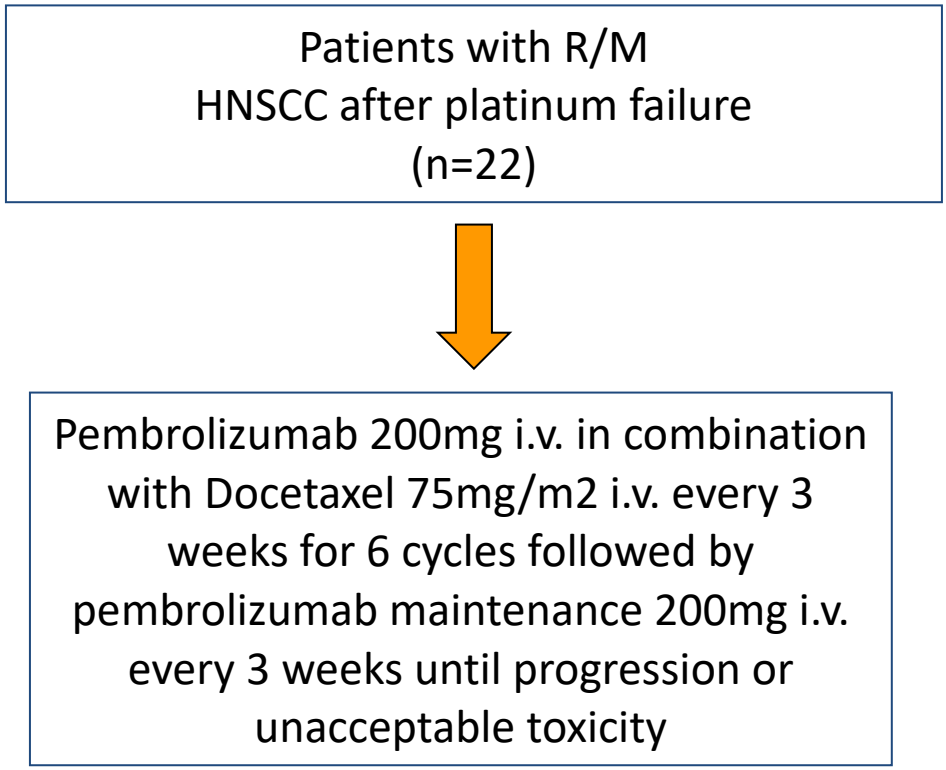
Subjects who request to discontinue study treatment will remain in the study and must continue to be followed for protocol specified follow-up procedures. The only exception to this is when a subject specifically withdraws consent for any further contact with the PI physician or persons previously authorized by subject to provide this information. Subjects should notify the investigator of the decision to withdraw consent from future follow-up in writing, whenever possible. The withdrawal of consent should be explained in detail in the medical records by the investigator, as to whether the withdrawal is from further treatment with study drug only or also from study procedures and/or post treatment study follow-up, and entered on the appropriate CRF page. In the event that vital status (whether the subject is alive or dead) is being measured, publicly available information should be used to determine vital status only as appropriately directed in accordance with local law.

6.6. Lost to follow-up

All reasonable efforts must be made to locate subjects to determine and report their ongoing status. This includes follow-up with persons authorized by the subject as noted above. Lost to follow-up is defined by the inability to reach the subject after a minimum of three documented phone calls, faxes, or emails as well as lack of response by subject to one registered mail letter. All attempts should be documented in the subject's medical records. If it is determined that the subject has died, the site will use permissible local methods to obtain the date and cause of death. If investigator's use of third-party representative to assist in the follow-up portion of the study has been included in the subject's informed consent, then the investigator may use a Sponsor-retained third-party representative to assist site staff with obtaining subject's contact information or other public vital status data necessary to complete the follow-up portion of the study. The site staff and representative will consult publicly available sources, such as public health registries and databases, in order to obtain updated contact information. If after all attempts, the subject remains lost to follow-up, then the last known alive date as determined by the investigator should be reported and documented in the subject's medical records.

6.7. Study design schematic

Figure 1: Study design



The treatment to be used in this trial is outlined below in Table 1

Table 1: Trial Treatment

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
Docetaxel	75mg/m2	Q3W	IV infusion	Day 1 of each 3 week cycle	Standard of care

Trial treatment should begin as close as possible to the date on which treatment is allocated/assigned.

6.8. Pembrolizumab Dose Modification Guidelines for Drug Related Adverse Event

Adverse events (both non-serious and serious) associated with docetaxel/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 Table 2 below.

Table 2: Pembrolizumab dose Modification Guidelines for Drug-Related Adverse Events

General instructions:

1. Corticosteroid taper should be initiated upon AE improving to Grade 1 or less and continue to taper over at least 4 weeks.
2. For situations where pembrolizumab has been withheld, pembrolizumab can be resumed after AE has been reduced to Grade 1 or 0 and corticosteroid has been tapered. Pembrolizumab should be permanently discontinued if AE does not resolve within 12 weeks of last dose or corticosteroids cannot be reduced to ≤10 mg prednisone or equivalent per day within 12 weeks.
3. For severe and life-threatening irAEs, IV corticosteroid should be initiated first followed by oral steroid. Other immunosuppressive treatment should be initiated if irAEs cannot be controlled by corticosteroids.

Immune-related AEs	**Toxicity grade or conditions (CTCAEv4.0)**	**Action taken to pembrolizumab**	**irAE management with corticosteroid and/or other therapies**	**Monitor and follow-up**
Pneumonitis	Grade 2	Withhold	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	• Monitor participants for signs and symptoms of pneumonitis

	Grade 3 or 4, or recurrent Grade 2	Permanently discontinue		• Evaluate participants with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment • Add prophylactic antibiotics for opportunistic infections
Diarrhea / Colitis	Grade 2 or 3	Withhold	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	• Monitor participants for signs and symptoms of enterocolitis (ie, diarrhea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (ie, peritoneal signs and ileus). • Participants with ≥ Grade 2 diarrhea suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis. • Participants with diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion.
	Grade 4	Permanently discontinue		
AST / ALT elevation or Increased bilirubin	Grade 2	Withhold	• Administer corticosteroids (initial dose of 0.5- 1 mg/kg prednisone or equivalent) followed by taper	• Monitor with liver function tests (consider weekly or more frequently until liver enzyme value returned to baseline or is stable
	Grade 3 or 4	Permanently discontinue	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	
Type 1 diabetes mellitus (T1DM) or Hyperglycemia	Newly onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of β-cell failure	Withhold	• Initiate insulin replacement therapy for participants with T1DM • Administer anti-hyperglycemic in participants with hyperglycemia	• Monitor participants for hyperglycemia or other signs and symptoms of diabetes.
Hypophysitis	Grade 2	Withhold	• Administer corticosteroids and initiate hormonal replacements as clinically indicated.	• Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency)
	Grade 3 or 4	Withhold or permanently discontinue[1]		
Hyperthyroidism	Grade 2	Continue	• Treat with non-selective beta-blockers (eg, propranolol) or thionamides as appropriate	• Monitor for signs and symptoms of thyroid disorders.
	Grade 3 or 4	Withhold or permanently discontinue[1]		
Hypothyroidism	Grade 2-4	Continue	• Initiate thyroid replacement hormones (eg, levothyroxine or liothyroinine) per standard of care	• Monitor for signs and symptoms of thyroid disorders.
Nephritis and Renal dysfunction	Grade 2	Withhold	• Administer corticosteroids (prednisone 1-2 mg/kg or equivalent) followed by taper.	• Monitor changes of renal function
	Grade 3 or 4	Permanently discontinue		
Myocarditis	Grade 1 or 2	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes

	Grade 3 or 4	Permanently discontinue		
All other immune-related AEs	Intolerable/ persistent Grade 2	Withhold	• Based on type and severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3	Withhold or discontinue based on the type of event. Events that require discontinuation include and not limited to: Gullain-Barre Syndrome, encephalitis		
	Grade 4 or recurrent Grade 3	Permanently discontinue		
1. Withhold or permanently discontinue pembrolizumab is at the discretion of the investigator or treating physician. **NOTE:** For participants with Grade 3 or 4 immune-related endocrinopathy where withhold of pembrolizumab is required, pembrolizumab may be resumed when AE resolves to ≤ Grade 2 and is controlled with hormonal replacement therapy or achieved metabolic control (in case of T1DM).				

6.9. Docetaxel Dose Modification Guidelines for Drug Related Adverse Events

If necessary, treatment can be delayed for toxicity for a maximum of 2 weeks. In case of treatment delay both drugs have to be delayed during combination therapy within cycle 1-4. Thereafter, docetaxel can be discontinued because of intolerable toxicity and pembrolizumab maintenance therapy can be initiated.

Every effort will be made to administer the full dose regimen to maximize dose-intensity.
If possible, toxicities should be managed symptomatically. If toxicity occurs, the appropriate treatment will be used to ameliorate signs and symptoms including anti-emetics for nausea and vomiting, anti-diarrheals for diarrhea, and antipyretics and/or antihistamines for drug fever.

Table 3: Dose levels for docetaxel dose reduction

Dose Level	DOCETAXEL Q3 WEEKS
0	75 mg/m2
-1	60 mg/m2
-2	45 mg/m2

Hematologic Toxicity:

- **Neutropenia and/or its complications:**

Adverse event	Action to be taken
- Grade 4 neutropenia* for 7 days or more - Grade 3-4 neutropenia* with oral fever >38.5°C - Infection with grade 3-4 neutropenia*	If the patient develops one of these adverse events, the next infusion should be given with a one-level dose reduction.

- **Thrombocytopenia:**

In case of grade ≥ 3 platelet-toxicity, delay maximum 2 weeks until platelets recover to ≥ 100 x 109/l, then treat with a one-level dose reduction.

- **Allergy (anaphylactic and hypersensitivity reactions) due to Docetaxel:**

Hypersensitivity reactions that occur despite pre-medication are very likely to occur within a few minutes of start of the first or of the second infusion of docetaxel. Therefore, during the 1st and the 2nd infusion, careful evaluation of general sense of well-being and blood pressure and heart rate monitoring will be performed for at least the first 10 minutes, so that immediate intervention is possible in response to symptoms of an untoward reaction.
Facilities and equipment for resuscitation must be immediately available: antihistamine, corticosteroids, aminophylline, epinephrine.
If a reaction occurs, the specific treatment that is medically indicated for a given symptom (e.g. epinephrine in case of anaphylactic shock, aminophylline in case of bronchospasm, etc.) will be instituted.

- **Nausea/Vomiting:**

A prophylactic anti-emetic treatment should be given to the patients from the first cycle. Anti-emetic prophylaxis with 5-HT3 Antagonists (i.e. ondansetron) should be given to all patients.
If despite even more aggressive antiemetic medication (i.e.aprepitant), grade ≥ 3 nausea/vomiting still occur, reduce the dose of study drug by one dose level. If despite dose reduction, nausea/vomiting still occur at grade ≥ 3, the patient will go off study.

- **Liver toxicity:**

In case of increase of ASAT and/or ALAT to >3-5 x ULN or bilirubin to >1.5-3 ULN, delay study drug treatment for up to 2 weeks until ASAT and/or ALAT return to ≤ 3 x ULN and bilirubin to 1.5≤ ULN. Then re-treat at one dose level lower. If no recovery to < 3 x ULN and bilirubin to 1.5< ULN within two weeks delay, patient will go off protocol therapy.

- **Docetaxel-induced fluid retention:**

In case of fluid retention (peripheral edema and/or effusions) during treatment with docetaxel, the signs and symptoms should be graded as mild, moderate, severe or life-threatening.

NO DOSE REDUCTION IS PLANNED.

The patient's body weight will be recorded and followed as frequently as possible to document any weight gain which could be related to edema.

- **Alopecia and nail changes:**

NO DOSE REDUCTION PLANNED.

- **Stomatitis:**

Grade ≤ 2: no dose reduction, study chemotherapy should be withheld until resolution to grade ≤ 1.
If grade 3 stomatitis occurs, study drug should be withheld until resolution to grade ≤ 1. Treatment may then be resumed, but the dose of study drug should be reduced by one dose level for all subsequent doses.
In case of grade 4 stomatitis, the patient will go off study.

- **Peripheral neuropathy:**

In case of signs or symptoms experienced by the patient, dose modification should be performed as follows:
Grade ≤ 1: no change.
Grade 2: re-treat with a one-level dose reduction (no further dose reduction is planned).
Grade ≥ 3: patient will go off protocol therapy.

6.10. Concomitant Medications and chemotherapy pre-medication

Chemotherapy pre-medication

Prior to docetaxel/pembrolizumab therapy subjects receive pre-medication with dexamethasone 8 mg on the day of therapy and 5-HT3 antagonists on day 1-3 according to the site standard. Additional glucocorticoids are prohibited (see section below).

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. All concomitant medication will be recorded on the case report form (CRF) including all prescription, over-the-counter (OTC), herbal supplements, and IV medications and fluids. If changes occur during the trial period, documentation of drug dosage, frequency, route, and date may also be included on the CRF.

All concomitant medications received within 28 days before the first dose of trial treatment and 30 days after the last dose of trial treatment should be recorded. Prohibited Concomitant Medications

Subjects are prohibited from receiving the following therapies during the Screening and Treatment Phase of this trial:

- 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 other purposes as specified above or other than to modulate symptoms from an event of clinical interest of suspected immunologic etiology.

6.11. Study flow chart

Table 4: Overview of procedures

	Baseline	During treatment			After treatment	
Investigation	Within 4 weeks prior to pembrolizumab/docetaxel start	On day of each docetaxel/ pembrolizumab administration or within 72 hours before	10 (+/-2) days after each cycle	Every 12 weeks	End of treatment (within 4 weeks after last treatment administration)	Until PD every 12 weeks
Informed consent	♦					
Clinical examination	♦	♦	♦		♦	♦
Medical history, demographics	♦					
ECOG status	♦	♦	♦		♦	
Adverse events assessment	♦	♦	♦		♦	♦
EORTC QLQ C-30 and EORTC QLQ-H&N35.	♦	♦				
ECG	♦					
Hematology	♦	♦	♦		♦	
Serum chemistry incl. thyroid function	♦	♦	♦		♦	
Urinalysis for proteinuria	♦	♦			♦	

HIV test	♦					
Hepatitis serology	♦					
Pregnancy test	♦ (within 24 hours before 1st pembrolizumab infusion)					
CT/MRI scan	♦			♦		♦
Tumor biopsy for NGS and p16 staining	♦					
Blood sample (15ml)	♦			♦		
Survival						♦

7. ETHICAL CONSIDERATIONS

7.1. Good clinical practice

This study will be conducted in accordance with Good Clinical Practice (GCP), as defined by the International Conference on Harmonisation (ICH) and in accordance with the ethical principles underlying European Union Directive 2001/20/E.

The study will be conducted in compliance with the protocol. The protocol and any amendments and the subject informed consent will receive Institutional Review Board/Independent Ethics Committee (IRB/IEC) approval/favorable opinion prior to initiation of the study.

Personnel involved in conducting this study will be qualified by education, training, and experience to perform their respective tasks.

7.2. Institutional Review Board/Independent Ethics Committee

Before study initiation, the investigator must have a written and dated approval/favorable opinion from the IRB/IEC for the protocol, consent form, subject recruitment materials (eg, advertisements), and any other written information to be provided to subjects. The investigator should provide the IRB/IEC with reports, updates and other information (eg, expedited safety reports, amendments, and administrative letters) according to regulatory requirements or institution procedures.

7.3. Informed consent

Investigators will ensure that subjects are clearly and fully informed about the purpose, potential risks, and other critical issues regarding participation in this clinical study. Only patients who have signed the informed consent formed for this trial will be enrolled.

8. STUDY MEDICATIONS

8.1. Investigational Product

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.

Clinical Supplies will be provided by Merck as summarized in Table 5.

Table 5: Product descriptions

Product Name &Potency	**Dosage Form**
Pembrolizumab 50 mg	Lyophilized Powder for Injection
Pembrolizumab 100 mg/ 4mL	Solution for Injection

8.2. HANDLING AND DISPENSING

The product storage manager should ensure that the study drug is stored in accordance with the environmental conditions (temperature, light, and humidity) as determined by MSD. If concerns regarding the quality or appearance of the study drug arise, the study drug should not be dispensed

and contact MSD immediately. Investigational product documentation must be maintained that includes all processes required to ensure drug is accurately administered. This includes documentation of drug storage, administration and, as applicable, storage temperatures, reconstitution, and use of required processes (eg, required diluents, administration sets). Infusion-related supplies (eg, IV bags, in-line filters, 0.9% NaCl solution) will not be supplied by MSD and should be purchased locally if permitted by local regulations. For non-investigational product, if marketed product is utilized, it should be stored in accordance with the package insert, summary of product characteristics (SmPC), or similar. Please refer to the current version of the Investigator Brochure and/or pharmacy reference sheets for complete storage, handling, dispensing, and infusion information for pembrolizumab.

8.3. Product description pembrolizumab

For details regarding drug storage, preparation, administration, and use time please refer to the pembrolizumab Investigator Brochure and/or pharmacy reference sheets.

8.4. Pembrolizumab administration

MK-3475 will be administered as a 30 minute IV infusion. 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). Further details on preparation and administration of pembrolizumab (MK-3475) are provided in the Pharmacy Manual.

The pharmacists will prepare the MK-3475 medication for administration. The Procedures Manual contains specific instructions for MK-3475 dose calculation, reconstitution, preparation of the infusion fluid, and administration. This document is available for reference by the pharmacist and study personnel.

8.5. Packaging and Labeling Information

Clinical supplies will be affixed with a clinical label in accordance with regulatory requirements.

8.6. Clinical Supplies Disclosure

This trial is open-label; therefore, the subject, the trial site personnel, the Sponsor and/or designee are not blinded to treatment. Drug identity (name, strength) is included in the label text; random code/disclosure envelopes or lists are not provided.

8.7. Storage and handling

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.

8.8. Returns and Reconciliation

The investigator is responsible for keeping accurate records of the clinical supplies received from Merck or designee, the amount dispensed to and returned by the subjects and the amount remaining at the conclusion of the trial.

Upon completion or termination of the study, all unused and/or partially used investigational product will be destroyed at the site per institutional policy. It is the Investigator's responsibility to arrange for disposal of all empty containers, provided that procedures for proper disposal have been established according to applicable federal, state, local and institutional guidelines and procedures, and provided that appropriate records of disposal are kept.

8.9. Docetaxel administration

Docetaxel will be provided by the AKH hospital pharmacy as routine ready to use infusion bag and will be administered as a 60 minute IV infusion prior to pembrolizumab. Patients will receive docetaxel intravenous infusions via infusion pump.

8.10. Supportive Care guidelines

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 and in greater detail in the ECI guidance document. 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. Thetreatment 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 is instructed to follow the ECI reporting guidance but does not need to follow the treatment guidance (as outlined in the ECI guidance document). Refer to Section 6.8 for dose modification.

It may be necessary to perform conditional procedures such as bronchoscopy, endoscopy, or skin photography as part of evaluation of the event. Suggested conditional procedures, as appropriate, can be found in the ECI guidance document.

- **Pneumonitis**:
    - For **Grade 2 events**, treat with systemic corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.
    - For **Grade 3-4 events**, immediately treat with intravenous steroids. Administer additional anti-inflammatory measures, as needed.
    - Add prophylactic antibiotics for opportunistic infections in the case of prolonged steroid administration.

- **Diarrhea/Colitis**:
  Subjects should be carefully monitored for signs and symptoms of enterocolitis (such as diarrhea, abdominal pain, blood or mucus in stool, with or without fever) and of bowel perforation (such as peritoneal signs and ileus).

    - All subjects who experience diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion. For Grade 2 or higher diarrhea, consider GI consultation and endoscopy to confirm or rule out colitis.
    - For **Grade 2 diarrhea/colitis** that persists greater than 3 days, administer oral corticosteroids.

- For **Grade 3 or 4 diarrhea/colitis** that persists > 1 week, treat with intravenous steroids followed by high dose oral steroids.
- When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.

- **Type 1 diabetes mellitus (if new onset, including diabetic ketoacidosis [DKA]) or ≥ Grade 3 Hyperglycemia, if associated with ketosis (ketonuria) or metabolic acidosis (DKA)**

  - For **T1DM** or **Grade 3-4** Hyperglycemia
    - Insulin replacement therapy is recommended for Type I diabetes mellitus and for Grade 3-4 hyperglycemia associated with metabolic acidosis or ketonuria.
    - Evaluate patients with serum glucose and a metabolic panel, urine ketones, glycosylated hemoglobin, and C-peptide.

- **Hypophysitis**:

  - For **Grade 2** events, treat with corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.
  - For **Grade 3-4** events, treat with an initial dose of IV corticosteroids followed by oral corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.

- **Hyperthyroidism or Hypothyroidism**:
  Thyroid disorders can occur at any time during treatment. Monitor patients for changes in thyroid function (at the start of treatment, periodically during treatment, and as indicated based on clinical evaluation) and for clinical signs and symptoms of thyroid disorders.

  - **Grade 2** hyperthyroidism events (and **Grade 2-4** hypothyroidism):
    - In hyperthyroidism, non-selective beta-blockers (e.g. propranolol) are suggested as initial therapy.
    - In hypothyroidism, thyroid hormone replacement therapy, with levothyroxine or liothyroinine, is indicated per standard of care.
  - **Grade 3-4** hyperthyroidism
    - Treat with an initial dose of IV corticosteroid followed by oral corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.

- **Hepatic**:
  - For **Grade 2** events, monitor liver function tests more frequently until returned to baseline values (consider weekly).
    - Treat with IV or oral corticosteroids
  - For **Grade 3-4** events, treat with intravenous corticosteroids for 24 to 48 hours.
  - When symptoms improve to Grade 1 or less, a steroid taper should be started and continued over no less than 4 weeks.

- **Renal Failure or Nephritis**:
  - For **Grade 2** events, treat with corticosteroids.
  - For **Grade 3-4** events, treat with systemic corticosteroids.
  - When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4weeks.

- **Management of Infusion Reactions**: Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion.

Table 6 below shows treatment guidelines for subjects who experience an infusion reaction associated with administration of pembrolizumab (MK-3475).

Table 6 Infusion Reaction Treatment Guidelines

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator.	None
Grade 2 Requires infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for < =24 hrs	**Stop Infusion and monitor symptoms.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDS Acetaminophen Narcotics Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator.	Subject may be premedicated 1.5h (± 30 minutes) prior to infusion of pembrolizumab (MK-3475) with: Diphenhydramine 50 mg po (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg po (or equivalent dose of antipyretic).

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
	If symptoms resolve within one hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g., from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the subject should be premedicated for the next scheduled dose. **Subjects who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further trial treatment administration.**	
Grades 3 or 4 Grade 3: Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates) Grade 4: Life-threatening; pressor or ventilatory support indicated	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDS Acetaminophen Narcotics Oxygen Pressors Corticosteroids Epinephrine Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. **Subject is permanently discontinued from further trial treatment administration.**	No subsequent dosing
Appropriate resuscitation equipment should be available in the room and a physician readily available during the period of drug administration.		

8.11. Diet/Activity/Other Consideration

- **Diet**

Subjects should maintain a normal diet unless modifications are required to manage an AE such as diarrhea, nausea or vomiting.

- **Contraception**

Pembrolizumab may have adverse effects on a fetus in utero. Furthermore, it is not known if pembrolizumab has transient adverse effects on the composition of sperm. Non-pregnant, non-breast-feeding women may be enrolled if they are willing to use 2 methods of birth control or are considered highly unlikely to conceive. Highly unlikely to conceive is defined as 1) surgically sterilized, or 2) postmenopausal (a woman who is ≥45 years of age and has not had menses for greater than 1 year will be considered postmenopausal), or 3) not heterosexually active for the duration of the study. The two birth control methods can be either two barrier methods or a barrier method plus a hormonal method to prevent pregnancy. Subjects should start using birth control from study Visit 1 throughout the study period up to 120 days after the last dose of study therapy.

The following are considered adequate barrier methods of contraception: diaphragm, condom (by the partner), copper intrauterine device, sponge, or spermicide. Appropriate hormonal contraceptives will include any registered and marketed contraceptive agent that contains an estrogen and/or a progestational agent (including oral, subcutaneous, intrauterine, or intramuscular agents).

Subjects should be informed that taking the study medication may involve unknown risks to the fetus (unborn baby) if pregnancy were to occur during the study. In order to participate in the study they must adhereto the contraception requirement (described above) for the duration ofthe study and during the follow-up period defined in section 7.2.2-Reporting of Pregnancy and Lactation to the Sponsor and to Merck. If there is any question that a subject will not reliably comply with the requirements for contraception, that subject should not be entered into the study.

- **Use in Pregnancy**

If a subject inadvertently becomes pregnant while on treatment with pembrolizumab, the subject will immediately be removed from the study. The site will contact the subject at least monthly and document the subject's status until the pregnancy has been completed or terminated. The outcome of the pregnancy will be reported to the Sponsor and to Merck without delay and within 24 hours to the Sponsor and within 2 working days to Merck if the outcome is a serious adverse experience (e.g., death, abortion, congenital anomaly, or other disabling or life-threatening complication to the mother or newborn).

The study investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the fetus or newborn to the Sponsor. If a male subject impregnates his female partner the study personnel at the site must be informed immediately and the pregnancy reported to the Sponsor and to Merck and followed as described above and in Section 7.2.2.

- **Use in Nursing Women**

It is unknown whether pembrolizumab is excreted in human milk. Since many drugs are excreted in human milk, and because of the potential for serious adverse reactions in the nursing infant, subjects who are breast-feeding are not eligible for enrollment.

8.12. Subject Withdrawal/Discontinuation Criteria

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. Specific details regarding discontinuation or withdrawal are provided in Section 7.1.4 – Other Procedures.

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: For unconfirmed radiographic disease progression, please see Section 5.2.2

  Note: A subject may be granted an exception to continue on treatment with confirmed radiographic progression if clinically stable or clinically improved, please see Section 7.1.2.7.1
- Unacceptable adverse experiences as described in Section 5.2.1.2
- 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
- Completed 24 months of uninterrupted treatment with pembrolizumab or 35 administrations of study medication, whichever is later.

  Note: 24 months of study medication is calculated from the date of first dose. Subjects who stop pembrolizumab after 24 months may be eligible for up to one year of additional study treatment if they progress after stopping study treatment provided they meet the requirements detailed in Section 7.1.5.5
- Administrative reasons

8.13. Criteria for Early Trial Termination

Early trial termination will be the result of the criteria specified below:

1. Quality or quantity of data recording is inaccurate or incomplete
2. Poor adherence to protocol and regulatory requirements

3. Incidence or severity of adverse drug reaction in this or other studies indicates a potential health hazard to subjects

4. Plans to modify or discontinue the development of the study

9. STATISTICAL CONSIDERATIONS

9.1. Sample Size Calculation

The primary objective of this Phase II study is to evaluate the proportion of patients responding to pembrolizumab plus docetaxel. An exact binominal test with a nominal 0.050 one-sided significance level will have 84% power to detect the difference between the null hypothesis proportion, $\pi 0$ of 0.15 and the alternative proportion, πA of 0.40 when the sample size is 22. This corresponds to a rejection of the Null hypothesis, if 7 or more successes are observed in 22 treated patients.
Continuous variables will be summarized using descriptive statistics and Kaplan Meier curves will be calculated to estimate OS and PFS. The Overall Response Rate (CR/PR together) will be described by absolute frequencies and percentages. The corresponding one-sided exact 95 % confidence interval will by calculated.

9.2. Study population

9.2.1. Full analysis set Assessment of Efficacy

All registered patients who started treatment will be included in the full analysis set (FAS) when assessing efficacy. For assessing patients´ response or progression of disease all patients with at least one tumor assessment (CT or MRI) after start of treatment are included. Patients lost to follow-up before their first imaging assessment will be replaced by another eligible patient.

The Overall Response Rate (CR/PR together) will be described by absolute frequencies and percentages. The corresponding one-sided exact 95 % confidence interval will by calculated.

If there are 7 or more successes (CR or PR) out of the 22 patients the study is considered to be a success and the null hypothesis (Clinical Benefit Rate is ≤15 %) will be rejected in favour of the alternative hypothesis of a higher Overall Response Rate.

9.2.2. Safety Analyses set

All registered patients receiving at least one treatment dose are included in the safety analyses set.

9.2.3. Assessment of Safety

A complete patient Adverse Event listing, including details (intensity, relation to drug, etc.) for all patients enrolled in this trial will be given. Adverse Event (including abnormal laboratory values) intensity and relationship to trial drug will be presented as summary tables. Serious Adverse Events (grade 3-4), will be summarised in a brief case history.

9.2.4. Secondary Objectives

The Best OR categories will be described by frequencies and percentages. Individual patients response over time of will be reported as case studies. Kaplan Meier curves will be calculated to estimate OS. Patients lost to follow up will be censored at the date of last known survival status. Changes in quality of life measurements will be reported by frequencies and percentages.

9.2.5. Exploratory Objectives

Exploratory endpoints will be analysed in a descriptive way only. Categorical data will be described by frequencies and percentages. Continuous data are summarized by mean and standard deviation in case of normal distribution and by median, minimum and maximum otherwise. Repeat measurements will be graphically shown by line plots for every patient.

10. Adverse Event

An adverse event is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. 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 a medicinal product or protocol-

specified procedure, whether or not considered related to the medicinal product or protocol-specified procedure. 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 Merck's product, is also an adverse event.

Changes resulting from normal growth and development that do not vary significantly in frequency or severity from expected levels are not to be considered adverse events. Examples of this may include, but are not limited to, teething, typical crying in infants and children and onset of menses or menopause occurring at a physiologically appropriate time.

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

Adverse events may occur during the course of the use of Merck product in clinical trials or within the follow-up period specified by the protocol, or prescribed in clinical practice, from overdose (whether accidental or intentional), from abuse and from withdrawal.

Adverse events may also occur in screened subjects during any pre-allocation baseline period as a result of a protocol-specified intervention, including washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

Progression of the cancer under study is not considered an adverse event unless it is considered to be drug related by the investigator.

All adverse events will be recorded from the time the consent form is signed through 30 days following cessation of treatment and at each examination on the Adverse Event case report forms/worksheets. The reporting timeframe for adverse events meeting any serious criteria is described below.

10.1. Definition of an overdose for this protocol and reporting pf overdose to the sponsor and MERCK

For purposes of this trial, an overdose of pembrolizumab will be defined as any dose of 1,000 mg or greater (≥5 times the indicated dose). No specific information is available on the treatment of overdose of pembrolizumab. Appropriate supportive treatment should be provided if clinically indicated. In the event of overdose, the subject should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

If an adverse event(s) is associated with ("results from") the overdose of a Merck product, the adverse event(s) is reported as a serious adverse event, even if no other seriousness criteria are met.

If a dose of Merck's product meeting the protocol definition of overdose is taken without any associated clinical symptoms or abnormal laboratory results, the overdose is reported as a non-serious Event of Clinical Interest (ECI), using the terminology "accidental or intentional overdose without adverse effect."

All reports of overdose with and without an adverse event must be reported within 24 hours to the Sponsor and within 2 working days hours to Merck Global Safety. (Attn: Worldwide Product Safety; FAX 215 993-1220)

10.2. Reporting of pregnancy and lactation to the sponsor and to MERCK

Although pregnancy and lactation are not considered adverse events, it is the responsibility of investigators or their designees to report any pregnancy or lactation in a subject (spontaneously reported to them), including the pregnancy of a male subject's female partner that occurs during the trial or within 120 days of completing the trial completing the trial, or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier. All subjects and female partners of male subjects who become pregnant must be followed to the completion/termination of the pregnancy. Pregnancy outcomes of spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage and stillbirth must be reported as serious events (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported.

Such events must be reported within 24 hours to the Sponsor and within 2 working days to Merck Global Safety. (Attn: Worldwide Product Safety; FAX 215 993-1220)

10.3. Immediate reporting of adverse events to the sponsor and to MERCK

10.3.1. Serious adverse events and Suspected unexpected serious adverse reaction (SUSARS)

A serious adverse event is any adverse event occurring at any dose or during any use of Merck's product that:

- Results in death;
- Is life threatening;
- Results in persistent or significant disability/incapacity;
- Results in or prolongs an existing inpatient hospitalization;
- Is a congenital anomaly/birth defect;
- Is a new cancer (that is not a condition of the study);

- Is associated with an overdose;
- Is an other important medical event

Any serious adverse event, or follow up to a serious adverse event, including death due to any cause other than progression of the cancer under study that occurs to any subject from the time the consent is signed through 90 days following cessation of treatment, or the initiation of new anti-cancer therapy, whichever is earlier, whether or not related to Merck product, must be reported within 24 hours to the Sponsor and within 2 working days to Merck Global Safety.

Pembrolizumab SUSARs represent Serious Adverse Events related to pembrolizumab (=Adverse Reactions), considered "unexpected" with regard to the valid investigator brochure for pembrolizumab.

SUSARS and non-serious Events of Clinical Interest will be forwarded to Merck Global Safety and will be handled in the same manner as SAEs.

The sponsor is solely responsible for sending the reports on SAEs and SUSARs to all participating investigators, to Regulatory agencies and Ethics Committees concerned in accordance with international and local laws and regulations as well as ICH/GCP guidelines.

Additionally, any serious adverse event, considered by an investigator who is a qualified physician to be related to Merck product that is brought to the attention of the investigator at any time outside of the time period specified in the previous paragraph also must be reported immediately to the Sponsor and to Merck.

SAE reports and any other relevant safety information are to be forwarded to the Merck Global Safety facsimile number: +1-215-993-1220

A copy of all 15 Day Reports and Annual Progress Reports is submitted as required by FDA, European Union (EU), Pharmaceutical and Medical Devices agency (PMDA) or other local regulators. Investigators will cross reference this submission according to local regulations to the Merck Investigational Compound Number (IND, CSA, etc.) at the time of submission. Additionally investigators will submit a copy of these reports to Merck & Co., Inc. (Attn: Worldwide Product Safety; FAX 215 993-1220) at the time of submission to FDA.

All subjects with serious adverse events must be followed up for outcome.

10.4. Events of clinical interest

Selected non-serious and serious adverse events are also known as Events of Clinical Interest (ECI) and must be recorded as such on the Adverse Event case report forms/worksheets and reported within 24 hours to the Sponsor and within 2 working days to Merck Global Safety. (Attn: Worldwide Product Safety; FAX 215 993-1220) Events of clinical interest for this trial include:

1. an overdose of Merck product, as defined in Section Definition of an Overdose for This Protocol and Reporting of Overdose to the Sponsor, 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. The trial site guidance for assessment and follow up of these criteria can be found in the Investigator Trial File Binder (or equivalent).

1. Additional adverse events:

   A separate guidance document has been provided entitled "Event of Clinical Interest Guidance Document" (previously entitled, "Event of Clinical Interest and Immune-Related Adverse Event Guidance Document"). This document provides guidance regarding identification, evaluation and management of ECIs and irAEs.

   ECIs (both non-serious and serious adverse events) identified in this guidance document from the date of first dose through 90 days following cessation of treatment, or 30 days after the initiation of a new anticancer therapy, whichever is earlier, need to be reported within 24 hours to the Sponsor and within 2 working days to Merck Global Safety. (Attn: Worldwide Product Safety; FAX 215 993-1220), regardless of attribution to study treatment, consistent with standard SAE reporting guidelines.

   Subjects should be assessed for possible ECIs prior to each dose. Lab results should be evaluated and subjects should be asked for signs and symptoms suggestive of an immune-related event. Subjects who develop an ECI thought to be immune-related should have additional testing to rule out other etiologic causes. If lab results or symptoms indicate a possible immune-related ECI, then additional testing should be performed to rule out other etiologic causes. If no other cause is found, then it is assumed to be immune-related.

10.5. Evaluating adverse event

An investigator who is a qualified physician will evaluate all adverse events according to the NCI Common Terminology for Adverse Events (CTCAE), version 4.0. Any adverse event which changes CTCAE grade over the course of a given episode will have each change of grade recorded on the adverse event case report forms/worksheets.

All adverse events regardless of CTCAE grade must also be evaluated for seriousness.

10.6. Sponsor responsibility for reporting serious adverse events

All Adverse Events will be reported to regulatory authorities, IRB/IECs and investigators in accordance with all applicable global laws and regulations.

11. Insurance Policy

In accordance with the provisions of the law and ICH GCP, the sponsor has an insurance policy intended to guarantee against possible damages resulting from research. The studies and/or experiments performed on behalf of the Medical University of Vienna are specifically and expressly guaranteed. It is advisable to underline that non compliance with the research legal conditions are clauses of guarantee exclusion.

12. Publication

This trial is intended for publication, even if terminated prematurely. Publication may include any or all of the following: posting of a synopsis online, abstract and/or presentation at a scientific conference, or publication of a full manuscript. Any publications of the results, either in part or in total by investigators or their representatives will require pre-submission review by the Sponsor and Merck.

13. Financial considerations and research funding

This trial is supported by a research grant by Merck. Merck does not pay incentives to enroll subjects in this trial. The investigators have no conflict of interest to declare.

Table 7: Evaluating Adverse Events

An investigator who is a qualified physician, will evaluate all adverse events as to:

V4.0 CTCAE Grading	**Grade 1**	**Mild; asymptomatic or mid symptoms; clinical or diagnostic observations only; intervention not indicated.**
	Grade 2	**Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL.**
	Grade 3	**Severe or medically significant but not immediately life-threatening; hospitalization or prolongation or hospitalization indicated; disabling; limiting self-care ADL.**
	Grade 4	**Life threatening consequences; urgent intervention indicated.**
	Grade 5	**Death related to AE**
Seriousness	A serious adverse event is any adverse event occurring at any dose or during any use of Merck product that:	
	†**Results in death**; or	
	†**Is life threatening; or** places the subject, in the view of the investigator, at immediate risk of death from the event as it occurred (Note: This does not include an adverse event that, had it occurred in a more severe form, might have caused death.); or	
	†**Results in a persistent or significant disability/incapacity** (substantial disruption of one's ability to conduct normal life functions); or	
	†**Results in or prolongs an existing inpatient hospitalization** (hospitalization is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation. (Note: Hospitalization [including hospitalization for an elective procedure] for a preexisting condition which has not worsened does not constitute a serious adverse event.); or	
	†**Is a congenital anomaly/birth defect** (in offspring of subject taking the product regardless of time to diagnosis);or	
	Is a new **cancer;** (that is not a condition of the study) **or**	
	Is an overdose (whether accidental or intentional). Any adverse event associated with an overdose is considered a serious adverse event. An overdose that is not associated with an adverse event is considered a non-serious event of clinical interest and must be reported within 24 hours.	
	Other important medical events that may not result in death, not be life threatening, or not require hospitalization may be considered a serious adverse event when, based upon appropriate medical judgment, the event may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed previously (designated above by a †).	
Duration	Record the start and stop dates of the adverse event. If less than 1 day, indicate the appropriate length of time and units	
Action taken	Did the adverse event cause the Merck product to be discontinued?	
Relationship to test drug	Did the Merck product cause the adverse event? The determination of the likelihood that the Merck product caused the adverse event will be provided by an investigator who is a qualified physician. The investigator's signed/dated initials on the source document or worksheet that supports the causality noted on the AE form, ensures that a medically qualified assessment of causality was done. This initialed document must be retained for the required regulatory time frame. The criteria below are intended as reference guidelines to assist the investigator in assessing the likelihood of a relationship between the test drug and the adverse event based upon the available information. **The following components are to be used to assess the relationship between the Merck product and the AE**; the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely the Merck product caused the adverse event (AE):	
	Exposure	Is there evidence that the subject was actually exposed to the Merck product such as: reliable history, acceptable compliance assessment (pill count, diary, etc.), expected pharmacologic effect, or measurement of drug/metabolite in bodily specimen?
	Time Course	Did the AE follow in a reasonable temporal sequence from administration of the Merck product? Is the time of onset of the AE compatible with a drug-induced effect (applies to trials with investigational medicinal product)?
	Likely Cause	Is the AE not reasonably explained by another etiology such as underlying disease, other drug(s)/vaccine(s), or other host or environmental factors

Relationship to Merck product (continued)	**The following components are to be used to assess the relationship between the test drug and the AE: (continued)**	
	Dechallenge	Was the Merck product discontinued or dose/exposure/frequency reduced? If yes, did the AE resolve or improve? If yes, this is a positive dechallenge. If no, this is a negative dechallenge. (Note: This criterion is not applicable if: (1) the AE resulted in death or permanent disability; (2) the AE resolved/improved despite continuation of the Merck product; or (3) the trial is a single-dose drug trial); or (4) Merck product(s) is/are only used one time.)
	Rechallenge	Was the subject re-exposed to the Merck product in this study? If yes, did the AE recur or worsen? If yes, this is a positive rechallenge. If no, this is a negative rechallenge. (Note: This criterion is not applicable if: (1) the initial AE resulted in death or permanent disability, or (2) the trial is a single-dose drug trial); or (3) Merck product(s) is/are used only one time). NOTE: IF A RECHALLENGE IS PLANNED FOR AN ADVERSE EVENT WHICH WAS SERIOUS AND WHICH MAY HAVE BEEN CAUSED BY THE MERCK PRODUCT, OR IF REEXPOSURE TO THE MERCK PRODUCTPOSES ADDITIONAL POTENTIAL SIGNIFICANT RISK TO THE SUBJECT, THEN THE RECHALLENGE MUST BE APPROVED IN ADVANCE BY THE U.S. CLINICAL MONITOR AS PER DOSE MODIFICATION GUIDELINES IN THE PROTOCOL.
	Consistency with Trial Treatment Profile	Is the clinical/pathological presentation of the AE consistent with previous knowledge regarding the Merck product or drug class pharmacology or toxicology?
The assessment of relationship will be reported on the case report forms /worksheets by an investigator who is a qualified physician according to his/her best clinical judgment, including consideration of the above elements.		
Record one of the following		**Use the following scale of criteria as guidance (not all criteria must be present to be indicative of a Merck product relationship).**
Yes, there is a reasonable possibility of Merck product relationship.		There is evidence of exposure to the Merck product. The temporal sequence of the AE onset relative to the administration of the Merck product is reasonable. The AE is more likely explained by the Merck product than by another cause.
No, there is not a reasonable possibility Merck product relationship		Subject did not receive the Merck product OR temporal sequence of the AE onset relative to administration of the Merck product is not reasonable OR there is another obvious cause of the AE. (Also entered for a subject with overdose without an associated AE.)

14. APPENDICES

- **ECOG Performance Status**

Grade	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.
*As published in Am. J. Clin. Oncol.: *Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982.* The Eastern Cooperative Oncology Group, Robert Comis M.D., Group Chair.	

- **Common Terminology Criteria for Adverse Events V4.0 (CTCAE)**

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for adverse event reporting. (http://ctep.cancer.gov/reporting/ctc.html)

- **Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 Criteria for Evaluating Response in Solid Tumors**

RECIST version 1.1 will be used in this study for assessment of tumor response. While either CT or MRI may be utilized, as per RECIST 1.1, CT is the preferred imaging technique in this study.

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Amendment 1 to the protocol V3.0

Exploratory analysis of cytokine profile in HNSCC patients treated with docetaxel and pembrolizumab

It has been published recently, that serum cytokine levels are altered in HNSCC patients and correlate with disease progression[1]. Apart from that, it there is growing evidence that not only cytokines such as interferon gamma but also soluble PD-L1 levels are of prognostic and predictive value in patients treated with CPI[2,3].

Based on this recent evidence we propose a retrospective exploratory analysis of the serum samples collected within the Pem-Doc study prior to publication in order to better understand the treatment responses.

In particular we plan to measure the serum levels of interferon gamma; Interleukin 6, interleukin 17A, soluble PD-L1, major-histocompatibility-complex (MHC) class I-related chain genes A and B employing a ProcartaPlex 6-plex immunoassay. Soluble serum parameters will be quantified at baseline and at the initial restaging for patients with disease control and non-responders. Potential differences between paired data will be calculated using Wilcoxon signed-rank tests.

Since this is a retrospective exploratory analysis of stored serum samples there will be no additional risks for the remaining patients.

Next generation sequencing

As already described in the protocol next generation sequencing will be performed. However, the Oncomine Comprehensive Assay v3 (Thermo Fisher Scientific, Waltham, MA, USA) instead of the Qiagen Comprehensive Cancer GeneRead DNAseq Targeted Panel will be used, since this assay is the one currently employed (for routine purposes as well) at the Department of Pathology due to superior performance.

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