Clinical Trial Protocol
IO102-IO103-022 (IOB-022)
MK3475-D38 (KN-D38)

A Phase II Multi-Arm (basket) Trial Investigating the Safety and Efficacy of IO102-IO103 in Combination with Pembrolizumab, as First-line Treatment for Patients with Metastatic Non-Small Cell Lung Cancer (NSCLC), Squamous Cell Carcinoma of Head and Neck (SCCHN), or Metastatic Urothelial Bladder Cancer (mUBC)

Sponsor:	**IO Biotech ApS** **Ole Maaløes Vej 3** **DK-2200 Copenhagen N, Denmark**
Trial ID:	**IO102-IO103-022 (IOB-022)/ MK3475-D38 (KN-D38)**
EU Trial No:	**2024-511561-10-00**
IND No:	**Not applicable**
Version:	**8.0**
Date:	**21-Jun-2024**

1 Clinical Trial Protocol Statement

1.1 Sponsor's Approval of Clinical Trial Protocol

This clinical trial will be conducted in compliance with the clinical trial protocol, ICH-GCP and the applicable regulatory requirements,including Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014.

1.2 Co-ordinating Investigator's Approval of Clinical Trial Protocol

I have read and agree to the IO102-IO103-022 (IOB-022)/MK3475-D38 (KN-D38) clinical trial "A Phase II Multi-Arm (basket) Trial Investigating the Safety and Efficacy of IO102-IO103 in Combination with Pembrolizumab, as First-Line Treatment for Patients with Metastatic Non-Small Cell Lung Cancer (NSCLC), Squamous Cell Carcinoma of Head and Neck (SCCHN), or Metastatic Urothelial Bladder Cancer (mUBC)". I am aware of my responsibilities as the Co-ordinating Investigator under the guidelines of Good Clinical Practice (GCP, 2001), local regulations (as applicable) and the trial protocol. I agree to conduct this clinical trial according to these guidelines and to appropriately direct and assist the staff under my control, who will be involved in this clinical trial.

Jonathan Riess

International Coordinating Investigator

1.3 Acknowledgement Statement Investigators

I have read and agree to the IO102-IO103-022 (IOB-022)/MK3475-D38 (KN-D38) clinical trial "A Phase II Multi-Arm (basket) Trial Investigating the Safety and Efficacy of IO102-IO103 in Combination with Pembrolizumab, as First-line Treatment for Patients with Metastatic Non-Small Cell Lung Cancer (NSCLC), Squamous Cell Carcinoma of Head and Neck (SCCHN), or Metastatic Urothelial Bladder Cancer (mUBC)". I am aware of my responsibilities as an Investigator under the guidelines of Good Clinical Practice (GCP, 2001), local regulations (as applicable) and the trial protocol. I agree to conduct this clinical trial according to these guidelines and to appropriately direct and assist the staff under my control, who will be involved in this clinical trial.

Signature: Date of Signature:

Name:

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List of Abbreviations and Acronyms

Abbreviation	Definition
5-FU	5-Fluorouracil
ADR	Adverse Drug Reaction
AE	Adverse Event
AEOSI	Adverse Events of Special Interest
ALK	Anaplastic Lymphoma Kinase
ALT	Alanine Aminotransferase
APC	Antigen Presenting Cells
aPTT	Activated Partial Thromboplastin Time
AST	Aspartate Aminotransperase
β-hCG	Beta-Human Chorionic Gonadotropin
BCC	Basal Cell Carcinoma
BCG	Bacillus Calmette–Guérin
BRAF	Proto-oncogene B-Raf
CI	Confidence Interval
CIT	Cancer Immunotherapy
CNS	Central Nervous System
CPS	Combined Positive Score
CR	Complete Response
CrCl	Calculated Creatinine Clearance
CRF	Case Report Form
CRO	Clinical Research Organisation
CRR	Complete Response Rate
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Event
CTFG	Clinical Trials Facilitation and Coordination Group
CTLA-4	Cytotoxic T-Lymphocyte Associated Protein 4
DCR	Disease Control Rate
DoR	Duration of Response
EBV	Epstein-Barr Virus
EC	Ethics Committee
ECG	Electrocardiogram
ECI	Events of Clinical Interest
ECOG PS	Eastern Cooperative Oncology Group Performance Status
EDC	Electronic Data Capture
EGFR	Epidermal Growth Factor Receptor
EMA	European Medicines Agency
EOT	End of Treatment
ESMO	European Society for Medical Oncology
FDA	Food and Drug Administration
FFPE	Formalin Fixed Paraffin Embedded
FSH	Follicle Stimulating Hormone
FU	Follow Up
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
GFR	Glomerular Filtration Rate
GLP	Good Laboratory Practise
HbsAg	Hepatitis B Surface Antigen
HCP	Health Care Professional
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus

HLA	Human Leucocyte Antigen
HMA	European Union Heads of Medicines Agencies
HPV	Human Papillomavirus
HR	Hazard Ratio
IB	Investigator's Brochure
ICF	Informed Consent Form
ICI	Immune Checkpoint Inhibitor
ICH	International Conference on Harmonization
iCPD	Confirmed Progressive Disease according to iRECIST
IDO	Indoleamine 2,3-dioxygenase
IEC	Independent Ethics Committees
IgG4	Humanized Immunoglobulin G4
IHC	Immunohistochemistry
IIT	Investigator Initiated Trials
IMP	Investigational Medicinal Product
IND	Investigational New Drug
INR	International Normalized Ratio
iPFS	Immune-Related Progression-Free Survival
irAE	Immune-Related AE
IRB	Institutional Review Board
iRECIST	Immune-Related Response Evaluation Criteria In Solid Tumors
IUD	Intrauterine Device
iUPD	Unconfirmed Progressive Disease according to iRECIST
IUS	Intrauterine Hormone-releasing System
IV	Intravenous
KRAS	Kirsten Rat Sarcoma viral oncogene homolog
LDH	Lactate Dehydrogenase
M	Metastatic
MCBS	Magnitude of Clinical Benefit Scale
MedDRA	Medical Dictionary for Regulatory Activities
MHC	Major Histocompatability Complex
MM	Multiple Myeloma
MRI	Magnetic Resonance Imaging
mUBC	Metastatic Urothelial Bladder Cancer
MUGA	Multi-Gated Acquisition
N	Nonmissing data
NE	Not Evaluable
NSCLC	Non-Small Cell Lung Cancer
ORR	Objective Response Rate
OS	Overall Survival
OTC	Over The Counter
PBMC	Peripheral Blood Mononuclear Cells
PD	Progressive Disease
PD-1	Programmed Cell Death 1
PD-L1	Programmed Death Ligand 1
PD-L2	Programmed Cell Death Ligand 2
PFR	Progression-Free Rate
PBPK	Physiologically-based PK
PFS	Progression-Free Survival
PoC	Proof of Concept
PK	Pharmacokinetic
PR	Partial Response

PT	Prothrombin Time
PV	Pharmacovigilance
Q2W	Every 2 Weeks
Q3W	Every 3 Weeks
QOL	Quality Of Life
R	Recurrence
RECIST	Response Evaluation Criteria In Solid Tumors
RNA	Ribonucleic Acid
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SC	Subcutaneously
SCCHN	Squamous Cell Carcinoma of Head and Neck
SD	Stable Disease
SEER	Surveillance, Epidemiology, and End Results
SmPC	Summary of Product Characteristics
SOP	Standard Operating Procedures
SPC	Summary of Product Characteristics
SUSAR	Suspected, Unexpected Serious Adverse Reaction
TC	Tumor Cell
TCC	Transitional Cell Carcinoma
TCR	T Cell Receptor
TEAE	Treatment Emergent Adverse Events
TIL	Tumor Infiltrating Lymphocytes
TL	Target Lesion
TPS	Tumor Proportion Score
TSH	Thyroid Stimulating Hormone
TTR	Time to Response
UBC	Urothelial Bladder Cancer
UC	Urothelial Carcinoma
UCC	Urothelial Cell Carcinoma
ULN	Upper Limit of Normal
VGPR	Very Good Partial Response
WFI	Water for Injection
WOCBP	Woman Of Childbearing Potential
WT	Wild Type

2 Protocol Summary

Short Protocol Title	**A Phase II Multi-Arm (basket) Trial Investigating the Safety and Efficacy of IO102-IO103 in Combination with Pembrolizumab, as First-Line Treatment for Patients with Metastatic Non-Small Cell Lung Cancer (NSCLC), Squamous Cell Carcinoma of Head or Neck (SCCHN), or Metastatic Urothelial Bladder Cancer (mUBC)**
Trial No	IOB-022/MK3475-D38 (KN-D38)
Protocol Date and Version	Version 7.0; 24-Apr-2023
Trial Phase	II
Sponsor	IO Biotech ApS Ole Maaløes Vej 3, DK-2200 Copenhagen N Denmark
Background information	Naturally occurring indoleamine 2,3-dioxygenase (IDO)/programmed death ligand 1 (PD-L1) specific T cells recognize MHC-bound IDO/PD-L1 peptides, and are able to eliminate IDO expressing or PD-L1 expressing immunoregulatory cells and cancer cells. Activation of IDO or PD-L1 specific T cells through injection with the IDO and PD-L1 peptides will boost natural killing of cancer cells and counteract immunoregulatory mechanisms in the tumor microenvironment. Thus, IDO/PD-L1 specific T cells may both directly support anti-cancer immunity by killing target T cells but also indirectly by releasing pro-inflammatory cytokines in the microenvironment to boost additional anti-cancer immunity. Both IDO and PD-L1 represent two key checkpoint molecules in the context of anti-tumor immunity. Mouse surrogate IDO peptide (for IO102) and PD-L1 peptide (for IO103) have both shown anti-tumor therapeutic effect in murine cancer models and synergy of the two peptide injections has been observed in a cancer model where IDO and PD-L1 expression was confirmed in different cell populations within tumor microenvironment. The dual-antigen approach addresses the known heterogeneity of IDO and PD-L1 expression in human cancers (where cell populations overexpressing these molecules do not necessarily overlap) and therefore heterogeneity in immune resistance mechanisms in individual patients. A CT26 cancer model demonstrated that IDO peptide injection in combination with an anti-PD-1 works in a synergistic manner, leading to complete response. The overall immune modulation induced by the peptide injection renders tumor microenvironment more inflamed, thus enhancing the therapeutic action of the anti-PD-1 antibody. An ongoing investigator sponsored Phase I/II trial (MM1636) of IO102-IO103 plus nivolumab have shown highly encouraging efficacy and a favorable safety profile in the cohort of anti PD-1 naïve patients with metastatic melanoma (NCT 03047928). Preliminary data from an ongoing randomized Phase I/II trial (Study No. IO102-012/KN-764, NCT03562871) in a cohort with PD-L1 Tumor Proportion Score (TPS) ≥50% treated with IO102 + pembrolizumab demonstrated that patients with metastatic NSCLC and a PD-L1 TPS ≥50% receiving IO102 plus pembrolizumab stayed longer on treatment compared to patients receiving pembrolizumab monotherapy and without adding new safety signals.

	Based on above, it is hypothesized that dual antigen therapy with IO102-IO103 plus pembrolizumab will improve the efficacy of anti PD-1 antibody in patients with a PD-L1 TPS of ≥50% There is therefore a strong rationale for investigation of the dual antigen (IO102-IO103) in combination with PD-1 in the first line setting of patients with metastatic NSCLC and in other solid tumor indications such as SCCHN or mUBC. Identifying patients who would respond to the combination of IO102-IO103 and pembrolizumab is key to successful management of patients with mUBC and SCCHN. For these two indications, although both TPS and Combined Positive Scores (CPS) will be collected, patient inclusion will be based on CPS as this has been identified as most relevant and likely indicator to response and therefore provide benefit from the trial treatment. Further rationale is provided in Section 7.
Trial Objectives	**Primary objective:** The primary objective is to investigate the efficacy of IO102-IO103 in combination with pembrolizumab in the frontline treatment of each of the different solid tumor indications (NSCLC adenocarcinoma PD-L1 TPS ≥50%, SCCHN PD-L1 CPS ≥20, or metastatic UBC PD-L1 CPS ≥10) with the intent to expand a specific cohort if a clinically relevant signal is observed. **Secondary objective:** The secondary objective is to investigate the safety of IO102-IO103 in combination with pembrolizumab in each of the 3 disease indications. **Exploratory objectives:** Analysis of tumour tissue and blood samples will be undertaken to evaluate biomarkers that inform regarding trial drug activity or may predict response to treatment.
Trial Endpoints	**Primary endpoint** Overall objective response rate (ORR) according to RECIST v. 1.1 **Secondary endpoints** • Progression-Free Survival (PFS) according to RECIST v. 1.1 • Duration of response (DOR) • Complete response rate (CRR) • Disease control rate (DCR) • Time to response (TTR) • Safety **Exploratory endpoints** • Overall survival (OS) • PFS according to iRECIST (iPFS) • Analysis of the tumor microenvironment for IDO and PD-L1 expression and lymphocyte infiltration • Circulating tumor DNA as a surrogate measure of tumor burden • Assessment of peripheral immune cell function and treatment-specific T cell responses • ORR and PFS according to independent central review, if applicable
Diagnosis/population	A. NSCLC adenocarcinoma (metastatic disease) with PD-L1 expression TPS ≥50%. B. SCCHN (recurrent or metastatic disease) with PD-L1 CPS ≥ 20. C. UBC (metastatic disease) with PD-L1 CPS ≥ 10.

Inclusion Criteria	1. Patients with histologically or cytologically confirmed: Metastatic NSCLC (adenocarcinoma) (Cohort A), who have not received prior systemic treatment for their metastatic disease and who have: • No known sensitizing genetic aberrations where there are approved therapies (such as ALK, ROS1, EGFR, BRAF V600E, MET skipping mutations, and RET mutations or rearrangements) or SCCHN (Cohort B) with no prior systemic therapy administered in the recurrent or metastatic setting (with the exception of systemic therapy completed >6 months prior if given as part of multimodal treatment for locally advanced disease) and who have: • SCCHN considered incurable by local therapies. Tumors of nasopharyngeal origin (any histology) are excluded • Documented results of p16/HPV status for oropharyngeal cancer (per institution standard) or Metastatic UBC (Cohort C) with no prior therapy and not eligible for any platinum-containing chemotherapy: • Urothelial cancer of the renal pelvis, ureter, bladder or urethra (transitional cell and mixed transitional/non transitional cell histologies permitted but transitional cell histology must be the dominant histology) For all cohorts, any solitary metastases must be biopsied to confirm diagnosis of metastases from primary indication. 2. PD-L1 TPS or PD-L1 CPS (as confirmed prior to enrolment using the PD-L1 IHC DAKO 22C3 PharmDx assay, using local or central services): • Cohort A (NSCLC adenocarcinoma): PD-L1 TPS ≥50% • Cohort B (SCCHN): PD-L1 CPS ≥20; HPV +/- • Cohort C (mUBC): PD-L1 CPS ≥10 3. A female participant is eligible to participate if she is not pregnant not breastfeeding, and at least one of the following conditions applies: • Not a woman of childbearing potential (WOCBP) • A WOCBP who agrees to follow contraceptive guidance starting with the screening visit and through 120 days after last dose of pembrolizumab or 180 days after last dose of chemotherapy. Note: A WOCBP, i.e., fertile, following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilisation methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy. Tubal ligation is *not* a method of permanent sterilisation. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.

	4. The participant (or legally acceptable representative if applicable) provides written informed consent for the trial in accordance with International Conference on Harmonization Good Clinical Practice Guideline (ICH-GCP) and local legislation prior to admission to the trial. 5. At least 18 years of age on day of signing informed consent. 6. Have measurable disease per RECIST v. 1.1 as assessed by local site investigator/radiologist. Lesions situated in a previously irradiated area are considered measurable if progression has been demonstrated in such lesions. 7. Have provided archival tumor tissue sample or newly obtained core or excisional biopsy of a tumor lesion not previously irradiated. Formalin-fixed, paraffin embedded (FFPE) tissue blocks are preferred to slides. 8. Have an ECOG performance status of 0 to 1. 9. If participant received major surgery, they must have recovered adequately from the adverse events and/or complications from the intervention prior to starting trial treatment. 10. Have adequate organ function as defined below. Specimens must be collected within 10 days prior to the start of trial treatment. Adequate organ function as defined by: • Haematology: Absolute neutrophil count ≥1500/µL or ≥1.5 × 10^9/L Platelets ≥100,000/µL or ≥100 × 10^9/L Hemoglobin ≥9.0 g/dL or ≥5.6 mmol/L. Criteria must be met without packed red blood cell transfusion within the prior 2 weeks. Participants can be on stable dose of erythropoietin (≥ approximately 3 months) • Renal: Creatinine ≤1.5 × upper limit of normal (ULN), or Measured or calculated creatinine clearance (CrCl) ≥50 mL/min for patients with creatinine levels >1.5 × institutional ULN; GFR can also be used in place of creatinine or CrCl • Hepatic: Total bilirubin ≤1.5 × ULN or direct bilirubin ≤ ULN for patients with total bilirubin levels >1.5 × ULN Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤2.5 × ULN (≤5 × ULN for patients with liver metastases) Alkaline phosphatase ≤2.5 × ULN

	• Endocrine: No uncontrolled endocrinopathies • Coagulation: International normalised ratio or prothrombin time (PT) and activated partial thromboplastin time (aPTT) ≤ 1.5 × ULN unless patient is receiving anticoagulant therapy as long as PT or aPTT is within therapeutic range of intended use of anticoagulants 11. Patients who are hepatitis B surface antigen (HBsAg) positive are eligible if they have received hepatitis B virus (HBV) antiviral therapy for at least 4 weeks and have undetectable HBV viral load prior to treatment initiation. Note: Patients should remain on anti-viral therapy throughout trial treatment and follow local guidelines for HBV anti-viral therapy after completion of trial treatment. Hepatitis B screening tests are not required unless: a. Known history of HBV infection b. As mandated by local health authority 12. Patients with history of hepatitis C virus (HCV) infection are eligible if HCV viral load is undetectable at screening. Note: Patients must have completed curative anti-viral therapy at least 4 weeks before treatment initiation. Hepatitis C screening tests are not required unless: a. Known history of HCV infection b. As mandated by local health authority
Exclusion Criteria	Cohorts A, B, and C: 1. A WOCBP who has a positive urine pregnancy test (within 72 hours) prior to treatment. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required. 2. Has received prior therapy with an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent or with an agent directed to another stimulatory or co-inhibitory T cell receptor (e.g., CTLA-4, OX 40, CD137) AND was discontinued from that treatment due to a Grade 3 or higher immune-related AE (irAE). 3. Has received prior systemic anti-cancer therapy in the first line setting for the participant's metastatic disease (treatment with chemotherapy and/or radiation as part of neoadjuvant/adjuvant therapy is allowed as long as completed at least 6 months prior to diagnosis of metastatic disease). 4. Has not recovered from all AEs due to previous therapies to ≤ Grade 1 or baseline. Participants with ≤ Grade 2 neuropathy are eligible. 5. Has received any prior radiotherapy, with the exception of palliative radiotherapy to non-target lesions, within 2 weeks prior to the start of trial

	treatment or radiotherapy to the lung >30 Gy within 6 months of start of trial treatment. Participants must have recovered from all radiation-related adverse events and not have had radiation pneumonitis requiring corticosteroids. 6. Have a life expectancy of <3 months and/or rapidly progressing disease. 7. Have received a live or live attenuated vaccine within 30 days prior to the first dose of trial treatment. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster (chicken pox), yellow fever, rabies, Bacillus Calmette–Guérin (BCG), and typhoid vaccine. Administration of killed vaccines, mRNA based (e.g., covid-19) and vector based vaccines are allowed. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (e.g., FluMist®) are live attenuated vaccines and are not allowed. 8. Is currently participating in or has participated in a study of an investigational agent or has used an investigational device within 4 weeks prior to the first dose of study treatment. Note: Participants who have entered the follow-up phase of an investigational study may participate as long as it has been 4 weeks after the last dose of the previous investigational agent. 9. Has a diagnosis of immunodeficiency 10. Received any of the following medications or procedures within 2 weeks prior to first dose of trial treatment: chronic systemic steroid therapy (in dosing exceeding 10 mg daily of prednisone equivalent) or any other form of immunosuppressive therapy 11. Has a known additional malignancy that is progressing or has required active treatment within the past 2 years. Note: Participants with basal cell carcinoma of the skin, squamous cell carcinoma of the skin or carcinoma in situ (e.g., breast carcinoma, cervical cancer in situ) that have undergone potentially curative therapy are not excluded. 12. Has CNS metastases and/or carcinomatous meningitis. Participants in Cohort A (NSCLC) with previously treated brain metastases may participate provided they are clinically stable and without requirement of steroid treatment for at least 14 days prior to first dose of trial treatment. 13. Has severe hypersensitivity (≥ Grade 3) to IO102 or IO103, pembrolizumab and/or any of their excipients. 14. Has an active autoimmune disease that has required systemic treatment in 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) is not considered a form of systemic treatment and is allowed. 15. Has a history of (non-infectious) pneumonitis that required steroids or has current pneumonitis/insterstitial lung disease. 16. Has an active infection requiring systemic therapy.

	17. Has a known history of human immunodeficiency virus (HIV) infection. No HIV testing is required unless mandated by local health authority. 18. Known adrenal insufficiency function (that is basal cortisol level <140nmol/L or <5 μg/dL). 19. Has known active Hepatitis B virus (defined as Hepatitis B surface antigen [HBsAg] reactive and/or detectable HBV DNA) or known active Hepatitis C virus (HCV) (defined as anti-HCV Ab positive and detectable HCV ribonucleic acid [RNA] [qualitative]) infection. Note: No testing for Hepatitis B and Hepatitis C is required unless a. Known history of HBV or HCV infection b. Mandated by local health authority. Patients who have a history of hepatitis will be screened using serology to confirm status. 20. Has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the trial, interfere with the patient's participation for the full duration of the trial, or is not in the best interest of the patient to participate, in the opinion of the treating investigator. 21. Has known psychiatric or substance abuse disorders that would interfere with the patient's ability to cooperate with the requirements of the trial. 22. Is pregnant or breastfeeding or expecting to conceive within the projected duration of the trial, starting with the screening visit through 180 days after last dose of trial treatment. 23. Has had an allogeneic tissue/solid organ transplant. 24. Has progressive disease (PD) within six months of completion of curatively intended systemic treatment for locoregionally advanced SCCHN.
Number of patients	1. Cohort A (NSCLC adenocarcinoma). Approximately 30 patients will be enrolled and treated. 2. Cohort B (SCCHN). Approximately 30 patients will be enrolled and treated. 3. Cohort C (mUBC). Approximately 30 patients will be enrolled and treated.
Number of countries and sites	3 to 5 countries (UK, Spain, USA plus additional) with approximately 25 sites
Estimated total duration of trial and timing of statistical analyses	Screening phase: up to 28 days Treatment period up to 2 years Each patient will receive treatment for up to 2 years. Following completion of trial treatment, patients will be followed until the last patient has been treated for 35 cycles plus 30 days follow-up or until death, withdrawal of consent, or lost-to-follow-up. After the end of trial treatment each patient will be followed for a minimum of 30 days for adverse event (AE) monitoring. Serious adverse events (SAE) and Events of Clinical Interest (ECI) will be collected for up to 90 days following cessation of treatment or 30 days following cessation of treatment if the patient initiates new anticancer therapy, whichever is earlier.

	This is an open label trial therefore analysis of each cohort will occur independently of the others. For each treatment cohort, the primary analysis will be performed 6 months after the last patient started treatment.
Investigational and concomitant products, route of administration, dose and schedule	Investigational agents: IO102-IO103 is an immunotherapeutic targeting the immunoregulatory enzymes IDO and PD-L1 emulsified with adjuvant (Montanide ISA 51 VG). Pembrolizumab is a potent humanized monoclonal immunoglobulin G4 (IgG4) with high specificity of binding to the PD-1 receptor. Route of administration and dose: IO102-IO103: SC administration (IO102 85µg SC and IO103 85µg SC every 3 weeks (Q3W) in combination with pembrolizumab (IV administration 200 mg Q3W). Schedule: IO102-IO103: - Induction period: SC administrations of IO102-IO103 will be given on days 1 and 8 of cycles 1 and 2. In total, 4 doses of each will be administered during the first 2 cycles. - Maintenance period: from cycle 3, SC administrations will be given on day 1 of each 3 week cycle for a max of 33 cycles. - A total of 37 administrations during 2 years. Pembrolizumab: - Day 1 of each 3 week cycle for a max of 35 cycles (2 years) - A total of 35 administrations during 2 years. During the COVID-19 pandemic: To minimize or eliminate immediate hazards and to protect the life and well-being of research participants (e.g. to limit exposure to COVID-19) it is advised to assess and manage the risk of COVID-19 to the patient, taking into consideration prior exposure to the SARS-COV2 virus, vaccination status, age and co-morbitities. Scheduled visits are advised to be delayed as appropriate in the situation of a patient who has a positive COVID-19 test or where an outbreak occurs at the investigational hospital. See Appendix III for further details. All COVID-19 related deviations from the protocol will be recorded as COVID-19 deviations.
Selection of doses in the trial	IO102-IO103 will be used as add-on therapy to pembrolizumab. The dose of IO102-IO103 planned to be studied in this trial is 85 µg of each peptide administered as an emulsion for SC injection. The dose is based on previous experience in clinical trials and is expected to achieve both immunological and clinical responses. No dose selection is applied in the trial.
Statistical Methods	ORR, CRR and DCR, will be assessed and 95% confidence intervals will be calculated using the Clopper-Pearson exact methodology. PFS rate (PFR) at 6 months as well as the endpoint duration of response with corresponding 95% intervals, will be estimated using Kaplan-Meier methods. The trial will assess the opportunity for a positive risk benefit in three indications (NSCLC adenocarcinoma, SCCHN and mUBC) based on ORR for each indication; if a clinically meaningful signal is observed based on the primary endpoint, then there will be an opportunity to consider expanding that particular indication beyond proof of concept, either by adding in more patients or cohorts.

	Interim analyses for each cohort will be considered after 15 patients are treated with ≥2 cycles in the cohort and have either completed at least 2 post-baseline tumor assessments or have discontinued. Details of the interim analyses will be defined in the Statistical Analysis Plan.
Sample Size Calculation	This is an exploratory study and all calculations are done using a 1-side 15% significance level based on 30 patients in each cohort to be enrolled and treated. **Cohort A (NSCLC adenocarcinoma PD-L1 TPS ≥50%)** For patients with PD-L1 ≥50% treated with pembrolizumab, the ORR is estimated to be 39% (Mok *et al.*, 2019). If the true ORR for IO102-IO103 plus pembrolizumab is 55% there is a power of 77% to detect a difference between 39% and 55% with 30 patients. If there are 17 responders from the 30 patients, the ORR point estimate will be 57% and the 95% Clopper-Pearson confidence interval will be 37% - 75%. **Cohort B (SCCHN, PD-L1 CPS ≥ 20)** For patients with CPS ≥20 treated with pembrolizumab, the ORR is estimated to 23% (Burtness *et al.*, 2019). If the true ORR for IO102-IO103 plus pembrolizumab is 35% there is a power of 68% to detect a difference between 23% and 35% with 30 patients. If there are 11 responders from the 30 patients, the ORR point estimate will be 37% and the 95% Clopper-Pearson confidence interval will be 20% - 56%. **Cohort C (mUBC, PD-L1 CPS ≥ 10)** Patients with CPS ≥10 treated with pembrolizumab, the ORR is estimated to 47% (Vuky *et al.*, 2020). If the true ORR for IO102-IO103 plus pembrolizumab is 60% there is a power of 65% to detect a difference between 47% and 60% with 30 patients. If there are 18 responders from the 30 patients, the ORR point estimate will be 60% and the 95% Clopper-Pearson confidence interval will be 41% - 77%.
Efficacy Assessments	Efficacy will be assessed by imaging tumors using CT scans and per RECIST v. 1.1. A baseline scan will be performed at screening, every 9 weeks the first year of treatment and thereafter every 12 weeks until patient end treatment, either by completion of treatment or withdrawal.

3 Trial Procedures

Table 1 Schedule of Trial Procedures (Year 1)

	Screening		Trial treatment period – Year 1																		
Trial Treatment Period Week Number (+/- 3 days)	**-4 wk to D-1**	**-1 wk to D-1**	**1**	**2**	**4**	**5**	**7**	**10**	**13**	**16**	**19**	**22**	**25**	**28**	**31**	**34**	**37**	**40**	**43**	**46**	**49**
Day	**D-28 to D-1**	**D-7 to D-1**	**1**	**8**		**29**															
Pembrolizumab Cycle Number:			**P1**		**P2**		**P3**	**P4**	**P5**	**P6**	**P7**	**P8**	**P9**	**P10**	**P11**	**P12**	**P13**	**P14**	**P15**	**P16**	**P17**
Visit number:	**1**		**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**
Informed consent main and biomarker	X																				
Demographics[1]	X																				
Medical history	X																				
Disease Stage (NSCLC, UBC or SCCHN, previous treatment)	X																				
In-/exclusion criteria check	X																				
Echocardiogram or MUGA		X																			
Pregnancy test[2]		X			X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
ECOG PS	X		X					X			X			X			X			X	
Tumor imaging[3]	X[3a,b]							X[3c, e]			X[3c, e]			X[3c, e]			X[3c, e]			X[3c, e]	
Clinical disease Assessment	X							X			X			X			X			X	
Tumor tissue biopsy or archival tissue sample[4]	X							(X)													
Biomarker blood sampling	X				X			X			X										
PD-L1 status (DAKO 22C3)	X																				
Clinical chemistry[5]	X	X	X		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Haematology[6]	X	X	X		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pembrolizumab (200 mg IV)			X		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Table 1 Schedule of Trial Procedures (Year 1)

	Screening		Trial treatment period – Year 1																		
Trial Treatment Period Week Number (+/- 3 days)	**-4 wk to D-1**	**-1 wk to D-1**	**1**	**2**	**4**	**5**	**7**	**10**	**13**	**16**	**19**	**22**	**25**	**28**	**31**	**34**	**37**	**40**	**43**	**46**	**49**
Day	**D-28 to D-1**	**D-7 to D-1**	**1**	**8**		**29**															
Pembrolizumab Cycle Number:			**P1**		**P2**		**P3**	**P4**	**P5**	**P6**	**P7**	**P8**	**P9**	**P10**	**P11**	**P12**	**P13**	**P14**	**P15**	**P16**	**P17**
Visit number:	**1**		**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**
IO102 (85µg SC) and IO103 (85µg SC)			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urinalysis[7]	X		X				X		X		X		X		X		X		X		X
Thyroid function tests[8]	X		X				X		X		X		X		X		X		X		X
Coagulation Tests[9]	X		X				X		X		X		X		X		X		X		X
Vital signs[10]	X		X		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical examination[11] (full or directed)	X		X		X		X		X				X				X				X
12-lead ECG[12]	X		X						X				X				X				X
Adverse events		X[13]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medication	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pharmacokinetic blood sampling[17]			X																		

Table 2 Schedule of Trial Procedures (Year 2 and/or end of trial treatment)

	Trial treatment period – Year 2 Trial treatment																		EoT	Post Trial treatment (Endpoint FUP)
Week number (+/- 3 days)	**52**	**55**	**58**	**61**	**64**	**67**	**70**	**73**	**76**	**79**	**82**	**85**	**88**	**91**	**94**	**97**	**100**	**103**	**EoT[14] or 107**	**Every 12 wk[15]**
Pembrolizumab Cycle Number:	**P18**	**P19**	**P20**	**P21**	**P22**	**P23**	**P24**	**P25**	**P26**	**P27**	**P28**	**P29**	**P30**	**P31**	**P32**	**P33**	**P34**	**P35**		
Visit number:	**21**	**22**	**23**	**24**	**25**	**26**	**27**	**28**	**29**	**30**	**31**	**32**	**33**	**34**	**35**	**36**	**37**	**38**	**39**	
Pregnancy test[2]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
ECOG PS			X				X				X				X				X	
Tumor imaging[3]			X[3c,e]				X[3c,e]				X[3c,e]				X[3c,e]				X[3c,d,e]	X[3d,e]
Clinical disease Assessment			X				X				X				X				X	
Pembrolizumab (200mg IV)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
IO102 (85µg SC) and IO103 (85µg SC)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Clinical chemistry[5]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Haematology[6]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Urinalysis[7]		X		X		X		X		X		X		X		X			X	
Thyroid function tests[8]		X		X		X		X		X		X		X		X			X	
Coagulation Tests[9]		X		X		X		X		X		X		X		X			X	
Vital signs[10]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Physical examination[11] (full or directed				X				X				X				X			X	
12-lead ECG[12]				X				X				X				X			X	
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[18]
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Subsequent anti-cancer treatment																			X	X
Date of death/Survival follow-up																			X	X

General instructions:

- X denotes an assessment for all patients.
- (X) denotes an optional assessment for all patients.
- EOT – end of treatment visit occurs after cessation of all Trial treatment or completion of 24 months (last treatment at 96 weeks) trial therapy. If cessation of Trial treatment is caused by reasons other than Disease Progression, Tumor Imaging and Disease Assessments will continue until Disease Progression.
- P# represents the pembrolizumab cycle number.

Footnotes:

1. Demography includes: gender, ethnic origin, race, year of birth.
2. A urine pregnancy test is mandatory for female patients of childbearing potential within 72 hours prior to start of treatment. Repeat every 3 weeks during the treatment period, as well as at the end of relevant systemic exposure, i.e. 120 days after last dose of pembrolizumab. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test (β-hCG) will be required.
3. Tumor (radiological) imaging: CT scans of abdomen, chest and pelvis. A MRI scan can be used if CT contrast is contra-indicated. The same radiographic procedure must be used throughout the trial. Assess disease response according to RECIST v. 1.1. After PD or response per iRECIST, repeat imaging for confirmation is required. Repeat imaging at between 4 and 8 weeks to confirm PD; and repeat imaging at >4 weeks to confirm response.
   a. Imaging must be done before administration of trial treatment.
   b. At screening, include a brain scan to exclude active metastases or leptomeningeal metastases.
   c. Pseudo progression should be considered if progression observed in the absence of clinical deterioration, and if suspected, tumor assessments can continue until progression is confirmed (iRECIST).
   d. For patients who discontinue trial treatment, tumor imaging should be performed at the time of treatment discontinuation (±4 week window). If previous imaging was obtained within 4 weeks prior to the date of discontinuation, then imaging at treatment discontinuation is not mandatory. Continue tumor imaging every 12 weeks until progression.
   e. +/-7 days
4. Two samples of tumor tissue are required to be provided at screening and these can be either archival (within 3 months, and in absence of adjuvant or neo-adjuvant treatment) or newly acquired biopsy tissue. Use of archival tissue >3 months old, may be considered after communication with and agreement by the Sponsor. One of the samples (FFPE block or slides) is for PD-L1 status which will be assessed prior to enrolment using the DAKO 22C3 assay. The PD-L1 status can be assessed locally for eligibility and enrollment but one sample (FFPE block or slides) is required for central confirmation. Tissue sampling for biomarkers at week 10 is optional and contingent on patient signing biomarker consent form and depends on the presence of a suitable lesion.
5. Clinical chemistry includes: albumin, alkaline phosphatase, alanine aminotransferase (ALT), aspartate aminotransperase (AST), lactate dehydrogenase (LDH), , uric acid, calcium, glucose, phosphorus, potassium, sodium, magnesium, total bilirubin, direct bilirubin if total bilirubin is >ULN, total protein, urea. In addition, troponin (per institutional standard) will be measured at Screening.
6. Haematology includes:, hemoglobin, platelet count, white blood cell (total and differential).
7. Urinanalysis will be performed at screening, trial treatment and every 6 weeks during trial treatment and as clinically indicated and includes: blood, glucose, protein, specific gravity, microscopic examination (if abnormal results noted), creatinine (plasma or serum) or measured or calculated creatinine clearance (CrCl). GFR can be used instead of creatinine or CrCl.
8. Thyroid function testing (TSH, T_3 or FT_3, FT_4) at screening, start of trial treatment and every 6 weeks during trial treatment, and as clinically indicated.
9. Coagulation Tests includes: prothrombin time (PT INR), partial thromboplastin time (activated) aPTT
10. Vital Signs include blood pressure, heart rate, respiration rate, weight and temperature. Height will be measured at screening only.
11. Physical examination:
    a. Full examination at Screening and every 12 weeks. Check and describe any significant abnormal physical examinations or findings: heart, lung, general, skin (other than the melanoma), oral cavity, chest, lymph nodes.
    b. Directed examination at other timepoints or as clinically indicated to include: symptom driven examination.
12. 12-lead ECG is performed at screening, at the start of the trial treatment, and every 12 weeks during trial treatment and as clinically indicated.
13. AEs occurring after informed consent to be recorded
14. End of Treatment visit has to be conducted for all patients at the timepoint of permanent discontinuation of trial treatment.

15. Patients are to be followed-up post trial treatment every 12 weeks for survival status until the last patient in has been treated for 35 cycles plus 30 days follow up or until disease progression, death, withdrawing consent, or becoming lost to follow-up. If a patient cannot be contacted for survival follow up, information may also be obtained by other means in accordance with local regulations, e.g., contact with patients' health care providers, public sources, e.g. death registry, obituary listing, etc. when it is available and verifiable.
16. For female patients of childbearing potential a urine pregnancy test is mandatory at 120 days after last dose of pembrolizumab. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test (β-hCG) will be required.
17. Pharmacokinetic blood sampling will be performed in a subset of up to 10 patients. See Section 12.4 for details.
18. AEs to be recorded until at least 100 days after the last administration of trial treatment.

4 Trial Design

4.1 Trial Design

This is a non comparative, open label, multi-cohort (basket) trial of IO102-IO103 in combination with pembrolizumab in three indications: non-small cell lung cancer (NSCLC) adenocarcinoma, squamous cell carcinoma of the head and neck (SCCHN) or metastatic urothelial bladder carcinoma (mUBC).

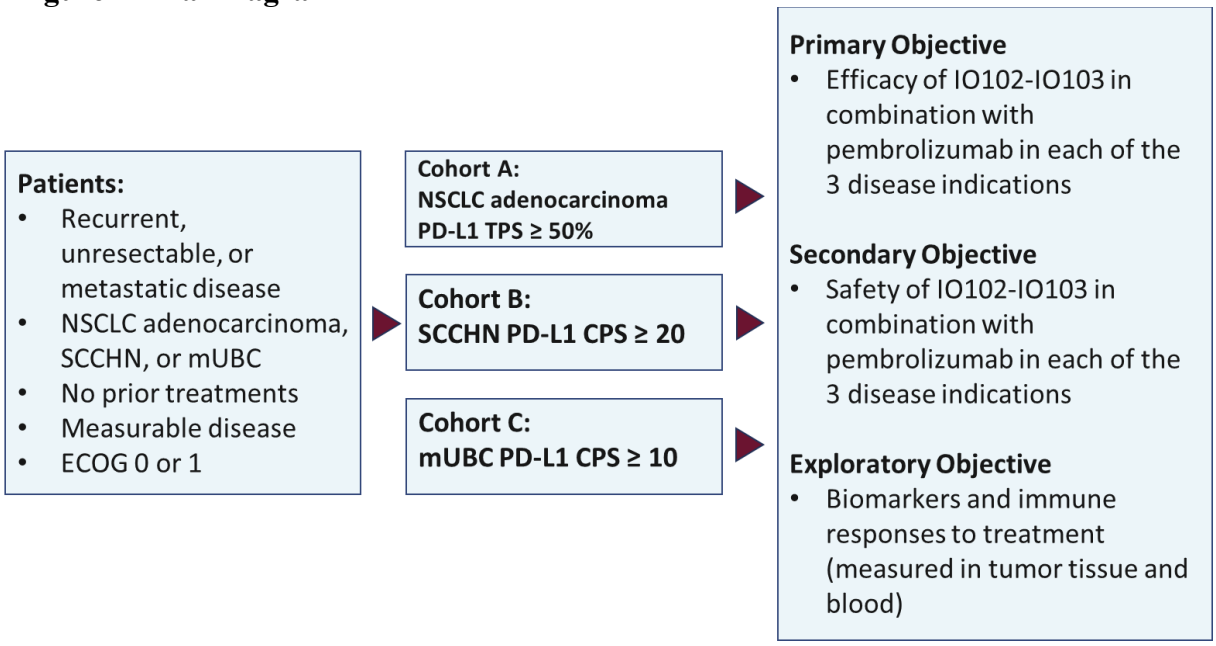
The primary objective of the trial is to investigate the efficacy of IO102-IO103 in combination with pembolizumab in the frontline treatment in each of the different solid tumor indications with the intent to expand a specific cohort if a clinically meaningful signal is observed based on primary endpoint as defined in Section 17.

The primary endpoint is ORR according to RECIST v. 1.1. Disease evaluation by CT scan or MRI will be done locally for all patients based on RECIST v. 1.1 prior to administration of trial treatment, every 9 weeks post baseline the first year of treatment followed by every 12 weeks until disease progression. A copy of the CT scan or MRI will be provided to the sponsor. The same modality of radiological examination must be used throughout the trial.

The clinical trial is unblinded and will consist of 3 cohorts:

- Cohort A: Patients with NSCLC adenocarcinoma (metastatic disease) and programmed cell death ligand 1 (PD-L1) expression TPS ≥50%.
- Cohort B: Patients with SCCHN (recurrent or metastatic disease) and PD-L1 CPS ≥20
- Cohort C: Patients with mUBC (metastatic disease) and PD-L1 CPS ≥10

Figure 1 Trial Diagram



Approximately 90 patients will be enrolled and treated; approximately 30 patients in each cohort.

All eligible patients will receive treatment for up to 2 years with IO102-IO103 (IO102 85µg and IO103 85µg) subcutaneously (SC) every 3 weeks (Q3W) in combination with pembrolizumab intravenously (IV) 200mg Q3W.

IO102-IO103 will be administered one hour prior to pembrolizumab as follows:

- Induction period: On Day 1 and 8 of the first 2 cycles. In total 4 administrations will be provided during the first 2 cycles.
- Maintenance period: On Day 1 of each subsequent 3 week cycle for a maximum of 33 cycles starting from cycle 3.

A maximum of 37 administrations will be provided for each patient during the trial.

Pembrolizumab will be administered on Day 1 of each 3 week cycle in accordance with standard of care for a maximum of 35 cycles (2 years). A maximum of 35 administrations will be provided for each patient during the trial.

Patients will be followed-up post-treatment every 12 weeks for disease status, including initiating a non-trial cancer treatment, until the last patient in has been treated for 35 cycles plus 30 days follow up or until disease progression, death, withdrawing consent, start new anti cancer treatment or becoming lost to follow-up. End of trial is defined as last patient last visit.

Adverse events (AEs) will be assessed using CTCAE v. 5.0. A steering committee will be established by the Sponsor to oversee the study conduct and perform reviews of safety data after approximately 5 patients have received the first cycle of study treatment and then after 25% (approximately 22 of the 90 patients planned) have received the first cycle of study treatment. Thereafter, safety data will be monitored periodically and according to the steering committee charter throughout the trial. Steering committee members will include Sponsor representatives, Investigators and, when required, other external experts.

AEs will be monitored for a minimum of 30 days after patients discontinue trial treatment. SAE and Adverse Events of special interest (AEOSI) data will be collected for up to 90 days following discontinuation of trial treatment or 30 days following discontinuation of trial treatment if the patient initiates new anticancer therapy, whichever is earlier.

Specific procedures to be performed during the trial, as well as their prescribed times and associated visit windows, will be outlined in the Trial Procedures Table 1 and Table 2. Details of each procedure will be provided in Trial Procedures, Section 10.6 and Section 12.

5 Trial Objectives

5.1 Primary Objective

The primary objective is to investigate the efficacy of IO102-IO103 in combination with pembolizumab in the frontline treatment of each of the different solid tumor indications (NSCLC adenocarcinoma PD-L1 TPS ≥50%, SCCHN PD-L1 CPS ≥20 , or mUBC CPS ≥10) with the intent to expand a specific cohort if a significant clinically relevant signal is observed.

5.2 Secondary Objectives

The secondary objective is to investigate the safety of IO102-IO103 in combination with pembrolizumab in each of the 3 disease indications.

5.3 Exploratory Objectives

The exploratory objectives are to evaluate biomarkers that inform regarding trial drug activity or may predict response to treatment.

Biomarkers, will be measured in tumor tissue and blood (whole, serum or plasma) provided during screening and on-treatment. Specific objectives are:

- To evaluate and establish the pharmacodynamic activity of IO102 and IO103 on T cells, the tumor microenvironment, and IDO activity in cellular and/or molecular assays
- To evaluate biomarkers that may predict response to IO102 and IO103 including pretreatment IDO and PD-L1 expression, the composition of tumor infiltrating lymphocytes, tumor mutational burden, and HLA type

6 Trial Endpoints

6.1 Primary Endpoint

The primary endpoint is ORR according to RECIST v. 1.1.

6.2 Secondary Endpoints

The Key secondary endpoints are the following:

- Progression-free survival (PFS) according to RECIST v. 1.1
- Duration of response (DOR)
- Complete response rate (CRR)
- Disease control rate (DCR)
- Time to response (TTR)

Safety endpoints:

- Incidence of participants with AEs [Up to 3 years]
- Incidence of participants with SAEs [Time Frame: Up to 3 years]
- Incidence of treatment-related AEs [Time Frame: Up to 3 years]
- Incidence of treatment-related SAEs [Time Frame: Up to 3 years]
- Incidence of AEs causing discontinuation of trial treatment

6.3 Exploratory Endpoints

- Overall survival (OS)
- PFS according to iRECIST (iPFS)
- Analysis of the tumor microenvironment for IDO and PD-L1 expression and lymphocyte infiltration
- Circulating tumor DNA as a surrogate measure of tumor burden
- Assessment of peripheral immune cell function and treatment-specific T cell responses
- ORR and PFS according to independent central review, if applicable

7 Background

7.1 Therapeutic Background

7.1.1 NSCLC Background

7.1.1.1 Epidemiology

Lung cancer remains the leading cause of cancer deaths worldwide, accounting for approximately 12% of all new cancers in 2018 (Bray *et al.*, 2018). In 2021 in the United States, it is estimated that there are 235,760 new cases of lung cancer (119,100 in men and 116,660 in women) and 131,880 lung cancer deaths (Siegel *et al.*, 2021). Similar data from Europe estimate that in 2018 there were 387,900 lung cancer deaths (267,300 in men and 120,600 in women) (Ferlay *et al.*, 2019).

NSCLC is the predominant subtype, accounting for approximately 85% of all cases (Molina *et al.*, 2008; Howlader *et al.*, 2014). NSCLC can be divided into two major histologic types: adenocarcinoma and squamous cell carcinoma (Travis *et al.*, 2011). Adenocarcinoma histology accounts for more than half of all NSCLC, while squamous cell histology accounts for approximately 25% of NSCLC (Langer *et al.*, 2010). The remaining cases of NSCLC are represented by large-cell carcinoma, neuroendocrine tumors, sarcomatoid carcinoma, and poorly differentiated histology.

Genetic changes that have prognostic and/or predictive significance in NSCLC include mutations in the epidermal growth factor receptor (EGFR) gene, rearrangements in the anaplastic lymphoma kinase (ALK) gene, and mutations in the Kirsten rat sarcoma viral oncogene homolog (KRAS) gene. The rates of these mutations differ between adenocarcinoma and squamous cell carcinoma. For example, EGFR kinase domain mutations have been reported in 10%-40% of patients with adenocarcinoma NSCLC but are infrequently observed in patients with squamous NSCLC (Herbst, Heymach and Lippman, 2008). The ALK fusion oncogene, recognized as a driver of lung tumorigenesis, is observed in approximately 7% of patients with adenocarcinoma but is rare in squamous histology (Herbst, Heymach and Lippman, 2008; Langer *et al.*, 2010). In addition, KRAS mutations can be observed in up to 30% of adenocarcinoma NSCLC, while they are rare in squamous NSCLC (Travis et al. 2011).

7.1.1.2 First-Line Immunotherapy as Monotherapy for Advanced NSCLC with high (≥ 50%) PD-L1 Expression

Chemotherapy-based regimens are associated with substantial toxicities and are generally poorly tolerated by elderly patients and by patients with poor performance status. Therefore, novel therapies that deliver an improved therapeutic index are needed for NSCLC. Pursuing personalized cancer immunotherapy (CIT), several Phase III trials have been conducted to investigate chemotherapy-free regimens involving anti-PD-L1/PD-1 inhibitors versus standard cytotoxic chemotherapy in treatment-naive patients with PD-L1-positive NSCLC without an activating EGFR mutation or ALK gene rearrangement. These randomized trials have demonstrated that a high level of programmed cell death ligand 1 (PD-L1) expression predicts response to pembrolizumab, atezolizumab and cemiplimab. This level of PD-L1 expression may be seen in approximately 30 % of advanced NSCLCs (Reck *et al.*, 2016).

The KEYNOTE-024 trial demonstrated significant improvement in survival with pembrolizumab monotherapy over standard platinum-based doublets in advanced NSCLC with high PD-L1 expression (tumor proportion score [TPS] ≥50% assessed using the PD-L1 immunohistochemistry

[IHC] 22C3 pharmDx assay), with OS HR = 0.63 (95% CI: 0.44% to 0.91%), p <0.002, median OS 30.0 versus 14.2 months; and PFS HR = 0.50, p <0.001, median PFS 10.3 versus 6.0 months (Reck *et al.*, 2016, 2019).

In KEYNOTE-042 trial, patients with a tumor proportion score (TPS) ≥1% (determined using the PD-L1 IHC 22C3 pharmDx assay) were enrolled, survival outcomes of pembrolizumab compared with chemotherapy doublets in the two primary patient populations with a TPS ≥50% and a TPS ≥1% were OS HR = 0.69, p <0.0003, median OS: 20.0 versus 12.2 months, and OS HR = 0.81, p <0.0018, median OS: 16.7 versus 12.1 months, respectively. However, patients in a prespecified exploratory subgroup with TPS 1%-49% appeared to have similar OS in the two arms: HR = 0.92, median OS 13.4 versus 12.1 months; 95% CI: 0.77 to 1.11 months (Mok *et al.*, 2019). Based on results from these studies, pembrolizumab is approved for the the first line treatment of patients with metastatic NSCLC without an activating EGFR mutation or ALK gene rearrangement, whose tumors express PD-L1 (TPS ≥1%) in the United States and in patients whose tumors express high PD-L1 (TPS ≥50%) in the European Union.

Recently, atezolizumab monotherapy has also demonstrated a statistically significant and clinically meaningful improvement in OS compared with platinum-based doublet chemotherapy as first line treatment of metastatic NSCLC that expresses high PD-L1 in the IMpower110 trial (Herbst *et al.*, 2020). IMpower110 is a Phase III, randomized, open-label trial evaluating the efficacy and safety of atezolizumab monotherapy compared with platinum-based doublet chemotherapy in PD-L1-selected, chemotherapy-naive patients with advanced non-squamous or squamous NSCLC without EGFR or ALK mutations (wild type [WT]).

Only patients whose tumors expressed PD-L1 (defined as tumor cell [TC]1/2/3 or immune cell [IC]1/2/3, as determined by the VENTANA® SP142 IHC Assay) were eligible. A total of 572 patients were enrolled and were randomized in a 1:1 ratio to receive atezolizumab monotherapy, cisplatin, or carboplatin (per investigator discretion) combined with either pemetrexed (non-squamous) or gemcitabine (squamous), followed by maintenance therapy with pemetrexed alone (non-squamous) or best supportive care (squamous). The trial enrolled patients with an EGFR mutation or ALK translocation who had disease progression or intolerable toxicity to treatment with a tyrosine kinase inhibitor; these patients were excluded from the analysis population, which included WT patients only (554 WT patients). The primary efficacy endpoint was OS by PD-L1 subgroup (TC3/IC3-WT; TC2/3 IC2/3-WT; and TC1/2/3 IC1/2/3-WT), as determined using the VENTANA PD-L1 SP142 IHC assay. Key secondary endpoints included investigator-assessed PFS, ORR, and DOR.

At the time of the interim OS analysis (clinical cutoff date: 10 September 2018), atezolizumab monotherapy showed a statistically significant and clinically meaningful improvement in OS compared with chemotherapy in patients with high PD-L1 expression (TC3/IC3-WT) with a stratified HR (95% CI) of 0.595 (0.398 to 0.890), p <0.0106, median OS 20.2 months versus 13.1 months (see Table 1). Because the OS statistical testing boundary was not crossed in the TC2/3 or IC2/3-WT or TC1/2/3 or IC1/2/3-WT subgroups at this interim analysis, the trial will continue to the OS final analysis for these subgroups.

IMpower110 also demonstrated a clinically meaningful improvement in investigator-assessed PFS for atezolizumab in patients with high PD-L1 expression (TC3/IC3-WT) with a stratified HR (95% CI) of 0.630 (0.449 to 0.884) and median PFS of 8.1 months versus 5.0 months. Atezolizumab monotherapy was also associated with improved ORR in the TC3/IC3-WT subgroup, with durable responses compared to chemotherapy.

More recently, cemiplimab, a PD-1 inhibitor, improved OS and PFS compared with chemotherapy in patients with advanced NSCLC with PD-L1 of ≥50 % without an EGFR, ROS1, or ALK genetic aberration (Sezer *et al.*, 2021), and has the Food and Drug Administration (FDA) approval for this indication.

In the EMPOWER-Lung 1 trial, among 563 patients with advanced NSCLC with PD-L1 of ≥50 %, cemiplimab 350 mg every three weeks improved OS relative to platinum-doublet chemotherapy (median, not reached versus 14.2 months, respectively; HR 0.57, 95% CI 0.42-0.77), as well as PFS (8.2 versus 5.7 months; HR 0.54, 95% CI 0.43-0.68) (Sezer *et al.*, 2021). OS and PFS were also improved in the intention-to-treat population of 710 patients (which additionally included patients with PD-L1 expression that had not been confirmed or had been established as <50 %), despite 74 % crossover. Grade ≥3 toxicities were 28 % with cemiplimab and 39 % with chemotherapy.

Overall, chemotherapy-free options with first line immunotherapy offers patients with advanced NSCLC expressing PD-L1 significant survival benefits as well as a more tolerable toxicity profile. Despite improvements and benefits with PD-L1/PD-1-targeting agents, nearly all patients experience disease progression. Consequently, new molecules and combinations, including novel immunotherapy combinations, are needed to address this unmet medical need.

7.1.2 SCCHN Background

7.1.2.1 Epidemiology

SCCHN develop from the mucosal epithelium in the oral cavity, pharynx and larynx and are the most common malignancies that arise in the head and neck. The burden of SCCHN varies across countries and regions and has generally been correlated with exposure to tobacco-derived carcinogens, excessive alcohol consumption, or both. Increasingly, tumors that arise in the oropharynx are linked to prior infection with oncogenic strains of HPV, primarily HPV-16, and, to a lesser extent, HPV-18 and other strains (Isayeva *et al.*, 2012; Michaud *et al.*, 2014; Stein *et al.*, 2015). HPV-positive SCCHN generally has a more favourable prognosis than HPV-negative SCCHN (Johnson *et al.*, 2020).

Median age of diagnosis for non-virally associated SCCHN is 66 years, whereas the median age of diagnosis for HPV-associated oropharyngeal cancer and Epstein-Barr virus (EBV)-associated nasopharyngeal cancer is ~53 years and ~50 years, respectively (Windon *et al.*, 2018). The survival for SCCHN has improved modestly over the past three decades; for example, the 5-year survival increased from 55% during the period 1992-1996 to 66% during the period 2002-2006 when analysed across all age groups and anatomical sites within the Surveillance, Epidemiology, and End Results (SEER) registry (Pulte and Brenner, 2010).

7.1.2.2 Frontline treatment options for locoregional recurrence and metastatic SCCHN

Patients with locoregional recurrence (R) who are not amenable to surgery and/or radiotherapy as well as those with metastatic (M) disease are eligible for systemic treatment (Machiels *et al.*, 2021). Standard of care has for more than a decade been platinum base chemotherapy plus cetuximab based on results from the EXTEREME trial (Vermorken *et al.*, 2008). Addition of cetuximab to cisplatin-5-fluorouracil (5-FU) increased OS from 7.4 months with platinum-5-FU to 10.1 months with platinum,

5-FU and cetuximab. In the EXTREME trial, the corresponding ORR increased from 20 to 30% and the PFS increased from 3.3 to 5.6 weeks. The EXTREME regimen is associated with a 82% frequency of Grade 3/4 toxicities. Paclitaxel or docetaxel-based regimens are also used, but have yet to be compared head-to-head with the EXTREME regimen. Recent studies showed that the median OS of the EXTREME regimen may be prolonged (approximately 11 months) than that seen in original studies which showed a median OS published in 2008 of approximately 10 months (Vermorken *et al.*, 2014; Bossi *et al.*, 2017; Ferris *et al.*, 2018).

Since R/M first line patients have somewhat heterogeneous characteristics, National Comprehensive Cancer Network (NCCN 2021) guidelines (Guidelines Detail (nccn.org)) highlight the importance of considering individualized systemic therapies based on patient characteristics, given the toxicity of the EXTREME regimen. NCCN guidelines offer consideration of the use of alternative combination regimens including platinum plus taxane, cisplatin plus cetuximab and cisplatin plus 5-FU, or the use of these agents as monotherapies.

According to the guidelines of the European Society for Medical Oncology (ESMO), in the first-line treatment of recurrent SCCHN, EXTREME is standard of care for patients with contraindications to anti-PD-1 inhibitors and in patients with a tumor not expressing PD-L1. EXTREME can also be considered as second-line treatment after progression on an immune checkpoint inhibitor in fit patients considered eligible for platinum-based chemotherapy (Machiels *et al.*, 2021).

7.1.2.3 Pembrolizumab in frontline SCCHN

The standard of care first-line therapy for recurrent and/or metastatic disease has changed recently. The KEYNOTE-048 trial showed that the combination of platinum based chemotherapy plus pembrolizumab significantly improved OS compared with the EXTREME regimen (cisplatin or carboplatin plus 5-FU plus cetuximab): median OS 13.0 versus 10.7 months (p=0.0034) (Burtness *et al.*, 2019). Objective response rate (ORR) and PFS were similar between the chemotherapy plus cetuximab and chemotherapy plus pembrolizumab arms [ORR 35.6% and 36.3%, PFS 4.9 and 5.1 months, Grade 3-5 adverse events (AEs) 85.1% versus 83.3%, respectively].

Pembrolizumab monotherapy also improved median OS in patients with PD-L1-expressing SSCHN: 14.9 versus 10.7 months in the CPS ≥20 subgroup and 12.3 versus 10.3 months in the CPS ≥1 subgroup. As expected, pembrolizumab monotherapy was better tolerated than the EXTREME regimen (Grade 3-5 AEs 54.7% versus 83.3%, respectively). However, PFS with pembrolizumab monotherapy was not significant compared with EXTREME: 3.4 versus 5.0 months in CPS ≥20 and 3.2 versus 5.0 months in CPS ≥1. Similarly, ORR for pembrolizumab monotherapy versus EXTREME regimen was 23.3% versus 36.1% and 19.1% versus 34.9% in the CPS ≥20 and CPS ≥1 groups, respectively.The 6 month estimates for PFS in patients with CPS >20 was 32% in the pembrolizumab alone arm and 45% in the cetuximab plus chemotherapy arm.

Therefore, based on the KEYNOTE-048 results, two different approaches are validated for patients with locoregional relapse not amenable to locoregional salvage treatment and/or with distant metastases (Machiels *et al.*, 2021). A ‘chemo-free’ approach with pembrolizumab monotherapy in patients with CPS ≥1 SCCHN should be considered, especially when a rapid tumor shrinkage is not needed. A second option, independent of PD-L1 status, is the combination of pembrolizumab and chemotherapy (cisplatin or carboplatin plus 5-FU), particularly in symptomatic patients or when a rapid tumor shrinkage is needed (Machiels *et al.*, 2021).

The FDA recently approved pembrolizumab in combination with chemotherapy as first-line treatment regardless of PD-L1 expression and pembrolizumab alone for patients with PD-L1-expressing tumors (CPS ≥1). In contrast, the European Medicines Agency (EMA) has approved pembrolizumab with or without chemotherapy only for patients with a CPS ≥1 [I, A; ESMO-Magnitude of Clinical Benefit Scale (ESMO-MCBS) v1.1 score: 4] (Machiels *et al.*, 2021).

7.1.3 mUBC Background

7.1.3.1 Epidemiology

Urothelial carcinoma (UC, also termed transitional cell carcinoma [TCC], urothelial bladder cancer or urothelial cell carcinoma [UCC] of the urinary tract) describes a range of tumors that arise from the urothelial endothelium, which includes the bladder, renal pelvis, ureter, and urethra. The worldwide incidence of bladder cancer exceeds 300,000 cases annually, ranking it as the seventh most common cancer worldwide (Jemal *et al.*, 2011). TCC is the most common histologic subtype associated with bladder cancer and accounts for greater than 90% of all urothelial carcinoma cases in the industrialized world, whereas non-urothelial subtypes, including squamous cell, adenocarcinoma, and small cell carcinoma, are more frequent in other areas of the world (Chalasani, Chin and Izawa, 2009).

7.1.3.2 Frontline treatment options for mUBC

Cisplatin-based combination chemotherapy is the preferred standard first-line treatment for medically fit patients patients with previously untreated metastatic urothelial bladder carcinoma based on randomized trials (Logothetis *et al.*, 1990; Loehrer *et al.*, 1992; Saxman *et al.*, 1997; Von der Maase *et al.*, 2000; Von Der Maase *et al.*, 2005; Sternberg *et al.*, 2006; Galsky, Hahn, Rosenberg, Sonpavde, Hutson, Oh, Dreicer, Vogelzang, C. Sternberg, *et al.*, 2011). The median survival with these regimens is 13 to 15 months, and 5% to 15% of patients attain long-term survival. However, the presence of pre-existing co morbidities such as renal dysfunction, poor performance status, neuropathy and heart failure usually confers cisplatin ineligibility (Dash *et al.*, 2006; Galsky, Hahn, Rosenberg, Sonpavde, Hutson, Oh, Dreicer, Vogelzang, C. N. Sternberg, *et al.*, 2011; Galsky, Hahn, Rosenberg, Sonpavde, Hutson, Oh, Dreicer, Vogelzang, C. Sternberg, *et al.*, 2011) and up to 50% of patients are ineligible for a cisplatin based regimen.

Immune checkpoint inhibitors have revolutionized the field of oncology, providing a novel mechanism for anticancer therapy. PD-1-targeting antibodies pembrolizumab and nivolumab and PD-L1-targeting antibodies atezolizumab and avelumab have been approved for use in advanced urothelial cancer in the post-platinum setting or in the upfront setting in platinum-ineligible patients. While this represents a significant step forward in management of urothelial cancers, most patients do not have an objective response to these therapies. PD-L1 expression is not a consistently predictive biomarker, but is recommended for checkpoint utilization in select circumstances.

In addition to approval for patients who progress following platinum-based chemotherapy, atezolizumab and pembrolizumab are approved in the first-line setting for mUBC. Both agents were initially approved as first-line treatment for cisplatin-ineligible patients on the basis of the Phase II IMvigor210 (Balar, Galsky, *et al.*, 2017) and KEYNOTE-052 (Balar, Castellano, *et al.*, 2017) trials. Subsequently, the randomized phase III IMvigor130 trial of atezolizumab and KEYNOTE-361 trial of pembrolizumab enrolled platinum-eligible patients with locally advanced/metastatic UC and no prior systemic therapy to receive atezolizumab/pembrolizumab with or without platinum-based chemotherapy versus platinum-based chemotherapy alone (Suzman *et al.*, 2019). In June 2018, interim analyses of these two trials showed that patients with low PD-L1 expression receiving atezolizumab or pembrolizumab monotherapy had decreased survival compared with patients with

low PD-L1 expression who received platinum-based chemotherapy, leading to a change in drug approval (Suzman *et al.*, 2019). Currently, atezolizumab and pembrolizumab are indicated as first-line treatment for locally advanced /metastatic UC patients who are cisplatin-ineligible and whose tumors express PD-L1 or patients who are not eligible for any platinum therapy regardless of PD-L1 status.

There is also growing evidence to suggest that the clinical benefit of the combination of immune checkpoint inhibitors with chemotherapy in the first-line setting may be limited. Results from IMvigor130 evaluating the combination of atezolizumab plus chemotherapy demonstrated a PFS benefit over chemotherapy alone (8.2 versus 6.3 months; HR 0.82, 95% CI 0.70–0.96) but this benefit was small and of questionable clinical significance (Grande *et al.*, 2019). Thus, there remains a significant unmet medical need for well-tolerated active therapies in this population.

7.1.3.3 Pembrolizumab in mUBC

The phase II KEYNOTE-052 trial studied pembrolizumab as first-line treatment for 370 cisplatin-ineligible patients with metastatic urothelial carcinoma (Balar, Castellano, *et al.*, 2017) ORR was 24% in all patients who received at least one dose of pembrolizumab. The ORR was higher (38%) in patients with a CPS of 10 or more. The ongoing Phase III KEYNOTE-361 trial (NCT02853305) is randomizing treatment-naive metastatic urothelial cancer patients 1:1:1 to receive pembrolizumab, pembrolizumab plus investigator's choice of chemotherapy (containing cisplatin), or chemotherapy alone. Patients who are cisplatin-ineligible are randomized to a carboplatin-based regimen. The indication label for pembrolizumab includes cisplatin-ineligible patients, as long as they have a CPS ≥10 by an FDA-approved test or patients who are not eligible for any platinum-containing chemotherapy regardless of PD-L1 status.

7.2 IDO and PD-L1 Antigens as Targets

Cancer cells are naturally attacked by cells of the immune system, including cytotoxic T cells. Cancer cells can induce a state of tolerance whereby they can escape this immune system response. This effect is brought about by many different mechanisms; some of the most important are through overexpression of the PD-1, PD-L1 molecules and the metabolic enzyme IDO. The PD-1 receptor is expressed on various cells, including T cells. The blocking of PD-1 on T cells by PD-1 blocking antibodies protects the T cells from the inactivation signal from PD-L1 expressed by cancer cells or immune regulatory cells. Pembrolizumab is a PD-1 blocking antibody that has been shown to provide an objective clinical response rate in 45% of the patients with melanoma (Pedoeem et al., 2014) 39% of patients with NSCLCwith TPS ≥50% (Mok et al. 2019), 23% of patients with SCCHN CPS ≥20 (Burtness et al. 2019) and 32% of patients with mUBC CPS ≥10 (Powles et al. 2021)

The expression of the metabolic enzyme IDO is induced on various host cells and tumor cells upon exposure to IFN-γ. Activation of IDO inhibits cytotoxic T cells by depleting the microenvironment of amino acids crucial to the function of lymphocytes (Van Allen *et al.*, 2014).

Spontaneous T cell reactivity against IDO and PD-L1 in the tumor microenvironment and in the peripheral blood of various cancer patients and healthy donors has been identified (Søorensen *et al.*, 2009; Sørensen *et al.*, 2011; S. Munir *et al.*, 2013; Shamaila Munir, Andersen, Met, *et al.*, 2013; Shamaila Munir, Andersen, Svane, *et al.*, 2013; Ahmad *et al.*, 2016). The IDO reactive $CD8^+$ T cells were cytotoxic and could kill both cancer cells and immune regulatory dendritic cells *in vitro*. The PD-L1 reactive $CD8^+$ T cells were also cytotoxic and were able to kill cancer cells and myeloid derived suppressor cells (MDSCs). Therefore, boosting specific T cells that recognize immune regulatory proteins, such as IDO and PD-L1, may directly modulate immune regulation (Sørensen *et al.*, 2009; Sørensen *et al.*, 2011; S. Munir *et al.*, 2013; Shamaila Munir, Andersen, Met, *et al.*, 2013;

Shamaila Munir, Andersen, Svane, *et al.*, 2013; Ahmad *et al.*, 2016). Due to the distinctive mechanisms of action, the combination of treatment with a monoclonal antibody targeting PD-1 and PD-L1 and IDO peptides are expected to have synergistic effects. There is nothing to suggest that combining pembrolizumab with the experimental IDO and PD-L1 peptide injection should be more toxic than treatment with pembrolizumab alone. The PD-L1 peptide (PD-L19-27; IO103) and IDO peptide (IDO194-214; IO102) both contain $CD8^+$ T cell epitopes as well as $CD4^+$ T cell epitopes. IO102-IO103 consisting of IDO and PD-L1 peptides boosts the natural immunity mediated by IDO and PD-L1 specific T cells. These can attack and kill regulatory immune cells and cancer cells as well as support additional anti-cancer immunity by the release of helper cytokines.

7.3 Pharmaceutical Background

7.3.1 IO102 and IO103

IO102 is an immunotherapeutic targeting the immunoregulatory enzyme IDO, a critical endogenous cellular factor that contributes to immune suppression and tumor immune escape. IDO activity constitutes a counter regulatory mechanism induced by proinflammatory signals, which is a crucial mechanism in cancer. Patients with cancer may exhibit increased IDO expression, which can be detected both in immune cells and tumor cells. IDO is involved in the regulation of the immune response by suppressing T-cell function as well as enabling local tumor immune escape. In cancer, IDO can either be expressed directly by the tumor cells themselves or induced indirectly in the host antigen presenting cells by the tumor. In these settings, IDO mediates an acquired immune tolerance towards tumors, allowing tumors to evade immune responses by the host. Furthermore, high IDO expression has been shown to be correlated with a poor prognosis and shorter OS in various malignancies. Therefore, IDO is an attractive target in therapeutic interventions aimed at restoring the immune response towards the tumor and may serve as a widely applicable target for a therapeutic cancer immunotherapeutic.

IO103 is an immunotherapeutic targeting the PD-L1 antigen. It is a single PD-L1-derived peptide designed to engage and activate PD-L1–specific T-cells. IO103 consists of a 19-amino acid peptide from the signal peptide of PD-L1.

Refer to the most recent versions of the Investigator's Brochure (IB) for IO102-IO103 for detailed information on the trial treatments and full pre-clinical and clinical data.

7.3.2 Pembrolizumab

Pembrolizumab is a potent humanized immunoglobulin G4 (IgG4) monoclonal antibody with high specificity of binding to the PD-1 receptor, thus inhibiting its interaction with PD-L1 and programmed cell death ligand 2 (PD-L2). Based on preclinical in vitro data, pembrolizumab has high affinity and potent receptor blocking activity for PD-1. Pembrolizumab has an acceptable preclinical safety profile and is in clinical development as an IV immunotherapy for advanced malignancies. Pembrolizumab is indicated for the treatment of patients across a number of indications. For more details on specific indications, refer to the IB for pembrolizumab.

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 immunoglobulin superfamily member related to cluster of differentiation 28 (CD28) and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) that has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (PD-L1 and/or PD-L2) (Greenwald et al., 2005).

The structure of murine PD-1 has been resolved (Zhang *et al.,* 2004). PD-1 and its family members are type I transmembrane glycoproteins containing an Ig-variable–type (IgV-type) domain responsible for ligand binding and a cytoplasmic tail 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, and an immunoreceptor tyrosine-based switch motif. Following T-cell stimulation, PD-1 recruits the tyrosine phosphatases, SHP-1 and SHP-2, to the immunoreceptor tyrosine-based switch motif within its cytoplasmic tail, leading to the dephosphorylation of effector molecules such as CD3 zeta (CD3ζ), protein kinase C-theta (PKCθ), and zeta-chain-associated protein kinase (ZAP70), which are involved in the CD3 T-cell signaling cascade (Okazaki et al., 2001; Chemnitz *et al*., 2004). The mechanism by which PD-1 down-modulates T-cell responses is similar to, but distinct from, that of CTLA-4, because both molecules regulate an overlapping set of signaling proteins (Francisco *et al*., 2010). As a consequence, the PD-1/PD-L1 pathway is an attractive target for therapeutic intervention in NSCL, SCCHN and mUBC.

Pembrolizumab has an acceptable preclinical safety profile and is in clinical development as an IV immunotherapy for advanced malignancies. Pembrolizumab is indicated for the treatment of patients across a number of indications. For more details on specific indications refer to the IB for pembrolizumab.

7.4 Nonclinical and Clinical Trials

7.4.1 Pembrolizumab Pre-Clinical and Clinical Trials

Therapeutic studies in mouse models have shown that administration of antibodies blocking PD-1/PD-L1 interaction enhances infiltration of tumor-specific CD8+ T cells and ultimately leads to tumor rejection, either as a monotherapy or in combination with other treatment modalities (Hirano *et al*., 2005; Blank *et al*., 2004; Curran *et al*., 2010; Pilon *et al*., 2010). Anti-mouse PD-1 or anti-mouse PD-L1 antibodies have demonstrated antitumor responses in models of squamous cell carcinoma, pancreatic carcinoma, melanoma, acute myeloid leukemia and colorectal carcinoma (Curran *et al*., 2010; Pilon *et al*., 2010; Zhang *et al*., 2004). In such studies, tumor infiltration by CD8+ T cells and increased IFN-γ, granzyme B and perforin expression were observed, indicating that the mechanism underlying the antitumor activity of PD-1 checkpoint inhibition involved local infiltration and activation of effector T cell function *in vivo* (Curran, 2010). Experiments have confirmed the *in vivo* efficacy of anti-mouse PD-1 antibody as a monotherapy, as well as in combination with chemotherapy, in syngeneic mouse tumor models (see the IB for pembrolizumab).

7.4.2 IO102 Pre-Clinical

In summary, *ex vivo* proof-of-concept (PoC) studies demonstrate that the IO102 IDO peptide injection:

- has the ability to bind stably to human leucocyte antigen (HLA) to allow efficient antigen presentation by antigen presenting cells (APC);
- is recognised by the peptide-specific T cells, leading to activation of IDO-specific T cells;
- can activate IDO-specific T cells to differentiate into effector T cells and demonstrate cytotoxicity in the case of $CD8^+$ T cells.

In addition, *in vivo* PoC studies in syngeneic mouse tumor models reveal that IDO-targeting vaccine induces expansion of IDO-specific T cells in mice, leading to demonstrable anti-tumor therapeutic responses accompanied by reduction of IDO^+immune suppressive cells in the tumor. In addition, efficacy of IDO peptide injection in a syngeneic mouse colon carcinoma model, CT26, is further

improved by co-administration of anti-PD-1 antibody.

Two repeat dose toxicology studies (one Good Laboratory Practise (GLP)-compliant) with IO102 in mice applying doses up to 50 µg SC weekly for 8 weeks have shown that IO102 peptide injection was well tolerated without causing any dermal reactions at the injection sites or any systemic toxicity.

7.4.3 IO102 Clinical Trials

IO102 and its predecessor, IO101 have been studied in humans in the following clinical trials:

The first immune modulating peptide to be investigated was a short peptide IO101. This was a 9-amino acid peptide, which was investigated in a Phase I trial in patients with metastatic NSCLC. The IO101 peptide is an HLA-A2-restricted, IDO-derived $CD8^+$ T-cell epitope. IO101 comprises only the MHC class I-restricted $CD8^+$ T-cell epitope that is entirely contained within a longer peptide, the IO102. The IO102 comprises of both $CD8^+$ T-cell epitopes and $CD4^+$ T-cell epitopes.

Fifteen HLA-A2 positive patients with Stage III-IV NSCLC in disease stabilization after standard chemotherapy (at least 28 days after last dose of chemotherapy) were treated with the IO101 IDO peptide, 85 µg once every 2 weeks (Q2W) for 12 weeks and subsequently once Q4W until disease progression or death.

The IO101 peptide injection was well tolerated with no treatment related AEs of CTCAE Grade >2. In terms of longer follow-up (>5 years), the IO101 was well tolerated with no severe AEs for administration up to 5 years (Iversen *et al.*, 2014, Kjeldsen *et al.,* 2018). Two of 15 patients were long-term survivors with ongoing clinical response 6 years after the first treatment and with presence of IDO-specific T cells in the blood at several time points.

IO102 was studied in a first in human trial (Bjoern *et al.,* 2016) in combination with ipilumumab in patients with malignant melanoma (MM1304). Ten patients with histologically verified unresectable Stage III or IV malignant melanoma were treated with IO102 at a dose of 250 µg once weekly for 4 weeks and subsequently once Q2W for a total of 7 administrations. In addition, the patients received ipilimumab administered IV at a dose of 3 mg/kg bodyweight. In total, four series of ipilimumab were given, 3 weeks apart.

All 10 patients received at least 5 administrations of the IO102 peptide injection. One patient had received IFN-α in an adjuvant setting before entering the trial. None of the patients had received any prior systemic therapy for metastatic disease. At the first evaluation at 12 weeks, 5/10 treated patients were in stable disease, 1 of whom had an unconfirmed PR with a 44% reduction of target lesion (TL) diameter. Five patients progressed and were referred to other treatments. Two of the 5 patients with SD at the first evaluation were confirmed, 2 progressed by the second evaluation, and 1 patient died between the first and second evaluations. The death was considered unrelated to IO102.

Future trials will evaluate the safety and efficacy of IO102-IO103 in a range of tumors including melanoma and HNSCC (NCT: 04445064). Please refer to current IO102-IO103 IB.

Review of the ipilimumab safety data only revealed findings already known for the compound. IO102 was well tolerated with no associated CTCAE Grade 3/4 AEs reported.

7.4.4 IO103 Pre-Clinical Studies

In summary: *ex-vivo/in vitro* PoC studies demonstrate that the IO103 PD-L1 peptide:

- has the ability to bind stably to HLA to allow efficient antigen presentation by APC;
- is recognized by PD-L1-specific T cells, leading to activation of PD-L1-specific T cells;
- can activate PD-L1-specific T cells to differentiate into effector T cells that demonstrate

(MacKie *et al.,* 2009) cytotoxicity in the case of $CD8^+$ T cells and (Schadendorf *et al.,* 2018) enhancement of activity of other effector T cells.

In addition, *in vivo* PoC studies reveal that PD-L1 peptide treatment IO103 induces expansion of PD-L1-specific T cells in mice, leading to demonstrable anti-tumor activity in a syngeneic mouse tumor model (CT26). In addition, in the same model, administration of IDO- and PD-L1 peptides together leads to additive anti-tumor therapeutic response.

7.4.5 IO103 Clinical Trials

IO103 monotherapy has been studied in 2 investigator-initiated trials – 1 in multiple myeloma (MM) and 1 in basal cell carcinoma (BCC).

The multiple myeloma trial (NCT03042793, MY0001) has been completed and was a first in human, open-label, single-center trial investigating safety, immunological response, and clinical response of treatment with PD-L1 peptide emulsified with Montanide adjuvant in patients with multiple myeloma (MM) after high-dose chemotherapy with stem cell support (Jørgensen *et al.*, 2020). Patients received IO103 every 2 weeks (Q2W) for the first 10 weeks and thereafter monthly for 9 months *e.g.* 15 administrations in total. Before treatment, 4 patients were in CR or better, and 5 patients were in very good partial response (VGPR). Following treatment, 3 patients showed an improved depth of response during therapy, and a further patient exhibited spontaneous basal cell carcinoma (BCC) clearance and was macroscopically complete. The rate of relapses was as expected for the population.

Grade I/II self-limiting injection site reactions (itching, tenderness and redness), were reported in 9/10 patients. During treatment, a total of 9 Grade 3 AEs were reported and none have been deemed related to the treatment with IO103. The level of infections and other AEs were as expected in the period after high-dose chemotherapy and autologous stem cell transplantations. No Grade 4 or 5 toxicities were reported.

IO103 was tested as monotherapy in patients with resectable BCC based on the regression of 2 BCCs seen in the myeloma trial. The aim of the trial was to assess the safety and efficacy IO103 therapy in 10 patients with BCC. Patients were treated with IO103 together with Montanide as adjuvant up to 9 times during 6 months. Regression in tumor size of at least 30% was seen in 5 of 18 tumors, 2 of which showed complete regression of individual tumors but not all tumors in single individuals. Treatments resulted in immune responses against the therapy in blood samples from 9/10 patients and in skin samples from 5/9 patients. The monotherapy of IO103 was well tolerated as the most frequent AEs were local injection site reactions which were easily manageable (Jørgensen *et al.*, 2020).

See the IB for further clinical trial details.

7.4.6 IO102-IO103 – Clinical Trial

Currently, 1 ongoing trial investigates IO102-IO103 in combination with nivolumab standard of care in patients with melanoma.

The clinical trial is a Phase I/II trial and includes 30 patients with metastatic melanoma in a first line setting (NCT03047928, MM1636). This ongoing open-label, single-center trial started in October 2017 and is investigating safety and efficacy of combination therapy with nivolumab and the IDO/PD-L1 (IO102-IO103) antigen**.** The IO102-IO103 antigen is administered from the start of nivolumab treatment, i.e., bi-weekly for the first 6 administrations and thereafter every 4th week for up to 1 year.
Baseline characteristics of the 30 patients are representative of a typical trial population of metastatic melanoma. Of note, 13 (43%) patients had PD-L1 negative tumors (PD-L1<1%) and 18 (60%) had visceral metastatic/M1c disease. Additionally, 19 (63%) patients' tumors were BRAF WT and 11

(37%) carried a BRAF mutation. Twenty-four patients (80.0%) had an objective response, and 22 of these patients have a radiologically confirmed objective response (73.3%) assessed by RECIST v. 1.1 at least 4 weeks after the first response observation. Of the 17 patients with PD-L1 positive disease, 15 obtained a confirmed objective response (88.2%) while in the 13 patients with PD-L1 negative disease, 7 obtained a confirmed objective response (53.8%). Complete responses were seen in 8 patients with M1c disease and four of these patients had a PD-L1-negative tumor. Of the 22 patients with a confirmed objective response, 14 patients had disease progression. Overall, 8 patients died, 1 due to AEs considered unrelated to IO102-IO103 treatment; the remaining patients discontinued due to progression and died. Median PFS was 25.3 months. The 85 μg doses were well tolerated in combination with nivolumab, with no DLTs. Based on the similarities between nivolumab and pembrolizumab, the doses are expected to be well tolerated with pembrolizumab, with no need for a safety run-in.

A summary is included in the most recent IO102-IO103 IB. Results have been published (Kjeldsen *et al.*, 2021) and presented at ESMO (Svane, 2020) and AACR (Kjeldsen *et al.*, 2022).

8 Rationales

8.1 Rationale for Pembrolizumab Dose and Schedule

The planned dose of pembrolizumab for this trial is 200 mg every Q3W. Based on the totality of data generated in the Keytruda development program, 200 mg Q3W is an appropriate dose of pembrolizumab for adults across all indications. As outlined below, this dose is justified by:

- Clinical data from 8 randomized studies in melanoma and NSCLC indications demonstrating flat dose- and exposure-efficacy relationships from 2 mg/kg Q3W to 10 mg/kg every 2 Q2W representing an approximate 5 to 7.5 fold exposure range (refer to the IB for pembrolizumab)
- Population pharmacokinetic (PK) analysis showing that both fixed dosing and weight-based dosing provides similar control of PK variability with considerable overlap in the distributions of exposures, supporting suitability of 200 mg Q3W
- Clinical data showing meaningful improvement in benefit-risk including overall survival at 200 mg Q3W across multiple indications, and
- Pharmacology data showing full target saturation in both systemic circulation (inferred from PK data) and tumor (inferred from physiologically-based PK [PBPK] analysis) at 200 mg Q3W.

Among the 8 randomized dose-comparison studies, a total of 2262 participants were enrolled with melanoma and non-small cell lung cancer (NSCLC), covering different disease settings (treatment naïve, previously treated, PD-L1 enriched, and all-comers) and different treatment settings (monotherapy and in combination with chemotherapy). Five studies compared 2 mg/kg Q3W versus 10 mg/kg Q2W (KN001 Cohort B2, KN001 Cohort D, KN002, KN010, and KN021), and 3 studies compared 10 mg/kg Q3W versus 10 mg/kg Q2W (KN001 Cohort B3, KN001 Cohort F2 and KN006). All of these studies demonstrated flat dose- and exposure-response relationships across the doses studied representing an approximate 5- to 7.5-fold difference in exposure. The 2 mg/kg (or 200 mg fixed-dose) Q3W provided similar responses to the highest doses studied. Subsequently, flat dose-exposure-response relationships were also observed in other tumor types including head and neck cancer, bladder cancer, gastric cancer and classical Hodgkin Lymphoma, confirming 200 mg Q3W as the appropriate dose independent of the tumor type. These findings are consistent with the mechanism

of action of pembrolizumab, which acts by interaction with immune cells, and not via direct binding to cancer cells.

Additionally, pharmacology data clearly show target saturation at 200 mg Q3W. First, PK data in KN001 evaluating target-mediated drug disposition conclusively demonstrated saturation of PD-1 in systemic circulation at doses much lower than 200 mg Q3W. Second, a PBPK analysis was conducted to predict tumor PD-1 saturation over a wide range of tumor penetration and PD-1 expression. This evaluation concluded that pembrolizumab at 200 mg Q3W achieves full PD-1 saturation in both blood and tumor.

Finally, population PK analysis of pembrolizumab, which characterized the influence of body weight and other participant covariates on exposure, has shown that the fixed-dosing provides similar control of PK variability as weight-based dosing, with considerable overlap in the distribution of exposures from the 200 mg Q3W fixed dose and 2 mg/kg Q3W dose. Supported by these PK characteristics and given that fixed-dose has advantages of reduced dosing complexity and reduced potential of dosing errors, the 200 mg Q3W fixed-dose was selected for evaluation across all pembrolizumab protocols.

8.2 Rationale for IO102-IO103 Dose and Schedule

IDO is a cytosolic enzyme responsible for tryptophan catabolism and conversion of tryptophan into kynurenine. It is overexpressed by a variety of tumor cell types and antigen-presenting cells and plays an important role in immunosuppression mainly through suppression of cytotoxic T-lymphocyte activation; tryptophan depletion inhibits T-lymphocyte proliferation and activation and suppresses the immune system. PD-L1 is overexpressed on many human cancer cell types, including malignant melanoma. PD-L1 binding to its cognate receptor PD-1 on T-cells suppresses the immune system and results in increased immune evasion and decreased cytotoxic T-lymphocyte activation.

IO102 and IO103 stimulate activation of human T-cells against IDO and PD-L1 expressing cells, respectively, and they have been demonstrated to activate proinflammatory immune responses and cytotoxic killing of immunosuppressive cells in vitro. Thus, treatment with IDO and PD-L1 peptides in patients with cancer may activate the immune system to eradicate IDO- and PDL1expressing tumor and immune cells in the tumor microenvironment (TME), facilitating the activation and proliferation of effector T-cells against tumor cells.

Data from murine preclinical tumor models directly support this notion, where the antitumor activity of both IDO and PD-L1 targeting antigen immunotherapeutic has been demonstrated. Importantly, treatment with IDO and PD-L1 peptides demonstrates combinational antitumor response in a tumor model where IDO and PD-L1 molecules are expressed by different cell types within the TME.

As noted above, both IDO and PD-L1 represent key checkpoint molecules in the context of antitumor immunity. While both molecules are regulated and induced by IFNγ secreted by lymphocytes (Spranger et al., 2013) and could be expressed by both myeloid cells and tumor cells in the TME, their expression does not necessarily overlap in the same cells.
A trial by Krähenbühl confirmed that the expression profile of IDO and PD-L1 was nonoverlapping in melanoma biopsies before and after targeted therapy versus immune therapy (Krähenbühl *et al.,* 2018).

In summary, IO102-IO103 targets two separate, but interlinked key cancer immune resistance pathways (IDO and PD-L1, respectively). Thus, treatment with IO102 and IO103 results in targeting 2 separate escape mechanisms that are not confined in the same cell populations. Further, an attack on either or both IDO-positive and PD-L1–positive target cells in the TME would lead to IFNγ secretion by activated T-cells, resulting in elevation of IDO/PD-L1 expression in the

surrounding cells, rendering them sensible prone to further for attack by IO102-IO103 dual-antigen treatment induced T cells.

The proposed doses of IO102 and IO103 to be studied in this trial are 85 µg. The 85 µg doses were well tolerated in combination with nivolumab, with no DLTs. Based on the similarities between nivolumab and pembrolizumab, the doses are expected to be well tolerated with pembrolizumab, with no need for a safety run-in (Svane, 2020). This dose is aligned with the net peptide administered to patients with advanced melanoma in trial MM1636, which corresponds to the gross weight of the peptide administered (100 µg). The formulations for IO102 and IO103 are comparable to those used previously in clinical trials (NCT03562871 and NCT03047928 for IO102; NCT03714529 for IO103) and can be expected to achieve both immunological and clinical responses.

No dose selection is applied in the trial. Identifying the maximum tolerated dose has been challenging for cancer vaccines. The sponsor's clinical experience is that with administration of 100 µg or 250 µg of IO102, an expected immunological response measured by analyzing induced dual-antigen immunotherapeutic specific cellular response in the treated patients is generated (Iversen *et al.*, 2014, Bjoern *et al.,* 2016). Especially relevant in these settings is the finding that close to 100% of all treated patients in the MM1636 trial (please refer to section 7.4.6) have demonstrated induction of dual-antigen immunotherapeutic specific T cell response (measured by IFNγ enzyme-linked immunospot assay). As the expression of both PD-L1 and IDO are induced strongly by IFNγ, and as both are immunotherapeutics, both IO102 and IO103 are expected to have a similar mode of action. It is the sponsor's conclusion that the dose regimen of IO102-IO103 chosen for the proposed trial is relevant to achieve both immunological and clinical responses.

The schedule selected is driven by the expected synergy with pembrolizumab, evidence from MM1636 and other trials (data on file), and convenience for the patient to avoid unnecessary visits (as well as administrations). The schedule includes an induction period where 2 additional administrations of the dual-antigen are given on Day 8 of cycles 1 and 2 to ensure expansion of dual-antigen specific T-cells.

8.3 Rationale for Trial Population

8.3.1 Rationale for Trial Population - NSCLC

Pembrolizumab has shown significant clinical benefit in patients with metastatic NSCLC independent of histology.

Use of pembrolizumab for patients with PD-L1 expression ≥50 % is supported by the phase III KEYNOTE-024 trial, in which 305 treatment-naïve patients with advanced NSCLC having at least 50 % tumor cell PD-L1 staining were randomly assigned to pembrolizumab monotherapy (200 mg IV Q3W) versus standard platinum-doublet chemotherapy (Reck *et al.*, 2016). At a median follow-up of 11.2 months, PFS, the primary endpoint, was prolonged with pembrolizumab compared with platinum-doublet chemotherapy (median PFS, 10.3 versus 6 months; HR 0.50, 95% CI 0.37-0.68), and ORRs were improved (45 versus 28 %). The median duration of response was not reached in the pembrolizumab group and was 6.3 months in the chemotherapy group. Severe (≥ Grade 3) treatment-related adverse effects were lower among patients receiving pembrolizumab (27 versus 53 %). Any-grade pneumonitis was reported in 5.8 % of patients treated with pembrolizumab, with severe pneumonitis in 2.6 %. Although PFS was prolonged, there is still a significant unmet need in this population for more durable responses.

In the Phase III KEYNOTE-042 trial of patients with treatment-naïve, advanced, EGFR/ALK WT NSCLC and at least 1% tumor PD-L1 expression, pembrolizumab monotherapy is being compared

with platinum-doublet chemotherapy, chosen according to histology. Of note, this trial did not permit crossover. At a median follow-up of 12.8 months, results are as follows (Mok *et al.*, 2019). OS, the primary endpoint, was prolonged among patients receiving pembrolizumab compared with those receiving chemotherapy as follows:

- TPS ≥50 % (599 patients), 20 versus 12 months (HR 0.69, 95% CI 0.56-0.85)

There was no statistically significant PFS benefit among patients receiving pembrolizumab compared with those receiving chemotherapy, except for those with the highest level of PD-L1 expression (TPS ≥50 %; median PFS, 7.1 versus 6.4 months [HR 0.81, 95% CI 0.67-0.99]). As in KEYNOTE-024, pembrolizumab was better tolerated than chemotherapy, with grade 3 to 5 adverse events occurring in 18% of those receiving pembrolizumab and 41 % of those receiving chemotherapy.

Pembrolizumab is approved by the FDA for the front-line treatment of patients with advanced EGFR/ALK wild-type NSCLC whose tumors have ≥1 % PD-L1 expression based on the 22C3 pharmDx test (Merck and Corp., 2020).

The RR results obtained in this trial will be compared to an historical RR of 40%. A 40% RR is at the average of RRs observed with existing agents as monotherapy - especially immune checkpoint inhibitors - tested in the first line setting in metastatic NSCLC patients . Considering the effect of pembrolizumab on duration of response and the population being studied, a RR of 55% is considered clinically important for the combination of pembrolizumab with IO102-IO103.

8.3.2 Rationale for Trial Population - SCCHN

A large number of patients with head and neck cancer initially present with locally advanced, Stage III/IV disease that is initially treated with combinations of chemotherapy, radiation and/or surgery. This initial treatment is generally designated as “definitive” therapy, which typically combines chemoradiation and surgery and can result in disease control rates ranging between 33 and 86% of patients. Patients who progress after initial definitive therapy require subsequent treatment for recurrent (R) disease. Patients who initially present with metastatic (M) disease generally receive the same therapy as those with recurrent disease after definitive treatment.

Despite the recent progress with immune-checkpoint inhibitors in R/M SCCHN, only about 30% of patients respond to current therapy regimens, with a median OS of 15 months, even when combined with chemotherapy (Vermorken *et al.*, 2008; Burtness *et al.*, 2019). Hence, there remains a high unmet need in R/M SCCHN for regimens with a more favorable therapeutic index, to improve treatment efficacy and decrease treatment-related toxicity. A 6-month estimate of PFS in patients with a CPS ≥20 would be estimated to be 39% in patients treated with IO102-IO103 plus pembrolizumab.

8.3.3 Rationale for Trial Population - mUBC

Inoperable locally-advanced/metastatic urothelial bladder carcinoma has an extremely poor prognosis with a high unmet medical need. Platinum-based chemotherapy is the current standard of care for patients with previously untreated mUBC. Systemic chemotherapy in mUBC is, however, characterized by significant toxicity with poor OS and low response rates and limited durability in a frail population of advancing age and multiple co-morbidities.

Many patients are not eligible to receive treatment with cisplatin-based chemotherapy due to their poor health status and need more effective therapeutic options.

Immunotherapy in mUBC has shown significant promise. Frontline treatment with pembrolizumab in patients who are ineligible to receive cisplatin has demonstrated durable responses (Rosenberg *et al.*, 2016; Balar, Castellano, *et al.*, 2017). However, response rates and overall survival remain poor.

8.4 Overall Risk/Benefit Assessment

Pembrolizumab has a positive benefit-risk profile and is well tolerated in the approved indications. The most common pembrolizumab adverse reactions (reported in ≥20% of patients) include pruritus, diarrhea, and cough. In the pembrolizumab monotherapy trials, the incidence of Grade 3-5 drug-related AEs across studies is 13.8%. Pembrolizumab immune-mediated Adverse Events of Special Interest (AEOSIs) are relatively uncommon. The most frequently reported AEOSI is hypothyroidism, with an overall incidence of 8.5%. Furthermore, most AEOSIs are mild to moderate in severity, and are generally readily manageable with appropriate care in the clinical setting.

Pembrolizumab has been generally well-tolerated; adverse events with potentially immune-mediated causes that are consistent with an immunotherapeutic agent, including rash, hypothyroidism, hepatitis/elevated transaminases, colitis, and myasthenia gravis, have been observed in ongoing studies of pembrolizumab. To date, these events have been amenable to monitoring and treatment. Details of the pembrolizumab risks are highlighted in the IB for pembrolizumab.

A clinical trial (MM1636) evaluated IO102-IO103 in combination with nivolumab in the intended advanced melanoma patient population at the intended dose, and has demonstrated clinically relevant improvements in the ORR, including sub-groups of patients and in terms of the complete response rate and the duration of response. Details are included in the most recent IO102-IO103 IB.

It is considered a high risk that the patients get injections site reactions, but they are manageable and reversible by use of local treatment with steroid ointments and or antihistamines. The AEs reported in the MM1636 trial included injection site reactions (in 76.7% patients, the majority were Grade 1 or 2), and the remaining AEs were related to anti-PD-1 monotherapy. The safety profile of the IO102-IO103 dual-antigen immunotherapeutic is considered favorable.

Apart from injection site reactions AEs, there is a potential risk for a small increase in radiation exposure during the assessment of disease with radiological scans and tumor tissue biopsies. The imaging schedule of every 3 months used in this trial is usually considered standard intervals for tumor assessments with standard of care treatment.

At screening, it is possible for patients to utilize archival samples (obtained within 3 months and without previous exposure to anticancer therapy). Archival tissue that is obtained more than 3 months from screening, may be considered on after communication with and agreement by the Sponsor. Acquisition of on-trial repeat biopsies is largely dependent on a suitable lesion being available and the willingness of the patient. Patients have a risk of bleeding, infection, and pain during a biopsy and will be informed about these risks. Patients will be carefully selected if they are suitable for a re-biopsy.

As described in detail above, the combination of the IDO/PD-L1 antigen IO102-IO103 and the immune checkpoint inhibitor (ICI) nivolumab is safe with encouraging early efficacy data: an ORR of 73.3% was reached and 46.7% achieved a complete response in patients with melanoma. The safety profiles for nivolumab and pembrolizumab are similar and therefore the combination with IO102-IO103 with pembrolizumab will likely yield a similar safety profile to that of combining with nivolumab. Hence, treatment with IO102-IO103 may offer potential benefits compared to ICIs such

as pembrolizumab alone, as preliminary evidence suggests that treatment with IO102-IO103 may result in a better antitumor response with ICIs. Except for local reactions at injection site, toxicity was comparable to patients receiving nivolumab monotherapy. Additional details regarding specific benefits and risks for patients participating in this clinical trial may be found in the patient information sheet.

In summary, treatment with pembrolizumab in combination with IO102-IO103 offers the potential for clinical benefit in previously untreated patients with solid tumors. Given the promising efficacy and good safety profile of immune checkpoint inhibitors such as nivolumab in combination with IO102-IO103 treatment, the benefit-risk assessment for this basket trial in combination with pembrolizumab is regarded as positive.

AEs will be assessed using CTCAE v. 5.0.

To minimize or eliminate immediate hazards and to protect the life and well-being of research participants (e.g., to limit exposure to COVID-19) it is advised to assess and manage the risk of COVID-19 to the patient, taking into consideration prior exposure to the SARS-COV2 virus, vaccination status, age and co-morbitities. Scheduled visits are advised to be delayed as appropriate in the situation of a patient who has a positive COVID-19 test or where an outbreak occurs at the investigational hospital. See Appendix III for further details. All COVID-19 related deviations from the protocol will be recorded as COVID-19 deviations. Patients most at risk of rapidly progressing disease are excluded, and all patients are required to have a life expectancy of at least 3 months.

9 Trial Population

9.1 Entry Criteria

9.1.1 Diagnosis/Condition for Entry into the Trial

- Cohort A. NSCLC adenocarcinoma (metastatic disease) with PD-L1 expression TPS ≥50%.
- Cohort B. SCCHN (recurrent or metastatic disease) with PD-L1 CPS ≥20.
- Cohort C. mUBC (metstatic disease) with PD-L1 CPS ≥10

9.1.2 Patient Inclusion Criteria

1. Patients with histologically or cytologically confirmed:

   Metastatic NSCLC (adenocarcinoma) (Cohort A), who have not received prior systemic treatment for their metastatic disease and who have:
   - No known sensitizing genetic aberrations where there are approved therapies (such as ALK, ROS1, EGFR, BRAF V600E, MET skipping mutations, and RET mutations or rearrangements)

   or

   SCCHN (Cohort B) with no prior systemic therapy administered in the recurrent or metastatic setting (with the exception of systemic therapy completed >6 months prior if given as part of multimodal treatment for locally advanced disease) and who have:
   - SCCHN considered incurable by local therapies. Tumors of nasophyngeal origin (any histology) are excluded

- Documented results of p16/HPV status for oropharyngeal cancer (per institution standard)

or

Metastatic UBC (Cohort C) with no prior therapy and not eligible for any platinum-containing chemotherapy:

- Urothelial cancer of the renal pelvis, ureter, bladder or urethra (transitional cell and mixed transitional/non transitional cell histologies permitted but transitional cell histology must be the dominant histology)

For all cohorts, any solitary metastases must be biopsied to confirm diagnosis of metastases from primary indication.

2. PD-L1 TPS or PD-L1 CPS (as confirmed prior to enrolment using the PD-L1 IHC DAKO 22C3 pharmDx assay, using local or central services):
   - Cohort A (NSCLC adenocarcinoma): PD-L1 TPS ≥ 50%
   - Cohort B (SCCHN): PD-L1 CPS ≥20; HPV +/-
   - Cohort C (mUBC): PD-L1 CPS ≥10
3. A female participant is eligible to participate if she is not pregnant not breastfeeding, and at least one of the following conditions applies:

- Not a woman of childbearing potential (WOCBP)
- A WOCBP who agrees to follow contraceptive guidance starting with the screening visit and through 120 days after last dose of pembrolizumab or 180 days after last dose of chemotherapy.

Note: A WOCBP, i.e., fertile, following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilisation methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy. Tubal ligation is *not* a method of permanent sterilisation. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.

4. The participant (or legally acceptable representative if applicable) provides written informed consent for the trial in accordance with ICH-GCP and local legislation prior to admission to the trial.
5. At least 18 years of age on day of signing informed consent.
6. Have measurable disease per RECIST v. 1.1 as assessed by local site investigator/radiologist. Lesions situated in a previously irradiated area are considered measurable if progression has been demonstrated in such lesions.

7. Have provided archival tumor tissue sample or newly obtained core or excisional biopsy of a tumor lesion not previously irradiated. Formalin-fixed, paraffin embedded (FFPE) tissue blocks are preferred to slides.

8. Have an ECOG performance status of 0 to 1.

9. If participant received major surgery, they must have recovered adequately from the adverse events and/or complications from the intervention prior to starting trial treatment.

10. Have adequate organ function as defined below. Specimens must be collected within 10 days prior to the start of trial treatment.

    Adequate organ function as defined by:

    - Haematology:

      Absolute neutrophil count ≥1500/μL or ≥1.5 × 10^9/L

      Platelets ≥ 100,000/μL or ≥ 100 × 10^9/L

      Hemoglobin ≥ 9.0 g/dL or ≥ 5.6 mmol/L. Criteria must be met without packed red blood cell transfusion within the prior 2 weeks. Participants can be on stable dose of erythropoietin (≥ approximately 3 months).

    - Renal:

      Creatinine ≤1.5 × ULN, or

      Measured or calculated creatinine clearance (CrCl) ≥50 mL/min for patients with creatinine levels >1.5 × institutional ULN;

      GFR can also be used in place of creatinine or CrCl

    - Hepatic:

      Total bilirubin ≤1.5 × ULN or direct bilirubin ≤ ULN for patients with total bilirubin levels >1.5 × ULN

      Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤2.5 × ULN (≤5 × ULN for patients with liver metastases)

      Alkaline Phosphatase ≤2.5 × ULN

    - Endocrine:

      No uncontrolled endocrinopathies

    - Coagulation:

International normalised ratio (INR) or prothrombin time (PT) and activated partial thromboplastin time (aPTT) ≤1.5 × ULN unless patient is receiving anticoagulant therapy as long as PT or aPTT is within therapeutic range of intended use of anticoagulants

11. Patients who are hepatitis B surface antigen (HBsAg) positive are eligible if they have received hepatitis B virus (HBV) antiviral therapy for at least 4 weeks and have undetectable HBV viral load prior to treatment initiation.

    Note: Patients should remain on anti-viral therapy throughout trial treatment and follow local guidelines for HBV anti-viral therapy after completion of trial treatment. Hepatitis B screening tests are not required unless:
    a. Known history of HBV infection
    b. As mandated by local health authority

12. Patients with history of hepatitis C virus (HCV) infection are eligible if HCV viral load is undetectable at screening.

    Note: Patients must have completed curative anti-viral therapy at least 4 weeks before treatment initiation. Hepatitis C screening tests are not required unless:
    a. Known history of HCV infection
    b. As mandated by local health authority

9.2 Patient Exclusion Criteria

Cohorts A, B, and C:

1. A WOCBP who has a positive urine pregnancy test (within 72 hours) prior to treatment. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.

2. Has received prior therapy with an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent or with an agent directed to another stimulatory or co-inhibitory T-cell receptor (e.g., CTLA-4, OX 40, CD137) AND was discontinued from that treatment due to a Grade 3 or higher immune-related AE (irAE).

3. Has received prior systemic anti-cancer therapy in the first line setting for the participant's metastatic disease (treatment with chemotherapy and/or radiation as part of neoadjuvant/adjuvant therapy is allowed as long as completed at least 6 months prior to diagnosis of metastatic disease).

4. Has not recovered from all AEs due to previous therapies to ≤ Grade 1 or baseline. Participants with ≤ Grade 2 neuropathy are eligible.

5. Has received any prior radiotherapy, with the exception of palliative radiotherapy to non-target lesions, within 2 weeks prior to start of trial treatment or radiotherapy to the lung >30 Gy within 6 months of start of trial treatment. Participants must have recovered from all radiation-related adverse events and not have had radiation pneumonitis requiring corticosteroids.

6. Have a life expectancy of <3 months and/or rapidly progressing disease.

7. Have received a live or live attenuated vaccine within 30 days prior to the first dose of trial treatment. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster (chicken pox), yellow fever, rabies, Bacillus Calmette–Guérin (BCG), and typhoid vaccine. Administration of killed vaccines, mRNA based (e.g., covid-19) and vector based vaccines are allowed. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (e.g., FluMist®) are live attenuated vaccines and are not allowed.

8. Is currently participating in or has participated in a study of an investigational agent or has used an investigational device within 4 weeks prior to the first dose of study treatment. Note: Participants who have entered the follow-up phase of an investigational study may participate as long as it has been 4 weeks after the last dose of the previous investigational agent.

9. Has a diagnosis of immunodeficiency

10. Received any of the following medications or procedures within 2 weeks prior to first dose of trial treatment: chronic systemic steroid therapy (in dosing exceeding 10 mg daily of prednisone equivalent) or any other form of immunosuppressive therapy.

11. Has a known additional malignancy that is progressing or has required active treatment within the past 2 years.

    Note: Participants with basal cell carcinoma of the skin, squamous cell carcinoma of the skin or carcinoma in situ (e.g., breast carcinoma, cervical cancer in situ) that have undergone potentially curative therapy are not excluded.

12. Has CNS metastases and/or carcinomatous meningitis. Participants in Cohort A (NSCLC) with previously treated brain metastases may participate provided they are clinically stable and without requirement of steroid treatment for at least 14 days prior to first dose of trial treatment.

13. Has severe hypersensitivity (≥ Grade 3) to IO102 or IO103, pembrolizumab and/or any of their excipients.

14. Has an active autoimmune disease that has required systemic treatment in 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) is not considered a form of systemic treatment and is allowed.

15. Has a history of (non-infectious) pneumonitis that required steroids or has current pneumonitis / insterstitial lung disease.

16. Has an active infection requiring systemic therapy.

17. Has a known history of human immunodeficiency virus (HIV) infection. No HIV testing is required unless mandated by local health authority.

18. Known adrenal insufficiency function (that is basal cortisol level <140nmol/L or <5 µg/dL).

19. Has known active Hepatitis B virus (defined as Hepatitis B surface antigen [HBsAg] reactive and/or detectable HBV DNA) or known active Hepatitis C virus (HCV) (defined as anti-HCV Ab positive and detectable HCV ribonucleic acid [RNA] [qualitative]) infection.

    Note: No testing for Hepatitis B and Hepatitis C is required unless
    a. Known history of HBV or HCV infection
    b. Mandated by local health authority.

    Patients who have a history of hepatitis will be screened using serology to confirm status.

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

21. Has known psychiatric or substance abuse disorders that would interfere with the patient's ability to cooperate with the requirements of the trial.

22. Is pregnant or breastfeeding or expecting to conceive within the projected duration of the trial, starting with the screening visit through 180 days after last dose of trial treatment.

23. Has had an allogeneic tissue/solid organ transplant.

24. Has progressive disease (PD) within six months of completion of curatively intended systemic treatment for locoregionally advanced SCCHN.

9.3 Patient Withdrawal from Trial Treatment and Withdrawal from Trial Participation

9.3.1 Withdrawal from Trial Treatment

Discontinuation of trial treatment does not represent withdrawal from the trial. See Section 9.3.2 for guidance on withdrawal from trial.

A patient must be discontinued from IO102-IO103 and pembrolizumab but may continue to be monitored in the trial for any of the following reasons:

- Disease progression according to iRECIST.

  NOTE: If the participant is achieving a clinically meaningful benefit, an exemption to continue trial treatment may be considered following consultation with the Sponsor. In this case, if trial treatment is continued, tumor imaging should continue to be performed following the intervals as outlined in schedule of assessments

- The patient becomes pregnant
- Initiation of new anti-cancer treatment
- The patient withdraws consent to further interventional treatment.
- Completion of 35 cycles of administration of trial treatments

During the 2-year treatment period, a patient may be withdrawn from IO102-IO103 and pembrolizumab, or may continue treatment with pembrolizumab alone or IO102-IO103 alone if the investigator considers there is clinical benefit:

- The Investigator believes that for safety reasons it is in the best interest of the patient discontinue dosing
- The patient is not in compliance with trial treatment administration
- Significant AEs based on the Investigator or Sponsor's medical director judgment.
- Need for concomitant medication that is not permitted during this trial (see Section 11.7.2)
- The patient wishes to discontinue trial treatment
- Discontinuation of trial treatment may be considered for patients who have attained a confirmed CR and have been treated for at least 8 cycles (at least 24 weeks).

Patients are not permitted to be withdrawn from only one of IO102 or IO103 for any reason.

9.3.2 Patient Withdrawal from Trial Participation

In accordance with the Declaration of Helsinki (in accordance with the applicable country's acceptance), each patient is free to withdraw from the trial at any time. The Investigator also has the right to withdraw a patient from the trial due to non compliance with trial requirements.

Patients withdrawn from the trial should perform the EOT assessments and post-trial treatment (Endpoint FUP) assessments as defined in Table 1 and Table 2.

The primary reason for trial withdrawal should be recorded in the electronic case report form (eCRF). Withdrawal due to AEs should be distinguished from withdrawal due to insufficient response.

Patients withdrawn from the clinical trial due to pregnancy are required to follow the instructions as outlined in Section 13.8.

10 Trial Design

10.1 Overall Trial Design

Non comparative, open label, multi-cohort (basket) trial of IO102-IO103 in combination with pembrolizumab in 3 indications (NSCLC adenocarcinoma, SCCHN, and mUBC). A clinically meaningful efficacy signal will allow expansion as appropriate. For more details, please refer to Section 4.1.

10.2 Randomisation or Treatment Allocation

Not applicable as there is no randomization in the trial.

10.2.1 Stratification of Patients

There will be no stratification of patients

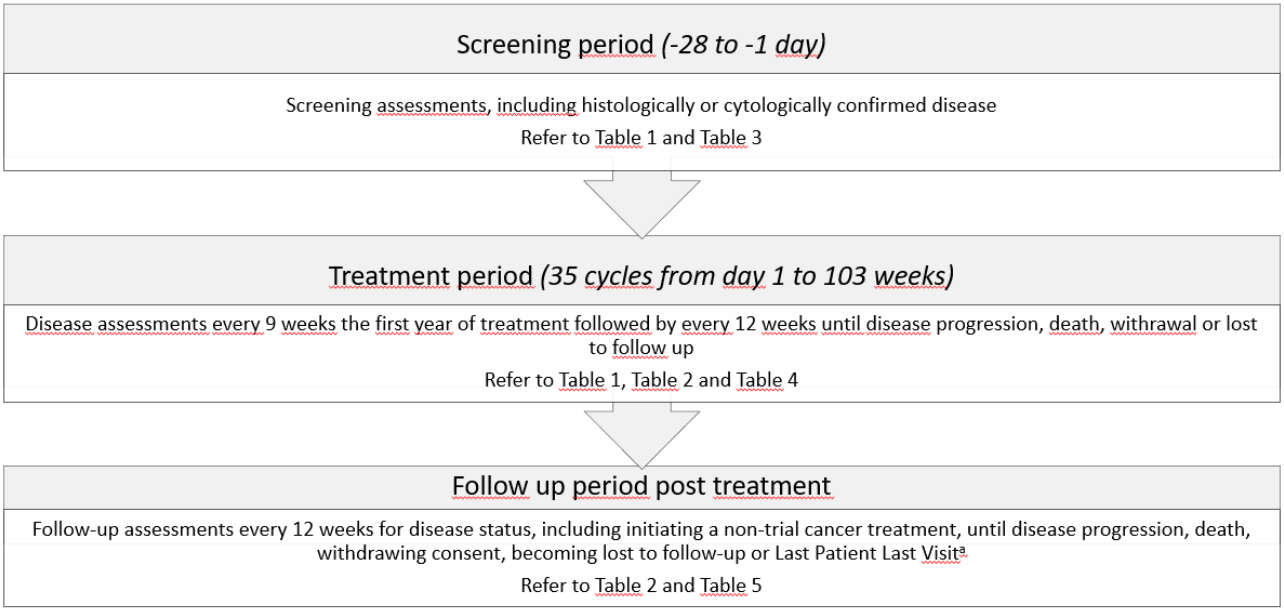
10.3 Sample Size

Approximately 90 patients will be enrolled and treated; approximately 30 patients in each cohort.

Assuming a screen failure rate of 30%, approximately 130 patients are expected to enter screening.

10.4 Trial Design Flow Diagram

Figure 2 Trial Flow Diagram



[a]Last Patient Last Visit is defined as when the last patient in has been treated for 35 cycles plus 30 days follow up or until disease progression, death, withdrawing consent, or becoming lost to follow-up.

10.5 Trial Duration and Participating Centres

The duration of the trial will include a screening phase lasting up to 28 days, a treatment period of 24 months and a follow-up period lasting until the last patient in has completed the trial treatment plus 30 days follow up or until PD, death, withdrawal of consent or lost-to-follow-up.

The trial will require approximately 3 years from the time the first patient signs the ICF until the last patient last visit.

Approximately 25 sites in 3 to 5 countries are planned to participate in the trial.

The end of trial is defined as the date of last patient last visit.

10.6 Schedule of Events

10.6.1 Screening Assessments and Procedures

Table 3 Assessments and Procedures in Screening

Informed Consent	The patient must be fully informed about the trial and sign the Main Informed Consent Form (ICF). The ICF must be signed before any trial specific assessments or procedures are conducted.
Demographics	• Year of birth is to be recorded in the eCRF (date of birth can be recorded on samples, vials etc. to facilitate the identification of patient samples). • Gender • Ethnic origin and race • Height (cm) and weight (kg)
Medical history	Details of all previous or concomitant conditions or surgical procedures.
Disease Stage (NSCLC adenocarcinoma, UBC or SCCHN, previous treatment)	• Tumor classification • Date of first diagnosis • Prior treatments, including all surgical or chemotherapy/targeted or immunotherapy interventions; date of start/stop, regimen administered and response to treatment.
Pregnancy test	For WOCBP, a urine pregnancy test must be conducted within 72 hours prior to administration of trial treatment. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test (β-hCG) will be required.
ECOG PS	ECOG performance status. See Appendix I.
Tumor imaging	CT scans of abdomen, chest and pelvis must be done prior to administration of trial treatment. A MRI scan can be used if CT contrast is contra-indicated. The same radiographic procedure must be used throughout the trial. At screening, a brain scan must be included to exclude active metastases or leptomeningeal metastases.
Clinical disease Assessment	Disease response is assessed according to RECIST v. 1.1. After PD or response per iRECIST, repeat imaging for confirmation is required. Repeat imaging between 4 and 8 weeks to confirm PD; and repeat imaging at >4 weeks to confirm response
Tumor tissue biopsy or archival tissue sample	Blood sample and archival tumor tissue sample or newly obtained core or excisional biopsy of a tumor lesion not previously irradiated. Formalin-fixed, paraffin embedded tissue blocks are preferred to slides. Used for analysis of PD-L1 (clone 22C3) and immunomodulatory markers by multiplexed IHC, immune gene signature, and tumor mutational burden.
Biomarker blood sampling	A blood sample for the purpose of assessing biomarkers.

PD-L1 status (DAKO 22C3)	The PD-L1 status of the patient must be evaluated using the PD-L1 IHC pharmDx assay. See Section 12.2.4.1.
Clinical chemistry	Clinical chemistry parameters to be collected are described in Table 11. All screening laboratory assessments must be performed or repeated within 7 days prior to treatment initiation.
Haematology	Haematology parameters to be collected are described in Table 11. All screening laboratory assessments must be performed or repeated within 7 days prior to treatment initiation.
Urinalysis	Urinalysis parameters to be collected are described in Table 11.
Thyroid function tests	Thyroid Function Test parameters to be collected are described in Table 11.
Coagulation Tests	Coagulation Test parameters to be collected are described in Table 11.
Vital signs	• Blood pressure (suprine systolic and diastolic) • Heart rate • Respiration rate • Weight • Body temperature • Height
Physical examination (full)	A full physical examination of heart, lung, general, skin, oral cavity, chest, lymph nodes. Any abnormalities should be provided on the Medical History record.
12-lead electrocardiogram (ECG)	Date and time of ECG and interpretation are collected
Echocardiogram or multi-gated acquisition (MUGA) scan	Date and time of echocardiogram/MUGA and interpretation are collected
Concomitant medication	If the patient is receiving any medication for conditions mentioned on the Medical History page, details need to be recorded on the Concomitant therapies record.
Adverse Events	Record any AEs that have occurred since the date of informed consent, including AEs following procedures such as tumor biopsy or blood sampling. These AEs will not be considered drug related.

10.6.2 Trial Treatment Period

The following assessments must be completed during the trial treatment period or at the End of Treatment (EoT) visit.

Table 4 Assessments and Procedures during Trial Treatment Period

Assessment or procedure:	Trial Treament Period:
ECOG PS	Every 9 weeks during the first year of treatment and then every 12 weeks
Tumor imaging	Every 9 weeks during the first year of treatment and then every 12 weeks for the second year of treatment
Clinical disease Assessment	Every 9 weeks during the first year of treatment and then every 12 weeks for the second year of treatment After PD or response per iRECIST 1.1, repeat imaging for confirmation is required. Repeat imaging between 4 and 8 weeks to confirm PD; and repeat imaging at >4 weeks to confirm response
Tumor tissue biopsy or archival tissue sample	At week 10 if a suitable lesion is available and patient has consented
Biomarker blood sampling	At week 4, 10 and 19
Clinical chemistry	All visits except visits 2 and 5 Laboratory samples can be collected up to 48 hours prior to treatment administration and must be known and acceptable prior to dosing.
Haematology	At all visits except visits 2 and 5 Laboratory samples can be collected up to 48 hours prior to treatment administration and must be known and acceptable prior to dosing.
Pembrolizumab (200 mg IV)	Pembrolizumab will be administered on Day 1 of each 3 week cycle in accordance with standard of care
IO102 (85µg SC) and IO103 (85µg SC)	IO102-IO103 will be administered on Day 1 of each 3 week cycle and additionally on day 8 and 29 during the first 2 cycles.
Urinalysis	Every 6 weeks before trial treatment administration.
Thyroid function tests	Every 6 weeks before trial treatment administration.
Coagulation Tests	Every 6 weeks before trial treatment administration.
Vital signs	• Blood pressure (suprine systolic and diastolic) • Heart rate • Respiration rate • Weight • Body temperature At all visits except visits 2 and 5. Vital signs must be assessed before trial treatment administration.

Physical examination (full or directed)	Full physical examination is performed every 12 weeks of heart, lung, general, skin, oral cavity, chest, lymph nodes. Directed physical examination is performed at visit 1, 4, 6 and 12 and as clinically indicated to include symptom driven examination.
12-lead ECG	Every 12 weeks before trial treatment administration.
Adverse events	Any new AEs or changes to existing AEs must be recorded at all visits
Concomitant medication	Any new concomitant medication or changes to existing concomitant medication must be recorded at all visits
Pregnancy test	Urine pregnancy tests to be repeated every 3 weeks during the treatment period, as well as at EOT. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test (β-hCG) will be required
Pharmacokinetic blood sampling (only applicable to patients who have consented to PK blood sampling)	Blood samples for the purpose of measuring drug concentration.

10.6.3 Post-Trial Treatment Period

The following assessments and procedures are required every 12 weeks after permanent discontinuation of the trial treatments (that is discontinuation of IO102-IO103 and pembrolizumab).

Table 5 Assessments and Procedures after Discontinuation of Trial Treatments

Assessment or Procedure:	Frequency
Tumor imaging	Every 12 weeks until disease progression (iRECIST) or death, withdrawal of consent, start of new anticancer therapy or end of trial
Clinical disease Assessment	Every 12 weeks until disease progression (iRECIST) or death withdrawal of consent, start of new anticancer therapy or end of trial
Adverse events	Every 12 weeks
Subsequent anti-cancer treatment	Every 12 weeks
Date of death/Survival follow-up	Every 12 weeks
Pregnancy test	For female patients of childbearing potential a urine pregnancy test is mandatory at 120 days after last dose of pembrolizumab. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test (β-hCG) will be required.

11 Trial Treatment

The trial treatments are IO102-IO103 dual-antigen immunotherapeutic and pembrolizumab.

Pembrolizumab is available as a 100 mg/4 mL solution for injection and may be obtained from commercial supplies (and reimbursed by IO Biotech) or provided by IO Biotech. Clinical supplies of pembrolizumab provided by Merck Sharp & Dohme, LLC, Rahway, NJ, USA may also be used. The contents of the label will be in accordance with all applicable regulatory requirements.

11.1 Investigational Medicinal Products

The investigational medicinal products (IMPs) are outlined in Table 6 and Table 7. Trial treatments will be administered after all baseline procedures and assessments have been completed and the patients have been confirmed eligible for the trial.

Table 6 Investigational Medicinal Products Summary

Product Name & Potency	Dosage Form
IO102 [redacted]	Powder for solution for injection
IO103 [redacted]	Powder for solution for injection
Pembrolizumab (MK-3475) 100 mg/vial	Solution for injection

Table 7 IO102-IO103 and Pembrolizumab Dose and Schedule

Drug	Dose Frequency	Route of Administration	Regimen
IO102-IO103	Day 1 Q3W, with additional administration on day 8 during the first 2 cycles.	Subcutaneous	Induction period: Day 1 of each 3 week cycle. Additional IO102-IO103 administrations on day 8 during the first 2 cycles. In total 4 injections during the first 2 cycles. Maintenance period: SC administrations on day 1 of each 3 week cycle for a max of 33 cycles. A total of 37 administrations. IO102-IO103 will be administered 1 hour +/- 15 minutes prior to pembrolizumab. IO102-IO103 are administered separately in any order.
Pembrolizumab	Q3W	IV infusion	Day 1 of each 3 week cycle for a max of 35 cycles (2 years)

11.2 Packaging and Labeling

Labeling will be in accordance with all applicable regulatory requirements.

11.3 Storage and Preparation of Trial Treatment

11.3.1 Storage and Preparation of IO102

The IO102 drug product is a freeze-dried powder and must be stored according to the instructions in the IB. Storage temperature must be monitored.

IO102 in the form of a freeze-dried powder consists of powder for solution for injection. Before administration, IO102 must be reconstituted with water for injection (WFI) and subsequently emulsified with an adjuvant Montanide ISA 51 VG (Seppic, France).

IO102, WFI and adjuvant (Montanide) will be supplied by the Sponsors. Instructions for preparing and administering IO102 will be provided in a separate Pharmacy Manual.

11.3.2 Storage and Preparation of IO103

The IO103 drug product is a freeze-dried powder and must be stored according to the instructions in the IB. Storage temperature must be monitored.

IO103 in the form of freeze-dried powder consists of powder for solution for injection. Before administration, IO103 must be reconstituted with WFI and subsequently emulsified with the adjuvant Montanide ISA 51 VG (Seppic, France).

IO103, WFI and adjuvant (Montanide) will be supplied by the Sponsor. Instructions for preparing and administering IO103 will be provided in a separate Pharmacy Manual.

11.3.3 Preparation and Storage of Pembrolizumab

Refer to the Pharmacy Manual for storage and preparation of pembrolizumab.

11.4 Treatment and Dose Schedule

The trial treatments will be administered after all procedures and assessments have been completed.

Patients will receive their trial treatment Q3W as described in Table 7. Patients will additionally receive IO102-IO103 on day 8 and 29 during the first 2 cycles.

IO102-IO103 will be administered by SC injection at a dose of 85µg each dose. The injection is made by SC administration in the upper arm of the patient (single location, 5 cm [2 inches] apart). Abdomen can alternatively be used as injection site in case the patient has reactions from previous injections.

Pembrolizumab will be administered using IV infusion on Day 1 of each 3-week treatment cycle after all procedures and assessments have been completed. Pembrolizumab will be administered as a dose of 200 mg using 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 between -5 minutes and +10 minutes is permitted (i.e., infusion time is 30 minutes (-5 min/+10 min)).

The Pharmacy Manual contains specific instructions for the preparation and administration of the trial treatments.

11.4.1 Timing of Trial Treatment Administration

IO103-IO102 will be administered as two separate SC injections, one hour +/- 15 minutes prior to pembrolizumab. IO102-IO103 injections can be administered in any order, however both must be given to constitute complete treatment with IO102-IO103.

11.4.2 Dose Modification and Toxicity Management Guidelines

11.4.2.1 IO102-IO103

There is currently no information about dose modification or dose delay requirements for IO102-IO103. In the situation of toxicity considered related to, or possibly related to IO102-IO103, the investigation can consider whether to stop the IO102-IO103 treatment.

In case of Grade ≥ 3 injection site reactions such as ulceration or necrosis, administration of IO102-IO103 will stop and no further administration will occur. With the Sponsor's agreement, the patient can continue to receive pembrolizumab if the injection site reaction has improved and there is evidence of clinical benefit.

Treatment with IO102-IO103 or pembrolizumab cannot be re-started once the decision is taken to permanently withdraw the patient from trial treatment.

Management of Injection Site Reactions Associated with IO102-IO103

Injection site reactions have been experienced by the majority of patients who have received treatment with IO102-IO103 (melanoma trial: MM1636; 23/30 [77%] patients), IO102 as monotherapy (melanoma trial: MM1304; 6/10 [60%] patients) and IO103 as monotherapy (basal cell carcinoma trial: BB1801; 10/10 [100%] patients and myeloma trial: MY0001; 9/10 [90%] patients).

The majority of the injection site reactions were Grade 1 or 2 in severity, short-term and local at the injection site (e.g., injection site tenderness, redness, swelling, itching and granulomas). One patient treated with IO102-IO103 experienced a Grade 3 granuloma that required resection.

Injection site reactions that typically manifested as transient adverse events and in most cases, symptoms responded to oral antihistamines, and symptoms remitted after completion of treatment.

Injection site reactions ≥Grade 2 associated with IO102-IO103 will be documented in the eCRF. Any pathology report of a biopsy should be available as a source document.

It is recommended that oral antihistamines are used to manage local injection site reactions associated with IO102-IO103. Local corticosteroid treatment is allowed in the presence of symptoms lasting ≥48 hours after the IO102-IO103 injection. The medical need to use local corticosteroids over several cycles should be discussed with the Sponsor.

11.4.2.2 Pembrolizumab

Immune-related AEs Associated with Pembrolizumab

Events of special interest include immune related adverse events and infusion reactions. Adverse events associated with pembrolizumab exposure may represent an immunologic etiology. These irAEs may occur shortly after the first dose or several months after the last dose of pembrolizumab treatment and may affect more than one body system simultaneously. Therefore, early recognition and initiation of appropriate treatment is critical to reduce complications. Based on existing clinical trial data, most irAEs were reversible and managed with interruptions of pembrolizumab, administration of corticosteroids and/or other supportive care. For suspected irAEs, the investigator will be required to ensure adequate evaluation to confirm etiology or exclude other causes. Additional procedures or tests such as bronchoscopy, endoscopy, skin biopsy may be included as part of the evaluation. Based on the severity of irAEs, the investigator may choose to withhold or permanently discontinue pembrolizumab,

or administer corticosteroids. Dose modification and toxicity management guidelines for irAEs associated with pembrolizumab are provided in the respective SmPC.

Dose Modification and Toxicity Management of Infusion Reactions Related to Pembrolizumab
AEs associated with pembrolizumab combination exposure, including coadministration with additional compounds may represent an immune-related response. These irAEs may occur shortly after the first dose or several months after the last dose of pembrolizumab combination treatment and may affect more than one body system simultaneously. Therefore, early recognition and initiation of treatment is critical to reduce complications. Based on existing clinical trial data, most irAEs were reversible and could be managed with interruptions of pembrolizumab combination treatment, administration of corticosteroids and/or other supportive care. For suspected irAEs, ensure adequate evaluation to confirm etiology or exclude other causes. Additional procedures or tests such as bronchoscopy, endoscopy, skin biopsy may be included as part of the evaluation. Dose modification and toxicity management guidelines for irAEs associated with pembrolizumab are provided in Table 8.

Attribution of Toxicity:
When trial interventions are administered in combination, attribution of an adverse event to a single component is likely to be difficult. Therefore, while the investigator may attribute a toxicity event to the combination, to IO102-IO103 alone, or to pembrolizumab alone, for adverse events listed in Table 8, both interventions must be held according to the criteria in Table 8 Dose Modification and Toxicity Management Guidelines for Immune-related AEs Associated with Pembrolizumab.

Holding Trial Interventions:
When trial interventions are administered in combination, if the AE is considered immune-related, both interventions should be held according to recommended dose modifications.

Restarting Trial Interventions:
Participants may not have any dose modifications (no change in dose or schedule) of pembrolizumab in this trial, as described in Table 8.

If the toxicity does not resolve or the criteria for resuming treatment are not met, the participant must be discontinued from all trial interventions.

If the toxicities do resolve and conditions are aligned with what is defined in Table 8, the combination of IO102-IO103 and pembrolizumab may be restarted at the discretion of the investigator. In these cases where the toxicity is attributed to the combination or to IO102-IO103 alone, re-initiation of pembrolizumab as a monotherapy may be considered after communication with and agreement by the Sponsor.

Table 8 Dose Modification and Toxicity Management Guidelines for Immune-related AEs Associated with Pembrolizumab

General instructions: 1. Severe and life-threatening irAEs should be treated with IV corticosteroids followed by oral steroids. Other immunosuppressive treatment should begin if the irAEs are not controlled by corticosteroids. 2. Pembrolizumab must be permanently discontinued if the irAE does not resolve or the corticosteroid dose is not ≤10 mg/day within 12 weeks of the last pembrolizumab-treatment. 3. The corticosteroid taper should begin when the irAE is ≤ Grade 1 and continue at least 4 weeks.

4. If pembrolizumab has been withheld, pembrolizumab may resume after the irAE decreased to ≤ Grade 1 after corticosteroid taper.

irAEs	Toxicity grade (CTCAE v. 5.0)	Action with pembrolizumab	Corticosteroid and/or other therapies	Monitoring and follow-up
Pneumonitis	Grade 2	Withhold	Administer corticosteroids (initial dose of 1 to 2 mg/kg prednisone or equivalent) followed by taper Add prophylactic antibiotics for opportunistic infections	Monitor participants for signs and symptoms of pneumonitis Evaluate participants with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment
	Recurrent Grade 2, Grade 3 or 4	Permanently discontinue		
Diarrhea / Colitis	Grade 2 or 3	Withhold	Administer corticosteroids (initial dose of 1 to 2 mg/kg prednisone or equivalent) followed by taper	Monitor participants for signs and symptoms of enterocolitis (ie, diarrhea, abdominal pain, blood or mucus in stool with or without fever) and of 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
	Recurrent Grade 3 or Grade 4	Permanently discontinue		
AST or ALT elevation or Increased Bilirubin	Grade 2 [a]	Withhold	Administer corticosteroids (initial dose of 0.5 to 1 mg/kg prednisone or equivalent) followed by taper	Monitor with liver function tests (consider weekly or more frequently until liver enzyme value returned to baseline or is stable)
	Grade 3 [b] or 4 [c]	Permanently discontinue	Administer corticosteroids (initial dose of 1 to 2 mg/kg prednisone or equivalent) followed by taper	

Type 1 diabetes mellitus (T1DM) or Hyperglycemia	New onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of b-cell failure	Withhold [d]	Initiate insulin replacement therapy for participants with T1DM Administer antihyperglycemc in participants with hyperglycemia	Monitor participants for hyperglycemia or other signs and symptoms of diabetes
Hypophysitis	Grade 2	Withhold	Administer corticosteroids and initiate hormonal replacements as clinically indicated	Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency)
	Grade 3 or 4	Withhold or permanently discontinue [d]		
Hyperthyroidism	Grade 2	Continue	Treat with nonselective beta-blockers (eg, propranolol) or thionamides as appropriate	Monitor for signs and symptoms of thyroid disorders
	Grade 3 or 4	Withhold or permanently discontinue [d]		
Hypothyroidism	Grade 2, 3 or 4	Continue	Initiate thyroid replacement hormones (eg, levothyroxine or liothyronine) per standard of care	Monitor for signs and symptoms of thyroid disorders
Nephritis: grading according to increased creatinine or acute kidney injury	Grade 2	Withhold	Administer corticosteroids (prednisone 1 to 2 mg/kg or equivalent) followed by taper	Monitor changes of renal function
	Grade 3 or 4	Permanently discontinue		
Neurological Toxicities	Grade 2	Withhold	Based on severity of AE administer corticosteroids	Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3 or 4	Permanently discontinue		
Myocarditis	Grade 2, 3 or 4	Permanently discontinue	Based on severity of AE administer corticosteroids	Ensure adequate evaluation to confirm etiology and/or exclude other causes
Exfoliative Dermatologic Conditions	Suspected SJS, TEN, or DRESS	Withhold	Based on severity of AE administer corticosteroids	Ensure adequate evaluation to confirm etiology or exclude other causes
	Confirmed SJS, TEN, or DRESS	Permanently discontinue		
All Other irAEs	Persistent Grade 2	Withhold	Based on severity of AE administer corticosteroids	Ensure adequate evaluation to confirm etiology or exclude other causes
	Grade 3	Withhold or discontinue based on the event [e]		

	Recurrent Grade 3 or Grade 4	Permanently discontinue		

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

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

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

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

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

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

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

11.4.3 Dose Modification and Toxicity Management of Infusion-Reactions Related to Pembrolizumab

Pembrolizumab may cause severe or life-threatening infusion-reactions including severe hypersensitivity or anaphylaxis. Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion. Dose modification and toxicity management guidelines on pembrolizumab associated infusion reaction are provided in Table 9.

Table 9 Pembrolizumab Infusion Reaction Dose Modification and 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 participant is deemed medically stable in the opinion of the investigator.	None
Grade 2 Requires therapy or infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤24 hrs.	• **Stop Infusion.** • 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 participant is deemed medically stable in the opinion of the investigator. • If symptoms resolve within 1 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 participant should be premedicated for the next scheduled dose. **Participants who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further trial treatment**	Participant may be premedicated 1.5h (± 30 minutes) prior to infusion of trial intervention with: Diphenhydramine 50 mg po (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg po (or equivalent dose of analgesic).
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 ventilator support indicated	• **Stop Infusion.** • Additional appropriate medical therapy may include but is not limited to: • Epinephrine** • IV fluids • Antihistamines • NSAIDs • Acetaminophen • Narcotics • Oxygen • Pressors • Corticosteroids • Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator. • Hospitalization may be indicated. **In cases of anaphylaxis, epinephrine should be used immediately. Participant is permanently discontinued from further trial treatment.	No subsequent dosing
Appropriate resuscitation equipment should be available at the bedside and a physician readily available during the period of drug administration. For further information, please refer to the Common Terminology Criteria for Adverse Events v5.0 (CTCAE) at http://ctep.cancer.gov.		

11.4.4 Other Allowed Dose Interruption for IO102-IO103 and Pembrolizumab

IO102-IO103 and pembrolizumab may be interrupted for situations other than treatment-related AEs such as medical or surgical events and/or unforeseen circumstances not related to trial intervention. However, trial intervention is to be restarted within 21 days of the originally scheduled dose and within 42 days of the previously administered dose, unless otherwise discussed with the Sponsor. The reason for interruption is to be documented in the patient's trial record.

11.5 Compliance Check and Drug Accountability

11.5.1 IO102-IO103

The Investigator must ensure that a designated person at the trial site/pharmacy receives the trial treatments from the Sponsor and that all such deliveries are:

- Recorded
- Handled and stored safely and properly
- Only dispensed to trial patients according to the protocol
- Returned to distributor if unused.

The Investigator or designee must keep an inventory and accountability logs for the trial treatments, including all IO102-IO103 components. The inventory must include details of receipt and dispensing to the patient, batch and identification numbers. Accounting must be made of any treatments deliberately or accidently destroyed. Discrepancies between the number of vials received and dispensed must be reconciled and documented.

Empty, Used Vials
After completion of accountability logs for the trial treatments, used/partially used vials may be discarded locally in accordance with site specific procedures

Unused Vials

All unused vials must be kept and returned to the storage facility identified by the Sponsor after the reconciliation of delivery records with accountability logs by the Site Monitor, unless specific written agreement with the Sponsor or designee is in place for local destruction of unused vials.

All trial supplies are to be accounted for on an accountability log. It is essential that all used and unused supplies are retained for verification (by the Sponsor or Sponsor’s representative). The Investigator should ensure adequate records are maintained via the accountability log.

11.5.2 Pembrolizumab

The Investigator must ensure that a designated person at the trial site/pharmacy handles drug accountability of pembrolizumab according to institutional standard operating procedures and policies..

11.6 Unblinding Procedures

Not applicable as the trial is unblinded.

11.7 Concomitant Medications and Vaccinations (Allowed and Prohibited)

11.7.1 Allowed Medication and Procedures

All treatments that the investigator considers necessary for a participant's welfare may be administered at the discretion of the investigator provided they meet the permitted medications criteria (not supplied by the sponsor) in keeping with the community standards of medical care.

All concomitant medication will be recorded on the eCRF including all prescription, over-the-counter (OTC) products, herbal supplements, and IV medications and fluids. If changes occur during the trial period, documentation of drug dosage, frequency, route, and date should also be included on the eCRF.
All concomitant medications received within 28 days prior to the first dose of trial treatment and up to 30 days after the last dose of trial treatment should be recorded. Concomitant medications administered beyond 30 days after the last dose of trial treatment should only be recorded for SAEs and ECIs as defined in Section 13.3 and 13.7.

11.7.2 Disallowed Medication and Procedures

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

Listed below are specific restrictions for concomitant therapy or vaccination during the course of the trial:

- Antineoplastic systemic chemotherapy or biological therapy
- Immunotherapy not specified in this protocol
- Chemotherapy not specified in this protocol
- Investigational agents other than IO102, IO103
- Radiation therapy, with the following exception: Palliative radiation to non-target lesions is permitted.
- Live vaccines within 30 days prior to the first dose of trial treatment and while participating in the trial. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster, yellow fever, rabies, BCG, and typhoid vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (e.g., FluMist®) are live attenuated vaccines and are not allowed. COVID-19 vaccines, in general are not live or attenuated vaccines, and in most cases are permitted.

  Systemic glucocorticoids for any purpose other than to modulate symptoms from an AE that is suspected to have an immunologic etiology. The use of physiologic doses of corticosteroids may be approved after consultation with the Sponsor.

  Note: Inhaled steroids are allowed for management of asthma.

Patients who, in the assessment by the investigator, require the use of any of the aforementioned treatments for clinical management must be discontinued.

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

11.7.3 Diet/Contraception and Other Considerations

11.7.3.1 Diet

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

11.7.3.2 Contraception

IO102-IO103 and pembrolizumab may have adverse effects on a fetus in utero.

Participants 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, participants of childbearing potential must adhere to the contraception requirement from the day of study medication initiation (or 14 days prior to the initiation of study medication for oral contraception) throughout the study period up to at least 120 days after the last dose of study medication. If there is any question that a participant of childbearing potential will not reliably comply with the requirements for contraception, that participant should not be entered into the study.

According to the Recommendations related to contraception and pregnancy testing in clinical trials v.1.1 dated 21 Septemeber 2020, developed by the Clinical Trials Facilitation and Coordination Group (CTFG) of European Union Heads of Medicines Agencies (HMA), the following definitions and recommendations related to contraception and pregnancy testing in clinical trials are used:

- WOCBP:

  Woman is considered of childbearing potential, i.e. fertile, following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilisation methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy.

- Postmenopausal state is defined as:

  12 months with no menses without alternative medical cause

  High follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a post-menopausal state in women not using hormonal contraception or hormonal replacement therapy. However in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.

Postmenopausal women and females who are permanently sterilised (bilateral oophorectomy or hysterectomy confirmed with medical records of the actual procedure or confirmed by an ultrasound, bilateral salpingectomy, vasectomy) do not need to use contraception to be eligible for the trial.

Based on the recommendations of the Clinical Trials Facilitation and Coordination Group related to contraception and pregnancy testing in clinical trials (CTFG, 2020) a WOCBP must use a highly effective contraception method. Highly effective contraception have a failure rate of <1% per year and include the following:

- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:
  - Oral
  - Intravaginal
  - Transdermal

- Progestogen-only hormonal contraception, associated with inhibition of ovulation:
  - Oral
  - Injectable
  - Implantable
- intrauterine device (IUD)
- intrauterine hormone-releasing system (IUS)
- bilateral tubal occlusion.
- vasectomised partner (provided that partner is the sole sexual partner of the WOCBP trial patient and that the vasectomised partner has received medical assessment of the surgical success)
- true sexual abstinence (defined as refraining from heterosexual intercourse during the entire period of risk associated with the trial treatments).

Male patients do not need to use contraception during the trial.

11.7.3.3 Use in Pregnancy and Lactating Women

If a patient inadvertently becomes pregnant while on trial treatment, the patient will be immediately discontinued from trial treatment. The site will contact the patient at least monthly and document the patient's status until the pregnancy has been completed or terminated. The outcome of the pregnancy will be reported to the sponsor without delay and within 24 hours 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 trial 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.

It is unknown whether any of the trial treatments are 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, patients who are breast-feeding are not eligible for enrollment.

12 Clinical Assessments

The following sections describe the methods of assessments and list the type of data to be recorded in the CRF. A detailed schedule for the different assessments is given in Table 1 and Table 2 (Schedule of Trial Procedures).

12.1 Eastern Cooperative Oncology Group Performance Scale

Eastern Cooperative Oncology Group (ECOG) Performance Scale will be recorded at times indicated in Table 1 and Table 2. The ECOG Performance Scale is provided in Appendix I.

12.2 Efficacy Assessments

12.2.1 Tumor (Disease) Evaluation

Tumor imaging is strongly preferred to be acquired by computed tomography (CT). Contrast-enhanced magnetic resonance imaging (MRI) may be used when CT with iodinated contrast is contraindicated, or when mandated by local practice.

The same imaging technique regarding modality, ideally the same scanner, and the use of contrast should be used in a patient throughout the trial to optimize the reproducibility of the assessment of existing and new tumor burden and improve the accuracy of the assessment of response or progression based on imaging.

Imaging should include at least the chest, abdomen, and pelvis; however, other sites may be imaged at the recommendation of the investigator, if clinically applicable.

Tumor images must be sent to the central imaging vendor for collect and hold purposes. A central read of images may be performed if a signal of interest is detected in one or more cohorts.

Confirmation of measurable disease based on RECIST v. 1.1 at Screening will be used to determine patient eligibility (RECIST 1.1 is detailed in Appendix II).

All scheduled and unscheduled scans must be submitted to the central imaging vendor for potential external independent assessment.

12.2.1.1 Initial Tumor Imaging

Initial tumor imaging at Screening must be performed within 28 days prior to the date of planned first dose of trial treatment. The site trial team must review screening images to confirm the patient has measurable disease per RECIST v. 1.1.

Tumor imaging performed as part of routine clinical management is acceptable for use as screening tumor imaging if it is of diagnostic quality and performed within 28 days prior to the date of planned first dose of trial treatment

12.2.1.2 Tumor Imaging During the Trial Treatment Period

The first post-baseline imaging assessment should be performed at 9 weeks (±7 days) from the date of first dose of trial treatment. Subsequent tumor imaging should be performed every 9 weeks (±7 days) for first year on treatment followed by every 12 weeks (±7 days) during the second year on treatment until End of Trial or more frequently if clinically indicated. After End of Trial, imaging will continue to be performed every 12 weeks (±7 days) until the last patient in has completed 35 treatment cycles or has confirmed disease progresssion.

Imaging timing should follow calendar days and should not be adjusted for delays in cycle starts. Imaging should continue to be performed until disease progression is identified by the investigator. Imaging should not be delayed due to interruptions or delays in the delivery of each cycle or in the event of the extension of pembrolizumab cycle intervals.

Objective response should be confirmed by a repeat imaging assessment. Tumor imaging to confirm PR or CR should be performed at least 4 weeks after the first indication of a response is observed. Patients will then return to regular scheduled imaging, starting with the next scheduled imaging time point. Patients who receive additional imaging for confirmation do not need to undergo the next scheduled tumor imaging if it is less than 4 weeks later; tumor imaging may resume at the subsequent scheduled imaging time point.

Per iRECIST disease progression should be confirmed by the site 4 to 8 weeks after site-assessed first radiologic evidence of PD (iUPD) in clinically stable patients. Patients who have unconfirmed disease progression may continue on treatment at the discretion of the investigator until progression is confirmed by the site, provided they have met the conditions detailed in Section 12.2.3. Patients who receive confirmatory imaging do not need to undergo the next scheduled tumor imaging if it is less than 4 weeks later; tumor imaging may resume at the subsequent scheduled imaging time point, if clinically stable. Patients who have confirmed disease progression by iRECIST, as assessed by the site, will discontinue trial treatment. Exceptions are detailed in Section 12.2.3.

12.2.1.3 Tumor Imaging after Discontinuation of Trial Treatment(s)

For patients who discontinue trial treatment, tumor imaging should be performed at the time of treatment discontinuation (±4 week window). If previous imaging was obtained within 4 weeks prior to the date of discontinuation, then imaging at treatment discontinuation is not mandatory. For patients who discontinue trial treatment due to documented disease progression, this is the final required tumor imaging if the investigator elects not to implement iRECIST.

For patients who discontinue trial treatment without documented disease progression, every effort should be made to continue monitoring disease status by tumor imaging every 12 weeks until the start of a new anticancer treatment, disease progression, pregnancy, death, withdrawal of consent, or the end of the trial, whichever occurs first.

12.2.2 Response Evaluation

RECIST v. 1.1 will be used to assess disease progression. iRECIST is based on RECIST 1.1, but adapted to account for the unique tumor response seen with immunotherapeutic drugs. iRECIST will be used by the Investigator to assess tumor progression, and make treatment decisions. Patients are expected to continue with the trial treatment until the progressive disease or for another reason as described in Section 9.3.1, such as toxicity or completion of trial treatment, etc. This allowance to continue treatment despite initial disease progression takes into account the observation that some patients can have a transient tumor flare in the first few months after the start of immunotherapy, and then experience subsequent disease response.

If repeat imaging does not confirm disease progression per iRECIST, as assessed by the Investigator, and the patient continues to be clinically stable, the regular imaging schedule should be maintained and trial treatment may continue.

If repeat imaging confirms disease progression per iRECIST, trial treatment should be discontinued (Section 9.3.1); however, if the patient is achieving a clinically meaningful benefit, an exception to continue trial treatment may be considered following consultation with the Sponsor. In this case, if trial treatment is continued, tumor imaging should continue to be performed following the intervals as outlined in Table 1 and Table 2.

12.2.3 Overall Survival

OS is defined as the duration of time from date of enrollment to death from any cause. After disease progression, all patients are expected to be followed every 12 weeks to confirm their survival status. These follow-up visits/contacts continue until the last planned overall survival analysis.

12.2.4 Biomarker Assessments

12.2.4.1 Tumor Tissue

Samples should be obtained and processed according to the Laboratory Manual.

Samples of formalin-fixed paraffin embedded (FFPE) tumor tissue are required to be provided at screening and these can be either archival (within 3 months prior to signing the informed consent form, and in absence of adjuvant or neoadjuvant treatment) or newly acquired core, incisional, or excisional biopsy of a tumor lesion that was not previously irradiated. Use of archival tissue >3 months old may be considered after communication with, and agreement by, the Sponsor.

FFPE tissue blocks are preferred to slides. Newly obtained biopsies are preferred to archival tissue. If submitting unstained cut slides, newly cut slides should be submitted to the testing laboratory within 14 days from the date slides are cut (details pertaining to tumor tissue submission can be found in the Laboratory Manual).

Biomarkers will be measured from the sample(s) of tumor tissue provided. They will include (but are not limited to) biomarkers applicable to all patients (see Table 10).

The PD-L1 status can be assessed locally for eligibility and enrollment in the study, but samples (FFPE block or slides) are required for central confirmation. Tissue sampling for biomarkers at Week 10 is optional and contingent on patient signing biomarker consent form and depends on the presence of a suitable lesion

Subsequent tissue sampling for biomarkers (Week 10) is voluntary and depends on the presence of a suitable lesion. Provision of tissue at this timepoint is not a prerequisite for participation in the trial, however sequential biopsies are highly encouraged.

Table 10 Tumor Tissue Testing and Requirements (All Patients)

Test	Local/central laboratory	Number of slides	Schedule
PD-L1 expression (Dako 22c3 PharmDx)	Local and central confirmation	3	Screening
Analysis of the tumor microenvironment by multiplexed analysis of target expression and lymphocyte infiltration	Central	8	Screening and Week 10
Tumor Mutational Burden	Central	5	Screening

12.2.4.2 Blood Biomarkers

Biomarkers will be analyzed centrally from blood samples and derivatives (whole, serum, plasma, PBMC) collected at the timepoints indicated in Table 1. Local PBMC preparation is required unless explicitly exempted by Sponsor. Blood biomarkers will include:

- Assessment of peripheral immune cell function (PBMC) and treatment-specific T-cell responses
- Analysis of circulating tumor DNA
- IDO activity (serum/plasma) including kynurenine/tryptophan (Kyn/Trp) ratio.
- HLA typing

For these assessments, blood sample(s) totaling approximately 60-70 mL will be obtained at Screening and Week 4, Week 10 and Week 19, and sent for analysis at a central laboratory.

Except for PD-L1 analysis used for eligibility and enrollment, all other molecular and cellular analyses are for scientific research use only and will not be included in the clinical trial report.

12.3 Safety Assessment

AEs will be assessed using CTCAE v. 5.0.

12.3.1 Adverse Events

An AE is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered causally related to the trial treatment. An undesirable medical condition can be symptoms (e.g., nausea, chest pain), signs (e.g., tachycardia, enlarged liver) or the abnormal results of an investigation (e.g., laboratory findings, electrocardiogram). In clinical trials an AE can include an undesirable medical condition occurring at any time, including run in or washout periods, even if no investigational medicinal product has been administered.

Adverse events will be monitored from the time that the patient provides written informed consent and

throughout the trial duration, until 30 days post last dose of trial treatment and will be elicited by direct, non leading questioning or by spontaneous reports.

Adverse event will be graded and recorded throughout the trial and during the follow-up period according to NCI CTCAE (Version 5.0).

Further details for AE reporting can be found in Section 13.

12.3.2 Physical Examination

Full physical examinations will be conducted at times indicated in Table 1 and Table 2. Any clinically significant physical examination findings (abnormalities) observed during the screening period should be recorded under medical history (if resolved). Any clinical significant physical examination findings observed after the first trial treatment dose will be reported as AEs. Any physical examination findings (abnormalities) persisting at the end of the trial will be followed by the Investigator until resolution or until reaching a clinically stable endpoint.

Directed physical examinations will be conducted for cycles that do not require a full physical examination as indicated in Table 1 and Table 2 the Investigator or qualified designee will perform a directed physical examination as clinically indicated.

12.3.3 Vital Signs

Vital Signs include blood pressure, heart rate, respiration rate, weight and temperature. Height will be measured at screening only. Vitals signs will be recorded at times indicated in Table 1 and Table 2. The method of vital signs assessment must be kept consistent throughout the trial.

12.3.4 12-Lead Electrocardiogram

A standard 12-lead ECG will be performed using local standard procedures at times indicated in Table 1 and Table 2. Any clinically significant findings at screening should be recorded in medical history.

12.3.5 Eastern Cooperative Oncology Group Performance Scale

Eastern Cooperative Oncology Group (ECOG) Performance Scale will be recorded at times indicated in Table 1 and Table 2. The ECOG Performance Scale is provided in Appendix I.

12.3.6 Safety Laboratory Parameters

12.3.6.1 Biochemistry, Hematology and Urinalysis

All safety laboratory analysis will be performed at a laboratory facility local to the trial site.

Laboratory tests for hematology, biochemistry and urinalysis are specified in Table 11 and the timing is specified in Table 1 and Table 2.

All safety screening laboratory evaluations should be performed or repeated within 7 days prior to treatment initiation; all other screening assessments are performed within 28 days.

Rescreening is permitted, if applicable and after discussion with the Sponsor.

Laboratory samples can be collected up to 48 hours prior to the scheduled trial treatment and results must be known and acceptable prior to dosing.

12.3.6.2 Thyriod Function Tests and Coagulation Tests

Thyroid Function and coagulation tests will be performed locally and are specificed in Table 11, and the timing is specified in Table 1 and Table 2.

Laboratory samples can be collected up to 48 hours prior to the scheduled trial treatment and results must be known and acceptable prior to dosing.

Table 11 Laboratory Tests

Hematology	Chemistry	Urinalysis	Other
Hemoglobin	Albumin	Blood	TSH
Platelet count	Alkaline phosphatase	Glucose	T_3 or FT_3
White blood cell (total and differential)	ALT	Protein	FT_4
	AST	Specific gravity	Prothrombin time (PT INR)
	LDH	Microscopic examination (if abnormal results noted)	Partial thromboplastin time (activated) aPTT
	Uric acid	Creatinine or measured or calculated creatinine clearance (CrCl) [+++]	Serum β-hCG [†]
	Calcium		
	Glucose		
	Phosphorus		
	Potassium	Urine pregnancy test[†]	
	Sodium		
	Magnesium		
	Total bilirubin		
	Direct bilirubin if total bilirubin is >ULN		
	Total protein		
	Creatinine[+++]		
	Urea		
	Troponin (Screening only)[#]		

[†] Perform on women of childbearing potential only. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test will be required.
[#] Per institutional standard.
[+++] Creatinine can be measured in plasma or serum. Measured or calculated creatinine clearance (CrCl). CrCl should be calculated per institutional standard. If no local guideline is available, CrCl should be calculated using the Cockcroft-Gault Method. GFR can also be used in place of creatinine or CrCl.

12.3.7 Demographics and Other Baseline Characteristics

The following will be collected:

- Year of birth
- Age
- Race and ethnic origin
- Gender

12.3.8 Medical History and Concomitant Illness

The medical history for each patients that has provided written informed consent will be obtained. Medical history will include all active conditions and previous conditions within the last 10 years that are considered relevant or clinically significant by the Investigator.

12.3.9 Echocardiogram/Multi-Gated Acquisition Scan

An echocardiogram or MUGA scan will be performed within 7 days prior to treatment initiation. Clinically significant findings will recorded as medical history.

12.3.10 Body Weight and Height

The trial patients' body weight and height will be collected.

12.3.11 Pregnancy Test

Urine pregnancy test will be collected within 72 hours prior to trial treatment, every 3 weeks during the trial treatment, at the End of Treatment, as well at 120 days after the last dose of pembrolizumab. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test (β-hCG) will be required. Women with childbearing potential must be willing to use adequate birth control starting from the screening visit and through 120 days after last dose of pembrolizumab or 180 days after last dose of treatment with IO102-IO103.

12.4 Pharmacokinetic Assessment

PK samples will be taken from up to 10 patients at the following timepoints on Day 1 of the first cycle: Pre-dose and the following times after IO102-IO103 peptide administration: 15 minutes, 1 hour, 2 hours and 4 hours post-dose. A separate ICF will be used for this sub-study. Plasma samples will be analyzed using liquid chromatography tandem mass spectrometry (LC-MS/MS).

13 Adverse Events

13.1 Adverse Event Definitions

An Adverse Event (AE), an Adverse Drug Reaction (ADR) and a Serious Adverse Event (SAE) are defined according to ICH Guideline E2A. AEs will be assessed using CTCAE v. 5.0.

An AE is any untoward medical occurrence in a patient administered the Trial treatment(s) and which does not necessarily have to have a causal relationship with this Trial treatments(s). An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), for example, symptom, or disease temporally associated with the use of the Trial treatment(s), whether or not considered related to the Trial treatment(s).

Progression of the cancer under study is not considered an adverse event unless it results in hospitalization or death.

An ADR is any noxious and unintended response to a Trial treatment(s) at least possibly related to any dose of the Trial treatment(s).

An SAE is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening (this refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it was more severe)
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly or birth defect

- Is judged medically important (this refers to an event that may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed)

A non-SAE is any AE that does not meet the definition of an SAE.

The following will not be considered an AE:

- Pre-planned procedure (documented at Visit 1) unless the condition for which the procedure was planned has worsened from the first trial related activity after the patient has signed the informed consent form
- Symptoms and events associated with diease progression will not be reported as an adverse event.
- Concomitant illness identified as a result of screening procedures. However, if symptoms are worsened and/or become serious, this must be reported as a SAE.
- Hospital admissions for social reasons such as pre-planned cosmetic surgery not associated with the underlying disease.

13.2 Adverse Event Assessment Definitions

13.2.1 Severity

The investigator should assess the severity of all AEs according to the following definitions:

Grade 1. Mild: Discomfort noticed, but no disruption of normal daily activity. Prescription drug not ordinarily needed for relief of symptom but may be given because of personality of patient.

Grade 2. Moderate: Discomfort sufficient to reduce or affect normal daily activity. Patient is able to continue in study; treatment for symptom may be needed.

Grade 3. Severe: Incapacitating, severe discomfort with inability to work or to perform normal daily activity. Severity may cause cessation of treatment with test drug; treatment for symptom may be given and/or patient hospitalized.

Grade 4. Life-Threatening: Symptom(s) place the patient at immediate risk of death from the reaction as it occurred; it does not include a reaction that, had it occurred in a more serious from, might have caused death.

Grade 5. Fatal: Event caused the death of the patient.

Note the distinction between seriousness and severity: The term severe is used to describe the intensity of the event and a severe event is not necessarily serious. CTCAE v. 5.0 (or later versions if updated) will be used to define severity. The seriousness criteria serve as a guide for defining regulatory reporting obligations see Section 13.1.

13.2.2 Relationship to Trial Treatment

Assessment of causality is based on the following considerations: associative connections (time and/or place), pharmacological explanations, previous knowledge of the drug, presence of characteristic clinical or pathological phenomena, exclusion of other causes, and/or absence of alternative explanations.

The investigator will be asked to assess causal relationship to each of the trial treatments (pembrolizumab, IO102-IO103) according to the following classifications:

- Probably related
- Possibly related

- Unlikely related

13.2.3 Outcome

The investigator will be asked to record the most appropriate outcome of the following:

- Recovered/resolved
- Recovering/resolving
- Not recovered/not resolved
- Recovered with sequelae
- Fatal
- Unknown

13.3 Reporting of Adverse Events

At each visit the patient will be asked about AEs in an objective manner, e.g.: "Have you experienced any problems since the last visit?"

Only medically qualified personnel (investigators) must assess AEs.

AEs will be assessed according to CTCAE v. 5.0 (or later) and must be reported on the AE form. The diagnosis should be recorded, if available. If no diagnosis is available each sign and symptom should be recorded as individual AEs.

All other relevant documents supporting the reported SAE (e.g. diagnostic procedures, hospital records, autopsy reports) must be sent using the same method as the reported SAE.

- All AEs, SAEs and other reportable safety events that occur after the consent form is signed but before treatment /allocation must be reported by the investigator if the participant is receiving placebo run-in or other run-in treatment, if the event cause the participant to be excluded from the study, or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, or a procedure.
- All AEs or ECIs (Events of Clinical Interest) from the time of treatment/ allocation through 30 days following cessation of study treatment must be reported by the investigator.
- All AEs meeting serious criteria, from the time of treatment/ allocation through 90 days following cessation of study treatment, or 30 days following cessation of study treatment if the participant initiates new anticancer therapy, whichever is earlier must be reported by the investigator.
- All pregnancies and exposure during breastfeeding, from the time of treatment/ allocation through 120 days following cessation of study treatment, or 30 days following cessation of study treatment if the participant initiates new anticancer therapy must be reported by the investigator.
- Additionally, any SAE brought to the attention of an investigator at any time outside of the time period specified above must be reported immediately to the Sponsor if the event is considered to be drug-related.

The independent ethics committees and regulatory authorities will be notified by the Sponsor or Sponor's delegate of SAEs according to current regulation and local requirements.

All Suspected, Unexpected Serious Adverse Reactions (SUSARs) are subject to expedited reporting to regulatory authorities by the Sponsor or Sponsor's pharmacovigilance vendor.

13.4 Follow-up on Adverse Events

All AEs should be followed until they are resolved or stable the patient's participation in the trial ends, whichever comes first.

SAEs and severe, non-serious AEs considered related to trial drug should be followed on a regular basis according to the investigator's clinical judgment until a final outcome has been established.

13.5 Sponsor Responsibility for Reporting SAEs

The Sponsor is responsible for the ongoing safety evaluation of the trial treatment.

The sponsor is responsible for the prompt notification to all concerned investigators, the ECs/Institutional Review Boards (IRBs) and Competent Authorities where IO102 and/or IO103 studies are ongoing, of findings that affect the health of the patients, impact on the conduct of the study or alter the Competent Authority's authorisation to continue the study in accordance with Directive CTR 536/2014 or local law as applicable.

The sponsor has to keep detailed records of all AEs reported to him by the investigators and to perform an evaluation with respect to seriousness, causality and expectedness. These records shall be submitted to the Competent Authorities in the countries where the clinical study is being conducted, if they so request.

Each individual AE should be evaluated by the Sponsor, with regard to its seriousness and causal relationship to the IMP. The sponsor will assess whether or not the AE is unexpected.

13.6 Definition of an Overdose and Reporting of an Overdose

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

Overdose with IO102-IO103 is unlikely, due to the SC route of administration. There is no information available regarding overdose with IO102-IO103.

13.7 Events of Clinical Interest

Selected non-serious and serious adverse events are also known as ECI and must be reported to the Sponsor within 24 hours of awareness.

Events of clinical interest for this trial include:

- An overdose of Sponsor's product, as defined in Section 13.6 that is not associated with clinical symptoms or abnormal laboratory results.
- An elevated AST or ALT lab value that is greater than or equal to 3× the upper limit of normal and an elevated total bilirubin lab value that is greater than or equal to 2× the upper limit of normal and, at the same time, an alkaline phosphatase lab value that is less than 2× 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 made available. It may also be appropriate to conduct additional evaluation for an underlying etiology in the setting of abnormalities of liver blood tests including AST, ALT, bilirubin, and alkaline phosphatase that do not meet the criteria noted above. In these cases, the decision to proceed with additional evaluation will be made through consultation between the trial investigators

and the sponsor. However, abnormalities of liver blood tests that do not meet the criteria noted above are not ECIs for this trial.

13.8 Reporting of Pregnancies

If a participant inadvertently becomes pregnant while on treatment with IO102-IO103 and/or pembrolizumab, the participant will be immediately discontinued from study treatment. The site will contact the participant at least monthly and document the participant's status until the pregnancy has been completed or terminated. The outcome of the pregnancy will be reported to the Sponsor without delay and within 24 hours 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.

In addition, the investigator must attempt to collect pregnancy information on any female partners of male trial patients who become pregnant while the patient is enrolled in the trial. Pregnancy information must be reported to sponsor as described above.

All pregnancies and exposure during breastfeeding, from the time of treatment through 120 days following cessation of trial treatment, or 30 days following cessation of trial treatment if the participant initiates new anticancer therapy whichever is earlier.

14 Changes to Trial Conduct

14.1 Protocol Amendments

Before implementation of substantial protocol changes, approval/favorable opinion must be obtained from the appropriate national Competent Authority(ies) and IRBs/IECs, unless the amendment is considered an urgent safety measure in which case, the amendment will be implemented immediately and before approval. Amendments considered administrative or logistical may be implemented without IRBs/IECs or national Competent Authority(ies) approval.

14.2 Clinical Trial Pausing

The clinical trial may be paused for reasons considered to change the risk of patients to be entered or already entered to the trial. Conditions that may warrant pausing of the clinical trial include, but are not limited to the following:

- The death (other than death related to disease progression) of a patient within 30 days of receiving trial treatment that is considered at least possibly related to trial treatment.

14.3 Premature Termination of the Trial

In case of premature termination of the trial, Competent Authorities and independent ethics committees will be notified in writing, including the reason for premature termination.

Conditions that may warrant premature termination of the trial include, but are not limited to the following:

- The discovery of an unexpected and significant or unacceptable risk to the patients enrolled in the trial
- Failure of the investigators to enroll patients at an acceptable rate in the trial as a whole
- A decision of the sponsor to discontinue development of the IO102-IO103 combination or one of the two components of the combination.

14.4 Premature Termination of a Cohort or Trial Site

The sponsor can decide to prematurely terminate single cohorts and/or sites. Conditions that may warrant termination include, but are not limited to the following:

- Insufficient adherence to protocol requirements
- Failure to enroll patients at an acceptable rate and/or with steering committee agreement

15 Data Handling and Retention of Documents

15.1 Source Data

For all data recorded, the source document must be defined in a source document agreement or similar document at each trial site. There must only be one source defined at any time for any data elements.

Source data should as a general rule be recorded in the patients's medical record or other defined document normally used at the trial site. Source data not normally collected as a routine part of the clinical practice at the site may be entered on a worksheet. Clinical assessments/safety evaluations must be signed by medically qualified investigators.

If the worksheet does not become part of the patient's medical record, the following should as a minimum be added to the patient's medical record:

- Date(s) of conducting the informed consent process (date of enrolment) including date of provision of patient information
- A statement from the investigator to verify that each of the eligibility criteria are met for each patient
- Patient ID
- Randomisation code number (if applicable)
- The fact that the patient is participating in a clinical trial in NSCLC adenocarcinoma, SCCHN, and mUBC including treatment with IO102-IO103 and pembrolizumab for up to 24 months
- Other relevant medical information

The trial monitor will check the CRFs for accuracy and completeness by verifying data recorded in the CRF against source data to ensure such records are consistent.

15.2 Coding of Data

Medical history and AEs will be coded using the most current version of Medical Dictionary for Regulatory Activities (MedDRA).

Concomitant medication will be coded using most current version of WHO Drug Reference List.

16 Retention of Documents

The monitor will instruct the investigator to maintain source documents and the signed informed consent form for each patient.

Furthermore, the monitor will instruct the investigator to archive essential documents for the duration defined in the ICH Guideline E6 (Note for Guidance on Good Clinical Practice) or for 15 years, whichever comes first.

The duration of archiving defined in the ICH Guideline E6 is as follows:

Essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational

product. These documents should be retained for a longer period however if required by the applicable regulatory requirements or by an agreement with the sponsor.

The sponsor will notify the investigator when retention of the trial-related records is no longer required.

17 Statistical Methods

All output will be generated for each cohort (NSCLC adenocarcinoma, SCCHN and mUBC).

The data will be summarized in tables, as appropriate, showing the number of patients with nonmissing data (N), mean, standard deviaton, median, minimum and maximum for continous data and showing counts and percentage for the categorical data. Data will also be listed as deemed appropriate.

The Statistical Analysis Plan (SAP) will describe in detail the analyses presented below.

ORR, CRR and DCR, will be assessed and 95% confidence intervals will be calculated using the Clopper-Pearson exact methodology.

PFS rate (PFR) at 6 months as well as the endpoint duration of response with corresponding 95% intervals, will be estimated using Kaplan-Meier methods using the treated patient population.

17.1 Timing of Analyses

For each treatment cohort, the primary analysis will be performed 6 months after the last patient started treatment.

Interim analyses for each cohort will be considered after 15 patients are treated with ≥2 cycles in the cohort and have either completed at least 2 post-baseline tumor assessments or have discontinued. Details of the interim analyses will be defined in the SAP.

17.2 Sample Size and Power Considerations

A minimum of 2 cycles of vaccination is considered necessary to induce benefit over monotherapy pembrolizumab; additional patients may be enrolled to ensure at least 30 patients are treated for 2 cycles and more. This is an exploratory study and for all 3 cohorts a 1-side 15% significance level is used and sample sizes have been considered.

Cohort A (NSCLC adenocarcinoma PD-L1 TPS ≥50%)

For patients with PD-L1 TPS ≥ 50% with pembrolizumab, ORR is estimated to be 39% (Mok *et al.*, 2019).

If the true ORR for IO102-IO103+pembrolizumab is 55% there is a power of 77% to detect a difference between 39% and 55% with 30 patients. If there are 17 responders from the 30 patients, the ORR point estimate will be 57% and the 95% Clopper-Pearson confidence interval will be 37% - 75%.

Cohort B (SCCHN, PD-L1 CPS ≥20)

For patients with CPS ≥20 with pembrolizumab, ORR is estimated to 23% (Burtness *et al.*, 2019).

If the true ORR for IO102-IO103+pembrolizumab is 35% there is a power of 68% to detect a difference between 23% and 35% with 30 patients. If there are 11 responders from the 30 patients, the ORR point estimate will be 37% and the 95% Clopper-Pearson confidence interval will be 20% - 56%.

Cohort C (mUBC, PD-L1 CPS ≥10)

Patients with CPS ≥10 with pembrolizumab, ORR is estimated to 47% (Vuky *et al.*, 2020).

If the true ORR for IO102-IO103+pembrolizumab is 60% there is a power of 65% to detect a difference between 47% and 60% with 30 patients. If there are 18 responders from the 30 patients, the ORR point estimate will be 60%, and the 95% Clopper-Pearson confidence interval will be 41% - 77%.

17.3 Approach to Endpoint Analyses

Statistical analyses will be performed on the treated set, including all patients that receive at least one dose of IMP, and the minimum exposure set, including all patients that receive at least 2 cycles of IO102-IO103. A per-protocol set may be defined prior to database lock for sensitivity analysis of efficacy endpoints.

17.3.1 Primary endpoint

The primary endpoint is ORR according to RECIST v. 1.1.

ORR will be assessed and 95% confidence intervals will be calculated using the Clopper-Pearson exact methodology.

The primary analysis will be based on the treated patient population, but supported with analysis of the minimum exposure patient population.

17.3.2 Other endpoints

The endpoint of the PFS will be estimated using Kaplan-Meier methods.

DCR and CRR will be assessed and 95% confidence intervals will be calculated using the Clopper-Pearson exact methodology.

For overall survival the percentage of patients who are alive at 6 monthly intervals after first dose will be presented based on the Kaplan-Meier estimates.

DOR and iPFS will be illustrated using Kaplan-Meier plots with time to censoring marked on the curves. Median time of response/median progreesion free time with corresponding 95% CI will be estimated using Kaplan-Meier methods.

TTR will be presented in a cumulative plot i.e. inverted Kaplan-Meier plot. Time to censoring will be marked on the curves and median time to response will be estimated if applicable using Kaplan-Meier methods.

17.4 Analysis Data Sets

The following 2 analysis sets will be defined:

- **Treated set:** patients who receive at least one dose of any study medication.
- **Minimum exposure set:** all treated patients who did not discontinue IO102-IO103 treatment prior to the second dose of Cycle 2 (Day 8 of Cycle 2 administration).

Additional analysis sets may be defined in the SAP.

Patients enrolled but not treated will be included in listings and patient profiles only.

17.5 Definition of Efficacy Endpoints

17.5.1 Primary Endpoints

ORR is based on disease evaluation done locally for all patients in accordance with RECIST v. 1.1 prior to administration of trial treatment and every 9 weeks post baseline the first year of treatment followed by every 12 weeks until disease progression and is the percentage of patients that has a complete or partial response.

Response (complete response or partial response) should be confirmed by a repeat imaging assessment. Tumor imaging to confirm PR or CR should be performed at least 4 weeks after the first indication of a response is observed.

17.5.2 Secondary Endpoints

The list of secondary efficacy endpoints evaluated in the trial is

- PFS according to RECIST v. 1.1
- DoR
- CRR
- DCR
- OS
- TTR

17.5.3 Progression Free Survival (PFS)

PFS is defined as the time from first treatment with IMP to the first documented disease progression (based on disease evaluation done locally for all patients in accordance with RECIST v. 1.1) or death from any cause. If a patient is not known to have progressed or died then they will be censored at the date of the last disease assessment. If a patient progresses after they have 2 or more consecutively missed disease assessment visits then they will be censored at the date of the last non missing disease assessment.

17.5.4 Progression Free Survival according to iRECIST (iPFS)

PFS is defined as the time from first treatment with IMP to the first documented disease progression (based on iRECIST) or death from any cause.

Per iRECIST disease progression should be confirmed by the site 4 to 8 weeks after site-assessed first radiologic evidence of PD (iUPD). The event date used for calculation for progression free survival should be the first date when the progression criterion is met (iUPD) providing that progression is confirmed at the next assessment (see Appendix II).

If a patient is not known to have progressed or died then they will be consored at the date of the last disease assessment. If a patient progresses after they have 2 or more consecutively missed disease assessment visits then they will be censored at the date of the last non missing disease assessment.

17.5.5 Duration of Response (DoR)

Duration of response will be measured from the date of first observed objective response until disease progression or death (whichever is earlier). Date of progression and censoring will be handled in the same way as for PFS (evaluation done locally for all patients in accordance with RECIST v. 1.1). The time of the initial response will be defined as the latest of the dates contributing towards the first visit response of PR or CR.

If a patient does not progress following a response, then their duration of response will use the PFS censoring time.

17.5.6 Complete Response Rate (CRR) and Disease Control Rate (DCR)

CRR is defined as the number (%) of patients with a visit response of CR. Evaluation of response will be done locally for all patients in accordance with RECIST v. 1.1.

DCR is defined as the number (%) of patients with a visit response of PR or CR or SD. Evaluation of response will be done locally for all patients in accordance with RECIST v. 1.1.

17.5.7 Overall Survival (OS)

Overall survival is defined as the time from first dose of IMP until death from any cause. Patients not known to have died will be censored at the date last known to be alive. After disease progression, all patients are expected to be followed every 12 weeks to confirm their survival status. These follow-up visits/contacts continue until the last planned overall survival analysis.

17.5.8 Time to Response (TTR)

In the subset of responding patients, TTR is defined as the time from first dose of IMP until the date of the first observed partial or complete response. Evaluation of response will be done locally for all patients in accordance with RECIST v. 1.1.

17.5.9 ECOG Performance Status

ECOG performance status is a scale measuring the disease impacts a patient's daily living abilities. The scale takes on the values 0, 1, 2, 3, 4 and 5 and measures the impact from from fully active (equals 0) to dead (equals 5).

17.5.10 Exploratory Endpoints

Exploratory endpoints are biomarkers, measures of immune markers, Progression Free Survival according to iRECIST (iPFS), and ORR and PFS according to independent central review, if applicable.

The presentation of the exploratory endpoints will be described in detail in the statistical analysis plan.

17.6 Statistical/Analytical Issues

17.6.1 Missing Data

For the assessment of ORR, CRR and DCR, a patient without sufficient tumor assessment data (Not Evaluable [NE] as disease response) will be considered as a non-responder.

Procedures for dealing with missing data will be described in detail in the statistical analysis plan.

17.6.2 Examination of Subgroups

Important demographic and baseline value-defined subgroups will be examined and the results presented, e.g., comparison of effects by smoking status, age, sex and baseline value. A detailed description will be provided in the statistical analysis plan

17.7 Safety Analysis

All safety output will be based on the treated set.

17.7.1 Adverse Events

A treatment emergent adverse events (TEAE) is defined as any event which is not present prior to exposure to study medication, and starts no later than 30 days after last trial treatment for non-serious events and no later than 90 days after last trial treatment for serious events, or any event already present that worsens in either intensity or frequency following exposure to IMP.

An overview of all AEs including severity, relationship to IMP, serious AEs (SAEs) and AEs leading to withdrawals or death will be presented.

TEAEs will be summarized by system organ class (according to MedDRA current version) and preferred term (according to MedDRA current version) displaying number of patients, number and percentage of patients having the AE as well as number of AEs. Furthermore, AEs will be summarized according to severity, relationship, outcome and seriousness. AEs causing discontinuation of trial treatment will be summarized by SOC and preferred term.

Summaries will be done across all cycles.

SAEs and AEs leading to withdrawal will be listed and tabulated, if appropriate.

All data will be listed.

17.7.2 Electrocardiogram

ECG assessments will be summarized by visit.

17.7.3 Vital Signs

Blood pressure, pulse, temperature and body weight will be summarized by visit.

17.7.4 Laboratory Safety Assessments

Laboratory parameters will be graded according to CTCAE grading. CTCAE changes in laboratory parameters will be presented by shift tables showing baseline values against values at treatment visits.

Mean changes from baseline over time will also be summarized and plots produced for each laboratory parameter. Plots will show mean and error bars (+/- SE).

A liver related scatterplot (eDISH plot - part 1) of alanine aminotransferase by bilirubin will be presented. All patients with alanine aminotransferase $\geq 3 \times$ ULN and bilirubin $\geq 2 \times$ ULN (eDISH plot - part 2 – patients in Hy's law range, if any) will have their liver parameters presented in a plot by visit and patient.

17.8 Pharmacokinetic Analysis

PK data (drug concentration) will be summarized descriptively.

18 Good Clinical Practice

This trial will be carried out in compliance with the protocol, GCP, Standard Operating Procedures (SOPs) of the CROs and applicable regulatory requirements.

The investigator agrees, when signing this protocol, to adhere to the instructions and procedures described in it, to the principles of Good Clinical Practice and to applicable regulatory requirements.

19 Ethics

19.1 Independent Ethics Committees / Competent Authorities

Before implementing this trial, the protocol, the proposed patient information and patient consent form, and other documents as required, will be reviewed by properly constituted Independent Ethics Committees (IECs) and by the national Competent Authorities.

A signed and dated statement that the protocol and patient information and patient consent form have been approved by the IECs and regulatory authorities will be obtained before trial initiation.

For each individual IEC the name and occupation of the chairman and the members of the IEC will be collected as well as a statement that the IEC works in accordance with ICH GCP.

IECs will receive updates on trial progress according to local regulations.

19.2 Informed Consent

The patient's signed and dated informed consent to participate in the trial will be obtained prior to any trial related procedure being carried out.

Before any trial related procedure the investigator will explain to the potential patient the aims, methods, reasonably expected benefits and potential hazards of the trial and any discomfort participation in the trial may entail. Patient will be informed that participation in the trial is voluntary and that the patient may withdraw from the trial at any time and for any reason. Patient will be informed that if they choose not to participate, this will not affect the care the patient will receive for the treatment of his or her disease. Finally, patients will be informed that their records may be accessed by health authorities and authorized sponsor staff without violating the confidentiality of the patient, to the extent permitted by the applicable laws or regulations.

All patients will be given opportunity to ask questions and will be given sufficient time to consider before consenting. The patients may choose to be accompanied, e.g. by a family member, during the information process. After having consented, a copy of the informed consent form will be given to the patient.

All patients will be asked to consent to the genomic analyses which include at least the following analyses:

- Tumor mutational burden
- Immune gene signatures
- T-cell receptor sequencing

Patients participating in the PK blood sampling will be required to sign a separate consent form.

20 Audits and Inspections

A representative of the sponsor may visit the trial sites at any time during the trial or after completion of the trial to conduct an audit of the trial. These audits will require access to all trial records, including source documents, for inspection and comparison with the CRFs. Patient privacy will, however, be respected. The investigator and other trial personnel will be responsible for being present and available for consultation during routinely scheduled site audit visits conducted by the sponsor's representative.

Similar auditing procedures (inspections) may also be conducted by agents of regulatory health authorities, either as part of a national GCP compliance program or to review the results of this trial in support of a regulatory submission. The investigator should notify the sponsor's representative or sponsor immediately, if he/she has been contacted by a regulatory agency concerning an upcoming inspection.

21 Monitoring

Before trial initiation a monitor from sponsor's representative will review the protocol and the CRF with the investigators and their trial personnel. During the trial the monitor will visit the trial site regularly to check the completeness of patient records, the accuracy of entries in CRFs, the adherence to the protocol and to GCP,

the progress of enrolment and the handling and accounting of the trial treatments. Key trial personnel must be available to assist the monitor during these visits.

The investigator must give the monitor direct access to source data/documents (e.g. relevant hospital or medical records) to confirm their consistency with the entries in eCRFs. No information in these records about the identity of the patients must leave the trial site.

If there are institutional restrictions on visitors remote monitoring may be necessary. The procedures associated with remote monitoring are discussed in the Monitoring Plan.

22 Reporting of Results

22.1 Integrated Clinical Trial Report

Data will be reported in an integrated clinical trial report in compliance with the requirements of the current version of ICH E3: Structure and Content of Clinical Study Report.

The signatory investigator will review and sign the integrated clinical trial report.

22.2 Use of Information

All unpublished information relating to this trial and/or to the trial drug is considered confidential by the sponsor and shall remain the sole property of the sponsor.

The investigator must accept that the sponsor may use the information from this clinical trial in connection with the development of the IMP(s), and therefore, may disclose it as required to other investigators, to government licensing authorities, to regulatory agencies of other governments, stock exchange market, and commercial partners.

22.3 Publication of Results

Basic information of this trial will be posted by the Sponsor on the website: www.clinicaltrials.gov before the first patient enters the trial.

The sponsor is committed to publishing the trial results, whether positive or negative, in a peer-reviewed journal.

The criteria for authorship as set out by the Committee of Medical Journal Editors (www.icmje.org) will be applied.

The contributorship model will be applied and contributors who do not meet the criteria for authorship will be listed in an acknowledgments section with descriptions of the role of each contributor in order to ensure indexation in the National Library of Medicine.

Publications are subject to the following conditions:

- Data are the property of the Sponsor and cannot be published without prior authorization from the Sponsor.
- Publications should be drafted with protection of individual privacy, intellectual property and contract rights in mind, and also conform to legislation and current national practices in patent and other laws.
- The primary publication (i.e. the results from all centers) should be published before, or in parallel with, any secondary publications.
- Publications shall not disclose any Sponsor confidential information or property.

23 Insurance and Liability

The sponsor has subscribed to an insurance policy covering, in its terms and provision, its legal liability for injuries caused to participating patients and arising out of trial procedures performed in accordance this

protocol, in accordance with applicable law and with the ICH Guideline E6 (Note for Guidance on Good Clinical Practice).

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25 Appendices

APPENDIX I - Eastern Cooperative Oncology Group (ECOG) Performance Score

Grade	ECOG Performance status
0	Fully active. Able to carry on all pre-disease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature (e.g. light house work, office work).
2	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	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

APPENDIX II - Disease Assessment by RECIST v. 1.1 and Progressive Disease Assessment by iRECIST

RECIST v. 1.1 evaluation and definitions of disease response

Complete Response (CR)	Disappearance of all TLs since baseline. Any pathological lymph nodes selected as TLs must have a reduction in short axis to <10 mm.
Partial Response (PR)	At least a 30% decrease in the sum of the diameters of TLs, taking as reference the baseline sum of diameters
Stable Disease (SD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD
Progression of disease (PD)	At least a 20% increase in the sum of diameters of TLs and an absolute increase of at least 5 mm, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study).
Not Evaluable (NE)	Only relevant if any of the TLs were not assessed or not evaluable or had a lesion intervention at this visit. Note: if the sum of diameters meets the progressive disease criteria, progressive disease overrides not evaluable as a TL response

Assessment at Screening and Prior to Disease Progression by RECIST v. 1.1
Until radiographic disease progression based on RECIST v. 1.1, there is no distinct iRECIST assessment.

Overall visit response algorithm

Target lesions	Non-target lesions	New lesions	Overall response
CR	CR	No or NE	CR
CR	NA	No or NE	CR
CR	Non CR/Non PD	No or NE	PR
CR	NE	No or NE	PR
PR	Non PD or NE or NA	No or NE	PR
SD	Non PD or NE or NA	No or NE	SD
NE	Non PD or NE or NA	No or NE	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

RECIST v. 1.1 and iRECIST defined disease progression

Assessment and Decision at RECIST v. 1.1 Progression
For patientes who show evidence of radiological PD by RECIST v. 1.1 as determined by the Investigator, the Investigator may continue the patient on trial treatment until repeat imaging is obtained as described in the Table below (that is, using iRECIST for patient management). This decision by the Investigator should be based on the patients's overall clinical condition.

Disease assessment:	**Definition of Response criteria**	**Timing of radiological assessment**	**Key criteria to be met**
At progressive disease	RECIST v. 1.1	Timing according to the radiological scan schedule	At least a 20% increase in the sum of diameters of TLs and an absolute increase of at least 5 mm, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). New lesions and/or unequivocal increase in non-target lesions will also contribute. This is referred to as iUPD (unconfirmed progressive disease according to iRECIST)
At confirmation progressive disease	iRECIST	At least 4 weeks, but not more than 8 weeks after iUPD	iCPD (**confirmed progressive disease according to iRECIST**): continued increase in tumor burden where RECIST v. 1.1 definitions of progression has been met in target, non-target or new lesions. **Progression in target disease worsens with an increase of at least 5mm in the absolute sum and/or unequivocal increase in non-target tumor burden and/or increase in previously identified new lesions and/or further new lesions**.

APPENDIX III - Management of Patients During the Coronavirus Disease 2019 (COVID-19) Pandemic

The safety and protection of patients from the SARS-CoV-2 virus which causes COVID-19 is a priority.

In general, the risk of COVID-19 for fully SARS-CoV-2 vaccinated patients is considered less than the risk of not treating the patient for advanced cancer.

During the COVID-19 pandemic, it is recommended that:

- the overall risk of COVID-19 to the patient is considered (taking into consideration age, vaccination status, co-morbidities etc.);
- all patients have a negative PCR or lateral flow test before consent (that is - before starting the 28 day screening period prior to treatment initiation);
- patients continue to confirm their negative status using either lateral flow or PCR before each clinical trial related hospital visit. The Sponsor will reimburse reasonable costs for COVID-19 tests.

Patients who have not yet consented to enter the clinical trial.

It is recommended to delay patient consent to enter the trial in the situation where either the patient has a positive PCR test for COVID-19, or if there is considered to be a COVID-19 outbreak at the hospital site or institution. The duration of delay is at the discretion of the investigator or in accordance with the institution's policy, but should be at least 2 weeks.

Patients who have consented to participate in the clinical trial.

It is recommended that scheduled visit to the hospital and/or administration of IO102-IO103 and/or pembrolizumab be delayed for 2 weeks in the situation where a patient reports a positive lateral flow or PCR test.

In the situation of a hospital specific COVID-19 outbreak, the visit to the hospital should be delayed until the outbreak is curtailed and contingency plans implemented as necessary.

Contingency plans are designed to protect the patient, their family and hospital staff in the situation of a COVID-19 outbreak at the hospital and the delay to the scheduled visit likely to be more than 2 weeks. Contingency plans can include, but are not limited to:

- Home visits by health care professional(s) (HCP) able to administer IO102-IO103 and conduct physical examination and take blood, as per the protocol schedule.
- Telephone contact to discuss AEs and other relevant clinical discussion.

Patients should be asked to return to the hospital for their trial treatment administration and trial specific procedures at the earliest opportunity, in accordance with the institution's policy.
Reimbursement of reasonable taxi fares and other unplanned expenses will be made by the Sponsor in order to avoid public transportation.

For these patients, the delay to the scheduled visit, or home visit by HCP must be documented in the patient's medical notes and **identified as a COVID-19 protocol deviation**.

Activities such as remote monitoring and remote source data verification (SDV) and maintenance of General Data Protection Regulation (UK/EU GDPR) during the COVID-19 pandemic are documented in the Monitoring Manual or Monitoring Plan.

Signature Page for IO102-IO103-022 Protocol Version 8.0 v1.0