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Statistical Analysis Plan

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)

Trial ID: IO102-IO103-022

Version: 2.0 Final; Date: 06 Feb 2025

Signature page

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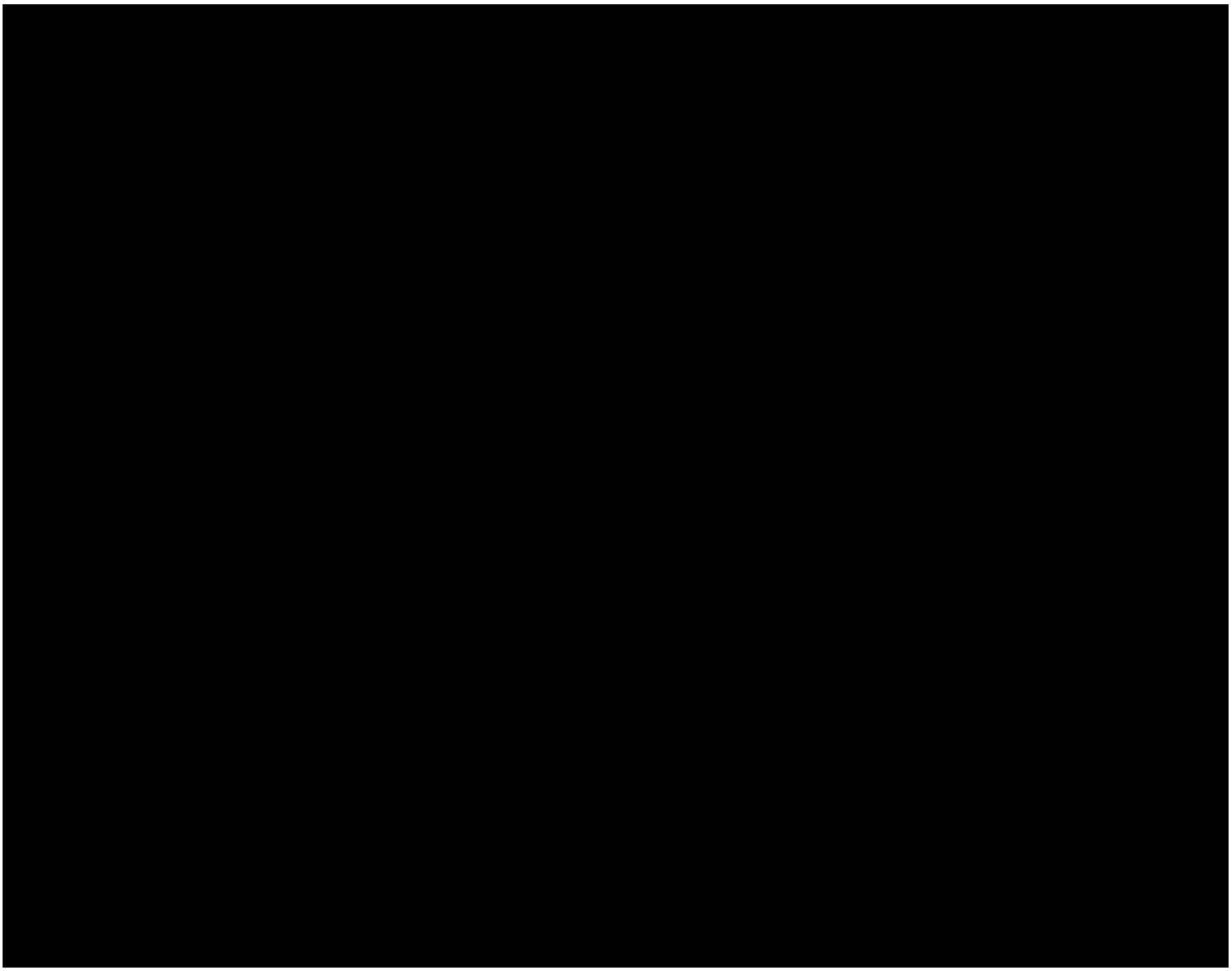

Amendment History

Version number	Date	Summary of Major Change
Version 1.0	02 Nov 2021	Original version, based on Protocol 3.0
Version 1.1	06 Apr 2022	Revision according to protocol amendment 4.1 • Changed the primary endpoint from co-primary endpoints (ORR and PFS) to a single endpoint (ORR). PFS will be analyzed as a secondary endpoint
Version 2.0	06 Feb 2025	Revision according to protocol amendment 8.0 • Changed OS analysis from secondary endpoint to exploratory endpoint • Clarified censoring rules for PFS analysis • Updated specifications for biomarker analysis • Added pharmacokinetic analysis • Added details on lab data categorization and analysis plan • Added specifications for reporting immune-mediated adverse events and injection site reaction

Table of Contents

1 List of Abbreviations

AE	Adverse Event
ALAT	Alanine Aminotransferase
ASAT	Aspartate Aminotransferase
CI	Confidence Interval
CPS	Combined Positive Score
CR	Complete Response
CRF	Case Report Form
CRR	Complete Response Rate
CSR	Clinical Study Report
CT	Computerized Tomography
CTCAE	Common Terminology Criteria for Adverse Events
DBL	Data Base Lock
DCR	Disease Control Rate
DoR	Duration of Response
ECOG	Eastern Cooperative Oncology Group
EEP	Efficacy Evaluable Population
HCP	Health Care Professional
IMP	Investigational Medicinal Product
iPFS	Progression Free Survival according to iRECIST
iRECIST	Immune-Related Response Evaluation Criteria in Solid Tumors
SPP	Intention-To-Treat
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic Resonance Imaging
mUBC	Metastatic Urothelial Bladder Cancer
N	Number of Patients
NSCLC	Non-Small Cell Lung Cancer
ORR	Objective Response Rate
OS	Overall Survival
PD	Progression Disease
PR	Partial Response
PFS	Progression Free Survival
PFR	Progression Free Rate
PFR6	Progression Free Rate at 6 months
PP	Per Protocol

PT	Preferred Term
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SCCHN	Squamous Cell Carcinoma of Head and Neck
SD	Stable Disease
SOC	System Organ Class
TEAE	Treatment Emergent Adverse Event
TS	Treated Set
TPS	Tumor Proportion Score
TTR	Time to Response

2 Introduction

The statistical analysis plan (SAP) for trial IO102-IO103-022 is based on the protocol version 8.0 dated 21 June 2024.

The SAP describes in detail the analyses to be conducted and highlights any deviations from the analysis described in the protocol, if any. Deviations from methods described in this SAP, if any, will be specified in the clinical trial report.

Before releasing data for analysis of the study, data review and classification meeting(s) will be held to classify patients with respect to analysis populations. The product of the classification meetings will be a detailed description of the analysis populations.

The analysis is performed based on:

- The clinical database, which includes the electronic Case Report Forms (eCRF)
- List of important protocol deviations
- Analysis populations documented as part of the data base lock (DBL) minutes.

3 Trial Characteristics

3.1 Trial Objectives

Whilst the following describes the trial objectives, at the end of the study the sponsor will consider the totality of the evidence from all available data.

3.1.1 Primary Objective

This is an exploratory study. The primary objective is to investigate the efficacy of IO102-IO103 in combination with pembrolizumab in the frontline treatment of each of the different metastatic solid tumor indications (NSCLC PD-L1 Tumor Proportion Score (TPS) ≥50%, SCCHN PD-L1 Combined Positive Score (CPS) ≥20, or mUBC CPS ≥10.

3.1.2 Secondary Objectives

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

3.1.3 Exploratory Objectives

The primary exploratory objectives are to evaluate baseline biomarkers that may predict response to treatment, and to assess IO102-IO103-specific immunity. Biomarkers, which will be measured from formaldehyde-fixed paraffin embedded (FFPE) tumor tissue include:

- Comprehensive genomic sequencing (next generation sequencing) to provide information on tumor mutational burden (TMB) and ~500 genes associated with cancer
- Baseline gene expression profiling via Nanostring, to elucidate gene signatures and individual gene expression patterns
- PD-L1 and IDO immunohistochemistry

and blood (whole, serum or plasma) provided during screening and on-treatment include, but are not limited to:

- To evaluate and establish activity of IO102 and IO103 in cellular and/or molecular assays
- To evaluate the dynamics of the molecular interaction between the tumor and its microenvironment (multiplex/special IHC, Immune Phenotyping, Transcriptomics) to elucidate the therapeutic mechanism of action of IO102 and IO103

To seek a correlation between tumor/immune parameters and clinical response to enable selection of patient and gain understanding of potential mechanisms of resistance to therapy

3.2 Trial Design

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

The primary endpoint is ORR by investigator assessment 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. The same modality of radiological examination must be used throughout the trial.

The clinical trial is open-label and consists of 3 cohorts:

- Cohort A: Patients with NSCLC, metastatic Stage IV and PD-L1 expression TPS ≥50%.
- Cohort B: Patients with SCCHN (recurrent or metastatic disease) with PD-L1 CPS ≥20
- Cohort C: Patients with mUBC, metastatic Stage IV and PD-L1 CPS ≥10

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 the 3 arms has completed the trial treatment and 30 days for safety follow-up, or until progression of disease (PD), death, withdrawal of consent or lost-to-follow-up, whichever is earlier.

All eligible patients will receive treatment for up to 2 years with IO102-IO103 (IO102 85µg and IO103 85µg) subcutaneously (SC) on day 1 and day 8 of the first 2 cycles and on day 1 of each subsequent 3-week cycle in combination with pembrolizumab intravenously (IV) 200 mg Q3W. IO102-IO103 will be administered one hour prior to pembrolizumab. A maximum of 37 administrations will be provided for each patient during the trial.

The details of the trial procedures can be found in Section 3 of the protocol.

4 Analysis Data Sets

The following 2 analysis sets will be defined.

- Treated Set (TS): patients who receive at least one dose of any study medication. Since all enrolled patients are treated, this is also the intent-to-treat set.
- Minimum Exposure Set (MES) set: MES is defined as all treated patients who did not discontinue IO102-IO103 treatment prior to the second dose of cycle 2 (Day 8 of cycle 2 administration).

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

Safety endpoints will be analyzed with the Treated Set. The efficacy analyses (ORR, PFS, CRR, DOR, DCR, and TTR) will be performed using the MES set. ORR will also be analyzed using the Treated Set as a sensitivity analysis.

4.1 Important protocol deviations

Before DBL all protocol deviations will be evaluated and classified as important or not important. Important protocol deviations can lead to patients not included in the Per-Protocol Set to be defined at DBL. The decisions will be documented in the DBL meeting minutes. Protocol deviations will be summarized, and a listing of important protocol deviations will be prepared.

5 Planned Statistical Methods and Data Presentations

5.1 Timing of analyses

An interim analysis can be conducted for each cohort, when the primary endpoint of ORR can be analyzed 6 months after the last patient of the corresponding arm started treatment. Additional interim analysis may be added as needed. The interim analysis will be based on snapshots of the database unless otherwise justified. Data summaries in tables, figures and listings of the corresponding cohort including baseline characteristics, safety, and efficacy, will be prepared and presented in publications and conference presentations.

Final analysis of the study will be conducted when all patients of the study has completed up to 35 cycles of trial treatment plus 30 days for safety follow-up, or until progression of disease (PD), death, withdrawal of consent or lost-to-follow-up, whichever is earlier. Data will be summarized and reported in a clinical study report (CSR).

5.2 Statistical Considerations

All outputs mentioned in the remainder of the SAP will be generated for all three cohorts (NSCLC, SCCHN and mUBC) separately.

Baseline is defined as the last assessment with available data prior to exposure of trial drug.

Numerical data will be presented using number of patients, mean, standard deviation, median, range (minimum and maximum).

All summary tables for categorical variables will display counts, percentages, and number of missing data (if relevant) by cohort.

The Kaplan-Meier survival curves and 25^{th}, 50^{th} (median), and 75^{th} percentiles will be provided along with their 2-sided 95% CI for time- to-event data.

All statistical analyses will be conducted using SAS version 9.4 or higher. Generally, no imputation of missing data will be applied in analyzing efficacy endpoints. Missing/partial dates of events will be handled as described in section 6.

All safety endpoints will be presented using descriptive statistics and no formal statistical tests will be applied.

5.3 Patient Disposition

An overall summary table of the patient disposition will be prepared with number of patients in the following categories (and sub-categories):

- Treated Set patients

- Minimum Exposure Set
- Off-treatment and reasons for off-treatment
- Off-trial and reasons for off-trial

Patient disposition data will be listed for all treated patients to include informed consent date, treatment and study completion status with reasons for treatment discontinuation /study withdrawal. A listing of screen failures and reasons for screen failures will be prepared.

5.4 Demographics and Baseline Characteristics

Demographics and baseline characteristics consist of age, gender, race, ethnicity, height, weight, BMI, ECOG, smoking status and other parameters such as time since initial diagnosis of disease, primary tumor stage at initial diagnosis, stage at study entry, PD-L1 TPS/CPS score and category, prior adjuvant treatment, LDH status, Liver metastasis based on the treated set.

5.5 Medical History

The medical history for each patient that has provided written informed consent will be obtained according to protocol definition.

Medical history is coded using Medical Dictionary for Regulatory Activities (MedDRA) most current version and will be summarized by SOC and PT by each cohort and overall in the treated set. A listing of medical history for each patient will be provided in the TS.

5.6 Prior Cancer Therapy

Prior cancer therapy, including chemotherapy, hormone therapy, immune therapy, targeted therapy along with the number of regimens (0, 1, 2, ≥3) administered, prior cancer radiation and prior cancer surgeries will be summarized by frequency and percentage of patients within each category. The data will be summarized and listed for the Treated Set.

5.7 Exposure

All descriptive data will be presented separately for each cohort for the Treated Set.

Duration of exposure to the treatment is the total duration (days) from the first dose to the last dose (inclusive) of treatment and is calculated as:

Date of last dose - Date of first dose of trial treatment + 1

IO102-IO103 will not be continued as monotherapy without pembrolizumab. However, with the Sponsor's agreement, the patient can continue to receive pembrolizumab if there is evidence of clinical benefit.

Duration of exposure to IO102-IO103 and pembrolizumab will be calculated separately as well as a combination.

Number of doses received, cycles of treatment, duration of treatment, duration of pembrolizumab, duration of IO102-IO103 will be summarized for each cohort in the Treated Set. Numbers of dose delays and discontinuations, infusion interrupted and reason for these will be summarized. Dose intensity for pembrolizumab and IO102-IO103 will also be summarized.

All exposure data will be listed.

5.8 Prior and Concomitant medication

Prior and concomitant medication information is collected from screening and during the trial. Prior and concomitant medications will be coded using the current version of WHODrug and will be summarized with frequencies and percentages of patients who received medications by ATC class (ATC level 3) and preferred term and will be listed as well.

If a medication has an end date and end time that occur before the first dose date and time, that medication will be considered a prior medication. If a medication has a start date and start time that occur before the first dose date and time but an end date and end time that occur after first dose date and time, that medication will be considered concomitant. If a medication has a start date, start time, end date, and end time that occur on/after the first dose date and time, that medication will be considered concomitant. Should a missing start date, start time, end date, or end time leading to ambiguity in whether a medication is prior or concomitant, the medication will be considered concomitant. Missing/partial date and time will be imputed as described in section 6.

Prior and concomitant medication will be summarized based on the Treated Set.

5.9 Analysis and Presentation of Efficacy Endpoints

5.9.1 Disease Assessment and RECIST

The response is based on disease evaluation by CT scan or MRI done locally for all patients based on RECIST v.1.1 guideline prior to administration of trial treatment and every 9 weeks post baseline during the first year of treatment followed by every 12 weeks until disease progression. After PD or response per RECIST 1.1, repeat imaging for confirmation is required. Repeat imaging is done between 4 and 8 weeks to confirm PD (per iRECIST), and at least 4 weeks after to confirm response.

Best overall response (BOR) is defined as the best overall response assessment of target, non-target and new lesions from the start of trial treatment until disease progression/recurrence or start of subsequent anti-cancer therapy. Valid response assessments (ranked from best to worst) are complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD), not evaluable (NE) in accordance with RECIST v.1.1. If a patient dies with no evidence of CR, PR, SD or progressive disease per RECIST v1.1 then BOR will be assigned as PD unless the death is >26 weeks from the last tumor assessment (or baseline if no post baseline tumor assessments) in which case BOR will be assigned as NE.

According to RECIST v1.1, when no imaging/measurement is done at all at a particular visit, the patient is not evaluable (NE) at that visit. For PFS analysis, if no imaging/measurement is done at all at the protocol defined visit, the assessment will be considered missing.

If a patient has had a tumor assessment which cannot be evaluated due to on-study intervention (e.g., palliative radiotherapy of symptomatic lesions, palliative surgery) or because of missing anatomy not covering all lesions, the patient will be assigned NE at that visit unless there is evidence of progression in which case the response will be assigned as PD. Not evaluable in this scenario will be considered equivalent to a non-PD assessment.

The confirmation of CR/PR requires a second response assessment of the same or better level at least 4 weeks apart with no intervening PD (date of 2nd response assessment date of the 1st

response assessment +1>28 days). If there are “NE” assessments between responses, the RECIST 1.1 guidance suggests it is reasonable to consider a patient with response pattern of PR-NE-PR as a confirmed response. There “NE” will not be considered as intervening PD.

Sensitivity analysis for ORR, DoR and DCR will be performed using the same analysis method regardless of confirmation.

5.9.2 Analysis and Presentation of the Primary Endpoints

The primary endpoint is Objective Response Rate (ORR) according to RECIST v1.1. ORR is defined as the percentage of patients with a BOR of either CR or PR and should be confirmed by a repeat imaging assessment performed at least 4 weeks after the first indication of a response is observed. The denominator will be the number of patients in the MES

Patients without a post-baseline tumor assessment will be classed as non-responders. Response will be assessed based on all evaluable assessments up to and including progression per RECIST v 1.1 before starting subsequent anti-cancer therapy.

A two-sided 95% Clopper-Pearson [5] CI for ORR will be calculated. Bayesian hierarchical modeling approach will be explored to estimate the probability of treatment effects across 3 patient cohorts [8]

5.9.3 Analysis and Presentation of the Secondary Endpoints

The list of secondary efficacy endpoints evaluated in the trial is

- Progression Free Survival (PFS)
- Duration of Response (DoR)
- Complete Response Rate (CRR)
- Disease Control Rate (DCR)
- Time to Response (TTR)

Important biomarker subgroups (such as PD-L1 score categories) or baseline characteristic subgroups (such as disease stage, baseline tumor burden, etc.) may be explored for primary and secondary endpoints, if applicable.

5.9.3.1 Progression Free Survival

PFS is defined as the time from start of treatment to the first documented disease progression (based on disease evaluation done locally 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. Censoring rules and details regarding the handling of missing assessments for PFS primary analysis are presented in the table below.

Censoring Rules for PFS Primary Analysis

Scenario	Date of Progression or Censoring	Outcome

PD or death	Date of PD or death, whichever is earlier	Event
No documented PD or death	Date of last non-PD assessment, or Day 1 if no post-baseline tumor assessment	Censored

PFS will be presented in a Kaplan-Meier plot with time to censoring marked on the curves and number of patients at risk presented at each timepoint.

A summary of PFS table will also be provided to include the median, 25th, and 75th percentiles for PFS for each cohort. PFS rate at landmark times (e.g. 6 months, 12 month and 18 months) will be determined based on the Kaplan-Meier estimates and presented in the summary table as well.

CIs for the median progression free times are calculated using the method by Brookmeyer and Crowley [6]. CIs for point estimates of the survival distribution are calculated using the method by Kalbfleisch and Prentice [7]. Progression Free Survival based on RECIST 1.1 swimmer plot will be provided.

5.9.3.2 Duration of Response

Objective response is defined as either complete response (CR) or partial response (PR) and 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.

Duration of response is defined for patients who had objective response and 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. Median duration of response and quartiles of the duration of response and 95% confidence intervals will be calculated similarly as the analysis for PFS.

5.9.3.3 Complete Response Rate

Complete Response Rate (CRR) is defined as the percentage of patients achieved complete response. The denominator will be the number of patients in the MES.

CR should be confirmed by a repeat imaging assessment performed at least 4 weeks after the first indication of a response is observed.

The 95% Clopper-Pearson confidence intervals will be calculated for CRR in each cohort.

5.9.3.4 Disease Control Rate

Disease Control Rate (DCR) is defined as the percentage of patients with a BOR of CR, PR or SD. The denominator will be the number of patients in the MES.

CR and PR should be confirmed by a repeat imaging assessment performed at least 4 weeks after the first indication of a response is observed. If not CR/PR, at least one visit response of SD at least 8 weeks from start of study medication is observed. The 95% Clopper-Pearson confidence intervals will be calculated for DCR in each cohort.

5.9.3.5 Time to Response

Time to response will be measured for patients who had a confirmed objective response, from the start of treatment until the date of first observed CR or PR.

The cumulative rate of response will be presented using Kaplan-Meier curve. The median and 95% confidence intervals will be presented. Only patients who have a confirmed objective response will be included in the summary.

5.9.4 Analysis and Presentation of Exploratory Endpoints

Exploratory endpoints are

- Biomarkers
- PFS according to iRECIST (iPFS)
- Overall survival (OS)

5.9.4.1 Biomarkers

Biomarkers, which will be measured from tumor tissue and blood (whole, serum or plasma) provided during screening and on-treatment (Tumor: Week 10; Blood; Week 4, 10 and 19), include:

- PD-L1 expression using multiplex analysis on the same sample to evaluate spatial distribution, or serial sections (FFPE tumor).
- Assessment of Tumor Infiltrating Lymphocytes (TILs) by multiplex IHC or similar (FFPE tumor).
- IDO activity (serum/plasma) including kynurenine/tryptophan (Kyn/Trp) ratio.
- Tumor mutational burden (FFPE tumor and blood) (TMB).
- Immune gene signature (FFPE tumor).
- Immunological monitoring such as vaccine specific T-cell responses and other immunological related measures (PBMC from blood).
- HLA haplotyping.
- T-cell receptor sequencing (DNA isolated from FFPE and PBMC).

Associations between biomarkers and clinical response may be explored. Biomarker analysis except for PD-L1 (used for eligibility and enrollment) will be analyzed and summarized in a separate biomarker analysis report, if applicable.

5.9.4.2 Progression Free Survival According to iRECIST

iPFS is defined as the time from first treatment with IMP to the first documented disease progression and confirmed by the subsequent visit assessment based on iRECIST or death from any cause. The same analysis method for PFS will be used for iPFS. to the first documented disease progression

5.9.4.3 Overall Survival

Overall survival is defined as the time from start of treatment 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 death or the last date of survival follow-up.

Overall survival will be estimated using the Kaplan-Meier method. A plot including the Kaplan-Meier curves and number of patients at risk per time point will be presented.

5.10 Statistical Methodology for Safety Endpoints

Safety analysis will be conducted in the Treated Set. Safety evaluations will be based on clinically significant changes or abnormalities in the patient's test results and investigator reported AEs.

Safety data will include

- Adverse events
- Electrocardiogram (ECG)
- Vital signs
- Physical examination
- Laboratory safety assessments
- ECOG Performance Status

5.10.1 Adverse Events

AEs will be reported in the eCRF from signing of informed consent and onwards. AEs will be graded using CTCAE v5.0. The diagnosis should be recorded, if available. If no diagnosis is available each sign and symptom should be recorded as individual AEs. AEs will be coded using the most current version of Medical Dictionary for Regulatory Activities (MedDRA). Attribution to both pembrolizumab and IO102-IO103 will be reported by the investigator as unlikely, possible or probably related. Treatment-related AEs are reported as either possible or probably related to either pembrolizumab, IO102-IO103 or both. A treatment emergent adverse event (AE) is defined as any event that has an onset date, or a worsening in severity or becomes serious on or after the first dose of study medication and up to 100 days after the last dose of study medication.

An overall summary of the number and percentage of patients in each of the categories listed below will be presented.

- All AEs
- All SAEs
- AE related to any study medication
- Grade 3 or 4 AEs

- Grade 3 or 4 AEs related to any study medication
- SAE related to any study medication
- AEs leading to discontinuation of either trial medication (action taken for pembrolizumab or IO102-IO103 reported as drug withdrawn)
- AEs leading to death
- Related AEs leading to death
- Immune mediated adverse event (imAE)
- Injection site reactions

For each of the above categories, data will be further summarized by MedDRA system organ class and preferred term. In addition, tables of AEs will be summarized by preferred term, by decreasing frequency. Patients with more than one AE within a particular PT are counted only once for that PT.

AEs that are immune related or potentially immune related will be evaluated. The immune mediated adverse events (imAE) in this study are defined by the pre-specified list of preferred terms developed by Merck in the AEOSI for pembrolizumab (latest version prior to DBL will be used for the CSR). Infusion reactions are deemed not immune-mediated and will not be included in the summary of immune-mediated events.

Injection site reactions are of special interest and will be summarized with a group of MedDRA terms which are reviewed by the study team and will be included in the CSR report.

A by-patient listing of all AEs will also be prepared, where AE start/end date, seriousness, CTCAE grade, action taken, outcome, the causality will be included in the listing.

5.10.2 Laboratory Safety Data

All data recorded in the eCRF will be listed. Lab values will be converted to standard units and normalized using local lab reference ranges.

$$Normalized\ value = (value - LLN) \times \frac{ULN_{std} - LLN_{std}}{ULN - LLN} + LLN_{std}$$

This normalization transformation will be used for all lab tests other than cell counts. Normalization is used to account for different reference ranges (lower limit of normal or LLN and upper limit of normal or ULN) for different laboratories.

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

Frequency of patients with possible clinically significant abnormalities will be summarized. Possible clinically significant abnormalities are defined as CTCAE grade of 2 or greater, with an increase of at least one grade from baseline, except as noted in Appendix A

An elevated AST or ALT lab value >= 3x the upper limit of normal and an elevated total

bilirubin lab value >= 2x the upper limit of the normal and, at the same time, ALP lab value < 2x the upper limit of normal will be summarized for each cohort.

A liver related scatterplot (eDISH plot - part 1) of alanine aminotransferase by bilirubin will be presented. All patients with alanine aminotransferase ≥ 3 × UNL and bilirubin ≥ 2 × UNL (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.

The labs to be reported can be found in Appendix A.

5.10.3 ECG

ECG abnormalities will be presented in a data listing.

5.10.4 Vital Signs and Physical examination

Any clinically significant findings (abnormalities) of vital signs or physical examination observed during the screening period should be recorded under medical history (if resolved). Any clinically significant findings of vital signs or physical examination observed after the first trial treatment dose will be reported as AEs.

Vital sign values will be presented in a by-patient listing.

5.10.5 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 fully active (equals 0) to dead (equals 5).

The change from baseline to best value during treatment in ECOG will be tabulated.

5.11 Pharmacokinetic Analysis

PK samples will be taken from up to 10 patients at the following timepoints on Day 1 of the first cycle: pre-dose and after IO102-IO103 administration: 15 mins, 1 hour, 2 hours, and 4 hours post-dose. PK data will be analyzed and summarized in a separate report.

6 Handling of Missing Data

Missing or partial dates for an event will be imputed following the below rules. All missing data not covered here will not be imputed. Analyses will be performed considering all data observed for the respective analysis sets.

The imputed dates will be flagged in the analysis datasets (ADaM) but the listings of events will present the actual dates as recorded on the eCRF.

6.1 Conventions for Missing /partial Dates for Prior/Concomitant Medications

If a medication has a completely missing start date it will be considered a prior medication, and if a medication has a completely missing stop date it will be considered a concomitant medication. If a partial start or stop date occurs, the following imputation process will be implemented:

Partial Missing Start or Stop Date	Imputation for Start Date	Imputation for Stop Date
Day missing, month and year present	• Month and/or year different to month and year of first study drug dose: Impute day with "01" • Month and/or year same as month and year of first study drug dose: Impute day with same day as first dose of study drug.	Impute day with last day of the month
Day and month missing, year present	• Year different to year of first study drug dose: Impute day and month with "01JAN" • Year same as year of first study drug dose: Impute month and day with same month and day as first dose of study drug.	Impute day and month with "31DEC"
Month missing, day and year present	• Year different to year of first study drug dose: Impute month with "JAN" • Year same as year of first study drug dose: Impute month with same month as first dose of study drug.	Impute with "DEC"
Caveats	• If any imputed start date leads to a start date that is after the stop date, then the start date will be imputed with the date of the stop of medication. • No stop date will be imputed if the treatment is ongoing.	

6.2 Conventions for Missing/partial Adverse Event Dates

If an AE has a completely missing start and stop date, it will be considered treatment emergent; if the stop date is not missing, but the start date is completely missing, it will be considered treatment emergent unless the stop date occurs prior to the first dose of study drug.

For purpose of calculation of duration of AE, if a completely missing start and stop date occurs then it will be considered to have started on the date of first dose and stopped at the date of study termination. If stop date is present, and start date is completely missing, the start date will be imputed with the date of first dose of study drug unless the stop date occurs prior to first dose of study drug; in this case the start date will be imputed with the stop date. If start date is present and a completely missing stop date occurs, it will be considered to have stopped at the date of study termination for the patient.

For assessing treatment emergent or calculation of duration of AE, if a partial start or stop date occurs, the following imputation process will be implemented:

Partial Missing Start or Stop Date	Imputation for Start Date	Imputation for Stop Date
Day missing, month and year present	• Month and/or year different to month and year of first study drug dose: Impute day with "01".	Impute day with last day of the month

Partial Missing Start or Stop Date	Imputation for Start Date	Imputation for Stop Date
	• Month and/or year same as month and year of first study drug dose: Impute day with same day as first dose of study drug.	
Day and month missing, year present	• Year different to year of first study drug dose: Impute day and month with "01JAN". • Year same as year of first study drug dose: Impute month and day with same month and day as first dose of study drug.	Impute day and month with "31DEC"
Month missing, day and year present	• Year different to year of first study drug dose: Impute month with "JAN". • Year same as year of first study drug dose: Impute month with same month as first dose of study drug.	Impute with "DEC"
Caveats	• If any imputed start date leads to a start date that is after the stop date, then the start date will be imputed with the date of the stop of AE.	

7 Reference List

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8 Appendix

8.1 Appendix A: List of Lab Tests

	Category	Units	Direction	Clinical Significance Rule
Clinical Chemistry				
Alanine Aminotransferase (Serum)	A	U/L	High	CTCAE >=2
Albumin (Serum)	C	g/L		
Alkaline Phosphatase (Serum)	A	U/L	High	CTCAE >=2
Aspartate Aminotransferase (Serum)	A	U/L	High	CTCAE >=2
Bilirubin (Serum)	A	umol/L	High	CTCAE >=2
Blood Urea Nitrogen (Serum)	C	mmol/L		
Calcium (Serum)	C	mmol/L		
Creatinine (Serum)	A	umol/L	High	> 1.5xULN and > baseline
Direct Bilirubin (Serum)	C	umol/L		
Glucose (Serum Random)	A	mmol/L	Low High	Low: Standard[1] High: >10 mmol/L and > baseline
Lactate Dehydrogenase (Serum)	A	U/L	High	> ULN and >baseline
Magnesium (Serum)	C	mmol/l		
Phosphate (Serum)	C	mmol/l		
Potassium (Serum)	C	mmol/l		
Protein (Serum)	C	g/L		
Sodium (Serum)	A	mmol/L	Low	< 130 mmol/L and < baseline
Urate (Serum)	C	umol/L		
Hematology				
Basophils (Blood)	C	10^9/L		
Eosinophils (Blood)	C	10^9/L		
Hemoglobin (Blood)	A	g/L	Low	Standard[1]
Leukocytes (Blood)	A	10^9/L	Low	Standard[1]
Lymphocytes (Blood)	A	10^9/L	Low	Standard[1]
Monocytes (Blood)	C	10^9/L		
Neutrophils (Blood)	A	10^9/L	Low	Standard[1]

	Category	Units	Direction	Clinical Significance Rule
Platelets (Blood)	A	10^9/L	Low	Standard[1]
Urinalysis				
Creatinine Clearance (Urine)	C	mL/min		
Specific gravity (Urine)	C	n/a		
Thyroid Function				
Free T3 (FT3) (Blood)	A	pmol/L	Low High	Low: < LLN and < baseline High: > ULN and > baseline
Free thyroxine (FT4) (Blood)	A	pmol/L	Low High	Low: < LLN and < baseline High: > ULN and > baseline
Thyroid stimulating hormone (TSH) (Blood)	A	mU/L	Low High	Low: < LLN and < baseline High: > ULN and > baseline
Total triiodothyronine (T3) (Blood)	A	nmol/L	Low High	Low: < LLN and < baseline High: > ULN and > baseline
Coagulation				
Activated Partial Thromboplastin Time (Plasma)	C	sec		
Prothrombin Intl. Normalized Ratio (Plasma)	C	n/a		

[1]CTCAE grade 2 or higher with an increase of at least one grade from baseline. Symptoms are not considered.

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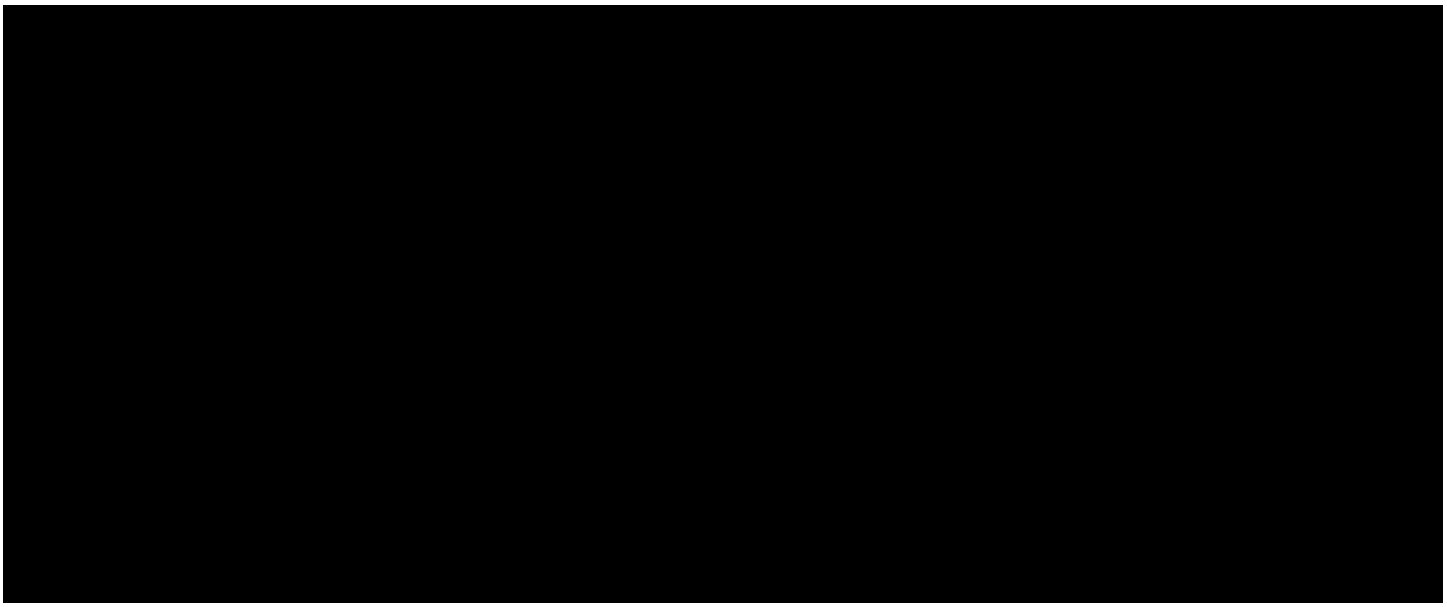

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