Statistical Analysis Plan (SAP)

Protocol Title:	A phase 2, open-label, single-arm, multicenter study of SOT101 in combination with pembrolizumab to evaluate the efficacy and safety in patients with selected advanced/refractory solid tumors
Protocol Version No./Date:	Amendment 1.0/20-Apr-2023
CRF Version No./Date:	1.0/28-Feb-2022
SAP Version No./Date:	2.0/01-Feb-2024

1.0 Approvals

Sponsor	[redacted]
Sponsor Name:	
Representative/ Title:	
Signature /Date:	
ICON	
Biostatistician / Title:	
Signature /Date:	

[redacted]

2.0 Change History

Version/Date	Change Log
0.1	Created as new
0.2	Updated per Sotio and SME review
0.3	Updated per Sotio review
0.4	Updated per SME review
0.5	Updated per Sotio and SME review
1.0	Updated for signature per Sotio feedback
1.1	Updated per MSD feedback
1.2	Amended SAP based on PA#1, addition of PK analyses and updates based on ADaM development findings and IDMC requests.
1.3	Updated per Sotio review
1.4	Updated per Sotio review
2.0	Prepared for signature

3.0 Table of Contents

[redacted]

[redacted]

4.0 Purpose

The Statistical Analysis Plan (SAP) describes the statistical methods to be used during the reporting and analyses of data collected under SOTIO Biotech AG Protocol Amendment 1 SC104 final version dated 20 April 2023.

5.0 Scope

The SAP outlines the following:

- Study objectives
- Study design
- Study endpoints
- Applicable study definitions
- Statistical methods

6.0 Introduction

This SAP should be read in conjunction with the study protocol and case report forms (CRFs). This version of the plan has been developed using protocol amendment 1.0 dated 20 April 2023 and CRFs version 1.0 dated 28 February 2022. Any further changes to the protocol or CRFs may necessitate updates to the SAP.

The SAP will be finalized prior to database lock.

Each version of the SAP requires approval by the sponsor.

6.1 Changes from Protocol

The following changes to the protocol have been applied:

Endpoint of “Circulating tumor cell (CTC) count conversion from >5 to <5 cells per 7.5 mL of blood” for metastatic castration-resistant prostate cancer (mCRPC) only will be analyzed as a conversion from ≥5 to <5 cells per 7.5 mL of blood.

Endpoint of “Confirmed PSA decline of ≥50%” will not only evaluate the response at 6 months post-trial entry: all timepoints will be considered as per the schedule of assessments (Section 1.3.3 of Study Protocol).

Additional sensitivity analyses and exploratory endpoints:

As a sensitivity analysis for Best Overall Response (BOR) as per RECIST 1.1: BOR will also be performed as per Prostate Cancer Clinical Trials Working Group 3 (PCWG3)-modified RECIST 1.1 to study the effect of progressive disease in bone on the BOR, for patients with mCRPC.

As a sensitivity analysis to Clinical Benefit Rate (CBR) as per RECIST 1.1: CBR will also be performed for all patients in mCRPC – with both measurable and non-measurable disease – as per PCWG3-modified RECIST 1.1, to study the effect of progressive disease in bone on the CBR.

Other sensitivity analyses using All Subjects as Treated (ASaT) population on selected efficacy endpoints.

As per the EMA guideline on the evaluation of anticancer medicinal products in man, the endpoint PFS2 has been added as an exploratory endpoint.

Following Futility Analysis in August 2023, recruitment to the study was stopped. Exploratory Endpoints will no longer be analyzed.

[redacted]

7.0 Study Objectives and Endpoints

7.1 Primary Objective

- To estimate the antitumor efficacy of SOT101 in combination with pembrolizumab

7.2 Secondary Objectives

- To assess the safety and tolerability of SOT101 in combination with pembrolizumab according to Common Terminology Criteria for Adverse Events (CTCAE) version 5.0
- To further evaluate the antitumor efficacy of SOT101 in combination with pembrolizumab
- (Population) pharmacokinetics (PK) of SOT101 in combination with pembrolizumab
- To determine the immunogenicity of SOT101 in combination with pembrolizumab

7.3 Exploratory Objectives

- To identify immune and molecular (including genomic, metabolic, and/or proteomic) biomarker(s) in archival and/or fresh tumor tissue and blood that may be indicative of clinical response/resistance, safety, pharmacodynamic (PD) activity, and/or the mechanism of action of SOT101 and pembrolizumab
- To determine the immunogenicity of pembrolizumab in combination with SOT101
- (Population) PK of pembrolizumab in combination with SOT101
- To further evaluate the antitumor efficacy of SOT101 in combination with pembrolizumab

7.4 Endpoint Attributes

Objective	Endpoint(s)
Primary	
• To estimate the antitumor efficacy of SOT101 in combination with pembrolizumab	• Objective response rate (ORR) according to Response Evaluation Criteria In Solid Tumors version 1.1 (RECIST 1.1) in patients with measurable disease
Secondary	
• To assess the safety and tolerability of SOT101 in combination with pembrolizumab according to Common Terminology Criteria for Adverse Events (CTCAE) version 5.0	• Type, frequency, and severity of treatment-emergent AEs (TEAEs); AEs of special interest (AESIs); safety laboratory findings; vital signs; electrocardiography (ECG) findings
• To further evaluate the antitumor efficacy of SOT101 in combination with pembrolizumab	• ORR according to RECIST for immune-based therapeutics (iRECIST) (iORR) in patients with measurable disease • Best overall response according to RECIST 1.1 (BOR) and iRECIST (iBOR) in patients with measurable disease

Objective	Endpoint(s)

	• Duration of response according to RECIST 1.1 (DoR), iRECIST (iDoR) and Prostate Cancer Clinical Trials Working Group 3 (PCWG3)-modified RECIST 1.1 (metastatic castration-resistant prostate cancer [mCRPC] only)
	• Clinical benefit rate according to RECIST 1.1 (CBR), iRECIST (iCBR) and PCWG3-modified RECIST 1.1 (mCRPC only)
	• Progression-free survival (PFS) according to RECIST 1.1, iRECIST (iPFS), and PCWG3-modified RECIST 1.1 (mCRPC only)
	• Time to response according to RECIST 1.1 (TtR) and iRECIST (iTtR) in patients with measurable disease
	• mCRPC only:
	  ○ Circulating tumor cell (CTC) count conversion from ≥ 5 to < 5 cells per 7.5 mL of blood
	  ○ Confirmed prostate-specific antigen (PSA) decline of ≥ 50%
	  ○ Time to confirmed PSA progression

• (Population) pharmacokinetics (PK) of SOT101 in combination with pembrolizumab	• Concentrations of SOT101 over time
• To determine the immunogenicity of SOT101 in combination with pembrolizumab	• Incidence, titer, and time course of anti-drug antibodies (ADAs) against SOT101
Exploratory	
• To identify immune and molecular (including genomic, metabolic, and/or proteomic) biomarker(s) in archival and/or fresh tumor tissue and blood that may be indicative of clinical response/resistance, safety, pharmacodynamic (PD) activity, and/or the mechanism of action of SOT101 and pembrolizumab	• Changes in the expression of immune biomarkers as compared to baseline in tumor tissue • Circulating tumor DNA fraction (mCRPC only) • Status of immune, molecular, disease-related, and other exploratory biomarkers in blood and archival and/or freshly obtained tumor tissue
• To determine the immunogenicity of pembrolizumab in combination with SOT101	• Incidence, titer, and time course of ADAs against pembrolizumab
• (Population) PK of pembrolizumab in combination with SOT101	• Concentrations of pembrolizumab over time
• To further evaluate the antitumor efficacy of SOT101 in combination with pembrolizumab	• Overall survival (OS)

8.0 Study Design

This is a phase 2, open-label, single-arm, multicenter study of SOT101 in combination with pembrolizumab to evaluate the efficacy and safety in patients with selected advanced/refractory solid tumors.

Participation of each patient will consist of the Screening, Treatment, and Follow-up study periods.

Eligible patients will be treated in cohorts by the following histologically or cytologically confirmed solid tumor indications, line of treatment.

- Non-small cell lung cancer (NSCLC)
  - For the second-line or third-line treatment of patients with advanced and/or metastatic NSCLC with disease progression on or after an immune checkpoint inhibitor-containing regimen and/or a platinum-containing regimen, with no epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK) genomic tumor aberrations
- Colorectal cancer
  - For the first-line treatment of patients with unresectable or metastatic Microsatellite Instability-High/Mismatch Repair Deficient (MSI-H/dMMR) colorectal cancer
- Cutaneous squamous cell carcinoma (cSCC)
  - For the first-line treatment of patients with recurrent or metastatic cSCC or second-line if refractory or relapsed after an immune checkpoint inhibitor-containing regimen (based on data from study SC103)
- Advanced hepatocellular carcinoma
  - For the second-line or later-line treatment of patients with advanced hepatocellular carcinoma having progressed on or after a checkpoint inhibitor-containing regimen
- Metastatic castration-resistant prostate cancer (mCRPC)
  - For the second-line or later-line treatment of patients with mCRPC after recurrence or failure of docetaxel
- Ovarian cancer
  - For the second-line or later-line treatment of patients with advanced ovarian cancer after recurrence or failure on platinum-based therapy within 6 months

During the treatment period, patients will be treated with SOT101 together with pembrolizumab until any of the criteria for treatment discontinuation is met.

Patients will be treated with SOT101 12 µg/kg subcutaneously on day 1 (±1 day for the cycle start), day 2, day 8, and day 9 in combination with pembrolizumab 200 mg intravenously (IV) on day 1 in 3-week cycles after all procedures and assessments have been completed.

Pembrolizumab will be administered as an IV infusion via peripheral or central venous line starting within 30 minutes after the first dose (day 1) of SOT101 in each 3-week cycle.

After termination of study interventions, patients will be evaluated at an End of treatment visit.

All patients will come to the clinic 30 (±2) days and 90 (+2) days after their last dose of SOT101 and/or pembrolizumab (whichever occurs later).

Patients will be followed up for survival every 3 months (±2 weeks) during year 1 and then every 6 months (±2 weeks) until one year after the last patient's last dose of SOT101 and/or pembrolizumab (whichever occurs later).

8.1 Sample Size Considerations

The number of patients per indication to be treated for at least one cycle is based on a Bayesian calculation: for each indication separately, Markov chain Monte Carlo has been used for the sample size determination. Assuming a desired ORR for the number of responses, and a uniform prior distribution between 0 and 1, there will be at least 80% posterior probability to achieve an effect above the minimal ORR:

- Indication 1 (NSCLC): 50 patients
- Indication 2 (MSI-H/dMMR colorectal cancer): 57 patients
- Indication 3 (cSCC): 57 patients
- Indication 4 (advanced hepatocellular carcinoma): 55 patients (not applicable in France)
- Indication 5 (mCRPC): 51 patients
- Indication 6 (recurrent ovarian cancer): 50 patients

This results in a total of 320 patients.

8.2 Randomization

Random assignment is not being used in this study.

9.0 Analysis Sets

9.1 Screened Population

The screened population is defined as all patients who sign the main study informed consent form.

9.2 Enrolled Population

The enrolled population is defined as all patients who sign the main study informed consent form and all eligibility criteria are met as confirmed by approver during screening assessments and who proceed to be enrolled in the study. This population will be used to describe patient disposition and protocol deviations and may include patients who do not receive study treatment.

9.3 All-subjects-as-treated population

The all-subjects-as-treated (ASaT) population will consist of all patients exposed to SOT101 or pembrolizumab.

All safety analyses will be performed on the ASaT population. The ASaT population will also be used for selected efficacy analyses.

9.4 Pharmacokinetic Population

The PK population will consist of all patients who are PK-evaluable, defined as all patients in the ASaT population who have at least one post-dose SOT101 concentration measurement above the lower limit of quantitation (LLQ).

The PK team will provide input to the determination of patients with evaluable samples. Further evaluation and review of PK data will be performed to establish evaluability of patient data on a record level prior to database lock. Non-evaluable records will be flagged in the database together with reason for non-evaluability.

9.5 Efficacy Population

The efficacy population will consist of all patients exposed to the combination therapy for at least one treatment cycle. This is defined as patients with 4 doses of SOT101 and 1 dose of pembrolizumab in Cycle 1, or patients exposed to both SOT101 and pembrolizumab in Cycle 1 who started Cycle 2.

This will be the main population for the analyses of the primary endpoint and secondary efficacy endpoints.

9.6 Per Protocol Population

The per protocol (PP) population is defined as all patients who had least one full treatment cycle of SOT101 and pembrolizumab (with 4 doses of SOT101 and 1 dose of pembrolizumab in Cycle 1), did not violate any eligibility criteria, and did not have any major protocol deviations.
Protocol deviations will be assessed at a data review meeting prior to database lock.

10.0 Conventions and Derivations

10.1 Study Treatment

The study treatment defined is the combination of SOT101 12 µg/kg subcutaneously and 200 mg pembrolizumab IV infusion.

Patients will be treated with SOT101 12 µg/kg subcutaneously on day 1 (±1 day for the cycle start), day 2, day 8, and day 9 in combination with pembrolizumab 200 mg IV on day 1 in 3-week cycles.

Pembrolizumab will be administered as an IV infusion via peripheral or central venous line starting within 30 minutes after the first dose (day 1) of SOT101 in each 3-week cycle.

Start of study treatment is defined as the date and time of first dose of either SOT101 or pembrolizumab, whichever occurs earliest. Per protocol this should be SOT101.

10.2 Baseline

Unless otherwise specified, baseline is defined as the last non-missing value prior to the first administration of either study treatment.

10.3 Change from Baseline

Change from baseline (CFB) will be calculated as (post-baseline – baseline). CFB will be calculated for patients with both a baseline and post-baseline value as applicable.

10.4 Percentage Change From Baseline

Percentage CFB will be calculated as (CFB/baseline) *100, where applicable.

If a baseline value is 0 for a parameter, then percentage CFB will not be calculated for that parameter.

10.5 Definition of Study Day

All study days on or after the start of study treatment will be calculated as:

- Date of assessment – date of start of study treatment + 1.

Study days that occur before the start of study treatment will be calculated as:

- Date of assessment – date of start of study treatment.

In cases of missing and/or incomplete dates, no study days will be calculated.

10.6 Study Period

Periods of the study are defined as follows:

Screening: From the date of informed consent form signature to the start of study treatment.

On-treatment (i.e. combination treatment period): From the day of the start of study treatment to the day prior to the end of treatment visit, the end of study date, or start of new anti-cancer therapy, whichever is earliest.

Follow-up: Begins from the date of the end of treatment visit or start of new anti-cancer therapy, whichever is earliest.

10.7 Cycle

Cycle number will be taken from the database. Unscheduled visits will be in listings only and identified with a numbering system that reflects the cycle they occur in by comparing the visit date against the scheduled visits and numbering in order of unscheduled visit e.g. Unscheduled Cycle 1 Day 1.01, Unscheduled Cycle 1 Day 8.01 etc. Unscheduled visits occurring on the same day as other visits will be kept as separate records.

Tumor assessments are not performed regularly per cycle, these will be identified in the ADaM datasets by actual week of study by calculating (date of assessment – date of study start+1)/7 and rounding up.

Additionally for the purposes of summarizing by scheduled week, labels for assessments falling into the scheduled week of study will be derived e.g. 'Week 6 assessment (Weeks 4 to 8)', 'Week 12 assessment (weeks 10 to 14) ' etc., by assigning the assessments within the protocol specified window of every 6 weeks ± 2 weeks. Labels for assessments falling outside of the assessment windows would be labelled 'Not Assigned'. In the case of multiple tumor assessments in a time window, evaluable assessments closest to the planned assessment time (or the closest non-evaluable assessment if all non-evaluable) will be considered the scheduled assessment. In the case of two assessments within a window being exactly the same distance from the centre of the window, the earliest assessment will be assigned as the scheduled assessment. Contributing assessments (e.g. target lesion assessment) should be labelled consistently with the overall tumor assessment.

10.8 Age group

Age at informed consent will be categorized as <18 years, ≥ 18 years to < 65 years, ≥ 65 years to < 85 years, ≥ 85 years, with no rounding applied for assigning to categories, meaning patient will be in group ≥ 85 years once s/he has in the Demography CRF page age at least 85 or higher.

10.9 Body Surface Area

BSA will be calculated using the DuBois formula: $Weight^{0.425}$ x $Height^{0.725}$ x 0.007184

10.10 Time since Initial Diagnosis at ICF Signature

The time since initial diagnosis (months) will be calculated as the date of informed consent minus the date of initial diagnosis and converted to months.

The date of initial diagnosis is from the Cancer History CRF page.

10.11 Number of previous lines of systemic therapy

The number of previous lines of systemic therapy is calculated as the number of therapy regimens in the metastatic setting recorded per patient from the Prior Systemic Anti-Cancer Therapy Regimen CRF page.

[redacted]

10.12 Prior and Concomitant Medications and Procedures

The medications that are taken prior to the start of study treatment and discontinued prior to the start of study treatment are defined as prior medications. Procedures occurring prior to the start of study treatment are defined as prior procedures.

The concomitant medications are defined as medications that have started after the start of study treatment or if they were started prior to the start of study treatment but are ongoing beyond the start of study treatment. Concomitant procedures are those procedures occurring after the start of study treatment.

Refer to Section 10.15 below for how to handle partial or missing dates in the assessment of whether or not a medication was taken or a procedure occurred prior to or concomitantly with the study treatment.

10.13 Derivation of Efficacy Variables

Tumor assessments will be performed by investigators and assessed per iRECIST[1] for all tumor indications with the exception of patients in the mCRPC indication who will be assessed using iRECIST and Prostate Cancer Clinical Trials Working Group 3 (PCWG3)-modified RECIST 1.1[2].

10.13.1 RECIST 1.1 Response Assessment

Up to the first unconfirmed progressive disease (iUPD), the RECIST 1.1 disease response assessment will be derived from the iRECIST response assessment form as follows:

iRECIST	**RECIST 1.1**
iCR	CR
iPR	PR
iSD	SD
iUPD	PD
Non-iCR/Non-iUPD	Non-CR / Non-PD
NE	NE
NED	NED

After the first iUPD, the RECIST 1.1 overall response will no longer be derived.

10.13.2 PCWG3-modified RECIST 1.1 Response Assessment

Patients with mCRPC, tumor response as per the PCWG3-modified RECIST 1.1 will be derived from the iRECIST assessment for soft tissue, and the PCWG3 bone assessment. The assessment responses for soft tissue response (according to RECIST 1.1 criteria, after derivation from iRECIST) and bone response (according to PCWG3 criteria) will be combined to give an overall radiological objective response per assessment in mCRPC indication cohort patient per PCWG3-modified RECIST 1.1. The PCWG3-modified RECIST 1.1 disease response assessment will be derived from the Disease Response CRF form as follows.

Soft Tissue Response from above derivation (RECIST 1.1)	**Bone Scan result (PCWG3)**	**PCWG3-modified RECIST 1.1 Response**
PD	Any	PD
Any	PD	PD
Any (except PD)	PDu	PDu
NE	Non-PD, NED, or NE	NE

Soft Tissue Response from above derivation (RECIST 1.1)	Bone Scan result (PCWG3)	PCWG3-modified RECIST 1.1 Response
SD	Non-PD, NED, or NE*	SD
Non-CR / Non-PD	Non-PD, NED, or NE*	Non-CR / Non-PD
PR	Non-PD, NED, or NE*	PR
CR	Non-PD or NE*	PR (if target lesions were present at baseline) Non-CR / Non-PD (if no target lesions at baseline
CR	NED	CR
NED	NE	NE
NED	Non-PD	Non-CR / Non-PD
NED	NED	NED

*If the bone scan is entirely missing or was not done then the overall response is NE

10.13.3 Best Overall Response (BOR and iBOR)

Per RECIST (v 1.1): The best overall response (BOR) according to RECIST v 1.1 will be programmatically derived from the first dose date until the first documented disease progression, death, or start of new anti-cancer therapy. BOR will be determined according to the following rules in a stepwise manner for subjects with measurable disease:

Step	Condition
Step 1: **BOR of CR** If a BOR of CR is not determined, Step 2 will be performed.	At least two consecutive determinations of CR more than 4 weeks apart, or if not consecutive, with no other assessment between the two determinations other than unable to evaluate (NE), CR.
Step 2: **BOR of PR** If a BOR of PR is not determined, Step 3 will be performed.	At least two consecutive determinations of PR or CR, more than 4 weeks apart, or if not consecutive, with no other assessment between the two determinations other than NE, CR, PR.
Step 3: **BOR of SD** If a BOR of SD is not determined, Step 4 will be performed.	At least one SD assessment (or better), ≥ 6 weeks (≥ 42 days) after start of study treatment; if not, at least one follow-up scan (i.e., consecutive scan) evaluated as SD (or better) is required to determine a BOR of SD. If not consecutive scans, with no other assessment between the two determinations other than NE, CR, PR, SD.
Step 4: **BOR of PD** If a BOR of PD is not determined, Step 5 will be performed.	At least one (i.e., any) PD after baseline.

Step	Condition
Step 5: **BOR of NED** If a BOR of NED is not determined, Step 6 will be performed.	If no measurable disease at baseline and all subsequent assessments will be NED.
Step 6: **BOR of NE**	Measurable disease at baseline, but not all or any target lesions have been evaluated, or if derivation of BOR from Step 1 to 5 does not apply.

Based on the table above, the following examples cover the possibilities for best overall response considering the first tumor assessment as response (CR, PR), and subsequent or consecutive tumor assessments:

Overall response First time point	Overall response Subsequent time point	BEST overall response
CR	CR	CR
CR	PR	SD, or PR**
CR	SD	SD
CR	PD	SD*, or PD
CR	NE	SD*, or NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD*, or PD
PR	NE	SD*, or NE

* Provided minimum criteria for SD duration is met

** Sometimes (i)CR may be claimed when subsequent scans suggest small lesions were likely still present and in fact the patient had (i)PR, not (i)CR at the first time point. Under these circumstances, the original (i)CR should be changed to (i)PR in the eCRF and the best response is (i)PR. If that is not the case, the (i)BOR of (i)SD will be determined considering two consecutive assessments better than (i)SD. This applies to both RECIST 1.1 and iRECIST.

- **Per PCWG3-modified RECIST 1.1:** the BOR derivation will be performed exactly as per RECIST 1.1, with the following exceptions: The derivation will be performed for all subjects, including those without measurable disease; Step 3 will be derived as BOR of Non-CR / Non-PD (instead of SD) for patients with non-measurable disease. Step 5 will consider first the possibility of PDu without any subsequent confirmation of PD, in this case, the BOR as per PCWG3-modified RECIST 1.1 will be PDu:

Step	Condition
Step 1: **BOR of CR** (measurable disease only) If a BOR of CR is not determined, Step 2 will be performed.	At least two consecutive determinations of CR more than 4 weeks apart, or if not consecutive, with no other assessment between the two determinations other than unable to evaluate (NE), CR.

Step	Condition
Step 2: **BOR of PR** (measurable disease only) If a BOR of PR is not determined, Step 3 will be performed.	At least two consecutive determinations of PR or CR, more than 4 weeks apart, or if not consecutive, with no other assessment between the two determinations other than NE, CR, PR.
If measurable disease: Step 3: **BOR of SD** If a BOR of SD is not determined, Step 4 will be performed. or If non-measurable disease: Step 3: **BOR of Non-CR/Non-PD** If a BOR of **Non-CR/Non-PD** is not determined, Step 4 will be performed.	At least one SD assessment (or better), ≥ 6 weeks (≥ 42 days) after start of study treatment; if not, at least one follow-up scan (i.e., consecutive scan) evaluated as SD (or better) is required to determine a BOR of SD. If not consecutive scans, with no other assessment between the two determinations other than NE, CR, PR, SD. At least one Non-CR/Non-PD assessment (or better), ≥ 6 weeks (≥ 42 days) after start of study treatment; if not, at least one follow-up scan (i.e., consecutive scan) evaluated as Non-CR/Non-PD (or better) is required to determine a BOR of Non-CR/Non-PD. If not consecutive scans, with no other assessment between the two determinations other than NE, Non-CR/Non-PD.
Step 4: **BOR of PD** If a BOR of PD is not determined, Step 5 will be performed.	At least one (i.e., any) PD after baseline.
Step 5: **BOR of PDu** (non-measurable disease only) If a BOR of PDu is not determined, Step 6 will be performed.	At least one (i.e. any) PDu assessment after baseline.
Step 6: **BOR of NED** (non-measurable disease only) If a BOR of NED is not determined, Step 7 will be performed.	If no measurable disease at baseline and all subsequent assessments will be NED.
Step 7: **BOR of NE**	Measurable disease at baseline, but not all or any target lesions have been evaluated, or if derivation of BOR from Step 1 to 6 does not apply.

- **Per iRECIST:** The BOR according to iRECIST (iBOR) is defined as the best overall timepoint response recorded from the first dose date until confirmed disease progression, death, or start of new anti-cancer therapy, considering any requirement for confirmation. iBOR will be programmatically derived according to the following rules in a stepwise manner for patients with measurable disease only:

Step	Condition
Step 1: i**BOR of iCR** If an iBOR of iCR is not determined, Step 2 will be performed.	At least two consecutive determinations of iCR more than 4 weeks apart, or if not consecutive, with no other assessment between the two determinations other than unable to evaluate (NE), iCR.
Step 2: i**BOR of iPR** If an iBOR of iPR is not determined, Step 3 will be performed.	At least two consecutive determinations of iPR or iCR, more than 4 weeks apart, or if not consecutive, with no other assessment between the two determinations other than NE, iCR, iPR.
Step 3: i**BOR of iSD** If an iBOR of iSD is not determined, Step 4 will be performed.	At least one iSD assessment (or better), ≥ 6 weeks (≥ 42 days) after start of study treatment; if not, at least one follow-up scan (i.e., consecutive scan) evaluated as iSD (or better) is required to determine an iBOR of iSD. If not consecutive scans, with no other assessment between the two determinations other than NE, iCR, iPR, iSD.
Step 4: i**BOR of iCPD** If an iBOR of iCPD is not determined, Step 5 will be performed.	At least one (i.e., any) iCPD after baseline.
Step 5: i**BOR of iUPD** If an iBOR of iUPD is not determined, Step 6 will be performed.	At least one (i.e., any) iUPD after baseline.
Step 6: i**BOR of NED** If an iBOR of NED is not determined, Step 7 will be performed.	If no measurable disease at baseline and all subsequent assessments will be NED.
Step 7: i**BOR of NE**	Measurable disease at baseline, but not all or any target lesions have been evaluated, or if derivation of iBOR from Step 1 to 6 does not apply.

10.13.4 Objective Response Rate (ORR and iORR)

- Per RECIST (v1.1): The ORR is the proportion of patients who achieved BOR of CR or PR.
- Per iRECIST: The iORR is defined as the proportion of patients who achieved iBOR of iCR or iPR.

10.13.5 Tumor Burden

Change in Tumor burden will be calculated as the percent CFB in target lesions per time point. Per RECIST criteria this will only be done for target lesions defined at baseline.

It will be derived as:

- ((Sum of target lesions at post-baseline assessment – sum of target lesions at baseline)/sum of target lesions at baseline) x 100

[redacted]

The absolute maximum reduction in target lesions from baseline will be derived across all the post-baseline assessments until documented disease progression or start of new anti-cancer therapy, whichever is earliest.

10.13.6 Duration of Response (DOR and iDOR)

- Per RECIST (v1.1): Duration of response is defined as the time from first documentation of overall response leading to a confirmed CR or PR until the time of first documentation of overall response of disease progression (PD) or death.
- Per iRECIST: Duration of response is defined as the time from first documentation of overall response leading to a confirmed iCR or iPR until the time of disease progression or death. The date of disease progression will be the first instance of iUPD that is confirmed by a later iCPD, this can occur on the subsequent assessment or after a series of persistent iUPD assessments. The date of iUPD will also be used as disease progression if the iUPD assessment is followed by:
    - if the patient stops protocol treatment because they were judged to be clinically unstable, or
    - no further tumor assessments are done,

      or
    - the next timepoint responses are all iUPD, and iCPD never occurs ,

      or
    - if the patient dies from their cancer.

  An iUPD assessment followed by subsequent non-PD assessments will not be considered as the start of progression. Stopping protocol treatment due to clinical instability is identified as subjects discontinuing from SOT101 with reason ‘clinical progression’.
- Per PCWG3-modified RECIST 1.1: Duration of response is defined as the time from first documentation of overall response leading to a confirmed CR or PR until the time of first documentation of overall response of (confirmed) disease progression (PD) or death.

Clinical deterioration alone will not be considered as documented disease progression. Only tumor assessments performed before or on the start of any new anti-cancer treatment (including radiation therapy to the tumor lesion (s)) will be considered in the assessment of DOR and iDOR.

10.13.7 Clinical Benefit Rate (CBR and iCBR)

- Per RECIST (v1.1): The CBR is the proportion of patients who achieved BOR of CR, PR, or SD.
- Per iRECIST: The iCBR is defined as the proportion of patients who achieved iBOR of iCR, iPR or iSD.
- Per PCWG3-modified RECIST (v1.1):
    - Patients with measurable disease: as per RECIST 1.1
    - Patients with measurable and non-measurable disease: The CBR is the proportion of patients who achieved BOR of CR, PR, SD, Non-CR/Non-PD, NED.

10.13.8 Progression-Free Survival (PFS and iPFS)

- Per RECIST (v1.1): A PFS time is defined as the time from the first day of study treatment until the first date of radiological disease progression (PD) or death.

[redacted]

- Per iRECIST: An iPFS time is defined as the time from the first day of study treatment until the first date of confirmed disease progression or death. The date of disease progression would be the date of the first iUPD that is confirmed by a later iCPD. This can occur on the subsequent assessment or after a series of persistent iUPD assessments. The date of iUPD will also be used as disease progression if the iUPD assessment is followed by:
    - if the patient stops protocol treatment because they were judged to be clinically unstable, or
    - no further tumor assessments are done,

      or
    - if the next timepoint responses are all iUPD, and iCPD never occurs,

      or
    - if the patient dies from their cancer.

  An iUPD assessment followed by subsequent non-PD assessments will not be considered as the start of progression. Stopping protocol treatment due to clinical instability is identified as subjects discontinuing from SOT101 with reason 'clinical progression'.
- Per PCWG3-modified RECIST 1.1: PFS time is defined as the time from the first day of study treatment until the date of PCWG3-modified RECIST 1.1 defined confirmed disease progression or death.

Clinical deterioration alone will not be considered as documented disease progression. Only tumor assessments performed before the start of any new anti-cancer treatment (including radiation therapy to the tumor lesion (s)) will be considered in the assessment of PFS/iPFS.

10.13.9 Time to Response (TtR and iTtR)

- Per RECIST (v1.1): TtR is defined as the time from the first day of study treatment until the first date of confirmed PR or CR. The date of confirmed response would be the date of the first PR or CR that is confirmed by a later PR or CR.

- Per iRECIST: iTtR is defined as the time from the first day of study treatment until the first date of iPR or iCR. The date of confirmed response would be the date of the first iPR or iCR that is confirmed by a later iPR or iCR.

Time to response is only calculated for patients with measurable disease.

10.13.10 CTC Response

The CTC response is defined as the proportion of patients with CTC count conversion from $\geq$5 at baseline to $<$5 cells at any post-baseline timepoint per 7.5 mL of blood. This endpoint applies to the mCRPC cohort only.

10.13.11 PSA Response

The PSA response is defined as the proportion of patients with PSA decline of ≥50% from baseline at any post-baseline timepoint. This endpoint applies to the mCRPC cohort only.

10.13.12 Time to Confirmed PSA Progression

Time to confirmed PSA progression is defined as the time from the first day of study treatment to the date of PSA progression, where PSA progression is defined as the date when an increase of 25% or more and an absolute increase of 2 ng/mL or more from the nadir (or baseline, whichever is lowest) are documented.

For patients who have a decline in PSA during treatment, PSA progression must be confirmed by a second value 3 or more weeks later increased with respect to the nadir PSA (or baseline, whichever is lowest). The date of the first PSA progression will be used; in patients with an unconfirmed PSA progression, date of the first PSA progression will be used if followed by treatment discontinuation.

This endpoint applies to the mCRPC cohort only.

10.13.13 Overall Survival (OS) – Exploratory Analysis, not to be reported

OS is defined as the time from the first day of study treatment until the date of death. Patients with missing data will be censored at the last known date to be alive.

10.13.14 Progression-Free Survival 2 (PFS2)[5] – Exploratory Analysis, not to be reported

PFS2 time is defined as the time from the first day of study treatment to date of second disease progression while on subsequent systemic anti-cancer therapy, or death from any cause, whichever first.

10.13.15 Last Known Date to Be Alive

The last known date to be alive will be derived for patients at the analysis cutoff using the latest complete date among the following:

- Patient assessment dates (blood draws [laboratory, PK], vital signs, ECOG performance status, ECG, tumor assessments, tumor measurement, or tumor biopsy dates)
- Start and end dates of anti-cancer therapies administered after study treatment discontinuation
- AE start and end dates
- Concomitant medication start and end dates
- Concurrent procedure date
- Date of death collected on the ‘Death Details’ electronic Case Report Form (eCRF)
- Date of last contact collected on the ‘Survival Status’ eCRF where status is ‘alive’; or date last known to be alive if status is ‘unknown’
- Study treatment start and end dates
- Date of discontinuation on disposition eCRF pages (do not use if reason for discontinuation is lost to follow-up).

Only dates associated with actual contact of the patient will be used in the derivation. Dates associated with a technical operation unrelated to patient status such as the date a blood sample was processed will not be used. Assessment dates after the cutoff date will not be applied to derive the last contact date, if applicable.

10.14 Derivations for Exposure Variables

The following variables will be derived for SOT101 and pembrolizumab respectively.

Variable	Definition for SOT101	Definition for pembrolizumab	Definition for combination therapy
Duration of exposure (days)	Last dose date – Start dose date +1	Last dose date – Start dose date +1	Last dose date of either SOT101 or Pembrolizumab, whichever is later – Start dose date of SOT101 or

			pembrolizumab, whichever is earlier +1
Cycle started	A patient is considered to have started a cycle if they received at least one dose of SOT101 in that cycle, per the Study Exposure CRF page.	A patient is considered to have started a cycle if they received at least one dose of pembrolizumab in that cycle, per the Study Exposure CRF page.	A patient is considered to have started a cycle if they received at least one dose of SOT101 and pembrolizumab in that cycle, per the Study Exposure CRF page.
Completed Cycle	A cycle is considered completed if the patient received 4 doses of SOT101 and 1 dose of pembrolizumab in that cycle, or the patient started the next cycle and received at least one dose of SOT101 in that cycle.	A cycle is considered completed if the patient received 4 doses of SOT101 and 1 dose of pembrolizumab in that cycle, or the patient started the next cycle and received pembrolizumab in that cycle.	
Duration of cycle (days)	The day prior to the date of cycle start (day 1 in each cycle) will be considered as the end of the previous cycle. For the last cycle, 21 days will be used.		
Planned cumulative dose (*applicable unit*)	(12 (µg/kg/dose) * 4 doses) * Number of cycles started (µg/kg)	200 mg * Number of cycles started (mg)	
Real dose administered (*applicable unit*)	(2 x Total volume administered) / patient weight (µg/kg)	As per CRF (mg)	
Actual cumulative dose (all cycles)	Sum of the real doses (µg/kg) administered	Sum of the real doses (mg) administered	
Actual cumulative dose for completed cycles* (Not presented, required for calculation of ADI)	Sum of the real doses (µg/kg) administered considering only completed cycles	Sum of the real doses (mg) administered considering only completed cycles	
Duration of exposure (days) for completed cycles *	Considering only completed cycles: End date of last completed cycle – Start dose date of SOT101 or Pembrolizumab, whichever is earlier + 1		
Intended dose Intensity	12 (µg/kg/dose) * 4 doses/ 21 day (µg/kg /day)	200 mg/ 21 day (mg/day)	
Actual dose intensity (ADI) (µg/kg /day) or (mg/day) *	Considering only completed cycles; Actual cumulative dose/ Duration of exposure (days)		
Actual dose intensity by cycle (µg/kg /day) or (mg/day) *	Considering only completed cycles: Actual cumulative dose in that cycle / Duration of cycle (days)		
Relative dose intensity by cycle (%)	Considering only completed cycles:		

	100 * (Actual dose Intensity for that cycle/Intended dose intensity for that cycle)	
Overall Relative dose intensity (%) *	Considering only completed cycles: 100 * (Actual dose Intensity /Intended dose)	
Compliance with planned dose (%)	100 * (Actual cumulative dose / Planned cumulative dose at that cycle, taking into account per protocol dose reductions)	

* Only completed cycles as defined should be considered for derivation

10.15 Safety Variables

10.15.1 Treatment-emergent AEs

All AEs will be recorded in the database but not all on-treatment events will be considered as treatment-emergent e.g. if they are an improvement of an existing condition. A treatment-emergent AE (TEAE) is defined as an AE that started or worsened after the start of study treatment.

10.15.2 AEs of Special Interest

AEs of special interest (AESIs) will be identified from AE CRF page.

The following AEs are defined for this protocol as AESIs:

1. An overdose of pembrolizumab, as defined in section 6.7 of the protocol.

2. An elevated AST or ALT laboratory value that is greater than or equal to 3×ULN and an elevated total bilirubin laboratory value that is greater than or equal to 2×ULN and, at the same time, an alkaline phosphatase laboratory value that is less than 2×ULN, 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 study investigators and the sponsor's medical monitor for the trial. However, abnormalities of liver blood tests that do not meet the criteria noted above are not AESIs for this trial.

10.15.3 Physical Examinations, ECGs, and Other Observations Related to Safety

Additional safety assessments include physical examinations, ECOG, ECG measurements including left ventricular ejection fraction (LVEF), and pregnancy test.

10.16 Handling of Missing Data

No imputation of missing data will be performed other than specified in this section.

10.16.1 Imputation of Missing Dates for AEs and Concomitant Medication and Procedures

For the purposes of assigning AEs and concomitant medications to study periods the following algorithm will be used for missing or partial dates (AE start/stop dates and concomitant medication start/stop dates):

The actual (non-imputed) value for date will be presented in all data listings and imputed dates will only be used for programming purposes, such as TEAE derivation.

Start date
If the start date is completely missing (i.e., the day, month, and year are all unknown), the start date will be set to the date of the first dose of study medication

Missing day only

- If the month and year of the incomplete date are the same as the month and year of the **first dose date**, then the day of the **first dose date** will be assigned to the missing day.
- If either the year is before the year of the **first dose date** or if years are the same but the month is before the month of the **first dose date**, then the last day of the month will be assigned to the missing day.
- If either the year is after the year of the **first dose date** or if both years are the same but the month is after the month of the **first dose date**, then the first day of the month will be assigned to the missing day.

Missing month only

- The day will be treated as also missing and both month and day will be replaced according to the below procedure.

Missing day and month

- If the year of the incomplete date is the same as the year of the **first dose date**, then the day and month of the **first dose date** will be assigned to the missing fields.
- If the year of the incomplete date is not the same as the year of the **first dose date**, then January 1 will be assigned to the missing fields.

If the stop date is complete and the imputed start date is after the stop date, then the start date will be imputed using the stop date

Stop date
Missing day only

- If the month and year of the incomplete date are the same as the month and year of the **last visit date**, then the day of the **last visit date** will be assigned to the missing day.
- If either the year is before the year of the **last visit date** or if both years are the same but the month is before the month of the **last visit date**, then the last day of the month will be assigned to the missing day.
- If either the year is after the year of the **last visit date** or if both years are the same but the month is after the month of the **last visit date**, then the first day of the month will be assigned to the missing day.

Missing month only

- The day will be treated as missing and both month and day will be replaced according to the below procedure.

Missing day and month

- If the year of the incomplete date is the same as the year of the **last visit date**, then the day and month of the **last visit date** will be assigned to the missing fields.
- If the year of the incomplete date is before the year of the **last visit date**, then 31st December will be assigned to the missing fields.
- If the year of the incomplete date is after the year of the **last visit date**, then 1st January will be assigned to the missing fields.

Completely missing stop dates where a record is not ongoing, will not be imputed.

Incomplete start dates of follow-up anti-cancer therapy will be imputed as follows:

- If only 'day' is missing, then impute with the first day of the month.
- If 'day' and 'month' are missing and 'year' is not missing and is the same as the year of the last dose, then impute as date of last dose.
- If the imputed start date is greater than the last contact date, then set to the last contact date.

Incomplete dates of death will be imputed as follows:

- If only 'day' is missing, then impute with the first day of the month.
- If 'day' and 'month' are missing and 'year' is not missing and is the same as the year of the last contact date, then impute as the date of the last contact +1 day.
- If 'day' and 'month' are missing and 'year' is not missing and is greater than the year of the last contact date, then impute as 1st January of that year.
- If the imputed death date is less than the last contact date, then set to the last contact date + 1 day.

10.16.2 Imputation of Diagnosis and Prior Disease History

The partial start date for initial diagnosis will be assigned to 15th day of the month (if only day is missing) or July 1st (if both month and day are missing).

For completely missing dates no imputation will be performed.

10.16.3 Missing Response Data

Patients with missing response data will be considered non-responders, unless specified otherwise.

10.16.4 Imputation of Laboratory Values with Character Symbol

Missing laboratory data will not be imputed. However, laboratory values of the form of "< x" (i.e., below the lower limit of quantification) or "> x" (i.e., above the upper limit of quantification) will be imputed as "x" for the purpose of calculation of summary statistics and comparing to normal ranges. These values will still be displayed as "< x" or "> x" in the listings.

10.17 Time Conversion

Time conversion will follow the rules described below:

- 1 week = 7 days,
- 1 month = 30.4375 days,
- 1 year = 365.25 days.

11.0 Interim Analyses

An analysis for futility will be performed when the sample size is considered enough for such analysis and for each indication, as described below in this section (for further details please refer to study protocol). Efficacy data and outputs will also be a part of the IDMC review.

The criteria for conclusion of futility, for each indication, are as follows:

[redacted]

- Indication 1 (Advanced and/or metastatic non-small cell lung cancer [NSCLC]):
  - N = 21 patients if the number of responses is less than 2 (r < 2)
- Indication 2 (Microsatellite instability-high [MSI-H] or mismatch repair deficient [dMMR] colorectal cancer):
  - N = 12 patients if the number of responses is less than 4 (r < 4)
- Indication 3 (Recurrent or metastatic cutaneous squamous cell carcinoma [cSCC]):
  - N = 12 patients if the number of responses is less than 4 (r < 4)
- Indication 4 (Advanced hepatocellular carcinoma):
  - N = 19 patients if the number of responses is less than 2 (r < 2)
- Indication 5 (Metastatic castration-resistant prostate cancer [mCRPC]):
  - N = 35 patients if the number of responses is less than 1 (r < 1)
- Indication 6 (Recurrent ovarian cancer):
  - N = 21 patients if the number of responses is less than 2 (r < 2)

For the purposes of interim analyses, in the case of ongoing patients with any unconfirmed response and for whom a confirmatory scan is still pending:

- Responders (PR, CR) or patients with SD that, at the time of the futility analysis, did not yet have a second (confirmatory) tumor assessment performed will be considered to have an Unconfirmed response (PR, CR) or Unconfirmed SD as BOR, respectively. Such BORs will be presented with "Unconfirmed" label.
- ORR will also include Unconfirmed PR and Unconfirmed CR in the numerator.

For the purpose of conducting the interim analysis, a temporary futility analysis population will be defined based on the patients which are deemed necessary for such interim analysis as described above. This population flag will be removed once all futility analyses have been performed.

12.0 Statistical Methods

All data collected during this study will be displayed in data listings on the largest population for which data is available, unless otherwise specified. Data listings will be sorted by indication and patient ID as a minimum, additional sorting variables will be specified as appropriate in the listing shell. Listings will include all relevant derived variables – those variables will be marked as "(derived)". Each listing will also contain a flag for the related population: for safety data, if the patient is in the ASaT population; for efficacy outputs, if the patient is in the efficacy and ASaT populations, etc. When listing options from the CRF in the case of 'Other: Specify', concatenate the specify text e.g. 'Other: XXXXXXXXX'; in the case of missing end date due to an ongoing event, medication or procedure, the text 'ongoing' will be inserted in place of the end date.

Descriptive statistics (number of observations [n], mean, median, standard deviations [STD], minimum, Q1, Q3 [or interquartile range as indicated below], and maximum values) for continuous variables will be presented. Mean, median, Q1 and Q3 will be presented to 1 decimal more than original data. STD will be presented to 2 decimals more than original data. Minimum and maximum will match the decimal points in the original data. For categorical variables, summary measures will include the frequency and percentage (with 1 decimal place) of patients in each category. Percentages will not be displayed for zero counts.

Where appropriate the set of summary tables will be reported for each indication separately. Some outputs may be indication specific and only produced for that indication.

The analyses will be descriptive, no formal testing of statistical hypotheses is planned.

[redacted]

All data summaries and tabulations will be prepared with SAS® Version 9.4 or higher.

12.1 Patient Disposition

The number and percentage of patients and each population to which they belong will be presented, together with the reason for exclusion from each population.

The number and percentage of patients screened (and reason for screen failure), enrolled, and treated in the study will be presented, together with the:

- number and percentage of patients who discontinued from the study and a breakdown of the corresponding reasons for discontinuation
- number and percentage of patients who discontinued study treatment with the corresponding reasons.

Disposition will be summarized descriptively for all screened patients, overall for the study and for each indication separately.

The number of patients screened, enrolled, and treated by country and center will also be presented.

12.2 Demographic and Baseline Characteristics

Demographic and baseline characteristics data will be summarized descriptively for each indication separately for the ASaT population. Each summary will be repeated for the efficacy and per protocol populations.

12.2.1 Demographics

Demographic characteristics will be summarized using the following information from the Demographics CRF page: Sex, ethnicity, race, age at informed consent and age group. From other CRF pages also, baseline weight (kg), baseline height (m), baseline BSA (m^2), baseline BMI (kg/m^2) and baseline Eastern Cooperative Oncology Group (ECOG) status will be summarized.

12.2.2 Primary Disease History

Primary disease history will be listed and summarized using the information from the Cancer History CRF page. Variables to be summarized include location of primary tumor, time since diagnosis at ICF signature, stage of disease at diagnosis, and prior treatment with checkpoint inhibitors. The number of previous lines of systemic therapy will be summarized. Prior mutations and other genetic analysis data will be listed only.

12.3 Prior Therapy for Primary Diagnosis

A tabulation of prior systemic anti-cancer therapies coded according to WHODrug dictionary (version March 22 B3 or later) will be presented in the Efficacy, ASaT and Per Protocol populations. Prior systemic anti-cancer therapies will be tabulated and categorized by medication group (ATC level 2) and preferred term using counts and percentages.

A tabulation of non-systemic anti-cancer therapies coded according to MedDRA (version 24.1 or later) will be presented for the Efficacy, ASaT and Per Protocol populations. Prior non-systemic anti-cancer therapies will be tabulated and categorized by System Organ Class and Preferred Term using counts. Systemic and non-systemic therapies will be presented separately. Radiation therapy is not coded and will be listed only.

Full details of prior systemic anti-cancer therapies will be listed only.

[redacted]

12.4 Medical History

Medical history will be coded according to Medical Dictionary for Regulatory Activities (MedDRA, Version 24.1 or later).

Medical history will be tabulated by system organ class (SOC) and preferred term (PT) using counts and percentages for the ASaT population.

12.5 Treatments

12.5.1 Exposure to Study Treatments

Descriptive statistics will be provided for the duration of exposure (days), the total number of cycles started, the total number of doses administered, number of patients with at least one dose adjustment (SOT101 only), cumulative dose, actual dose intensity and relative dose intensity on each study treatment. Summaries will be performed on the ASaT,efficacy and per protocol populations. Compliance per protocol will be listed only. Relative Dose Intensity by cycle will be plotted per patient using box plots overlaid with a mean profile line, and only presented for cycles with at least 20 patients data available.

The total number of doses administered will be summarized as well as the frequency of patients with 1, 2, 3, 4, 5, 6, 7, 8, or ≥9 injections.

Information regarding patients' dosing regimens, including total volume administered and dose adjustments, will be listed only.

12.5.2 Prior and Concomitant Medications, and Procedures

Medications received priorly and concomitantly with study drug, categorized by medication group (ATC level 2) and preferred term according to WHODrug (Latest Version), will be summarized for the ASaT population.

Prior and concomitant procedures will be coded according to MedDRA and summarized by System Organ Class and Preferred Term.

Prior and concomitant medications and procedures will be tabulated separately using counts and percentages to display the number and percentage of patients using at least one medication.

Full detail of medications and procedures will be presented in listings only.

12.6 Protocol Deviations

Protocol deviations will be documented by category (as per the latest study Protocol Deviation Guidance document). All deviations will be reviewed, categorized, designated important or not important, and finalized prior to database lock. Important protocol deviations will be defined as those potentially impacting safety or efficacy assessments and analyses. Additional details of what will be considered important protocol deviation can be found in the Protocol Deviation Guidance document.

Important protocol deviations for patients in the enrolled population will be summarized by deviation category. All protocol deviations will be listed only.

Any COVID-19-specific protocol deviations will be listed separately.

12.7 Efficacy Analyses

All efficacy analyses will be summarized descriptively for each indication separately on the efficacy population, the ASaT population, and the Per protocol population where applicable.

[redacted]

Subgroup analyses may be performed on selected populations and efficacy endpoints. These will include the subgroups of CPI naïve vs. CPI pre-treated, patients with higher risk factors such as ECOG >= 2 vs. ECOG < 2, or more than 2 previous lines of therapy.

12.7.1 Objective Disease Response

Descriptive statistics (frequency and percentage) for ORR and iORR, and the two-sided exact 95% Clopper-Pearson confidence interval[4] (CI) for the iORR/ORR will be presented for patients with measurable disease in each indication separately. Primarily, patients with missing data will be considered to be non-responders.

Sensitivity analyses on iORR and ORR will be performed including the use of:

- ASaT and PP populations
- No imputation of missing data (i.e. only patients with evaluable post-baseline tumor assessment)

12.7.2 Tumor Burden

A summary table of tumor burden by scheduled assessment window will be presented along with an accompanying listing. A waterfall plot of maximum percent reduction in the sum of diameter of target lesions from baseline will be created for each indication separately. These plots will display the best percentage CFB in the sum of the diameter of all target lesions for each patient.

A spaghetti plot of percent reduction in the sum of target lesions from baseline will be created to plot the change in tumor burden over time (in weeks from start of treatment) for each patient.

A swimmer plot showing an overview of tumor assessments in relation to treatment exposure, follow up and treatment status (ongoing/stopped) will be created.

12.7.3 BOR and iBOR

BOR/iBOR will be summarized using descriptive statistics (frequency and percentage) for each indication separately.

Additionally, BOR will also be explored as per PCWG3-modified RECIST 1.1 for patients in mCRPC, with both measurable and non-measurable disease.

A sensitivity analysis will be performed for BOR and iBOR using the ASaT and Per Protocol populations.

12.7.4 DOR and iDOR

DOR/iDOR will be summarized using Kaplan-Meier estimates for each indication separately. Log-log 95% confidence intervals for estimates of the percentiles will be presented.

Responders will be considered to have an ongoing response if they: i) have not progressed, and ii) have not started a new anti-cancer therapy, and iii) have not been lost to follow-up, and iv) are alive.
Patients with missing data will be censored/considered as having an event as specified below:

Situation	Date of progression or censoring	Outcome
No progression, no death. No start of new anti-cancer therapy.	Date of the last evaluable tumor assessment.	Censored
No progression, no death. Start of new anti-cancer therapy.	Date of the last tumor assessment with non-progression before the start of new anti-cancer therapy.	Censored

[redacted]

Situation	Date of progression or censoring	Outcome
Progression or death after one missed adequate tumor assessment.	Date of progression or death, whichever is earliest (if both occur).	Progressed
Progression or death after more than one (consecutively) missed adequate tumor assessments.	Date of the last evaluable tumor assessment.	Censored

DOR will be calculated based on RECIST 1.1, iRECIST, and PCWG3-modified RECIST for the mCRPC cohort only for those patients with measurable disease at baseline.

12.7.5 CBR and iCBR

CBR/iCBR will be summarized using descriptive statistics (frequency and percentage) together with a 95% CI for each indication separately.

CBR will be calculated based on PCWG3-modified RECIST for the mCRPC cohort separately for those patients with measurable disease at baseline and for all mCRPC patients.

Primarily, patients with missing data will be considered to be non-responders.

A sensitivity analysis will be performed for CBR and iCBR using the ASaT and Per Protocol populations; and without imputing for missing response.

12.7.6 PFS and iPFS

PFS/iPFS will be summarized using Kaplan-Meier estimates for each indication separately. A sensitivity analysis will be performed using the ASaT population.

PFS will be calculated based on PCWG3-modified RECIST for the mCRPC cohort for those patients with both measurable and non-measurable disease.

Patients with missing data will be censored/considered as having an event as specified below:

Situation	Date of progression or censoring	Outcome
Incomplete or no baseline tumor assessments.	Date of the first day of study treatment	Censored
Start of new anti-cancer therapy.	Date of the last tumor assessment with non-progression before the start of new anti-cancer therapy.	Censored
Death before the first disease progression assessment.	Date of death.	Progressed

Situation	Date of progression or censoring	Outcome
Death between adequate tumor assessment visits.	Date of death.	Progressed
Progression or death after one (consecutively) missed adequate tumor assessment[a].	Date of progression or death, whichever is earliest (if both occur).	Progressed
Progression or death after more than one (consecutively) missed adequate tumor assessments.	Date of the last evaluable tumor assessment.	Censored
No progression, no death.	Date of the last evaluable tumor assessment, or first date of study treatment if no post-baseline tumor assessments.	Censored

[a]Identified as 12 weeks between the date of last evaluable tumor assessment and the date of the event.

12.7.7 TtR and iTtR

TtR/iTtR will be summarized using Kaplan-Meier estimates for each indication separately. A sensitivity analysis will be performed using the ASaT population. Patients with missing data will be censored at the last tumor assessment date, date of death, or date of first dose of study treatment (if incomplete or no baseline tumor assessments), whichever occurs latest.

12.7.8 CTC Response

The CTC response will be summarized using descriptive statistics (frequency and percentage) together with a 95% CI for the mCRPC indication cohort. Patients with missing data will be considered as non-responders.

12.7.9 PSA Response

The PSA response will be summarized using descriptive statistics (frequency and percentage) together with a 95% CI for the mCRPC indication cohort.

Responses will need confirmation by a second consecutive value obtained 4 or more weeks after the first value indicated a response. Evaluable patients with no confirmed response as defined above will be classified as non-responders.

12.7.10 Time to Confirmed PSA Progression

Time to confirmed PSA progression will be summarized using Kaplan-Meier estimates for the mCRPC indication. Patients with missing data will be censored at the PSA assessment date, date of death, or date of first dose of study treatment (if incomplete or no baseline PSA assessments), whichever occurs latest.

12.7.11 OS – Exploratory Analysis: Not to be reported

OS will be summarized using Kaplan-Meier estimates for each indication separately. Patients with missing data will be censored at the last time known to be alive. OS will be analyzed on the ASaT and Efficacy Populations.

12.7.11.1 Duration of Follow-up – Exploratory Analysis: Not to be reported

A reverse Kaplan-Meier analysis will be performed on OS to estimate the median follow-up incorporating censoring rules and flipping event/censored events.

12.7.12 PFS2 – Exploratory Analysis: Not to be reported

PFS2 will be summarized using Kaplan-Meier estimates for each indication separately for all patients in the ASaT and Efficacy populations.

Patients alive and for whom a second disease progression has not been observed will be censored at the last time known to be alive and without second objective disease progression. Death is considered an event, regardless of whether subsequent anti-cancer therapy has been started. Patients progressing on subsequent anti-cancer therapy without experiencing progression on SOT101 will also be considered to have experienced an event.

12.8 Safety Analyses

AEs will be graded according to the NCI CTCAE version 5.0.

All safety analyses will be summarized separately for each indication and overall. Safety analyses will be performed in the ASaT population unless otherwise specified.

12.8.1 Adverse Events

AEs will be coded according to MedDRA (Version 24.1or later) by SOC, PT, and severity grade using NCI CTCAE version 5.0.

Linked AEs will be identified via the AE ID recorded as change in severity of an existing AE on the AE CRF page. Multiple AE records with differing attributes can comprise a single linked AE occurrence. Linked AEs will be selected for analysis in tables based on their worst case scenario attribute e.g. maximum CTC grade, causal relationship, seriousness, and treatment emergence out of all records.

The ordering (the worst to best) for the following characteristics will be applied:

- Relationship: suspected, not suspected.
- Toxicity Grade: Grade 5 to Grade 1.

In the case of multiple actions taken across linked AEs, the AEs will appear in all relevant tables, however for the figures the worst case shall be taken based on the following hierarchy:

- Action taken with SOT101: permanently discontinued, temporarily discontinued, dose reduced, other action, no action taken.
- Action taken with pembrolizumab: permanently discontinued, delay of administration, other action, no action taken.

AE records within a linked AE can be given different treatment-emergence status. Treatment emergence for linked AEs will be established as those records in the linked AE with a worsening of severity from the preceding pre-treatment record. Any AE subsequently linked to an on-treatment AE would be considered treatment-emergent.

12.8.1.1 TEAEs

A breakdown of the number and percentage of patients reporting each AE categorized by SOC and PT will be presented. Note that patients are only counted once within each SOC or PT if an AE was reported more than once.

The following summaries of TEAEs will be presented by SOC and PT, where related is defined as a 'suspected' relationship to study treatment, combination treatment related is defined as being related to either SOT101 or pembrolizumab (or both), and discontinuation of combination treatment means discontinuation of either SOT101 or pembrolizumab (or both):

- Patients reporting at least one TEAE
- TEAEs occurring in ≥5% of patients
- Patients reporting at least one SOT101-related TEAE
- Patients reporting at least one Combination treatment related TEAE
- Patients reporting at least one CTCAE Grade 3 or greater TEAE
- Patients reporting at least one CTCAE Grade 3 or greater SOT101-related TEAE
- Patients reporting at least one CTCAE Grade 3 or greater combination treatment-related TEAE
- Patients with at least one AESI
- Patients with TEAEs leading to dose reduction or temporary discontinuation of SOT101
- Patients with TEAEs leading to dose reduction of SOT101
- Patients with TEAEs leading to temporary discontinuation of SOT101
- Patients with TEAEs leading to delay of administration of pembrolizumab,
- Patients with TEAEs leading to permanent discontinuation of SOT101
- Patients with TEAEs leading to permanent discontinuation of pembrolizumab
- Patients with TEAEs leading to permanent discontinuation of combination therapy
- Patients with treatment-related TEAEs leading to permanent discontinuation of SOT101
- Patients with non-serious TEAEs reported in ≥5% of patients

The following summaries will be presented by PT in descending order of frequency:

- Patients reporting at least one TEAE
- Patients reporting at least one SOT101-related TEAE
- Patients reporting at least one combination treatment-related TEAE
- TEAEs occurring in ≥5% of patients
- Patients reporting at least one CTCAE grade 3 or greater TEAE for PTs occurring in at least 5% of patients,

The following summaries will be presented by SOC, PT, and maximum CTCAE grade:

- Patients reporting at least one TEAE
- Patients reporting at least one SOT101-related TEAE.

All AEs (including non-treatment-emergent events) recorded on the CRFs will be listed using the ASaT population. The following listings will be produced separately:

- All AEs
- AEs leading to death
- Treatment-emergent SAEs
- TEAEs leading to permanent discontinuation of SOT101
- TEAEs leading to temporary discontinuation of SOT101
- TEAEs leading to permanent discontinuation of pembrolizumab
- TEAEs leading to temporary discontinuation of pembrolizumab
- TEAEs leading to dose reduction of SOT101
- TEAEs of special interest

The following summaries will be presented by PT in descending order of frequency, and maximum CTCAE grade broken down into the categories Any Grade, Grade 1/2, Grade 3, Grade 4 and Grade 5:

- Any TEAE
- Any SOT101-related TEAE.
- Any Combination-treatment related TEAE
- TEAEs reported in ≥10% of patients

Additionally a bar chart showing TEAEs occurring in ≥10% of subjects will be presented, sorted by most prevalent TEAE and with the bar broken down to represent CTCAE grades 1 or 2, 3, or 4.

12.8.1.2 SAEs and Deaths

The following summaries of SAEs, including AEs that lead to death, will be presented by SOC and PT:

- Patients with at least one SAE
- Patients with at least one SOT101-related SAE
- Patients with at least one combination treatment-related SAE
- Patients with an AE leading to death
- Patients with a treatment-related TEAE leading to death (related to SOT101)
- Patients with a treatment-related TEAE leading to death (related to combination treatment)

The following summaries will be presented by PT in descending order of frequency:

- Patients reporting at least one SAE
- Patients reporting at least one treatment-related SAE (related to SOT101) Patients reporting at least one combination treatment-related SAE (related to either SOT101 or Pembrolizumab)

12.8.2 Laboratory Data

12.8.2.1 Laboratory Parameters

Clinical laboratory parameters to be collected on-study are referenced in the protocol section 8.2.5**Error! Reference source not found.**. Standard International units documented in the local laboratory conventions will be used for all laboratory parameters.

Quantitative data will be summarized using descriptive statistics of actual values and CFB for each scheduled visit over study. Only selected parameters will be summarized and plotted: Hemoglobin, Platelets, Neutrophils, Lymphocytes for hematology; ALT, Albumin, Alkaline phosphatase, AST, Total Bilirubin, Creatinine, Creatinine clearance, Lactate dehydrogenase, and C-reactive protein for chemistry. D-Dimer for Coagulation.

All laboratory data will be summarized in International System (SI) units. Conversion for local laboratories will be performed in the RAVE Lab Tool according to the study Local Lab Conventions. In general, laboratory data will be presented by visit. Values at unscheduled visits will be included in the summary of maximum for all cycles and minimum for all cycles, which will present the largest and smallest values observed for each patient on-treatment for each test.

The actual values for each scheduled visit up to and including cycle 10 for selected laboratory parameters will be plotted for each indication. Box plots will be produced showing the summary data per indication per scheduled assessment, including an overlaid mean profile line and approximate LLN and ULN lines indicated (see Appendix I).

Laboratory values evaluated as abnormal will be presented in separate listing.

12.8.2.2 Hy's Law

Hepatic function abnormality defined by an increase in AST and/or ALT to ≥ 3 × ULN concurrent with an increase in total bilirubin to ≥ 2 × ULN but without increase in alkaline phosphatase (i.e., alkaline phosphatase < 2 × ULN) meets the criteria for Hy's law and raises the concern for drug-induced liver injury when no other cause is identified.

The number and percentage of patients meeting Hy's Law at each scheduled visit during the on-treatment period will be summarized.

An eDISH figure displaying patients who reach 3xULN for ALT or AST, plus 2xULN for total bilirubin and thus are at risk for a drug induced liver injury according to Hy's law will be presented for all patients. A listing of patients at risk will also be presented.

12.8.2.3 TSH assessment

Results will be summarized and listed for thyroid parameters: TSH, Free T4, Total T3 and Free T3.

12.8.3 Vital Signs

The following vital signs will be summarized: heart rate (beats/min), systolic blood pressure (SBP; mmHg), diastolic blood pressure (DBP; mmHg), and body temperature (C).

The selected vital signs will be summarized descriptively at each study timepoint where they are collected. CFB values will be summarized for the on-treatment time points. All vital signs will be listed.

The actual values and CFB for each scheduled study visit for selected vital signs parameters will be plotted at each time point up to and including Cycle 10 using a line plot including confidence intervals around the mean.

[redacted]

12.8.4 ECOG Performance Status

A tabulation of ECOG performance status by timepoint will be provided, including the number and percentage of patients reporting each ECOG category at each scheduled time point.

12.8.5 Physical Examinations, ECGs, and Other Observations Related to Safety

Summaries of these safety assessments will be tabulated by indication at each assessment timepoint.

12.8.5.1 Physical Examination

Physical examination data will be listed only.

12.8.5.2 Electrocardiogram

Summaries will be generated for patients based on International Council for Harmonization (ICH) E14 category, with QTcF in categories <450msec, 450-480msec, or increased to value >480 and ≤500 msec, and value >500 msec, and patients with CFB in QTcF increased by ≤30 msec, >30 to ≤60 msec, and by >60 msec.

The actual values and CFB for each scheduled study visit for selected ECG parameters will be plotted at each time point up to and including cycle 10 using a box-whisker plot including an overlaid mean profile line.

12.8.5.3 LVEF

LVEF data will be summarized. Observed values and CFB will be presented for each planned visit.

12.8.5.4 Pregnancy Test

Pregnancy testing data will be listed only.

12.8.5.5 Long Term Follow-up

Survival status data will be listed for the ASaT population. Additionally, all subsequent anti-cancer therapy will be summarized and listed.

12.8.5.6 Death Report

Death report data will be summarized for the enrolled population. Primary and secondary causes of death will be summarized using a combination of coded terms (MedDRA coded PT and SOC terms) and the CRF responses. .

12.9 Serum PK Summaries

All PK analyses will be performed using the PK population.

Descriptive statistics (number of patients, mean, geometric mean, 95% CI for the geometric mean,, STD, coefficient of variation [%CV], median, min, and max) will be used to summarize the serum concentrations descriptively by scheduled timepoint and actual dose received. Summaries will be performed by actual dose received, defined as the actual dose received on the day of PK sampling. All concentrations data will be listed by planned dose level and scheduled timepoints, with the actual dose level received at each timepoint presented at record level.

Serum concentrations of SOT101 below the quantifiable limit (BQL) will be set to 0 in the computation of mean concentration values. The following rules apply:

- If there are less than 3 quantifiable values in a data series, only the minimum, maximum and n will be presented. The other summary statistics will be denoted as not calculated (NC).

- If any of the values at a certain timepoint are BLQ, the geometric mean and geometric coefficient of variation (CV) will be denoted as NC.

PK parameters will be calculated as described in the PK Analysis Plan (PKAP). The units of concentration and resulting PK parameters, with amount or concentration in the unit, will be presented as they are received from the analytical laboratory. PK parameters will be summarized descriptively by timepoint and actual dose received, by indication and overall (number of patients, mean, geometric mean, STD, coefficient of variation [%CV], median, min, and max). Line plots of SOT101 concentration including error bars for ±SD by timepoint and indication will be presented by profile day showing plots for C1D1, C1D9, C2D1 and C2D9. C1D2 pre-dose will be present on the C1D1 figure as the 24h dose.

12.10 Immunogenicity

The presence or absence of anti-drug antibodies, neutralizing ADA's and titer categorizations will be summarized by timepoint and actual dose level, by indication and overall for SOT101. Immunogenicity data will be listed. Any additional immunogenicity analyses will be described separately.

12.11 Other Endpoints

Pharmacodynamic endpoints will be reported separately..

13.0 References

1. Seymour L, Bogaerts J, Perrone A, Ford R et al. iRECIST: guidelines for response criteria for use in trials testing immunotherapeutics. Lancet Oncol. 2017 March; 18(3); e143-e152.
2. Scher H, Morris M, Stadler WM et al. The Prostate Cancer Working Group 3 (PCWG3) consensus for trials in castration-resistant prostate cancer (CRPC). Journal of Clinical Oncology 33, no 15_suppl. May 20 2015; 5000-5000
3. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). European journal of cancer. 2009;45(2):228-47.
4. Clopper C, Pearson ES. The use of confidence or fiducial limits illustrated in the case of the binomial. Biometrika. 1934;26:404-1
5. EMA Guideline on the evaluation of anticancer medicinal products in man, Appendix 1. Jul 1 2013.

14.0 Glossary of Abbreviations

Glossary of Abbreviations:	
ADA	Anti-drug antibody
AE	Adverse event
AESI	Adverse event of special interest
ALK	Anaplastic lymphoma kinase
ALT	Alanine transaminase
ASaT	All-patients-as-treated
AST	Aspartate transaminase
ATC	Anatomic Therapeutic Classification
BOR	Best overall response (according to RECIST 1.1)
CBR	Clinical benefit rate (according to RECIST 1.1)
CFB	Change from baseline
CI	Confidence interval
CR	Complete Response
CRF	Case Report Form
cSCC	Cutaneous squamous cell carcinoma
CSR	Clinical Study Report
CTC	Circulating tumor cell
CTCAE	Common Terminology Criteria for Adverse Events
DEC	Dose Escalation Committee
dMMR	Mismatch repair deficient
DoR	Duration of response (according to RECIST 1.1)
ECG	Electrocardiography
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EGFR	Epidermal growth factor receptor
iBOR	Best overall response (according to iRECIST)
iCBR	Clinical benefit rate (according to iRECIST)
ICF	Informed Consent Form
iCPD	Confirmed progressive disease (according to iRECIST)
iCR	Complete response (according to iRECIST)
ICH	International Council for Harmonization

IDMC	Data Monitoring Committee
iDoR	Duration of response (according to iRECIST)
INR	International normalized ratio
iORR	Objective response rate (according to iRECIST)
iPFS	Progression-free survival (according to iRECIST)
iPR	Partial response (according to iRECIST)
iSD	Stable disease (according to iRECIST)
iRECIST	Response Evaluation Criteria In Solid Tumors for immune-based therapeutics
iUPD	Unconfirmed progressive disease (according to iRECIST)
IV	Intravenous
LLQ	Lower limit of quantitation
LVEF	Left ventricular ejection fraction
mCRPC	Metastatic castration-resistant prostate cancer
MSI-H/dMMR	Microsatellite Instability-high/Mismatch Repair Deficient
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NE	Not evaluable
NSCLC	Non-small cell lung cancer
ORR	Objective response rate
OS	Overall survival
PCWG3	Prostate Cancer Clinical Trials Working Group 3
PD	Progressive Disease
PFS	Progression-free survival (according to RECIST 1.1)
PK	Pharmacokinetics
PP	Per protocol
PR	Partial response (according to RECIST 1.1)
PSA	Prostate-specific antigen
PT	Preferred term
Q1	25th percentile
Q3	75th percentile
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Stable disease (according to RECIST 1.1)

SOC	System organ class
STD	Standard deviation
TEAE	Treatment-emergent adverse event
TSH	Thyroid stimulating hormone
TtR	Time to response
ULN	Upper limits of normal

Appendix 1: Approximate limits for normal ranges used in figures of safety data

Parameter	Lower limit	Upper limit
Albumin (g/L)	34	54
Creatinine (umol/L)	53	114.9
Creatinine Clearance (ml/min)	88	137
Total Bilirubin (umol/L)	1.71	20.5
ALT (U/L)	0	105
AST (U/L)	0	105
ALP (U/L)	43.8	120
Hemoglobin (g/L)	100	166
Neutrophils (10E9/L)	1.0	8.0
Neutrophils (%)	55	70
Lymphocytes (10E9/L)	1.0	4.0
Lymphocytes (%)	20	40
LDH (UI/L)	105	350
Platelet count (10E9/L)	100	400
CRP (mg/dl)		0.5
SysBP (mmHg)	90	140
DiaBP (mmHg)	60	80
HR (beats/min)	60	100
RR (breaths/min)	12	18
Body temp (ºC)		38