1 TITLE PAGE

Study Protocol number	SC103
Study Protocol title	A multicenter open-label phase 1/1b study to evaluate the safety and preliminary efficacy of SO-C101 as monotherapy and in combination with pembrolizumab in patients with selected advanced/metastatic solid tumors
Sponsor	SOTIO Biotech AG Hochbergerstrasse 60C 4057 Basel Switzerland
Investigational medicinal products	SO-C101 Pembrolizumab
Indication	Selected advanced/metastatic solid tumors
Phase	1/1b
IND number	140011
EudraCT number	2018-004334-15
GCP statement	This study will be conducted in accordance with current Good Clinical Practice (GCP), the provisions of International Council for Harmonisation (ICH) Guidelines, the Declaration of Helsinki and its amendments, and applicable laws and regulations of all countries with sites participating in the study.
Confidentiality statement	This document contains proprietary information and trade secrets of SOTIO Biotech AG. This information may not be used, divulged, published, copied, or otherwise disclosed to any third party without the prior written consent of SOTIO Biotech AG.

SIGNATURES / PROTOCOL APPROVAL AND RELEASE

We, the undersigned, have read this Protocol and its appendices and agree that they contain all the necessary information required for the conduct of this study.

For SOTIO Biotech AG:

[redacted]

SIGNATURES / PROTOCOL APPROVAL AND RELEASE

I, the undersigned, have read this Protocol and its appendices and agree that they contain all the necessary information required for the conduct of this study.

Coordinating investigator:

Prof. Aurélien Marabelle, M.D., Ph.D.
Clinical Director
Cancer Immunotherapy Program
Institute Gustave Roussy
Villejuif, France

Signature: ……

Date: ……

INVESTIGATOR'S DECLARATION AND SIGNATURE

I have read this Protocol and I agree that it contains all the necessary details for carrying out this clinical study. I will conduct this clinical study as described and I will complete it within the time designated. I verify that I am suitably qualified by education, scientific medical training, and experience to conduct this clinical study. Documentation of my qualifications and professional affiliations are contained in my up-to-date curriculum vitae.

I will provide the supplied copies of the Protocol and all information relating to pre-clinical and previous clinical experience (e.g., Investigator's Brochure) to all staff in my unit who will participate in this clinical study. I will discuss this material with them to ensure that they are fully conversant with the Protocol, the medical treatment, and the conduct of the clinical study, and that they will handle the data and information generated in the clinical study confidentially.

I will conduct the clinical study in accordance with the current version of the Declaration of Helsinki (adopted by the 18th World Medical Association General Assembly, Helsinki, Finland, June 1964 and amended by the 64th World Medical Association General Assembly, Fortaleza, Brazil, October 2013) and ICH guidelines on GCP (E6[R2] Step 4 version dated 09-Nov-2016), and the moral, ethical, and scientific principles that justify medical research. The clinical study will be conducted in accordance with the relevant laws and regulations relating to clinical studies and the protection of patients of the country in which the clinical study will be performed. All patients will be informed comprehensively about the nature of the clinical study and will give their written consent to participate before entry into the clinical study. They will be informed that they may withdraw from the clinical study at their discretion at any time. I will use only the information sheet and consent form approved by SOTIO Biotech AG (hereinafter referred to as "sponsor" or "SOTIO") and the Institutional Review Board (IRB) or Ethics Committee (EC) which has reviewed this clinical study. I will supply SOTIO with any material written by myself (e.g., summary of clinical study) which is given to the IRB/EC in support of the application.

Where applicable and required, the information contained in the electronic Case Report Forms (eCRFs) will be transcribed from my records, reports, and manuscripts. The eCRF may be the original source document for certain items. Either I or an appointed person will attest to the authenticity of the data and accuracy and completeness of the transcription by signing the eCRFs. I agree to the audit and monitoring procedures that involve verification of clinical study records against the original records by direct access. Should it be requested by government regulatory agencies, I will make available additional background data from my records, and where allowed from the hospital or institution where the clinical study was conducted. I certify that any laboratory, excluding the central laboratory (laboratories) appointed for the clinical study, in which laboratory parameters will be determined, is subject to regular external quality control.

I consent that SOTIO and its designees can collect, process, transfer, use, and store my personal data and details relating to my professional activities for the purposes of this clinical study.

I understand that the eCRFs and other data pertinent to this clinical study are the property of SOTIO and are confidential. I will provide SOTIO with clinical study data in a way that prevents identification of any patient.

Investigator's signature: _____
Date: _____
Printed name: _____
Street address: _____
Telephone number: _____

Contact information

Sponsor's medical monitor: _____
24-hr emergency telephone number: _____

Other contact information

Full contact details for each investigational site, the sponsor, and key coordinating and operational personnel involved in this clinical study will be maintained in the Trial Master File and in the Investigator Site File.

2 CLINICAL PROTOCOL SYNOPSIS

Investigational medicinal products	1. SO-C101 2. Pembrolizumab
Protocol number	SC103
Study phase	1/1b
Study title	A multicenter open-label phase 1/1b study to evaluate the safety and preliminary efficacy of SO-C101 as monotherapy and in combination with pembrolizumab in patients with selected advanced/metastatic solid tumors
Background and rationale	Over the past decade, the power of the immune system to kill malignant tumors using cancer immunotherapy has emerged as a promising approach to treat a broad range of human cancers. Therapy with recombinant interleukin (IL)-2, a T-cell and natural killer-cell growth factor, was one of the earliest forays in immunotherapy that yielded some successes. IL-15 is a member of the common γ-chain family of cytokines that shares functional activities with IL-2. The main nonredundant role of IL-15 in immune homeostasis is in the maintenance of long-lasting T-cell immunity by supporting the proliferation and survival of memory CD8+ T cells. The effects of IL-15 are mediated by interactions with IL-15 receptor (IL-15R) chains α, ß, and γ. IL-15 can bind to the IL-15Rαβγ complex of responding cells (cis-presentation) or complex with IL-15Rα present on accessory cells and bind the IL-15Rβγ complex on responding cells (trans-presentation). Trans-presentation represents the main route of IL-15 signaling. While initially showing promise as a cancer therapeutic, the efficacy of IL-15 was limited by its short *in vivo* half-life. More recently, various approaches have been developed to improve the *in vivo* half-life and efficacy of IL-15, largely by generating IL-15/IL-15Rα conjugates. In order to make use of the enhanced biological activity of the IL-15/IL-15Rα complex for the treatment of cancer and to overcome the need for endogenous IL-15Rα or coadministration of IL-15 with IL-15Rα, we engineered a fusion protein which consists of the N-terminal sushi domain of human IL-15Rα covalently coupled via a linker of 20 amino acids to human IL-15 (receptor-linker-IL-15 [SO-C101]). Before being acquired by SOTIO, SO-C101 was referred to as RLI-15.

	In vitro, SO-C101 was superior to IL-15 in driving cell proliferation and survival. In experiments with human T cells, SO-C101 bound with high affinity to IL-15Rβγ and the kinetics of SO-C101 internalization was slower than that of IL-15. IL-15 and SO-C101 dose-dependently activated similar signaling pathways. However, the kinetics and duration of these activations were markedly different; SO-C101-induced signaling was slower to start but lasted longer than signaling induced by IL-15. Clinical studies conducted with compounds with a similar mode of action; e.g., ALT-803, an IL-15/IL-15Rα complex fused to an IgG1 Fc in which IL-15 is additionally mutated; showed that ALT-803 has a favorable safety profile and is able to induce a robust immune-stimulatory response. In addition, ALT-803 in combination with nivolumab showed promising clinical activity. This study is planned based on the encouraging results of the pre-clinical studies with SO-C101 and the clinical unmet need for patients who do not respond or develop resistance to programmed cell death protein 1 (PD-1) and programmed cell death ligand 1 (PD-L1) antibody treatment. The combination of SO-C101 with immune checkpoint inhibitors is hypothesized to extend the therapeutic benefit to a larger proportion of patients. This study will assess the safety and tolerability of SO-C101 administered as monotherapy and in combination with an anti-PD-1 antibody (pembrolizumab) in patients with selected relapsed/refractory advanced/metastatic solid tumors. SO-C101 will be administered on treatment days either as a once daily dose (dosing schedule 1) or twice a day as 2 divided doses (50%:50%) with the second dose on each treatment day being administered 8 hours (±15 min) after the first dose (dosing schedule 2). This first-in-human (FIH) study of SO-C101 will consist of the following parts: 1. **Part A** will assess the safety and tolerability of SO-C101 monotherapy for dosing schedule 1 to define the maximum tolerated dose (MTD) and/or the recommended phase 2 dose (RP2D) 2. **Part A1** will assess the safety and tolerability of SO-C101 monotherapy for dosing schedule 2 to define the MTD and/or the RP2D 3. **Part B** will assess the safety and tolerability of SO-C101, dosing schedule 1, in combination with pembrolizumab and the MTD and/or RP2D 4. **Part B1** will assess the safety and tolerability of SO-C101, dosing schedule 2, in combination with pembrolizumab and the MTD and/or RP2D

	5. **Part D** will be a dose expansion part at the RP2D dose level identified in Part A to further assess the safety, tolerability, and preliminary efficacy of the RP2D of SO-C101 monotherapy for dosing schedule 1 in selected indications 6. **Part D1** will be a dose expansion part at the RP2D dose level identified in Part A1 to further assess the safety, tolerability, and preliminary efficacy of the RP2D of SO-C101 monotherapy for dosing schedule 2 in selected indications
Objectives	**PART A (SO-C101 dosing schedule 1, monotherapy, dose escalation)** **Primary objectives** • To assess the safety and tolerability of SO-C101 given as monotherapy • To determine the MTD and/or RP2D of SO-C101 given as monotherapy **Secondary objectives** • To characterize the pharmacokinetics (PK) of SO-C101 • To characterize the pharmacodynamics (PD) of SO-C101 in peripheral blood • To determine the preliminary efficacy of SO-C101 monotherapy as measured by objective response rate (ORR), duration of response (DOR), clinical benefit rate (CBR), and progression-free survival (PFS) according to Response Evaluation Criteria in Solid Tumors for immune-based therapeutics (iRECIST) • To determine the immunogenicity of SO-C101 given as monotherapy **Exploratory objectives** • To explore the mechanistic effects of SO-C101 on selected immune cell populations in tumor tissue samples • To assess overall survival (OS) at 6 months after the End of treatment (EoT) visit **PART A1 (SO-C101 dosing schedule 2, monotherapy, dose escalation)** **Primary objectives** • To assess the safety and tolerability of SO-C101 given as monotherapy • To determine the MTD and/or RP2D of SO-C101 given as monotherapy **Secondary objectives** • To characterize the PK of SO-C101 • To characterize the PD of SO-C101 in peripheral blood

	• To determine the preliminary efficacy of SO-C101 monotherapy as measured by ORR, DOR, CBR, and PFS according to iRECIST • To determine the immunogenicity of SO-C101 as monotherapy **Exploratory objectives** • To explore the mechanistic effects of SO-C101 on selected immune cell populations in tumor tissue samples • To assess OS at 6 months after the EoT visit **PART B (SO-C101 dosing schedule 1, combined with pembrolizumab, dose escalation)** **Primary objectives** • To assess the safety and tolerability of SO-C101 when combined with pembrolizumab • To determine the MTD and/or RP2D of SO-C101 when combined with pembrolizumab **Secondary objectives** • To characterize the PK of SO-C101 when combined with pembrolizumab • To characterize the PD of SO-C101 in peripheral blood when combined with pembrolizumab • To assess the preliminary efficacy of the combination of SO-C101 with pembrolizumab as measured by ORR, DOR, CBR, and PFS according to iRECIST • To determine the immunogenicity of SO-C101 in combination with pembrolizumab **Exploratory objectives** • To explore the mechanistic effects of SO-C101 in combination with pembrolizumab on selected immune cell populations in tumor tissue samples • To assess OS at 6 months after the EoT visit **PART B1 (SO-C101 dosing schedule 2, combined with pembrolizumab, dose escalation)** **Primary objectives** • To assess the safety and tolerability of SO-C101 when combined with pembrolizumab • To determine the MTD and/or RP2D of SO-C101 when combined with pembrolizumab **Secondary objectives** • To characterize the PK of SO-C101 when combined with pembrolizumab • To characterize the PD of SO-C101 in peripheral blood when combined with pembrolizumab

	• To assess the preliminary efficacy of the combination of SO-C101 twice daily with pembrolizumab as measured by ORR, DOR, CBR, and PFS according to iRECIST • To determine the immunogenicity of SO-C101 in combination with pembrolizumab **Exploratory objectives** • To explore the mechanistic effects of SO-C101 in combination with pembrolizumab on selected immune cell populations in tumor tissue samples • To assess OS at 6 months after the EoT visit **Part D (SO-C101 dosing schedule 1, monotherapy, dose expansion at the RP2D identified in Part A)** **Primary objective** • To assess the safety and tolerability of SO-C101 **Secondary objectives** • To characterize the PK of SO-C101 • To characterize the PD of SO-C101 in peripheral blood • To assess the preliminary efficacy of SO-C101 as measured by ORR, DOR, CBR, and PFS according to iRECIST • To determine the immunogenicity of SO-C101 **Exploratory objectives** • To explore the mechanistic effects of SO-C101 on selected immune cell populations in tumor tissue samples • To assess OS at 6 months after the EoT visit **Part D1 (SO-C101 dosing schedule 2, monotherapy, dose expansion at the RP2D identified in Part A1)** **Primary objective** • To assess the safety and tolerability of SO-C101 **Secondary objectives** • To characterize the PK of SO-C101 • To characterize the PD of SO-C101 in peripheral blood • To assess the preliminary efficacy of SO-C101 as measured by ORR, DOR, CBR, and PFS according to iRECIST • To determine the immunogenicity of SO-C101 **Exploratory objectives** • To explore the mechanistic effects of SO-C101 on selected immune cell populations in tumor tissue samples • To assess OS at 6 months after the EoT visit

Endpoints	**PART A (SO-C101 dosing schedule 1, monotherapy, dose escalation)** **Primary endpoints** • Safety and tolerability of SO-C101 as evaluated by the incidence of dose-limiting toxicities (DLTs), incidence of SO-C101-related adverse events (AEs), serious AEs (SAEs), AEs leading to premature discontinuation of SO-C101, deaths, and clinical laboratory test abnormalities • MTD is defined as the dose level associated with ≥33% of DLT-evaluable patients experiencing a DLT. If the MTD is reached, the RP2D will be conventionally defined as the dose level just below this non-tolerated dose level. If the MTD is not reached, the RP2D will be selected based on integrated evaluation of safety, tolerability, clinical benefit, PK and PD data, for all dose levels tested. **Secondary endpoints** • PK of SO-C101 • Immune response characterized by the changes in expression of immune markers in peripheral blood mononuclear cells (PBMCs) • ORR, DOR, CBR, and PFS according to iRECIST • Detection of anti-drug antibodies (ADAs) **Exploratory endpoints** • Changes in the expression of immune biomarkers as compared to baseline in tumor tissue • OS at 6 months after the EoT visit **PART A1 (SO-C101 dosing schedule 2, monotherapy, dose escalation)** **Primary endpoints** • Safety and tolerability of SO-C101 as evaluated by the incidence of DLTs, incidence of SO-C101-related AEs, SAEs, AEs leading to premature discontinuation of SO-C101, deaths, and clinical laboratory test abnormalities • MTD is defined as the dose level associated with ≥33% of DLT-evaluable patients experiencing a DLT. If the MTD is reached, the RP2D will be conventionally defined as the dose level just below this non-tolerated dose level. If the MTD is not reached, the RP2D will be selected based on integrated evaluation of safety, tolerability, clinical benefit, PK and PD data, for all dose levels tested. **Secondary endpoints** • PK of SO-C101 • Immune response characterized by the changes in expression of immune markers in PBMCs

	• ORR, DOR, CBR, and PFS according to iRECIST • Detection of ADAs **Exploratory endpoints** • Changes in the expression of immune biomarkers as compared to baseline in tumor tissue • OS at 6 months after the EoT visit **PART B (SO-C101 dosing schedule 1, combined with pembrolizumab, dose escalation)** **Primary endpoints** • Safety and tolerability of SO-C101 combined with pembrolizumab as evaluated by the incidence of DLTs, SO-C101-related AEs, SAEs, AEs leading to premature SO-C101 discontinuation, deaths, and clinical laboratory test abnormalities • MTD defined as the dose level associated with ≥33% of DLT-evaluable patients experiencing a DLT. If the MTD is reached, the RP2D will be conventionally defined as the dose level just below this non-tolerated dose level. If the MTD is not reached, the RP2D will be selected based on integrated evaluation of safety, tolerability, clinical benefit, PK and PD data, for all dose levels tested. **Secondary endpoints** • PK of SO-C101 combined with pembrolizumab • Immune response after administration of SO-C101 in combination with pembrolizumab characterized by the changes in expression of immune markers in PBMCs • ORR, DOR, CBR, and PFS according to iRECIST • Detection of ADAs **Exploratory endpoints** • Changes in the expression of immune biomarkers after administration of SO-C101 in combination with pembrolizumab as compared to baseline in tumor tissue • OS at 6 months after the EoT visit **PART B1 (SO-C101 dosing schedule 2, combined with pembrolizumab, dose escalation)** **Primary endpoints** • Safety and tolerability of SO-C101 combined with pembrolizumab as evaluated by the incidence of DLTs, SO-C101-related AEs, SAEs, AEs leading to premature SO-C101 discontinuation, deaths, and clinical laboratory test abnormalities • MTD defined as the dose level associated with ≥33% of DLT-evaluable patients experiencing a DLT. If the MTD is reached, the RP2D will be conventionally defined as the dose

	level just below this non-tolerated dose level. If the MTD is not reached, the RP2D will be selected based on integrated evaluation of safety, tolerability, clinical benefit, PK and PD data, for all dose levels tested. **Secondary endpoints** • PK of SO-C101 combined with pembrolizumab • Immune response after administration of SO-C101 in combination with pembrolizumab characterized by the changes in expression of immune markers in PBMCs • ORR, DOR, CBR, and PFS according to iRECIST • Detection of ADAs **Exploratory endpoints** • Changes in the expression of immune biomarkers after administration of SO-C101 in combination with pembrolizumab as compared to baseline in tumor tissue • OS at 6 months after the EoT visit **PART D (SO-C101 dosing schedule 1, monotherapy, dose expansion at the RP2D identified in Part A)** **Primary endpoint** • Safety and tolerability of SO-C101 as evaluated by the incidence of SO-C101-related AEs, SAEs, AEs leading to premature SO-C101 discontinuation, deaths, and clinical laboratory test abnormalities **Secondary endpoints** • PK of SO-C101 • Immune response after administration of SO-C101 characterized by the changes in expression of immune markers in PBMCs • ORR, DOR, CBR, and PFS according to iRECIST • Detection of ADAs **Exploratory endpoints** • Changes in the expression of immune biomarkers after administration of SO-C101 as compared to baseline in tumor tissue • OS at 6 months after the EoT visit **PART D1 (SO-C101 dosing schedule 2, monotherapy, dose expansion at the RP2D identified in Part A1)** **Primary endpoint** • Safety and tolerability of SO-C101 as evaluated by the incidence of SO-C101-related AEs, SAEs, AEs leading to premature SO-C101 discontinuation, deaths, and clinical laboratory test abnormalities

	Secondary endpoints • PK of SO-C101 • Immune response after administration of SO-C101 characterized by the changes in expression of immune markers in PBMCs • ORR, DOR, CBR, and PFS according to iRECIST • Detection of ADAs **Exploratory endpoints** • Changes in the expression of immune biomarkers after administration of SO-C101 as compared to baseline in tumor tissue • OS at 6 months after the EoT visit
Overall study design	This study will assess the safety and tolerability of two administration schedules of SO-C101 administered as monotherapy (Part A, Part A1, Part D, and Part D1) and in combination with an anti-PD-1 antibody (pembrolizumab) (Part B and Part B1) in patients with selected relapsed/refractory advanced/metastatic solid tumors who are refractory to or intolerant of existing therapies known to provide clinical benefit for their condition. Part A, Part A1, Part B, and Part B1 will enroll patients with the following relapsed/refractory advanced/metastatic tumors: renal cell carcinoma, non-small cell lung cancer, small-cell lung cancer, bladder cancer, melanoma, Merkel-cell carcinoma, skin squamous-cell carcinoma, microsatellite instability high solid tumors, triple-negative breast cancer, mesothelioma, thyroid cancer, thymic cancer, cervical cancer, biliary tract cancer, hepatocellular carcinoma, ovarian cancer, gastric cancer, head and neck squamous-cell carcinoma, and anal cancer. Part D and Part D1 will enroll patients with relapsed/refractory advanced/metastatic renal cell carcinoma, patients with relapsed/refractory advanced/metastatic skin squamous-cell carcinoma, and patients with relapsed/refractory advanced/metastatic melanoma. The study will have the following parts: • Part A will be a FIH SO-C101 monotherapy dose escalation part for dosing schedule 1. • Part A1 will be a SO-C101 monotherapy dose escalation part for dosing schedule 2 which will start once the RP2D of SO-C101, dosing schedule 1, is identified in Part A; the starting daily dose of Part A1 will be 1 dose level below the RP2D identified in Part A. The dose will be split into two identical (50%:50%) daily doses with the second dose on each treatment day being administered 8 hours (±15 min) after the first dose. • Part B will study SO-C101 dosing schedule 1 in combination with pembrolizumab and will start after dose level 5 in Part A is

completed and deemed safe and will use SO-C101 monotherapy level 3 dose, dosing schedule 1, as the starting dose in combination with pembrolizumab.

- Part B1 will study SO-C101 dosing schedule 2 in combination with pembrolizumab and will start once the RP2D of SO-C101, dosing schedule 1, in combination with pembrolizumab is identified in Part B; the starting daily dose of Part B1 will be 1 dose level below the RP2D identified in Part B. The dose will be split into two identical (50%:50%) daily doses with the second dose on each treatment day being administered 8 hours (±15 min) after the first dose.
- Part D will be a dose expansion part which will start once the RP2D of SO-C101, dosing schedule 1, is identified in Part A; SO-C101 will be given at the Part A RP2D.
- Part D1 will be a dose expansion part which will start once the RP2D of SO-C101, dosing schedule 2, is identified in Part A1; SO-C101 will be given at the Part A1 RP2D.

Part A will start first with SO-C101 monotherapy dose escalation for dosing schedule 1 which will continue until the MTD and/or RP2D of SO-C101 monotherapy for dosing schedule 1 is defined. After this, Part A1 (dosing schedule 2) will start with the starting daily dose at 1 dose level below the RP2D identified in Part A and will continue until the MTD and/or RP2D of SO-C101 monotherapy given as per dosing schedule 2 is defined.

Part B will start once monotherapy SO-C101 dose level 5 (6.0 µg/kg) in Part A is completed and deemed safe. The starting dose of Part B will be Part A dose level 3 (1.5 µg/kg) which will be combined with a fixed dose of pembrolizumab (200 mg intravenously [IV] every 3 weeks). If an MTD in Part A is reached before dose level 5, then the starting dose of SO-C101 in Part B will be decided based on the review of all available safety/PD/PK data.

After the start of Part B, the study will continue recruiting to Part A and Part B in parallel. The Part B SO-C101 dose will be following the increasing safe dose levels of monotherapy SO-C101 from Part A. Under no circumstances will the Part B SO-C101 dose exceed the highest dose deemed safe in Part A. Part B dose escalation will continue until the MTD and/or RP2D of SO-C101 in combination with pembrolizumab is defined. This approach will allow for combination safety/PK/PD to be tested and optimized timely and effectively.

Part A ➡ MTD/RP2D schedule 1 monotherapy
➡ Part D: Part A expansion at the dosing schedule 1 monotherapy RP2D in selected indication(s)
➡ Part A1: Schedule 1 monotherapy RP2D dose split* ➡ MTD/RP2D schedule 2 monotherapy
➡ Part D1: Part A1 expansion at the dosing schedule 2 monotherapy RP2D in selected indication(s)

Part B ➡ MTD/RP2D schedule 1 in combination with pembrolizumab
➡ Part B1: Schedule 1 combination RP2D dose split* ➡ MTD/RP2D schedule 2 in combination with pembrolizumab

**Dose split into two identical (50%:50%) daily doses with the second dose on each treatment day being administered 8 hours (±15 min) after the first dose*

	This study is planned to allow patients to crossover from Part A and Part A1 to Part B or Part B1 when they have objective progressive disease in Part A and Part A1 and there is a dose deemed safe in Part B or Part B1. The investigator should also be of the opinion that these patients will derive benefit from combination treatment in Part B or Part B1. These patients will NOT be part of the dose escalation cohorts of Part B or Part B1; therefore, they will not be part of the DLT evaluation in Part B or Part B1. The crossover will only be allowed when all of the following criteria are met: • Unconfirmed progressive disease as per iRECIST in Part A and Part A1 • Eligibility for Part A and Part A1 (except fresh biopsy requirement) still holds and patients have no known hypersensitivity to any of the ingredients in the pembrolizumab drug product (Keytruda™) • There are no safety concerns as deemed by the investigator and the patient should not have had a DLT in Part A and Part A1 • A completed safe dose level identified in Part B or Part B1. If there are more than one safe dose levels identified, the patient will be allowed to be assigned to the highest dose level deemed safe. For each patient considered for the crossover, the investigator will discuss this with the sponsor's medical monitor. After the RP2D of SO-C101 dosing schedule 1 in combination with pembrolizumab is identified in Part B, Part B1 dose escalation investigating SO-C101 dosing schedule 2 will start. Part B1 will start with the starting daily dose at 1 dose level below the RP2D identified in Part B until the MTD and/or RP2D of SO-C101 dosing schedule 2 in combination with pembrolizumab is defined. Part D (dose expansion) will start after the RP2D of SO-C101 monotherapy for dosing schedule 1 is identified in Part A. SO-C101 will be given as per dosing schedule 1 at the RP2D identified in Part A. Part D1 (dose expansion) will start after the RP2D of SO-C101 monotherapy for dosing schedule 2 is identified in Part A1. SO-C101 will be given as per dosing schedule 2 at this RP2D. The study will recruit patients to all ongoing study parts in parallel. The sponsor will allocate slots for the patients to be recruited to the dose-escalation study parts.
Part A (SO-C101 dosing schedule 1, monotherapy, dose escalation)	Patients will be treated with escalating doses of SO-C101 given as per dosing schedule 1 via the subcutaneous (SC) route following the dose escalation scheme below. A starting dose of 0.25 µg/kg was selected in Part A of this study. If this starting dose is not tolerated, then a lower dose could be considered.

Dose level	SO-C101 dose given once a day (µg/kg/administration)	Dose increase
1	0.25 µg/kg	Starting dose
2	0.75 µg/kg	200%
3	1.5 µg/kg	100%
4	3.0 µg/kg	100%
5	6.0 µg/kg	100%
6	9.0 µg/kg	50%
7	15.0 µg/kg	67%
8	12.0 µg/kg	-20%

Patients will be treated with SO-C101 given once a day on day 1 (±1 day; Wednesday), day 2 (Thursday), day 8 (Wednesday), and day 9 (Thursday) of the 21-day cycle. The start of the treatment (day 1) is planned to be on a Wednesday to allow biomarker sampling (fresh PBMCs transfer to the central laboratory) on weekdays. However, as long as the two doses per week are given on consecutive days (day 1 and day 2) and the second week dosing (day 8 and day 9) takes place 7 days after day 1, there will be ±1 day flexibility for the day 1 dosing to take place on a Tuesday or on a Thursday.

SC injection sites will be rotated to different areas of the body (upper and lower extremities, each of the 4 quadrants of the abdomen) to minimize the summated potential local effects of SO-C101 administration.

This dosing schedule will be revised in light of the emerging clinical data from initial cohorts and if these data reveal substantial differences from non-clinical data, adjustment of the planned dose levels will be considered by the Dose Escalation Committee (DEC) and the Independent Advisory Panel (IAP).

This schedule should be strictly adhered to with no dose delays/reductions to be allowed for especially cycle 1 for maximum exposure for safety evaluation for DLTs. If any visits are missed for obtaining PK/PD/safety laboratory parameters during cycle 1, patients will be reviewed individually by the sponsor's medical monitor and investigators for their evaluability for DLT assessment.

SO-C101 monotherapy dose escalation for dosing schedule 1 will continue until the MTD and/or RP2D is reached as per the dose escalation schema. If the MTD is not reached at the end of the planned dose escalation cohorts, the recruitment will stop to assess RP2D. Additional doses and schedules could be opened as required based on the RP2D assessment results to define the optimal dose and schedule for further clinical studies.

	Patients recruited in Part A will continue treatment at their assigned dose level. Intra-patient dose escalation beyond the dose initially assigned to a patient is not permitted during cycle 2. However, patients receiving treatment with SO-C101 given as per dosing schedule 1 beyond cycle 2 may continue treatment at the next higher dose level if it is assessed to be safe by the DEC and IAP and if the following criteria are met: • No safety concerns as deemed by the investigator • No DLT at the initial dose level assigned • No unacceptable AEs, defined as drug-related clinically meaningful, uncontrolled grade 3 or any grade 4 toxicities at the current dose level • No dose reduction at the current dose level • Completed at least two cycles at the assigned dose • The investigator should also be of the opinion that these patients will derive benefit from treatment at the higher dose level of SO-C101 given as per dosing schedule 1 If these requirements are met, the patient can be dose escalated to the next dose level after discussion with the sponsor's medical monitor. These patients after intra-patient dose increase will NOT be part of the higher dose escalation cohorts; therefore, after intra-patient dose increase, they will not be part of the DLT evaluation. Intra-patient escalation up to the RP2D level is allowed and can be done step-by step if the patient stays at the higher dose level and meets the criteria for escalation as specified above. If treatment discontinuation is due to disease progression, crossover to the combination treatment (Part B or Part B1) could be considered. Patients will be discontinued from study treatment for any of the following events: • Radiographic disease progression (confirmed progressive disease per iRECIST [iCPD]) • Clinical disease progression (investigator assessment) • AE (intercurrent illness or study treatment-related toxicity, including DLTs, that would, in the judgment of the investigator, affect assessments of clinical status to a significant degree or require discontinuation of study treatment) • Patient may withdraw from the study at any time for any reason; the investigator must make every effort to determine the reason for this decision and record it in source documentation of the patient • Death • Pregnancy

	• Concomitant treatment with a prohibited medication, including further lines of cancer therapy • Patient non-compliance • Lost to follow-up • Study terminated by the sponsor
Part A1 (SO-C101 dosing schedule 2, monotherapy, dose escalation)	Patients will be treated with escalating doses of SO-C101 given as per dosing schedule 2 via the SC route. The starting daily dose will be 1 level below the RP2D identified in Part A. The dose will be split into two identical (50%:50%) daily doses with the second dose on each treatment day being administered 8 hours (±15 min) after the first dose. If this starting dose is not tolerated, then a lower dose could be considered. Further dose levels will be considered based on safety data and decisions taken during Dose Escalation Meetings (DEMs). Patients will be treated with SO-C101 given twice a day 8 hours (±15 min) apart on day 1 (±1 day; Wednesday), day 2 (Thursday), day 8 (Wednesday), and day 9 (Thursday) of the 21-day cycle. The start of the treatment (day 1) is planned to be on a Wednesday to allow biomarker sampling (fresh PBMCs transfer to the central laboratory) on weekdays. However, as long as the four doses per week are given on consecutive days (day 1 and day 2) and the second week dosing (day 8 and day 9) takes place 7 days after day 1, there will be ±1 day flexibility for the day 1 dosing to take place on a Tuesday or on a Thursday. SC injection sites will be rotated to different areas of the body (upper and lower extremities, each of the 4 quadrants of the abdomen) to minimize the summated potential local effects of SO-C101 administration. This dosing schedule will be revised in light of the emerging clinical data from initial cohorts and if these data reveal substantial differences from non-clinical data, adjustment of the planned dose levels will be considered by the DEC and the IAP. This schedule should be strictly adhered to with no dose delays/reductions to be allowed for especially cycle 1 for maximum exposure for safety evaluation for DLTs. If any visits are missed for obtaining PK/PD/safety laboratory parameters during cycle 1, patients will be reviewed individually by the sponsor's medical monitor and investigators for their evaluability for DLT assessment. SO-C101 monotherapy dose escalation for dosing schedule 2 will continue until the MTD and/or RP2D is reached. If the MTD is not reached, the recruitment will stop to assess RP2D. Additional doses and schedules could be opened as required based on the RP2D assessment results to define the optimized dose and schedule for further clinical studies.

	Patients recruited in Part A1 will continue treatment at their assigned dose level. Intra-patient dose escalation beyond the dose initially assigned to a patient is not permitted during cycle 2. However, patients receiving treatment with SO-C101 given as per dosing schedule 2 beyond cycle 2 may continue treatment at the next higher dose level if it is assessed to be safe by the DEC and IAP and if the following criteria are met: • No safety concerns as deemed by the investigator • No DLT at the initial dose level assigned • No unacceptable AEs, defined as drug-related clinically meaningful, uncontrolled grade 3 or any grade 4 toxicities at the current dose level • No dose reduction at the current dose level • Completed at least two cycles at the assigned dose • The investigator should also be of the opinion that these patients will derive benefit from treatment at the higher dose level of SO-C101 given as per dosing schedule 2 If these requirements are met, the patient can be dose escalated to the next dose level after discussion with the sponsor's medical monitor. These patients after intra-patient dose increase will NOT be part of the higher dose escalation cohorts; therefore, after intra-patient dose increase, they will not be part of the DLT evaluation. Intra-patient escalation up to the RP2D level is allowed and can be done step-by step if the patient stays at the higher dose level and meets the criteria for escalation as specified above. If treatment discontinuation is due to disease progression, crossover to the combination treatment (Part B or Part B1) could be considered. Patients will be discontinued from study treatment for any of the following events: • Radiographic disease progression (iCPD) • Clinical disease progression (investigator assessment) • AE (intercurrent illness or study treatment-related toxicity, including DLTs, that would, in the judgment of the investigator, affect assessments of clinical status to a significant degree or require discontinuation of study treatment) • Patient may withdraw from the study at any time for any reason; the investigator must make every effort to determine the reason for this decision and record it in source documentation of the patient • Death • Pregnancy • Concomitant treatment with a prohibited medication, including further lines of cancer therapy

<table>
<tr><td></td><td>

- Patient non-compliance
- Lost to follow-up
- Study terminated by the sponsor

</td></tr>
<tr><td>Part B
(SO-C101 dosing schedule 1, combined with pembrolizumab, dose escalation)</td><td>

Part B treatment will consist of SO-C101 given as per dosing schedule 1 in combination with pembrolizumab following the dose escalation scheme below.

The SO-C101 starting dose for cohort 1 of Part B, the combination with pembrolizumab, will be 1.5 µg/kg provided that dose level 5 (6.0 µg/kg) in Part A is tolerated and deemed safe. If the dose level of 6.0 µg/kg is not deemed safe, then Part B will start at the lower dose level deemed safe. If this starting dose is not tolerated, then SO-C101 dose level -1 of Part B (0.75 µg/kg) will be tested.

<table>
<tr><th>Dose level</th><th>SO-C101 dose given once a day (µg/kg/administration)</th><th>Dose increase</th><th>Pembrolizumab</th></tr>
<tr><td>-1</td><td>0.75 µg/kg</td><td>(-50%)</td><td>200 mg</td></tr>
<tr><td>1</td><td>1.5 µg/kg</td><td>Starting dose</td><td>200 mg</td></tr>
<tr><td>2</td><td>3.0 µg/kg</td><td>100%</td><td>200 mg</td></tr>
<tr><td>3</td><td>6.0 µg/kg</td><td>100%</td><td>200 mg</td></tr>
<tr><td>4</td><td>9.0 µg/kg</td><td>50%</td><td>200 mg</td></tr>
<tr><td>5</td><td>12.0 µg/kg</td><td>33%</td><td>200 mg</td></tr>
</table>

Patients will be treated with escalating doses of SO-C101 given once a day on day 1 (±1 day; Wednesday), day 2 (Thursday), day 8 (Wednesday), and day 9 (Thursday) together with a fixed dose of pembrolizumab (200 mg IV every 3 weeks) given on the day 1 administration of SO-C101. Pembrolizumab will be administered within 30 minutes after the first dose of SO-C101 and as outlined in the package insert. The start of the treatment (day 1) is planned to be on a Wednesday to allow biomarker sampling (fresh PBMCs transfer to the central laboratory) on weekdays. However, as long as the two doses of SO-C101 per week are given on consecutive days (day 1 and day 2) and the second week SO-C101 dosing (day 8 and day 9) takes place 7 days after day 1, there will be ±1 day flexibility.

This schedule should be strictly adhered to with no dose delays/reductions to be allowed for especially in cycle 1 for maximum exposure for safety evaluation for DLTs. If any visits are missed for obtaining PK/PD/safety laboratory parameters during cycle 1, patients will be reviewed individually by the sponsor's medical monitor and investigators for their evaluability for DLT assessment.

SO-C101 combination dose escalation for dosing schedule 1 will continue until the MTD and/or RP2D is reached as per the dose

</td></tr>
</table>

	escalation schema. If the MTD is not reached at the end of the planned dose escalation cohorts, the recruitment will stop to assess RP2D. Additional doses and schedules could be opened as required based on the RP2D assessment results to define the optimal dose and schedule for further clinical studies. In case SO-C101 needs to be stopped for reasons other than disease progression, pembrolizumab treatment can continue for up to 1 year as assessed by the DEC if the patient does not progress and can tolerate the treatment. In case pembrolizumab needs to be stopped, SO-C101 treatment can continue until disease progression or unacceptable toxicity. SC injection sites will be rotated to different areas of the body (upper and lower extremities, each of the 4 quadrants of the abdomen) to minimize the summated local effects of SO-C101 administration. Once Part B is open for recruitment and the first combination cohort is deemed safe, patients who had objective disease progression in Part A and Part A1 will be allowed to crossover to Part B given that there are no safety concerns. Patients recruited in Part B will continue SO-C101 given as per dosing schedule 1 and pembrolizumab treatment at the assigned dose level of SO-C101. Intra-patient dose escalation beyond the dose initially assigned to a patient is not permitted during cycle 2. However, patients receiving treatment with SO-C101 given as per dosing schedule 1 beyond cycle 2 may continue treatment at the next higher dose level if it is assessed to be safe by the DEC and IAP and if the following criteria are met: • No safety concerns as deemed by the investigator • No DLT at the initial dose level assigned • No unacceptable AEs, defined as drug-related clinically meaningful, uncontrolled grade 3 or any grade 4 toxicities at the current dose level • No dose reduction at the current dose level • Completed at least two cycles at the assigned dose • The investigator should also be of the opinion that these patients will derive benefit from treatment at the higher dose level of SO-C101 If these requirements are met, the patient can be dose escalated to the next dose level after discussion with the sponsor's medical monitor. These patients after intra-patient dose increase will NOT be part of the higher dose escalation cohorts; therefore, after intra-patient dose increase, they will not be part of the DLT evaluation. Intra-patient escalation up to the RP2D level is allowed and can be done step-by step if the patient stays at the higher dose level and meets the criteria for escalation as specified above.

	Patients will be discontinued from study treatment for any of the following events: • Radiographic disease progression (iCPD) • Clinical disease progression (investigator assessment) • AE (intercurrent illness or study treatment-related toxicity, including DLTs, that would, in the judgment of the investigator, affect assessments of clinical status to a significant degree or require discontinuation of study treatment) • Patient may withdraw from the study at any time for any reason; the investigator must make every effort to determine the reason for this decision and record it in source documentation of the patient • Death • Pregnancy • Concomitant treatment with a prohibited medication, including further lines of cancer therapy • Patient non-compliance • Lost to follow-up • Study terminated by the sponsor
Part B1 (SO-C101 dosing schedule 2, combined with pembrolizumab, dose escalation)	Part B1 treatment will consist of SO-C101 given as per dosing schedule 2 in combination with pembrolizumab. The starting daily dose will be 1 level below the RP2D identified in Part B. The dose will be split into two identical (50%:50%) daily doses with the second dose on each treatment day being administered 8 hours (±15 min) after the first dose. If this starting dose is not tolerated, then a lower dose could be considered. Further dose levels will be considered based on safety data and decisions taken during DEMs. Patients will be treated with escalating doses of SO-C101 given twice a day 8 hours (±15 min) apart on day 1 (±1 day; Wednesday), day 2 (Thursday), day 8 (Wednesday), and day 9 (Thursday) together with a fixed dose of pembrolizumab (200 mg IV every 3 weeks) given with the first administration of SO-C101 on day 1. Pembrolizumab will be administered within 30 minutes after the first dose of SO-C101 and as outlined in the package insert. The start of the treatment (day 1) is planned to be on a Wednesday to allow biomarker sampling (fresh PBMCs transfer to the central laboratory) on weekdays. However, as long as the four doses of SO-C101 per week are given on consecutive days (day 1 and day 2) and the second week SO-C101 dosing (day 8 and day 9) takes place 7 days after day 1, there will be ±1 day flexibility. This schedule should be strictly adhered to with no dose delays/reductions to be allowed for especially in cycle 1 for maximum exposure for safety evaluation for DLTs. If any visits are missed for obtaining PK/PD/safety laboratory parameters during cycle 1, patients will be reviewed individually by the sponsor's

	medical monitor and investigators for their evaluability for DLT assessment. SO-C101 combination dose escalation for dosing schedule 2 will continue until the MTD and/or RP2D is reached. If the MTD is not reached, the recruitment will stop to assess RP2D. Additional doses and schedules could be opened as required based on the RP2D assessment results to define the optimal dose and schedule for further clinical studies. In case SO-C101 needs to be stopped for reasons other than disease progression, pembrolizumab treatment can continue for up to 1 year as assessed by the DEC if the patient does not progress and can tolerate the treatment. In case pembrolizumab needs to be stopped, SO-C101 treatment can continue until disease progression or unacceptable toxicity. SC injection sites will be rotated to different areas of the body (upper and lower extremities, each of the 4 quadrants of the abdomen) to minimize the summated local effects of SO-C101 administration. Once Part B1 is open for recruitment and the first combination cohort is deemed safe, patients who had objective disease progression in Part A and Part A1 will be allowed to crossover to Part B1 given that there are no safety concerns. Patients recruited in Part B1 will continue SO-C101 given as per dosing schedule 2 and pembrolizumab treatment at the assigned dose level of SO-C101. Intra-patient dose escalation beyond the dose initially assigned to a patient is not permitted during cycle 2. However, patients receiving treatment with SO-C101 given as per dosing schedule 2 beyond cycle 2 may continue treatment at the next higher dose level if it is assessed to be safe by the DEC and IAP and if the following criteria are met: • No safety concerns as deemed by the investigator • No DLT at the initial dose level assigned • No unacceptable AEs, defined as drug-related clinically meaningful, uncontrolled grade 3 or any grade 4 toxicities at the current dose level • No dose reduction at the current dose level • Completed at least two cycles at the assigned dose • The investigator should also be of the opinion that these patients will derive benefit from treatment at the higher dose level of SO-C101 If these requirements are met, the patient can be dose escalated to the next dose level after discussion with the sponsor's medical monitor. These patients after intra-patient dose increase will NOT be part of the higher dose escalation cohorts; therefore, after intra-patient dose increase, they will not be part of the DLT evaluation.

	Intra-patient escalation up to the RP2D level is allowed and can be done step-by step if the patient stays at the higher dose level and meets the criteria for escalation as specified above. Patients will be discontinued from study treatment for any of the following events: • Radiographic disease progression (iCPD) • Clinical disease progression (investigator assessment) • AE (intercurrent illness or study treatment-related toxicity, including DLTs, that would, in the judgment of the investigator, affect assessments of clinical status to a significant degree or require discontinuation of study treatment) • Patient may withdraw from the study at any time for any reason; the investigator must make every effort to determine the reason for this decision and record it in source documentation of the patient • Death • Pregnancy • Concomitant treatment with a prohibited medication, including further lines of cancer therapy • Patient non-compliance • Lost to follow-up • Study terminated by the sponsor
Part D (SO-C101 dosing schedule 1, monotherapy, dose expansion at the RP2D identified in Part A)	Part D treatment will consist of SO-C101 monotherapy given as per dosing schedule 1 at the RP2D identified in Part A. Patients will be treated with SO-C101 given once a day on day 1 (±1 day; Wednesday), day 2 (Thursday), day 8 (Wednesday), and day 9 (Thursday). The start of the treatment (day 1) is planned to be on a Wednesday to allow biomarker sampling (fresh PBMCs transfer to the central laboratory) on weekdays. However, as long as the two doses of SO-C101 per week are given on consecutive days (day 1 and day 2) and the second week SO-C101 dosing (day 8 and day 9) takes place 7 days after day 1, there will be ±1 day flexibility for the day 1 dosing to take place on a Tuesday or on a Thursday. SC injection sites will be rotated to different areas of the body (upper and lower extremities, each of the 4 quadrants of the abdomen) to minimize the summated local effects of SO-C101 administration. Patients will be discontinued from study treatment for any of the following events: • Radiographic disease progression (iCPD) • Clinical disease progression (investigator assessment) • AE (intercurrent illness or study treatment-related toxicity that would, in the judgment of the investigator, affect assessments of

	clinical status to a significant degree or require discontinuation of study treatment) • Patient may withdraw from the study at any time for any reason; the investigator must make every effort to determine the reason for this decision and record it in source documentation of the patient • Death • Pregnancy • Concomitant treatment with a prohibited medication, including further lines of cancer therapy • Patient non-compliance • Lost to follow-up • Study terminated by the sponsor
Part D1 (SO-C101 dosing schedule 2, monotherapy, dose expansion at the RP2D identified in Part A1)	Part D1 treatment will consist of SO-C101 monotherapy given as per dosing schedule 2 at the RP2D identified in Part A1. Patients will be treated with SO-C101 given twice a day 8 hours (±15 min) apart on day 1 (±1 day; Wednesday), day 2 (Thursday), day 8 (Wednesday), and day 9 (Thursday). The start of the treatment (day 1) is planned to be on a Wednesday to allow biomarker sampling (fresh PBMCs transfer to the central laboratory) on weekdays. However, as long as the four doses of SO-C101 per week are given on consecutive days (day 1 and day 2) and the second week SO-C101 dosing (day 8 and day 9) takes place 7 days after day 1, there will be ±1 day flexibility for the day 1 dosing to take place on a Tuesday or on a Thursday. SC injection sites will be rotated to different areas of the body (upper and lower extremities, each of the 4 quadrants of the abdomen) to minimize the summated local effects of SO-C101 administration. Patients will be discontinued from study treatment for any of the following events: • Radiographic disease progression (iCPD) • Clinical disease progression (investigator assessment) • AE (intercurrent illness or study treatment-related toxicity that would, in the judgment of the investigator, affect assessments of clinical status to a significant degree or require discontinuation of study treatment) • Patient may withdraw from the study at any time for any reason; the investigator must make every effort to determine the reason for this decision and record it in source documentation of the patient • Death • Pregnancy

	• Concomitant treatment with a prohibited medication, including further lines of cancer therapy • Patient non-compliance • Lost to follow-up • Study terminated by the sponsor

DLT definition	DLTs will be AEs as specified below and graded according to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events version 5.0. Attribution to SO-C101 will not be used and the AEs listed below will be considered DLTs unless clearly not related to SO-C101 (i.e., events clearly due to the cancer disease, other comorbid illness, or unequivocally related to concomitant medications). The DLT evaluation period is the first treatment cycle of 21 days. Every DLT in the study will be discussed with the study investigators and every effort will be made to ensure all clinical assessments are carried out and documented appropriately and, wherever possible, histological assessments are also performed to identify and understand the safety profile of SO-C101 as monotherapy and in combination with pembrolizumab.
	AEs that are considered DLTs
	• All grade 5 events not clearly related to disease progression or any other causes will be considered DLTs.
	• Any grade 3 or higher **non-hematologic toxicity** regardless of duration will be considered a DLT: with the **exceptions** below that are **NOT** considered DLTs:
	  ○ Grade 3 nausea, vomiting, or diarrhea that can be controlled within 72 hours
	  ○ Grade 3 fatigue less than 5 days
	  ○ Grade 3 or higher correctable electrolyte abnormalities that last less than 72 hours and not associated with clinical complications
	  ○ Grade 3 or higher amylase or lipase not associated with clinical manifestations of pancreatitis
	• Hy's law cases will be considered DLTs.
	• Grade 3 aspartate transaminase (AST) or alanine transaminase (ALT) or grade 3 bilirubinemia that lasts more than 5 days
	• **Hematologic DLTs** will include the following:
	  ○ Grade 4 neutropenia or thrombocytopenia lasting more than 7 days
	  ○ Febrile neutropenia
	  ○ Grade 3 or higher thrombocytopenia with bleeding
	• Any grade 4 immune-related AEs regardless of duration

	• Any grade 3 or grade 4 non-infectious pneumonitis regardless of duration • Any grade 3 immune-related AEs, excluding colitis, hepatitis, and pneumonitis, that do not downgrade to grade ≤2 within 3 days after onset of the event despite maximal supportive care including systemic corticosteroids or downgrade to grade 1 or baseline within 14 days • Any grade 2 pneumonitis that does not resolve to grade 1 within 3 days of the initiation of maximal supportive care • Recurrent grade 2 pneumonitis in Part B and Part B1 • Grade 3 colitis **AEs that <u>are NOT</u> considered DLTs** • Grade 3 endocrinopathy that is managed with or without systemic corticosteroid therapy and/or hormone replacement therapy • Inflammatory reaction attributed to a local antitumor response (grade 3 tumor pain caused by acute inflammatory reaction at tumor-bearing sites, e.g., like sites of metastatic disease or lymph nodes) that resolves to grade 1 within 3 weeks • Concurrent vitiligo or alopecia of any AE grade Other clinically significant toxicities, including a single event or multiple occurrences of the same event, may be considered as DLTs. AEs occurring after treatment cycle 1 may be considered DLT-like events upon DEC discussion. If required, a DEM will be set up to assess these events.
Observation of patients after administration of SO-C101; Part A, Part B, and Part D	**Cycle 1** ***Dose on day 1*** In cycle 1 of Part A, Part B, and Part D, patients will be hospitalized for 24 hours after the first dose of SO-C101 on day 1 and will be closely observed for any AEs in the hospital. Vital signs (body temperature, heart rate, respiratory rate, and systolic and diastolic blood pressure) will be documented at the following frequency at minimum unless clinically required otherwise: • Prior to each SO-C101 dose • 15 minutes (±5 minutes) after dosing • 30 minutes (±5 minutes) after dosing • 60 minutes (±10 minutes) after dosing, and then • Every 60 minutes (±15 minutes) after dosing up until 8 hours following SO-C101 administration

	Subsequent doses During observation after subsequent doses of SO-C101, vital signs (body temperature, heart rate, respiratory rate, and systolic and diastolic blood pressure) will be documented at the following frequency at minimum until discharge from the clinic: • Prior to each SO-C101 dose • 15 minutes (±5 minutes) after dosing • 30 minutes (±5 minutes) after dosing • 60 minutes (±10 minutes) after dosing, and then • Every 60 minutes (±15 minutes) after dosing up until 4-6 hours following SO-C101 administration **From cycle 2 onwards** For the subsequent cycles of Part A, Part B, and Part D, patients will be observed in the hospital up to 4-6 hours following SO-C101 administration. During post-SO-C101 observation, vital signs (body temperature, heart rate, respiratory rate, and systolic and diastolic blood pressure) will be documented at the following frequency until discharge from the clinic: • Prior to each SO-C101 dose • 15 minutes (±5 minutes) after dosing • 30 minutes (±5 minutes) after dosing • 60 minutes (±10 minutes) after dosing, and then • Every 60 minutes (±15 minutes) after dosing up until 4-6 hours following SO-C101 administration If patients feel unwell at any point in time during the study after being discharged from the hospital, they should contact their study investigator as indicated in the Informed Consent Form (ICF).
Observation of patients after administration of SO-C101; Part A1, Part B1, and Part D1	**Cycle 1 day 1 and cycle 1 day 2** In Part A1, Part B1, and Part D1, patients will be hospitalized from day 1 to day 3 of cycle 1 and will be closely observed for any AEs in the hospital. Vital signs (body temperature, heart rate, respiratory rate, and systolic and diastolic blood pressure) will be documented at the following frequency at minimum unless clinically required otherwise: • Prior to the first dose of SO-C101 • 15 minutes (±5 minutes) after dosing • 30 minutes (±5 minutes) after dosing

	• 60 minutes (±10 minutes) after dosing, and then • Every 60 minutes (±15 minutes) after dosing up until 8 hours following SO-C101 first administration • Prior to the second dose of SO-C101 • 15 minutes (±5 minutes) after the second dosing • Every 60 minutes (±15 minutes) after dosing up until 6 hours following the second SO-C101 administration (e.g., 14 hours after the first dose) **Subsequent dosing days** During observation after subsequent doses of SO-C101, vital signs (body temperature, heart rate, respiratory rate, and systolic and diastolic blood pressure) will be documented at the following frequency at minimum until discharge from the clinic: • Prior to the first dose of SO-C101 • 15 minutes (±5 minutes) after dosing • 30 minutes (±5 minutes) after dosing • 60 minutes (±10 minutes) after dosing, and then • Every 60 minutes (±15 minutes) after dosing up until 4-6 hours following the first SO-C101 administration • Prior to the second dose of SO-C101 at 8 hours after the first dose • 15 minutes (±5 minutes) after the second dosing • Every 60 minutes (±15 minutes) after dosing up until 4 hours following the second SO-C101 administration (e.g., 12 hours after the first dose) If patients feel unwell at any point in time during the study after being discharged from the hospital, they should contact their study investigator as indicated in the ICF.
Dose escalation	**Enrollment into the dose cohorts in Part A, Part A1, Part B, and Part B1** The DLT evaluation period is the first treatment cycle (21 days). A patient evaluable for DLT will be a patient who has completed cycle 1 and received all planned treatments without any treatment delays or interruptions: for Part A, received all 4 doses of SO-C101 as planned; for Part A1, received all 8 doses of SO-C101 as planned; for Part B, received all 4 doses of SO-C101 and 1 dose of pembrolizumab as planned; for Part B1, received all 8 doses of SO-C101 and 1 dose of pembrolizumab as planned. Patients who do not fulfill these criteria for any other reason than DLT should be replaced.

	After completion of the DLT evaluation period with the adequate number of evaluable patients, all data as specified in the DEM Charter will be reviewed during a DEM by the DEC. The same data will also be reviewed by the IAP as described in the IAP Charter. The decision as to whether an AE should be considered as DLT and/or whether a dose level is to be considered intolerable will be made by the DEC with endorsement from the IAP. The DEC consists of the study investigators and the sponsor's medical monitor. The IAP consists of two independent clinical experts and an independent statistician. In the event of a confirmed non-tolerable dose in any cohort, the sponsor will inform all sites immediately so that the patients will not be exposed to doses of SO-C101 that have been determined to exceed the MTD. Patients who will not be DLT evaluable will be replaced. Replaced patients can continue with study treatment. The dose escalation plan will follow the traditional 3+3 design as described by Le Tourneau et al. Initially, three patients will be enrolled for each dose level and if none of the three patients in a cohort experiences a DLT, another three patients will be treated at the next higher dose level. However, if one of the first three patients experiences a DLT, three more patients will be treated at the same dose level. The dose escalation continues until at least two patients in a cohort of three to six patients experience DLTs (i.e., ≥33% of patients with a DLT at that dose level). If an MTD is reached, then the dose escalation will be stopped. The DEC will then decide whether any additional patients need to be enrolled in any dose level(s) not exceeding the MTD to gain confidence at the dose which will be considered as the RP2D. **Staggered (sentinel) dosing will be employed as described below:** For each dose level, the first patient for the cohort will receive the first cycle of SO-C101 on day 1, day 2, day 8, and day 9. This patient will be observed for safety for 7 days afterwards, starting from day 9. If there are no safety concerns at the end of these 7 days, the responsible investigator will notify the sponsor's medical monitor and the second and third patients will be allowed to be dosed. The second and third patients will not be dosed on the same day. If there is a concern at the end of these 7 days of observation for safety of the first patient, the study investigator will notify the sponsor's medical monitor as soon as possible and the sponsor will notify all sites and a DEM will be organized. The DEC will review, discuss, and decide on the next steps of the study.
MTD and RP2D definitions	If the MTD is reached, the RP2D is conventionally defined as the dose level just below this non-tolerated dose level. If ≤1 of 6 patients (or 0 of 3) in all dose cohorts experience a DLT, then the MTD will not have been reached. If the MTD is not reached, then the RP2D will be selected based on integrated evaluation of safety, tolerability,

	clinical benefit, and PK and PD data for all dose levels tested. An expansion cohort of up to 12 patients at the RP2D could be considered to obtain more experience if required. The DEC will evaluate the data and select the RP2D according to the following guidelines: 1. The RP2D will not exceed the MTD. 2. Toxicities other than DLTs will be considered, including: AEs assessed as related to SO-C101 treatment but not considered dose limiting, the nature and frequency of toxicities, and the emergence of any specific category of toxicities. 3. Evidence of clinical activity, as available 4. Available PK/PD data 5. If 2 or more potential RP2D dose levels cannot be distinguished using the criteria above, cohort expansion for optimized RP2D determination may take place at up to 2 dose levels to obtain data for up to 6 additional patients per dose level. The selection of RP2D will be based on this larger dataset. If serious related toxicities are observed in later cycles beyond cycle 1, a reduction of the MTD and/or RP2D may be considered. This determination will be made by the investigators and the sponsor's medical monitor, taking into account all available data.
Study periods	**PART A, PART A1, PART B, AND PART B1** **Screening period** Patients will be screened within a period of not more than 21 days, which will start when the ICF has been signed and end on day 1 of cycle 1. If screening is not completed within this period, next steps (continue/discontinue the patient in the study) will be discussed with the sponsor's medical monitor. **Treatment periods** *DLT evaluation period* The DLT evaluation period will be the first treatment cycle of 21 days. *Continued treatment period* Patients without DLT during the DLT evaluation period will continue treatment with SO-C101 monotherapy or SO-C101 together with pembrolizumab until any of the criteria for treatment discontinuation are met. Intra-patient dose escalation beyond the dose initially assigned to a patient is not permitted during cycle 2. However, patients receiving treatment with SO-C101 beyond cycle 2 may continue treatment at the next higher dose level if it is assessed to be safe by the DEC and IAP and if the criteria for intra-patient dose increase are met. These patients after intra-patient dose increase will NOT be part of the higher dose escalation cohorts; therefore, after intra-patient dose

	increase, they will not be part of the DLT evaluation. Intra-patient escalation up to the RP2D level is allowed and can be done step-by step if the patient stays at the higher dose level and meets the criteria for escalation. In Part B and Part B1, in case SO-C101 needs to be discontinued for reasons other than disease progression, pembrolizumab treatment will continue for up to 1 year until any of the criteria for treatment discontinuation are met. If pembrolizumab needs to be discontinued for reasons other than disease progression, SO-C101 treatment will continue until any of the criteria for treatment discontinuation are met. *EoT visit* After termination of study treatments (SO-C101 and/or pembrolizumab), patients will be evaluated at the EoT visit, which will be scheduled within 7 days (+7 days) after the final administration of SO-C101 and/or pembrolizumab (whichever occurs later). **Follow-up period** Every effort should be taken to monitor all AEs and concomitant medications for 90 days after the final dose of SO-C101 and/or pembrolizumab (whichever occurs later); all patients will come to the clinic 30 (±2) days, 60 (±2) days, and 90 (±2) days after the final dose of SO-C101 and/or pembrolizumab. Patients who discontinue SO-C101 therapy prior to iCPD or start of a new anticancer therapy will continue to have regular tumor assessments until: • iCPD, or • start of a new anticancer therapy, or • 6 months (±2 weeks) after the EoT visit, whichever occurs earliest, unless patients withdraw consent. Patients will be followed up for survival at 3 months (±2 weeks) and 6 months (±2 weeks) after the EoT visit (end of the patients' study participation). **PART D AND PART D1** **Screening period** Patients will be screened within a period of not more than 21 days, which will start when the ICF has been signed and end on day 1 of cycle 1. If screening is not completed within this period, next steps (continue/discontinue the patient in the study) will be discussed with the sponsor's medical monitor. **Treatment period** Patients will be treated with SO-C101 until any of the criteria for treatment discontinuation are met. After termination of SO-C101,

	patients will be evaluated at the EoT visit, which will be scheduled within 7 days (+7 days) after the final administration of SO-C101. **Follow-up period** Every effort should be taken to monitor all AEs and concomitant medications for 90 days after the final dose of SO-C101; all patients will come to the clinic 30 (±2) days, 60 (±2) days, and 90 (±2) days after the final dose of SO-C101. Patients who discontinue SO-C101 therapy prior to iCPD or start of a new anticancer therapy will continue to have regular tumor assessments until: • iCPD, or • start of a new anticancer therapy, or • 6 months (±2 weeks) after the EoT visit, whichever occurs earliest, unless patients withdraw consent. Patients will be followed up for survival at 3 months (±2 weeks) and 6 months (±2 weeks) after the EoT visit (end of the patients' study participation).
End of the study	Each study part will end when the last patient in this study part completes the last visit, including follow-up calls. The study will end when the last patient completes the last visit, including follow-up calls.
Early termination of the study	The sponsor reserves the right to discontinue the study for medical reasons or any other reason at any time. If the study is prematurely terminated or suspended, the sponsor will promptly inform the investigators/institutions, regulatory agencies, and Institutional Review Board (IRB) or Ethics Committee (EC) of the termination or suspension and the reason(s) for the termination or suspension. The investigator reserves the right to discontinue the study should his/her judgment so dictate. If the investigator terminates or suspends the study without prior agreement of the sponsor, the investigator should inform the institution where applicable, and the investigator/institution should promptly inform the sponsor and the IRB/EC and provide the sponsor and the IRB/EC with a detailed written explanation of the termination or suspension.
Stopping rules for all parts	If a patient experiences a **life-threatening** SAE considered by the investigator to be related to SO-C101 (i.e., excluding events unequivocally related to cancer) or if >30% of the treated patients discontinue because of toxicities considered by the investigator to be related to SO-C101, the dosing of all patients in the study will be temporarily stopped until the IAP (and DEC for dose escalation parts only) have reviewed the safety data and determined if it is safe to continue and at which dose.

Inclusion/ exclusion criteria	**INCLUSION CRITERIA** Inclusion criteria for all study parts are the same with the exception of the pre-specified tumor type (inclusion criterion 2), please see below. 1. Age ≥18 years 2. Part A, Part A1, Part B, and Part B1: Patients with selected histologically or cytologically confirmed advanced and/or metastatic solid tumors (renal cell carcinoma, non-small cell lung cancer, small-cell lung cancer, bladder cancer, melanoma, Merkel-cell carcinoma, skin squamous-cell carcinoma, microsatellite instability high solid tumors, triple-negative breast cancer, mesothelioma, thyroid cancer, thymic cancer, cervical cancer, biliary tract cancer, hepatocellular carcinoma, ovarian cancer, gastric cancer, head and neck squamous-cell carcinoma, and anal cancer) who are refractory to or intolerant of existing therapies known to provide clinical benefit for their condition. Patients who were not previously treated with (naïve) or who have relapsed/refractory disease on immune checkpoint inhibitors are eligible. Part D and Part D1: Patients with histologically or cytologically confirmed advanced and/or metastatic renal cell carcinoma, patients with histologically or cytologically confirmed advanced and/or metastatic skin squamous-cell carcinoma, and patients with relapsed/refractory advanced/metastatic melanoma who are refractory to or intolerant of existing therapies known to provide clinical benefit for their condition. Patients who have relapsed/refractory disease on immune checkpoint inhibitors are eligible. 3. Performance status: Eastern Cooperative Oncology Group (ECOG) performance score 0-1. Patients with ECOG performance score 2 will be discussed with the sponsor's medical monitor to be agreed for inclusion. 4. Immunosuppressive doses of systemic medications (such as steroids) or absorbed topical or inhaled steroids (doses ≤10 mg/day of prednisone or equivalent) are allowed. Doses above 10 mg/day of prednisone or equivalent must be discontinued at least 2 weeks before investigational medicinal product administration. 5. Estimated life expectancy of ≥3 months 6. Washout periods: 4 weeks for chemotherapy, 4 weeks or 5 half-lives (whichever shorter) for biologic agents including immuno-oncology therapy and 4 weeks from major surgeries, definitive radiotherapy and 2 weeks after palliative radiotherapy 7. Have at least one measurable lesion per iRECIST in a non-irradiated port. If in a previously irradiated port, must have

	demonstrated progression since best response to radiation therapy. 8. Have fully recovered from previous treatment to grade ≤1 toxicity (excluding alopecia) or have stable grade 2 neuropathy 9. Adequate organ system function: 9.1. Left ventricular ejection fraction by echocardiogram >50% 9.2. Patients with thyroid disease are eligible if euthyroid on suppressive or replacement therapy and asymptomatic thyroid-stimulating hormone increase to be allowed 9.3. Creatinine clearance ≥30 mL/min using Cockcroft-Gault equation 9.4. Hemoglobin at least 10 g/dL 9.5. Prothrombin time and activated partial thromboplastin time ≤1.5× upper limit of normal (ULN) 10. ALT/AST ≤2.5×ULN and total bilirubin ≤2×ULN in patients without liver metastasis (benign hereditary hyperbilirubinemias, e.g., Gilbert's syndrome, are permitted, those patients must have total bilirubin <3 mg/dL). In patients with liver metastasis, ALT/AST ≤5×ULN is allowed but total bilirubin must be ≤2×ULN. 11. Negative serum pregnancy test if woman of child-bearing potential (WOCBP; non-childbearing is defined as greater than one year postmenopausal or surgically sterilized). WOCBP must adhere to using a medically accepted method of birth control and agree to continue its use during the study or be surgically sterilized (e.g., hysterectomy or tubal ligation) and males must agree to use barrier method of birth control while on study. WOCBP must agree to use highly effective contraception during treatment and for at least 30 days after SO-C101 discontinuation (Part A, Part A1, Part D, and Part D1) or 4 months after pembrolizumab discontinuation (Part B and Part B1) unless the last dose of SO-C101 is later than 4 months after the last pembrolizumab administration in Part B and Part B1. In such a case, the highly effective contraception must be used for at least 30 days after SO-C101 discontinuation. Highly effective contraception includes: • Placement of an intrauterine device or intrauterine hormone-releasing system • Established hormonal contraceptive methods: oral, intravaginal, transdermal, injectable, or implant. Females who are using hormonal contraceptives must have been on a stable dose of the same hormonal contraceptive product for at least 4 weeks prior to dosing and must continue to use the same contraceptive during the study and for 30 days after SO-C101 discontinuation (Part A, Part A1, Part D, and Part D1) or 4 months after last pembrolizumab discontinuation (Part B and Part B1) unless the last dose of SO-C101 is later than 4

	months after the last pembrolizumab administration in Part B and Part B1. In such a case, female patients must have been on a stable dose of the same hormonal contraceptive for at least 30 days after SO-C101 discontinuation. • Bilateral tubal occlusion Female patients exempt from this requirement are patients who practice total abstinence or have a sole male partner who is vasectomized with confirmed azoospermia. If currently abstinent, the patient must agree to use a double barrier method (condom plus diaphragm or cervical/vault cap with spermicide) if they become sexually active during the study, and for 30 days after SO-C101 discontinuation (Part A, Part A1, Part D, and Part D1) or 4 months after pembrolizumab discontinuation (Part B and Part B1) unless the last dose of SO-C101 is later than 4 months after the last pembrolizumab administration in Part B and Part B1. In such a case, the patient must agree to use a double barrier method during treatment and for at least 30 days after SO-C101 discontinuation. Male patients must agree to use a condom during treatment and for 30 days after SO-C101 discontinuation (Part A, Part A1, Part D, and Part D1) or 4 months after pembrolizumab discontinuation (Part B and Part B1) unless the last dose of SO-C101 is later than 4 months after the last pembrolizumab administration in Part B and Part B1. In such a case, the patient must agree to use a condom during treatment and for at least 30 days after SO-C101 discontinuation. 12. Accessible tumor tissue available for fresh biopsy 13. Ability to understand and sign written informed consent to participate in the study **EXCLUSION CRITERIA** **Exclusion criteria for all study parts** 1. Patient with untreated central nervous system metastases and/or leptomeningeal carcinomatosis; participants with previously treated stable (no progression on magnetic resonance imaging done 4 or more weeks apart) brain metastases are **eligible** 2. Has a known additional malignancy that is progressing and/or requires active treatment 3. Prior exposure to drugs that are agonists of IL-2- or IL-15-like **but not limited** to recombinant human IL-15 (NCI), ALT-803 (ALTOR), NKTR-214 (Nektar) 4. Patients with a history of and current interstitial lung disease or fibrosis and pneumonitis; patients with clinically significant or oxygen requiring chronic obstructive pulmonary disease or any chronic inflammatory disease (sarcoidosis etc.) 5. Has received a live vaccine within 30 days of planned start of study therapy. Note: Seasonal influenza vaccines for injection

	are generally inactivated flu vaccines and are allowed; however, intranasal influenza vaccines (e.g., Flu-Mist) are live attenuated vaccines, and are not allowed. 6. Absolute white blood cell count $\leq 2.0\times10^9$/L 7. Absolute neutrophil count $\leq 1.0\times10^9$/L 8. Platelet count $\leq 100\times10^9$/L 9. Pregnant or breastfeeding women 10. Receiving any other investigational treatment 11. Any active autoimmune disease or a documented history of autoimmune disease, poorly controlled asthma, or history of syndrome that required systemic steroids (except the allowed doses) or immunosuppressive medications, except for patients with vitiligo or resolved childhood asthma/atopy. Patients with clinically controlled asthma who routinely require fixed doses intermittent use of bronchodilators and/or micro-doses of steroids are **allowed**. 12. Co-morbidities: 12.1. History of hematopoietic malignancy including chronic lymphocytic leukemia (excluding childhood leukemia) 12.2. History of coronary heart disease 12.3. Evidence of clinically active infection requiring systemic (any route) antibiotic therapy. All prior infections must have resolved following optimal therapy. 12.4. History of or serology positive for HIV or active hepatitis B or C. Cured hepatitis B and hepatitis C infections are eligible. 12.5. Uncontrolled hypertension (systolic >160 mm Hg and/or diastolic >110 mm Hg) or clinically significant (i.e., active) cardiovascular disease, cerebrovascular accident/stroke, or myocardial infarction within 6 months prior to first study medication; unstable angina; congestive heart failure of New York Heart Association grade 2 or higher; or uncontrolled cardiac arrhythmia requiring medication. Patients with uncontrolled hypertension should be medically managed on a stable regimen to control hypertension prior to study entry. 12.6. Clinically significant peripheral artery disease 12.7. Prolongation of QTcF >450 msec 12.8. History of medical or psychiatric disease which, in the view of the investigator, would preclude safe treatment or acceptable study compliance 13. Any ongoing toxicity from prior anti-cancer treatment that, in the judgment of the investigator, may interfere with study treatment

	14. Other illness that, in the opinion of the investigator, would exclude the patient from participating in this study, including uncontrolled diabetes mellitus, cardiac disease **Exclusion criteria for Part B and Part B1 only** • Is hypersensitive to any of the ingredients of pembrolizumab drug product (Keytruda™) • History of solid organ transplantation or hematopoietic stem cell transplantation
Dose escalation meetings	A DEM will only take place once there are 3 or 6 DLT-evaluable patients to complete the cohort. A DEM will take place after the last patient of the cohort has completed the first cycle (21 days) with or without DLTs and is evaluable for DLT assessment. After completion of the DLT period, all available safety data will be reviewed by the IAP as well as the DEC. The decision as to whether AEs should be considered as DLTs and/or whether a dose level is to be considered intolerable will be made by the DEC endorsed by IAP. The IAP will consist of two independent clinical experts and an independent statistician. The working principles of the IAP will be defined in the IAP Charter. In the event of a confirmed non-tolerable dose in any cohort, the sponsor will inform all sites immediately so that patients will not be exposed to doses of SO-C101 that have been determined to exceed the MTD. At every DEM, all accumulating safety data from previous cohorts will also be reviewed and any safety issues arising during this longer follow-up period will be taken into consideration by the DEM panel as well as the IAP.
Statistical methods and data analysis	Each study part will be analyzed separately following its objectives. Further statistical analyses pooling data of more study parts can be included in the Statistical Analysis Plan (SAP). **Safety population** All patients exposed to SO-C101 in Part A, Part A1, Part D, and Part D1. All patients exposed to SO-C101 or pembrolizumab in Part B and Part B1. **PK/PD population** All PK/PD-evaluable patients. **Efficacy population** All patients exposed to SO-C101 (exposure for at least one treatment cycle) who had at least one evaluable tumor assessment per iRECIST after the initiation of SO-C101 treatment.

	Statistical part of study design and sample size estimation **Part A** The traditional 3+3 design dose escalation will be applied until the MTD is identified. Therefore, 3 to 6 DLT-evaluable patients per dose level will be included in a cohort. The estimated number of patients is 27-54. **Part A1** The traditional 3+3 design dose escalation will be applied until the MTD is identified. Therefore, 3 to 6 DLT-evaluable patients per dose level will be included in a cohort. The estimated number of patients is 6-15. **Part B** The traditional 3+3 design dose escalation will be applied until the MTD is identified. Therefore, 3 to 6 DLT-evaluable patients per dose level will be included in a cohort. The estimated number of patients is 21-42. **Part B1** The traditional 3+3 design dose escalation will be applied until the MTD is identified. Therefore, 3 to 6 DLT-evaluable patients per dose level will be included in a cohort. The estimated number of patients is 6-15. **Part D and Part D1** The number of patients in Part D together with or without Part D1 to be treated for at least one cycle is set to a maximum of 20 per indication (60 in total). This number of patients is deemed to be appropriate to provide further safety, PK, PD, and efficacy data per indication at the RP2D dose level identified in Part A (SO-C101, dosing schedule 1, monotherapy) and the RP2D dose level identified in Part A1 (SO-C101, dosing schedule 2, monotherapy). In case biomarker data in Part A1 suggest a more competitive efficacy as compared to once daily dosing, a switch to twice daily dosing (Part D1) will be made during the course of the study without affecting the overall number of patients enrolled. **Analyses** Analyses will be descriptive. Further details will be specified in the SAP.
Planned duration	It is expected that the enrollment duration will be 31-48 months (14-22 months Part A, 3-9 months Part A1, 11-18 months Part B, 3-9 months Part B1, 6-12 months Part D, and 12-18 months Part D1) and for each patient the estimated average treatment duration will be 12-24 weeks in Part A, Part A1, Part D, and Part D1; and 24-36 weeks in Part B and Part B1. Patients who will respond to therapy will continue with treatment until any of the criteria for treatment discontinuation are met.

3 TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

LIST OF IN-TEXT FIGURES

4 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Term
ADA	Anti-drug antibody
AE	Adverse event
ALC	Absolute lymphocyte count
ALT	Alanine transaminase
ALT-803	IL-15/IL-15Rα complex fused to an IgG1 Fc
aPTT	Activated partial thromboplastin time
AST	Aspartate transaminase
AUC	Area under the curve
BCL-2	B-cell lymphoma 2
CA	Competent authority
CBR	Clinical benefit rate
CD	Cluster of differentiation
CFR	Code of Federal Regulations
CLS	Capillary leak syndrome
C_{max}	Maximum (or peak) serum concentration
CRA	Clinical research associate
CRO	Contract Research Organization
CRP	C-reactive protein
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DEC	Dose Escalation Committee
DEM	Dose Escalation Meeting
DL	Dose level
DLT	Dose-limiting toxicity
DOR	Duration of response
EC	Ethics Committee
EC50	Half maximal effective concentration
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EEA	European Economic Area
EGFR	Epidermal growth factor receptor
EoT	End of treatment
Fc	Fragment crystallizable
FDA	US Food and Drug Administration
FIH	First-in-human
Foxp3	Forkhead box P3
GCP	Good Clinical Practice
HbA1c	Glycated hemoglobin

Abbreviation	Term
HDIL-2	High-dose IL-2
hs-cTnT test	High-sensitivity cardiac troponin T test
IAP	Independent Advisory Panel
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation
iCPD	Confirmed progressive disease per iRECIST
IFN	Interferon
Ig	Immunoglobulin
IL	Interleukin
IL-2R	IL-2 receptor
IL-15R	IL-15 receptor
IMP	Investigational medicinal product
IND	Investigational new drug
INV	Investigator
IRB	Institutional Review Board
iRECIST	Response Evaluation Criteria In Solid Tumors for immune-based therapeutics
iUPD	Unconfirmed progressive disease per iRECIST
IV	Intravenous(ly)
JAK	Janus kinase
KRAS	Kirsten Ras oncogene
MABEL	Minimal anticipated biological effect level
MAD	Maximum administered dose
MAPK	Mitogen-activated protein kinase
MedDRA	Medical Dictionary for Regulatory Activities
MM	Malignant melanoma
mRCC	Metastatic renal cell carcinoma
MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose
NCI	National Cancer Institute
NK cell	Natural killer cell
NKG2D	Natural killer group 2 member D receptor
NKp30	Natural cytotoxicity receptor
NKT cell	Natural killer T cell
NKTR-214	IL-2 conjugated with multiple releasable chains of polyethylene glycol
NOAEL	No-observed-adverse-effect level
ORR	Objective response rate
OS	Overall survival
PAD	Pharmacologic active dose

Abbreviation	Term
PBMC	Peripheral blood mononuclear cell
PD	Pharmacodynamic(s)
PD-1	Programmed cell death protein 1
PD-L1	Programmed cell death ligand 1
PFS	Progression-free survival
PI3K	Phosphatidylinositol-4,5-bisphosphate 3-kinase
PK	Pharmacokinetic(s)
PT	Prothrombin time
Q1	25th percentile
Q3	75th percentile
rhIL-15	Recombinant human IL-15
RLI-15	Synonymous to SO-C101; fusion protein receptor-linker-IL-15
RO	Receptor occupancy
RP2D	Recommended phase 2 dose
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SC	Subcutaneous(ly)
SmPC	Summary of Product Characteristics
SOC	System organ class
SO-C101	Fusion protein receptor-linker-IL-15
SOP	Standard Operating Procedure
STAT	Signal transducer and activator of transcription
T3	Triiodothyronine
T4	Thyroxine
TC	Teleconference
T_{max}	Time to reach maximum concentration
Treg	Regulatory T cell
TSH	Thyroid-stimulating hormone
ULN	Upper limit of normal
WBC	White blood cell
WOCBP	Woman of child-bearing potential

**Abbreviations of commonly used weight, height, and volume measures are not listed above.*

5 ETHICS

5.1 Institutional Review Board/ Ethics Committee

The Protocol, Informed Consent Form (ICF), and appropriate related documents must be reviewed and approved by an Institutional Review Board (IRB) or Ethics Committee (EC) constituted and functioning in accordance with International Council for Harmonisation (ICH) Guideline E6 Good Clinical Practice (GCP)[1] and any local regulations, and by the competent authority (CA). Any Protocol amendment or revision to the ICF will be resubmitted to the IRB/EC and to the CA for review and approval, except for changes involving only logistical or administrative aspects of the study (e.g., change of clinical research associates [CRAs], change of telephone numbers). Documentation of IRB/EC compliance with ICH E6 and any local regulations regarding constitution and review conduct will be provided to the sponsor.

A signed letter of study approval from the IRB/EC chairman must be sent to the principal investigator or, if regionally required, the head of the medical institution with a copy to the sponsor before study start and the release of investigational medicinal products (IMPs) to the site by the sponsor or its designee. If the IRB/EC decides to suspend or terminate the study, the investigator (or if regionally required, the head of the medical institution) will immediately send the notice of study suspension or termination by the IRB/EC to the sponsor.

Study progress is to be reported to IRB/ECs and to CAs annually (or as required) by the investigator or sponsor, depending on local regulatory obligations. If the investigator is required to report to the IRB/EC, he/she will forward a copy to the sponsor at the time of each periodic report.

The investigator(s) or the sponsor will submit, depending on local regulations, periodic reports and inform the IRB/EC (or if regionally required, the investigator and the relevant IRB/EC via the head of the medical institution) and the CA of any reportable adverse events (AEs) per ICH guidelines and local IRB/EC standards of practice. Upon completion of the study, the investigator or sponsor will provide the IRB/ECs and the CAs with a brief report of the outcome of the study, if required.

At the end of the study, the sponsor should notify the IRB/EC and CA as regionally required.

5.2 Ethical conduct of the study

This study will be conducted in accordance with Standard Operating Procedures (SOPs) of the sponsor (or designee), which are designed to ensure adherence to applicable regulatory requirements, and in accordance with the current version of the Declaration of Helsinki (adopted by the 18th World Medical Association General Assembly, Helsinki, Finland, June 1964 and amended by the 64th World Medical Association General Assembly, Fortaleza, Brazil, October 2013) and ICH guidelines on GCP (E6[R2] Step 4 version dated 09-Nov-2016).

5.3 Patient information and informed consent

As part of administering the informed consent document, the investigator must explain to each patient the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits involved, any potential discomfort, potential alternative procedure(s) or course(s) of treatment available to the patient, and the extent of maintaining confidentiality of the patient's records. Each patient must be informed that

participation in the study is voluntary, that he/she may withdraw from the study at any time, and that withdrawal of consent will not affect his/her subsequent medical treatment or relationship with the investigator.

This informed consent should be given by means of a standard written statement, written in nontechnical language. The patient should understand the statement before signing and dating it and will be given a copy of the signed document.

After the ICF and any other written information to be provided to patients is read and explained to the patient, the patient will be asked to sign and date the ICF before any study-specific procedures are performed. No patient can enter the study before his/her informed consent has been obtained.

The patient should be informed in a timely manner if new information becomes available that may be relevant to the patient's willingness to continue participation in the study. The communication of this information should be documented.

6 INVESTIGATORS AND SPONSOR

This study will be conducted by qualified investigators under the sponsorship of SOTIO Biotech AG (the sponsor). Some study activities can be delegated by the sponsor to vendors as appropriate.

The coordinating investigator for this study is:

Prof. Aurélien Marabelle, M.D., Ph.D.

Clinical Director

Cancer Immunotherapy Program

Institute Gustave Roussy

Villejuif, France

7 INTRODUCTION

7.1 Background and rationale

Over the past decade, the power of the immune system to kill malignant tumors using cancer immunotherapy has emerged as a promising approach to treat a broad range of human cancers. The involvement of the immune system in the tumor control is well accepted and immunotherapy is taking a major place in the treatment of cancers recently. However, various mechanisms are developed by the tumor to escape from immune cell attack, and immunotherapy has to meet a number of challenges. To elicit an effective antitumor response, three steps must be achieved: 1) effective processing and presentation of tumor antigens by dendritic cells; 2) generation of a protective T-cell response, as well as activation of other immune partners such as natural killer (NK) cells, natural killer T (NKT) cells, and B cells; and finally 3) overcoming of the immune suppression induced by the tumor and its microenvironment.[2] Several current cancer immunotherapies that have been investigated for their efficacy include cytokine therapy, adoptive cell transfer, cancer vaccines, and monoclonal antibodies.

Therapy with recombinant interleukin (IL)-2, a T-cell and NK-cell growth factor, was one of the earliest successes in immunotherapy. IL-2 (International Nonproprietary Name: aldesleukin) was approved in some countries in the EU to treat metastatic renal cell carcinoma (mRCC) and by the US Food and Drug Administration (FDA) to treat mRCC and malignant melanoma (MM). The FDA approval of high-dose IL-2 (HDIL-2) for the treatment of mRCC and MM was based on data derived from multiple pivotal trials administering IL-2 of 600,000-720,000 IU/kg with up to 15 bolus infusions every 8 hours, based on patients' tolerance. In 255 patients with mRCC, the objective response rate (ORR) was 15% with 7% complete responders.[3,4] Despite the proven efficacy of HDIL-2 in treating mRCC and MM patients, its use remains relatively restricted due to toxicity. Due to the short serum half-life and the need to achieve an immune-modulatory effect in the tissues, IL-2 must be given in high doses that induce severe systemic toxicities, including capillary leak syndrome (CLS), pulmonary edema, hypotension, acute renal insufficiency and rarely myocarditis. Nonetheless, this success validated the concept that stimulating T-cell and NK-cell responses could yield effective and durable responses.

IL-15 is a cytokine that has many overlapping functions as IL-2 including the ability to promote antitumor responses but with distinct advantages over IL-2. While both IL-2 and IL-15 signal through the common IL-2 receptor (IL-2R) chains β and γ (IL-2Rβγ or IL-15 receptor [IL-15R] βγ) complex, which is responsible for intracellular signaling through the JAK/STAT, MAPK, and PI3K pathways in T cells and NK cells, only IL-2 engages the high-affinity IL-2R chain α (IL-2Rα). As IL-2Rα is expressed on regulatory T cells (Tregs), IL-15 does not induce the expansion of these immunosuppressive cells.[5-7] Because IL-15 can engage IL-2Rβγ without engaging IL-2Rα on Tregs, it is thought to have an improved therapeutic index compared with IL-2.[8-10] Overall, IL-15 is a T-cell growth factor that: 1) induces the activation and proliferation of CD8+ T cells and NK cells, 2) maintains long-term memory T cells with relatively less effect on Tregs, and 3) inhibits activation-induced cell death. These advantages led IL-15 to be ranked first among various novel strategies by a National Cancer Institute (NCI) immunotherapy workshop as the agent with the greatest potential to impact clinical oncology.[11]

Despite the promising preclinical responses of recombinant IL-15,[12] success in the clinical setting was limited by its short *in vivo* half-life until recently. To date, three main modifications of IL-15 have been made to generate more potent soluble

IL-15 agonists: 1) combining IL-15 with a soluble IL-15R chain α (IL-15Rα) or the sushi domain of IL-15Rα; 2) fusing IL-15Rα to the Fc portion of human IgG1; 3) mutating IL-15 to increase its affinity to IL-2Rβγ. All formulations of IL-15 agonists have demonstrated increased strength and duration of IL-15R signaling and subsequent enhanced antitumor immunity in nonclinical studies. Recently, emerging clinical data as single agent or in combination with programmed cell death protein 1 (PD-1)- or programmed cell death ligand 1 (PD-L1)-blocking antibodies showed that IL-2Rβγ agonists at doses capable of inducing antitumor immune responses are safe and feasible in the outpatient setting and that the cytokine complex might be safely combined with PD-1 immunotherapy.[2]

In order to make use of the enhanced biological activity of the IL-15/IL-15Rα complex for the treatment of cancer and to overcome the need for endogenous IL-15Rα or co-administration of IL-15 with IL-15Rα, we engineered a fusion protein which consists of the N-terminal sushi domain of human IL-15Rα covalently coupled via a linker of 20 amino acids to human IL-15 (receptor-linker-IL-15 [RLI-15]; SO-C101).

7.2 Nonclinical summary

The antitumor activity of SO-C101 was investigated in several syngeneic mouse tumor models, including subcutaneously (SC) growing as well as disseminated, metastatic tumor models. SO-C101 was investigated as monotherapy as well as in combination with an anti-PD-1 antibody. The beneficial effect of combining SO-C101 treatment with anti-PD-1 treatment supports the clinical evaluation of this combination treatment approach.

7.2.1 SO-C101 monotherapy

SO-C101 promoted mobilization, expansion, and activation of human NK and CD8+ T cells in humanized mice and murine NK and CD8+ T cells in syngeneic mice.[13,14]

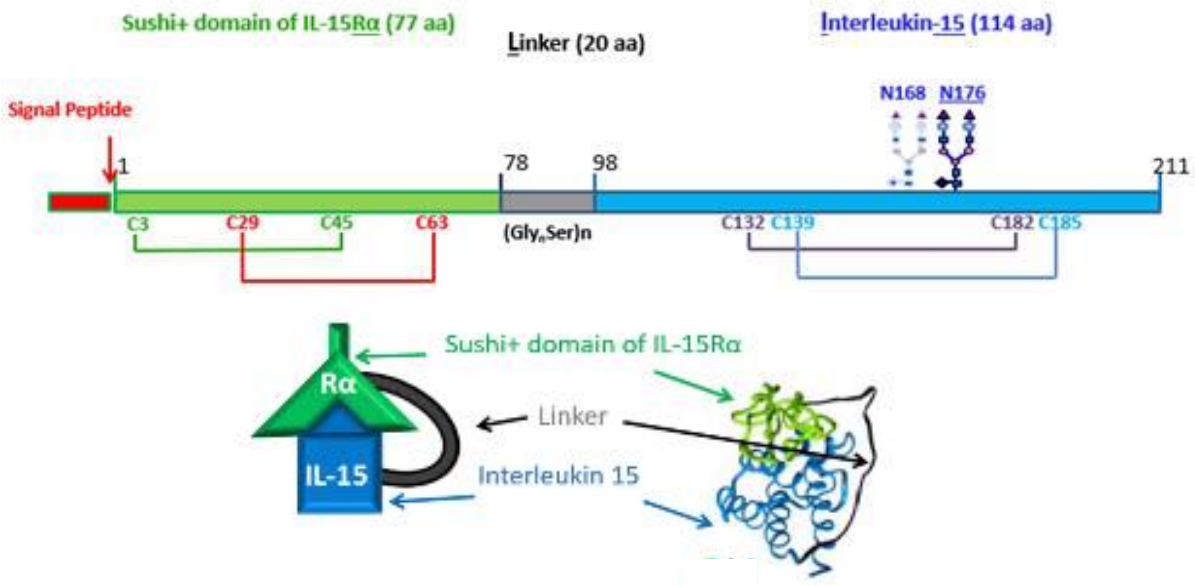
This NK- and CD8+ T-cell activation correlated with the potent anticancer therapeutic effects of SO-C101 in the following metastatic and solid tumor models in mice:

- In the B16F10 metastatic melanoma model in C57BL/6 mice, SO-C101 reduced the number of lung metastases after intravenous (IV) injection of mouse B16F10 cells as well as the number of liver metastases after intrasplenic injection and increased overall survival (OS)[15]
- In the orthotopic HCT-116 human colon tumor mouse model engrafted in the cecum of nude mice, systemic SO-C101 administration strongly inhibited primary tumor growth and metastatic dissemination to the peritoneum and other organs such as liver, lung, and spleen[15]
- In the RENCA orthotopic tumor model, SO-C101 inhibited primary tumor growth and displayed a significant anti-metastatic activity in a metastatic model setting[16]

7.2.2 SO-C101 mechanism of action

SO-C101 is a fusion protein which consists of the N-terminal sushi domain of human IL-15Rα covalently coupled via a linker of 20 amino acids to human IL-15 (Figure 7.1).[17,18] Before being acquired by SOTIO, SO-C101 was referred to as RLI-15.

Figure 7.1: Structure of SO-C101 (RLI-15)



SO-C101 and IL-15 dose-dependently activate similar signaling pathways. However, the kinetics and duration of this activation are markedly different; SO-C101-induced signaling is slower to start, but lasts longer than signaling induced by IL-15.[18]

7.2.3 SO-C101 in combination with an anti-PD-1 antibody

SO-C101 exhibited a profound synergistic effect with an anti-PD-1 antibody in several mouse tumor models:

- In the CT-26 colorectal carcinoma model, SO-C101 limited primary tumor growth when initiated at an early time of tumor development; at a later time, combination with an anti-PD-1 antibody showed synergistic activity with SO-C101, but not with IL-15[19]
- In the syngeneic TRAMP-C2 prostate mouse tumor model in C57BL/6 mice, treatment with SO-C101 alone decreased tumor growth. SO-C101 in combination with an anti-PD-1 antibody decreased the tumor growth more profoundly in an early treatment setting in comparison to the SO-C101 monotherapy; moreover, 70% of mice remained completely tumor-free when treated with SO-C101 in combination with anti-PD-1[16]
- Late therapeutic treatment of TRAMP-C2 tumors with SO-C101 and an anti-PD-1 antibody decreased the tumor growth significantly; flow cytometry analyses showed high numbers of interferon (IFN)-γ-producing CD8+ T cells in splenocytes which indicated the induction of systemic immunity at the end of the treatment period with SO-C101 and the anti-PD-1 antibody[16]

7.2.4 Pharmacology

A binding affinity of SO-C101 to IL-15Rβγ between 200 pM and 800 pM was determined. Binding of SO-C101 to IL-15Rβγ induced intracellular signaling, cell activation, and proliferation, comparable to IL-15-induced cell activation via the high affinity IL-15Rαβγ. The half maximal effective concentration (EC50) of SO-C101 to induce cell proliferation was lower than its binding affinity, indicating that less than 50% of receptor occupancy (RO) was required to induce half maximal cell proliferation. Human NK cells were more sensitive

to SO-C101-mediated activation than CD8+ T cells as demonstrated by the difference in their EC50 of approximately 10 pM for NK cells and 100 pM for CD8+ T cells.

Besides inducing cell proliferation, SO-C101 promoted the functional activation of NK and CD8+ T cells as demonstrated by cell surface expression of activating receptors, increased IFN-γ release, and cytolytic activity. Activated CD8+ T cells are known to recognize major histocompatibility complex-presented peptides derived from mutated or overexpressed proteins via their T-cell receptor on the surface of tumor cells. NKp30 and NKG2D expression confers cytotoxicity against induced self-proteins expressed on tumor cells by NK and CD8+ T cells. These SO-C101-mediated effects are in support of the activation of both innate and adaptive cellular immune responses against tumor cells.

The non-human primate cynomolgus monkey (*Macaca fascicularis*) is regarded as the relevant species for *in vivo* studies, based on the following observations: 1) the amino acid sequences of human IL-15 and IL-15Rαβγ show a high degree of identity to their respective cynomolgus monkey counterparts (IL-15: 96.3%, IL-15Rα: 88.6%, IL-15Rβ: 94.2%, IL-15Rγ: 97.6%); 2) SO-C101 activated cynomolgus NK and CD8+ T cells *in vitro* with equivalent potency to human NK and CD8+ T cells; and 3) doses promoting NK and CD8+ T-cell activation *in vivo* were 26-fold and 16-fold, respectively, lower in the cynomolgus monkey than in the mouse (based on allometrically scaled doses).

Studies in rodents were used to investigate the antitumor activity of SO-C101, but not regarded to determine pharmacologic active and safe doses for investigations in humans. As mentioned above, activation of NK and CD8+ T cells correlated with antitumor activity of SO-C101 in several mouse tumor models, which was augmented by anti-PD-1 combination therapy. This positive pharmacodynamic (PD) drug-drug interaction was wanted and will be explored in study SC103 for its potential to increase NK- and CD8+ T-cell activation and tumor regression. Importantly, the combination of SO-C101 with an anti-PD-1 antibody produced rather additive effects, reducing the risk of an exacerbated PD response and a potentially associated safety concern. SO-C101 effectively activated NK and CD8+ T cells dose dependently at doses between 4.0 µg/kg and 25.0 µg/kg in cynomolgus monkeys. Consistent with *in vitro* and mouse *in vivo* studies, CD4+ T cells and regulatory CD4+CD25+Foxp3+ T cells were less or not significantly activated. Importantly, SC administration was more effective than IV infusion in activating NK and CD8+ T cells. This was likely caused by the difference in SO-C101 pharmacokinetics (PK); SC administration resulted in a longer circulation time of biologically active serum concentrations compared to IV administration. Two daily administrations within one week were optimal for NK- and CD8+ T-cell activation. Following two daily administrations on day 1 and day 2, NK- and CD8+ T-cell activation was comparably low on day 3, further increased until day 5 and resumed back to baseline by day 9. Importantly, NK- and CD8+ T-cell activation followed a different kinetics than the SO-C101 serum concentrations that induced this activation. Repeated administration over two weeks promoted the increase of lymphocyte counts and the number of circulating NK and CD8+ T cells. As these numbers did not further increase during subsequent dosing, the schedule for treatment of patients in study SC103 was selected accordingly.

For more information, see the Investigator's Brochure (IB).

7.2.5 Pharmacokinetics

SO-C101 PK was mainly investigated in cynomolgus monkeys as this species is the most relevant for the correlation between PK and PD as well as for the assessment of SO-C101

safety. Absorption and serum kinetics following single and repeated SO-C101 administration to cynomolgus monkeys SC or as a 15- or 60-minute IV infusion was investigated and an absorption, distribution, and excretion study was performed with [125-iodine]-SO-C101. The doses employed covered the low pharmacologic range up to doses resulting in toxicological findings.

Following SC injection, maximum (or peak) serum concentration (C_{max}) and area under the curve (AUC) increased over the entire dose range investigated. The increase of both C_{max} and AUC was about 2-fold higher than dose-proportional at lower doses and closer to dose-proportional at higher doses. C_{max} was observed between 1.5 and 3 hours following SC injection. C_{max} following SC injection was between 6- to 10-fold lower, compared to IV infusion. The terminal half-life of SO-C101 was in the range of approximately 2 hours to almost 4 hours and was comparable after the SC and IV routes of administration. The bioavailability of SO-C101 following SC administration compared to a 60-minute IV infusion was at 35% to 40% relatively constant over the dose range tested.

The volume of distribution of SO-C101 following IV infusion was low and ranged between 37 mL/kg to 351 mL/kg between studies and groups, indicating a distribution mainly to the body fluid compartment. Clearance following IV administration ranged between 81 mL/h/kg and 239 mL/h/kg, indicating that SO-C101 was not highly excreted via the liver.

A difference in PK properties of SO-C101 between genders was not observed across all studies. Also, a high comparability of the SO-C101 PK was observed when SO-C101 was administered repeatedly and the analysis was performed on different study days. Accumulation of SO-C101 following repeated administration was not observed. This is in line with the relatively short half-life of SO-C101 and the daily administration schedule investigated. SO-C101 was mainly eliminated via the kidney. This is supported by the molecular size of SO-C101 (22 to 25 kDa) and the kidney clearance threshold above this molecular size. About 50% of the administered SO-C101 dose was detectable in urine 24 hours following a single SC administration.

For more information, see the IB.

7.2.6 Toxicology and safety pharmacology

The safety of SO-C101 was investigated in three repeated dose toxicity studies performed in cynomolgus monkeys. These studies employed a more frequent treatment schedule (up to 4 weekly administrations for 4 weeks) than planned in study SC103 (2 administrations per week). The SC route of administration, intended for the treatment of patients, was investigated in a maximum tolerated dose (MTD) study and in the pivotal 28-day Good Laboratory Practice study at 3 dose levels.

Immune activation was observed in the toxicity studies which is seen as the main cause for the effects observed. Infiltration of mononuclear cells, mostly lymphocytic, into tissues was a prominent result of SO-C101-mediated systemic immune activation. Tissue infiltrates of vascular and perivascular localization and minimal to slight intensity were observed in all organs analyzed. This infiltration was considered non-adverse as it did not result in degenerative effects in the target tissues. The SC dose of 80.0 µg/kg was described as the no-observed-adverse-effect level (NOAEL) and the SC dose of 100.0 µg/kg was described as the MTD. The symptoms leading to the definition of the MTD were hunched posture, reduced activity, raised hair, subdued behavior, occasional vomit, and mild tremors. This was accompanied by slight weight loss and transient increases in body temperature after SO-C101 administration.

SO-C101 produced changes in hematology and clinical chemistry parameters which were potentially linked to the observed systemic immune activation and tissue infiltration. Most evident was the dose-dependent and transient increase in C-reactive protein (CRP) levels after each administration. Other changes potentially indicating immune-mediated effects on the liver were increases in triglyceride and bilirubin as well as decreases in albumin (observed at the NOAEL), increases in aspartate transaminase (AST) and alanine transaminase (ALT) activity, and decreases in total protein, albumin:globulin ratio and inorganic phosphate. Creatinine and urea levels, potentially indicating the inflammation to the kidney, were only slightly increased in one study.

Hematology changes, besides the increase in NK or NKT cells and CD8+ T cells, included a decrease in neutrophils and red blood cells, the latter accompanied by a reduction in hemoglobin and an increase in reticulocyte counts. The nature of these changes and how much the immune activation by SO-C101 contributes to these changes are unclear. Changes in platelet counts and coagulation parameters were not observed at the NOAEL but at the MTD. Fibrinogen was increased (up to 2-fold in one study), but potentially reflecting a marker of the underlying immune activation.

The above described clinical chemistry and hematology changes did not reflect organ toxicities induced over the 4-week treatment with SO-C101. There was a dose effect observed with less incidence of effects and a lower magnitude at the low dose tested (20.0 µg/kg). Laboratory parameters returned to normal levels after the 4-week recovery period. The incidence and severity of mononuclear inflammatory cells infiltrates were decreased, indicating partial reversibility.

SO-C101 showed the potential to induce the release of IL-6, IL-8, and IFN-γ from human whole blood cells *in vitro*. Consistently throughout the studies in cynomolgus monkeys addressing SC administration, the release of IL-6, IFN-γ, and macrophage chemoattractant protein 1 was observed, possibly reflecting a direct consequence of SO-C101-mediated stimulation of NK and CD8+ T cells. Thus, the cytokines observed following SO-C101 administration may contribute to the immune-mediated findings observed in the toxicology studies.

The analysis of behavioral parameters as a surrogate central nervous system safety pharmacology parameter did not identify any SO-C101-mediated changes. Similarly, SO-C101-mediated effects on respiration rate were not observed. An increase in body temperature and heart rate was observed in a cardiac and respiratory safety pharmacology study approximately between 2.5 and 23 hours after SC administration which was accompanied with shortening of the QT interval in the 80.0 µg/kg SC group (maximal change by -10% to -14% following correction for heart rate). Blood pressure and other ECG parameters such as QP interval and QRS complex interval were generally not changed with biological relevance following SO-C101 administration and no heart arrhythmias were observed. It seems likely that QT intervals were rather indirectly affected as a response to increased heart rate, body temperature and the underlying immune activation stimulated by SO-C101.

SC administration of SO-C101 was well tolerated. Generally, no irritation, edema, or erythema was observed at the sites of injection. Microscopically, vascular and perivascular infiltration, mainly of lymphocytes, was observed at the injection sites with minimal to slight intensity.

For more information, see the IB.

7.3 Justification for the SC route as the route of administration

Study SC103 is planned to investigate only the SC administration of SO-C101, based on nonclinical PK/PD studies with SO-C101 and clinical data on agents with a similar mode of action.

SO-C101 was well absorbed following SC administration and demonstrated 35% to 40% bioavailability compared to 60-minute infusion. Absorption following SC injection resulted in a relatively longer circulation time of active SO-C101 concentrations, translating into stronger NK- and CD8+ T-cell activation compared to IV infusion. Furthermore, C_{max} was 6- to 8-fold lower but not more variable between animals when compared to IV infusion. Based on these findings, the SC route is considered to be pharmacologically more effective than the IV route and is regarded as safe.

Recently published clinical data on agents with a similar mode of action also support the SC route of administration. Studies published using the recombinant human IL-15 (rhIL-15) and ALT-803 (IL-15/IL-15R α complex) showed that SC dosing was safe and tolerable compared to IV administration due to a lower C_{max} and more sustained levels of the compound in the circulation.[20,21] The initial first-in-human (FIH) solid tumor trial of rhIL-15 using daily IV bolus infusion for 12 consecutive days unexpectedly and severely demonstrated toxicities and produced diminutive immune activation and little potential for use as monotherapy or in combination with other agents. However, the FIH trial of SC administration of rhIL-15 successfully completed dose escalation cohorts and SC administration allowed for an MTD ≥6 times higher compared to IV bolus administration.[12]

7.4 Justification for dose scheduling

7.4.1 Dosing schedule 1

Based on the PK/PD study results in cynomolgus monkeys, SO-C101 is planned to be given SC once daily on two consecutive days (day 1, day 2, day 8, and day 9 of a 21-day cycle) per week for two weeks followed by a week of rest that forms the three-weekly cycles. Alternative schedules of dosing may be planned after review of the patients in the first couple of cohorts. The schedule of two consecutive SC administrations in one week is based on the finding that administration on day 1 and day 2 in a treatment week resulted in optimal NK- and CD8+ T-cell activation in cynomolgus monkeys. A treatment period longer than two weeks did not further increase NK- and CD8+ T-cell numbers but rather reduced their cell counts. Based on these findings (see section 7.2.4), a treatment period of two weeks was selected for study SC103.

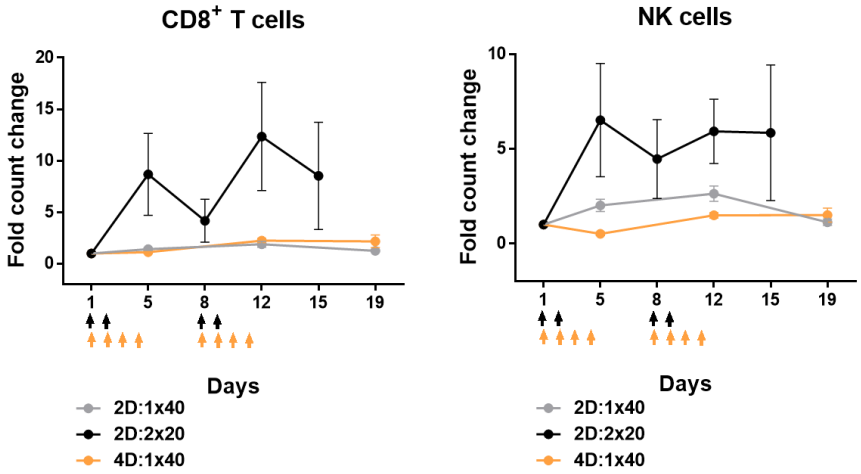
7.4.2 Dosing schedule 2

In order to explore the potential for improving the activation and expansion of NK and CD8+ T cells, two alternative SC dosing schedules were investigated in cynomolgus monkeys: i) once-daily SO-C101 administration for 4 consecutive treatment days, and ii) twice-daily SO-C101 administration for 2 consecutive days (studies SO-C101-1186E and SO-C101-1141E). In addition, the twice-daily SO-C101 administration was investigated in mice and this allowed testing the anti-tumor activity (studies SO-C101-1182E and SO-C101-1183E).

In cynomolgus monkeys, the administration of 20 µg/kg of SO-C101 twice a day 8 hours apart was more effective than 40 µg/kg of SO-C101 once a day for 2 or 4 consecutive days in increasing the numbers of CD8+ T cells and NK cells in peripheral blood (Figure 7.2).

Notably, the increase in cell counts promoted by twice-daily SO-C101 was stronger for CD8+ T cells than for NK cells.

Figure 7.2: Peripheral blood cell counts of CD8+ T cells and NK cells after once-daily and twice-daily SO-C101 administration in cynomolgus monkeys

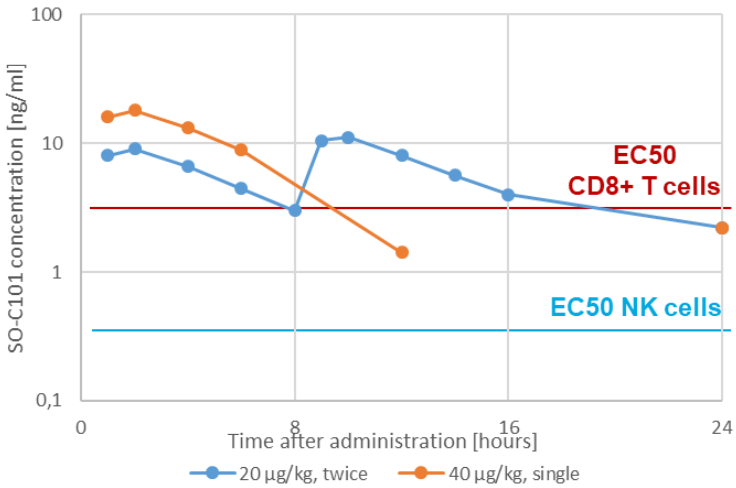


2D:1×40: animals were dosed once daily with 40 µg/kg/dose for 2 consecutive days; 2D:2×20: animals were dosed twice daily 8 hours apart with 20 µg/kg/dose for 2 consecutive days; 4D:1×40: animals were dosed once daily with 40 µg/kg/dose for 4 consecutive days. Administration days are indicated by arrows.

The percentage of CD8+ T cells and NK cells was determined by flow cytometry from blood at pre-dose, days 5, 8, 12, and 15. Data represent means ± standard error of mean.

The PK of SO-C101 following a single administration of 40 µg/kg promoted systemic concentrations above 2.5 ng/mL for about 9 hours whereas 2 doses of 20 µg/kg, 8 hours apart, promoted concentrations above 2.5 ng/mL for approximately 16 hours (Figure 7.3). The reference concentration of 2.5 ng/mL reflects the EC50 required for CD8+ T-cell activation. The longer exposure to SO-C101 at concentrations above 2.5 ng/mL is seen as the cause of the higher increase in the peripheral blood cell counts of CD8+ T cells and NK cells observed after twice-daily SO-C101 administration (Figure 7.2).

Figure 7.3: SO-C101 serum concentrations after once-daily and twice-daily SO-C101 administration in cynomolgus monkeys



No clinical signs were reported following the once-daily (40 µg/kg per dose) or twice-daily (20 µg/kg per dose) SO-C101 administration. The observed changes in hematology parameters were more pronounced after twice-daily SO-C101 administration than after once-daily SO-C101 administration. However, these changes were not clinically relevant.

In mice, two daily administrations of the same cumulative dose of SO-C101 as used in a single administration per day were more effective in inducing CD8+ T-cell and NK-cell frequencies and were more effective in reducing the tumor volume in MC38 tumor-bearing mice.

In conclusion, the preclinical observations indicate that the twice-daily SO-C101 administration of half of the daily dose is safe and leads to a prolonged exposure to SO-C101 at concentrations resulting in stronger PD effects as determined by an increased activation and proliferation of CD8+ T cells and NK cells.

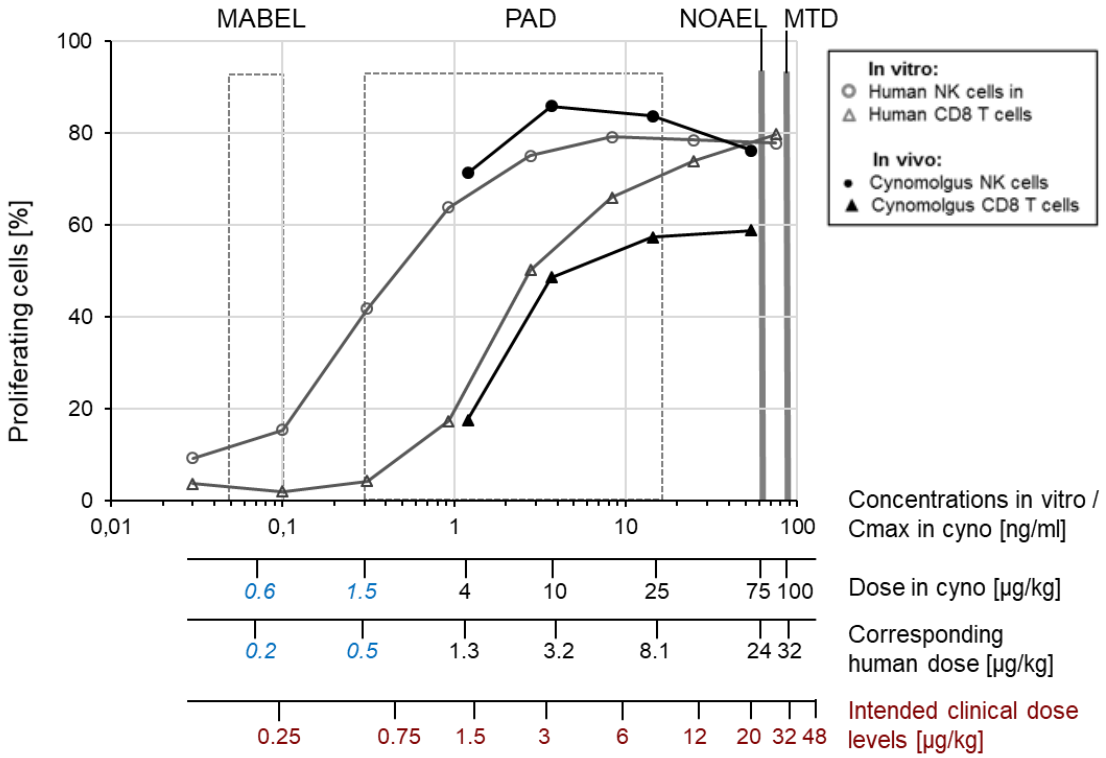
7.5 Justification for the starting dose and dose escalation steps in Part A

A starting dose of 0.25 µg/kg was selected for Part A. This starting dose is anticipated to represent a minimal active dose level. The selection of the starting dose was based on the activation of human NK and CD8+ T cells *in vitro* as well as on the responses observed in cynomolgus monkeys following SC administration of SO-C101 (Figure 7.4). This integrated approach is supported by the correlation between *in vitro* dose-response and the relationship between C_{max} and NK- and CD8+ T-cell activation levels in cynomolgus monkeys. This allowed to determine the dose range reaching from the minimal anticipated biological effect level (MABEL) to the anticipated pharmacologic active dose (PAD), and the NOAEL in cynomolgus monkeys. These doses were translated into human doses by allometric scaling using 3.1 as a factor. Importantly, the pharmacologic activity of SO-C101 as shown in Figure 7.4 was used for determining the starting dose and the escalation steps planned for clinical study SC103 because this was a more sensitive approach compared to RO (see also section 7.2.4).

Accordingly, a starting dose of 0.25 µg/kg was selected. This dose is expected to promote about 20% NK-cell activation without affecting CD8+ T cells. At an anticipated C_{max} of 0.1 ng/mL, the calculated RO would be between 0.5% and 2%, using the determined K_d range of 200 – 800 pM and the Hill equation.[22] Based on the dose effect as shown in Figure 7.4, the selected starting dose of 0.25 µg/kg is anticipated to represent the upper end of the MABEL range.

Recent analyses of starting doses in FIH studies together with subsequent findings at higher doses concluded that in case of immune agonistic antibodies excluding CD3 agonists, generally a starting dose achieving 20% to 80% RO was considered safe.[23] In the case of CD3-containing agonistic bispecifics, a FIH starting dose of 10% RO was not considered safe. Instead, a dose achieving up to 50% pharmacologic activity was acceptable with 6 artificial dose escalations until a human MTD when a tetravalent construct with high affinity for CD3 was excluded.[24] The selected SO-C101 starting dose of 0.25 µg/kg is expected to achieve below 10% RO (0.5% to 2% RO using the K_d of 200 and 800 pM) and 20% activation of NK cells, but no T-cell activation. Furthermore, this dose is about 100-times lower than the human equivalent of the NOAEL. Thus, the approach for selecting the SO-C101 starting dose is considered to be safe while reducing the number of patients dosed with non-active doses and is more conservative, compared to starting doses described in recent evaluations of immune agonistic biologics.[23,24]

Figure 7.4: Dose relationship of SO-C101-mediated NK- and CD8+ T-cell activation *in vitro* and in cynomolgus monkeys



Data from studies with human cells in vitro and from cynomolgus monkey studies with SC administration of SO-C101. Activity is shown versus the in vitro SO-C101 concentration and the C_{max} observed in vivo. Human equivalent doses were calculated by allometric scaling using 3.1 as a factor. MABEL: minimal anticipated biological effect level, PAD: pharmacologic active dose range, NOAEL: no adverse effect level, MTD: maximum tolerated dose.

The subsequent dose levels as shown in Table 7.1 were selected to gradually increase NK-cell activation to 60% and to start inducing CD8+ T-cell activation to <10%, respectively, at dose level 2 and to further increase activation to 100% until dose level 6. Dose level 7 would still be below the human equivalent of the NOAEL (26.0 µg/kg). Dose escalation in study SC103 will be made dependent on the safety observed at each dose level. Furthermore, PK parameters as well as NK- and CD8+ T-cell activation analyzed in patients in each dose cohort will be considered in the dose escalation decision.

Table 7.1: SO-C101 starting dose and dose escalation steps in study SC103 (Part A)

Dose level	SO-C101 dose	Dose increase	Expected NK cell activity [%]	Expected CD8+ activity [%]
1	0.25 µg/kg	Starting dose	20	0
2	0.75 µg/kg	200%	60	<10%
3	1.5 µg/kg	100%	80	25
4	3.0 µg/kg	100%	100	60

Dose level	SO-C101 dose	Dose increase	Expected NK cell activity [%]	Expected CD8+ activity [%]
5	6.0 µg/kg	100%	100	80
6	9.0 µg/kg	50%	100	100
7	15.0 µg/kg	67%	100	100
8	12.0 µg/kg*	-20%	100	100

Expected NK- and CD8+ T-cell activation was determined from Figure 7.4, based on data obtained in cynomolgus monkeys and the corresponding human doses, determined by allometric scaling.

** Identified on 08-Jun-2021 as the RP2D for monotherapy SO-C101 administered as a once daily dose.*

7.6 Justification for the starting dose in Part A1

In Part A1, the daily dose of SO-C101 will be administered as 2 divided doses. By this means, maximum plasma levels of SO-C101 will be reduced whilst keeping exposure in a similar range but avoiding long time intervals with subtherapeutic plasma concentrations during the night after dosing (see section 7.4.2 and Figure 7.3).

It is expected that the twice-daily dosing schedule will promote CD8+ T-cell and NK-cell expansion more effectively than the once-daily dosing schedule. The increase in CD8+ T-cell and NK-cell counts observed in study SC103 was not linked to safety concerns. To reduce the likelihood of adverse effects, the daily starting dose in Part A1 will be 1 dose level below the recommended phase 2 dose (RP2D) identified in Part A. Thus, the daily starting dose will be an already proven safe daily dose.

7.7 Justification for the starting dose in Part B

A starting dose of 1.5 µg/kg is selected for the combination with pembrolizumab, provided that dose level 5 (6.0 µg/kg) in Part A is tolerated and deemed safe. Thus, the starting dose in Part B will be 4-fold below the already tested dose in humans (SO-C101 monotherapy in Part A) which is moreover still more than 4-fold below the human equivalent of the NOAEL (26.0 µg/kg). If the dose level of 6.0 µg/kg in Part A is not deemed safe, then Part B will start at the lower dose level deemed safe from Part A. The Dose Escalation Committee (DEC) will review all available safety data as per the Dose Escalation Meeting (DEM) Charter from the first 5 cohorts of Part A before the start of Part B. The dose escalation scheme for Part B is shown in Table 9.2.

7.8 Justification for the starting dose in Part B1

In Part B1, the daily dose of SO-C101 will be administered as 2 divided doses. By this means, maximum plasma levels of SO-C101 will be reduced whilst keeping exposure in a similar range but avoiding long time intervals with subtherapeutic plasma concentrations during the night after dosing (see section 7.4.2 and Figure 7.3).

It is expected that the twice-daily dosing schedule will promote CD8+ T-cell and NK-cell expansion more effectively than the once-daily dosing schedule. Similarly as in Part A1, it is currently planned that the daily starting dose in Part B1 will be 1 dose level below the

RP2D identified in Part B if the safety profile in Part B supports this. Thus, the daily starting dose will be an already proven safe daily dose.

7.9 Study design rationale

We hypothesize that combined checkpoint inhibition and appropriate cytokine therapy will lead to synergistic outcomes in the induction and/or maintenance of the antitumor responses by activation of both innate and adaptive cellular immune responses against tumor cells. The SO-C101-mediated effects overcome 1) insufficient generation of antitumor T cells; 2) inadequate function of tumor-specific T cells; or 3) impaired formation of T-cell memory.[25] SO-C101, besides inducing NK- and CD8+ T-cell proliferation, promotes their functional activation as demonstrated by cell surface expression of activating receptors, increased IFN-γ release, and cytolytic activity. The efficacy/safety data from clinical studies conducted with compounds in clinical development with a similar mode of action, e.g., ALT-803 (an IL-15/IL-15Rα complex fused to an IgG1 Fc) have shown a favorable safety profile and induction of a robust immune-stimulatory response,[21,26] especially in combination with nivolumab. The monotherapy and combination studies indicated that new conjugates showed no cytokine release syndrome, CLS, hemodynamic instability, or systemic organ failures. The AE profile observed in these studies was anticipated, monitorable, and manageable.

Increasing recognition of the potential of immunotherapeutic combinations and the fact that some immuno-oncology agents may yield only modest clinical activity as monotherapy yet be highly active in the context of a therapeutic combination have led to the deployment of innovative trial designs.[27,28] One of these approaches integrates the combination assessment into the initial clinical development using the so called “bifurcated design” which is pursued in this study.

In this study, SO-C101 monotherapy dose escalation for dosing schedule 1 will be executed first through several dose levels in Part A to allow adequate dosing and follow-up for the monotherapy safety to be established using the traditional 3+3 design[29] (see section 9.7). Provided that safety is acceptable (see section 9.7), the study will “bifurcate” to two distinct paths (Part A and Part B) for subsequent escalation. After this point, the study will continue in parallel and recruit to both Part A and Part B given as per dosing schedule 1. Under no circumstances will the SO-C101 dose in Part B exceed the highest dose deemed safe in Part A (see Figure 8.1).

After the RP2D of SO-C101 given as per dosing schedule 1 is identified in Part A, the study will continue to Part A1 and Part D. Part A1 will be a SO-C101 monotherapy dose escalation part for dosing schedule 2. The starting daily dose of SO-C101 in Part A1 will be 1 dose level below the RP2D identified in Part A. The dose will be split into two identical (50%:50%) daily doses with the second dose on each treatment day being administered 8 hours (±15 min) after the first dose. Part D will be a dose expansion part in which SO-C101 monotherapy will be given as per dosing schedule 1 at the Part A RP2D with the same schedule as in Part A.

After the RP2D of SO-C101 given as per dosing schedule 2 is identified in Part A1, Part D1 will start. Part D1 will be a dose expansion part in which SO-C101 monotherapy will be given as per dosing schedule 2 at the Part A1 RP2D with the same schedule as in Part A1.

After the RP2D of SO-C101 given as per dosing schedule 1 in combination with pembrolizumab is identified in Part B, Part B1 will start. Part B1 will be a dose escalation part in which SO-C101 given as per dosing schedule 2 will be administered in combination

with pembrolizumab. The starting daily dose of SO-C101 in Part B1 will be 1 dose level below the RP2D identified in Part B. The dose will be split into two identical (50%:50%) daily doses with the second dose on each treatment day being administered 8 hours (±15 min) after the first dose.

The study will recruit patients to all ongoing study parts in parallel. The sponsor will allocate slots for the patients to be recruited to the dose-escalation study parts.

The patient population for all parts will be patients who are refractory to or intolerant of existing therapies known to provide clinical benefit for their condition. The basis of selecting these tumors was to include solid tumors with known sensitivity for anti-PD-(L)1 monotherapies also called PD-Lomas.[30] PD-Lomas where ORR ≥10% was reported were selected to demonstrate potential efficacy signal for the effect of SO-C101 added to Keytruda™.

Part A, Part A1, Part B, and Part B1 will enroll patients with the following relapsed/refractory advanced/metastatic tumors: renal cell carcinoma, non-small cell lung cancer, small-cell lung cancer, bladder cancer, melanoma, Merkel-cell carcinoma, skin squamous-cell carcinoma, microsatellite instability high solid tumors, triple-negative breast cancer, mesothelioma, thyroid cancer, thymic cancer, cervical cancer, biliary tract cancer, hepatocellular carcinoma, ovarian cancer, gastric cancer, head and neck squamous-cell carcinoma, and anal cancer.

Dose escalation in Part A, Part A1, Part B, and Part B1 will continue until the MTD and/or RP2D of the monotherapy SO-C101 and SO-C101 in combination with pembrolizumab are defined. This approach will allow for combination safety/PK/PD to be tested and optimized timely and effectively.

Part D and Part D1 will enroll patients with relapsed/refractory advanced/mRCC, patients with relapsed/refractory advanced/metastatic skin squamous-cell carcinoma, and patients with relapsed/refractory advanced/metastatic melanoma.

As the monotherapy clinical activity is expected to be limited and as explained above, there is a clear rationale that the combination will be more efficacious, this study will allow patients in Part A and Part A1 to crossover to Part B or Part B1 when they have objective progressive disease but no safety concerns (see section 8.1.9).[31] These patients will be allowed to crossover to Part B or Part B1 only when there is a dose level deemed safe in combination with pembrolizumab by the DEC during a DEM (see the DEM Charter). These patients will not be part of the Part B or Part B1 dose-limiting toxicity (DLT) assessment as they have already received SO-C101 in Part A or Part A1. This will offer an opportunity for patients in the monotherapy dose escalation parts (Part A, Part A1) to receive a potentially more effective therapy.

In order to allow patients treated at lower dose levels of SO-C101 to receive effective treatment in Part A, Part A1, Part B, and Part B1, patients will be allowed to continue treatment at the next higher dose level if it is assessed to be safe by the DEC and an Independent Advisory Panel (IAP) and if the criteria listed in section 8.1.8 are met.

After the combination RP2D of SO-C101 with pembrolizumab is identified in Part B and Part B1, ongoing patients in Part B and Part B1 can receive SO-C101 at the respective combination RP2D together with pembrolizumab if the criteria listed in section 8.1.8 are met.

The sponsor has also introduced additional safety monitoring to capture potential longer-term side effects of monotherapy and the combination as follows:

1. Safety monitoring beyond cycle 1: All patients will be monitored for potential late immune-related toxicities during the study and for 90 days after treatment discontinuation (see section 9.7.7.3). This will allow to capture potential late onset immune-mediated reactions with monotherapy SO-C101 and in combination with pembrolizumab such as immune-mediated pneumonitis; immune-mediated colitis, immune-mediated hepatitis, immune-mediated nephritis, infusion-related reactions; immune-mediated endocrinopathies: hypophysitis; thyroid disorders; and type 1 diabetes mellitus.
2. Time period before the start of Part B: As detailed above, Part B will only start after dose level 5 is deemed safe in Part A. At this point, the patients at dose level 3 in Part A (1.5 µg/kg) will be on treatment for at least 5 cycles / minimum 4.5 months and there will be a minimum of 15 patients dosed at 5 dose levels (0.25, 0.75, 1.5, 3.0, and 6.0 µg/kg). This time period seems to be in line with the median time to onset of immune-mediated toxicities of pembrolizumab, although the range could be quite wide.[32]
3. An IAP consisting of two experienced clinicians in immuno-oncology and an independent statistician will be monitoring and reviewing all safety data.
4. Additional cardiac eligibility and safety assessments (see section 9.11.6.4.7). IL-15 was shown to increase hyaluronic acid secretion by endothelial cells and induce angiogenesis. IL-15 could be an important mediator in the progression of atherosclerosis by its pro-inflammatory activities.[33,34] Findings from completed clinical studies with ALT-803 have shown one patient with grade 4 congestive heart failure (monotherapy at the highest dose level of 20.0 µg/kg given via the SC route) and one patient with grade 3 myocardial infarction in combination with nivolumab.[35]

Taken together, the mechanism of action of SO-C101, the results from the pre-clinical studies where SO-C101 in combination with PD-1 inhibitors have shown synergy, and the emerging encouraging clinical data with similar agents warrant SO-C101 to be studied in combination with an anti-PD-1 agent. Amongst potential anti-PD-1 agents, pembrolizumab is licensed both in frontline and in relapsed/refractory setting in many indications in the US and in the EU. This study aims to define the optimum RP2D of SO-C101 as monotherapy and in combination with pembrolizumab in a safe and efficient manner which in our view would be possible with the current study design.

8 STUDY DESIGN AND OBJECTIVES

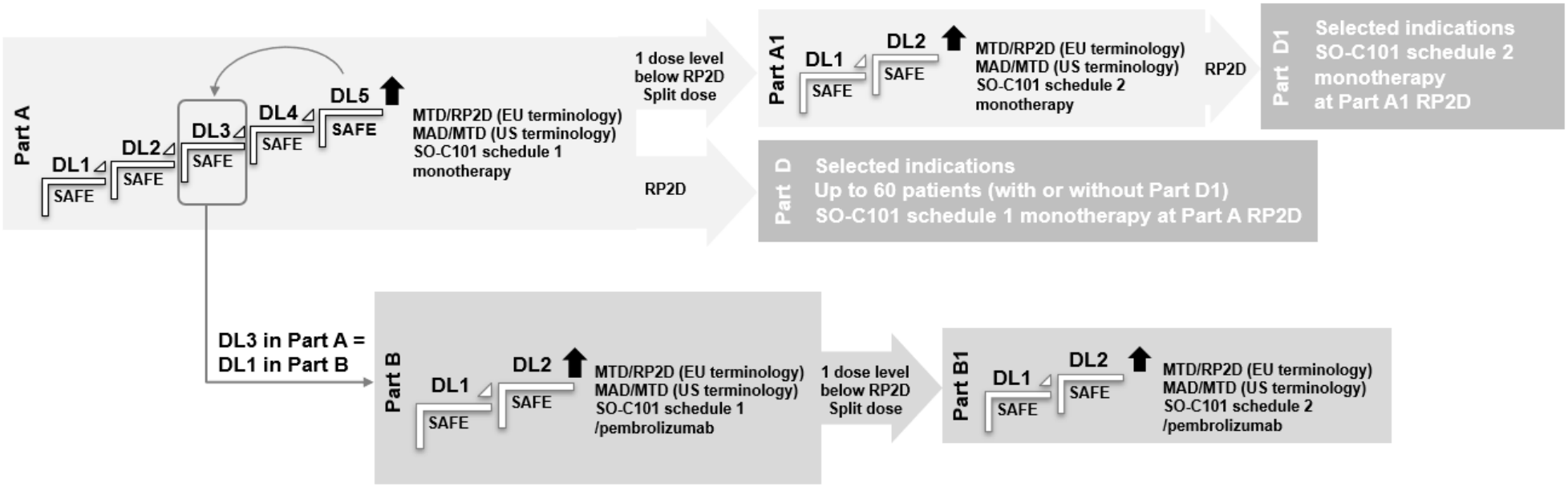
8.1 Study design

This study will assess the safety and tolerability of SO-C101 administered as monotherapy (Part A, Part A1, Part D, and Part D1) and in combination with an anti-PD-1 antibody (pembrolizumab) (Part B and Part B1) in patients with selected relapsed/refractory advanced/metastatic solid tumors who are refractory to or intolerant of existing therapies known to provide clinical benefit for their condition. Part A, Part A1, Part B, and Part B1 will enroll patients with the following relapsed/refractory advanced/metastatic tumors: renal cell carcinoma, non-small cell lung cancer, small-cell lung cancer, bladder cancer, melanoma, Merkel-cell carcinoma, skin squamous-cell carcinoma, microsatellite instability high solid tumors, triple-negative breast cancer, mesothelioma, thyroid cancer, thymic cancer, cervical cancer, biliary tract cancer, hepatocellular carcinoma, ovarian cancer, gastric cancer, head and neck squamous-cell carcinoma, and anal cancer. Part D and Part D1 will enroll patients with relapsed/refractory advanced/mRCC, patients with relapsed/refractory advanced/metastatic skin squamous-cell carcinoma, and patients with relapsed/refractory advanced/metastatic melanoma.

The study will have the following parts:

- Part A will be a FIH SO-C101 monotherapy dose escalation part for dosing schedule 1.
- Part A1 will be a SO-C101 monotherapy dose escalation part for dosing schedule 2 which will start once the RP2D of SO-C101 given as per dosing schedule 1 is identified in Part A; the starting daily dose of Part A1 will be 1 dose level below the RP2D identified in Part A. The dose will be split into two identical (50%:50%) daily doses with the second dose on each treatment day being administered 8 hours (±15 min) after the first dose.
- Part B will be a dose escalation part which will study SO-C101 given as per dosing schedule 1 in combination with pembrolizumab and will start after dose level 5 in Part A is completed and deemed safe and will use SO-C101 monotherapy level 3 dose as the starting dose in combination with pembrolizumab (Figure 8.1).
- Part B1 will be a dose escalation part which will study SO-C101 given as per dosing schedule 2 in combination with pembrolizumab and will start once the RP2D of SO-C101 given as per dosing schedule 1 in combination with pembrolizumab is identified in Part B; the starting daily dose of Part B1 will be 1 dose level below the RP2D identified in Part B. The dose will be split into two identical (50%:50%) daily doses with the second dose on each treatment day being administered 8 hours (±15 min) after the first dose.
- Part D will be a dose expansion part which will start once the RP2D of SO-C101 given as per dosing schedule 1 is identified in Part A; SO-C101 will be given at the Part A RP2D with the same schedule as in Part A.
- Part D1 will be a dose expansion part which will start once the RP2D of SO-C101 given as per dosing schedule 2 is identified in Part A1; SO-C101 will be given at the Part A1 RP2D with the same schedule as in Part A1.

Figure 8.1: Overall design



DL, dose level; MAD, maximum administered dose; MTD, maximum tolerated dose; RP2D, recommended phase 2 dose

8.1.1 Dosing schedule

SO-C101 will be administered on treatment days either as a once daily dose (dosing schedule 1) or twice a day as 2 divided doses (50%:50%) with the second dose on each treatment day being administered 8 hours (±15 min) after the first dose (dosing schedule 2).

8.1.2 Part A – Monotherapy SO-C101 dosing schedule 1 dose escalation

Part A will start first with SO-C101 monotherapy dose escalation for dosing schedule 1 which will continue until the MTD and/or RP2D of SO-C101 monotherapy given as per dosing schedule 1 is defined.

8.1.3 Part A1 – Monotherapy SO-C101 dosing schedule 2 dose escalation

Part A1 will start with the starting daily dose at 1 dose level below the RP2D identified in Part A (which will be split into two identical [50%:50%] daily doses) until the MTD and/or RP2D of SO-C101 monotherapy given as per dosing schedule 2 is defined.

8.1.4 Part B – SO-C101 dosing schedule 1 dose escalation in combination with pembrolizumab

Part B will start once monotherapy SO-C101 dose level 5 (6.0 µg/kg) in Part A is completed and deemed safe. The starting dose of Part B will be Part A dose level 3 (1.5 µg/kg) which will be combined with a fixed dose of pembrolizumab (200 mg IV every 3 weeks). If an MTD in Part A is reached before dose level 5, then the starting dose of SO-C101 in Part B will be decided based on the review of all available safety/PD/PK data. After the start of Part B, the study will continue recruiting to Part A and Part B in parallel. The Part B SO-C101 dose will be following the increasing safe dose levels of monotherapy SO-C101 from Part A. Under no circumstances will the Part B SO-C101 dose exceed the highest dose deemed safe in Part A (see Figure 8.1). Part B dose escalation will continue until the MTD and/or RP2D of SO-C101 in combination with pembrolizumab is defined. This approach will allow for combination safety/PK/PD to be tested and optimized timely and effectively.

8.1.5 Part B1 – SO-C101 dosing schedule 2 dose escalation in combination with pembrolizumab

After the RP2D of SO-C101 given as per dosing schedule 1 in combination with pembrolizumab is identified in Part B, Part B1 will start with the starting daily dose at 1 dose level below the RP2D identified in Part B (which will be split into two identical [50%:50%] daily doses) until the MTD and/or RP2D of SO-C101 given as per dosing schedule 2 in combination with pembrolizumab is defined.

8.1.6 Part D – Monotherapy SO-C101 dosing schedule 1 dose expansion

Part D will start after the RP2D of SO-C101 monotherapy given as per dosing schedule 1 is identified in Part A. SO-C101 will be given as per dosing schedule 1 at this RP2D.

8.1.7 Part D1 – Monotherapy SO-C101 dosing schedule 2 dose expansion

Part D1 will start after the RP2D of SO-C101 monotherapy given as per dosing schedule 2 is identified in Part A1. SO-C101 will be given as per dosing schedule 2 at this RP2D.

8.1.8 Intra-patient dose increase

Intra-patient dose escalation beyond the dose initially assigned to a patient is not permitted during cycle 2. However, patients receiving treatment with SO-C101 beyond cycle 2 may continue treatment at the next higher dose level if it is assessed to be safe by the DEC and IAP and if the following criteria are met:

- No safety concerns as deemed by the investigator
- No DLT at the initial dose level assigned
- No unacceptable AEs, defined as drug-related clinically meaningful, uncontrolled grade 3 or any grade 4 toxicities at the current dose level
- No dose reduction at the current dose level
- Completed at least two cycles at the assigned dose
- The investigator should also be of the opinion that these patients will derive benefit from treatment at the higher dose level of SO-C101

If these requirements are met, the patient can be dose escalated to the next dose level after discussion with the sponsor's medical monitor. These patients after intra-patient dose increase will NOT be part of the higher dose escalation cohorts; therefore, after intra-patient dose increase, they will not be part of the DLT evaluation.

Intra-patient escalation up to the RP2D level in Part A, Part A1, Part B, and Part B1 is allowed and can be done step-by step if the patient stays at the higher dose level and meets the criteria for escalation as specified above.

8.1.9 Crossover of patients from Part A and Part A1 to Part B or Part B1

This study is planned to allow patients to crossover from Part A and Part A1 to Part B or Part B1 when they have objective progressive disease in Part A and Part A1 and there is a dose deemed safe in Part B or Part B1. The investigator should also be of the opinion that these patients will derive benefit from combination treatment in Part B or Part B1. These patients will **NOT** be part of the dose escalation cohorts of Part B or Part B1; therefore, they will not be part of the DLT evaluation in Part B or Part B1.

The crossover will only be allowed when all of the following criteria are met:

- Unconfirmed progressive disease (iUPD) as per Response Evaluation Criteria In Solid Tumors for immune-based therapeutics (iRECIST)[36] in Part A and Part A1
- Eligibility for Part A and Part A1 (except fresh biopsy requirement) still holds and patients have no known hypersensitivity to any of the ingredients in the pembrolizumab drug product (Keytruda™)
- There are no safety concerns as deemed by the investigator and the patient should not have had a DLT in Part A and Part A1
- A completed safe dose level identified in Part B or Part B1; if there are more than one safe dose levels identified, the patient will be allowed to be assigned to the highest dose level deemed safe

For each patient considered for the crossover, the investigator will discuss this with the sponsor's medical monitor.

If all of the above criteria are met, the following procedures will be applied:

- Patient will attend the End of treatment (EoT) visit for Part A or Part A1
- Patient will sign the ICF for Part B or Part B1

Once a patient starts Part B or Part B1, all Part B or Part B1 study procedures starting from cycle 1 day 1 will be followed except:

- PK
- Part B or Part B1 screening biopsy (the second biopsy in cycle 2 in Part B or Part B1 is optional for crossover patients)

8.2 Objectives

8.2.1 Part A (SO-C101 dosing schedule 1, monotherapy, dose escalation)

8.2.1.1 Primary objectives

- To assess the safety and tolerability of SO-C101 given as monotherapy
- To determine the MTD and/or RP2D of SO-C101 given as monotherapy

8.2.1.2 Secondary objectives

- To characterize the PK of SO-C101
- To characterize the PD of SO-C101 in peripheral blood
- To determine the preliminary efficacy of SO-C101 monotherapy as measured by ORR, duration of response (DOR), clinical benefit rate (CBR), and progression-free survival (PFS) according to iRECIST
- To determine the immunogenicity of SO-C101 given as monotherapy

8.2.1.3 Exploratory objectives

- To explore the mechanistic effects of SO-C101 on selected immune cell populations in tumor tissue samples
- To assess OS at 6 months after the EoT visit

8.2.2 Part A1 (SO-C101 dosing schedule 2, monotherapy, dose escalation)

8.2.2.1 Primary objectives

- To assess the safety and tolerability of SO-C101 given as monotherapy
- To determine the MTD and/or RP2D of SO-C101 given as monotherapy

8.2.2.2 Secondary objectives

- To characterize the PK of SO-C101
- To characterize the PD of SO-C101 in peripheral blood
- To determine the preliminary efficacy of SO-C101 monotherapy as measured by ORR, DOR, CBR, and PFS according to iRECIST
- To determine the immunogenicity of SO-C101 as monotherapy

8.2.2.3 Exploratory objectives

- To explore the mechanistic effects of SO-C101 on selected immune cell populations in tumor tissue samples
- To assess OS at 6 months after the EoT visit

8.2.3 Part B (SO-C101 dosing schedule 1, combined with pembrolizumab, dose escalation)

8.2.3.1 Primary objectives

- To assess the safety and tolerability of SO-C101 when combined with pembrolizumab
- To determine the MTD and/or RP2D of SO-C101 when combined with pembrolizumab

8.2.3.2 Secondary objectives

- To characterize the PK of SO-C101 when combined with pembrolizumab
- To characterize the PD of SO-C101 in peripheral blood when combined with pembrolizumab
- To assess the preliminary efficacy of the combination of SO-C101 with pembrolizumab as measured by ORR, DOR, CBR, and PFS according to iRECIST
- To determine the immunogenicity of SO-C101 in combination with pembrolizumab

8.2.3.3 Exploratory objectives

- To explore the mechanistic effects of SO-C101 in combination with pembrolizumab on selected immune cell populations in tumor tissue samples
- To assess OS at 6 months after the EoT visit

8.2.4 Part B1 (SO-C101 dosing schedule 2, combined with pembrolizumab, dose escalation)

8.2.4.1 Primary objectives

- To assess the safety and tolerability of SO-C101 when combined with pembrolizumab
- To determine the MTD and/or RP2D of SO-C101 when combined with pembrolizumab

8.2.4.2 Secondary objectives

- To characterize the PK of SO-C101 when combined with pembrolizumab
- To characterize the PD of SO-C101 in peripheral blood when combined with pembrolizumab
- To assess the preliminary efficacy of the combination of SO-C101 twice daily with pembrolizumab as measured by ORR, DOR, CBR, and PFS according to iRECIST
- To determine the immunogenicity of SO-C101 in combination with pembrolizumab

8.2.4.3 Exploratory objectives

- To explore the mechanistic effects of SO-C101 in combination with pembrolizumab on selected immune cell populations in tumor tissue samples
- To assess OS at 6 months after the EoT visit

8.2.5 Part D (SO-C101 dosing schedule 1, monotherapy, dose expansion at the RP2D identified in Part A)

8.2.5.1 Primary objective

- To assess the safety and tolerability of SO-C101

8.2.5.2 Secondary objectives

- To characterize the PK of SO-C101
- To characterize the PD of SO-C101 in peripheral blood
- To assess the preliminary efficacy of SO-C101 as measured by ORR, DOR, CBR, and PFS according to iRECIST
- To determine the immunogenicity of SO-C101

8.2.5.3 Exploratory objectives

- To explore the mechanistic effects of SO-C101 on selected immune cell populations in tumor tissue samples
- To assess OS at 6 months after the EoT visit

8.2.6 Part D1 (SO-C101 dosing schedule 2, monotherapy, dose expansion at the RP2D identified in Part A1)

8.2.6.1 Primary objective

- To assess the safety and tolerability of SO-C101

8.2.6.2 Secondary objectives

- To characterize the PK of SO-C101
- To characterize the PD of SO-C101 in peripheral blood
- To assess the preliminary efficacy of SO-C101 as measured by ORR, DOR, CBR, and PFS according to iRECIST
- To determine the immunogenicity of SO-C101

8.2.6.3 Exploratory objectives

- To explore the mechanistic effects of SO-C101 on selected immune cell populations in tumor tissue samples
- To assess OS at 6 months after the EoT visit

9 INVESTIGATIONAL PLAN

9.1 Part A (SO-C101 dosing schedule 1, monotherapy, dose escalation)

Patients will be treated with escalating doses of SO-C101 given as per dosing schedule 1 via the SC route following the dose escalation scheme below (Table 9.1). A starting dose of 0.25 µg/kg was selected in Part A of this study. If this starting dose is not tolerated, then a lower dose will be considered. Justification for the starting dose is described in section 7.5.

Table 9.1: SO-C101 dosing schedule 1 dose increments, Part A

Dose level	SO-C101 dose given once a day (µg/kg/administration)	Dose increase
1	0.25 µg/kg	Starting dose
2	0.75 µg/kg	200%
3	1.5 µg/kg	100%
4	3.0 µg/kg	100%
5	6.0 µg/kg	100%
6	9.0 µg/kg	50%
7	15.0 µg/kg	67%
8	12.0 µg/kg*	-20%

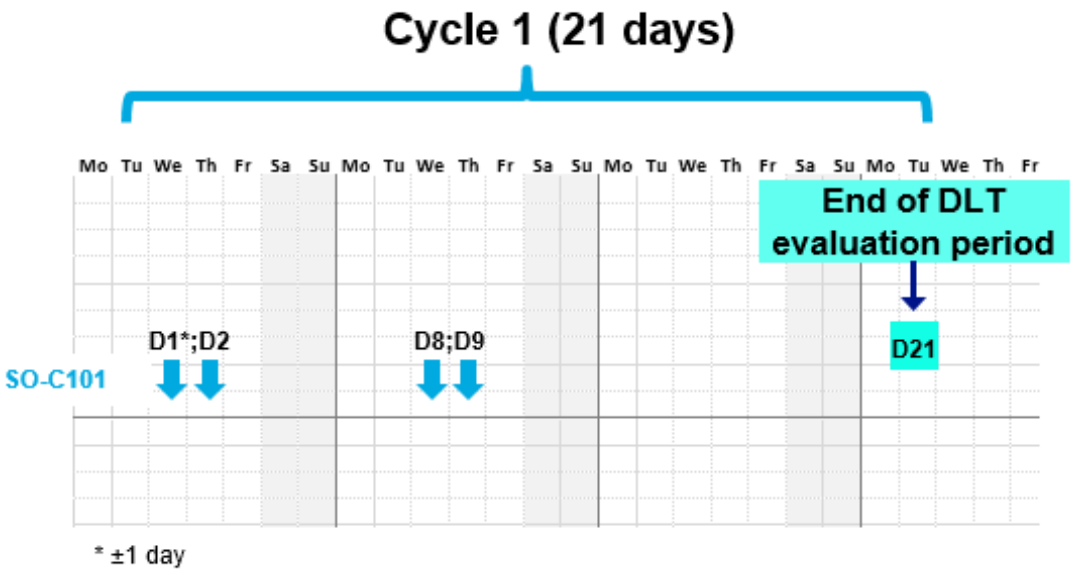
** Identified on 08-Jun-2021 as the RP2D for monotherapy SO-C101 administered as a once daily dose.*

Patients will be treated with SO-C101 given once a day on day 1 (±1 day; Wednesday), day 2 (Thursday), day 8 (Wednesday), and day 9 (Thursday) of the 21-day cycle (see Figure 9.1). The start of the treatment (day 1) is planned to be on a Wednesday to allow biomarker sampling (fresh peripheral blood mononuclear cells [PBMCs] transfer to the central laboratory) on weekdays. However, as long as the two doses per week are given on consecutive days (day 1 and day 2) and the second week dosing (day 8 and day 9) takes place 7 days after day 1, there will be ±1 day flexibility for the day 1 dosing to take place on a Tuesday or on a Thursday.

SC injection sites will be rotated to different areas of the body (upper and lower extremities, each of the 4 quadrants of the abdomen) to minimize the summated potential local effects of SO-C101 administration.

This dosing schedule will be revised in light of the emerging clinical data from initial cohorts and if these data reveal substantial differences from non-clinical data, adjustment of the planned dose levels will be considered by the DEC (see the DEM Charter and section 9.7.3) and the IAP.

Figure 9.1: Part A: SO-C101 dosing schedule 1



This schedule should be strictly adhered to with no dose delays/reductions to be allowed for especially cycle 1 for maximum exposure for safety evaluation for DLTs (Figure 9.1; for DLT evaluation, see section 9.7.1). If any visits are missed for obtaining PK/PD/safety laboratory parameters during cycle 1, patients will be reviewed individually by the sponsor's medical monitor and investigators for their evaluability for DLT assessment (Table 9.6).

SO-C101 dosing schedule 1 monotherapy dose escalation will continue until the MTD and/or RP2D is reached as per the dose escalation schema (Table 9.1). If the MTD is not reached at the end of the planned dose escalation cohorts, the recruitment will stop to assess RP2D as described in section 9.7.2. Additional doses and schedules could be opened as required based on the RP2D assessment results to define the optimal dose and schedule for further clinical studies.

Patients recruited in Part A will continue treatment at their assigned dose level until any of the criteria listed in section 9.11.10 are met. Intra-patient dose escalation beyond the dose initially assigned to a patient is not permitted during cycle 2. However, patients receiving treatment with SO-C101 given as per dosing schedule 1 beyond cycle 2 may continue treatment at the next higher dose level if it is assessed to be safe by the DEC and IAP and if the criteria listed in section 8.1.8 are met. These patients after intra-patient dose increase will NOT be part of the higher dose escalation cohorts; therefore, after intra-patient dose increase, they will not be part of the DLT evaluation. Intra-patient escalation up to the RP2D level is allowed and can be done step-by step if the patient stays at the higher dose level and meets the criteria for escalation as specified in section 8.1.8.

If a patient's treatment discontinuation is due to disease progression, crossover to the combination treatment (Part B or Part B1) could be considered. See section 8.1.9.

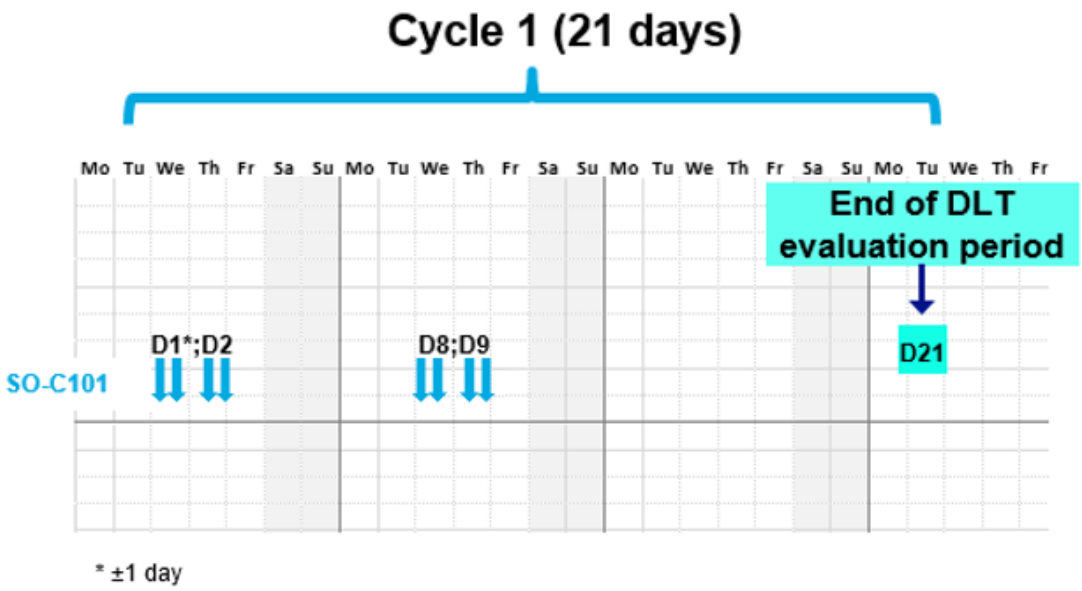
9.2 Part A1 (SO-C101 dosing schedule 2, monotherapy, dose escalation)

Patients will be treated with escalating doses of SO-C101 given as per dosing schedule 2 via the SC route. The starting daily dose will be 1 level below the RP2D identified in Part A. The dose will be split into two identical (50%:50%) daily doses with the second dose on each treatment day being administered 8 hours (±15 min) after the first dose. If this starting dose is not tolerated, then a lower dose could be considered. Further dose levels will be

considered based on safety data and decisions taken during DEMs. Justification for the starting dose is described in section 7.6.

Patients will be treated with SO-C101 given twice a day 8 hours (±15 min) apart on day 1 (±1 day; Wednesday), day 2 (Thursday), day 8 (Wednesday), and day 9 (Thursday) of the 21-day cycle (see Figure 9.2). The start of the treatment (day 1) is planned to be on a Wednesday to allow biomarker sampling (fresh PBMCs transfer to the central laboratory) on weekdays. However, as long as the four doses per week are given on consecutive days (day 1 and day 2) and the second week dosing (day 8 and day 9) takes place 7 days after day 1, there will be ±1 day flexibility for the day 1 dosing to take place on a Tuesday or on a Thursday.

Figure 9.2: Part A1: SO-C101 dosing schedule 2



SC injection sites will be rotated to different areas of the body (upper and lower extremities, each of the 4 quadrants of the abdomen) to minimize the summated potential local effects of SO-C101 administration.

This dosing schedule will be revised in light of the emerging clinical data from initial cohorts and if these data reveal substantial differences from non-clinical data, adjustment of the planned dose levels will be considered by the DEC (see the DEM Charter and section 9.7.3) and the IAP.

This schedule should be strictly adhered to with no dose delays/reductions to be allowed for especially cycle 1 for maximum exposure for safety evaluation for DLTs (Figure 9.2; for DLT evaluation, see section 9.7.1). If any visits are missed for obtaining PK/PD/safety laboratory parameters during cycle 1, patients will be reviewed individually by the sponsor's medical monitor and investigators for their evaluability for DLT assessment (Table 9.6).

SO-C101 dosing schedule 2 monotherapy dose escalation will continue until the MTD and/or RP2D is reached. If the MTD is not reached, the recruitment will stop to assess RP2D. Additional doses and schedules could be opened as required based on the RP2D assessment results to define the optimal dose and schedule for further clinical studies.

Patients recruited in Part A1 will continue treatment at their assigned dose level until any of the criteria listed in section 9.11.10 are met. Intra-patient dose escalation beyond the dose initially assigned to a patient is not permitted during cycle 2. However, patients receiving

treatment with SO-C101 given as per dosing schedule 2 beyond cycle 2 may continue treatment at the next higher dose level if it is assessed to be safe by the DEC and IAP and if the criteria listed in section 8.1.8 are met.

These patients after intra-patient dose increase will NOT be part of the higher dose escalation cohorts; therefore, after intra-patient dose increase, they will not be part of the DLT evaluation. Intra-patient escalation up to the RP2D level is allowed and can be done step-by step if the patient stays at the higher dose level and meets the criteria for escalation as specified in section 8.1.8.

If a patient's treatment discontinuation is due to disease progression, crossover to the combination treatment (Part B or Part B1) could be considered. See section 8.1.9.

9.3 Part B (SO-C101 dosing schedule 1, combined with pembrolizumab, dose escalation)

Part B treatment will consist of SO-C101 given as per dosing schedule 1 in combination with pembrolizumab following the dose escalation scheme below (Table 9.2). Justification for the starting dose is described in section 7.7.

The SO-C101 starting dose for cohort 1 of Part B, the combination with pembrolizumab, will be 1.5 µg/kg provided that dose level 5 (6.0 µg/kg) in Part A is tolerated and deemed safe. If the dose level of 6.0 µg/kg is not deemed safe, then Part B will start at the lower dose level deemed safe. If this starting dose is not tolerated, then SO-C101 dose level -1 of Part B (0.75 µg/kg) will be tested.

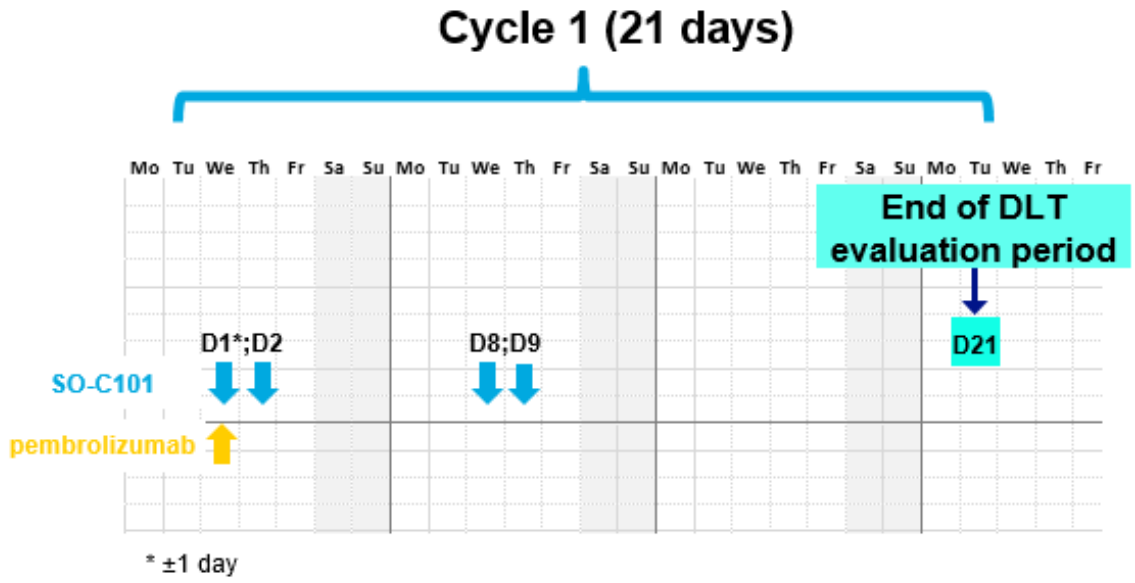
Table 9.2: SO-C101 dosing schedule 1 dose increments in combination with pembrolizumab, Part B

Dose level	SO-C101 dose given once a day (µg/kg/administration)	Dose increase	Pembrolizumab
-1	0.75 µg/kg	(-50%)	200 mg
1	1.5 µg/kg	Starting dose	200 mg
2	3.0 µg/kg	100%	200 mg
3	6.0 µg/kg	100%	200 mg
4	9.0 µg/kg	50%	200 mg
5	12.0 µg/kg	33%	200 mg

Patients will be treated with escalating doses of SO-C101 given once a day on day 1 (±1 day; Wednesday), day 2 (Thursday), day 8 (Wednesday), and day 9 (Thursday) together with a fixed dose of pembrolizumab (200 mg IV every 3 weeks) given on the day 1 administration of SO-C101. Pembrolizumab will be administered within 30 minutes after the first dose of SO-C101 and as outlined in the package insert[37,38] (see Figure 9.3). The start of the treatment (day 1) is planned to be on a Wednesday to allow biomarker sampling (fresh PBMCs transfer to the central laboratory) on weekdays. However, as long as the two doses of SO-C101 per week are given on consecutive days (day 1 and day 2) and the second

week SO-C101 dosing (day 8 and day 9) takes place 7 days after day 1, there will be ±1 day flexibility for the day 1 dosing to take place on a Tuesday or on a Thursday.

Figure 9.3: Part B: SO-C101 dosing schedule 1 and pembrolizumab



This schedule should be strictly adhered to with no dose delays/reductions to be allowed for especially cycle 1 for maximum exposure for safety evaluation for DLTs (Figure 9.3; for DLT evaluation, see section 9.7.1). If any visits are missed for obtaining PK/PD/safety laboratory parameters during cycle 1, patients will be reviewed individually by the sponsor's medical monitor and investigators for their evaluability for DLT assessment (Table 9.7).

SO-C101 combination dose escalation for dosing schedule 1 will continue until the MTD and/or RP2D is reached as per the dose escalation schema. If the MTD is not reached at the end of the planned dose escalation cohorts, the recruitment will stop to assess RP2D. Additional doses and schedules could be opened as required based on the RP2D assessment results to define the optimal dose and schedule for further clinical studies.

Patients will continue SO-C101 given as per dosing schedule 1 and pembrolizumab treatment at the assigned dose level of SO-C101 until any of the criteria listed in section 9.11.10 are met.

Intra-patient dose escalation beyond the dose initially assigned to a patient is not permitted during cycle 2. However, patients receiving treatment with SO-C101 given as per dosing schedule 1 beyond cycle 2 may continue treatment at the next higher dose level if it is assessed to be safe by the DEC and IAP and if the criteria listed in section 8.1.8 are met. These patients after intra-patient dose increase will NOT be part of the higher dose escalation cohorts; therefore, after intra-patient dose increase, they will not be part of the DLT evaluation.

In case SO-C101 needs to be stopped for reasons other than disease progression, pembrolizumab treatment can continue for up to 1 year as assessed by the DEC if the patient does not progress and can tolerate the treatment (see also Table 9.8 and Table 9.13). In case pembrolizumab needs to be stopped, SO-C101 treatment can continue until disease progression or unacceptable toxicity.

SC injection sites will be rotated to different areas of the body (upper and lower extremities, each of the 4 quadrants of the abdomen) to minimize the summated local effects of SO-C101 administration.

Once Part B is open for recruitment and the first combination cohort is deemed safe, patients who had objective disease progression in Part A and Part A1 will be allowed to crossover to Part B given that there are no safety concerns and the criteria and procedures are followed as described in section 8.1.9.

Intra-patient escalation up to the RP2D level is allowed and can be done step-by step if the patient stays at the higher dose level and meets the criteria for escalation as specified in section 8.1.8.

9.4 Part B1 (SO-C101 dosing schedule 2, combined with pembrolizumab, dose escalation)

Part B1 treatment will consist of SO-C101 given as per dosing schedule 2 in combination with pembrolizumab. The starting daily dose will be 1 level below the RP2D identified in Part B. The dose will be split into two identical (50%:50%) daily doses with the second dose on each treatment day being administered 8 hours (±15 min) after the first dose. If this starting dose is not tolerated, then a lower dose could be considered. Further dose levels will be considered based on safety data and decisions taken during DEMs. Justification for the starting dose is described in section 7.8.

Patients will be treated with escalating doses of SO-C101 given twice a day 8 hours (±15 min) apart on day 1 (±1 day; Wednesday), day 2 (Thursday), day 8 (Wednesday), and day 9 (Thursday) together with a fixed dose of pembrolizumab (200 mg IV every 3 weeks) given with the first administration of SO-C101 on day 1. Pembrolizumab will be administered within 30 minutes after the first dose of SO-C101 and as outlined in the package insert[37,38] (see Figure 9.4). The start of the treatment (day 1) is planned to be on a Wednesday to allow biomarker sampling (fresh PBMCs transfer to the central laboratory) on weekdays. However, as long as the four doses of SO-C101 per week are given on consecutive days (day 1 and day 2) and the second week SO-C101 dosing (day 8 and day 9) takes place 7 days after day 1, there will be ±1 day flexibility.

This schedule should be strictly adhered to with no dose delays/reductions to be allowed for especially in cycle 1 for maximum exposure for safety evaluation for DLTs (Figure 9.4; for DLT evaluation, see section 9.7.1). If any visits are missed for obtaining PK/PD/safety laboratory parameters during cycle 1, patients will be reviewed individually by the sponsor's medical monitor and investigators for their evaluability for DLT assessment (Table 9.7).

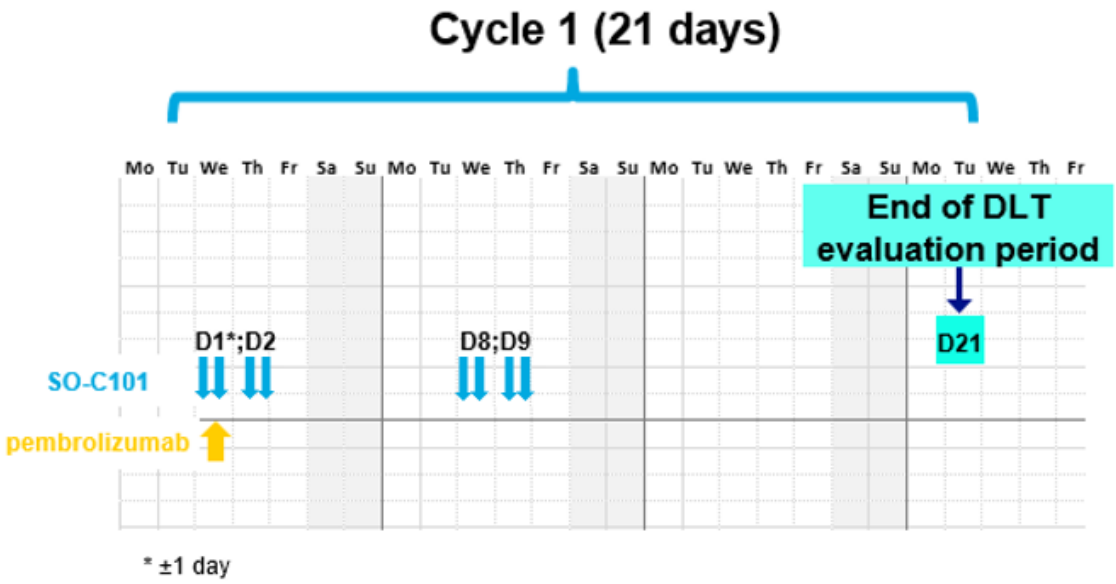
SO-C101 combination dose escalation for dosing schedule 2 will continue until the MTD and/or RP2D is reached. If the MTD is not reached, the recruitment will stop to assess RP2D. Additional doses and schedules could be opened as required based on the RP2D assessment results to define the optimal dose and schedule for further clinical studies.

Patients will continue SO-C101 given as per dosing schedule 2 and pembrolizumab treatment at the assigned dose level of SO-C101 until any of the criteria listed in section 9.11.10 are met.

Intra-patient dose escalation beyond the dose initially assigned to a patient is not permitted during cycle 2. However, patients receiving treatment with SO-C101 given as per dosing schedule 2 beyond cycle 2 may continue treatment at the next higher dose level if it is assessed to be safe by the DEC and IAP and if the criteria listed in section 8.1.8 are met.

These patients after intra-patient dose increase will NOT be part of the higher dose escalation cohorts; therefore, after intra-patient dose increase, they will not be part of the DLT evaluation.

Figure 9.4: Part B1: SO-C101 dosing schedule 2 and pembrolizumab



In case SO-C101 needs to be stopped for reasons other than disease progression, pembrolizumab treatment can continue for up to 1 year as assessed by the DEC if the patient does not progress and can tolerate the treatment (see also Table 9.8 and Table 9.13). In case pembrolizumab needs to be stopped, SO-C101 treatment can continue until disease progression or unacceptable toxicity.

SC injection sites will be rotated to different areas of the body (upper and lower extremities, each of the 4 quadrants of the abdomen) to minimize the summated local effects of SO-C101 administration.

Once Part B1 is open for recruitment and the first combination cohort is deemed safe, patients who had objective disease progression in Part A and Part A1 will be allowed to crossover to Part B1 given that there are no safety concerns and the criteria and procedures are followed as described in section 8.1.9.

Intra-patient escalation up to the RP2D level is allowed and can be done step-by step if the patient stays at the higher dose level and meets the criteria for escalation as specified in section 8.1.8.

9.5 Part D (SO-C101 dosing schedule 1, monotherapy, dose expansion at the RP2D identified in Part A)

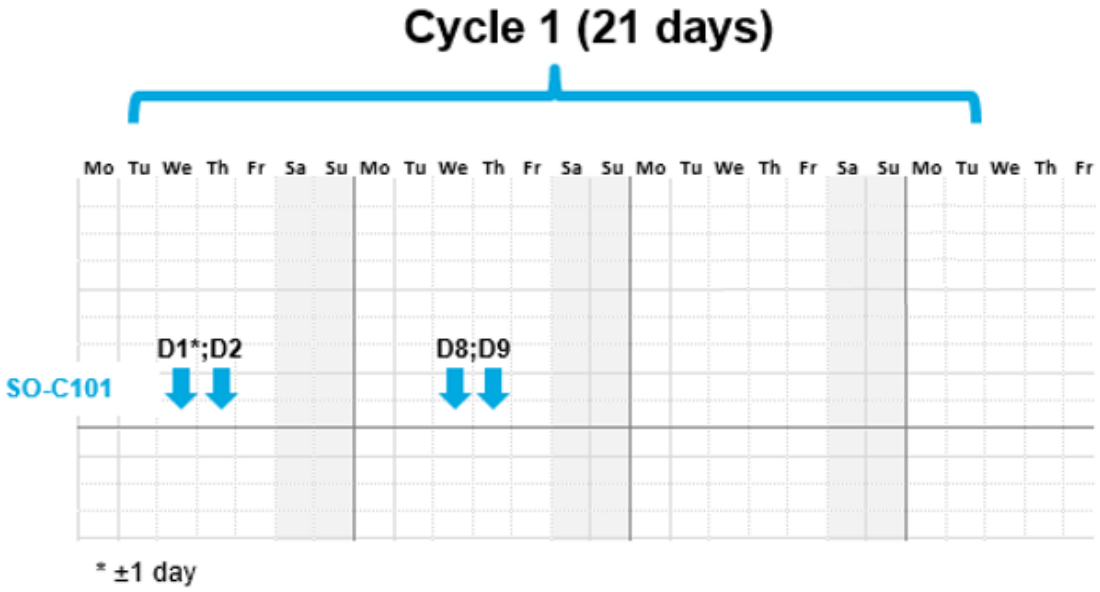
Part D treatment will consist of SO-C101 dosing schedule 1 given as monotherapy at the RP2D identified in Part A.

Patients will be treated with SO-C101 given once a day on day 1 (±1 day; Wednesday), day 2 (Thursday), day 8 (Wednesday), and day 9 (Thursday; see Figure 9.5).

The start of the treatment (day 1) is planned to be on a Wednesday to allow biomarker sampling (fresh PBMCs transfer to the central laboratory) on weekdays. However, as long as the two doses of SO-C101 per week are given on consecutive days (day 1 and day 2) and

the second week SO-C101 dosing (day 8 and day 9) takes place 7 days after day 1, there will be ±1 day flexibility for the day 1 dosing to take place on a Tuesday or on a Thursday.

Figure 9.5: Part D: SO-C101 dosing schedule 1



This schedule should be strictly adhered to with no dose delays/reductions to be allowed for especially in cycle 1 for maximum exposure for safety evaluation. If any visits are missed for obtaining PK/PD/safety laboratory parameters during cycle 1, patients will be reviewed individually by the sponsor's medical monitor and investigators. Patients will continue SO-C101 until any of the criteria listed in section 9.11.10 are met.

SC injection sites will be rotated to different areas of the body (upper and lower extremities, each of the 4 quadrants of the abdomen) to minimize the summated local effects of SO-C101 administration.

Data collected in Part D will be regularly reviewed by the IAP and discussed with the sponsor. Details will be provided in the IAP Charter.

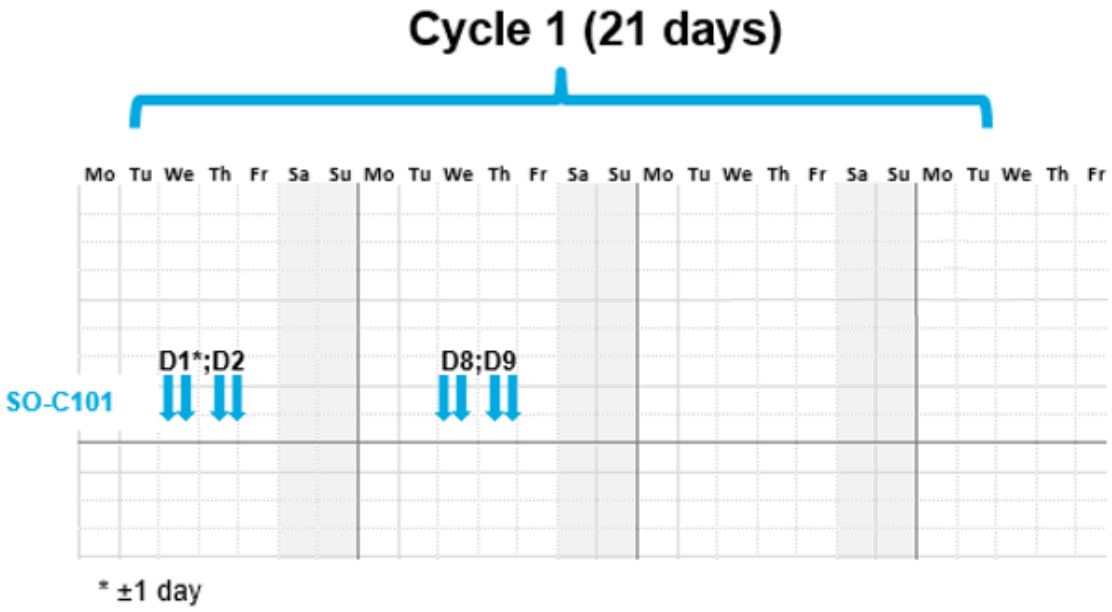
9.6 Part D1 (SO-C101 dosing schedule 2, monotherapy, dose expansion at the RP2D identified in Part A1)

Part D1 treatment will consist of SO-C101 given as per dosing schedule 2 as monotherapy at the RP2D identified in Part A1.

Patients will be treated with SO-C101 given twice a day 8 hours (±15 min) apart on day 1 (±1 day; Wednesday), day 2 (Thursday), day 8 (Wednesday), and day 9 (Thursday; see Figure 9.6).

The start of the treatment (day 1) is planned to be on a Wednesday to allow biomarker sampling (fresh PBMCs transfer to the central laboratory) on weekdays. However, as long as the four doses of SO-C101 per week are given on consecutive days (day 1 and day 2) and the second week SO-C101 dosing (day 8 and day 9) takes place 7 days after day 1, there will be ±1 day flexibility for the day 1 dosing to take place on a Tuesday or on a Thursday.

Figure 9.6: Part D1: SO-C101 dosing schedule 2



This schedule should be strictly adhered to with no dose delays/reductions to be allowed for especially in cycle 1 for maximum exposure for safety evaluation. If any visits are missed for obtaining PK/PD/safety laboratory parameters during cycle 1, patients will be reviewed individually by the sponsor's medical monitor and investigators. Patients will continue SO-C101 until any of the criteria listed in section 9.11.10 are met.

SC injection sites will be rotated to different areas of the body (upper and lower extremities, each of the 4 quadrants of the abdomen) to minimize the summated local effects of SO-C101 administration.

Data collected in Part D1 will be regularly reviewed by the IAP and discussed with the sponsor. Details will be provided in the IAP Charter.

9.7 Dose escalation plan and study periods

The DLT evaluation period is the first treatment cycle (21 days). A patient evaluable for DLT will be a patient who has completed cycle 1 and received all planned treatments without any treatment delays or interruptions: for Part A, received all 4 doses of SO-C101 as planned; for Part A1, received all 8 doses of SO-C101 as planned; for Part B, received all 4 doses of SO-C101 and 1 dose of pembrolizumab as planned; for Part B1, received all 8 doses of SO-C101 and 1 dose of pembrolizumab as planned. Patients who do not fulfill these criteria for any other reason than DLT should be replaced.

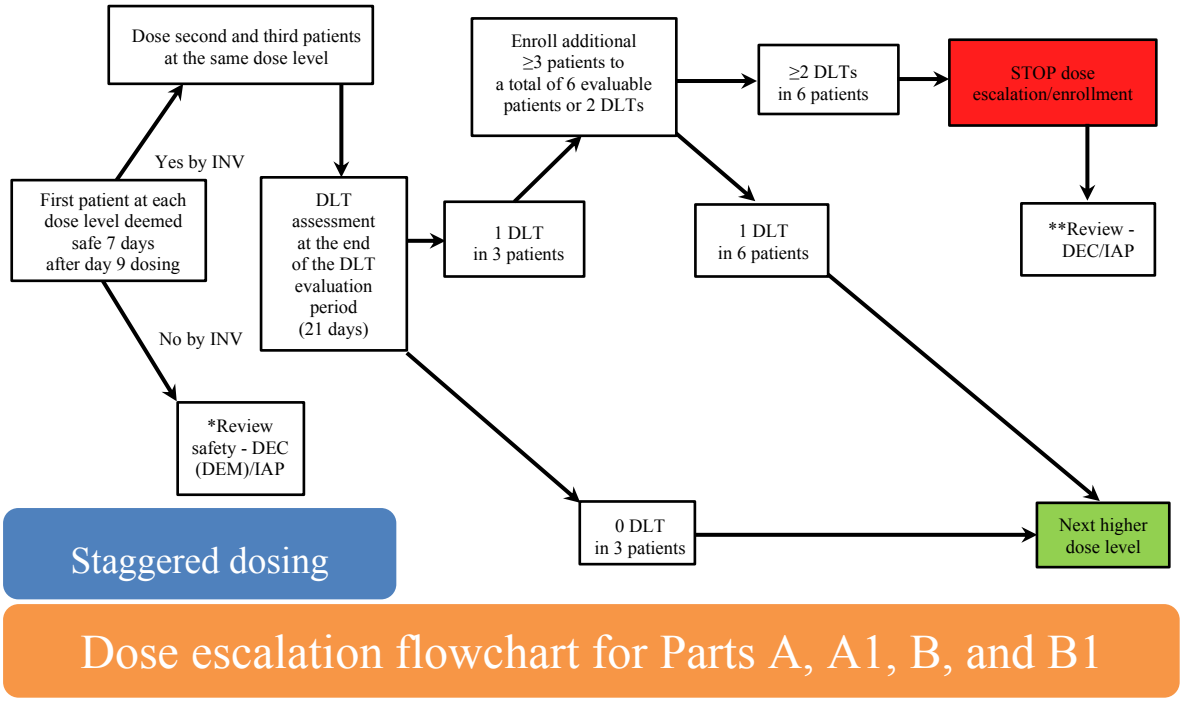
After completion of the DLT evaluation period with the adequate number of evaluable patients as defined below (see Figure 9.7), all data as specified in the DEM Charter will be reviewed during a DEM by the DEC. The same data will also be reviewed by the IAP as described in the IAP Charter. The decision as to whether an AE should be considered as DLT and/or whether a dose level is to be considered intolerable will be made by the DEC with endorsement from the IAP. The DEC consists of the study investigators and the sponsor's medical monitor. The IAP consists of two independent clinical experts and an independent statistician.

In the event of a confirmed non-tolerable dose in any cohort, the sponsor will inform all sites immediately so that the patients will not be exposed to doses of SO-C101 that have

been determined to exceed the MTD (see also the DEM Charter and sections 9.7.5 and 9.7.6). Patients who will not be DLT evaluable will be replaced. Replaced patients can continue with study treatment until any of the criteria listed in section 9.11.10 are met.

The dose escalation plan will follow the traditional 3+3 design as described by Le Tourneau et al.[29] This Protocol uses the European and Japanese definition of MTD and RP2D; see also section 12.6. Initially, three patients will be enrolled for each dose level and if none of the three patients in a cohort experiences a DLT, another three patients will be treated at the next higher dose level. However, if one of the first three patients experiences a DLT, three more patients will be treated at the same dose level. The dose escalation continues until at least two patients in a cohort of three to six patients experience DLTs (i.e., ≥33% of patients with a DLT at that dose level). If an MTD is reached, then the dose escalation will be stopped. The DEC will then decide whether any additional patients need to be enrolled in any dose level(s) not exceeding the MTD to gain confidence at the dose which will be considered as the RP2D.

Figure 9.7: Dose escalation flowchart (staggered dosing and 3+3 design)



* The DEC will review, discuss, and decide on the next steps of the study endorsed by the IAP.

**At this review meeting, the DEC will decide (with IAP endorsement) whether any additional patients need to be enrolled in any dose level(s) not exceeding the MTD to gain confidence at the dose which will be considered as the RP2D.

INV: Investigator

Staggered (sentinel) dosing will be employed as described below:

For each dose level, the first patient for the cohort will receive the first cycle of SO-C101 on day 1, day 2, day 8, and day 9. This patient will be observed for safety for 7 days afterwards, starting from day 9. If there are no safety concerns at the end of these 7 days, the responsible investigator will notify the sponsor's medical monitor and the second and third patients will be allowed to be dosed. The second and third patients will not be dosed on the same day. If there is a concern at the end of these 7 days of observation for safety of the first patient, the study investigator will notify the sponsor's medical monitor as soon as

possible and the sponsor will notify all sites and a DEM will be organized. The DEC will review, discuss, and decide on the next steps of the study.

9.7.1 DLT definitions for Part A, Part A1, Part B, and Part B1

DLTs will be AEs as specified below and graded according to the NCI's Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. Attribution to SO-C101 will not be used and the AEs listed below will be considered DLTs unless clearly not related to SO-C101 (i.e., events clearly due to the cancer disease, other comorbid illness, or unequivocally related to concomitant medications). The DLT evaluation period is the first treatment cycle of 21 days. Every DLT in the study will be discussed with the study investigators and every effort will be made to ensure all clinical assessments are carried out and documented appropriately and, wherever possible, histological assessments are also performed to identify and understand the safety profile of SO-C101 as monotherapy and in combination with pembrolizumab.

9.7.1.1 AEs that are considered DLTs

- All grade 5 events not clearly related to disease progression or any other causes will be considered DLTs.
- Any grade 3 or higher **non-hematologic toxicity** regardless of duration will be considered a DLT: with the **exceptions** below that are **NOT** considered DLTs:
  - Grade 3 nausea, vomiting, or diarrhea that can be controlled within 72 hours
  - Grade 3 fatigue less than 5 days
  - Grade 3 or higher correctable electrolyte abnormalities that last less than 72 hours and not associated with clinical complications
  - Grade 3 or higher amylase or lipase not associated with clinical manifestations of pancreatitis
- Hy's law cases will be considered DLTs (see section 12.3)
- Grade 3 AST or ALT or grade 3 bilirubinemia that lasts more than 5 days
- **Hematologic DLTs** will include the following:
  - Grade 4 neutropenia or thrombocytopenia lasting more than 7 days
  - Febrile neutropenia
  - Grade 3 or higher thrombocytopenia with bleeding
- Any grade 4 immune-related AEs regardless of duration
- Any grade 3 or grade 4 non-infectious pneumonitis regardless of duration
- Any grade 3 immune-related AEs, excluding colitis, hepatitis, and pneumonitis, that do not downgrade to grade ≤2 within 3 days after onset of the event despite maximal supportive care including systemic corticosteroids or downgrade to grade 1 or baseline within 14 days
- Any grade 2 pneumonitis that does not resolve to grade 1 within 3 days of the initiation of maximal supportive care
- Recurrent grade 2 pneumonitis in Part B and Part B1
- Grade 3 colitis

9.7.1.2 AEs that are NOT considered DLTs

- Grade 3 endocrinopathy that is managed with or without systemic corticosteroid therapy and/or hormone replacement therapy
- Inflammatory reaction attributed to a local antitumor response (grade 3 tumor pain caused by acute inflammatory reaction at tumor-bearing sites, e.g., like sites of metastatic disease or lymph nodes) that resolves to grade 1 within 3 weeks
- Concurrent vitiligo or alopecia of any AE grade

Other clinically significant toxicities, including a single event or multiple occurrences of the same event, may be considered as DLTs.

AEs occurring after treatment cycle 1 may be considered DLT-like events upon DEC discussion. If required, a DEM will be set up to assess these events.

9.7.2 Maximum tolerated dose and selection of the recommended phase 2 dose

If the MTD is reached, the RP2D is conventionally defined as the dose level just below this non-tolerated dose level. If ≤1 of 6 patients (or 0 of 3) in all dose cohorts experience a DLT, then the MTD will not have been reached. If the MTD is not reached, then the RP2D will be selected based on integrated evaluation of safety, tolerability, clinical benefit, and PK and PD data for all dose levels tested. An expansion cohort of up to 12 patients at the RP2D could be considered to obtain more experience if required.

The DEC will evaluate the data and select the RP2D according to the following guidelines:

1. The RP2D will not exceed the MTD.
2. Toxicities other than DLTs will be considered, including AEs assessed as related to SO-C101 treatment but not considered dose limiting, the nature and frequency of toxicities, and the emergence of any specific category of toxicities.
3. Evidence of clinical activity, as available
4. Available PK/PD data
5. If 2 or more potential RP2D dose levels cannot be distinguished using the criteria above, cohort expansion for optimized RP2D determination may take place at up to 2 dose levels to obtain data for up to 6 additional patients per dose level. The selection of RP2D will be based on this larger dataset. If serious related toxicities are observed in later cycles beyond cycle 1, a reduction of the MTD and/or RP2D may be considered. This determination will be made by the investigators and the sponsor's medical monitor, taking into account all available data.

9.7.3 Dose escalation meetings

A DEM will only take place once there are 3 or 6 DLT-evaluable patients to complete the cohort. A DEM will take place after the last patient of the cohort has completed the first cycle (21 days) with or without DLTs and is evaluable for DLT assessment.

After completion of the DLT period, all available safety data will be reviewed by the IAP as well as the DEC. The decision as to whether AEs should be considered as DLTs and/or whether a dose level is to be considered intolerable will be made by the DEC with endorsement from the IAP (for details, see the DEM Charter). The IAP will consist of two independent clinical experts and an independent statistician. The working principles of the IAP will be defined in the IAP Charter. In the event of a confirmed non-tolerable dose in

any cohort, the sponsor will inform all sites immediately so that patients will not be exposed to doses of SO-C101 that have been determined to exceed the MTD.

At every DEM, all accumulated safety data from previous cohorts will also be reviewed and any safety issues arising during this longer follow-up period will be taken into consideration by the DEM panel as well as the IAP.

9.7.4 Safety monitoring beyond cycle 1

9.7.4.1 Part A and Part A1

Starting from cycle 2, patients will be monitored for all AEs including late immune-related toxicities which might be associated with SO-C101 administration for 90 days after the last dose of SO-C101 (see section 9.7.7.3). Any late toxicities will be considered in the determination of the MTD/RP2D and dose schedules for Part A, Part A1, Part B, and Part B1.

9.7.4.2 Part B and Part B1

Patients will be monitored at the same visits and assessments as specified in Part A and Part A1 with special attention paid to the potentiation of immune-mediated reactions during the combination treatment with SO-C101.

The following immune-mediated reactions were reported in patients treated with pembrolizumab: immune-mediated pneumonitis; immune-mediated colitis; immune-mediated hepatitis; immune-mediated nephritis; infusion-related reactions; immune-mediated endocrinopathies: hypophysitis, thyroid disorders, and type 1 diabetes mellitus.[37,38]

Patients will be monitored for 90 days after the last dose of SO-C101 and/or pembrolizumab (whichever occurs later) for any late toxicities (see section 9.7.7.3). These toxicities will be considered for the assessment of MTD/RP2D in Part B and Part B1.

9.7.5 Patient recruitment management

Patient allocation and recruitment to all cohorts in Part A, Part A1, Part B, and Part B1 will be actively managed by the sponsor as described in the Cohort Management Manual. The study will recruit patients to all ongoing study parts in parallel. Recruitment will be based on pre-specified slot allocation to ensure equal chance for all sites to enroll patients into the study. The study investigators will be informed about available slot allocation on an ongoing basis by e-mails or during teleconferences (TCs) with sites.

9.7.6 Communication plan

Study investigators will inform the sponsor's medical monitor via an immediate phone call in case of an urgent safety signal including, but not limited to, DLTs, life-threatening immune reactions, and serious safety-related protocol deviations. The sponsor's medical monitor will immediately inform all sites and any preventative measure will be put in place including stopping recruitment temporarily if required. In case of a DLT, this immediate phone call will be followed by submission of required information within 24 hours via electronic Case Report Form (eCRF) or via email. The sponsor's medical monitor will immediately inform all sites and the IAP and a DEM will be planned.

Regular study TCs will be held among study investigators (designated sub-investigators) and the sponsor's medical monitor. The aim is to review potential patients for recruitment

and allow communication flow of updates on ongoing patients in the study including any emerging safety issues. The study investigator or designated sub-investigator will also inform the sponsor's medical monitor at these regular TCs of any important toxicities or DLT-like events occurring in the subsequent cycles. This will allow any appropriate actions to be implemented.

Ad-hoc meetings with the study investigators or designees may also be arranged to discuss any safety concerns during the study.

9.7.7 Study periods in Part A, Part A1, Part B, and Part B1

9.7.7.1 Screening period

Patients will be screened within a period of not more than 21 days, which will start when the ICF has been signed and end on day 1 of cycle 1. If screening is not completed within this period, next steps (continue/discontinue the patient in the study) will be discussed with the sponsor's medical monitor.

9.7.7.2 Treatment periods

9.7.7.2.1 DLT evaluation period

The DLT evaluation period will be the first treatment cycle of 21 days.

9.7.7.2.2 Continued treatment period

Patients without DLT during the DLT evaluation period will continue treatment with SO-C101 monotherapy or SO-C101 together with pembrolizumab until any of the criteria listed in section 9.11.10 are met.

Intra-patient dose escalation beyond the dose initially assigned to a patient is not permitted during cycle 2. However, patients receiving treatment with SO-C101 beyond cycle 2 may continue treatment at the next higher dose level if it is assessed to be safe by the DEC and IAP and if the criteria listed in section 8.1.8 are met. These patients after intra-patient dose increase will NOT be part of the higher dose escalation cohorts; therefore, after intra-patient dose increase, they will not be part of the DLT evaluation.

Intra-patient escalation up to the RP2D level is allowed and can be done step-by step if the patient stays at the higher dose level and meets the criteria for escalation in section 8.1.8.

In Part B and Part B1, in case SO-C101 needs to be discontinued for reasons other than disease progression, pembrolizumab treatment will continue for up to 1 year until any of the criteria listed in section 9.11.10 are met. If pembrolizumab needs to be discontinued for reasons other than disease progression, SO-C101 treatment will continue until any of the criteria listed in section 9.11.10 are met.

9.7.7.2.3 EoT visit

After termination of study treatments (SO-C101 and/or pembrolizumab), patients will be evaluated at the EoT visit, which will be scheduled within 7 days (+7 days) after the final administration of SO-C101 and/or pembrolizumab (whichever occurs later).

9.7.7.3 Follow-up period

Every effort should be taken to monitor all AEs and concomitant medications for 90 days after the final dose of SO-C101 and/or pembrolizumab (whichever occurs later); all patients

will come to the clinic 30 (±2) days, 60 (±2) days, and 90 (±2) days after the final dose of SO-C101 and/or pembrolizumab.

Patients who discontinue SO-C101 therapy prior to confirmed progressive disease per iRECIST (iCPD) or start of a new anticancer therapy will continue to have regular tumor assessments until:

- iCPD, or
- start of a new anticancer therapy, or
- 6 months (±2 weeks) after the EoT visit,

whichever occurs earliest, unless patients withdraw consent.

Patients will be followed up for survival at 3 months (±2 weeks) and 6 months (±2 weeks) after the EoT visit (end of the patients' study participation).

9.7.8 Study periods in Part D and Part D1

9.7.8.1 Screening period

Patients will be screened within a period of not more than 21 days, which will start when the ICF has been signed and end on day 1 of cycle 1. If screening is not completed within this period, next steps (continue/discontinue the patient in the study) will be discussed with the sponsor's medical monitor.

9.7.8.2 Treatment period

Patients will be treated with SO-C101 until any of the criteria for treatment discontinuation are met. After termination of SO-C101, patients will be evaluated at the EoT visit, which will be scheduled within 7 days (+7 days) after the final administration of SO-C101.

9.7.8.3 Follow-up period

Every effort should be taken to monitor all AEs and concomitant medications for 90 days after the final dose of SO-C101; all patients will come to the clinic 30 (±2) days, 60 (±2) days, and 90 (±2) days after the final dose of SO-C101.

Patients who discontinue SO-C101 therapy prior to iCPD or start of a new anticancer therapy will continue to have regular tumor assessments until:

- iCPD, or
- start of a new anticancer therapy, or
- 6 months (±2 weeks) after the EoT visit,

whichever occurs earliest, unless patients withdraw consent.

Patients will be followed up for survival at 3 months (±2 weeks) and 6 months (±2 weeks) after the EoT visit (end of the patients' study participation).

9.7.9 End of the study

It is expected that the enrollment duration will be 31-48 months (14-22 months Part A, 3-9 months Part A1, 11-18 months Part B, 3-9 months Part B1, 6-12 months Part D, and 12-18 months Part D1) and for each patient the estimated average treatment duration will be 12-24 weeks in Part A, Part A1, Part D, and Part D1; and 24-36 weeks in Part B and Part B1.

Patients who will respond to therapy will continue with treatment as specified in sections 9.7.7 and 9.7.8.

Each study part will end when the last patient in this study part completes the last visit, including follow-up calls. The study will end when the last patient completes the last visit, including follow-up calls.

9.7.10 Early termination of the study

The sponsor reserves the right to discontinue the study for medical reasons or any other reason at any time. If the study is prematurely terminated or suspended, the sponsor will promptly inform the investigators/institutions, regulatory agencies, and IRB/ECs of the termination or suspension and the reason(s) for the termination or suspension.

The investigator reserves the right to discontinue the study should his/her judgment so dictate. If the investigator terminates or suspends the study without prior agreement of the sponsor, the investigator should inform the institution where applicable, and the investigator/institution should promptly inform the sponsor and the IRB/EC and provide the sponsor and the IRB/EC with a detailed written explanation of the termination or suspension. Study records must be retained.

9.7.11 Stopping rules for all parts

If a patient experiences a **life-threatening** serious AE (SAE) considered by the investigator to be related to SO-C101 (i.e., excluding events unequivocally related to cancer) or if >30% of the treated patients discontinue because of toxicities considered by the investigator to be related to SO-C101, the dosing of all patients in the study will be temporarily stopped until the IAP (and DEC for dose escalation parts only) have reviewed the safety data and determined if it is safe to continue and at which dose.

9.8 Selection of study population

9.8.1 Inclusion criteria for all study parts

Inclusion criteria for all study parts are the same with the exception of the pre-specified tumor type (inclusion criterion 2), please see below.

1. Age ≥18 years
2. Part A, Part A1, Part B, and Part B1: Patients with selected histologically or cytologically confirmed advanced and/or metastatic solid tumors (renal cell carcinoma, non-small cell lung cancer, small-cell lung cancer, bladder cancer, melanoma, Merkel-cell carcinoma, skin squamous-cell carcinoma, microsatellite instability high solid tumors, triple-negative breast cancer, mesothelioma, thyroid cancer, thymic cancer, cervical cancer, biliary tract cancer, hepatocellular carcinoma, ovarian cancer, gastric cancer, head and neck squamous-cell carcinoma, and anal cancer) who are refractory to or intolerant of existing therapies known to provide clinical benefit for their condition. Patients who were not previously treated with (naïve) or who have relapsed/refractory disease on immune checkpoint inhibitors are eligible.

   Part D and Part D1: Patients with histologically or cytologically confirmed advanced and/or mRCC, patients with histologically or cytologically confirmed advanced and/or metastatic skin squamous-cell carcinoma, and patients with relapsed/refractory advanced/metastatic melanoma who are refractory to or intolerant of existing therapies

known to provide clinical benefit for their condition. Patients who have relapsed/refractory disease on immune checkpoint inhibitors are eligible.

3. Performance status: Eastern Cooperative Oncology Group (ECOG) performance score 0-1. Patients with ECOG performance score 2 will be discussed with the sponsor's medical monitor to be agreed for inclusion (see appendix 12.4).
4. Immunosuppressive doses of systemic medications (such as steroids) or absorbed topical or inhaled steroids (doses ≤10 mg/day of prednisone or equivalent) are allowed. Doses above 10 mg/day of prednisone or equivalent must be discontinued at least 2 weeks before IMP administration.
5. Estimated life expectancy of ≥3 months
6. Washout periods: 4 weeks for chemotherapy, 4 weeks or 5 half-lives (whichever shorter) for biologic agents including immuno-oncology therapy and 4 weeks from major surgeries, definitive radiotherapy and 2 weeks after palliative radiotherapy
7. Have at least one measurable lesion per iRECIST in a non-irradiated port. If in a previously irradiated port, must have demonstrated progression since best response to radiation therapy.
8. Have fully recovered from previous treatment to grade ≤1 toxicity (excluding alopecia) or have stable grade 2 neuropathy
9. Adequate organ system function:
   9.1. Left ventricular ejection fraction by echocardiogram >50%
   9.2. Patients with thyroid disease are eligible if euthyroid on suppressive or replacement therapy and asymptomatic thyroid-stimulating hormone (TSH) increase to be allowed
   9.3. Creatinine clearance ≥30 mL/min using Cockcroft-Gault equation (see appendix 12.2)
   9.4. Hemoglobin at least 10 g/dL
   9.5. Prothrombin time (PT) and activated partial thromboplastin time (aPTT) ≤1.5× upper limit of normal (ULN)
10. ALT/AST ≤2.5×ULN and total bilirubin ≤2×ULN in patients without liver metastasis (benign hereditary hyperbilirubinemias, e.g., Gilbert's syndrome, are permitted, those patients must have total bilirubin <3 mg/dL). In patients with liver metastasis, ALT/AST ≤5×ULN is allowed but total bilirubin must be ≤2×ULN.
11. Negative serum pregnancy test if woman of child-bearing potential (WOCBP; non-childbearing is defined as greater than one year postmenopausal or surgically sterilized).

    WOCBP must adhere to using a medically accepted method of birth control and agree to continue its use during the study or be surgically sterilized (e.g., hysterectomy or tubal ligation) and males must agree to use barrier method of birth control while on study. WOCBP must agree to use highly effective contraception during treatment and for at least 30 days after SO-C101 discontinuation (Part A, Part A1, Part D, and Part D1) or 4 months after pembrolizumab discontinuation (Part B and Part B1) unless the last dose of SO-C101 is later than 4 months after the last pembrolizumab administration in Part B and Part B1. In such a case, the highly effective contraception must be used for at least 30 days after SO-C101 discontinuation. Highly effective contraception includes:

    - Placement of an intrauterine device or intrauterine hormone-releasing system

- Established hormonal contraceptive methods: oral, intravaginal, transdermal, injectable, or implant. Females who are using hormonal contraceptives must have been on a stable dose of the same hormonal contraceptive product for at least 4 weeks prior to dosing and must continue to use the same contraceptive during the study and for 30 days after SO-C101 discontinuation (Part A, Part A1, Part D, and Part D1) or 4 months after last pembrolizumab discontinuation (Part B and Part B1) unless the last dose of SO-C101 is later than 4 months after the last pembrolizumab administration in Part B and Part B1. In such a case, female patients must have been on a stable dose of the same hormonal contraceptive for at least 30 days after SO-C101 discontinuation.
- Bilateral tubal occlusion

Female patients exempt from this requirement are patients who practice total abstinence or have a sole male partner who is vasectomized with confirmed azoospermia. If currently abstinent, the patient must agree to use a double barrier method (condom plus diaphragm or cervical/vault cap with spermicide) if they become sexually active during the study, and for 30 days after SO-C101 discontinuation (Part A, Part A1, Part D, and Part D1) or 4 months after pembrolizumab discontinuation (Part B and Part B1) unless the last dose of SO-C101 is later than 4 months after the last pembrolizumab administration in Part B and Part B1. In such a case, the patient must agree to use a double barrier method during treatment and for at least 30 days after SO-C101 discontinuation.

Male patients must agree to use a condom during treatment and for 30 days after SO-C101 discontinuation (Part A, Part A1, Part D, and Part D1) or 4 months after pembrolizumab discontinuation (Part B and Part B1) unless the last dose of SO-C101 is later than 4 months after the last pembrolizumab administration in Part B and Part B1. In such a case, the patient must agree to use a condom during treatment and for at least 30 days after SO-C101 discontinuation.

12. Accessible tumor tissue available for fresh biopsy
13. Ability to understand and sign written informed consent to participate in the study

9.8.2 Exclusion criteria

9.8.2.1 Exclusion criteria for all study parts

1. Patient with untreated central nervous system metastases and/or leptomeningeal carcinomatosis; participants with previously treated stable (no progression on magnetic resonance imaging [MRI] done 4 or more weeks apart) brain metastases are **eligible**
2. Has a known additional malignancy that is progressing and/or requires active treatment
3. Prior exposure to drugs that are agonists of IL-2- or IL-15-like **but not limited** to rhIL-15 (NCI), ALT-803 (ALTOR), NKTR-214 (Nektar)
4. Patients with a history of and current interstitial lung disease or fibrosis and pneumonitis; patients with clinically significant or oxygen requiring chronic obstructive pulmonary disease or any chronic inflammatory disease (sarcoidosis etc.)
5. Has received a live vaccine within 30 days of planned start of study therapy. Note: Seasonal influenza vaccines for injection are generally inactivated flu vaccines and are allowed; however, intranasal influenza vaccines (e.g., Flu-Mist) are live attenuated vaccines, and are not allowed.

6. Absolute white blood cell (WBC) count $\leq 2.0 \times 10^9$/L
7. Absolute neutrophil count $\leq 1.0 \times 10^9$/L
8. Platelet count $\leq 100 \times 10^9$/L
9. Pregnant or breastfeeding women
10. Receiving any other investigational treatment
11. Any active autoimmune disease or a documented history of autoimmune disease, poorly controlled asthma, or history of syndrome that required systemic steroids (except the allowed doses) or immunosuppressive medications, except for patients with vitiligo or resolved childhood asthma/atopy. Patients with clinically controlled asthma who routinely require fixed doses intermittent use of bronchodilators and/or micro-doses of steroids are **allowed**.
12. Co-morbidities:
    - 12.1. History of hematopoietic malignancy including chronic lymphocytic leukemia (excluding childhood leukemia)
    - 12.2. History of coronary heart disease
    - 12.3. Evidence of clinically active infection requiring systemic (any route) antibiotic therapy. All prior infections must have resolved following optimal therapy.
    - 12.4. History of or serology positive for HIV or active hepatitis B or C. Cured hepatitis B and hepatitis C infections are eligible.
    - 12.5. Uncontrolled hypertension (systolic >160 mm Hg and/or diastolic >110 mm Hg) or clinically significant (i.e., active) cardiovascular disease, cerebrovascular accident/stroke, or myocardial infarction within 6 months prior to first study medication; unstable angina; congestive heart failure of New York Heart Association grade 2 or higher; or uncontrolled cardiac arrhythmia requiring medication. Patients with uncontrolled hypertension should be medically managed on a stable regimen to control hypertension prior to study entry.
    - 12.6. Clinically significant peripheral artery disease
    - 12.7. Prolongation of QTcF >450 msec[39]
    - 12.8. History of medical or psychiatric disease which, in the view of the investigator, would preclude safe treatment or acceptable study compliance
13. Any ongoing toxicity from prior anti-cancer treatment that, in the judgment of the investigator, may interfere with study treatment
14. Other illness that, in the opinion of the investigator, would exclude the patient from participating in this study, including uncontrolled diabetes mellitus, cardiac disease

9.8.2.2 Exclusion criteria for Part B and Part B1 only

- Is hypersensitive to any of the ingredients of pembrolizumab drug product (Keytruda™)
- History of solid organ transplantation or hematopoietic stem cell transplantation

9.9 Treatments

9.9.1 Treatments administered

9.9.1.1 SO-C101 (all study parts)

SO-C101 will be administered SC once a day (Part A, Part B, Part D) or twice a day 8 hours (±15 min) apart (Part A1, Part B1, Part D1) on day 1 (±1 day), day 2, day 8, and day 9 of the 21-day cycle. One treatment cycle will be 21 days (see also sections 9.1, 9.2, 9.3, 9.4, 9.5, and 9.6). The time of administration will be recorded in the eCRF.

SO-C101 will be supplied as solution for injection at a concentration of 2 mg/mL. See also section 11.9.

9.9.1.2 Pembrolizumab (Part B, Part B1)

The dose of pembrolizumab will be fixed (200 mg IV every 3 weeks) and will be administered together with the first SO-C101 administration on day 1. See also sections 9.3, 9.4, and 11.9.

9.9.2 Treatment modifications

Any treatment-related toxicity will be managed by concomitant medication (as appropriate) or by treatment interruption, dose reduction, and treatment discontinuation, or a combination of these.

No treatment modifications of SO-C101 will be allowed during the first cycle for all dose cohorts in Part A, Part A1, Part B, and Part B1 and for all patients in Part D and Part D1. In the following cycles, these might be allowed (for dose increase, see section 8.1.8; for treatment interruption, dose reduction, and treatment discontinuation, or a combination of these, see below). Any treatment modifications must be discussed with the sponsor's medical monitor prior to administration of SO-C101 to the patient.

Treatment modifications of pembrolizumab (Part B and Part B1) are allowed according to the approved label.[37,38] Whenever SO-C101 is interrupted in Part B and Part B1 due to immune-mediated toxicity, pembrolizumab should also be interrupted.

Patients who experience a DLT in cycle 1 in Part A, Part A1, Part B, and Part B1 may be allowed to continue SO-C101 at a reduced dose after discussion with the sponsor's medical monitor if this is judged to be in their best interest.

During SO-C101 treatment, SO-C101 dose interruptions and reductions due to toxicity will be implemented according to the instructions presented in Table 9.3 for all AEs excluding specific AEs as detailed in Table 9.4.

Table 9.3: Guidelines for SO-C101 dose adjustments after cycle 1

SO-C101-related toxicity[1]	During therapy	Approximate dose adjustment
Grade 1		
All occurrences	Continue SO-C101 treatment	Maintain dose level
Grade 2		
First occurrence		Maintain dose level

SO-C101-related toxicity[1]	During therapy	Approximate dose adjustment
Second occurrence (same toxicity)	Interrupt SO-C101 until resolved to grade ≤1 or baseline[2]	Reduce by one dose level of starting dose
Third occurrence (same toxicity)		Reduce by two dose levels of starting dose
Fourth occurrence (same toxicity)		Discuss with sponsor's medical monitor
Grade 3		
First occurrence	Interrupt SO-C101 until resolved to grade ≤1 or baseline[2]	Reduce by one dose level of starting dose
Second occurrence (same toxicity)		Reduce by two dose levels of starting dose
Third occurrence (same toxicity)	Discontinue SO-C101 treatment	Not applicable
Grade 4: Discontinue SO-C101 treatment[3]		

1. Excluding alopecia and nausea, vomiting or diarrhea not receiving adequate treatment, and AEs such as pneumonitis, colitis, and ALT/AST and bilirubin elevations as specified in Table 9.4
2. Any dosage interruptions of more than 7 days should be discussed with the sponsor's medical monitor to establish if longer dose interruption is needed; a delay of SO-C101 for more than 14 days due to any treatment-related toxicity must be discussed with the sponsor's medical monitor before treatment can be resumed. If systemic corticosteroids for the treatment of immune-mediated AEs are required at doses above 10 mg of prednisone or equivalent for less than 4 weeks, the study drugs should be held. If systemic corticosteroids at doses above 10 mg of prednisone or equivalent are required for more than 4 weeks, then the study drugs should be discontinued.
3. Exclude grade 4 hematologic toxicity of less than 72 hours duration

Retreatment with SO-C101 is contraindicated in patients who have experienced grade 4 toxicities and third occurrences of grade 3 toxicities during the study.

The treatment modifications below apply to all SO-C101 treatment administrations (all study parts). Where specified as delay or hold (after cycle 1), SO-C101 will be delayed/held week to week. For details, see Table 9.4.

Table 9.4: SO-C101 modifications after cycle 1 for specific AEs – delay/hold

Event	Grade/Severity	SO-C101 modifications
Kidney dysfunction	Creatinine clearance <30 mL/min	Delay the scheduled SO-C101 treatment one week each for up to two weeks until a recovery is sufficient to resume SO-C101 treatment, otherwise, discontinue SO-C101 treatment.
Febrile neutropenia		
Thrombocytopenia with bleeding or anemia		
Absolute lymphocyte count (ALC)	>50,000/mL	
WBC	>60,000/mL	

Event	Grade/Severity	SO-C101 modifications
Systolic hypotension	<90 mm	Manage with bolus fluid administration of up to 1.5 L over 24 hours. If systolic hypotension (<90 mm) of grade <3 persists at time of next scheduled SO-C101 treatment, an attempt should be made to correct this with bolus fluids administration of up to 1.5 L over 6 hours. If this corrects the hypotension, the SO-C101 treatment can be given. If it does not correct, SO-C101 treatment should be delayed one week each for up to 2 weeks until recovery is sufficient to resume SO-C101 treatment, otherwise discontinue SO-C101 treatment.
Allergic reactions/acute infusion reaction	Grade 2 with bronchospasm or any grade 3-4	Permanently discontinue SO-C101 treatment.
	Grade 1 or 2 (without bronchospasms)	Delay SO-C101 treatment until symptoms subside.
Pneumonitis	Grade 2	Hold SO-C101 treatment. Resume 1 dose level lower once improved to grade 1 or resolved.
	Grade 3 or 4	Permanently discontinue SO-C101 treatment.
Colitis	Grade 2 or 3	Hold SO-C101 treatment. Resume 1 dose level lower once improved to grade 1 or resolved.
	Grade 4	Permanently discontinue SO-C101 treatment.
ALT or AST	Grade 2	Hold SO-C101 treatment. Resume 1 dose level lower once improved to grade 1 or resolved.
	Grade 3	Permanently discontinue SO-C101 treatment.
Total bilirubin	Grade 2	Hold SO-C101 treatment. Resume 1 dose level lower once improved to grade 1 or resolved
	Grade 3	Permanently discontinue SO-C101 treatment.

9.9.3 SO-C101

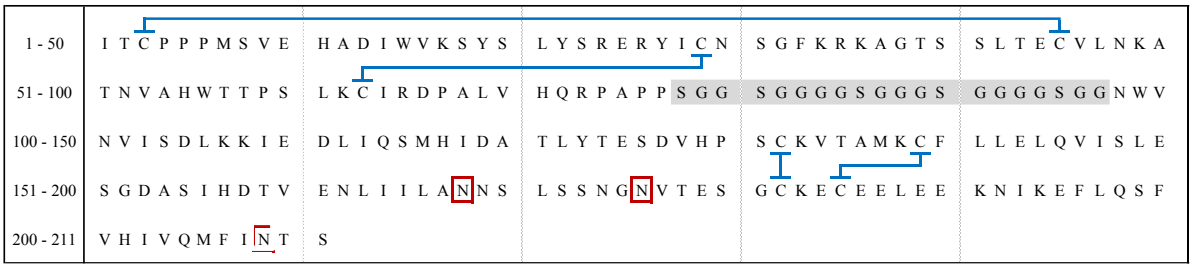
9.9.3.1 Name, structural formula

SO-C101 is a fusion protein. The N-terminal part of SO-C101 is comprised of 77 amino acids identical in sequence to the high-affinity binding site of IL-15Rα, referred to as the sushi domain. The C-terminal part is comprised of 114 amino acids identical in sequence to human IL-15. The two parts of SO-C101 are joined by a linker of 20 amino acids consisting of solely glycine and serine amino acids.

SO-C101 is thus comprised of 211 amino acids and has a theoretical intact monoisotopic mass of 22,666 Da. Based on published structural information and confirmed by experimental data, two di-sulphide bridges are within the N-terminal sushi domain and two di-sulphide bridges are in the C-terminal IL-15. Additionally, two N-glycosylation sites were experimentally confirmed with asparagine 176 carrying the majority of the N-glycans.

The amino acid sequence of SO-C101 is shown in Figure 9.8.

Figure 9.8: Amino acid sequence of SO-C101



In Figure 9.8, the di-sulphide bridges on the two parts of the fusion protein are shown with blue links between the relevant cysteines (C), the N-linked glycosylation sites are highlighted with a red box around the relevant asparagine (N) residues, and the linker between the two parts of the fusion protein is highlighted by grey shading.

9.9.3.2 Labeling for SO-C101

SO-C101 will be provided by the sponsor as clinical open-labeled supply labeled in accordance with text that is in full regulatory compliance with each participating country. The primary and secondary label will be translated into the required language(s) for each of those countries.

9.9.3.3 SO-C101 storage conditions

SO-C101 will be stored in accordance with the labeled storage conditions. Temperature monitoring is required at the storage location to ensure that SO-C101 is maintained within an established temperature range. The investigator or designee (or if regionally required, the head of the medical institution) is responsible for ensuring that the temperature is monitored throughout the total duration of the study and that records are maintained; the temperature should be monitored continuously by using either an in-house validated data acquisition system, a mechanical recording device, such as a calibrated chart recorder, or by manual means, such that minimum and maximum thermometric values over a specific time period can be recorded and retrieved as required.

9.9.4 Pembrolizumab

Pembrolizumab is commercially available. Always refer to the current/latest approved package insert/US prescribing information (for the US) and the Summary of Product Characteristics (SmPC; for the EU, available at: https://www.ema.europa.eu/documents/product-information/keytruda-epar-product-information_en.pdf) for comprehensive treatment information including, but not limited to, treatment preparation and administration as well as full pharmacologic and safety information.[37,38]

9.9.4.1 Pembrolizumab description

Pembrolizumab is a humanized monoclonal antibody that blocks the interaction between PD-1 and its ligands and can restore antitumor immune activity in solid tumors and hematologic malignancies.

9.9.4.2 Pembrolizumab identity

Pembrolizumab is supplied as Keytruda™ 1 vial of 100 mg/4 mL (25 mg/mL) – concentrate for solution for infusion.

9.9.4.3 Pembrolizumab: safety information

Pembrolizumab is commercially available. For full safety information, please always refer to the current package insert/US prescribing information (for the US) and to the current SmPC.[37,38]

9.9.4.4 Pembrolizumab immunogenicity

In clinical studies in patients treated with pembrolizumab 2 mg/kg every three weeks, 200 mg every three weeks, or 10 mg/kg every two or three weeks, 36 (1.8%) of 2034 evaluable patients tested positive for treatment-emergent antibodies to pembrolizumab, of which 9 (0.4%) patients had neutralizing antibodies against pembrolizumab. There was no evidence of an altered PK or safety profile with anti-pembrolizumab binding or neutralizing antibody development.[37]

9.9.5 Comparator drug

Not applicable

9.9.6 Method of assigning patients to treatment groups

See sections 9.1, 9.2, 9.3, 9.4, 9.5, 9.6, and 9.7.5.

9.9.7 Selection of doses in the study

See sections 9.1, 9.2, 9.3, 9.4, 9.5, and 9.6.

9.9.8 Selection and timing of dose for each patient

See sections 9.1, 9.2, 9.3, 9.4, 9.5, and 9.6.

9.9.9 Blinding

This is an open-label study; the treatment will not be blinded.

9.10 Supportive care and concomitant medication

SO-C101 is to be administered in a hospital setting under supervision of the investigator. An intensive care facility and skilled specialists must be available.

Supportive care can be provided based on investigator judgment according to local institutional guidelines. For pembrolizumab, the approved label should be followed.[37,38]

SO-C101 should not be administered to the patients with significant cardiac, pulmonary, renal and hepatic, or central nervous system impairment.

SC injection sites will be rotated to different areas of the body (upper and lower extremities, each of the 4 quadrants of the abdomen) to minimize the summated local effects of SO-C101 administration.

The investigator should instruct patients to notify the investigational site about any new medications taken since screening. All medications and non-drug therapies (including physical therapy, pre-medications, and blood transfusions) administered after screening must be listed in the eCRF. See also section 9.10.4.1 for prohibited medications.

9.10.1 Management of cytokine release syndrome

The management intervention guidelines described in this section can be modified by the individual study center as medically necessary or as appropriate without requiring a Protocol amendment or being considered a protocol deviation.

SO-C101 is a fusion protein, which comprises a variant of the IL-15 molecule, which is a common γ-chain cytokine and shares the IL-2R β and γ chains for signaling. SO-C101 therefore could have similar immunostimulatory properties as IL-2. SO-C101 treatment could potentially cause cytokine release syndrome as commercially available IL-2, although the risk is low.

Cytokine release syndrome may begin immediately after treatment administration, may be marked by increased capillary permeability to protein and fluids, and may reduce vascular tone. In most patients, this will result in a concomitant drop in mean arterial blood pressure within 2 to 12 hours after the start of treatment. With continued treatment, clinically significant hypotension (defined as systolic blood pressure below 90 mm Hg or a 20 mm Hg drop from baseline systolic pressure) and hypoperfusion may occur. In addition, extravasations of protein and fluids into the extra-vascular space will lead to the formation of edema and creation of new effusions. Potentially life-threatening complications of cytokine release syndrome could include cardiac dysfunction, adult respiratory distress syndrome, neurologic toxicity, renal and/or hepatic failure, and disseminated intravascular coagulation. Of particular concern is cardiac dysfunction, which can have a rapid onset and be severe, but is typically reversible.

Medical management of cytokine release syndrome begins with careful monitoring of the patient's fluids and organ perfusion status. This is achieved by frequent determination of blood pressure and pulse, and by monitoring organ functions, which includes assessment of mental status and urine output. Occurrence of hypovolemia will be monitored. Flexibility in fluid and pressor management is essential for maintaining organ perfusion and blood pressure. Therefore, extreme caution should be used in treating patients with fixed requirements for large volumes of fluid. Administration of IV fluids, either colloid or crystalloid is recommended for treatment of hypovolemia. Correction of hypovolemia may require large volumes of IV fluids but caution is required because unrestrained fluid administration may exacerbate problems associated with edema formation or effusions.

With extra-vascular fluid accumulation, edema is common and ascites, pleural or pericardial effusions may develop. Management of these events depends on a careful balancing of the effects of fluid shifts so that neither the consequences of hypovolemia (e.g., impaired organ perfusion) nor the consequences of fluid accumulations (e.g., pulmonary edema) exceed the patient's tolerance. Pulmonary edema, another manifestation of CLS, can lead to respiratory failure.

For further management guidelines please refer to Proleukin that is approved in some countries in the EU for the treatment of mRCC[40] and in the US by the FDA to treat mRCC and MM.[41]

For consensus guidelines on management, please also refer to "High-dose interleukin-2 (Aldesleukin) – expert consensus on best management practices-2014".[42] See also appendix 12.5.

9.10.2 Life-threatening toxicities

Life-threatening toxicities, if they are attributed to inflammatory reactions of SO-C101 in the judgment of the investigators, may be ameliorated by an IV administration of dexamethasone or other steroid-based medications. However, the use of systemic steroid medications may result in loss of the therapeutic effects of SO-C101. Patients receiving steroid medication may continue to receive the study treatment if, in the opinion of the investigator, there is potential clinical benefit and the patient is motivated to do so.

9.10.3 Overdosing

Side effects following administration of SO-C101 during the pre-clinical studies appeared to be dose related. Exceeding the recommended dose in the study can be associated with increased toxicity. Symptoms which persist after stopping the treatment with SO-C101 should be closely monitored and treated supportively. For the life-threatening toxicities, IV administration of dexamethasone is recommended.

9.10.4 Prohibitions and restrictions during the study period

9.10.4.1 Prohibited medications

Concomitant use of drugs known to prolong the QT/QTc interval is prohibited during the study. Some of the medications known to prolong the QT interval are[43]: amiodarone, azithromycin, ciprofloxacin, chlorpromazine, citalopram, domperidone, donepezil, escitalopram, fluconazole, haloperidol, levofloxacin, levomepromazine, methadone, ondansetron, and sulpiride. A complete list of medications known to prolong the QT interval can be found at www.crediblemeds.org.

Administration of live vaccines during treatment with SO-C101 (Part A, Part A1, Part D, Part D1) and with SO-C101 and pembrolizumab (Part B and Part B1) is prohibited.

Administration of another IMP during treatment with SO-C101 (Part A, Part A1, Part D, Part D1) and with SO-C101 and pembrolizumab (Part B and Part B1) is prohibited.

Another anticancer therapy during treatment with SO-C101 (Part A, Part A1, Part D, Part D1) and with SO-C101 and pembrolizumab (Part B and Part B1) is prohibited. Palliative radiotherapy of, e.g., painful bone metastases not defined as indicator lesions is allowed.

9.10.4.2 Warnings and precautions

Systemic steroid medications may result in loss of therapeutic effects of SO-C101 and should be avoided. However, in the event of a life-threatening inflammatory reaction to SO-C101, the IV administration of dexamethasone or other steroid-based medication is warranted. Corticosteroids have been shown to reduce cytokine-induced side effects including fever, renal insufficiency, hyperbilirubinemia, confusion, and dyspnea. However, low doses of steroids such as prednisone ≤10 mg per day or equivalent are acceptable. For Part B and Part B1: the approved label of pembrolizumab should be followed. If systemic corticosteroids for the treatment of immune-mediated AEs are required at doses above 10 mg of prednisone or equivalent for less than 4 weeks, the study drugs should be held. If systemic corticosteroids at doses above 10 mg of prednisone or equivalent are required for more than 4 weeks, then the study drugs should be discontinued.

Reference is made also to the Proleukin label that is approved in some countries in the EU for the treatment of mRCC (Proleukin UK label/SmPC at: https://www.medicines.org.uk/emc/ product/291) and in the US by the FDA to treat mRCC and MM (Proleukin US prescribing information at: https://www.proleukin.com/downloads/PR001I_Package%20Insert%20Clean.pdf).

As Proleukin is a marketed medicine and an immunocytokine which may share a similar mechanism of action to SO-C101 albeit with an adverse safety profile, it appears reasonable to refer to the same warnings and precautions relating to the concurrent administration of medicinal products with hepatotoxic, nephrotoxic, myelotoxic, or cardiotoxic effects which may increase the toxicity of SO-C101 in these systems.[40,41] These medications should be avoided during treatment with SO-C101. Beta-blockers and other antihypertensives may potentiate the hypotension seen with cytokine therapy. Therefore, administration of these medications should be avoided during SO-C101 administration but may be used at the discretion of the investigator.

9.10.4.3 Drug-drug interaction potential

PK drug interaction studies were not carried out with SO-C101. Based on its biologic nature, a competition with drug-metabolizing enzymes and transporters is not expected. In addition, SO-C101 does not contain Ig domains such as Fc parts minimizing the risk of interference with concomitant monoclonal antibody therapies.

9.10.4.4 Food

No food interaction is expected as the route of administration is not oral.

9.10.5 Treatment compliance

Treatment for each patient will be recorded during the study. CRAs will review treatment compliance during site visits and at the completion of the study.

9.10.6 IMP supplies and accountability

9.10.6.1 IMP supply

Study treatments must be received by designated personnel at the study site and kept in a secured location to which only designated site staff have access.

The investigator will not allow the IMPs to be used other than as directed by this Protocol. IMPs will not be dispensed to any individual who is not enrolled in the study.

9.10.6.2 IMP accountability

The investigator and the study staff (or if regionally required, the head of the medical institution or the designated pharmacist) will be responsible for the accountability of all IMPs (shipment, dispensing, inventory) following the sponsor's instructions and adherence to GCP guidelines as well as local or regional requirements.

The investigator will not allow the IMPs to be used other than as directed by this Protocol. IMPs will not be dispensed to any individual who is not enrolled in the study.

The site must maintain an accurate and timely record of the following: receipt of all IMPs, dispensing of IMPs to the patient, collection and reconciliation of unused IMPs that are not dispensed to patients.

9.10.6.3 IMP disposal and destruction

At study close out or as appropriate during the study, the investigator will ensure return of reconciled IMPs (used and unused) to the sponsor, third party, or (where applicable) destruction of reconciled IMPs at the site.

This includes, but may not be limited to:

- Documentation of receipt of IMPs
- IMP dispensing reconciliation log
- IMP accountability log
- Documentation of returns to the sponsor
- Certificates of destruction for any destruction of IMPs that occurs at the site

All forms will be provided by the sponsor. Any comparable forms that the site wishes to use must be approved by the sponsor. The IMP and inventory records must be made available, upon request, for inspection by a designated representative of the sponsor or a representative of a health authority (e.g., FDA). Unused IMPs/study supplies that were shipped to the site but not dispensed to patients are to be returned to the sponsor's designated central or local depot(s) during the study or at the conclusion of the study unless provision is made by the sponsor for destruction of IMPs and containers at the site. Destruction at the site will only occur under circumstances where regulation or supply type prohibits the return of IMPs to the central or local depot(s). Approval for destruction to occur at the site must be provided by the sponsor in advance. Upon completion of IMP accountability and reconciliation procedures by the site's personnel and documentation procedures by the sponsor's personnel, IMPs that are to be returned to the sponsor's designated central or local depot(s) must be boxed and sealed and shipped back to the central or local depot(s) following all local regulatory requirements. In some regions, the IMPs may be removed from the site and hand delivered to the central or local depot by sponsor representatives. Where IMPs are approved for destruction at the site, destruction will occur following the site's standard procedures and certificates of destruction will be provided to the sponsor. IMP accountability will be reviewed during site visits and at the completion of the study.

9.11 Study assessments

The timing of study assessments and procedures is detailed in Table 9.6, Table 9.7, Table 9.8, Table 9.9, Table 9.10, Table 9.11, Table 9.12, Table 9.13, Table 9.14, Table 9.15, Table 9.16, and Table 9.17.

9.11.1 Demography, disease history, and other baseline assessments

Demography information includes age at screening, gender, race, and ethnicity.

All medically significant medical and surgical history must be noted in the eCRF. Information on history of current malignancy will be collected, including primary tumor location, histology/cytology, initial diagnosis date, lines of previous treatment, start and stop dates of the treatments prior to this study, and any prior mutations/genetic analysis (i.e., EGFR, KRAS mutations, BCL-2) and the date of the latest disease progression if not coinciding with the stop date.

Other baseline assessments will be done as described in Table 9.6 and Table 9.7.

9.11.2 Tumor assessments

Tumor assessments will be performed by investigators and assessed per iRECIST for all tumor indications. The sponsor may request that images acquired for tumor assessments be sent to an imaging core laboratory for archiving and potential independent analysis.

Disease response and disease progression will be evaluated in this study using iRECIST criteria by contrast enhanced computed tomography (CT) scans of the chest, abdomen, pelvis and/or MRI.

The baseline disease assessment will be performed before the initiation of study treatment and response assessments will be performed as indicated in Table 9.6, Table 9.7, and Table 9.8. For crossover patients, the last tumor assessment in Part A or Part A1 serves as baseline in Part B or Part B1.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. If there is a change in modality, then the study site may be asked to explain the reason for the change in the eCRF. A change in modality may be considered a protocol deviation.

If a dose modification causes a delay in SO-C101 administration, the schedule of radiographic assessment will remain every 6 weeks (±2 weeks).

9.11.3 Pharmacokinetic assessments

Instructions on PK sample collection, handling, storage, and shipment of samples is detailed in the study-specific Laboratory Manual provided to the study site.

The timing of PK sample collection is detailed in Table 9.14, Table 9.15, Table 9.16, and Table 9.17.

9.11.4 Pharmacodynamic and other biomarker assessments

SO-C101 activates and expands preferentially NK cells and CD8+ T cells which are the major effectors of SO-C101-mediated antitumor response. The assessment of the biological activity of SO-C101 might support the decisions for selection of monotherapy dose as well as combination dose with pembrolizumab during dose escalation in Part A, Part A1, Part B, and Part B1. PD markers will be assessed in blood PBMCs and paired tumor tissue.

9.11.4.1 Peripheral blood

9.11.4.1.1 Peripheral blood mononuclear cell analysis

9.11.4.1.1.1 Aim

To determine the SO-C101 dose-dependent activity on immune cell populations in peripheral blood

9.11.4.1.1.2 Rationale

SO-C101-induced NK- and CD8+ T-cell activation and proliferation is a direct and immediate measure of the PD response to SO-C101 administration. The analysis will be used to monitor SO-C101 activity at the individual dose levels and over repeated administrations.

9.11.4.1.1.3 Method

Flow cytometry analyses of PBMCs will be conducted from fresh blood in a volume of up to 9 mL delivered to central laboratory for analysis within 24 hours.

9.11.4.1.1.4 Pharmacodynamic markers

Immune cells (leukocytes including NK, CD8+ and CD4+ T cells or myeloid cells) will be detected based on described specific markers including various subpopulations. Moreover, selected functional markers specific for the immune cell populations will be examined.

9.11.4.1.2 Cytokine analysis

Changes in the plasma cytokine concentration of pro-inflammatory and immunosuppressive cytokines may correlate with the administration of SO-C101. Relevant cytokines will be measured in blood.

9.11.4.2 Tumor biopsy

Tumor biopsies will be collected during screening and during cycle 2 to determine the SO-C101-dependent activation and/or expansion of immune cells to be correlated with the antitumor efficacy of the SO-C101 monotherapy or SO-C101 in combination with pembrolizumab. Additional tumor biopsy can be done at the time of a clinically significant event (not mandatory assessment).

Paraffin-embedded blocks will be prepared at the sites from the tumor biopsies for immunohistochemistry and/or by gene profiling analyses and sent to the central laboratory in ambient temperature.

Archived, fixed tumor tissue can be collected if fresh biopsy at screening is not available.

9.11.5 Safety assessments

9.11.5.1 Adverse events and pregnancies

9.11.5.1.1 Definitions

9.11.5.1.1.1 Adverse events

ICH Guideline E2A defines an AE as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment.

According to the FDA (21CFR312.32), an AE means any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug-related.

An AE can therefore be any unfavorable and unintended sign (e.g., tachycardia, enlarged liver), symptom (e.g., nausea, chest pain), abnormal result of an investigation (e.g., laboratory finding), or disease temporarily associated with the use of a medicinal product, whether or not considered related to the medicinal product.

9.11.5.1.1.2 Serious adverse events

A SAE is any untoward medical occurrence that at any dose fulfills one or more of the following criteria:

- Results in death
- Is immediately life-threatening

  The term "life-threatening" in the definition of "serious" refers to an event in which the patient was at immediate risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Is another medically significant event defined as an event that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent any of the above listed outcomes

9.11.5.1.1.3 Excluded events

Hospitalization for the following reasons will not be regarded as serious (not immediately reportable):

- Routine treatment or monitoring of the disease under study, including hospitalization due to study-related procedures, not associated with any deterioration of the patient's status
- Elective or pre-planned treatment (before signing the ICF) for a pre-existing condition that is unrelated to the disease under study and has not worsened since signing the ICF
- Social reasons, respite care, and in the absence of a medical condition (e.g., for observational purposes without any intervention)

9.11.5.1.1.4 Severity/intensity vs. seriousness

ICH E2A: The term "severe" is often used to describe the intensity (severity) of a specific event (as mild, moderate, or severe myocardial infarction); the event itself, however, may be of a relatively minor medical significance (such as a severe headache). This is not the same as "serious", which is based on patient/event outcome or action criteria usually associated with events that pose a threat to a patient's life or functioning. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

9.11.5.1.1.5 Pregnancy of study patients or their partners

Patients who are fertile must use a medically accepted birth control method during their participation in this clinical study and for at least 30 days after SO-C101 discontinuation (Part A, Part A1, Part D, and Part D1) or 4 months after pembrolizumab discontinuation (Part B and Part B1) unless the last dose of SO-C101 is later than 4 months after the last pembrolizumab administration in Part B and Part B1. In such a case, the medically accepted birth control method must be used for at least 30 days after SO-C101 discontinuation. Female patients exempt from this requirement are patients who practice total abstinence or have a male partner who is vasectomized with confirmed azoospermia.

If currently abstinent, the patient must agree to use a double barrier method as described above if they become sexually active during the study, and for 30 days after SO-C101 discontinuation (Part A, Part A1, Part D, and Part D1) or 4 months after pembrolizumab discontinuation (Part B and Part B1) unless the last dose of SO-C101 is later than 4 months after the last pembrolizumab administration in Part B and Part B1. In such a case, the double barrier method must be used for at least 30 days after SO-C101 discontinuation. See also section 9.8.1.

Pregnancy is not considered an AE unless it meets any criteria for becoming serious (see the definitions in section 9.11.5.1.1.2). However, patients must inform the investigator of any newly identified pregnancy or pregnancy of their partners without delay.

Consent to report information on the outcome of the pregnancy of male patients' partners needs to be obtained from the pregnant partners.

9.11.5.1.2 Safety monitoring periods

9.11.5.1.2.1 Reporting

Every effort should be taken to collect all (S)AEs, from the date of the patient's signing the ICF until 90 days after the final administration of SO-C101 and/or pembrolizumab, whichever occurs later.

Additionally, any SAE brought to the attention of an investigator at any time outside of the reporting period specified above must be reported immediately to the sponsor if the event is considered to be causally related to the SO-C101 and/or pembrolizumab.

In Part A, Part A1, Part D, and Part D1, pregnancies must be reported from the date of the patient's signing the ICF until up to 30 days after the final administration of SO-C101.

In Part B and Part B1, pregnancies must be reported from the date of the patient's signing the ICF until up to 30 days after the final administration of SO-C101 or 4 months after the final administration of pembrolizumab, whichever occurs later.

9.11.5.1.2.2 Follow-up

The investigator assesses at each visit (or more frequently, if necessary) if there are any changes in AE diagnosis, severity, suspected causal relationship to clinical study medication/procedure, interventions required to treat the event, and AE outcome.

AEs are monitored (followed up) until resolution, stabilization (becoming a permanent condition), or 6 months (±2 weeks) after the EoT visit of the patient (end of the patient's study participation).

All SAEs will be followed up until the event has resolved or stabilized (permanent condition).

Pregnancies will be monitored by the investigator to determine the outcome, including spontaneous abortion or voluntary termination, birth details, and the presence or absence of any birth defects, congenital abnormalities, or maternal and newborn complications. Every infant has to be followed up for 2 months after delivery.

9.11.5.1.3 Assessing adverse events

Information about adverse reactions (causally related events) known for SO-C101 will be found in the IB or will be communicated between IB updates in the form of "Dear Investigator Letter".

9.11.5.1.3.1 Causality

The investigator needs to assess the causal relationship of any AE to:

- SO-C101
- Pembrolizumab (Part B and Part B1 only)
- Other suspected cause(s) of the event (e.g., concurrent disease, concomitant medication)

This assessment is based on the investigator's clinical judgment, taking into account all relevant information available at the time of AE reporting including (but not limited to):

- Temporal association of the event onset with administration of the medication/procedure
- Known type of reaction for any of the administered IMPs
- Disappearance or abating of symptoms when the IMP is discontinued or the dose is reduced
- Reappearance of symptoms when the IMP is re-administered
- Event may or may not be caused by the patient's health condition
- Presence of risks or factors not related to study treatment that are known to be associated with the occurrence of the event

Causal relationship of all AEs will be classified as follows:

- **Not suspected**: it is not plausible that the AE is caused by medication/procedure and a likely alternative explanation exists.

No reasonable possibility of a causal or temporal relationship.

- Suspected: it is plausible that the AE is caused by medication/procedure.

Reasonable possibility of a causal relationship.

For the purposes of safety reporting, ***'reasonable possibility'*** *means there is evidence to suggest a causal relationship between one of the IMPs/procedure and the AE.*

9.11.5.1.3.2 Severity/intensity

Severity or intensity of an AE has to be assessed according to the NCI CTCAE (v5.0). A grading scale is provided for AE terms displaying grades 1 through 5 with unique clinical descriptions of severity for each AE.

Grading refers to the severity of the AE.

9.11.5.1.3.3 Reporting by the investigational site

Any AE (including SAEs), whether or not considered to be causally related to the study medication and regardless of its seriousness, must be reported (described and recorded) in the AE section of the patient's eCRF on an ongoing basis.

A standardized question such as "Have you had any health problems since your last visit or since you were last questioned?" will be given by the investigator or the investigational site personnel at each contact with the patient.

Only clinically relevant (per investigator's discretion) abnormal laboratory values, vital signs, or examination abnormalities need to be documented as AEs. Whenever possible, a diagnosis rather than symptoms should be provided on the AE eCRF page (e.g., anemia instead of low hemoglobin).

Physical examination findings will be compared with the baseline status and any significant change, as assessed by the investigator, must be documented as an AE.

A surgical procedure is not an AE but a therapeutic measure for a condition that necessitates surgery. Therefore, the condition for which the surgery is required has to be reported as an AE.

Any pre-planned surgery (i.e., planned before signature of the ICF) or other intervention permitted by the Clinical Study Protocol and the condition leading to that measure are not AEs. In such cases, the underlying condition needs to be documented in the patient's eCRF medical history.

Death itself is not an AE but the outcome of an event, which needs to be described using medical terminology. Information about death will be captured on the respective eCRF page along with relevant details (date of death, immediate and underlying causes of death).

9.11.5.1.3.4 Documenting in eCRFs

The reported term should be a medical diagnosis or sign/symptom of the event, not a procedure. Each symptom in a constellation of symptoms should be listed separately if the investigator has not made a preliminary/tentative diagnosis.

Fluctuations or re-occurrences of a condition, which are considered normal for the patient and are recorded in the patient's eCRF medical history, do not need to be reported as an AE. However, if the condition deteriorates during the study, it needs to be captured as an AE.

If the same AE occurs repeatedly, it must be assessed and documented separately each time.

If possible, each AE should be evaluated to determine:

- Event term or a description of the AE in medical terms (not as reported by the patient)

- Severity grade or intensity of the event as assessed by the investigator (1-5 per NCI CTCAE [v5.0])
- Its causal relationship to SO-C101 as assessed by the investigator (suspected; not suspected)
- Its causal relationship to pembrolizumab (Part B and Part B1 only) as assessed by the investigator (suspected; not suspected)
- Other suspected cause(s) of the event (e.g., concurrent disease, concomitant medication)
- Event duration, including onset date and end date
- Action taken with SO-C101 due to the reported event (no action taken; treatment interrupted; dose modified; permanently discontinued)
- Action taken with pembrolizumab due to the reported event (no action taken; dose delayed; permanently discontinued) (Part B and Part B1 only)
- Other action taken (no action taken; pharmacological treatment applied; non-pharmacological therapy applied; other)
- Event seriousness (non-serious or serious AE)
- Event outcome (resolved, resolved with sequelae, not resolved, resolving, fatal, unknown)

9.11.5.1.3.5 Immediately reportable events

The investigator or any investigational site staff must immediately (**within 24 hours of awareness at the latest**) notify/report to the Pharmacovigilance department any initial or medically relevant follow-up information about these events:

- SAE
- Pregnancy of the patient or patient's female partner

The initial notification can be done over the phone on +420 725 385 443. This notification must be followed within an additional 24 hours by a written report (i.e., a completed SAE Report Form or Pregnancy Data Collection Form), providing all available information and a detailed narrative description. A formless notification (without a report form) is not required if the initial/follow-up information is reported on the appropriate form within 24 hours of knowledge.

The investigator must not wait to receive additional information to fully document the event before notifying the Pharmacovigilance department **primarily via the eCRF system**; or via:

Email: safety@sotio.com

Fax: +420 224 175 498

Phone: +420 725 385 443

Follow-up information must be sent within the same timelines using the same contact details as outlined above.

Additionally, refer to Safety Reporting Instructions for Sites for information on how to report these events.

9.11.5.1.3.6 Minimum notification/reporting requirements

The following information must be provided for a valid notification/report:

1. Identification of the notifying/reporting person (e.g., name of the reporter)
2. Identification of the patient (e.g., subject identification)
3. Concerned IMP or clinical study (e.g., SC103)
4. Reason for notification/reporting (i.e., SAE or pregnancy)
5. Event term

*In addition, providing the **assessment of the causal relationship** is necessary for comprehensive evaluation by the sponsor and potential regulatory submission.*

9.11.5.1.3.7 Report forms

The SAE Report Form is **primarily completed within the eCRF system** for the study and submitted to the Pharmacovigilance department. In case the eCRF system is not available/accessible, a paper SAE Report Form is filled out and sent to the Pharmacovigilance department (see details above).

For reporting of pregnancies, the paper Pregnancy Data Collection Form is to be used. Completion guidelines provide information on format and details of the information required.

Originals of the paper report forms must be kept in the site study file.

The report forms need to be completed in English.

All immediate reports from the investigational site to the Pharmacovigilance department (i.e., SAEs and patients' or partners' pregnancies) must also be recorded in the site's source documentation and in the eCRF as appropriate.

9.11.6 Safety monitoring of the patients during the study

As this is a FIH study, patients will be closely monitored for any adverse reactions to identify RP2D/MTD in Part A, Part A1, Part B, and Part B1. Safety monitoring of the patients during the study will include assessments, examinations, and laboratory tests as described below. The DLT evaluation period is specified as the first treatment cycle of 21 days. During this first treatment cycle, each patient at every dose level will be monitored closely before and after each dose of SO-C101. After cycle 1, the assessments, examinations, and laboratory tests will continue as specified in section 9.11.7 for the assessment of cumulative effect of SO-C101 (all study parts) and/or overlapping immune-related reactions of SO-C101 and pembrolizumab (Part B and Part B1) during the study.

9.11.6.1 Physical examination and body weight and height and body surface area

General physical examination with organ/system-specific physical examination will be carried out by a licensed physician (or the physician's assistant or a nurse practitioner).

For screening, a complete physical examination will be performed including head, eyes, ear, nose, throat, neck, cardiovascular, chest/lungs, abdomen (including liver and spleen size), extremities, neurological, skin, and lymph nodes. For subsequent visits according to the protocol schedule (Table 9.6, Table 9.7, and Table 9.8), a physical examination with the focus on abdomen (including liver and spleen size), lymph nodes, and any other system that

may contribute to clinical disease assessments is to be done. An ECOG performance status will be assigned as indicated in Table 9.6, Table 9.7, and Table 9.8.

Body height and body weight will be measured. Body height will be measured only at screening. Body weight will be measured before the start of each treatment cycle and as indicated in Table 9.6, Table 9.7, and Table 9.8.

Body surface area will be automatically calculated using Dubois and Dubois formula.[44]

9.11.6.2 Assessment of vital signs

Vital signs will include blood pressure (systolic and diastolic, after ≥15 minutes of rest), body temperature, heart rate, and respiratory rate. See also section 9.11.6.3.

9.11.6.3 Observation of patients after administration of SO-C101

9.11.6.3.1 Part A, Part B, and Part D

9.11.6.3.1.1 Cycle 1

9.11.6.3.1.1.1 Dose on day 1

In cycle 1 of Part A, Part B, and Part D, patients will be hospitalized for 24 hours after the first dose of SO-C101 on day 1 and will be closely observed for any AEs in the hospital.

Vital signs (body temperature, heart rate, respiratory rate, and systolic and diastolic blood pressure) will be documented at the following frequency at minimum unless clinically required otherwise:

- Prior to each SO-C101 dose
- 15 minutes (±5 minutes) after dosing
- 30 minutes (±5 minutes) after dosing
- 60 minutes (±10 minutes) after dosing, and then
- Every 60 minutes (±15 minutes) after dosing up until 8 hours following SO-C101 administration

9.11.6.3.1.1.2 Subsequent doses

During observation after subsequent doses of SO-C101, vital signs (body temperature, heart rate, respiratory rate, and systolic and diastolic blood pressure) will be documented at the following frequency at minimum until discharge from the clinic:

- Prior to each SO-C101 dose
- 15 minutes (±5 minutes) after dosing
- 30 minutes (±5 minutes) after dosing
- 60 minutes (±10 minutes) after dosing, and then
- Every 60 minutes (±15 minutes) after dosing up until 4-6 hours following SO-C101 administration

9.11.6.3.1.2 From cycle 2 onwards

For the subsequent cycles of Part A, Part B, and Part D, patients will be observed in the hospital up to 4-6 hours following SO-C101 administration.

During post-SO-C101 observation, vital signs (body temperature, heart rate, respiratory rate, and systolic and diastolic blood pressure) will be documented at the following frequency until discharge from the clinic:

- Prior to each SO-C101 dose
- 15 minutes (±5 minutes) after dosing
- 30 minutes (±5 minutes) after dosing
- 60 minutes (±10 minutes) after dosing, and then
- Every 60 minutes (±15 minutes) after dosing up until 4-6 hours following SO-C101 administration

If patients feel unwell at any point in time during the study after being discharged from the hospital, they should contact their study investigator as indicated in the ICF.

9.11.6.3.2 Part A1, Part B1, and Part D1

9.11.6.3.2.1 Cycle 1 day 1 and cycle 1 day 2

In Part A1, Part B1, and Part D1, patients will be hospitalized from day 1 to day 3 of cycle 1 and will be closely observed for any AEs in the hospital.

Vital signs (body temperature, heart rate, respiratory rate, and systolic and diastolic blood pressure) will be documented at the following frequency at minimum unless clinically required otherwise:

- Prior to the first dose of SO-C101
- 15 minutes (±5 minutes) after dosing
- 30 minutes (±5 minutes) after dosing
- 60 minutes (±10 minutes) after dosing, and then
- Every 60 minutes (±15 minutes) after dosing up until 8 hours following SO-C101 first administration
- Prior to the second dose of SO-C101
- 15 minutes (±5 minutes) after the second dosing
- Every 60 minutes (±15 minutes) after dosing up until 6 hours following the second SO-C101 administration (e.g., 14 hours after the first dose)

9.11.6.3.2.2 Subsequent dosing days

During observation after subsequent doses of SO-C101, vital signs (body temperature, heart rate, respiratory rate, and systolic and diastolic blood pressure) will be documented at the following frequency at minimum until discharge from the clinic:

- Prior to the first dose of SO-C101
- 15 minutes (±5 minutes) after dosing

- 30 minutes (±5 minutes) after dosing
- 60 minutes (±10 minutes) after dosing, and then
- Every 60 minutes (±15 minutes) after dosing up until 4-6 hours following the first SO-C101 administration
- Prior to the second dose of SO-C101 at 8 hours after the first dose
- 15 minutes (±5 minutes) after the second dosing
- Every 60 minutes (±15 minutes) after dosing up until 4 hours following the second SO-C101 administration (e.g., 12 hours after the first dose)

If patients feel unwell at any point in time during the study after being discharged from the hospital, they should contact their study investigator as indicated in the ICF.

9.11.6.4 Assessment of laboratory parameters

The standard clinical laboratory analyses described below are to be performed by a local laboratory. Results from laboratory analysis performed by a local laboratory will be documented in the eCRF. Results from laboratory analysis performed by a central laboratory (see sections 9.11.3 and 9.11.4) will be provided to the sponsor or a third party. Details on the collection of samples and reporting of results by the laboratory/laboratories are provided to the investigator in the Laboratory Manual. More frequent evaluations may be performed at the investigator's discretion if medically indicated; results of these additional tests should be recorded in eCRFs.

The sponsor must be provided with a copy of the certification and a tabulation of the normal ranges for the local laboratory/laboratories. Laboratory values that are out of reference ranges should be evaluated for their clinical significance. Laboratory abnormalities which do not meet the criteria of clinical significance, as judged by the investigator, should not be reported as AEs.

It should be noted that severity and seriousness are different criteria for the evaluation of AEs (please see more details in section 9.11.5.1.3.2). Therefore, grade 3 and grade 4 laboratory events (evaluated per NCI CTCAE [v5.0]) do not automatically classify as SAEs unless they meet seriousness criteria as per definition (see section 9.11.5.1.1.2) or per investigator's discretion.

Clinically relevant laboratory abnormalities will be followed up until they return to normal, become stabilized (permanent condition), or until 6 months (±2 weeks) after the EoT visit of the patient (end of the patient's study participation).

The timing of the below mentioned laboratory tests to be done during the study is specified in Table 9.6, Table 9.7, Table 9.8, Table 9.9, Table 9.10, Table 9.11, Table 9.12, Table 9.13, Table 9.14, Table 9.15, Table 9.16, and Table 9.17.

9.11.6.4.1 Coagulation

Coagulation tests will include PT, aPTT, international normalized ratio, D-dimer, and fibrinogen.

9.11.6.4.2 Hematology

Hematology panel will include hemoglobin, glycated hemoglobin HbA1c at study entry, hematocrit, red blood cell count, reticulocytes, WBC count (with full differentiation), ALC, and platelet count.

9.11.6.4.3 Biochemistry

Blood chemistry tests will include Na, K, Cl, phosphate, Mg, Ca, albumin, total protein, ALT, AST, bilirubin (direct, total), alkaline phosphatase, lactate dehydrogenase, creatinine clearance (see appendix 12.2), creatinine, glucose (preferably fasting), urea or blood urea nitrogen, cholesterol, triglyceride, CRP, uric acid, amylase, and lipase.

9.11.6.4.4 Urinalysis

The following parameters are to be analyzed: pH, glucose, protein, bilirubin, urobilinogen. Microscopic examination: red blood cell count, WBC, epithelial cells, bacteria.

In case of proteinuria ≥100 mg/dL at screening, a 24-hour urine analysis will have to be performed (prior to the start of SO-C101 treatment) to document 24-hour proteinuria levels and a urine test will continue during the treatment period. In case of increase of proteinuria with ≥300 mg/dL (at any time), a 24-hour urine analysis will be performed.

9.11.6.4.5 Thyroid function

Thyroid function will be monitored by means of TSH, free triiodothyronine (T3), and free thyroxine (T4) testing.

9.11.6.4.6 Pregnancy

Premenopausal women and postmenopausal women who have been amenorrheic for less than 12 months will be tested for pregnancy.

9.11.6.4.7 Cardiac function

During the study, patients with signs or symptoms of chest pain, murmurs, gallops, irregular rhythm, or palpitations must be further assessed if clinically indicated, including the need for hospitalization (for details, see Table 9.5). Standard 12-lead ECG will be done locally at the site for assessment of any change in QTcF interval and other parameters. Cardiac troponin T will be monitored by high-sensitivity cardiac troponin T (hs-cTnT) test during the study to exclude any signs of myocardial injury. Echocardiography will be performed for the assessment of the heart function during the study, primarily for monitoring of left ventricular ejection fraction and other parameters.

Table 9.5: Cardiac function assessment

Visit	Assessments
Screening	ECG, echocardiography, and cardiac troponin T
Cycle 1	ECG: before each dose of SO-C101 and 4 hours (+30 min) after dosing (note: for schedule 2 both the first and second doses of SO-C101) Cardiac troponin T, schedule 1: days 1 and 8 before each dose of SO-C101 and on days 2 and 9 at least 3 hours after SO-C101

Visit	Assessments
	Cardiac troponin T, schedule 2: days 1 and 8 before the first daily dose of SO-C101 in the morning only and on days 2 and 9 at least 3 hours after the second daily dose of SO-C101
Subsequent cycles	ECG: cycles 2 and 3: before each dose of SO-C101 and 4 hours (+30 min) after dosing; cycle 4 onwards: on day 1 before SO-C101 dosing and 4 hours (+30 min) after dosing (note: for schedule 2 both the first and second doses of SO-C101) Cardiac troponin T, schedule 1: on day 1 before SO-C101 and day 9 at least 3 hours after Cardiac troponin T, schedule 2: on day 1 before the first daily dose of SO-C101 in the morning only and on day 9 at least 3 hours after the second daily dose of SO-C101 Echocardiography: from cycle 2 at the end of each second cycle (allowed interval from day 9 of the current cycle to day 2 of the next cycle)
EoT	ECG, echocardiography, and cardiac troponin T

9.11.6.4.8 Kidney function

Kidney function will be assessed by creatinine clearance estimated by the Cockroft-Gault formula (see appendix 12.2) at screening and during the study and the evaluation of creatinine levels in serum during the study as specified in Table 9.6 and Table 9.7.

Urine test will be done to assess levels of protein, glucose in urine, and potential urinary tract infections.

9.11.6.4.9 Liver and pancreatic functions

Liver and pancreatic functions will be assessed by any changes in liver enzymes, amylase, and lipase in blood and the presence/absence of bilirubin and urobilinogen in urine.

9.11.6.4.10 Adverse events

Patients in Part A, Part A1, Part B, and Part B1 in cycle 1 will be closely monitored for potential DLTs. In the following treatment cycles, patients will be followed up closely and any cumulative toxicity or any DLT-like AEs will be reviewed on a continuous basis during every DEM.

Patients in Part B and Part B1 will be monitored at the same visits and assessments as specified in SO-C101 monotherapy parts with special attention paid to the potentiation of immune-mediated reactions during the combination treatment with SO-C101.

For Part B and Part B1, patient monitoring following pembrolizumab administration will follow the established standard of care.

The following immune-mediated reactions were reported in patients treated with pembrolizumab:[37,38] immune-mediated pneumonitis; immune-mediated colitis, immune-mediated hepatitis, immune-mediated nephritis, infusion-related reactions;

immune-mediated endocrinopathies: hypophysitis, thyroid disorders, and type 1 diabetes mellitus.

Pneumonitis: Patients will be monitored for new or worsening cough, chest pain, or shortness of breath through the assessment of vital signs and AEs.

Colitis: Patients should be monitored for AEs, e.g., diarrhea or severe abdominal pain.

Hepatitis: Patients should be monitored for AEs, e.g., severe nausea or vomiting, or easy bruising or bleeding. Patients should be monitored for changes in hepatic function. Based on severity of liver enzyme elevations, withhold or discontinue pembrolizumab.

Hypophysitis: Patients should be monitored for AEs with special attention to the following: persistent or unusual headache, extreme weakness, dizziness or fainting, or vision changes.

Hyperthyroidism and hypothyroidism: Patients should be monitored for changes in thyroid function (TSH, free T3, and free T4).

Type 1 diabetes mellitus: Patients should be monitored for the level of glucose.

Nephritis: Patients should be monitored for kidney function.

Infusion-related reactions will be assessed by physical examination and AE collection and observation.

In case of any immune-mediated reactions observed in Part B and Part B1 in association with pembrolizumab administration, please refer to instructions for treatment modifications as specified in section 9.9.2.

9.11.6.4.11 Anti-drug antibodies

Samples for anti-drug antibodies (ADAs) will be collected to assess SO-C101 and pembrolizumab tolerance, correlation with PK, and potential AEs associated with ADAs and for the prediction of ADA production.

9.11.7 Schedule of procedures/assessments

Table 9.6, Table 9.7, and Table 9.8 present the schedule of procedures/assessments for the study. Table 9.9, Table 9.10, Table 9.11, Table 9.12, Table 9.13, Table 9.14, Table 9.15, Table 9.16, and Table 9.17 show the timing of blood samples collection.

All attempts should be made to collect the samples on time. Missed sample collections are considered protocol deviations.

Table 9.6: Schedule of procedures/assessments, Part A, Part A1, Part D, and Part D1 (SO-C101 monotherapy)

Cycle		**Cycle 1 to 3***						**From cycle 4 onwards****				**End of treatment visit** Within 7 (+7) days after the final dose of SO-C101	**Follow-up**
Visit	**Screening** Up to 21 days before day 1 of cycle 1	**Day 1**	**Day 2**	**Day 6**	**Day 8**	**Day 9**	**Day 13**	**Day 1**	**Day 2**	**Day 8**	**Day 9**		
Informed consent[1]	X												
Demography[2]	X												
Cancer[3] **and medical history**	X												
Height	X												
Pregnancy test	X (blood)	X (urine or blood)						X (urine or blood)					
Physical examination[4]	X	X	X	X	X	X	X	X	X	X	X	X	X[5]
Body weight and body surface area[6]	X	X						X				X	X[5]
Vital signs[7]	X	X	X	X	X	X	X	X	X	X	X	X	X[5]
Urinalysis[8]	X	X			X			X		X		X	
Creatinine clearance[9]	X	X		X		X		X		X			
ECG	X	X[10]	X[10]		X[10]	X[10]		X[10]				X	
Echocardiography[11]	X	End of each second cycle, starting from cycle 2 (allowed interval from day 9 of the current cycle to day 2 of the next cycle)										X	
ECOG performance score	X	X	X	X	X	X	X	X	X	X	X	X	
Tumor assessment (CT/MRI, MRI)[12]	X	Every 6 weeks (±2 weeks)											
SO-C101 administration[13]		X	X		X	X		X	X	X	X		
Tumor biopsy[14]	X	X											
AEs	X	X	X	X	X	X	X	X	X	X	X	X	X[5]
Concomitant medication/ non-drug therapies	X	X	X	X	X	X	X	X	X	X	X	X	X[5]
Survival information													X[15]

* Part A, Part D: All visits and dosing days will have a time window of ±1 day as long as the two doses of SO-C101 per week are given on consecutive days (day 1 and day 2) and the second week SO-C101 dosing (day 8 and day 9) takes place 7 days after day 1, which should be strictly followed for cycle 1 and, if possible, for the following cycles.

Part A1, Part D1: All visits and dosing days will have a time window of ±1 day as long as the four doses of SO-C101 per week are given on consecutive days (day 1 and day 2) and the second week SO-C101 dosing (day 8 and day 9) takes place 7 days after day 1, which should be strictly followed for cycle 1 and, if possible, for the following cycles.

** Criteria for removal from study treatment are listed in section 9.11.10

1. No study-specific procedures are to be performed prior to ICF signature
2. Demography implies the collection of information on age at screening, gender, race, and ethnicity
3. Primary tumor location, histology/cytology, initial diagnosis date, lines of previous treatment, start and stop dates of the treatments prior to this study, and any prior mutations/genetic analysis (i.e., EGFR, KRAS mutations, BCL-2) and the date of the latest disease progression if not coinciding with the stop date
4. To be done before SO-C101 dose and afterwards as clinically required
5. Every 30 (±2) days until 90 (±2) days after the last dose of SO-C101
6. To be measured before the first SO-C101 dose at day 1 of each cycle
7. Vital signs include blood pressure (systolic and diastolic, after ≥15 minutes of rest), body temperature, heart rate, and respiratory rate. During post-SO-C101 observation, vital signs (body temperature, heart rate, respiratory rate, systolic and diastolic blood pressure) will be documented as described in section 9.11.6.3.
8. Urine test will be performed prior to day 1. In case of ≥100 mg/dL proteinuria at screening, a 24-hour urine analysis will have to be performed (prior to the start of SO-C101 treatment) to document 24-hour proteinuria levels and a urine test will continue during the treatment period. In case of increase of proteinuria ≥300 mg/dL (at any time), a 24-hour urine analysis will be performed.
9. From serum creatinine, calculated by the Cockcroft-Gault formula (appendix 12.2); cycles 1 and 2: days 1 and 9 prior to SO-C101 administration and on day 6; cycle 3: day 1 (prior to SO-C101 administration) and on day 6; from cycle 4 and onwards on days 1 and 8 prior to SO-C101 administration
10. Before SO-C101 administration and 4 hours (+30 min) after SO-C101 administration (note: in Part A1 and Part D1 both the first and second doses of SO-C101)
11. End of each second cycle (i.e., cycle 2, 4, 6…); allowed interval from day 9 of the current cycle to day 2 of the next cycle
12. Until iCPD, until the start of a new anticancer therapy, or until 6 months (±2 weeks) after the EoT visit (whichever occurs earliest) unless patients withdraw consent
13. Time to be recorded; treatment days in Part A and Part D: once a day; treatment days in Part A1 and Part D1: twice a day 8 hours (±15 min) apart
14. Paired tumor biopsy (screening and during cycle 2) and at the time of a clinically significant event and at the time of progression or response (not mandatory); archived, fixed tumor tissue can be collected if fresh biopsy at screening is not available; Part A1, Part D, and Part D1: preferably/ if possible at cycle 2 day 13 (if not, will not be a deviation)
15. At 3 months (±2 weeks) and 6 months (±2 weeks) after the EoT visit (end of the patient's study participation)

Table 9.7: Schedule of procedures/assessments, Part B and Part B1 (SO-C101 combined with pembrolizumab)

Cycle		**Cycle 1 to 3***						**From cycle 4 onwards****				**End of treatment visit** Within 7 (+7) days after the final dose of SO-C101 and/or pembrolizumab	**Follow-up**
Visit	**Screening** Up to 21 days before day 1 of cycle 1	**Day 1**	**Day 2**	**Day 6**	**Day 8**	**Day 9**	**Day 13**	**Day 1**	**Day 2**	**Day 8**	**Day 9**		
Informed consent[1]	X												
Demography[2]	X												
Cancer[3] **and medical history**	X												
Height	X												
Pregnancy test	X (blood)	X (urine or blood)						X (urine or blood)					
Physical examination[4]	X	X	X	X	X	X	X	X	X	X	X	X	X[5]
Body weight and body surface area[6]	X	X						X				X	X[5]
Vital signs[7]	X	X	X	X	X	X	X	X	X	X	X	X	X[5]
Urinalysis[8]	X	X			X			X		X		X	
Creatinine clearance[9]	X	X		X		X		X		X			
ECG	X	X[10]	X[10]		X[10]	X[10]		X[10]				X	
Echocardiography[11]	X	End of each second cycle, starting from cycle 2 (allowed interval from day 9 of the current cycle to day 2 of the next cycle)										X	
ECOG performance score	X	X	X	X	X	X	X	X	X	X	X	X	
Tumor assessment (CT/MRI, MRI)[12]	X	Every 6 weeks (±2 weeks)											
SO-C101 administration[13]		X	X		X	X		X	X	X	X		
Pembrolizumab administration[14]		Every 3 weeks (day 1) according to the prescribing information											
Tumor biopsy[15]	X	X											
AEs	X	X	X	X	X	X	X	X	X	X	X	X	X[5]
Concomitant medication/ non-drug therapies	X	X	X	X	X	X	X	X	X	X	X	X	X[5]
Survival information													X[16]

* Part B: All visits and dosing days will have a time window of ±1 day as long as the two doses of SO-C101 per week are given on consecutive days (day 1 and day 2) and the second week SO-C101 dosing (day 8 and day 9) takes place 7 days after day 1.
Part B1: All visits and dosing days will have a time window of ±1 day as long as the four doses of SO-C101 per week are given on consecutive days (day 1 and day 2) and the second week SO-C101 dosing (day 8 and day 9) takes place 7 days after day 1.

** Criteria for removal from study treatment are listed in section 9.11.10

1. No study-specific procedures are to be performed prior to ICF signature
2. Demography implies the collection of information on age at screening, gender, race, and ethnicity
3. Primary tumor location, histology/cytology, initial diagnosis date, lines of previous treatment, start and stop dates of the treatments prior to this study, and any prior mutations/genetic analysis (i.e., EGFR, KRAS mutations, BCL-2) and the date of the latest disease progression if not coinciding with the stop date
4. To be done before SO-C101 dose and afterwards as clinically required
5. Every 30 (±2) days until 90 (±2) days after the last dose of SO-C101 and/or pembrolizumab, whichever occurs later
6. To be measured before the first SO-C101 dose at day 1 of each cycle
7. Vital signs include blood pressure (systolic and diastolic, after ≥15 minutes of rest), body temperature, heart rate, and respiratory rate. During post-SO-C101 observation, vital signs (body temperature, heart rate, respiratory rate, systolic and diastolic blood pressure) will be documented as described in section 9.11.6.3.
8. Urine test will be performed prior to day 1. In case of ≥100 mg/dL proteinuria at screening, a 24-hour urine analysis will have to be performed (prior to the start of SO-C101 treatment) to document 24-hour proteinuria levels and a urine test will continue during the treatment period. In case of increase of proteinuria ≥300 mg/dL (at any time), a 24-hour urine analysis will be performed.
9. From serum creatinine, calculated by the Cockcroft-Gault formula (appendix 12.2); cycles 1 and 2: days 1 and 9 prior to SO-C101 administration and on day 6; cycle 3: day 1 (prior to SO-C101 administration) and on day 6; from cycle 4 and onwards on days 1 and 8 prior to SO-C101 administration
10. Before SO-C101 administration and 4 hours (+30 min) after SO-C101 administration (note: in Part B1 both the first and second doses of SO-C101)
11. End of each second cycle (i.e., cycle 2, 4, 6…); allowed interval from day 9 of the current cycle to day 2 of the next cycle
12. Until iCPD, until the start of a new anticancer therapy, or until 6 months (±2 weeks) after the EoT visit (whichever occurs earliest) unless patients withdraw consent
13. Time to be recorded; treatment days in Part B: once a day; treatment days in Part B1: twice a day 8 hours (±15 min) apart
14. Time to be recorded; pembrolizumab will be administered within 30 minutes following SO-C101 administration
15. Paired tumor biopsy (screening and during cycle 2) and at the time of a clinically significant event and at the time of progression or response (not mandatory); archived, fixed tumor tissue can be collected if fresh biopsy at screening is not available; Part B1: preferably/ if possible at cycle 2 day 13 (if not, will not be a deviation)
16. At 3 months (±2 weeks) and 6 months (±2 weeks) after the EoT visit (end of the patient's study participation)

Table 9.8: Schedule of procedures/assessments, Part B and Part B1 (for patients who continue on pembrolizumab only after discontinuation of SO-C101)

Visit	**Day 1** of each cycle	**End of treatment visit*** Within 7 (+7) days after the final dose of pembrolizumab	**Follow-up**
Pregnancy test	X (urine or blood)		
Physical examination[1]	X	X	X[5]
Body weight and body surface area[2]	X	X	X[5]
Vital signs[3]	X	X	X[5]
Urinalysis[4]	X	X	
ECG[6]	X	X	
Echocardiography[7]		X	
ECOG performance score	X	X	
Tumor assessment (CT/MRI, MRI)[8]	Every 6 weeks (±2 weeks)		
Pembrolizumab administration	Every 3 weeks (day 1) according to the prescribing information		
AEs	X	X	X[5]
Concomitant medication/ non-drug therapies	X	X	X[5]
Survival information			X[9]

* Criteria for removal from study treatment are listed in section 9.11.10

1, 2, 3, and 4 to be done before pembrolizumab dose on day 1 of each cycle

3. Vital signs include blood pressure (systolic and diastolic, after ≥15 minutes of rest), body temperature, heart rate, and respiratory rate
4. Urine test will be performed prior pembrolizumab administration on day 1. In case of ≥100 mg/dL proteinuria at screening, a 24-hour urine analysis will have to be performed to document 24-hour proteinuria levels and a urine test will continue during the treatment period. In case of increase of proteinuria ≥300 mg/dL (at any time), a 24-hour urine analysis will be performed.
5. Every 30 (±2) days until 90 (±2) days after the last dose of pembrolizumab
6. ECG to be performed on day 1 before pembrolizumab administration
7. Echocardiography should be done at the EoT visit
8. Until iCPD, until the start of a new anticancer therapy, or until 6 months (±2 weeks) after the EoT visit (whichever occurs earliest) unless patients withdraw consent
9. At 3 months (±2 weeks) and 6 months (±2 weeks) after the EoT visit (end of the patient's study participation)

Table 9.9: Blood samples collection, Part A

All attempts should be made to collect the samples on time. Missed sample collections are considered protocol deviations. The numbers in brackets are the expected blood sampling volumes in mL.

		Cycle 1							Cycle 2							Cycle 3							From cycle 4*			EoT
Day	**Screening**	**1**	**2**	**6**	**8**	**9**	**13**	**15**	**1**	**2**	**6**	**8**	**9**	**13**	**15**	**1**	**2**	**6**	**8**	**9**	**13**	**15**	**1**	**8**	**9**	
SO-C101 administration[1]		X	X		X	X			X	X		X	X			X	X		X	X			X	X	X	
PBMCs[2]		X (9)	X (9)	X (9)	X (9)	X (9)	X (9)	X (9)	X (9)		X (9)	X (9)		X (9)	X (9)	X (9)		X (9)			X (9)	X (9)				X (9)
Serum (PK)	Please see Table 9.14																									
Serum (cytokine)[3]		X (8)	X (8)		X (8)	X (8)			X (8)	X (8)		X (8)	X (8)													
Serum (immunogenicity)[4]		X (5)						X (5)	X (5)							X (5)							X (5)			X (5)
PBMCs (for genetic test)		X (5)																								
HIV, hepatitis B and C	X (5)																									
Hematology (full complete blood count incl. ALC)	X (3)	X (3)	X (3)	X (3)	X (3)	X (3)	X (3)	X (3)	X (3)		X (3)	X (3)		X (3)	X (3)	X (3)		X (3)	X (3)		X (3)	X (3)	X (3)	X (3)		X (3)
Biochemistry (incl. CRP)	X (8)	X (8)	X (8)	X (8)		X (8)	X (8)		X (8)		X (8)		X (8)	X (8)		X (8)		X (8)					X (8)	X (8)		X (8)
CRP					X (1)					X (1)		X (1)														
Coagulation	X (5)	X (5)			X (5)				X (5)			X (5)				X (5)			X (5)				X (5)	X (5)		X (5)
TSH, free T3, free T4	X (1)	X (1)							X (1)							X (1)							X (1)			X (1)
Hs-cTnT test[5]	X (1)	X (1)	X (1)		X (1)	X (1)			X (1)				X (1)			X (1)				X (1)			X (1)		X (1)	X (1)
Serum pregnancy	X (5)																									

* Criteria for removal from study treatment are listed in section 9.11.10

1. Time to be recorded
2. All samples for PBMCs have to be collected before dosing (pre-dose) on the dosing day
3. Cycle 1: day 1 and day 2 (pre-dose and 2 hours [±30 min], 4 hours [±30 min], 6 hours [±30 min] post dose), day 8 and day 9 (pre-dose and 2 hours [±30 min], 4 hours [±30 min], 6 hours [±30 min] post dose); cycle 2: day 1 and day 2 (pre-dose and 2 hours [±30 min], 4 hours [±30 min], 6 hours [±30 min] post dose), day 8 and day 9 (pre-dose and 2 hours [±30 min], 4 hours [±30 min], 6 hours [±30 min] post dose)
4. Pre-dose SO-C101 on day 1 in each cycle up to cycle 12 (inclusive) and cycle 1 day 15; testing at the EoT visit to be done
5. Hs-cTnT test (cardiac troponin T test): cycle 1: days 1 and 8 before each dose of SO-C101 and on days 2 and 9 at least 3 hours after SO-C101; subsequent cycles: on day 1 before SO-C101 and day 9 at least 3 hours after SO-C101

Table 9.10: Blood samples collection, Part A1, Part D, and Part D1

All attempts should be made to collect the samples on time. Missed sample collections are considered protocol deviations. The numbers in brackets are the expected blood sampling volumes in mL.

		Cycle 1							Cycle 2						Cycle 3						Cycle 4			From cycle 5*			EoT
Day	**Screening**	**1**	**2**	**6**	**8**	**9**	**13**	**15**	**1**	**2**	**6**	**8**	**9**	**13**	**1**	**2**	**6**	**8**	**9**	**13**	**1**	**8**	**9**	**1**	**8**	**9**	
SO-C101 administration[1]		X	X		X	X			X	X		X	X		X	X		X	X		X	X	X	X	X	X	
PBMCs[2]		X (9)		X (9)	X (9)		X (9)		X(9)		X(9)	X(9)		X(9)	X (9)		X (9)			X (9)							X (9)
Serum (PK)	Please see Table 9.15																										
Serum (cytokine)[3]		X (14)	X (14)		X (10)	X (10)			X (10)	X (10)		X (10)	X (10)														
Serum (immunogenicity)[4]		X (5)						X (5)	X (5)						X (5)						X (5)			X (5)			X (5)
PBMCs (for genetic test)		X (5)													X (5)												
HIV, hepatitis B and C	X (5)																										
Hematology (full complete blood count incl. ALC)	X (3)	X (3)	X (3)	X (3)	X (3)	X (3)	X (3)	X (3)	X (3)		X (3)	X (3)		X (3)	X (3)		X (3)	X (3)		X (3)	X (3)	X (3)		X (3)	X (3)		X (3)
Biochemistry (incl. CRP)	X (8)	X (8)	X (8)	X (8)		X (8)	X (8)		X (8)		X (8)		X (8)	X (8)	X (8)		X (8)				X (8)	X (8)		X (8)	X (8)		X (8)
CRP					X (1)					X (1)		X (1)															
Coagulation	X (5)	X (5)			X (5)				X (5)			X (5)			X (5)			X (5)			X (5)	X (5)		X (5)	X (5)		X (5)
TSH, free T3, free T4	X (1)	X (1)							X (1)						X (1)						X (1)			X (1)			X (1)
Hs-cTnT test[5]	X (1)	X (1)	X (1)		X (1)	X (1)			X (1)				X (1)		X (1)				X (1)		X (1)		X (1)	X (1)		X (1)	X (1)
Serum pregnancy	X (5)																										

* Criteria for removal from study treatment are listed in section 9.11.10

1. Time to be recorded
2. All samples for PBMCs have to be collected before dosing (pre-dose) on the dosing day
3. Cycle 1: day 1 and day 2 (pre-dose and 2 hours [±30 min], 4 hours [±30 min], 6 hours [±30 min], 8 hours [±30 min], 12 hours [±30 min], 16 hours [±30 min] post dose); day 8 and day 9 (pre-dose and 4 hours [±30 min], 6 hours [±30 min], 8 hours [±30 min], 10 hours [±30 min] post dose); cycle 2: day 1 and day 2 (pre-dose and 4 hours [±30 min], 6 hours [±30 min], 8 hours [±30 min], 10 hours [±30 min] or 12 hours [±30 min] post dose if the patient is hospitalized on day 1); day 8 and day 9 (pre-dose and 4 hours [±30 min], 6 hours [±30 min], 8 hours [±30 min], 10 hours [±30 min] or 12 hours [±30 min] post dose if the patient is hospitalized on day 8); in Part A1 and Part D1, 8 hours post dose has to be collected before the second dose of SO-C101.
4. Pre-dose SO-C101 on day 1 in each cycle up to cycle 12 (inclusive) and cycle 1 day 15; testing at the EoT visit to be done
5. Hs-cTnT test (cardiac troponin T test) in Part A1 and Part D1: cycle 1: days 1 and 8 before the first daily dose of SO-C101 in the morning only and on days 2 and 9 at least 3 hours after the second daily dose of SO-C101; subsequent cycles: on day 1 before the first daily dose of SO-C101 in the morning only and on day 9 at least 3 hours after the second daily dose of SO-C101; in Part D: cycle 1: days 1 and 8 before each dose of SO-C101 and on days 2 and 9 at least 3 hours after SO-C101; subsequent cycles: on day 1 before SO-C101 and day 9 at least 3 hours after SO-C101

Table 9.11: Blood samples collection, Part B

All attempts should be made to collect the samples on time. Missed sample collections are considered protocol deviations. The numbers in brackets are the expected blood sampling volumes in mL.

		Cycle 1							Cycle 2							Cycle 3							From cycle 4*			EoT
Day	**Screening**	**1**	**2**	**6**	**8**	**9**	**13**	**15**	**1**	**2**	**6**	**8**	**9**	**13**	**15**	**1**	**2**	**6**	**8**	**9**	**13**	**15**	**1**	**8**	**9**	
SO-C101 administration[1]		X	X		X	X			X	X		X	X			X	X		X	X			X	X	X	
Pembrolizumab administration[1]		X							X							X							X			
PBMCs[2]		X (9)	X (9)	X (9)	X (9)	X (9)	X (9)	X (9)	X (9)		X (9)	X (9)		X (9)	X (9)	X (9)		X (9)			X (9)	X (9)				X (9)
Serum (PK)	Please see Table 9.14																									
Serum (cytokine)[3]		X (8)	X (8)		X (8)	X (8)			X (8)	X (8)		X (8)	X (8)													
Serum (immunogenicity)[4]		X (5)						X (5)	X (5)							X (5)							X (5)			X (5)
PBMCs (for genetic test)		X (5)																								
HIV, hepatitis B and C	X (5)																									
Hematology (full complete blood count incl. ALC)	X (3)	X (3)	X (3)	X (3)	X (3)	X (3)	X (3)	X (3)	X (3)		X (3)	X (3)		X (3)	X (3)	X (3)		X (3)	X (3)		X (3)	X (3)	X (3)	X (3)		X (3)
Biochemistry (incl. CRP)	X (8)	X (8)	X (8)	X (8)		X (8)	X (8)		X (8)		X (8)		X (8)	X (8)		X (8)		X (8)					X (8)	X (8)		X (8)
CRP					X (1)					X (1)		X (1)														
Coagulation	X (5)	X (5)			X (5)				X (5)			X (5)				X (5)			X (5)				X (5)	X (5)		X (5)
TSH, free T3, free T4	X (1)	X (1)							X (1)							X (1)							X (1)			X (1)
Hs-cTnT test[5]	X (1)	X (1)	X (1)		X (1)	X (1)			X (1)				X (1)			X (1)				X (1)			X (1)		X (1)	X (1)
Serum pregnancy	X (5)																									

* Criteria for removal from study treatment are listed in section 9.11.10

1. Time to be recorded; pembrolizumab will be administered within 30 minutes following SO-C101 administration
2. All samples for PBMCs have to be collected before dosing (pre-dose) on the dosing day
3. Cycle 1: day 1 and day 2 (pre-dose and 2 hours [±30 min], 4 hours [±30 min], 6 hours [±30 min] post dose), day 8 and day 9 (pre-dose and 2 hours [±30 min], 4 hours [±30 min], 6 hours [±30 min] post dose); cycle 2: day 1 and day 2 (pre-dose and 2 hours [±30 min], 4 hours [±30 min], 6 hours [±30 min] post dose), day 8 and day 9 (pre-dose and 2 hours [±30 min], 4 hours [±30 min], 6 hours [±30 min] post dose)
4. Pre-dose SO-C101 on day 1 in each cycle up to cycle 12 (inclusive) and cycle 1 day 15; testing at the EoT visit to be done
5. Hs-cTnT test (cardiac troponin T test): cycle 1: days 1 and 8 before each dose of SO-C101 and on days 2 and 9 at least 3 hours after SO-C101; subsequent cycles: on day 1 before SO-C101 and day 9 at least 3 hours after SO-C101

Table 9.12: Blood samples collection, Part B1

All attempts should be made to collect the samples on time. Missed sample collections are considered protocol deviations. The numbers in brackets are the expected blood sampling volumes in mL.

		Cycle 1							Cycle 2						Cycle 3						Cycle 4			From cycle 5*			EoT
Day	**Screening**	**1**	**2**	**6**	**8**	**9**	**13**	**15**	**1**	**2**	**6**	**8**	**9**	**13**	**1**	**2**	**6**	**8**	**9**	**13**	**1**	**8**	**9**	**1**	**8**	**9**	
SO-C101 administration[1]		X	X		X	X			X	X		X	X		X	X		X	X		X	X	X	X	X	X	
Pembrolizumab administration[1]		X							X						X						X			X			
PBMCs[2]		X (9)		X (9)	X (9)		X (9)		X(9)		X(9)	X(9)		X(9)	X (9)		X (9)			X (9)							X (9)
Serum (PK)	Please see Table 9.15																										
Serum (cytokine)[3]		X (14)	X (14)		X (10)	X (10)			X (10)	X (10)		X (10)	X (10)														
Serum (immunogenicity)[4]		X (5)						X (5)	X (5)						X (5)						X (5)			X (5)			X (5)
PBMCs (for genetic test)		X (5)													X (5)												
HIV, hepatitis B and C	X (5)																										
Hematology (full complete blood count incl. ALC)	X (3)	X (3)	X (3)	X (3)	X (3)	X (3)	X (3)	X (3)	X (3)		X (3)	X (3)		X (3)	X (3)		X (3)	X (3)		X (3)	X (3)	X (3)		X (3)	X (3)		X (3)
Biochemistry (incl. CRP)	X (8)	X (8)	X (8)	X (8)		X (8)	X (8)		X (8)		X (8)		X (8)	X (8)	X (8)		X (8)				X (8)	X (8)		X (8)	X (8)		X (8)
CRP					X (1)					X (1)		X (1)															
Coagulation	X (5)	X (5)			X (5)				X (5)			X (5)			X (5)			X (5)			X (5)	X (5)		X (5)	X (5)		X (5)
TSH, free T3, free T4	X (1)	X (1)							X (1)						X (1)						X (1)			X (1)			X (1)
Hs-cTnT test[5]	X (1)	X (1)	X (1)		X (1)	X (1)			X (1)				X (1)		X (1)				X (1)		X (1)		X (1)	X (1)		X (1)	X (1)
Serum pregnancy	X (5)																										

* Criteria for removal from study treatment are listed in section 9.11.10

1. Time to be recorded
2. All samples for PBMCs have to be collected before dosing (pre-dose) on the dosing day
3. Cycle 1: day 1 and day 2 (pre-dose and 2 hours [±30 min], 4 hours [±30 min], 6 hours [±30 min], 8 hours [-30 min], 12 hours [±30 min], 16 hours [±30 min] post dose); day 8 and day 9 (pre-dose and 4 hours [±30 min], 6 hours [±30 min], 8 hours [-30 min], 10 hours [±30 min] post dose); cycle 2: day 1 and day 2 (pre-dose and 4 hours [±30 min], 6 hours [±30 min], 8 hours [-30 min], 10 hours [±30 min] or 12 hours [±30 min] post dose if the patient is hospitalized on day 1); day 8 and day 9 (pre-dose and 4 hours [±30 min], 6 hours [±30 min], 8 hours [-30 min], 10 hours [±30 min] or 12 hours [±30 min] post dose if the patient is hospitalized on day 8); 8 hours post dose has to be collected before the second dose of SO-C101.
4. Pre-dose SO-C101 on day 1 in each cycle up to cycle 12 (inclusive) and cycle 1 day 15; testing at the EoT visit to be done
5. Hs-cTnT test (cardiac troponin T test): cycle 1: days 1 and 8 before the first daily dose of SO-C101 in the morning only and on days 2 and 9 at least 3 hours after the second daily dose of SO-C101; subsequent cycles: on day 1 before the first daily dose of SO-C101 in the morning only and on day 9 at least 3 hours after the second daily dose of SO-C101

Table 9.13: Blood samples collection (Part B and Part B1; for patients who continue on pembrolizumab only after discontinuation of SO-C101)

All attempts should be made to collect the samples on time. Missed sample collections are considered protocol deviations. The numbers in brackets are the expected blood sampling volumes in mL.

	Cycle 1	Cycle 2	From cycle 3*	EoT
Day	**1**	**1**	**1**	
Pembrolizumab administration[1]	X	X	X	
Hematology[2]	X (3)	X (3)	X (3)	X (3)
Biochemistry[3]	X (8)	X (8)	X (8)	X (8)
Coagulation[4]	X (5)	X (5)	X (5)	X (5)
TSH, free T3, free T4[5]	X (1)	X (1)	X (1)	X (1)

* Criteria for removal from study treatment are listed in section 9.11.10

1. Time to be recorded; Part B and Part B1: pembrolizumab will be administered on day 1

2, 3, 4, 5 Before pembrolizumab administration on day 1 in each cycle

Table 9.14: PK sampling, Part A and Part B

All attempts should be made to collect the samples on time. Missed sample collections are considered protocol deviations. The numbers in brackets are the expected blood sampling volumes in mL.

Cycle, day	Time point (pre-dose or time after SO-C101 administration)	SO-C101 PK	
		Part A	Part B
Cycle 1 day 1	Pre-dose to SO-C101 and pembrolizumab (as applicable)	X (1)	X (1)
	30 min (±5 min)	X (1)	X (1)
	1 h (±15 min)	X (1)	X (1)
	2 h (±15 min)	X (1)	X (1)
	4 h (Parts A, B: ±15 min)	X (1)	X (1)
	8 h (±15 min)	X (1)	X (1)
	12 h (±1 h)	X (1)	X (1)
	16 h (±1 h)	X (1)	
	20 h (±1 h)	X (1)	
	24 h (±6 h), pre-dose to cycle 1 day 2	X (1)	X (1)
Cycle 1 day 9	Pre-dose to SO-C101	X (1)	X (1)
	30 min (±5 min)	X (1)	X (1)
	1 h (±15 min)	X (1)	X (1)
	2 h (±15 min)	X (1)	X (1)
	4 h (±15 min)	X (1)	X (1)
	6 h (±15 min)	X (1)	X (1)
Cycle 2 day 1	Pre-dose to SO-C101 and pembrolizumab (as applicable)	X (1)	X (1)
	30 min (±5 min)	X (1)	X (1)
	1 h (±15 min)	X (1)	X (1)
	2 h (±15 min)	X (1)	X (1)
	4 h (Parts A, B: ±15 min)	X (1)	X (1)
	6 h (±15 min)	X (1)	X (1)
Cycle 2 day 9	Pre-dose to SO-C101	X (1)	X (1)
	30 min (±5 min)	X (1)	X (1)
	1 h (±15 min)	X (1)	X (1)
	2 h (±15 min)	X (1)	X (1)
	4 h (±15 min)	X (1)	X (1)
	6 h (±15 min)	X (1)	X (1)
Cycle 3 day 1	Pre-dose to SO-C101 and pembrolizumab (as applicable)	X (1)	X (1)
	30 min (±5 min)	X (1)	X (1)
	1 h (±15 min)	X (1)	X (1)
	2 h (±15 min)	X (1)	X (1)
	4 h (±15 min)	X (1)	X (1)
	6 h (±15 min)	X (1)	X (1)

Table 9.15: PK sampling, Part A1, Part B1, Part D (patients 1-5 in each indication), and Part D1 (patients 1-5 in each indication)

All attempts should be made to collect the samples on time. Missed sample collections are considered protocol deviations. The numbers in brackets are the expected blood sampling volumes in mL.

Patients will be hospitalized on PK sampling days (cycle 1 day 1, cycle 1 day 2, and cycle 3 day 1).

Cycle, day	Time point (pre-dose or time after SO-C101 administration)	SO-C101 PK
Cycle 1 day 1	Pre-dose to SO-C101 and pembrolizumab (as applicable)	X (1)
	1 h (±15 min)	X (1)
	2 h (±15 min)	X (1)
	4 h (±15 min)	X (1)
	8 h (±15 min) pre-dose*	X (1)
	9 h (±15 min)	X (1)
	10 h (±15 min)	X (1)
	12 h (±1 h)	X (1)
	16 h (±1 h)	X (1)
	20 h (±1 h)	X (1)
Cycle 1 day 2	Pre-dose to SO-C101	X (1)
	1 h (±15 min)	X (1)
	2 h (±15 min)	X (1)
	4 h (±15 min)	X (1)
	8 h (±15 min) pre-dose*	X (1)
	9 h (±15 min)	X (1)
	10 h (±15 min)	X (1)
	12 h (±1 h)	X (1)
	16 h (±1 h)	X (1)
	20 h (±1 h)	X (1)
	24 h (±6 h)	X (1)
Cycle 3 day 1	Pre-dose to SO-C101 and pembrolizumab (as applicable)	X (1)
	1 h (±15 min)	X (1)
	2 h (±15 min)	X (1)
	4 h (±15 min)	X (1)
	8 h (±15 min) pre-dose*	X (1)
	9 h (±15 min)	X (1)
	10 h (±15 min)	X (1)
	12 h (±1 h)	X (1)
	16 h (±1 h)	X (1)
	20 h (±1 h)	X (1)
	24 h (±6 h), pre-dose to cycle 3 day 2	X (1)

* In Part A1, Part B1, and Part D1, 8 hours post dose must be collected before the second dose of SO-C101

Table 9.16: PK sampling, Part D (starting with patient 6 in each indication)

All attempts should be made to collect the samples on time. Missed sample collections are considered protocol deviations. The numbers in brackets are the expected blood sampling volumes in mL.

Cycle, day	Time point (pre-dose or time after SO-C101 administration)	SO-C101 PK
Cycle 1 day 1	Pre-dose to SO-C101	X (1)
	1 h (±15 min)	X (1)
	4 h (±15 min)	X (1)
Cycle 1 day 2	Pre-dose to SO-C101	X (1)
	1 h (±15 min)	X (1)
	4 h (±15 min)	X (1)
Cycle 3 day 1	Pre-dose to SO-C101	X (1)
	1 h (±15 min)	X (1)
	4 h (±15 min)	X (1)

Table 9.17: PK sampling, Part D1 (starting with patient 6 in each indication)

All attempts should be made to collect the samples on time. Missed sample collections are considered protocol deviations. The numbers in brackets are the expected blood sampling volumes in mL.

Cycle, day	Time point (pre-dose or time after SO-C101 administration)	SO-C101 PK
Cycle 1 day 1	Pre-dose to SO-C101	X (1)
	1 h (±15 min)	X (1)
	4 h (±15 min)	X (1)
	8 h (±15 min) pre-dose*	X (1)
	12 h (±1 h)	X (1)
Cycle 1 day 2	Pre-dose to SO-C101	X (1)
	1 h (±15 min)	X (1)
	4 h (±15 min)	X (1)
	8 h (±15 min) pre-dose*	X (1)
	12 h (±1 h)	X (1)
Cycle 3 day 1	Pre-dose to SO-C101	X (1)
	1 h (±15 min)	X (1)
	4 h (±15 min)	X (1)
	8 h (±15 min) pre-dose*	X (1)

* 8 hours post dose must be collected before the second dose of SO-C101

9.11.8 Appropriateness of measurements

All clinical assessments are standard measurements commonly used in oncology studies.

The safety assessments to be performed in this study, including hematology analyses, blood chemistry tests, urinalysis, and assessment of AEs are standard evaluations to ensure patient safety.

9.11.9 Withdrawal of patients from the study

A patient may elect to withdraw from the study at any time for any reason. All patients who withdraw from the study are to complete the EoT visit as indicated in Table 9.6, Table 9.7, and Table 9.8.

A patient who has ceased to return for visits will be followed up by mail, phone, or other means to gather information such as the reason for failure to return, the status of treatment compliance, the presence or absence of AEs, and clinical courses of signs and symptoms.

9.11.10 Treatment discontinuation

Patients will be discontinued from study treatment for any of the following events:

- Radiographic disease progression (iCPD)(see section 9.11.11 for guidance regarding the continuation of treatment after disease progression)
- Clinical disease progression (investigator assessment)
- AE (intercurrent illness or study treatment-related toxicity, including DLTs [Part A, Part A1, Part B, and Part B1], that would, in the judgment of the investigator, affect assessments of clinical status to a significant degree or require discontinuation of study treatment)
- Patient may withdraw from the study at any time for any reason; the investigator must make every effort to determine the reason for this decision and record it in source documentation of the patient
- Death
- Pregnancy
- Concomitant treatment with a prohibited medication, including further lines of cancer therapy
- Patient non-compliance
- Lost to follow-up
- Study terminated by the sponsor

See also section 9.7.11.

9.11.11 Guidance for continuation of study treatment beyond iRECIST-defined disease progression

Response will be assessed using iRECIST. As a minority of patients treated with immunotherapy may derive clinical benefit despite evidence of disease progression, the following guidance is provided for continuation of study treatment beyond iUPD.[45]

Patients receiving study treatment will be permitted to continue study treatment beyond iUPD, as assessed by the investigator, as long as they meet the following criteria:

- Investigator-assessed clinical benefit, and do not have rapid disease progression
- Tolerance of SO-C101
- Tolerance of pembrolizumab (Part B and Part B1 only)
- Stable performance status
- Treatment beyond progression will not delay an imminent intervention to prevent serious complications of disease progression (e.g., central nervous system metastases).
- Investigator notifies the patient of any reasonably foreseeable risks or discomforts, or other alternative treatment options.
- The decision to continue treatment beyond iUPD should be discussed with the sponsor's medical monitor and documented in the study records.
- A radiographic assessment/scan should be performed within 6 weeks (±2 weeks). The assessment of clinical benefit should be balanced by clinical judgment as to whether the patient is clinically deteriorating and unlikely to receive any benefit from continued treatment with study treatment.
- If the investigator feels that the patient continues to achieve clinical benefit by continuing treatment, the patient should remain in the study and continue to receive monitoring according to the study calendar.
- In the case of iCPD: If the investigator believes that continued treatment is appropriate, imaging is not required after iCPD.

9.12 Data quality assurance

This study will be organized, performed, and reported in compliance with the Protocol, SOPs, working practice documents, and applicable regulations and guidelines. Site audits will be made periodically by the sponsor's or the Contract Research Organization (CRO)'s qualified compliance auditing team, which is an independent function from the study team responsible for the conduct of the study.

9.12.1 Data collection

Data required by the Protocol will be collected on the eCRFs, part of a validated data management system that is compliant with all regulatory requirements. As defined by ICH guidelines, the eCRF is an electronic document designed to record all of the protocol-required information to be reported to the sponsor on each study patient. Data collection in the eCRF should follow the instructions described in the eCRF Completion Guidelines. The investigator has ultimate responsibility for the collection and reporting of all clinical data entered on the eCRF. The investigator or designee as identified on Form FDA 1572 must sign the completed eCRF to attest to its accuracy, authenticity, and completeness. Completed, original eCRFs are the sole property of the sponsor and should not be made available in any form to third parties without written permission from the sponsor, except for authorized representatives of the sponsor or appropriate regulatory authorities and IRB/ECs.

9.12.2 Clinical data management

All software applications used in the collection of data will be properly validated following standard computer system validation that is compliant with all regulatory requirements. All

data, both eCRF and external data (e.g., laboratory data), will be entered into a clinical system.

9.13 Statistical methods

Each study part will be analyzed separately following its objectives. Part D and Part D1 are monotherapy parts including patients with the same indications. Therefore, data of both parts will be pooled for the purpose of exploratory analysis (within each indication separately). Further exploratory analyses including data of more study parts pooled can be included in the Statistical Analysis Plan (SAP).

The analyses will be descriptive. Descriptive statistics will be performed for continuous variables using number, mean, standard deviation, median, Q1 (25th percentile), Q3 (75th percentile), minimum, and maximum, unless otherwise specified. Categorical variables will be summarized as number (percent) of patients. Kaplan-Meier estimations of time-to-event data will be performed, together with estimation of median (if reached).

If appropriate regarding the number of patients, the descriptive statistics will be presented with 95% confidence intervals.

The intra-patient increase of the SO-C101 dose is allowed from Protocol version 6.1 onwards. The analyses are planned by dose level for all dose levels pooled. The main analyses are planned to be performed based on the initial dose level. However, changing the dose level will be also taken into account, especially in outputs presenting safety data in dose escalation study parts (where AEs will be presented by initial dose level and also by dose level administered before AE onset). Details will be specified in the SAP which will take into account the frequency and intensity of dose increases.

The statistical analyses of study data are described in this section. Further details of the analytical plan will be provided in the SAP which will be finalized before database lock. Statistical analyses will be performed using SAS software or other validated statistical software as required.

9.13.1 Study endpoints

9.13.1.1 Part A

9.13.1.1.1 Primary endpoints

- Safety and tolerability of SO-C101 as evaluated by the incidence of DLTs, incidence of SO-C101-related AEs, SAEs, AEs leading to premature discontinuation of SO-C101, deaths, and clinical laboratory test abnormalities
- MTD is defined as the dose level associated with ≥33% of DLT-evaluable patients experiencing a DLT. If the MTD is reached, the RP2D will be conventionally defined as the dose level just below this non-tolerated dose level. If the MTD is not reached, the RP2D will be selected based on integrated evaluation of safety, tolerability, clinical benefit, PK and PD data, for all dose levels tested.

9.13.1.1.2 Secondary endpoints

- PK of SO-C101
- Immune response characterized by the changes in expression of immune markers in PBMCs

- ORR, DOR, CBR, and PFS according to iRECIST
- Detection of ADAs

9.13.1.1.3 Exploratory endpoints

- Changes in the expression of immune biomarkers as compared to baseline in tumor tissue
- OS at 6 months after the EoT visit

9.13.1.2 Part A1

9.13.1.2.1 Primary endpoints

- Safety and tolerability of SO-C101 as evaluated by the incidence of DLTs, incidence of SO-C101-related AEs, SAEs, AEs leading to premature discontinuation of SO-C101, deaths, and clinical laboratory test abnormalities
- MTD is defined as the dose level associated with ≥33% of DLT-evaluable patients experiencing a DLT. If the MTD is reached, the RP2D will be conventionally defined as the dose level just below this non-tolerated dose level. If the MTD is not reached, the RP2D will be selected based on integrated evaluation of safety, tolerability, clinical benefit, PK and PD data, for all dose levels tested.

9.13.1.2.2 Secondary endpoints

- PK of SO-C101
- Immune response characterized by the changes in expression of immune markers in PBMCs
- ORR, DOR, CBR, and PFS according to iRECIST
- Detection of ADAs

9.13.1.2.3 Exploratory endpoints

- Changes in the expression of immune biomarkers as compared to baseline in tumor tissue
- OS at 6 months after the EoT visit

9.13.1.3 Part B

9.13.1.3.1 Primary endpoints

- Safety and tolerability of SO-C101 combined with pembrolizumab as evaluated by the incidence of DLTs, SO-C101-related AEs, SAEs, AEs leading to premature SO-C101 discontinuation, deaths, and clinical laboratory test abnormalities
- MTD defined as the dose level associated with ≥33% of DLT-evaluable patients experiencing a DLT. If the MTD is reached, the RP2D will be conventionally defined as the dose level just below this non-tolerated dose level. If the MTD is not reached, the RP2D will be selected based on integrated evaluation of safety, tolerability, clinical benefit, PK and PD data, for all dose levels tested.

9.13.1.3.2 Secondary endpoints

- PK of SO-C101 combined with pembrolizumab

- Immune response after administration of SO-C101 in combination with pembrolizumab characterized by the changes in expression of immune markers in PBMCs
- ORR, DOR, CBR, and PFS according to iRECIST
- Detection of ADAs

9.13.1.3.3 Exploratory endpoints

- Changes in the expression of immune biomarkers after administration of SO-C101 in combination with pembrolizumab as compared to baseline in tumor tissue
- OS at 6 months after the EoT visit

9.13.1.4 Part B1

9.13.1.4.1 Primary endpoints

- Safety and tolerability of SO-C101 combined with pembrolizumab as evaluated by the incidence of DLTs, SO-C101-related AEs, SAEs, AEs leading to premature SO-C101 discontinuation, deaths, and clinical laboratory test abnormalities
- MTD defined as the dose level associated with ≥33% of DLT-evaluable patients experiencing a DLT. If the MTD is reached, the RP2D will be conventionally defined as the dose level just below this non-tolerated dose level. If the MTD is not reached, the RP2D will be selected based on integrated evaluation of safety, tolerability, clinical benefit, PK and PD data, for all dose levels tested.

9.13.1.4.2 Secondary endpoints

- PK of SO-C101 combined with pembrolizumab
- Immune response after administration of SO-C101 in combination with pembrolizumab characterized by the changes in expression of immune markers in PBMCs
- ORR, DOR, CBR, and PFS according to iRECIST
- Detection of ADAs

9.13.1.4.3 Exploratory endpoints

- Changes in the expression of immune biomarkers after administration of SO-C101 in combination with pembrolizumab as compared to baseline in tumor tissue
- OS at 6 months after the EoT visit

9.13.1.5 Part D

9.13.1.5.1 Primary endpoint

- Safety and tolerability of SO-C101 as evaluated by the incidence of SO-C101-related AEs, SAEs, AEs leading to premature SO-C101 discontinuation, deaths, and clinical laboratory test abnormalities

9.13.1.5.2 Secondary endpoints

- PK of SO-C101

- Immune response after administration of SO-C101 characterized by the changes in expression of immune markers in PBMCs
- ORR, DOR, CBR, and PFS according to iRECIST
- Detection of ADAs

9.13.1.5.3 Exploratory endpoints

- Changes in the expression of immune biomarkers after administration of SO-C101 as compared to baseline in tumor tissue
- OS at 6 months after the EoT visit

9.13.1.6 Part D1

9.13.1.6.1 Primary endpoint

- Safety and tolerability of SO-C101 as evaluated by the incidence of SO-C101-related AEs, SAEs, AEs leading to premature SO-C101 discontinuation, deaths, and clinical laboratory test abnormalities

9.13.1.6.2 Secondary endpoints

- PK of SO-C101
- Immune response after administration of SO-C101 characterized by the changes in expression of immune markers in PBMCs
- ORR, DOR, CBR, and PFS according to iRECIST
- Detection of ADAs

9.13.1.6.3 Exploratory endpoints

- Changes in the expression of immune biomarkers after administration of SO-C101 as compared to baseline in tumor tissue
- OS at 6 months after the EoT visit

9.13.2 Definitions of analysis sets

9.13.2.1 Safety population

All patients exposed to SO-C101 in Part A, Part A1, Part D, and Part D1.

All patients exposed to SO-C101 or pembrolizumab in Part B and Part B1.

9.13.2.2 PK/PD population

All PK/PD-evaluable patients.

9.13.2.3 Efficacy population

All patients exposed to SO-C101 (exposure for at least one treatment cycle) who had at least one evaluable tumor assessment per iRECIST after the initiation of SO-C101 treatment.

9.13.3 Patient disposition

The number (percentage) of enrolled and treated patients will be summarized as well as patients who completed the study/discontinued from the study and reasons for withdrawal. The number (percentage) of patients who completed the study treatment/discontinued from the study treatment and reasons for discontinuation will also be summarized by treatment cohort.

9.13.4 Demographic and other baseline characteristics

Demographic and other baseline characteristics will be summarized and listed for each treatment cohort.

9.13.5 Prior and concomitant therapy

All investigator terms (verbatim terms) for medications recorded in the eCRF will be coded to an 11-digit code using the World Health Organization Drug Dictionary drug codes. Cancer-related prior medications will be defined as medications that stopped before the first dose of the IMP. Concomitant medications will be defined as medications that i) started before the first dose of SO-C101/pembrolizumab and were continuing at the time of the first dose of SO-C101/pembrolizumab, or ii) started on or after the date of the first dose of SO-C101/pembrolizumab. Medications started after the patient's last dose of SO-C101/pembrolizumab (whichever is administered last) will be labeled as post-treatment medications. A listing of prior, concomitant, and post-treatment medications will be included in the Clinical Study Report.

9.13.6 Primary endpoints analyses in dose escalation parts

The safety/tolerability profile of SO-C101 will be assessed. The incidence of treatment-emergent AEs and SAEs together with all other safety parameters will be summarized, by dose cohort. The incidence of DLTs (on DLT-evaluable patients, see section 9.7) by dose level will be tabulated. The MTD will be determined per Protocol definition. The RP2D will be selected as described in section 9.7.2.

9.13.7 Efficacy analyses

Analysis of efficacy endpoints will be descriptive as described above in section 9.13.

Efficacy population will be used.

Part D and Part D1 are planned to include a maximum of 60 patients (in total; up to 20 patients treated for at least one cycle in each indication). Overview of data per indication will be part of efficacy evaluation.

9.13.8 Pharmacokinetic analyses

9.13.8.1 SO-C101 PK evaluation

Evaluation of PK will be performed on the PK/PD population. Serum concentrations of SO-C101 will be tabulated and summarized by dose level, day, and time. The following PK parameters will be calculated: C_{max}, time to reach maximum concentration (T_{max}) following SO-C101 administration, AUC, and if data permit, elimination half-life, total body clearance, volume of distribution, and accumulation ratio.

9.13.8.2 Pembrolizumab PK evaluation

Evaluation of PK will be performed on the PK/PD population. Serum concentrations of pembrolizumab will be normalized to dose 1 mg/kg and then analyzed as follows:

Dose-normalized concentrations will be tabulated and summarized by dose level, day, and time. The following PK parameters will be calculated based on dose-normalized concentrations: C_{max}, T_{max}, AUC, and if data permit, elimination half-life, total body clearance, volume of distribution, and accumulation ratio.

Original (measured) and dose-normalized concentrations will be listed.

9.13.9 Pharmacodynamic and other biomarker analyses

Evaluation of PD will be performed on the PK/PD population. PD and other biomarker analyses may be performed and reported separately. Details of these analyses will be described in a separate analysis plan.

9.13.10 Safety analyses

Evaluation of safety will be performed on the Safety population. Safety data to be evaluated include all AEs, clinical laboratory results, vital signs, ECGs, and the results of physical examinations.

9.13.10.1 Extent of exposure

The number of cycles/days on treatment, quantity of SO-C101 and pembrolizumab administered, and the number of patients requiring dose reductions, treatment interruption, and treatment discontinuation due to AEs will be summarized.

9.13.10.2 Adverse events

The AE verbatim descriptions (event terms as reported by the investigator from the eCRF) will be classified into standardized medical terminology using the Medical Dictionary for Regulatory Activities (MedDRA). AEs in the eCRF will be coded to the MedDRA (version current at the time of database lock) lower level term closest to the verbatim term. AEs will be presented by MedDRA preferred term nested within primary system organ class (SOC). A treatment-emergent AE is defined as an AE that:

- emerges during treatment, having been absent at pretreatment (screening), or
- reemerges during treatment, having been present at pretreatment (screening), or
- worsens in severity during treatment relative to the pretreatment state.

Only those AEs that were treatment emergent will be included in summary tables. All AEs, treatment emergent or otherwise, will be presented in patient data listings.

The treatment-emergent AEs will be summarized by treatment cohort and their incidence will be reported as the number (percentage) of patients with treatment-emergent AEs by SOC and preferred term. A patient will be counted only once within a SOC and preferred term, even if the patient experienced more than one treatment-emergent AE within a specific SOC and preferred term. The number (percentage) of patients with treatment-emergent AEs will also be summarized by maximum severity (NCI CTCAE grades) and by relationship to SO-C101 and, in Part B and Part B1, to pembrolizumab (Suspected [related] and Not suspected [not related]), respectively.

9.13.10.3 Vital signs

Descriptive statistics for vital signs parameters and changes from baseline will be presented by day and time after dosing and treatment cohort.

9.13.11 Determination of sample size

9.13.11.1 Part A (SO-C101 dosing schedule 1, monotherapy, dose escalation)

The traditional 3+3 design dose escalation will be applied until the MTD is identified. Therefore, 3 to 6 DLT-evaluable patients per dose level will be included in a cohort. The estimated number of patients is 27-54.

9.13.11.2 Part A1 (SO-C101 dosing schedule 2, monotherapy, dose escalation)

The traditional 3+3 design dose escalation will be applied until the MTD is identified. Therefore, 3 to 6 DLT-evaluable patients per dose level will be included in a cohort. The estimated number of patients is 6-15.

9.13.11.3 Part B (SO-C101 dosing schedule 1, combined with pembrolizumab, dose escalation)

The traditional 3+3 design dose escalation will be applied until the MTD is identified. Therefore, 3 to 6 DLT-evaluable patients per dose level will be included in a cohort. The estimated number of patients is 21-42.

9.13.11.4 Part B1 (SO-C101 dosing schedule 2, combined with pembrolizumab, dose escalation)

The traditional 3+3 design dose escalation will be applied until the MTD is identified. Therefore, 3 to 6 DLT-evaluable patients per dose level will be included in a cohort. The estimated number of patients is 6-15.

9.13.11.5 Part D (SO-C101 dosing schedule 1, monotherapy, dose expansion at the RP2D identified in Part A) and Part D1 (SO-C101 dosing schedule 2, monotherapy, dose expansion at the RP2D identified in Part A1)

The number of patients in Part D together with or without Part D1 to be treated for at least one cycle is set to a maximum of 20 per indication (60 in total). This number of patients is deemed to be appropriate to provide further safety, PK, PD, and efficacy data per indication at the RP2D dose level identified in Part A (SO-C101, dosing schedule 1, monotherapy) and the RP2D dose level identified in Part A1 (SO-C101, dosing schedule 2, monotherapy). In case biomarker data in Part A1 suggest a more competitive efficacy as compared to once daily dosing, a switch to twice daily dosing (Part D1) will be made during the course of the study without affecting the overall number of patients enrolled.

9.13.12 Interim analysis

No interim analyses are planned. Data are monitored on an ongoing basis.

9.13.13 Other statistical/analytical issues

Not applicable

10 REFERENCE LIST

1. International Council for Harmonisation. E6 Good Clinical Practice Guideline. 2016; https://database.ich.org/sites/default/files/E6_R2_Addendum.pdf. Accessed October 02, 2020.
2. Mellman I, Coukos G, Dranoff G. Cancer immunotherapy comes of age. *Nature.* 2011;480(7378):480-489.
3. Fyfe G, Fisher RI, Rosenberg SA, Sznol M, Parkinson DR, Louie AC. Results of treatment of 255 patients with metastatic renal cell carcinoma who received high-dose recombinant interleukin-2 therapy. *Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology.* 1995;13(3):688-696.
4. Klapper JA, Downey SG, Smith FO, Yang JC, Hughes MS, Kammula US, Sherry RM, Royal RE, Steinberg SM, Rosenberg S. High-dose interleukin-2 for the treatment of metastatic renal cell carcinoma : a retrospective analysis of response and survival in patients treated in the surgery branch at the National Cancer Institute between 1986 and 2006. *Cancer.* 2008;113(2):293-301.
5. Liao W, Lin J-X, Leonard WJ. Interleukin-2 at the crossroads of effector responses, tolerance, and immunotherapy. *Immunity.* 2013;38(1):13-25.
6. Waldmann TA. The biology of interleukin-2 and interleukin-15: implications for cancer therapy and vaccine design. *Nature Reviews Immunology.* 2006;6(8):595-601.
7. Cheng G, Yu A, Malek TR. T-cell tolerance and the multi-functional role of IL-2R signaling in T-regulatory cells. *Immunological Reviews.* 2011;241(1):63-76.
8. Kobayashi H, Carrasquillo JA, Paik CH, Waldmann TA, Tagaya Y. Differences of biodistribution, pharmacokinetics, and tumor targeting between interleukins 2 and 15. *Cancer Research.* 2000;60(13):3577-3583.
9. Waldmann TA, Lugli E, Roederer M, Perera LP, Smedley JV, Macallister RP, Goldman CK, Bryant BR, Decker JM, Fleisher TA, Lane HC, Sneller MC, Kurlander RJ, Kleiner DE, Pletcher JM, Figg WD, Yovandich JL, Creekmore SP. Safety (toxicity), pharmacokinetics, immunogenicity, and impact on elements of the normal immune system of recombinant human IL-15 in rhesus macaques. *Blood.* 2011;117(18):4787-4795.
10. Katsanis E, Xu Z, Panoskaltsis-Mortari A, Weisdorf DJ, Widmer MB, Blazar BR. IL-15 administration following syngeneic bone marrow transplantation prolongs survival of lymphoma bearing mice. *Transplantation.* 1996;62(6):872-875.
11. Cheever MA. Twelve immunotherapy drugs that could cure cancers. *Immunological Reviews.* 2008;222:357-368.
12. Miller JS, Morishima C, McNeel DG, Patel MR, Kohrt HE, Thompson JA, Sondel PM, Wakelee HA, Disis ML, Kaiser JC, Cheever MA, Streicher H, Creekmore SP, Waldmann TA, Conlon KC. A first-in-human phase 1 study of subcutaneous outpatient recombinant human IL-15 (rhIL-15) in adults with advanced solid tumors. *Clinical Cancer Research: An Official Journal of the American Association for Cancer Research.* 2017.
13. Huntington ND, Alves NL, Legrand N, Lim A, Strick-Marchand H, Mention J-J, Plet A, Weijer K, Jacques Y, Becker PD, Guzman C, Soussan P, Kremsdorf D, Spits

H, Di Santo JP. IL-15 transpresentation promotes both human T-cell reconstitution and T-cell-dependent antibody responses in vivo. *Proceedings of the National Academy of Sciences of the United States of America.* 2011;108(15):6217-6222.

14. Huntington ND, Legrand N, Alves NL, Jaron B, Weijer K, Plet A, Corcuff E, Mortier E, Jacques Y, Spits H, Di Santo JP. IL-15 trans-presentation promotes human NK cell development and differentiation in vivo. *The Journal of Experimental Medicine.* 2009;206(1):25-34.

15. Bessard A, Solé V, Bouchaud G, Quéméner A, Jacques Y. High antitumor activity of RLI, an interleukin-15 (IL-15)-IL-15 receptor alpha fusion protein, in metastatic melanoma and colorectal cancer. *Molecular Cancer Therapeutics.* 2009;8(9):2736-2745.

16. SOTIO data on file.

17. Mortier E, Quéméner A, Vusio P, Lorenzen I, Boublik Y, Grötzinger J, Plet A, Jacques Y. Soluble interleukin-15 receptor alpha (IL-15R alpha)-sushi as a selective and potent agonist of IL-15 action through IL-15R beta/gamma. Hyperagonist IL-15 x IL-15R alpha fusion proteins. *The Journal of Biological Chemistry.* 2006;281(3):1612-1619.

18. Bouchaud G, Garrigue-Antar L, Solé V, Quéméner A, Boublik Y, Mortier E, Perdreau H, Jacques Y, Plet A. The exon-3-encoded domain of IL-15ralpha contributes to IL-15 high-affinity binding and is crucial for the IL-15 antagonistic effect of soluble IL-15Ralpha. *Journal of Molecular Biology.* 2008;382(1):1-12.

19. Desbois M, Le Vu P, Coutzac C, Marcheteau E, Béal C, Terme M, Gey A, Morisseau S, Teppaz G, Boselli L, Jacques Y, Béchard D, Tartour E, Cassard L, Chaput N. IL-15 trans-signaling with the superagonist RLI promotes effector/memory CD8+ T cell responses and enhances antitumor activity of PD-1 antagonists. *Journal of Immunology (Baltimore, Md: 1950).* 2016;197(1):168-178.

20. Conlon KC, Lugli E, Welles HC, Rosenberg SA, Fojo AT, Morris JC, Fleisher TA, Dubois SP, Perera LP, Stewart DM, Goldman CK, Bryant BR, Decker JM, Chen J, Worthy TYA, Figg WD, Peer CJ, Sneller MC, Lane HC, Yovandich JL, Creekmore SP, Roederer M, Waldmann TA. Redistribution, hyperproliferation, activation of natural killer cells and CD8 T cells, and cytokine production during first-in-human clinical trial of recombinant human interleukin-15 in patients with cancer. *Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology.* 2015;33(1):74-82.

21. Wrangle JM, Velcheti V, Patel MR, Garrett-Mayer E, Hill EG, Ravenel JG, Miller JS, Farhad M, Anderton K, Lindsey K, Taffaro-Neskey M, Sherman C, Suriano S, Swiderska-Syn M, Sion A, Harris J, Edwards AR, Rytlewski JA, Sanders CM, Yusko EC, Robinson MD, Krieg C, Redmond WL, Egan JO, Rhode PR, Jeng EK, Rock AD, Wong HC, Rubinstein MP. ALT-803, an IL-15 superagonist, in combination with nivolumab in patients with metastatic non-small cell lung cancer: a non-randomised, open-label, phase 1b trial. *The Lancet Oncology.* 2018;19(5):694-704.

22. Goutelle S, Maurin M, Rougier F, Barbaut X, Bourguignon L, Ducher M, Maire P. The Hill equation: a review of its capabilities in pharmacological modelling. *Fundamental & Clinical Pharmacology.* 2008;22(6):633-648.

23. Saber H, Gudi R, Manning M, Wearne E, Leighton JK. An FDA oncology analysis of immune activating products and first-in-human dose selection. *Regulatory toxicology and pharmacology: RTP.* 2016;81:448-456.

24. Saber H, Del Valle P, Ricks TK, Leighton JK. An FDA oncology analysis of CD3 bispecific constructs and first-in-human dose selection. *Regulatory toxicology and pharmacology: RTP.* 2017;90:144-152.

25. Sharma P, Hu-Lieskovan S, Wargo JA, Ribas A. Primary, adaptive, and acquired resistance to cancer immunotherapy. *Cell.* 2017;168(4):707-723.

26. Bernatchez C, Haymaker C, Tannir NM, Kluger H, Tetzlaff M, Bentebibel SE, Jackson N, Gergel I, Tagliaferri M, Zalevsky J, Hoch U, Imperiale M, Aung S, Hwu P, Sznol M, Hurwitz M, Diab A. A CD122-biased agonist increases CD8+ T cells and natural killer cells in the tumor microenvironment; making cold tumors hot with NKTR-214. 2018; http://www.nektar.com/application/files/7714/7887/7212/2016_SITC_NKTR-214-clinical_poster.pdf. Accessed December 20, 2019.

27. Bates SE, Berry DA, Balasubramaniam S, Bailey S, LoRusso PM, Rubin EH. Advancing clinical trials to streamline drug development. *Clinical Cancer Research: An Official Journal of the American Association for Cancer Research.* 2015;21(20):4527-4535.

28. Emens LA, Butterfield LH, Hodi FS, Marincola FM, Kaufman HL. Cancer immunotherapy trials: leading a paradigm shift in drug development. *Journal for Immunotherapy of Cancer.* 2016;4:42.

29. Le Tourneau C, Lee JJ, Siu LL. Dose escalation methods in phase I cancer clinical trials. *J Natl Cancer Inst.* 2009;101(10):708-720.

30. Hirsch L, Zitvogel L, Eggermont A, Marabelle A. PD-Loma: a cancer entity with a shared sensitivity to the PD-1/PD-L1 pathway blockade. *British Journal of Cancer.* 2019;120(1):3-5.

31. Ott PA, Hodi FS, Kaufman HL, Wigginton JM, Wolchok JD. Combination immunotherapy: a road map. *Journal for Immunotherapy of Cancer.* 2017;5.

32. Davies M, Duffield EA. Safety of checkpoint inhibitors for cancer treatment: strategies for patient monitoring and management of immune-mediated adverse events. *ImmunoTargets and Therapy.* 2017;6:51-71.

33. Raines EW, Ferri N. Thematic review series: The immune system and atherogenesis. Cytokines affecting endothelial and smooth muscle cells in vascular disease. *Journal of Lipid Research.* 2005;46(6):1081-1092.

34. Wuttge DM, Eriksson P, Sirsjö A, Hansson GK, Stemme S. Expression of interleukin-15 in mouse and human atherosclerotic lesions. *The American Journal of Pathology.* 2001;159(2):417-423.

35. Margolin K, Morishima C, Velcheti V, Miller JS, Lee SM, Silk AW, Holtan SG, Lacroix AM, Fling SP, Kaiser JC, Egan JO, Jones M, Rhode PR, Rock AD, Cheever MA, Wong HC, Ernstoff MS. Phase I trial of ALT-803, a novel recombinant IL15 complex, in patients with advanced solid tumors. *Clinical cancer research : an official journal of the American Association for Cancer Research.* 2018;24(22):5552-5561.

36. Seymour L, Bogaerts J, Perrone A, Ford R, Schwartz LH, Mandrekar S, Lin NU, Litière S, Dancey J, Chen A, Hodi FS, Therasse P, Hoekstra OS, Shankar LK, Wolchok JD, Ballinger M, Caramella C, de Vries EGE, group Rw. iRECIST: guidelines for response criteria for use in trials testing immunotherapeutics. *The Lancet Oncology*. 2017;18(3):e143-e152.

37. Keytruda SmPC EU. https://www.ema.europa.eu/en/documents/product-information/keytruda-epar-product-information_en.pdf. Accessed May 13, 2021.

38. Keytruda US Prescribing Information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/125514s097lbl.pdf. Accessed May 13, 2021.

39. U.S. Food and Drug Administration. E14 clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for non-antiarrhythmic drugs: Guidance for industry. 2018; https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073153.pdf. Accessed October 22, 2018.

40. Proleukin SmPC. https://www.medicines.org.uk/emc/product/291/smpc. Accessed May 11, 2021.

41. Proleukin US Prescribing Information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/103293s5130lbl.pdf. Accessed May 11, 2021.

42. Dutcher JP, Schwartzentruber DJ, Kaufman HL, Agarwala SS, Tarhini AA, Lowder JN, Atkins MB. High dose interleukin-2 (Aldesleukin) - expert consensus on best management practices-2014. *Journal for Immunotherapy of Cancer*. 2014;2(1):26.

43. Meid AD, Bighelli I, Machler S, Mikus G, Carra G, Castellazzi M, Lucii C, Martinotti G, Nose M, Ostuzzi G, Barbui C, Haefeli WE. Combinations of QTc-prolonging drugs: towards disentangling pharmacokinetic and pharmacodynamic effects in their potentially additive nature. *Therapeutic Advances in Psychopharmacology*. 2017;7(12):251-264.

44. Du Bois D, Du Bois EF. A formula to estimate the approximate surface area if height and weight be known. 1916. *Nutrition (Burbank, Los Angeles County, Calif)*. 1989;5(5):303-311; discussion 312-313.

45. Yu P, Steel JC, Zhang M, Morris JC, Waldmann TA. Simultaneous blockade of multiple immune system inhibitory checkpoints enhances antitumor activity mediated by interleukin-15 in a murine metastatic colon carcinoma model. *Clinical Cancer Research: An Official Journal of the American Association for Cancer Research*. 2010;16(24):6019-6028.

46. Council of Europe Committee of Ministers. Recommendation CM/Rec (2016)6 of the committee of ministers to member states on research on biological materials of human origin. 2016; https://search.coe.int/cm/Pages/result_details.aspx?ObjectId=090000168064e8ff. Accessed December 20, 2019.

11 PROCEDURES AND INSTRUCTIONS (ADMINISTRATIVE PROCEDURES)

11.1 Changes to the Protocol

Any change to the Protocol requires a written Protocol amendment or administrative change that must be approved by the sponsor before implementation. Amendments specifically affecting the safety of patients, the scope of the investigation, or the scientific quality of the study require submission to health or regulatory authorities as well as additional approval by the applicable IRBs/ECs. These requirements should in no way prevent any immediate action from being taken by the investigator, or by the sponsor, in the interest of preserving the safety of all patients included in the study. If the investigator determines that an immediate change to or deviation from the Protocol is necessary for safety reasons to eliminate an immediate hazard to the patients, the sponsor's medical monitor (or appropriate study team member) and the IRB/EC for the site must be notified immediately. The sponsor must notify the health or regulatory authority as required per local regulations.

Protocol amendments that affect only administrative aspects of the study may not require submission to health or regulatory authority or the IRB/EC, but the CA and IRB/EC should be kept informed of such changes as required by local regulations. In these cases, the sponsor may be required to send a letter to the IRB/EC and the CAs detailing such changes.

11.2 Adherence to the Protocol

The investigator will conduct the study in strict accordance with this Protocol.

11.3 Monitoring procedures

The sponsor's/CRO's CRA will maintain contact with the investigator and designated staff by telephone, letter, or email between study visits. Monitoring visits to each site will be conducted by the assigned CRA as described in the monitoring plan. The investigator will allow the CRA to inspect the clinical, laboratory, and pharmacy facilities to assure compliance with GCP and local regulatory requirements. The eCRFs and patients' corresponding original medical records (source documents) are to be fully available for review by the sponsor's representatives at regular intervals. These reviews verify adherence to study Protocol and data accuracy in accordance with local regulations. All records at the site are subject to inspection by the local auditing agency and IRB/EC review.

The investigator has to maintain source documents for each patient in the study, consisting of visit records (clinic, office, and hospital), laboratory data, ECG, echocardiography, images and the results of any other tests or assessments. The investigator must also keep one original signed and dated ICF (a signed and dated copy is given to the patient).

11.4 Recording of data

An eCRF is required and must be completed for each patient by qualified and authorized personnel. All data on the eCRF must reflect the corresponding source document. Any correction to entries made on the eCRF must be documented in a valid audit trail where the correction is dated, the individual making the correction is identified, the reason for the change is stated, and the original data are not obscured. Only data required by the Protocol for the purposes of the study should be collected. The investigator must sign the eCRFs.

11.5 Identification of source data

All data to be recorded on the eCRF must reflect the corresponding source documents.

11.6 Retention of records

Notwithstanding the circumstances of completion or termination of the study, the investigator is responsible for retaining all study documents, including but not limited to the Protocol, the IB, and regulatory agency registration documents (e.g., Form FDA 1572, ICFs, and IRB/EC correspondence). The site should plan to retain study documents, as directed by the sponsor, for at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 3 years have elapsed since the formal discontinuation of clinical development of the IMP.

It is requested that at the completion of the required retention period, or should the investigator retire or relocate, the investigator contact the sponsor, allowing the sponsor the option of permanently retaining the study records.

11.7 Confidentiality of personal data

In order to ensure that personal information of each patient is kept confidential and protected, names and any other information that allows direct identification of a patient will not be in the eCRFs or included in any records or samples provided to the sponsor or sponsor's authorized representatives; such information will be pseudonymised, i.e., all such information will be replaced by a specific code (patient number) assigned by a study doctor and all patients will be identified in eCRFs or any other records or samples by a patient number only.

The personal information collected for the purposes of this study will be held by the study sites, the sponsor and sponsor's authorized representatives, which together are responsible for processing of personal information in accordance with the General Data Protection Regulation (EU) 2016/679 and any corresponding local legislation.

The sponsor and its authorized representatives will analyze and use the personal information they receive for the purposes of this study only. These include:

- checking patients' suitability to take part in the study,
- monitoring patients' health during treatment with SO-C101 as monotherapy and in combination with pembrolizumab,
- comparing and pooling study results,
- establishing whether SO-C101 as monotherapy and in combination with pembrolizumab meets the appropriate standards of safety set by the authorities,
- establishing whether SO-C101 as monotherapy and in combination with pembrolizumab is effective,
- supporting the clinical development of SO-C101 as monotherapy and in combination with pembrolizumab,
- supporting the licensing application for regulatory approval of SO-C101 as monotherapy and in combination with pembrolizumab anywhere in the world,

- supporting the marketing, distribution, sale and use of SO-C101 as monotherapy and in combination with pembrolizumab anywhere in the world,
- complying with specific regulations governing clinical trials.

Participation of patients in this study is voluntary and they may withdraw from the study at any time by informing the investigator. Their participation in the study will then end and the study personnel will stop collecting personal information from the patients, but the sponsor will need to retain and use the pseudonymised personal information and associated research results that have already been collected from the patient. The sponsor must do this to comply with its legal and regulatory obligations, to maintain the scientific integrity of the study, and to complete the marketing authorization process for SO-C101 as monotherapy and in combination with pembrolizumab. It may be necessary to retain certain aspects of pseudonymised (coded) personal information for at least 25 years following the end of the study to comply with applicable laws and regulatory requirements and to ensure the scientific integrity of the study.

If necessary for the study purposes mentioned above, the sponsor may communicate such pseudonymised personal information to third parties (such as service providers, contractors, and research institutions that support the study) and regulatory or other governmental agencies that need to check the results of the study.

These third parties may be located in countries of the European Economic Area (EEA), the United States, and other countries that are outside of the EEA. Some non-EEA countries may not offer the same level of privacy protection. However, the sponsor will keep personal information it receives as confidential as possible within the limits of the law. The sponsor will implement appropriate contractual measures, including the standard data protection contractual clauses, to ensure that the relevant recipients outside the EEA provide an adequate level of protection to personal information as set out in this form and as required by applicable law.

The sponsor, either alone or together with other researchers, may publish or present the results of the study; however, personal information will not be disclosed in any publication or presentation. See also section 11.10.

All persons have certain rights to gain access to and correct any inaccuracies in the personal information held about them. In certain circumstances, they can also request restriction of processing of their personal information, object to certain types of processing of their personal information, request their personal information be erased and have their personal information provided to them or a third party in a digital format. The sponsor shall comply with the above requests to the fullest extent consistent with other legal and regulatory obligations and where required by law.

Personal data cannot be erased, even after patients finish or terminate their participation in the study, in order to guarantee the validity of the clinical research and to comply with statutory duties and drug authorization requirements.

Representatives from government agencies, the local EC and sponsor or its authorized representatives may also need access to medical records and study records for the purpose of checking data collected for the study.

The sponsor shall process all personal information of the patients in the study in accordance with the General Data Protection Regulation (EU) 2016/679, any applicable local legislation and the internal data protection policies reflecting organizational and technical arrangements to avoid unauthorized access, disclosure, dissemination, alteration, or loss of information

and personal data processed, namely the Data Protection Regulation and Incident Management Regulation. The organizational and technical measures introduced by the sponsor in relation to a protection of personal information of the patients involve the above mentioned pseudonymisation of personal information, appropriate controls to restrict its employees access to the personal information, a physical access control to any premises where the personal information is stored, an electronic access and system control logging for any systems containing personal information, data entry and data transfer control, availability control (back-up and recovery concept), network protection including firewalls and penetration testing procedures for regular testing, industry-standard security policies and procedures including assessment and evaluation of processes and regular training procedures. In the event of any security breach, the Incident management procedures would be implemented and the sponsor would notify such breach within statutory term as applicable.

11.8 Auditing procedures and inspection

In addition to the routine monitoring procedures, audits of clinical research activities will be conducted in accordance with the sponsor's SOPs to evaluate compliance with the principles of ICH GCP and all applicable local regulations. If a government regulatory authority requests an inspection during the study or after its completion, the investigator must inform the sponsor immediately.

11.9 Handling of IMPs

All IMPs will be supplied to the study sites by the sponsor. IMP supplies must be kept in an appropriate secure area (e.g., locked cabinet) and stored according to the conditions specified on the IMP labels. The investigator (or a designated pharmacist) must maintain an accurate record of the shipment and dispensing of the IMP in an IMP accountability ledger, a copy of which must be given to the sponsor at the end of the study. An accurate record of the date and amount of the IMP dispensed to each patient must be available for inspection at any time. The CRA will visit the site and review these documents along with all other study conduct documents at appropriate intervals once IMPs have been received by the site.

All IMP supplies are to be used only for this study and not for any other purpose. The investigator (or site personnel) must not destroy any IMP labels or any partly used or unused IMP supply before approval to do so by the sponsor. At the conclusion of the study and as appropriate during the study, the investigator (or a designated pharmacist) will return all used and unused IMP containers, IMP labels, and a copy of the completed IMP disposition form to the sponsor's CRA (or designated contractor) or, when approval is given by the sponsor, will destroy supplies and containers at the site. See also section 9.10.6.

11.10 Publication of results

All manuscripts, abstracts, or other modes of presentation arising from the results of this study must be reviewed and approved in writing by the sponsor in advance of submission pursuant to the terms and conditions set forth in the executed Clinical Trial Agreement between the sponsor/CRO and the institution/investigator. The review is aimed at protecting the sponsor's proprietary information existing either at the date of the commencement of the study or generated during the study.

The detailed obligations regarding the publication of any data, material results, or other information, generated or created in relation to the study shall be set out in the agreement between each investigator and the sponsor or CRO, as appropriate.

11.11 Disclosure and confidentiality of information about the study

The contents of this Protocol and any amendments and results obtained during the study should be kept confidential by the investigator, the investigator's staff, and the IRB/EC and will not be disclosed in whole or in part to others, or used for any purpose other than reviewing or performing the study, without the written consent of the sponsor. No data collected as part of this study will be used in any written work, including publications, without the written consent of the sponsor. These obligations of confidentiality and non-use shall in no way diminish such obligations as set forth in either the Confidentiality Agreement or Clinical Trial Agreement executed between the sponsor/CRO and the institution/investigator.

All persons assisting in the performance of this study must be bound by the obligations of confidentiality and non-use set forth in either the Confidentiality Agreement or Clinical Trial Agreement executed between the institution/investigator and the sponsor/CRO.

11.12 Patient insurance and indemnity

The sponsor will provide insurance for any patients participating in the study in accordance with all applicable laws and regulations.

11.13 Future research

Biological samples collected during this study may be stored for future research by the sponsor. Storage conditions will be in compliance with the standards for repositories of biological samples, according to the "Recommendation CM/Rec (2016)6 of the Committee of Ministers to member States on research on biological materials of human origin".[46]

The repository will have independent monitoring that will guarantee protection of the data and the patients' interests (see also section 11.7). The samples will not be transferred or sold to third parties. The exploratory studies that will be conducted with the samples will undergo a rigorous independent review evaluating both ethical and scientific aspects.

11.14 Document history

Version	Date
10.0	29-Jul-2021 (effective date 01-Nov-2021)
9.0	16-Jul-2021
8.0	11-Feb-2021
7.0	25-Nov-2020
6.1	13-May-2020
6.0	25-Mar-2020 (version 6.0 was never implemented)
5.0	05-Nov-2019
4.0	10-Apr-2019
3.0	20-Mar-2019
2.0	17-Jan-2019
1.0	12-Nov-2018

11.15 Protocol amendment (version 10.0) summary of changes versus version 9.0

Change number	Description of change	Rationale for change	Section affected in Protocol version 10.0
1	Change of sponsorship	Change of sponsorship (effective date 01-Nov-2021)	1 TITLE PAGE, SIGNATURES / PROTOCOL APPROVAL AND RELEASE, INVESTIGATOR'S DECLARATION AND SIGNATURE, 6 INVESTIGATORS AND SPONSOR, 9.12.1 Data collection, 11.7 Confidentiality of personal data, 11.8 Auditing procedures and inspection

12 APPENDICES

List of appendices

12.1 New York Heart Association Classification

Class I	No symptoms and no limitation in ordinary physical activity, e.g., shortness of breath when walking, climbing stairs.
Class II	Mild symptoms (mild shortness of breath and/or angina) and slight limitation during ordinary activity.
Class III	Marked limitation in activity due to symptoms, even during less-than-ordinary activity, e.g., walking short distances (20-100 m). Comfortable only at rest.
Class IV	Severe limitations. Experiences symptoms even while at rest. Mostly bedbound patients.
Class V	No class listed above or unable to determine.

12.2 Creatinine clearance estimation

For males, creatinine clearance is estimated using the Cockcroft-Gault formula as follows:

Creatinine clearance = [(140 − age) × weight]/(72 × serum creatinine)

Where age is in years, weight is in kilograms, and serum creatinine is in mg/dL. Actual, not ideal weight is to be used.

For females, creatinine clearance is estimated by multiplying the result of the above formula by 0.85.

12.3 Hy's law

Drugs are likely to cause a high rate (10-50%) of fatal liver injury or need for transplant in patients with acute hepatocellular injury sufficient to cause jaundice. Hy's law is a rule of thumb that a patient is at high risk of a fatal drug-induced liver injury if given a medication that causes hepatocellular injury (not cholestatic injury) with jaundice.

Hy's law cases have three components:

- The drug causes hepatocellular injury, generally defined as an elevated ALT or AST by 3-fold or greater above the ULN. Often with aminotransferases much greater (5-10×ULN).
- Among patients showing such aminotransferase elevations, they also have elevation of their serum total bilirubin of greater than 2×ULN, without findings of cholestasis (defined as serum alkaline phosphatase activity less than 2×ULN).
- No other reason can be found to explain the combination of increased aminotransferase and serum total bilirubin, such as viral hepatitis, alcohol abuse, ischemia, preexisting liver disease, or another drug capable of causing the observed injury.

12.4 Assessment of performance status

ECOG performance status should be documented according to Table 12.1.

Table 12.1: ECOG performance status scale

Grade	ECOG
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled, cannot carry on any self-care; totally confined to bed or chair
5	Dead

12.5 Clinical management recommendations for HD IL-2 therapy[42]

Issue	Considerations	Management
Venous access	Central line (for possible vasopressors)	**Typical**
	Double or triple lumen	PICC line placement
	Power inject and large volume capacity	Remove temporary lines at end of cycle
	Minimize catheter associated infection	**Variations**
		Broviac/Hickman catheter
		Subclavian/IJ catheter
IV fluids	Maintenance of volume with CLS	**Typical**
	Boluses for blood pressure support	D5NS or D5LR 10 ml – 125 ml/hr
	Administration of drugs	PRN KCL, HCO3, Mg replacement
	Replacement of electrolytes	**Variations**
	IL-2 only compatible with D5W	D5W, NS, 0.45% NaCl
Infections	No active infections	**Typical**
	Prevention	Gram + prophylactic antibiotic
	IV catheter likeliest source	**Variations**
	Avoid unnecessary in-dwelling catheters	Expanded coverage per hospital
Chills/rigors	Chills and rigors occur 1–2 hrs after IL-2	**Fever-Typical**
		Prophylaxis
Fever	Fever is common 2–4 hrs after IL-2	Acetaminophen 650 mg 30 min pre-dose, q 4–6 hrs and prn
		Indomethacin 25 mg q 6–8 hrs
Constitutional symptoms	Muscle joint aches continuous and progressive during IL-2 treatment	**Fever-Variation**
		Naproxen
		Ibuprofen
		Chills-Typical
		Meperidine 25 mg IV q 15 m prn
		Morphine 2–4 mg IV q 15 m prn
Nausea/vomiting	Episodic occurrence throughout therapy	**Typical- Prophylaxis**
	Nausea > vomiting	Ondansetron 0.15 mg/kg q 8 hrs
		Variations
		Granisetron 1 mg daily
		Ondansetron at longer interval
		Compazine 10 mg po q 6 hrs
		Use of antinausea agents prn
Epigastric distress	Gastritis induced by stress, medications	**Typical**
		H2 blocker prophylaxis
		Variation
		PPI prophylaxis
Mucositis/stomatitis	Progressive with continued treatment	**Typical**
		No prophylaxis
		Oncology mouthwash
Diarrhea	Can be profuse and increases with therapy	**Typical**
	5HT-3 antagonist anti-emetic prophylaxis	Imodium
	may have positively impacted	Lomotil
		Narcotic
		Break between IL-2 doses

Issue	Considerations	Management
		Variations
		5HT-3 antagonist prophylaxis
Patient monitoring	I & O, Weight	Per shift and daily
	Blood pressure, pulse, respirations, temp	Q 2-4 hrs
	Blood work	Daily
	EKG	Continuous cardiac monitoring
	O2 Saturation	Q 2–4 hrs
	Mental status examination	Q 8 hrs
		Increase frequency as needed
Aldesleukin/Interleukin-2 dose and administration	IL-2 incompatible with salt solutions.	**Typical:** 600,000 IU/kg infused over 15 minutes Q 8 hrs up to 14 doses.
	Dissolve in sterile water for injection Dilute into 50 cc D5W	**Variations:** 720,000 IU/kg Q 8 hrs Q 12 hrs < 14 maximum doses
	Stop infusion, flush IV tubing with 50 cc D5W before and after each dose.	
Hypotension	Maintain systolic BP 80–90 mm hg	Fluid boluses, 250–500 ml NS
	Blood pressure nadirs 4–6 hrs after each dose with diminished recovery with cumulative dosing	2xday
		Increase maintenance fluid rate
		Phenylephrine 0.1-4.0 mcg/kg/min
		Hold next dose
	Prior to each dose anticipate ability to respond to next nadir	DC IL-2
		Variations:
		Dopamine 1-6 ug/kg/min
	Progressive refractoriness to support measures	Pressors with minimal fluids
		Fluids without pressors
Cardiac arrhythmias	**Sinus tachycardia**	Manage BP and fever
	Common and progresses over a cycle	
	Peaks 2–4 hrs after dose with fever and hypotension	
	Must resolve prior to next dose	
	Supraventricular tachycardia, atrial fibrillation	Medical Conversion
	Less common	Cardizem as needed
	Atrial fibrillation	Digoxin
	Ventricular tachycardia	Medical Conversion
		Acute treatment
		Discontinue IL-2
Renal function		**Typical**
	Oliguria	Output less than 50–100 cc/8 hrs Fluid bolus, if no improvement next shift hold IL-2 dose
	Rising creatinine	Creatinine >3-4
		Stop NSAIDS and nephrotoxic antiobiotics
	Urine output and creatinine resolve after discontinuation of IL-2	Hold overnight dose
		If am creatinine improved continue
	If only one kidney always consider obstruction of ureter	**Variations**
		Dopamine 1–6 mcg/kg/min
		Furosemide

Issue	Considerations	Management
Pulmonary	Tachypnea/Dyspnea	**Typical**
	Diagnose etiology and treat	Oxygen 2–4 L nasal cannula, increasing up to 35% rebreather
	Hypoxic causes-Fluid overload, capillary leak, bronchospasm	Reassurance or sedative for anxiety, treat bronchospasm or acidosis if appropriate
	Non hypoxic causes	Hold IL-2 dose if O_2sat < 95%
	Anxiety, fever, acidosis	
	Maintain O_2sat > 92-5%	**Variation**
		Furosemide
		Bronchodilators
		Monitor bicarbonate
Peripheral edema	Expect to gain 5-10% body weight	Elevation, compression, limit fluid support in subsequent cycles
	Treat edema symptomatically	Diuretics upon conclusion of IL-2 dosing are not necessary but may speed process
	Entrapment of peripheral nerves in upper extremity may need therapy	Treat peripheral nerve pain
Neurotoxicity		**Typical**
	Protean manifestations	Formal neuro checks
	Gradual onset with sudden worsening near end of cycle	Enlist family evaluation
	May persist after cessation of therapy	Lorazepam and Haloperidol
	Delusions, Visual hallucinations	Hold IL-2 liberally for suspected neurotoxicity
		Warn patient of vivid dreams after discharge
Dermatologic		**Typical**
	Rash, erythema, dry desquamation	Emollient lotions and creams Oatmeal bath
	Pruritus	Antihistamines
	Moist dermatitis	Hold IL-2 dose
		Variations
		Crisco
		Gabapentin
		Naloxone
		Narcotics
		Nonalcohol, no steroid topicals
Metabolic	Hypomagnesemia, hypocalcemia (but low albumin – so corrected may be WNL), Hypokalemia-	Daily electrolyte panels
	Acidosis due to diarrhea, hypoperfusion	Correct electrolytes cautiously prn
	Hypothyroidism a slow onset problem	Magnesium and HCO3, particularly if diarrhea a problem
		HCO3 < 18 meq/L hold dose of IL-2
		Check TSH at beginning of cycle
		RL as support fluids may decrease need for HCO3
Hepatic	↑Bilirubin (up to 10)	Monitor daily
	↓Albumin (down to 1.8)	No intervention except if SGOT SGPT are >5x
	↑Hepatic aminotransferases	Resolves spontaneously
		Stop acetaminophen if bilirubin > 5

Issue	Considerations	Management
Hematologic	↓Platelets	Transfuse platelets if < 20 K
	Lymphs ↓during IL-2, ↑post therapy	Other abnormalities require no intervention
	Eosinophils progressively ↑with several cycles	Significant anemia needs evaluation for cause
Endocrine	Hypothyroidism – slow onset after completion of treatment	Check TFTs at beginning of cycle and monitor TFTs with subsequent visits
	Requires serial monitoring	

12.6 Definition of MTD and RP2D as used in the study Protocol

Since different definitions of MTD and RP2D are used in the United States compared to Europe and Japan, the sponsor is providing clarification on the definitions used in the study Protocol.

In section 9.13.1 of the Protocol, MTD is defined "*as the dose level associated with ≥33% of DLT-evaluable patients experiencing a DLT. If the MTD is reached, the RP2D will be conventionally defined as the dose level just below this non-tolerated dose level. If the MTD is not reached, the RP2D will be selected based on integrated evaluation of safety, tolerability, clinical benefit, PK and PD data, for all dose levels tested*.'' The sponsor is using the MTD/RP2D definition for Europe and Japan.

According to the study Protocol, "*The dose escalation plan follows the traditional 3+3 design as described by Le Tourneau et al.*" Le Tourneau et al. define MTD and RP2D as follows:

- Phase I trials conducted in the United States: the highest dose level at which <33% of patients experience DLT. The MTD is the highest dose with ≤1 of 6 (< 33%) patients with DLT and is the highest tolerated dose.
- Phase I trials conducted in Europe and Japan: the lowest dose level at which ≥33% of patients experience DLT (a misnomer in the sense that the MTD is actually not a tolerable dose). The dose escalation continues until at least 2 patients in a cohort of 3 to 6 patients experience DLTs (i.e., ≥33% of patients with a DLT at that dose level).
- In phase I trials with toxicity endpoint conducted in the United States RP2D is defined as the MTD.
- In phase I trials with toxicity endpoint conducted in Europe and Japan RP2D is one dose level below MTD.

12.7 Protocol amendment history

The Protocol amendment (version 10.0) summary of changes versus version 9.0 for the current amendment is in section 11.15.

12.7.1 Version 9.0 (16-Jul-2021): Protocol changes implemented

Change number	Description of change	Rationale for change	Section affected in Protocol version 9.0
1	Adjustment of the schedule of procedures/assessments to clarify that patients will visit the site on day 15 as follows: Part A: In cycles 1, 2, 3 Part A1: In cycle 1 Part B: In cycles 1, 2, 3 Part B1: In cycle 1 Part D: In cycle 1 Part D1: In cycle 1	To clarify that patients in study SC103 will visit the trial sites on day 15 only when blood sample collection is scheduled. They do not need to visit the site on day 15 only for AEs and concomitant medication/non-drug therapies recording.	9.11.7 Schedule of procedures/assessments
2	Definition of the end of study parts	To define that each study part will end when the last patient in this study part completes the last visit, including follow-up calls	2 CLINICAL PROTOCOL SYNOPSIS, 9.7.9 End of the study
3	Deletion of Part C	Part C will be replaced by a separate trial	2 CLINICAL PROTOCOL SYNOPSIS, 7.9 Study design rationale, 8 STUDY DESIGN AND OBJECTIVES, 9 INVESTIGATIONAL PLAN
4	Shortening of survival follow-up to 6 months after the EoT visit	No need to observe patients for longer than 6 months after the EoT visit	2 CLINICAL PROTOCOL SYNOPSIS, 8.2 Objectives, 9.7 Dose escalation plan and study periods, 9.11.5.1.2 Safety monitoring periods, 9.11.6.4 Assessment of laboratory parameters, 9.11.7 Schedule of procedures/assessments, 9.13.1 Study endpoints
5	Cancellation of assessments (physical examination, body weight and surface area, vital signs, and ECOG) during efficacy follow-up	Following the decision that 90 days of safety follow-up is enough, collection of physical examination, body weight and surface area, vital signs, and ECOG at efficacy follow-up visits will be cancelled; collection of physical examination, body	9.11.7 Schedule of procedures/assessments

Change number	Description of change	Rationale for change	Section affected in Protocol version 9.0
		weight and surface area, and vital signs will be done during safety follow-up	
6	Replacement of safety, efficacy, and survival follow-up periods with one follow-up period	The three different follow-up periods were confusing to the study sites	2 CLINICAL PROTOCOL SYNOPSIS, 9.7.7 Study periods in Part A, Part A1, Part B, and Part B1, 9.7.8 Study periods in Part D and Part D1, 9.11.7 Schedule of procedures/assessments
7	Clarification until when tumor assessments are to be done	To clarify that "until disease progression …." in fact means "until iCPD or start of a new anti-cancer treatment"	2 CLINICAL PROTOCOL SYNOPSIS, 9.7.7 Study periods in Part A, Part A1, Part B, and Part B1, 9.7.8 Study periods in Part D and Part D1
8	Clarification that tumor assessments are not to be done after iCPD	Not needed for the evaluation of study objectives	9.11.7 Schedule of procedures/assessments, 9.11.11 Guidance for continuation of study treatment beyond iRECIST-defined disease progression
9	Update of information on the chemical structure of SO-C101	New experimental information on the chemical structure of SO-C101	7.2.2 SO-C101 mechanism of action, 9.9.3.1 Name, structural formula
10	Clarification that serum (immunogenicity) testing is to be stopped after cycle 12 (testing at the EoT visit to be done)	Serum (immunogenicity) testing not needed beyond cycle 12	9.11.7 Schedule of procedures/assessments
11	Change of PBMC immunomonitoring and PBMC genetic testing time points in Part A1, Part B1, Part D, and Part D1	To be able to compare the two dosing schedules	9.11.7 Schedule of procedures/assessments
12	Adjustment of the time window for serum (cytokine) sampling 8 hours post dose in Part A1, Part D, and Part D1 from -30 min to ±30 min	To harmonize time windows for all serum (cytokine) sampling time points in Part A1, Part D, and Part D1	9.11.7 Schedule of procedures/assessments
13	Adjustment of the time window for PK sampling 4 and 8 hours post dose in Part A1, Part B1, Part D, and Part D1 from +30 min and -15 min, respectively, to ±15 min	To harmonize time windows for all PK sampling time points in Part A1, Part B1, Part D, and Part D1	9.11.7 Schedule of procedures/assessments

Change number	Description of change	Rationale for change	Section affected in Protocol version 9.0
14	Clarification that for crossover patients, the last tumor assessment in Part A or Part A1 serves as baseline in Part B or Part B1	To clarify baseline for tumor assessments after crossover from Part A or Part A1 to Part B or Part B1	9.11.2 Tumor assessments
15	Wording changes in section 5.2 Ethical conduct of the study	To improve readability and remove redundancies	5.2 Ethical conduct of the study
16	Wording changes in statistical parts	To improve readability and remove redundancies	2 CLINICAL PROTOCOL SYNOPSIS, 9.13 Statistical methods
17	Adjustment of the time window for the start of treatment (day 1) in Part A1, Part B1, Part D, and Part D1 from +1 day to ±1 day	To align the time window for day 1 in Part A1, Part B1, Part D, and Part D1 with the time window for day 1 in Part A and Part B	2 CLINICAL PROTOCOL SYNOPSIS, 9.2 Part A1 (SO-C101 dosing schedule 2, monotherapy, dose escalation), 9.4 Part B1 (SO-C101 dosing schedule 2, combined with pembrolizumab, dose escalation), 9.5 Part D (SO-C101 dosing schedule 1, monotherapy, dose expansion at the RP2D identified in Part A), 9.6 Part D1 (SO-C101 dosing schedule 2, monotherapy, dose expansion at the RP2D identified in Part A1), 9.9.1.1 SO-C101 (all study parts), 9.11.7 Schedule of procedures/ assessments
18	Adjustment of the sample size of Part D and Part D1 from a total of 20 patients per part to a total of up to 60 patients in total (Part D and Part D1)	To be able to collect more safety data on the RP2D of SO-C101 monotherapy and better characterize signals of efficacy	2 CLINICAL PROTOCOL SYNOPSIS, 7.9 Study design rationale, 8.1 Study design, 9.7.5 Patient recruitment management, 9.11.7 Schedule of procedures/ assessments, 9.13.7 Efficacy analyses, 9.13.11 Determination of sample size
19	Addition of information on the RP2D identified in Part A	To update the information on the study status	2 CLINICAL PROTOCOL SYNOPSIS, 7.5 Justification for the starting dose and dose escalation steps in Part A, 7.6 Justification for the starting dose in Part A1, 9.1 Part A (SO-C101 dosing schedule

Change number	Description of change	Rationale for change	Section affected in Protocol version 9.0
			1, monotherapy, dose escalation), 9.3 Part B (SO-C101 dosing schedule 1, combined with pembrolizumab, dose escalation), 12.7 Number of patients with at least one grade 3-4 TEAE suspected to be related to SO-C101 as per investigators' judgement reported in study SC103 up to dose level 9 in Part A and dose level 1 in Part B
20	Deletion of Senior Medical Director and change of Statistician	Change of personnel	SIGNATURES / PROTOCOL APPROVAL AND RELEASE
21	Minor wording changes and punctuation adjustments	To improve clarity and readability	Throughout the document

12.7.2 Version 8.0 (11-Feb-2021): Protocol changes implemented

Change number	Description of change	Rationale for change	Section affected in Protocol version 8.0
1	Definition of stopping rules for expansion parts (Part C, Part D, Part D1)	To clearly define stopping rules also for patients in Part C, Part D, and Part D1	2 CLINICAL PROTOCOL SYNOPSIS; 7.9 Study design rationale; 9.6 Part D (SO-C101 dosing schedule 1, monotherapy, dose expansion at the RP2D identified in Part A); 9.7 Part D1 (SO-C101 dosing schedule 2, monotherapy, dose expansion at the RP2D identified in Part A1); 9.8.12 Stopping rules for all parts; 9.12.10 Treatment discontinuation

12.7.3 Version 7.0 (25-Nov-2020): Protocol changes implemented

Change number	Description of change	Rationale for change	Section affected in Protocol version 7.0
1	Addition of Part A1 and Part B1 to investigate an additional dosing schedule for SO-C101: administration twice a day as 2 divided doses (instead of as 1 daily dose) with the second dose on each treatment day administered 8 hours (±15 min) after the first dose	Based on animal PK/PD study results, the once daily dose of SO-C101 will be administered as two divided doses and investigated in new study parts, Part A1and Part B1. Nonclinical studies demonstrated that when the total daily dose previously given as a once daily dose is administered as two equally divided doses twice daily (50% each of the once daily dose), this led to stronger PD activity, namely the activation of CD8+ T cells and NK cells as observed by their increase in absolute cell counts in cynomolgus monkeys (studies SO-C101-1186E, SO-C101-1141E). This increase in immune stimulation seems to contribute to a reduced tumor cell growth in tumor-bearing mice. PK evaluations suggest that the stronger PD effect is mediated by the longer exposure to SO-C101 concentrations that activate CD8+ T cells and NK cells.	2 CLINICAL PROTOCOL SYNOPSIS, 7.4 Justification for dose scheduling, 7.6 Justification for the starting dose in Part A1, 7.8 Justification for the starting dose in Part B1, 7.9 Study design rationale, 8.1 Study design, 8.2 Objectives, 9.1 Part A (SO-C101 dosing schedule 1, monotherapy, dose escalation), 9.2 Part A1 (SO-C101 dosing schedule 2, monotherapy, dose escalation), 9.3 Part B (SO-C101 dosing schedule 1, combined with pembrolizumab, dose escalation), 9.4 Part B1 (SO-C101 combined with pembrolizumab, dosing schedule 2, dose escalation), 9.8 Dose escalation plan and study periods, 9.9 Selection of study population, 9.10 Treatments, 9.11 Supportive care and concomitant medication, 9.12 Study assessments, 9.14 Statistical methods, 12.7 Number of patients with at least one grade 3-4 TEAE suspected to be related to SO-C101 as per investigators' judgement reported in study SC103 up to dose level 9 in Part A and dose level 1 in Part B
2	Addition of Part D, a dose expansion part, testing SO-C101 monotherapy schedule 1 RP2D from Part A in selected indications for additional safety and PK data	Given the limited number of subjects in the Part A dose escalation population, the aim is to collect more data on the safety profile of the compound.	1 TITLE PAGE, 2 CLINICAL PROTOCOL SYNOPSIS, 7.9 Study design rationale, 8.1 Study design, 8.2 Objectives, 9.6 Part D (SO-C101 dosing schedule 1, monotherapy, dose expansion at the RP2D identified in Part

Change number	Description of change	Rationale for change	Section affected in Protocol version 7.0
			A), 9.8 Dose escalation plan and study periods, 9.9 Selection of study population, 9.10 Treatments, 9.11 Supportive care and concomitant medication, 9.12 Study assessments, 9.14 Statistical methods
3	Addition of Part D1, a dose expansion part, testing SO-C101 monotherapy schedule 2 RP2D from Part A1 in selected indications for additional safety and PK data	Given the limited number of subjects in the Part A1 dose escalation population, the aim is to collect more data on the safety profile of the compound.	1 TITLE PAGE, 2 CLINICAL PROTOCOL SYNOPSIS, 7.9 Study design rationale, 8.1 Study design, 8.2 Objectives, 9.7 Part D1 (SO-C101 dosing schedule 2, monotherapy, dose expansion at the RP2D identified in Part A1), 9.8 Dose escalation plan and study periods, 9.9 Selection of study population, 9.10 Treatments, 9.11 Supportive care and concomitant medication, 9.12 Study assessments, 9.14 Statistical methods
4	Update of dose escalation levels in Part A and Part B	The dose escalation levels planned at the beginning of the study have seen some changes based on adjustments proposed, discussed and approved during the dose escalation meetings. The dose levels reflect the status at the time of this protocol amendment release and may require additional changes in the future.	2 CLINICAL PROTOCOL SYNOPSIS, 7.5 Justification for the starting dose and dose escalation steps in Part A, 9.1 Part A (SO-C101 dosing schedule 1, monotherapy, dose escalation), 9.3 Part B (SO-C101 dosing schedule 1, combined with pembrolizumab, dose escalation)
5	Clarification that Part C dosing schedule will be decided based on data about dosing schedule 1 and schedule 2 collected in other study parts	Clarification	2 CLINICAL PROTOCOL SYNOPSIS, 7.9 Study design rationale, 8.1 Study design, 9.10 Treatments
6	Clarification that all patients should have total bilirubin ≤2×ULN (i.e., including patients with liver metastases)	Clarification	2 CLINICAL PROTOCOL SYNOPSIS, 9.9 Selection of study population
7	Clarification that a DEM will take place after the last patient of the cohort has completed the first cycle (21 days) with or without DLTs and is evaluable for DLT assessment (this does	Clarification	2 CLINICAL PROTOCOL SYNOPSIS, 9.8.3 Dose escalation meetings

Change number	Description of change	Rationale for change	Section affected in Protocol version 7.0
	not have to be within 5-7 working days as stated in previous versions of the protocol)		
8	Clarification that regular study TCs will be held among study investigators (designated sub-investigators) and the sponsor's medical monitor (this does not have to be every week as stated in previous versions of the protocol)	Clarification	9.8.5 Patient recruitment management, 9.8.6 Communication plan
9	Clarification of the toxicities due to which retreatment with SO-C101 is contraindicated (grade 4 toxicities and third occurrences of grade 3 toxicities)	Clarification	9.10.2 Treatment modifications
10	Clarification that after grade 2 allergic reactions/acute infusion reaction with bronchospasm or any grade 3-4 allergic reactions/acute infusion reaction, SO-C101 is to be permanently discontinued	Clarification	9.10.2 Treatment modifications
11	ECG after SO-C101 administration changed from 2 hours after SO-C101 dosing to 4 hours after dosing	ECG to be done close to the Cmax observed in patients	9.12.6.4.7 Cardiac function, 9.12.7 Schedule of procedures/assessments
12	Clarification that AEs and concomitant medications are also to be recorded on Day 15	Clarification	9.12.7 Schedule of procedures/assessments
13	Clarification that patients must be followed for AEs and concomitant medications 90 days after the last dose of SO-C101 and/or pembrolizumab (as applicable), whichever occurs later (i.e., during efficacy follow-up or survival follow-up if this overlaps with safety follow-up)	Clarification	9.12.7 Schedule of procedures/assessments
14	Paired tumor biopsy is to be collected also at the time of progression or response	To be able to collect more PK/biomarker data	9.12.7 Schedule of procedures/assessments
15	Deletion of the sentence "Delayed sample collections will not be considered deviations, but the delay should be noted on the collection worksheet."	Samples not collected as per defined time matters and will be assessed. Protocol deviations are recorded if a sample is collected out of the time window.	9.12.7 Schedule of procedures/assessments

Change number	Description of change	Rationale for change	Section affected in Protocol version 7.0
16	Addition of a 5 min time window to the 30 min PK sampling time point	To prevent protocol deviations	9.12.7 Schedule of procedures/assessments
17	Change of chief medical officer	Change of personnel	SIGNATURES / PROTOCOL APPROVAL AND RELEASE
18	Minor wording changes and punctuation adjustments	To improve clarity and readability	Throughout the document

12.7.4 Version 6.1 (13-May-2020): Protocol changes implemented (note: version 6.0 was never implemented)

Change number	Description of change	Rationale for change	Section affected in Protocol version 6.1
1	Addition of an expansion cohort, Part C; SO-C101 combined with pembrolizumab at the combination RP2D identified in Part B or at the combination RP2D and at a lower dose of SO-C101 (up to 20-40 patients). Ongoing patients in Part A and Part B can receive SO-C101 at the RP2D if specific criteria are met. Crossover of patients from Part A or Part B to Part C will not be allowed.	The aim is to evaluate potential efficacy signal(s) earlier.	CLINICAL PROTOCOL SYNOPSIS, 7.8 Study design rationale, 8.1 Study design, 8.1.3 Part C – SO-C101 dose expansion in combination with pembrolizumab, 8.1.4 Intra-patient dose increase, 8.2.3 Part C (SO-C101 combined with pembrolizumab, dose expansion at the combination RP2D identified in Part B or at the combination RP2D and at a lower dose), 9.1 Treatment: Part A (SO-C101 monotherapy), 9.2 Treatment: Part B (SO-C101 combined with pembrolizumab, dose escalation), 9.3 Treatment: Part C (SO-C101 combined with pembrolizumab, dose expansion at the combination RP2D identified in Part B or at the combination RP2D and at a lower dose), 9.4.3.1 Safety monitoring beyond cycle 1, 9.4.7 Study periods in Part A and Part B, 9.4.8 Study periods in Part C, 9.4.9 End of the study, 9.5 Selection of study population, 9.6.1 Treatments administered, 9.6.2 Treatment modifications, 9.7.4.1 Prohibited medications, 9.7.4.2 Warnings

Change number	Description of change	Rationale for change	Section affected in Protocol version 6.1
			and precautions, 9.8.5.1.1.5 Pregnancy of study patients or their partners, 9.8.5.1.2.1 Reporting, 9.8.5.1.3.1 Causality, 9.8.5.1.3.4 Documenting in eCRFs, 9.8.6 Safety monitoring of the patients during the study, 9.8.6.3 Observation of patients after administration of SO-C101, 9.8.6.4.10 Adverse events, 9.8.7 Schedule of procedures/assessments, 9.8.10 Treatment discontinuation, 9.8.11 Guidance for continuation of study treatment beyond iRECIST-defined disease progression, 9.10 Statistical methods, 9.10.1.3 Part C, 9.10.2 Definitions of analysis sets, 9.10.10.2 Adverse events, 9.10.11.3 Part C (SO-C101 combined with pembrolizumab, dose expansion)
2	Addition of SO-C101 PK samples at 16 hours and 20 hours post-dose on cycle 1 day 1 for all patients in Part A and 12 patients in Part C	To be able to better describe the PK profile and calculate all PK parameters (current time points not sufficient to assess PK parameters during the elimination phase e.g. calculate t_{max}, $t_{1/2}$…)	9.8.7 Schedule of procedures/assessments
3	Addition of PK and immunogenicity analyses for pembrolizumab in Part C	To be able to describe the PK profile and immunogenicity of pembrolizumab in combination with SO-C101	9.8.6.4.11 Anti-drug antibodies, 9.10.8 Pharmacokinetic analyses
4	Addition of an option to increase the dose of SO-C101 administered to a patient in case this patient is in the study in Part A or Part B for at least 2 cycles and a higher dose of SO-C101 is deemed safe after the Dose escalation meeting; possible to increase the patient's dose of SO-C101 to this "new one"	To allow patients treated at lower dose levels of SO-C101 to receive treatment at doses which may be more effective. Permitting intra-patient dose escalation is appealing because it gives some patients the opportunity to be treated at safe higher doses from which they may potentially derive more clinical benefit.	CLINICAL PROTOCOL SYNOPSIS, 7.8 Study design rationale, 8.1.4 Intra-patient dose increase, 9.1 Treatment: Part A (SO-C101 monotherapy), 9.2 Treatment: Part B (SO-C101 combined with pembrolizumab, dose escalation), 9.4.7 Study periods in Part A and Part B, 9.6.2 Treatment modifications, 9.10 Statistical methods

Change number	Description of change	Rationale for change	Section affected in Protocol version 6.1
5	Removal of information about a legally acceptable representative	As per request from WIRB at Yale and to align with inclusion criterion 13 ("Ability to understand and sign written informed consent to participate in the study")	5.3 Patient information and informed consent
6	Addition of body surface area calculation	To be able to assess the effect of body size on PK and PD of SO-C101 to determine the appropriate dosing approach	9.8.6.1 Physical examination, body weight, body surface area and height, 9.8.7 Schedule of procedures/assessments
7	Archived, fixed tumor tissue can be collected if fresh biopsy at screening is not available	Preferably only biopsy samples collected during the study will be collected and analyzed	9.8.4.2 Tumor biopsy, 9.8.7 Schedule of procedures/assessments
8	Addition of the following coagulation parameters: D-dimer and fibrinogen	Given that coagulation and inflammation are closely linked, D-dimer and fibrinogen are added to coagulation parameters for dynamic monitoring of potential cytokine release syndrome symptoms in addition to PTT, aPTT and international normalized ratio	9.8.6.4.1 Coagulation
9	Addition of total protein to the biochemistry panel	Decrease in total protein can be a sign of kidney or liver function impairment or a sign of capillary leak associated with cytokine release syndrome	9.8.6.4.3 Biochemistry
10	Addition of senior medical director	Change of personnel	SIGNATURES / PROTOCOL APPROVAL AND RELEASE
11	Minor wording and punctuation corrections	To improve clarity and readability	Throughout the document

12.7.5 Version 5.0 (05-Nov-2019): Protocol changes implemented

Change number	Description of change	Rationale for change	Section affected in Protocol version 5.0
1	Revision of DLT criteria and exclusion criteria. Deletion of DLT criteria: - Grade 4 lymphopenia - Grade 3 lymphopenia lasting more than 7 days - Grade 3 or higher anemia	Revision of DLT criteria: Lymphopenia grade 3 and lymphopenia grade 4 are usually not considered a toxicity that qualifies as DLT and are frequently part of the conglomerate clinical presentation of advanced malignant disease. Lymphopenia may also result from treatment with steroids, which is allowed to a certain extent in SC103. Grade 3 or higher anemia: since the protocol specifies a hemoglobin concentration of ≥ 10 g/dL as eligibility criterion and the DLT period is defined to	CLINICAL PROTOCOL SYNOPSIS, 9.3.1.1 AEs that are considered DLTs, 9.4.2 Exclusion criteria for both Part A and Part B

Change number	Description of change	Rationale for change	Section affected in Protocol version 5.0
	Deletion of "ALC ≤ 0.5×10^9/L" from the list of exclusion criteria	be 21 days, it is highly unlikely that grade 3 or higher anemia will be observed during the DLT period. Deletion of "ALC ≤ 0.5×10^9/L" from the list of exclusion criteria: Recent published evidence indicates that there is no association between initial ALC count and response to anti-PD-1/PD-L1 in cancer patients in phase I (Sun et al. Eur. J. Cancer 84: 202, 2017)	
2	Harmonization of the safety follow up period with the FDA requirement for 90 days follow-up.	FDA: "The DLT evaluation period appears reasonable for the purposes of patient enrollment into escalating dose cohorts. However, continue to monitor all patients for approximately ninety days after treatment discontinuation for late immune-related toxicities that have been associated with immunotherapy products. Any such late toxicity will need to be considered in the determination of the maximal tolerated dose/RP2 dose and dose schedule to be taken forward into part B of the study."	CLINICAL PROTOCOL SYNOPSIS, 7.8 Study design rationale, 9.3.3.1.1 Part A, 9.3.3.1.2 Part B, 9.3.6.3 Safety follow-up period, 9.7.5.1.2.1 Reporting, 9.7.7 Schedule of procedures/assessments
3	Addition of a PK time point at 12 hours (+/- 1 hour) post dose at C1D1	An additional PK sample at 12 hours post dose to be collected at C1D1 for PK parameter calculation.	9.7.7 Schedule of procedures/assessments
4	Section 9.7.6.4.10 Adverse events: Patients in Part B will be monitored at the same visits and assessments as specified in Part A with the special attention to the potentiation of immune-mediated reactions (AEs of special interest) during the combination treatment with SO-C101. No AESIs are monitored since DLTs cover most of the situation/s which might be of our interest. Therefore, we proposed to omit the expression 'AEs of special interest' from the current wording.	Currently there are no AESIs defined per protocol as this is a phase I FIH safety study.	9.7.6.4.10 Adverse events
5	biliary ~~track~~ tract cancer	Correction of a typographical error	CLINICAL PROTOCOL SYNOPSIS, 7.8 Study design rationale, 8.1 Study design, 9.4.1 Inclusion criteria for both Part A and Part B

Change number	Description of change	Rationale for change	Section affected in Protocol version 5.0
6	Request from the clinical site MD Anderson Cancer Center to clarify the definition of MTD/RP2D used for this study protocol, that is, to include a clarification that the sponsor is using the alternative EU/Japan definition of MTD/RP2D for this study and that this definition is a misnomer in the sense that the MTD is actually not a tolerable dose, as this definition is not the traditional definition for phase I studies in the United States.	Request from the IRB of the clinical site MD Anderson Cancer Center	9.3 Dose escalation plan for Part A and Part B, 12.6 Definition of MTD and RP2D as used in the study Protocol
7	Update of the TEAE definition in section 9.9.10.2 of the protocol	Clarification of the TEAE definition	9.9.10.2 Adverse events
8	Addition of a time window for ECG	Clarification	9.7.7 Schedule of procedures/assessments
9	Addition of a time window for cytokine sampling	Clarification	9.7.7 Schedule of procedures/assessments
10	Minor wording and punctuation corrections	To improve clarity and readability	Throughout the document
11	Update of contact details for AE reporting	To reflect internal changes in the company	9.7.5.1.3.5 Immediately reportable events, 9.7.5.1.3.7 Report forms
12	For information on pembrolizumab safety refer to SmPC/US prescribing information	Label updates	9.5.4 Pembrolizumab, 9.5.4.3 Pembrolizumab: safety information
13	Change of chief medical officer	Change of personnel	SIGNATURES / PROTOCOL APPROVAL AND RELEASE

12.7.6 Version 4.0 (10-Apr-2019): Protocol changes implemented

Change number	Description of change	Rationale for change	Section affected in Protocol version 4.0
1	Monitoring of vital signs after dose 1 in cycle 1 for 8 hours instead of for 4-8 hours	Need to monitor all patients after the first dose for 8 hours	Synopsis, 9.7.6.3.1.1 Dose on day 1
2	Safety population in Part B to include patients exposed to SO-C101 or pembrolizumab instead of SO-C101 only	Usual definition of a safety population	Synopsis, 9.9.2.1 Safety population
3	Introduction of a PK/PD population	Population for PK and PD analyses	Synopsis, 9.9.2.2 PK/PD population, 9.9.8 Pharmacokinetic analyses, 9.9.9 Pharmacodynamic and other biomarker analyses

Change number	Description of change	Rationale for change	Section affected in Protocol version 4.0
4	Urea or blood urea nitrogen to be tested instead of blood urea nitrogen only	Need to accommodate sites' standard practices	9.7.6.4.3 Biochemistry
5	Clarification that free triiodothyronine and free thyroxine will be tested	Clarification	9.7.6.4.5 Thyroid function, 9.7.6.4.10 Adverse events, 9.7.7 Schedule of procedures/assessments
6	ECG to be done in cycles 1- 3 before each dose of SO-C101 and 2 hours after dosing, and from cycle 4 onwards on day 1 before SO-C101 dosing and 2 hours after dosing; *instead of* on days 1, 2, 8, 9 in cycle 1 before each dose of SO-C101 and 2 hours after dosing, and in subsequent cycles on day 1 before SO-C101 dosing	Further to FDA comment in FDA letter dated 03-Apr-2019: "*Specify the specific ECG collection time points with time matched PK samples at baseline (pre-dose), and at the anticipated time of maximum plasma concentration following administration of the first dose and following administration of multiple doses of SO-C101.*"	9.7.6.4.7 Cardiac function, 9.7.7 Schedule of procedures/assessments
7	Pregnancy test allowed to be done from urine or blood on day 1 of each cycle instead of from urine only	Need to accommodate sites' standard practices	9.7.7 Schedule of procedures/assessments
8	Serum (cytokine) volume increase from 4 to 8 mL per sampling	Need to accommodate FACS analysis requirements	9.7.7 Schedule of procedures/assessments
9	Renal clearance and fraction excreted will not be tested	Renal clearance and excretion of SO-C101 will be analyzed following further optimization of detection methodology. Based on pre-clinical studies in cynomolgus monkeys, the rate of excretion was moderate, mean 46% of the administered radioactivity, recovered by 24 h post dose, main route of excretion was via urine with ~ 61% recovered by 72 h. Further analysis of urine samples by ELISA failed to detect SO-C101, likely because SO-C101 was contained in the urine as cleavage products that were not detectable by the ELISA method. For details refer to Investigator Brochure v.3.0 section 4.3.5 Excretion. Therefore, the following parameters: renal clearance and excretion fraction are not planned to be analyzed in this study.	9.9.8 Pharmacokinetic analyses
10	Minor wording and punctuation corrections	To improve clarity and readability	Throughout the document
11	MedDRA version to be the one current at the time of database lock instead of version 21.1	MedDRA version to be decided at the time of database lock	9.9.10.2 Adverse events
12	Change of study statistician	Change of personnel	SIGNATURES / PROTOCOL APPROVAL AND RELEASE

12.7.7 Version 3.0 (20-Mar-2019): Protocol changes implemented

Change number	Description of change	Rationale for change	Section affected in Protocol version 3.0
1	Clarification of the definition of dose-limiting toxicity	Revised according to the FDA's recommendation and grade 3 ALT or AST and grade 3 bilirubinemia longer than 5 days have been included as DLT criteria grade 3 inflammatory local tumor reaction criteria was amended to *"Inflammatory reaction attributed to a local antitumor response (grade 3 tumor pain caused by acute inflammatory reaction at tumor-bearing sites, e.g., like sites of metastatic disease or lymph nodes) that resolves to grade 1 within 3 weeks."*	Synopsis, 9.3.1.1 AEs that are considered DLTs, 9.3.1.2 AEs that are NOT considered DLTs
2	Clarification that whenever SO-C101 is interrupted in Part B due to immune-mediated toxicity, pembrolizumab should also be interrupted	Revised according to the FDA's recommendation, since in Part B it might be impossible to distinguish which study drug caused the specific toxicity. The protocol wording was adjusted for Part B as follows: *"whenever SO-C101 treatment is interrupted for immune-medicated toxicity, treatment with pembrolizumab will be interrupted as well"*.	9.5.2 Treatment modifications
3	Modification of Table 9.3 Guidelines for SO-C101 dose adjustments beyond cycle 1	Updated footnote #2 to Table 9.3 to reflect the Agency's recommendation namely that *"study drugs should be held if systemic corticosteroids at doses above 10 mg prednisone equivalent are required for any duration, and that study drug should be discontinued if systemic corticosteroids at doses above 10 mg prednisone are required for > 4 weeks"*. Section 9.5.2 and Section 9.6.4.2 were also amended in line with this change.	9.5.2 Treatment modifications, 9.6.4.2 Warnings and precautions
4	Modification of Table 9.4 SO-C101 modifications after cycle 1 – delay/hold	Table 9.4 has been revised to clarify SO-C101 dose modifications in case of grade 3 AST or ALT or grade 3 bilirubinemia with recommendation for dose reduction for 1 dose lower in case of grade 2 ALT, AST or bilirubinemia and permanent discontinuation of treatment with SO-C101 in case of same toxicities of grade 3. "Treatment modifications" of the protocol to give clear guidance to investigators with reference to Table 9.3 and Table 9.4: *"During SO-C101 treatment, SO-C101 dose interruptions and reductions due to toxicity will be implemented according to the instructions presented in Table 9.3 for all AEs excluding specific AEs as detailed in Table 9.4."*	9.5.2 Treatment modification

Change number	Description of change	Rationale for change	Section affected in Protocol version 3.0
5	Clarification regarding prohibited medications and warnings and precautions	Prohibited medications were clarified according to the FDA's request to specify nephrotoxic, myelotoxic, cardiotoxic or hepatotoxic medications and specify medications known to prolong the QT interval.	9.6.4.1 Prohibited medications
6	Clarification re use of systemic corticosteroids for immune-mediated AEs at the doses above 10 mg of prednisone or equivalent	Added a clarification about the use of systemic corticosteroids for treatment of immune-medicated AEs at doses above 10 mg of prednisone or equivalent for less than 4 weeks, the study drugs should be held. If systemic corticosteroids at doses above 10 mg of prednisone or equivalent are required for more than 4 weeks, then the study drug should be discontinued.	9.5.2 Treatment modifications, 9.6.4.2 Warnings and precautions

12.7.8 Version 2.0 (17-Jan-2019)

12.7.8.1 Protocol changes implemented further to the initial EU VHP

Change number	Description of change	Rationale for change	Section affected in Protocol version 2.0
1	Part B will study SO-C101 in combination with pembrolizumab and will start after dose level ~~4~~5 in Part A is completed and deemed safe (bifurcated design) and will use SO-C101 monotherapy level ~~2~~3 dose as the starting dose in combination with pembrolizumab. ~~Part B patient population will be the same as in Part A except that it will include patients who are considered relapsed/refractory with prior ICI therapy as well as ICI naïve patients.~~	**VHP outcome (grounds for non-acceptance 17):** According to the protocol, patients who received immune checkpoint inhibitors (ICI) or not (ICI naïve) will be included in Part B; so inclusion criterion number 2 should be amended to include "Part B only: Patients who were not previously treated with (naïve) or who have relapsed/refractory disease on ICI are eligible". **Response:** The study is aimed to enroll a similar patient population in Part A and Part B to understand the benefit of the combination. Thus, inclusion criterion #2 in the protocol was written to apply for patients both in Part A and Part B: "Inclusion criterion #2: Patients who were not previously treated with (naïve) or who have relapsed/refractory disease on immune checkpoint inhibitors are eligible" However, we have noticed the discrepancy below in the protocol, which we believe caused the	CLINICAL PROTOCOL SYNOPSIS, 7.8 Study design rationale, 8.1 Study design

Change number	Description of change	Rationale for change	Section affected in Protocol version 2.0
		confusion in the definition of patient populations for Part A and Part B, and amended as follows in Synopsis, Section 7.8 and Section 8.1: "Part B will study SO-C101 in combination with pembrolizumab and will start after dose level 4 in Part A is completed and deemed safe (bifurcated design) and will use SO-C101 monotherapy level 2 dose as the starting dose in combination with pembrolizumab. ~~Part B patient population will be the same as in Part A except that it will include patients who are considered relapsed/refractory with prior ICI therapy as well as ICI naïve patients~~"	
2	11.13 Future research Biological samples collected during this study may be stored for future research by the sponsor. Storage conditions will be in compliance with the standards for repositories of biological samples, according to the "Recommendation CM/Rec (2016)6 of the Committee of Ministers to member States on research on biological materials of human origin".43 The repository will have independent monitoring that will guarantee protection of the data and the patients' interests (see also section 11.7). The samples will not be transferred or sold to third parties. The exploratory studies that will be conducted with the samples will undergo a rigorous independent review evaluating both ethical and scientific aspects.	**VHP outcome (grounds for non-acceptance 20):** Regarding the possibility of samples being kept for future research in a Biomedical Repository, it should be provide information about Repository's Policies. The policy information should reflect compliance with the standards for repositories of biological samples, according to the "Recommendation CM/Rec (2016)6 of the Committee of Ministers to member States on research on biological materials of human origin," available at https://search.coe.int/cm/Pages/result_details.aspx?ObjectId=090000168064e8ff. In particular, it should specify if 1) the repository has independent monitoring that guarantees protection of the data and the patients' interests, 2) there will be an independent review (ethical and scientific) of the studies that are going to be conducted with the samples, and 3) the samples will not be transfer neither sold to third parties. **Response:** Section 11.13 Future research has been added to the protocol to provide information about the Biomedical Repository Policies for future research.	11.13 Future research
3	11.7 Confidentiality of personal data In order to ensure that personal information of each patient is kept confidential and protected, names and any other information that allows direct identification of a patient	**VHP outcome (grounds for non-acceptance 21):** The sponsor should include a Confidentiality section in the protocol to ensure that confidentiality of personal data of the patients remain protected in accordance with Regulation (EU)	11.7 Confidentiality of personal data

Change number	Description of change	Rationale for change	Section affected in Protocol version 2.0
	will not be in the eCRFs or included in any records or samples provided to the sponsor or sponsor's authorized representatives; such information will be pseudonymised, i.e., all such information will be replaced by a specific code (patient number) assigned by a study doctor and all patients will be identified in eCRFs or any other records or samples by a patient number only. The personal information collected for the purposes of this study will be held by the study sites, the sponsor and sponsor's authorized representatives, which together are responsible for processing of personal information in accordance with the General Data Protection Regulation (EU) 2016/679 (GDPR) and any corresponding local legislation. The sponsor and its authorized representatives will analyze and use the personal information they receive for the purposes of this study only. These include: checking patients' suitability to take part in the study, • monitoring patients' health during treatment with SO-C101 as monotherapy and in combination with pembrolizumab, • comparing and pooling study results, • establishing whether SO-C101 as monotherapy and in combination with pembrolizumab meets the appropriate standards of safety set by the authorities, • establishing whether SO-C101 as monotherapy and in combination with pembrolizumab is effective, • supporting the clinical development of SO-C101 as monotherapy and in combination with pembrolizumab, • supporting the licensing application for regulatory approval of SO-C101 as monotherapy and in combination with pembrolizumab anywhere in the world, • supporting the marketing, distribution, sale and use of SO-C101 as monotherapy and in combination with pembrolizumab anywhere in the world, • complying with specific regulations governing clinical	2016/679 including a description of personal data protection measures such as patient identification code or identification code list, among others requirements. **Response:** Further to this request, a new section, section 11.7 Confidentiality of personal data, has now been added to the protocol.	

Change number	Description of change	Rationale for change	Section affected in Protocol version 2.0
	trials. Participation of patients in this study is voluntary and they may withdraw from the study at any time by informing the investigator. Then the participation in the study will end and the study personnel will stop collecting personal information from the patients, but the sponsor will need to retain and use the pseudonymised personal information and associated research results that have already been collected from the patient. The sponsor must do this to comply with its legal and regulatory obligations, to maintain the scientific integrity of the study, and to complete the marketing authorization process for SO-C101 as monotherapy and in combination with pembrolizumab. It may be necessary to retain certain aspects of pseudonymised (coded) personal information for at least 25 years following the end of the study to comply with applicable laws and regulatory requirements and to ensure the scientific integrity of the study. If necessary for the study purposes mentioned above, the sponsor may communicate such pseudonymised personal information to third parties (such as service providers, contractors and research institutions that support the study), and regulatory or other governmental agencies that need to check the results of the study. These third parties may be located in countries of the European Economic Area (EEA), the United States, and other countries that are outside of the EEA. Some non-EEA countries may not offer the same level of privacy protection. However, the sponsor will keep personal information it receives as confidential as possible within the limits of the law. The sponsor will implement appropriate contractual measures, including the standard data protection contractual clauses, to ensure that the relevant recipients outside the EEA provide an adequate level of protection to personal information as set out in this form and as required by applicable law. The sponsor,		

Change number	Description of change	Rationale for change	Section affected in Protocol version 2.0
	either alone or together with other researchers, may publish or present the results of the study; however, personal information will not be disclosed in any publication or presentation. See also section 11.10. All persons have certain rights to gain access to and correct any inaccuracies in the personal information held about them. In certain circumstances, they can also request restriction of processing of their personal information, object to certain types of processing of their personal information, request their personal information be erased and have their personal information provided to them or a third party in a digital format. The sponsor shall comply with the above requests to the fullest extent consistent with other legal and regulatory obligations and where required by law. Personal data cannot be erased, even after patients finish or terminate their participation in the study, in order to guarantee the validity of the clinical research and to comply with statutory duties and drug authorization requirements. Representatives from government agencies, the local ethics committee and sponsor or its authorized representatives may also need access to medical records and study records for the purpose of checking data collected for the study. The sponsor shall process all personal information of the patients in the study in accordance with the General Data Protection Regulation (EU) 2016/679 (GDPR), any applicable local legislation and the internal data protection policies reflecting organizational and technical arrangements to avoid unauthorized access, disclosure, dissemination, alteration, or loss of information and personal data processed, namely the Data Protection Regulation and Incident Management Regulation. The organizational and technical measures introduced by the sponsor in relation to a protection of personal information of the patients involve the above mentioned		

Change number	Description of change	Rationale for change	Section affected in Protocol version 2.0
	pseudonymisation of personal information, appropriate controls to restrict its employees access to the personal information, a physical access control to any premises where the personal information is stored, an electronic access and system control logging for any systems containing personal information, data entry and data transfer control, availability control (back-up and recovery concept), network protection including firewalls and penetration testing procedures for regular testing, industry-standard security policies and procedures including assessment and evaluation of processes and regular training procedures. In the event of any security breach, the Incident management procedures would be implemented and the sponsor would notify such breach within statutory term to the Office for Personal Data Protection of the Czech Republic and to all relevant study investigators. The sponsor has appointed a Data Protection Officer who can be contacted by post at SOTIO a.s., Jankovcova 1518/2, 170 00 Prague 7, the Czech Republic or via e-mail at gdpr@sotio.com.		
4	The sponsor shall process all personal information of the patients in the study in accordance with the General Data Protection Regulation (EU) 2016/679 (GDPR), any applicable local legislation and the internal data protection policies reflecting organizational and technical arrangements to avoid unauthorized access, disclosure, dissemination, alteration, or loss of information and personal data processed, namely the Data Protection Regulation and Incident Management Regulation. The organizational and technical measures introduced by the sponsor in relation to a protection of personal information of the patients involve the above mentioned pseudonymisation of personal information, appropriate controls to restrict its employees access to the personal information, a physical access control to any	**VHP outcome (grounds for non-acceptance 22):** It should be provided information about Data Protection Policies that should reflect organizational and technical arrangements to avoid unauthorized access, disclosure, dissemination, alteration or loss of information and personal data processed; moreover, it should specify the measures that will be implemented in case of data security breach. **Response:** In the newly created section 11.7 in the protocol, information about Data Protection Policies that reflects organizational and technical arrangement is provided: “The sponsor shall process all personal information of the patients in the study in accordance with the General Data	11.7 Confidentiality of personal data

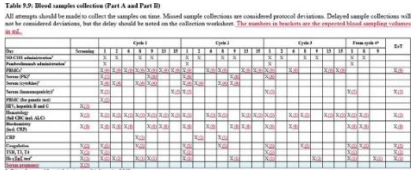
Change number	Description of change	Rationale for change	Section affected in Protocol version 2.0
	premises where the personal information is stored, an electronic access and system control logging for any systems containing personal information, data entry and data transfer control, availability control (back-up and recovery concept), network protection including firewalls and penetration testing procedures for regular testing, industry-standard security policies and procedures including assessment and evaluation of processes and regular training procedures. In the event of any security breach, the Incident management procedures would be implemented and the sponsor would notify such breach within statutory term to the Office for Personal Data Protection of the Czech Republic and to all relevant study investigator.	Protection Regulation (EU) 2016/679 (GDPR), any applicable local legislation and the internal data protection policies reflecting organizational and technical arrangements to avoid unauthorized access, disclosure, dissemination, alteration, or loss of information and personal data processed, namely the Data Protection Regulation and Incident Management Regulation. The organizational and technical measures introduced by the sponsor in relation to a protection of personal information of the patients involve the above mentioned pseudonymisation of personal information, appropriate controls to restrict its employees access to the personal information, a physical access control to any premises where the personal information is stored, an electronic access and system control logging for any systems containing personal information, data entry and data transfer control, availability control (back-up and recovery concept), network protection including firewalls and penetration testing procedures for regular testing, industry-standard security policies and procedures including assessment and evaluation of processes and regular training procedures. In the event of any security breach, the Incident management procedures would be implemented and the sponsor would notify such breach within statutory term to the Office for Personal Data Protection of the Czech Republic and to all relevant study investigator."	
5	Reduction of the starting dose from 0.5 µg/kg to 0.25 µg/kg and increase of the number of cohorts from 8 to 9 in Part A	**VHP outcome (grounds for non-acceptance 25):** As activation of NK cells occurs at lower doses, please consider a starting dose which confers around 25% activation of NK cells. Indeed, as mentioned in the meeting minutes, the sponsor use a PAD approach based only on the activation of CD8+ T cell while the NK activation should be taken into consideration. **Response:** The sponsor revised the starting dose, based on the Agencies comments and Question 25. The starting dose in Part A was	CLINICAL PROTOCOL SYNOPSIS, 7.6 Justification for the starting dose and dose escalation steps in Part A, Justification for the starting dose in Part B, Study design rationale, 8.1.2 Part B – SO-C101 dose escalation in combination with pembrolizumab, 9.1 Treatment: Part A (SO- C101 monotherapy), 9.2 Treatment: Part B (SO- C101 combined with pembrolizumab), 9.3.7 End of the

Change number	Description of change	Rationale for change	Section affected in Protocol version 2.0
		reduced from 0.5 µg/kg to 0.25 µg/kg. This revised starting dose is anticipated to promote 20% NK cell activation, while not affecting CD8 T cell activation. The receptor occupancy (RO) was calculated to be at 0.5% to 6%. The sponsor considers this new starting dose as safe for Part A of the planned clinical study SC-103. The subsequent dose levels were accordingly revised. The revised starting doses and the dose escalation steps as well as their justification are described in sections 7.6 and 7.7 of the SC-103 clinical study protocol.	study, Table 9.3: Guidelines for SO-C101 dose adjustments beyond cycle 1, 9.9.11 Determination of sample size
6	For each dose level, firstly one patient will be enrolled and will receive the first ~~two~~ four doses of SO-C101 (day 1, ~~and~~ day 2, day 8, and day 9). This patient will be observed for safety for 7 days after the fourth dose, starting from day ~~1~~9. If there are no safety concerns at the end of these ~~first~~ 7 days, the responsible investigator will notify the sponsor's medical monitor and the second and third patients will be allowed to be dosed. The second and third patients will not be dosed on the same day.	**VHP outcome (grounds for non-acceptance 26):** Sponsor should amend the protocol to modify staggered (sentinel) dosing approach regarding first dose administration of second patient in order to let enough time to observed any delay effect of the IMP. Therefore, the second patient should be dosed 7 days after the 4th administration (Day 9) of the first patient instead of the 7 days after the 1st administration (Day 1) of the first patient. **Response:** The study protocol has been amended per the recommendation above, and the new amended text is provided below: "For each dose level, the first patient will be enrolled and will receive the first four doses of SO-C101 (day 1, day 2, day 8, and day 9). This patient will be observed for safety for 7 days after the fourth dose, starting from day 9. If there are no safety concerns at the end of those 7 days, the responsible investigator will notify the sponsor's medical monitor and the second and third patients will be allowed to be dosed. The second and third patients will not be dosed on the same day."	CLINICAL PROTOCOL SYNOPSIS, 9.3 Dose escalation plan for Part A and Part B, Figure 9.3: Dose escalation flowchart (staggered dosing and 3 + 3 design)
7	9.6.1 Management of cytokine release syndrome The management intervention guidelines described in this section can be modified by the individual study center as medically necessary or as appropriate without requiring a protocol amendment or being considered a protocol	**VHP outcome (grounds for non-acceptance 27):** The sponsor is required to add to the protocol the management in case of patients experiencing a cytokine release syndrome as the risk cannot be excluded even if it is low.	9.6.1 Management of cytokine release syndrome, 12.5 Clinical management recommendations for HD IL-2 therapy

Change number	Description of change	Rationale for change	Section affected in Protocol version 2.0
	deviation. SO-C101 is a fusion protein, which comprises a variant of the IL-15 molecule, which is a common γ-chain cytokine and shares the IL-2 receptor β and γ chains for signaling. SO-C101 therefore could have similar immunostimulatory properties as IL-2. SO-C101 treatment could potentially cause cytokine release syndrome as commercially available IL- 2, although the risk is low. Cytokine release syndrome may begin immediately after treatment administration and may be marked by increased capillary permeability to protein and fluids and reduces vascular tone. In most patients, this will result in a concomitant drop in mean arterial blood pressure within 2 to 12 hours after the start of treatment. With continued treatment, clinically significant hypotension (defined as systolic blood pressure below 90 mm Hg or a 20 mm Hg drop from baseline systolic pressure) and hypoperfusion may occur. In addition, extravasations of protein and fluids into the extra-vascular space will lead to the formation of edema and creation of new effusions. Potentially life-threatening complications of CRS could include cardiac dysfunction, adult respiratory distress syndrome, neurologic toxicity, renal and/or hepatic failure, and disseminated intravascular coagulation. Of particular concern is cardiac dysfunction, which can be rapid onset and severe, but is typically reversible. Medical management of cytokine release syndrome begins with carefully monitoring of the patient's fluids and organ perfusion status. This is achieved by frequent determination of blood pressure and pulse, and by monitoring organ functions, which includes assessment of mental status and urine output. Occurrence of hypovolemia will be monitored. Flexibility in fluid and pressor management is essential for maintaining organ perfusion and blood pressure. Therefore, extreme caution should be used in treating patients with fixed requirements for large volumes of fluid. Administration of IV fluids, either colloid or	**Response:** New section 9.6.1 Management of cytokine release syndrome has been added to the Protocol.	

Change number	Description of change	Rationale for change	Section affected in Protocol version 2.0
	crystalloid is recommended for treatment of hypovolemia. Correction of hypovolemia may require large volumes of IV fluids but caution is required because unrestrained fluid administration may exacerbate problems associated with edema formation or effusions. With extra-vascular fluid accumulation, edema is common and ascites, pleural or pericardial effusions may develop. Management of these events depends on a careful balancing of the effects of fluid shifts so that neither the consequences of hypovolemia (e.g., impaired organ perfusion) nor the consequences of fluid accumulations (e.g., pulmonary edema) exceed the patient's tolerance. Pulmonary edema, another manifestation of capillary leak syndrome, can lead to respiratory failure. For further management guidelines please refer to Proleukin that is approved in some countries in the EU for the treatment of mRCC[39] and in the US by the FDA to treat mRCC and malignant melanoma.[40] For consensus guidelines on management, please also refer to "High-dose interleukin-2 (Aldesleukin) – expert consensus on best management practices-2014".[41] See also appendix 12.5.		
8	10. Alanine transaminase (ALT)/ aspartate transaminase (AST) ≤2.5×ULN and total bilirubin ≤2×ULN in patients without liver metastasis (benign hereditary hyperbilirubinemias, e.g., Gilbert's syndrome, are permitted, those patients must have total bilirubin <3 mg/dL). In patients with liver metastasis, ALT/AST ≤5×ULN is allowed.	**VHP outcome (grounds for non-acceptance 28):** The sponsor is required to amend inclusion criterion number 11 to specify bilirubin upper limit of normal (ULN) in patients with Gilbert's syndrome. **Response:** The inclusion criteria for patients with Gilbert's syndrome has been modified and upper limit of total bilirubin <3 mg/dL has been specified.	CLINICAL PROTOCOL SYNOPSIS, 9.4.1 Inclusion criteria
9	13.10. Part B only: History of solid organ transplantation or hematopoietic stem cell transplantation	**VHP outcome (grounds for non-acceptance 29):** The sponsor is required to amend the protocol to add the history of solid organ transplantation or HSCT as exclusion criterion to avoid the risks of immuno-associated events of pembrolizumab (SmPC of Keytruda).	CLINICAL PROTOCOL SYNOPSIS, 9.4.2 Exclusion criteria

Change number	Description of change	Rationale for change	Section affected in Protocol version 2.0
		Response: The protocol exclusion criteria has been amended to follow this recommendation and Exclusion criterion #13.10 has been added to the protocol as follows for Part B: Part B only: History of solid organ transplantation or HSCT	
10	Removal of distinction between non-immune-related and immune-related DLTs	**VHP outcome (grounds for non-acceptance 30):** The sponsor is required to clarify what is implied by "non-immune-related AEs that are considered DLTs" (section 9.3.1.1) as both IMPs are involved in immune mechanisms. The sponsor should clarify how it will be distinguished between DLTs that are considered non-immune-related grade ≥3 liver toxicity and immune-related grade ≥3 liver toxicity. **Response:** The sponsor revised the wording for the DLT criteria in the protocol in light of this questions and removed the "non-immune- related DLT" or "immune-related DLT" distinction as highlighted by the agency as both IMPs are involved in immune mechanisms. Every DLT in the study will be discussed with the study investigators and every effort will be made to ensure all clinical assessments are carried out and documented appropriately as well as wherever possible histological assessments are also performed to identify and understand the safety profile of the SO-C101 as monotherapy and in combination with pembrolizumab.	CLINICAL PROTOCOL SYNOPSIS, 9.3.1 DLT definitions Part A and Part B
11	The treatment modifications below apply to all study treatment visits (Part A and Part B) when SO-C101 ~~or pembrolizumab are~~ is given. Where specified as delay or hold (after cycle 1), ~~the study treatment~~ ~~(pembrolizumab and/or~~ SO-C101~~)~~ will be delayed/held week to week. For details, see Table 9.4. In Table 9.4: SO-C101 ~~Study~~ treatment	**VHP outcome (grounds for non-acceptance 31):** The sponsor is required to clarify the protocol to specify if table 9.4 provides for doses modifications of Keytruda as this table does not follow Keytruda SmPC recommendations (especially for grade 3 recurrent colitis and liver toxicity). However, it is specify in section 9.5.2 that "treatment modifications of pembrolizumab are allowed according to the approved label".	9.5.2 Treatment modifications, Table 9.4: SO-C101Treatment modifications after cycle 1 – delay/hold

Change number	Description of change	Rationale for change	Section affected in Protocol version 2.0
		Response: Table 9.4 was meant to be related to SO-C101 dose modifications only; however, the title of the table was misleading. This table is now modified to refer to dose modification for SO-C101 administration and this has been clarified in the protocol. For Keytruda administration, the Keytruda SmPC recommendations must be followed.	
12		**VHP outcome (grounds for non-acceptance 32):** The sponsor is required to add to Table 9.9 "blood sample collection" the expected blood sampling volumes since many samples are planned in addition to the usual management of patients (pharmacokinetics, cytokines, PBMC). **Response:** The corresponding blood volume for each sample has been added into Tables 9.9 and 9.10 of the protocol.	Table 9.9: Blood samples collection (Part A and Part B), Table 9.10: Blood samples collection (Part B; for patients who continue on pembrolizumab only after discontinuation of SO- C101)

12.7.8.2 Additional "non-VHP GNA" changes

Change number	Description of change	Rationale for change	Section affected in Protocol version 2.0
1	Özlem Ataman, M.D., Ph.D. Head of Translational Research and Early Clinical Development ~~Acting~~ ~~Chief Medical Officer~~	Job title changed	SIGNATURES / PROTOCOL APPROVAL AND RELEASE
2	Revision of the solid tumor indications to include solid tumors of renal cell carcinoma, non-small cell lung cancer, small-cell lung cancer, bladder cancer, melanoma, Merkel-cell carcinoma, skin squamous-cell carcinoma, microsatellite instability high solid tumors, triple-negative breast cancer, mesothelioma, thyroid cancer, thymic cancer, cervical cancer, biliary track cancer, hepatocellular carcinoma, ovarian cancer, gastric cancer, head and neck squamous-cell carcinoma, and anal cancer	Tumor indications to be included in the study has been revised to include solid tumors with known sensitivity for anti-PD-(L)1 monotherapies among the so called "PD- Lomas". PD-Lomas where ORR ≥10% was reported were selected to demonstrate potential efficacy signal for the effect of SO- C101 added to Keytruda.	1 TITLE PAGE, CLINICAL PROTOCOL SYNOPSIS, 7.8 Study design rationale, 8.1 Study design, 9.4.1 Inclusion criteria, 9.7.2 Efficacy assessments, 9.7.2.1 Radiologic evaluation of disease

Change number	Description of change	Rationale for change	Section affected in Protocol version 2.0
3	Addition of a signature page for the coordinating investigator	To show approval of the Protocol by the coordinating investigator	SIGNATURES / PROTOCOL APPROVAL AND RELEASE
4	~~- Grade 3 or higher leukocytosis~~	To align the synopsis with the body of the Protocol	CLINICAL PROTOCOL SYNOPSIS
5	The coordinating investigator for this trial is: Prof. Aurélien Marabelle, M.D., Ph.D. Clinical Director Cancer Immunotherapy Program Institute Gustave Roussy Villejuif, France	To mention the coordinating investigator in the Protocol	6 INVESTIGATORS AND SPONSOR
6	Clarification of the required time of observation of patients after SO- C101 administration	To clarify further the time period of the observation after SO-C101 administration	CLINICAL PROTOCOL SYNOPSIS, 9.7.6.3 Observation of patients after administration of SO-C101
7	Addition of creatinine clearance calculation in addition to serum creatinine evaluation as follows: - cycles 1 and 2: days 1 and 9 prior to SO-C101 administration and on day 6; - - cycle 3: day 1 (prior to SO-C101 administration) and on day 6; - from cycle 4 and onwards on days 1 and 8 prior to SO-C101 administration.	To add creatinine clearance calculation in addition to serum creatinine evaluation	9.7.6.4.8 Kidney function, Table 9.6: Schedule of procedures/assessments, Part A (SO-C101 monotherapy)
8	Deletion of information about posting of summary of study results to https://www.clinicaltrialsregister.eu/ and https://clinicaltrials.gov/.	Not mandatory/required	11.10 Publication of results
9	Minor wording corrections and clarifications	To improve readability and clarify ambiguities	Throughout the Protocol