AMENDED CLINICAL STUDY PROTOCOL

CL1-95012-001

A FIRST IN HUMAN PHASE 1/2 OPEN-LABEL, MULTICENTER, DOSE ESCALATION AND EXPANSION STUDY OF PRS-344/S095012 IN PATIENTS WITH SOLID TUMORS

Product Number / Name	PRS-344/S095012
Protocol Number	CL1-95012-001
Public Study Title	A study of PRS-344/S095012 (PD-L1x4-1BB bispecific antibody) in patients with solid tumors
EudraCT Number	2019-003456-36
IND Number	
Study Phase	Phase 1 / 2
Sponsor Contact	Institut de Recherches Internationales Servier (I.R.I.S.) 22 route 128 91190 Gif-sur-Yvette FRANCE
Version and Date	Version 9.0 – 22 of January 2024

CCI **Statement**

VERSION LIST

Protocol No.	Substantial amendment No.	Final version date	Countries concerned	Nature of modifications
1.0	NA	25 May 2021	ALL	Not Applicable
2.0	1	28 June 2021	ALL	• **Section 7.2. Inclusion and exclusion criteria** Modification of inclusion criteria n°10. • **Section 7.3. Patients or Partners of Patients of Reproductive Potential** Precision on contraceptive methods for male patients. • **Section 9. STUDY ASSESSMENTS** Clarifications in assessment Tables (9) 1, 2. • **Section 8.9 Concomitant Medications** Addition of specific caution for CYP450 substrates with a narrow therapeutic index.
3.0	2	15 October 2021	ALL	• Infusion time reduced from 120 minutes to 60 minutes. • **Section 6.4** Clarification on SRC – A SRC charter will be provided in a separate document. • **Section 6.4.4** Section added to authorize intra-patient dose escalation under certain conditions. • **Section 6.7** Section added to give recommendations in case of patient's COVID-19 infection. • **Section 6.9** Section added to clarify the rules to be applied in case of treatment administration delay. • **Section 7.2** Modification of exclusion criteria n°10, 13, 18, 19, 20, 25. • **Sections 7.2 and 7.3** Modification of the duration for male contraception from 6 months to 4 months after the last dose. • **Section 9 Assessment tables** o Addition of timepoints for regular assessment of ACTH and Thyroid hormones. o Precision for efficacy assessment timepoint, at the time decision is made to stop the treatment (+/-14 days). o Enlargement of the time for the collection of the fresh baseline biopsies from 3 days to 14 days prior to first administration o Precision about predose for blood samples for PK, laboratory tests, pharmacodynamic biomarkers: within 4 hours prior to IMP administration. • **Section 9.1.3** Addition of timepoints for vital signs in case of previous IRR or CRS.

				• **Section 9.1.8.5** Addition of the option to use CKD-EPI formula for GFR estimation. • **Section 9.5.1** Enlargement of the time for the collection of the fresh baseline biopsies from 3 days to 14 days prior to first administration. • **Section 10.4.1** Clarification on timeframe for AE reporting. Correction of typing mistakes.
4.0*	3	22 February 2022	USA	• **Section 4.2.5** Precision on previous clinical experience. • **Section 6.4.3** Precision on the use of data from backfilled patients. • **Section 6.4.5** Modification of patient replacement rules. • **Section 6.4.6** Precisions on the DLT definition. • **Section 6.7** Modification of rules for restart of treatment after COVID-19 infection. • **Section 6.8** Rewording of the whole section for sake of clarity, and to remove inconsistencies. • **Section 6.9** Modification to be in accordance with Section 6.5.4. • **Section 7.2** Modification of inclusion criteria n°8, 11, 16, 18, 19, 20, 25, 30, 32, 34 and 39. Addition of inclusion criteria n°42 and 43 and removal of inclusion criterion n°30 and 31. • **Section 7.3** Homogenization of time window for contraceptive measures. • **Section 8.4** Precision on IMP administration. • **Section 8.9.3** Clarification on the prophylactic use of growth factors. • **Section 8.10** Removal of inconsistency • **Section 9 Assessment tables** o Addition of time points for ECOG evaluation during treatment period and corresponding change in Section 9.1.6. o Window for laboratory tests and PK samples. • **Section 9.4.1** End of administration includes flushing step. • Correction of typing mistakes.

4.1	3.1	29 March 2022	ALL	• **Section 6.4.6**
				  ○ Clarifications on the DLT definition.
				  ○ Addition of a recommendation for subsequent cohorts in case of CRS of Grade ≥ 2 during DLT period.
				• **Section 6.5**
				  ○ Patients that are intolerant to chemotherapy or immunotherapy cannot be enrolled in this study.
				  ○ Dose of irinotecan for UGT1A1 heterozygous patients.
				  ○ Safety lead-in design for combination with irinotecan modified.
				• **Section 6.8**
				Precisions on dose modification recommendations for irinotecan.
				• **Section 6.8.3**
				Modification of Table (6.8.3) 1 for management of hepatotoxicity.
				• **Section 6.8.4**
				Addition of a new table for management of specific immune-related AEs.
				• **Section 7.2**
				Addition of an exclusion criteria for expansion.
				• **Section 9**
				Addition of a PK sample 1 hour after all administrations, including in Cycle 3 & onwards. Update of Appendix 5 accordingly.
				• Correction of typing mistakes.
				• Correction of numbering of Section 6.

5.0	4	05 September 2022	ALL	• **Section 4.2.5**
				Addition of a cross-reference to the Investigator's Brochure.
				• **Section 6.1**
				Update of the duration of infusion of PRS-344/S095012.
				• **Section 6.2.2**
				Update of the duration of infusion of PRS-344/S095012.
				• **Section 6.3.1**
				Update of the duration of infusion of PRS-344/S095012.
				• **Section 6.8.2**
				  ○ Addition of measures for the management of CRS.
				  ○ Update of the sample medium for cytokines evaluation.
				• **Section 8.4**
				Update of the duration of infusion of PRS-344/S095012.
				• **Section 8.9.1**
				Addition of a cross-reference to CRS management.
				• **Section 9.1.8.7**
				Deletion of ketones and acetone assessment from the dipstick analysis.
				• **Section 10.4.1**
				Review of reporting rules for adverse event.

				• **Section 10.4.2** Update of Investigator's responsibilities. • **Section 12.1** Update of sign-off timing of e-CRF. • **Appendix 5** Update of blood volumes collected.
6.0	5	25 January 2023	ALL	• **Section 4.2.3** Rewording of some information on toxicology. • **Section 4.2.5** Update of the clinical experience of PRS-344/S095012. • **Section 4.3.2** Deletion of information on the rationale of FIH starting dose and addition of a cross-reference to the Investigator's Brochure. Addition of Section 4.3.2.2 for the rationale for doses in phase 2. • **Section 4.3.3** Update of the rationale for disease indications and deletion of information relating to combination therapy for phase 2. • **Section 4.4** Update of the overall benefit/risk with the phase 2 and setting up of DMC for phase 2. • **Section 5.1** Addition of the determination of RP2D as primary objective of phase 1 and of some details for secondary objectives and endpoints. • **Section 5.2** Update of objectives and endpoints of phase 2 (including the central assessment of the primary endpoint, the addition of endpoints and a secondary objective, the transition from a secondary objective to an exploratory objective and the addition of an exploratory objective). • **Sections 6.1 and 6.4.7** Deletion of anti-tumor activity (efficacy) considerations to determine the RP2D. • **Sections 6.1, 6.4.2 and 6.4.6** Clarification on DLT observation period: 28 days in case of CCI schedule and 21 days in case of Q3W schedule. • **Section 6.1** Clarification that the dose of PRS-344/S095012 in phase 1 will be determined during end of cohort meetings, based on safety data and available PK data. • **Sections 6.1, 6.2.2, 6.3.1** Deletion of information on the infusion duration of PRS-344/S095012. • **Sections 6.1, 6.3.3, 6.4.7, 6.5, 6.6.2, 7.1, 8.4, 9.1.7, 9.1.8.3, 9.2.1, 9.5.2, 9.5.4, 11.1, 11.4*, 11.5.3, Figure (6) 1, Table (9) 2*, Appendix 7*:** Modification of the indications of expansion arms, study design, dose levels, stopping rules, number of patients, study assessments and statistical sections of phase 2. *Added item

				• **Sections 6.2.1, 6.2.2, 6.4.3, 7.2 (inclusion criteria n°7 and 45) and 9.5.1 and Tables (9) 1, (9) 2* and 9 (3)** Addition of clarifications on baseline and on-treatment tumor biopsies according to the parts and arms of the study (including the mandatory or optional character, the possibility of an archived tumor biopsy at baseline under specific conditions, as well as the need of a biopsy within 30 days of CR determined by the investigator for confirmation of the CR in patients deemed eligible by digital photography only (arm 3)). *Added item • **Sections 6.2.3, 7.3 and 9 and Tables (9) 1, (9) 2* and 9 (3)** Revision of assessments during the FU period and their timepoints. *Added item • **Sections 6.2.3, 6.6.3, 9.1.2 and 9.2.1 and Table (9) 2*** Addition of the photographic assessment (and not only radiologic) of the disease for patients with skin tumors only evaluated by photography. *Added item • **Section 6.4.6** Addition of the MAD in the RP2D definition for consistency with Section 6.4.7. • **Section 6.4.7** Clarification that dose(s) of PRS-344/S095012 for phase 2 will be recommended during end of cohort meetings and discussed by the DMC. • **Section 6.6.3** Addition of one criterion for treatment withdrawal. • **Section 6.7** Update of the conditions for resuming the study treatment(s) in case of COVID-19 infection. • **Section 6.8** Deletion of information relating to irinotecan dose modifications. • **Sections 6.8.2 and 8.9** Deletion of information relating to the use of tocilizumab, corticosteroids and other immunosuppressive monoclonal antibodies for the management of CRS and addition of these treatments as concomitant medications. • **Section 6.8.2** Possibility to set up a premedication to mitigate the risk of CRS for all patients at the investigator's discretion, if necessary. • **Sections 6.8.2 and 8.4** Possibility of extension of the infusion duration of PRS-344/S095012 for safety reasons after the approval by the Sponsor. • **Section 7.2** To define inclusion criteria n°3, 5 and 7 as dose escalation specific inclusion criteria and to update them as needed.

				To update inclusion criteria n°13 and 14 defined as dose expansion specific inclusion criteria and to add inclusion criteria n° 45 and 46. Specification/modification of inclusion criterion n°8. Deletion of inclusion criterion n°12. Specification/modification of exclusion criteria n°16, 24, 25 and 29. To shift exclusion criterion n°43 (UGT1A1 enzyme deficiencies) to 44, because already one exclusion criterion n°43 (hepatitis infections). To delete exclusion criteria n°40, 41 and 44 (formerly 43), specific to the dose expansion part. • **Section 8.4** Deletion of information related to modalities of administration of irinotecan. • **Section 8.9.1** Specification of premedication for IRR and CRS. • **Section 8.10** Addition of prohibited therapies. • **Section 9 – Table (9) 1** Update of the table of assessment schedule for phase 1 CCI and addition of C1D8 timepoint for flow cytometry and deletion of C2D1 timepoint. • **Section 9 – Table (9) 2*** Addition of the table of the assessment schedule for phase 2 CCI . *Added item • **Section 9 – Table (9) 3 [formerly Table (9) 2]** Update of the table of assessment schedule for phase 1 Q3W and addition of C1D8 timepoint for flow cytometry and deletion of C1D15 timepoint. • **Section 9.1.8.1 and Tables (9) 1, (9) 2* and (9) 3** Addition of CD8 and/or CD4 lymphocytes counts if feasible on site. *Added item • **Section 9.2.1 and Tables (9) 1, (9) 2* and (9) 3** Update of timepoints for tumor assessments according to schedule of administration. *Added item • **Section 9.2.1** Clarifications on tumor assessment methods. • **Section 9.2.2 and Tables (9) 1 and (9) 3** Deletion of assessments of tumor markers. • **Section 9.2.2 (formerly Section 9.2.3)** Specification of the modalities for remote monitoring of survival to comply with the synopsis. • **Section 9.3** Addition that back-up samples for ADA will be stored to allow complementary analyses. • **Section 9.4.2** Specification of the pharmacokinetic analysis.

				• **Sections 9.4 and 9.5** Clarification that biomarker analyses (all exploratory) and PK analyses may change during the course of the trial according to new scientific data. • **Section 9.5.1** and **Table (9) 3 [formerly Table (9)2]** Modification of the collection timepoint of the on-treatment biopsy in case of Q3W schedule from C2D1 to C2D8-15. • **Section 9.5.3** Possibility to use left over and back up samples for analysis of a cytokine or any other circulating protein of interest, for better understanding of the activity of the study drug. • **Section 10.2.1** Addition of European Union Clinical Trial regulation 536/2014 as reference for definition of seriousness, where applicable. • **Section 10.4.1** Deletion of CRS / IRR among list of AE that should be reported in e-CRF within 24 hours. • **Sections 10.4.3 and 14.8.2*** Description of DMC for phase 2. *Added item • **Sections 11.2 and 11.3.4 and Appendix 6** Update of the definition of *DLT evaluable population.* • **Section 11.2** Addition of the *response evaluable population*. • **Sections 10.4.2.5, 12.1, 12.2 and 12.5** Clarifications of data review and database management. • **Section 14.3** Clarifications on optional ICF signatures. • **Section 14.5** Clarifications on the type of visit. • **Section 14.8.1*** Creating a section to describe Safety Review Committee. *Added item • **Section 16** Appendix 5: update of the table for phase 1 CCI and addition of tables for phase 2 and phase 1 Q3W. These modifications have been also accordingly implemented in the synopsis.
7.0	6	17 April 2023	ALL	• **Section 4.2.5** Update of the clinical experience with PRS-344/S095012. • **Section 4.3.3** Update of the rationale for indication selection for phase 2. • **Section 4.4** Update of the overall benefit/risk assessment of PRS-344/S095012.

				• **Section 6.1** Harmonization between different sections of the protocol of the definition of the patient population to be evaluated arm 3 (CSCC – CPI relapsed/refractory). • **Section 6.8.2** Update of the recommendations for Cytokine Release Syndrome management. • **Section 6.8.3** Update of the recommendations for management of immune-related hepatotoxicity. • **Section 6.8.4** Addition of recommendations to assist with identification / diagnosis of hemophagocytic lymphohistiocytosis. • **Section 6.8.5** Update of the recommendations for immune-related adverse event management. • **Section 7.2** Update of inclusion criteria n°8 and 14. Addition of inclusion criteria n°47 and 48. Update of exclusion criteria n°20, 25 and 29. Addition of exclusion criterion n°49. • **Section 9 – Tables 9 (1), 9 (2), 9 (3)** Update of the collection of blood samples for PK of PRS-344/S095012. Addition of blood samplings for cytokine analysis at D1 of Cycle 3 & subsequent odd cycles. • **Section 9.1.7** Addition of the assessment of the Royal Marsden Prognosis Score during screening. • **Section 9.1.9.2** Addition of glucose, ferritin (screening) in the biochemistry. • **Section 14.9** Addition of information on the reporting of a suspected serious breach. • **Section 15** Update of the list of references. • **Section 16** Update of tables "cumulative blood volume collected per patient per period/cycle" (Appendix 5). Addition of a scale - Royal Marsden Prognosis Score - in Appendix 8. These modifications have been also accordingly implemented in the synopsis.

8.0	7**	21 August 2023	ALL	**Integration of non-substantial amendment 2:** correction in the Royal Marsden Prognosis Score table (Appendix 8). **Update of the Sponsor's address (I.R.I.S).** **Addition of obinutuzumab pretreatment:** • **Section 4 Introduction** o Re-organisation of the section to further describe up-to-date clinical experience in a dedicated sub-section 4.4. o Update of safety data in section 4.4.1. o Addition of section 4.4.2 dedicated to efficacy data. o Addition of the section 4.4.3, dedicated to pharmacokinetic and pharmacodynamic data of PRS-344/S095012. o Addition of a section 4.5, describing the rationale for ADA mitigation strategy. o Numeration of section Overall Benefit/Risk is updated to 4.6 and section is updated. • **Section 6.1 Overall Study Design** Addition of obinutuzumab infusion. • **Section 6.3.1 Schedule of Administration** Addition of obinutuzumab infusion. • **Section 6.8.1** Management of infusion-related reactions • **Section 7.1** Update of the number of patients to be included. • **Section 7.2 Inclusions and Exclusions criteria** o Modification of inclusion criteria n°47, 8c, 9, 48. o Addition of inclusion criteria n° 50, 51, 52. o Precision of the inclusion criteria 7a. o Deletion of the exclusion criteria 43. • **Section 8.9 Concomitant medications** o Addition of a section 8.9.1 Pretreatment with obinutuzumab. o Following sections numeration is corrected accordingly. • **Section 9, Assessment tables** o Update of the schedule of administration with the addition of obinutuzumab Table (9) 1, Table (9) 2 Table (9) 3. o Correction of typos. • **Section 9.3, Immunogenicity assessment** o Precision regarding possible additional PK and ADA measures. • **Section 10.2.3, Assessment of cause-effect relationship** o AE's relationship with obinutuzumab to be assessed in an AE form. • **Section 11.1** Sample size is precised in regard to the obinutuzumab strategy.
9.0	8**	22 January 2024	ALL	• **Section 6.8.4** o Addition of specific criteria for HLH diagnosis and treatment guidelines.

				• **Section 6.8.5 – Table (6.8.5) 1** o Addition of American Society of Clinical Oncology (ASCO) guideline in the management of specific immune-related AEs. • **Sections 8.6 and 8.8** o Update of the tool for accountabilities of treatments and treatment compliance. • **Section 9 – Tables 9 (1), 9 (2), 9 (3), 9.1.8.2** o Addition of ferritin in each of the biochemistry panels. • **Section 16 (Appendix 9)** o Addition of specific criteria for HLH diagnosis and treatment guidelines. • **Update of Sponsor contacts** • **Correction of typing mistakes**
9.0	9**	22 January 2024	FRA-EC	See modifications from amendments 7 and 8 above.

** Note = the version 4.0 was submitted only to the USA for initial submission and was not accepted as such. Following questions, a version 4.1 was approved by the USA. This version 4.1 was then submitted to all other countries with an Amendment 3.*

*** The amendments 7 and 8 have been pooled together in the amendment 9 for single French Ethics Committee (FRA-EC) submission and assessment.*

PROTOCOL APPROVAL SIGNATURE PAGE

Protocol: CL1-95012-001
Version: V9.0
Title: A first-in-human Phase 1/2 open-label, multicenter, dose escalation and expansion study of PRS-344/S095012 in patients with solid tumors.

Date:

Amendment:

Reviewed and Approved by:	
Name, Title: PPD , MD, Vice President, Clinical Sciences – I.R.I.S.	
Signature 	Date 29 January 2024

PROTOCOL ACCEPTANCE FORM

Protocol: CL1-95012-001 V9.0
Title: A first in human Phase 1/2 open-label, multicenter, dose escalation and expansion study of PRS-344/S095012 in patients with solid tumors.

Date:

Amendment:

I have carefully read this protocol and agree that it contains all the necessary information required to conduct this study. I agree to conduct this study as described and according to the Declaration of Helsinki, ICH Guidelines for GCP, and all applicable regulatory requirements.

Investigator's Signature	Date
Name (printed)	

1. SYNOPSIS

Title of Study: A first in human Phase 1/2 open-label, multicenter, dose escalation and expansion study of PRS-344/S095012 in patients with solid tumors.

Protocol No.: CL1-95012-001
Public Study title: A study of PRS-344/S095012 (PD-L1x4-1BB bispecific antibody) in patients with solid tumors

Investigators:
Investigators are listed in a separate document.

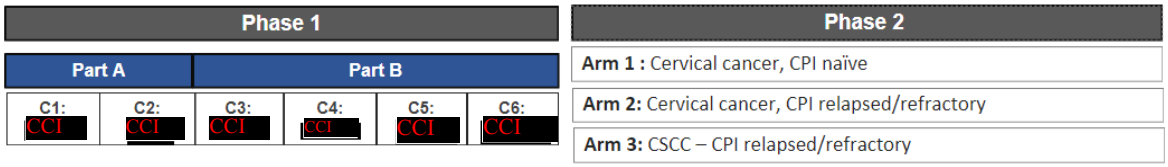
Study center(s):
This is an international multicenter study to be conducted in the United States of America (USA), Europe and Australia.
Approximately 10 sites will be opened in phase 1 and approximately 60 sites in phase 2.

Study period:
The duration of the study will be approximately [redacted] years for dose escalation and [redacted] years for dose expansion.

- Maximum study duration for each participating patient: each patient will participate in the study until disease progression, loss to follow-up, an adverse event leading to withdrawal, significant non-compliance with the study protocol, withdrawal of consent, end of study, or death from any cause. For all patients, the maximum duration of the treatment period will not exceed [redacted] year for patients with complete response (CR) and [redacted] years for patients with partial response (PR). Longer treatment duration may be permitted if patient benefits outweigh the risks according to the investigator's judgment and after consultation with the sponsor.
- Study initiation date (date of first visit, first patient): Q3 2021.
- Study Completion Date (end of phase 2): 2027.

Methodology
This is a first-in-human (FIH), phase 1/2, multicenter, open-label, dose escalation and dose expansion study designed to determine the safety and activity of PRS-344/S095012 in patients with advanced and/or metastatic solid tumors.

Figure (1) 1 - CL1-95012-001 Study design



Dose levels are provisional and will depend on the Bayesian Logistic Regression Model (BLRM) recommendation and cumulative safety data observed. C = Cohort; CPI = checkpoint inhibitors; CSCC: cutaneous squamous cell carcinoma

Phase 1 will be conducted in patients for whom standard treatment options are not available, no longer effective, or not tolerated and consists of dose escalation in 2 parts (A and B), where the safety of PRS-344/S095012 will be investigated as the primary objective. Part A is an accelerated dose escalation following a [redacted]. In part B, the design for dose escalation will be supported by a Bayesian Logistic Regression Model (BLRM), where [redacted] to [redacted] patients per dose level will be enrolled. The starting dose will be a flat dose of [redacted] mg given [redacted]. To further understand the safety, pharmacokinetic (PK)/ pharmacodynamic or early signals of activity of PRS-344/S095012, backfilling of previously evaluated dose levels will be allowed as described below. If necessary or appropriate and agreed upon during an end of cohort meeting, an alternative administration schedule of Q3W may be investigated in new cohorts. The dose limiting toxicity (DLT) observation period will be 28 days [redacted] for the [redacted] schedule and 21 days for the Q3W schedule.

Phase 2 will evaluate the potential efficacy of PRS-344/S095012 in 3 disease-specific expansion arms:

- *Arm 1 (cervical cancer – checkpoint inhibitor (CPI) naïve):* patients with recurrent, persistent and/or metastatic cervical cancer, who have not been previously treated with a CPI, and whose disease has progressed on any prior line of treatment.

- *Arm 2 (cervical cancer – CPI-relapsed/refractory):* patients with recurrent, persistent and/or metastatic cervical cancer, who have received and progressed on any line of a CPI as monotherapy or in combination.

Note: for cervical cancer in arms 1 and 2, acceptable histologies are squamous carcinoma, adenocarcinoma, and adenosquamous carcinoma; sarcomas and neuro-endocrine carcinomas are not eligible.

- *Arm 3 (cutaneous squamous cell carcinoma* (*CSCC) – CPI-relapsed/refractory):* patients with advanced or metastatic CSCC who have received and progressed on CPI treatment.

This expansion phase will follow a Clustered Bayesian Hierarchical Model (CBHM) with one or more futility analyses.
A Data Monitoring Committee (DMC) will be put in place for the phase 2 part of the study.
Patients will receive PRS-344/S095012 CCI as monotherapy.
Additional arms could be initiated in the same population/indication with the Q3W administration schema if considered relevant and decided during end of cohort meeting and/or approved DMC.
Additional settings or combinations may be added through an amendment to the protocol and after Competent Authority, Institutional Review Board (IRB) and Ethics Committee (EC) approvals.

Study Objectives and endpoints

Phase 1	
Primary objectives	**Endpoints**
- To evaluate the safety and tolerability profile of single-agent PRS-344/S095012	- Incidence of DLTs - Incidence and severity of adverse events (AEs) - Discontinuation of study treatment due to an AE - Laboratory, electrocardiogram (ECG) and vital sign measurements
- To determine the maximum tolerated dose (MTD) or maximum administered dose (MAD) and the recommended phase 2 dose (RP2D) of PRS-344/S095012	- Incidence of DLTs
Secondary objectives	**Endpoints**
- To characterize the PK of PRS-344/S095012	- Serum PK parameters of PRS-344/S095012
- To evaluate the immunogenicity of PRS-344/S095012	- Detection of anti-drug antibodies (ADA) against PRS-344/S095012 and their titration when applicable
- To assess the preliminary anti-tumor activity of PRS-344/S095012 as per the investigator, according to Response Evaluation Criteria in Solid Tumors (RECIST) v1.1	- Objective Response (OR): Defined as Complete Response (CR) plus Partial Response (PR) - Duration of Response (DoR): defined as the time from first demonstration of response to progression or death, whichever occurs first - Progression-free Survival (PFS): Defined as the time from the first dose of treatment to first documented disease progression or death due to any cause, whichever occurs first - Overall Survival (OS): Defined as the time from first dose of study drug to death due to any cause
Exploratory objectives	**Exploratory objectives**
To evaluate the intra-tumor pharmacodynamics of PRS-344/S095012 through the analysis of pre- and on-treatment tumor biopsies	- Programmed death-ligand 1 (PD-L1), CD8, and 4-1BB expression in the tumor microenvironment by immunohistochemistry (IHC) - Immune cell subsets and activation status (such as but not limited to expression of Ki67 and Granzyme in CD8 T cells) by IHC And/or gene expression profiling in the tumor such as but not limited to interferon gamma (IFNγ) gene signature

- To characterize treatment-induced pharmacodynamic effects in peripheral blood	- Immuno-phenotyping of T cell subsets and their activation (such as, but not limited to, CD4, CD8, regulatory T cells, naïve and memory subsets, Ki67) and changes by flow cytometry - Cytokine levels - Soluble 4-1BB level
- To analyze potential predictive biomarkers of response from tumor and blood samples	- PD-L1, 4-1BB, and CD8 expression in the tumor - And/or tumor mutational burden (TMB) in the tumor and/or blood, microsatellite instability (MSI) status, specific mutations in the tumor (or in the blood if feasible, with an optional sample) - And/or gene expression profiling in the tumor and/or blood
- To assess any potential PK/pharmacodynamic relationship through a population modelling approach that may support the selection of the RP2D and schedule of administration	- PK and pharmacodynamic parameters in PK/pharmacodynamic models and simulation outcomes to support RP2D and schedule of administration.
Phase 2	
Primary objective	**Endpoint**
- To evaluate the potential anti-tumor activity and efficacy of PRS-344/S095012, as per central assessment according to RECIST v1.1 criteria based on appropriate clinical standards for the specified tumor type	- Arms 1 and 2: OR as per central assessment according to RECIST v1.1 criteria - Arm 3: OR as per central assessment and composite response criteria (digital medical photography and/or imaging as per RECIST v1.1)
Secondary objectives	**Endpoints**
- To further describe the efficacy	- All arms: OR as per investigator assessment - Disease Control (DC) - DoR - PFS - OS - Time to Response (TTR)
- To further characterize the safety and tolerability of PRS-344/S095012	- AEs, serious adverse events (SAEs) - Laboratory, ECG, vital signs
- To further characterize the PK profile of PRS-344/S095012	- Serum concentrations of PRS-344/S095012
- To further characterize immunogenicity of PRS-344/S095012	- Detection of ADA against PRS-344/S095012 and their titration when applicable
Exploratory objectives	**Endpoints**
- To evaluate potential predictive biomarkers of response from tumor and/or blood samples	- PD-L1, and potentially other markers like 4-1BB, and CD8 expression in the tumor - And/or TMB in the tumor and/or blood, MSI status, specific mutations in the tumor (or in the blood if feasible, with an optional sample) - And/or gene expression profiling in the tumor and/or blood
- To evaluate pharmacodynamic changes in the tumor and blood samples	- Immune cell quantity and phenotype characterization in the blood and in the tumor - And/or cytokine levels - And/or soluble 4-1BB levels

Number of Patients Planned

Phase 1 - Dose escalation:

Parts A and B: Approximately CCI patients will be enrolled in these parts of the study. The exact number of patients will depend on the number of dose cohorts that will be opened.

Patients enrolled in order to backfill previously evaluated dose levels: Approximately CCI additional patients may be enrolled to as many as CCI previously evaluated dose levels, in order to further characterize their safety, PK or PD.

Phase 2 - Dose expansion: Approximately CCI patients will be enrolled in each of the arms. Additional arms may be considered later via an amendment to the protocol.

- Arm 1: approximately CCI patients, cervical cancer, CPI-naïve.
- Arm 2: approximately CCI patients, cervical cancer, CPI-relapsed / refractory.
- Arm 3: approximately CCI patients, CSCC, CPI-relapsed / refractory.

Criteria for Inclusion/Exclusion

Inclusion criteria

1. The participating patient signs a written informed consent obtained prior to performing any study procedure, including screening procedures.
2. Age ≥ 18 years on the day the consent is signed.
4. Patients should have a documented disease progression on prior therapy before entry into this study.
6. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.
47a. Royal Marsden Prognosis Score of 0 to 1 (score based on lactate dehydrogenase (LDH) value, albumin value and number of sites of metastasis, see Appendix 8).
42. Patients must have a life expectancy of at least 3 months following first investigational medicinal product (IMP) administration.
8d. Adequate organ function as assessed by laboratory tests within 7 days prior to pretreatment with obinutuzumab:
   - Absolute neutrophil count (ANC) ≥ 1500/µL.
   - Platelet count ≥ 75 000/µL (this criterion must be met without the use of transfusion or thrombopoietin for at least two weeks prior to study drug administration).
   - Hemoglobin ≥ 8g/dL (this criterion must be met without the use of transfusion or erythropoietin within the two weeks prior to study drug administration).
   - Lymphocyte count ≥ 800/µL.
   - Gamma-globulin level > 6g/L (by serum protein electrophoresis) or IgG level > 4g/L (by measurement of quantitative immunoglobulins).
   - Glomerular filtration rate (GFR) or measured or calculated creatinine clearance (CrCl) ≥ 30mL/min.
   - Total bilirubin ≤1.5×upper limit of normal (ULN) (or total serum bilirubin < 3×ULN for patients with Gilbert's disease).
   - Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 2.5×ULN (5 X ULN for patients with liver metastases).

9a. A female patient must use a highly effective method of birth control during study treatment, for 120 days after the last dose of the PRS-344/S095012, or 18 months after the last obinutuzumab infusion, whichever comes the latest.
10b. A male patient with childbearing potential partners must use a condom during the study and for at least 4 months after the last dose of the study treatment, or 6 months after the last obinutuzumab infusion, whichever comes the latest. Patients who are sterile or vasectomized must use a condom during sexual intercourse with a childbearing potential partner in order to avoid exposure of an existing embryo/foetus. In addition, contraception should be considered for their female partner. Contraceptive measures do not apply if the patient is sexually abstinent. Sperm donation will not be allowed during the study and for 4 months after the last dose of study treatment, or 6 months after the last obinutuzumab infusion, whichever comes the latest.
11a. Human immunodeficiency virus (HIV)-infected patients must have well-controlled HIV or be on adequate antiretroviral therapy (ART).
48a. Tests should be negative for Cytomegalovirus (CMV), Epstein-Barr virus (EBV), Hepatitis B virus (HBV), and Hepatitis C virus (HCV) infection, according to local standards:
   - Negative CMV DNA testing in serum or plasma by a sensitive quantitative molecular method.
   - Absence of serum immunoglobulin (Ig)M antibodies against EBV-VCA (Viral Capside Antigen).
   - Negative serologic testing for hepatitis B surface antigen (HbsAg) or a negative result by a sensitive quantitative molecular method for HBV-DNA in serum or plasma.
   - Negative HCV RNA testing in serum or plasma by a sensitive quantitative molecular method.

52. Negative test results for human T-lymphotropic virus 1 (HTLV 1). HTLV testing is only required for participants from countries in which HTLV 1 infection is endemic (Japan, countries in the Caribbean basin, South America, Central America, sub-Saharan Africa, and Melanesia).

Dose escalation, specific additional inclusion criteria:

3. Patients with a histological diagnosis of an unresectable, locally advanced or metastatic solid tumor for which standard treatment options are not available, no longer effective, or not tolerated.

5a. Patients must have measurable disease per RECIST 1.1 as assessed by the local site investigator/imaging. Lesions situated in a previously irradiated area are considered measurable only if progression has been demonstrated in such lesions.

7b. Patients with no available archived material must have one or more tumor lesions amenable to biopsy.
Note: archival tissue taken < 9 months before the start of treatment can be used. If a patient consents to an on-treatment biopsy (which is optional but highly encouraged), pre-treatment tumor tissue should be available ideally from a fresh biopsy taken before the start of treatment or, if available, from archival tissue taken < 6 months before S095012 administration without any intercurrent treatment.
Patients enrolled to a previously evaluated dose level (back-fill patients): an on-treatment tumor tissue biopsy is required. A pre-treatment fresh tumor biopsy is also required unless archival tumor tissue was obtained < 6 months before the start of treatment and there was no intervening cancer treatment given during this time.

Dose expansion, specific additional inclusion criteria:

The criterion No. 12 is deleted as per amendment No. 5.

13. Patients with histologically diagnosed:

- *Arm 1 and 2*: recurrent, persistent, and/or metastatic cervical cancer. Acceptable histologies are squamous carcinoma, adenocarcinoma, and adenosquamous carcinoma.
  Note: Sarcomas and neuro-endocrine carcinomas are not eligible.
- *Arm 3:* locally advanced or metastatic cutaneous squamous cell carcinoma.

14a. Patients must have received:

- *Arm 1 (cervical cancer, CPI-naïve):* at least 1 prior line of platinum-based combination therapy. Patients must not have received any prior treatment with an immune checkpoint inhibitor (anti-PD-1, PD-L1 or anti-CTLA-4 [cytotoxic T lymphocyte-associated protein 4]) and do not have access to an approved immune checkpoint inhibitor. Surgery, radiation therapy, and additional chemotherapy must not be considered appropriate alternative treatment options for these patients.
- *Arm 2 (cervical cancer, CPI-relapsed/refractory):* at least 1 prior line of systemic therapy with an immune checkpoint inhibitor as monotherapy or in combination with chemotherapy and/or any other systemic therapies. Surgery, radiation therapy, and additional chemotherapy must not be considered appropriate alternative treatment options for these patients.
- *Arm 3 (CSCC, CPI-relapsed/refractory):* at least 1 prior line of systemic therapy with an immune checkpoint inhibitor as monotherapy or in combination with chemotherapy and/or any other systemic therapies. Surgery, radiation therapy, and additional chemotherapy must not be considered appropriate alternative treatment options for these patients.

45. Biopsy requirements

- *Arms 1 and 2 (cervical cancer):* fresh baseline biopsies are mandatory, on-treatment biopsies are optional.
  Note: fresh baseline biopsies are not mandatory if archived tumor biopsy specimens collected no later than 6 months without intercurrent treatment before screening are available. If no archived material is available, a fresh biopsy must be collected at baseline.
- *Arm 3 (skin cancer):* fresh baseline biopsies are mandatory, on-treatment biopsies are mandatory unless medically contra-indicated.
  Note 1: fresh baseline biopsies are not mandatory if archived tumor biopsy specimens collected no later than 6 months without intercurrent treatment before screening are available. If no archived material is available, a fresh biopsy must be collected at baseline.
  Note 2: For patients deemed eligible by digital photography only, an additional biopsy is required within 30 days of CR determined by the investigator for confirmation of the CR.

46. Patients must have at least one measurable target lesion as per RECIST 1.1 and/or World Health Organization (WHO) criteria for only externally visible skin tumors confirmed by central review. Lesions situated in a previously irradiated area are considered measurable only if progression has been demonstrated in such lesions.

Exclusion criteria

15. Pregnant and lactating women.

16b. Patients with previously treated brain metastases that may be considered active. Patients may participate provided they are radiologically stable, clinically asymptomatic and are off immunosuppressive therapies for at least 4 weeks prior to first IMP administration. Low and stable dose of steroid (≤ 10 mg/day prednisone or equivalent) is allowed.

17. Patients with primary central nervous system (CNS) malignancy.

18a. Patients with Child-Pugh Class B8 or higher liver cirrhosis.

19a. Patients who have received prior:

a. Chemotherapy, Small molecule inhibitors, Monoclonal Antibodies, Antibody-drug conjugates, and/or other similar investigational agent: at least 3 weeks or 5 half-lives prior to first IMP administration, whichever is shorter.
b. Radioimmunoconjugates or other similar experimental therapies: at least 6 weeks or 5 half-lives prior to first IMP administration, whichever is shorter.

20b. Patients must have recovered from any AE (from previous anti-cancer therapy) to Common Terminology Criteria for Adverse Events (CTCAE) V5.0 Grade 1 or lower. Grade 2 alopecia, peripheral neuropathy, decreased haemoglobin, and electrolyte changes are acceptable. Patients receiving replacement hormone therapy due to previous AEs will not be excluded from participation in this study if the associated AE has recovered to Grade 1 with replacement therapy prior to first IMP administration.

21. Patients who have received a 4-1BB agonist in the past.

22. Patients who have had major surgery within 4 weeks prior to first administration of IMP.

23. Patients with an active autoimmune disease that is currently requiring systemic anti-inflammatory treatment (such as disease-modifying anti-rheumatic drugs [DMARDs], steroids, or immunosuppressants), except vitiligo, alopecia areata, asthma/atopy and psoriasis treated and controlled by topical therapies. Patients with auto-immune endocrinopathies that are well treated by replacement hormone therapies (*e.g.* thyroxine, insulin, physiological steroids for adrenal or pituitary deficits) are eligible.

24a. Patients with a history of immune-related adverse events (irAEs) from a previous line of treatment must have recovered to CTCAE Grade ≤ 1 and have also stopped any immunosuppressive/steroid therapy > 10 mg prednisone per day. Patients with prior history of Grade ≥ 3 immune-related pneumonitis, colitis, hepatitis, or myocarditis are excluded.

25c. Patients who have received either systemic corticosteroids (> 10 mg per day of prednisone or equivalent) or other immunosuppressive medications during the 2 months prior to the first dose of the study drug. Higher single doses of corticosteroids given as premedication against infusion-related reactions are allowed. Treatment with local steroids (inhaled, intranasal, injected) are allowed.

26. Patients who have received an allogenic solid organ or bone marrow transplant.

27. Patients with a history of interstitial lung disease, pneumonitis requiring systemic steroids for treatment, or current pneumonitis.

28. Patients with a clinically significant cardiovascular disease or condition, including:

a. New York Heart Association (NYHA) classification III or IV, known symptomatic coronary artery disease, or symptoms of coronary artery disease on systems review, or known cardiac arrhythmias (atrial fibrillation or supraventricular tachycardia [SVT]).
b. Any concomitant serious health condition, which, in the opinion of the investigator, would place the patient at undue risk from the study, including uncontrolled hypertension and/or diabetes, clinically significant pulmonary disease (*e.g.*, chronic obstructive pulmonary disease requiring hospitalization within 3 months) or neurological disorder (*e.g.*, seizure disorder active within 3 months).

29b. Patients with an active infection with a viral, bacterial, or fungal pathogen requiring systemic treatment within seven days before first IMP administration. Any patient requiring systemic treatment for CMV or EBV within 2 months before IMP administration should be excluded. Refer to inclusion criterion 11a and exclusion criterion 32a for HIV infections, and to inclusion criterion 48a for CMV, EBV and hepatitis B and C infections.

32a. Patients with HIV who have Castleman's disease.

33. Patients who have received a live vaccine within four weeks prior to first IMP administration. Examples of live vaccines include but are not limited to measles, mumps, rubella, varicella zoster, yellow fever, rabies, Bacillus Calmette-Guérin (BCG), and typhoid vaccine. Seasonal injected influenza vaccines (which are generally killed virus vaccines) and live replicative vaccines are allowed; intranasal influenza vaccines are live attenuated vaccines and are not allowed.

34. Patients who have received any Covid-19 vaccine within 14 days prior to first IMP administration or who have a dose planned during the DLT observation period.

35. Patients with a history of clinically significant hypersensitivity to monoclonal antibodies or infused therapeutic proteins or any component of the study drugs.
36. Patients with significant pulmonary compromise including a requirement for continuous supplemental oxygen to maintain adequate oxygenation.
37. Patient with history of, or current evidence of, any condition, surgical or medical therapy, or laboratory abnormalities that might confound the results of the study, make study drug administration hazardous, interfere with the patient's involvement for the full duration of the study, or make it difficult to monitor AEs such that in the opinion of the treating physician it is not in the best interest of the patient to participate in the study.
38. Any psychiatric or substance abuse condition rendering the patient unable to understand the nature, scope, and possible consequence of the study and or evidence of an uncooperative attitude.
39. Patients with any other active malignancy within 3 years prior to first IMP administration, except for adequately treated basal cell or squamous cell skin cancer, or carcinoma in situ.
49. Patients with a history of an opportunistic infection within a year prior to first IMP administration.
50. History of progressive multifocal leukoencephalopathy.
51. Active tuberculosis requiring treatment within 3 years prior to the start of treatment or a suspicion of latent tuberculosis by the investigator.

Test Product, Dose, and Mode of Administration

PRS-344/S095012 drug product is a concentrate for solution for infusion for intravenous (IV) administration. It is supplied in 20 mL US Pharmacopeia and European Pharmacopeia Type I glass vials filled with 16 mL of product at a concentration of 25 mg/mL. Each vial for administration contains 400 mg of PRS-344/S095012. For dosing, the required volume of product is diluted as described in the Pharmacy Manual.

In dose escalation, PRS-344/S095012 will be administered CCI as an IV infusion. The dose of PRS-344/S095012 will be determined during end of cohort meetings, based on safety data and available PK data. Based on observed safety, PK and pharmacodynamic profiles, a Q3W schedule may be used.

In dose expansion, PRS-344/S095012 will be administered CCI. The dose of PRS-344/S095012 will be recommended during an end of cohort meeting and this recommendation will be discussed by the DMC before the start of any expansion arm.

Additional arms could be initiated in the same population/indication with the Q3W administration schema if considered relevant and decided during end of cohort meeting and/or approved DMC.

In the study, the targeted duration of infusion of PRS-344/S095012 is up to 2 hours. The infusion duration will be defined per cohort during end of cohort meetings.

Pretreatment with obinutuzumab

Within two weeks before the first dose of PRS-344/S095012 is administered, patients will be treated with obinutuzumab as an IV infusion, with the aim of CCI. Obinutuzumab will be given as CCI of infusion, at the earliest on CCI and at the latest on CCI. Alternatively, obinutuzumab may be given as CCI, at the earliest on CCI and CCI, and at the latest on CCI, according to the investigator's preference. The administration of obinutuzumab will otherwise generally follow the instructions in the product label for the infusion duration and for premedication with a corticosteroid, an anti-pyretic, and an antihistamine to mitigate infusion-related reactions (IRRs) that may be caused by obinutuzumab.

Study design

Phase 1 - Dose escalation

Part A: Accelerated dose escalation following CCI

During part A, CCI per dose level will be enrolled. Dose escalation will be conducted in semi-logarithmic increments at most though smaller dose increments may be utilized. Dose escalation scheme will be as follows:

- If no IMP-related AE ≥ Grade 2, IMP-related cytokine-release syndrome (CRS) of any grade or DLT occurs during the 28-day DLT observation period, escalation to the next dose level in CCI cohort may be decided after the review of the available CCI data by a Safety Review Committee (SRC), composed of the Sponsor's medical representative and investigator(s).

- In the event of any IMP-related AE ≥ Grade 2, IMP-related CRS of any grade or DLT occurring during the 28-day DLT observation period, CCI additional patients will be enrolled at the same dose level and the design will be switched to part B design. Dosing of the first and second additional patients will be staggered by a minimum of 24 hours.

Part B: Dose escalation by BLRM

In part B, dose escalation will start at no greater than the CCI dose level; lower in case of IMP-related AE ⩾ Grade 2, IMP-related CRS of any grade, or DLT occurring in part A. The CCI threshold is based on the Human Equivalent Dose (HED) of the minimal therapeutic dose determined *in vivo* in a relevant mouse model. Dose escalation will be supported by a BLRM.

A cohort will be considered complete if a minimum of [redacted] patients are evaluable for safety at the end of the DLT observation period. Dosing of the first and second additional patients at any dose level will be staggered by a minimum of 24 hours.

The safety of the dose level and the determination of the next dose level will be decided by the SRC during dose escalation meeting based on the review of all available patient data and following the BLRM recommendation(s). All dose escalation will be conducted in semi-logarithmic increments at most. Smaller dose increments may be utilized and at any time the dose increment can be reduced.

Backfilled cohorts

To further understand the safety and PK/pharmacodynamics of PRS-344/S095012, backfilled cohort(s) will be allowed, where additional patients may be enrolled in prior dose levels if:

- An acceptable safety profile (DLT observation period) has been observed in the cohort, which is being backfilled.
- Patients consent to have mandatory fresh paired biopsies collected at baseline (unless an archived tumor biopsy (< 6 months old) without intercurrent treatment is available) and on treatment.

All patients enrolled in the backfilled cohorts will follow the same safety assessments as the patients enrolled in the main dose escalation, including monitoring and reporting of the DLTs. These data will be taken into account in the BLRM to adjust recommendations for the next dose levels and for RP2D determination.

Intra-patient dose escalation

Based on the clinical judgment of the investigator, and with approval of the Sponsor's medical representative, intra-patient dose escalation may be permitted for patients who experience disease stabilization, unconfirmed progressive disease (PD) or confirmed PR or CR. The proposed new dose level must have been determined to be tolerable and safe after the DLT observation period. Intra-patient dose escalation should not occur before the 2nd RECIST assessment.

Dose-limiting Toxicity (DLT)

All AEs (related and unrelated to treatment) will be continuously monitored and graded based on the CTCAE v5.0; except for CRS that will be graded according to American Society for Transplantation and Cellular Therapy (ASTCT) CRS consensus Grading.

A DLT is defined as an AE, occurring during the DLT observation period of phase 1, assessed as unrelated to disease progression, intercurrent illness, concomitant medications or other etiology, considered as related to the IMP by the investigator and satisfying at least one criterion below.

The DLT observation period will be a 28-day period in the CCI schedule and a 21-day period in the Q3W schedule.

DLTs include the following:

- Grade ≥ 3 neutropenia lasting ≥ 5 days.
- Any febrile neutropenia (*i.e.*, ANC < 1000/mm3 with single temp of > 38.3 degrees C [101 degrees F] or a sustained temperature of ≥ 38 degrees C [100.4 degrees F] for more than one hour).
- Grade ≥ 3 thrombocytopenia with clinically significant hemorrhage.
- Grade ≥ 3 cytokine release syndrome.
- Grade ≥ 3 non-hematologic AEs, except the following:
  - Grade ≥ 3 nausea, vomiting, or diarrhea lasting < 72 hours despite maximal medical therapy.
  - Grade 3 asymptomatic, electrolyte abnormalities lasting less than 72 hours that are not clinically complicated, and/or resolve spontaneously or with conventional medical interventions.

- Grade 3 creatine phosphokinase (CPK), creatinine, gamma-glutamyl transferase (GGT).
- Grade 3 amylase, lipase without clinical significance and lasting < 7 days.
- Grade 3 hyperglycemia if clinically stable.
- Grade ≥ 3 fatigue lasting < 5 days.
- Grade 3 AST or ALT elevations lasting < 7 days that are not clinically complicated
- Grade 3 non-hepatic-related increases in alkaline phosphatase.

- AST or ALT > 3 x ULN (or > 3 x baseline in subjects with baseline elevation) AND total bilirubin > 2 x ULN (or > 2 x baseline in subjects with baseline elevation) or clinical jaundice, without initial findings of cholestasis AND no other immediately apparent identifiable possible causes of elevated liver enzymes and hyperbilirubinemia.
- Treatment delays > 2 weeks from the scheduled next dose due to any AE related to the IMP.

Maximum tolerated dose

The MTD is the highest drug dosage that is unlikely (< 25% posterior probability) to cause any DLT in more than 33% of the treated patients in the first cycle of PRS-344/S095012. A minimum of six patients evaluable for safety must be included in a dose level for it to be declared as the MTD.

Escalation can stop prior to MTD determination if deemed appropriate based on PK, safety and PK/Pharmacodynamic profiles.

Recommended phase 2 dose

The RP2D will not be higher than the MTD, if determined, or higher than the MAD in phase 1 and will be based on PK and PK/ pharmacodynamic considerations as well as the cumulative safety profile as reviewed during investigator/Sponsor cohort reviews with the Sponsor having the final decision.

Phase 2 – Dose expansion

Phase 2 will evaluate the potential efficacy of PRS-344/S095012 in 3 disease-specific arms as described in the Methodology section.

Dose expansion arms may be initiated at the end of dose escalation once the RP2D has been determined based on safety, PK and available pharmacodynamics. Alternatively, depending on safety, PK, pharmacodynamics and efficacy available data, one or more dose expansion arm(s) may be initiated before the end of dose escalation. In this case, dose escalation can still proceed up to the MTD or MAD if not reached at that time. During any interim analysis, the dose of PRS-344/S095012 could be escalated to a higher dose, not exceeding the MTD, in a new arm of patients if determined as safe and after recommendation of the DMC. Selected dose(s) of PRS-344/S095012 administered in the dose expansion arm(s) will be recommended by the SRC during an end of cohort meeting. This recommendation will be discussed by the DMC before starting the expansion part. All those discussions/recommendations will be reported in meeting minutes. Doses tested in the phase 2 part of the study will not exceed the MTD determined during the phase 1 part of the study or the highest safe dose evaluated during the phase 1 part of the study.

A CBHM with one or more futility analyses will be adopted for the expansion part. According to the futility analysis result, recruitment could be:

- Stopped, if results are considered futile.
- Continued, if results are considered not futile. In that case, additional participants will be enrolled in the next stage and treated at the corresponding dose until the next interim analysis or predefined end of study.

At the end of the study, anti-tumor activity results on the overall participants included in all stages will be analysed.

In addition to efficacy assessments, the safety profile of PRS-344/S095012 will be reviewed regularly during the study with appropriate stopping rules and processes for safety review (see details in Section 6.6). The sponsor may stop any arm at any time for any reason. As new data emerge on the CL1-95012-001 study and from other ongoing studies of antibody(ies) with a similar mechanism of action, new tumor type(s) and treatments (*i.e.*, monotherapy or combination with immuno-oncology (IO) treatment, chemotherapy or targeted therapy) may be added to this study, through protocol amendment.

Duration of treatment

The study includes a CCI [redacted], which corresponds to the DLT observation period in phase 1. However, after Cycle 1, in case of acceptable safety/tolerability profiles, patients may receive additional cycles of PRS-344/S095012 until one of the following criteria applies:

- Confirmed radiographic/photographic disease progression. Patients should continue until a subsequent (at least 4 weeks) radiographic/photographic confirmation of progression. Patients may continue beyond confirmed PD if benefits are expected to outweigh risks in the opinion of the investigator and in consultation with the Sponsor.
- Unacceptable adverse events according to investigator's judgment (including intervening illness that prevents further administration of treatment).
- Significant patient noncompliance with the protocol.
- Patient decision to withdraw from the treatment or study.
- Pregnancy.
- Investigator decision to withdraw the patient from the treatment or study.
- Patient is lost to follow-up.
- Death.
- Sponsor decision to end the study early.
- [redacted] year from CR and [redacted] years for patients with PR (although treatment may continue if benefits are expected to outweigh risks in consultation with Sponsor)
- Any other protocol deviation that results in a significant risk to the patient's safety.

Regardless of the supposed role of the research (IMP, or experimental procedure), all AEs/SAEs will be reported at any time after the first IMP administration and up to 30 calendar days after the patient's last IMP administration.
All IMP-related AE (implying immune-mediated AEs) and all deaths (regardless of the supposed role of the research (IMP, or experimental procedure)) will be reported up to 90 calendar days after the patient's last IMP administration.
All SAEs related to the research will be reported without time limit. SAE reporting may occur after the end of the study.

End of Study

The end of the study is defined as the last patient's last visit, which includes the long-term safety follow-up visit, 90 days after the last IMP administration or the date of the last contact attempt if the last participant is declared lost to follow-up.

Criteria for Evaluation

Safety measurements

Patients will be monitored for safety throughout the study. Timepoints are described in the schedules of assessments.
The safety and tolerability of PRS-344/S095012 will be evaluated by the:

- Incidence of DLTs.
- AEs and SAEs.
- Vitals signs (blood pressure, heart rate, respiratory rate and body temperature).
- Weight and height.
- Physical examination.
- ECOG.
- 12-lead ECG.
- Hematology, coagulation laboratory studies.
- Biochemistry (including liver function tests).

Laboratory tests abnormalities and AEs will be graded as per CTCAE v5.0.

Pharmacokinetic measurements

Blood PK samples will be collected to characterize the PK of PRS-344/S095012 before and after dosing of the product. Full descriptions of timepoints are provided in the schedules of assessments.

For dose escalation, PK parameters such as C_{inf}, T_{inf}, t_{last}, C_{last}, AUC_{last}, AUC, λz, and $t_{1/2}$ will be determined using non-compartmental pharmacokinetic analysis (NCA).

For dose escalation and dose expansion, concentration-time data of PRS-344/S095012 for each dose group will be summarized using descriptive statistics (*i.e.*, number of subjects, mean, standard deviation, geometric mean and coefficient of variation, median, minimum and maximum).

Immunogenicity measurements

Serum samples will be collected to assess the immunogenicity of PRS-344/S095012.

Antitumor activity measurements

The antitumor activity of the treatment will be assessed by RECIST version 1.1 or WHO criteria for CCI [redacted] tumors (only arm 3 phase 2) every [redacted] weeks initially. After CCI [redacted] weeks of treatment, antitumor activity will be assessed every CCI [redacted] weeks until discontinuation of treatment. Imaging/photography should be done at the time the decision is made to stop the treatment (+/- 14 days). After discontinuation of treatment for any reasons other than PD, it is recommended to assess the tumor by imaging/photography every 12 weeks (+/- 14 days) until PD, initiation of another treatment for the patient's cancer, loss to follow-up, end of study, withdrawal of consent, or death (whichever comes first).

In case PRS-344/S095012 is administered Q3W on a 21-day cycle, tumor assessments will be performed every 6 weeks for 50 weeks and then every 12 weeks and at the time decision is made to stop the treatment (+/-14 days). After discontinuation of treatment, it is recommended to assess the tumor by imaging every 12 weeks (+/- 14 days).

Tumor responses will be assessed locally by the investigator. In phase 2, tumor responses will be assessed centrally and locally.

Disease assessment will be performed by computed tomography (CT) or magnetic resonance imaging (MRI) scans with contrast, or other objective measures consistent with RECIST 1.1. The same methods used at baseline that identify sites of disease should be used uniformly for all subsequent assessments.

For patients with visible tumors (arm 3), assessments will also be performed through medical digital photography and evaluation will be performed using clinical response criteria and composite response criteria for externally visible tumors.

Objective responses (CR, PR, stable disease [SD], or PD) will be determined as per RECIST 1.1 or WHO criteria for externally visible skin tumors.

Survival follow-up may be done remotely by using various wired and wireless telecommunication technologies, including but not limited to phone, internet and shared electronic medical records, and will continue until death, withdrawal of consent, or closure of study.

For patients who progressed, treatment may continue beyond progression. A confirmation scan will be conducted at least four weeks after the initial scan indicating progression to confirm progression.

Antitumor activity of PRS-344/S095012 will be measured by OR, DC, DoR, PFS, OS, TTR.

Pharmacodynamic and biomarker measurement

Tumor biopsies

In the *dose escalation (parts A and B)*, for patients enrolled to a new dose level: archival tissue taken < 9 months before the start of treatment can be used. If a patient consents to an on-treatment biopsy (which is optional but highly encouraged), pre-treatment tumor tissue should be available ideally from a fresh biopsy taken before the start of treatment or, if available, from archival tissue taken < 6 months before S095012 administration without any intercurrent treatment.

For patients enrolled to a previously evaluated dose level (back-fill patients): an on-treatment tumor tissue biopsy is required. A pre-treatment fresh tumor biopsy is also required unless archival tumor tissue was obtained < 6 months before the start of treatment and there was no intervening cancer treatment given during this time.

In *phase 2, in arms 1 and 2*, a fresh biopsy will be collected at baseline, unless an archived tumor biopsy (< 6 months old) without intercurrent treatment is available. On-treatment biopsies are optional and will be done between D22 and D28 of Cycle 1 when the patient consents.

In *phase 2, in arm 3*, a fresh biopsy will be collected at baseline, unless an archived tumor biopsy (< 6 months old) without intercurrent treatment is available. Fresh on-treatment biopsy is mandatory and will be collected between D22 and D28 of cycle 1, unless medically contra-indicated. For patients deemed eligible by CCI , an additional biopsy is required within 30 days of CR determined by the investigator for confirmation of the CR.

These tumor biopsies will be used to investigate pharmacodynamic changes or mechanisms of response to treatment and potential predictive markers.

- Immunohistochemistry (IHC) to assess immune cell landscape, target expression, phenotype and activation status of immune cell subsets.
- And/or ribonucleic acid (RNA) profiling as potential predictive biomarkers of response or pharmacodynamic markers on tumors.
- And/or DNA whole exome sequencing to evaluate potential predictive biomarkers of response.

Blood samples
Sequential blood samples will be collected in all patients according to the schedules of assessments and the following analyses may be performed, depending on results obtained during the course of the trial:

- Immunophenotyping by flow cytometry: Lymphocyte subtypes and activation status (only for phase 1 and arm 3 of phase 2) will be measured as well as drug-target binding on lymphocytes (only for phase 1).
- And/or measurement of soluble 4-1BB and cytokines in plasma.
- And/or DNA/RNA extraction and sequencing.

Statistical Methods

Safety analysis
Analysis set:

All patients who have received at least one administration of PRS-344/S095012 will be included in the safety analysis (safety population). In phase 1, a patient will be included in the DLT evaluable population if he/she receives at least 80% of the required PRS-344/S095012 dose and completes the DLT observation period or experiences a DLT.

Statistical analysis:
As this is a descriptive safety, tolerability, and PK study, no statistical analysis will be performed to determine the sample size for dose escalation. The statistical analysis for safety will be descriptive. However, for dose escalation, a BLRM will be implemented to support the dose escalation, selection of tested dose levels of PRS-344/S095012 and calculation of the MTD. All details will be described in the Statistical Analysis Plan.

Efficacy analysis
For phase 1 dose escalation, the statistical analysis of preliminary antitumor activity will be descriptive. All patients who have received at least one administration of PRS-344/S095012 will be included in the efficacy analysis.

In phase 2, all patients who have received at least one administration of PRS-344/S095012, have measurable disease at baseline, and meet any of the following conditions: 1) at least one post-baseline disease assessment; 2) documented clinical progression; 3) death will be included in the efficacy analysis (response evaluable population).
In dose expansion arms, a CBHM (Jiang *et al*, 2021) will be adopted with the potential to borrow information among arms that belong to the same cluster (responsive or non-responsive) given observed data. The futility threshold of a CCI Objective Response Rate (ORR) was derived from historical data obtained from patients treated in the same line of therapy. Approximately CCI patients will be enrolled in each arm. One interim analysis is planned in each arm after there are CCI response-evaluable patients. An additional interim analysis may be performed in each arm dependent upon recruitment status and trial progress. At the time of a planned analysis, the corresponding arm will be stopped if the following futility criterion is met, where q_1, q_2 and q_3 represent the true (unknown) ORR of arms 1 to 3, respectively.

Analysis	Criteria
Interim analysis (N=CCI)	Pr ($q_1 \leq$ CCI | *Data*) > 0.398
Final analysis (N=CCI)	Pr ($q_1 \leq$ CCI | *Data*) > 0.22

All details of the methodology employed for results analysis will be described in the Statistical Analysis Plan.

Pharmacokinetic analysis

All patients who have samples collected to provide interpretable PK results, and who have no deviations that might affect the PK interpretation will be included in the PK analysis.

Pharmacokinetic parameters will be estimated using non-compartmental analysis methods and described in a separate data analysis plan (DAP). Descriptive statistics (*i.e.*, number of subjects, mean, standard deviation, geometric mean and coefficient of variation, median, minimum, and maximum) will be used to summarize PK parameters in each part.

Further PK analyses may be conducted using a population PK approach. PK/Pharmacodynamics analyses may be used to explore the potential relationship between efficacy, safety, and/or biomarker endpoints and PRS-344/S095012 exposure. Any modelling analysis based on final data will be described in a separate pharmacometric analysis plan and reported in a standalone report.

Specific COVID-19 information

In case of highly suspected COVID-19 infection (based on typical symptoms or typical chest CT scan images) or confirmed COVID-19 infection (based on positive COVID-19 biological testing), the study treatment(s) should be immediately interrupted. The study treatment(s) could be restarted if patient is asymptomatic and a period of at least 7 days after the diagnosis has been respected, and with a negative test (if the testing is required by the institutional site).

Data Monitoring Committee

The DMC is composed of independent experts and will meet regularly at the start, during and at the end of the phase 2 part of the study. Further details on DMC composition, meetings and decision-making process are provided in the DMC charter.

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3. LIST OF ABBREVIATIONS ACRONYMS AND DEFINITIONS OF TERMS

The following abbreviations are used in this study protocol.

Abbreviations, Acronyms and Definitions of Terms

Abbreviation or Specialist Term	Explanation
ACTH	Adreno corticotropic hormone
ADA	Antidrug antibody
ADCC	Antibody-dependent cell-mediated cytotoxicity
AE	Adverse event
ALT	Alanine aminotransferase
ALP	Alkaline phosphatase
ANC	Absolute neutrophil count
aPTT	Activated partial thromboplastin time
ART	Antiretroviral therapy
ASCO	American Society of Clinical Oncology
AST	Aspartate aminotransferase
ASTCT	American Society for Transplantation and Cellular Therapy
AUC	Area under the curve
AUC_{last}	Area under the curve from time zero to the last measurable concentration sampling point (t_{last})
BHM	Bayesian hierarchical model
BOR	Best overall response
BPM	Beats per minute
BLRM	Bayesian logistic regression model
BRPM	Breaths per minute
bTMB	blood Tumor mutational burden
BUN	Blood urea nitrogen
°C	Degrees centigrade/celsius
C	Cycle
CA	Competent authority
CBC	Complete blood count
CBHM	Clustered Bayesian Hierarchical Model
CEA	Carcinoembryonic Antigen
CFR	Code of Federal Regulations
CK	Creatine kinase

Abbreviation or Specialist Term	Explanation
CI	Confidence interval
CL	Clearance
C_{last}	Last observed plasma concentration
CLL	Chronic Lymphocytic Leukemia
C_{inf}	Observed concentration at the end of the infusion
CMV	Cytomegalovirus
CNS	Central nervous system
CPI	Checkpoint inhibitors
CPK	Creatine phosphokinase
CPS	Combined positivity score
CR	Complete response
CrCl	Creatinine clearance
CRF	Case Report Form
CRO	Contract research organization
CRS	Cytokine-release syndrome
CSCC	Cutaneous squamous cell carcinoma
CSF	Colony-stimulating factor
CT	Computed tomography (scan)
CTCAE v5.0	Common Terminology Criteria for Adverse Events Version 5.0
CTLA-4	Cytotoxic T lymphocyte-associated protein 4
D1, etc.	Day 1, et cetera
DAP	Data analysis plan
DC	Disease Control
DILI	Drug-induced liver injury
dL	Deciliter
DLBCL	Diffuse large B-cell lymphoma
DLT	Dose-limiting toxicity
DMARDs	Disease-modifying anti-rheumatic drugs
DMC	Data monitoring committee
DNA	Deoxyribonucleic acid
DoR	Duration of response
EBV	Epstein-Barr virus
EC	Ethics Committee
EBV-VCA	Epstein-Barr virus - Viral Capsid Antigen

Abbreviation or Specialist Term	Explanation
ECG	Electrocardiogram
e-CRF	Electronic case report form
ECOG	Eastern Cooperative Oncology Group
e.g.	For example
FAP	Fibroblast activation protein-α
FDA	Food and Drug Administration
FL	Follicular Lymphoma
G1	Grade 1
G2	Grade 2
G3	Grade 3
G4	Grade 4
FHL	Familial hemophagocytic lymphohistiocytosis
FIH	First-in-human
FT3	Free triiodothyronine
FT4	Free thyroxine
FU	Follow-up
GCP	Good clinical practice
GFR	Glomerular filtration rate
GGT	Gamma-glutamyl transferase
h	Hour
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HED	Human equivalent dose
HepBsAg	Hepatitis B surface antigen
HIV	Human immunodeficiency virus
HLH	Hemophagocytic lymphohistiocytosis
HPV	Human papilloma virus
IB	Investigator's brochure
ICF	Informed Consent Form
ICH	International Council for Harmonization
i.e.	Id est
IEC	Independent Ethics Committee
IFNγ	Interferon gamma
Ig	Immunoglobulin
IHC	Immunohistochemistry

Abbreviation or Specialist Term	Explanation
IMP	Investigational medicinal product
IL	Interleukin
INR	International normalized ratio
I.R.I.S.	Institut de recherches internationales Servier
irAEs	Immune-related adverse event
IRB	Institutional review board
IRR	Infusion-related reaction
IV	Intravenous
kg	Kilogram
LDH	Lactate dehydrogenase
LFT	Liver Function Test
mM	Millimolar
mAb	Monoclonal antibody
MAD	Maximum administered dose
min	Minute
mg	Milligram
mL	Milliliter
MLR	Mixed lymphocyte reaction
mm	Millimeter
MRI	Magnetic resonance imaging
MSI	Microsatellite instability
MTD	Maximum tolerated dose
N	Number
NGAL	Neutrophil gelatinase-associated lipocalin
NK	Natural killer
NHL	Non-Hodgkin’s lymphoma
nM	Nanomolar
NSAID	Non-steroidal anti-inflammatory drug
NYHA	New York Heart Association
OR	Objective response
ORR	Objective response rate
OS	Overall survival
PBMC	Peripheral Blood Mononuclear Cells
PD	Progressive disease
PD-1	Programmed death-1 (receptor)

Abbreviation or Specialist Term	Explanation
PD-L1(+)	Programmed death-ligand 1 (positive)
PET	Positron emission tomography
PFS	Progression-free survival
PK	Pharmacokinetics
PR	Partial response
PS	Performance status
PS80	Polysorbate 80
PT	Prothrombin time
QW	Every week
Q2W	Every two weeks
Q3W	Every three weeks
Q4W	Every four weeks
QTc	Baseline-corrected QT value
QTcF	QT using Fridericia correction
RBC	Red blood cell
RECIST	Response Evaluation Criteria in Solid Tumors
RMP	Royal Marsden Prognosis
RNA	Ribonucleic acid
RP2D	Recommended phase 2 dose
RTSM	Randomisation and Trial Supply Management
S4-1BB	Soluble 4-1BB
SA	Single agent
SAE	Serious adverse event
SAP	Statistical Analysis Plan
scFv	Single-chain antibody fragment
SD	Stable disease
SITC	Society for immunotherapy of cancer
SRC	Safety review committee
SUSAR	Suspected unexpected serious adverse reaction
$t_{1/2}$	Elimination half-life
T_{inf}	Time corresponding to the C_{inf}
TCR	T-cell receptor
TMB	Tumor mutational burden
TNF-α	Tumor necrosis factor alpha
TRAE	Treatment related adverse event

Abbreviation or Specialist Term	Explanation
TSH	Thyroid-stimulating hormone
TTR	Time to response
ULN	Upper limit of normal
US	United States
USA	United States of America
WBC	White blood cell
WHO	World Health Organization
XLP	X-linked lymphoproliferative syndrome
Y	Year

4. INTRODUCTION

PRS-344/S095012 is a monoclonal antibody (mAb)-like bispecific protein targeting the programmed death-ligand 1 (PD-L1) and the immune receptor 4-1BB. PRS-344/S095012 is constituted by the genetic fusion of a backbone-engineered anti-PD-L1 antibody and an agonistic 4-1BB-targeting moiety. Antitumor activity of S095012/PRS-344 combines both the checkpoint inhibition via the PD-1/PD-L1 axis and the activation of the 4-1BB mediated anticancer effect to provide a potent costimulatory signal to tumor antigen-specific T cells.

All details are provided in the Investigator's Brochure.

4.1. Rationale for Bispecific Targeting of PD-L1 and 4-1BB

PD-L1

Programmed death-ligand 1 (PD-L1), also known as CD274 or B7 Homolog 1, is a membrane-bound protein primarily expressed on hematopoietic cells such as monocytes, dendritic cells, and activated T cells (Keir *et al.*, 2008). In addition, PD-L1 is highly expressed on a wide range of different tumor types as an immune evasion mechanism (Taube *et al.*; 2012; Parsa *et al*, 2007) and it is often described to be an indicator of tumor aggressiveness and predictor of worse clinical outcome (Thompson *et al.*, 2004; Inman *et al;*, 2007; Ghebeh *et al.*, 2007; Hino *et al.*, 2010; Chen *et al.*, 2013; Hamanishi *et al.*, 2007). PD-L1 interacts with its receptor Programmed Death-1 (PD-1), which is mainly expressed on activated T cells and natural killer (NK) cells (Agata *et al.*, 1996; Vibhakar *et al.*, 1997). PD-1/PD-L1 interaction has an inhibitory role on T cells, by limiting the T-cell receptor (TCR) downstream signaling pathway (Yokosuka *et al.*, 2012; Hui *et al.*, 2017; Patsoukis *et al.*, 2012) that leads to a decreased T cell activation, proliferation, survival, and cytokine production.

The PD-1/PD-L1 pathway has a strong clinical validation for the treatment of human tumors. Currently, six PD-1/PD-L1 targeting antibodies have been approved for the treatment of solid tumors and hematological malignancies: three PD-1 targeting antibodies (pembrolizumab, nivolumab, and cemiplimab) and three PD-L1 targeting antibodies (avelumab, atezolizumab, and durvalumab). These antibodies have clearly demonstrated clinical benefit in various tumor types, but only in a fraction of patients.

4-1BB

4-1BB is mainly expressed on activated $CD8^+$ and $CD4^+$ T cells, activated B cells, and NK cells (Li and Liu, 2013). 4-1BB plays an important role in the regulation of immune responses. 4-1BB ligand (4-1BBL) is the only known natural ligand of 4-1BB and is constitutively expressed on several types of antigen-presenting cells. 4-1BB-positive T cells are activated by engaging a $4\text{-}1BBL^+$ cell. The 4-1BB clustering leads to activation of the receptor and downstream signaling (Snell *et al.*, 2011; Yao *et al.*, 2013). In a T cell, pre-stimulated by the T cell receptor binding to a cognate major histocompatibility complex (MHC) target, co-stimulation via 4-1BB leads to further enhanced activation, survival, and proliferation as well as the production of pro-inflammatory cytokines and an improved capacity to kill.

The benefit of 4-1BB co-stimulation for the elimination of tumors has been clearly demonstrated in *in vivo* mouse models. Forced expression of 4-1BBL on a tumor leads to tumor rejection (Melero *et al.*, 1998). Likewise, the forced expression of an anti-4-1BB single-chain antibody fragment (scFv) leads to a $CD4^+$ T-cell and NK cell-dependent elimination of the tumor (Ye *et al.*, 2002; Zhang *et al.*, 2006; Yang *et al.*, 2007). A systemically administered anti-4-1BB antibody has also been demonstrated to delay tumor growth (Martinet *et al.*, 2002).

Finally, the potential of 4-1BB targeting has also been shown in nonclinical combination therapy studies where additional anti-tumor benefit was demonstrated by the combination of 4-1BB agonism with a checkpoint blockade (Wei *et al.*, 2013; Curran *et al.*, 2011; Guo *et al.*, 2013) or NK cell-targeting antibodies (Kohrt *et al.*, 2011; Stagg *et al.*, 2011).

4-1BB requires receptor clustering for activation, and an optimal 4-1BB-targeting agent in the treatment of cancer should induce clustering of 4-1BB, in a tumor localized fashion on tumor-infiltrating lymphocytes. 4-1BB agonist antibodies currently in clinical development present some limitations, as 4-1BB clustering is promoted by Fcγ receptor-positive cells, which are not selectively tumor-localized but distributed throughout the body (Bulliard *et al.*, 2013; Bulliard *et al.*, 2014). The toxicity data of urelumab, a 4-1BB monoclonal antibody indicate that such a non-selective activation may lead to unacceptable toxicity.

Based on these data, the combination of PD-1/PD-L1 blockade and activation of the 4-1BB immunostimulant pathway therefore appears to be a very promising pathway to improve clinical responses.

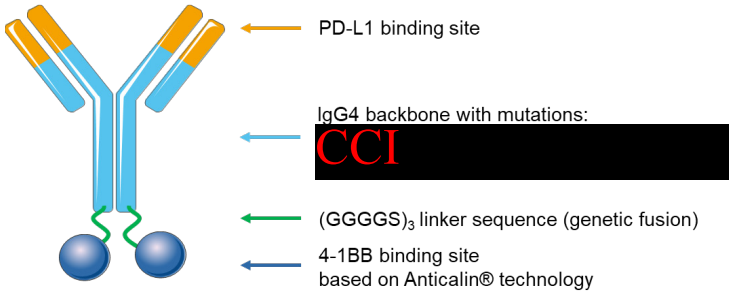
Hypothesis of mechanism of antitumoral activity of PRS-344/S095012
PRS-344/S095012 that targets PD-L1 receptor on one arm and 4-1BB receptor on the other arm, allows bringing 4-1BB positive activated cytolytic T cells near PD-L1 positive tumor cells, maximizing the killing of the target tumor cells. It combines PD-1/PD-L1 axis inhibition and PD-L1-dependent 4-1BB activation to enhance T cell effector functions. This dual mechanism of action allows to (1) stimulate only T cells activated by T cell receptor stimulation, not bystander non-activated T cells; (2) induce 4-1BB co-stimulation of human primary T cells which is dependent on the presence of PD-L1 on target cells; (3) blocks the PD-1/PD-L1 pathway; (4) enhance T cell activation.

4.2. PRS-344/S095012 background information

4.2.1. Structure

PRS-344/S095012 is an antibody-like bispecific molecule consisting of a genetic fusion of a backbone-engineered anti-PD-L1 antibody and an agonistic 4-1BB-targeting moiety (Figure (4.2.1) 1). This moiety consists of a so-called Anticalin® protein, a 22 kDa single domain protein based on the extracellular human protein "Neutrophil-gelatinase associated lipocalin" (NGAL) that has been engineered to bind 4-1BB with high affinity and selectivity. The antibody moiety contains an CCI backbone with CCI mutations to further reduce FcγR interactions and the CCI PRS-344/S095012 is recombinantly expressed in a derivative of the Chinese hamster ovary cell line CCI

Figure (4.2.1) 1 - PRS-344/S095012 drug substance



Of note, each moiety of the molecule (anti-PD-L1 antibody and 4-1BB-targeting Anticalin protein as part of another bispecific molecule) is currently independently studied in phase 1 clinical studies in the United States of America (USA).

4.2.2. Pharmacology

Biological activity of PRS-344/S095012 was demonstrated in a series of *in vitro* experiments based on cells of human origin and *in vivo* using mice models. PRS-344/S095012 binds simultaneously both human PD-L1 with picomolar affinity and human 4-1BB with single digit nanomolar affinity. No binding to Fcγ receptors was observed, as expected based on the engineered IgG4 backbone, resulting in an absence of detectable antibody-dependent cell-mediated cytotoxicity (ADCC) activity in the presence of PD-L1 positive cells.

In vitro, PRS-344/S095012 can enhance stimulation of activated T cells in a series of *in vitro* experimental models based on human cells (CD8-based mixed lymphocyte reaction (MLR), SEB assays and coculture assays with tumor cells). Key findings support that PRS-344/S095012:

- Stimulates only pre-activated T cells, not bystander non-activated T cells; consistent with PD-1, PD-L1 and 4-1BB upregulation only occurring in activated T cells.
- Induces 4-1BB co-stimulation of human T cells, dependent on the presence of PD-L1 on target cells.
- Blocks the PD-1/PD-L1 pathway.
- Enhances T cell co-stimulation in a dose dependent manner.

Three relevant *in vitro* assays demonstrated that PRS-344/S095012 has a trend towards a 2-fold higher potency compared to the PD-L1/4-1BB bispecific antibody GEN1046.

In vivo, PRS-344/S095012 was investigated on a humanized mouse model that expresses human 4-1BB engrafted with MC38 tumor cells line expressing huPD-L1. In this model, PRS-344/S095012 doses above 1 mg/kg resulted in statistically significant tumor growth inhibition compared to anti-PD-L1 antibody alone.

All details are provided in the Investigator's Brochure (IB).

4.2.3. Toxicology

The non-clinical safety assessment for PRS-344/S095012 did not identify any toxicities predictive of potential human safety concerns up to a dose level CCI in cynomolgus monkey. The cynomolgus monkey was selected as the most relevant species to assess potential toxicity of CCI and off-target toxicities of PRS-344/S095012 *in vivo*, despite an absence of cross-reactivity CCI . Animals received 5 weekly intravenous (IV) administrations of CCI . The study included cardiovascular and respiratory safety pharmacology endpoints. The death of one female CCI group 4 hours following the fifth administration was attributed to an immune complex-mediated type III hypersensitivity reaction. In general, immunogenicity in monkey is not predictive of the antidrug antibodies (ADA) incidence or severity of immune complex disease in humans (Mease *et al.*, 2017; Kronenberg *et al.*, 2017; Leach *et al.*, 2014; Vahle *et al.*, 2018).

Potential cross-reactivity of PRS-344/S095012 tested in a selected panel of human tissues showed as expected specific positive, predominantly membranous, staining of mononuclear cells and epithelial cells in lymphoid tissues. Staining in a few non-lymphoid epithelia was observed (trophoblasts in the placenta, Hassall's corpuscles and reticular epithelium in the thymus, and crypt epithelium in the tonsil). Overall, this pattern was considered consistent with the reported expression of PD-L1 and 4-1BB (Brown *et al.*, 2003; Freeman *et al.*, 2000; Lyford-Pike *et al.*, 2013; Padda *et al.*, 2015; Petroff *et al.*, 2003; Thibult *et al.*, 2013; Veras *et al.*, 2017; Lindstedt *et al.*, 2003; Mittler *et al.*, 2004; Pauly *et al.*, 2002; Schwarz *et al.*, 1995; Zhang *et al.*, 2004). *In vitro* cytokine release assays were performed on human peripheral blood mononuclear cells (PBMC). PRS-344/S095012 induced a very limited increase in cytokines CCI . A minimal increase of more than one cytokine was observed for CCI CCI (for interferon gamma (IFN-γ), Interleukin (IL)-2, IL-6 and tumor necrosis factor alpha (TNF-α)) and for CCI (for IFN-γ, IL-1β, IL-2, IL-4, IL-6, IL-10 and TNF-α).

For more details, refer to the Investigator's Brochure.

4.2.4. Pharmacokinetics

The pharmacokinetics (PK) of PRS-344/S095012 has been evaluated in cynomolgus monkeys across a range of dose levels from CCI . PK was dose-proportional between CCI . The pharmacokinetic parameters in cynomolgus monkeys were consistent with monoclonal antibodies with a low elimination clearance CCI and a small total volume of distribution CCI . The terminal half-life in was CCI (Gauderat, 2020). The non-compartmental analysis of PRS-344/S095012 and CCI (parent antibody) concentration-time profiles showed that the 4-1BB-binding Anticalin moiety only moderately influences the half-life and clearance of the molecule (Andersen, 2019). The half-life of PRS-344/S09512 in humans is anticipated to be CCI .

In these studies, ADA were detected in all animals treated with PRS-344/S095012, having an influence on overall exposure, especially at low doses. Immunogenicity of PRS-344 will be closely monitored in the clinical study.

4.2.4.1. Monospecific, PD-L1-Targeting Monoclonal Antibodies

Three therapeutic antibodies targeting PD-L1 (atezolizumab, avelumab and durvalumab) are currently registered as standard of care for selected indications (*e.g.* non-small cell lung cancer, small-cell lung cancer, Merkel cell carcinoma, triple-negative breast cancer, renal cell carcinoma and urothelial bladder cancer). They are further investigated in monotherapy or in combination in other indications. Collected from the prescribing information leaflet, the most common adverse reactions in patients receiving anti-PD-L1 therapy monotherapy are immune-related adverse events (irAEs) such as pneumonitis, hepatitis, diarrhea/colitis, endocrinopathies (refer to IB for further details). None of them reached a maximum tolerated dose (MTD) during the dose escalation phase.

4.2.4.2. Monospecific 4-1BB-Targeting Monoclonal Antibodies

Two therapeutic antibodies targeting 4-1BB have been tested in early clinical development phases, utomilumab (PF-05082566) and urelumab (BMS-663513) (Ahrens *et al.*, 2014; Fisher *et al.*, 2012; Jure-Kunkel *et al.*, 2007).

Urelumab
Urelumab is an IgG4 monoclonal antibody that binds 4-1BB and does not interfere with the 4-1BB/4-1BBL interaction. It was investigated in monotherapy in an open-label, ascending, multi-dose (0.3, 1, 3, 6, 10, or 15 mg/kg) phase 1/2 study (NCT00309023) conducted in patients with locally advanced or metastatic solid tumors (Sznol et al., 2008). In the dose escalation phase, the *repor*ted toxicity was manageable, with fatigue, transaminitis, neutropenia, rash, and diarrhea being the most common AEs (Sznol *et al.*, 2008). In 106 of 115 patients enrolled, the most frequent Grade 2 laboratory abnormalities were increases in alanine aminotransferase (ALT) (15%) and aspartate aminotransferase (AST) (12%), leukopenia (8%), neutropenia (6%), thrombocytopenia (4%), and hyperbilirubinemia (1%) (Sznol et al., 2008). The follow-up monotherapy phase 2 study (NCT00612664; 1 to 5 mg/kg every three weeks (Q3W)) was stopped due to the high incidence of Grade 4 hepatitis (Ascierto *et al.*, 2010). Clinical activity represented by partial responses (PRs) and sustained stable diseases (SDs) was observed in the expansion cohort (objective response rate [ORR] 7/54). The MTD of urelumab has been established at 0.1 mg/kg.

Utomilumab
Utomilumab is a fully humanized IgG2 monoclonal antibody that binds 4-1BB in a manner that blocks the binding of endogenous 4-1BBL to 4-1BB. It was investigated in monotherapy in a dose escalation (0.006 to 0.3 mg/kg) phase 1 study (NCT01307267) (Segal *et al.*, 2014). In this study, utomilumab was well tolerated and showed SD with a best overall response in 22% of the patients suffering from various types of cancer. In a further study, utomilumab was tested at doses ranging from 0.03 to 10 mg/kg and in combination with 375 mg/m^2 rituximab in patients with relapsed or refractory CD20-positive NHL (Gopal *et al.*, 2015). No dose-limiting or severe immune-related toxicities were observed. For the patients treated at doses up to 2.4 mg/kg, the ORR was 21% (8/38), and 37% in rituximab-refractory patients.

4.2.4.3. Combination of 4-1BB and PD-(L)1 Targeting Molecules

Clinical development of urelumab (BMS-663513) was pursued in combination with nivolumab in phase 1/2 clinical studies, focusing on safety and efficacy at lower doses (3 mg and 8 mg every four weeks [Q4W]). In this setting, no significant additive toxicity was observed, with 17% Grades 3 to 4 IMP-related AEs. In metastatic melanoma patients, ORR was 50% in patients with PD-L1 ≥ 1% and 47% in patients with PD-L1 ≤ 1%.

4.2.4.4. Bispecific Molecules targeting 4-1BB and tumor antigen or PD-L1

Duobody-PD-L1×4-1BB (GEN1046)
GEN1046 is an Fc-silenced, bispecific next-generation checkpoint immunotherapy that potentiates activated T cells through PD-L1 blockade and simultaneous PD-L1-dependent 4-1BB co-stimulation. Its mechanism of action is similar to PRS-344/S095012, in that it, too, causes conditional binding of 4-1BB after PD-L1 engagement.

In the FIH study (NCT03917381), GEN1046 is being investigated in advanced solid tumors to explore safety, PK, Pharmacodynamic and anti-tumor activity.

Patients have been treated with GEN1046 Q3W IV (61 patients) at escalating dose levels ranging from 25 mg to 1200 mg as single agent (SA). Most common Treatment Related Adverse Events (TRAEs) ≥ G3 were transaminase elevation (9.8%), hypothyroidism (1.6%), and fatigue (1.6%). Treatment related G3 transaminase elevations decreased upon corticosteroid administration; no treatment-related bilirubin increases or G4 transaminase elevations have occurred. Six DLTs were observed across the dose range, including G4 febrile neutropenia (at 25 and 80 mg), G3 nephritis (140 mg), G3 ALT increase (at 140 mg), G3 AST/ALT increase (200 mg) and G3 transaminase increase (800 mg). An MTD was not reached. Importantly, cytokine release, tachycardia, hypotension or hypoxia has not been reported at any dose level. Overall, a manageable safety profile was observed on treatment with GEN1046 as single agent (SA). The study is currently enrolling patients in several expansion cohorts in a range of solid tumor indications (Garralda *et al.*, 2020). The study noted clinical activity and pharmacodynamic effects of GEN1046 across several dose levels.

FAP targeted 4-1BB agonist (RO7122290)
RO7122290 is a bispecific antibody-like fusion protein based on a trimeric 4-1BB ligand and a targeting Fab moiety recognizing fibroblast activation protein-α (FAP) abundantly expressed by cancer-associated fibroblasts in many tumors. Upon TCR/CD3 engagement, simultaneous binding of FAP and 4-1BB results in clustering and stimulation of T- and NK- cells at the tumor site, thereby leading to potent anti-tumor activity in a panel of preclinical models.

In a FIH study (NCT03869190), RO7122290 is being investigated in FAP positive tumors as single agent (SA) and in combination with atezolizumab (anti-PD-L1 monoclonal antibody) to explore the safety, PK, pharmacodynamic and anti-tumor activity to establish the recommended dose for expansion.

Patients are treated with RO7122290 weekly (QW) at escalating dose levels ranging from 5 – 2000 mg IV (62 pts) as SA and 45 – 2000 mg IV in combination with atezolizumab at 1200 mg Q3W (39 pts). Most common AEs ≥ G3 as SA were asthenia, (6.5%), AST elevation and pneumonia (each 4.8%), whereas pneumonia, pneumonitis (each 10.3%), neutro- and lymphocytopenia (each 7.7%) were most frequent in combination with atezolizumab. Three DLTs were observed including febrile neutropenia G3 (45 mg SA), CRS G3 (130 mg SA) and pneumonitis G3 (500 mg plus atezolizumab). An MTD has not been reached.

Overall, an acceptable safety profile is observed as SA or combination with anti-PD-L1 (ESMO 2020, EUDRACT Number: 2017-003961-83).

HER2 targeted 4-1BB agonist (PRS-343)
PRS-343, a first-in-class bispecific antibody-Anticalin fusion protein, targets HER2 on cancer cells and costimulatory immune receptor 4-1BB on T cells. Importantly, PRS-343 and PRS-344/S095012 share the same IgG4 backbone and 4-1BB-binding Anticalins. In the phase 1 trials (NCT03330561 and NCT03650348) in patients with HER2+ solid tumors, patients have been treated with PRS-343 Q3W in sequential dose cohorts from 0.0005 to 8 mg/kg IV as SA and from 0.05 mg/kg to 8 mg/kg in combination with atezolizumab. PRS-343 has also been evaluated in alternate administration schedules of CCI and Q1W at 8 mg/kg and CCI in doses ranging from 8 to 18 mg/kg. A total of 123 patients with various HER2+ cancers have been enrolled across both clinical trials. Overall, the most frequent TRAEs were mild to moderate infusion related reaction, nausea, chills, vomiting, dyspnea, and fatigue (Ku *et al.*, 2020).

In the SA part, a G4 IRR was observed at 5 mg/kg PRS-343 Q3W dose and schedule. One patient sustained a G2 decreased ejection fraction and another patient had G3 decreased ejection fraction and heart failure; both events recovered without sequelae. To date, it is notable that no significant AST / ALT increases have been demonstrated with monotherapy PRS-343 up to a dose of 18 mg/kg. In the combination study, TRAEs above Grade 3 included one patient with a Grade 4 AST which was treated with corticosteroids and had a reflare with Grade 3 hepatic transaminitis. In the context of concurrent progressive disease, the patient declined further supportive measures and subsequently died. Additional TRAEs included Grade 4 hemolytic anemia (unrelated to PRS-343, related to atezolizumab). No DLTs have been noted to date either in the monotherapy or the combination study. The significant difference in hepatotoxicity is notable for PRS-343, an anticalin linked bispecific antibody, when compared to the other two bispecifics discussed above.

4.3. Rationale

4.3.1. Rationale for the Clinical Study

PRS-344/S095012 shows potent activity on tumor cell killing through enhanced T cells stimulation both *in vitro* and *in vivo*. Moreover, PRS-344/S095012 has shown a significantly higher potency *in vitro* to promote enhanced T cell stimulation compared to the anti-PD-L1 benchmark atezolizumab, as a single agent or in combination with an anti-4-1BB benchmark (see Investigator's Brochure for further details). PRS-344/S095012 induces dose-dependent tumor growth inhibition in a relevant mouse model with physiological activation of endogenous T cells in the tumor, and that was higher than that of an anti-PD-L1 antibody. These data provide the scientific rationale for evaluating the safety, tolerability and potential anti-tumor activity of PRS-344/S095012 in cancer patients.

4.3.2. Rationale for study dose selection

4.3.2.1. Rationale for FIH dose selection

The starting dose of CCI was determined given the overall preclinical package.

Further details regarding the rationale for selection of the FIH starting dose are included in the Investigator's Brochure.

4.3.2.2. Rationale for doses in phase 2

Selected dose(s) of PRS-344/S095012 administered in the dose expansion arm(s) will be recommended by the SRC during an end of cohort meeting. This recommendation will be discussed by the Data Monitoring Committee (DMC) before starting the expansion part of the study.
Doses tested in the phase 2 part of the study will not exceed the MTD determined during the phase 1 part of the study or the highest safe dose evaluated during the phase 1 part of the study. The expansion arms may be initiated at the end of dose escalation once the RP2D has been determined based on safety, PK and available pharmacodynamics data. Alternatively, depending on safety, PK, pharmacodynamics and efficacy available data, one or more dose expansion arm(s) may be initiated before the end of dose escalation. In this case, dose escalation can still proceed up to the MTD or maximum administered dose (MAD) if not reached at that time. During any interim analysis, the dose of PRS-344/S095012 could be escalated to a higher dose, not exceeding the MTD, in a new arm of patients if determined as safe during the phase 1 part and after recommendation of the DMC.

4.3.3. Rationale for indication selection for phase 2

Cervical cancer is the fourth most common cancer amongst women worldwide (Buskwofie *et al.*, 2020). There were an estimated 604 000 new cervical cancer cases and 342 000 deaths worldwide in 2020 (source: WHO). Early-stage disease can often be cured with surgery and/or chemoradiation and has a good prognosis (Marth *et al.*, 2017). Although current therapies in first line represents effective treatment modalities, up to one third of patients will develop progressive or recurrent tumors, the pelvis being the most common site of failure (Bellone *et al.*, 2007; Leitao and Chi, 2002; Friedlander *et al.*, 2002). For women with extrapelvic disease, the 5-year survival rate is only 17%. For women with recurrent disease, prognosis is even worse with 5-year survival rates of less than 5% (Howlader *et al.*, 2015). The major risk factors associated with cervical cancer development include human papilloma virus (HPV) infection, immune system deficiency, smoking, having multiple full-term pregnancies, long-term use of oral contraception and diet (Tsu and Jeronimo, 2016; Crosbie *et al.*, 2013).

In cervical cancer, pembrolizumab was first approved as a 2L therapy in patients expressing PD-L1 (CPS > 1%) through accelerated approval in the USA in 2018 with 14.3% ORR (95% confidence interval (CI): 7.4, 24.1). Subsequently, pembrolizumab received Food and Drug Administration (FDA) approval in 2021 for its use in combination with chemotherapy, with or without bevacizumab, for patients with persistent, recurrent or metastatic cervical cancer whose tumors express PD-L1 (CPS ≥1). This was supported by the phase III trial, KEYNOTE-826, conducted in 617 patients receiving first-line chemotherapy for persistent, recurrent, or metastatic cervical cancer (approximately two-thirds of whom also received bevacizumab). The addition of pembrolizumab improved median progression-free survival (PFS) versus placebo (10.4 versus 8.2 months; hazard ratio for disease progression or death 0.65, 95% CI 0.53-0.79), without negatively impacting health-related quality of life. Additionally, overall survival (OS) at 24 months was 50 percent in the pembrolizumab group and 40 percent in the placebo group (hazard ratio 0.67, 95% CI 0.54-0.84). Objective response rates were 66 and 51 percent, respectively (Colombo *et al*, 2021).
Cemiplimab also showed positive phase 3 results as a second line therapy in patients with cervical cancer, regardless of PD-L1 levels, with a 16.4% ORR (95% CI: 12.5 to 21.1) compared to 6.3% in patients treated with chemotherapy (95% CI: 3.8 – 9.6). Median PFS was also longer in the cemiplimab group than in the chemotherapy group, with a hazard ratio of 0.75 (95% CI, 0.63 to 0.89; two-sided p < 0.001).

Cutaneous squamous cell carcinoma (CSCC) accounts for approximately 20% of all skin cancers (Stratigos *et al.*, 2020) with an estimated global incidence of 2.4 million cases in 2019 (Chong *et al.*, 2022; Zhang *et al.*, 2021). Prognosis for CSCC patients with localized disease is highly favorable (5-year survival rates are 99% with micrographic surgery) (Lansbury *et al.*, 2013). However, in patients with advanced disease, there is in general a poor prognosis (Brantsch *et al.*, 2008; Schmults *et al.*, 2013).

PD-1 targeting checkpoint inhibitors (CPIs) such as pembrolizumab and cemiplimab and nivolumab trigger a high ORR in locally advanced or metastatic CSCC (Hughes *et al.*, 2021; Migden *et al.*, 2018). In the expansion cohorts of a phase 1 study, a response to cemiplimab was observed in 13 of 26 patients (50%; 95% CI, 30 to 70). In the metastatic-disease cohort of the phase 2 study, a response was observed in 28 of 59 patients (47%; 95% CI, 34 to 61) (Migden *et al.*, 2018). Anti-PD-L1 therapy is active in this disease as well. In an open-label phase II trial, 24 patients with metastatic and/or locally advanced CSCC received nivolumab at 3 mg/kg every two weeks until disease progression, unacceptable toxicity, or one year of treatment. At median follow-up of 18 months, objective responses were seen in 14 patients (58 percent), which were all partial responses; the median duration of response was not reached. Median PFS and OS were 13 and 21 months, respectively. Nivolumab was well tolerated in this study which included older adults (Munhoz, 2022). However, for patients who relapse or do not respond to CPIs, no standard therapy is available, and there is a high unmet medical need in this patient population.

Studies have demonstrated that approximately 50% of patients with metastatic CSCC are PD-L1 positive (García-Díez et al., 2018) and among cervical cancer patients, *up t*o 90% are PD-L1 positive (Colombo *et al.*, 2021).

Additionally, the tumor mutational burden (TMB) is high in cervical cancer due to HPV infection (Otter *et al.*, 2019) and in CSCC (Corchado-Cobos *et al.*, 2020). Therefore, the use of immunotherapy could be a good treatment option in cervical cancer and CSCC, as cancers with a higher TMB are known to be more responsive to immunotherapy (Chan *et al.*, 2019).

Taken in consideration the previously described preclinical data, we suggest that PRS-344/S095012 has the potential to efficiently inhibit tumor growth in immunogenic tumors, including but not restricted to, cervical cancer and CSCC, beyond what can be achieved with anti PD (L) agents alone. As PRS-344/S095012 is designed to target PD-L1 and promote tumor localized 4-1BB agonistic activity, it could overcome resistance to anti PD (L)1 therapies, in addition to increasing the clinical activity of monotherapy anti PD (L)1 in anti-PD (L)1 naïve tumors.

4.4. Clinical Experience

4.4.1. Safety data with PRS-344/S095012

PRS-344/S095102 has been given as a CCI infusion CCI, with CCI of therapy defined as CCI of treatment and follow-up. As of July 7th, 2023 (cut-off date for Investigator's Brochure version 4), CCI patients had been enrolled and treated with PRS-344/S095012 in the dose escalation part of the study across doses of CCI per infusion. Of these patients, CCI were evaluable for dose-limiting toxicity.

The principal toxicities of treatment included CCI and CCI. A patient treated at the CCI dose level developed CCI after his first and only infusion of PRS-344/S095012, and this event CCI.

Table (4.4.1) 1 summarizes the DLTs that have been observed in the study. Of note is that additional patients were treated at the CCI dose level, not because of CCI, but because of IRRs occurring with CCI PRS-344/S095012. In an effort to mitigate IRRs, CCI. Nevertheless, CCI, and CCI; see the discussion about CCI and CCI below).

CCI that occurred at the CCI dose level required CCI, in order to CCI. Under the amended study additional patients are currently being enrolled to the CCI dose level before CCI.

Table (4.4.1) 1 - Summary of DLTs

Dose	DLT / Preferred term	Number of DLT-evaluable patients	Total number of patients treated
CCI	None G4 neutropenia > 5 days G3 fatigue >5 days G4 thrombocytopenia G5 (fatal) HLH	CCI	

Table (4.4.1) 2 summarizes the treatment-related adverse events that have occurred in the CCI patients treated to date. Of note, CCI events of interest do not appear in the table because CCI treated patient. CCI concerns CCI treated at the CCI dose level who experienced a CCI from CCI . CCI to the CCI that is further described below.

Table (4.4.1) 2 - Treatment-related AEs (TRAEs) in all patients treated with PRS-344/S095012 (N = CCI)

	All Grade n (%)	Grade 3 n (%)	Grade 4 n (%)
Any TRAEs	CCI		
TRAEs in ≥ 5% of pts by PT			
Aspartate aminotransferase increased			
Cytokine release syndrome			
Fatigue			
Infusion related reaction			
Nausea			
Alanine aminotransferase increased			
Pyrexia			
Night sweats			
Blood bilirubin increased			
Diarrhoea			
Gamma-glutamyltransferase increase			
Thrombocytopenia			
Vomiting			
Abdominal distension			
Abdominal pain			
Arthralgia			
Chills			
Constipation			
Immune thrombocytopenia			
Lymphocyte count decreased			
Myalgia			
Neutropenia			
Neutrophil count decreased			
Oedema peripheral			
Platelet count decreased			
Pruritus			
Rash			
Rash pruritic			

PT = Preferred term (AE MedDRA coded name), n = number of patients, % = percentage of all patients treated with study drug.

Note, CCI (cf below) is not detailed in this table as occurring in less than 5% of treated patients.

Table (4.4.1) 3 summarizes the IRR and CRS events that have been observed in the study. CCI of all patients experienced CRS, with CCI occurring in CCI patients. Treatment discontinuation because of CRS occurred in CCI, who experienced CCI.
CCI of patients experienced an IRR, with CCI occurring in CCI. No patient discontinued study treatment because of an IRR. Patients CCI before the first PRS-344/S095012 infusion. However, CCI.

Table (4.4.1) 3 - Cytokine release syndrome and infusion-related reactions

	All	CCI	CCI	CCI	CCI
N patients	CCI				
CRS events (n, %)					
All	CCI				
G1					
G2					
G3					
G4					
IRR events (n,%)					
All					
G1					
G2					
G3					
G4					

Table (4.4.1) 4 summarizes the treatment-related CCI toxicity observed in the study. CCI of all patients experienced treatment-related CCI, with CCI of all patients experienced treatment-related CCI and CCI were reversible, CCI.

Table (4.4.1) 4 - Hematologic toxicity related to treatment

	All	CCI	CCI	CCI	CCI
N patients	CCI				
Thrombopenia events (n, %)					
All					
G1					
G2					
G3					
G4					
Neutropenia events (n,%)					
All					
G1					
G2					
G3					
G4					
Febrile neutropenia					
CCI					

As noted above, a patient treated with a single CCI dose of PRS-344/S095012 developed CCI. The complications of CCI included CCI . The patient had received CCI doses of a CCI for more than CCI to receiving PRS-344/S095012, and was consequently CCI . Although CCI had been CCI daily over the CCI the administration of PRS-344/S095012, he was still CCI , as evidenced by CCI It was hypothesized that his CCI . He was also considered to be CCI because of CCI , with CCI tissue metastases.

Because of this case of CCI, measures were taken to CCI if they had recently received CCI of CCI or CCI . Measures were also taken to CCI from the study if they CCI of CCI or CCI with CCI or CCI The Royal Marsden Prognosis Score was also used to CCI patients with a CCI from the study.

Table (4.4.1) 5 summarizes the CCI related to treatment. CCI in CCI and CCI have been grade CCI in severity and CCI .

Table (4.4.1) 5 - CCI related to treatment

	All	CCI	CCI	CCI	CCI
N patients	CCI				
AST events (n, %)					
All					
G1					
G2					
G3					
G4					
ALT events (n,%)					
All					
G1					
G2					
G3					
G4					
Bilirubin events (n,%)					
All					
G1					
G2					
G3					
G4					

CCI

4.4.2. Efficacy data with PRS-344/S095012

In the first CCI treated with PRS-344/S095012 CCI were observed. CCI patients had CCI for CCI cycles of treatment.

In summary, the toxicities associated with PRS-344/S095012 have been largely related to its underlying mechanism of action, with activation of immunologic activity. IRRs are associated with CCI, and CCI is related to CCI (see the discussion below regarding PK and PD in the following section). As noted in the section describing PRS-344/S095012's PK and PD, the rapid development of CCI, and the consequent CCI to PRS-344/S095012, CCI.

4.4.3. Pharmacokinetic and pharmacodynamic data of PRS-344/S095012

After the first administration, PRS-344/S095012 exhibited CCI in exposure ($AUC_{0\text{-}336h}$, C_{max}) between the CCI, with a trend towards CCI in its apparent half-life CCI dose, in line with CCI. Exposure-related CCI and CCI were also observed within this range of doses. However, CCI to PRS-344/S095012 was found to CCI due to CCI. Indeed, CCI have been observed CCI with available CCI data, and CCI are strongly correlated with CCI. Consequently, CCI of PRS-344/S095012 CCI, and an CCI of its CCI is CCI. CCI the CCI is therefore important forCCI. This experience CCI of CCI into the study, CCI

4.5. Rationale for CCI strategy

4.5.1. Obinutuzumab CCI

Obinutuzumab is a type II anti-CD20 monoclonal antibody that is used in the treatment of patients with B-cell malignancies, specifically in patients with chronic lymphocytic leukemia (CLL) and follicular lymphoma (FL). Its primary mechanism of action is to deplete B-cells by binding to the CD20 antigen and inducing direct cell death and antibody-dependent cell-mediated cytotoxicity. While the reduction in malignant B-cells expressing the CD20 antigen results in a high degree of efficacy in CLL and FL, the reduction in normal B-cells results in immunosuppression, including an increased risk of reactivation of viral infections. The other principal toxicity of obinutuzumab is infusion-related reactions (IRRs), for which a corticosteroid-containing premedication regimen is required.

When obinutuzumab is given for the treatment of FL a dose of 1000 mg IV is given on Days 1, 8 and 15 of the firstCCI of treatment, followed by 1000 mg monthly. A randomized phase 2 study in patients with CLL compared a 2000 mg dose of obinutuzumab with a 1000 mg dose (Byrd *et al*, 2016). The two doses had similar safety profiles. Although the objective response rate was higher with the 2000 mg dose, progression-free survival was not significantly different, and hence the 1000 mg dose is standardly used in the treatment of both CLL and FL.

More recently obinutuzumab has been evaluated both in preclinical models and in patients as a means of CCI against highly immunogenic biologic agents (Bacac *et al*, 2021).

In monkeys, obinutuzumab given as a single 30 mg/kg dose prevented de novo antibody generation against tetanus toxoid, while rituximab (a type I anti-CD20 antibody) did not significantly affect antibody generation. Importantly, memory recall responses (measles/rubella vaccine) were not affected by treatment with either agent, consistent with the lack of CD20 expression on memory B-cells.

In patients with CCI obinutuzumab was evaluated for its ability to CCI CCI which is highly expressed in CCI and other CCI tumors. In the case of an CCI , a CCI dose of obinutuzumab given approximately 13 days before the bispecific molecule CCI in CCI patients CCI of treatment (CCI). In the case of an CCI molecule, the same pre-treatment prevented CCI in CCI patients, for as many as CCI . As expected, the administration of obinutuzumab was associated with depletion of B-cells in the peripheral blood, but there were no safety issues related to this depletion. Evaluation of this strategy with obinutuzumab continues with other bispecific molecules (NCT04826003) administering either a single 2000 mg dose or two consecutive 1000 mg doses of obinutuzumab one week before infusion of the bispecific.

It remains unclear whether obinutuzumab needs to be CCI after the first dose(s). CCI may last for a year or longer after obinutuzumab administration. Therefore, as patients remain on study, samples will continue to be collected at the beginning of each new cycle of treatment to assess CCI . This information may be helpful in determining CCI may be warranted. Giving only a single dose of obinutuzumab also limits the duration of CCI .

4.5.2. Initial evaluation of obinutuzumab pretreatment in CCI

Obinutuzumab will first be administered with CCI nd that has CCI . Although CCI are expected to have only a limited impact on CCI after the first administration of treatment, making it unlikely that obinutuzumab will change the dose recommendation, a cautious approach is warranted: greater toxicity could be observed in the CCI and CCI cycles of treatment CCI .

Approximately CCI patients will be treated with PRS-344/S095012 preceded by obinutuzumab administration, with the objective of having safety, PK, PD and ADA data over CCI . It is anticipated that as many as CCI of the patients initially treated may not complete CCI cycles of treatment because of CCI or CCI . The experience over CCI cycles of treatment in CCI patients should provide enough data to preliminarily assess whether the continued used of obinutuzumab is warranted. In the table below are four hypothetical outcomes and their corresponding interpretations, using a Wilson score confidence interval.

Number of patients without CCI / Number of patients treated	80% Wilson score interval	Interpretation
CCI	(0.51, 0.94)	80% certainty that the confidence interval of (0.51, 0.94) covers the true CCI rate of CCI.
	(0.75, 1)	80% certainty that the confidence interval of (0.75, 1) covers the true CCI rate of CCI.
	(0.57, 0.95)	80% certainty that the confidence interval of (0.57, 0.95) covers the true CCI rate of CCI.
	(0.79, 1)	80% certainty that the confidence interval of (0.79, 1) covers the true CCI rate of CCI.

If either CCI or CCI patients are observed to have CCI over CCI cycles of treatment, we will be able to conclude that the confidence interval of (0.75 or 0.79, 1) covers the true CCI rate of CCI (with 80% confidence, which is acceptable in an early phase trial). If CCI patient CCI or CCI), then the confidence interval will be wider, with the lower bound in the range of 50%. In this case we would proceed to CCI to CCI that we can CCI. If CCI or CCI patients CCI, then the confidence interval will lie between 0.3 and 0.9, and we would conclude that reaching the goal of CCI in 80% of patients was unlikely. The CCI for PRS-344/S095102 will also be evaluated, in order to put the CCI into perspective. It is possible that in some cases CCI will have little or no impact on CCI. If obinutuzumab is found to be effective in CCI and is safe, then CCI of PRS-344/S095012 CCI with obinutuzumab pretreatment.

4.6. Overall Benefit/Risk

During this study, there will be an ongoing assessment of the risks of treatment with periodic evaluation of safety data. The study will be discontinued in the event of any (new) finding indicating a risk that would render continuation of the study unjustifiable. A Safety Review Committee (SRC) comprised of the Investigator(s) and the Sponsor's Medical and Safety Representative(s) will meet to evaluate clinical and laboratory safety data on an ongoing basis and to make decisions regarding the advisability of continuing accrual to a dose cohort and/or escalating the dose and allowing accrual to a next higher dose cohort in phase 1. The SRC will also recommend the starting dose for the phase 2 part of the trial. This starting dose and the beginning of the phase 2 part of the trial will be discussed by the DMC (See Section 14.8.2 for more details on the DMC). These recommendations will be recorded in meeting minutes.

To mitigate potential risks, the phase 1 part of the study is designed to detect DLTs, if any, and to define an MTD or MAD and/or selected dose(s) (RP2D) of PRS-344/S095012 in accordance with the dose escalation rules described in this protocol. For each new cohort, enrollment of the 1st and the 2nd patients will be staggered by a minimum of 24 hours to evaluate acute safety before allowing the enrollment of further patients at a new dose level. If the dose administered in a cohort is well tolerated, dose escalation may proceed, and enrollment of subsequent cohorts may occur. The options to slow infusions, delay dosing, and discontinue administration of study drug(s) in the event of specific AEs are outlined in Section 6.6.

Patients participating in this study will be closely monitored for all AEs, with particular attention to IRRs, CRS, neutropenia, thrombocytopenia, increases in transaminases and any other potential immune-related toxicities. Following the occurrence of a case of HLH in the phase 1 part of this study, new inclusion and exclusion criteria were added to the protocol to avoid the enrolment of patients with severe immunosuppression, evidence of reactivation or infection with CMV or EBV, or high tumor burdens. Advice was also provided for the early detection of HLH. Patients will be followed for 90 days after the last dose; in the case of an unresolved AE, the patient will be continuously followed until resolution or stabilization.

The use of obinutuzumab CCI [redacted] has been considered for its potential benefit and risks. Based on the published experience, obinutuzumab has proven to be CCI [redacted], both in a preclinical model and in patients. Hence the probability that CCI [redacted] is considered to be high.

The selective effect of obinutuzumab on B-cells is preferable to the more generalized immunosuppression that would be caused by the chronic administration of corticosteroids or a cytotoxic agent. Moreover, unlike these broadly immunosuppressive agents, obinutuzumab is not considered likely to increase the risk of HLH, since B-cells and antibodies are not believed to play a role in the pathogenesis of this disease.

In addition, more broadly immunosuppressive agents could antagonize the desired activity of PRS-344/S095012 by directly affecting T cells, which are the target cells of PRS-344/S095012. In mouse models, depletion of B cells using anti-CD20 antibodies did not impair the antitumor activity of an anti-PD1 agent. This suggests that B cells are not required for the activity of the PD-L1 inhibitory part of PRS-344/S095012 (Damsky *et al*, 2019).

Nevertheless, treatment of patients with obinutuzumab carries an increased risk of infection because of its depletion of B cells. In order to mitigate this risk patients are excluded from treatment if they have evidence of ongoing or latent infections with hepatitis B or C, or reactivation of EBV or CMV infections. Patients with a history of an opportunistic infection are also excluded from treatment with obinutuzumab. Obinutuzumab has been associated with progressive multifocal leukoencephalopathy (PML), and investigators and patients must be aware of this risk.

In phase 2, the primary objective is the detection of anti-tumor activity. Nevertheless, the safety of the treatment will be closely monitored. Potential dose adjustment, premedication or safety management will be implemented accordingly.

For additional information, please refer to the latest version of the Investigator's Brochure, to Gazyvaro® Product information - Annexe 1 European Summary of Product characteristics, and Gazyva® AUS Product Information.

5. STUDY OBJECTIVES AND ENDPOINTS

5.1. Phase 1

5.1.1. Primary Objectives and Endpoints

Objectives	Endpoints
- To evaluate the safety and tolerability profile of single-agent PRS-344/S095012	- Incidence of DLTs - Incidence and severity of adverse events (AEs) - Discontinuation of study treatment due to an AE - Laboratory, electrocardiogram (ECG) and vital sign measurements
- To determine the MTD or MAD and RP2D of PRS-344/S095012	- Incidence of DLTs

5.1.2. Secondary Objectives and Endpoints

Objectives	Endpoints
- To characterize the PK of PRS-344/S095012	Serum PK parameters of PRS-344/S095012
- To evaluate the immunogenicity of PRS-344/S095012	- Detection of ADA against PRS-344/S095012 and their titration when applicable
- To assess the preliminary anti-tumor activity of PRS-344/S095012 as per the investigator, according to Response Evaluation Criteria in Solid Tumors (RECIST) v1.1	- Objective Response (OR): Defined as Complete Response (CR) plus Partial Response (PR) - Duration of Response (DoR): defined as the time from first demonstration of response to progression or death, whichever occurs first - Progression-free Survival (PFS): Defined as the time from the first dose of treatment to first documented disease progression or death due to any cause, whichever occurs first - Overall Survival (OS): Defined as the time from first dose of study drug to death due to any cause

5.1.3. Exploratory Objectives and Endpoints

Objectives	Endpoints
- To evaluate the intra-tumor pharmacodynamics of PRS-344/S095012 through the analysis of pre- and on-treatment tumor biopsies	- PD-L1, CD8, and 4-1BB expression in the tumor microenvironment by immunohistochemistry (IHC) - Immune cell subsets and activation status (such as but not limited to expression of Ki67 and Granzyme in CD8 T cells) by IHC - And/or gene expression profiling in the tumor such as but not limited to IFNγ gene signature
- To characterize treatment-induced pharmacodynamic effects in peripheral blood	- Immuno-phenotyping of T cell subsets and their activation (such as, but not limited to, CD4, CD8, regulatory T cells, naïve and memory subsets, Ki67) and changes by flow cytometry. - Cytokine levels - Soluble 4-1BB level
- To analyze potential predictive biomarkers of response from tumor and blood samples	- PD-L1, 4-1BB, and CD8 expression in the tumor - And/or tumor mutational burden (TMB), in the tumor and/or blood, microsatellite instability (MSI) status, specific mutations in the tumor (or in the blood if feasible, with an optional sample) - And/or gene expression profiling in the tumor and/or blood

Objectives	Endpoints
- To assess any potential PK/pharmacodynamic relationship through a population modelling approach that may support the selection of the RP2D and schedule of administration	- PK and pharmacodynamic parameters in PK/pharmacodynamic models and simulation outcomes to support RP2D and schedule of administration

5.2. Phase 2

5.2.1. Primary Objective and endpoint

Objective	Endpoint
- To evaluate the potential anti-tumor activity and efficacy of PRS-344/S095012, as per central assessment according to RECIST v1.1 criteria based on appropriate clinical standards for the specified tumor type	- Arms 1 and 2: OR as per central assessment according to RECIST v1.1 criteria - Arm 3: OR as per central assessment and composite response criteria (digital medical photography and/or imaging as per RECIST v1.1)

5.2.2. Secondary Objectives and endpoints

Objectives	Endpoints
- To further describe the efficacy	- All arms: OR as per investigator assessment - Disease Control (DC) - DoR - PFS - OS - TTR (Time to Response)
- To further characterize the safety and tolerability of PRS-344/S095012	- AEs, serious adverse event (SAEs) - Laboratory, ECG, vital signs
- To further characterize the PK profile of PRS-344/S095012.	- Serum concentrations of PRS-344/S095012.
- To further characterize immunogenicity of PRS-344/S095012	- Detection of ADA against PRS-344/S095012 and their titration when applicable

5.2.3. Exploratory Objectives and endpoints

Objectives	Endpoints
- To evaluate potential predictive biomarkers of response from tumor and/or blood samples	- PD-L1, and potentially other markers like 4-1BB, and CD8 expression in the tumor - And/or TMB in the tumor and/or blood, MSI status, specific mutations in the tumor (or in the blood if feasible, with an optional sample) - And/or gene expression profiling in the tumor and/or blood
- To evaluate pharmacodynamic changes in the tumor and blood samples	- Immune cell quantity and phenotype characterization in the blood and in the tumor - And/or cytokine levels - And/or soluble 4-1BB levels

6. INVESTIGATIONAL PLAN

6.1. Overall Study Design

This is a first-in-human (FIH), phase 1/2, multicenter, open-label, dose escalation and dose expansion study designed to determine the safety and activity of PRS-344/S095012 in patients with advanced and/or metastatic solid tumors. The study design is outlined in Figure (6.1) 1.

Phase 1 will evaluate the safety and tolerability of PRS-344/S095012 in patients for which standard treatment options are not available, no longer effective, or not tolerated.

PRS-344/S095012 will be administered as SA through IV infusion CCI initially. The dose of PRS-344/S095012 will be determined during end of cohort meetings, based on safety data and available PK data. A Q3W administration schedule may be evaluated in new cohorts, if necessary or appropriate and agreed upon during an end of cohort meeting. The starting dose will be a flat dose of CCI mg dosed CCI. The DLT observation period will be 28 days CCI for the CCI schedule and 21 days for the Q3W schedule. The phase 1 part of the study consists of dose escalation conducted in 2 parts (part A and part B). Part A is an accelerated dose escalation following a CCI. Part B is a dose escalation in multiple patient cohorts, guided by a Bayesian Logistic regression model (BLRM).

In phase 1, backfilling will be allowed (*i.e.* the possibility to enrol additional patients in prior cohorts as long as an acceptable safety profile has been observed in the cohort being backfilled), refer to Section 6.4.3 for further details. The RP2D will be determined based on safety, PK and pharmacodynamic data observed during phase 1.

Phase 2 will evaluate the potential efficacy of PRS-344/S095012 in 3 disease-specific expansion arms:

- **Arm 1 (cervical CPI-naïve):** patients with recurrent, persistent and/or metastatic cervical cancer, who have not been previously treated with a CPI, and whose disease has progressed on any prior line of treatment.
- **Arm 2 (cervical cancer – CPI-relapsed/refractory)**: patients with recurrent, persistent and/or metastatic cervical cancer, who have received and progressed on any line of a CPI as monotherapy or in combination.

Note: for cervical cancer in arms 1 and 2, acceptable histologies are squamous carcinoma, adenocarcinoma, and adenosquamous carcinoma; sarcomas and neuro-endocrine carcinomas are not eligible.

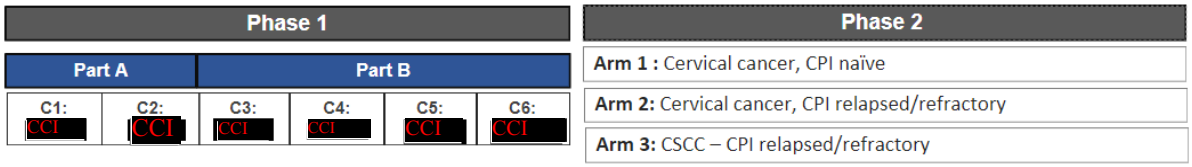
- **Arm 3 (CSCC – CPI-relapsed/refractory):** patients with advanced or metastatic Cutaneous Squamous Cell Carcinoma (CSCC) who have received and progressed on CPI treatment.

Patients will receive PRS-344/S095012 as monotherapy CCI. Obinutuzumab will be administered as single dose or a single dose split over 2 consecutive days, administered fourteen to seven days before the first dose of PRS-344/S095012, as per investigator's judgment.

This expansion phase will follow a Clustered Bayesian Hierarchical Model (CBHM) with one or more futility analyses.

In addition to efficacy assessments, the safety profile of PRS-344/S095012 will be reviewed regularly during the study with appropriate stopping rules and processes for safety review. The sponsor may stop any arm at any time for any reason (See Section 6.6.2). As new data emerge from the CL1-95012-001 study and from other ongoing studies of antibody(ies) with a similar mechanism of action, new tumor type(s) and treatments (*i.e.*, monotherapy or combination with immuno-oncology (IO) treatment, chemotherapy or targeted therapy) may be added to this study, through protocol amendment.

Figure (6.1) 1 - CL1-95012-001 Study design



Dose levels are provisional and will depend on the BLRM recommendation and cumulative safety data observed. C = Cohort; CPI = checkpoint inhibitors, CSCC: cutaneous squamous cell carcinoma.

6.2. Study Plan

The study will be divided into the following periods for each patient:

6.2.1. Screening Period

Upon signing the Informed Consent Form (ICF), patients will be evaluated between Day-28 to Day-14 (+7 days) against study inclusion and exclusion criteria. Screening assessments and evaluations will be performed before the pretreatment with obinutuzumab is administered. In phase 1, baseline fresh biopsies are not mandatory for patients in the dose escalation cohorts, if archived tumor biopsy specimens collected no more than 9 months before screening are available. Fresh biopsies at baseline are mandatory for patients enrolled in order to backfill previously evaluated dose levels unless archival tumor tissue less than 6 months old is available and the patient has not received any anti-cancer treatment since the biopsy was taken. In phase 2, a fresh baseline biopsy will be mandatory for all patients in all arms unless archival tumor tissue less than 6 months old is available and the patient has not received any anti-cancer treatment since the biopsy was taken.

6.2.2. Treatment Period

Patients will be allocated to different dose levels in dedicated cohorts in phase 1 or to dedicated arms in phase 2 and will receive doses of PRS-344/S095012 administered by IV infusion on CCI A Q3W administration schedule may be evaluated in a new cohort of patients in phase 1, if emerging PK, pharmacodynamics, and safety data from CCI schedule indicate that a different dosing regimen is more appropriate. Further details are provided in Section 6.3.1.

Treatment is planned to be provided until disease progression. Treatment may be administered beyond progression according to the criteria described in Section 9.2.1. However, patients may be discontinued from treatment with the study drug earlier according to the criteria described in Section 6.6.3.

On-treatment biopsies are optional for patients in dose escalation and in arms 1 and 2 of phase 2 and mandatory for patients enrolled in backfilled cohorts of phase 1 as well as for patients in arm 3 of phase 2, unless medically contraindicated. In arm 3, for patients deemed eligible by digital photography only, an additional biopsy is required within 30 days of CR determined by the investigator for confirmation of the CR.

End-of-treatment

End of treatment corresponds to the 3-month safety follow up visit as described in Section 6.2.3.

6.2.3. Follow up (FU) Period

1-month Safety FU visit

Patients will be evaluated 30 days after the last IMP administration. During this visit, patient safety will be evaluated through physical examination, vital signs, ECG and laboratory assessments as specified in Table (9) 1, Table (9) 2 and Table (9) 3, in order to assess any ongoing AEs.

Long-term Safety FU visits

Patients will be evaluated 60 and 90 days after the last IMP administration. During this visit, patient safety will be evaluated through physical examination, vital signs, ECG and laboratory assessments as specified in Table (9) 1, Table (9) 2 and Table (9) 3, in order to assess any ongoing AEs. Disease status and survival (12 weeks after last IMP intake) will be documented during the 90-day visit. New information will be documented in the Adverse Event page. Any patient who develops immune-related toxicity will receive an appropriate assessment and/or performed the adequate test(s) to treat the event(s). In case of unresolved AE, the patients will be continuously followed until resolution or stabilization, or until the end of the study whatever comes first. SAEs related to the IMP will be reported without time limit.

Disease Status and Survival FU visits

Disease Status and survival must be followed every 12 weeks (+/- 14 days). Disease status will be monitored through radiologic/photographic assessments up to progressive disease (PD) or if the patient receives another treatment for the cancer disease. Patient Survival will be followed via phone calls or contact with physician. During this period, the following information should also be recorded in the electronic Case Report Form (e-CRF):

- In case of imaging (for example positron emission tomography [PET] Scan), date and response status.
- In case of death of the patient, date of the event.
- If the patient starts a new medication for the cancer disease, date of first administration, treatment name and best response.

In any cases other than consent withdrawal, patient should have safety follow-up and be followed until the end of the trial for disease status and survival. If the patient withdraws his/her consent, no FU visit will be planned.

6.2.4. End of Study

The end of the study is defined as the last patient's last visit, which includes the long-term safety follow-up visit, 90 days after the last dose of IMP or the date of the last contact attempt if the last participant is declared lost to follow-up.

6.3. Doses and Schedule of Administration

6.3.1. Schedule of Administration

PRS-344/S095012 will be administered as intravenous infusion CCI , with at least 12 days between 2 infusions CCI schedule). In this schedule, patients will receive PRS-344/S095012 on Day 1 and Day 15 of each 28-day CCI.

In order to CCI obinutuzumab will be administered either as a single dose of CCI mg or two doses of CCI mg given over two consecutive days. If a single dose is given, obinutuzumab will be administered at the earliest CCI before the first dose of PRS-344/S095012 (C1D1), and at the latest CCI) before C1D1. If obinutuzumab is administered over two consecutive days, it will be done at the earliest on CCI and CCI and at the latest on CCI and CCI .

During the dose escalation phase of the study, according to emerging safety, PK and pharmacodynamic data, a Q3W schedule of administration may be evaluated after discussion between the sponsor and the investigators. According to dose optimisation recommendations, a new cohort of patients may be enrolled utilizing the new schedule at a dose level resulting in a cumulative exposure that does not exceed the maximum dose considered safe after the DLT observation period. Subsequent escalation may proceed using the Q3W schedule. In the Q3W schedule, patients will receive PRS-344/S095012 on Day 1 of each 21-day cycle.

6.3.2. Starting Dose

The rationale for the starting dose is described in Section 4.3.2.

The starting dose of PRS-344/S095012 will be a CCI mg flat dose. The dose of PRS-344/S095012 will be adjusted or interrupted as appropriate based on treatment modifications defined in Section 6.8.

6.3.3. Dose Levels

Phase 1 dose escalation (parts A and B) will be conducted with semi-logarithmic increments as maximum, as illustrated in Table (6.3.3) 1. However, it is possible that intermediate or higher dose levels will be added during the study and that smaller dose increments may be utilized.

The first dose level evaluated in part B will depend on safety events observed in part A and will start at CCI mg at most.

The RP2D will be determined based on safety, tolerability, PK and pharmacodynamic data. In any case, this dose will not exceed the maximum dose tested in phase 1.

Table (6.3.3) 1 - PRS-344/S095012 Dose Levels increments and predicted maximum serum concentration

Dose Level	Dose (mg)	Predicted maximum serum concentration at the end of first infusion (µg/mL)
1	CCI	CCI
2		
3		
4		
5		
6		

The phase 2 part of the study may be initiated at the end of dose escalation once the RP2D has been determined based on safety, PK and available pharmacodynamics. Alternatively, depending on safety, PK, pharmacodynamics and efficacy available data, one or more dose expansion arm(s) may be initiated before the end of dose escalation. In this case, dose escalation can still proceed up to the MTD or MAD if not reached at that time. During any interim analysis, the dose of PRS-344/S095012 could be escalated to a higher dose, not exceeding the MTD, in a new arm of patients if determined as safe and after recommendation of the DMC. See Section 6.4.7 for the starting dose of phase 2.

6.4. Phase 1 - Dose Escalation

In parts A and B, dose escalation to a subsequent cohort will be based on the review of all AEs, DLTs, and safety tests that occur/are performed within the DLT observation period. The decision will be taken by the SRC composed of the investigator(s) and the medically responsible representative(s) of the sponsor during dose escalation meetings. Dose escalation meetings will be held at the end of the DLT observation period of all patient cohorts concerned. Further details on SRC composition, meetings and decision-making processes are provided in the SRC charter.

6.4.1. Part A: Accelerated Titration Design

In this part, dose escalation will be carried out in single-patient cohorts based on a CCI. The first patient will be administered a flat starting dose of CCI mg CCI Dose escalation will be conducted in semi-logarithmic increments.

Dose Escalation Rules
Dose escalation to a subsequent cohort will be based on the review of all AEs, DLT and safety assessments that occur/are performed within the 28-day DLT observation period. The decision will be made as follows:

- If no IMP-related AE ≥ Grade 2, IMP-related cytokine-release syndrome (CRS) of any grade or DLT occurs during the 28-day DLT observation period, the decision will be made by SRC, to escalate to the next dose level in a single-patient cohort.
- If any IMP-related AE ≥ Grade 2 or IMP-related CRS of any grade or DLT occurs during the DLT observation period, three additional patients will be enrolled at the same dose level. Dosing of the first and second patients will be staggered by a minimum of 24 hours.

Once the 3 additional patients have completed the 28-day DLT observation period, the SRC will review all safety data (AEs, DLTs, and safety tests) from all 4 patients (as well as the cumulative safety data from preceding cohort, if any). With the support of BLRM predictions, three possibilities will be considered:

a. Stop the dose escalation.
   Note: in this situation, no part B will be conducted, and patients will be enrolled in phase 2 at a dose that does not exceed the MTD.
b. Escalate to the next dose level in multiple patient cohorts (part B).
c. Stay at the same dose level in multiple patient cohorts (part B).

6.4.2. Part B: Multiple-Patient Dose Escalation

In part B, an adaptive BLRM design will be used for dose escalation. Part B will start at the CCI mg dose level at maximum or lower in case of IMP-related AE ≥ Grade 2, IMP-related CRS of any grade, or DLT occurring in part A. The CCI mg threshold is based on the Human Equivalent Dose (HED) of the minimal therapeutic dose determined in vivo in a relevant mouse model.

A cohort will be considered complete if a minimum of 3 patients are evaluable for safety at the end of the DLT observation period. The DLT observation period will be a 28-day period in the CCI schedule and a 21-day period in the Q3W schedule.

At any dose level, dosing between the first and the second patients will be staggered by a minimum of 24 hours.

Once a cohort is complete, the SRC will review safety, tolerability, AE and the BLRM recommendations during a dose escalation meeting. If a dose is deemed safe, the dose may be escalated to the next dose level according to a semi-logarithmic increment as a maximum. The SRC may decide at any time to reduce the dose increment.

During phase 1, when feasible, PK samples will be analyzed at the end of part A and then after every 2 cohorts in part B. Investigators and sponsor's representatives may decide to perform additional analyses if needed.

The populations evaluable for safety and for DLT are defined in Section 11.2.

6.4.3. Backfilled cohorts

To further understand the safety and PK or pharmacodynamics of PRS-344/S095012, backfilled cohort(s) will be allowed, where additional patients may be enrolled in prior dose levels if:

- An acceptable safety profile (DLT observation period) has been observed in the cohort which is being backfilled.
- Patients consent to have mandatory fresh paired biopsies collected at baseline (unless an archived tumor biopsy (< 6 months old) without intercurrent treatment is available) and on treatment.

In these backfilled cohort(s), similar safety monitoring (including DLT observation period) will be conducted as for the patients participating in the main dose escalation. Data of patients from backfilled cohorts will be taken into account in the BLRM model to adjust recommendations for the next dose levels and the determination of the RP2D.

6.4.4. Intra-patient dose escalation

Based on the clinical judgment of the investigator, and with approval of the Sponsor's medical representative, intra-patient dose escalation may be permitted for patients treated in the dose escalation part of the study if:

- The proposed new dose level has been determined to be tolerable and safe after the DLT observation period (*i.e.*, the next higher dose is being evaluated).
- It does not occur before the 2nd RECIST assessment.
- The patient experiences disease stabilization, unconfirmed PD or confirmed PR or CR.

Patients with confirmed PD should be withdrawn from the study (Section 6.6.3). Patients with unconfirmed objective response (PR or CR) should continue to receive the same dose level of PRS-344/S095012.

6.4.5. Patient Replacement Rules

During phase 1, patients enrolled in the main dose escalation part of this study may be replaced to ensure that the required number of evaluable patients per cohort are recruited. Replacement may occur for:

- Patients who discontinue during the first cycle due to any reason other than a DLT and/or study-related toxicity.
- Patients who received less than 80% of the required study drug dose for reasons other than safety and do not have a DLT during the DLT observation period.

The following patients will not be replaced:

- Patients who discontinue due to a DLT.
- Patients who discontinue after full evaluation of the DLT observation period.

6.4.6. Dose-limiting Toxicities

Definition of DLT

A DLT is defined as an AE, occurring during the DLT observation period of phase 1, assessed as unrelated to disease progression, intercurrent illness, concomitant medications or other etiology, considered as related to the IMP by the investigator and satisfying at least one criterion below.

- Grade ≥ 3 neutropenia lasting ≥ 5 days.
- Any febrile neutropenia.
- (*i.e.*, ANC < 1000/mm^3 with single temp of > 38.3 degrees C [101 degrees F] or a sustained temperature of ≥ 38 degrees C [100.4 degrees F] for more than one hour).
- Grade ≥ 3 thrombocytopenia with clinically significant hemorrhage.
- Grade ≥ 3 cytokine release syndrome.
- Grade ≥ 3 non-hematologic AEs, except the following:
  - Grade ≥ 3 nausea, vomiting, or diarrhea lasting < 72 hours despite maximal medical therapy.
  - Grade 3 asymptomatic, electrolyte abnormalities lasting less than 72 hours that are not clinically complicated, and/or resolve spontaneously or with conventional medical interventions.
  - Grade 3 creatine phosphokinase (CPK), creatinine, gamma-glutamyl transferase (GGT).
  - Grade 3 amylase, lipase without clinical significance and lasting < 7 days.

  - Grade 3 hyperglycemia if clinically stable.
  - Grade ≥ 3 fatigue lasting < 5 days.
  - Grade 3 AST or ALT elevations lasting < 7 days that are not clinically complicated.
  - Grade 3 non-hepatic-related increases in alkaline phosphatase.
- AST or ALT > 3 x upper limit of normal (ULN) (or > 3 x baseline in subjects with baseline elevation) AND total bilirubin > 2 x ULN (or > 2 x baseline in subjects with baseline elevation) or clinical jaundice, without initial findings of cholestasis AND no other immediately apparent identifiable possible causes of elevated liver enzymes and hyperbilirubinemia.
- Treatment delays > 2 weeks from the scheduled next dose due to any AE related to the IMP.

The DLT observation period will be a 28-day period in the CCI schedule and a 21-day period in the Q3W schedule.
All AEs (related and unrelated to treatment) will be continuously monitored, graded based on Common Terminology Criteria for Adverse Events (CTCAE) v5.0; except for CRS that will be graded according to American Society for Transplantation and Cellular Therapy (ASTCT) CRS Consensus Grading and reported as described in Section 10.

Prophylactic use of growth factors and blood products is not permitted. In case of use during the DLT observation period, this will constitute a DLT.

Isolated laboratory changes without associated clinical signs or symptoms may not be included in this definition. These abnormalities will be discussed and reviewed by the investigators and the sponsor's representative. AEs that are not classified as DLT as per definition above could be considered as DLT if agreed by the investigators and the sponsor's medical monitor.

Occurrence of grade ≥ 2 CRS during the DLT observation period of a given cohort may trigger evaluation of a priming dose schedule (*i.e.* initial lower dose of PRS-344/S095012 followed by escalation to the full treatment dose) in a separate cohort.

DLT management
Patients who experience a DLT must discontinue study drug immediately, ***unless*** the following situations occurs:
- The investigator believes that the patient has derived a significant clinical benefit from treatment. In this case, the investigator may consider continuing treatment at the next lowest dose level according to the dose escalation scheme upon recovery from the DLT (baseline or Grade ≤ 1), in consultation with the sponsor's medical representative.
- The investigator believes that the event can be adequately monitored to avoid recurrence of the toxicity. In this case, the patient may be offered continued treatment with PRS-344/S095012.

All DLTs will be reported to the sponsor within 24 hours via DLT form in the e-CRF. After having filled in the DLT form, fill in the "Adverse Event" page of the e-CRF, without waiting for the results of the clinical outcome or of additional investigations (Section 10). When data of the DLT form are submitted, an e-mail will be immediately and automatically sent to the sponsor.

Decision process and decision rules
Before initiation of a new dose level, the SRC composed of the medical responsible person(s) from the Sponsor and investigator(s) will meet to review the toxicities in terms of DLT and safety observed in all patients, and to decide jointly the next dose level to be tested or to stop the dose escalation. All attempts will be made to reach consensus in the decision. Further details on SRC composition, meetings and decision-making process are provided in the SRC charter.

Maximum Tolerated Dose
The MTD is the highest drug dosage that is unlikely (< 25% posterior probability) to cause any DLT in more than 33% of the treated patients in the first cycle of PRS-344/S095012. A minimum of six patients evaluable for safety must be included in a dose level for it to be declared as the MTD.

Escalation can stop prior to MTD determination if deemed appropriate based on PK, safety and PK/ pharmacodynamic profiles. The RP2D will not be higher than the MTD, if determined, or higher than the MAD in phase 1 and will be based on PK and PK/Pharmacodynamic considerations as well as the cumulative safety profile as reviewed during investigator/Sponsor cohort reviews with the Sponsor having the final decision.

6.4.7. Determination of PRS-344/S095012 recommended phase 2 dose

The RP2D will be determined based on safety data, pharmacokinetics and pharmacodynamic effect of PRS-344/S095012 observed in phase 1, including patients enrolled in backfilled cohorts. Modeling and simulation approaches may also be employed. Data from potential other clinical studies conducted with PRS-344/S095012 will also be used for the determination of the PRS-344/S095012 RP2D. In any case, the RP2D administered in phase 2 will not exceed the MTD or MAD determined in phase 1.

Dose expansion arm(s) may be initiated at the end of dose escalation once the RP2D has been determined based on safety, PK and available pharmacodynamics. Alternatively, depending on safety, PK, pharmacodynamics and efficacy available data, one or more dose expansion arm(s) may be initiated before the end of dose escalation. In this case, dose escalation can still proceed up to the MTD or MAD if not reached at that time. During any interim analysis, the dose of PRS-344/S095012 could be escalated to a higher dose, not exceeding the MTD, in a new arm of patients if determined as safe and after recommendation of the DMC. Selected dose(s) of PRS-344/S095012 administered in the dose expansion arm(s) will be recommended by the SRC during an end of cohort meeting. This recommendation will be discussed by the DMC before starting the expansion part of the study. All those discussions/recommendations will be reported in meeting minutes. Doses tested in the phase 2 part of the study will not exceed the MTD determined during the phase 1 part of the study or the highest safe dose evaluated during the phase 1 part of the study.

6.5. Phase 2 - Dose Expansion

Phase 2 will evaluate the potential efficacy of PRS-344/S095012 in 3 disease-specific arms as described in Section 6.1.
Patients will receive PRS-344/S095012 CCI as monotherapy.
Additional arms could be initiated in the same population/indication with the Q3W administration schema if considered relevant and decided during end of cohort meeting and/or approved DMC.

Additional settings or combination may be added through an amendment to the protocol and after Competent Authority (CA), Institutional Review Board (IRB) and Ethics Committee (EC) approvals.

A CBHM with one or more futility analyses will be adopted for the expansion part. According to the futility analysis result, recruitment could be:

- Stopped, if results are considered futile.
- Continued, if results are considered not futile. In that case, additional participants will be enrolled in the next stage and treated at the corresponding dose until the next interim analysis or predefined end of study.

At the end of the study, anti-tumor activity results on the overall participants included in all stages will be analysed.

In addition to efficacy assessments, the safety profile of PRS-344/S095012 will be reviewed regularly during the study with appropriate stopping rules and processes for safety review (see details in Section 6.6). The sponsor may stop any arm at any time for any reason. As new data emerge on the CL1-95012-001 study and from other ongoing studies of antibody(ies) with a similar mechanism of action, new tumor type(s) and treatments (*i.e.*, monotherapy or combination with immuno-oncology (IO) treatment, chemotherapy or targeted therapy) may be added to this study, through protocol amendment.

6.6. Stopping rules and Criteria for Treatment Withdrawal

6.6.1. Stopping rules for dose escalation

See Section 6.4. Sponsor can also stop the dose escalation at any time for any reason.

6.6.2. Stopping rules for dose expansion

Interim analyses will be performed to assess stopping for futility and safety.

Regular interim analyses will be conducted for each arm. Safety and efficacy data will be reviewed by the DMC. Enrollment and further dosing will stop according to efficacy criteria outlined in Section 6.5.
Enrollment during the dose expansion part of the study may also be paused because of unacceptable toxicity. Specifically, after 10 participants have been treated at the RP2D for at least 1 cycle or experienced a DLT during dose expansion, and if the posterior probability is greater than 0.8 that the true DLT rate during the treatment period (regardless of cycles) is greater than 33%, enrollment will be paused and the RP2D will be re-evaluated by the investigators and sponsor. Whether the RP2D is decreased or not, the posterior probability of DLT will be evaluated in increments of 10 participants who have been treated at the RP2D for at least 1 cycle or experienced a DLT during dose expansion. These calculations of the posterior probability of DLT, performed separately within each expansion arm (if the second expansion arm is initiated), will use the beta-binomial model, with a prior distribution of beta (0.5, 0.5), and include the DLT-evaluable participants treated at the RP2D during both dose escalation and dose expansion.

Enrollment and further dosing will continue during the interim analysis. Enrollment and further treatment will be based on DMC recommendations as to further conduct of the study. In accordance with Food and Drug Administration (FDA) guideline (FDA, 2018), the sponsor will interact with the regulatory authority, prior to enrolling more than 40 evaluable patients per arm.
In addition, enrollment may be stopped at any time during the study per Sponsor decision (or by the sponsor following a request from the DMC), even if futility and safety analysis support further enrollment.

6.6.3. Criteria for treatment withdrawal

PRS-344/S095012 treatment will be stopped for the following reasons:

- Confirmed radiographic/photographic disease progression. Patients should continue until a subsequent (at least 4 weeks) radiographic/photographic confirmation of progression. Patients may continue beyond confirmed PD if benefits are expected to outweigh risks in the opinion of the investigator and in consultation with the Sponsor.
- Unacceptable AE according to investigator's judgment (including intervening illness that prevents further administration of treatment).
- Significant patient noncompliance with protocol.
- Pregnancy.
- Patient decision to withdraw from the treatment or study.
- Patients may leave the study at any time for any reason if they wish to do so, without consequence. Patients will be asked if they are willing to continue the safety and disease / Survival follow up.
- Investigator decision to discontinue treatment or study.
- Patient lost to follow-up.
- Death.
- Sponsor decision to stop the study early.
- [redacted] year from CR and [redacted] years for patients with PR (although treatment may continue if benefits are expected to outweigh risks in consultation with Sponsor).
- Any other protocol deviation that results in a significant risk to the patient's safety.

Patients may voluntarily withdraw from the study or treatment at any time and for any reason. A patient's participation in the study may by ended according to the investigator's clinical judgment and the reason for patient withdrawal will be documented in the source data and noted on the e-CRF.

If such withdrawal occurs, or if the patient fails to return for visits, the investigator must determine the primary reason for the patient's withdrawal from the study and record that information in the e-CRF. If the reason for withdrawal is an AE, patient monitoring should continue until the outcome is evident. The specific event or test result(s) must be recorded in the e-CRF.

At a minimum, all patients who discontinue treatment will be contacted for a Safety Follow-up as described in Section 6.2.3.

Patients who discontinue for any reason, except withdrawal of the consent, will be followed for survival. Those who discontinue for any reason *other* than PD or withdrawal of the consent, will be followed for the Disease Status, (by radiologic/photographic assessment), then for Survival after PD. Full details on the follow up visits according to the treatment discontinuation reasons are provided in Section 6.2.3.

In all cases, it should be clearly documented in the source data and noted on the e-CRF if patients withdrew their consent and will not enter the follow-up phase, or if patients stop the study treatment but will continue further participation in the study.

6.7. COVID-19 Information

In case of highly suspected COVID-19 infection (based on typical symptoms or typical chest CT scan images) or confirmed COVID-19 infection (based on positive COVID-19 biological testing), the study treatment(s) should be immediately interrupted.

The study treatment(s) could be restarted if patient is asymptomatic and a period of at least 7 days after the diagnosis has been respected, and with a negative test (if the testing is required by the institutional site).

6.8. Safety Management and Criteria for Dose Adjustment

Due to its immune agonist and antagonist activities, PRS-344/S095012 may trigger immune-related adverse events as already observed with other members of the same class. Management of these toxicities should follow standard medical and institutional practices, with the support of recommendations from the Society for Immunotherapy of Cancer (SITC) (Puzanov *et al.*, 2017; Brahmer *et al.*, 2021) and ASTCT recommendation for CRS management, as outlined in the following sections.

Dose modifications for PRS-344/S095012 should follow general dose modifications as described below.

6.8.1. Management of Infusion-related Reactions

Infusion-related reactions associated with PRS-344/S095012 administration should be managed according to the standard practice of medicine. General guidelines for the management of such reactions are provided in this section. Infusion-related reactions (IRRs) will be defined according to CTCAE v5.0 (Appendix 2: Grading of IRR (according to CTCAE v5.0). IRR associated to obinutuzumab should be managed according to the product label and local standard guidelines.

In case of IRR, a specific form should be completed in the e-CRF.

Patients should be monitored closely for the development of IRRs during PRS-344/S095012 administration. Medications and supportive measures for the treatment of such reactions should be available for immediate use during the study drug administration. Resuscitation equipment and other supplies for the emergency management of an allergic/toxic reaction must be available.

Table (6.8.1) 1 - PRS-344/S095012 treatment modification and medication for IRR

NCI-CTCAE Grade **(See description in Appendix 2** Grading of IRR (according to CTCAE v5.0)	**Treatment modification and medication**
Grade 1 – mild	• Increase monitoring frequency of vital signs as medically indicated as patients are deemed medically stable • The administration may be continued however the rate of infusion may be reduced to 50% at the discretion of the investigator. • If the symptoms resolve, the administration rate can be increased, as tolerated, to the baseline rate. • The patient may receive appropriate further treatment for IRRs if clinically indicated per the site's standard practice for management of IRRs.
Grade 2 – moderate	• Stop IMP infusion • Increase monitoring of vital signs as medically indicated • If symptoms resolve quickly or decrease to Grade 1, resume infusion at 50% of original rate with close monitoring of any worsening, otherwise hold dosing until resolution of symptoms with mandated premedication for the next scheduled visit. If the patient's symptoms do not return, and vital signs are stable, the administration rate for the next scheduled administration may be increased, as tolerated, to the baseline rate. • Consider treatment with corticosteroids if symptoms persist. At the next infusion, consider H_2-blockers (*e.g.*, famotidine or ranitidine) as clinically indicated. • If patient has a second occurrence of Grade ≥ 2 IRR on the reduced-rate infusion with the suggested medication, stop the infusion and consider removing the patient from treatment • If worsens to Grade 3 or 4, follow treatment modification guidelines accordingly
Grade 3 or Grade 4 – severe or life-threatening	• Stop IMP infusion immediately and disconnect infusion tubing from the patient with additional appropriate medical measures and close monitoring until deemed medically stable by attending Investigator. Hospitalization and/or close monitoring is recommended • Administration of glucocorticoids may be required • Permanently withdraw patient from IMP treatment and do not administer any further IMP treatment

6.8.2. Management of Cytokine Release Syndrome

Cytokine release syndrome associated with PRS-344/S095012 administration should be managed according to the standard practice of medicine. General guidelines for the management of such reactions are provided in this section. CRS will be graded according to ASTCT CRS Consensus Grading (Lee *et al.*, 2019) (Appendix 3). In case of CRS, a specific CRS form should be completed in the e-CRF where all symptoms related to this CRS will be reported (except neurologic symptoms which should be reported in a separate AE form).

Table (6.8.2) 1 - PRS-344/S095012 treatment modification and medication for CRS

ASTCT Grade (See description in Appendix 3)	**Treatment modification and medication**
Grade 1	• Assess for infection. • Corticosteroids should NOT be used for Grade 1 CRS. • Administer acetaminophen or ibuprofen for fever. • Monitor the patient for worsening of condition.
Grade 2	• Stop IMP infusion • If symptoms resolve (≤ Grade 1) and upon the clinical judgment of the treating physicians, administration of the IMP can be resumed • Monitor cardiac and other organ functions closely • Administer IV fluids, diphenhydramine hydrochloride IV or institutional equivalent, acetaminophen (paracetamol) or ibuprofen PO for fever, and oxygen and bronchodilators for bronchospasm, as appropriate and if not administered previously. • Intervene with immunosuppressive agents if the patient is judged to be unable to tolerate the altered hemodynamics and organ stresses associated with the syndrome. • Tocilizumab may be used for Grade 2 CRS that does not resolve with other measures within two hours of starting treatment for the Grade 2 CRS, or that requires the use of supplemental oxygen > 4 L/min by nasal cannula or low dose vasopressors. • Corticosteroids may be used for Grade 2 CRS that does not respond to other measures, including tocilizumab, until resolution • Monitor for worsening condition.

Table (6.8.2) 1 (Cont'd)- PRS-344/S095012 treatment modification and medication for CRS

ASTCT Grade (See description in Appendix 3)	Treatment modification and medication
Grade 3 or Grade 4 – severe or life-threatening	• Permanently discontinue PRS-344/S095012 treatment • Administer IV fluids, diphenhydramine hydrochloride (or institutional equivalent) IV, acetaminophen (paracetamol) or ibuprofen PO for fever, and oxygen and bronchodilators for bronchospasm, as appropriate. • Provide appropriate circulatory support, including vasopressors as medically indicated. • Monitor cardiac and other organ functions closely • Monitor the patient very closely, *e.g.* in an intensive care unit • If possible, a blood sample should be obtained at the time of diagnosis of IRR/CRS for the evaluation of circulating cytokines. Follow-up samples should also be obtained at the time of resolution of symptoms (see Section 9.5.3). The appropriate diagnostic or treatment procedures should not be delayed or hindered by obtaining such samples. • If possible, a blood sample should be obtained within 24h after the diagnosis of CRS for the evaluation of PK and ADA. (see Sections 9.3 and 9.4.1). The appropriate diagnostic or treatment procedures should not be delayed or hindered by obtaining such samples. • Administer tocilizumab if not administered previously. If administered previously, an additional dose may be used for prolonged or recurrent episodes. For Grade 4, higher doses of corticosteroids (dexamethasone 30 mg or equivalent) could be used.

Please refer to Sections 8.9.3 and 8.9.5 for further information on the use of tocilizumab and corticosteroids.

If a patient presents CRS, the following measures should be taken:

- In case of CRS, whatever the grade of the event, premedication is recommended for the next infusion of the patient who experiences the event. This premedication should be put in place at the discretion of the investigator. Section 8.9.2 provides guidance for the premedication.
- The availability of tocilizumab on site should be checked before any infusion.
- The targeted duration of infusion is up to 2 hours. The infusion duration will be defined per cohort during end of cohort meetings in order to mitigate the risk of CRS according to safety data obtained for ongoing participants. The infusion duration may be increased for safety reasons after the approval by the Sponsor.

If needed, a recommendation for the use of premedication at the investigator's discretion for all patients may be discussed during a meeting with SRC (safety review meeting or end of cohort meeting) during phase 1 or DMC during phase 2. The treatment used in this premedication will be determined during an SRC meeting or DMC meeting.

6.8.3. Management of hepatotoxicity

Hepatotoxicity should be considered when abnormalities are observed in liver function tests (LFTs: AST, ALT and bilirubin), according to CTCAE v5.0 (Appendix 4).

Table (6.8.3) 1 - PRS-344/S095012 treatment modification and medication for hepatotoxicity

Toxicity and CTCAE Grade	Treatment modification and medication
Grade 1 LFT abnormality (any enzyme)	• PRS-344/S095012 may be continued. • A hepatic function panel should be performed at least once weekly. • If liver enzyme and function tests are stable, the frequency of blood tests can be reduced.
Grade 2 LFT abnormality (any enzyme)	• Hold treatment with PRS-344/S095012. • Monitor hepatic function every 3 to 5 days. • Rule out viral hepatitis, autoimmune disease biliary obstruction, new metastasis or thrombosis. • Consider prednisone 0.5-1 mg/kg/day (or the equivalent dose of methyl prednisolone) with a 4-week taper. • Resume PRS-344/S095012 treatment when corticosteroid treatment tapers to 10 mg/day of prednisone and recovery to Grade ⩽ 1 or Baseline, based on Investigator's clinical judgement.
In patients <u>without</u> liver metastasis	
• AST or ALT increases to more than 3 and up to 8 times ULN or • Total bilirubin increases to more than 1.5 up to 3 times ULN	• Hold treatment with PRS-344/S095012* • Monitor hepatic function every 3 to 5 days. • Rule out viral hepatitis, autoimmune disease, biliary obstruction, new metastasis or thrombosis. • Consider prednisone 0.5 – 1 mg/kg/day (or the equivalent dose of methyl prednisolone) with a 4-week taper.
• AST or ALT increases to more than 8 times ULN or • Total bilirubin increases to more 3 times ULN	• Permanently discontinue PRS-344/S095012 treatment. • Monitor liver function at least every 1 to 2 days. • Start prednisone 1-2 mg/kg/day. If refractory after 3 days, consider other immunosuppressors. • If liver enzymes improve, taper corticosteroids over 4 weeks. • Consider obtaining liver biopsy.
In patients <u>with</u> liver metastasis	
• Baseline AST or ALT is more than 1 and up to 3 times ULN and increases to more than 5 and up to 10 times ULN or • Baseline AST or ALT is more than 3 and up to 5 times ULN and increases to more than 8 up to 10 times ULN	• Hold treatment with PRS-344/S095012* • Monitor hepatic function every 3 to 5 days. • Rule out viral hepatitis, autoimmune disease, biliary obstruction, new metastasis or thrombosis. • Consider prednisone 0.5 – 1 mg/kg/day (or the equivalent dose of methyl prednisolone) with a 4-week taper.
• AST or ALT increases to more than 10 times ULN or • Total bilirubin increases to more than 3 times ULN	• Permanently discontinue PRS-344/S095012 treatment. • Monitor liver function at least every 1 to 2 days. • Start prednisone 1-2 mg/kg/day. If refractory after 3 days, consider other immunosuppressors. • If liver enzymes improve, taper corticosteroids over 4 weeks. • Consider obtaining liver biopsy.

** Resume in patients with complete or partial resolution (Grades 0 to 1) after corticosteroid taper. Permanently discontinue if no complete or partial resolution within 12 weeks of initiating steroids or inability to reduce prednisone to 10 mg per day or less (or equivalent) within 12 weeks of initiating steroids*

In all cases, close monitoring and evaluation should be initiated upon detection and confirmation of early signals of possible drug-induced liver injury (DILI):

- Obtain a detailed history of symptoms, concurrent diseases, concomitant medications (including non-prescription medications and herbal and dietary supplement preparations), alcohol use, recreational drug use and special diets.
- Obtain additional tests to evaluate liver function, as appropriate (*e.g.* total bilirubin, direct and indirect bilirubin, alkaline phosphatase, Gamma-glutamyl transferase, international normalized ratio (INR), albumin).
- Investigate:
  - Seropositivity for acute viral hepatitis type A, B, C, D and E, EBV and further hepatotrophic viruses, as appropriate.
  - Autoimmune disease through the quantification of serum immunoglobulin with IgG concentrations > 1.5 x ULN, serum autoantibodies (such as antinuclear antibodies, anti-smooth muscle antibodies, or anti-liver-kidney microsomal antibodies) at titers greater than 1:80; seronegativity for anti-mitochondrial antibodies.
  - Alcoholic hepatitis, non-alcoholic fatty liver disease, hypoxic/ischemic hepatopathy, and biliary tract disease.
- In case of immune-related hepatotoxicity that leads to treatment withdrawal, PK and ADA samples should be taken within 24h after the diagnosis (see Sections 9.3 and 9.4.1). The appropriate diagnostic or treatment procedures should not be delayed or hindered by obtaining such samples.

6.8.4. Management of Hemophagocytic lymphohistiocytosis

HLH should be diagnosed and treated as an emergency. The following recommendations are provided in order to help the identification / diagnosis of such event (those recommendations do not prevail the medical judgement):

- If a patient develops grade 2 or greater neutropenia, thrombocytopenia or anemia, which may suggest the diagnosis of HLH, more frequent assessments of peripheral blood counts (CBCs) may be warranted.
- If a patient develops grade 3 or higher cytopenias, blood samples should be collected for measurements of serum ferritin, triglycerides, and fibrinogen. Where available, soluble IL-2 and soluble CD163 should be measured as well.
- For patients suspected of having HLH, based on clinical presentation and blood tests, bone marrow aspiration and biopsy should be performed to confirm or rule out the diagnosis.
- If a patient is found to have HLH, blood samples should be collected to measure the prevailing concentrations of PRS-344/S095012, ADAs, and cytokines.
- If a patient is diagnosed with HLH, it is strongly recommended to permanently withdraw the treatment with PRS-344/S095012.

Guidelines for the diagnosis of HLH and its treatment are provided in Appendix 9. These guidelines are based on the HLH-2004 consensus criteria, which were further revised in 2014 for HLH associated with malignancies.

6.8.5. Management of other Adverse Events

Other immune-related adverse events are known to occure with the use of immunotherapy such anti-PD-(L)1 and CTLA monoclonal antibodies. Beyond the AEs described above, other dermatologic, gastroenterological, endocrine, pulmonary, rheumatologic/musculoskeletal, cardiovascular, hematologic, renal, neurologic and ophthalmologic immune-related toxicities have also been described.

Management of these toxicities should follow standard medical and institutional practices and the SITC and American Society of Clinical Oncology (ASCO) (Schneider *et al*., 2021) recommendations when applicable. Guidelines for the management of specific immune-related AEs are provided in Table (6.8.5) 1. General guidelines for the management of other related AEs are provided in Table (6.8.5) 2.

If possible, a blood sample should be obtained within 24h after the diagnosis of any immune-related adverse event that leads to interruption or discontinuation of study treatment for the evaluation of PK and ADA (see Sections 9.3 and 9.4.1). The appropriate diagnostic or treatment procedures should not be delayed or hindered by obtaining such samples.

Table (6.8.5) 1 - PRS-344/S095012 treatment modification and medication for specific immune-related AEs

Adverse Reaction	Severity of Event	Treatment modification	Mitigation measure, management and medication
Pneumonitis	Grade 1	Hold treatment with PRS-344/S095012* or proceed with close monitoring	Refer to ASCO Guideline (Schneider *et al.*, 2021), Table 3
	Grade 2	Hold treatment with PRS-344/S095012 *	
	Grade 3	Permanently discontinue PRS-344/S095012 treatment	
Colitis	Grade 2 or 3	Hold treatment with PRS-344/S095012*	Refer to ASCO Guideline (Schneider *et al.*, 2021), Table 2
	Grade 4	Permanently discontinue PRS-344/S095012 treatment	
Endocrinopathies	Grade 2	Consider holding depending on the event	Refer to ASCO Guideline (Schneider *et al.*, 2021), Table 4
	Grade 3 or 4	Withhold until clinically stable or permanently discontinue depending on severity	
Nephritis with Renal Dysfunction	Grade 2 or 3 increased blood creatinine	Hold treatment with PRS-344/S095012*	Refer to ASCO Guideline (Schneider *et al.*, 2021), Table 6
	Grade 4 increased blood creatinine	Permanently discontinue PRS-344/S095012 treatment	
Exfoliative Dermatologic Conditions	Suspected Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) or drug reaction with eosinophilia and systemic symptoms (DRESS)	Hold treatment with PRS-344/S095012*	Refer to ASCO Guideline (Schneider *et al.*, 2021), Section 1
	Confirmed SJS, TEN, DRESS	Permanently discontinue PRS-344/S095012 treatment	
Myocarditis	Grade 2, 3, or 4	Permanently discontinue PRS-344/S095012 treatment	Refer to ASCO Guideline (Schneider *et al.*, 2021), Table 9
Neurological Toxicities	Grade 2	Hold treatment with PRS-344/S095012*	Refer to ASCO Guideline (Schneider *et al.*, 2021), Table 7
	Grade 3 or 4	Permanently discontinue PRS-344/S095012 treatment	

** Resume in patients with complete or partial resolution (Grades 0 to 1) after corticosteroid taper. Permanently discontinue if no complete or partial resolution within 12 weeks of initiating steroids or inability to reduce prednisone to 10 mg per day or less (or equivalent) within 12 weeks of initiating steroids*

Table (6.8.5) 2 - PRS-344/S095012 Dose adjustment for Adverse Events (other than IRR, CRS, hepatoxicity and specific immune-related AEs)

Severity of Event	Treatment modification and medication
Grade 1	• Maintain PRS-344/S095012 dose level, except for some neurologic, hematologic, and cardiac toxicities. • Provide treatment to control symptoms, if applicable.
Grade 2	• Tolerable Grade 2 toxicities: Maintain PRS-344/S095012 treatment. • Intolerable Grade 2 toxicities: o Hold PRS-344/S095012 treatment, with consideration of resuming when symptoms revert to Grade 1 or less. o Corticosteroids may be administered (initial dose of 0.5 to 1 mg/kg/day of prednisone or equivalent). Upon 2nd occurrence, dose of PRS-344/S095012 may be reduced by one dose level.
Grade 3	• Suspend PRS-344/S095012 treatment • Discontinuation or dose modification to be determined by discussion between investigator(s) and Medical Monitor on a case-by-case basis. • High-dose corticosteroids (prednisone 1 to 2 mg/kg/day or methylprednisolone 1 to 2 mg/kg/day) treatment should be initiated. Corticosteroids should be tapered over the course of at least 4 to 6 weeks. Some refractory cases may require infliximab or other immunosuppressive therapy.
Grade 4	• Permanently discontinue PRS-344/S095012 treatment • For single laboratory value out of normal range without any clinical correlates, permanent discontinuation of PRS-344/S095012 treatment is not required. In this case, study intervention should be held until the etiology is determined. If the event is not considered immune-related and resolves to Grade ≤ 1, restarting study intervention may be considered.

6.9. Dose delay

In case of delays of IMP administration of more than CCI days, the patient should be withdrawn from the study. For patients that show clinical benefit (*i.e.* stable disease), a case-by-case discussion between sponsor and investigators may lead to the patient continuing the study if judged beneficial to the patient.

These rules apply during the entire study treatment.

Any delays in dosing and the reasons for such delays must be documented in the e-CRF.

7. STUDY POPULATION

7.1. Number of Patients

Phase 1 - Dose escalation (parts A and B): Approximately CCI patients will be enrolled for dose escalation. The final number of patients will depend on the number of dose cohorts that will be opened before reaching the MTD (if found), MAD or RP2D. For part A, one to four evaluable patients will be enrolled per dose level.

Patients enrolled in order to backfill previously evaluated dose levels: Approximately CCI additional patients may be enrolled to as many as CCI previously evaluated dose levels, in order to further characterise their safety, PK or PD.

Phase 2 – Dose expansion: Approximately CCI patients will be enrolled in each of the arms. Additional arms may be considered later via an amendment to the protocol.

- Arm 1: approximately CCI, cervical cancer, CPI-naïve.
- Arm 2: approximately CCI, cervical cancer, CPI-relapsed / refractory.
- Arm 3: approximately CCI, CSCC, CPI-relapsed / refractory.

7.2. Inclusion and Exclusion Criteria

Note: the criteria are numbered according to the order of first appearance in the protocol. The letter "a" means a first change in the criterion, the letter "b" a second change, etc. Through amendment N°5, the presentation of criteria has been reviewed to have dedicated sub-sections for phase 1 and phase 2 specific criteria.

Inclusion criteria

1. The participating patient signs a written informed consent obtained prior to performing any study procedure, including screening procedures.
2. Age ≥ 18 years on the day the consent is signed.
4. Patients should have a documented disease progression on prior therapy before entry into this study.
6. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.
47a. Royal Marsden Prognosis Score of 0 to 1 (score based on LDH value, albumin value and number of sites of metastasis, see Appendix 8).
42. Patients must have a life expectancy of at least 3 months following first IMP administration.
8d. Adequate organ function as assessed by laboratory tests within 7 days prior to pretreatment with obinutuzumab:

- Absolute neutrophil count (ANC) ≥ 1500/µL
- Platelet count ≥ 75 000/µL (this criterion must be met without the use of transfusion or thrombopoietin for at least two weeks prior to study drug administration).
- Hemoglobin ≥ 8g/dL (this criterion must be met without the use of transfusion or erythropoietin within the two weeks prior to study drug administration).
- Lymphocyte count ≥ 800/µL.
- Gamma-globulin level > 6g/L (by serum protein electrophoresis) or IgG level > 4g/L (by measurement of quantitative immunoglobulins).

- Glomerular filtration rate (GFR) or measured or calculated creatinine clearance (CrCl) ≥ 30mL/min.
- Total bilirubin ≤ 1.5×ULN (or total serum bilirubin < 3×ULN for patients with Gilbert's disease).
- AST and ALT ≤ 2.5×ULN (5×ULN for patients with liver metastases).

9a. A female patient must use a highly effective method of birth control during study treatment, for 120 days after the last dose of the PRS-344/S095012, or 18 months after the last obinutuzumab infusion, whichever comes the latest.

10a. A male patient with childbearing potential partners must use a condom during the study and for at least 4 months after the last dose of the study treatment, or 6 months after the last Obinutuzumab infusion, whichever comes the latest. Patients who are sterile or vasectomized must use a condom during sexual intercourse with a childbearing potential partner in order to avoid exposure of an existing embryo/foetus. In addition, contraception should be considered for their female partner. Contraceptive measures do not apply if the patient is sexually abstinent. Sperm donation will not be allowed during the study and for 4 months after the last dose of study treatment, or 6 months after the last obinutuzumab infusion, whichever comes the latest.

11a. Human immunodeficiency virus (HIV)-infected patients must have well-controlled HIV or be on adequate antiretroviral therapy (ART).

48a. Tests should be negative for Cytomegalovirus (CMV), Epstein-Barr virus (EBV), Hepatitis B virus (HBV), and Hepatitis C virus (HCV) infection, according to local standards:

- Negative CMV DNA testing in serum or plasma by a sensitive quantitative molecular method.
- Absence of serum immunoglobulin (Ig)M antibodies against EBV-VCA (Viral Capside Antigen).
- Negative serologic testing for hepatitis B surface antigen (HbsAg) or a negative result by a sensitive quantitative molecular method for HBV-DNA in serum or plasma.
- Negative HCV RNA testing in serum or plasma by a sensitive quantitative molecular method.

52. Negative test results for human T-lymphotropic virus 1 (HTLV 1). HTLV testing is only required for participants from countries in which HTLV 1 infection is endemic (Japan, countries in the Caribbean basin, South America, Central America, sub-Saharan Africa, and Melanesia).

Dose escalation, specific additional inclusion criteria:

3. Patients with a histological diagnosis of an unresectable, locally advanced or metastatic solid tumor for which standard treatment options are not available, no longer effective, or not tolerated.

5a. Patients must have measurable disease per RECIST 1.1 as assessed by the local site investigator/imaging. Lesions situated in a previously irradiated area are considered measurable only if progression has been demonstrated in such lesions.

7b. Patients with no available archived material must have one or more tumor lesions amenable to biopsy.

Note: archival tissue taken < 9 months before the start of treatment can be used. If a patient consents to an on-treatment biopsy (which is optional but highly encouraged)), pre-treatment tumor tissue should be available ideally from a fresh biopsy taken before the start of treatment or, if available, from archival tissue taken < 6 months before S095012 administration without any intercurrent treatment.

Patients enrolled to a previously evaluated dose level (back-fill patients): an on-treatment tumor tissue biopsy is required. A pre-treatment fresh tumor biopsy is also required unless archival tumor tissue was obtained < 6 months before the start of treatment and there was no intervening cancer treatment given during this time.

Dose expansion, specific additional inclusion criteria:

The criterion No. 12 is deleted as per amendment No. 5.

13. Patients with histologically diagnosed:

- *Arm 1 and 2*: recurrent, persistent, and/or metastatic cervical cancer. Acceptable histologies are squamous carcinoma, adenocarcinoma, and adenosquamous carcinoma.
  Note: Sarcomas and neuro-endocrine carcinomas are not eligible.
- *Arm 3:* locally advanced or metastatic cutaneous squamous cell carcinoma.

14. Patients must have received:

- *Arm 1 (cervical cancer, CPI-naïve)*: at least 1 prior line of platinum-based combination therapy. Patients must not have received any prior treatment with an immune checkpoint inhibitor (anti-PD-1, PD-L1 or anti-CTLA-4 [cytotoxic T lymphocyte-associated protein 4]) and do not have access to an approved immune checkpoint inhibitor. Surgery, radiation therapy, and additional chemotherapy must not be considered appropriate alternative treatment options for these patients.
- *Arm 2 (cervical cancer, CPI-relapsed/refractory):* at least 1 prior line of systemic therapy with an immune checkpoint inhibitor as monotherapy or in combination with chemotherapy and/or any other systemic therapies. Surgery, radiation therapy, and additional chemotherapy must not be considered appropriate alternative treatment options for these patients.
- *Arm 3* (CSCC, *CPI-relapsed/refractory*): at least 1 prior line of systemic therapy with an immune checkpoint inhibitor as monotherapy or in combination with chemotherapy and/or any other systemic therapies. Surgery, radiation therapy, and additional chemotherapy must not be considered appropriate alternative treatment options for these patients.

45. Biopsy requirements

- *Arms 1 and 2 (cervical cancer):* fresh baseline biopsies are mandatory, on-treatment biopsies are optional.
  Note: fresh baseline biopsies are not mandatory if archived tumor biopsy specimens collected no later than 6 months without intercurrent treatment before screening, are available. If no archived material is available, a fresh biopsy must be collected at baseline.
- *Arm 3 (skin cancer):* fresh baseline biopsies are mandatory, on-treatment biopsies are mandatory unless medically contra-indicated.
  Note 1: fresh baseline biopsies are not mandatory if archived tumor biopsy specimens collected no later than 6 months without intercurrent treatment before screening, are available. If no archived material is available, a fresh biopsy must be collected at baseline.
  Note 2: For patients deemed eligible by digital photography only, an additional biopsy is required within 30 days of CR determined by the investigator for confirmation of the CR.

46. Patients must have at least one measurable target lesion as per RECIST 1.1 and/or World Health Organization (WHO) criteria for only externally visible skin tumors confirmed by central review. Lesions situated in a previously irradiated area are considered measurable only if progression has been demonstrated in such lesions.

Exclusion criteria

15. Pregnant and lactating women.

16b. Patients with previously treated brain metastases that may be considered active. Patients may participate provided they are radiologically stable, clinically asymptomatic and are off immunosuppressive therapies for at least 4 weeks prior to first IMP administration. Low and stable dose of steroid (≤ 10 mg/day prednisone or equivalent) is allowed.

17. Patients with primary central nervous system (CNS) malignancy.

18a. Patients with Child-Pugh Class B8 or higher liver cirrhosis.

19a. Patients who have received prior:

a. Chemotherapy, small molecule inhibitors, monoclonal antibodies, antibody-drug conjugates, and/or other similar investigational agent: at least 3 weeks or 5 half-lives prior to first IMP administration, whichever is shorter.
b. Radioimmunoconjugates or other similar experimental therapies: at least 6 weeks or 5 half-lives prior to first IMP administration, whichever is shorter.

20b. Patients must have recovered from any AE (from previous anti-cancer therapy) to CTCAE V5.0 Grade 1 or lower. Grade 2 alopecia, peripheral neuropathy, decreased haemoglobin, and electrolyte changes are acceptable. Patients receiving replacement hormone therapy due to previous AEs will not be excluded from participation in this study if the associated AE has recovered to Grade 1 with replacement therapy prior to first IMP administration.

21. Patients who have received a 4-1BB agonist in the past.

22. Patients who have had major surgery within 4 weeks prior to first administration of IMP.

23. Patients with an active autoimmune disease that is currently requiring systemic anti-inflammatory treatment (such as disease-modifying anti-rheumatic drugs [DMARDs], steroids, or immunosuppressants), except vitiligo, alopecia areata, asthma/atopy and psoriasis treated and controlled by topical therapies. Patients with auto-immune endocrinopathies that are well treated by replacement hormone therapies (*e.g.* thyroxine, insulin, physiological steroids for adrenal or pituitary deficits) are eligible.

24a. Patients with a history of immune-related adverse events (irAEs) from a previous line of treatment must have recovered to CTCAE Grade $\leq$ 1 and have also stopped any immunosuppressive/steroid therapy > 10 mg prednisone per day. Patients with prior history of Grade $\geq$ 3 immune-related pneumonitis, colitis, hepatitis, or myocarditis are excluded.

25c. Patients who have received either systemic corticosteroids (> 10 mg per day of prednisone or equivalent) or other immunosuppressive medications during the 2 months prior to the first dose of the study drug. Higher single doses of corticosteroids given as premedication against infusion-related reactions are allowed. Treatment with local steroids (inhaled, intranasal, injected) are allowed.

26. Patients who have received an allogenic solid organ or bone marrow transplant.

27. Patients with a history of interstitial lung disease, pneumonitis requiring systemic steroids for treatment, or current pneumonitis.

28. Patients with a clinically significant cardiovascular disease or condition, including:

a. New York Heart Association (NYHA) classification III or IV, known symptomatic coronary artery disease, or symptoms of coronary artery disease on systems review, or known cardiac arrhythmias (atrial fibrillation or supraventricular tachycardia [SVT]).
b. Any concomitant serious health condition, which, in the opinion of the investigator, would place the patient at undue risk from the study, including uncontrolled hypertension and/or diabetes, clinically significant pulmonary disease (*e.g.*, chronic obstructive pulmonary disease requiring hospitalization within 3 months) or neurological disorder (*e.g.*, seizure disorder active within 3 months).

29b. Patients with an active infection with a viral, bacterial, or fungal pathogen requiring systemic treatment within seven days before first IMP administration. Any patient requiring systemic treatment for CMV or EBV within 2 months before IMP administration should be excluded. Refer to inclusion criterion 11a and exclusion criterion 32a for HIV infections, and to inclusion criterion 48a for CMV, EBV, hepatitis B and C infections.

32a. Patients with HIV who have Castleman's disease.

33. Patients who have received a live vaccine within four weeks prior to first IMP administration. Examples of live vaccines include but are not limited to measles, mumps, rubella, varicella zoster, yellow fever, rabies, Bacillus Calmette-Guérin (BCG), and typhoid vaccine. Seasonal injected influenza vaccines (which are generally killed virus vaccines) and live replicative vaccines are allowed; intranasal influenza vaccines are live attenuated vaccines and are not allowed.
34. Patients who have received any Covid-19 vaccine within 14 days prior to first IMP administration or who have a dose planned during the DLT observation period.
35. Patients with a history of clinically significant hypersensitivity to monoclonal antibodies or infused therapeutic proteins or any component of the study drugs.
36. Patients with significant pulmonary compromise including a requirement for continuous supplemental oxygen to maintain adequate oxygenation.
37. Patients with history of, or current evidence of, any condition, surgical or medical therapy, or laboratory abnormalities that might confound the results of the study, make study drug administration hazardous, interfere with the patient's involvement for the full duration of the study, or make it difficult to monitor AEs such that in the opinion of the treating physician it is not in the best interest of the patient to participate in the study.
38. Any psychiatric or substance abuse condition rendering the patient unable to understand the nature, scope, and possible consequence of the study and or evidence of an uncooperative attitude.
39. Patients with any other active malignancy within 3 years prior to first IMP administration, except for adequately treated basal cell or squamous cell skin cancer, or carcinoma in situ.
49. Patients with a history of an opportunistic infection within a year prior to first IMP administration.
50. History of progressive multifocal leukoencephalopathy.
51. Active tuberculosis requiring treatment within 3 years prior to the start of treatment or a suspicion of latent tuberculosis by the investigator.

Dose expansion, specific additional exclusion criteria:
Of note, the previous criteria for dose expansion (No. 40, 41 and 43) are deleted as per amendment No. 5.

7.3. Patients or Partners of Patients of Reproductive Potential

Pregnancy is an exclusion criterion and women of childbearing potential must not be considering getting pregnant during the study. Female patients of childbearing potential must have a negative serum or urine pregnancy test within 72 hours prior to start of study drug. A serum or urine pregnancy test will be performed at the safety FU visits.

To be considered of non-childbearing potential, a female patient must meet at least one of the following criteria:

- Postmenopausal (*i.e.* amenorrhoeic for at least two years) AND a follicle-stimulating hormone value within the institution's postmenopausal range at screening.
- Hysterectomy OR bilateral oophorectomy.
- Tubal ligation at least 5 years prior to screening with no subsequent pregnancies.

Fertile female patients must practice a highly effective method of contraception during treatment and for 120 days following the last dose of study drug. Highly effective contraception result in a low failure rate (*i.e.* less than 1% per year) when used consistently and correctly, such:

- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:
  - Oral.
  - Intravaginal.
  - Transdermal.
- Progestogen-only hormonal contraception associated with inhibition of ovulation:
  - Oral.
  - Injectable.
  - Implantable.
- Intrauterine device (IUD).
- Intrauterine hormone-releasing system (IUS).
- Bilateral tubal occlusion.
- Vasectomized partner.
- Sexual abstinence (when this is in line with the preferred and usual lifestyle of the patient).

In case of use of oral contraception women should have been stable on the same contraceptive drug (same active principle) for at least 6 months prior to the first study treatment administration.

A male patient with childbearing potential partners must use a condom during the study and until at least 4 months after the last dose of the study treatment. Patients that are sterile or vasectomized must use a condom during sexual intercourse with a childbearing potential partner in order to avoid exposure of an existing embryo/foetus. In addition, contraception should be considered for their female partner.
Contraceptive measures do not apply if the patient is sexual abstinent. Sperm donation will not be allowed during the study and for 4 months after the last dose of study treatment.

Patients will be instructed to notify the investigator if pregnancy is discovered either during or within 4 months of the last dose of study drug.

7.4. Waivers of Inclusion/Exclusion Criteria

No waivers of these inclusion or exclusion criteria will be granted by the investigator and the sponsor or its designee for any patient enrolling into the study.

8. DESCRIPTION OF STUDY TREATMENT

8.1. Physical Description of the IMP

The IMP is PRS-344/S095012 and its structure is described in Section 4.2.1. Table (8.1) 1 summarizes the characteristics of the IMP. Further details are provided in the Pharmacy Manual.

Table (8.1) 1 - Investigational Medicinal Product

	Investigational Medicinal Product
Product name:	PRS-344/S095012
Dosage form:	Concentrate for solution for infusion filled in a US Pharmacopeia and European Pharmacopeia Type I glass vial configuration (FluroTech® stopper and aluminum crimp). CCI mL vials with a nominal fill volume of 16 mL for IV administration.
Unit dose	Each vial contains CCI mg of PRS-344/S095012 with a protein concentration of CCI mg/mL in CCI
Route of administration	Intravenous infusion
Storage conditions	2 °C to 8 °C

Vials containing PRS-344/S095012 drug product will be labelled according to national regulations for investigational products.

8.2. Method of Assigning Patients to Treatment Groups

Patients will be assigned to a dose cohort by the sponsor or sponsor's designee at the time of submission of the patient enrollment form according to the study design. All details are described in the Cohort Management Plan.

8.3. Packaging, Labeling and Storage of PRS-344/S095012

The IMP will be packaged and labeled according to current Good Manufacturing Practices (GMP). Details of the packaging and labeling of the clinical supplies are found in the Pharmacy Manual.

PRS-344/S095012 must be stored refrigerated at 2°C to 8°C in its original package in an appropriate storage facility accessible only to the pharmacist(s), the investigator, or a duly designated person. All the details on the storage and shelf life (stability) of the PRS-344/S095012 vials are described in the Pharmacy Manual.

The investigator or designated pharmacist is responsible for the daily IMP temperature monitoring using FONT-CIRT-FORM-311 "Therapeutic Unit temperature log sheet - centre" (recording Min-Max temperature every working day) or an equivalent document. In case of temperature deviation, the investigator/pharmacist should immediately:

- Place the affected IMP(s) in quarantine.
- Alert the monitor or the local project manager if the monitor is absent, forward to them all the needed information and implement ALL the instructions received.

Furthermore, the investigator or designated pharmacist must put in place an adequate corrective/preventive action once the first temperature deviation occurs to avoid recurrence.
IMP management will be verified on a regular basis by the study monitor.

8.4. Preparation and administration of PRS-344/S095012

Preparation of the IMP
During the preparation of the study medication, care must be taken to ensure sterility of the prepared solution as the product does not contain any anti-microbial preservative or bacteriostatic agent.
PRS-344/S095012 should be diluted in saline with the addition of CCI [redacted]
All the details for the preparation, including dilution steps and material compatibilities are provided in the Pharmacy Manual.

Administration of the IMP
PRS-344/S095012 will be administered at the dosage indicated in Section 6.3.3 or according to the dose decided for each cohort in phase 1 or at the beginning of each arm in phase 2. The investigator or his/her designee (experienced in the use of IV agents) will be responsible for administering the appropriate dose of PRS-344/S095012 to all patients.

PRS-344/S095012 will be administered by the IV route, via an indwelling venous catheter. The targeted duration of infusion is up to CCI [redacted] The infusion duration will be defined per cohort during end of cohort meetings. The infusion duration may be increased for safety reasons after the approval by the Sponsor. The reason for increasing the duration of infusion will be reported in the e-CRF. The infusion set must contain an in-line filter (0.22-micron pore size). Infusion line should be flushed, using saline. The catheter may be placed into a peripheral vein (if accessible), administration via central venous catheter or port (if in place) is allowed.

DO NOT administer PRS-344/S095012 as an IV push or bolus injection.

Volume of infusion
- The CCI [redacted] mg dose will be administered in a total volume of 50 ml.
- Doses above CCI [redacted] mg will be administered in a total volume of 200 ml.

All details about study medication handling, preparation and administration are described in the Pharmacy Manual, including the appropriate material compatibility.

8.5. Patient Monitoring During PRS-344/S095012 Administration

Patient vital signs should be measured as described in Section 9.1.3. All supportive measures consistent with optimal patient care will be provided throughout the study according to institutional standards.
Precautions for anaphylaxis should be taken during PRS-344/S095012 administration. Emergency resuscitation equipment and medications should be readily available. Additional supportive measures should also be available and may include, but are not limited to, epinephrine, antihistamines, corticosteroids, IV fluids, vasopressors, oxygen, bronchodilators, diphenhydramine and acetaminophen.

8.6. Accountability of Protocol-specified Treatments

IMPs receipt, dispensing according to the experimental design of the study, accountability and collection are the responsibility of the investigator and/or pharmacist of the medical institution.

Study personnel will maintain accurate records of IMPs shipments/receipts and its administration and will track it into the validated tracking system (RTSM).

The investigator and/or the pharmacist of the medical institution and/or a designated person from their study team must complete in real time the validated tracking system (RTSM).

The investigator and/or the pharmacist of the medical institution should only use the IMPs provided for the patients involved in the study. Remaining treatments (used and unused IMPs) will subsequently be collected and stored according to the local procedures and requirements, by the person responsible for the IMP management.

The site is responsible for the return or destruction of IMPs as required. A drug management system will manage IMPs inventory at all sites.

Destruction or return of IMP may be possible (after sponsor authorization) when the product has been used, has expired or no sooner than the last visit of the last treated patient. Destruction or return of the IMP is the responsibility of the investigator. Certified destruction will be performed according to standard modalities for that class of product and the attestation must be sent to the sponsor. More details on destruction process are provided in the Pharmacy Manual.

All defects or deterioration of IMPs or the packaging are to be reported to the study monitor. The investigator will notify the monitor of all complaints set out (change appearance…).

In the event of an anticipated return of IMPs to the sponsor (batch recall), the sponsor will prepare an information letter intended for the investigator and/or pharmacist of the medical institution. This letter will be sent by the person locally responsible for the study to each study center.

IMP management will be verified on a regular basis by the study monitor.

8.7. Blinding of Treatment

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

8.8. Treatment Compliance

The IMPs will be administered by designated and qualified personnel at the study site to ensure compliance. The number of injectable vials and volume infused are to be counted by the investigator or a designated person from his/her team and recorded in the e-CRF and RTSM.

8.9. Concomitant Medications

Patients are allowed to continue the medications that they are taking at baseline (unless specifically prohibited by the selection criteria). Patients may also receive concomitant medications that are medically indicated as standard of care for the treatment of symptoms concomitant disease and intercurrent illnesses. Patients may also receive therapy to mitigate any side effects of the study medication as clinically indicated, as well as best supportive care as per institutional guidelines. This may include, but is not limited to, antiemetics, antidiarrheals, anticholinergics, antispasmodics, antipyretics, antihistamines, analgesics, antibiotics, and other medications intended to treat symptoms. The investigator should instruct the patient not to take any additional medications (including over-the-counter products) during the study without prior consultation with the investigator. A specific caution must be taken for patients who are receiving medicinal products that are CYP450 substrates with a narrow therapeutic index. These patients should be closely monitored for potential adverse effects.

All concomitant medications will be recorded in the e-CRF.

8.9.1. Pretreatment with obinutuzumab

Premedication Prior to obinutuzumab administration

The use of corticosteroids, analgesics, non-steroidal anti-inflammatory drugs (NSAIDs) and/or antihistamines is required to minimize IRR reactions associated with the administration of obinutuzumab. Premedication must be administered prior to obinutuzumab administration. A list of the mandatory premedications is provided in the table provided below.

Premedication Requirements for obinutuzumab

Premedication	Timing of administration
Prednisolone 100 mg IV administered by IV infusion (or equivalent)	Completed at least 60 minutes prior to the obinutuzumab infusion
Oral analgesic antipyretic (e.g. 1000 mg acetaminophen/paracetamol).	At least 30 minutes prior to the obinutuzumab infusion
Antihistaminic medicine (e.g., diphenhydramine 50 -mg)	At least 30 minutes prior to the obinutuzumab infusion

Preparation

The obinutuzumab Drug Product will be supplied as a 50 mL single dose glass vial containing 1000-mg liquid concentrate in 40 mL (25 mg/mL) for infusion. In addition to the drug substance, the solution also contains histidine/histidine-HCl, trehalose dihydrate and poloxamer 188. All details regarding packaging, labeling, storage and preparation are described in the Pharmacy Manual.

Administration

Obinutuzumab should be administered under the close supervision of an experienced physician and in an environment where full resuscitation facilities are immediately available.

Obinutuzumab will be administered either as a single dose of CCI mg or two doses of CCI mg on two consecutive days, as per investigator's judgment. Within the first option, obinutuzumab will be administered at the earliest CCI before the first dose of PRS-344/S095012 (C1D1), and at the latest CCI before C1D1. If obinutuzumab is administered over two consecutive days, it will be done at the earliest on CCI and at the latest on CCI before C1D1.

All details regarding the infusion rate of obinutuzumab are detailed in the Pharmacy Manual.

Surveillance

Hypotension may occur because of an IRR adverse event. Therefore, it is recommended that antihypertensive drugs not be given on the morning of, and throughout the infusion of obinutuzumab, even if clinically indicated. Patients with a history of cardiac disease should be monitored closely.

8.9.2. Premedication for infusion-related reactions and cytokine-release syndrome

Management of IRRs or CRS according to grade is described in Sections 6.8.1 and 6.8.2. Additional information on the use of tocilizumab is provided in Section 8.9.2.

In case of IRR or CRS, whatever the grade of the event, premedication is recommended for the next infusion to the patient who has experienced the event. This premedication should be put in place at the discretion of the investigator.

Patients who experience IRRs or G1 and G2 CRS should be premedicated with acetaminophen, ibuprofen, histamine 1 (H1) blocker (diphenhydramine or other analogue), and/or histamine 2 (H2) blocker (famotidine or other analogue), as per standard practice.

8.9.3. Tocilizumab

In case of CRS, the availability of tocilizumab on site should be checked before any infusion. Treatment with tocilizumab should be considered according to local guidelines for adverse events management.

8.9.4. Other immunosuppressive monoclonal antibodies

Other immunosuppressive monoclonal antibodies like anti-TNFα monoclonal antibodies (infliximab), soluble TNFα receptor (etanercept) and IL1R-based inhibitors (anakinra) may be considered according to institution guidelines.

8.9.5. Corticosteroids

Although systemic corticosteroids and TNFα inhibitors may attenuate the potential beneficial immunologic effects of treatment with PRS-344/S095012, they may be administered at the discretion of the treating physician, if clinically indicated. If practicable, alternatives to corticosteroids should be considered.

The use of inhaled corticosteroids and mineralocorticoids (*e.g.* fludrocortisone) for patients with orthostatic hypotension or adrenocortical insufficiency is allowed. Megestrol administered as an appetite stimulant is acceptable while the patient is enrolled in the study. Steroid replacement for physiological insufficiency is allowed (as long as not exceeding 10 mg/day prednisone or equivalent).

8.9.6. Hematopoietic Growth Factor and Blood Products

Erythropoietin, darbepoetin alfa, and/or hematopoietic colony-stimulating factors for treatment of cytopenias may be administered according to institutional guidelines. The prophylactic use of these agents is not permitted unless agreed with the sponsor.

Transfusion thresholds for blood product support will be in accordance with institutional guidelines.

8.10. Prohibited Therapies

The following therapies are prohibited during the study (unless otherwise noted):

- Investigational drugs and devices.
- Radiation therapy (not including palliative radiotherapy at focal sites).
- Anticancer therapy other than PRS-344/S095012.
- Patients must not receive live, attenuated vaccines (*e.g.* FluMist®) within four weeks prior to first day of treatment, at any time during the study, or through 90 days after the last dose of PRS-344/S095012 but may receive inactivated vaccine. Influenza vaccination should be given during influenza season only.
- Patients must not receive Covid-19 vaccine within 14 days prior to first day of treatment and at any time during the DLT observation period (Cycle 1).
- Any other medical conditions or therapeutic interventions at investigator's discretion that could interfere with efficacy or safety of the drug (vitamin K, herbals…).

9. STUDY ASSESSMENTS

The procedures and assessments that will be performed during this study are described in this section and summarized in the schedule of assessments (Table (9) 1, Table (9) 2,Table (9) 3).

Detailed instructions regarding centralized laboratory procedures, including the collection and handling of samples, are included in the study Laboratory Manual provided by the sponsor.

Table (9) 1 - Phase 1 - CCI Dosing, CCI - Schedule of Assessments

Evaluations	Screening period (A0)	Treatment Period																Follow Up Period (FU)		
	D-28 to D-14 (+7 days)	Cycle 0 (C0)	Cycle 1 (C1) (DLT Observation Period)							Cycle 2 (C2)						Cycle 3 & onwards		1-month Safety FU (30± 3 days)	Long-term Safety FU (60 and 90 days ± 7 days)	Disease and Survival Status (every 12 weeks ± 14 days)
		D-14 (+7 days) to D-1	CCI													D1 ±1	D15 ±1			
Administrative Procedures																				
Informed consent	x																			
Inclusion/exclusion criteria	x																			
Demographics	x																			
Medical history	x																			
Prior oncology treatment history	x																			
Prior medication review [1]	x																			
Pretreatment																				
Obinutuzumab		x[29]																		
Treatment																				
PRS-344/S095012 administration			x				x			x				x		x	x			
Efficacy																				
Tumor imaging [2]	x														x					(x)
Survival Status																				x

Table (9) 1 (Cont'd) - Phase 1 - CCI Dosing, CCI - Schedule of Assessments

Evaluations	Screening period (A0)	Treatment Period															Follow Up Period (FU)		
	D-28 to D-14 (+7 days)	Cycle 0 (C0)	Cycle 1 (C1) (DLT Observation Period)							Cycle 2 (C2)						Cycle 3 & onwards		1-month Safety FU (30± 3 days)	Long-term Safety FU (60 and 90 days ± 7 days)	Disease and Survival Status (every 12 weeks ± 14 days)
		D-14 (+7 days) to D-1	CCI													D1 ±1	D15 ±1			
Safety																				
AEs/SAEs [3]	x[4]	Ongoing throughout the study																		
Concomitant medications	Ongoing assessment																			
Concomitant procedures	Ongoing assessment																			
ECOG Performance Status	x		x[5]							x[6]						x[6]				
Royal Marsden Prognosis Score	x		x[12]																	
Physical examination [7]			x(f)				x(d)			x(d)				x(d)		x(d)	x(d)	x(d)	x(d)	
Vital signs, weight, height [8]	x		x			x	x	x		x				x		x	x	x	x	

Table (9) 1 (Cont'd) - Phase 1 CCI Dosing, CCI - Schedule of Assessments

Evaluations	Screening period (A0)	Treatment Period														Follow Up Period (FU)		
		Cycle 0 (C0)	Cycle 1 (C1) (DLT Observation Period)							Cycle 2 (C2)						Cycle 3 & onwards				
	D-28 to D-14 (+7 days)	D-14 (+7 days) to D-1	CCI													D1 ±1	D15 ±1	1-month Safety FU (30± 3 days)	Long-term Safety FU (60 and 90 days ± 7 days)	Disease and Survival Status (every 12 weeks ± 14 days)
12-lead ECG	x		x[9]				x[10]			x[9]						x[10]		x	x	
Laboratory tests																				
Hematology [11]	x		x[12]			x	x[12]	x		x[12]				x[12]		x[12]		x	x	
Biochemistry [13]	x		x[12]	x	x	x	x[12]	x		x[12]	x	x	x	x[12]		x[12]	x[12]	x	x	
Coagulation [14]	x		x[12]							x[12]						x[12]		x	x	
Urinalysis [15]	x		x[12]							x[12]						x[12]		x	x	
Pregnancy test [16]	x		x[12]							x[12]						x[12]		x	x	
HIV, hepatitis B and C, CMV, EBV [17]	x																			
Thyroid function [18]	x		x[12]							x[12]						x[12]		x	x	
ACTH [19]	x		x[12]							x[12]						x[12]		x	x	
Pharmacokinetic measurements																				
Serum for PRS-344/S095012 PK [20, 21]			x	x	x	x	x			x	x	x	x	x		x	x	x		
Serum for anti-PRS-344/S095012 Antibodies (ADA) [21]			x[22]				x[22]			x[22]				x[22]		x[22]		x	x	

Table (9) 1 (Cont'd) - Phase 1 - [redacted] Dosing, [redacted] Schedule of Assessments

Evaluations	Screening period (A0) D-28 to D-14 (+7 days)	Treatment Period														Follow Up Period (FU)		
		Cycle 0 (C0)	Cycle 1 (C1) (DLT Observation Period)							Cycle 2 (C2)						Cycle 3 & onwards		1-month Safety FU (30± 3 days)	Long-term Safety FU (60 and 90 days ± 7 days)	Disease and Survival Status (every 12 weeks ± 14 days)
		D-14 (+7 days) to D-1	[redacted]													D1 ±1	D15 ±1			
Pharmacodynamics biomarkers																				
Tumor biopsy	x[23]							x[24]												
Blood for flow cytometry [25, 21]			x			x	x	x												
Blood for cytokine analysis [26, 21]			x		x	x	x	x		x						x				
Blood for soluble 4-1BB analysis [27, 21]			x	x	x	x	x	x		x	x	x	x	x		x	x			
Blood for genomic			x																	
Optional samples [28, 21]																				
Blood for DNA			x				x	x		x										
Blood for RNA			x				x	x		x										
Blood for plasma preparation (bTMB)			x																	
Blood for exosomal PD-L1			x																	

1 At the time of screening
2 Based on RECIST 1.1 for all solid tumors via CT/MRI. Assessment every eight weeks and the time of decision to stop treatment (+/- 14 days). If an imaging was made within 2 weeks before the decision, imaging may not be repeated. After 50 weeks of treatment, patients will be assessed every 12 weeks until discontinuation of treatment. After discontinuation of treatment for any reasons other than PD, it is recommended to assess the tumor by imaging every 12 weeks (+/- 14 days) until PD, initiation of another treatment for the patient's cancer, loss to follow-up, end of study, withdrawal of consent, or death (whichever comes first). After drug withdrawal, data will be collected in the e-CRF if available.
3 All AEs to be reported up to the 30-day FU visit; AEs related to the IMP, and death regardless of the relationship with IMP or experimental procedure to be reported up to 90 days after last administration; SAEs related to the research to be reported without time limit.
4 Once inform consent is signed and before the first IMP administration, all fatal events and all events related to experimental procedure to be reported.
5 Performance status not needed on C1D1 prior to PRS-344/S095012 IV administration if it has been assessed within 7 days before C1D1
6 Within 24 hours prior to PRS-344/S095012 IV administration
7 Full physical examination (f) at C1D1 should be performed within 72 hours of dosing. Directed examination (d) should be performed on C1D15, on D1 and D15 of subsequent cycles and at the safety FU visits.
8 Vital signs (HR, BP, body temperature, respiratory rate) predose and 15±5 minutes, 30±10 minutes, and at end of PRS-344/S095012 administration, including flush (±20 minutes). Vital signs will be also measured 6 hours after the end of PRS-344/S09012 administration including flush on C1D1 and 2 hours after the end of administration including flush on C1D15 and C2D1. Weight at screening, before each administration and at the safety follow up visits. Height at screening only.
9 Triplicate 12-lead ECG taken within 5 to 10 minutes predose and at 3 hours and 6 hours post dose on C1D1 and C2D1

10 12-lead ECG taken within 5 to 10 minutes predose and at 3 hours and 6 hours post dose on C1D15 and on D1 of Cycle 3 and onwards
11 Hemoglobin, hematocrit, platelets, white blood cells, neutrophils, lymphocytes (if feasible on site, CD8 and/or CD4 lymphocytes counts will be done), eosinophils, basophils, and monocytes.
12 Within 24 hours prior to PRS-344/S095012 IV administration. On C1D1, assessment may not be repeated if screening assessment was performed within 72 hours prior to PRS-344/S095012 IV administration.
13 Sodium, potassium, chloride, bicarbonate, calcium, magnesium, blood urea nitrogen (BUN)/urea, creatinine, total protein, albumin, ALP, AST, ALT, total bilirubin, direct bilirubin (if abnormal total bilirubin), amylase, lipase, uric acid, creatine kinase, GGT, LDH, glucose, and ferritin.
14 PT (prothrombin time), aPTT (activated partial thromboplastin time), fibrinogen and INR
15 If dipstick test is positive, urinary biochemistry tests will be performed.
16 For women of childbearing potential only. Serum pregnancy test at screening and urinary test before each cycle and serum or urinary test at the Safety FU visits
17 Serologies testing will be performed according to local standards.
18 Thyroid function: TSH, FT3, FT4 (anti-thyroglobulin antibodies will be measured if TSH is abnormal). Thyroid function will be assessed during screening, on D1 of each cycle up to Cycle 3 and then on D1 of every second cycle, and at the Safety FU visits.
19 ACTH hormone will be assessed during screening, on D1 of each cycle up to Cycle 3 and then on D1 of every second cycle and at the Safety FU visits.
20 For Cycle 1 and Cycle 2: on D1 at predose within 4 hours prior to PRS-344/S095012 IV administration, within 3 minutes before the end of administration including flush, 1h ±10min, 3h ±10min, 6h ±30min after the end of administration, and on D2 (24h ±6h), D3 (48h ±6h), D8 (168h ± 12 h) and D15 (pre-dose within 4 hours prior to PRS-344/S095012 IV administration and 1h ±10min after the end of administration). For Cycle 3 and subsequent odd cycles, on D1 at predose within 4 hours prior to PRS-344/S095012 IV administration and between 4 to 24 hours after end of infusion and on D15 at predose within 4 hours prior to PRS-344/S095012 IV administration and 1h ±10min after the end of administration. For Cycle 4 and subsequent even cycles, on D1 and D15 at pre-dose within 4 hours prior to PRS-344/S095012 IV administration and 1h ±10min after the end of administration.
21 Pre-dose samples should be taken within 4 hours prior to PRS-344/S095012 IV administration. In case of immune-related adverse event leading to IMP withdrawal, a PK/ADA samples should be taken within 24h following the diagnosis of adverse event.
22 At predose
*23 For patients in **dose escalation**, if available, archived material (< 9 months old) will be provided at baseline. If not available, a fresh biopsy will be collected within 14 days prior to first administration. For patients enrolled in **backfilled cohorts**, a fresh biopsy will be collected at baseline (within 14 days prior to first administration), unless an archived tumor biopsy (< 6 months old) without intercurrent treatment is available.*
*24 For patients in **dose escalation**, on-treatment biopsy is optional. If patient consents, a fresh biopsy will be collected in Cycle 1 between D22 and D28 and a fresh biopsy will have to be collected as well at baseline (unless an archived tumor biopsy (< 6 months old) without intercurrent treatment is available). For patients enrolled in **backfilled cohorts**, a fresh biopsy will be collected in any case on-treatment in Cycle 1 between D22 and D28.*
25 Blood for the Flow cytometry: Cycle 1 D1 predose, D8, D15 predose and D22.
26 Blood for cytokine: Cycle 1 D1 predose, 48h (D3), 168h (D8), D15 predose, D22 and Cycle 2 D1 predose. For Cycle 3 and subsequent odd cycles, on D1 at predose within 4 hours prior to PRS-344/S095012 IV administration and between 4 to 24 hours after end of infusion.
27 Blood for soluble 4-1BB: Cycle 1 and 2: D1 predose, 24h (D2), 48h (D3), 168h (D8), D15 predose, D22 (Cycle 1 only). Cycle 3 and onwards: D1 predose, D15 predose
28 If the patient consents, additional blood for DNA and blood for RNA samples will be collected on Cycle 1 D1 predose, D15 predose, D22 and Cycle 2 D1 predose. Additional blood samples for bTMB-plasma preparation and exosomal PD-L1 detection will be collected on Cycle 1 D1 predose.
29 The administration is performed in [redacted] *mg* [redacted] *or in* [redacted] *of obinutuzumab* [redacted] *before the first administration of PRS-344/S095012.*

Table (9) 2 - Phase 2 - CCI Dosing CCI - Schedule of Assessments

Evaluations	Screening period (A0)	Treatment Period											Follow Up Period (FU)		
		Cycle 0 (C0)	Cycle 1 (C1)				Cycle 2 (C2)				Cycle 3 & onwards		1-month Safety FU (30 ± 3 days)	Long-term Safety FU (60 and 90 ± 7 days)	Disease and Survival Status (every 12 weeks ± 14 days)
	D-28 to D-14 (+7 days)	D-14 (+7 days) to D-1	CCI												
Administrative Procedures															
Informed consent	x														
Inclusion/exclusion criteria	x														
Demographics	x														
Medical history	x														
Prior oncology treatment history	x														
Prior medication review	x														
Pretreatment															
Obinutuzumab		x[17]													
Treatment															
PRS-344/S095012			x		x		x		x		x	x			
Efficacy															
Tumor imaging/photography [2]	x									x					(x)
Survival Status															x

Table (9) 2 (Cont'd) - Phase 2 - [redacted] Dosing [redacted] - Schedule of Assessments

Evaluations	Screening period (A0)	Treatment Period										Follow Up Period (FU)		
		Cycle 0	Cycle 1 (C1)			Cycle 2 (C2)				Cycle 3 & onwards				
	D-28 to D-14 (+7 days)	D-14 (+7 days) to D-1	[redacted]							D1 ±1	D15 ±1	1-month Safety FU (30 ± 3 days)	Long-term Safety FU (60 and 90 ± 7 days)	Disease and Survival Status (every 12 weeks ± 14 days)
Safety														
AEs/SAEs	x (to be reported: all deaths and AE related to study procedures)	Ongoing throughout the study (to be reported: all AEs up to 1-month FU visit, AEs related to IMP and all deaths up to 3-month FU visit, SAEs related to the research without time limit)												
Concomitant medications	Ongoing assessment													
Concomitant procedures	Ongoing assessment													
ECOG Performance Status	x		x not needed if assessed within 7 days before C1D1				x Predose (up to 24 hours)				x Predose (up to 24 hours)			
Royal Marsden Prognosis Score	x		x not needed if assessed within 3 days before C1D1											

Table (9) 2 (Cont'd) - Phase 2 - CCI Dosing CCI - Schedule of Assessments

Evaluations	Screening period (A0)	Treatment Period											Follow Up Period (FU)		
		Cycle 0	Cycle 1 (C1)				Cycle 2 (C2)				Cycle 3 & onwards				
	D-28 to D-14 (+7 days)	D-14 (+7 days) to D-1	CCI								D1 ±1	D15 ±1	1-month Safety FU (30 ± 3 days)	Long-term Safety FU (60 and 90 ± 7 days)	Disease and Survival Status (every 12 weeks ± 14 days)
Physical examination (f) full; (d) directed	x(f)												x(d)	x(d)	
Vital signs, weight, height [3]	x		x	x	x	x	x		x		x	x	x	x	
12-lead ECG (predose)	x		x Triplicate				x Triplicate				x		x	x	
Laboratory tests: Predose, up to 24 hours before infusion on days with infusion (C1D1 not needed in screening assessment less than 72 hours before visit)															
Hematology [4]	x		x	x	x	x	x		x		x		x	x	
Biochemistry [5]	x		x	x	x	x	x		x		x	x	x	x	
Coagulation [6]	x						x				x		x	x	
Urinalysis [7]	x						x				x		x	x	
Pregnancy test [8]	x		x				x				x		x	x	
HIV, hepatitis B and C, CMV, EBV [9]	x														
Thyroid function [10]	x						x				x[11]		x	x	
ACTH	x						x				x[11]		x	x	

Table (9) 2 (Cont'd) - Phase 2 - CCI Dosing, CCI - Schedule of Assessments

Evaluations	Screening period (A0)	Treatment Period										Follow Up Period (FU)		
	D-28 to D-14 (+7 days)	Cycle 0	Cycle 1 (C1)				Cycle 2 (C2)				Cycle 3 & onwards	1-month Safety FU (30 ± 3 days)	Long-term Safety FU (60 and 90 ± 7 days)	Disease and Survival Status (every 12 weeks ± 14 days)
		D-14 (+7 days) to D-1	CCI								D1±1	D15 ±1			
Pharmacokinetic measurements															
Serum for PRS-344/S095012 PK [12, 13]			x	x	x	x	x	x	x		x	x	x		
Serum for anti-PRS-344/S095012 Antibodies (ADA) [13]			x				x				x		x	x	
Pharmacodynamics biomarkers: samples taken on the day of administration will be done as predose samples															
Tumor biopsy	x[14]					x[15]									
Blood for flow cytometry (Arm 3 only)			x	x											
Blood for cytokine analysis [13,16]			x	x	x	x	x	x	x		x				
Blood for soluble 4-1BB			x	x	x	x	x	x	x						
Blood for genomic			x												
Optional samples (optional informed consent)															
Blood for DNA			x		x	x	x								
Blood for RNA			x		x	x	x								
Blood for plasma preparation (bTMB)			x												

1 Depending on on-going PK and PD data, this visit or part of samples could be cancelled.
2 Based on RECIST 1.1 for all solid tumors via CT/MRI or WHO criteria for externally visible skin tumors. Assessment every eight weeks during treatment period and the time of decision to stop treatment (+/- 14 days). If an imaging/photography was made within 2 weeks before the decision, imaging/photography may not be repeated. After 50 weeks of treatment, patients will be assessed every 12 weeks until discontinuation of treatment. After discontinuation of treatment for any reasons other than PD, it is recommended to assess the tumor by imaging/photography every 12 weeks (+/- 14 days) until PD, initiation of another treatment for the patient's cancer, loss to follow-up, end of study, withdrawal of consent, or death (whichever comes first). After drug withdrawal, data will be collected in the e-CRF if available
3 Vital signs (HR, BP, body temperature, respiratory rate) predose and 15±5 minutes, 30±10 minutes, and at end of PRS-344/S095012 administration, including flush (±20 minutes). Vital signs will be also measured 6 hours after the end of PRS-344/S09012 administration including flush on C1D1 and 2 hours after the end of administration including flush on C1D15 and C2D1. Weight at screening, before each administration and at the safety FU visits. Height at screening only.
4 Hemoglobin, hematocrit, platelets, white blood cells, neutrophils, lymphocytes (if feasible on site, CD8 and/or CD4 lymphocytes counts will be done), eosinophils, basophils, and monocytes.
5 Sodium, potassium, chloride, bicarbonate, calcium, magnesium, blood urea nitrogen (BUN)/urea, creatinine, total protein, albumin, ALP, AST, ALT, total bilirubin, direct bilirubin (if abnormal total bilirubin), amylase, lipase, uric acid, creatine kinase, GGT, LDH, glucose, and ferritin.
6 PT (prothrombin time), aPTT (activated partial thromboplastin time), fibrinogen and INR
7 If dipstick test is positive, urinary biochemistry tests will be performed.
8 For women of childbearing potential only. Serum pregnancy test at screening and urinary test before each cycle and serum or urinary test at the Safety FU visits.
9 Serologies testing will be performed according to local standards.
10 Thyroid function: TSH, FT3, FT4. (Anti-thyroglobulin antibodies will be measured if TSH is abnormal).
11 Started from Cycle 3, assessment to be done every second cycle
12 For Cycle 1 and Cycle 2: on D1 at predose (within 4 hours prior to PRS-344/S095012 IV administration), within 3 minutes before the end of administration including flush, 1h ±10min, 3h ±10min, D8 (168h ± 12 h) and D15 (pre-dose within 4 hours prior to PRS-344/S095012 IV administration and 1h ±10min after the end of administration). For Cycle 3 and subsequent odd cycles, on D1 at predose within 4 hours prior to PRS-344/S095012 IV administration and between 4 to 24 hours after end of infusion and on D15 predose within 4 hours prior to PRS-344/S095012 IV administration and 1h ±10min after the end of administration. For Cycle 4 and subsequent even cycles, on D1 and D15 pre-dose (within 4 hours prior to PRS-344/S095012 IV administration) and 1h ±10min after the end of administration.
13 Pre-dose samples should be taken within 4 hours prior to PRS-344/S095012 IV administration. In case of immune-related adverse event leading to IMP withdrawal, a PK/ADA samples should be taken within 24h following the diagnosis of adverse event.
14 If available archived material (<6 months old without intercurrent treatment) will be provided at baseline. If not available, a fresh biopsy will be collected within 14 days prior to first administration.
15 On-treatment biopsy is optional in arms 1 and 2 and mandatory in arm 3. A dedicated consent is to be signed if patient consents for arms 1 and 2. A fresh biopsy will be collected in Cycle 1 between D22 and D28 and a fresh biopsy will have to be collected as well at baseline (unless an archived tumor biopsy (< 6 months old) without intercurrent treatment is available). For patients deemed eligible by digital photography only (arm 3), an additional biopsy is required within 30 days of CR determined by the investigator for confirmation of the CR.
16 Blood for cytokine: Cycle 1 D1 predose,, 168h (D8), D15 predose, D22 and Cycle 2 D1 predose, C2D8, C2D15. For Cycle 3 and subsequent odd cycles, on D1 at predose within 4 hours prior to PRS-344/S095012 IV administration and between 4 to 24 hours after end of infusion.
17 The infusion is performed in CCI *mg* CCI *or in* CCI *of obinutuzumab* CCI *mg* CCI CCI *before the first administration of PRS-344/S095012.*

Table (9) 3 - Phase 1 - Q3W Dosing, 21-Day Cycles - Schedule of Assessments

Evaluations	Screening period (A0)	Treatment Period											Follow Up Period (FU)		
	D-28 to D-14 (+7 days)	Cycle 0 (C0)	Cycle 1 (C1) (DLT Observation Period)					Cycle 2 (C2)					All subsequent cycles	1-month Safety FU (30 ± 3 days)	Long-term Safety FU (60 and 90 days ± 7 days)	Disease and Survival Status (every 12 weeks ± 14 days)
		D-14 (+7 days) to D-1	D1	D2	D3	D8	D15 ±1	D1	D2	D3	D8	D15 ±1	D1±1			
Administrative Procedures																
Informed consent	x															
Inclusion/exclusion criteria	x															
Demographics	x															
Medical history	x															
Prior oncology treatment history	x															
Prior medication review[1]	x															
Pretreatment																
Obinutuzumab		x[29]														
Treatment																
PRS-344/S095012 administration			x					x					x			
Efficacy																
Tumor imaging [2]	x												x			(x)
Survival Status																x

Table (9) 3 (Cont'd) - Phase 1 - Q3W Dosing, 21-Day Cycles - Schedule of Assessments

Evaluations	Screening period (A0)	Treatment Period											Follow Up Period (FU)		
	D-28 to D-14 (+7 days)	Cycle 0 (C0)	Cycle 1 (C1) (DLT Observation Period)					Cycle 2 (C2)					All subsequent cycles	1-month Safety FU (30 ± 3 days)	Long-term Safety FU (60 and 90 days ± 7 days)	Disease and Survival Status (every 12 weeks ± 14 days)
		D-14 (+7 days) to D-1	D1	D2	D3	D8	D15 ±1	D1	D2	D3	D8	D15 ±1	D1±1			
Safety																
AEs/SAEs[3]	x[4]	Ongoing throughout the study														
Concomitant treatment	Ongoing assessment															
Concomitant procedures	Ongoing assessment															
ECOG Performance Status	x		x[5]					x[6]					x[6]			
Royal Marsden Prognosis Score	x		x[11]													
Physical examination[7]			x(f)					x(d)					x(d)	x(d)	x(d)	

Table (9) 3 (Cont'd) - Phase 1 - Q3W Dosing, 21-Day Cycles - Schedule of Assessments

Evaluations	Screening period (A0)	Treatment Period											Follow Up Period (FU)		
	D-28 to D-14 (+7 days)	Cycle 0 (C0)	Cycle 1 (C1) (DLT Observation Period)					Cycle 2 (C2)					All subsequent cycles	1-month Safety FU (30 ± 3 days)	Long-term Safety FU (60 and 90 days ± 7 days)	Disease and Survival Status (every 12 weeks ± 14 days)
		D-14 (+7 days) to D-1	D1	D2	D3	D8	D15 ±1	D1	D2	D3	D8	D15 ±1	D1±1			
Vital signs, weight, height[8]	x		x			x		x			x		x	x	x	
12-lead ECG	x		x[9]					x[9]					x	x	x	
Laboratory tests																
Hematology [10]	x		x[11]			x	x	x[11]				x	x[11]	x	x	
Biochemistry [12]	x		x[11]	x	x	x	x	x[11]	x	x	x	x	x[11]	x	x	
Coagulation [13]	x		x[11]					x[11]					x[11]	x	x	
Urinalysis [14]	x		x[11]					x[11]					x[11]	x	x	
Pregnancy test [15]	x		x[11]					x[11]					x[11]	x	x	
HIV, hepatitis B and C, CMV, EBV [16]	x															
Thyroid function [17]	x		x[11]					x[11]					x[11]	x	x	
ACTH[18]	x		x[11]					x[11]					x[11]	x	x	
Pharmacokinetic measurements																
Serum for PRS-344/S095012 PK[19,20]			x	x	x	x	x	x	x	x	x	x	x	x		
Serum for anti-PRS-344/S095012 antibodies[20]			x[21]					x[21]					x[21]	x	x	

Table (9) 3 (Cont'd) - Phase 1 - Q3W Dosing, 21-Day Cycles - Schedule of Assessments

Evaluations	Screening period (A0)	Treatment Period											Follow Up Period (FU)		
	D-28 to D-14 (+7 days)	Cycle 0 (C0)	Cycle 1 (C1) (DLT Observation Period)					Cycle 2					All subsequent cycles	1-month Safety FU (30 ± 3 days)	Long-term Safety FU (60 and 90 days ± 7 days)	Disease and Survival Status (every 12 weeks ± 14 days)
		D-14 (+7 days) to D-1	D1	D2	D3	D8	D15 ±1	D1	D2	D3	D8	D15 ±1	D1±1			
Tumor biopsy	x[22]										x[23]					
Blood for flow cytometry[24,20]			x			x		x			x					
Blood for cytokine analysis[25, 20]			x		x	x	x	x					x			
Blood for soluble 4-1BB[26, 20]			x	x	x	x	x	x	x	x	x	x	x			
Blood for genomic			x													
Blood for DNA			x				x	x			x					
Blood for RNA			x				x	x			x					
Blood for plasma preparation (bTMB)			x													
Blood for exosomal PD-L1			x													

1 At the time of screening

2 Based on RECIST 1.1 for all solid tumors via CT/MRI. Assessment every six weeks and at the time decision is made to stop the treatment (+/-14 days). If an imaging was made within 2 weeks before the decision, imaging may not be repeated. After 50 weeks, patients will be assessed every 12 weeks until discontinuation of treatment. After discontinuation of treatment for any reasons other than PD, it is recommended to assess the tumor by imaging every 12 weeks (+/- 14 days) until PD, initiation of another treatment for the patient's cancer, loss to follow-up, end of study, withdrawal of consent, or death (whichever comes first). After drug withdrawal, data will be collected in the e-CRF if available.

3 All AEs to be reported up to the 30-day FU visit; AEs related to the IMP, and death regardless of the relationship with IMP or experimental procedure to be reported up to 90 days after last administration; SAEs related to the research to be reported without time limit.

4 Once inform consent is signed and before the first IMP administration, all fatal events and all events related to experimental procedure to be reported.

5 Performance status not needed on C1D1 prior to PRS-344/S095012 administration if it has been assessed within 7 days before C1D1

6 Within 24 hours prior to PRS-344/S095012 IV administration

7 Full physical examination (f) on C1D1 should be performed within 72 hours of dosing Directed examination (d) should be performed on D1 of subsequent cycles and at the safety FU visits.

8 Vital signs (HR, BP, body temperature, respiratory rate) predose and 15±5 minutes, 30±10 minutes, and at end of PRS-344/S095012 administration including flush (±20 minutes). Vital signs will be also measured 6 hours after the end of PRS-344/S09012 administration including flush on C1D1 and 2 hours after the end of administration including flush on C2D1. Weight at screening, before each administration and at the safety FU visits. Height at screening only.

9 Triplicate 12-lead ECG taken within 5 to 10 minutes predose and at 3 hours and 6 hours post dose on C1D1 and C2D1

10 Hemoglobin, hematocrit, platelets, white blood cells, neutrophils, lymphocytes (if feasible on site, CD8 and/or CD4 lymphocytes counts will be done), eosinophils, basophils, and monocytes.
11 Within 24 hours prior to PRS-344/S095012 IV administration. On C1D1, assessment may not be repeated if screening assessment was performed within 72 hours prior to PRS-344/S095012 IV administration.
12 sodium, potassium, chloride, bicarbonate, calcium, magnesium, blood urea nitrogen/urea, creatinine, total protein, albumin, ALP, AST, ALT, total bilirubin, direct bilirubin (if abnormal total bilirubin), amylase, lipase, uric acid, creatine kinase, GGT, LDH, glucose, and ferritin.
13 PT (prothrombin time), aPTT (activated partial thromboplastin time), fibrinogen and INR
14 If dipstick test is positive, urinary biochemistry tests will be performed.
15 For women of childbearing potential only. Serum pregnancy test at screening and urinary test only at predose and serum or urinary test at the Safety FU visits.
16 Serologies testing will be performed according to local standards.
17 Thyroid function: TSH, FT3, FT4. (Anti-thyroglobulin antibodies will be measured if TSH is abnormal). Thyroid function will be assessed during screening, on D1 of each cycle up to Cycle 3 and then on D1 of every second cycle, and at the Safety FU visits.
18 ACTH hormone will be assessed during screening, on D1 of each cycle up to Cycle 3 and then on D1 of every second cycle and at the Safety FU visits.
19 For Cycle 1 and Cycle 2: on D1 at predose, within 3 minutes before the end of administration including flush, 1 h±10min, 3 h±10min and 6 h±30min after end of administration, and on D2 (24h±6h), D3 (48h±6h), D8 (168h±12h) and D15 (360h ± 12h). For Cycle 3 and subsequent odd cycles, on D1 at predose within 4 hours prior to PRS-344/S095012 IV administration and between 4 to 24 hours after end of infusion. For Cycle 4 and subsequent even cycles on D1 at pre-dose within 4 hours prior to PRS-344/S095012 IV administration and 1 h±10min after the end of administration.
20 Predose samples should be taken within 4 hours prior to IMP administration. In case of immune-related adverse event leading to IMP withdrawal, a PK/ADA samples should be taken within 24h following the diagnosis of adverse event.
21 At predose
*22 For patients in **dose escalation**, if available archived material (< 9 months old) will be provided at baseline. If not available, a fresh biopsy will be collected within 14 days prior to first administration. For patients enrolled in **backfilled cohorts**, a fresh biopsy will be collected at baseline (within 14 days prior to first administration), unless an archived tumor biopsy (< 6 months old) without intercurrent treatment is available.*
*23 For patients in **dose escalation**, on-treatment biopsy is optional. If patients consent, a fresh biopsy will be collected in Cycle 2 between D8 and D15 and a fresh biopsy will have to be collected as well at baseline (unless an archived tumor biopsy (< 6 months old) without intercurrent treatment is available). For patients enrolled in **backfilled cohorts**, a fresh biopsy will be collected in any case on-treatment in Cycle 2 between D8 and D15.*
24 Blood for flow cytometry: Cycle 1 predose D1, D8, and Cycle 2 predose D1, D8
25 Blood for cytokines: Cycle 1 D1 predose, 48h (D3), 168h (D8), D15 predose, and Cycle 2 D1 predose. For cycle 3 and subsequent odd cycles, on D1 at predose within 4 hours prior to PRS-344/S095012 IV administration and between 4 to 24 hours after end of infusion.
26 Blood for soluble 4-1BB: Cycle 1 and 2: D1 predose, 24h (D2), 48h (D3), 168h (D8), D15 after administration. Cycle 3 and onwards: D1 predose
27 If the patient consents, additional blood samples for DNA and blood samples for RNA will be collected on Cycle 1 predose D1, D15, and Cycle 2 predose D1, D8. Additional blood samples for bTMB-plasma preparation and exosomal PD-L1 detection will be also collected on C1D1.
29 The infusion is performed i[redacted] or in[redacted] of obinutuzumab[redacted] before the first administration of PRS-344/S095012

9.1. Safety Assessments

All AEs must be followed up and fully and precisely documented in order to ensure that the sponsor has the necessary information to continuously assess the benefit-risk balance of the clinical study. All safety assessments will be done locally at the clinical site, except cytokine analysis that will be analyzed centrally by a third-party laboratory.

9.1.1. Adverse Event Assessment

The investigator has the responsibility for assessing the safety of the patients and for compliance with the protocol to ensure study integrity. Patients will be monitored for AEs during the study as described in Section 10.4. AEs (including laboratory abnormalities) will be graded according to the CTCAE v5.0 grading system (except for CRS, graded as per ASTCT) and recorded on the e-CRF.

Complete details for monitoring AEs, including the definition of IMP-related AEs, are provided in Section 10.

9.1.2. Demographic/ Prior Treatments/ Medical History

Patient demographics, significant medical history including prior cancer treatments will be recorded. Any ongoing condition observed prior to the initiation of treatment will be recorded, including prior assessment of radiographic/photographic progression on prior checkpoint inhibitors.

9.1.3. Vital Signs

Vital signs will be measured at the timepoints described in Table (9) 1, Table (9) 2 and Table (9) 3.

These assessments include body temperature (C or F), systolic and diastolic blood pressure readings (mmHg), pulse (beats per minute [BPM]), and respiratory rate (breaths per minute [BRPM]).

Vital signs will be measured after a minimum of 5 minutes rest, immediately prior to IV administration, then at 15 ± 5 minutes, 30 ± 10 minutes, and at the end of administration, including the flushing of the infusion catheter (±20 minutes). The actual time of the vital sign measurements should be accurately documented. If the administration is interrupted and/or subsequently restarted, vital signs should be assessed every 60 ± 5 minutes. In addition, vital signs will be measured on C1D1 6 hours after the end of IMP administration including the infusion catheter flush, before patient discharge; and on C1D15 (except for Q3W schedule) and C2D1, 2 hours after the end of IMP administration including the infusion catheter flush, before patient discharge. If a patient experiences an IRR/CRS during any cycle, the observation period should be extended until resolution and for subsequent cycles extended to 6 hours for that patient, as clinically indicated until patient demonstrate tolerance to infusion.

The frequency or the length of the monitoring period may be modified if clinically indicated, *e.g.* if in the opinion of the investigator, the vital sign results, at the time of event onset, are clinically significant. In such a case, the patient's vital sign measurements should continue to be recorded until they have returned to normal or to pre-treatment levels and an AE recorded. The same position should be used each time vital signs are measured for a given patient, and blood pressure should be measured from the arm contralateral to the site of study drug administration. Body temperature should be measured according to normal institutional practice.

When vital signs are to be collected at the same timepoint as a blood collection, vital signs should be collected first. All vital signs will be obtained after the patient has been resting for at least 5 minutes.

9.1.4. Weight and Height

Height will be measured only during screening. Weight will be measured at the timepoints specified in Table (9) 1, Table (9) 2 and Table (9) 3 and the patient should be in light indoor clothes.

9.1.5. Physical Examination

Physical examinations may be "full" which will include an assessment of all the major body systems or, after the initial screening examination, directed to particular body organ systems based on what the investigator deems necessary to focus on during the physical examination. Physical examinations will be performed at the timepoints specified in Table (9) 1, Table (9) 2 and Table (9) 3.

The timepoints at which the full *versus* directed examination is performed are specified in Table (9) 1, Table (9) 2 and Table (9) 3.

ECOG Performance Status
ECOG performance status (PS) will be assessed during screening and treatment period as specified in Table (9) 1, Table (9) 2 and Table (9) 3.

Care will be taken to accurately score PS during screening for study eligibility purposes. Additional consideration should be given to borderline ECOG PS to avoid enrolling patients with significant impairment.

9.1.6. Royal Marsden Prognosis Score

The RMP Score (Arkenau *et al.*, 2009; Appendix 8) will be assessed during screening as specified in Table (9) 1, Table (9) 2 and Table (9) 3.

The purpose of the RMP Score is to exclude patients from this study who are unlikely to be able to complete 2 or more cycles of therapy because of the highly advanced nature of their malignancies.

9.1.7. Electrocardiogram

12-lead ECGs will be performed at the timepoints specified in Table (9) 1, Table (9) 2 and Table (9) 3 and ideally before any venipuncture. 12-lead ECG aligned with PK assessments (taken within 5 to 10 minutes pre-dose [for phases 1 and 2] and at 3 hours and 6 hours post-dose [only for phase 1] on C1D1 and C2D1) will be done in triplicate. When ECGs are to be recorded at the same timepoint as a blood collection, ECGs should be recorded first. At each measurement, resting, and supine 12-lead ECGs will be recorded within 5 to10 minutes total time. The ECG measurement performed predose on Day 1 will serve as the patient's baseline-corrected QT (QTcF) value for all post-dose comparisons. The investigator will be responsible for verifying the accuracy of the electronic QTc interval recording using the Fridericia correction formula:

- Fridericia correction (QTcF) = QT ÷ cube root of the RR interval.

In calculations of QTcF, QT is measured in milliseconds and RR, the duration of the entire cardiac cycle, is measured in seconds.

In some cases, it may be appropriate to repeat abnormal ECGs. If a machine-read QTcF value is prolonged, repeat measurements may not be necessary if a physician's interpretation determines that the QTcF value is accurate.

All ECG measurements must be collected within 10 minutes of the scheduled collection time, except for the 6-hour post treatment measurement, which must be collected within 30 minutes of the collection time.

9.1.8. Laboratory Assessments

Blood and urine samples will be collected at the timepoints specified in Table (9) 1, Table (9) 2 and Table (9) 3.

All laboratory assessments will be performed locally. Cumulative blood volumes are described in Appendix 5. Screening results will be assessed by the investigator for the evaluation of study eligibility. Additional clinical laboratory tests can be performed at any time during the study at the investigator's discretion. Clinically significant IMP-related findings at the Safety Follow-Up Visits should be followed to resolution or stabilization.

All blood and urine collections for clinical laboratory tests occurring on the same day as study drug administration must be performed prior to IMP administration.

9.1.8.1. Hematology

The laboratory tests to be performed at the timepoints specified in Table (9) 1, Table (9) 2 and Table (9) 3 are hemoglobin, hematocrit, platelets, white blood cells (WBCs), neutrophils, lymphocytes (if feasible on site, CD8 and/or CD4 lymphocytes counts will be done), eosinophils, basophils, and monocytes. Hematology results must be reviewed by the investigator prior to the start of treatment with study drug.

9.1.8.2. Biochemistry

The laboratory tests to be performed at the timepoints specified in Table (9) 1, Table (9) 2 and Table (9) 3 are sodium, potassium, chloride, bicarbonate, calcium, magnesium, blood urea nitrogen (BUN)/urea, creatinine, total protein, albumin, alkaline phosphatase (ALP), AST, ALT, GGT, total bilirubin and direct bilirubin (if total bilirubin is abnormal), lactate dehydrogenase (LDH), amylase, lipase, uric acid, creatine kinase (CK), glucose and ferritin.

9.1.8.3. Adrenal and Thyroid functions

Thyroid functions will be tested on blood samples. Thyroid function tests include thyroid stimulating hormone (TSH, also known as thyrotropin), free T4 (FT4; thyroxine) and free T3 (FT3; triiodothyronine). In case of abnormal results, anti-thyroglobulin antibodies will be assessed. Adrenal function test consists in adreno corticotropic hormone (ACTH) assessment. Thyroid and adrenal functions will be assessed during screening, on D1 of each cycle up to Cycle 3 (except on C1D1 for phase 2) and then on D1 of every second cycle and at the Safety FU visits as outlined in Table (9) 1, Table (9) 2 and Table (9) 3.

Viral status
Viral status will be performed at baseline as outlined in Table (9) 1, Table (9) 2 and Table (9) 3.

HIV, hEp B and hEp C will be tested as mandated by local authorities.

9.1.8.4. Creatinine Clearance Estimation

Creatinine clearance will be estimated from Serum creatinine using the Cockcroft and Gault formula, as following:

$$CrCl = \frac{140 - Age}{7.2 \times [Cr]} \times body\ weight \times k'$$

Where,
CrCl is the estimated creatinine clearance in mL/min
[Cr] is the serum creatinine concentration in mg/L
Age is given in years
Weight is given in kilograms
k' is 1 for men and 0.85 for women

Alternatively, the GFR can be estimated using the Modification of Diet in Renal Disease (MDRD) or the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula as follows:

- MDRD formula:

$$GFR = 186 \times [Cr]^{-1.154} \times Age^{-0.203}\ (\times 0.742\ if\ female)$$

- CKD-EPI formula:

$$GFR = 141 \times \min([Cr]/k, 1)^{\alpha} \times \max([Cr]/k, 1)^{-1.209} \times 0.993^{Age} \ (\times 1.018 \ if \ female)$$

Where,
GFR is the glomerular filtration rate in mL/min
[Cr] is the serum creatinine concentration in mg/dL
Age is given in years
k is 0.9 for men and 0.7 for women
α is -0.411 for men and -0.329 for women
min indicates the minimum of [Cr]/k or 1
max indicates the minimum of [Cr]/k or 1

However, the estimation of creatinine clearance and/or GFR must be done using the same methodology for a given patient.

9.1.8.5. Coagulation

The fibrinogen, aPTT, INR and PT laboratory tests are to be performed at the timepoints specified Table (9) 1, Table (9) 2 and Table (9) 3.

These tests are to be repeated more frequently (*e.g.* twice weekly) if clinically indicated (*e.g.* INR and PT for patients on anticoagulants).

9.1.8.6. Urinalysis

Urinalysis will be performed at the timepoints specified in Table (9) 1, Table (9) 2 and Table (9) 3 on a freshly voided clean sample. A dipstick will be performed which includes the assessment of proteins, glucose, hemoglobin, bilirubin, urobilinogen, nitrite and leucocytes as well as testing of pH and specific gravity. If clinically warranted or warranted by the results of the Urine Test (dipstick), urinary biochemistry tests will be performed (Specific Gravity, pH, Protein, Glucose, Ketones, Nitrite), as well as microscopy with WBCs, red blood cells (RBCs), bacteria, epithelial cells, and casts.

For patients with a urostomy, urine may be collected using one of the two following methods:

- **Method 1** (may be performed by the patient): Remove pouch and clean with warm water as usual. Hold the collection pot under the stoma (but not touching it or the skin underneath) while catching the urine that dribbles out. Wait until 10 to 20 mL of urine is collected and replace pouch.
- **Method 2** (performed by a health care professional): Remove pouch and clean with warm water as usual. Using a sterile technique, insert a small catheter (size 10 Fr) 4 to 6 cm into the stoma. Place the other end of the catheter into the sterile pot to collect the urine. Wait until 10 to 20 mL of urine is collected and replace pouch.

9.1.8.7. Pregnancy Screen

A urine or serum sample will be collected from women of childbearing potential for pregnancy testing at the timepoints specified in Table (9) 1, Table (9) 2 and Table (9) 3.

If a urine test result is either positive or equivocal, a confirmation test will be done with a serum test performed within 72 hours of the urine test and before any drug administration or study procedures.

9.2. Efficacy assessments

9.2.1. Tumor Assessments

Tumor assessments based on RECIST version 1.1 or WHO criteria for externally visible skin tumors (only arm 3 phase 2) will be performed locally in phase 1 and locally and centrally in phase 2 at the timepoints specified in Table (9) 1, Table (9) 2 and Table (9) 3.

This will be assessed every 8 weeks initially. After 50 weeks of treatment, patients will be assessed every 12 weeks until discontinuation of treatment. Imaging/photography should be done at the time the decision is made to stop the treatment (+/-14 days). After discontinuation of treatment for any reasons other than PD, it is recommended to assess the tumor by imaging/photography every 12 weeks (+/- 14 days) until PD, initiation of another treatment for the patient's cancer, loss to follow-up, end of study, withdrawal of consent, or death (whichever comes first). After withdrawal, data will be collected in the e-CRF if available.

In case PRS-344/S095012 is administered Q3W on a 21-day cycle, tumor assessments will be performed every 6 weeks for 50 weeks and then every 12 weeks until discontinuation of treatment and at the time the decision is made to stop the treatment (+/-14 days). After discontinuation of treatment for any reasons other than PD, it is recommended to assess the tumor by imaging every 12 weeks (+/- 14 days) until PD, initiation of another treatment for the patient's cancer, loss to follow-up, end of study, withdrawal of consent, or death (whichever comes first). After withdrawal, data will be collected in the e-CRF if available.

Tumor responses will be assessed by the investigator. In phase 2, images will be also stored and analyzed centrally by a third party until patient withdrawal.

Disease assessment will be performed by computed tomography (CT) or magnetic resonance imaging (MRI) scans with contrast or, if clinically indicated, other validated imaging methods (*i.e.* PET-CT, bone scan, X-ray), of the chest, abdominal and pelvic areas, and other body areas if applicable. Brain scans (CT or MRI with contrast) will be performed if applicable. The same methods used at baseline that identify sites of disease should be used uniformly for all subsequent assessments. Additional disease assessments may be obtained, if clinically indicated.

For image acquisition specifications, including instruction in the event of allergy to contrast dye, refer to RECIST v1.1 (Specifications for Standard Anatomical Radiological Imaging) (Eisenhauer *et al.*, 2009). Objective responses (CR, PR, SD, or PD) will be determined as per RECIST 1.1 (Eisenhauer *et al.*, 2009) or WHO criteria for externally visible skin tumors.

Additional radiographic examinations by other validated imaging methods can be performed if clinically indicated.

For patients with visible tumors (arm 3), assessments will also be performed through medical digital photography and evaluation will be performed using clinical response criteria and composite response criteria for externally visible tumors (see Appendix 7).

Treatment beyond progression

Immunotherapeutic agents such as PRS-344/S095012 may produce antitumor effects by potentiating endogenous cancer-specific immune responses. The response patterns seen with such an approach may extend beyond the typical time course of responses seen with cytotoxic agents and can manifest as a clinical response after an initial increase in tumor burden or even the appearance of new lesions.

After the first evidence of disease progression determined by radiologic imaging/photography, patients may continue to receive study treatment at the discretion of the investigator while waiting for confirmation of progressive disease if they are clinically stable, defined as meeting all the following criteria, and after discussion with the medical monitor.

- Absence of signs and symptoms (including worsening of laboratory values) that are thought to be associated with disease progression and that are not requiring intensified management of disease related symptoms, including increased analgesia, radiotherapy or other palliative care.
- Tolerance of PRS-344/S095012.
- Stable ECOG PS.
- Treatment beyond progression will not delay an imminent intervention to prevent serious complications of disease progression (for example, central nervous system metastases).

If the criteria are met, patients may continue treatment (unless clinically unstable) until a subsequent (at least 4 weeks after the initial assessment of progression and no later than 8 weeks) radiographic/photographic confirmation of that progression since immune-related pseudo progression is possible. Clinically stable patients may continue beyond confirmed PD if benefits are expected to outweigh risks in the opinion of the investigator and in consultation with the Sponsor. All details are provided in the iRECIST guidelines (Seymour *et al.*, 2017).

9.2.2. Survival Status

Patients will be followed up for survival every 12 weeks (± 14 days), until withdrawal of consent, end of study, or patient's death. This survival follow-up may be done remotely by using various wired and wireless telecommunication technologies, including but not limited to phone, internet and shared electronic medical records.

9.3. Immunogenicity Assessments

Venous blood samples for the assessment of the presence of anti-drug antibodies (ADA) will be drawn at the timepoints presented in Table (9) 1, Table (9) 2 and Table (9) 3.

Blood samples should be collected from the arm opposite from the PRS-344/S095012 administration site, or from another site if collected within 24 hours of dosing.

Blood samples for PK and ADA analysis will also be collected in the event of an immune-related adverse event that leads to IMP withdrawal. These samples should be taken up to 24h following the diagnosis of the event. If additional timepoints or additional circulating protein analysis are necessary for better understanding CCI [redacted], left over and back up samples may be used for such analyses.

Samples will be analyzed centrally by a third-party laboratory. ADA samples will also be collected in the event of a clinically significant AE (such as IRR/anaphylaxis) or if ADA is suspected, at which time those samples could be used to measure any relevant biomarkers, to understand better the IRR/AE. After the primary clinical study report data cut-off date is reached, no additional ADA samples will be collected for those patients still ongoing on the study.

Back-up samples for ADA will be stored for a maximal period of 15 years to allow complementary analyses as part of the drug immunogenicity assessment. This could include ADA reanalysis with a modified bioanalytical method, new methods to characterize pre-existing ADA or the neutralizing potential of ADA or any other method used to study ADA or their impact on safety or efficacy.

Please refer to the Laboratory Manual for full details on collection and processing of blood ADA samples.

9.4. Pharmacokinetic Assessments

If new scientific evidence becomes available during the course of the trial, the planned pharmacokinetic analysis may be adjusted or omitted accordingly and the data of the existing biological samples may be used for additional analyses.

9.4.1. Blood Sample Collection

Venous blood samples for the PK analysis of IMP will be drawn at the timepoints presented in Table (9) 1, Table (9) 2 and Table (9) 3.

End of administration includes the catheter flushing step. Blood samples should be collected from the arm opposite from the PRS-344/S095012 administration site, or from another site if collected within 24 hours of dosing.

Blood for PK and ADA analysis will also be collected in the event of an immune-related adverse event that leads to IMP withdrawal. These samples should be taken up to 24h following the diagnosis of the event. If additional timepoints or additional circulating protein analysis are necessary for better understanding of the PK/ADA of the study drug or obinutuzumab, left over and back up samples may be used for such analyses.

Samples will be analyzed centrally by a third-party laboratory for the quantification of PRS-344/S095012 levels using a validated bioanalytical method.

Residual ADA and PK serum samples used for ADA or PK analysis may also be used for exploratory, alternative, PK assay development and analysis as well as PK analyses related to PRS-344/S095012 treatment.

Please refer to the Laboratory Manual for details on collection and processing of blood PK samples.

9.4.2. Pharmacokinetic analysis

The pharmacokinetic analysis will be performed under the responsibility of the Servier Quantitative Pharmacology department (I.R.I.S.). The dataset needed for final analysis will be prepared by extraction under the supervision of the Clinical Data Management Department using SAS® program and following the clinical PK project leader specifications. The analysis will be performed on the Pharmacokinetic analysis population.

The PK analysis population includes those patients who have samples collected that provide interpretable PK results, with no deviations that might affect the interpretation of the PK. The PK analysis population will be determined during the data review meeting. Any suspicious concentration will be investigated and kept in the PK analysis, if possible. All excluded concentrations will be justified in the report.

For dose escalation and dose expansion, concentration-time data of PRS-344/S095012 for each dose group will be summarized using descriptive statistics (*i.e.*, number of subjects, mean, standard deviation, geometric mean and coefficient of variation, median, minimum and maximum).

For dose escalation, non-compartmental pharmacokinetic analysis (NCA) will be performed under the supervision of the Quantitative Pharmacology department (I.R.I.S) using Phoenix WinNonlin® version 6.4 or later or Excel 2010 or later on the individual serum concentration-time data of PRS-344/S095012 for each patient, using the theoretical administration and sampling times for preliminary analysis and the exact administration and sampling times for final analysis. Serum PK parameters such as: C_{inf}, T_{inf}, t_{last}, C_{last}, AUC_{last}, AUC, λ_z, and $t_{1/2}$ will be determined. The NCA will be described in a separate Data Analysis Plan (DAP).

PRS-344/S095012 concentrations may also be analyzed by a population modeling approach to assess the PK of PRS-344/S095012 and to investigate potential sources of variability through a covariate analysis. In addition, PK/Pharmacodynamic analyses may be used to explore the potential relationship between efficacy, safety, and/or biomarker endpoints and PRS-344/S095012 exposure. Any modeling analysis based on final data will be described in a separate pharmacometric analysis plan and reported in a standalone report. Interim pharmacometric analyses may be performed.

All leftover samples (such as PK samples, ADA samples) collected during the study can be retained up to 15 years after completion of the study, thereafter all samples will be destroyed.

All analyses will be related to and used only in connection with the data collected in the present study or other PRS-344/S095012-related studies, for potential future studies to explore the biology of the patient's tumor, or for the development of bioanalytical methods. The identity of the patient will remain confidential. The analyses will not have any medical consequences for the patient and/or their relatives.

9.5. Pharmacodynamic Assessments

Analyses will be performed at one or more central laboratories (Specialty Laboratories). A detailed Laboratory Manual specifying sample collection, handling, storage, and shipment will be provided to the study sites; retention time for specimens will be specified therein.

All biomarker analyses are exploratory. If new scientific evidence becomes available during the course of the trial, biomarker analyses may change, and existing biological samples may be used for additional analyses, or planned analyses may be adjusted or omitted.

All leftover samples (such as plasma samples for cytokines and s4-1BB, PBMC samples, and, if applicable, biopsy samples) collected during the study can be retained up to 15 years after completion of the study; thereafter, all samples will be destroyed.

All analyses will be related to and used only in connection with the data collected in the present study or other PRS-344/S095012-related studies, for potential future studies to explore the biology of the patient's tumor, or for the development of bioanalytical methods. The identity of the patient will remain confidential. The analyses will not have any medical consequences for the patient and/or their relatives.

9.5.1. Tumor Biopsies

Dose escalation part
In part A and part B, archived tumor biopsies (< 9 months old) will be collected at baseline. If not available, a fresh biopsy will be collected. On-treatment biopsies are optional. If the patient consent(s), fresh paired tumor biopsies will be collected at baseline (within 14 days prior to the first administration) (unless an archived tumor biopsy (< 6 months old) without intercurrent treatment is available) and on treatment (from Day 22 to Day 28 of Cycle 1).
In the backfilled cohorts, collection of paired fresh tumor biopsies will be required for each patient at baseline (unless an archived tumor biopsy (< 6 months old) without intercurrent treatment is available) and whilst on-treatment (between Day 22 and Day 28 of Cycle 1).

Phase 2
In phase 2, in arms 1 and 2, a fresh biopsy will be collected at baseline, unless an archived tumor biopsy (< 6 months old) without intercurrent treatment is available. On-treatment biopsies are optional and will be done between D22 and D28 of Cycle 1 when the patient consents.
In arm 3, a fresh biopsy will be collected at baseline, unless an archived tumor biopsy (< 6 months old) without intercurrent treatment is available. Fresh on-treatment biopsy is mandatory and will be collected between D22 and D28 of Cycle 1, unless medically contra-indicated. For patients deemed eligible by digital photography only, an additional biopsy is required within 30 days of CR determined by the investigator for confirmation of the CR.

The eligible patients must have one or more discrete tumor lesions amenable to core needle biopsy, either on primary tumors or metastatic lesions, at baseline (if no available archived material) and on-treatment (if mandatory), and consent to assessments (unless unsafe on treatment).

In case PRS-344/S095012 is administered Q3W on a 21-day cycle, on-treatment biopsy will be collected between D8 and D15 of Cycle 2.

The time of the pre- and on-treatment (if any) biopsies will be recorded. Whenever possible, the biopsy under treatment is required to be performed in the same lesion as the initial biopsy. At each timepoint, the core needle biopsies will be paraffin embedded (details are provided in in the Laboratory Manual).

Pharmacodynamic assessment on tumor biopsies

The baseline and on-treatment tumor tissue biopsies will be used to investigate pharmacodynamic changes or mechanisms of response to treatment and potential predictive biomarkers. It is planned to perform:

- Immunohistochemistry (IHC) to assess immune cell landscape, target expression, phenotype and activation status of immune cell subsets (*e.g.* CD8, CD3, PDL1, Ki67), as feasible. Preclinical data with PRS344/S095012 supports such tumor biopsy analysis as an increase in CD8+ tumor-infiltrating lymphocytes was observed in a xenograft model. If only the baseline tumor tissue biopsy is available, it will be used to assess PD-L1 IHC, as a potential predictive biomarker and potentially other markers (*e.g.* CD8, CD3).
- And/or ribonucleic acid (RNA) profiling as potential predictive biomarkers of response or pharmacodynamic markers on tumors, using RNA sequencing or using a gene expression panel covering innate and adaptive immune markers including T cell activation and inhibition, chemokines and cytokines. Any IMP-related signatures generated will have the potential to inform pharmacodynamic and patient stratification strategy for future studies.
- And/or DNA whole exome sequencing to evaluate potential predictive biomarkers of response (for example, if relevant: TMB, MSI status, specific mutations) on the baseline biopsies. A blood sample (blood for genomic) will be collected to have the germline DNA as a reference to determine the TMB in the tumor.

9.5.2. Blood Samples for flow cytometry

Dose escalation part

Peripheral blood mononuclear cells (PBMC) will be collected for immunophenotyping through flow cytometry.

Patients will have venous blood samples drawn at the timepoints specified in Table (9) 1 and Table (9) 3 for the preparation of PBMCs, where lymphocyte subtypes and activation status will be measured as well as drug-target binding on lymphocytes (as feasible) by flow cytometry.

Samples will be analyzed centrally by a third-party laboratory.

Phase 2

Only patients in arm 3 (cutaneous squamous cell carcinoma) will have blood drawn for flow cytometry, at the timepoints specified in Table (9) 2 Fresh whole blood sample will be sent for analysis on the same day to the third-party laboratory. Lymphocyte subtypes and activation status will be measured.

Complete instructions for processing, handling of blood samples and shipment of samples will be provided in the Laboratory Manual.

9.5.3. Blood Samples for Soluble 4-1BB and cytokines

All patients will have venous blood samples drawn at the timepoints specified in Table (9) 1, Table (9) 2 and Table (9) 3 for measurement of soluble 4-1BB and cytokines. Plasma will be extracted from these blood samples with K3 EDTA anti-coagulant.

For cytokines, assessments may include (but are not limited to) IL2, IL-6, IL8, IL-10, TNF-α, IFN-γ and IP-10. Blood will also be collected in the event of a clinically significant AE (such as IRR/anaphylaxis/CRS) for cytokine analysis at additional timepoints if indicated by safety findings. If additional timepoints or additional circulating protein analysis are necessary for better understanding of the activity of the study drug, left over and back up samples may be used for analysis of a cytokine or any other circulating protein of interest.

Samples will be analyzed centrally by a third-party laboratory. Complete instructions for processing, handling of blood samples and shipment of samples will be provided in the Laboratory Manual.

9.5.4. Optional Analyses

If the patient consents (optional), additional blood samples will be collected at the timepoints specified in Table (9) 1, Table (9) 2 and Table (9) 3.

Samples will be stored for potential further research analysis, on the effect of PRS-344/S095012 on the cancer, or on disease understanding, or for the development of bioanalytical methods. The analysis would be performed by a third-party laboratory.

Blood for DNA and RNA preservation will be collected at Cycle 1 predose D1 and D15, D22 and at Cycle 2 predose D1 for CCI schedule. Two additional blood samples will be collected at Cycle 1 D1 and cell free plasma will be prepared (see the Laboratory Manual for sample processing details) for potential analysis of blood tumor mutational burden (bTMB) (phases 1 and 2) and PD-L1 expression on exosomes (only phase 1), if relevant, or for other pharmacodynamic or predictive biomarkers.

For the Q3W schedule, blood collection timepoints for optional blood samples are indicated in Table (9) 3.

Samples will be stored in a Biorepository contract research organization (CRO) for a maximum of 15 years after the end of the study. The consent given to this assessment can be withdrawn at any time without compromising the participation in the overall clinical study investigations. All samples will be destroyed within a maximum of 15 years after the end of the study or earlier if requested or in case of consent withdraw. In that case, related samples will be destroyed before any optional assessment is completed. The samples will not be used for any investigations not specified in this protocol or for the elaboration of a DNA bank.

Focus of future studies may include, but is not limited to, general characterization of groups or subgroups of cancer indications or testing of other anticancer drugs. Analyses may include the same, but may not be limited to, the modalities mentioned above, *i.e.*, presence of cells, expression/mutations of genes and/or expression/enzymatic activity of proteins in the obtained samples.

Complete instructions for processing and handling of blood samples are provided in the Laboratory Manual.

10. ADVERSE EVENT MANAGEMENT

10.1. Definitions

10.1.1. Definition of Adverse Event

An adverse event is defined as any untoward medical occurrence in a subject participating in a clinical study, whether or not there is a causal relationship with the IMP and/or experimental procedures, occurring or detected from the date the patient signs the information consent form, irrespective of the period of the study (periods without administration of the study drug [*e.g.* run-in period] are also included).

An adverse event can therefore be:

- Any unfavorable and unintended sign (including an abnormal finding from an additional examination such as lab tests, X-rays, ECG, …) which is deemed clinically relevant by the investigator.
- Any symptom or disease.
- Any worsening during the study of a symptom or a disease already present when the patient entered the study (increase in frequency and/or intensity). In case of studied disease, only fatal outcome should be reported as an adverse event.

and reported by the patient, detected during a study visit or at an additional examination or occurred since the previous study visit (including any relevant events reported in patient's diary or safety evaluation scale).

NOTE:

- Any **hospitalization for administration of antitumoral treatment and/or associated protocol (during or after the study) or other care measures for cancer (*e.g.* overnight hospital stay to receive a blood or platelets transfusion), for social reasons, educational purpose** (*e.g.* learning of diabetes management by the patient) or routine check-up should not be considered as an adverse event and should not be reported in the Case Report Form (CRF).
- Any clinically significant abnormal laboratory findings or other abnormal safety assessments, which are associated with the studied disease should not be considered as an adverse event unless judged by the investigator to be more severe than expected for the participant's condition.
- Non-fatal progressive disease should not be considered as an adverse event.
- The following procedures, whether planned before the study or not, whether leading to a hospitalization or not, **should not be reported in the CRF and kept in the source data (or patient file):**
  - Therapeutic procedures related to a non-aggravated medical history (*e.g.* cataract extraction not due to an aggravation of the cataract during the study, hemodialysis sessions related to renal insufficiency not aggravated during the study).
  - Prophylactic procedures (*e.g.* sterilization, wisdom teeth removal).
  - Comfort procedures (*e.g.* cosmetic surgery).
  - Control procedures of a pre-existing condition without aggravation (*e.g.* colonoscopy to control the remission of colon cancer).

10.1.2. Definition of Serious Adverse Event

Any adverse event that at, any dose:
- Results in death.
- Is life threatening. (1)
- Requires in-patient hospitalization or prolongation of existing hospitalization.
- Is medically important. (2)
- Results in persistent or significant disability or incapacity. (3)
- Is a congenital abnormality or birth defect. (4)

(1) *Life-threatening in this context refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.*

(2) *Any event that might not be life-threatening or result in death or hospitalization but might jeopardize the patient or might require intervention to prevent one of these outcomes (for example: edema or allergic bronchospasm that required intensive treatment at home, blood dyscrasia, convulsions that do not result in hospitalization, or development of drug dependence or drug abuse). The investigator should exercise his/her scientific and medical judgment to decide whether such an event requires expedited reporting to sponsor.*

(3) *Disability/incapacity in this context refers to any event that seriously disrupts the ability of the patient to lead a normal life, in other words leads to a persistent or permanent significant change, deterioration, injury or perturbation of the patient's body functions or structure, physical activity and/or quality of life.*

(4) *Congenital anomaly or birth defect refers to the exposure to the IMP before conception (in men or women) or during pregnancy that res*ulted in an adverse outcome in the child.

10.1.3. Definition of Overdose

This refers to any administration of a quantity of IMP (PRS-344/S095012) which is above the maximum dose recommended in the study protocol, independently of the occurrence of any adverse event.

The quantity should be considered per administration or cumulatively regarding the maximum dose recommended in the study protocol. For instance, if a patient from cohort 1 is supposed to receive a dose of CCI mg of IMP but he/she receives by mistake a higher dose than planned, it should be considered as an overdose.

10.1.4. Definition of Adverse Event of Special Interest

Not applicable.

10.1.5. Definition of Events Requiring an Immediate Notification (ERIN)

An event must be notified immediately (*i.e.* without delay and within 24 hours after investigator becoming aware of the event, at the latest) to the sponsor if it is:
- A Serious Adverse Event.
- An overdose of the IMP even if asymptomatic.
- Any intake of the IMP by a person around the patient.
- Pregnancy of the patient.

10.2. Classification of an Adverse Event (Seriousness, Severity, Causality, Expectedness)

It is important that the investigator provides his/her opinion on the **seriousness**, the **intensity** of the event as well as the **cause-effect relationship** between an adverse event and the research IMP. This evaluation must be made by the investigator and reported in the AE form. In addition, the sponsor will be responsible for the evaluation of the **expectedness** of the event (Section 10.4.3).

10.2.1. Assessment of Seriousness

The seriousness should be evaluated according to international guidance (see definition Section 10.1.2, in accordance with ICH Topic E2A and European Directive 2001/20/EC of 4 April 2001 or the European Union Clinical Trial Regulation 536/2014).

Death is an outcome of an SAE and not an SAE itself. When death is an outcome, report the event(s) resulting in death as the SAE term (*e.g.* "pulmonary embolism"). If the cause of death is unknown, report "Death, unknown cause" as the SAE term.

10.2.2. Assessment of Severity

The severity of all AEs will be graded according to the National Cancer Institute Common Toxicity Criteria for Adverse Event (NCI-CTCAE) on a five points scale (Grade 1 to 5):

- Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- Grade 2: Moderate; minimal, local or non-invasive intervention indicated; limiting age-appropriate instrumental ADL[1].
- Grade 3: Severe or medically significant but not immediately life threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL[2].
- Grade 4: Life-threatening consequences; urgent intervention indicated.
- Grade 5: Death related to AE.

[1] Instrumental Activities of Daily Living (ADL) refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
[2] Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden".

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria under Section 10.2.1. An AE of severe intensity may not be considered serious automatically.

For CRS, ASTCT Consensus grading will be used for grading (Lee *et al.*, 2019).

10.2.3. Assessment of the cause- effect relationship

The investigator must make an assessment in the AE form whether the AE is related or not to the research, meaning:

- Adverse event related to IMP(s) (PRS-344/S095012 and obinutuzumab).

- Adverse event related to study protocol *i.e.* related to:
  - A procedure scheduled in the study protocol (*i.e.* exercise test, MRI, etc.), or
  - A change or withdrawal of previous / concomitant treatment related to the conditions of the protocol or
  - A product other than the IMP, taken as part of the protocol.

Moreover, the investigator has to assess if the AE is related to disease progression. Cases ticked "related" by the investigator or judged by the sponsor as having a reasonable suspected causal relationship to the IMP (AE linked to the mechanism of action of the IMP…), will be considered as suspected Adverse Drug Reaction. In general, if a relationship between AE and IMP is at least reasonably possible (*i.e.* the relationship cannot be ruled out) it is to be considered as "related".

10.3. Laboratory Abnormalities

All laboratory abnormalities considered as clinically significant during the study will be reported as an adverse event and graded using CTCAE V5.0 included under a reported AE term describing a clinical syndrome (*e.g.* elevated BUN and creatinine in the setting of an AE of "renal failure").

If a laboratory abnormality cannot be reported as a clinical syndrome, AND if the laboratory abnormality results in a therapeutic intervention (*i.e.* concomitant medication or therapy, dose interruption or reduction), is a DLT, or is judged by the investigator to be of other clinical relevance, then the laboratory abnormality should be reported as an AE.

In addition, investigators can determine for laboratory abnormalities, which are in the range of grade 1 or 2 CTCAE abnormalities, whether they are clinically significant or not and can document this correspondingly as an AE or not in the e-CRF. Patients experiencing AEs or / clinically significant laboratory abnormalities will be assessed and appropriate evaluations performed until all parameters have returned to baseline levels or are consistent with the patient's then-current physical condition.

10.4. Reporting Procedures

10.4.1. Time frame for AE reporting

Any event meeting the above-mentioned definitions (see Section 10.1) must be reported to the sponsor on an **adverse event form** if it occurred:

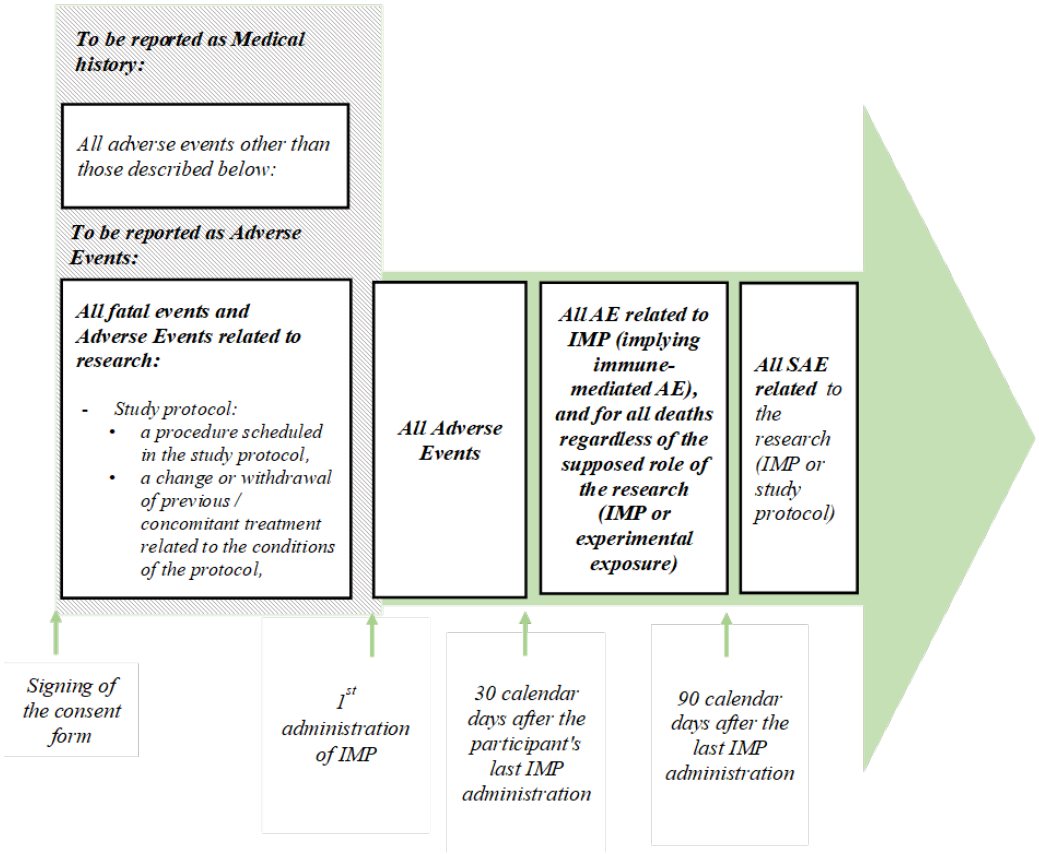
- Before the first IMP administration, for fatal events and all events related **to any procedure/condition required by the study protocol.**
- At any time after the IMP administration and up to 30 calendar days after the patient's last IMP administration for all AE, regardless of the supposed role of the research (IMP, or experimental procedure).
- Up to 90 calendar days after the patient's last IMP administration for all AEs related to the IMP (implying immune-mediated AEs), and for all deaths, regardless of the supposed role of the research (IMP, or experimental procedure).
- Irrespective of the time of onset in case of serious adverse event related to the research. SAE reporting may occur after end of study.

Of note, events occurring between the signature of the informed consent and the first administration of the IMP, for which the investigator does not consider an association with the research must be reported as ***medical history*** *in the dedicated form of the e-CRF. Fatal events, related or not to the research, occurring after ICF signature and before first IMP administration, must be reported on an AE form.*

In general, AEs should be reported as soon as possible in the e-CRF, through the completion of an AE form. All ERINs (related and unrelated) should be reported in the e-CRF within 24h of the investigator's knowledge whatever the grade, as these events may lead to immediate action of the sponsor such as change of the study design (switch from part A to part B), dose adjustments or increase/reduced infusion rate. In this situation and after duly completion of the AE form of the e-CRF, an email notification will be automatically sent to the sponsor.

Figure 10.4.1) 1 illustrates the types of events that need to be reported as AE or Medical History according to the study period.

Figure (10.4.1) 1 - Rules for AE reporting



10.4.2. Responsibilities of the Investigator

For any adverse event and special situation mentioned above the investigator must:

- **Note in the patient's medical file** the date on which he/she learned of the event (at a follow-up visit or a telephone contact with the patient or a third person, …) and any other relevant information which he/she has learned of the event.
- **Assess** the event in terms of seriousness, intensity and causality.

- **Report the event to the sponsor** using the AE form (in case of ERIN, the reporting should be done immediately).
- **Document** the event with additional useful information (see Section 10.4.2.1).
- Ensure the **follow-up** of the event.
- **Fulfil his/her regulatory obligations** to the CAs and/or to the Ethic committees (IRB/ Independent Ethic Committee (IEC)), in accordance with local regulations.
- **Demonstrate the oversight on data reported** and ensure the whole content's accuracy, completeness and legibility in accordance with the Good Clinical Practices (GCP) (see Section 12.1).

Moreover, the investigator must report to the sponsor and/or to the IRB/IEC and/or to the Competent Authorities in accordance with the local regulation, any new information that might materially influence the benefit-risk assessment of the IMP or that would be sufficient to consider changes in the IMP administration or in the overall conduct of the clinical investigation.

10.4.2.1. Documentation of the Event

The investigator must ensure that all events are well documented. He/she should provide the sponsor, on request, with anonymized copies of relevant the documents (*e.g.* autopsy report and terminal medical reports (ICH E6 R2).

10.4.2.2. Follow-up of Adverse Events

The investigator must ensure that follow-up of the patient is appropriate to the nature of the event, and that it continues until resolution or the end of the study, whatever comes first.

Any change in terms of diagnosis, severity, seriousness, measures taken, causality or outcome regarding an adverse event already reported must be written up in a new complete evaluation of the event documented on an "Adverse Event" page previously created for the event.

If the adverse event has not resolved at the patient's final visit in the study, the patient must be followed up suitably and any information on the outcome of the event will be noted on an "Adverse Event" page previously created for the event.

If the follow-up of the patient is not done by the investigator him/herself (hospitalization, followed by a specialist or the patient's general practitioner, …), the investigator will do everything to establish/maintain contact with the person/department in charge of follow-up of the patient.

10.4.2.3. Special situations (pregnancy, overdoses, intake of IMP by a person around the patient)

Pregnancy
If a female patient in the study becomes pregnant, the investigator must:

- Immediately stop the test drug.
- Report the pregnancy on an "Adverse Event" page as well as on the specific paper pregnancy form (1st page) to be notified immediately (ERIN).

- Follow-up this pregnancy and provide the sponsor with information concerning this follow-up (using the 2nd page of the specific paper pregnancy form).

If the partner of a patient becomes pregnant during the study, the pregnancy should not be reported in the e-CRF. The investigator should **immediately** contact the sponsor (contact details provided in the investigator's study file) who will inform him/her about the procedure(s) to be followed.

All reports of congenital abnormalities/birth defects are SAEs. Spontaneous miscarriages should also be reported and handled as SAEs.

Overdose of IMP

- In case of overdose, the investigator should report it on an "Adverse Event" page to be notified immediately (ERIN).
- Overdose should be followed-up to ensure that the information is as complete as possible with regards to:
  - Dose details (number of units, duration…) and details regarding other medicinal products or substance.
  - Context of occurrence, *i.e.* intentional (suicide attempt, other reason) or accidental (error in prescription, administration, dispensing, dosage).
  - Related signs and symptoms ("No related adverse events" to be reported otherwise).
  - Outcome.
  - As soon as possible, a blood sample should be collected to assess the blood concentration of IMP in case no PK samples are scheduled (Section 9) and analyzed following recommendation in Section 9.4.

Exposure to IMP by a person around the patient

This event should not be reported in the e-CRF. The investigator should immediately contact the sponsor (contact details provided in the investigator's study file) who will inform him/her about the procedure to be followed.

10.4.2.4. Recording Methods in the e-CRF

Adverse events must be documented on the "Adverse Event" page of the e-CRF.

In case of chronic disease:

- If the disease is known when the patient enters in the study, only worsening (increased frequency and/or intensity of the episodes/attacks) will be documented as an adverse event,
- If the disease is detected during the study and if repeated episodes enable diagnosis of a chronic disease, the episodes will be grouped on the "Adverse Event" page previously created for the event which will clearly describe the diagnosis.

10.4.2.5. Procedure for an event requiring an immediate notification.

In case of an event requiring an immediate notification, the investigator must:

- **Immediately,** after being informed of this event, **report the event in** the **patient's medical file** as well as on the **"Adverse Event" page** of the e-CRF according to the general instructions available in the e-CRF, ***without*** waiting for the results of the clinical outcome or of additional investigations. When data will be submitted into the e-CRF, an e-mail will be immediately and automatically sent to the sponsor.

- Fulfil his/her regulatory obligations to the Competent Authorities and/or to the IRB/IEC, in accordance with local regulations.

Moreover, on request, the investigator should provide the sponsor with the documents required in Section 10.4.2.1.

If an adverse event initially non-serious worsens and becomes a serious adverse event, this must be reported **immediately** on an "Adverse event" page of the e-CRF.
In case the e-CRF is unavailable when the investigator was informed of the ERIN, he/she should:

- **Immediately** fill in a paper "Adverse event" page:
  - For serious event on a paper "Adverse event – Initial information" page.
  - For event initially non-serious on a paper "Adverse event – Initial information" page, and the worsening of the event leading to seriousness on a paper "Adverse event – Additional information" page.
- Immediately send these pages by fax or by e-mail (scanned copies) to the person(s) designated in the contact details provided in the investigator's study file or outside working hours, the 24-hour phone line (+33(0)1.01.55.72.60.00 for a call from outside France), and/or the specific phone line as specified in the instruction provided to each center.
- As soon as the e-CRF becomes available, the investigator should enter these data in the "Adverse Event" page of the e-CRF.

10.4.3. Responsibilities of the sponsor

In accordance with international guidance, the assessment of the seriousness and the causality of adverse events are made by the investigator but also falls under the sponsor's duties, who is responsible for ensuring that all suspected and unexpected serious adverse reactions are reported to the Competent Authorities and the Ethics Committees.

The sponsor will review the seriousness of the adverse events and the causality of (at least) the serious adverse events, whether reported by the investigator or upgraded by the sponsor. The causality and the seriousness may be upgraded (but never downgraded). Anonymized copies of relevant documents may be asked for the event assessment. If the assessment of an event by the investigator and by the sponsor are different, both assessments will be reported in the clinical study report.

In addition, the sponsor is responsible for determining whether an AE is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the IMP.

Independently of the regulatory obligations of the investigator, the sponsor must report the pharmacovigilance data and any new safety finding likely to affect the benefit /risk balance of the product, required in ICH Good Clinical Practice guidelines and local regulations, to the appropriate Authorities, to all the investigators involved and to the trial subjects involved - through the investigators - as mentioned in Section 12.4 "Modification of the protocol and information and consent form".

The concerned Authorities will be notified as soon as possible by the sponsor, of the IEC recommendations if any, where relevant for the safety of patients (*i.e.* modification or termination of the study).

The concerned Authorities will be notified as soon as possible by the sponsor of the DMC recommendations if any, where relevant for the safety of participants (*i.e.* modification or termination of the study). See Section 14.8.2 for more details on the DMC.

11. STATISTICS

11.1. Sample Size

Phase 1 - Dose escalation
The number of patients will depend on the number of dose cohorts that will be enrolled before reaching the MTD. It is expected that approximatively CCI patients will be enrolled. The size and design of the dose escalation phase of the study is consistent with standard phase 1 accelerated dose escalation designs and multiple-patient cohort dose escalation based on the BLRM with the objective of determining the MTD/RP2D (Hansen *et al.*, 2014; Le Tourneau *et al.*, 2009). Thirty additional patients may be enrolled to backfill cohorts as mentioned in Section 6.4.3.

In addition, approximately 10-12 patients will be treated with PRS-344/S095012 preceded by obinutuzumab administration, with the objective of having safety, PK, PD and ADA data over 2 cycles of treatment for 5-6 patients (as mentioned in Section 4.3.2.2). CCI

CCI

Phase 2 - Expansion arms
Approximately 108 patients will be enrolled in arms 1 to 3, with approximately CCI patients in each arm. The planned sample size is considered adequate for controlling the chance of falsely claiming efficacy at <15% in each arm, *i.e.*, when the underlying ORR is futile. It also provides reasonable accuracy in claiming efficacy when the underlying ORR reflects an efficacious treatment effect.

11.2. Analysis Populations

The following analysis populations are defined:

Safety population: All patients who have received at least one administration of PRS-344/S095012.

DLT evaluable population: In phase 1, all patients who have received at least 80% of the required PRS-344/S095012 dose and completed the DLT observation period or who experienced a DLT.

Response evaluable population: In phase 2, all patients who have received at least one administration of PRS-344/S095012, have measurable disease at baseline, and meet any of the following conditions: 1) at least one post-baseline disease assessment; 2) documented clinical progression; 3) death.

PK analysis population: All patients who have samples collected to provide interpretable PK results, with no deviations that might affect the PK interpretation.

11.3. Phase 1 Dose Allocation Methodology

The primary objective of phase 1 parts A and B is to determine the safety and tolerability, MTD or MAD, of single-agent PRS-344/S095012 in patients with advanced and/or metastatic solid tumors for which standard treatment options are not available, no longer effective or not tolerated.

In part B of the study an adaptive BLRM with overdose control (EWOC) will be used to guide dose escalation and estimate the MTD(s) based on occurrence of DLT during Cycle 1. The BLRM is a well-established method to estimate the MTD in cancer patients. The adaptive BLRM will be guided by the escalation with overdose control principle to control the risk of DLT in future patients on study. The dose recommended by the model at any stage of the study is based on the entire history of all available DLT information from previous cohorts as opposed to only the number of DLTs observed in the last cohort of patients.

The MTD will be based on:

- The MTD estimated by the BLRM model stated above and,
- An overall clinical assessment of all available safety, tolerability, PK, pharmacodynamic data.

11.3.1. Statistical Model

The dose-DLT relationship will be described by a two-parameter logistic model:

$$logit(\pi_{(d)}) = \log(\alpha) + \beta \log(d/d^*), \alpha > 0, \beta > 0$$

where:

- $logit(\pi_{(d)}) = \log\left(\frac{\pi_{(d)}}{1-\pi_{(d)}}\right)$
- $\pi_{(d)}$ is the probability of a DLT at dose *d*.

Doses are rescaled as *d/d** with reference dose [redacted] of PRS-344/S095012. Thus, α is equal to the odds of toxicity at *d**. Note that for a dose equal to zero, the probability of toxicity is zero.

The MTD is the highest drug dosage that is unlikely (< 25% posterior probability) to cause DLT in more than 33% of the treated patients in the first cycle of PRS-344/S095012 treatment.

11.3.2. Provisional Dose Levels

Phase 1 dose escalation (parts A and B) will be conducted with semi-logarithmic increment as maximum, as illustrated in Table (6.3.3) 1. However, it is possible that intermediate or higher dose levels will be added during the study and that smaller dose increments may be utilized. The first dose level used for part B will depend on the safety events observed in part A and will start at CCI at most.

In phase 2, the RP2D will be determined based on safety, tolerability, PK and pharmacodynamic data. In any case, this dose will not exceed the maximum dose tested in phase 1.

11.3.3. Prior Specifications

The bivariate normal prior for the model BLRM parameters with a reference dose level of CCI is obtained as follows:
The following non-informative prior for (log(α), log(β)) was used:

- The median DLT rate at the PRS-344/S095012 reference dose (CCI) was assumed to be 20%.
- A doubling in dose was assumed to double odds of DLT.
- The standard deviation of log(α) was set to 2, and the standard deviation of log(β) to 1, which allows for considerable prior uncertainty for the dose-toxicity profile.
- The correlation between log(α) and log(β) was set to 0.

Table (11.3.3) 1 - Prior parameters for bivariate normal distribution of model parameters

Parameters	Means	Standard deviations	Correlation
log(α), log(β)	(-1.386, 0.000)	(2.000, 1.000)	0

Figure (11.3.3) 1 - Prior distribution of DLT rates

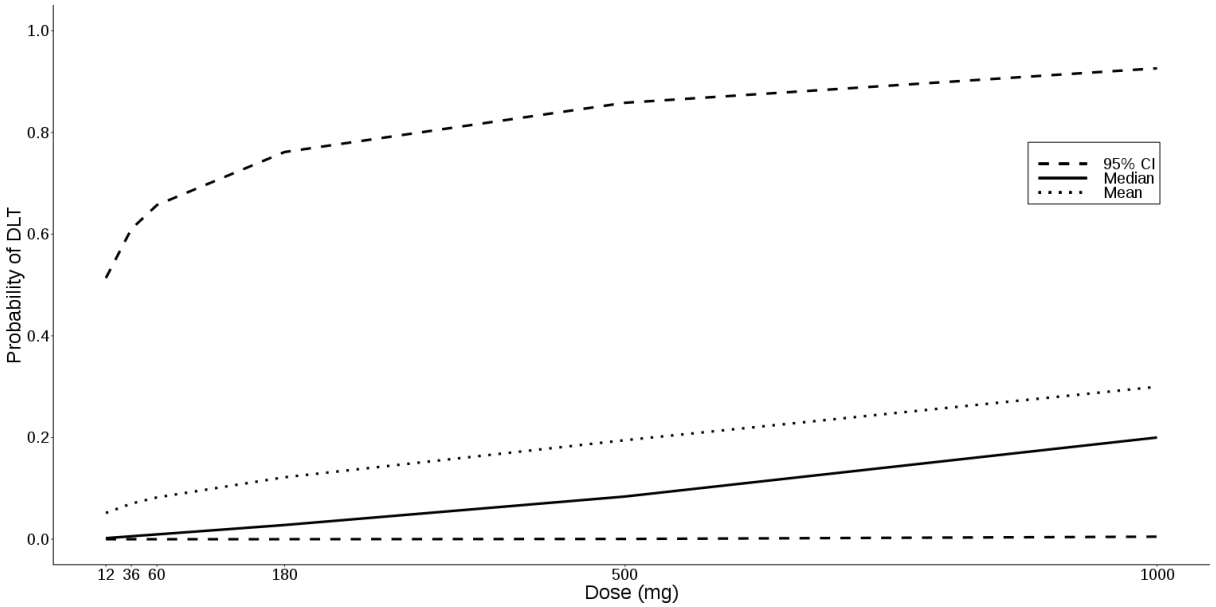


Table (11.3.3) 2 - Prior distribution summaries derived from priors

Doses (mg)	Prior probabilities that Pr(DLT) is in interval:			Mean	Standard Deviation	Quantiles		
	[0, 0.16)	[0.16, 0.33)	[0.33, 1]			2.5%	50%	97.5%
CCI	0.9079	0.0443	0.0478	0.0516	0.1329	0.0000	0.0020	0.5137
	0.8732	0.0593	0.0674	0.0701	0.1546	0.0000	0.0058	0.6102
	0.8504	0.0687	0.0809	0.0822	0.1670	0.0000	0.094	0.6572
	0.7754	0.0978	0.1269	0.1219	0.2000	0.0000	0.0279	0.7616
	0.6382	0.1430	0.2188	0.1948	0.2419	0.0005	0.0840	0.8584
	0.4554	0.1801	0.3645	0.2998	0.2806	0.0050	0.2001	0.9262

Note: bold values indicate doses not meeting the overdose criterion (more than 25% chance of excessive toxicity) with the prior information only.

11.3.4. Dose Recommended by the Bayesian Logistic Regression Model

The set of potential doses assessed with the model is defined in Section 6.3.3. The first dose level used for the part B will depend on the escalation occurred in part A and will not exceed CCI at most. The cohort will be opened for three to six patients.

All available data on DLTs (assessed in Cycle 1) will be used for updating the model. Before making a dose allocation decision, a minimum of three patients must be evaluable for safety and not prematurely withdrawn for reasons other than a DLT, which means that they have received at least 80% of the required PRS-344/S095012 dose and completed the DLT observation period or they have experienced a DLT.

After each cohort of patients is completed, the dose recommended by the BLRM will be based on posterior summaries including the mean, median, standard deviation, 95%-credible interval, and the probability that the true DLT rate for each dose lies in one of the following categories:

- [0,16%] under-dosing.
- [16%,33%] targeted toxicity.
- [33%,100%] excessive toxicity.

Following the principle of escalation with overdose control (EWOC), after each cohort of patients the doses fulfilling EWOC criterion (*i.e.* it is unlikely (< 25% posterior probability) that the DLT rate at the dose falls in the excessive toxicity interval) will be identified by the model. A dose not fulfilling EWOC criterion cannot be recommended. Admissible doses for the next cohort will not exceed semi-logarithmic increment increase from the previous dose. Note that the dose that maximizes the posterior probability of targeted toxicity is the best estimate of the MTD, but it may not be an admissible dose according to the overdose criterion if the amount of data is insufficient.

The dose recommended by the adaptive BLRM should be regarded as guidance and information to be integrated with a clinical assessment of the toxicity and available activity profiles observed at the time of the analysis in determining the next dose level to be investigated.

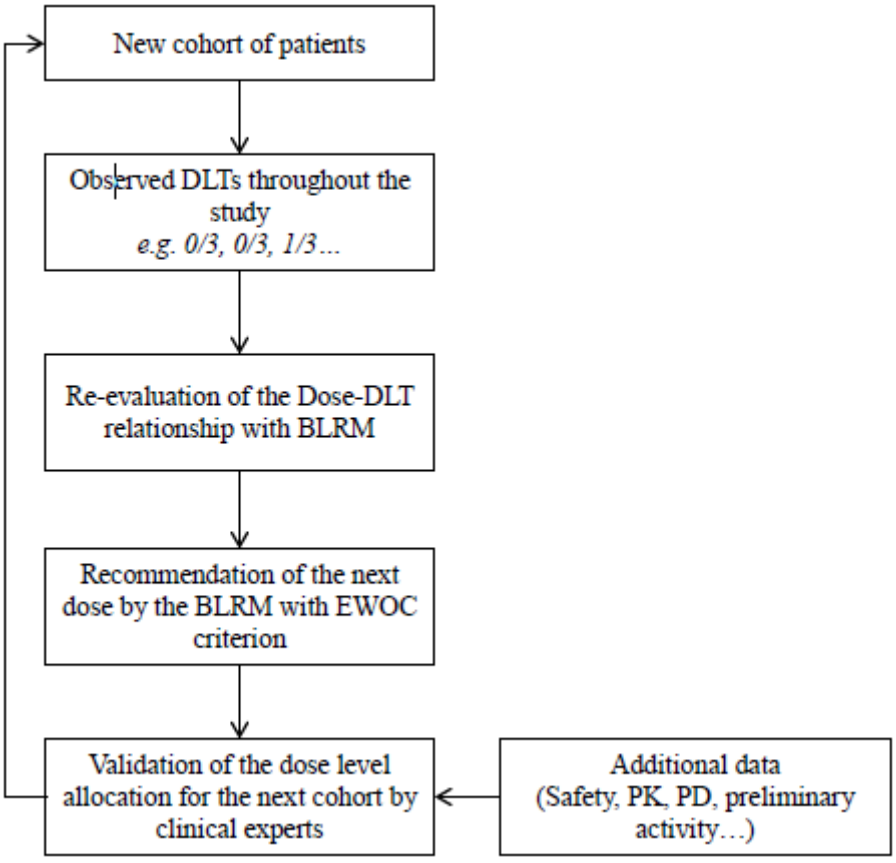
11.3.5. Dose Allocation Process

After each cohort of patients is completed and before including a new cohort of patients, a dose escalation meeting between the sponsor medical representative and the investigators will take place to decide jointly the next dose level to be tested according to:

- The dose proposed by the BLRM (based on DLT data) in part B.
- All available cumulative safety data.
- Available PK data.
- Available pharmacodynamic data.
- Available preliminary activity data.

The dose allocation process is described in Figure (11.3.5) 1.

Figure (11.3.5) 1 -BLRM Dose Allocation Process



11.3.6. Final Recommendations and Stopping Rules Recommended by the Bayesian Logistic Regression Model

Dose escalation will continue until identification of the MTD(s). This will occur when the following conditions are met:

1. At least six patients have been treated at this dose.
2. This dose satisfies one of the following conditions:
   a) The posterior probability of targeted toxicity at this dose exceeds 50% and is the highest among potential doses, or
   b) A minimum of 24 patients have already been treated on the study.
3. It is the dose recommended for patients, either per the model or by review of all clinical data by the SRC.

Of note, the dose escalation part could be stopped earlier during a dose escalation meeting according to the model estimations and a global assessment of the safety, PK, PD, and preliminary antitumor activity data. Note that it is possible that the MTD may not be reached in some situations.

11.4. Phase 2 Dose Expansion Design and Statistical Assumptions

In dose expansion arms, a CBHM (Jiang *et al.*, 2021) will be adopted. The principle of the method is to divide all arms into two clusters (subgroups) based on the observed data, where one cluster represents the responsive arms and the other cluster represents the non-responsive arms. We then apply the following Bayesian hierarchical model (BHM) to borrow information within each subgroup given the similarities among those arms. If a subgroup has only one arm, the BHM will be replaced by the beta-binomial model.

$$
\begin{aligned}
x_g \mid q_g &\sim Binomial(q_g),\\
\theta_g &= \log\left(\frac{q_g}{1-q_g}\right) - \log\left(\frac{q_{0,g}}{1-q_{0,g}}\right),\\
\theta_g \mid \theta, \sigma^2 &\sim N(\theta, \sigma^2),\\
\theta \sim N(\mu_0, \tau_0^2),\ \sigma^2 &\sim IG(a_0, b_0),
\end{aligned}
$$

where x_g is the number of responders in arm g, q_g is the underlying ORR in arm g, $q_{0,g}$ is the null response rate that is deemed futile in arm g, IG (-) denotes inverse-gamma distribution, μ_0, τ^2_0, a_0 and b_0 are hyperparameters.

The futility threshold of a [CCI] ORR was derived from historical data obtained from patients treated in the same line of therapy. Approximately [CCI] patients will be enrolled in each arm. One interim analysis is planned in each arm after there are [CCI] response-evaluable patients. An additional interim analysis may be performed in each arm dependent upon recruitment status and trial progress. At the time of a planned analysis, the corresponding arm will be stopped if the following futility criterion is met, where q_1, q_2 and q_3 represent the true (unknown) ORR of arms 1 to 3, respectively.

Analysis	Criteria
Interim analysis (N=[CCI])	Pr ($q_1 \leq$ [CCI] | *Data*) > 0.398
Final analysis (N=[CCI])	Pr ($q_1 \leq$ [CCI] | *Data*) > 0.22

All details of the methodology including the operating characteristics from simulation studies will be described in the Statistical Analysis Plan (SAP).

11.5. Criteria for Evaluation

11.5.1. Safety

Number and percentage of patients with occurrence of DLT will be described in the DLT evaluable population.

Emergent AEs, laboratory data and safety tests will be reviewed and summarized on an ongoing basis during the study. All EAEs and safety laboratory abnormalities of potential clinical concern will be described. Safety data will be presented in tabular and/or graphical format and summarized descriptively by dose cohort and time where appropriate, in the safety population. Absolute value data and changes from baseline data will be summarized as appropriate.

EAEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and severity of EAEs and laboratory abnormalities will be graded using CTCAE v5.0 as appropriate. The worst grade will be described per patient. To examine the evolution of toxicities the worst grade will be analyzed in relation to the grade presented by the patient at baseline (via shift tables).

Incidence tables of patients with EAEs will be presented for all EAEs by maximum severity, SEAEs, SAEs, EAEs assessed as related to study drug, and EAEs resulting in discontinuation of study drug.

Listings of relevant safety data sorted by dose cohort, patient and assessment date will be provided.

11.5.2. Pharmacokinetics and Immunogenicity

PK profiles of PRS-344/S095012 will be investigated during the study. The immunogenicity of PRS-344/S095012 (anti- PRS-344/S095012 antibody formation) will be investigated during the study.

Pharmacokinetic variables

See Section 9.4.2.

Immunogenicity–exposure and/or AE relationship

The concentration/adverse event – immunogenicity relationship will be explored graphically and tabulated to characterize a relationship between the changes from screening immunogenicity presence and serum concentration of PRS-344/S095012.

In addition, the potential correlation between immunogenicity and other endpoints (major safety, efficacy and biomarker parameters) may be evaluated. This will be done in two steps. First, a descriptive analysis will be performed graphically between immunogenicity change from screening values and major safety, efficacy, and biomarker parameters (either as categories or continuous variables). If any potential correlation is identified, further investigation may be performed using a mechanism-based modeling approach, as appropriate.

11.5.3. Efficacy

Overall responses (CR, PR, SD, or PD) will be determined as per RECIST 1.1 (Eisenhauer *et al.*, 2009). The primary analysis will use responses from central assessment. Supportive analyses using the unconfirmed/confirmed responses, and/or investigator reported responses will also be reported.

The following parameters will be derived (per RECIST 1.1 or composite criteria, as appropriate):

- Objective response rate (ORR) will be calculated as the proportion of patients who achieve CR or PR. Best overall response (BOR) will be determined per patient as the best response recorded (either CR, PR, SD or PD) from the start of the treatment until the disease progression/recurrence.
- Disease control rate (DCR) will be calculated as the proportion of patients who achieved SD, PR, or CR (based on patient's best response).
- Duration of Response (DoR) will be calculated as the time from the first documentation of CR or PR until the documented PD or death.
- Time to Response (TTR) will be calculated as the time from the first dose of PRS-344/S095012 to the first documentation of CR or PR.
- Progression-free survival (PFS) will be determined as the time from the first dose of PRS-344/S095012 to first documented disease progression or death due to any cause, whichever occurs first.
- Overall survival (OS) will be determined as the time from first PRS-344/S095012 dose to death due to any cause.

Treatment beyond progression
See Section 9.2.1.

11.5.4. Pharmacodynamics

The pharmacodynamic response will be assessed by analyzing lymphocyte subtypes in peripheral blood or lymphocyte markers in tumor biopsies, or cytokine/s4-1BB levels in plasma. The PK/ pharmacodynamic relationship and relationship to tumor response may be explored.

11.6. Statistical Methods

Tabular summaries of data will be descriptive in nature (*i.e.* number of patients [n], mean, standard deviation, median, minimum and maximum for continuous variables and n and percent for categorical variables). A more detailed description of analysis methods will be provided in the SAP to be completed prior to the clinical database lock.

12. DATA HANDLING AND RECORD KEEPING

12.1. Study data

A 21 CFR Part 11-compliant electronic data capture system is going to be used for this study. An electronic case report form (e-CRF) is designed to record the data required by the protocol and collected by the investigator.
The e-CRF will be produced by I.R.I.S. The investigator or a designated person from his/her team will be trained on the use of the e-CRF by the sponsor.
Data entry at the investigator's site will be performed by the investigator or by the designated person from his/her team after completion of the patient's Medical File.
Upon entry, data will be transmitted via the Internet from the study center to the study database.
The investigator or the designated person from his/her team agrees to complete the e-CRF, at each patient's visit, as well as all the other documents provided by the sponsor (*e.g.* documents relating to the IMP management).

Data recorded directly on e-CRF and considered as source data must be collected immediately in the e-CRF. Source data and source documents of the center should be clearly identified in a specific, detailed and signed document before the beginning of the study. The other e-CRF forms must be completed as soon as possible following each visit.

All corrections of data on the e-CRF must be made by the investigator or by the designated person from his/her team using electronic data clarifications according to the provided instructions. All data modification will be recorded using the audit trail feature of e-CRF software, including date, reason for modification and identification of the person who has made the change.

To ensure confidentiality and security of the data, usernames and passwords will be used to restrict system access to authorized personnel only, whether resident within the investigator's sites, the sponsor or third parties.

Data will be verified in accordance with the monitoring strategy defined for the study. After comparing these data to the source documents, the monitor will request correction / clarification from the investigator using electronic data clarifications that should be answered and closed as quickly as possible.

Data can be frozen during the study after their validation. However, the investigator has the possibility to modify data if deemed necessary via a request to the sponsor.

The investigator or authorised member for sign-off must confirm the authenticity of the data recorded in the e-CRF by signing-off the e-CRF in a timely manner as defined in the e-CRF completion guide.

After the data base lock, the investigator or an authorized member of his/her team will have to download from the e-CRF an electronic file containing patient data from his/her center for archiving it in the study file (see Section 12.5).

12.2. Data management

Data are collected via an e- CRF and stored in a secured database.
For data collected on the e-CRF, the Servier Clinical Data Management of I.R.I.S. is responsible for data processing including data validation performed according to a specification manual describing the checks to be carried out. As a result of data validation, data may require some changes. An electronic data clarification form is sent to the investigator who is required to respond to the query and make any necessary changes to the data.
For data transferred from the CRO in charge of central activities, the Servier Clinical Data Management of I.R.I.S. is responsible for data transfer: CRO provides electronic transfers of computerized data to the Clinical Data Management of I.R.I.S. Data are transferred according to a transfer protocol issued by the I.R.I.S. data manager.

The Servier Medical Review Department of I.R.I.S. is responsible for data coding including:
- Medical / surgical history, adverse events and procedures using MedDRA.
- Medications using World Health Organization, Drug Dictionary (WHO-Drug).

The coding process is described in a specification manual.
The investigator ascertains he/she will apply due diligence to avoid protocol deviations. Under no circumstances should the investigator contact the sponsor or its representatives monitoring the study, if any, to request approval of a protocol deviation, as no deviations are permitted. If the investigator feels a protocol deviation would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by the sponsor and approved by the IRB/IEC it cannot be implemented. All important protocol deviations will be recorded and reported in the clinical study report.

On one timepoint decided by the Sponsor during the study and at the end of the study, reviews of the data are performed according to the sponsor standard operating procedure. When the database has been declared to be complete and accurate, it will be locked and made available for data analysis.

12.3. Study Discontinuation and Site Closure

Both the sponsor and the investigator reserve the right to temporarily halt or discontinue the study at any time. Should this be necessary, both parties will arrange temporary halt or discontinuation procedures. The sponsor reserves the right to temporarily halt or to discontinue the study at any time for medical or administrative reasons. When feasible, a 30-day written notification will be given. The entire study will be stopped if:
- The protocol-specified treatment is considered too toxic to continue the study.
- Evidence has emerged that, in the opinion of the Sponsor or the Investigator(s), makes the continuation of the study unnecessary or unethical.
- The stated objectives of the study are achieved.
- The Sponsor discontinues the development of the study drug.

In terminating the study, the sponsor and the investigator will ensure that adequate consideration is given to the protection of the patients' interests. The on-going patients should be seen as soon as possible, and the same assessments as described in Section 9 should be performed. Under some circumstances, the investigator may be informed of additional procedures to be followed to ensure that adequate consideration is given to the protection of the patient's interests.

Regardless of the reason for termination, all data available for the patient at the time of discontinuation of follow up must be recorded on the e-CRF. All reasons for discontinuation of treatment must be documented.

In case of study suspension (temporary halt), the study may resume once concerns about safety, protocol compliance and data quality are addressed and satisfy the Sponsor, the IRB/Independent Ethics Committee (IEC) and Competent Authorities

12.4. Modification of the Study Protocol and Information and Consent Form

Protocol amendments, except when necessary to eliminate an immediate hazard to patients, must be made only with the prior approval of the sponsor. Agreement from the investigator must be obtained for all protocol amendments and amendments to the informed consent document.

The IRB or IEC must be informed of amendments and give approval before their implementation, when appropriate in accordance with local regulations. The sponsor will submit any study protocol amendments to the concerned regulatory authorities for approval and keep the investigator(s) updated as detailed in the ICH GCP guidelines, when appropriate in accordance with local regulations.

Moreover, any change to the information and consent form constitutes an amendment to this document and must be submitted for approval to the IRB/IEC(s), and if applicable to the Competent Authorities.

Such amendments may only be implemented after written approval of the IRB/IEC has been obtained and compliance with the local regulatory requirements, except for an amendment required to eliminate an immediate risk to the study patients. Each patient affected by the amendment must complete, date and sign two originals of the new version of the information and consent form together with the person who conducted the informed consent discussion. He/she will receive one signed original amendment to the information and consent form.

12.5. Archiving / Retention of Study Documents

The study site will maintain a study file, which should contain, at minimum, the IB, the protocol and any amendments, drug accountability records, correspondence with the IRB or IEC and the sponsor, and other study-related documents.

The investigator agrees to keep records and those documents that include (but are not limited to) the identification of all participating patients, medical records, study-specific source documents, source worksheets, all original signed and dated ICFs, copies of all e-CRFs, and detailed records of drug disposition to enable evaluations or audits from regulatory authorities and the sponsor or its designees.

The investigator shall retain those records required to be maintained for a period of five years after the date a marketing application in an ICH region is approved for the drug for the indication for which it is being investigated or, if no application is to be filed or if the application is not approved for such indication, until at least five years after the investigation is discontinued or longer if so required by local regulation.

However, these documents may need to be retained for a longer period if so required by the applicable regulatory requirement(s) or if needed by the sponsor. For instance, in EU, the investigator will keep all information relevant to the study for at least 25 years after the end of the study. In addition, the investigator must make provision for the patients' medical records to be kept for the same period.

No data should be destroyed **without** the agreement of the sponsor. Should the investigator wish to assign the study records to another party or move them to another location, the sponsor must be notified in writing of the new responsible person and/or the new location. The sponsor will inform the investigator, in writing, when the study-related records are no longer needed.

Patients' medical records and other original data will be archived in accordance with the archiving regulations or facilities of the investigational site and according to local CA regulations if appropriate.

On the timepoints decided by the Sponsor, the investigator or an authorized member of his/her team will download an electronic copy of each patient's data from the e-CRF and should keep it in a reliable, secure and durable location. The file includes all data and comments reported in the e-CRF, the history of all queries and signatures and the full audit trail reports.

The file must include appropriate restrictions (password protection) and adequate protection from loss, physical damage or deterioration for the duration of the archiving period.

12.6. Clinical Study Report

The study report will be drafted by the sponsor in compliance with sponsor's standard operating procedure. The sponsor's representative and the investigators must mutually agree on the final version. One copy of the final report must be dated and signed by the sponsor's representatives and investigators if required by local regulation.
The clinical study report, the summary of the results of the clinical trial together with a summary that is understandable to a layperson will be submitted where applicable within 1 year after the end of the clinical trial worldwide.

12.7. Study Publication

The conditions regulating the dissemination of any of the information derived from this study are described in the Clinical Trial Agreement. The sponsor assumes full responsibilities relating to this function and retains exclusive property rights over the results of the study, which it may use as it deems fit.

The sponsor will ensure that the key design elements of this protocol will be posted in a publicly accessible database such as clinicaltrials.gov. In addition, upon study completion and finalization of the study report, the results of this study will be either submitted for publication and/or posted in a publicly accessible database of clinical study results.

Any investigator-initiated publication and/or communication relative to the study and/or relative to the obtained results during the study or after the study end must be submitted – in advance - to the sponsor, in accordance with the guidelines set forth in the clinical trial agreement, the applicable publication policy or financial agreement.

The investigator, who submitted the project, will take the sponsor's comments into due consideration.

As the study is a multicenter one, the first publication will be performed only with data collected from several centers and analyzed under the responsibility of the sponsor. The investigator commits himself not to publishing or communicating data collected in only one center or part of the centers before the publication of the complete results of the study, unless prior written agreement from the other investigators and the sponsor has been provided. Data Sharing Policy is available at https://clinicaltrials.servier.com/data-request-portal/.
Researchers can ask for a study protocol, patient-level and/or study-level clinical trial data including clinical study reports (CSRs). They can ask for all interventional clinical studies:

- Submitted for new medicines and new indications approved after 1 January 2014 in the European Economic Area (EEA) or the USA.
- Where Servier or an affiliate are the Marketing Authorization Holders (MAH). The date of the first Marketing Authorization of the new medicine (or the new indication) in one of the EEA Member States will be considered within this scope.

The datasets generated and/or analyzed during the current study will be available upon request from www.clinicaltrials.servier.com after the Marketing Authorization has been granted.

Summary results and a lay summary will be published on www.clinicaltrials.servier.com within 12 months after the end of the study.

12.8. Quality Assurance Audits

An audit visit to clinical centers may be conducted at any time (during or after the end of the study) by a quality auditor appointed by the sponsor. The purpose of an audit, which is independent of and separate from routine monitoring or quality control functions, is to evaluate study conduct and compliance with the protocol, standard operating procedures, ICH GCPs, and the applicable regulatory requirements. The investigator and the sponsor may also be subject to an inspection by the FDA, European regulatory authorities, or other applicable regulatory authorities at any time.

The sponsor will inform the investigators concerned immediately upon notification of a pending study center inspection. Likewise, the investigator will inform the sponsor of any pending inspection.

The auditor and regulatory authorities will require authority from the investigator to have direct access to the patients' medical records. It is important that the investigator(s) and their staff cooperate with the auditor or regulatory authorities during this audit or inspection.

The investigator must allow the representatives of the Competent Authorities and the persons responsible for the audit:

- To inspect the site, facilities and material used for the study.
- To meet all members of his/her team involved in the study.

- To have direct access to study data and source documents.
- To consult all the documents relevant to the study.

If the computerized medical file is considered as not validated, the investigator undertakes to provide all the source-documents and the print-outs of the medical files of the patients and, if the computer system used allows, the record of the changes made during the study. If the computerized medical file is considered as validated, the investigator undertakes to:

- Give access to the representatives of the Competent Authorities and persons responsible for the audit to the computerized medical files of all patients,
- Provide the print-outs of the changes made during the study, if the tracking of the changes made to the medical files cannot be accessed in the computer.

If on-site auditing cannot be accomplished, remote source data verification may be performed in accordance with applicable regulations.

13. INSURANCE

The sponsor is insured under the liability insurance program subscribed to cover its liability as sponsor of clinical trials on a worldwide basis.

Where an indemnification system and/or a mandatory policy are in place, the sponsor will be insured under a local and specific policy in strict accordance with any applicable law.

All relevant insurance documentation is included in the file submitted for regulatory or IRB/IEC authorities' approval as necessary.

14. STUDY ADMINISTRATION

14.1. Regulatory and Ethical Considerations

This study will be conducted in compliance with the protocol, Good Clinical Practices (GCPs), including International Council for Harmonization (ICH) Technical Requirements for Registration of Pharmaceuticals for Human Use Guidelines, FDA/European CAs, regulatory requirements, and in accordance with the ethical principles of the Declaration of Helsinki (see Appendix 1).

14.1.1. Regulatory Authority Approvals

The sponsor or designee will submit the study protocol plus all relevant study documents to applicable CAs for approval before the study start. No patient will be admitted to the study until appropriate regulatory approval of the study protocol has been received.

Data generated in the USA will be handled in accordance with the Health Information Portability and Accountability Act (HIPAA). The study will be registered at www.clinicaltrials.gov using the Protocol Registration System.

14.1.2. Institutional Review Board(s)/Independent Ethics Committee(s)

This protocol and any material to be provided to the patient (such as advertisements, patient information sheets, or descriptions of the study used to obtain informed consent) will be submitted to (an) IRB(s)/IEC(s) by the investigator(s) or the sponsor in accordance with local regulations. This also applies to protocol amendments.

The sponsor will supply relevant data for the investigator to submit the study protocol/ICF and additional study documents to the IRB/IEC. The principal investigator will submit the study protocol/ICF for review and approval by an IRB/IEC, according to national law and/or local regulations, and will provide the IRB/IEC with all appropriate materials.

Verification of the IRB/IEC's unconditional approval of the study protocol and the written ICF will be transmitted to the sponsor. This approval must refer to the study by exact study protocol title and number, identify the documents reviewed, and state the date of the review.

The study will not start in a center before written approval by the corresponding IRB/IEC(s) has been obtained, the local regulatory requirements have been complied with, and the signature on the clinical study protocol of each contractual party involved has been obtained.

The IRB/IEC must be informed by the principal investigator of all subsequent study protocol amendments and of SAEs or suspected unexpected serious adverse reactions (SUSARs) occurring during the study that are likely to affect the safety of the patients or the conduct of the study.

14.2. Confidentiality of Information

All documents and information given to the investigator by the sponsor with respect to PRS-344/S095012 and study CL1-95012-001are strictly confidential.

The investigator expressly agrees that data on his/her professional and clinical experience is collected by the sponsor on paper and computer and stored for its sole use relating to its activities as the sponsor of clinical trials, in accordance with GCP.

He/she has a right to access, modify, and delete his/her own personal data by applying to the sponsor.
In case a patient wants to exercise his/her rights regarding personal data protection, he/she will contact the investigator. The investigator will forward the request to the sponsor.

The investigator agrees that he/she and the members of his/her team will use the information only in the framework of this study, for carrying out the protocol. This agreement is binding if the confidential information has not been disclosed to the public by the sponsor. The clinical study protocol given to the investigator may be used by him/her or his/her colleagues to obtain the informed consent of study patients. The clinical study protocol as well as any information extracted from it must not be disclosed to other parties without the written authorization of the sponsor.

The investigator must not disclose any information without the prior written consent from the sponsor, except to the representatives of the CAs, and only at their request. In the latter case, the investigator commits himself/herself to informing the sponsor prior to disclosure of information to these authorities.

A patient screening log and a full identification and enrollment list of each patient will be completed and kept in a safe place by the investigator who should agree to provide access on site to the auditor and/or the representatives of the CAs. The information will be treated in compliance with professional secrecy.

The patient pre-screening log must be completed from the moment the investigator checks that a patient could potentially take part in the study (by assessment of patient medical history during a visit or by examination of the medical file).

14.3. Patient Informed Consent

All information about the clinical study, including the patient information and the ICF, is prepared and used for the protection of the human rights of the patient according to ICH GCP guidelines and the Declaration of Helsinki (Appendix 1).

It is the responsibility of the investigator to obtain signed ICFs from each patient participating in this study after adequate explanation of the aims, methods, objectives, and potential hazards of the study and before undertaking any study-related procedures. According to local regulation, additional ICF signature may be required for biopsy on-treatment, additional blood samples for optional analyses and for genomic blood samples.

The ICF, prepared by the sponsor, must be approved along with the study protocol by the IRB or IEC. Any changes to the ICF required by the site must be acceptable to the sponsor.

The patient must be provided with the patient information and ICF consistent with the study protocol version being used and which has been approved by the relevant IRB or IEC. The ICF must be in a language fully comprehensible to the prospective patient. Patients (and/or relatives, guardians, impartial witness or legal representatives, if necessary) must be given sufficient time and opportunity to inquire about the details of the study and to discuss and decide on their participation in the study with the investigator concerned. The patient and the person explaining about the study and with whom they discuss the informed consent will sign and date the ICF. A copy of the signed ICF will be retained by the patient and the original signed ICF will be filed in the investigator file unless otherwise agreed.

14.4. Study Monitoring

Clinical site monitoring is conducted to ensure that the rights and well-being of human subjects are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol/amendment(s), with GCP, and with applicable regulatory requirement(s).

On behalf of the sponsor, a clinical research organization monitor will contact and visit the investigator at the study center before the entry of the first patient and at predetermined appropriate intervals during the study until after the last patient has completed. The monitor will also perform a study closure visit. Details of clinical site monitoring are documented in a Clinical Monitoring Plan (CMP). If on-site monitoring cannot be accomplished, remote source data verification may be performed in accordance with applicable regulations.

14.4.1. Before the study

The investigator will allow the monitor to visit the site and facilities where the study will take place to ensure compliance with the protocol requirements.

Training sessions may be organized for the investigators and/or instruction manuals may be given to the investigators.

14.4.2. During the study

In accordance with ICH GCP guidelines, the investigator must ensure provision of sufficient time, reasonable space, and adequate qualified personnel for the monitoring visits. The visits are for verifying adherence to the study protocol and the completeness, consistency, and accuracy of data entered on the e-CRF and other documents.

The investigator will make all source data (*i.e.*, the various study records, the e-CRFs, laboratory test reports, other patient records, drug accountability forms, and other pertinent data) available for the monitor and allow access to them throughout the entire study period. Monitoring is done by comparing the relevant site records of the patients with the entries on the e-CRF (*i.e.* source data verification). It is the monitor's responsibility to verify the adherence to the study protocol and the completeness, consistency, and accuracy of the data recorded on the e-CRFs.

By agreeing to participate in the study, the investigator agrees to cooperate with the monitor and to ensure that any problems detected during the monitoring visits are resolved.

The investigator will allow the monitor to:

- Review the study site's processes and procedures.
- Verify the appropriate clinical investigator supervision of study site staff and third-party vendors.
- Inspect the site, the facilities and the material used for the study.
- Meet all members of his/her team involved in the study.
- Consult the documents relevant to the study.
- Check that the electronic case report forms have been filled out correctly.
- Directly access source documents for comparison of data therein with the data in the electronic case report forms.
- Verify that the study is carried out in compliance with the protocol and local regulatory requirements.

All information dealt with during these visits will be treated as strictly confidential. Contact information for the study monitor is in the investigator file.

14.5. Organization of the center/ delegation of authority

Every person to whom the investigator delegates under his/her responsibility a part of the follow-up of the study (co-investigator, nurse…) and any other person involved in the study for this center (cardiologist, pharmacist…) must be noted in the "Organization of center" document / Delegation of authority.

This document should be filled in at the beginning of the study and updated at any change of a person involved in the study in the center.

The study design of this protocol may be adapted to integrate decentralized trial elements and initiatives. Any adaptations must aim to empower participants, be within the capability of research sites and respect the need for participant safety and study data integrity.

Country specific initiatives should be validated by the local study team with support from Quality Assurance and must include a detailed supervision plan and risk assessment. Where applicable the site must gain ethics approval prior to implementing any change to their normal participant care plan.

14.6. Documentation supplied to the sponsor

The investigator undertakes before the study begins:

- To provide his/her dated and signed Curriculum Vitae (CV) in English (2 pages recommended) or to complete, in English, the CV form provided by the sponsor and to send it to the sponsor, together with that of his/her co-investigator(s).
- To provide a detailed description of the methods, techniques, and investigational equipment, and the reference values for the parameters measured.
- To provide any other document required by local regulation (*e.g.* Food & Drug Administration 1572 form).
- To send a copy of the IRB/IEC's opinion with details of its composition and the qualifications of its constituent members, if applicable according to the local regulation.

The CVs of the other members of the team involved in the study (if possible, in English) will be collected during the study (at the least, those staff members involved in the patients' medical follow-up/study-related decision process and those persons involved in the measurement of the main assessment criteria).

14.7. Sponsor responsibilities

The sponsor undertakes to:

- Supply the investigator with adequate and sufficient information concerning the IMP to enable him/her to carry out the study.
- Supply the investigator with Investigator's Brochure if the test drug is not marketed.
- Obtain any authorization to perform the study and/or any import license for the IMP administered that may be required by the local authorities before the beginning of the study.
- Provide the investigator annually, or at another frequency defined by the local regulations, with a document describing study progress which is to be sent to the IRB/IEC(s).
- Take all the necessary precautions to maintain the safety of the processed data, in particular their confidentiality, their integrity and their availability, by assessing risks identified concerning personal data protection. The following measures will be implemented (non-exhaustive):
  - Management of authorization to access to personal data (e-CRF).
  - Identification and authentication measures before accessing personal data (e-CRF).
  - Traceability measures for the access to and modification of personal data (e-CRF).
  - Secured data transfer.
  - Time limit for storing personal data.

Handle any security breach by implementing an internal committee (including CISO, DPO, communication department…) to qualify the security incident (Information systems, nature and number of personal data impacted), to define an action plan for corrective actions and to notify all relevant persons (authority and/or if needed individuals).

14.8. Supervisory committees

14.8.1. Safety Review Committee

The SRC is composed of investigators of phase 1 part of the trial and the medically responsible representatives of the sponsor during dose escalation meetings. The main responsibilities of the SRC will be to determine the doses and schedule to be tested in the next cohort and to assess the safety profile of the study drug during the phase 1 part. Further details on SRC composition, responsibilities, meetings and decision-making process are provided in the SRC charter.

14.8.2. Data Monitoring Committee

The DMC is composed of independent experts in oncology. They will meet regularly at the start, during and at the end of the phase 2 part of the study. The main responsibilities of the DMC will be to review the efficacy and safety data on a regular basis and to provide written recommendations to the investigators and the Sponsor regarding the conduct of the study (modification or termination). The DMC will also provide recommendations on the selected dose and schedule of each expansion arm. Further details on DMC composition, responsibilities, meetings and decision-making process are provided in the DMC charter.

14.9. Serious breach

A serious breach is defined as any deviation of the approved protocol version or the clinical trial regulation that is likely to affect to a significant degree the safety and rights of a participant or the reliability and robustness of the data generated in the clinical trial. The investigator should ensure that the study site staff is able to identify the occurrence of a suspected serious breach and that any suspected serious breach is promptly reported to the sponsor or delegated party (contact point designated by the sponsor).

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16. APPENDICES

Appendix 1:World Medical Association Declaration of Helsinki

Ethical Principles for Medical Research Involving Human Subjects

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and amended by the:
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
52nd WMA General Assembly, Edinburgh, Scotland, October 2000
53th WMA General Assembly, Washington DC, USA, 2002 (Note of Clarification added)
55th WMA General Assembly, Tokyo, Japan, 2004 (Note of Clarification added)
59th WMA General Assembly, Seoul, Republic of Korea, October 2008
64th WMA General Assembly, Fortaleza, Brazil, October 2013

Preamble

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects**,** including research on identifiable human material and data.
   The Declaration is intended to be read as a whole and each of its constituent paragraphs should be applied with consideration of all other relevant paragraphs.
2. Consistent with the mandate of the WMA, the Declaration is addressed primarily to physicians. The WMA encourages others who are involved in medical research involving human subjects to adopt these principles

General Principles

3. The Declaration of Geneva of the WMA binds the physician with the words, “The health of my patient will be my first consideration,” and the International Code of Medical Ethics declares that, “A physician shall act in the patient's best interest when providing medical care.”
4. It is the duty of the physician to promote and safeguard the health, well-being and rights of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.
5. Medical progress is based on research that ultimately must include studies involving human subjects.
6. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best proven interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.
7. Medical research is subject to ethical standards that promote and ensure respect for all human subjects and protect their health and rights.
8. While the primary purpose of medical research is to generate new knowledge, this goal can never take precedence over the rights and interests of individual research subjects.

9. It is the duty of physicians who are involved in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects. The responsibility for the protection of research subjects must always rest with the physician or other health care professionals and never with the research subjects, even though they have given consent.
10. Physicians must consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.
11. Medical research should be conducted in a manner that minimizes possible harm to the environment.
12. Medical research involving human subjects must be conducted only by individuals with the appropriate ethics and scientific education, training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional.
13. Groups that are underrepresented in medical research should be provided appropriate access to participation in research.
14. Physicians who combine medical research with medical care should involve their patients in research only to the extent that this is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.
15. Appropriate compensation and treatment for subjects who are harmed as a result of participating in research must be ensured.

Risk, Burdens and Benefits

16. In medical practice and in medical research, most interventions involve risks and burdens. Medical research involving human subjects may only be conducted if the importance of the objective outweighs the risks and burdens to the research subjects.
17. All medical research involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and groups involved in the research in comparison with foreseeable benefits to them and to other individuals or groups affected by the condition under investigation.
    Measures to minimize the risks must be implemented. The risks must be continuously monitored, assessed and documented by the researcher.
18. Physicians may not be involved in a research study involving human subjects unless they are confident that the risks have been adequately assessed and can be satisfactorily managed.
    When the risks are found to outweigh the potential benefits or when there is conclusive proof of definitive outcomes, physicians must assess whether to continue, modify or immediately stop the study.

Vulnerable Groups and Individuals

19. Some groups and individuals are particularly vulnerable and may have an increased likelihood of being wronged or of incurring additional harm.
    All vulnerable groups and individuals should receive specifically considered protection.

20. Medical research with a vulnerable group is only justified if the research is responsive to the health needs or priorities of this group and the research cannot be carried out in a non-vulnerable group. In addition, this group should stand to benefit from the knowledge, practices or interventions that result from the research.

Scientific Requirements and Research Protocols

21. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.
22. The design and performance of each research study involving human subjects must be clearly described and justified in a research protocol.
    The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, potential conflicts of interest, incentives for subjects and information regarding provisions for treating and/or compensating subjects who are harmed because of participation in the research study.
    In clinical trials, the protocol must also describe appropriate arrangements for post-trial provisions.

Research Ethics Committees

23. The research protocol must be submitted for consideration, comment, guidance and approval to the concerned research ethics committee before the study begins. This committee must be transparent in its functioning, must be independent of the researcher, the sponsor and any other undue influence and must be duly qualified. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards, but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration.
    The committee must have the right to monitor on-going studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No amendment to the protocol may be made without consideration and approval by the committee. After the end of the study, the researchers must submit a final report to the committee containing a summary of the study's findings and conclusions.

Privacy and Confidentiality

24. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information.

Informed Consent

25. Participation by individuals capable of giving informed consent as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no individual capable of giving informed consent may be enrolled in a research study unless he or she freely agrees.

26. In medical research involving human subjects capable of giving informed consent, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, post-study provisions and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information.
    After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.
    All medical research subjects should be given the option of being informed about the general outcome and results of the study.
27. When seeking informed consent for participation in a research study the physician must be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent must be sought by an appropriately qualified individual who is completely independent of this relationship.
28. For a potential research subject who is incapable of giving informed consent, the physician must seek informed consent from the legally authorized representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the group represented by the potential subject, the research cannot instead be performed with persons capable of providing informed consent, and the research entails only minimal risk and minimal burden.
29. When a potential research subject who is deemed incapable of giving informed consent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorized representative. The potential subject's dissent should be respected.
30. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research group. In such circumstances the physician must seek informed consent from the legally authorised representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research must be obtained as soon as possible from the subject or a legally authorized representative.
31. The physician must fully inform the patient which aspects of their care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never adversely affect the patient-physician relationship.
32. For medical research using identifiable human material or data, such as research on material or data contained in biobanks or similar repositories, physicians must seek informed consent for its collection, storage and/or reuse. There may be exceptional situations where consent would be impossible or impracticable to obtain for such research. In such situations the research may be done only after consideration and approval of a research ethics committee.

Use of Placebo

33. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best proven intervention(s), except in the following circumstances:
    Where no proven intervention exists, the use of placebo, or no intervention, is acceptable; or
    Where for compelling and scientifically sound methodological reasons the use of any intervention less effective than the best proven one, the use of placebo, or no intervention is necessary to determine the efficacy or safety of an intervention
    and the patients who receive any intervention less effective than the best proven one, placebo, or no intervention will not be subject to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention.
    Extreme care must be taken to avoid abuse of this option.

Post-Trial Provisions

34. In advance of a clinical trial, sponsors, researchers and host country governments should make provisions for post-trial access for all patients who still need an intervention identified as beneficial in the trial. This information must also be disclosed to patients during the informed consent process.

Research Registration and Publication and Dissemination of Results

35. Every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject.
36. Researchers, authors, sponsors, editors and publishers all have ethical obligations with regards to the publication and dissemination of the results of research. Researchers have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. All parties should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results must be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest must be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

Unproven Intervention in Clinical Practice

In the treatment of an individual patient, where proven interventions do not exist, or other known interventions have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorized representative, may use an unproven intervention if in the physician's judgment it offers hope of saving life, re-establishing health or alleviating suffering. This intervention should subsequently be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information must be recorded and, where appropriate, made publicly available.

Appendix 2: Grading of IRR (according to CTCAE v5.0)

Adverse Event	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
IRR	Mild transient reaction: administration interruption not indicated; intervention not indicated.	Therapy or administration interruption indicated but responds promptly to symptomatic treatment (*e.g.* antihistamines, NSAIDS, steroids, IV fluids); prophylactic medications indicated for ≤ 24 hours.	Prolonged (*i.e.* not rapidly responsive to symptomatic medication, brief interruption of administration, or both); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae.	Life-threatening consequences; urgent intervention indicated.

Abbreviations: IRR=infusion-related reaction; IV=intravenous; NSAIDs=non-steroidal anti-inflammatory drugs.

Note: *An acute IRR may occur with an agent that causes cytokine-release (e.g. monoclonal antibodies or other biological agents). Signs and symptoms usually develop during or shortly after drug administration and generally resolve completely within 24 hours of completion of administration. Signs/symptoms may include: allergic reaction/hypersensitivity (including drug fever); arthralgia (joint pain); bronchospasm; cough; dizziness; dyspnea (shortness of breath); fatigue (asthenia, lethargy, malaise); headache; hypertension; hypotension; myalgia (muscle pain); nausea; pruritus/itching; rash/desquamation; rigors/chills; sweating (diaphoresis); tachycardia; tumor pain (onset or exacerbation of tumor pain due to treatment); urticaria (hives, welts, wheals); vomiting.*

Appendix 3: Grading of CRS (according to ASTCT CRS Consensus Grading)

CRS parameter	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
Fever[*]	Temperature ≥38°C	Temperature ≥38°C	Temperature ≥38°C	Temperature ≥ 38 C
with				
Hypotension	None	Not requiring vasopressors	Requiring a vasopressor with or without vasopressin	Requiring multiple vasopressors (excluding vasopressin)
And / or[†]				
Hypoxia	None	Requiring low-flow nasal cannula [‡]or blow-by	Requiring high-flow nasal cannula[‡], facemask or venture mask	Requiring positive pressure (*e.g.* CPAP, BiPAP, intubation and mechanical ventilation)

[*] *Fever is defined as temperature ≥ 38°C not attributable to any other cause. In patients who have CRS then receive anti-pyretic or anti-cytokine therapy such as tocilizumab or steroids, fever is no longer required to grade subsequent CRS severity. In this case, CRS grading is driven by hypotension and/or hypoxia.*

[†]*CRS grade is determined by the more severe event: hypotension or hypoxia not attributable to any other cause. For example, a patient with temperature of 39.5°C, hypotension requiring 1 vasopressor, and hypoxia requiring low-flow nasal cannula is classified as grade 3 CRS.*

[‡]*Low-flow nasal cannula is defined as oxygen delivered at ≤ 6L/minute. Low-flow also includes blow-by oxygen delivery, sometimes used in pediatrics. High-flow nasal cannula is defined as oxygen delivered at ≥ 6L/minute.*

Appendix 4: Definition of Liver function tests abnormalities (according to CTCTAE v.5.0)

Adverse Event	Grade 1	Grade 2	Grade 3	Grade 4
AST	> ULN - 3.0 x ULN if baseline was normal; 1.5 - 3.0 x baseline if baseline was abnormal.	> 3.0 - 5.0 x ULN if baseline was normal; > 3.0 - 5.0 x baseline if baseline was abnormal.	> 5.0 - 20.0 x ULN if baseline was normal; > 5.0 - 20.0 x baseline if baseline was abnormal.	> 20.0 x ULN if baseline was normal; > 20.0 x baseline if baseline was abnormal
ALT	> ULN - 3.0 x ULN if baseline was normal; 1.5 - 3.0 x baseline if baseline was abnormal.	> 3.0 - 5.0 x ULN if baseline was normal; > 3.0 - 5.0 x baseline if baseline was abnormal	> 5.0 - 20.0 x ULN if baseline was normal; > 5.0 - 20.0 x baseline if baseline was abnormal	> 20.0 x ULN if baseline was normal; > 20.0 x baseline if baseline was abnormal.
Blood Bilirubin	> ULN - 1.5 x ULN if baseline was normal; > 1.0 - 1.5 x baseline if baseline was abnormal.	> 1.5 - 3.0 x ULN if baseline was normal; > 1.5 - 3.0 x baseline if baseline was abnormal.	> 3.0 - 10.0 x ULN if baseline was normal; > 3.0 - 10.0 x baseline if baseline was abnormal.	> 10.0 x ULN if baseline was normal; > 10.0 x baseline if baseline was abnormal.

Appendix 5: Cumulative blood volume collected per patient per period/cycle in phase 1 / CCI schedule

Evaluations	**Screening Period**	**Treatment Period**													**Safety follow up**
		Cycle 1 (C1)						**Cycle 2 (C2)**					**Cycle 3 & onwards**		
		D1	**D2**	**D3**	**D8**	**D15**	**D22**	**D1**	**D2**	**D3**	**D8**	**D15**	**D1**	**D15**	
Laboratory tests															
Hematology	5ml	5ml			5ml	5ml	5ml	5ml				5ml	5ml		5ml*3
Biochemistry	5ml	5ml	5ml	5ml	5ml	5ml	5ml	5ml	5ml	5ml	5ml	5ml	5ml	5ml	5ml*3
Coagulation	5ml	5ml						5ml					5ml		5ml*3
Pregnancy test, HIV, hepatitis B and C, Thyroid function	5ml	5ml						5ml					5 ml		5ml*3
Pharmacokinetics															
Serum for PRS-344/S095012 PK		15ml	3ml	3ml	3ml	6ml		15ml	3ml	3ml	3ml	6ml	6ml	6ml	3ml
Serum for anti-PRS-344/S095012 antibodies (ADA)		3ml				3ml		3ml				3ml	3ml		3ml*3
Biomarkers															
Blood for cytokine analysis		2ml		2ml	2ml	2ml	2ml	2ml					4ml*		
Blood for soluble 4-1BB		2ml	2ml	2ml	2ml	2ml	2ml	2ml	2ml	2ml	2ml	2ml	2ml	2ml	
Blood for cytometry		16ml			16ml	16ml	16ml								
Blood for genomic		9ml													
Optional samples															
Blood for DNA		9ml				9ml	9ml	9ml							
Blood for RNA		3ml				3ml	3ml	3ml							
Blood for bTMB-plasma preparation		20ml													
Blood for exosomal PD-L1		3ml													

Volume of blood collected (ml)															
Per visit **(without optional samples)**	**20**	**67**	**10**	**12**	**33**	**39**	**30**	**42**	**10**	**10**	**10**	**21**	**31**** **/35***	**13**	**23 + 3 (PK only one visit)**
Per period/cycle	**20**	**191**						**93**					**44**/48***		**72**
Per visit **(including optional samples)**	**20**	**102**	**10**	**12**	**33**	**51**	**42**	**54**	**10**	**10**	**10**	**21**	**31**** **/35***	**13**	**23 + 3 (PK only one visit)**
Per period/cycle	**20**	**250**						**105**					**44**/48***		**72**

*For Cycle 3 and subsequent odd cycles; **For Cycle 4 and subsequent even cycles

Cumulative blood volume collected per patient per period/cycle in phase 2

Evaluations	**Screening Period**	**Treatment Period**									**Safety follow up**
		Cycle 1 (C1)				**Cycle 2 (C2)**			**Cycle 3 & onwards**		
		D1	**D8**	**D15**	**D22**	**D1**	**D8**	**D15**	**D1**	**D15**	
Laboratory tests											
Hematology	5ml	5ml	5ml	5ml	5ml	5ml		5ml	5ml		5ml *3
Biochemistry	5ml	5ml	5ml	5ml	5ml	5ml	5ml	5ml	5ml	5ml	5ml *3
Coagulation	5ml					5ml			5 ml		5ml *3
Pregnancy test, HIV, hepatitis B and C, Thyroid function	5ml	5ml				5ml			5 ml		5ml *3
Pharmacokinetics											
Serum for PRS-344/S095012 PK		15ml	3ml	6ml		15ml	3ml	6ml	6ml	6ml	3ml
Serum for anti-PRS-344/S095012 antibodies (ADA)		3ml				3ml			3ml		3ml*3
Biomarkers											
Blood for cytokine analysis		2ml	2ml	2ml	2ml	2ml	2ml	2ml	4ml*		
Blood for soluble 4-1BB		2ml	2ml	2ml	2ml	2ml	2ml	2ml			
Blood for cytometry		16ml	16ml								
Blood for genomic		9ml									
Optional samples											
Blood for DNA		9ml		9ml	9ml	9ml					
Blood for RNA		3ml		3ml	3ml	3ml					
Blood for bTMB-plasma preparation		20ml									

Volume of blood collected (ml)											
Per visit **(without optional samples)**	**20**	**62**	**33**	**20**	**14**	**42**	**12**	**20**	**29**/33***	**11**	**23 + 3 (PK only one visit)**
Per period/cycle	**20**	**129**				**74**			**40**/44***		**72**
Per visit **(including optional samples)**	**20**	**94**	**33**	**32**	**26**	**54**	**12**	**20**	**29**/33***	**11**	**23 + 3 (PK only one visit)**
Per period/cycle	**20**	**185**				**86**			**40**/44***		**72**

*For Cycle 3 and subsequent odd cycles; **For Cycle 4 and subsequent even cycles

Cumulative blood volume collected per patient per period/cycle in phase 1 / Q3W schedule

Evaluations	**Screening Period**	**Treatment Period**											**Safety follow up**
		Cycle 1 (C1)					**Cycle 2 (C2)**					**Cycle 3 & onwards**	
		D1	**D2**	**D3**	**D8**	**D15**	**D1**	**D2**	**D3**	**D8**	**D15**	**D1**	
Laboratory tests													
Hematology	5ml	5ml			5ml	5ml	5ml				5ml	5ml	5ml*3
Biochemistry	5ml	5ml	5ml	5ml	5ml	5ml	5ml	5ml	5ml	5ml	5ml	5ml	5ml*3
Coagulation	5ml	5ml					5ml						5ml*3
Pregnancy test, HIV, hepatitis B and C, Thyroid function	5ml	5ml					5ml					5 ml	5ml*3
Pharmacokinetics													
Serum for PRS-344/S095012 PK		15ml	3ml	3ml	3ml	6ml	15ml	3ml	3ml	3ml	6ml	6ml	3ml
Serum for anti-PRS-344/S095012 antibodies (ADA)		3ml					3ml					3ml	3ml*3
Biomarkers													
Blood for cytokine analysis		2ml		2ml	2ml	2ml	2ml					4ml*	
Blood for soluble 4-1BB		2ml	2ml	2ml	2ml	2ml	2ml	2ml	2ml	2ml	2ml	2ml	
Blood for cytometry		16ml			16 ml	16ml	16ml			16 ml			
Blood for genomic		9ml											
Optional samples													
Blood for DNA		9ml				9ml	9ml			9ml			
Blood for RNA		3ml				3ml	3ml			9ml			
Blood for bTMB-plasma preparation		20ml											
Blood for exosomal PD-L1		3ml											

Volume of blood collected (ml)													
Per visit **(without optional samples)**	**20**	**87**	**10**	**12**	**23**	**36**	**58**	**10**	**10**	**26**	**18**	**26**/30***	**23 + 3 (PK only one visit)**
Per period/cycle	**20**	**168**					**122**					**26**/30***	**72**
Per visit **(including optional samples)**	**20**	**122**	**10**	**12**	**23**	**48**	**70**	**10**	**10**	**44**	**18**	**26**/30***	**23 + 3 (PK only one visit)**
Per period/cycle	**20**	**215**					**152**					**26**/30***	**72**

*For Cycle 3 and subsequent odd cycles; **For Cycle 4 and subsequent even cycles

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Appendix 7: Clinical Response Criteria and Composite Response Criteria for Patients with Externally Visible Tumors

These criteria are designed primarily for patients in arm 3 with locally advanced CSCC. This appendix describes clinical response criteria for externally visible lesions that can be measured bi-dimensionally using digital medical photography. This appendix also provides composite response criteria for disease that is measurable by both clinical response criteria and RECIST 1.1.

Patients in arm 3 will be followed by digital medical photography, if applicable, if possible in addition to radiological assessments. The patients will undergo radiologic imaging at baseline, and this will also be performed serially at each response assessment unless the investigator deems that the baseline radiologic imaging was uninformative. Radiologic imaging will be essential in the evaluation of tumors which have subdermal components which cannot be adequately assessed by digital medical photography.

Standardized digital photographs of the externally visible component of all target lesions must be obtained at baseline and at the time of each subsequent tumor assessment. Investigators will also provide a clinical description of the externally visible target lesion(s) at baseline and at each tumor assessment, as well as comments on any changes in the lesion(s) since the previous assessment.

Special Issues for Externally Visible Tumors

1. Anatomic Defects

Regarding tumor around a surgical cavity/anatomic defect (*e.g.*, rhinectomy), such lesions should be considered non-measurable unless there is a nodular lesion measuring ≥10 mm in maximal bi-dimensional perpendicular diameters. The surgical cavity or anatomic defect should not be considered when measuring the lesion.

2. Indeterminate-Appearing Tissue

If there is uncertainty about whether a given lesion or area of a lesion represents malignancy *versus* benign process (*e.g.*, scarring, fibrosis), biopsies should be obtained. Indeterminate-appearing areas (*e.g.*, scarring, fibrosis) are included in the tumor measurements unless biopsies are obtained to establish benign status.

3. Local *versus* central review

An independent central review committee, with access to de-identified digital medical photography results and biopsy results, will provide response assessments as required by the sponsor to address study objectives. Central reviews will be scheduled by the sponsor but will not be continuous or "real-time." Clinical management decisions generally will be as per investigator response assessments and local pathology review. In the unlikely event that central review yields major differences with the local response assessment that could have implications for the ongoing management of an active patient on study, the situation will be discussed between the sponsor and the investigator in order to determine patient management.

4. Patients with other malignancies than locally advanced CSCC, who have externally visible tumors

Externally visible tumors will be followed as non-target lesions if there are other radiologically assessable tumors which fulfil the criteria of target lesions. If there are no such lesions, the externally visible lesions (lesion size ≥10 mm in baseline dimensional perpendicular axes) would be target lesions and followed as per clinical response criteria in this appendix.

Clinical Response Criteria for Externally Visible Tumors

1. Externally Visible Tumor Dimension

The externally visible component of target lesion(s) will be measured using bi-dimensional WHO criteria as the sum of the products (of individual target lesions) in the longest dimension and perpendicular second longest dimension – at each tumor assessment and will be documented using standardized digital photography. In the absence of substantial change in lesion geometry, subsequent visit measurements should be performed in the same axes and the investigator should refer to the previous visit's annotated photographs as a starting point to identify axis for measurement when making subsequent assessments. For patients deemed eligible by digital photography only, a biopsy is required within 30 days of CR determined by the investigator for confirmation of the CR.

Clinical response criteria for externally visible tumor(s) require bidimensional measurements according to WHO criteria, and are as follows:

- Complete response of externally visible disease (vCR): all target lesion(s) no longer.
- visible, maintained for at least 4 weeks. Documentation of vCR requires confirmation by biopsies of site(s) of externally visible target lesion(s) with histologic confirmation of no residual malignancy, per central pathology review. In the absence of such histologic confirmation, a patient cannot be deemed to have experienced vCR and the best response would be partial response.
- Partial response of externally visible disease (vPR): decrease of 50% (WHO criteria) or greater in the sum the products of perpendicular longest dimensions of target lesion(s), maintained for at least 4 weeks.
- Stable externally visible disease (vSD): not meeting criteria for vCR, vPR, or progressive disease.
- Progression of visible disease (vPD): increase of ≥ 25% (WHO criteria) in the sum of the products of perpendicular longest dimensions of target lesion(s).

2. New Lesions

A new cutaneous lesion consistent with CSCC will be considered as cPD if the lesion is ≥ 10 mm in both maximal perpendicular diameters and can be clearly documented as not being previously present, unless it is confirmed on biopsy not to be consistent with CSCC. If a new cutaneous lesion is not biopsied or if the histology is inconclusive, it should be considered CSCC and deemed cPD.

Overall Clinical Responses for All Possible Combinations of Clinical Tumor Responses

Externally Visible Tumor Dimension[a]	New Lesions[a]	Clinical Response
vCR	No	cCR[b]
vPR	No	cPR[c]
vSD	No	cSD[d]
vPD	Yes or No	cPD[e]
Any	Yes	cPD

[a] *See above for definitions*
[b] *Clinical Complete Response*
[c] *Clinical Partial Response*
[d] *Clinical Stable Disease*
[e] *Clinical Progression of Disease*

Composite Response Criteria

For patients who have disease that is measurable by BOTH clinical response criteria by digital medical photography and RECIST 1.1 using radiologic imaging.

Clinical Response (Digital Medical Photography	**RECIST 1.1 Response (Imaging)**	**Composite (Overall): Clinical + RECIST Response**
cCR	CR	CR
cCR	PR or SD	PR
cPR	CR, PR, or SD	PR
cSD	CR or PR	PR
SD	SD	SD
PD	Any	PD
Any	PD	PD

In addition, if all previously inoperable target lesions are rendered operable with clear margins obtained at the time of surgery, this will be considered a PR. If the investigator deems a previously unresectable lesion to be potentially resectable due to response, the Medical Monitor should be consulted prior to any surgical procedure being performed. A decision will be rendered by the sponsor as to whether the planned surgical intervention is compatible with study requirements. (This statement does not apply to patients in emergency life-threatening situations that require immediate surgery).

Appendix 8: Royal Marsden Prognosis Score

Variable	Theoretical Score	Patient Score
LDH		LDH
< ULN	0	X=
> ULN	1	
Albumin, g/L		Albumin
> 35	0	Y=
< 35	1	
Sites of metastasis		Sites of metastasis
0 - 2	0	Z=
> 2	1	
	Total	X+Y+Z=

LDH: lactate dehydrogenase; ULN: upper limit of normal

Appendix 9: HLH diagnostic criteria and treatment guidelines

Diagnosis criteria

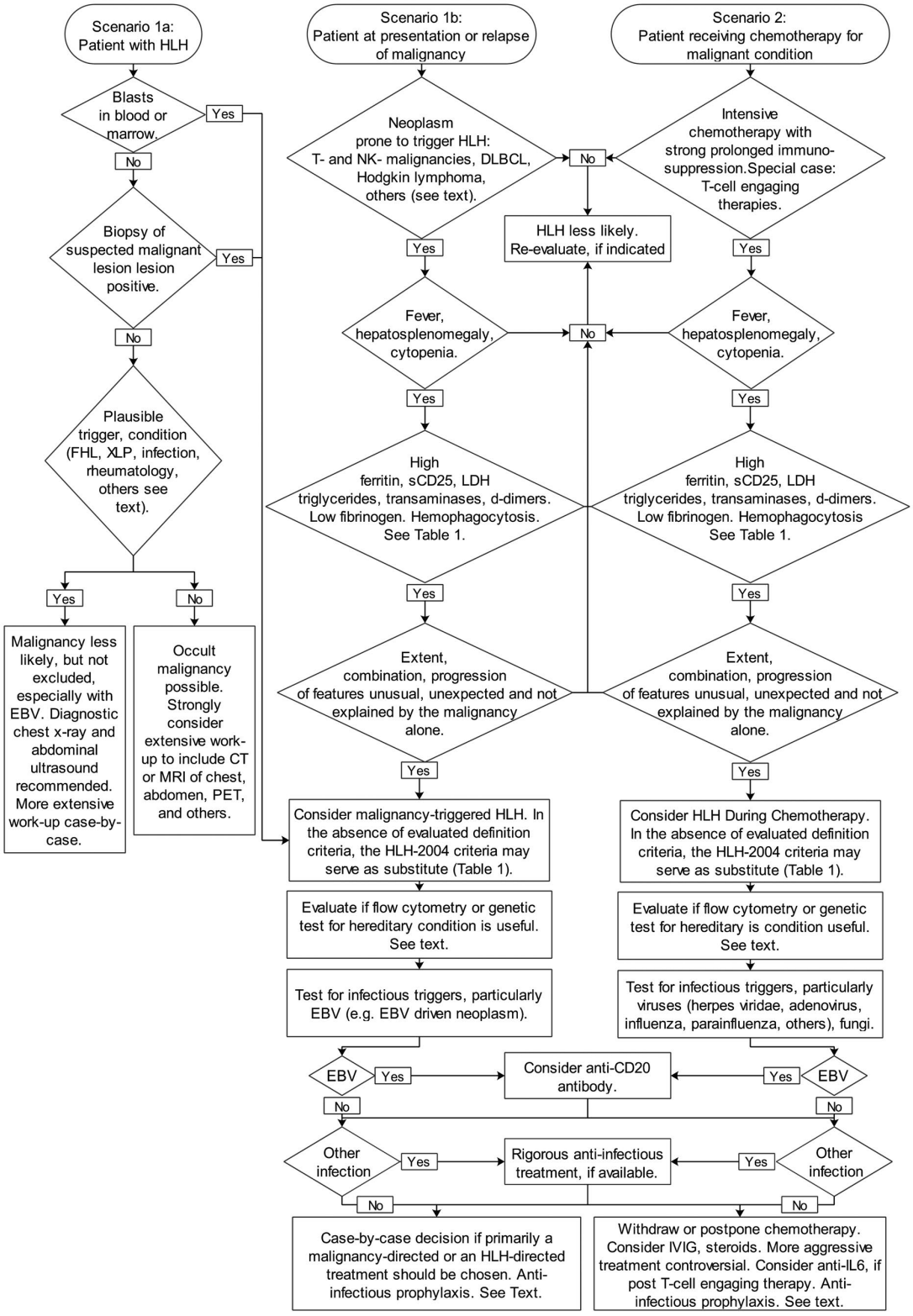
The diagnosis of HLH can be established if Criterion 1 or 2 is fulfilled (La Rosée *et al*., 2019; Lehmberg *et al*., 2015).

1. A molecular diagnosis consistent with HLH
2. Diagnostic criteria for HLH fulfilled (5 of the 8 criteria below) • Fever • Splenomegaly • Cytopenias (affecting ≥ 2 of 3 lineages in the peripheral blood) • Hemoglobin < 90 g/L (hemoglobin <100 g/L in infants <4 wk) • Platelets < $100x10^9$/L • Neutrophils < $1.0x10^9$/L • Hypertriglyceridemia and/or hypofibrinogenemia • Fasting triglycerides ≥ 3.0 mmol/L (i.e., ≥ 265 mg/dL) • Fibrinogen ≤ 1.5 g/L • Hemophagocytosis in bone marrow or spleen or lymph nodes. No evidence of malignancy. • Low or no NK cell activity (according to local laboratory reference) • Ferritin ≥ 500 µg/L • sCD25 (i.e., soluble IL-2 receptor) ≥ 2400 U/mL

Other features:

- Elevated transaminases and bilirubin,
- Elevated lactate dehydrogenase,
- Elevated D-dimers,
- Elevated cerebrospinal fluid and/or protein.

Flow chart for diagnosis and management of malignancy-associated hemophagocytic lymphohistiocytosis (Lehmberg *et al*., 2015).



DLBCL: diffuse large B-cell lymphoma; EBV: Epstein-Barr virus; FHL: familial hemophagocytic lymphohistiocytosis: HLH: hemophagocytic lymphohistiocytosis; XLP: X-linked lymphoproliferative syndrome