Clinical Study Protocol (CSP)

A Multicenter, Open-Label, Single-ARm, PHase II Clinical Trial to Evaluate the Efficacy and Safety of INCMGA00012 (retifanlimab) in Advanced Penile SquamoUS Cell Carcinoma. ORPHEUS

Phase II Study of the Efficacy of INCMGA00012 (retifanlimab) in Penile Squamous Cell Carcinoma

(ORPHEUS)

Study Drug(s):	INCMGA00012 (retifanlimab)
EudraCT#:	2019-001172-11
Clinical Trials.gov#:	NCT04231981
Study Code#:	MedOPP239
CSP Version and Date:	2.0, 24-Feb-2021
CSP Review History	
Initial Approved version:	Spain 1.2; 17 Feb 2020
	Italy 1.3; 11 Jun 2020

I. SPONSOR'S SIGNATURE PAGE

CSP Title: "A Multicenter, **O**pen-Label, Single-A**R**m, **PH**ase II Clinical Trial to **E**valuate the Efficacy and Safety of INCMGA00012 (retifanlimab) in Advanced Penile Squamo**US** Cell Carcinoma. **ORPHEUS**".

CSP Short Title: "Phase II Study of the Efficacy of INCMGA00012 (retifanlimab) in Penile Squamous Cell Carcinoma (ORPHEUS)".

Study Code: MedOPP239

CSP Version and Date: 2.0, 24-Feb-2021

Marta Martínez de Falcón		
Sponsor	Signature	Signature date (DD-Mmm-YYYY)
Xavier Garcia del Muro, *M.D. Ph.D.*		
Principal Investigator	Signature	Signature date (DD-Mmm-YYYY)
David Páez, *M.D. Ph.D.*		
Sponsor's Medical Monitor	Signature	Signature date (DD-Mmm-YYYY)

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Name	Role
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Dr David Páez	*Sponsor's Medical Monitor*
Dr Isabel Tena	*Sponsor's Medical Scientist*
Principal Investigators of the ORPHEUS Trial	

III. DECLARATION OF INVESTIGATORS

CSP Title: "A Multicenter, **O**pen-Label, Single-A**R**m, **PH**ase II Clinical Trial to **E**valuate the Efficacy and Safety of INCMGA00012 (retifanlimab) in Advanced Penile Squamo**US** Cell Carcinoma. **ORPHEUS**".

CSP Short Title: "Phase II Study of the Efficacy of INCMGA00012 (retifanlimab) in Penile Squamous Cell Carcinoma (ORPHEUS)".

Study Code: MedOPP239

I have received, reviewed and understood the following:

a) Protocol version: 2.0, dated on 24-Feb-2021;
b) Investigator's Brochure (IB) for INCMGA00012 (retifanlimab), with details of clinical and nonclinical data relevant to the study of the products in human subjects.

- I have been adequately informed about the development of the investigational products to date. I will confirm the receipt of updated IBs. I have read this study protocol and agree that it contains all the information required to conduct the study. I agree to conduct the study as set out in this protocol.
- I fully understand that any changes instituted by the investigator(s) without previous agreement with the Sponsor would constitute a violation of the protocol, including any ancillary studies or procedures performed on study patients (other than those procedures necessary for the wellbeing of the patients). I am aware that I cannot deviate from or apply changes to the protocol without prior approval or the favorable opinion of the Institutional Review Board (IRB) or Ethics Committee (EC) and/or before Sponsor's agreement to avoid immediate risk to the trial patients. If this occurs, I agree to inform the Sponsor as to the deviation or changes in writing and their reasons, as soon as possible.
- I will not enroll the first patient in the study until I have received approval from the appropriate IRB/EC and until all legal and regulatory requirements in my country have been fulfilled.
- The study will be conducted in accordance with the moral, ethical, and scientific principles governing clinical research as set out in the Declaration of Helsinki and its amendments, the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines (ICH E6[R2] GCP) and applicable regulations and laws.
- I agree to obtain, in the manner described in this protocol and in (ICH E6[R2] GCP), written informed consent form (ICF) by the patient or witnessed verbal ICF to participate for all patients whose participation in this study is proposed to and before any patient's study specific procedure is done.
- I will ensure that the study drug(s) supplied by the Sponsor are being used only as described in this protocol.

- I am aware of the requirements for the correct reporting of serious adverse events, and I commit to document and to report such events as required by the Sponsor and in accordance with Health Authority Regulatory requirements.
- I agree to supply – upon request – the Sponsor or Sponsor's representative with evidence of current laboratory accreditation, the name and address of the laboratory, and a list of normal values and ranges.
- I agree with the use of results of the study for the purposes of national and international registration, publication, and information for medical and pharmaceutical professionals.
- I agree to keep all source documents and case report forms as specified in the relevant sections of this protocol.
- I will provide all required Regulatory Authority forms, up-to-date curriculum vitae of myself, sub-investigators and of any member of my study team (if requested) before the study starts, which may be submitted to regulatory authorities.
- I am aware of the possibility of being audited by the Sponsor or its delegate or inspected by regulatory authorities for the performance of this study. I will permit monitoring, auditing and inspection and provide direct access to source data/documents and reports for these purposes.
- Furthermore, I confirm herewith that the Sponsor is allowed to enter and utilize my professional contact details and function in an electronic database for internal purposes and for submission to Health Authorities worldwide.

Name: _____

Signature: _____ Date: _____

IV. CSP SYNOPSIS

CSP Title:	"A Multicenter, **O**pen-Label, Single-A**R**m, **PH**ase II Clinical Trial to **E**valuate the Efficacy and Safety of INCMGA00012 (retifanlimab) in Advanced Penile Squamo**US** Cell Carcinoma. **ORPHEUS**".
CSP Short Title	"Phase II Study of the Efficacy of INCMGA00012 (retifanlimab) in Penile Squamous Cell Carcinoma (ORPHEUS)".
Study Code:	MedOPP239
EudraCT Number:	2019-001172-11
Investigational Medicine Product:	INCMGA00012 (retifanlimab)
Trial Design:	This is a multicenter, open-label, single-arm, phase II clinical trial.
Target Disease:	Unresectable locally advanced or metastatic penile squamous cell carcinoma (PSqCC).
Patients:	Men age ≥ 18 years with locally advanced unresectable or metastatic PSqCC stage 4 (i.e., T4 or N3 or M1) that are presenting with radiologic progression of disease (PD) following or not standard treatment with chemotherapy. PD must be based on Response Evaluation Criteria in Solid Tumors (RECIST) version (v.)1.1 criteria. Patients are not eligible if they are candidates for a local treatment with a curative intention. Patients must present Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) 0-1 and with adequate organ function. Formalin-fixed paraffin-embedded (FFPE) tumor biopsy and blood samples are mandatory for performing exploratory analyses.
Number of Patients:	18 patients.
Study Objectives	**Primary objective:** • To assess the efficacy –as determined by the objective response rate (ORR)– of INCMGA00012 (retifanlimab) in patients with unresectable locally advanced or metastatic PSqCC. **Secondary objectives:** • To assess the efficacy –as determined by clinical benefit rate (CBR), the progression-free survival (PFS), the 6-month progression-free survival (PFS), duration of response (DoR), time to progression (TTP), overall survival (OS), and maximum tumor shrinkage– of INCMGA00012 (retifanlimab) in these patients. • To evaluate the safety and tolerability of INCMGA00012 (retifanlimab) in these patients.

	Exploratory objectives: • To determine the efficacy –as determined by the ORR, CBR and 6-month PFS based on immune-related RECIST (irRECIST). • To evaluate predictive or prognostic, tumor- and/or immune-related biomarkers associated with disease activity status or response to treatment. • To identify possible mechanisms of resistance to study treatments through the comparative analysis of potential biomarkers from paired pre-treatment and post-progression tumor and/or blood samples. • To assess impact of INCMGA00012 (retifanlimab) on HIV control in participants who are known to be HIV-positive.
Study Endpoints	**Primary endpoint:** • ORR will be evaluated according to the investigator as per RECIST v.1.1. **Secondary endpoints:** • OS, and CBR, PFS, 6-month PFS, DoR, TTP, and maximum tumor shrinkage that will be evaluated as per RECIST v.1.1. • The safety and tolerability will be evaluated by incidence of adverse events (AEs), incidence of prespecified AEs, change from baseline in targeted vital signs, and change from baseline in targeted clinical laboratory test results. **Exploratory endpoints:** • ORR, CBR and 6-month PFS as per irRECIST. • Relationship between tumor- and/or immune-related biomarkers, and efficacy in tumor tissue and/or liquid biopsy. • Changes from baseline in the CD4-positive cell count and HIV viral load in participants who are known to be HIV-positive.
Selection criteria:	**Inclusion criteria:** Patients must meet ALL of the following inclusion criteria to be eligible for enrolment into the study: 1. Patients have been informed about the nature of study, and have agreed to participate in the study, and signed the informed consent form (ICF) prior to participation in any study-related activities. 2. Male patients ≥ 18 years of age at the time of signing ICF.

	3. Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) 0-1. 4. Life expectancy ≥12 weeks. 5. Histologically-proven PSqCC. 6. Locally advanced unresectable or metastatic stage 4 PSqCC that is not amenable to resection with curative intent (T4 or N3 or M1). 7. Radiological evidence of locally advanced or metastatic disease. 8. Patients must have measurable disease or evaluable disease according to Response Evaluation Criteria in Solid Tumors (RECIST) version (v.)1.1 criteria. 9. Patients must agree to provide a tumor tissue sample from a metastatic site or the primary tumor at the time of study entry, with the exception of patients whom tumor biopsies cannot be obtained (e.g., inaccessible tumor or subject safety concern) that may submit an archived tumor specimen only upon agreement from the Sponsor. If feasible, patients will also be given the option of providing a tumor tissue sample at disease progression from metastasis or primary tumor (if tumor biopsies cannot be obtained for inaccessible lesion or subject safety concern). 10. Willingness and ability to provide blood samples (liquid biopsy) at the time of inclusion, after 2 cycles of study treatment (C3D1), and upon PD or study termination. 11. Adequate organ function: a. Hematological: White blood cell (WBC) count > 3.0 x 10^9/L, absolute neutrophil count (ANC) ≥ 1.5 x 10^9/L, platelet count ≥ 75.0 x10^9/L, and hemoglobin > 9.0 g/dL. b. Hepatic: Bilirubin ≤ 1.5 times the upper limit of normal (× ULN) (< 3 x ULN in the case of Gilbert's disease); aspartate transaminase (AST), and alanine transaminase (ALT) ≤ 2.5 times × ULN (in the case of liver metastases ≤ 5 × ULN); Albumin > 2.5 mg/mL. c. Renal: Serum creatinine ≤ 1.5 x ULN; alternately measured or calculated creatinine clearance ≥30 mL/min with creatinine levels >1.5 × institutional ULN (glomerular filtration rate [GFR] can also be used in place of creatinine or creatinine clearance). d. Coagulation: Activated Partial Thromboplastin Time (aPTT) ≤1.5 X ULN and International Normalized Ratio (INR) or Prothrombin Time (PT) ≤1.5 X ULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants.

12. Patients who are willing and able to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures.
13. Subjects should agree to use an adequate method of contraception starting with the first dose of study therapy through 180 days after the last dose of study treatment.
14. Patients that have received prior chemotherapy regimens or radiotherapy for locally recurrent and/or metastatic disease are not excluded but patients naïve of systemic treatment can also be included.
15. For pretreated patients, last dose of chemotherapy administered ≥ 28 days from study entry.

Exclusion criteria

Patients will be excluded from the study if they meet ANY of the following criteria:

1. Locally PSqCC candidate for curative treatment.
2. Prior therapy with an anti–PD-1, anti–PD-L1, or anti–PD-L2 agent.
3. Known hypersensitivity to any of the excipients of INCMGA00012 (retifanlimab).
4. Receipt of anticancer therapy or participation in another interventional clinical study within 28 days before the first administration of study drug; 6 weeks for mitomycin C.
5. Radiotherapy within 14 days of first dose of study treatment with the following caveat: 28 days for pelvic radiotherapy.
6. Toxicity of prior therapy that has not recovered to ≤ Grade 1 or baseline (with the exception of any grade of alopecia and anemia not requiring transfusion support). Endocrinopathy, if well-managed, is not exclusionary and should be discussed with Sponsor's medical monitor.
7. Major surgery (defined as requiring general anesthesia) or significant traumatic injury within 4 weeks of start of study drug, or patients who have not recovered from the side effects of any major surgery, or patients who may require major surgery during the study.
8. Known active uncontrolled or symptomatic Central Nervous System (CNS) metastases, carcinomatous meningitis, or leptomeningeal disease as indicated by clinical symptoms, cerebral edema, and/or progressive growth. Patients with a history of CNS metastases or cord compression are eligible if they have been definitively treated (e.g., radiotherapy, stereotactic surgery) and are clinically stable off anticonvulsants and steroids for at least 4 weeks before randomization.
9. Cardiovascular: patients that have any of the following within 6 months of randomization: severe/unstable angina, myocardial infarction, symptomatic pericarditis, symptomatic congestive heart failure (New York Heart Association functional

	classification III-IV), cerebrovascular accident including transient ischemic attack, or symptomatic pulmonary embolism, coronary/peripheral artery bypass graft, ongoing cardiac dysrhythmias of National Cancer Institute–Common Terminology Criteria for Adverse Events (NCI–CTCAE) v.5.0 grade ≥2, including, ventricular arrhythmias –except for benign premature ventricular contractions–, supraventricular and nodal arrhythmias requiring a pacemaker or not controlled with medication, any conduction abnormality requiring a pacemaker or any cardiac arrhythmia not controlled with medication. 10. Metabolic: Uncontrolled hyper/hypothyroidism or diabetes mellitus type 1 (T1DM). Patients with hypothyroidism stable on hormone replacement will not be excluded from the trial. Patients with controlled T1DM on a stable insulin regimen may be eligible for this study. 11. Diagnosis of immunodeficiency or is receiving systemic steroid therapy or immunosuppressive therapy within seven days prior to study treatment initiation. 12. Active autoimmune disease that has required systemic treatment in past 2 years (i.e., with use of disease modifying agents, corticosteroids, or immunosuppressive drugs). *Note: Replacement therapy (e.g., thyroxine, insulin, or physiologic steroid replacement therapy (≤ 10 mg prednisone daily) for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment.* 13. Prior allogenic stem cell or solid organ transplantation. 14. Has received a live vaccine within 28 days of the planned start of study drug. *Note: Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chicken pox/zoster, yellow fever, rabies, Bacillus Calmette–Guérin (BCG), and typhoid vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (e.g., FluMist®) are live-attenuated vaccines and are not allowed.* 15. Active/history of pneumonitis requiring treatment with steroids or active/history of interstitial lung disease. 16. Active uncontrolled infection at the time of screening. 17. Latent tuberculosis determined by a positive TST followed by confirmation by pulmonologists. 18. Participants who are known to be human immunodeficiency virus (HIV)-positive, unless all of the following criteria are met: a. CD4-positive count ≥ 300/µL; b. Undetectable viral load; c. Receiving highly active antiretroviral therapy. 19. Active hepatitis A virus (HAV) (positivity for HAV IgM antibody), hepatitis B virus (HBV) (patients with negative hepatitis B surface antigen [HBsAg] test and a positive antibody to HBsAg [anti–HBsAg] test at screening are eligible) or hepatitis C virus (HCV) (patients with a positive antibody to hepatitis C [anti–

	HCV] are eligible only if polymerase chain reaction [PCR] is negative for virus hepatitis C ribonucleic acid [RNA]). 20. Known additional malignancy that is progressing or requires active treatment, or history of other malignancy within 3 years of study entry with the exception of cured basal cell or squamous cell carcinoma of the skin, superficial bladder cancer, prostate intraepithelial neoplasm, or other noninvasive or indolent malignancy, or cancers from which the participant has been disease-free for >1 year, after treatment with curative intent. 21. Patients have any other concurrent severe and/or uncontrolled medical condition that would, in the Investigator's judgment contraindicate patient participation in the clinical study.
Treatment:	After signing the ICF and confirmed eligibility, patients will receive INCMGA00012 (retifanlimab) 500 mg by intravenous infusion on Day1 of each cycle, once every four weeks for up to 2 years. Patients will receive treatment until disease progression, unacceptable toxicity, death, or discontinuation from the study treatment for any other reason. Patients discontinuing the study treatment period will enter a post-treatment follow-up period during which survival and new anti–cancer therapy information will be collected every 3 months (± 14 days) from the last dose of investigational product until the end of study (EoS).
Study Procedures, Efficacy and Safety Assessments:	**Patient visits**: Visits are organized in programmed cycles of 28 days (if there are no delays in treatment owing to the occurrence of an AE). After baseline, all visits must occur within ± 3 working days from the scheduled date, unless otherwise noted in the schedule of assessments, and every 12 weeks after documented PD. Assessments scheduled for Day 1 of each cycle must be performed within 72 hours prior to study treatment administration, unless otherwise indicated in the schedule of assessments, in order to confirm to the patient if treatment can be followed up. **Efficacy assessments:** Tumor assessments will be performed until radiographically and/or clinically documented PD as per RECIST criteria v.1.1, study treatment discontinuation, initiation of new anticancer therapy, or discontinuation of patient from overall study participation (i.e., death, patient's request, lost to follow-up), whichever occurs first.

	Clinical assessment. Examination of the penis and/or inguinal region: Radiographic assessment: [computerized tomography (CT) of the chest, abdomen, and pelvis or magnetic resonance imaging (MRI) of the abdomen and pelvis with a non-contrast CT scan of the chest in patients for whom CT scans with contrast are contraindicated] will be performed using RECIST v.1.1 every 8 weeks (± 7 days) from the first dose of study treatment up to 6 months (more frequently if clinically indicated). All subjects who remain on treatment for 6 months will subsequently have imaging performed every 12 weeks (± 7 days). Imaging should continue to be performed until radiologic evidence of PD, treatment discontinuation, the start of new anti–cancer treatment, withdrawal of consent, death, or the EoS, whichever occurs first. Bone scans will also be used to assess bone metastases. If a subject has a known history of bone metastases or has new bone pain during screening, a bone scan should be obtained prior to study entry. A bone scan at follow-up is required only if they develop new or worsening symptoms or if the site believes they have attained a complete response (CR). If a subject has no known metastatic disease in the bone or active symptoms, a bone scan at baseline is not needed. After PD by RECIST v.1.1, if the site Investigator determines the subject is clinically stable and will benefit from continued treatment, the subject will then be managed by irRECIST. Each assessment will be performed as scheduled according to the calendar regardless of any dosing delay to prevent the introduction of bias into the assessment of efficacy. Failure to perform any of the required disease assessments will result in the inability to determine disease status for that time point. Tumor samples for molecular analysis are required for patient participation and patients must agree to provide tissues from a metastatic site or the primary penile tumor at the time of study entry (that should be available for at least 60% of patients) and at the time of PD. Provision of previous archival tissue is acceptable for patients with non-measurable disease, or inaccessible lesions. Blood samples for molecular analysis will be collected at the time of baseline, after 2 cycles of study treatment (C3D1), and upon PD or EoS. **Safety assessments:** The occurrence and maximum grade of AEs observed throughout the study will be listed. Any AE that the Investigator reports as unrelated to the drug will also be reported. In this study, AEs will be assessed according to the NCI–CTCAE v.5.0.
Statistics:	The sample size calculation is based on an exact binomial test. The clinical trial is designed to demonstrate an ORR of at least 25% and

	to exclude a rate of less than 5% (p0=0.05, p1=0.25, α =0.05, β=0.80, A'hern's exact design). At least 3 responders (18.8%) among 16 evaluable patients will be adequate to justify the investigation of this strategy in further clinical trials. Considering a drop-out rate of 10%, a sample size of 18 patients will be needed to attain 80% power at nominal level of one-sided alpha of 0.05. The full analysis set will be considered the primary population for the analysis.
Study Periods	**Recruitment period:** Estimated at least 12 months in order to enroll 18 patients. **End of study:** EoS will occur 12 months after the last patient has been enrolled in the study (treatment start).

V. TABLE OF ABBREVIATIONS

Definition	Abbreviation
AE	Adverse event
ALK	Alkaline phosphatase
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
aPTT	Activated Partial Thromboplastin Time
AST	Aspartate aminotransferase
BCG	Bacillus Calmette–Guérin
CBR	Clinical benefit rate
CI	Confidence interval
CNS	Central Nervous System
CR	Complete response
CRF	Case report form
CRO	Clinical Research Organization
DEHP	(2-ethylhexyl) phthalate
DNA	Deoxyribonucleic acid
DoR	Duration of response
EC	Ethics Committee
ECI	Event of clinical interest
ECOG	Eastern Cooperative Oncology Group
EGFR	Epidermal Growth Factor Receptor
EMA	European Medicines Agency
EoS	End of study
EoT	End of treatment
ESA	Erythropoiesis-stimulating agents
FDA	Food and Drug Administration
FFPE	Formalin-fixed and paraffin-embedded
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
GFR	Glomerular filtration rate
GGT	Gamma-glutamyl transferase
HAV	Hepatitis A virus
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HNSqCC	Head and neck region
HPV	Human papillomavirus
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
ICI	Immune checkpoint inhibitor
IFN	Interferon
IMP	Investigational medicinal product
INR	International Normalized Ratio
irAE	Immune-related adverse event
IRB	Institutional Review Board
irRECIST	Immune-related RECIST
ITT	Intention-to-treat
mAb	Monoclonal antibody

Definition	Abbreviation
MMR	Mismatch repair
MTD	Maximum tolerated dose
NCCN	National Comprehensive Cancer Network
NCI–CTCAE	National Cancer Institute–Common Terminology Criteria for Adverse Events
NSCLC	Non-small cell lung cancer
ORR	Overall response rate
OS	Overall survival
PCR	Polymerase chain reaction
PD	Progressive disease
PD-1	Programmed cell death protein 1
PD-L1	Programmed Death-ligand 1
PES	Polypropylene and polyethersulfone
PFS	Progression-free survival
PP	Per protocol
PR	Partial response
PS	Performance Status
PSqCC	Penile squamous cell carcinoma
PT	Prothrombin Time
PVC	Polyvinylchloride
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	Ribonucleic acid
RT	Radiation therapy
SAE	Serious adverse event
SCAC	Squamous Carcinoma of the Anal Canal
SD	Stable disease
SqCC	Squamous cell carcinoma
T1DM	Diabetes mellitus type 1
TEAE	Treatment Emergent Adverse Event
TMB	Tumor mutational burden
TRAE	Treatment-related AE
TSH	Thyroid-stimulating hormone
TST	Mantoux tuberculin skin test
TTP	Time to progression
ULN	Upper limit of normal
UPN	Unique Patient Number
WBC	White blood cell

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1 STUDY BACKGROUND AND RATIONALE

1.1 Introduction

Squamous cell carcinoma (SqCC) is the most common primary neoplasm of the penis (95% of penile tumors), but only 0.4% to 0.6% of all malignant neoplasms among men in the United States and Europe. The incidence of penile SCC (PSqCC) is higher (up to 10%) among men in the developing countries of Asia, Africa, and South America (1). High risk human papillomavirus (HPV) is responsible for 30-80% of PSqCC tumors. HPV deoxyribonucleic acid (DNA) can be identified in around 30-80% of invasive penile cancer cases (2–5). Patients with stage IV PSqCC –defined by deep inguinal or pelvic lymph node involvement (stage N3) or distant metastases (M1)– have a 5-year overall survival (OS) rate <50% (6).

Patients with PSqCC present typically in their late 50s or 60s and the vast majority does with clinically localized disease, for which organ-preserving surgical excision and/or radiation are usually sufficient for primary treatment (7). The mainstay of treatment for advanced disease has been palliative cisplatin-based chemotherapy, with only marginal survival benefit in term of overall response rate (ORR) and transient responses (8,9). Best supportive care remains an option for advanced cases. For these cases or cases refractory to systemic therapy or radiation therapy (RT), the National Comprehensive Cancer Network (NCCN) panel strongly recommends consideration of clinical trial participation as data are limited in the second-line setting.

Although new therapies are being evaluated in PSqCC, very little information is available regarding due to limited knowledge of molecular alterations. Among them, Epidermal Growth Factor Receptor (EGFR) inhibitors, such as cetuximab have demonstrated a modest benefit in a retrospective study (10). Advances on progressive PSqCC present, thus, a therapeutic challenge and new approaches to increase efficacy in the field of PSqCC are urgently required. However, the rarity of this disease makes it difficult to perform prospective, randomized trials.

Recent published data have demonstrated that high levels of programmed cell death protein 1 (PD-1) and its ligand –Programmed Death-ligand 1 (PD-L1)– are found in the majority of primary and metastatic PSqCC patients (11–14) in line with other various SCC, suggesting that targeting immune checkpoint pathways may be beneficial in these patients. PSqCC, SCC of the head and neck region (HNSqCC) and cervical SCC have reasonably high tumor mutational burden (TMB), being ranked just behind melanoma, lung, bladder and esophageal and colorectal cancer (15,16). The use of immune checkpoint inhibitors (ICIs) such as nivolumab or pembrolizumab –two humanized antibodies against PD-1– has been a successful strategy in patients with many of these tumors gaining the approval by the U.S. Food and Drug Administration (FDA) for several indications.

In addition, a single institution study very recently demonstrated that PSqCC is genomically similar to other more common HPV-related tumors, with a TMB value as high as lung SqCC and HNSqCC but with no significant correlation with HPV infection (15).

For HPV-related cancers, immune responses appear to be driven by a combination of both viral and non-viral antigens (17) and the role of HPV in PD-1 pathway and the efficacy of ICIs is still controversial. These data provide a rational basis for further investigation of anti–PD-1 and anti–PD-L1 immunotherapeutic in patients with advanced PSqCC. Of the patients who do respond, many can have long-term survival and therefore there is much interest in identifying these patients using prognostic and predictive biomarkers (18).

1.2 PD-1 Checkpoint Inhibition and Cancer Treatment

The basis of immunotherapy is to boost the host immune response against the tumor. PD-1 cells to suppress T cell activation and therefore promote immune evasion. The importance of intact immune surveillance in controlling outgrowth of neoplastic transformation has been known for decades. Extensive evidence has demonstrated a correlation between tumor-infiltrating lymphocytes (TILs) in cancer tissue and prognosis in several tumor types (19–25).

The PD-1 receptor-ligand interaction is critical to suppress immune control. The normal function of PD-1, expressed on the cell surface of activated T cells under healthy conditions, is to down-modulate excessive immune responses. PD-1 (encoded by the gene *Pdcd1*) is an immunoglobulin (Ig) superfamily member related to CD28 and cytotoxic T lymphocyte–associated antigen 4 (CTLA-4), which has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (PD-L1 and/or PD-L2). Binding of PD-L1 to PD-1 inhibits T cell activation triggered through the T cell receptor in peripheral tissues, whereas PD-L2 is thought to control immune T cell activation in lymphoid organs (26).

PD-L1 and PD-L2 are constitutively expressed or can be induced in a variety of cell types. Their interaction with the PD-1 receptor on tumor-specific T cells plays a decisive role in immune evasion by tumors. As a consequence, the PD-1/PD-L1 pathway is an attractive target for therapeutic intervention in cancer.

The first immune checkpoint inhibitor to be approved for clinical use was the anti–CTLA4 antibody ipilimumab. Since then, anti–PD-1 (nivolumab and pembrolizumab) and anti–PD-L1 (atezolizumab) agents have been approved for various types of cancers.

1.3 Preclinical Studies with PD-1 ICIs

Preclinical data from mouse models have shown that administration of antibodies blocking PD-1/PD-L1 interaction increases infiltration of tumor-specific CD8-positive T cells and finally guides to tumor rejection, either as a monotherapy or in combination with other treatment modalities (27,28).

Anti–mouse PD-1 or PD-L1 antibodies have demonstrated antitumor responses in models of SqCC, pancreatic carcinoma, melanoma, breast carcinoma, acute myeloid leukemia, and colorectal carcinoma, among others. In these studies, tumor infiltration by CD8-positive T cells and increased interferon (IFN)-γ, granzyme B, and perforin expression were observed, reflecting that the principal mechanism that probably justify the antitumor activity of PD-1 checkpoint inhibition involved local infiltration and activation of effector T cell function *in vivo*.

1.4 Role of Immunotherapy in Urothelial Cancers and Squamous Non-Small Cell Lung Cancer

Nivolumab and pembrolizumab –two humanized IgG4 (S228P) monoclonal antibody that targets PD-1– received FDA accelerated approval for the treatment of urothelial carcinoma after unsuccessful front- and second-line chemotherapy (29–31). Both agents have been demonstrated to be superior in terms of efficacy and safety to other second-line approved agents (paclitaxel, docetaxel, or vinflunine). Nivolumab provided meaningful ORR and pembrolizumab was able to prolong OS in almost 3 months irrespective of PD-L1 expression. Atezolizumab also has demonstrated to be effective and safe as first-line agent for the treatment of patients with locally advanced and unresectable or metastatic urothelial cancer and comorbidities (32) and was approved as fist-line agent in 'unfit' patients. Currently, pembrolizumab in the first-line setting is being further assessed in the Phase III KEYNOTE-361 trial (NCT02335424).

Regarding squamous non-small cell lung cancer (NSCLC), nivolumab was able to almost double 1-year OS compared to standard chemotherapy (docetaxel) in patients with metastatic squamous NSCLC who had experienced progressive disease (PD) during or after one prior platinum-based chemotherapy (9.2 months, 95% confidence interval [CI] 7.3–13.3 vs. 6 months, 95% CI 5.1–7.3) (33) and is recommended by the FDA for patients with NSCLC in this setting, particularly in those with squamous histology. In these studies, PD-L1 expression –in line with other ICIs studies– was neither prognostic nor predictive biomarker of benefit, because some patients with negative PD-L1 status showed a response to PD-1 blockade.

Regarding PSqCC, recent observations address that the use of ICIs such as pembrolizumab is effective in PSqCC that present with DNA mismatch repair (MMR)-deficiency (34). These represent a very low proportion of patients, however.

Currently, several ongoing clinical trials are evaluating the role of the anti–PD-L1 in PSqCC patients. Whereas it is truth that for fit patients, another clinical trial (NCT04224740) –not still recruiting–, will be evaluating the role of the anti–PD-L1 pembrolizumab in combination with cisplatin-based chemotherapy as first-line (HERCULES), the majority of clinical trials are using immunotherapy as a single modality of treatment in both chemo-naive or pretreated with cisplatin-based chemotherapt patients. The NCT03686332 trial evaluating the role of atezolizumab to control locoregional lymph node disease is directed to chemo-naïve patients, whereas the

NCT03391479 trial is evaluating the role of avelumab in patients with advanced disease who are unfit for or have progressed after platinum-based chemotherapy. In the NCT02721732 study pembrolizumab is administered in patients –pretreated or not–, with tumors that cannot be removed by surgery or are metastatic, and the combination of nivolumab with ipilimumab in another study also includes chemo-naive PSqCC patients (NCT03333616 and NCT02834013). Regarding second-line, another study (NCT02837042) evaluating pembrolizumab following prior chemotherapy or advanced PSqCC has just been terminated. Regarding maintenance therapy, the PULSE study (NCT03774901) is evaluating the role of avelumab in patients who are in response or with stable disease after first line platinum-containing chemotherapy.

1.5 The Role of Immunotherapy in HPV-Related Cancer

HPV is implicated in a significant proportion of oropharyngeal cancers as well as most cervical, penile and anal cancers. Although the presence of TILs and PD-L1 expression is less common in the HPV-related throat/cervical tumors, patients with HPV-related tumors represent a considerable proportion of PD-L1-positive tumors given their high prevalence. Studies demonstrating the efficacy of immunotherapy in squamous HPV-related throat carcinoma are based on vaccines such as MEDI0457 (35) and AXAL (36) in monotherapy or in AXAL in combination for advanced HPV-related throat and cervical carcinoma.

However, for HPV-related cancers, immune responses is also driven by non-viral antigens (17) and all patients will eventually fail to the above mentioned therapies.

PD-1/PD-L1 are highly expressed among up to 70% HPV-related HNSqCC (37). Pembrolizumab is significantly more effective in term of ORR in relapsed/refractory patients with HNSqCC HPV-positive compared with HPV-negative (25%, 95% CI 7–52 vs. 14%, 95% CI 4-32) (38).

Nivolumab demonstrated a significant improvement in OS in platinum-resistant HNSqCC compared with standard chemotherapy (1-year OS 36% vs. 16.6%) and showed preliminary evidence that patients with PD-L1 expression 1% or $p16^{INK4a}$ positive tumors (indicating HPV positivity) may derive greater benefit from nivolumab (39). Despite these results, the role of HPV in PD-1 pathway is still controversial.

Regarding other HPV-related tumors, nivolumab and pembrolizumab have also demonstrated excellent activity in cervical cancer (18,40,41) and in patients with metastatic SqCC of the anal canal (42,43). Regarding cervical cancer, ORR induced by nivolumab was reported as high as 30% (phase I/II) (18,40). In the partial responders, the median duration of response was 5.4 months, irrespective of PD-L1 or HPV status (40). For pembrolizumab, the KEYNOTE 158 trial has demonstrated ORR of 14.1% (18). Interestingly, 91% of patients had response duration of greater than or equal to 6 months. No responses were observed in patients whose tumors had a

PD-L1 combined positive score (CPS) < 1 (defined as the total number of PD-L1–positive cells [tumor, lymphocytes, and macrophages] divided by the total number of tumor cells) (41). Following the results of the KEYNOTE 158 trial (18), pembrolizumab was recently approved for patients with recurrent or metastatic cervical cancer that progressed on or after chemotherapy whose tumors express PD-L1 (CPS ≥1). A higher benefit in HPV-positive patients was not confirmed.

Finally, two studies trying to stratify PD-L1 positivity for HPV status in PSqCC failed to show any correlation. Moreover, PD-L1 was expressed mainly in HPV-negative tumors (11,12). However, few patients were analyzed, and these results should be interpreted with caution. Ongoing trials continue to investigate the role of ICIs in these HPV-related tumors (NCT02635360, NCT03073525, NCT03614949, NCT03738228, and NCT03811015). Design of future clinical trials should include stratification based on HPV status.

1.6 INCMGA00012 (retifanlimab)

1.6.1 Preclinical Efficacy

INCMGA00012 –also known as MGA012 or retifanlimab– is a highly selective, hinge-stabilized humanized IgG4κ isotype monoclonal antibody (mAb) against PD-1 that is currently under development as a therapeutic candidate for the treatment of multiple solid tumors, both as a monotherapy and in combination with other potentially immunoactive agents. Upon binding PD-1, INCMGA00012 (retifanlimab) inhibits the interaction of PD-1 with PD-L1/PD-L2 and disrupts the negative signaling axis to restore T-cell function. Consistent with its intended mechanism of action and functional properties, INCMGA00012 (retifanlimab) has been shown to inhibit the binding of PD-L1 and PD-L2 to PD-1, to disrupt the PD-1/PD-L1 inhibitory axis, and to enhance IFN-γ secretion in staphylococcus enterotoxin B-stimulated human peripheral blood mononuclear cells with activity comparable to pembrolizumab and nivolumab replicas (generated by MacroGenics, Inc. and based on the published sequences of these antibodies) (

Figure 1 and ***Figure 2***). INCMGA00012 (retifanlimab) does not induce antibody-dependent cellular cytotoxicity or complement dependent cytotoxicity, mitogenic activity, hemolysis, or cytokine release. The clinical translational results demonstrate that retifanlimab is biologically active at all evaluated dose regimens and activity is as anticipated for a PD-L1 inhibitor.

Figure 1. INCMGA00012 (retifanlimab)-Mediated Inhibition of Soluble PD-L1 or PD-L2 Binding to a PD-1 Expressing Cell Line (NS0/PDCD1).

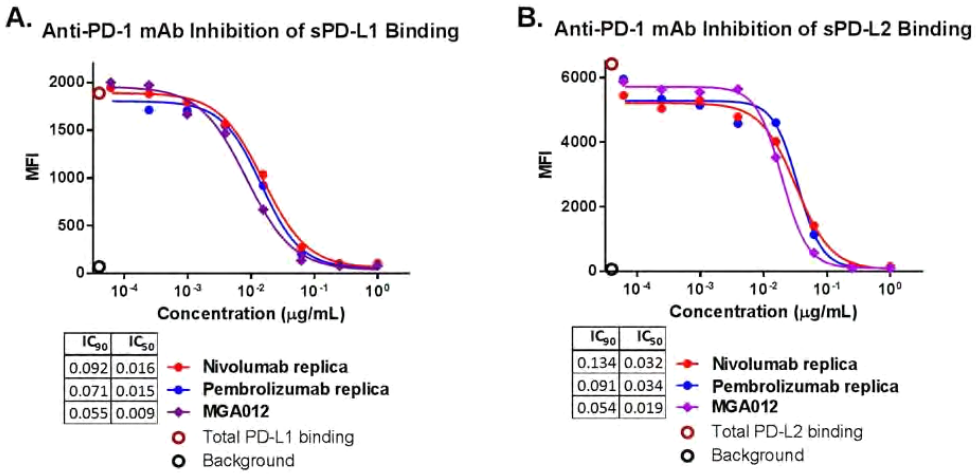
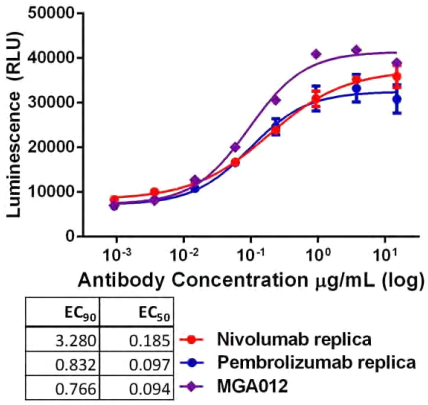


Figure 2. INCMGA00012 (retifanlimab)-Mediated Reversal of PD-1/PD-L1 Inhibitory Signaling as Measured by Luciferase Gene Expression in a Co-Culture Reporter Assay System.



1.6.2 Clinical Efficacy

As of 23 September 2020, 289 participants have received INCMGA00012 (retifanlimab) monotherapy in Study INCMGA 0012-101. Preliminary activity in terms of durable RECIST v1.1 response has also been seen in multiple other tumor types. Based on the available data, the efficacy profile of INCMGA00012 (retifanlimab) is expected to be consistent with that of other PD-(L)1 inhibitors.

INCMGA00012 (retifanlimab) has shown meaningful clinically activity in platinum-refractory Squamous Carcinoma of the Anal Canal (SCAC). Preliminary activity in terms of durable RECIST v1.1 responses has also been seen in multiple other tumor types (NSCLC (44), cervical cancer

(45), biomarker-unselected endometrial cancer (45), sarcoma (45), Merkel cell carcinoma (46), and endometrial carcinoma with high levels of MicroSatellite Instability (MSI-H) or deficient MisMatch Repair (dMMR) (47).

Efficacy in SCAC (Study INCMGA 0012-202)

As of 08 June 2020, 94 participants with locally advanced or metastatic SCAC whose cancer had progressed on or who were intolerant of platinum-based therapy had received retifanlimab 500 mg every 4 weeks (Q4W). The study excluded participants with autoimmune disease that required systemic immunosuppression and those with an ECOG performance score ≥ 2. Participants with well-controlled HIV infection (CD4+ count ≥ 300/μL and undetectable viral load) and receiving antiretroviral therapy were included. Prior PD-L1 therapy was not allowed.

Participants received retifanlimab 500 mg as an intravenous (IV) infusion Q4W for up to 2 years. Treatment continued until progression of disease, unacceptable toxicity, or completion of planned treatment. Participants with initial radiographic disease progression could receive additional doses of treatment in the absence of clinical deterioration until radiographic confirmation of progression. Assessment of tumor status was performed every 8 weeks throughout the treatment period.

As of 08 June 2020, the median duration of treatment was 85 days (range: 1 day to 19.4 months [592 days]). Eighteen participants (19.1%) were continuing to receive retifanlimab, and 54 participants (57.4%) remained in the study, either continuing to receive retifanlimab or being followed for survival and/or safety.

Median age was 64 years (range: 37 to 94 years), 64.9% of participants were female, 76.6% were Caucasian, and the ECOG performance score was 0 (41.5%) or 1 (58.5%). Most participants (80.9%) had distant metastases at baseline and the most common sites of disease were the lymph nodes (64.9%) and liver (41.5%). Nine participants (9.6%) were HIV-positive. All but 3 participants (97.0%) had received prior platinum-based chemotherapy. The majority of participants (87.2%) had also received prior radiotherapy, either as chemoradiotherapy (73.4%) or radiotherapy alone (17.0%).

The expansion study (Study INCMGA 0012-101, POD1UM-101, NCT03059823) contained 4 tumor-specific cohorts (endometrial, cervical, soft tissue sarcoma, and NSCLC) and 2 tumor-agnostic flat dose cohorts (500 and 750 mg once Q4W). All patients were ≥18 years old and had PD during or following 1–5 prior treatments, measurable disease per RECIST v1.1, and no prior immune checkpoint inhibitors. The primary endpoint was safety. Adverse events (AEs) were graded via National Cancer Institute–Common Terminology Criteria for Adverse Events

(NCI–CTCAE) v.4.03. Response was evaluated by RECIST v1.1 with treatment past progression allowed at the discretion of the investigator.

Results as of July 10, 2018, a total of 157 patients had been treated with INCMGA00012 (retifanlimab), of whom 127 patients in the tumor-specific cohorts (29 endometrial, 33 cervical, 32 sarcoma, and 33 NSCLC), and 15 each in the two tumor-agnostic flat-dose cohorts. Median (range) age was 59 (18–86) years. The majority of patients were female (66.9%), white (85.4%), and had present Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) of 1 (67.5%). RECIST responses (confirmed and unconfirmed) were observed in all 4 tumor types (6/25 evaluable patients with cervical cancer, 6/26 with NSCLC, 3/29 with endometrial cancer, and 1/22 with sarcoma).

INCMGA00012 (retifanlimab) in monotherapy as a first-line of treatment is being currently investigated in several phase 2 trials for other specific tumors: treatment-naïve NSCLC with EGFR-negative, alkaline phosphatase (*ALK*)- or *ROS*-negative (POD1UM-203; NCT03679767); urothelial carcinoma in non-eligible patients for cisplatin therapy (POD1UM-203; NCT03679767); unresectable or metastatic melanoma (POD1UM-203; NCT03679767); naïve metastatic merkel cell carcinoma (POD1UM-201; NCT03599713), naïve locally advanced or metastatic renal cell carcinoma with clear cell component (with or without sarcomatoid features) (POD1UM-203; NCT03679767), metastatic Merkel cell carcinoma (POD1UM201; NCT03599713), metastatic solid tumors stage IIIB not amenable to curative therapy to stage IV Non-small cell lung cancer advanced/metastatic unresectable malignant pleural mesothelioma (POD1UM-105; NCT03920839). Also, is being studied in combination in naive non-small cell lung cancer and squamous head and neck tumors. Regarding patients with stage III non-small cell lung cancer is being evaluated in combination with platinum-based chemotherapy INCMGA00012 (POD1UM-304; NCT04205812) or chemoradiation (POD1UM-301; NCT04203511). Regarding Squamous Cell Carcinoma of the Head & Neck is being evaluated in combination with Enoblituzumab (NCT04129320).

1.6.3 Clinical Safety

As of the data cutoff date (23 SEP 2020), 578 unique participants have been exposed to INCMGA00012 (retifanlimab) as monotherapy. An additional 96 participants have been exposed to INCMGA00012 (retifanlimab) in combination with other anticancer agents, in combination with epacadostat INCB024360 (53 participants), in combination with parsaclisib (22 participants), or in combination with pemigatinib INCB054828 (15 participants) and 6 participants in combination with INCB001158.

The safety data presented in the IB v.7.0 demonstrate that the safety profile of INCMGA00012 (retifanlimab) is acceptable and consistent with the profile described for the PD-(L)1 inhibitor

class. Adverse drug reactions in participants treated with INCMGA00012 (retifanlimab) monotherapy include the following:

- Very common: fatigue, asthenia, diarrhea, nausea, pruritus, and pyrexia.
- Common: hypothyroidism, rash, hyperthyroidism, alanine aminotransferase increased, myalgia, lipase increased,, influenza-like illness, infusion-related reaction, rash maculo-papular, dysgeusia, pneumonitis, and rash erythematous.
- Uncommon: colitis, nephritis, blood thyroid stimulating hormone decreased, pruritus generalized, rash macular, rash pruritic, adrenal insufficiency, blood thyroid stimulating hormone increased, dermatitis, interstitial lung disease, myositis, rash papular, autoimmune hepatitis, autoimmune thyroiditis, dermatitis acneiform, pancreatitis, rash pustular, thyroid disorder, diabetic ketoacidosis, hypophysitis, hypopituitarism, immune-mediated enterocolitis, iritis, myocarditis, palmar-plantar erythrodysesthesia syndrome, radiculopathy, thyroiditis, tri-iodothyronine decreased, tri-iodothyronine increased, type 1 diabetes mellitus, and uveitis.

Study INCMGA 0012-101 is an ongoing, open-label, dose-escalation and cohort expansion study in participants with relapsed/refractory, unresectable, locally advanced or metastatic solid tumors. As of 23 September 2020, 289 participants have been exposed to INCMGA00012 (retifanlimab) monotherapy. Treatment-emergent AEs (TEAEs) were reported in 272 participants (94.1%). TEAEs reported for ≥ 10% of participants included fatigue, anemia, diarrhea, nausea, asthenia, and vomiting. Grade 3 or higher TEAEs occurring in > 5 participants were anemia (6.6%), pulmonary embolism (2.8%), blood alkaline phosphatase increased and lipase increased (2.4%), and hyponatremia (2.1%). Fatal TEAEs occurred in 5 participants (0.3%; hemiparesis, nephritis, cardiovascular insufficiency, pulmonary embolism, and renal failure). All fatal TEAEs were considered not related to INCMGA00012 (retifanlimab) by the investigator. Serious TEAEs occurred in 85 participants (29.4%). Serious TEAEs that occurred for > 2 participants included urinary tract infection (1.4%), pleural effusion (1.4%), pulmonary embolism (1.4%), pneumonia (1.0%), and dyspnea (1.0%). TEAEs that led to discontinuation of INCMGA00012 (retifanlimab) occurred in 26 participants (9.0%): colitis 4 participants, 1.4%), pulmonary embolism (2 participants, 0.7% each), and autoimmune hepatitis, brain edema, cardiovascular insufficiency, diarrhea, dry mouth, failure to thrive, female genital tract fistula, general physical health deterioration, iritis, myocardial infarction, myocarditis, nephritis, edema peripheral, pneumonitis, pneumothorax, polymyalgia rheumatica, transaminases increased (tumor pain, and type 1 diabetes mellitus (1 participant, 0.3% each). No dose-limiting toxicities (DLTs) occurred, and the maximum tolerated dose (MTD) was not reached.

Study INCMGA 0012-104 is an ongoing, open-label, multicenter study of INCMGA00012 (retifanlimab) monotherapy, INCB001158 (arginase inhibitor) monotherapy, and INCMGA00012 (retifanlimab) + INCB001158 combination therapy in Japanese participants with advanced solid

tumors. As of 23 September 2020, 6 participants have been exposed to INCMGA00012 (retifanlimab) 500mg Q4W monotherapy in the study. TEAEs occurred in all 6 participants (100%). TEAEs reported for > 1 participant included rash (3 participants, 50.0%), constipation (2 participants 33.3%), amylase increased (2 participants [33.3%]), and pruritus (2 participants [33.3%]). Grade 3 or higher TEAEs occurred in 2 participants (33.3%) and included femoral neck fracture, ileus, lymphocyte count decreased, and pyelonephritis (1 participant [16.7%] each). No fatal TEAEs occurred in participants receiving retifanlimab monotherapy. Serious TEAEs occurred in 2 participants (33.3%) and included ileus, pyelonephritis, and femoral neck fracture (1 participant [16.7%] each). No serious TEAEs were considered related to INCMGA00012 (retifanlimab). There were no TEAEs that led to discontinuation of INCMGA00012 (retifanlimab). There have been no DLTs reported in participants receiving INCMGA00012 (retifanlimab) monotherapy in this study.

Study INCMGA 0012-201 is an ongoing open-label, single-arm, multicenter study in participants with advanced/metastatic Merkel cell carcinoma. As of 23 September 2020, 68 participants have been exposed to INCMGA00012 (retifanlimab) monotherapy. As of the data cutoff date, 4 participants (5.9%) have received ≥ 1 year of continuous treatment with INCMGA00012 (retifanlimab) monotherapy. In participants receiving retifanlimab monotherapy, TEAEs occurred in 50 participants (73.5%). TEAEs reported in ≥ 10% of participants included asthenia (14 participants [20.6%]), pruritus (13 participants [19.1%]), diarrhea (9 participants [13.2%]), nausea (9 participants [13.2%]), and pyrexia (8 participants [11.8%]). Grade 3 or higher TEAEs occurring in > 1 participant (2.9%) were anemia, asthenia, neutropenia, and pneumonia (2 participants [2.9%] each). Fatal TEAEs occurred in 3 participants (4.4%; acute respiratory failure, asthenia, and Chronic lymphocytic leukemia (CLL) [reported term: progression of CLL]). Only the event of CLL was considered related to retifanlimab. The event occurred in a 70-year-old participant with a 4-year ongoing medical history of CLL, for which the participant never received therapy. After 3 cycles of retifanlimab, the participant was hospitalized with Grade 3 anemia, Grade 2 thrombocytopenia, and Grade 1 neutropenia. Retifanlimab was then discontinued due to progression of CLL and Merkel cell carcinoma, and treatment for CLL was started with chlorambucil and obinutuzumab. The event was complicated by pleuropneumopathy that was resistant to antibiotics. The investigator indicated that the relationship to retifanlimab cannot be excluded due to rapid worsening of the hematologic disease. Serious TEAEs occurred in 13 participants (19.1%). The only serious TEAE to occur in >1 participant was asthenia (2 participants [2.9%]). TEAEs that led to discontinuation of retifanlimab occurred in 7 participants (10.3%): asthenia (with a fatal outcome), atrial fibrillation, CLL (with a fatal outcome [aforementioned progression of CLL]), infusion-related reaction, pancreatitis, polyarthritis, and radiculopathy (1 participant [1.5%] each).

Study INCMGA 0012-202 is an ongoing open-label, single-arm, multicenter study in participants with locally advanced or metastatic squamous carcinoma of the anal canal who have

progressed on or after a standard-of-care platinum-based chemotherapy regimen. As of 23 September 2020, 94 participants have been exposed to INCMGA00012 (retifanlimab) monotherapy. As of the data cutoff date, 3 participants (3.2%) have received ≥ 1 year of continuous treatment with INCMGA00012 (retifanlimab) monotherapy. TEAEs occurred in 90 participants (95.7%). TEAEs reported for ≥ 15.0% of participants were asthenia (22 participants [23.4%]), diarrhea (19 participants [20.2%]), anemia (18 participants [19.1%]), fatigue (17 participants [18.1%]), nausea (15 participants [16.0%]), and vomiting (15 participants [16.0%]). Grade 3 or higher TEAEs occurring in > 2 participants were anemia (6 participants [6.4%]), general physical health deterioration (4 participants [4.3%]), pelvic pain (4 participants [4.3%]), abdominal pain, asthenia, dyspnea, fatigue, hyponatremia, intestinal obstruction, proctalgia, and urinary tract infection (3 participants [3.2%]). Fatal TEAEs occurred in 10 participants (10.6%). Only 1 fatal event (lymphangiosis carcinomatosa) was considered by the investigator to be related to retifanlimab. Serious TEAEs occurred in 50 participants (53.2%). Serious TEAEs reported most frequently were abdominal pain, anemia, and urinary tract infection (all 4 participants [4.3%]). TEAEs that led to discontinuation of retifanlimab occurred in 7 participants (7.4%): coma hepatic, diffuse large B-cell lymphoma, immune-mediated enterocolitis, palmar-plantar erythrodysaesthesia syndrome, pleural effusion, pneumonitis, and pseudomonas infection (1 participant [1.1%] each).

Study INCMGA 0012-203 is an ongoing open-label, multicenter study in participants with advanced solid tumors. As of 23 September 2020, enrolment has been completed with 121 participants having received INCMGA00012 (retifanlimab) monotherapy. As of the data cutoff date, 6 participants (5.0%) have received ≥ 1 year of continuous treatment with retifanlimab monotherapy. In participants receiving retifanlimab monotherapy, TEAEs occurred in 106 participants (87.6%). TEAEs reported for ≥ 10% of participants included asthenia (21 participants [17.4%]), arthralgia (18 participants [14.9%]), decreased appetite (17 participants [14.0%]), pruritus (15 participants [12.4%]), rash (13 participants [10.7%]), and urinary tract infection (13 participants [10.7%]). Grade 3 or higher TEAEs occurring in > 2 participants were anemia (5 participants [4.1%]), pneumonia (5 participants [4.1%]), sepsis (4 participants [3.3%]), ALT increased (3 participants [2.5%]), and chronic obstructive pulmonary disease (3 participants [2.5%]). Fatal TEAEs occurred in 6 participants (5.0%), none of which were considered by the investigator to be related to retifanlimab. Serious TEAEs occurred in 31 participants (25.6%). Serious TEAEs that occurred in ≥ 2 participants were pneumonia (5 participants [4.1%]), chronic obstructive pulmonary disease (4 participants [3.3%]), sepsis (3 participants [2.5%]), hepatocellular injury, and pulmonary embolism (2 participants [1.7] each). TEAEs that led to discontinuation of retifanlimab occurred in 13 participants (10.7%): sepsis (2 participants [1.7%]), and alanine aminotransferase increased, azotemia, blood creatinine increased, cerebrovascular accident, chronic obstructive pulmonary disease, general physical health deterioration,

hemorrhage, hepatic failure, hepatocellular injury, myelodysplastic syndrome, and right ventricular failure (1 participant [0.8%] each).

1.6.3.1 General Information

Fatigue is the most common side effect observed with immune checkpoint inhibitors, with an estimated overall frequency around 20% percent for the anti–PD-1 and anti–PD-L1 agents. However, the most relevant toxicities in clinical practice associated with these agents are immune-related adverse events (irAE).

1.6.3.2 Dermatologic Toxicity

Skin toxicity is the most common irAE related to immune checkpoint inhibitors, and approximately 30-40% of patients treated with anti–PD-1 and anti–PD-L1 agents will develop dermatologic complications. This toxicity usually is the earliest irAE, with a median time to onset of 3.6 weeks after treatment initiation. Typical physical examination findings consist of a reticular and maculopapular erythematous rash on the trunk or extremities. Severe rashes such as Stevens-Johnson syndrome/toxic epidermal necrolysis have been also reported in rare cases.

1.6.3.3 Diarrhea

Diarrhea is a very common clinical AE in patients undergoing treatment with immune checkpoint inhibitors. The onset of this toxicity occurs later than dermatologic toxicity, approximately six weeks after treatment initiation. Diarrhea of any grade has been reported in approximately 14,4% of patients treated with these agents, although grade 3 and 4 immune-mediated colitis has been seen in only 1-2% of cases. Potential risk of gastrointestinal perforation should be taken into consideration on patients with immune-related colitis.

1.6.3.4 Hepatotoxicity

Elevations in serum levels of the hepatic enzymes, aspartate aminotransferase (AST) and alanine aminotransferase (ALT), have been observed with anti–PD-1 and anti–PD-L1 agents in less than 5% of patients with grade 3 and 4 events being extremely rare. Most episodes are asymptomatic laboratory abnormalities, but occasionally patients have an associated fever. Increases in total and direct bilirubin are exceptional, and usually occur in association with a prolonged period of AST and ALT elevations. The most frequent time of onset is around two or three months after initiation of treatment, although early or delayed events may also be seen.

1.6.3.5 Endocrinopathies

Inflammation of the pituitary, thyroid, or adrenal glands as a result of checkpoint blockade often presents with imprecise symptoms such as nausea, headache, fatigue, and vision changes. Although it has been difficult to establish the exact incidence of endocrinopathies associated with these compounds, clinically significant events are thought to occur in less than 5-10% of patients treated with anti–PD-1 and anti–PD-L1 agents. The most common endocrinopathies are hypophysitis and autoimmune thyroid disease, principally primary hypothyroidism secondary to a destructive thyroiditis. Hyperthyroidism associated with Graves disease and adrenal insufficiency has also been reported with these compounds.

1.6.3.6 Less Common irAEs

Other less common irAEs have been attributed to anti–PD-1 and anti–PD-L1 agents, including:

- Nephritis (renal insufficiency, granulomatous interstitial nephritis, and lupus membranous nephropathy).
- Respiratory complications (sarcoidosis, pneumonitis, and organizing inflammatory pneumonia).
- Eye disorders (episcleritis, conjunctivitis, uveitis, or ophthalmopathy associated with Graves' disease).
- Pancreatic alterations [asymptomatic elevated levels of serum amylase and lipase and type 1 diabetes mellitus (T1DM)].
- Neurologic syndromes (myasthenia gravis, Guillain-Barre syndrome, posterior reversible encephalopathy syndrome, aseptic meningitis, enteric neuropathy, and transverse myelitis).
- Hematologic disorders (red cell aplasia, neutropenia, and thrombocytopenia).

1.7 Rationale for Dose Selection of INCMGA00012 (retifanlimab)

INCMGA00012 (retifanlimab) will be administered at 500 mg Q4W. The selection of this dose was based on modeling of clinical PK data from the first-in-human monotherapy study, INCMGA 0012-101 (NCT03059823), in which 37 participants from dose escalation phase were treated at doses of 1 mg/kg every 2 weeks (Q2W), 3 mg/kg Q2W, 3 mg/kg Q4W, 10 mg/kg Q2W, and 10 mg/kg Q4W and clinical experience with flat dosing in the expansion cohorts of the same study. Simulations demonstrated that the median steady-state trough concentration of retifanlimab 500

mg Q4W and 375 mg Q3W was approximately 21.1 µg/mL, which is the median trough concentration for pembrolizumab 2 mg/kg Q3W (48).

These dose regimens were further supported by the linear PK of retifanlimab and the final population PK analysis from 506 participants in 5 studies where body weight was identified as a statistically significant covariate for V_C but not for CL. Lack of correlation between CL and body weight minimizes an advantage of weight-based dosing over flat dosing on PK variability, especially for total exposure, as body size was believed to be a major contributor to inter-individual PK variability for mAb therapies

Based on these observations, 500 mg Q4W was chosen as the dose regimen. Preliminary efficacy data demonstrate clinical activity of INCMGA00012 (retifanlimab) based on durable RECIST responses in multiple tumor types (45).

1.8 Study Rationale

Currently, patients with patients with PSqCCs presenting with advanced disease continue to present poor prognosis and OS of <1 year. Best supportive care remains an option for advanced in this setting and consideration of clinical trial is strongly recommended by the NCCN panel of experts.

The majority of primary PSqCC tumors express PD-L1. On the other hand, in a recent study it has been showed that PSqCC presents an identical genotype compared to other HPV-related SqCC tumors and very similar to squamous NSCLC. These data provide a rational basis for further investigation of anti–PD-1 and anti–PD-L1 immunotherapeutic in patients with advanced PSqCC. Of the patients who do respond, many can have long-term survival and therefore there is much interest in identifying these patients using prognostic and predictive biomarkers.

For HPV-related cancers, the role of HPV as molecular marker ICIs-based therapy is quite scarce and not conclusive and future clinical trials should include the HPV status in the evaluation of prognostic/predictive biomarkers.

Preliminary data with INCMGA00012 (retifanlimab) in ~200 patients have shown promising antitumor activity, resulting in response rates similar to those observed with other ICIs. However, no data are available so far with anti–PD-1 and anti–PD-L1 agents used in this tumor subtype. In order to determine if immunotherapy could benefit this population, this multicenter, open-label, phase II clinical trial will evaluate the efficacy and safety of the of anti–PD1 INCMGA00012 (retifanlimab) in patients with advanced PSqCC previously treated or not with chemotherapy. Unlike other currently ongoing studies, this trial will evaluate the activity of immunotherapy in a series of patients with advanced PSqCC regardless of their prior treatment and extension of the disease.

2 STUDY OBJECTIVES AND ENDPOINTS

2.1 Primary Objective

- To assess the efficacy –as determined by the objective response rate (ORR)– of INCMGA00012 (retifanlimab) in patients with unresectable locally advanced or metastatic PSqCC.

2.1.1 Primary Endpoint

- ORR will be evaluated according to the investigator as per RECIST v.1.1.

2.2 Secondary Objectives

- To assess the efficacy –as determined by the clinical benefit rate (CBR), PFS, 6-month PFS, duration of response (DoR), time to progression (TTP), OS, and maximum tumor shrinkage– of INCMGA00012 (retifanlimab) in these patients.
- To evaluate the safety and tolerability of INCMGA00012 (retifanlimab) in these patients.

2.2.1 Secondary Endpoints

- OS, and clinical benefit rate (CBR), PFS, 6-month PFS, DoR, TTP, and maximum tumor shrinkage that will be evaluated as per RECIST v.1.1.
- The safety and tolerability will be evaluated by incidence of AEs, incidence of prespecified AEs, change from baseline in targeted vital signs, and change from baseline in targeted clinical laboratory test results.

2.3 Exploratory Objectives

- To determine the efficacy –as determined by the ORR, CBR, and 6-month PFS based on immune-related RECIST (irRECIST).
- To evaluate predictive or prognostic, tumor- and/or immune-related biomarkers associated with disease activity status or response to treatment.
- To identify possible mechanisms of resistance to study treatments through the comparative analysis of potential biomarkers from paired pre-treatment and post-progression tumor and/or blood samples.

- To assess impact of INCMGA00012 (retifanlimab) on HIV control in participants who are known to be HIV-positive.

2.3.1 Exploratory Endpoints

- ORR, CBR, and 6-month PFS as per irRECIST.
- Relationship between tumor- and/or immune-related biomarkers, and efficacy in tumor tissue and/or liquid biopsy.
- Changes from baseline in the CD4-positive cell count and HIV viral load in participants who are known to be HIV-positive.

3 STUDY DESIGN

3.1 Description of Study Design

This is a multicenter, open-label, single-arm, phase II clinical trial to evaluate the efficacy and safety of the INCMGA00012 (retifanlimab) in progressive advanced PSqCC patients, previously treated or not with chemotherapy.

The study population consists of male patients age ≥ 18 years with advanced PSqCC that are presenting with progressive disease. Patients that have received prior treatment of locally recurrent and/or metastatic disease with platinum-based chemotherapy regimens are not excluded.

In the absence of progression of disease or unacceptable toxicity, treatment with INCMGA00012 (retifanlimab) will continue based on physician's criteria for up to 2 years.

Tumor assessments per RECIST v.1.1 and irRECIST will be performed approximately every eight weeks (± 7 days) for the first 6 months and every 12 weeks (± 7 days) thereafter until PD, treatment discontinuation, the start of new anti–cancer treatment, withdrawal of consent, death, or the end of study (EoS), whichever occurs first. Tumor assessments will be performed on the specified schedule regardless of treatment delays.

For estimation of ORR, CBR, DoR, and PFS tumor response will be based on RECIST v.1.1. In patients who continue treatment beyond radiographic PD per RECIST v.1.1, tumor response (ORR, CBR, and PFS) may continue to be assessed using irRECIST criteria until study treatment discontinuation.

Safety assessments will include the incidence, nature, and severity of AEs and laboratory abnormalities graded per the NCI–CTCAE v.5.0. Laboratory safety assessments will include the regular monitoring of hematology, blood chemistry, coagulation, and thyroid function testing. A schedule of assessments is provided in ***Appendix 1***.

3.2 Study Schedule Summary

The study will consist of a 28-day screening phase, a treatment phase, and a post-treatment phase (end of treatment [EoT] visit and EoS) that includes safety, efficacy, and survival follow-up.

3.2.1 Screening Phase

During this phase, subject eligibility is determined, including the documentation of baseline characteristics. This phase of the study will begin once the informed consent from (ICF) is signed by the patient and the procedures to be performed are described in ***Section 6*** of the protocol.

One re-screening is allowed in patients that are screening failure in this study. Patient has to re-consent the ICF before any study procedure is done.

3.2.2 Treatment Phase

Patients will receive study treatment according to the protocol and will be discontinued if one of the following situations arises:

- AEs which, according to the protocol or in the opinion of the Investigator, can cause serious or permanent damage or which rule out further treatment with the study drug.
- Progression of disease is confirmed radiologically and unequivocally assessed according to the RECIST criteria version 1.1 and/or irRECIST.
- Major study protocol non-compliance.
- Patient's withdrawal from the study.
- Death.
- Study is cancelled by the Sponsor.

3.2.3 End of Treatment Visit

EoT visit will be 28 days (± 7 days) after the last dose of study treatment.

3.2.4 Follow-up after treatment discontinuation

EoS will occur 12 months after the last patient has been enrolled in the study (treatment start).

Patients discontinuing the study treatment period will enter a post-treatment follow-up period during which survival and new anti–cancer therapy information will be collected every 3 months (± 14 days) from the last dose of investigational product until the end of study (EoS).

During this visit, status survival and post study anti–cancer therapy evaluation will be collected (telephone contact is acceptable).

LPLV: 12 months after first study dose of the last patient or progressive disease experienced in all patients or when the trial is terminated by the Sponsor, whichever is earlier.

4 PATIENT SELECTION

The following eligibility criteria can be used in the screening of patients for whom the protocol treatment is deemed suitable. In order to determine whether this protocol is suitable for a given patient, all medical and non-medical criteria should be taken into consideration.

Patient eligibility will be reviewed and documented by a suitable member of the Investigator's study team before the patients are enrolled in the study.

4.1 Study Population

Male patients age ≥ 18 years with progressive locally advanced –not amenable to curative treatment– or metastatic PSqqCC (i.e., T4 or N3 or M1) previously treated with chemotherapy regimens or patients naïve of systemic treatment.

The patient's signed ICF should be obtained before any trial related activities and according to local guidelines.

4.2 Inclusion Criteria

Patients must meet ALL the following inclusion criteria to be enrolled in the study:

1. Patients have been informed about the nature of study, and have agreed to participate in the study, and signed the informed consent form (ICF) prior to participation in any study-related activities.
2. Male patients ≥ 18 years of age at the time of signing ICF.
3. Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) 0-1.
4. Life expectancy ≥12 weeks.
5. Histologically-proven PSqCC.

6. Locally advanced unresectable or metastatic stage 4 PSqCC that is not amenable to resection with curative intent (T4 or N3 or M1).
7. Radiological evidence of locally advanced or metastatic disease.
8. Patients must have measurable disease or evaluable disease according to Response Evaluation Criteria in Solid Tumors (RECIST) version (v.)1.1 criteria.
9. Patients must agree to provide a tumor tissue sample from a metastatic site or the primary tumor at the time of study entry, with the exception of patients for whom tumor biopsies cannot be obtained (e.g., inaccessible tumor or subject safety concern) that may submit an archived tumor specimen only upon agreement from the Sponsor. If feasible, patients will also be given the option of providing a tumor tissue sample at disease progression from metastasis or primary tumor (if tumor biopsies cannot be obtained for inaccessible lesion or subject safety concern).
10. Willingness and ability to provide blood samples (liquid biopsy) at the time of inclusion, after 2 cycles of study treatment (C3D1), and upon PD or study termination.
11. Adequate organ function:

    - Hematological: White blood cell (WBC) count > 3.0 x 10^9/L, absolute neutrophil count (ANC) ≥ 1.5 x 10^9/L, platelet count ≥ 75.0 x10^9/L, and hemoglobin > 9.0 g/dL.
    - Hepatic: Bilirubin ≤ 1.5 times the upper limit of normal (× ULN) (< 3 x ULN in the case of Gilbert's disease); aspartate transaminase (AST), and alanine transaminase (ALT) ≤ 2.5 times × ULN (in the case of liver metastases ≤ 5 × ULN); Albumin > 2.5 mg/mL.
    - Renal: Serum creatinine ≤ 1.5 x ULN; alternately measured or calculated creatinine clearance ≥30 mL/min with creatinine levels >1.5 × institutional ULN (glomerular filtration rate [GFR] can also be used in place of creatinine or creatinine clearance).

    CLcr (mL/min) =(*Cockcroft-Gault equation: ([{140 – age in years} × {ACTUAL WEIGHT in kg}] divided by [{72 × serum creatinine in mg/dL} multiplied by 0.85 if female])).

    eGFR =175 x $(S_{Cr})^{-1.154}$ x $(age)^{-0.203}$ x 0.742 [if female] x1.212 [if Black]. From MDRD (49)

    - Coagulation: Activated Partial Thromboplastin Time (aPTT) ≤1.5 X ULN and International Normalized Ratio (INR) or Prothrombin Time (PT) ≤1.5 X ULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants.

12. Patients who are willing and able to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures.
13. Subjects should agree to use an adequate method of contraception starting with the first dose of study therapy through 180 days after the last dose of study treatment.

14. Patients that have received prior chemotherapy regimens or radiotherapy for locally recurrent and/or metastatic disease are not excluded but patients naïve of systemic treatment can also be included.
15. For pretreated patients, last dose of chemotherapy administered ≥ 28 days from study entry.

4.3 Exclusion criteria

Any patient meeting ANY of the following criteria will be excluded from the study:

1. Locally PSqCC candidate for curative treatment.
2. Prior therapy with an anti–PD-1, anti–PD-L1, or anti–PD-L2 agent.
3. Known hypersensitivity to any of the excipients of INCMGA00012 (retifanlimab).
4. Receipt of anticancer therapy or participation in another interventional clinical study within 28 days before the first administration of study drug; 6 weeks for mitomycin C.
5. Radiotherapy within 14 days of first dose of study treatment with the following caveat:
   a. 28 days for pelvic radiotherapy.
6. Toxicity of prior therapy that has not recovered to ≤ Grade 1 or baseline (with the exception of any grade of alopecia and anemia not requiring transfusion support). Endocrinopathy, if well-managed, is not exclusionary and should be discussed with Sponsor's medical monitor.
7. Major surgery (defined as requiring general anesthesia) or significant traumatic injury within 4 weeks of start of study drug, or patients who have not recovered from the side effects of any major surgery, or patients who may require major surgery during the study.
8. Known active uncontrolled or symptomatic Central Nervous System (CNS) metastases, carcinomatous meningitis, or leptomeningeal disease as indicated by clinical symptoms, cerebral edema, and/or progressive growth. Patients with a history of CNS metastases or cord compression are eligible if they have been definitively treated (e.g., radiotherapy, stereotactic surgery) and are clinically stable off anticonvulsants and steroids for at least 4 weeks before randomization.
9. Cardiovascular: patients that have any of the following within 6 months of randomization: severe/unstable angina, myocardial infarction, symptomatic pericarditis, symptomatic congestive heart failure (New York Heart Association functional classification III-IV), cerebrovascular accident including transient ischemic attack, or symptomatic pulmonary embolism, coronary/peripheral artery bypass graft, ongoing cardiac dysrhythmias of NCI–CTCAE v.5.0 grade ≥2, including, ventricular arrhythmias –except for benign premature ventricular contractions–, supraventricular and nodal arrhythmias requiring a pacemaker or not controlled with medication, any conduction abnormality requiring a pacemaker or any cardiac arrhythmia not controlled with medication.
10. Metabolic: Uncontrolled hyper/hypothyroidism or diabetes mellitus type 1 (T1DM). Patients with hypothyroidism stable on hormone replacement will not be excluded from the trial. Patients with controlled T1DM on a stable insulin regimen may be eligible for this study.

11. Diagnosis of immunodeficiency or is receiving systemic steroid therapy or immunosuppressive therapy within seven days prior to study treatment initiation.
12. Active autoimmune disease that has required systemic treatment in past 2 years (i.e., with use of disease modifying agents, corticosteroids, or immunosuppressive drugs).
    Note: Replacement therapy (e.g., thyroxine, insulin, or physiologic steroid replacement therapy (≤ 10 mg prednisone daily) for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment.
13. Prior allogenic stem cell or solid organ transplantation.
14. Has received a live vaccine within 28 days of the planned start of study drug.
    Note: Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chicken pox/zoster, yellow fever, rabies, Bacillus Calmette–Guérin (BCG), and typhoid vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (e.g., FluMist®) are live-attenuated vaccines and are not allowed.
15. Active/history of pneumonitis requiring treatment with steroids or active/history of interstitial lung disease.
16. Active uncontrolled infection at the time of screening.
17. Latent tuberculosis determined by a positive TST followed by confirmation by pulmonologists.
18. Participants who are known to be human immunodeficiency virus (HIV)-positive, unless all of the following criteria are met:
    a. CD4-positive count ≥ 300/μL;
    b. Undetectable viral load;
    c. Receiving highly active antiretroviral therapy.
19. Active hepatitis A virus (HAV) (positivity for HAV IgM antibody), hepatitis B virus (HBV) (patients with negative hepatitis B surface antigen [HBsAg] test and a positive antibody to HBsAg [anti–HBsAg] test at screening are eligible) or hepatitis C virus (HCV) (patients with a positive antibody to hepatitis C [anti–HCV] are eligible only if polymerase chain reaction [PCR] is negative for virus hepatitis C ribonucleic acid [RNA]).
20. Known additional malignancy that is progressing or requires active treatment, or history of other malignancy within 3 years of study entry with the exception of cured basal cell or squamous cell carcinoma of the skin, superficial bladder cancer, prostate intraepithelial neoplasm, or other noninvasive or indolent malignancy, or cancers from which the participant has been disease-free for >1 year, after treatment with curative intent.
21. Patients have any other concurrent severe and/or uncontrolled medical condition that would, in the Investigator's judgment contraindicate patient participation in the clinical study.

5 TREATMENT

5.1 Formulation, Packaging, and Handling

Study drug packaging will be overseen by the Sponsor's Clinical Trial Supplies department and bear a label with the identification required by local law, the protocol number, drug identification, and dosage. The packaging and labeling of the study drug will be in accordance with Sponsor standards and local regulations. Local packaging in some countries may be different.

The study drug must be stored according to the details on the Product Information. The drug label indicates the storage temperature. Upon arrival of investigational products at the site, site personnel should check them for damage, verify proper identity, quantity, integrity of seals, and temperature conditions, and report any deviations or product complaints upon discovery.

INCMGA00012 (retifanlimab) drug product for IV administration will be supplied in a glass vial for single use. Each vial contains INCMGA00012 (retifanlimab) at a concentration of 25 mg/mL. Upon receipt, INCMGA00012 (retifanlimab) vials are to be refrigerated at 2-8 ºC (36-46 ºF) in a locked storage area protected from light with limited access. Do not freeze. INCMGA00012 (retifanlimab) vials should not be used beyond the expiration date provided by the manufacturer.

5.2 Dosage and Administration

INCMGA00012 (retifanlimab) should be administered intravenously, at flat dose of 500 mg over one hour (± 15 minutes) or 30 minutes (± 15 min) using a filter on day 1 of each 28-day cycle (every 4 weeks). Infusion rate may be reduced if an infusion reaction occurs.

INCMGA00012 (retifanlimab) was observed to be compatible with the following materials: polyvinylchloride (PVC) with (2-ethylhexyl) phthalate (DEHP), PVC (without DEHP), polyolefin, polyethylene, polypropylene and polyethersulfone (PES). Study drug administration supplies (i.e., IV bags and tubing) should be made only of these materials.

INCMGA00012 (retifanlimab) will be prepared by adding the drug product directly to a bag containing 0.9% sodium chloride (normal saline) injection United States Pharmacopeia (or local equivalent) and delivered through an IV administration set including a 0.2 micron low protein binding preferably in-line filter made of PES. The final concentration range for INCMGA00012 (retifanlimab) must be within 0.3mg/mL to 12mg/mL in the normal saline IV bag. It is recommended to use 100 mL normal saline IV bags for infusion preparation, however, in case of supply constraints, 250 mL normal saline IV bags may be used if needed.

The total time at room temperature for prepared infusion solution should not exceed 6 hours inclusive of infusion time.

5.3 Treatment Modification

Safety and tolerability of all patients will be closely monitored throughout study treatment and the follow-up period using the NCI–CTCAE v.5.0. Patients will be assessed in order to detect any AEs before administering new study treatment during each treatment visit. Treatment will only be administered if clinical evaluation and local laboratory test results are acceptable.

Patients who have treatments withheld for more than 12 weeks must discontinue study treatment and are considered off study. Patients whose treatment is interrupted or permanently discontinued due to an AE, including abnormal laboratory value, must be followed until resolution or stabilization of the event, whichever comes first, which includes all study assessments appropriate to monitor the event.

Intrapatient dose reductions are not permitted for INCMGA00012 (retifanlimab). If a dose interruption is necessary for management of treatment-related TEAEs, INCMGA00012 (retifanlimab) will be reinitiated at the dose at which it was interrupted.

Patients should meet the following re-treatment criteria before proceeding with subsequent cycles:

- Hemoglobin ≥ 8 g/dL.
- ANC ≥ 1.0×10^9/L.
- Platelet count ≥ 75×10^9/L.
- ALT/AST/bilirubin level < Grade 2.
- Resolution of all immune-related TEAEs to ≤ Grade 1 (with the exception of hyperglycemia [allowed to Grade 2] and endocrinopathy that is controlled on hormonal replacement).
- Resolution of all non–immune-related TEAEs to ≤ Grade 1 or baseline (with the exception of Grade 2 alopecia and fatigue). Transient asymptomatic laboratory elevations ≤ Grade 3 do not require dose interruption if the participant is asymptomatic and if the elevation is clinically insignificant and has been discussed with the medical monitor.

If retreatment criteria are not met, then re-treatment should be delayed, and the participant should be re-evaluated weekly or more frequently as clinically indicated. INCMGA00012 (retifanlimab) may be interrupted for a maximum of 12 weeks due to toxicity.

5.4 Modification of the Amount of Study Drug Administered Due to Changes in Patient's Weight

INCMGA00012 (retifanlimab) is administered as a fixed dose irrespective of the patient´s body weight. AEs (both non-serious and serious) associated with INCMGA00012 (retifanlimab)

exposure may represent an immunologic etiology. These AEs may occur shortly after study treatment initiation or several months after the last dose of treatment. INCMGA00012 (retifanlimab) must be withheld for certain drug-related toxicities and severe or life-threatening AEs as per ***Table 1*** below. Dose reduction of INCMGA00012 (retifanlimab) is not permitted.

INCMGA00012 (retifanlimab) should be permanently discontinued:

- For grade 4 toxicity except for endocrinopathies that are controlled with replacement hormones.
- If steroid dosing cannot be reduced to ≤ 10 mg prednisone or equivalent per day within 12 weeks.
- If a treatment-related toxicity does not resolve to grade 0-1 within 12 weeks after last dose of INCMGA00012 (retifanlimab).
- If any event occurs a second time at grade ≥ 3 severity (also for recurrent grade 2 pneumonitis).

Table 1. Toxicity Management Guidelines for Immune-related AEs Associated with INCMGA00012 (retifanlimab).

Immune-Related Adverse Event	Toxicity Grade or Conditions (CTCAE v5.0)	Action Taken With INCMGA00012 (retifanlimab)	AE Management With Corticosteroid and/or Other Supportive Care Therapies
Pneumonitis	Grade 1	No action.	None.
	Grade 2	Withhold until ≤ Grade 1.	• Administer systemic corticosteroids per local practice followed by taper. • Evaluate participants with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment. • Add prophylactic antibiotics for opportunistic infections.
	Grades 3 or 4, or recurrent Grade 2	Permanently discontinue.	
Diarrhea/colitis	Grade 1	No action.	None.
	Grades 2 or 3	Withhold until ≤ Grade 1.	• Consider prompt initiation of standard anti-diarrheal agents. • Administer systemic corticosteroids per local practice followed by taper. • Consider prophylactic antibiotics per local practice. • Consider gastrointestinal consultation and performing endoscopy to rule out colitis.
	Grade 4 or recurrent Grade 3	Permanently discontinue.	
AST/ALT elevation and/or increased bilirubin/Hepatitis	Grade 1	No action.	None.
	Grade 2	Withhold until ≤ Grade 1.	• Administer systemic corticosteroids per local practice followed by taper. • Consider monitoring liver enzymes weekly (or more frequently) until liver enzyme value returns to baseline or is stable.
	Grade 3 or 4, or in participants with liver metastasis with baseline Grade 2 elevation of AST or ALT, hepatitis with AST or ALT increases ≥ 50% and lasts ≥ 1 week	Permanently discontinue.	
Endocrinopathies Type 1 diabetes mellitus	Grades 1 and 2	No action.	None.
	Grades 3 and 4 hyperthyroidism	No action.	For hypothyroidism, initiate thyroid replacement hormones (eg, levothyroxine or liothyronine) per standard of care.

Immune-Related Adverse Event	Toxicity Grade or Conditions (CTCAE v5.0)	Action Taken With INCMGA00012 (retifanlimab)	AE Management With Corticosteroid and/or Other Supportive Care Therapies
Hyperglycemia Hyperthyroidism Hypothyroidism Hypophysitis Adrenal insufficiency	Grades 3 or 4	Withhold until ≤ Grade 1. May restart INCMGA00012 (retifanlimab) if endocrinopathy has improved to ≤ Grade 2 and is controlled with hormone replacement, if indicated, and steroid taper is complete.	• For Type 1 diabetes mellitus, initiate insulin replacement therapy. • For hyperglycemia, administer antihyperglycemic. • For hyperthyroidism, treat with nonselective beta-blockers (eg, propranolol) or thionamides as appropriate. • For hypophysitis or adrenal insufficiency, administer corticosteroids and initiate hormonal replacements as clinically indicated.
Nephritis and renal dysfunction	Grade 1	No action.	None.
	Grade 2	Withhold until ≤ Grade 1.	Administer corticosteroids per local practice followed by taper.
	Grade 3 or 4	Permanently discontinue.	
Rash	Grade 1	No action.	None.
	Grade 2	No action.	Manage with topical steroids with or without drug interruption.
	Grade 3[i] or persistent Grade 2 (≥ 2 weeks) or suspected Stevens-Johnson syndrome or toxic epidermal necrolysis	Withhold until ≤ Grade 1.	Administer corticosteroids per local practice followed by taper.
	Grade 4 or confirmed Stevens-Johnson syndrome or toxic epidermal necrolysis	Permanently discontinue.	
Myocarditis	Grade 2	Withhold until ≤ Grade 1.	• Treatment with systemic corticosteroids should be initiated (initial dose of 1-2 mg/kg per day of prednisone or equivalent). Taper as appropriate. • Management of cardiac symptoms according to standard of care and with guidance from cardiology. Consider cardiac MRI and myocardial biopsy for diagnosis.
	Grades 3 or 4	Permanently discontinue.	
All other irAEs	Grade 3 or intolerable/ persistent Grade 2	Withhold until ≤ Grade 1.	Based on severity of AE, administer corticosteroids.
	Recurrent Grade 3	Consider discontinuation.	
	Grade 4	Permanently discontinue.	

Table 2. Guidelines for Management of Suspected Infusion Reactions.

Grade	Description[i)]	Treatment	Subsequent Infusions
1	Mild reaction; infusion interruption not indicated; intervention not indicated.	• Monitor vital signs closely until medically stable.	• Premedication with acetaminophen/paracetamol and a histamine blocker should be considered for participants who have had previous systemic reactions to protein product infusions or when recommended by institutional policy.
2	Requires infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, non-steroidal anti-inflammatory drugs [NSAIDS], narcotics, IV fluids); prophylactic medications indicated for ≤ 24 hours.	• First occurrence: Stop infusion and initiate appropriate medical measures (e.g., IV fluids, antihistamines NSAIDS, acetaminophen/paracetamol, narcotics, per institutional preferences). • Monitor vital signs until medically stable. • If symptoms resolve within 1 hour, infusion may be resumed at 50% of the original infusion rate. • Subsequent occurrences (after recommended prophylaxis): Permanently discontinue study treatment.	• Premedicate at least 30 minutes before infusion with antihistamines (e.g., diphenhydramine 50 mg orally) and acetaminophen/ paracetamol (500-1000 mg orally). • Additional supportive measures may be acceptable (per institutional preference) but should be discussed with medical monitor. • Next infusion should start at 50% of the original infusion rate. If no reaction, rate of infusion can be increase by 25% every 15 minutes until a rate of 100% has been reached. Subsequent infusions can begin at 100%.
3 or 4	**Grade 3:** Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates). **Grade 4:** Life-threatening; pressor or ventilatory support indicated.	• Stop infusion and initiate appropriate medical therapy (e.g., IV fluids, antihistamines NSAIDS, acetaminophen/ paracetamol, narcotics, oxygen, pressors, epinephrine, corticosteroids, per institutional preferences). • Monitor vital signs frequently until medically stable. Hospitalization may be indicated.	• Permanently discontinue study treatment.

[i)] Per NCI–CTCAE v5.0, appropriate resuscitation equipment should be available at the bedside and a physician readily available during the period of study treatment administration.

5.4.1 Drug Extravasation

As a general recommendation, in the event of extravasation, the following advice should be considered:

- Stop the infusion immediately.
- Do not remove the needle or cannula.
- Aspirate with the same needle as much infiltrated drug as possible from the subcutaneous site.
- Apply ice to area for 15 to 20 minutes every four to six hours for the first 72 hours.
- Paint the skin over the extravasated site with 100% dimethyl sulfoxide (or hyaluronidase) four times daily for two weeks.

Watch the area closely during the following days in order to determine whether a surgical excision and skin graft is necessary.

5.5 General Concomitant Medication and Additional Assistance Guidelines

Concomitant treatment and prior medication are defined as non-investigational medicinal product (IMP). Concomitant treatment includes any prescribed medication or phytotherapy between the 28 days prior to the administration of the first treatment dose and the last safety visit during treatment period. All concomitant treatments will be recorded. After this time, information will only be collected on any anti–cancer drugs taken by the patient until EoS.

Information on concomitant medication will include start date, end date, brand or generic name, route of administration, dose, and treatment indication. The following concomitant treatments are permitted during the study:

- Erythropoiesis-stimulating agents (such as Procrit®, Aranesp®, Epogen®) for the supportive treatment of anemia. Blood transfusions are permitted during the study.
- The prophylactic use of granulocyte-Colony Stimulating Factor is not allowed during the first treatment cycle but can be used for cases of neutropenia arising during treatment, in accordance with the NCCN guidelines.
- Bisphosphonates and denosumab for the prevention of skeletal events.
- Prophylactic or therapeutic anticoagulation therapy such as low-molecular weight heparin or warfarin at a stable dose level.
- Mineralcorticoids (e.g., fludrocortisone).
- Medications for the treatment of diarrhea, nausea, anorexia, or vomiting.
- Any medications deemed necessary to ensure patient safety and well-being may be administered at the discretion of the Investigator.

5.6 Prohibited Concomitant Medications

INCMGA00012 (retifanlimab) belongs to the class of IgG antibodies that are administered parenterally and cleared by protein catabolism, extrinsic factors such as food and drug-drug interactions are not anticipated to affect its exposure. Specifically, drugs that affect cytochrome P450 and other metabolizing enzymes are not expected to interfere with the catabolism of INCMGA00012 (retifanlimab) (50). It is unlikely that INCMGA00012 (retifanlimab) would be a victim or a perpetrator of PK drug-drug interactions (51,52). Dedicated drug-drug interaction studies of retifanlimab have not been performed.

INCMGA00012 (retifanlimab) is known to increase some proinflammatory cytokine levels. This is a known class effect of checkpoint inhibitory monoclonal antibodies (mAbs) (53)(54) but is unlikely to modulate CYP enzymes or drug transporters, based on clinical evidence with other agents of this class (50). It is unlikely that retifanlimab would be a perpetrator of drug-drug interactions, and the potential for clinically significant drug-drug interaction is low.

HIV antiretroviral medications, used according to protocols as appropriate by HIV-positive participants in retifanlimab studies, may be substrates, inhibitors, or inducers of the P-glycoprotein and multidrug-resistant protein transporters and the cytochrome P450 enzyme system. None of the highly active antiretroviral therapies are immunosuppressors (55). Since retifanlimab is not expected to be a victim or perpetrator of drug transporters or cytochrome P450 enzymes, the potential of drug-drug interaction between antiretroviral drugs and retifanlimab is low (51). No clinically important differences in the CL of retifanlimab were found in HIV-positive participants taking antiretroviral medications compared to participants who were not HIV-positive.

Glucocorticoid co-administration was explored as a time series covariate in the population pharmacokinetics model. Results show that glucocorticoid co-administration is not a predictor for retifanlimab clearance in the model.

Hormonal contraceptives are metabolized by the cytochrome P450 enzyme system, and retifanlimab is not expected to be a victim or perpetrator of cytochrome P450 enzymes. Therefore, the potential for pharmacokinetic drug interactions between hormonal contraceptives and retifanlimab is low (56).

Subjects are prohibited from receiving the following therapies during the screening and treatment phase of this trial:

- Immunotherapy not specified in the protocol.
- Chemotherapy not specified in the protocol.

- Targeted therapy
- RT.

  Note: RT is allowed during screening, as long as it is completed at least two weeks prior to first dose of study treatment and may be allowed to treat a symptomatic bone lesion or the brain after consultation with Sponsor.

- Herbal supplements.
- Probiotics.
- Live vaccines within 30 days prior to first dose of study treatment and while participating in the trial. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella, herpes zoster, yellow fever, rabies, BCG, and typhoid (oral) vaccines. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed. However, intranasal influenza vaccines (e.g., FluMist®) are live attenuated vaccines, and are not allowed.
- Immunosuppressive agents within seven days prior to first dose of study treatment.
- Steroids for any purpose other than to modulate symptoms from an event of clinical interest of suspected immunologic etiology.

  Note: The use of physiologic doses of steroids (≤ 10 mg prednisone daily) is allowed and does not require Sponsor consultation.

  Note: The use of systemic steroids to premedicate patients for whom computerized tomography (CT) scans with contrast are contraindicated is allowed. Magnetic resonance imaging (MRI) of abdomen and pelvis with a non-contrast CT scan of the chest may also be performed in these patients.

  Note: Local applications and inhaled steroids for management of asthma are allowed.

Subjects who, per Investigator's assessment, require any of the aforementioned medications for clinical management should be discontinued from study treatment. There are no prohibited therapies during the post-treatment follow-up phase.

5.7 Medication Errors and Overdose

Medication errors in this study may arise when the drug is administered at the wrong time or when the wrong dose strength is taken. Patient medication errors should be recorded on the relevant section in the case report form (CRF). In the event of an error in the administration of the medication, the Sponsor should be informed immediately.

Medication errors must be reported irrespective of the presence of an associated AE/SAE, including:

- Medication errors involving patient exposure to the IMP.
- Any possible medication errors or use of the medication not defined in the protocol which implicates the participating patient or not.

Regardless of whether the medication error is accompanied by an AE or not, in the judgment of the Investigator, the medication error should be properly documented and recorded.

5.8 Treatment Compliance

Patients will receive treatment under physician supervision. Personnel will check the administration volume and total administered dose. The administered dose of each treatment will be recorded in the source data and the appropriate CRF.

6 STUDY ASSESSMENTS AND PROCEDURES

6.1 Informed Consent Form

Written ICF from the patient must be signed before performing any study procedure. However, tumor assessments available and performed as part of clinical practice prior to obtaining ICF and within 28 days prior to treatment start may be used; such evaluations do not need to be repeated for screening. Bone scans performed within 60 days prior to treatment start are acceptable.

By giving their consent, patients will be informed as to the nature of the study drug and will receive pertinent information regarding the study objectives, possible benefits, and potential AEs. They will also receive information on the follow-up procedures and possible risks they will be exposed to. This document also informs patients about how biological samples will be obtained and collected and its legal implications. After receiving the document, the patient will read it (or receive information verbally before witnesses) and will sign the previously approved ICF. The patient will receive a signed copy of the ICF. The patient can withdraw his consent and discontinue the study; this will not affect any future medical treatment. One re-screening is allowed in patients that are screening failure in this study. Patient has to re-consent ICF before any study procedure is done.

At inclusion:

- The Sponsor will request the patient's demographic and clinical data related to screening criteria.

- Each patient will be given a Unique Patient Number (UPN) for this study, provided by the Sponsor. All data will be recorded in the appropriate CRF using this identification number. This number will be provided to the central laboratory to ensure traceability of study samples.

Confirmation of patient's eligibility for study participation will be recorded on the CRF.

6.2 Visit Schedule

All screening tests and evaluations must be completed and reviewed to confirm that patients meet all eligibility criteria within 28 days prior to the first administration of study medication (dosing).

The Investigator will maintain a screening log to record details of all patients screened and to confirm eligibility or record reasons for screening failure, as applicable.

Visits are organized in programmed cycles of 28 days (if there are no delays in treatment owing to the occurrence of an AE). All visits must occur within ± 3 working days from the scheduled date, unless otherwise noted in the schedule of assessments.

Assessments scheduled for day 1 (before treatment) of all cycles must be performed within 72 hours prior to study treatment administration, unless otherwise indicated in the schedule of assessments, to confirm to the patient if treatment can be followed up. If a mandatory procedure described in the protocol falls on a bank holiday and/or weekend, this procedure should be performed on the day before or after the holiday (i.e. within a period of ± 3 working days). The summary of all study assessments is included in ***Appendix 1***.

EoT visit will be performed within 28 days after last study treatment dose. Patients will be followed up for survival and post-study anticancer therapy evaluation every 3 months until the EoS. Telephone contact is acceptable.

6.3 Demographic Data and Medical History

Demographic data include age, and self-reported race/ethnicity. Medical history comprises clinically significant diseases, surgical interventions, history of cancer (including prior antineoplastic treatments and procedures), history of smoking, alcoholism, drug addiction, as well as any medications (e.g., prescribed drugs, over-the-counter drugs, medicinal plants, homeopathic remedies, or food supplements) used by the patient in the 28 days prior to screening visit.

6.4 Efficacy Assessments

6.4.1 Tumor and Response Evaluations

All measurable and evaluable lesions should be assessed and documented at the screening visit and re-assessed at each subsequent tumor evaluation. Tumor assessments will be performed at screening, every 8 weeks (± 7 days) for the first 6 months following first dose of study treatment, and every 12 weeks (± 7 days) thereafter until PD, treatment discontinuation, withdrawal of consent, the start of new anticancer treatment, death, or study termination by the Sponsor, whichever occurs first. The same radiographic procedures and technique must be used throughout the study for each patient.

Tumor assessment during the screening period should consist of clinical exam –with examination of the penis and/or inguinal region– and of anatomical imaging consisting of 1) CT scan of the chest, abdomen, and pelvis (MRI of the abdomen and pelvis with a non-contrast CT scan of the chest in patients for whom CT scans with contrast are contraindicated), 2) bone scan if a subject has a known history of bone metastases or has new bone pain during screening, and 3) any other imaging studies as clinically indicated by the treating physician [brain imaging during the trial should be performed in subjects with known brain metastases (every nine weeks for first year, then every 12 weeks) and those with worsening and/or new neurological symptoms].

Tumor assessment after the screening period should consist of clinical exam –with examination of the penis and/or inguinal region– and of anatomical imaging consisting of 1) CT scan of the chest, abdomen, and pelvis (MRI of the abdomen and pelvis with a non-contrast CT scan of the chest in patients for whom CT scans with contrast are contraindicated). In the event a positron emission tomography (PET)/CT scan is used for tumor assessments, CT portion of PET/CT is usually of lower quality, and should not be used instead of dedicated diagnostic CT. If the CT scan is of high quality, with oral and IV contrast, may be used with caution. Additional information from PET may bias CT assessment. 2) bone scan if a subject develops new or worsening symptoms or if the site believes they have attained a complete response (CR), and 3) any other imaging studies felt to be clinically indicated by the treating physician. All known sites of disease documented at screening should be re-assessed at each subsequent tumor evaluation.

After progression of disease by RECIST v.1.1, if the site Investigator determines the subject is clinically stable and will benefit from continued treatment, the subject will then be managed by irRECIST as described in ***Section 6.4.4*** of the protocol.

6.4.2 Response Assessment

CBR is defined as the number of patients with CR, partial response (PR) or stable disease (SD) (for at least 12 weeks) divided by the number of patients in the analysis set. Tumor response

will be defined as best response, based on local investigator's assessment according to RECIST criteria guidelines (version 1.1).

ORR is defined as the proportion of the subjects in the analysis set who have a CR or PR based on RECIST v.1.1:

- CR: Complete disappearance of all target lesions. Any pathological lymph nodes (target or non-target) must have reduction in short axis to < 10 mm.
- PR: At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.
- SD: Neither sufficient shrinkage to qualify for PR, nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.
- PD: At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum diameters while on study. The development of new, previously undetected lesions is also considered progression.

DoR is defined as the time from first documented CR or PR until disease progression or death from any cause, based on local investigator's assessment according to RECIST criteria v.1.1. In case of the patient first reaching PR and later CR, the duration of CR will be measured and reported separately, starting from the date when first documented, and ending when a progressive disease is diagnosed, or the patient dies.

Maximum tumor shrinkage is defined as the percentage of tumor shrinkage from baseline (obtained from the sum of the largest diameters of the target lesions), based on local investigator's assessment according to RECIST criteria v.1.1.

6.4.3 OS and PFS Definitions

OS is defined as the time from the date of first dose of study treatment until death by any cause or the last date the patient was known to be alive. Patients who are lost to follow-up and the patients who are alive at the date of data cut-off will be censored at the date the patient was last known alive.

PFS is defined as the time from the date of first dose of study treatment until the first documented PD based on RECIST v.1.1 or death due to any cause, whichever occurs first based on local investigator's assessment according to RECIST criteria v.1.1. Patients with no progression or death will be assessed until patient discontinues study treatment, so they will be censored at the date of their last evaluable imaging.

Finally, 6-months PFS rate is defined as the proportion of patients who are alive and progression-free at 6 months from the date of first dose of study treatment based on irRECIST criteria.

6.4.4 irRECIST

Immunotherapeutic agents such as INCMGA00012 (retifanlimab) may induce antitumor effects by potentiating endogenous cancer-specific immune responses. The response patterns observed with these compounds may be different to the typical time course of responses seen with classical cytotoxic agents and can manifest a clinical response after an initial increase in tumor burden or even the appearance of new lesions. Standard RECIST v.1.1 may, therefore, not provide a precise response assessment of immunotherapeutic agents such as INCMGA00012 (retifanlimab).

irRECIST is RECIST v.1.1 adapted to account for the unique tumor response seen with immunotherapeutic agents. In this way, in subjects who have initial evidence of radiological PD by RECIST v.1.1, it is at the discretion of the Investigator whether to continue a subject on study treatment until repeat imaging is obtained. Subjects may receive study treatment and tumor assessment should be repeated at least four weeks later in order to confirm PD by irRECIST. Any subject deemed clinically unstable should be discontinued from trial treatment at first radiologic evidence of PD and is not required to have repeat imaging for PD confirmation. Clinical stability is defined as the following:

- Absence of symptoms and signs indicating clinically significant PD, including worsening of laboratory values.
- No decline in ECOG performance status.
- Absence of rapid PD.
- Absence of progressive tumor at critical anatomical sites (e.g., cord compression) requiring urgent alternative medical intervention.

In determining whether or not the tumor burden has increased or decreased per irRECIST, the local site Investigator should consider all target and non-target lesions as well as any incremental new lesion(s). Scenarios where PD is confirmed at repeat imaging if any of the following occur by irRECIST:

- Tumor burden remains ≥ 20% and at least 5 mm absolute increase compared to nadir.
- Non-target disease resulting in initial PD is worse (qualitative assessment).
- New lesion resulting in initial PD is worse (qualitative assessment).
- Additional new lesion(s) since last evaluation.
- Additional new non-target progression since last evaluation.

If repeat imaging confirms PD due to any of the scenarios listed above, subjects will be discontinued from study therapy. If repeat imaging does not confirm PD by irRECIST and the

subject continues to be clinically stable, treatment may continue and follow the regular imaging schedule.

Note: If a subject with confirmed radiographic PD per irRECIST, but the subject is achieving a clinically meaningful benefit, and there is no further increase in the tumor burden at the confirmatory tumor imaging, an exception to continue treatment may be considered following consultation with the Sponsor. In this case, if treatment is continued, tumor imaging should continue to be performed following the intervals as outlined in ***Appendix 1****.*

Note: In subjects who discontinue study treatment without documented PD, every effort should be made to continue monitoring their disease status by tumor imaging following the intervals as outlined in ***Appendix 1*** *until the start of new anti–cancer treatment, PD, death, or the EoS, whichever occurs first.*

6.5 Safety and Tolerability Assessments

6.5.1 Laboratory Assessments

Laboratory tests will be performed in accordance to local standard treatment and clinical indications. These values will include:

- Hematological test [hemoglobin, hematocrit, red blood cell count, platelet count, WBC with differential count (ANC, lymphocytes, monocytes, eosinophils and basophiles)], coagulation, chemistry with renal function analysis (serum creatinine or measured/calculated creatinine clearance or GFR), liver function [AST, ALT, alkaline phosphatase (ALP), gamma-glutamyl transferase (GGT), total and direct bilirubin], glucose, sodium, potassium, calcium, chloride, magnesium, uric acid, total protein, albumin, and lactate dehydrogenase.
- Urinalysis (specific gravity, pH, glucose, protein, ketones, and blood).
- Thyroid function testing [thyroid-stimulating hormone (TSH), free T3, and free T4].
- HAV serology (positivity for HAV IgM antibody).
- HIV serology.
- HBV serology [HBsAg, anti–HBsAg].
- HCV serology (anti–HCV). In patients with a positive anti–HCV, HCV RNA detection and quantification by PCR will be additionally performed.
- Mantoux or Quantiferon tuberculin skin test (TST)

6.5.1.1 HIV Management Control

In participants who are known to be HIV-positive, additional HIV tests will be required every 8 weeks during 1st year of study treatment, every 3 months during the 2nd year and every 6 months during the follow-up period in order to monitor the following laboratory criteria:

a) CD4-positive count ≥ 300/μL;
b) Undetectable viral load.

Moreover, a final sample will be collected at the EoT visit or, if no separate EoT visit is performed, at the 28-day follow-up visit.

6.5.2 Pregnancy and Assessment of Fertility

Carcinogenicity studies have not been conducted and male participants should use barrier contraception (i.e., condom) or maintain sexual abstinence while receiving INCMGA00012 (retifanlimab) and up to 180 days following the end of the study treatment. Accidental exposure of pregnant partners through the insemination route is unlikely to result in fetal exposures of concern given the low C_{max} in semen that has been described with other IgG antibodies and the limited vaginal absorption that is likely to occur.

6.5.3 Physical Examination

A complete physical examination will include an examination of head, eyes, ears, nose, and throat, examination of the penis and/or inguinal region, as well as cardiovascular, dermatological, musculoskeletal, respiratory, digestive, genitourinary, and neurological systems. A limited physical exam will consist of a symptom-directed physical examination.

Changes to abnormalities identified during the baseline period should be recorded at all subsequent physical examinations. New or worsening abnormalities should be recorded as AEs, if applicable.

6.5.4 Vital Signs

These will include the measurement of height (only during screening), weight, respiratory rate, heart rate, blood pressure, and body temperature. Abnormal or significant changes in vital signs from baseline should be recorded as AEs, if appropriate.

6.5.5 ECOG PS

PS will be determined using the ECOG performance status scale (see ***Table 3***). Wherever possible, the patient's performance status should always be assessed by the same personnel throughout the study.

Table 3. ECOG PS Scale.

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

(http://www.ecog.org/general/perf_stat.html)

6.6 Translational Research

The molecular study involves the collection, processing, temporary storage, and shipment of samples from consenting patients enrolled in centers selected for participation in the study. The study plan includes collection and initial processing of tumor tissues and blood samples to a central laboratory that will be used to identify dynamic biomarkers that may be of prognostic value or predictive of response/resistance to INCMGA00012 (retifanlimab) treatment.

The exploratory analysis will be performed only if an adequate number of samples is available at the EoS. Since the identification of new markers that correlate with disease activity and the efficacy or safety of treatment is rapidly developing, the definitive list of analyses remains to be determined, but may include determination of markers such as but not limited to PD1, PD-L1, HIV, and HPV status.

Tumor-based biomarkers may include description of immune cells, gene expression profiling including tumor mutation burden, and/or measurement of protein levels for immune-related and tumor-related proteins.

Blood-based biomarkers may include serum cytokines, circulating immune cells, and circulating tumor cells.

6.6.1 Tumor Samples

Patients must agree to provide a tumor tissue sample from a metastatic site or primary tumor at the time of study entry, within 28 days prior to the first administration of study medication, with the exception of patients for whom tumor biopsies cannot be obtained (e.g., inaccessible tumor or subject safety concern) that may submit an archived primary/metastatic tumor specimen only upon agreement from the Sponsor.

If feasible, patients will also be given the option of providing a tumor tissue sample from metastasis or primary tumor obtained at disease progression.

Exploratory studies will be performed on tumor biopsies, or formalin-fixed and paraffin-embedded (FFPE) or frozen tumor samples (blocks), or unstained glass slides.

Details on tumor tissue samples preparation, processing, storage, and shipment will be provided in a separate study manual.

6.6.2 Blood Samples

Blood samples are required for all patients during the screening period, within 28 days prior to the first administration of study medication, after two cycles of study treatment, and upon progression or study termination.

Additional tests will be required for all participants who are known to be HIV-positive in order to confirm CD4-positive count and the undetectable viral load following timepoints shown in ***Section 6.5.1.1***.

6.7 Discontinuation of Patient, Study, or Site Participation

6.7.1 Patient Discontinuation

Patients have the right to withdraw from the study at any time for any reason. The Investigator also has the right to withdraw patients from the study in the event of intercurrent illness, AEs, and treatment failure after a prescribed procedure, protocol violation, administrative reasons, or for other reasons. An excessive rate of withdrawals can render the study uninterpretable; therefore, unnecessary withdrawal of patients should be avoided.

Should a patient decide to withdraw, all efforts should be made to complete and report the observations as thoroughly as possible. The Investigator should contact the patient or a responsible relative by telephone or through a personal visit to establish as completely as possible the reason for the withdrawal. A complete final evaluation at the time of the patient's withdrawal should be made with an explanation of why the patient is withdrawing from the study. If the reason

for removal of a patient from the study is an AE, the principal specific event will be recorded on the CRF.

In the case that the patient decides to prematurely discontinue study treatment, he should be asked if he can still be contacted for further information. The outcome of that discussion should be documented in both the medical records and in the CRF.

6.7.2 Study and Site Discontinuation

The Sponsor reserves the right to terminate this study at any time. Reasons for terminating the study may include, but are not limited to, the following:

- The incidence or seriousness of AEs in this or other studies indicates a potential health risk to patients.
- Patient enrollment is unsatisfactory.
- Data recording is inaccurate or incomplete.
- Excessively slow recruitment.
- Poor protocol adherence.
- Non-compliance with the International Conference on Harmonization (ICH) guideline for Good Clinical Practice (GCP).

7 SAFETY DEFINITIONS AND REPORTING REQUIREMENTS

Safety assessments will consist of monitoring and recording protocol-defined AEs, events of clinical interest (ECI), and SAEs; measurement of protocol-specified hematology, clinical chemistry, measurement of protocol-specified vital signs; and other protocol-specified tests that are deemed critical to the safety evaluation of the study drug(s).

The Sponsor or its designee is responsible for reporting relevant SAEs to competent authorities, other applicable regulatory authorities, and participating investigators, in accordance with ICH guidelines, and/or local regulatory requirements.

The Sponsor or its designee is responsible for reporting unexpected fatal or life-threatening events associated with the use of the study drug(s) to the regulatory agencies and competent authorities within seven calendar days after being notified of the event. The Sponsor or its designee will report other relevant SAEs associated with the use of the study medication to the appropriate competent authorities (according to local guidelines), investigators, by a written safety report within 15 calendar days of notification.

7.1 AEs Definitions

An AE is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and/or unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an IMP, regardless of whether it is considered related to the IMP or not.

An abnormal test finding should only be reported as an AE if meets any of the following criteria:

- Is associated with accompanying symptoms and a general diagnostic term, including the symptoms and the abnormal test finding, cannot be defined.
- Requires additional diagnostic testing or medical/surgical intervention, leads to a change in study drug(s) dosing or discontinuation from the study.
- Needs additional concomitant drug treatment.
- Is considered to be an AE by the investigator or by the Sponsor.

Diagnostic and therapeutic non-invasive and invasive procedures, such as surgery, should not be reported as AEs. However, the medical condition for which the procedure was performed should be reported if it meets the definition of an AE. For example, an acute appendicitis that begins during the AE reporting period should be reported as the AE and the resulting appendectomy should be recorded as treatment of the AE.

The causal relationship between an AE and the IMP will be defined as follows:

Unrelated: The temporal association between the AE and the administration of the IMP makes a causal relationship unlikely, or the subject/patient's clinical state or the study procedure/conditions provide a sufficient explanation for the AE.

Related: The temporal association between the AE and the administration of the IMP makes a causal relationship possible, and the subject/patient's clinical state or the study procedure/conditions do not provide a sufficient explanation for the AE.

Each AE must be assessed by the Investigator as to whether or not there is a reasonable possibility of causal relationship to the IMP.

The descriptions and grading scales found in the revised NCI–CTCAE v.5.0 criteria will be utilized for all toxicity reporting. A copy of the NCI–CTCAE v.5.0 criteria can be downloaded from the CTEP website:

(https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf).

Grade refers to the intensity (severity) of the AE. The CTCAE displays grades 1 through 5 with unique clinical descriptions of severity for each AE based on this general guideline:

- **CTCAE grade 1 Mild**: Asymptomatic or mild symptoms. It does not interfere with normal daily activities. Clinical or diagnostic observations only; intervention not indicated.
- **CTCAE grade 2 Moderate**: It causes some interference with daily activities; minimal, local or noninvasive intervention or treatment indicated.
- **CTCAE grade 3 Severe:** Medically significant but not immediately life-threatening. Normal daily activities are substantially impaired; hospitalization or prolongation of hospitalization indicated and/or intervention or treatment is required.
- **CTCAE grade 4 Life-threatening consequences**: Normal daily activities are substantially impaired; hospitalization and/or urgent intervention or treatment is indicated.
- **CTCAE grade 5 Fatal-death**: Death related to AE.
- Not applicable: Clinically significant and asymptomatic laboratory test abnormalities or abnormal assessments, for which no CTCAE grading guidance is applicable but which are considered as AEs.

  A mild, moderate, or severe AE may or may not be serious (see definition below). These terms are used to describe the intensity of a specific AE. However, a severe AE (such as severe headache) may be of relatively minor medical significance and is not necessarily serious. For example, nausea lasting several hours may be rated as severe, but may not be clinically serious. Fever of 39°C that is not considered severe may become serious if it prolongs hospital discharge by a day. Seriousness rather than severity serves as a guide for defining regulatory reporting obligations.

7.1.1 Infusion-related reactions

Infusion-related reactions may be associated with the administration of therapeutic antibodies and are known to occur with the PD-1 inhibitor class. As of the data cutoff date, infusion-related reactions occurred in 38 (6.6%) of the participants receiving retifanlimab monotherapy. The incidences of infusion-related reactions in participants receiving retifanlimab in Study INCMGA 0012-203 (30-minute infusions) and Studies INCMGA 0012-101, INCMGA 0012-104, INCMGA 0012-201, and INCMGA 0012-202 (60-minute infusions) were generally similar.

All infusion-related reactions were Grade 1 or 2 in severity with the exception of 2 Grade 3 infusion-related reactions Infusion-related reactions were observed in Study INCMGA 0012-101 regardless of whether prophylaxis was administered; therefore, routine prophylaxis is not recommended. Primary prophylaxis with antipyretics and histamine blockers should be strongly considered for participants who have had previous systemic reactions to protein product infusions or when recommended according to institutional policy. Secondary prophylaxis is recommended

for participants who have experienced infusion-related reactions to retifanlimab. Routine prophylaxis is not required. Monitor participants for signs and symptoms of infusion-related reactions. Interrupt or slow the rate of infusion or permanently discontinue retifanlimab based on severity of reaction. Participants who experience life-threatening infusion-related reactions should not be retreated with retifanlimab. Guidance for prophylaxis and management of infusion-related reactions is provided in all study protocols.

7.1.2 Expected Treatment Emergent Immune-Related Adverse Events (irAEs)

Immune-related adverse reactions, including severe cases, have occurred in participants receiving INCMGA00012 (retifanlimab). With the exception of endocrinopathies, the majority of immune-related adverse reactions occurring during treatment with retifanlimab were managed with interruptions of retifanlimab, administration of corticosteroids and/or supportive care. Immune-related adverse reactions may occur after the last dose of retifanlimab. Immune-related adverse reactions affecting more than one body system can occur simultaneously. irAEs in participants exposed to INCMGA00012 (retifanlimab) were generally consistent with approved PD-1 inhibitors in frequency and severity. Guidance for assessment, management, and reporting of these immune-related toxicities is provided in the study protocol.

Table 4. Treatment Emergent irAEs

Group Term, n (%)	Retifanlimab Monotherapy (N = 578)
Endocrine irAEs	
Hypothyroidism	47 (8.1)
Hyperthyroidism	27 (4.7)
Thyroiditis[a]	5 (0.9)
Adrenal insufficiency	3 (0.5)
Type 1 diabetes[b]	2 (0.3)
Hypophysitis[c]	2 (0.3)
Nonendocrine irAEs	
Skin reactions[d]	34 (5.9)
Pneumonitis[e]	10 (1.7)
Nephritis[f]	6 (1.0)
Colitis[g]	6 (1.0)
Hepatitis[h]	4 (0.7)
Myositis	3 (0.5)
Polyarthritis	3 (0.5)
Pancreatitis	2 (0.3)
Uveitis[i]	2 (0.3)
Myocarditis	1 (0.2)
Radiculopathy	1 (0.2)

irAE = immune-related adverse event; Q4W = every 4 weeks.
[a] Includes preferred terms of autoimmune thyroiditis, thyroid disorder, and thyroiditis.
[b] Includes preferred terms of diabetic ketoacidosis and Type 1 diabetes mellitus.
[c] Includes preferred terms of hypophysitis and hypopituitarism.
[d] Includes preferred terms of dermatitis, dermatitis bullous, palmar-plantar erythrodysaesthesia syndrome, pruritus, pruritus generalised, rash, rash erythematous, rash maculo-papular, rash pruritic, rash pustular, and toxic skin eruption.
[e] Includes preferred terms of interstitial lung disease and pneumonitis.
[f] Includes preferred terms of acute kidney injury and nephritis. Excludes the events of nephritis in the 4 participants for which there is insufficient evidence to support a diagnosis of immune-related nephritis.
[g] Includes preferred terms of colitis and immune-mediated enterocolitis.
[h] Includes preferred terms of autoimmune hepatitis and hepatitis, and 1 participant with concurrent Grade 3 elevations of AST and ALT (based on laboratory results) with immune-related hepatitis suspected by the investigator.
[i] Includes preferred terms of iritis and uveitis.

7.2 SAEs

Per definition, a SAE is defined as any AE that either:

- Results in death (i.e., the AE actually causes or leads to death).
- Is life-threatening (i.e., the AE, in the view of the investigator, places the subject/patient at immediate risk of death when it occurs).
- Requires inpatient hospitalization or prolongation of existing hospitalization.
- Results in persistent or significant disability/incapacity (disability is defined as a substantial disruption of a person ability to conduct normal life functions).

- Constitutes a congenital anomaly/birth defect (in a neonate/infant born to a mother exposed to the investigational product(s).

Definition of life-threatening: An AE is life-threatening if the subject/patient was at immediate risk of death from the event as it occurred, i.e., does not include an event that might have caused death if it had occurred in a more serious form. For instance, drug induced hepatitis that resolved without evidence of hepatic failure would not be considered life-threatening even though drug induced hepatitis can be fatal.

Definition of hospitalization: AEs requiring hospitalization should be considered serious. In general, hospitalization means that the subject/patient has been detained (usually involving an overnight stay) at the hospital or emergency ward for observation and/or treatment which would not have been appropriate at the study site. When in doubt as to whether hospitalization occurred or was necessary, the AE should be considered as serious.

Hospitalization for elective surgery or routine clinical procedures, which are not the result of an AE, do not need to be notified according to immediate reporting criteria. If anything untoward is reported during any procedure, this must be reported as an AE and either 'serious' or 'non-serious' attributed according to the usual criteria.

According to immediate reporting criteria, a hospitalization or prolongation of hospitalization in the absence of a precipitating clinical AE, do not need to be notified. Some examples include:

- Admission for treatment of a pre-existing condition not associated with the development of a new AE or with a worsening of the pre-existing condition (i.e., for work-up of persistent pretreatment lab abnormality).
- Social admission (i.e., subject/patient has no place to sleep).
- Administrative admission (i.e., for yearly physical examination).
- Protocol-specified admission during a study (i.e., for a procedure required by the study protocol).
- Optional admission not associated with a precipitating clinical AE (i.e., for elective cosmetic surgery).
- Hospitalization for observation without a medical AE.
- Pre-planned treatments or surgical procedures should be noted in the baseline documentation and/or for the individual subject/patient.
- Admission exclusively for the administration of blood products.

Definition of clinically/medically significant event: Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a SAE when, based upon appropriate medical judgment, they may jeopardize the subject/patient and may require medical

or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse. Clinically/medically significant events MUST be reported as SAEs.

In this clinical trial and as defined in this protocol, SAEs and hospitalizations unequivocally and solely related to established tumor progression of disease will NOT be treated as SAEs for reporting obligations.

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

For the time period beginning when the consent form is signed until treatment allocation first dose of study treatment, any ECI, or follow up to an ECI, that occurs to any subject must be reported within 24 hours to the Sponsor if it causes the subject to be excluded from the trial or is the result of a protocol-specified intervention.

For the time period beginning at treatment allocation first dose of study treatment through 90 days following cessation of treatment, or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier, any ECI, or follow up to an ECI, whether or not related to Incyte, must be reported within 24 hours to the Sponsor.

7.3 Events of clinical interest (ECI) for INCMGA00012 (retifanlimab)

The table 5 shows the expected SAE.

Table 5. SAEs

MedDRA System Organ Class Preferred Term	Overall SAR Frequency n (%) Frequency Category
Gastrointestinal disorders	
Colitis	4 (0.7) Uncommon
Respiratory, thoracic and mediastinal disorders	
Pneumonitis	3 (0.5) Uncommon

Note: Frequency is expressed as the number (n) and percentage (%) of the total number of participants (N) exposed to the study drug as monotherapy who have experienced the SAR.

Please refer to the most updated INCMGA00012 (retifanlimab) IB for further detailed information related to AEs.

Overdose of INCMGA00012 (retifanlimab) product. There are no human or animal data regarding overdose of INCMGA00012 (retifanlimab). Treatment of overdose should consist of general supportive measures".

All SAEs/ECIs that have not resolved by the EoS, or that have not resolved upon discontinuation of the subject/patient's participation in the study, must be followed until any of the following occurs:

- The event resolves.
- The event stabilizes.
- The event returns to baseline, if a baseline value/status is available.
- The event can be attributed to agents other than the investigational product or to factors unrelated to study conduct.
- It becomes unlikely that any additional information can be obtained (subject/patient or health care practitioner refusal to provide additional information, lost to follow-up after demonstration of due diligence with follow-up efforts).

7.4 AEs Reporting and Other Safety Related Issues Reporting

For serious and non-serious AEs, the reporting period to the Sponsor (or its designated representative) begins from the time that the patient provides ICF.

Reporting period for SAEs/ECIs that are NOT related with the study IMP INCMGA00012 (retifanlimab) and also all non-serious AEs is as follows:

- If patient discontinues treatment during the study, until 90 calendar days after the last administration of any of the study IMP.

All study patients will be carefully monitored for the occurrence of AEs (including SAEs and ECIs) during the above specified AE reporting period.

If the investigator becomes aware of a SAE/ECI at any time after the end of administration of study treatment and believes that it is POSSIBLY RELATED to INCMGA00012 (retifanlimab), the investigator should notify the serious adverse reaction to the Sponsor immediately irrespective of the time elapsed since last administration of the study IMP.

For all ≥ grade 3 AEs with causal relationship to the investigational product, a follow-up by the Investigator may be required until the event or its sequelae resolve or stabilize at the acceptable level to the Investigator, and the Sponsor concurs with that assessment.

Clearly related signs, symptoms, and abnormal diagnostic procedure results should be grouped together and reported as a single diagnosis or syndrome whenever possible. Any additional events that fall outside this definition should also be reported separately.

All AEs must be recorded in the CRF.

7.5 SAE Reporting and Timeframe

Reporting requirements will comply with all EU safety reporting requirements as detailed in current legislation and all applicable local regulations for safety reporting.

The investigator or investigator's team will report all protocol defined SAEs and ECIs to the Sponsor (MedSIR) no later than 24 hours of any site study team staff becoming aware of the event as follows:

- The full details of the SAE and/or ECI should be collected and fully documented using the SAE form and sent to the Sponsor (MedSIR).
- Follow-up information, copies of any relevant test results, event outcome and the opinion of the investigator as to the relationship between the IMP and the SAE and ECI, accompanied by other applicable documentation when it is requested, will be sent along with the SAE form, if available on the day the event is reported or as soon as possible if it is not.
- The original SAE reporting form and the confirmation from the Sponsor must be kept with the CRF documentation at the study site(s).

All SAE forms will be sent by the investigator or investigator's team to the Sponsor (MedSIR) according to the reporting instructions provided by MedSIR at the site initiation visit and filed in the Investigator's File.

SAEs and ECIs will be followed until resolved, a stable outcome is reached, subject/patient is lost to follow-up, or dies.

As sponsor, MedSIR will be responsible for ensuring that events are reported within the mandated timeframe to the European Medicines Agency (EMA), other competent authorities, Institutional Review Boards (IRBs)/ECs, and investigator(s), as necessary and in accordance with all applicable guidelines, approved directives and regulations. All safety reporting local regulatory requirements will be followed.

7.6 Expedited reporting to HAs, investigators, IRBs, and ECs

To determine reporting requirements for single SAE cases, MedSIR (as Sponsor) or its designee will assess the expectedness of these events using the following reference documents:

- INCMGA00012 (retifanlimab) IB.

MedSIR (as Sponsor) or its designee will compare the severity of each event and the cumulative event frequency reported for the study with the severity and frequency reported in the applicable reference document.

Reporting requirements will also be based on the investigator's assessment of causality and seriousness, with allowance for upgrading by the Sponsor as needed.

Within seven calendar days after being notified of the event, MedSIR (as Sponsor) or its designee will report unexpected fatal or life-threatening events associated with the use of the study drug to the regulatory agencies and competent authorities, to the investigators and Ethics Committees (ECs). MedSIR (as Sponsor) or its designee will report other unexpected SAEs associated with the use of the study medication to the appropriate competent authorities (according to local guidelines), investigators, and ECs by a written safety report within 15 calendar days of notification. All safety expedited reports will be reported in accordance with all regulatory reporting obligations (including timelines) and local regulatory requirements.

7.7 Other Safety-Related Reports

As Sponsor, MedSIR will assess constantly the benefit/risk rate of the trial that means a continuous evaluation of the safety profile of the drugs under investigation will be done using all available information. MedSIR will provide the regulatory agencies and competent authorities and the investigators with any relevant information that may affect the benefit/risk rate of the trial. An annual DSUR safety report for study INCMGA00012 (retifanlimab) will be prepared and distributed by MedSIR or its designee in accordance with all regulatory reporting obligations and local regulatory requirements.

In order to ensure the correct and necessary exchange of safety related information between MedSIR (as Sponsor) and Incyte a contract will be established and signed between MedSIR and these companies.

MedSIR or its designee will report any finding of noncompliance (as failure to follow any applicable regulation or institutional policies that govern human subjects' research) and/or serious noncompliance (as noncompliance that materially increases risks that result in substantial harm to subjects or others, or that materially compromises the rights or welfare of participants) according to any reporting obligation and local regulatory requirements.

7.8 Pregnancy Reporting

Irrespective of the treatment received by the subject/patient, any patient's partner pregnancy occurring during study treatment or during the 7 months following study drug discontinuation must be reported within 24 hours of investigator's knowledge of the event.

Pregnancies will be treated as SAEs and the investigator will complete a pregnancy form, and forward it to the sponsor according to the reporting instructions provided by MedSIR at the site initiation visit and filed in the Investigator's File.

The subject/patient will be asked to provide follow-up information on the outcome of the pregnancy, including premature termination should the case arise. Spontaneous miscarriage and congenital abnormalities will also be reported as SAEs.

The follow-up period will be deemed to have ended when the health status of the child has been determined at 12 months of the infant's life.

Additional follow up information on any INCMGA00012 (retifanlimab) exposed pregnancy and infant will be requested at specific time points (i.e., after having received the initial report, at the end of the second trimester, 2 weeks after the expected date of delivery, and at 3, 6, and 12 months of the infant's life).

Follow-up queries may be sent, asking for further information, if required for a comprehensive assessment of the case.

8 STASTICAL CONSIDERATIONS AND ANALYSIS PLAN

8.1 Sample Size

A total of 18 patients with unresectable locally advanced or metastatic PsqCC will be enrolled into this trial.

8.2 Justification of Sample Size

This is a multicenter, open-label, single arm, phase II trial evaluating the efficacy and safety of INCMGA00012 (retifanlimab) in unresectable locally advanced or metastatic PSqCC. The defined primary endpoint is ORR.

In the single arm phase II trial VinCap (57) patients with locally advanced PSqCC were treated with vinflunine. The trial evaluated CBR and ORR after 4 cycles. The 45.5% and 27.3% of patients achieved clinical benefit and objective response, respectively. These data suggest that excluding an ORR ≤5% while targeting the improvement of the ORR to ≥25% would be an adequate approach to assess a new antineoplastic strategy in this patient population.

The sample size calculation is based on an exact binomial test. The clinical trial is designed to demonstrate an ORR of at least 25% and to exclude a rate of less than 5% (p0=0.05, p1=0.25, α =0.05, β=0.80, A'hern's exact design). At least 3 responders (18.8%) among 16 evaluable patients will be adequate to justify the investigation of this strategy in further clinical trials. Considering a drop-out rate of 10%, a sample size of 18 patients will be needed to attain 80% power at nominal level of one-sided alpha of 0.05.

8.3 Analysis Sets

Full analysis and safety set.

The full analysis and safety set includes patients who receive at least one dose of study medication.

Per-protocol set

All patients that accomplish selection criteria, receive at least one drug exposure, and receive the protocol required study drug exposure and processing. Criteria for determining the "per protocol" (PP) group assignment would be established by the Steering Committee before the statistical analysis begins. This analysis will only occur if this set differs by ≥ 10% from the full analysis set.

Exploratory analysis set

All patients with biomarker evaluable samples with the assay and alternative platforms that accomplish selection criteria and receive at least one drug exposure.

Analysis set schedule

Primary, secondary and irRECIST endpoints will be analyzed on the full analysis set, and per-protocol populations. Full analysis set will be considered the primary population for the analysis. Biomarker and correlation between biomarkers and clinical outcomes will be analyzed on exploratory analysis set. Safety analysis will be performed on the safety set.

The estimands for the study based on ICH E9 (R1) addendum will be fully described in the statistical analysis plan.

8.4 Statistical Plan

8.4.1 Primary Efficacy Endpoint

The primary efficacy endpoint for the present study is the ORR. The ORR is defined as the number of patients with CR and PR divided by the number of patients in the analysis set. Tumor response will be defined as best response based on local investigator's assessment according to RECIST criteria v.1.1.

8.4.2 Secondary Efficacy Endpoints

The secondary efficacy variables are CBR, DoR, PFS, OS, and maximum tumor shrinkage. For an exhaustive definition of efficacy endpoints, please refer to the ***Section 6.4.2***.

8.4.3 Exploratory Endpoints

The exploratory endpoints are PFS, CBR, and ORR based on irRECIST (see ***Section 2.3.1***) and predictive biomarkers (such as but not limited to PD-1, PD-L1, HIV status).

The objective of the exploratory analyses of irRECIST is the characterization of INCMGA00012 (retifanlimab) clinical activity. We will also compare RECIST and irRECIST criteria for evaluation of the clinical response.

The objective of the statistical analyses of biomarkers is the identification of those markers or combinations of markers which show best association with positive clinical outcome of the study treatment. We will measure the clinical efficacy of that analysis in terms of ORR, CBR, PFS and irPFS.

8.4.4 Analysis of Baseline and Demographic Variables

The demographics and baseline characteristics including disease history and prior therapy are summarized using descriptive statistics.

8.4.5 Decision Rules and Adjustment of Alpha in The Study

The study would be defined as positive at final analysis, if the ORR in the INCMGA00012 (retifanlimab) arm is statistically significantly better ($p<0.05$) than expected under the null hypothesis (H0: ORR≤5%). Decisions will be based on exact binomial test.

For all secondary and exploratory tests, we will use two-sided p-values with alpha ≤ 0.05 level of significance. The p-values emerging from these analyses will not be interpreted in a confirmative sense; they will be considered of descriptive nature only.

8.4.6 Primary Efficacy Analysis

We will describe number and proportion of responders. We will estimate the ORR with the 95% Clopper-Pearson confidence intervals and the p-value with exact binomial test. Analysis will be performed on the full analysis and PP sets. ITT will be considered the primary set for the analysis.

8.4.7 Secondary Efficacy Outcomes

We will describe number and proportion of patients with clinical benefit and 6-month PFS. We will estimate the proportion with the 95% Pearson-Clopper confidence intervals. For time to event endpoints (PFS, OS, irPFS and DOR), we will use the Kaplan-Meier method. Number and proportion of events, median survival time and survival rates, with corresponding 95%CI, will be calculated in both arms. For continuous outcome (maximum tumor shrinkage) we will use statistics of central tendency (median with 95%CI) and dispersion [range and interquartile range]. We provide waterfall plots of maximum tumor shrinkage from baseline. The duration of response has also plotted with bar plots.

Analysis will be performed on the ITT, and PP sets. ITT will be considered the primary population for the analysis. For all tests, we will use two-sided p-values with alpha ≤ 0.05 level of significance.

8.4.8 Subgroup Efficacy Analysis

CBR, 6-month PFS, DoR, TTP, ORR, and OS according to RECIST v.1.1 together with ORR, CBR, and 6-month PFS according to irRECIST will be analyzed in patients' subgroups categorized based on baseline factors of potential prognostic value. The baseline factors will include but not limited to the following: (1) Prior treatments; (2) Number of previous regimens; (3) Type of previous regimens (e.g., platinum agents, radiotherapy); (4) Age; (5) Sites of metastases; (6) Race and geographic location (if applicable). We will utilize the Kaplan-Meier method and LogRank test. Multivariable Cox proportional hazards model for adjusting for multiple prognostic factors will be used to test the association between prognostic factors and the outcomes if sample size is adequate. Covariate estimates, *hr* and corresponding 95% Cis, applicable test statistics, and P-values will be presented. We will use the Breslow method for tie handling in survival

analysis. P-values and 95% CIs for *hr* will be based on Wald test. The assumption of proportional hazards will be assessed by plotting the hazards over time.

For binary outcomes we will use chi-squared test for binary outcomes followed by multivariate logistic regression for adjusting for multiple prognostic factors. We will examine the residuals to assess model assumptions.

For all tests, we will use two-sided P-values with alpha ≤ 0.05 level of significance and P-values ≤ 0.05 will indicate statistical significance. The P-values emerging from these analyses will not be interpreted in a confirmative sense but will be considered of descriptive nature only. Analysis will be performed on the ITT and PP sets. ITT will be considered the primary population for the analysis.

8.4.9 Exploratory Analysis

The exploratory analysis will be performed only if an adequate number of samples is available at the EoS. Markers (such as but not limited to PD1, PD-L1, HIV, and HPV status) will be evaluated on a univariate level regarding their potential for prediction of the clinical endpoints (ORR, CBR, PFS and irPFS).

Biomarker and response correlations with clinical covariates will be investigated. It will be checked whether covariates can improve the prediction and whether there is an interaction with the biomarkers. Further multivariate techniques (e.g. Multiple Logistic Regression, Cox regression and penalized regressions models) will be deliberated in order to study combinations of markers. Techniques to control false discovery rate and overfitting (cross-validation) may be considered. Analysis will he performed on exploratory analysis set.

8.5 Safety Outcomes

Patient safety and AEs will be assessed using the NCI–CTCAE v.5.0. Analysis of safety-related data will be considered at three levels:

- First, the extent of exposure (dose, duration, number of patients) will be examined to determine the degree to which safety can be assessed from the study.
- Second, we will describe and compare clinically relevant test, concomitant medications, and AEs reported in every study group. For AEs, we will report intensity, expectability, casualty, relation, body system, action taken, and outcome.
- Finally, SAEs, deaths, and study discontinuations will be described and examined.

8.6 Missing Data Management

Study variables could be missing for patients who withdrawn from the trial or for specific visits. We will report reasons for withdrawal. Patient with missing in response outcomes (ORR and CBR) will considered as no responders. Other outcomes will be managed with simple imputations methods. The effect that any missing data might have on results will be assessed via sensitivity analysis of study sets.

For PFS and DoR, patients without a date of disease progression or death will be analyzed as censored observations on the date of last tumor assessment. If no post-baseline tumor assessment is available, patients will be censored at the date of randomization + 1 day. Data for patients with an event who missed two or more scheduled assessments immediately prior to the event will be censored at the last tumor assessment prior to the missed visits.

For OS, patients who are not reported as having died will be analyzed as censored observations on the date they were last known to be alive. If no post-baseline data are available, OS will be censored at the date of randomization + 1 day.

8.7 Steering Committee Review

A Steering Committee will be established for this study. It will be composed of the investigators, the sponsor's medical scientist and the scientific global coordinator. Further details on the steering committee and its responsibilities will be provided in a separate document.

The Steering Committee will meet on demand to review, discuss, and evaluate all of the gathered efficacy and safety data. In case of any arising safety concern, these meetings can also be called at any time at request of a participating investigator. At these meetings, the Sponsor and the participating investigators must reach a consensus on study data. The Sponsor will prepare minutes from these meetings and circulate them to each investigator for comment prior to finalization.

Study site investigators and the Sponsor will review patient data at least every six months. Each study site investigator will monitor patient's data for serious toxicities on an ongoing basis.

9 ETHICAL CONSIDERATIONS

9.1 Regulatory and Ethics Compliance

The study will be performed and reported in accordance with the guidelines of the ICH, and the ethical principles laid down in the Declaration of Helsinki. The study will be also compliance with European Directive 2001/20/EC and any applicable local regulations.

9.2 IRBs/IECs

Conduct of the study must be approved by an appropriately constituted IRB/IEC. Approval is required for the study protocol, protocol amendments, ICFs, study subject information sheets, and advertising materials. The IRB/IEC must also be contacted in the event of any major protocol violation or any SAE.

It is the Investigator's responsibility to communicate with their local IRB/IEC to ensure accurate and timely information is provided at all phases during the study.

The Principal Investigator is responsible for providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC. Investigators are also responsible for promptly informing the IRB/EC/CA of any protocol amendments (approval is required before implementation of substantial amendments).

In addition to the requirements to report protocol-defined AEs to the Sponsor, investigators are required to promptly report to their respective IRB/EC/CA all unanticipated problems involving risk to human patients. Some IRBs/ECs/CA may want prompt notification of all SAEs, whereas others require notification only about events that are serious, assessed to be related to study treatment, and are unexpected. Investigators may receive written safety reports or other safety related communications from the Sponsor. Investigators are responsible for ensuring that such reports are reviewed and processed in accordance with regulatory requirements and with the policies and procedures established by their IRB/EC/CA and archived in the site's study file.

9.3 Informed Consent

For each study subject, written ICF will be obtained prior to any protocol related activities. As part of this procedure, the study site Investigator or designee must explain orally and in writing the nature, duration, and purpose of the study, and the action of the drug in such a manner that the study subject is aware of the potential risks, inconveniences, or adverse effects that may occur. The study subject should be informed that he is free to withdraw from the study at any time. The subject will receive all information that is required by local regulations and ICH guidelines.

The Consent Form must be signed and dated by the patient before his participation in the study. The case history or clinical records for each patient shall document the informed consent process and that written ICF was obtained prior to participation in the study.

A copy of each signed Consent Form must be provided to the patient.

All signed and dated Consent Forms must remain in each patient's study file and must be available for verification by study monitors at any time.

The ICF should be revised whenever there are changes to procedures outlined in the ICF or when new information becomes available that may affect the willingness of the patient to participate.

For any updated or revised Consent Forms, the case history for each patient shall document the informed consent process and that written ICF was obtained for the updated/revised Consent Form for continued participation in the study. The final revised IRB/EC-approved ICF must be provided to the Sponsor for regulatory purposes.

9.4 Data Protection

The Sponsor will ensure the confidentiality of patient's medical information in accordance with all applicable laws and regulations.

The Sponsor as Data Controller according to the EU Data Protection Directive (95/46/EC) and the General Data Protection Regulation (2016/679) (GDPR) on the protection of individuals with regard to the processing of personal data and on the free movement of such data confirms herewith compliance to Directive 95/46/EC and GDPR in all stages of Data Management.

Data generated by this study must be available for inspection upon request by representatives of national and local health authorities, the Sponsor monitors, representatives, and collaborators, and the IRB/EC for each study site, as appropriate.

10 SOURCE DOCUMENTATION, STUDY MONITORING, AND QUALITY ASSURANCE

10.1 Source Data Documentation

Source data refers to all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies).

Source documents are original documents, data, and records (i.e., hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial).

Sponsor's Quality Assurance group may assist in assessing whether electronic records generated from computerized medical record systems used at investigational sites can serve as source documents for the purposes of this protocol.

If a site's computerized medical record system is not adequately validated for the purposes of clinical research (as opposed to general clinical practice), applicable hardcopy source documents must be maintained to ensure that critical protocol data entered into the eCRFs can be verified.

At a minimum, source documentation must be available to substantiate subject identification, eligibility, and participation; proper informed consent procedures; dates of visits; adherence to protocol procedures; adequate reporting and follow-up of AEs; administration of concomitant medication; study receipt/dispensing/return records; study administration information; and date of completion and reason.

Data recorded on the CRF will be verified by checking the CRF entries against source documents (i.e., all original records, laboratory reports, medical records) in order to ensure data completeness and accuracy as required by study protocol. The Investigator and/or site staff must make CRFs and source documents of subjects enrolled in this study available for inspection by MedSIR or its representative at the time of each monitoring visit.

The source documents must also be available for inspection, verification, and copying, as required by regulations, officials of the regulatory health authorities (i.e., FDA, EMEA, and others), and/or ECs/IRBs. The Investigator and study site staff must comply with applicable privacy, data protection, and medical confidentiality laws for use and disclosure of information related to the study and enrolled subjects.

The patient must also allow access to the patients' medical records. Each patient should be informed of this prior to the start of the study.

10.2 Study Monitoring and Source Data Verification

Study progress will be monitored by MedSIR or its representative (i.e., a Clinical Research Organization [CRO]) as frequently as necessary to ensure:

- That the rights and well-being of human subjects are protected;
- The reported trial data are accurate, complete, and verifiable from the source documents; and
- The conduct of the trial is in compliance with the current approved protocol/amendment(s), GCP, and applicable regulatory requirements.

Contact details for the team involved in study monitoring will be identified in a handout located in the Investigator Site File.

Data recorded on the CRF will be verified by checking the CRF entries against source documents (i.e., all original records, laboratory reports, medical records, subject diaries) in order

to ensure data completeness and accuracy as required by study protocol. The Investigator and/or site staff must make CRFs and source documents of subjects enrolled in this study available for inspection by the Sponsor or its representative at the time of each monitoring visit.

10.3 Retention of Records

Investigators must retain all study records required by the applicable regulations in a secure and safe facility. The Investigator must consult a Sponsor representative before disposal of any study records and must notify the Sponsor of any change in the location, disposition, or custody of the study files.

Essential documents must be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. “Essential documents” are defined as documents that individually and collectively permit evaluation of the conduct of a trial and the quality of the data produced. These documents should be retained for a longer period, however, if required by the applicable e regulatory requirements or by an agreement with the Sponsor. The CHMP requires retention for the maximum period of time permitted by the institution, but not less than 15 years (ICH E6[R2], 4.9.5). It is the responsibility of the Sponsor to inform the Investigator/institution as to when these documents no longer need to be retained (ICH E6[R2], 5.5.12).

The study site Investigator must not dispose of any records relevant to this study without either (1) written permission from the Sponsor or (2) providing an opportunity for the Sponsor to collect such records. The study site Investigator shall take responsibility for maintaining adequate and accurate electronic or hard copy source documents of all observations and data generated during this study. Such documentation is subject to inspection by the Sponsor and the FDA and/or EMA (or respective individual EU country regulatory authorities).

These principles of record retention will also be applied to the storage of laboratory samples, provided that the integrity of the stored sample permits testing.

10.4 Data Quality Assurance

During and/or after completion of the study, quality assurance auditor (s) named by the MedSIR or the regulatory authorities may wish to perform on-site audits. The Investigators will be expected to cooperate with any audit and provide assistance and documentation (including source data) as requested.

The Sponsor’s representatives are responsible for contacting and visiting the Investigator for the purpose of inspecting the facilities and, upon request, inspecting the various records of

the clinical study (i.e., CRFs and other pertinent data) provided that patient confidentiality is respected.

The Investigator agrees to cooperate with the monitor to ensure that any problems detected in the course of these monitoring visits, including delays in completing CRFs, are resolved.

In accordance with ICH E6[R2] GCP and the Sponsor's audit plans, this study may be selected for audit by representatives from the Sponsor's (or designee's) Quality Assurance Department. Inspection of site facilities (i.e., pharmacy, drug storage areas, laboratories) and review of study-related records will occur to evaluate the study conduct and compliance with the protocol, ICH GCP (ICH E6 [R2]), and applicable country regulatory requirements.

11 DATA MANAGEMENT

11.1 Data Entry and Management

In this study, all data will be entered onto CRFs in a timely fashion by the Investigator and/or the Investigator's dedicated site staff.

The Investigator must review data recorded in the CRF to verify their accuracy.

Reconciliation of the data will be performed by the designated CRO. At the conclusion of the study, the occurrence of any protocol violations will be identified and recorded as part of the clinical database. After these actions have been completed and the database has been declared to be complete and accurate, it will be locked and will become available for statistical data analysis.

11.2 Data Clarification

As part of the conduct of the trial, MedSIR may have questions about the data entered by the site, referred to as queries. The monitors and the Sponsor or designees are the only parties that can generate a query.

11.3 Data Coding Procedures

Coding of AEs, medical history, and prior and concomitant medications will be performed using standard dictionaries as described in the Data Management Plan.

12 STUDY MANAGEMENT

12.1 Discontinuation of the Study

MedSIR reserves the right to discontinue the study for safety or administrative reasons at any time. Should the study be terminated and/or the site closed for whatever reason, all investigational drugs pertaining to the study must be returned to MedSIR. Any actions required to assess or maintain study subject safety will continue as required, in spite of termination of the study.

12.2 Changes to the Protocol

Any change or addition to this protocol requires a written protocol amendment or administrative letter that must be approved by MedSIR, the Scientific Global Coordinator, the study site Investigator, and the IRB/IE/CA before implementation. This requirement for approval should in no way prevent any immediate action from being taken by the study site Investigator or MedSIR in the interests of preserving the safety of all subjects included in the trial. If an immediate change to the protocol is felt to be necessary by the study site Investigator and is implemented for safety reasons, MedSIR should be notified as soon as possible (within 24 hours if possible) and the IRB/IEC/CA should be informed as necessary.

12.3 Publication Policy Protection of Trade Secrets

All information generated in this study must be considered highly confidential and must not be disclosed to any persons not directly concerned with the study without prior written permission from the Scientific Global Coordinator and MedSIR. However, authorized regulatory officials, the Scientific Global Coordinator or the study site Investigator, and MedSIR personnel (or their representatives) will be allowed full access to inspect and copy the records. All clinical investigational drug, patient bodily fluids, and/or other materials collected shall be used solely in accordance with this protocol, unless otherwise agreed to in writing by Scientific Global Coordinator or the study site Investigator and MedSIR.

The Sponsor will ensure that as far as possible results of this study will be published as scientific/clinical papers in high-quality peer-reviewed journals. Preparation of such manuscripts will be made with full collaboration of principal Investigators and in accordance with the current guidelines of Good Publication Practice.

The Sponsor must be notified of any intent to publish data collected from the study and prior approval from Sponsor must be obtained prior to publication.

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Appendix 1. Schedule of Study Assessments and Procedures.

Assessment Window (Days)	Screening	All cycles	End of Treatment visit	Progression of disease	End of Study (12 months after the first study dose of the last patient included)
	D –28 to –1	1(± 3 days)	28 days (± 3 days) after last dose		
Informed consent form[1]	X				
Review of eligibility criteria	X				
Demographic data and medical history[2]	X				
Physical examination	X	X	X		X
ECOG performance status	X	X	X		X
Weight, Height, and Vital signs[3]	X	X	X		X
Concomitant medications reporting[4]	X	X	X		
AE reporting[5]	X	X	X		
12-lead electrocardiogram	X	Performed as clinically indicated			
Assessment of symptoms	X	X	X		X
Tumor assessment[6]	X	See footnote ([7])			X
Hematology/Chemistry[8]	X	X ([9])	X		X
TSH, free T3, free T4	X	X ([9])			
Coagulation panel (aPTT, INR or PTT)	X				
Viral serology[10] and Mantoux or Quantiferon tuberculin skin test (TST) [11]	X				
Urinalysis[12]	X	Every 2 cycles[12]			
Tumor samples for exploratory research[13]	X			X	
Blood samples for exploratory research[14]	X	At C3D1	X		
INCMGA00012 (retifanlimab) infusion		X			
Survival and anti–cancer therapy follow-up				X	X

Abbreviations: AE: Adverse event; ALP: Alkaline phosphatase; ALT: Alanine aminotransferase; ANC: Absolute neutrophil count; aPTT: activated partial thromboplastin time; AST: Aspartate aminotransferase; CT: Computed tomography; DNA: Deoxyribonucleic acid; ECOG PS: Eastern Cooperative Oncology Group Performance Status; EoT: End of Treatment; GGT: Gamma-glutamyl transferase; HAV: Hepatitis A virus; HBV: Hepatitis B virus; HBcAb: Hepatitis B core antibody; HBsAg: Hepatitis B surface antigen; HCV: Hepatitis C virus; HIV: Human immunodeficiency virus; INR: International normalized ratio; MRI: Magnetic Resonance Imaging; NCI–CTCAE: National Cancer Institute–Common Terminology Criteria for Adverse Events; PTT: Partial thromboplastin time; RNA: Ribonucleic acid; TSH: Thyroid-stimulating hormone; WBC: White blood cells.

1. **Informed Consent Form:** Signed written Informed Consent Form obtained prior to any trial-specific procedure.
2. **Demographic data and medical history:** Demographic data include age and self-reported race/ethnicity. Medical history comprises clinically significant diseases, surgical interventions, history of cancer (including prior antineoplastic treatments and procedures), history of smoking, alcoholism, drug addiction, as well as any medications (e.g., prescribed drugs, over-the-counter drugs, medicinal plants, homeopathic remedies, or food supplements) used by the patient in the 28 days prior to screening visit.
3. **Weight, Height, and Vital signs**: Weight, height (only at screening), respiratory rate, blood pressure measurements (systolic and diastolic), pulse rate, and body temperature (oral, axillary, or tympanic temperature).
4. **Concomitant medication reporting:** Relevant concomitant medication will be recorded at screening and on an ongoing basis.
5. **AE reporting:** All AEs occurring during the trial and until 90 days after treatment discontinuation visit (EoT visit) have to be recorded with grading according to the NCI–CTCAE v.5.0 criteria.
6. **Tumor assessment**: All measurable and evaluable lesions should be assessed and documented at the screening visit. Evaluation consists of clinical exam with evaluation of the penis and/or inguinal region and anatomical imaging performed during the screening period should consist of:

   a) CT of the chest, abdomen, and pelvis or MRI of the abdomen and pelvis with a non-contrast CT scan of the chest in patients for whom CT scans with contrast are contraindicated; In the event a positron emission tomography (PET)/CT scan is used for tumor assessments, CT portion of PET/CT is usually of lower quality, and should not be used instead of dedicated diagnostic CT. If the CT scan is of high quality, with oral and IV contrast, may be used with caution. Additional information from PET may bias CT assessment.

   b) Bone scan if a subject has a known history of bone metastases or has new bone pain during screening;

   c) Any other imaging studies as clinically indicated by the treating physician.

   Tumor assessments will be performed at baseline, every 8 weeks (± 7 days) for the first 6 months following first dose of study treatment, and every 12 weeks (± 7 days) thereafter, with additional scans as clinically indicated. All known sites of disease documented at screening should be re-assessed at each subsequent tumor evaluation. The same radiographic procedures and technique must be used throughout the study for each patient (bone scan will be performed only if a subject develops new or worsening symptoms or if the site believes they have attained a complete response).
7. In subjects who discontinue study treatment without documented disease progression, every effort should be made to continue monitoring their disease status by tumor imaging following the intervals as outlined in footnote 3 until the start of new anti–cancer treatment, disease progression, death, or the end of the study, whichever occurs first.

8. **Hematology/Chemistry**: Blood test will be performed as per local standard of care and clinical indication before treatment administration. These values should be included: hemoglobin, hematocrit, red blood cell count, platelet count, and WBC count with differential count (ANC, lymphocytes, monocytes, eosinophils, and basophiles), coagulation, chemistry with renal function analysis (serum creatinine or measured/calculated creatinine clearance or GFR), liver function (AST, ALT, ALP, GGT, total and direct bilirubin), glucose, sodium, potassium, calcium, chloride, magnesium, uric acid, total protein, albumin, and lactate dehydrogenase.
9. Cycle 1 Day 1 panel assessments are not required if the panel was performed at screening within 72 hours prior to start of study treatment.
10. **Viral serology**: HAV (IgM antibody), HBsAg, total HBcAb, HCV antibody; additional tests for HBV DNA or HCV RNA will be required to confirm eligibility; HIV.
11. **Mantoux or Quantiferon tuberculin skin test (TST):** in case of positivity of the test results, the pulmonologists must rule out the presence of latent TBC. All patients with latent TBC will be excluded from the study.
12. **Urinalysis**: Urinalysis include specific gravity, pH, glucose, protein, ketones, and blood. Every 2 cycles: Cycle 1 day 1, Cycle 3 day 1, cycle 5 day 1, cycle 7 day 1, etc., before study treatment administration.
13. **Tumor samples for exploratory research:** A tumor tissue sample from a metastatic site or the primary tumor must be collected at the time of study entry, with the exception of patients for whom tumor biopsies cannot be obtained (e.g., inaccessible tumor or subject safety concern) that may submit an archived primary or metastatic tumor specimen only upon agreement from the Sponsor. If feasible, patients will also be given the option of providing a tumor tissue sample from metastasis or primary tumor obtained at disease progression or study termination.
14. **Blood samples for exploratory research:** Blood samples are required for all patients at the time of inclusion, after two cycles of study treatment, and upon progression or study termination.

    Note: Additional tests will be required for all participants who are known to be HIV-positive in order to confirm CD4-positive count and the undetectable viral load, every 8 weeks during 1st year of study treatment, every 3 months during the 2nd year and every 6 months during the follow-up period. A final sample will be collected at the EoT visit or, if no separate EoT visit is performed, at the 28-day follow-up visit.