CONFIDENTIAL INFORMATION

Statistical Analysis Plan (SAP)

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Title	A Multicenter, Open-Label, Single-ARm, PHase II Clinical Trial to Evaluate the Efficacy and Safety of INCMGA00012 in Advanced Penile SquamoUS Cell Carcinoma. **- ORPHEUS -** Phase II Study of the Efficacy of INCMGA00012 in Penile Squamous Cell Carcinoma
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STATISTICAL ANALYSIS PLAN (SAP)

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Signature Page

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Date: 25/05/2021

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The undersigned hereby declare that they have examined the Statistical Analysis Plan document and agree to its form and content.

Represented by:

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1.0	May 21, 2021	New

LIST OF ABBREVIATIONS

Abbreviation	Definition
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
BOR	BEST OVERALL RESPONSE
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
FAS	FULL ANALYSIS SET
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
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

Abbreviation	Definition
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
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
TTR	TIME TO RESPONSE
TTP	TIME TO PROGRESSION
ULN	UPPER LIMIT OF NORMAL
UPN	UNIQUE PATIENT NUMBER
WBC	WHITE BLOOD CELL

TABLE OF CONTENTS

1 INTRODUCTION

1.1 General

The purpose of this statistical analysis plan (SAP) is to provide a protocol specific description of the statistical analysis that will be performed to produce an integrated clinical/statistical report.

This SAP is based upon the following study documents:

- Protocol version: Version 1.1, 08-Nov-2019.
- eCRF last release version updated: 09-Feb-2021.

1.2 Type of Study

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

1.3 Study Population

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

1.4 Study Design

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

INCMGA00012 should be administered intravenously, at flat dose of 500 mg over one hour (± 15 minutes) or 30 minutes (-5/+ 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.

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

Tumor assessments per RECIST v.1.1 and irRECIST will be performed approximately every 8 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.

The primary endpoint is ORR.

For estimation of ORR, CBR, DoR, PFS, and OS, 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.

1.5 Study Schedule

Assessment Window (Days)	Screening	All cycles	End Of Treatment visit	Progression of disease	End of Study
	D –28 to –1	1(± 3 days)	28 days (± 3 days) after last dose		12 months after last study 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 tuberculin skin test (TST)[11]	X				
Urinalysis[12]	X	Every two cycles[12]			
Tumor samples for exploratory research[13]	X			X	
Blood samples for exploratory research[14]	X	At C3D1	X		
INCMGA00012 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. Concomitant medication reporting: Relevant concomitant medication will be recorded at screening and on an ongoing basis.
4. 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.
5. 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).
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; 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 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.

1.6 Sample Size

A total of 18 patients will be enrolled and the defined primary endpoint is ORR.

Justification of Sample Size:

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.

2 STUDY OBJECTIVES

2.1 Primary objective

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

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 response (TTR), OS, and maximum tumor shrinkage, of INCMGA00012 in these patients.
- To evaluate the safety and tolerability of INCMGA00012 in these patients.

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 on HIV control in participants who are known to be HIV-positive.

3 DEFINITION OF ENDPOINTS

3.1 Primary Endpoint

- The primary efficacy endpoint for the present study is the ORR.

3.2 Secondary Endpoints

- The secondary efficacy variables are CBR, DoR, TTR, PFS, OS and maximum tumor shrinkage by investigator RECIST response.

3.3 Safety Endpoints

- 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.

3.4 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.

4 ANALYSIS SETS

The following sets will be analyzed:

- **Screening:** Patients who were present at the screening visit.
- **Safety and FAS (Full Analysis Set) Set:** patients who receive at least one dose of study medication.

  Efficacy and Safety endpoints will be analyzed on the Safety/FAS set.

  FAS set will be considered the primary population for the analysis.
- **Per-protocol (PP) 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 FAS set.

  The primary and secondary efficacy analyses will be performed on the FAS and PP sets.
- **Exploratory Set:** All patients with biomarker evaluable samples with the assay and alternative platforms that accomplish selection criteria and receive at least one drug exposure.

  Exploratory analysis will be performed on exploratory set. A separate analysis report for such assessments will be written.

5 STATISTICAL METHODS

5.1 General Methodology

The statistical analysis will be conducted following the principles as specified in International Conference on Harmonization (ICH) Topic E9 (CPMP/ICH/363/96). The significance level will be α=0.05 for all tests. As an exploratory study, multiple testing without adjustment of the significance level is considered acceptable.

Definition of baseline: For each safety or efficacy parameter, the last valid assessment made before first study drug administration will be used as the baseline for all analyses of that safety or efficacy parameter unless otherwise specified.

Continuous data will be summarized in terms of the number of observations, mean, standard deviation (SD), median, minimum, maximum, and first and third quartiles, unless otherwise stated. Where data are collected over time, both the observed data and change from baseline will be summarized at each time point.

The minimum and maximum will be reported to the same number of decimal places as the raw data recorded in the database. The mean, median, and first and third quartiles will be reported to one more decimal place than the raw data recorded in the database. The SD will be reported to two more decimal places than the raw data recorded in the database. In general, the maximum number of decimal places reported shall be four for any summary statistic.

Categorical data will be summarized in terms of the number of subjects providing data at the relevant time point (n), frequency counts and percentages. Changes from baseline in categorical data will be summarized using shift tables where appropriate.

Percentages will be presented to one decimal place. A percentage of 100% will be reported as 100%. Percentages will not be presented for zero counts. Unless otherwise stated, percentages will be calculated using n as the denominator, for frequency tables not assessed by time point the set will be used as denominator. If sample sizes are small, the data displays will show the percentages, but any textual report (e.g., clinical study report) will describe frequencies only.

P-values greater than or equal to 0.001, in general, will be presented to three decimal places. However, if a P-value is only presented to four decimal places (by SAS) it will not be rounded again but will be presented to four decimal places. P-values less than 0.0001 will be presented as "<0.0001".

Confidence intervals will be presented to one more decimal place than the raw data. A two-sided significance level of 5% will be used for confidence intervals.

For binary endpoints, the 95% confidence intervals (CIs) will be constructed based on an exact binary distribution.

The Kaplan-Meier method will be used to estimate the time to event function, the median of time to event and the 95% confidence interval of the same will be calculated. These confidence intervals will be calculated based on the Greenwood method. Number and proportion of events, median survival time and survival rates, with corresponding 95%Cl will be calculated.

All scores and change from baseline will be summarized in terms of the number of observations, mean, standard deviation, 95%CI of mean, median, range and interquartile range. We will examine the residuals to assess model assumptions.

All report outputs will be produced using SAS® version 9.4 version in a secure and validated environment. All report outputs will be provided to the Sponsor in a single Microsoft Word document.

5.2 Subject Disposition

Descriptive statistics will be provided for the following:

- Overall number of subjects in the screening set, the number of patients eligible to participate in the study, and number of screen failures.
- Number and percent of subjects in each of the analysis sets.
- Number and percent of subjects excluded from each of the analysis sets along with reason for exclusion.
- Listing of subjects excluded from each of the analysis sets along with reason for exclusion.
- Listing of protocol deviations.
- Study termination:
    - Number and percent of subjects who completed the study.
    - Frequency of premature termination reasons.
    - Listing of all dropouts along with reason for termination, treatment group and time of termination.
- Follow-up time (months), defined as the time from start dose until the last available follow-up date.
- Follow-up Dates:
    - Database cut-off date.
    - Start date of treatment dose of the first patient.
    - Start date of treatment dose of the last patient.
    - End date of treatment dose of the last patient.
    - End date of follow-up of the last patient.

No statistical tests are planned for these data.

5.3 Baseline Characteristics

Baseline characteristics will be provided for the FAS and PP set.

Descriptive statistics, including number of subjects, mean, standard deviation (SD), median and range for continuous variables and frequency and percent for categorical variables will be provided.

Baseline Characteristics:

- Demographics
- Vital Signs
- Toxic background
- Oncological history
- General Medical History
- Prior concomitant medication
- History of Penile Cancer
- Previous surgeries for penile cancer
- Previous early/advanced disease treatment for penile cancer
- HR status
- Penile cancer stage
- Viral Serology and TST
- Urinalysis
- Physical examination
- ECOG
- 12-Lead ECG

No statistical tests are planned for these data.

A by-subject listing of all demographic and other baseline characteristics will be provided.

5.4 Efficacy Analysis

Efficacy results will be reported for the FAS and PP set.

All efficacy analysis will be exploratory.

5.4.1 Response Efficacy Definitions

5.4.1.1 RECIST V.1.1

Overall response according RECIST v1.1 will be obtained from target lesion response, non-target lesion response and new lesions, as follows:

Target Lesions	Non-target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not all evaluated	No	PR
PR	Non-CR/Non-PD or not all evaluated	No	PR
SD	Non-CR/Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

The following results will be reported in all patients and in patients with measurable disease.

- The unconfirmed Best Overall Response, defined as the best overall response recorded from the start of the study treatment until 35 days after last dose administration date and confirmation of response is not required.
    - When CR or PR is the best response across all time points, then best overall response will be CR or PR respectively.
    - When SD is the best response for ≥ 12 weeks the best overall response will be SD ≥ 12 w.
    - When SD is the best response for < 12 weeks the best overall response will be SD < 12 w.
    - When non-target disease only and Non-CR/Non-PD is the best response for ≥ 12 weeks the best overall response will be SD ≥ 12 w.
    - When non-target disease only and Non-CR/Non-PD is the best response for < 12 weeks the best overall response will be SD < 12 w.
    - When PD is the best response across all time points, best overall response will be PD.
    - When there is no evaluable tumor assessments best overall response will be NE.
- The confirmed Best Overall Response, defined as the best overall response recorded from the start of the study treatment until 35 days after last dose administration date and confirmation of response is required.
    - When CR or PR is the best response for ≥ 4 weeks then best overall response will be CR or PR respectively.
    - When SD is the best response for ≥ 12 weeks the best overall response will be SD ≥ 12 w.
    - When SD is the best response for < 12 weeks the best overall response will be SD < 12 w.
    - When non-target disease only and Non-CR/Non-PD is the best response for ≥ 12 weeks the best overall response will be SD ≥ 12 w.
    - When non-target disease only and Non-CR/Non-PD is the best response for < 12 weeks the best overall response will be SD < 12 w.
    - When PD is the best response across all time points, best overall response will be PD.
    - When there is no evaluable tumor assessments best overall response will be NE.
- Unconfirmed Objective Response Rate (ORR) is defined as the proportion of patients with best overall response of unconfirmed CR or unconfirmed PR.
- Unconfirmed Clinical Benefit Rate (CBR) is defined as the proportion of patients with best overall response of unconfirmed CR or unconfirmed PR or SD ≥ 12 w.
- Confirmed Objective Response Rate (ORR) is defined as the proportion of patients with best overall response of confirmed CR or confirmed PR.
- Confirmed Clinical Benefit Rate (CBR) is defined as the proportion of patients with best overall response of confirmed CR or confirmed PR or SD ≥ 12 w.
- PFS is defined as the time from start dose until death by any cause or objective tumor progression according to RECIST v.1.1 or clinical disease progression. Patients with no progression or death will be censored at the date of their last evaluable imaging previous 35 days after last dose administration date. Censoring rules are specified below:

Situation	**Date of progression or censoring**	**Outcome**
Progression documented between scheduled visits	Earliest of: • Date of assessment by investigator (if progression is based on clinical criteria); or • Date of assessment showing new lesion (if progression is based on new lesion);	Progressed

Situation	Date of progression or censoring	Outcome
	or • Date of last radiological assessment of measured lesions (if progression is based on increase in sum of measured lesions).	
Death before first progression disease (PD) assessment	Date of death.	Progressed
Death between adequate assessment visits	Date of death.	Progressed
No progression	Date of last radiological assessment of measured lesions.	Censored
Treatment discontinuation for undocumented progression	Date of last radiological assessment of measured lesions.	Censored
Treatment discontinuation for toxicity or other reason	Date of last radiological assessment of measured lesions.	Censored

- 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 RECIST criteria.
- The Overall Survival (OS) is defined as the time from start dose until death from any cause. Patients with no death will be censored on the last available follow-up date.
- The duration of response (DoR) is defined as the time from start dose of first tumor response (either CR or PR) to disease progression or death due to any cause. The DoR will be calculated for the patients with unconfirmed CR or PR.
- The Time to Progression (TTP) is defined as the time from start dose to objective tumor progression or clinical disease progression (TTP does not include deaths). Patients with no progression will be censored at the date of their last evaluable imaging previous 35 days after last dose administration date.
- The Time to Response (TTR) is defined as the time from start dose to unconfirmed ORR date. Patients without ORR will be censored at the date of their last evaluable imaging previous 35 days after last dose administration date.
- Maximum Tumor Shrinkage (best percentage of change from baseline in the size of target tumor lesions) is defined as the biggest percentage of tumor shrinkage from baseline (obtained from the sum of the largest diameters of the target lesions).

5.4.1.2 irRECIST

The following results will be reported in all patients and in patients with measurable disease:

- The response assessment of the tumor is defined as best response according to:
    - irCR: complete disappearance of all measurable and non-measurable lesions. Lymph nodes must decrease to < 10 mm in short axis. Confirmation of response is not mandatory.
    - irPR: decrease of ≥ 30% in Total Measured Tumor Burden (TMTB) relative to baseline, non-target lesions are irNN, and no unequivocal progression of new non-measurable lesions.
    - irSD: failure to meet criteria for irCR or irPR in the absence of irPD.
    - irNN: no target disease was identified at baseline and at follow-up the patient fails to meet criteria for irCR or irPD.
    - irPD: minimum 20% increase and minimum 5 mm absolute increase in TMTB compared to nadir, or irPD for non-target or new non-measurable lesions. Confirmation of progression is recommended minimum 4 weeks after the first irPD assessment.
    - irNE, used in exceptional cases where insufficient data exists.

- irORR is defined as the proportion of participants with irCR or irPR. Participants who do not have on-study radiographic tumor re-evaluation, who received anti-tumor treatment other than the study medication prior to reaching an irCR or irPR, or who died, progressed, or dropped out for any reason prior to reaching an irCR or irPR will be counted as non-responders in the assessment of irORR.
- irCBR is defined as the proportion of participants with irCR or irPR or irSD. Participants who do not have on-study radiographic tumor re-evaluation, who received anti-tumor treatment other than the study medication prior to reaching an irCR or irPR or irSD, or who died, progressed, or dropped out for any reason prior to reaching an irCR or irPR or irSD will be counted as non-responders in the assessment of irCBR.
- irPFS: is defined as the period from the date of treatment initiation to the date of the first documentation of objective progression of disease (irPD) or death due to any cause in absence of documented irPD. Confirmation of progression is recommended minimum 4 weeks after the first irPD assessment. Participants lacking an evaluation of tumor response after treatment initiation will have their PFS time censored on the date of treatment initiation with the duration of a day. Participants with documentation of irPD or death after a long interval (2 or more incomplete or non-evaluable assessments) since the last tumor assessment will be censored at the time of last objective assessment that did not show PD. The length of irPFS will be calculated as irPFS time (months) = [(progression, death date or censor date) – treatment initiation date +1]/30.4.
- 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.

5.4.2 Primary Efficacy Analysis

ORR will be estimated with the 95% Clopper-Pearson confidence intervals and the P-value with exact binomial test.

Primary efficacy results will be reported for the FAS and PP set. Full analysis set will be considered the primary set for the analysis.

Table 1. Primary Efficacy Estimands

Estimand	Population	Variable	Intercurrent event strategy	Summary measure
Primary	FAS set	Unconfirmed ORR	- Patient with missing Unconfirmed ORR outcome will considered as no responders. - Patients without any post-baseline assessment will be considered as non-responders.	The number and proportion of patients with response with the 95% Pearson-Clopper CI will be calculated.
Sensitivity 1 to Primary	PP set	Unconfirmed ORR	Same as above	Same as above

5.4.3 Decision Rules and Adjustment of Alpha for Primary Endpoint

The study would be defined as positive at final analysis, if the ORR in the INCMGA00012 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.

5.4.4 Secondary Efficacy Analysis

Secondary efficacy results will be reported for the FAS and PP set.

For binary endpoints, the number and proportion of patients with response with the 95% Pearson-Clopper CI will be calculated.

The time to event endpoints will be performed with maximum likelihood method (MLM) for exponential distribution test, at nominal level of 0.05. Number and percentage of events will be described. The median, 6-month, 1 and 2-year

survival rates and 95% confidence intervals will be provided based on exponential MLM and Kaplan-Meier method. Swimmer plots for time-to-event endpoints will be provided.

For continuous outcome (maximum tumor shrinkage) we will use statistics of central tendency (median with 95%CI) and dispersion (range and interquartile range). We will provide waterfall plots of maximum tumor shrinkage from baseline. The duration of response has also plotted with bar plots.

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

Table 2. Secondary Efficacy Estimands

Estimand	Population	Variable	Intercurrent event strategy	Summary measure
Secondary 1	FAS set	PFS	- Patients with no progression or death will be censored at the date of their last evaluable imaging previous 35 days after last dose administration date. - If no post-baseline tumor assessment is available, patients will be censored at the date of treatment initiation + 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.	Kaplan-Meier plot, number and proportion of events, median survival time, 6 months, 1- and 2-year survival rates with corresponding 95% CI. Swimmer plot will be provided.
Sensitivity 1 to Secondary 1	PP set	PFS	Same as above	Same as above
Secondary 2	FAS set	BOR	- When CR or PR is the best response across all time points, then best overall response will be unconfirmed CR or unconfirmed PR respectively. - When CR or PR is the best response for ≥ 4 weeks then best overall response will be confirmed CR or confirmed PR respectively. - When SD is the best response for ≥ 24 weeks the best overall response will be SD ≥ 24 w. - When SD is the best response for < 24 weeks the best overall response will be SD < 24 w. - When non-target disease only and Non-CR/Non-PD is the best response for ≥ 24 weeks the best overall response will be SD ≥ 24 w. - When non-target disease only and Non-CR/Non-PD is the best response for < 24 weeks the best overall response will be SD < 24 w. - When PD is the best response across all time points, best overall response will be PD. - When there is no evaluable tumor assessments best overall response will be NE.	The number and proportion of patients with response with the 95% Pearson-Clopper CI will be calculated.
Sensitivity to secondary 2	PP set	BOR	Same as above	Same as above
Secondary 3	FAS set	Confirmed ORR	- Patient with missing confirmed ORR outcomes will considered as no responders. - Patients without any post-baseline assessment will be considered as non-responders.	The number and proportion of patients with response with the 95% Pearson-Clopper CI will be calculated.

Estimand	Population	Variable	Intercurrent event strategy	Summary measure
Sensitivity to secondary 3	PP set	Confirmed ORR	Same as above	Same as above
Secondary 4	FAS set	Unconfirmed CBR	- Patient with missing Unconfirmed ORR outcome will considered as no responders. - Patients without any post-baseline assessment will be considered as non-responders.	The number and proportion of patients with response with the 95% Pearson-Clopper CI will be calculated.
Sensitivity to secondary 4	PP set	Unconfirmed CBR	Same as above	Same as above
Secondary 5	FAS set	Confirmed CBR	- Patient with missing confirmed ORR outcomes will considered as no responders. - Patients without any post-baseline assessment will be considered as non-responders.	The number and proportion of patients with response with the 95% Pearson-Clopper CI will be calculated.
Sensitivity to secondary 5	PP set	Confirmed CBR	Same as above	Same as above
Secondary 7	FAS set	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 tumor assessment is available, patients will be censored at the date of treatment initiation + 1 day.	Kaplan-Meier plot, number and proportion of events, median survival time, 1- and 2-year survival rates with corresponding 95% CI.
Sensitivity to secondary 7	PP set	OS	Same as above	Same as above
Secondary 8	FAS set	TTR	- Patients with no response will be censored at the date of their last evaluable imaging previous 35 days after last dose administration date.	Kaplan-Meier plot, number and proportion of events, median survival time, 1- and 2-year survival rates with corresponding 95% CI.
Sensitivity to secondary 8	PP set	TTR	Same as above	Same as above
Secondary 9	FAS patients with overall response	DoR	- Patients with no progression or death will be censored at the date of their last evaluable imaging previous 35 days after last dose administration date. - If no post-response tumor assessment is available, patients will be censored at the date of treatment response + 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.	Kaplan-Meier plot, number and proportion of events, median survival time, 1- and 2-year survival rates with corresponding 95% CI.
Sensitivity to secondary 9	PP patients with overall response	DoR	Same as above	Same as above
Secondary 11	FAS set	Maximum Tumor Shrinkage	Only observed cases will be used	Median, range, mean, standard deviation, and interquartile range. Waterfall plots describing the percentage of change in target tumor lesions
Sensitivity to secondary 11	PP set	Maximum Tumor Shrinkage	Same as above	Same as above

Estimand	Population	Variable	Intercurrent event strategy	Summary measure
Secondary 12	FAS set	irPFS	- Confirmation of progression is recommended minimum 4 weeks after the first irPD assessment - If no post-baseline tumor assessment is available, patients will be censored at the date of treatment initiation + 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.	Kaplan-Meier plot, number and proportion of events, median survival time, 6-month, 1- and 2-year survival rates with corresponding 95% CI.
Sensitivity to secondary 12	PP set	irPFS	Same as above	Same as above
Secondary 13	FAS set	irORR	- Patient with missing confirmed ORR outcomes will considered as no responders. - Patients without any post-baseline assessment will be considered as non-responders.	The number and proportion of patients with response with the 95% Pearson-Clopper CI will be calculated.
Sensitivity to secondary 13	PP set	irORR	Same as above	Same as above
Secondary 13	FAS set	irCBR	- Patient with missing confirmed ORR outcomes will considered as no responders. - Patients without any post-baseline assessment will be considered as non-responders.	The number and proportion of patients with response with the 95% Pearson-Clopper CI will be calculated.
Sensitivity to secondary 13	PP set	irCBR	Same as above	Same as above

5.4.5 Handling of Missing Data

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 will considered as no responders. Patients without any post-baseline assessment will be considered as non-responders or without clinical benefit.

The analysis of timed endpoints is based on a Kaplan-Meier method, therefore, not affected by patient withdrawals (as they are censored) provided that dropping out is unrelated to prognosis.

For the analysis of maximum tumor shrinkage only observed cases will be used.

The other variables will be managed with simple imputations methods (last observation carried forward). The effect that any missing data might have on results will be assessed via sensitivity analysis.

5.4.6 Subgroup Analysis

CBR, 6-month PFS, DoR, TTR, 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.

Forest plots will be presented to describe all these analyses.

Table 3. Time-to-Event Estimands

Estimand	Population	Variable	Intercurrent event strategy	Summary measure
PFS subgroup analysis	FAS set	PFS	Multivariate Cox proportional hazards model adjusted for baseline prognostic factors. Breslow method for tie handling in survival analysis will be used. P-values and the 95% confidence intervals for hazard ratio will be based on Wald test.	Forest plot will report for each baseline prognostic subgroup: - number and % of patients - adjusted HR (95%CI) - interaction p-value - median survival time - **6-month** survival rate (95%CI)
irPFS subgroups analysis	FAS set	irPFS	Same as above	Same as above
TTR subgroups analysis	FAS set	TTR	Same as above	Same as above
DoR subgroups analysis	FAS set	DoR	Same as above	Same as above
OS subgroups analysis	FAS set	OS	Same as above	Same as above

Table 4. Binary Outcomes Estimands

Estimand	Population	Variable	Intercurrent event strategy	Summary measure
ORR subgroup analysis	FAS set	ORR	Multivariate logistic regression model adjusted for baseline prognostic factors. P-values and the 95% confidence intervals for odds ratio will be based on Wald test.	Forest plot will report for each baseline prognostic subgroup: - % patients (95%IC) - adjusted OR (95%CI) - interaction p-value - proportion difference (95%CI)
CBR subgroup analysis	FAS set	CBR	Same as above	Same as above
irORR subgroup analysis	FAS set	irORR	Same as above	Same as above
irCBR subgroup analysis	FAS set	irCBR	Same as above	Same as above

5.4.7 Exploratory Analysis

These statistical analyses will be exploratory. Exploratory analyses will be performed on the exploratory analysis set. A separate analysis report for such assessments will be written.

We will 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.

The exploratory endpoints are PFS, CBR, and ORR based on irRECIST 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 clinical activity. 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 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.

5.5 Safety

All safety tables will list or summarize subjects on the safety set.

These safety assessments will be subjected to clinical review and summarized by appropriate descriptive statistics.

These data will include report of AEs, laboratory analysis, vital signs, ECOG PS, changes in ECG, time of trial dosing, and proportion of interruptions. Terms and severity of AE will be obtained and reported according to the NCI-CTCAE v.5. Statistical summaries of characteristics, frequency, grading, duration, and relationship with treatment will be presented.

5.5.1 Duration and Extent of Exposure of Study Treatment

The study treatment period is defined as the time between the study entry and the last dose of study therapy (INCMGA00012).

Duration and extent of exposure will be based on the safety set.

The following parameters will be calculated:

- b: "Actual Cycle Duration" is the difference between start and stop date dose.
- c: "Actual Cycle Dose Days" is the number of days with dose administration in the cycle, considering the interruptions.
- d: "Actual Total Dose" is the total dose a patient took in a cycle, considering interruptions and reductions.
- e: "Intended Daily Dose per Cycle".
- f: "Intended Cycle Duration".
- g: "Intended Cycle Dose Days".
- A: "Total number of cycles" = 1
- B: "Treatment Duration" = Sum over all cycles of (b).
- C: "Days on drug" = Sum over all cycles of (c).
- D: "Total Actual Total Dose" = Sum over all cycles of (d).

- E: "Mean Intended Daily Dose" = Mean over all cycles of (e).
- F: "Total Intended Duration" = Sum over all cycles of (f).
- G: "Total Intended Dose Days" = Sum over all cycles of (g).
- H: "Intended Total Dose" = G*E
- I: "Actual Average Daily Dose on Dose Days" = D/C
- J: "Ratio for Dose Interruption" = C/G
- K: "Ratio for Cycle Duration" = F/B
- L: "Actual Average Daily Dose Intensity" = I*J*K
- M: "Relative Dose Intensity (RDI)" = L/E*100

The treatment duration (months), number of cycles, days on Drug and Treatment compliance (%) will be summarized in terms of the number of observations, mean, standard deviation (STD), median, minimum and maximum.

Extent of exposure measured as RDI (dose level) will be described with median, interquartile range (IQR) and range. The RDI will be dichotomized in different cutoffs (≥50%, ≥70%, ≥80%, ≥90%, ≥100%) and described with frequencies and percentages.

5.5.2 Dose Delays, Reductions and Discontinuations

The following summaries will be provided:

- Subjects with at least one dose delay.
- Subjects with at least one dose delay due to adverse event.
- Subjects with at least one dose reduction.
- Subjects with at least one dose reduction due to adverse event.
- Subjects with permanently dose discontinuation.
- Subjects with permanently dose discontinuation due to adverse event.

5.5.3 Concomitant Medications

The number and percent of unique patients taking concomitant medications will be summarized by therapeutic classification, coded term, and dose level. Elective surgeries/procedures performed during the study will be presented in a listing.

The following are conventions that will be used to classify individual medications as prior and/or concomitant:

- Medications with stop dates prior to screening visit date will be considered prior.
- Medications with missing stop dates or stop dates the day of or after screening visit date will be considered concomitant, regardless of start date. Additionally, if the start date is prior to screening visit date or missing, the medication will also be considered prior.

Frequencies and by-subject listing of all prior and concomitant medications will be provided, containing variables listed on Prior/Concomitant Assessment eCRF, their corresponding categories (Prior or Concomitant), and WHO Anatomical Therapeutic Chemical (ATC) level 2 and ATC Name.

5.5.4 Adverse Events

All AEs will be recorded on the eCRF "Adverse Events" page and will be coded using the current version of MedDRA® to give a system organ class (SOC) and preferred term (PT) for each event. All adverse event safety data will be updated to the version of MedDRA that is current at the time of the database lock and statistical analyses. Adverse events will be coded with grades defined according to CTCAE V5.0 criteria.

Treatment-emergent AEs (i.e., those events occur after the first study medication administration and were not present at baseline or worsened in severity following the start of treatment) will be tabulated. The TEAE will be tabulated according to intensity and causality. If intensity of an AE or causality of an AE to the study medication is missing, a worst-case scenario will prevail (severe in intensity or probably related will be assumed). In the summary tables the number of subjects with events and the number of events will be presented.

The onset date of an AE will be compared to the date of first dose of study drug to determine whether the AE is treatment emergent. Adverse events with an onset date on or after the date of first dose of study drug will be classified as treatment emergent.

All deaths and SAEs, regardless of cause, from treatment start until 28 days after final dose of treatment. Non-fatal AEs occurring after treatment start regardless of cause, up until 28 days after final dose of treatment or until start of new anti-cancer treatment, whichever is first. Disease progression is not considered a treatment emergent adverse event unless the patient dies of disease prior to 28 days after discontinuation of treatment. Events that are continuations of baseline abnormalities are considered treatment emergent adverse events only if there is an increase in grade over baseline, or if there is an increase following a decrease during the study.

Treatment emergent adverse events with cause possibly, probably or definitely related to treatment as judged by the investigator. Events that are continuation of baseline abnormalities are not considered treatment related unless there is an increase in grade, or if there is an increase following a decrease, and the increase is judged by the investigator to be due to treatment.

Descriptive statistics will be used to characterize the profiles of treatment-related AEs, treatment-related deaths, SAEs, treatment-related delays, dose reductions, and/or treatment discontinuations. All AEs will be graded according to the current version of the NCI-CTCAE v.5 and the Medical Dictionary for Regulatory Activities (MedDRA).

The following summaries will be provided:

- Summary of Adverse Events
    - Subjects with at least one Adverse Event (AE)
    - Subjects with at least one Treatment Emergent AE (TEAE)
    - Subjects with at least one related study drug TEAE
    - Subjects with at least one grade 3 or 4 or 5 TEAE
    - Subjects with at least one related grade 3 or 4 or 5 TEAE
    - Subjects with at least one serious TEAE
    - Subjects with at least one related serious TEAE
    - Subjects with at least one non-serious TEAE
    - Subjects with at least one Adverse Event of Special Interest (AESI)
    - Deaths due to TEAE
    - Subjects with TEAE leading to Discontinuation of Study Treatment
    - Subjects dropped out due to AE.
- Summary by SOC and PT of the number and percentage of subjects reporting each:
    - Treatment Emergent Adverse Events
    - Treatment Emergent Adverse Events by Treatment and Hematologic
    - Treatment Emergent Adverse Event Related to Study Drug
    - Related Treatment Emergent Adverse Event by Treatment and Hematologic
    - AESI Treatment Emergent Adverse Events
    - Treatment Emergent Adverse Events with Grade 3 or 4 or 5

- Related Treatment-Emergent Adverse Event with Grade 3 or 4 or 5
- Serious Treatment Emergent Adverse Event
- Serious and Related Treatment Emergent Adverse Event
- Treatment Emergent Adverse Event by Maximum Severity
- Treatment Emergent Adverse Event Leading to Discontinuation of Study Drug

5.5.5 Clinical Laboratory Parameters

The following summaries will be produced for all hematology and biochemistry laboratory parameters:

- Shift tables of low, normal, high distribution (n; %) with respect normal ranges of center, at each post-baseline cycle by baseline (cycle 1 day 1) distribution.
- Shift tables of low, normal, high distribution (n; %) of clinically significant at each post-baseline cycle comparing with baseline (cycle 1 day 1) distribution.
- The value distribution will be displayed using a serial box plot at each cycle.

5.5.6 Vital Signs

The following summaries will be produced for all vital sign's parameters:

- Shift tables of low, normal, high distribution (n; %) at each post-baseline cycle by baseline (cycle 1 day 1) distribution.

5.5.7 Physical Examination

The following summaries will be produced for all physical examination's parameters:

- Shift tables of low, normal, high distribution (n; %) at each post-baseline cycle by baseline (cycle 1 day 1) distribution.

5.6 Interim Analysis of Safety

No interim analysis is planned.

5.7 Changes of Analysis from Protocol

- The level of significance α has been changed from $\leq$ to $=$ in some paragraphs.
- We have included the time to response as secondary endpoint. We have dropped the time to progression.

5.8 Deviations from SAP

Any deviations from the original statistical plan will be described and justified in the final clinical study report.

6 APPENDICES

6.1 Appendix 1 - SAS Codes

All report outputs will be produced using SAS® version 9.4 (TS1M5) version in a secure and validated environment.

ORR will be estimated with the 95% Clopper-Pearson confidence intervals and the P-value with exact binomial test.

```
proc freq data=FAS;
  tables ORR / binomial(exact p=.05) alpha=.05;
  title 'ORR (FAS)';
run;
```

6.2 List of Tables, Listings, Figures

A complete list of tables, listings and figures (TLFs) will be given in a separate document which can be updated without updating the SAP. The list will serve as a reference for both the Sponsor, the trial statistician and the statistical programmer and includes the totality of statistical output to be produced.

All output will be headed with an appropriate heading specifying the study ID and abbreviated study title.

All output will be dated and have page numbers in the form 'Page [x / y]' where x denotes the current page within an output and y the total number of pages of that output.

All statistical output will identify the underlying analysis sets and indicate the number of patients/events in this set (N) and the number of patient/events actuals contributing to the output (n). All statistical output will be presented per treatment (if applicable).

All patient listings will contain additionally to the patient identification the analysis set and the treatment.