Imugene Limited

IMU.ACS.001

HERIZON: A Phase 1b/2 Open-label Study of IMU-131 HER2/neu Peptide Vaccine Plus Standard of Care Chemotherapy with Randomization in Phase 2 in Patients with HER2/neu Overexpressing Metastatic or Advanced Adenocarcinoma of the Stomach or Gastroesophageal Junction

Statistical Analysis Plan

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Prepared by:

PPD, Inc

On behalf of Imugene Limited

Level 3/62 Lygon St

CARLTON VIC 3053

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List of Abbreviations

5-FU	5-fluorouracil
ADaM	Analysis Data Model
AEs	Adverse event(s)
ATC	Anatomical Therapeutic Chemical
AUC	Area Under Curve
B cell	B lymphocyte
BOR	Best overall response
CI	Confidence interval
CIV	continuous intravenous infusion
Cox-PH	Cox-proportional hazards regression model
CR	Complete Response
CRF	Case report form
CRP	C-reactive protein
CTCAE	National Cancer Institute's Common Toxicity Criteria for Adverse Events
CTS	Change in Tumor Size
DCR	Disease Control Rate
DOR	Duration of Response
EAIR	Exposure-adjusted incidence rate
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EoT	End of Treatment
EVAL	Evaluable Set
FAS	Full Analysis Set
GEJ	Gastroesophageal junction
GMFR	geometric mean fold rises
GMT	geometric mean titer
HER2/neu	Human epidermal growth factor receptor 2
HR	hazard ratio
ICF	Informed consent form
IDMC	Independent Data Monitoring Committee
IgG	Immunoglobulin G
IMU-131	Investigational product consisting of P467-CRM in Montanide adjuvant
ITT	Intent-to-Treat
IV	Intravenous(ly)
IxRS	Interactive Voice or Web Response System
LVEF	Left ventricular ejection fraction
MedDRA	Medical Dictionary for Regulatory Activities
NE	Not Evaluable
ORR	Objective Response Rate
OS	Overall survival
PD	Progressive Disease
PFS	Progression Free Survival
PP	Per-Protocol
PR	Partial Response
PT	preferred term

RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	recommended phase 2 dose
SAP	Statistical analysis plan
SD	Stable Disease
SOC	System organ class
T cell	T lymphocyte
TEAEs	Treatment-emergent Adverse Events
ToGA	Trastuzumab for Gastric Cancer
TTP	Time to Progression
WHODD	World Health Organization Drug Dictionary

1. Introduction

This Statistical Analysis Plan (SAP) describes the analyses and data presentations for Imugene Limited protocol IMU.ACS.001 "HERIZON: A Phase 1b/2 Open-label Study of IMU-131 HER2/neu Peptide Vaccine Plus Standard of Care Chemotherapy with Randomization in Phase 2 in Patients with HER2/neu Overexpressing Metastatic or Advanced Adenocarcinoma of the Stomach or Gastroesophageal Junction", which was amended on 17 Feb 2021 (Amendment No. 3). The protocol has a 2-part design: Phase 1b and Phase 2, and this SAP is specifically for the Phase 2 study. It contains definitions of analysis populations, derived variables and statistical methods for the analysis of efficacy, safety and immunogenicity.

The following analyses are planned in this study.

- Periodic safety analyses for Independent Data Monitoring Committee (IDMC) safety reviews
- The final analysis of progression free survival (PFS) after 24 evaluable PFS events have been realized
- The final analysis of overall survival (OS) after 24 deaths (at the end of study)

This SAP will only cover the secondary endpoint analysis at clinical cutoff of 24 evaluable PFS events and the primary endpoint analysis of OS at clinical cutoff of 24 OS events. The detail analyses for IDMC safety review is specified in the IDMC charter.

Throughout this SAP, the treatment group will be referred to as the IMU-131 plus chemotherapy group and chemotherapy alone group. The purpose of the SAP is to ensure the credibility of the study findings by pre-specifying the statistical approaches to any data analysis prior to database lock. This SAP will be finalized and signed prior to the clinical database lock for the final PFS analysis at 24 evaluable progression events. Any significant changes after final PFS analysis and prior to final database lock for primary endpoint OS analysis after 24 deaths will be documented in Final SAP Amendment.

All statistical analyses detailed in this plan will be conducted using SAS® 9.4 or later (SAS Institute Inc., Cary, North Carolina).

2. Objectives

2.1. Primary Objective

The primary objective of this study is to evaluate the clinical efficacy of IMU-131 plus chemotherapy compared to chemotherapy alone based on OS.

2.2. Secondary Objective

The secondary objectives of this study are as follows:

- To evaluate other efficacy measures of IMU-131 plus chemotherapy compared to chemotherapy alone including PFS, time to progression (TTP), disease control rate (DCR), objective response rate (ORR), duration of objective response (DOR) and change in tumor size (CTS) according to Response Evaluation Criteria In Solid Tumors version 1.1 (RECIST 1.1) for the progression evaluation of radiographic data.
- To evaluate the safety profile of IMU-131 plus chemotherapy compared to chemotherapy alone.

2.3. Exploratory Objective

The exploratory objective of this study is as follows:

- To evaluate humoral and cellular immunogenicity data of IMU-131 plus chemotherapy compared to chemotherapy alone including P467-specific antibodies (IgG), Her-2-specific antibodies (IgG), vaccine-specific cytokine levels and regulatory and effector T and B cells.
- To evaluate the arm-specific associations between clinical outcome, intra-tumor T cells, regulatory effector T and B cells, and serum and biochemical markers of tumor progression.
- To evaluate arm-specific associations between clinical outcome and HER2 and PD-L1 expression in tumor tissue.
- To evaluate inhibition of in-vitro tumor cell growth and intra-cellular signaling processes by Her-2-specific antibodies (IgG).

3. Investigational Plan

3.1. Overall Study Design and Plan

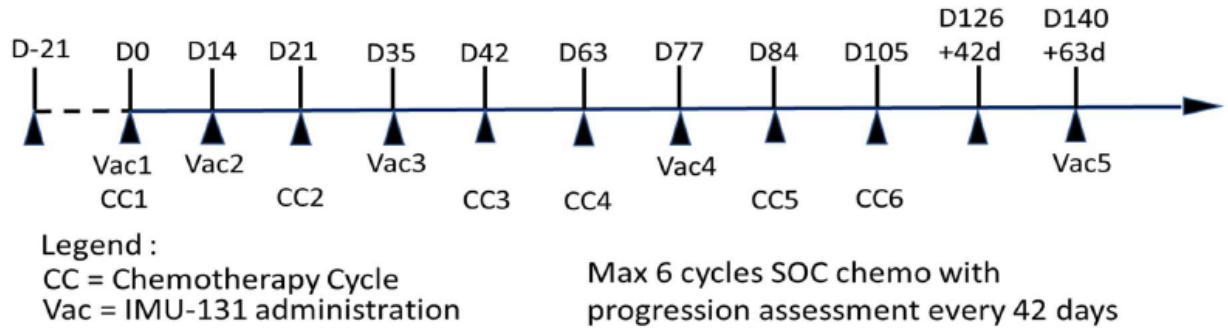
This phase 1b/2 protocol for patients with HER2/neu overexpressing metastatic or advanced adenocarcinoma of the stomach or GEJ has a 2-part design: Phase 1b and Phase 2.

Phase 1b is an open-label, multicenter, single arm, dose escalation study with up to 18 enrolled to evaluate safety, tolerability and immunogenicity and to assess the Recommended Phase 2 Dose (RP2D) of IMU-131 initiated 14 days prior to the start of chemotherapy.

Phase 2 is an open-label, randomized, multicenter study to assess the clinical activity, immunogenicity, safety and tolerability of IMU-131. Phase 2 will enroll 36 patients and be conducted in the same centers as Phase 1b, with the addition of new centers as required to fulfill recruitment. Patient will be randomly assigned in a 1:1 ratio to either 'IMU-131 plus chemotherapy' or 'chemotherapy alone' groups.

The length of Phase 2 will be approximately 30 months: 22 months' recruitment and an estimated 8 months' follow-up from completion of recruitment to realization of the required number of deaths. For a representation of the timeline of events in Phase 2 see Figure 1(Timeline for Phase 2).

Figure 1: Timeline for Phase 2



Screening Period

Screening assessments or procedures will be conducted within 3 weeks prior to the start of study treatment, across at least 2 clinic visits. At the first screening visit, the patient will be asked to sign the informed consent form (ICF), the eligibility criteria will be assessed and screening for HER2/neu overexpression will be completed. All other screening procedures will be conducted at subsequent screening visits.

Patient may be re-screened under certain situations as specified in the protocol. Before re-screening, patient must sign a new ICF and will keep the same screening number. Screening procedures and test results/eligibility checks will be updated as part of re-screening.

After completing all screening assessments, patients who meet all the inclusion and none of the exclusion criteria will proceed to the treatment period.

Treatment Period

Patient who are determined to be eligible for the study will be randomized on the Baseline/Day 0 visit. Treatment for both groups will begin at the Baseline/Day 0 visit.

Patients in the IMU-131 plus chemotherapy group will receive vaccination of IMU-131 at Baseline/Day 0, Day 14, Day 35, Day 77, Day 140 and then every 63 days until disease progression. Patients in both the IMU-131 plus chemotherapy group and the chemotherapy alone group will receive chemotherapy starting at the Baseline/Day 0 visit and then every 21 days for a maximum of 6 cycles as clinically indicated or until disease progression, whichever occurs sooner. Chemotherapy will be consisting of:

- Cisplatin by intravenous administration at 80 mg/m2 on the first day of each cycle and either 5-FU, 4000 mg/m2 CIV (administered as 1000 mg/m2/day as continuous infusion for 96 hours on days 1 to 4 of each cycle) or capecitabine for 14 days at 2000 mg/m2/day, orally (administered as 1000 mg/m2 twice daily morning and evening for a total of 2000 mg/m2/day on days 1 to 14 of each cycle);
- Or oxaliplatin, by intravenous administration at 130 mg/m2 on Day 1 of each cycle and capecitabine for 14 days at 2000 mg/m2/day, orally (administered as 1000 mg/m2 twice daily morning and evening for a total of 2000 mg/m2/day on days 1 to 14 of each cycle).

Patients who withdraw from the treatment or have progressive disease will undergo the End of Treatment (EoT) assessments as planned in the Schedule of Study Procedures.

Post-treatment Follow-up Period

After the EoT visit, the patient will be followed up every 42 days with radiographic assessment conducted (only for patients who withdrew from study before progressive disease was confirmed), survival follow-up assessment and post-study anti-cancer treatment recorded.

3.2. Study Endpoints

Primary Efficacy Endpoint

- OS measured from randomization to death due to any cause

Secondary Efficacy Endpoints

- PFS measured from randomization to date of earliest progressive disease (PD) based on blinded central review according to RECIST 1.1 criteria, or to date of death from any cause
- TTP measured from randomization to date of earliest PD based on blinded central review according to RECIST 1.1 criteria
- ORR measured from randomization as the proportion of patients achieving a best overall response of CR or PR based on blinded central review according to RECIST 1.1 criteria
- DCR measured from randomization as the proportion of patients achieving a best overall response of complete response (CR), partial response (PR) or stable disease (SD) based on blinded central review according to RECIST 1.1 criteria
- DOR measure from when earliest CR or PR is observed to PD or death due to any cause based on blinded central review according to RECIST 1.1 criteria
- Percentage CTS measured from baseline as the sum of diameters based on blinded central review according to RECIST 1.1 criteria

Exploratory Endpoints

- Values and changes from baseline in humoral and cellular immunogenicity data including P467-specific antibodies (IgG), Her 2-specific antibodies (IgG), vaccine-specific cytokine levels and regulatory and effector T and B cells
- Values and changes from baseline in serum and biochemical markers of tumor progression
- Values and changes from randomization in Her-2-specific antibodies (IgG) inhibition of in-vitro tumor cell growth
- Values and changes from baseline in intra-tumor T cells and biochemical markers from pre- and post-treatment tumor biopsies

Safety Endpoints

- Incidence of treatment-emergent adverse events (TEAE), Grade 3 or higher TEAEs, serious TEAEs, and TEAEs leading to study treatment discontinuation
- Incidence of treatment-emergent grade 3/4 clinical laboratory abnormalities
- Changes and shifts from baseline in clinical laboratory, vital signs, and electrocardiogram (ECG) parameters
- Change from baseline in ECOG performance grade
- Concomitant medication use
- Treatment compliance

4. General Statistical Considerations

4.1. Reporting Convention

4.2. Analysis Window

Baseline is defined as the last non-missing measurement prior to the first administration of any study treatment. For patients who were randomized but not treated, baseline will be the assessment taken on or before the randomization visit Baseline/ Day 0.

The day of the first dose of any study drug will be defined as study Day 0. Study day are calculated relative to Day 0, as the difference between the date of interest and Day 0.

For the post-baseline by-visit summaries of safety assessments, the nominal visits as captured on the eCRF page will be utilized.

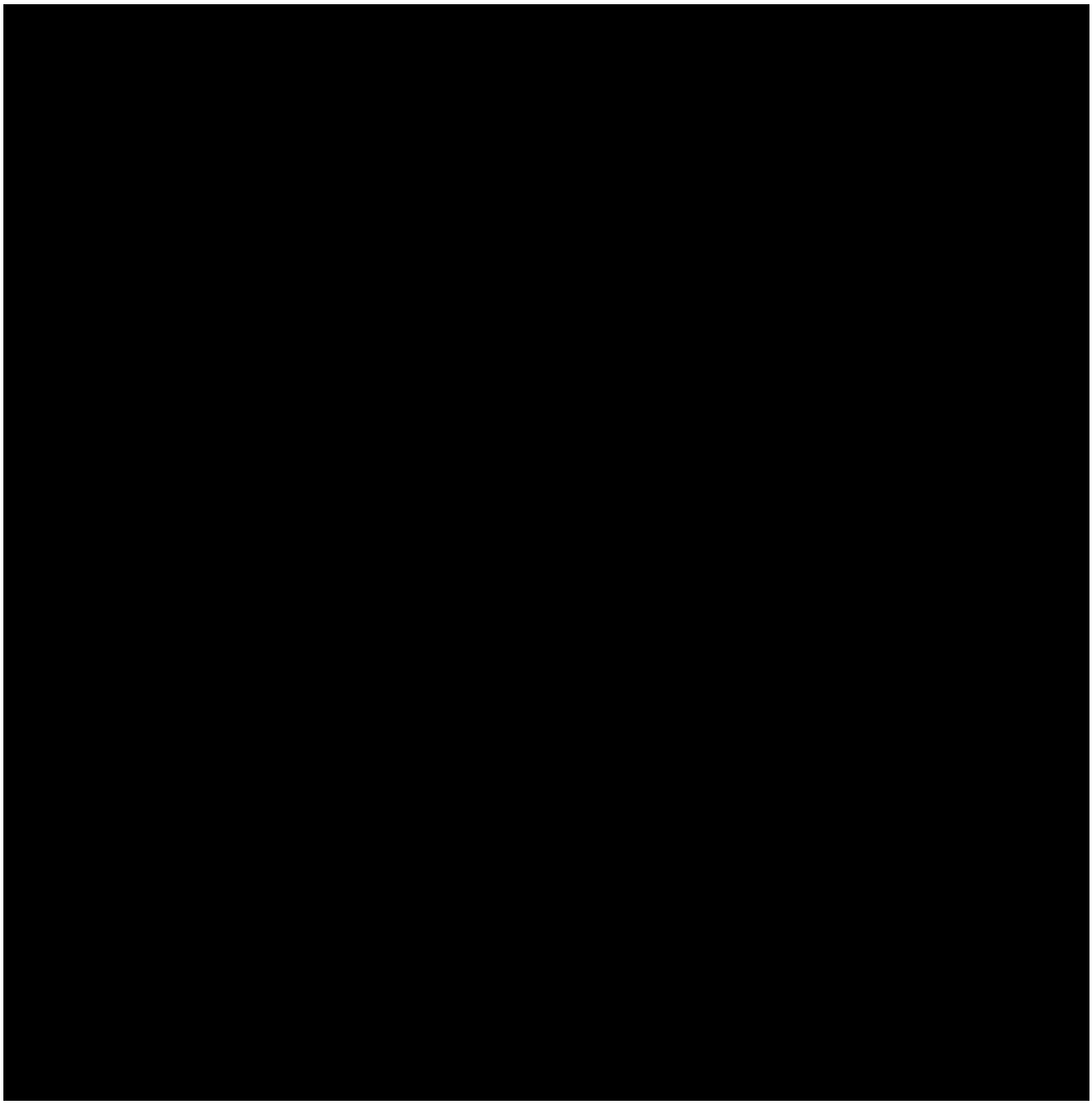
For the purpose of by-visit summaries of efficacy assessment (like the change in tumor size) and humoral immunogenicity data, the post-baseline visit mapping rules described in Table 4-1 and Table 4-2 will be used respectively. When multiple records fall in the same post-baseline visit window, the record with the study day closest to the target visit day will be chosen. In a case of a tie, the record with the earlier date will be chosen. Records that not chosen will be effectively

treated similarly to an unscheduled assessment and will still be included in all except the by-visit summaries.

[redacted]

4.3. Sample Size Calculation

[redacted]



4.4. Randomization, Stratification, and Blinding

Patients will be randomized using a permuted block randomization in a 1:1 ratio to receive IMU-131 plus chemotherapy or chemotherapy alone treatment. Randomization will be performed centrally using an Interactive Voice or Web Response System (IxRS) and stratified by tumor stage at screening (III vs. IV).

Phase 2 is an open-label study in which all the personnel will be unblinded except for the central radiography reviewers.

4.5. Analysis Set

The following analysis sets will be used:

ITT Set: All randomized patients. Patients will be analyzed as randomized. This analysis set will be used for primary efficacy analysis.

Evaluable Set (EVAL): All randomized patients who receive any amount of study treatment and have at least one evaluable post-baseline tumor response. Patients will be analyzed as randomized.

The Full Analysis Set (FAS): All randomized patients who receive any amount of study treatment. FAS analyses will be conducted on the basis of the randomized treatment.

Safety Set: All randomized patients who receive any amount of study treatment. Patients will be analyzed as treated. All the safety analyses will be based on the Safety set.

Per-protocol (PP) Set: A subset of the ITT set who will be selected based on the study drug experience (compliance and/or time on study drug) and major protocol deviations. The criteria for inclusion in the PP set will be finalized and documented prior to data base lock. Patients will be analyzed as randomized.

5. Patient Disposition

5.1. Disposition

A summary of patient's disposition will be presented based on the ITT set. The number and percentage of patients who received at least one dose of study treatment, and who discontinued study treatment will be presented by treatment group and in total, with specific primary reasons for treatment discontinuation presented as well. A similar summary will be repeated for study discontinuation.

The enrollment will be summarized by study site and treatment group.

The number and percentage of patients included in each analysis set will be provided. All the percentages will be based on the number of patients randomized.

A Listing of patient treatment and study disposition will be provided.

5.2. Protocol Deviations

The protocol deviations will be defined in a separated study deviation rules document and will be identified and assessed by clinical research investigators or designee throughout the study. Any major protocol violation will be assessed prior to database lock, and to be considered for exclusion from Per-protocol Set. The number and percentage of subjects with major protocol deviations will be summarized overall and for each treatment group by type of deviation based on the ITT set. A listing of protocol deviations will be provided.

6. Demographics and Baseline Characteristics

The demographics and baseline characteristics will be summarized by treatment group and in total based on the ITT set. No inferential statistics will be presented. Individual patient listings will be provided to support the summary tables.

6.1. Demographics

Descriptive statistics for the following demographic variables will be provided:

- Age at consent (years)
- Gender (Male, Female)
- Primary race (Blank or African American, American Indian or Alaska Native, Asian, Native Hawaiian or other Pacific Islander, White, Other, Not reported)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino, Not reported, Unknown)
- Height (cm)
- Weight (kg)
- Body mass index (BMI; kg/m^2): calculated as (weight in kilograms) / (height in meters) ^{2}

6.2. Baseline Disease Characteristics and Prior Gastric Cancer Therapy

Descriptive statistics for the following disease characteristics will be provided:

- Baseline ECOG performance status
- Baseline left ventricular ejection function (LVEF)
- Initial tumor diagnosis type (Adenocarcinoma of gastroesophageal junction, Adenocarcinoma of the stomach)
- Disease Extent at Initial Diagnosis (Resectable, Borderline Resectable, Unresectable locally advanced, Unresectable and metastatic)
- Tumor stage at screening (Stage III, Stage IV)
- Gross location of primary tumor (Type I, II, III, Not applicable)
- Time since the initial diagnosis (in days): calculated as date of informed consent – date of initial diagnosis + 1. If either month or month and day of initial diagnosis date is missing, use the January 1. If day is missing, use the first day of the month. Imputation will not be done for completely missing date.
- Number of target lesions at baseline
- Sum of lesion diameters (mm) of target lesions at baseline according to RECIST 1.1

The number and percentage of patients with prior gastric cancer therapy will be summarized as below:

- Prior gastric cancer surgery (yes, no)
- Prior gastric cancer drug therapy (yes, no)

- Prior gastric cancer radiotherapy (yes, no)

Listings of prior gastric cancer surgery, prior gastric cancer drug therapy and prior gastric cancer radiotherapy will be provided, presenting the detail information captured on the specific eCRF pages.

6.3. Medical History

Medical history will be coded according to the Medical Drug Regulatory Activities (MedDRA), version 21.0 or higher. A frequency summary of medical history will be provided by system organ class (SOC) and preferred term (PT).

7. Treatments and Medications

7.1. Prior and Concomitant Medications

Medications reported on the Prior and Concomitant Medications eCRF pages will be coded using World Health Organization Drug Dictionary (WHODD) March 2019 version and grouped into relevant categories based on the Anatomical Therapeutic Chemical (ATC) coding scheme.

A prior medication is defined as any medication taken prior to the first administration of any study treatment (i.e. intake was stopped prior to the first administration). A concomitant medication is defined as any medication that is ongoing on/after the first administration or taken on/after the first administration.

For the purpose of inclusion in prior and/or concomitant medication tables, incomplete medication start and stop dates will be imputed as described in Appendix 2.

If start date is completely missing and end date is not prior to the first dose, then the medication will be classified as concomitant. If the start date is completely missing and the end date is prior to the first dose of study drug, then the medication will be classified as prior. If the end date is completely missing, then the medication will be classified as concomitant. Medications for which both the start and end dates are completely missing will be classified as both prior and concomitant.

The number and percentage of patients with any prior medications will be summarized by ATC level 3 and generic drug name for each treatment group and in total. Similar frequency tables will be provided for concomitant medications. All summaries will be performed using the Safety set.

A listing of prior and concomitant medications will be provided.

7.2. Concomitant Procedures/Surgeries

Concomitant procedure/surgery will be coded using the MedDRA version 21.0 or higher. A concomitant procedure/surgery is defined as any procedure/surgery conducted on or after the first administration of study treatment. Procedure/surgery with a missing date will be classified as concomitant.

The number and percentage of patients with any concomitant procedure/surgery will be summarized by SOC and PT for each treatment group and in total using the Safety set.

A listing of concomitant procedure/surgery will be provided.

7.3. Study Treatments

7.3.1. Extent of Exposure

The treatment duration is defined as time interval in weeks between the date of first administration of any study treatment and the treatment end date inclusive, calculated as (treatment end date – date of the first administration of any study treatment + 1) / 7. The treatment end date will be the date of last IMU-131 injection if applicable, or the date of last chemotherapy treatment captured on the End of Treatment eCRF page, whichever is later. For patients who are still treatment ongoing at the clinical cutoffs, the treatment end date will be

earlier date of the clinical cutoff date and the maximum date among the exposure data captured on the IMU-131 Vaccination eCRF pages if applicable, and the specific Chemotherapy administration eCRF pages.

Descriptive summary of treatment duration will be provided by treatment group. The total number of vaccinations, and the total number of cycles of chemotherapy administrated per patient will be summarized descriptively by treatment group. All summaries will be performed using the Safety set.

7.3.2. Treatment Compliance

The treatment compliance of IMU-131 vaccination will be calculated as the actual total number of vaccinations administrated divided by the prescribed number of vaccinations up to the disease progression or the data cutoff date and then multiplying 100. The acceptable range for compliance is defined as between 80% - 100%.

Treatment compliance will be summarized descriptively and categorically in terms of < 80% and ≥80% to ≤100%.

8. Efficacy Analyses

All imaging will be assessed by both investigators and a blinded central radiography review vendor, according to Response Evaluation Criteria In Solid Tumors version 1.1 (RECIST 1.1). The blinded central review disease response assessments will be used as the primary measure for the efficacy endpoints, and the investigator disease assessments will be used as supportive measures for these analyses. All the disease assessments from the randomization until the clinical cutoff date or the end of study will be used in the deviation of the secondary efficacy endpoints, unless otherwise specified.

[redacted]

For all the time-to-event endpoints described in this section, the time interval will be reported in unit of week.

8.1. Primary Efficacy Endpoint

The overall survival (OS) is defined as the time from the randomization to the death due to any cause. Patients who have not died by the time of data cutoff or study end will be censored at the last known alive date, or the data cutoff date for final analysis if the last known alive date is not available yet.

OS time will be calculated as Date of death (or date of last known alive/cutoff date) minus Randomization date + 1.

[redacted]

[redacted]

8.2. Secondary Efficacy Endpoint

8.2.1. Progression-free Survival (PFS)

PFS is defined as time in days from the randomization to the date of disease progression or death due to any cause on or prior to the clinical cutoff date, whichever occurred earlier. The disease progression will be defined as the radiological disease progression as assessed by blinded central reviewers. Therefore, duration of PFS in days is defined as the time between the date of randomization and the date of the first occurrence of one of the following events:

- Radiological disease progression per RECIST 1.1 as assessed by the blinded central reviewers, i.e. a tumor response of PD is observed
- Death due to any cause

The calculation of PFS is a two steps process.

- Determination of date of disease progression, which is the date of assessment corresponding to the first date time that overall tumor response is "Progressive Disease" on the Overall Tumor Response-RECIST eCRF
- Calculation of duration from randomization to disease progression, death, or censoring date as described in Table 8-1 as follows. In cases where a patient's tumor is downstaged to become surgically resectable, this is considered a response to treatment with subsequent surgery being part of the patient's normal clinical care. Such cases are considered evaluable PFS event at time of confirmed progressive disease.

Table 8-1 Censoring Conventions for PFS

Situation	Date of Progression or Censoring	Outcome
Disease progression, and time interval between progression date and previous tumor assessment date with progression-free response is less than or equal to 98 days	Earliest of: • Date of first tumor assessment showing new lesion • Date of first tumor assessment with overall response of PD	Event
Disease progression, and time interval between the progression date and the previous tumor assessment date with progression-free response is greater than 98 days.	Latest of: • the last progression-free assessment date • randomization date	Censored
Death without any post-baseline radiological assessment, and time interval between death	Death date	Event

date and randomization date is less than or equal to 98 days		
Death without any post-baseline radiological assessment, and time interval between death date and randomization date is greater than 98 days	Randomization date	Censored
Death before documented progression, and time interval between death date and previous tumor assessment date with progression-free response is less than or equal to 98 days	Death date	Event
Death before documented progression, and time interval between death date and previous tumor assessment date with progression-free response is greater than 98 days	The last progression-free assessment date	Censored
No death or disease progression, no treatment discontinuation due to symptomatic deterioration, and no subsequent anti-cancer therapy (i.e., systemic anti-cancer therapy, anti-cancer surgery, curative radiotherapy).	Latest of • the last progression-free assessment date • randomization date	Censored
Subsequent anti-cancer treatment (i.e., systemic anti-cancer therapy, anti-cancer surgery, radiotherapy) started prior to progression	Latest of • the last progression-free assessment date prior to start of anti-cancer treatment • randomization date	Censored
Treatment discontinuation due to symptomatic deterioration prior to disease progression	Latest of • the last progression-free assessment date before treatment discontinuation date • randomization date	Censored

An adequate disease assessment is a schedule or unscheduled assessment where the overall tumor assessment as assessed by blinded central reviewers is not missing and not unevaluable.

Progression-free survival is calculated as follows.

PFS = Analysis date defined above – randomization date + 1

[redacted]

[redacted]

8.2.2. Time to Progression (TTP)

The time to progression is defined as the time from randomization to the disease progression on or prior to the clinical cutoff date.

Similar with PFS, the calculation of TTP is a two steps process.

- Determination of date of disease progression, which is the date of assessment corresponding to the first date time that overall tumor response is "Progressive Disease" on the Overall Tumor Response-RECIST eCRF
- Calculation of duration from randomization to disease progression, or censoring date as described in Table 8-2 as follows. In cases where a patient's tumor is downstaged to become surgically resectable, this is considered a response to treatment with subsequent surgery being part of the patient's normal clinical care. Such cases are considered evaluable for progression analysis at time of confirmed progressive disease.

Table 8-2 Censoring Conventions for TTP

Situation	Date of Progression or Censoring	Outcome
Disease progression, and time interval between progression date and previous tumor assessment date with progression-free response is less than or equal to 98 days	Earliest of: • Date of first tumor assessment showing new lesion • Date of first tumor assessment with overall response of PD	Event
Disease progression, and time interval between the progression date and the previous tumor assessment date with progression-free response is greater than 98 days.	Latest of: • the last progression-free assessment date • randomization date	Censored
Death without any post-baseline radiological assessment, and time interval between death date and randomization date is less than or equal to 98 days	Death date	Censored
Death without any post-baseline radiological assessment, and time interval between death date and randomization date is greater than 98 days	Randomization date	Censored

Death before documented progression, and time interval between death date and previous tumor assessment date with progression-free response is less than or equal to 98 days	Death date	Censored
Death before documented progression, and time interval between death date and previous tumor assessment date with progression-free response is greater than 98 days	The last progression-free assessment date	Censored
No death or disease progression, no treatment discontinuation due to symptomatic deterioration, and no subsequent anti-cancer therapy (i.e., systemic anti-cancer therapy, anti-cancer surgery, curative radiotherapy).	Latest of • the last progression-free assessment date • randomization date	Censored
Subsequent anti-cancer treatment (i.e., systemic anti-cancer therapy, anti-cancer surgery, radiotherapy) started prior to progression	Latest of • the last progression-free assessment date prior to start of anti-cancer treatment • randomization date	Censored
Treatment discontinuation due to symptomatic deterioration prior to disease progression	Latest of • the last progression-free assessment date before treatment discontinuation date • randomization date	Censored

Time to Progression is calculated as follows.

TTP = Analysis date defined above – randomization date + 1

8.2.3. Disease Control Rate (DCR)

The best overall response (BOR) for each patient will be derived based on blinded central review disease response assessments according to RECIST 1.1, using all the assessments from randomization until the data cutoff date or the end of study. If there is no post randomization

disease assessment, the BOR will be "No Post Randomization Assessment"; and if all the post randomization tumor responses are not evaluable, the BOR will be "Not Evaluable" (NE).

[redacted]

8.2.4. Objective Response Rate (ORR)

ORR is defined as the proportion of patients with a BOR of CR or PR after randomization.

[redacted]

8.2.5. Duration of Objective Response (DOR)

DOR is defined as the time from the earliest date when a tumor response of CR or PR is observed until the date of the first occurrence of disease progression or death due to any cause:

Patients who don't have disease progression or have not died on or prior to the analysis cutoff date will be censored at the last adequate disease assessment date, or the earliest date of the tumor response of CR or PR observed if no disease assessment is available afterwards. See Section 8.2.1 for the definition of disease progression and adequate disease assessment.

[redacted]

8.2.6. Investigator Disease Assessment (PFS, TTP, DCR, ORR, and DOR)

[redacted] The same analysis method as described in Section 8.2.1, Section 8.2.2, Section 8.2.3, Section 8.2.4, and Section 8.2.5 will be applied.

8.2.7. Change in Tumor Size (CTS)

[redacted]

8.2.8. Sensitivity Analysis

8.2.8.1. Clinical Disease Progression

Addition to original disease progression definition, clinical disease progression can be also considered as evidence of disease progression when there is no supportive radiographic assessment of PD. Clinical disease progression is "Progression Disease" leading to treatment discontinuation on eCRF end of treatment page identified by clinical assessment. The date of documented progression disease on eCRF end of treatment page will be used as the event date in a sensitivity analysis. The same full event and censoring rules show in Table 8-1 will be implemented as well but including clinical disease progression as evidence of disease progression when there is no supportive radiographic assessment of PD.

[redacted]

8.2.8.2. Death Due to Random Cause

Sensitivity analyses will be performed for the endpoints PFS and OS based on ITT set with assumption that patients dying due to any confirmed random event, like COVID-19, will be censored at the date of death. The same inferential analysis described in section 8.1 and section 8.2.1 will be performed for the endpoint OS and PFS, respectively.

8.2.8.3. Patients Randomized to Wrong Stratus

Patients who randomized to the wrong stratus as a result of post-randomization review will be analyzed using the actual tumor stage as stratus factor provided it can be credibly argued that there is no between-arm bias in the application of the post-randomization review and specifically that the results of the review are not influenced by arm assignment. The analysis of survival and PFS will be repeated for the following modification:

- Analyze patients who randomized to the wrong stratus due to the wrong stage classification determined at the time of randomization by the actual tumor stage. The actual tumor stage can be assessed in a subsequent stage assessment.

The same inferential analysis described in section 8.1 and section 8.2.1 will be performed for the endpoint OS and PFS, respectively.

Additional version of the survival analysis can be done by relaxing the censoring implemented as a result of cutoff and using vital status data collected after cutoff.

9. Safety Analyses

All the safety analyses will be performed using the Safety set.

9.1. Adverse Events

Adverse events (AE) will be coded using the MedDRA version 21.0 or higher. The severity of AEs will be graded according to National Cancer Institute's Common Toxicity Criteria for Adverse Events version 5.0 (CTCTAE v5.0).

A TEAE is defined as any AE occurring or worsening on or after the first administration of any study drug and within 30 days after the last administration date. Any AE for which the onset date is missing, and the end date is on or after the first dose of any study drug or missing will be counted as TEAE. For the purpose of inclusion in TEAE summaries, incomplete adverse event onset and end dates will be imputed as described in Appendix 2.

A treatment-related TEAE is defined as any TEAE which is reported as "Possible Related", "Probably Related" or "Definitely Related" to any study treatment on the eCRF pages. Any TEAE with a missing relationship or a relationship of "Not Applicable" will be considered as a treatment-related TEAE.

A TEAE leading to treatment discontinuation is defined as any TEAE which is reported with an action of 'Permanently discontinued' taken with any study treatment on the eCRF pages. A TEAE leading to treatment reduction or interruption is defined as any TEAE which is reported with an action of 'Dose decreased' or 'Stopped temporarily' taken with any study treatment on the eCRF pages.

Unless otherwise specified, for the frequency summaries of TEAE, the number and percentage of patients who experienced the specific event, and the number of events will be provided. For the number of patients with the specific event, patients with multiple occurrences of the specific event will be counted only once. For the number event, each occurrence of the specific event will be counted. The SOC will be presented in the descending order of the overall incidence and then alphabetically if two or more SOC have the same incidence; the PT within each SOC will be presented in the descending order of the overall incidence and then alphabetically if two or more PT have the same incidence.

Frequency tables for the following TEAE categories will be provided by SOC and PT for each treatment group and in total. An overview summary table for these TEAE categories will be provided.

- TEAEs
- TEAEs leading to treatment discontinuation
- TEAEs leading to treatment reduction or interruption
- Treatment-related TEAEs
- Serious TEAEs
- Grade 3 or higher TEAEs
- TEAEs leading to death

The TEAEs with a high level term of 'Injection site reactions' will be summarized by PT and treatment group.

The TEAEs will be summarized by SOC, PT, the worst CTCAE grade and treatment group. At each level of patient summarization, the patient will be counted at the most severe occurrence if patient reported multiple occurrences of the same event.

The TEAEs will also be summarized by the relationship to study treatment (as captured in the eCRF), SOC, PT and treatment group. At each level of the patient summarization, the patient will be counted at the most closely related occurrence if the patient reported multiple occurrences of the same event.

A frequency summary table for the most frequent TEAEs will be provided by PT and treatment group. The most frequent TEAEs are defined as the PTs with a minimum of 5% patients' incidence among the overall population.

Listings of all AEs (including non-TEAEs), serious TEAEs, TEAEs leading to death, Grade 3 or higher TEAEs will be provided.

9.2. Clinical Laboratory Evaluations

The local clinical laboratory data (i.e. chemistry, hematology) will be graded according to CTCAE v5.0, for applicable tests. Grade 0 will be assigned for values that fall outside of the grading criteria.

Actual value and change from baseline value will be descriptively summarized by visit and treatment group for each laboratory test. Shift tables in toxicity grades from baseline to each scheduled post-baseline visit will be provided as well for the laboratory tests with gradings. A shift table from baseline to the worst post-baseline grade will be provided for the laboratory tests with gradings. Unscheduled assessments will be considered as well when identifying the worst post-baseline grade.

Listings of laboratory data will be provided.

9.3. Vital Sign Measurements

Vital sign measurements include height (cm), weight (kg), temperature (^{o}C), blood pressure (mmHg) and pulse rate (beats/min). Descriptive statistics of baseline, actual value and change from baseline at each time point will be provided by visit and treatment group for vital signs except for height which will only be summarized at baseline.

A listing of vital sign data will be provided.

9.4. Electrocardiogram

ECG parameters include heart rate (beats/min), PR interval (msec), QRS duration (msec) and QTc interval (msec). The ECG results will be interpreted by investigator and recorded as: normal, abnormal not clinically significant, or abnormal clinically significant on eCRF pages. Descriptive statistics of continuous ECG parameters and shift summary of ECG result interpretation from baseline will be provided by visit.

A listing of ECG data will be provided.

9.5. LVEF Evaluation

Actual value and change from baseline in LVEF (%) will be summarized by scheduled visit and treatment group.

A listing of LVEF data will be provided.

9.6. ECOG Performance Status

The ECOG performance status will be summarized as a categorical variable by visit and treatment group. Descriptive summary table for change from baseline in ECOG performance grade will also be provided by visit.

A listing of ECOG performance grade will be provided.

10.Other Analyses

All the summaries will be performed using the Safety set.

10.1. Immunologic Assessments

Collection of blood samples for humoral immunity will be performed for all patients as scheduled in the Schedule of Study Procedures.

[redacted]

Listings of humoral immunogenicity data will be provided.

Analyses of cellular immunogenicity data are conducted by Imugene and is documented separately.

10.1.1. Time-adjusted Area Under Curve (AUC) of Her-2-specific Antibodies

[redacted]

[redacted]

Scatter plot to observe the relationship of time-adjusted AUC of Her-2-specific antibody from Baseline to Day 84 with change in tumor size from baseline to Day 84 will be presented.

10.2. Serum and Biochemical Markers of Tumor Progression

Analyses of serum and biochemical markers of tumor progression data are conducted by Imugene and is documented separately.

10.3. In-Vitro Inhibition of Tumor Cell Growth

Analyses of Her-2-specific antibodies (IgG) inhibition of in-vitro tumor cell growth data are conducted by Imugene and is documented separately.

10.4. Intra-tumor Analysis

Analyses of intra-tumor analysis data are conducted by Imugene and is documented separately.

11.Independent Data Monitoring Committee

An IDMC will regularly monitor the data from this Phase 2 study. The IDMC review meeting will be conducted after 8, 16 and 24 PFS events occur and at intervals of no less than once per year. The purpose of the data review is for safety evaluation. Further details of the IDMC review will be provided in the IDMC charter and separate analysis plan.

12. Secondary Endpoint Analysis

After 24 PFS events have been realized, the final analysis of PFS will be performed, which will also include an OS interim superiority analyses. A failure to meet statistical criterion for PFS will not prevent the final assessment of survival.

As for the final analysis of PFS, and OS interim analysis, in addition to the efficacy analysis on endpoints PFS and OS, it also includes:

- Summary of treatment discontinuation and study discontinuation;
- Summary of the demographics, baseline disease characteristics;
- Summary of study treatment exposure;
- Summary and analysis of other efficacy endpoints including TTP, DCR, ORR, DOR, CTS;
- Overview summary of TEAEs, summaries of all TEAEs by CTCAE grade, treatment-related TEAEs, TEAEs leading to treatment discontinuation, Injection site reaction TEAEs, serious TEAEs and TEAEs leading to death;
- Summary of local laboratory tests, ECG tests, LVEF and ECOG performance grade;
- Summary of AUC and time-adjusted AUC for Her-2-specific antibody and correlation of the Her-2-specific antibody with change in tumor size, PFS and OS;

The same analysis methods will be used as full analysis described in previous sections of this SAP.

[redacted]

13.Changes in the Planned Analysis

[redacted]

14.References

Brookmeyer, R. and Crowley, J. (1982) A confidence interval for the median survival time. Biometrics, 38, 29-41. doi:10.2307/2530286.

Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R. et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version1.1). Eur J Cancer. 2009; 45:228-47.

Shiroiwa T, Fukuda T, Shimozuma K. Cost-effectiveness analysis of trastuzumab to treat HER2-positive advanced gastric cancer based on the randomised ToGA trial. Br J Cancer, 2011;105(9):1273-8.

Wilson, E. B. (1927), “Probable Inference, the Law of Succession, and Statistical Inference,” Journal of the American Statistical Association, 22, 209–212.

15.Appendices

15.1. Appendix 1: Schedule of Study Procedures – Phase 2

	Screen	**Base-line**	**Week 2[K]** (+/- 3d)	**Week 3** (+/- 3d)	**Week 5[K]** (+/- 3d)	**Week 6** (+/- 3d)	**Week 9** (+/- 7d)	**Week 11[K]** (+/- 7d)	**Week 12** (+/- 7d)	**Week 15** (+/- 7d)	**Week 18** (+/- 7d)	**Week 20[K]** (+/- 7d)	**EoT Visit[P]** (+/- 7d)	**Post-treatment FU Visit** (+/- 7d)
Study Days	-21d to -1d	0	14	21	35	42	63	77	84 repeat every 84 days (+/- 7d)	105	126 repeat every 84 days (+/- 7d)	140 repeat every 63 days (+/- 7d)	At least 28 (+/- 7) days after last dose	Every 42 days after EoT
Survival/anti-cancer treatment														X
IMU-131 Vaccination		X	X		X			X				X		
Chemotherapy[F]		X		X		X	X		X	X				
Informed Consent	X													
Demographics and prior medications	X													
Medical History	X													
Cancer History	X													
Physical Exam[O]	X	X		X		X	X		X	X	X		X	
Weight and vital signs (temp, BP, pulse)[L]	X	X	X	X	X	X	X	X	X	X	X	X	X	
Height	X													
ECOG performance status	X	X							X				X	
Radiographic Assessment[E]		X				X			X		X			X[G]
Cardiac Assessment[H]	X								X				X	
Tumor biopsy[I]	X								X[J]				X[J]	
Urine Pregnancy Test[A]	X	X	X	X	X	X	X	X	X	X	X	X	X	
HIV, Hepatitis[M]	X													
Hematology, Chemistry[M]	X	X		X		X	X		X	X	X		X	
Exploratory endpoint labs[B]		X							X				X	
Immunology – humoral[C]		X		X		X	X		X		X		X	
Immunology - cellular[C]		X							X				X	

	Screen	**Base-line**	**Week 2[K]** (+/- 3d)	**Week 3** (+/- 3d)	**Week 5[K]** (+/- 3d)	**Week 6** (+/- 3d)	**Week 9** (+/- 7d)	**Week 11[K]** (+/- 7d)	**Week 12** (+/- 7d)	**Week 15** (+/- 7d)	**Week 18** (+/- 7d)	**Week 20[K]** (+/- 7d)	**EoT Visit[P]** (+/- 7d)	**Post-treatment FU Visit** (+/- 7d)
Study Days	-21d to -1d	0	14	21	35	42	63	77	84 repeat every 84 days (+/- 7d)	105	126 repeat every 84 days (+/- 7d)	140 repeat every 63 days (+/- 7d)	At least 28 (+/- 7) days after last dose	Every 42 days after EoT
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	
Concomitant Procedures	X	X	X	X	X	X	X	X	X	X	X	X	X	
Adverse Events		X	X	X	X	X	X	X	X	X	X	X	X	

A Negative urine pregnancy test required for women of childbearing potential at screening and prior to each vaccination. If positive urine test vaccination may be delayed until negative BHCG blood test.

B A 1 x 10 mL whole blood sample to assess vaccine-specific cytokine levels and in-vitro inhibition of tumor cell growth will be obtained from each patient at Days 0, 84 then every 84 days and at EoT visit.

C 1 x 10 mL (i.e. 1 tube) whole blood sample for humoral immunity at Baseline, Days 21, 42, 63, 84, 126 then every 42 days and EoT visit and 5 x 8 mL blood samples at Baseline, Days 84 then every 84 days and EoT visit for cellular immunity. To be taken prior to vaccination at Baseline visit.

D Chemotherapy will be administered as a concomitant therapy to all patients as a 21-day regimen consisting of: cisplatin by intravenous administration at 80 mg/m2 on the first day of each cycle and either 5-FU, 4000 mg/m2 CIV (administered as 1000 mg/m2/day as continuous infusion for 96 hours on days 1 to 4 of each cycle) or capecitabine for 14 days at 2000 mg/m2/day, orally (administered as 1000 mg/m2 twice daily morning and evening for a total of 2000 mg/m2/day on days 1 to 14 of each cycle), or capecitabine for 14 days at 2000 mg/m2/day, orally (administered as 1000 mg/m2 twice daily morning and evening for a total of 2000 mg/m2/day on days 1 to 14 of each cycle) and oxaliplatin, by intravenous administration at 130 mg/m2 on Day 1 of each cycle. Body weight to be measured and body surface area to be calculated based on weight and baseline height at the start of each 21-day chemotherapy cycle. Chemotherapy continues until ceased by the investigator as clinically indicated for the care of the patient. To document compliance while away from the clinic, patients will record capecitabine treatment in a patient diary.

E Radiographic assessment to occur within 14 days prior to Baseline Visit, then at Days 42, 84, 126 every 42 days thereafter. Radiographic assessment continues until disease progression according to RECIST 1.1 response criteria irrespective of whether patient has withdrawn from the study.

F Chemotherapy continues for up to 6 cycles until disease progression or until ceased by the investigator as clinically indicated for the care of the patient, whichever occurs first.

G Radiographic assessment according to RECIST 1.1 response criteria at post-treatment follow-up visit only for patients withdrawn from the study prior to disease progression.

H Cardiac assessment will be based on assessment of medical history, physical examination, 12-lead ECG results and evaluation LVEF by echocardiography or MUGA scan at Screening, Days 84 then every 84 days and at EoT visit.

I No tumor biopsy is required if a previous pathology result or archival tissue is available confirming HER2/neu expression consistent with Inclusion Criteria #6.

J Optional Day 84 and post-progression tumor biopsy (which may be provided at any time during the post-treatment follow-up period).

K Visit only for 'IMU-131 plus chemotherapy' group.

L Record temperate 30min (+/- 10mins) after each IMU-131 vaccination.

M Local laboratory testing. Safety lab samples can be drawn up to 72 hours before any on-study clinic visit.

O A targeted, symptom directed physical examination may be performed at visits occurring after the Baseline Visit.

P When progressive disease or withdrawal from study has been confirmed, EoT visit will be conducted at least 28 Days (+/- 7) after last dose of study medication. AEs to be checked at least 28 days after last study treatment per Section 9.2: Reporting Period.

15.2. Appendix 2: Imputation Rules for Medication/Adverse Event Date

Missing onset dates (where UK and UKN indicate unknown or missing day and month respectively)

- UK-MMM-YYYY:
    - If the month and year are different from the month and year of the first dose of study drug, assume 01-MMM-YYYY.
    - If the month and year are the same as the first dose of study drug month and year, and the end date (after any imputation) is on or after the first dose of study drug, then assume the date of the first dose of study drug.
    - If the month and year are the same as the first dose of study drug month, and year and the end date (after any imputation) is prior to the first dose of study drug, then assume the end date for the onset date.
- DD-UKN-YYYY/UK-UKN-YYYY:
    - If the year is different from the year of first dose of study drug, assume 01-JAN-YYYY of the collected year.
    - If the year is the same as the first dose of study drug year, and the end date (after any imputation) is on or after the first dose of study drug, then assume the date of the first dose of study drug.
    - If the year is the same as the first dose of study drug, and the end date (after any imputation) is prior to the first dose of study drug, then assume the end date for the onset date.

Missing end dates (where UK and UKN indicate unknown or missing day and month respectively):

- UK-MMM-YYYY: Assume the last day of the month;
- DD-UKN-YYYY/UK-UKN-YYYY: Assume 31-DEC-YYYY

All the imputed end date will not be later than the last day on study.

PPD	PPD Biostatistics and Programming
	Statistical Analysis Plan (SAP) Client Approval Form

Client:	Imugene Limited
Protocol Number:	IMU.ACS.001

Document Description:	Final Statistical Analysis Plan
SAP Title:	HERIZON: A Phase 1b/2 Open-label Study of IMU-131 HER2/neu Peptide Vaccine Plus Standard of Care Chemotherapy with Randomization in Phase 2 in Patients with HER2/neu Overexpressing Metastatic or Advanced Adenocarcinoma of the Stomach or Gastroesophageal Junction
SAP Version Number:	5.0
Effective Date:	12 July 2022

Author(s):

For PPD: [redacted]

Approved by:

[redacted]

Date *(DD-MMM-YYYY)*

Date *(DD-MMM-YYYY)*