nextHERIZON: AN OPEN-LABEL, SIGNAL GENERATING, PHASE 2 STUDY OF HER-VAXX IN COMBINATION WITH CHEMOTHERAPY OR PEMBROLIZUMAB IN PATIENTS WITH METASTATIC HER2/NEU OVER-EXPRESSING GASTRIC OR GASTROESOPHAGEAL JUNCTION (GEJ) ADENOCARCINOMAS WHO HAVE PREVIOUSLY RECEIVED TRASTUZUMAB AND PROGRESSED ON THIS TREATMENT

Compound:	IMU-131
Compound Name:	HER-Vaxx
Protocol Number:	IMU.131.203
IND Number:	27918
Sponsor:	Imugene Limited Suite 12.01, Level 12 4-6 Bligh Street SYDNEY NSW 2000 Australia
Amendment:	4
Amendment Date:	8 August 2023

Approver's Name and Title:	**Signature:**	**Date:**
[redacted]	[redacted]	Aug 10, 2023

The name, title, address and telephone number(s) of the sponsor's medical experts for the study are documented in the study contact list located in the investigator site file.

PROTOCOL ACCEPTANCE FORM

nextHERIZON: AN OPEN-LABEL, SIGNAL GENERATING, PHASE 2 STUDY OF HER-VAXX IN COMBINATION WITH CHEMOTHERAPY OR PEMBROLIZUMAB IN PATIENTS WITH METASTATIC HER2/NEU OVER-EXPRESSING GASTRIC OR GASTROESOPHAGEAL JUNCTION (GEJ) ADENOCARCINOMAS WHO HAVE PREVIOUSLY RECEIVED TRASTUZUMAB AND PROGRESSED ON THIS TREATMENT

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I agree to conduct the study in accordance with the current protocol.

_____

Principal Investigator's Name (print)

_____ _____

Principal Investigator's Signature Date

Please keep the signed original form in your investigator site file, and return a copy to your local study monitor.

DOCUMENT HISTORY

Document	Version Date	Summary of Changes
Original protocol	15 October 2021	N/A
Amendment 1	01 December 2021	- clarify prior treatment requirement for enrollment into Arms - add 15-day interval between enrollment of first 3 patients into Arm 2
Amendment 2	02 March 2022	Table 1: SoA updated S2.1.3/S2.2.4: Exploratory objectives and endpoints updated S3.5: Clarify maximum pembrolizumab treatment duration S4.3: Update exclusion criteria #4, #18 & #19 S5.4/Figure 2: Update treatment plan with additional blood sample collection. S6 and subsections: Move screening exploratory endpoint blood sample to Baseline/Day1, add biomarker blood sample collection to Days 1, 22, 43 and 64, allow for 72-hour collection window prior to Day 1. Add ECOG at Day 64. S6.4.10: Clarify intra-tumor analysis. S7.1.4: Clarify SAE follow-up period for pembrolizumab. S7.1.9: Clarify follow-up period for pregnancy. S8.4: Confirm expansion of either Arm if ≥ 4 of 15 patients have an objective response. Various typographical, administrative, and formatting changes and clarifications to wording to improve readability.

Document	Version Date	Summary of Changes
Amendment 3	11 July 2022	Table 1: SoA updated to align with modified schedules for Arm 1 Table 2: SoA updated to align with modified schedules for Arm 2 S1.6.2: Modified continuation treatment for Arm 1 and Arm 2 S2/Synopsis (Objectives & Endpoints): Modify chemotherapy for Arm 1 S3/ Synopsis (Study Design): - Modify chemotherapy for Arm 1 - Add safety run-in for Arm 1 - Modified dosing schedule for Arm 1 and Arm 2 S4.2/Synopsis (Exclusion Criteria)/: Modify Exclusion #16 S5/Synopsis (Duration of Patients Participation and Duration of Study): - Modify chemotherapy for Arm 1 - Add safety run-in for Arm 1 - Modified dosing schedule for Arm 1 and Arm 2 S6/Synopsis (Study Treatment (s) Dose and Route of Administration): Modify HER-Vaxx dose. Modify chemotherapy. Additional biomarker blood sample collection. S7: Investigational Plan updated to align with dosing schedule modifications S8.2.5: Updated Safety Contact Information Various typographical, administrative, and formatting changes and clarifications to wording to improve readability.
Amendment 4	8 August 2023	Updated Safety contact information. Modified contraception and pregnancy timelines. Updated eligibility to allow prior Enhertu treatment in Arm 1.

Document	Version Date	Summary of Changes
		Updated eligibility such that confirmation of HER2 status after trastuzumab failure only required for Arm 2 and for minimal number of patients for Arm 1. Clarified wording related to eligibility for Arm 1 +/- prior immune checkpoint inhibitors. Revised exclusion criteria related to Immune Checkpoint Inhibitors. Updated sponsor address Added additional ctDNA blood draws and updated Schedule of Activities. Updated schema per changes above and added dosing schema. Modified dosing for Arm 2 to align more closely with Arm 1. Added statement regarding future use of unused central laboratory samples. Other formatting and administrative changes

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LIST OF ABBREVIATIONS

°C	degree Celsius
µg	microgram
1L	first line
5-FU	5-fluorouracil
ADCC	Antibody-dependent cellular cytotoxicity
ADR	Adverse drug reaction
ADC	Antibody-Drug Conjugate
AE(s)	Adverse event(s)
AESI	Adverse events of special interest
AGC	Advanced Gastric Cancer
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
APAP	N-acetyl-para-aminophenol
AST	Aspartate aminotransferase
ATG	Anti-thymocyte globulin
B cell	B lymphocyte
BDISH	Brightfield double *in situ* hybridization
BHCG	Beta-human chorionic gonadotrophin
BSA	Body Surface Area
BUN	Blood urea nitrogen
CBC	Complete blood count
CBER	Center for Biologics Evaluation and Research
CD28	Cluster of differentiation 28
CD3ζ	Cluster of differentiation 3 zeta
CDC	Complement-dependent cytotoxicity
CEA	Carcinoembryonic antigen
CI	Confidence interval
CISH	Chromogenic in situ hybridization
CNS	Central nervous system
CrCl	Creatinine clearance
CSA	Clinical Study Agreement
ctDNA	circulating tumor cell DNA
CTLA4	Cytotoxic T-lymphocyte-associated protein 4
CONSORT	Consolidated Standards of Reporting Trials
CPS	combined positive *score*
CR	Complete Response
CRA	Clinical Research Associate
CRF	Case report form
CRO	Contract research organization

CRP	C-reactive protein
CSA	Clinical Study Agreement
CSR	Clinical Study Report
CT	Computed tomography
CTCAE	National Cancer Institute's Common Toxicity Criteria for Adverse Events
ctDNA	Circulating Tumor DNA
DILI	Drug-induced Liver Injury
DLT	Dose-limiting toxicity
DoR	Duration of Response
DRESS	Drug Rash with Eosinophilia and System Symptom
DSUR	Development safety update report
EAS	Evaluable analysis set
EC	Ethics Committee
ECG	Electrocardiogram
ECHO	Echocardiogram
ECI	Events of clinical interest
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EDC	Electronic data capture
EGF	epithelial growth factor
EGFR	Epidermal growth factor receptor
EoT	End of treatment
FAS	Full Analysis Set
FDA	Food and Drug Administration
FISH	Fluorescent in situ hybridization
FU	Follow Up
G	Gauge
GC	Gastric cancer
GCP	Good Clinical Practice
GEJ	Gastroesophageal junction
GFR	Glomerular filtration rate
GGT	Gamma glutamyl transpeptidase
GI	Gastrointestinal
HBsAg	Hepatitis B surface antigen
HCV	Hepatitis C virus
HER2/neu	Human epidermal growth factor receptor 2
HIV	Human Immunodeficiency Virus
HR	Hazard ratio
IB	Investigator's Brochure
ICF	Informed Consent Form

ICH	International Conference on Harmonization
ICI	Immune checkpoint inhibitor
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Commitee
IFNγ	Interferon gamma
IgG	Immunoglobulin G
IgG4	Immunoglobulin G4
Ig-V type	Ig-variable–type
IHC	Immunohistochemistry
IM	Intramuscular(ly)
IMP	Investigational Medicinal Product
IMU	Imugene Limited, Australia
IMU-131	Investigational product consisting of P467-CRM in Montanide adjuvant
IND	Investigational New Drug
INDSR	Investigational New Drug Safety Report
IO	Immuno-oncology
irAE	Immune related AE
IRB/IEC	Institutional review board/independent ethics committee
ISF	Investigational Site File
ITT	Intent-to-Treat
IUD	intrauterine device
IUS	Intrauterine system
IV	Intravenous(ly)
LDH	Lactate dehydrogenase
LFT	liver function test
LLN	Lower limit of normal
LVEF	Left ventricular ejection fraction
mAb	monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram
mGC	Metastatic Gastric Cancer
mL	milliliter
mm	millimeter
MSS	Microsatellite stable status
MUGA	Multiple gated acquisition (scan)
N	number
NCCN	National Comprehensive Cancer Network®
NCI	National Cancer Institute
NGS	Next generation sequencing
NSAID	Nonsteroidal anti-inflammatory drugs

NSCLC	Non-small cell lung cancer
ORR	Objective Response Rate
OS	Overall survival
PBPK	Physiologically-based PK
PBMC	Peripheral blood mononuclear cell
PBS	Phosphate-buffered saline
PD	Progressive Disease
PD-1	Programmed cell death 1
PD-L1	Programmed death-ligand 1
PD-L2	Programmed death-ligand 2
PEV6C	First generation formulation of IMU-131
PFS	Progression Free Survival
PK	Pharmacokinetics
PKCθ	Protein kinase C theta
PPAS	Per-protocol analysis set
PR	Partial Response
pRBC	Packed red blood cell
PT	Preferred term
PVG	Pharmacovigilance
Q2W	Once every 2 weeks
Q3W	Once every 3 weeks
RBC	Red blood cell
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	Ribonucleic acid
RoW	Rest of World
SAE(s)	Serious adverse event(s)
SAF	Safety Analysis Set
SAP	Statistical analysis plan
SAR	Serious Adverse Reaction
SD	Stable Disease
SJS	Stevens-Johnson Syndrome
SmPC	Summary of Product Characteristics
SoC	Standard of Care
SOC	System organ class
SRC	Safety Review Committee
SUSAR	Suspected Unexpected Serious Adverse Reaction
T1DM	Type 1 Diabetes Mellitus
T cell	T lymphocyte
TEAEs	Treatment-emergent Adverse Events
TEN	Toxic Epidermal Necrolysis

TMB	Tumor mutational burden
TMDD	Target-mediated drug disposition
TME	Tumor microenvironment
ToGA	Trastuzumab for Gastric Cancer
T-regs	Regulatory T-cells
TTP	Time to Progression
ULN	Upper limit of normal
USPI	United States Prescribing Information
VEGFR	Vascular endothelial growth factor receptor
WBC	White blood cell
WHO	World Health Organization
WOCBP	Women of childbearing potential
ZAP70	Zeta-chain-associated protein kinase

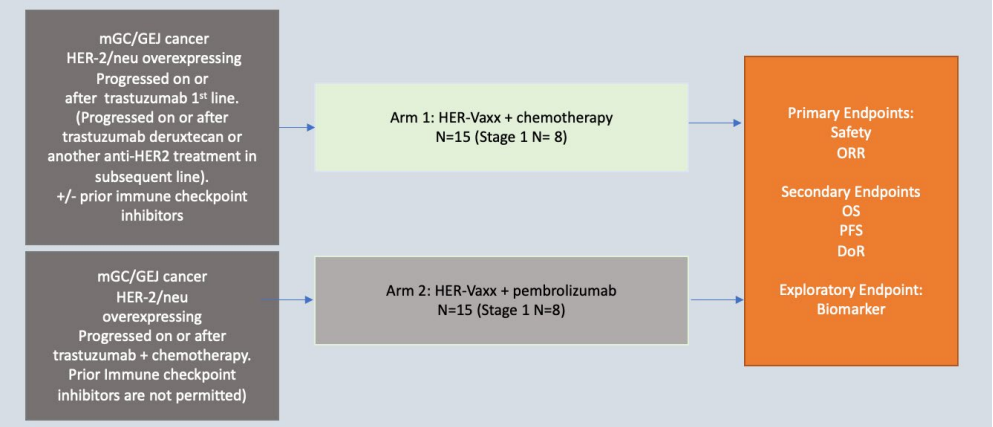
CLINICAL PROTOCOL SYNOPSIS

Study Number and Title	**IMU.131.203** nextHERIZON: An open-label, signal generating, phase 2 study of HER-Vaxx in combination with chemotherapy or pembrolizumab in patients with metastatic HER2/neu over-expressing gastric or gastroesophageal junction (GEJ) adenocarcinomas who have previously received trastuzumab and progressed on this treatment
Sponsor	Imugene Limited
IND Number	027918
Clinical Phase	Phase 2
Indication / Target population	Human epidermal growth factor receptor 2 (HER2/neu) overexpressing advanced or metastatic adenocarcinoma of the stomach or gastroesophageal junction. The intended population is: • Patients who have progressed on or after trastuzumab and other HER2 targeted treatments for their advanced or metastatic disease • Arm 1 only: Patients with documented HER-2 positivity at diagnosis. A post-progression biopsy either fresh or archival tissue, or pathology report should be provided. • Arm 2 only: Patients who have confirmed HER2/neu overexpression since progression on or after trastuzumab by tumor biopsy (post-progression fresh or archival tissue, or post-progression pathology report). • Sponsor may approve use of liquid (blood-based) biopsy where tumor biopsy is not clinically indicated
Number of Sites	Approximately 15 sites globally
Number of Patients	A total of approximately 30 evaluable patients (15 in each Arm).
Rationale	Gastric cancer (GC) is one of the most common cancers worldwide and the third leading cause for cancer death. About 10 to 20% of GC are HER2/neu over-expressing (IARC, 2021). Gastric cancer is often diagnosed at an advanced stage, defined as unresectable locoregional or metastatic disease, which has extremely poor prognosis with 5-year survival not exceeding 5 to 20% (ACS, 2021). Despite significant progress in the treatment of metastatic GC, most patients with metastatic disease succumb to the disease. Therefore, improving the treatment options and effectiveness is critical in changing the outcomes for patients with advanced and metastatic gastric cancer. For patients with advanced and metastatic, HER2/neu over-expressing GC or GEJ adenocarcinoma, the addition of trastuzumab to standard cisplatin/

	fluoropyrimidine chemotherapy improved overall survival (OS) significantly with a Hazard Ratio (HR) of 0.65 (Bang, 2010). Ramucirumab is a human IgG1 monoclonal antibody receptor antagonist designed to bind to the extracellular domain of VEGFR-2. The phase III RAINBOW trial evaluated the efficacy and safety of ramucirumab plus paclitaxel vs placebo plus paclitaxel in patients with locally advanced or metastatic gastric or GEJ adenocarcinoma who have progressed after first-line chemotherapy (Wilke, 2014). OS was significantly longer in the ramucirumab plus paclitaxel group than in the placebo plus paclitaxel group (median 9·6 months [95% CI: 8·5,10·8] vs 7·4 months [95% CI: 6·3,8·4], hazard ratio 0·807 [95% CI: 0·678, 0·962]; p=0·017). PFS was significantly increased in the treatment group compared to the control group (4.4 months [95% CI: 4.2, 5.3] vs 2.9 months [95% CI: 2.8,3.0], hazard ratio 0·64 [95% CI: 0·54, 0·75]; p<0·001). Confirmed objective response rate (ORR) was 28% (95% CI: 23, 33) in the ramucirumab plus paclitaxel Arm compared with 16% (95% CI: 13, 20) for those receiving placebo plus paclitaxel. Ramucirumab plus paclitaxel is now approved as a second-line treatment option for patients with metastatic gastric cancer, who failed first-line treatment with platinum- and fluoropyrimidine-based combinations or trastuzumab in combination with cisplatin and 5-fluorouracil/cisplatin and capecitabine. Most recently there have been two Food and Drug Administration (FDA) approvals that will change the treatment landscape for metastatic GC (mGC)/GEJ. On January 15th, 2020, the FDA granted approval for Enhertu® (trastuzumab deruxtecan), as treatment in HER2/neu over-expressing GC patients who have received a prior trastuzumab based therapy. On May 5th, 2021, the FDA granted accelerated approval to Keytruda® (pembrolizumab) in combination with trastuzumab, fluoropyrimidine- and platinum-containing chemotherapy for the 1L treatment of patients with locally advanced unresectable or metastatic HER2/neu positive gastric or GEJ adenocarcinoma. The approval was based on the prespecified interim analysis of the first 264 patients of the ongoing KEYNOTE-811 (NCT03615326) study, a multicenter, randomized, double blind, placebo-controlled study in patients with HER2/neu positive- advanced gastric or GEJ adenocarcinoma who had not previously received systemic therapy for metastatic disease. Despite the recent advances for the treatment in HER2/neu overexpressing GC/GEJ cancer, there remains an unmet need for treatments that are well tolerated and may include alternative treatment to chemotherapy or to treatment with trastuzumab-deruxtecan. The safety and immunogenicity of the HER-Vaxx (IMU-131) have been shown in a Phase 1b dose finding and an ongoing randomized controlled Phase 2 HERIZON study (IMU.ACS.001), treating patients with advanced and metastatic GC and GEJ with HER-Vaxx + chemotherapy. The study showed an OS benefit with a HR of 0.558 (2-sided 80% CI: 0.349 0.895) at updated final analysis. Safety was shown to be similar between the treatment Arms, with no significant vaccination related toxicity (Maglakelidze, 2023).

	To overcome resistance to immunotherapy within GI cancer, one promising strategy is to increase the number of cytotoxic immune cells within the tumor microenvironment (TME) via the use of polyclonal vaccines such as HER-Vaxx. Active immunization with HER-Vaxx has induced high and long-lasting antibody levels and expanded lymphocytes' subpopulations, such as interferon gamma (IFNγ) producing CD4 and CD8 T cells (Tobias, 2017). Therefore, the introduction of HER-Vaxx in patients that have progressed on or after trastuzumab or other HER-2 targeted treatments may overcome potential HER-2 resistance. Based on pre-clinical synergy HER-Vaxx may also synergize with pembrolizumab and therefore serve as a potentially better tolerated and chemotherapy-free treatment opportunity in metastatic patients that progressed under their previous therapy.
Study Treatment(s)	IMU-131 The investigational product, IMU-131, will be supplied as drug substance P467-CRM197 (aqueous phase vaccine) and Montanide ISA 51 VG (adjuvant). P467-CRM197 is composed of 3 individual B-cell epitopes (P467) selected from the HER2/neu structure and conjugated to CRM197. P467-CRM197 emulsified with Montanide ISA 51 VG forms IMU-131 (HER-Vaxx). Chemotherapy (Arm 1) Chemotherapy will be ramucirumab plus paclitaxel. Chemotherapy (ramucirumab and paclitaxel) will be sourced or reimbursed by the Sponsor as required by local health authority regulations. Pembrolizumab (Arm 2) Pembrolizumab is a humanized immunoglobulin G4 (IgG4) monoclonal antibody (mAb) with high specificity of binding to the programmed cell death 1 (PD-1) receptor, thus inhibiting its interaction with programmed cell death ligand 1 (PD-L1) and programmed cell death ligand 2 (PD-L2). Pembrolizumab will be sourced or reimbursed by the Sponsor where required by local health authority regulations.
Study Design	This study will evaluate safety and efficacy of HER-Vaxx in combination with chemotherapy or pembrolizumab in patients with mGC/GEJ cancer who have progressed on or after trastuzumab treatment. The study includes two treatment Arms that will be analyzed independently using a 2-Stage design: • Arm 1: HER-Vaxx in combination with chemotherapy (ramucirumab plus paclitaxel) • Arm 2: HER-Vaxx in combination with pembrolizumab. Eligibility for Arm 1 requires patients with mGC/GEJ adenocarcinoma overexpressing HER-2/neu who have progressed on or after trastuzumab in combination with chemotherapy as first line therapy; patients that

	subsequently progressed on or after trastuzumab deruxtecan or another anti-HER2 treatment are eligible for enrolment in Arm 1. Arm 1 eligibility does not depend on prior treatment with immune checkpoint inhibitors (ICIs). Eligibility for Arm 2 requires that patients be naïve to immune checkpoint inhibitors and have progressed on or after first line treatment with a HER-2 targeted therapy including trastuzumab in combination with standard of care chemotherapy. For each Arm, after 8 evaluable patients are enrolled (Stage 1), if 1 or more patients respond (i.e., experience complete response [CR] or partial response [PR]), an additional 7 evaluable patients will be enrolled in that Arm (Stage 2). If there are no responses in Stage 1, then preliminary anti-tumor activity in the group will not have been identified and no further patients will be enrolled in that Arm. If the Arm continues to Stage 2, a total of 15 evaluable patients will be studied for that Arm. The Arm will be considered successful if ≥ 4 treated patients respond, and the Arm may be expanded to enroll 25 patients. This design is applied to each Arm separately. Arm 1 requires that a minimum of 5 of 8 patients in Stage 1 and additional 5 patients (i.e. 10 of the total 15 patients enrolled) in Stage 2 must have HER2/neu overexpression as assessed by the central lab or post-progression pathology report. Arm 2 requires that all patients enrolled must have post-progression HER2/neu overexpression confirmed locally for eligibility and subsequently assessed by the central lab or post-progression pathology report. Stage 1 of each Arm will include a safety run-in phase with staggered enrolment with the first 3 patients receiving their first treatment dose at least 15 days apart. After 3 patients are treated with the combination and are considered evaluable for the safety run-in period as defined below, a Safety Review Committee (SRC) consisting of study investigators and Sponsor medical monitor will assess the combination to ensure it is safe before enrolling the remaining patients. **Safety evaluation for combination in Arm 1 and Arm 2** **Arm 1: HER-Vaxx in combination with chemotherapy (ramucirumab plus paclitaxel)** This combination safety evaluation will be based on three evaluable patients at a single dose level of HER-Vaxx plus chemotherapy (ramucirumab plus paclitaxel). An initial 3 patients will be treated and observed for the occurrence of dose-limiting toxicities (DLTs) for a period of 29 days (including 3 doses of HER-Vaxx and at least 1 cycle of chemotherapy). Safety data will be reviewed by the SRC before further patients are enrolled. **Arm 2: HER-Vaxx in combination with pembrolizumab.** This combination safety evaluation will be based on three evaluable patients at a single dose level of HER-Vaxx plus pembrolizumab. An initial 3 patients will be treated and observed for the occurrence of DLTs for a period of 29 days

	(including 3 doses of HER-Vaxx and at least 1 dose of pembrolizumab). Safety data will be reviewed by the SRC before further patients are enrolled. Evaluation of DLTs and enrolment decisions for each: • If less than one-third of evaluable patients experience a DLT (i.e., 0 out of 3, or 1 out of 6), recruitment into the Arm may proceed. • If 1 out of the first 3 patients experiences a DLT, 3 more patients will be entered into the Arm. If 0 of these 3 additional patients experience a DLT, recruitment into the Arm may proceed. • If a DLT is observed in one-third or more patients (i.e., 2 or more of 6 patients) recruitment into the Arm will be stopped. The occurrence of any DLT will be assessed during the first 29 days. DLTs will be graded according to National Cancer Institute [NCI]-Common Terminology Criteria for Adverse Events [CTCAE] version 5.0. **nextHERIZON study design:**  ORR = objective response rate; OS = overall survival; PFS= progression free survival; DoR = duration of response
Objectives	**<u>Primary Safety Objective</u>:** • To evaluate the safety and tolerability of HER-Vaxx in combination with chemotherapy (ramucirumab plus paclitaxel) or pembrolizumab. **<u>Primary Efficacy Objective</u>:** • To evaluate the ORR of HER-Vaxx in combination with chemotherapy or pembrolizumab according to RECIST 1.1. **<u>Secondary Objectives</u>:** • To evaluate additional efficacy and survival measures (OS, PFS, DoR) of HER-Vaxx in each Arm.

	Exploratory Objectives: • To evaluate humoral and cellular immunogenicity data of HER-Vaxx plus chemotherapy (ramucirumab plus paclitaxel) or pembrolizumab. • To evaluate immunogenicity and biochemical markers of tumor progression to clinical outcomes of ORR, OS, PFS, and DoR. • To evaluate Arm-specific associations between clinical outcome and HER2/neu expression, PD-L1 expression and tumor mutational burden (TMB).
Endpoints	**Primary Safety Endpoints**: • Frequency and severity of AEs graded by Common Terminology Criteria for Adverse Events (CTCAE) v5.0. • Frequency and severity of immune-related AEs. • Frequency of patients discontinuing study treatment due to AEs. • Changes and shifts from baseline in clinical laboratory, vital signs, echocardiogram or multiple gated acquisition (MUGA) scan and electrocardiogram (ECG) parameters. **Primary Efficacy Endpoint**: • ORR measured from baseline as the proportion of patients achieving a confirmed best overall response of CR or PR according to RECIST v1.1 based on local review. **Secondary Efficacy Endpoints:** • DoR measured from earliest CR or PR until first documentation of PD based on RECIST v1.1, or death due to any cause. • PFS defined as the time from first dose of study drug to first documentation of progressive disease (PD) based on RECIST v1.1, or to death from any cause. • OS defined as the time from first dose of study drug to death from any cause. **Exploratory Endpoints:** • Values and changes from baseline in humoral and cellular immunogenicity including P467-specific antibodies, HER2-specific antibodies, vaccine-specific cytokine levels and regulatory and effector T and B cells. • Evaluation and Arm-specific associations of serum and biochemical markers of tumor progression and immunogenicity, including humoral and cellular responses, with measures of clinical response including ORR, DoR, PFS, and OS. • Analysis of HER2/neu expression, PD-L1 expression and TMB in pre- and post-treatment tumor biopsies / liquid biopsies (ctDNA/NGS).

Duration of Patients Participation and Duration of Study	Study treatment will continue until disease progression (i.e., if in the opinion of investigator there is no clinical benefit of further treatment after radiographic progression), unacceptable toxicities, withdrawal from study treatment for other reasons, or death. The end of treatment (EoT) visit will be completed at least 30 days after last study treatment. All patients will be followed for survival every 12 weeks from date of EoT for up to 3 years.
Inclusion Criteria	Patients must meet all the following inclusion criteria to be eligible for enrolment into the study: 1. Informed of the investigational nature of this study and provided written informed consent for the study in accordance with institutional, local, and national guidelines; 2. Age ≥18 years of age on day of signing informed consent; 3. Eastern Cooperative Oncology Group (ECOG) performance status 0 - 1; 4. Life expectance of a minimum of 3 months; 5. Confirmed diagnosis of advanced or metastatic HER2/neu overexpressing gastric or GEJ adenocarcinoma; 6. Progressed on or after trastuzumab therapy in combination with standard of care chemotherapy as first line therapy: a. **Arm 1 only**: Patients who subsequently progressed on or after trastuzumab deruxtecan or another anti-HER2 treatment are eligible. Prior therapy with ICIs is allowed, however eligibility does not depend on prior treatment with ICIs. b. **Arm 2 only**: Patients must be naïve to ICIs. 7. At least one measurable lesion as defined by RECIST 1.1 criteria and assessed by the local investigator; 8. **Arm 1 only:** Patients with documented HER-2 positivity at diagnosis. A post-progression tumor biopsy (post-progression fresh or archival tissue) or post-progression pathology report should be provided for a minimum of 5 of 8 patients in Stage 1 and 10 of total 15 after completion of Stage 2 are required; **Arm 2 only:** HER2/neu overexpression (3+ by immunohistochemistry [IHC] or if IHC 2+ confirmed by fluorescent *in situ* hybridization [FISH], brightfield double *in situ* hybridization [BDISH] or chromogenic *in situ* hybridization [CISH]) using post-progression fresh or archival tissue, or post-progression pathology report. Sponsor may approve use of liquid (blood-based) biopsy where tumor biopsy is not clinically indicated; 9. Adequate left ventricular ejection function at baseline, defined as left ventricular ejection fraction (LVEF) > 50% by echocardiogram or MUGA scan;

	10. Adequate hematologic function: a. ANC ≥ 1500/μL b. Platelet count ≥ 100 000/μL c. Hemoglobin ≥ 9 g/dL or ≥ 5.6 mmol/L • Note: Criteria must be met without packed red blood cell (pRBC) transfusion within the prior 2 weeks. Patients can be on stable dose of erythropoietin (≥ approximately 3 months); 11. Adequate hepatic function: a. Total bilirubin ≤ 1.5 x upper limit of normal [ULN] OR direct bilirubin ≤ ULN for patients with total bilirubin levels > 1.5 ULN; b. Alanine aminotransferase (ALT) and aspartate transaminase (AST) ≤ 2.5 x ULN if no liver involvement or ALT and AST ≤ 5 x ULN with liver involvement; 12. Adequate renal function: creatinine ≤ 1.5 x ULN OR measured or calculated creatine clearance (glomerular filtration rate [GFR] can also be used in place of creatinine or creatinine clearance [CrCl] as calculated by institutional standards) ≥30 mL/min for patients with creatinine levels >1.5 × institutional ULN; 13. Male patients must agree not to donate sperm and to use a highly effective method of contraception throughout the study and for at least 180 days after the last dose of assigned treatment; Female patients of childbearing potential must agree to use a highly effective method of contraception throughout the study and for at least 180 days after the final dose of HER-Vaxx, at least 92 days after the final dose of ramucirumab, at least 120 days after the final dose of pembrolizumab, and for 180 days after the final dose of paclitaxel. A patient is of childbearing potential if, in the opinion of the Investigator, she is biologically capable of having children and is sexually active. 14. A female patient is eligible to participate if she is not pregnant, not breastfeeding, and at least one of the following conditions applies: a. Not a woman of childbearing potential (WOCBP); b. A WOCBP who agrees to use highly effective method of contraception during the treatment period and for at least 180 days after the final dose of HER-Vaxx, at least 92 days after the final dose of ramucirumab, at least 120 days after the final dose of pembrolizumab, and for 180 days after the final dose of paclitaxel; 15. Willing and able to comply with all aspects of the protocol.

Exclusion Criteria	Patients presenting with any of the following will not be included in the study: 1. Prior non-investigational therapy for advanced Gastric Cancer within 14 days or major surgery within 28 days prior to Day 1 a. Patients must have recovered from all adverse events (AEs) due to previous therapies to ≤ Grade 1 or baseline. Participants with ≤ Grade 2 neuropathy may be eligible. Patients with endocrine-related AEs Grade ≤ 2 requiring treatment or hormone replacement may be eligible; b. If participant has received major surgery, they must have recovered adequately from the procedure and/or complications from the surgery prior to starting study treatment; 2. Has received prior radiotherapy within 2 weeks of start of study treatment or have had a history of radiation pneumonitis; Note: Participants must have recovered from all radiation-related toxicities. Three months of clinical stability is required post radiotherapy for CNS disease. A 1-week washout is permitted for palliative radiation (≤ 2 weeks of radiotherapy) to non-central nervous system (CNS) disease; 3. Arm 2 only: Has received prior therapy with immune checkpoint inhibitors (e.g. anti-PD-1, anti-PD-L1, or anti-PD-L2); 4. Previous malignant disease (other than primary malignancy) within the last 5 years, except basal or squamous cell carcinoma of the skin or cervical carcinoma in situ; 5. Concurrent active malignancy except for adequately controlled limited basal cell carcinoma of the skin; 6. Clinically significant cardiovascular disease, or other diseases that in the Investigator's opinion may influence the patient's tolerance to study treatment; 7. Pleural effusion or ascites requiring more than weekly drainage; 8. Known allergy to any of the study medications, their analogues, or excipients; 9. Prior organ transplantation, including allogenic stem-cell transplantation; 10. Chronic immunosuppressive therapy including, but not exclusively, steroids (a maximum of 10 mg prednisone a day or equivalent is permitted) or any other form of immunosuppressive therapy within 7 days prior the first dose of study drug; 11. Active, known, or suspected autoimmune disease. Participants with vitiligo, type I diabetes mellitus, residual hypothyroidism due to autoimmune condition only requiring hormone replacement, psoriasis not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger are permitted to enroll;

	12. Has a history of (non-infectious) pneumonitis / interstitial lung disease that required steroids or has current pneumonitis / interstitial lung disease; 13. Serious medical or psychiatric illness that could, in the Investigator's opinion, potentially interfere with the completion of the treatment according to the protocol. Patients with known alcohol or drug abuse are not eligible; 14. Known history of human immunodeficiency virus (HIV) infection or Hepatitis B (defined as Hepatitis B surface antigen [HBsAg] reactive) or known active Hepatitis C virus (defined as HCV Ribonucleic acid (RNA) [qualitative] is detected) infection; Note: No testing for HIV, Hepatitis B and Hepatitis C is required unless mandated by a local health authority; 15. Current participation or has participated in a study of an investigational agent or has used an investigational device within 3 weeks prior to the first dose of study treatment; Note: Patients who have entered the follow-up phase of an investigational study may participate as long as it has been 3 weeks after the last dose of the previous investigational agent; 16. Any vaccination within 14 days prior to starting study treatment; Arm 2 only: Planned live or live attenuated vaccinations. 17. Pregnant or lactating females; 18. Documented hypersensitivity to any component of study treatment or excipients.
Study Treatment(s) Dose and Route of Administration	The dose of HER-Vaxx to be used in combination with chemotherapy or pembrolizumab will be 100 µg. HER-Vaxx will be administered Intramuscular(ly) (IM) into the deltoid region of the upper arm with a 25-38 mm (1-1.5 inches), 21-23G needle as per the Schedule of Activities until treatment discontinuation criterion is met. HER-Vaxx will be administered at least 48 hours prior to initiation of chemotherapy or administered at least 30-60 minutes prior to the administration of pembrolizumab depending on assigned Arm (when scheduled on the same day). **Arm 1:** Patients will receive HER-Vaxx on Days 1 and 15 of Cycle 1, Day 1 of Cycles 2 and 3, then Day 1 of every second cycle from Cycle 3 onwards (Cycle 3 Day 1, Cycle 5 Day 1, etc.). Patients will also receive intravenous (IV) administration of chemotherapy (ramucirumab 8 mg/kg IV on Days 8 and 22 of a 28-day cycle + paclitaxel 80 mg/m^2 IV on Days 8, 15, and 22 of a 28-day cycle), at least 48 hours following the IM administration of HER-Vaxx (when scheduled on the same day) and continue to receive chemotherapy treatment for as long as clinically indicated. HER-Vaxx may continue independently of chemotherapy until treatment discontinuation criterion is met. Similarly, if HER-

	Vaxx has been discontinued, chemotherapy may continue independently until treatment discontinuation criterion is met. **Arm 2:** Patients will receive HER-Vaxx on Days 1 and 15 of Cycle 1, Day 1 of Cycles 2 and 3, then Day 1 of every 3rd cycle from Cycle 3 onward (Cycle 3 Day 1, Cycle 6 Day 1, etc.). Cycle 1 is a 28-day cycle and all subsequent cycles are 21-day cycles. Patients will also receive IV pembrolizumab (200 mg Q3W starting on Cycle 1, Day 8 and continuing on Day 1 of every cycle from Cycle 2 onward) at least 30--60 min following the IM administration of HER-Vaxx (when scheduled on the same day) and will continue treatment until treatment discontinuation criterion is met. HER-Vaxx may continue independently until treatment discontinuation criterion is met if pembrolizumab has been discontinued. Similarly, if HER-Vaxx has been discontinued, pembrolizumab may continue independently until treatment discontinuation criterion is met for a maximum of 35 cycles (approximately 2 years).
Concomitant Medications	Permitted medications include, but are not limited to: 1. Anti-emetics or anti-diarrheal agents as required 2. N-acetyl-para-aminophenol drugs (APAP, [paracetamol/acetaminophen]) 3. Nonsteroidal anti-inflammatory drugs (NSAIDs) The use of APAP and NSAIDs should be assessed on a per-patient basis. Guidelines for the use of paracetamol (acetaminophen) and NSAIDs are as follows: **Paracetamol** • Paracetamol may be used for the treatment and first signs of flu-like signs and symptoms, that may be associated with HER-Vaxx vaccination. • Dosing of paracetamol: The recommended dose is 500 or 1000 mg every 6 to 8 hours. The MAXIMUM daily (24-hour) dose must NOT exceed 3000mg and requires adequate hepatic function. **NSAIDs** • The decision to use oral NSAIDs should be made for each individual patient, with attention to the patient's renal and hydration status at the time of HER-Vaxx administration or the time of imaging scans with contrast. • Dosing of NSAIDs (e.g., oral ibuprofen, other NSAIDs permitted): The recommended dose is 400 or 600 mg ibuprofen (or an equivalent dose for other NSAIDs) every 8 hours. The MAXIMUM daily (24-hour) dose must NOT exceed 1800 mg ibuprofen (or an equivalent dose for other NSAIDs) and for a total of two days only.

	The following medications/treatments are **prohibited** during the study: • Other investigational drug. • Continuous systemic treatment with either corticosteroids or other immunosuppressive or immuno-modulatory medications unless required to treat an immune adverse event. o Note: inhaled or topical steroids and physiological replacement doses of up to 10 mg daily prednisone equivalents are permitted. • Total doses greater than 24 mg dexamethasone equivalent of oral corticosteroids per chemotherapy cycle. • Both treatment Arms: Any vaccination within 14 days prior to any study treatment and during first treatment cycle. • Arm 2 only: Live or live attenuated vaccines while participating in the study are not allowed. Note: Inactivated vaccines are allowed after the first treatment cycle. • Other anti-cancer therapy (i.e., chemotherapy; hormonal therapy; extensive, non-palliative radiation therapy, or standard or investigational agents).
Statistical Analysis	Summary statistics for continuous variables will include the number of patients (*n*), mean, standard deviation, median, minimum, and maximum. Summary statistics for categorical variables will include the frequency and percentage of patients in each category. Summary statistics for time to event data will include the number of patients, estimated median and its 95% CI, 25th percentile, 75th percentile, minimum, and maximum times to event, number of events (total and censored). Results will be summarized by Arm. All data will be listed. Baseline is assumed to be the last observation prior to first dose of study drug. The safety analysis set (SAF) consists of all patients who receive at least one dose of study treatment. All safety and tolerability evaluations will be based on this analysis set. The full analysis set (FAS), which includes all enrolled participants who receive at least 1 administration of study treatment, will be used for analyses of OS and may be used for additional analyses of selected efficacy endpoints. The evaluable analysis set (EAS), which includes all participants who receive at least 1 administration of study treatment and have an evaluable baseline tumor assessment and who have at least one evaluable post-baseline tumor response assessment as per RECIST v1.1 or were discontinued due to toxicity, will be the primary analysis set for analyses of response-based anti-tumor activity endpoints. The ORR along with the associated 95% CI based on the Clopper-Pearson exact method, will be reported. The Kaplan-Meier method will be used to summarize

	OS, PFS and DoR. The EAS will be the primary analysis set for analysis of ORR, PFS, and DoR. The FAS will be the primary analysis set for analysis of OS. All safety analyses will be conducted in the SAF. Adverse events (AEs) will be coded according to the current version of the Medical Dictionary for Regulatory Activities (MedDRA). The severity of AEs will be graded according to NCI CTCAE, v5.0. Treatment-emergent adverse events (TEAEs) are defined as any AE with onset or worsening of a pre-existing condition after the first dose of study drug through 30 days for AEs and 90 days for SAEs/irAEs following the last dose of study drug. Events including TEAEs, AEs leading to dose reduction/interruption, AEs related to study drug, serious adverse events (SAEs), AEs leading to study drug discontinuation, and fatal AEs will be summarized by system organ class (SOC) and preferred term (PT). A summary of AEs of NCI CTCAE Grade 3 or higher, as well as the most frequent AEs (by preferred term), and AEs by relationship to study treatment, will be provided. A listing of DLTs will be reported for the safety run-in phase of both Arms. Values and changes from baseline in clinical laboratory results will be summarized by visit. Clinical laboratory values will be graded according to the NCI CTCAE, for applicable tests. Shifts in toxicity grades from baseline grade will be summarized. Shifts from baseline in ECOG performance status also will be summarized.
Sample Size	For each Arm, after 8 evaluable patients are enrolled (Stage 1), an additional 7 evaluable patients will be enrolled in that Arm (Stage 2) if 1 or more patients respond (i.e., experience CR or PR). If there are no responses in Stage 1, then preliminary anti-tumor activity in the group will not have been identified and no further patients will be enrolled in that Arm. If the Arm continues to Stage 2, a total of 15 evaluable patients will be studied for that Arm. The Arm will be considered successful if $\geq$ 4 treated patients respond, and the Arm may be expanded to enroll 25 patients. This design is applied to each Arm separately and is based on a 2-Stage Simon Minimax design for a total of 15 evaluable patients (null hypothesis that ORR $\leq$ 11% versus the alternative hypothesis that ORR $\geq$ 40% with alpha=0.07268 and power=90.463%).

SCHEDULE OF ACTIVITIES

The Schedule of Activities tables provide an overview of the protocol visits and procedures for each Arm. Refer to Study Procedures (Section 7) for detailed information on each procedure and assessment required for compliance with the protocol.

Table 1. Schedule of Activities Arm 1 (HER-Vaxx + Chemotherapy)

Cycle	Screening (S)	Cycle 1(T)				Cycle 2(T)				Cycle 3 Onwards(T)				End of Treatment(E)	Survival Follow Up (U)
Day	D-21 to D-1	Day 1	Day 8	Day 15	Day 22	Day 1	Day 8	Day 15	Day 22	Day 1	Day 8	Day 15	Day 22		
Cumulative Day	D-21 to D-1	1	8	15	22	29	36	43	50	57	64	71	78		
Visit window	-	-	(+/- 3d)	(+/- 3d)	(+/- 3d)	(+/- 3d)	(+/- 3d)	(+/- 3d)	(+/- 3d)	(+/- 3d)	(+/- 3d)	(+/- 3d)	(+/- 3d)	(+/- 7d)	(+/- 7d)
Informed Consent	X														
Eligibility	X	X(A)													
Tumor biopsy (B)	X					X								X	
Demographics	X														
Medical History	X														
Physical Exam (C)	X	X	X	X	X	X	X	X	X	X(C)	X	X	X	X	
Weight & Vital Signs(D)	X	X	X	X	X	X	X	X	X	X(D)	X	X	X	X	
Height	X									-					
ECOG	X	X								-				X	
Radiographic Assessment(F)		X	X(F)												
Cardiac Assessment(G)	X									C4D1(G)				X	
Pregnancy Test (H)	X	X				X				X(H)				X	
HIV, Hepatitis B/C (I)	X									-					
Hematology, Chemistry(J)	X	X	X	X	X	X	X	X	X	X(J)	X	X	X	X	
Thyroid Function Tests(K)	X	X								X(K)				X	
Exploratory Biomarker (L)		X	X		X			X		X(L)				X	

Cycle	Screening [S]	Cycle 1[T]				Cycle 2[T]				Cycle 3 Onwards[T]				End of Treatment[E]	Survival Follow Up [U]
Day	**D-21 to D-1**	**Day 1**	**Day 8**	**Day 15**	**Day 22**	**Day 1**	**Day 8**	**Day 15**	**Day 22**	**Day 1**	**Day 8**	**Day 15**	**Day 22**		
Cumulative Day	**D-21 to D-1**	**1**	**8**	**15**	**22**	**29**	**36**	**43**	**50**	**57**	**64**	**71**	**78**		
Visit window	**-**	**-**	**(+/- 3d)**	**(+/- 3d)**	**(+/- 3d)**	**(+/- 3d)**	**(+/- 3d)**	**(+/- 3d)**	**(+/- 3d)**	**(+/- 3d)**	**(+/- 3d)**	**(+/- 3d)**	**(+/- 3d)**	**(+/- 7d)**	**(+/- 7d)**
Immunology – humoral [M]		X	X		X			X		X				X	X
Immunology – cellular [N]	X	X	X		X			X		X[N]				X	
ctDNA [O]		X				X				X				X	
HER-Vaxx [P]		X		X		X				X[P]					
Ramucirumab[Q]			X		X		X		X		X		X		
Paclitaxel[Q]			X	X	X		X	X	X		X	X	X		
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Adverse Events[R]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[R]
Survival/ anti-cancer treatment															X

Table 1 Footnotes

A. If screening assessments (Hematology, Blood Chemistry, Thyroid Function Test, Eastern Cooperative Oncology Group [ECOG], Cellular Immunology & Pregnancy Test) are performed within 72 hours of the first study treatment administration, the assessments do not have to be repeated on Cycle 1, Day 1.
B. Documentation of HER-2 positivity at diagnosis is required. A screening visit or archival tumor biopsy (either fresh or archival tissue) or post-progression pathology report should be provided. Cycle 2 and End of Treatment tumor biopsies are optional. The Cycle 2 optional tumor biopsy can be taken on any day during Cycle 2.
C. A limited, symptom-directed physical examination may be performed post Cycle 1, Day 1. Physical exam to be performed at each HER-Vaxx and chemotherapy treatment visit. In HER-Vaxx treatment cycles (C3 C5, C7..), physical exam to be performed at each visit in the cycle (while chemotherapy continues). In non-HER-Vaxx treatment cycles (C4, C6 C8 ..), physical exam not required at D1, but required at D8, D15, D22 (while chemotherapy continues).
D. Weight and Vital Signs (blood pressure, respiratory rate, heart rate and temperature) to be recorded prior to receiving study treatment. In addition, record temperature 30 min (±10 mins) after each HER-Vaxx vaccination. For Arm 1, weight to be used for body surface area (BSA) calculation as per institutional practice. Weight & vital signs must be performed at each HER-Vaxx and chemotherapy treatment visit. In HER-Vaxx treatment cycles (C3 C5, C7..), weight & vital signs to be performed at each visit in the cycle (while chemotherapy continues). In non-HER-Vaxx treatment cycles (C4, C6 C8 ..), weight & vital signs not required at D1, but required at D8, D15, D22 (while chemotherapy continues).
E. The end of treatment (EoT) visit will be completed at least 30 days after last study treatment.
F. Radiographic assessments: Cycle 1 assessment can be performed up to 14 days prior to Cycle 1 Day 1 and then every 6 weeks from Cycle 1, Day 1 within a +/- 3 day window until disease progression, or withdrawal for any other reason. Radiographic assessment is according to Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 response criteria. Upon PD, a scan will be scheduled 4 to 6 weeks after initial PD scan to confirm progression. After discontinuation from the study for any reason other than disease progression, radiographic change will be collected every 12 weeks until determination of progressive disease.

G. Cardiac assessment includes 12-lead ECG and echocardiography or multiple gated acquisition (MUGA) scan. Assessment to be performed at Screening, Cycle 4, Day 1 and then Day 1 every 3 cycles and EoT. Significant abnormal cardiac assessments should be evaluated by a cardiologist.
H. Highly sensitive urine pregnancy test (sensitivity of at least 25 mIU/mL) for all female patients of childbearing potential will be collected once each cycle prior to study treatment and/or chemotherapy:
    - on Day 1 of each odd-numbered cycle, starting Cycle 3.
    - on Day 8 of each even-numbered cycle, starting Cycle 4.

    If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required. Treatment may be delayed until negative beta-human chorionic gonadotrophin (BHCG) blood test is received.
I. Testing for human immunodeficiency virus (HIV), Hepatitis B and Hepatitis C is not required unless mandated by a local health authority.
J. Local hematology and chemistry laboratory testing to be collected prior to receiving any study treatment. Local labs can be drawn up to 72 hours before any on-study clinic visit. Local labs to be taken at each HER-Vaxx and chemotherapy treatment visit. In HER-Vaxx treatment cycles (C3, C5, C7, etc.), safety labs are to be taken at each visit in the cycle (while chemotherapy continues). In non-HER-Vaxx treatment cycles (C4, C6, C8, etc.), safety labs are not required at D1, but are required at D8, D15, D22 (while chemotherapy continues).
K. Thyroid function test to be performed prior to receiving study treatment. Thyroid function test is performed on Day 1 every 2nd cycle from Cycle 3 onward.
L. Whole blood for exploratory biomarkers (all exploratory biomarkers except ctDNA which is captured separately per footnote O) to be collected prior to administration of study treatment. Exploratory biomarkers to be collected on Day 1 every 2nd cycle from Cycle 3 onward.
M. Whole blood for humoral immunity samples to be collected prior to administration of study treatment. Blood samples for humoral immunity to be collected on Day 1 of every cycle from Cycle 3 onward and every 12 weeks for up to 1 year during Survival Follow Up.
N. Whole blood for cellular immunity peripheral blood mononuclear cell (PBMC) samples to be collected prior to administration of study treatment. Cellular immunity samples to be collected on day 1 of every 2nd cycle from Cycle 3 onward.
O. Whole blood for ctDNA HER-2 genotyping will be collected prior to administration of study treatment on Day 1 of every cycle.
P. HER-Vaxx to be administered as indicated for Cycles 1 through 3 and on Day 1 of every 2nd cycle from Cycle 3 (i.e. Cycles 3, 5, 7, …) onward until treatment discontinuation criterion is met. Patients to be observed for 30 minutes post HER-Vaxx administration. Note: Please ensure that HER-Vaxx is administered at least 48 hours before starting paclitaxel (when scheduled on the same day).
Q. Ramucirumab 8 mg/kg IV on Days 8 and 22 of a 28-day cycle + paclitaxel 80 mg/m^2 on Days 8, 15, and 22 of a 28-day cycle, for as long as clinically indicated. Paclitaxel to be administered at least 48 hours after administration of HER-Vaxx (when scheduled on the same day).
R. During Survival Follow-Up serious adverse events (SAEs) considered related to study treatment are to be reported 90 days after the final dose of study treatment or until initiation of new systemic anti-cancer therapy, whichever occurs first.
S. Screening can occur across multiple clinic visits within the 21-day screening period.
T. Each cycle is 28 days.
U. After study discontinuation and completion of the End of Treatment visit, patients will be followed for survival every 12 weeks (± 7 days) for up to 3 years.

Table 2. Schedule of Activities Arm 2 (HER-Vaxx + Pembrolizumab)

Cycle	Screening [T]	Cycle 1[U]				Cycle 2[U]		Cycle 3[U]	Cycle 4 Onwards[U]	End of Treatment[F]	Survival Follow Up [V]
Day	**D -21 to D -1**	**Day 1**	**Day 8**	**Day 15**	**Day 22**	**Day 1**	**Day 15**	**Day 1**	**Day 1**		
Cumulative Day	**D-21 to D-1**	**1**	**8**	**15**	**22**	**29**	**43**	**50**	**71**		
Visit window	**-**	**-**	**(+/- 3d)**	**(+/- 3d)**	**(+/- 3d)**	**(+/- 3d)**	**(+/- 3d)**	**(+/- 3d)**	**(+/- 3d)**	**(+/- 7d)**	**(+/- 7d)**
Informed Consent	X										
Eligibility	X	X[A]									
HER2+ Assessment[B]	X										
Tumor biopsy [C]	X					X				X	
Demographics	X										
Medical History	X										
Physical Exam [D]	X	X	X	X		X		X	X	X	
Weight and vital signs [E]	X	X	X	X		X		X	X	X	
Height	X										
ECOG	X	X								X	
Radiographic Assessment[G]		X	X[G]								
Cardiac Assessment[H]	X								X[H]	X	
Pregnancy Test [I]	X	X				X		X	X	X	
HIV, Hepatitis B/C [J]	X										
Hematology, Chemistry[K]	X	X	X	X		X		X	X	X	
Thyroid Function Tests[L]	X	X					X		X[L]	X	
Exploratory Biomarker [M]		X	X		X		X		X[M]	X	
Immunology – humoral [N]		X	X		X		X		X	X	X
Immunology – cellular [O]	X	X	X		X		X		X[O]	X	
ctDNA [P]		X				X		X	X	X	
HER-Vaxx [Q]		X		X		X		X[Q]		X	
Pembrolizumab[R]			X			X		X	X		
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	
Adverse Events[S]	X	X	X	X	X	X	X	X	X	X	X[S]
Survival/anti-cancer treatment											X

Table 2 Footnotes

A. If screening assessments (Hematology, Blood Chemistry, Thyroid Function Test, Eastern Cooperative Oncology Group [ECOG], Cellular Immunology, & Pregnancy Test) are performed within 72 hours of the first study treatment administration, the assessments do not have to be repeated on Cycle 1, Day 1.
B. Human epidermal growth factor receptor 2 (HER2/neu+) assessment prior to enrollment. Confirmed HER2/neu overexpression (3+ by immunohistochemistry (IHC) or if IHC 2+ confirmed by fluorescent in situ hybridization [FISH], brightfield double in situ hybridization [BDISH] or chromogenic *in situ* hybridization [CISH]) using post-progression fresh or

archival tissue, or post-progression pathology report. Sponsor may approve inclusion based on liquid (blood based) biopsy to assess patients' HER2/neu positivity where tumor biopsy is not clinically indicated.

C. A post-progression fresh or archival tumor biopsy sample or post-progression pathology report will be obtained for all patients to confirm eligibility. Cycle 2 and End of Treatment tumor biopsies are optional. The optional tumor biopsy can be taken on any day during Cycle 2.
D. A limited, symptom-directed physical examination may be performed post Cycle 1, Day 1. The physical exam must be performed prior to receiving any study treatment.
E. Weight and Vital Signs (blood pressure, respiratory rate, heart rate and temperature) to be recorded prior to receiving study treatment. In addition, record temperature 30 min (±10 mins) after each HER-Vaxx vaccination.
F. The end of treatment (EoT) visit will be completed at least 30 days after last study treatment.
G. Radiographic assessments: Cycle 1 assessment can be performed up to 14 days prior to Cycle 1, Day 1 within a +/- 3 day window and then every 6 weeks from Cycle 1, Day 1 until disease progression, or withdrawal for any other reason. Radiographic assessment is according to response evaluation criteria in solid tumors (RECIST) version 1.1 response criteria. Upon PD, a scan will be scheduled 4 to 6 weeks after initial PD scan to confirm progression. After discontinuation from the study for any reason other than disease progression, radiographic change will be collected every 12 weeks until determination of progressive disease.
H. Cardiac assessment includes 12-lead ECG and echocardiography or multiple gated acquisition (MUGA) scan. Assessments to be performed at Screening, Cycle 4 Day 1, then every 4 cycles and at EoT. Significant abnormal cardiac assessments should be evaluated by a cardiologist.
I. Highly sensitive urine pregnancy test (sensitivity of at least 25 mIU/mL) for all female patients of childbearing potential will be collected once each cycle prior to study drug treatment. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required. Treatment may be delayed until negative beta-human chorionic gonadotrophin (BHCG) blood test is received.
J. Testing for Human Immunodeficiency Virus (HIV), Hepatitis B and Hepatitis C is not required unless mandated by a local health authority.
K. Local hematology and chemistry laboratory testing to be collected at each study treatment visit prior to receiving any study treatment. Local labs can be drawn up to 72 hours before any on-study clinic visit.
L. Thyroid function test to be performed prior to receiving study treatment. Thyroid function test to be performed on day 1 every 2nd cycle from Cycle 4 onward (i.e., cycles 4, 6, 8, 10…).
M. Whole blood for exploratory biomarkers (all exploratory biomarkers except ctDNA which is captured separately per footnote O) to be collected prior to receiving study treatment. Exploratory biomarker samples to be collected every 3rd cycle from Cycle 4 onward (i.e., cycles 4, 7, 10…).
N. Humoral samples to be collected prior to receiving study treatment. Blood samples for humoral immunity to be collected on Day 1 of every cycle from Cycle 4 onward and every 12 weeks for up to 1 year during Survival Follow Up.
O. Cellular immunity peripheral blood mononuclear cell (PBMC) to be collected prior to receiving study treatment. Cellular immunity samples to be collected every 3rd cycle from Cycle 4 onwards.
P. Whole blood for ctDNA HER-2 genotyping will be collected prior to administration of study treatment on Day 1 of every cycle.
Q. HER-Vaxx to be administered as indicated for Cycles 1 through 3 and on day 1 of every 3rd cycle from Cycle 3 onward (i.e., cycles 3 6, 9, 12…) until treatment discontinuation criterion is met. Patients to be observed for 30 minutes post HER-Vaxx administration. Note: Please ensure that HER-Vaxx is administered at least 30-60 minutes before starting pembrolizumab (when scheduled on the same day).
R. Pembrolizumab 200 mg administered until treatment discontinuation criterion met for a maximum of 35 cycles. Pembrolizumab to be administered at least 30-60 minutes following administration of HER-Vaxx (when scheduled on the same day).
S. During Survival Follow-Up Serious adverse events (SAEs) considered related to study treatment are to be reported 90 days after the final dose of study treatment or until initiation of new systemic anti-cancer therapy, whichever occurs first.
T. Screening can occur across multiple clinic visits within the 21-day screening period.
U. Cycle 1 is 28 days. Cycles from Cycle 2 onwards are 21 days.
V. After study discontinuation and completion of the End of Treatment visit, patients will be followed every 12 weeks (± 7 days) for up to 3 years.

1. INTRODUCTION

1.1 HER-Vaxx (IMU-131) and Pembrolizumab

The investigational product, IMU-131, will be supplied as drug substance P467-CRM197, which is composed of 3 individual B-cell epitopes (P467) selected from Human epidermal growth factor receptor 2 (HER2/neu) structure and conjugated to CRM197, which becomes HER-Vaxx when emulsified with excipient Montanide (ISA 51 VG Sterile). IMU- 131 induces the patient's own B cells to produce endogenous anti-HER2/neu antibodies.

HER-Vaxx (IMU-131) is being developed for the treatment of patients with HER2/neu overexpressing metastatic or advanced adenocarcinoma of the stomach or GEJ (referred to as advanced gastric cancer [AGC]). Refer to Investigator's Brochure (IB) for detailed background information on HER-Vaxx (IMU-131).

Pembrolizumab is a potent humanized Immunoglobulin G4 (IgG4) monoclonal Antibody (mAb) with high specificity of binding to the programmed cell death 1 (PD1) receptor, thus inhibiting its interaction with programmed cell death ligand 1 (PD-L1) and programmed cell death ligand 2 (PD-L2). Based on preclinical in vitro data, pembrolizumab has high affinity and potent receptor blocking activity for PD1. Pembrolizumab has an acceptable preclinical safety profile and is in clinical development as an IV immunotherapy for advanced malignancies. Keytruda® (pembrolizumab) is indicated for the treatment of patients across a number of indications. For more details on specific indications and for detailed background information refer to the Summary of Product Characteristics (SmPC).

1.2 Background and Rationale

HER-Vaxx is being developed for the treatment of patients with HER2/neu overexpressing metastatic or advanced adenocarcinoma of the stomach or gastroesophageal junction, referred to as AGC.

The transmembrane tyrosine kinase receptor HER2/neu is also known as Neu, Erb-2, CD340, or p185 is a member of the epidermal growth factor receptor (EGFR/ErbB) family. HER2/neu is weakly detectable in epithelial cells of normal tissues but is overexpressed in 15% to 25% of several cancers (Zhang, 2009). In patients with gastric cancer, the receptor has been found to be overexpressed in 15% to 25% of patients (Hofmann, 2008; Park, 2006; Yano, 2006) where it is associated with a poor prognosis, more aggressive disease, and shorter survival. Where it is overexpressed, HER2/neu is typically the primary driver of proliferation for the malignant cells. The overexpression seems to be stable and homogenous in primary tumors as well as their metastases. These findings suggest HER-2/neu may be an attractive target of cancer immunotherapy.

AGC occurs primarily in an inoperable state with metastatic spread to distant lymph nodes or to inner organs and – if operable – tends to recur frequently. The 5-year survival rate of patients with Stage IIIc and IV gastric cancer is only 9% and 4%, respectively (Wagner, 2007) For initial systemic treatment for metastatic and locally advanced HER2-positive AGC, trastuzumab, an HER2/neu inhibitory mAb, is administered in combination with chemotherapy doublets (Roy, 2009). Addition of trastuzumab to the chemotherapy regimen, significantly

improved median overall survival (OS): 13.5 vs 11.1 months (p=0.0048). Based on these data, the combination of trastuzumab plus 5- Fluorouracil (5-FU) and cisplatin chemotherapy has become registered as the standard therapeutic option in first line (1L) setting. However, trastuzumab has been associated with a serious decline in heart function for some patients, and other potentially serious side effects include infusion reactions, pulmonary edema, and respiratory distress.

The elucidation of various molecular pathways involved in the development of AGC has led to a multitude of studies of targeted therapies. Following the success of the ToGA trial, agents such as those targeting the vascular endothelial growth factor (VEGF) angiogenesis pathway have been investigated. Ramucirumab is a human IgG1 monoclonal antibody receptor antagonist designed to bind to the extracellular domain of VEGFR-2. The phase III RAINBOW trial evaluated the efficacy and safety of ramucirumab plus paclitaxel vs placebo plus paclitaxel in patients with locally advanced or metastatic gastric or GEJ adenocarcinoma who have progressed after first-line chemotherapy (Wilke, 2014). OS was significantly longer in the ramucirumab plus paclitaxel group than in the placebo plus paclitaxel group (median 9·6 months [95% CI: 8·5,10·8] vs 7·4 months [95% CI: 6·3,8·4], hazard ratio 0·807 [95% CI: 0·678, 0·962]; p=0·017). PFS was significantly increased in the treatment group compared to the control group (4.4 months [95% CI: 4.2, 5.3] vs 2.9 months [95% CI: 2.8,3.0], hazard ratio 0·64 [95% CI: 0·54, 0·75]; p<0·001). Confirmed ORR was 28% (95% CI: 23, 33) in the ramucirumab plus paclitaxel Arm compared with 16% (95% CI: 13, 20) for those receiving placebo plus paclitaxel. Ramucirumab plus paclitaxel is now approved as a second-line treatment option for patients with metastatic gastric cancer, who failed first-line treatment with platinum- and fluoropyrimidine-based combinations or trastuzumab in combination with cisplatin and 5-fluorouracil/cisplatin and capecitabine.

Despite the recent advances for the treatment in HER2/neu overexpressing gastric cancer (GC)/GEJ cancer and the approvals for Enhertu® and Keytruda® as > 1L treatment options, there remains an unmet need for treatments that are well tolerated and induce durable responses.

To overcome resistance to immunotherapy within AGC, one promising strategy is to increase the number of cytotoxic immune cells directly within the tumor microenvironment (TME) via the use of polyclonal vaccines such as HER-Vaxx. Active immunization with HER-Vaxx has induced high and long-lasting antibody levels and expanded lymphocytes' subpopulations, such as interferon gamma (IFNγ) producing CD4 and CD8 T cells (Weir, 2011; Alanji, 2006; Matsushita, 2013). Therefore, the introduction of HER-Vaxx after 1L treatment in patients that have progressed on trastuzumab may overcome potential resistance against trastuzumab in combination with chemotherapy. It may also synergize with pembrolizumab and therefore serve as a potentially better tolerated and chemotherapy-free treatment opportunity in metastatic patients that progressed under their previous therapy.

1.3 Clinical Rationale for HER-Vaxx (IMU-131, HER2/neu Peptide Vaccine)

Polyclonal antibodies generated against IMU-131 peptides bind three separate regions of the HER2 receptor in domains III and IV thereby inhibiting intracellular signaling as well as inducing antibody dependent cellular cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC).

In vitro and *in vivo* animal experiments with an earlier formulation of IMU-131, PEV6C, have corroborated this approach and have shown the ability to generate an effective antibody response by human B-cells (Wiedermann, 2010). These antibodies were able to induce ADCC and CDC and to inhibit the proliferation of HER2/neu overexpressing tumor cells *in vitro*. PEV6C was also able to effectively inhibit the emergence of HER2/neu overexpressing breast tumors in a transgenic mouse model (Wiedermann, 2010).

IMU-131 is a HER2/neu antigen peptide – adjuvant emulsion (P467-CRM197 – Montanide emulsion) which is injected intramuscularly (IM) into the patient to stimulate innate immunity in response and is processed by antigen presenting cells. The immune system then generates specific adaptive immunity to the HER2/neu antigen peptides. This ultimately leads to the development of B cells that secrete endogenous HER2/neu-specific antibodies that block binding HER2 signaling. Blocking HER2 signaling inhibits proliferation and results in apoptosis in HER2/neu overexpressing tumor cells. Antibody binding to HER2/neu positive cells also signals for additional immunologic clearance through ADCC and CDC. Immunization with this multi-epitope vaccine performed in a c-neu transgenic mouse model demonstrated that the vaccine led to delayed onset of tumor growth and reduced tumor progression *in vivo* (Wiedermann, 2021), providing the rationale to move into human clinical testing.

Several strategies of combining cancer vaccines with chemotherapy have been tested. These studies have revealed that immune-stimulatory cancer vaccines can be safely used in combination with immunosuppressive chemotherapies to condition the immune system and to create an environment where cancer vaccines have a better chance of success. Among the chemotherapies tested to enhance immune responses from vaccines, the underlying mechanism of supporting the immune response of vaccines are favorably described for 5-FU- and cisplatin-based regimens and provide a rationale for the combination of both chemotherapies with an immune-stimulatory vaccine (Weir, 2011). Gastric cancer patients have been successfully immunized with G17DT immunogen resulting in anti-gastrin titers while receiving simultaneous cisplatin and 5-FU chemotherapy (Weidermann, 2021). Matsushita et al (2013) in a Phase 1 study treated patients with AGC using a vaccine containing a mixture of synthetic peptides and oral tegafur/uracil leucovorin. Among the 10 treated patients the responses were 1 partial response (PR) and 7 patients with stable disease (SD).

In the Phase 1 clinical trial of IMU-131 predecessor, PEV6C which was studied in combination with docetaxel in breast cancer patients without HER2/neu overexpression, eight of 10 patients exhibited an increase in HER2/neu-specific antibody titers directed against vaccine peptides as well as native HER2/neu protein. A marked increase in cellular immune responses was observed in the majority of vaccinated patients. In addition, the number of CD4+CD25+Foxp3+ T regulatory cells was markedly reduced following vaccination, suggesting the vaccine was effective in overcoming immunological tolerance to HER2/neu. These data support that the 3 peptide sequences contained in IMU-131 are effective in generating antibodies against HER2/neu as well as inducing additional immunologic changes that increase the activity of cellular immunity and reduce immunologic tolerance to HER2/neu expressing cells (Weidermann, 2021).

Between 08-May-2017 to 08-Feb-2023, 61 patients (14 in Phase 1b and 36 in Phase 2 and 11 in the Phase 2 Extension) diagnosed with metastatic or advanced, HER-2/neu overexpressing, gastric or GEJ adenocarcinoma were enrolled in the IMU-131 clinical development program

(HERIZON [IMU.ACS.001]), of which 47 patients (14 in Phase 1b, 19 in Phase 2, 11 Phase 2 Extension) were dosed with IMU-131. The preliminary immunology and clinical response data from Phase 2 reveal that the addition of HER-Vaxx to chemotherapy significantly prolonged survival. Safety data to date indicate that IMU-131 is well tolerated with no significant local or systemic reactions, and no need for pretreatment or for modification to the dose or treatment schedule due to safety (Weidermann, 2021, Maglakelidze, 2023). The updated final analysis showed an OS benefit with a HR of 0.558 (2-sided 80% CI: 0.349,0.895). Safety, in terms of hematological and non-hematological adverse events, was shown to be similar between the treatment Arms, with no significant vaccination-related toxicity (Maglakelidze, 2023).

The safety and immunological data from HERIZON supports a dose of 100 µg peptide P467 antigen equivalent conjugated to CRM197 in a Montanide emulsion (HER-Vaxx [IMU-131]) as a 1.0 mL injection on Days 0, 14, 35 followed by a booster 42 days later and subsequent boosters every 63 days. The 100 µg dose induced consistently high P467 Abs and HER2 Ab with an observed correlation of titer levels with clinical response.

The investigation of HER-Vaxx plus pembrolizumab is planned in Arm 2 of this study. Nonclinical data demonstrate a synergistic effect of combination HER2 and PD-1 vaccines which resulted in almost 90% of tumor growth inhibition in an HER2+ syngeneic mouse model (Kaumaya, 2020). Preliminary clinical data documented that treatment of HER-Vaxx can induce the upregulation of PD-L1 directly in the tumor tissue, turning a ‘cold’ tumor ‘hot’. Within Arm 2, pembrolizumab will be administered in combination with HER-Vaxx independent of tumor mutational burden (TMB) / microsatellite stable status (MSS)/ programmed death-ligand 1 (PD-L1) status of the tumor.

The proposed dose regimen for both treatment arms in the nextHERIZON study is based on empirical data from the Phase 1b/2 HERIZON study, pre-clinical data demonstrating the immunostimulatory effects of HER-Vaxx, and theoretical grounds for priming of the immune system prior to administering potentially immunosuppressive chemotherapy or immunostimulatory therapy with a checkpoint inhibitor.

The initiation of combination therapy with either standard of care chemotherapy (ramucirumab + paclitaxel) or pembrolizumab, depending on the treatment group, begins one week after the first priming dose of HER-Vaxx. Treatment with chemotherapy for Arm 1 begins on study day 8, with a second dose of HER-Vaxx given on study day 15. This chemotherapy regimen continues for each 28-day cycle. Treatment with pembrolizumab for Arm 2 is administered every 21 days following the study day 8 dose. A similar staggered, priming approach to combination therapy with HER-Vaxx and standard of care chemotherapy using platinum and fluoropyrimidine-based chemotherapy regimens was successfully used in the HERIZON study with good safety and tolerability and stimulation of anti-HER2neu antibodies by HER-Vaxx (refer to the IB).

1.4 Pembrolizumab Pharmaceutical and Therapeutic Background

The importance of intact immune surveillance function in controlling outgrowth of neoplastic transformations has been known for decades (Disis, 2010). Accumulating evidence shows a correlation between tumor-infiltrating lymphocytes in cancer tissue and favorable prognosis in various malignancies. In particular, the presence of CD8+ T-cells and the ratio of CD8+ effector T cells/FoxP3+ regulatory T-cells (T-regs) correlates with improved prognosis and

long-term survival in solid malignancies, such as ovarian, colorectal, and pancreatic cancer; hepatocellular carcinoma; malignant melanoma; and renal cell carcinoma. Tumor-infiltrating lymphocytes can be expanded ex vivo and reinfused, inducing durable objective tumor responses in cancers such as melanoma (Dudley, 2005; Hunder, 2008).

The PD-1 receptor-ligand interaction is a major pathway hijacked by tumors to suppress immune control. The normal function of PD-1, expressed on the cell surface of activated T cells under healthy conditions, is to down-modulate unwanted or excessive immune responses, including autoimmune reactions. PD-1 (encoded by the gene Pdcd1) is an immunoglobulin (Ig) superfamily member related to cluster of differentiation 28 (CD28) and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) that has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (PD-L1 and/or PD-L2) (Greenwald, 2005; Okazaki, 2001).

The structure of murine PD-1 has been resolved (Zhang, 2004). PD-1 and its family members are type I transmembrane glycoproteins containing an Ig-variable–type (IgV type) domain responsible for ligand binding and a cytoplasmic tail responsible for the binding of signaling molecules. The cytoplasmic tail of PD-1 contains 2 tyrosine-based signaling motifs, an immunoreceptor tyrosine-based inhibition motif, and an immunoreceptor tyrosine-based switch motif. Following T-cell stimulation, PD-1 recruits the tyrosine phosphatases, SHP-1 and SHP-2, to the immunoreceptor tyrosine-based switch motif within its cytoplasmic tail, leading to the dephosphorylation of effector molecules such as CD3 zeta (CD3ζ), protein kinase C-theta (PKCθ), and zeta-chain-associated protein kinase (ZAP70), which are involved in the CD3 T-cell signaling cascade (Zhang, 2004; Chemnitz, 2004; Shepard, 2004; Riley, 2009). The mechanism by which PD-1 down-modulates T cell responses is similar to, but distinct from, that of CTLA-4, because both molecules regulate an overlapping set of signaling proteins (Parry, 2005; Francisco, 2010) As a consequence, the PD 1/PD-L1 pathway is an attractive target for therapeutic intervention in HER2/neu overexpressing metastatic or advanced gastric or gastro-esophageal cancer.

1.5 Pre-clinical and Clinical Trials for Pembrolizumab

Therapeutic studies in mouse models have shown that administration of antibodies blocking PD-1/PD-L1 interaction enhances infiltration of tumor-specific CD8+ T cells and ultimately leads to tumor rejection, either as a monotherapy or in combination with other treatment modalities (Blank, 2004; Weber, 2010; Strome, 2003; Spranger, 2014; Curran, 2010; Pilon-Thomas, 2010). Anti-mouse PD-1 or anti-mouse PD-L1 antibodies have demonstrated antitumor responses in models of squamous cell carcinoma, pancreatic carcinoma, melanoma, acute myeloid leukemia and colorectal carcinoma (Strome, 2003; Curran, 2010; Pilon-Thomas, 2010; Nomi, 2007). In such studies, tumor infiltration by CD8+ T cells and increased IFN-γ, granzyme B and perforin expression were observed, indicating that the mechanism underlying the antitumor activity of PD-1 checkpoint inhibition involved local infiltration and activation of effector T cell function in vivo (Pilon-Thomas, 2010; Hirano, 2005). Experiments have confirmed the *in vivo* efficacy of anti-mouse PD-1 antibody as a monotherapy, as well as in combination with chemotherapy, in syngeneic mouse tumor models.

1.6 Risks and Benefits for nextHERIZON

It is anticipated that the information gained from this study will contribute to the development of a safe and effective anti-HER2/neu peptide vaccine. It is unknown whether patients will benefit from participation in this study. The investigational product-related risks to patients in this study are associated with the general risk of vaccination, however HER-Vaxx in the HERIZON study revealed no systemic or immune related toxicities with only mild local injection site reactions. The combination of HER-Vaxx plus chemotherapy showed a similar adverse event profile as chemotherapy alone.

The general risks to patients will arise from their common chemotherapy (Arm 1) or from risks associated with pembrolizumab (Arm 2). Serious and potentially fatal specific and general risks are associated with ramucirumab plus paclitaxel (Arm 1), that will be administered to patients on this study. These treatments are standard care for this disease (NCCN, 2022) and are given in a standard fashion that is familiar to all Investigators. All patients are likely to experience chemotherapy-associated adverse events (AEs).

The risks of pembrolizumab administration are detailed in the Summary of Product Characteristics (SmPC) and label of the compound (Keytruda® SmPC). Pembrolizumab has been documented to cause immune-mediated adverse reactions and infusion-related reactions, for which a series of measures including dose modifications are recommended (Keytruda® SmPC/label, Section 6.3.4. and 6.3.5).

1.6.1. Vaccination-specific Potential Risks Include the Following

Local reactions: An inflammatory reaction as manifested by redness, swelling, and/or tenderness may occur at the site of vaccine injection. Local reactions are expected to resolve within days to weeks without medical intervention and sequelae.

Systemic reactions: May include flu-like symptoms with low-grade fever, chills, and malaise. Experience to date with other peptide vaccines suggests that if such reactions occur, they resolve in days to weeks without therapy or limitation of daily activity. Serum sickness reactions due to deposition of antigen-antibody complexes or idiosyncratic immune responses not dependent on immune complexes could develop, resulting in damage to organs such as the liver or kidney. Such immune-mediated reactions have not been reported to date for HER2/neu peptide vaccines. Temporary ascending paralysis, the Guillain-Barré syndrome, may occur with any vaccine, although it is very rare.

The elicitation of polyclonal antibody responses may also elicit antibodies capable of binding Fc receptors and fixing complement making serum sickness and serum sickness-like reactions due to deposition of antigen-antibody complexes theoretically possible. These reactions manifest 5-10 days after treatment and consist of skin rashes, joint pains and fever and have been described for exogenously administered antibodies such as snake anti-venom, horse anti-thymocyte globulin (ATG), rabies and tetanus anti-serum. In this setting the large amounts of antibody can bind to the target antigens and cause immune complex deposition in the tissues. Symptoms and signs typically resolve after cessation of the treatment and may require treatment with high dose corticosteroids for severe reactions. However, non-clinical data indicate HER-Vaxx induces low levels of endogenous antibodies which are not expected to produce circulating immune complexes. Idiosyncratic immune responses not dependent on

immune complexes could also develop, resulting in damage to organs, such as the liver or kidney.

Allergic reactions and anaphylaxis: Allergic and anaphylactic reactions are also possible.

No such reactions have been observed to date.

1.6.2. Management of Risks

The design of this Phase 2 study supports appropriate medical monitoring of patients. Physical monitoring of patients occurs after each vaccination and at regular intervals during each study. Safety Review Committee (SRC) meetings during dose combination, as well as site teleconferences between the medical monitor, sponsor representatives and investigational site staff will occur regularly during the study.

To minimize the risk to patients and maximize safety, the following factors have been incorporated into the study design:

- Detailed safety and laboratory assessments will be performed.
- Review of safety data and dose-limiting toxicities (DLTs) by the SRC
- All clinical observations will be evaluated by the Investigator on an ongoing basis.
- Each patient must stay on site for at least 30 min after HER-Vaxx administration on each treatment day.
- The study agent(s) must be administered in a clinical setting where emergency resuscitative equipment and personnel trained in the management of anaphylaxis are immediately available to treat systemic reactions under the direct supervision of a physician.
- To minimize the potential risk of the combination treatment, the first 3 patients in each Arm are planned to be treated at least 15 days apart and observed for DLTs over 29 days. Decisions on the extensions of the safety run-in or the inclusion of the remaining patients will be made by the SRC. Dose modifications for pembrolizumab are described in Section 6.3.4 and 6.3.5 below.

Complete information for HER-Vaxx (IMU-131) or pembrolizumab is provided in the IB and SmPC respectively.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1 Objectives

2.1.1. Primary Safety Objective

- To evaluate the safety and tolerability of HER-Vaxx in combination with chemotherapy (ramucirumab plus paclitaxel) or pembrolizumab.

2.1.2. Primary Efficacy Objective

- To evaluate the objective response rate (ORR) of HER-Vaxx in combination with chemotherapy or pembrolizumab according to RECIST 1.1.

2.1.3. Secondary Objective

- To evaluate additional efficacy and survival measures (OS, progression free survival [PFS], duration of response [DoR]) of HER-Vaxx in each Arm.

2.1.4. Exploratory Objectives

- To evaluate humoral and cellular immunogenicity data of HER-Vaxx plus chemotherapy (ramucirumab plus paclitaxel) or pembrolizumab.
- To evaluate immunogenicity and serum and biochemical markers of tumor progression to clinical outcomes of ORR, PFS and DoR.
- To evaluate Arm-specific associations between clinical outcome and HER2/neu expression, PD-L1 expression, and TMB.

2.2 Endpoints

2.2.1. Primary Safety Endpoints

- Frequency and severity of adverse events (AEs) graded by Common Terminology Criteria for Adverse Events (CTCAE) v5.0.
- Frequency and severity of immune-related AEs.
- Frequency of patients discontinuing study treatment due to AEs.
- Changes and shifts from baseline in clinical laboratory, vital signs, echocardiogram or multiple gated acquisition (MUGA) scan and electrocardiogram (ECG) parameters.

2.2.2. Primary Efficacy Endpoint

- ORR measured from baseline as the proportion of patients achieving a confirmed best overall response of complete response (CR) or partial response (PR) according to RECIST v1.1 based on local review.

2.2.3. Secondary Efficacy Endpoints

- DoR measured from earliest CR or PR until first documentation of PD based on RECIST v1.1 or death due to any cause.
- PFS defined as the time from first dose of study drug to first documentation of progressive disease (PD) based on RECIST v1.1, or to death from any cause.
- OS defined as the time from first dose of study drug to death from any cause.

2.2.4. Exploratory Endpoints

- Values and changes from baseline in humoral and cellular immunogenicity including P467-specific antibodies, HER2-specific antibodies, vaccine-specific cytokine levels and regulatory and effector T and B cells.
- Evaluation and Arm-specific associations of serum and biochemical markers of tumor progression and immunogenicity, including humoral and cellular responses, with measures of clinical response including ORR, OS, PFS and DoR.
- Analysis of HER2/neu expression, PD-L1 expression and TMB in pre- and post-treatment tumor biopsies/liquid biopsies (circulating tumor DNA [ctDNA]/next generation sequencing [NGS]).

3. STUDY DESIGN

3.1 Overall Study Design

This study will evaluate safety and efficacy of HER-Vaxx in combination with chemotherapy (ramucirumab plus paclitaxel) or pembrolizumab in patients with metastatic GC (mGC)/GEJ cancer who have progressed on or after trastuzumab treatment.

For Arm 2, all patients must be re-assessed for their HER2/neu status prior to enrollment into the study due to potential HER2/neu loss during their previous treatment with trastuzumab (Seo, 2019). Patients must have confirmed HER2/neu overexpression since last progression by tumor biopsy (post-progression fresh or archival tissue, or post-progression pathology report). Sponsor may approve inclusion based on liquid (blood-based, ctDNA/NGS) biopsy to assess patients' HER2/neu positivity where tumor biopsy is not clinically indicated.

The study will include 2 treatment Arms that will be independently assessed for their endpoints.

- Arm 1: HER-Vaxx + chemotherapy (ramucirumab and paclitaxel)
- Arm 2: HER-Vaxx + pembrolizumab

Eligibility for Arm 1 requires patients with mGC/GEJ adenocarcinoma overexpressing HER-2/neu who have progressed on or after trastuzumab in combination with chemotherapy as first line therapy; patients that subsequently progressed on or after trastuzumab deruxtecan or another anti-HER2 treatment are eligible for enrolment in Arm 1. Arm 1 eligibility does not depend on prior treatment with immune checkpoint inhibitors (ICIs).

Eligibility for Arm 2 requires that patients be naïve to immune checkpoint inhibitors and have progressed on or after first line treatment with a HER-2 targeted therapy including trastuzumab in combination with standard of care chemotherapy.

In both Arms, HER-Vaxx may continue independently of chemotherapy or pembrolizumab until treatment discontinuation criterion is met. In Arm 1, chemotherapy may continue independently until treatment discontinuation criterion is met if HER-Vaxx has been discontinued. In Arm 2, pembrolizumab may continue independently of HER-Vaxx until treatment discontinuation criterion is met, for a maximum of 35 cycles (approximately 2 years).

For each Arm, after 8 evaluable patients are enrolled (Stage 1), if 1 or more patients respond (i.e., experience CR or PR), an additional 7 evaluable patients will be enrolled in that Arm (Stage 2). If there are no responses in Stage 1, then preliminary anti-tumor activity in the group will not have been identified and no further patients will be enrolled in that Arm. If the arm continues to Stage 2, a total of 15 evaluable patients will be studied for that Arm. The Arm will be considered successful if ≥ 4 treated patients respond, and the arm may be expanded to enroll 25 patients. This design is applied to each arm separately.

Arm 1 requires a minimum of 5 of 8 patients in Stage 1 and additional 5 patients (i.e. 10 of the total 15 patients enrolled) in Stage 2 must have HER2/neu overexpression as assessed by the central lab or post-progression pathology report.

Arm 2 requires that all patients enrolled must have post-progression HER2/neu overexpression confirmed locally for eligibility and subsequently assessed by the central lab or post-progression pathology report.

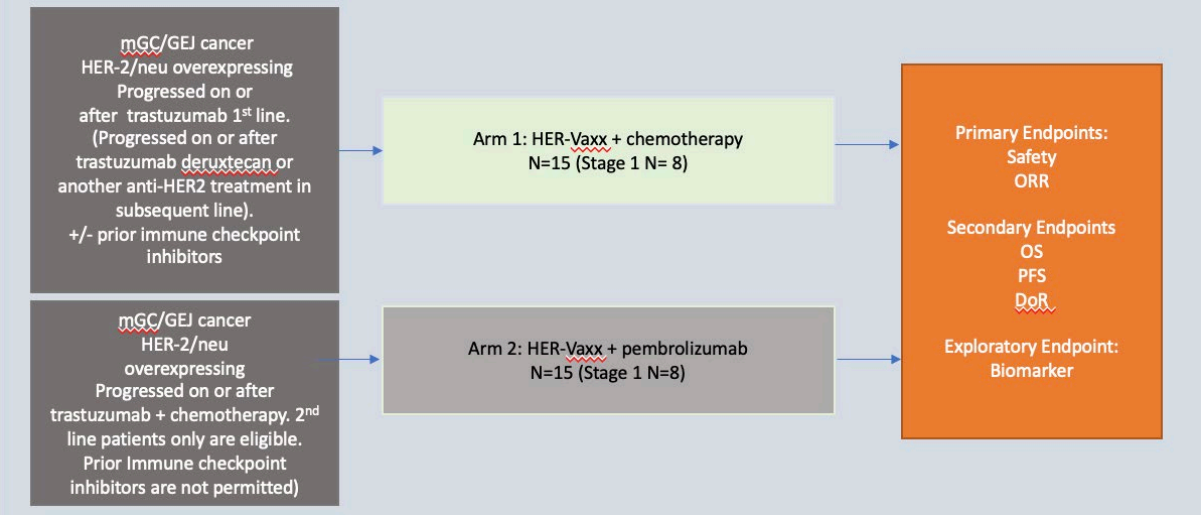
Stage 1 of each arm will include a safety run-in phase with staggered enrollment, with the first 3 patients receiving their first treatment dose at least 15 days apart. After 3 patients are treated with the combination and are considered evaluable for the safety run-in period as defined below, a SRC consisting of study investigators, , and Sponsor medical monitor will assess the combination to ensure an acceptable safety profile has been established before enrolling the remaining patients.

The primary objectives are to evaluate safety as well as ORR independently for each treatment arm. Additional anti-tumor activity in terms of OS, PFS and DoR serve as secondary objectives.

Exploratory objectives include biomarker evaluation and arm-specific associations of biomarkers, including humoral and cellular responses, with measures of clinical response including ORR, OS, PFS and DoR.

The nextHERIZON study set up is provided in Figure 1.

Figure 1. Study Schema



Chemotherapy (ramucirumab 8 mg/kg IV on Days 8 and 22 of a 28-day cycle + paclitaxel 80 mg/m2 IV on Days 8, 15, and 22 of a 28-day cycle). ORR = objective response rate; OS = overall survival; PFS= progression free survival; DoR = duration of response.

3.1.1. Safety and HER2 Antibody Consideration

Both Arms will include a safety run-in phase with staggered enrollment with the first 3 patients receiving their first treatment dose at least 15 days apart. After 3 patients are treated with the combination, and are considered evaluable for the safety run-in period as defined below, a SRC consisting of study investigators, , and Sponsor medical monitor will assess the combination to ensure an acceptable safety profile has been established before enrolling the remaining patients.

3.1.2. Safety Evaluation for Combination in Arm 1 and Arm 2

Arm 1: HER-Vaxx in combination with chemotherapy (ramucirumab plus paclitaxel)

This combination safety evaluation will be based on three evaluable patients at a single dose level of HER-Vaxx plus chemotherapy (ramucirumab plus paclitaxel). An initial 3 patients will be treated and observed for the occurrence of DLTs for a period of 29 days (including 3 doses of HER-Vaxx and at least 1 cycle of chemotherapy). Safety data will be reviewed by the SRC before further patients are enrolled.

Arm 2: HER-Vaxx in combination with pembrolizumab

This combination safety evaluation will be based on three evaluable patients at a single dose level of HER-Vaxx plus pembrolizumab. An initial 3 patients will be treated and observed for the occurrence of DLTs for a period of 29 days (including 3 doses of HER-Vaxx and at least 1 dose of pembrolizumab). Safety data will be reviewed by the SRC before further patients are enrolled.

3.1.2.1. DLT Evaluation for both Arms

Evaluation of DLTs and enrollment decisions in each Arm:

- If less than one-third of evaluable patients experience a DLT (i.e., 0 out of 3, or 1 out of 6) recruitment into the Arm may proceed.
- If 1 out of the first 3 patients experiences a DLT, 3 more patients will be entered into the Arm. If 0 of these 3 additional patients experience a DLT, recruitment into the Arm may proceed.
- If a DLT is observed in one-third or more patients (i.e., 2 or more of 6 patients) recruitment into the Arm will be stopped.

3.1.2.2. DLT Definition

For the study, the occurrence of any of the following toxicities during the first 29 days will be considered a DLT, if assessed by the investigator to be possibly, probably, or definitely related to study treatment administration:

- Grade 3 or 4 cardiac toxicity
- Grade 4 nonhematologic toxicity (not laboratory).
- Grade 4 hematologic toxicity lasting ≥ 7 days, except thrombocytopenia:
    - Grade 4 thrombocytopenia of any duration
    - Grade 3 thrombocytopenia associated with clinically significant bleeding
- Any nonhematologic adverse event (AE) ≥ Grade 3 in severity should be considered a DLT, with the following exceptions: Grade 3 fatigue lasting ≤ 3 days; Grade 3 diarrhea, nausea, or vomiting without use of anti-emetics or anti-diarrheals per standard of care; Grade 3 rash without use of corticosteroids or anti-inflammatory agents per standard of care.

- Any Grade 3 or Grade 4 non-hematologic laboratory value if:
    - Clinically significant medical intervention is required to treat the patients or
    - The abnormality leads to hospitalization, or
    - The abnormality persists for > 1 week.
    - The abnormality results in a Drug-induced Liver Injury (DILI)
    - Exceptions: Clinically nonsignificant, treatable, or reversible laboratory abnormalities including liver function tests, uric acid, etc.
- Febrile neutropenia Grade 3 or Grade 4:
    - Grade 3 is defined as absolute neutrophil count (ANC) < 1000/mm3 with a single temperature of > 38.3 degrees C (101 degrees F) or a sustained temperature of ≥ 38 degrees C (100.4 degrees F) for more than 1 hour
    - Grade 4 is defined as ANC < 1000/mm^3 with a single temperature of > 38.3 degrees C (101 degrees F) or a sustained temperature of ≥38 degrees C (100.4 degrees F) for more than 1 hour, with life-threatening consequences and urgent intervention indicated.
- Prolonged delay (> 2 weeks) in initiating Cycle 2 due to treatment-related toxicity.
- Grade 5 toxicity.

DLTs will be graded according to NCI- CTCAE version 5.0 (Appendix B).

3.2 Safety Review Committee

Safety data from both Arms will be reviewed by the SRC on an ongoing basis for the duration of the study.

The decision to continue enrollment or extend the safety run-in will be taken by the SRC after reviewing all available safety data (including DLTs) from the first 3 evaluable patients that are part of the safety run-in and have completed the DLT observation period. The safety run-in can be extended by another 3 patients, or all additional patients can be enrolled for Stage 1 based on the occurrence of DLTs.

On an on-going basis, the SRC will review the safety data and make recommendations on the continuation of the study following the procedures outlined in the SRC charter.

The SRC is comprised of study investigators and Sponsor medical monitor. All decisions will be documented in the form of minutes.

Based on the review of available data on safety, the SRC will make recommendations regarding further conduct and the scientific and ethical integrity of the study. The SRC will provide one of the following recommendations:

- Arm 1 / Arm 2 is to be continued
- Arm 1 / Arm 2 is to be stopped

- Modification of the study to address safety and dosing issues.

The Sponsor will act upon these recommendations as appropriate, i.e., the final decision will rest with the Sponsor. The Sponsor designee will notify the study team of the final decision regarding the SRC recommendations, including any actions to be taken. The study team will communicate the SRC recommendations and/or final decision of the Sponsor to all Investigators, the Institutional Review Boards (IRBs) / Independent Ethics Committees (IECs) and the Food and Drug Administration (FDA), if applicable. Refer to SRC charter for details.

3.3 Measures to Minimize Bias

This is an open-label non-randomized study; blinding and randomization are not applicable.

3.4 Duration of Patient Participation

Study treatment will continue until disease progression (i.e., if in the opinion of investigator there is no clinical benefit of further treatment after radiographic progression), unacceptable toxicities, withdrawal from study treatment for other reasons, or death.

The end of treatment (EoT) visit will be completed at least 30 (± 7) days after last study treatment.

All patients will be followed for survival from date of End of Treatment (EoT) every 12 weeks (± 7 days) for up to 3 years.

4. STUDY PATIENT POPULATION

4.1 Inclusion Criteria

Patients must meet all the following inclusion criteria to be eligible for enrolment into the study:

1. Informed of the investigational nature of this study and provided written informed consent for the study in accordance with institutional, local, and national guidelines;
2. Age ≥ 18 years of age on day of signing informed consent;
3. Eastern Cooperative Oncology Group (ECOG) performance status 0-1;
4. Life expectance of a minimum of 3 months;
5. Confirmed diagnosis of advanced or metastatic HER2/neu overexpressing gastric or GEJ adenocarcinoma;
6. Progressed on or after trastuzumab therapy in combination with standard of care chemotherapy as first line therapy:
    a. **Arm 1 only**: Patients who subsequently progressed on or after trastuzumab deruxtecan or another anti-HER2 treatment are eligible. Prior therapy with ICIs is allowed, however eligibility does not depend on prior treatment with ICIs.
    b. **Arm 2 only**: Patients must be naïve to ICIs.
7. At least one measurable lesion as defined by RECIST v1.1 criteria and assessed by the local investigator;
8. **Arm 1 only**: Patients with documented HER-2 positivity at diagnosis. A post-progression tumor biopsy (post-progression fresh or archival tissue) or post-progression pathology report should be provided for a minimum of 5 of 8 patients in Stage 1 and 10 of total 15 after completion of Stage 2 are required; **Arm 2 only**: HER2/neu overexpression (3+ by immunohistochemistry [IHC] or if IHC 2+ confirmed by fluorescent *in situ* hybridization [FISH], brightfield double *in situ* hybridization [BDISH] or chromogenic *in situ* hybridization [CISH]) using post-progression fresh or archival tissue, or post-progression pathology report. Sponsor may approve use of liquid (blood-based) biopsy where tumor biopsy is not clinically indicated;
9. Adequate left ventricular ejection function at baseline, defined as left ventricular ejection fraction (LVEF) > 50% by echocardiogram or MUGA scan;
10. Adequate hematologic function:
    a. Absolute neutrophil count (ANC) ≥ 1500/µL
    b. Platelet count ≥ 100 000/µL
    c. Hemoglobin ≥ 9 g/dL or ≥ 5.6 mmol/L

    Note: Criteria must be met without packed red blood cell (pRBC) transfusion within the prior 2 weeks. Patients can be on stable dose of erythropoietin (≥ approximately 3 months);
11. Adequate hepatic function:
    a. Total bilirubin ≤ 1.5 x upper limit of normal [ULN] OR direct bilirubin ≤ ULN for patients with total bilirubin levels > 1.5 ULN;

b. Alanine aminotransferase (ALT) and aspartate transaminase (AST) ≤ 2.5 x ULN if no liver involvement or ALT and AST ≤ 5 x ULN with liver involvement;

12. Adequate renal function: creatinine ≤ 1.5 x ULN OR measured or calculated creatine clearance (GFR can also be used in place of creatinine or creatinine clearance (CrCl) as calculated by institutional standards) ≥ 30 mL/min for patients with creatinine levels > 1.5 × institutional ULN;
13. Male patients must agree not to donate sperm and to use a highly effective method of contraception throughout the study and for at least 180 days after the last dose of assigned treatment. Females (childbearing potential) must agree to use a highly effective method of contraception throughout the study and for at least 180 days after the final dose of HER-Vaxx, at least 92 days after the final dose of ramucirumab, at least 120 days after the final dose of pembrolizumab, and for 180 days after the final dose of paclitaxel. A patient is of childbearing potential if, in the opinion of the Investigator, she is biologically capable of having children and is sexually active.
14. A female patient is eligible to participate if she is not pregnant, not breastfeeding, and at least one of the following conditions applies:
    a. Not a woman of childbearing potential (WOCBP)
    b. A WOCBP who agrees to use highly effective method of contraception during the treatment period and for at least 180 days after the final dose of HER-Vaxx, at least 92 days after the final dose of ramucirumab, at least 120 days after the final dose of pembrolizumab, and for 180 days after the final dose of paclitaxel;
15. Willing and able to comply with all aspects of the protocol.

4.2 Exclusion Criteria

Patients presenting with any of the following will not be included in the study:

1. Prior therapy for advanced Gastric Cancer within 14 days or major surgery within 28 days prior to Day 1;
    a. Patients must have recovered from all adverse events (AEs) due to previous therapies to ≤ Grade 1 or baseline. Participants with ≤ Grade 2 neuropathy may be eligible. Patients with endocrine-related AEs Grade ≤ 2 requiring treatment or hormone replacement may be eligible;
    b. If participant has received major surgery, they must have recovered adequately from the procedure and/or complications from the surgery prior to starting study treatment;
2. Has received prior radiotherapy within 2 weeks of start of study treatment or have had a history of radiation pneumonitis;

    Note: Participants must have recovered from all radiation-related toxicities. Three months of clinical stability is required post radiotherapy for CNS disease.
    A 1-week washout is permitted for palliative radiation (≤2 weeks of radiotherapy) to non-central nervous system (CNS) disease;

3. Arm 2 only: Has received prior therapy with Immune Checkpoint Inhibitors (e.g. anti-PD-1, anti-PD-L1, anti-PD-L2);
4. Previous malignant disease (other than primary malignancy) within the last 5 years, except basal or squamous cell carcinoma of the skin or cervical carcinoma *in situ*;
5. Concurrent active malignancy except for adequately controlled limited basal cell carcinoma of the skin;
6. Clinically significant cardiovascular disease, or other diseases that in the Investigator's opinion may influence the patient's tolerance to study treatment;
7. Pleural effusion or ascites requiring more than weekly drainage;
8. Known allergy to any of the study medications, their analogues, or excipients;
9. Prior organ transplantation, including allogenic stem-cell transplantation;
10. Chronic immunosuppressive therapy including, but not exclusively, steroids (a maximum of 10 mg prednisone a day or equivalent is permitted) or any other form of immunosuppressive therapy within 7 days prior the first dose of study drug;
11. Active, known, or suspected autoimmune disease. Participants with vitiligo, type I diabetes mellitus, residual hypothyroidism due to autoimmune condition only requiring hormone replacement, psoriasis not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger are permitted to enroll;
12. Has a history of (non-infectious) pneumonitis/interstitial lung disease that required steroids or has current pneumonitis / interstitial lung disease;
13. Serious medical or psychiatric illness that could, in the Investigator's opinion, potentially interfere with the completion of the treatment according to the protocol. Patients with known alcohol or drug abuse are not eligible;
14. Known history of human immunodeficiency virus (HIV) infection or Hepatitis B (defined as Hepatitis B surface antigen [HBsAg] reactive) or known active Hepatitis C virus (defined as HCV Ribonucleic acid (RNA) [qualitative] is detected) infection;

    Note: No testing for HIV, Hepatitis B and Hepatitis C is required unless mandated by a local health authority.

15. Current participation or has participated in a study of an investigational agent or has used an investigational device within 3 weeks prior to the first dose of study treatment;

    Note: Patients who have entered the follow-up phase of an investigational study may participate as long as it has been 3 weeks after the last dose of the previous investigational agent.

16. Any vaccination within 14 days prior to starting study treatment; Arm 2 only: Planned live or attenuated vaccinations.
17. Pregnant or lactating females;
18. Documented hypersensitivity to any component of study treatment or excipients.

4.3 Contraception Guidelines

All male and female patients who, in the opinion of the investigator, are biologically capable of having children and are sexually active, must agree to use a highly effective method of contraception consistently and correctly for the duration of the active treatment period and for at least 180 days after the final dose of HER-Vaxx, at least 92 days after the final dose of ramucirumab, at least 120 days after the final dose of pembrolizumab, and for 180 days after the final dose of paclitaxel. The investigator, in consultation with the patient, will select the most appropriate method of contraception for the individual patient from the permitted list of contraception methods, and instruct the patient in its consistent and correct use. The investigator, at each study visit, will confirm and document consistent and correct use. In addition, the investigator will instruct the patient to call immediately if the selected birth control method is discontinued or if pregnancy is known or suspected.

Highly effective methods of contraception are those that, alone or in combination, result in a failure rate of less than 1% per year when used consistently and correctly (i.e., perfect use) and include (refer to 2020_09_HMA_CTFG_Contraception_guidance_Version_1.1_updated.pdf):

1. Established use of oral, injected or implanted hormonal (combined estrogen and progestogen containing or progestogen-only) methods of contraception.

2. Correctly placed intrauterine device (IUD) or intrauterine system (IUS).

3. Male sterilization with appropriately confirmed absence of sperm in the post-vasectomy ejaculate.

4. Bilateral tubal occlusion

5. Sexual abstinence.

4.3.1. Use in Nursing Women

It is unknown whether pembrolizumab or HER-Vaxx is excreted in human milk. Since many drugs are excreted in human milk, and because of the potential for serious adverse reactions in the nursing infant, patients who are breastfeeding are not eligible for enrollment.

5. TREATMENT, PATIENT, STUDY AND SITE DISCONTINUATION

5.1 Study Treatment Discontinuation

Patients may be permanently discontinued from study treatment if they experience any of the following:

- Intolerable toxicity related to study treatment, including development of an immune-mediated adverse event determined by the investigator to be unacceptable given the individual patient's potential response to therapy and severity of the event
- Any medical condition that may jeopardize the patient's safety if he or she continues study treatment
- Investigator or Sponsor determination that treatment discontinuation is in the best interest of the patient
- Use of another non-protocol anti-cancer therapy
- Pregnancy
- Loss of clinical benefit as determined by the investigator after an integrated assessment of radiographic and biochemical data, local biopsy results (if available), and clinical status (e.g., symptomatic deterioration such as pain secondary to disease)

  Note: Patients may discontinue study treatment and be withdrawn from the study based on symptomatic clinical disease progression without documented radiographic evidence after discussion with the Sponsor / Medical Monitor
- Radiographic disease progression per RECIST v1.1 or symptomatic deterioration attributed to disease progression

  Note: Therapy may continue beyond progression if the treating physician feels that the patient is deriving benefit. A repeat early scan will be done 4 weeks after this determination to verify the patient’s status.
- Contraindications to Repeated Administration of HER-Vaxx

  If any of the following AEs arise during the study they constitute contraindications to further administration of HER-Vaxx, and patients should discontinue HER-Vaxx treatment permanently and be withdrawn from the study immediately, with appropriate safety follow-up by the investigator until resolution of the event, as with any AE (see Section 8):

  - Anaphylactic reaction following the administration of vaccine(s).
  - Any clinically relevant immunosuppressive or immuno-deficient condition.

The following events constitute contraindications to administration of HER-Vaxx. If an adverse event, the event must be reported and the patient followed as with any adverse event.

Withdrawal of patients experiencing the following events is at the discretion of the investigator as indicated below:

- Acute illness at the time of vaccination
    - Acute illness is defined as the presence of a moderate or severe illness with or without fever. All vaccines can be administered to persons with a minor illness such as diarrhea, mild upper respiratory infection with or without low-grade febrile illness, i.e., temperature < 38°C.
    - Withdrawal is at the discretion of the investigator if acute illness will not resolve in sufficient time to allow for vaccination schedule to continue.
- Temperature ≥ 38°C at the time of vaccination
    - Withdrawal is at the discretion of the investigator if raised temperature will not resolve in sufficient time to allow for vaccination schedule to continue.

The primary reason for study treatment discontinuation should be documented on the appropriate electronic case report form (eCRF).

5.2 Patient Discontinuation from the Study

Patients have the right to voluntarily withdraw from the study at any time for any reason. In addition, the investigator has the right to withdraw a patient from the study at any time.

Reasons for patient discontinuation from the study may include, but are not limited to, the following:

- Patient withdrawal of consent
- Study termination or site closure
- Adverse event
- Loss to follow-up

Every effort should be made to obtain a reason for patient discontinuation from the study. The primary reason for discontinuation from the study should be documented on the appropriate eCRF.

If a patient withdraws from the study, the study staff may use a public information source (e.g., county records) to obtain information about survival status.

5.3 Study Discontinuation

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

- A decision by the Sponsor to suspend or discontinue testing, evaluation, or development of the product. If the SRC recommends, based on review of the safety or effectiveness data, that the risks of study treatment exceed its potential benefit to study patients, the Sponsor may decide to terminate all patient treatment in this study.

- The decision by the Sponsor to discontinue the study based on the response observations associated with the 2-Stage design of this study, for both Arms independently (Section 9.4).
- The SRC may at any moment recommend temporary suspension of enrollment and treatment of patients in this study.
- Occurrence of a second DLT in any Arm during the DLT period will result in study stop and safety review by the SRC.
- Occurrence of a Grade 5 HER-Vaxx (IMU-131) or combination related adverse event.
- Occurrence of an AE meeting DLT criteria for hematological and non-hematological events in more than one-third of enrolled patients or two Grade 4 adverse events and at least possibly related to HER-Vaxx or the combination of HER-Vaxx and pembrolizumab (as per Section 3.1.2).

Immune related AEs will be monitored throughout the study as per National Comprehensive Cancer Network® [NCCN] guideline insights (Thompson, 2020).

- Immune related AEs: any Grade ≥ 3 event that does not resolve to Grade 1 (or baseline) within 7 days from the onset of the event, or any Grade ≥ 3 organ toxicity involving major organ systems that persists for greater than 72 hours, or any Grade ≥ 4 event will be reviewed and the SRC together with the Sponsor will decide on:
    - Halting patient dosing or study enrollment until the toxicity data can be further studied
    - Evaluating additional patients in a particular Arm to make the study more sensitive to characterizing adverse events
    - Exclusion of certain patients thought to be more at-risk for a particular adverse event.

The identification of a study-stopping for HER-Vaxx criterion in a patient will result in the permanent discontinuation of this patient and enrollment into the affected arm will be temporarily held until an appropriate evaluation of the cause of toxicity has been determined and a corrective action plan is established if needed. Under the condition, that any DLTs are classified as possibly related to HER-Vaxx, the investigators will decide on continuation of the study after consultation of the SRC, in mutual agreement with the Sponsor.

The Sponsor medical monitor should be notified immediately i.e. within 24 hours of learning of their occurrence, and the patient should be followed for safety as clinically indicated until the toxicity resolves and, in the opinion of the investigator, no further follow-up regarding the toxicity is needed (minimum of at least 30 days after last dose of HER-Vaxx).

The Investigator will be notified by the Sponsor if the study is terminated or placed on hold. The relevant IRBs/IECs and FDA will also be informed according to appropriate regulatory requirements.

If the study is prematurely terminated or suspended for any reason, the Investigator/Institution should promptly inform the study patients and should assure appropriate therapy and follow-up for the patients.

Enrollment in an Arm will be terminated if no responses are observed in the first 8 evaluable patients within an Arm as per Section 9.4 or 9.7.

5.4 Site Discontinuation

The Sponsor has the right to close a site at any time. Reasons for closing a site may include, but are not limited to, the following:

- Excessively slow recruitment
- Poor protocol adherence
- Inaccurate or incomplete data recording
- Non-compliance with the International Council for Harmonisation (ICH) guideline for Good Clinical Practice
- No study activity (i.e., all patients have completed the study and all obligations have been fulfilled)

6. STUDY TREATMENT

6.1 Manufacturing and Labelling

6.1.1. Vaccine Supply

The aqueous phase vaccine (P467-CRM197) is manufactured by PiChem Forschungs- und Entwicklungs GmbH, Austria. The adjuvant (Montanide ISA 51 VG) is manufactured by Elaiapharm, France.

The Quality Control Standards and Requirements for the aqueous phase vaccine (P467-CRM197) and the adjuvant (Montanide ISA 51 VG) are described in separate release protocols/Certificate of Analysis and the required approvals have been obtained.

6.1.1.1. Formulation and Packaging

The investigational product, HER-Vaxx, will be supplied as P467-CRM197 (aqueous phase vaccine) and Montanide ISA 51 VG (adjuvant). P467-CRM197 is supplied as a single vial of 200 µg aqueous phase vaccine in 1 mL PBS buffer. Montanide is supplied as single 3 mL vial of Montanide ISA 51 VG.

Arm 1: Chemotherapy (ramucirumab plus paclitaxel) will be sourced or reimbursed by the Sponsor if required by local health authority regulations or institutional policy.

Arm 2: Pembrolizumab is an investigational medicinal product (IMP) and will be provided or reimbursed by the Sponsor as required by local health authority regulations.

6.2 Preparation and Dispensing

Preparation of IMU-131 should be completed by appropriately trained and qualified pharmacy or site staff. Training and qualification will be provided by the Sponsor or their delegate and documented in the study file.

Detailed IMU-131 preparation and dispensing instructions can be found in the pharmacy manual. A droplet test will be used to confirm IMU-131 has been prepared correctly.

Chemotherapy (ramucirumab plus paclitaxel) will be administered IV per SOC and Investigator assessment.

Pembrolizumab for injection will be prepared for IV administration as per SmPC/label.

Only qualified personnel who are familiar with procedures that minimize undue exposure to them and to the environment should undertake the preparation, handling, and safe disposal of chemotherapeutic agents.

6.3 Dose Selection

6.3.1. Dose Selection HER-Vaxx

The dose of HER-Vaxx to be used in combination with chemotherapy or pembrolizumab will 100 µg.

A 1.0ml volume of HER-Vaxx will be administered Intramuscular(ly) (IM) as per the Schedule of Activities until treatment discontinuation criterion is met. The dose and dosing schedule have been selected based on available data from the IMU.ACS.001 study and are designed to compare booster dose schedules (ie., doses administered after first 3 doses) on production of HER2 specific antibodies.

6.3.2. Dose Selection Chemotherapy

Ramucirumab plus paclitaxel is now approved as a second-line treatment option for patients with metastatic gastric cancer, who failed first-line treatment with platinum- and fluoropyrimidine-based combinations or trastuzumab in combination with cisplatin and 5-fluorouracil/cisplatin and capecitabine. Patients in Arm 1 will receive intravenous (IV) administration of chemotherapy (ramucirumab 8 mg/kg IV+ paclitaxel 80 mg/m^2 IV) as per the Schedule of Activities.

6.3.3. Dose Selection Pembrolizumab

The planned dose of pembrolizumab for this study is 200 mg every 3 weeks (Q3W) as per the Schedule of Activities.

Based on the totality of data generated in the Keytruda development program, 200 mg Q3W is an appropriate dose of pembrolizumab for adults across all indications. As outlined below, this dose is justified by:

- Clinical data from 8 randomized studies in melanoma and non-small cell lung cancer (NSCLC) indications demonstrating flat dose- and exposure-efficacy relationships from 2 mg/kg Q3W to 10 mg/kg every 2 weeks (Q2W) representing an approximate 5 to 7.5 fold exposure range
- Population pharmacokinetic (PK) analysis showing that both fixed dosing and weight-based dosing provides similar control of PK variability with considerable overlap in the distributions of exposures, supporting suitability of 200 mg Q3W
- Clinical data showing meaningful improvement in benefit-risk including overall survival at 200 mg Q3W across multiple indications, and
- Pharmacology data showing full target saturation in both systemic circulation (inferred from PK data) and tumor (inferred from physiologically-based PK [PBPK] analysis) at 200 mg Q3W.

Among the 8 randomized dose-comparison studies, a total of 2262 patients were enrolled with melanoma and non-small cell lung cancer (NSCLC), covering different disease settings (treatment naïve, previously treated, PD-L1 enriched, and all-comers) and different treatment settings (monotherapy and in combination with chemotherapy). Five studies compared 2 mg/kg Q3W versus 10 mg/kg Q2W (KN001 Cohort B2, KN001 Cohort D, KN002, KN010, and KN021), and 3 studies compared 10 mg/kg Q3W versus 10 mg/kg Q2W (KN001 Cohort B3, KN001 Cohort F2 and KN006). All of these studies demonstrated flat dose- and exposure-response relationships across the doses studied representing an approximate 5- to 7.5 fold difference in exposure. The 2 mg/kg (or 200 mg fixed-dose) Q3W provided similar responses to the highest doses studied. Subsequently, flat dose-exposure-response relationships were also observed in other tumor types including head and neck cancer, bladder cancer, gastric cancer

and classical Hodgkin Lymphoma, confirming 200 mg Q3W as the appropriate dose independent of the tumor type. These findings are consistent with the mechanism of action of pembrolizumab, which acts by interaction with immune cells, and not via direct binding to cancer cells.

Additionally, pharmacology data clearly show target saturation at 200 mg Q3W. First, PK data in KN001 evaluating target-mediated drug disposition (TMDD) conclusively demonstrated saturation of PD-1 in systemic circulation at doses much lower than 200 mg Q3W. Second, a PBPK analysis was conducted to predict tumor PD-1 saturation over a wide range of tumor penetration and PD-1 expression. This evaluation concluded that pembrolizumab at 200 mg Q3W achieves full PD-1 saturation in both blood and tumor.

Finally, population PK analysis of pembrolizumab, which characterized the influence of body weight and other patient covariates on exposure, has shown that the fixed-dosing provides similar control of PK variability as weight-based dosing, with considerable overlap in the distribution of exposures from the 200 mg Q3W fixed dose and 2 mg/kg Q3W dose. Supported by these PK characteristics and given that fixed-dose has advantages of reduced dosing complexity and reduced potential of dosing errors, the 200 mg Q3W fixed-dose was selected for evaluation across all pembrolizumab protocols.

6.3.4. Dose Modification and Toxicity Management for Immune-related AEs Associated with Pembrolizumab

AEs associated with pembrolizumab exposure may represent immunologic etiology. These Immune related AEs (irAEs) may occur shortly after the first dose or several months after the last dose of pembrolizumab treatment and may affect more than one body system simultaneously. Therefore, early recognition and initiation of treatment is critical to reduce complications. Based on existing clinical study data, most irAEs were reversible and could be managed with interruptions of pembrolizumab, administration of corticosteroids, and/or other supportive care. For suspected irAEs, ensure adequate evaluation to confirm etiology or exclude other causes. Additional procedures or tests such as bronchoscopy, endoscopy, skin biopsy may be included as part of the evaluation. Based on the severity of irAEs, withhold or permanently discontinue pembrolizumab and administer corticosteroids. Dose modification and toxicity management guidelines for irAEs associated with pembrolizumab are provided in Table 3.

Table 3. Dose Modification and Toxicity Management Guidelines for Immune-related AEs Associated with Pembrolizumab

General instructions:

1. Severe and life-threatening irAEs should be treated with IV corticosteroids followed by oral steroids. Other immunosuppressive treatment should begin if the irAEs are not controlled by corticosteroids.
2. Pembrolizumab must be permanently discontinued if the irAE does not resolve or the corticosteroid dose is not ≤10 mg/day within 12 weeks of the last pembrolizumab-treatment.
3. The corticosteroid taper should begin when the irAE is ≤ Grade 1 and continue at least 4 weeks.
4. If pembrolizumab has been withheld, pembrolizumab may resume after the irAE decreased to ≤ Grade 1 after corticosteroid taper.

irAEs	Toxicity grade (CTCAE V5.0)	Action with pembrolizumab	Corticosteroid and/or other therapies	Monitoring and follow-up
Pneumonitis	Grade 2	Withhold	• Administer corticosteroids (initial dose of 1 to 2 mg/kg prednisone or equivalent) followed by taper • Add prophylactic antibiotics for opportunistic infections	• Monitor patients for signs and symptoms of pneumonitis • Evaluate patients with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment
	Recurrent Grade 2, Grade 3 or 4	Permanently discontinue		
Diarrhea / Colitis	Grade 2 or 3	Withhold	• Administer corticosteroids (initial dose of 1 to 2 mg/kg prednisone or equivalent) followed by taper	• Monitor patients for signs and symptoms of enterocolitis (ie, diarrhea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (ie. peritoneal signs and ileus) • Patients with ≥Grade 2 diarrhea suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis
	Recurrent Grade 3 or Grade 4	Permanently discontinue		

irAEs	Toxicity grade (CTCAE V5.0)	Action with pembrolizumab	Corticosteroid and/or other therapies	Monitoring and follow-up
				• Patients with diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion
AST or ALT elevation or Increased Bilirubin	Grade 2 [a]	Withhold	• Administer corticosteroids (initial dose of 0.5 to 1 mg/kg prednisone or equivalent) followed by taper	• Monitor with liver function tests (consider weekly or more frequently until liver enzyme value returned to baseline or is stable)
	Grade 3 [b] or 4 [c]	Permanently discontinue	• Administer corticosteroids (initial dose of 1 to 2 mg/kg prednisone or equivalent) followed by taper	
Type 1 diabetes mellitus (T1DM) or Hyperglycemia	New onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of β-cell failure	Withhold [d]	• Initiate insulin replacement therapy for patients with T1DM • Administer antihyperglycemc in patients with hyperglycemia	• Monitor patients for hyperglycemia or other signs and symptoms of diabetes
Hypophysitis	Grade 2	Withhold	• Administer corticosteroids and initiate hormonal replacements as clinically indicated	• Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency)
	Grade 3 or 4	Withhold or permanently discontinue [d]		
Hyperthyroidism	Grade 2	Continue	• Treat with nonselective beta-blockers (eg, propranolol) or thionamides as appropriate	• Monitor for signs and symptoms of thyroid disorders
	Grade 3 or 4	Withhold or permanently discontinue [d]		

irAEs	Toxicity grade (CTCAE V5.0)	Action with pembrolizumab	Corticosteroid and/or other therapies	Monitoring and follow-up
Hypothyroidism	Grade 2, 3 or 4	Continue	• Initiate thyroid replacement hormones (eg, levothyroxine or liothyronine) per standard of care	• Monitor for signs and symptoms of thyroid disorders
Nephritis: grading according to increased creatinine or acute kidney injury	Grade 2	Withhold	• Administer corticosteroids (prednisone 1 to 2 mg/kg or equivalent) followed by taper	• Monitor changes of renal function
	Grade 3 or 4	Permanently discontinue		
Neurological Toxicities	Grade 2	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3 or 4	Permanently discontinue		
Myocarditis	Grade 2, 3 or 4	Permanently discontinue	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes •
Exfoliative Dermatologic Conditions	Suspected SJS, TEN, or DRESS	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology or exclude other causes
	Confirmed SJS, TEN, or DRESS	Permanently discontinue		
All Other irAEs	Persistent Grade 2	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology or exclude other causes
	Grade 3	Withhold or discontinue based on the event [e]		
	Recurrent Grade 3 or Grade 4	Permanently discontinue		

AE(s)=adverse event(s); ALT= alanine aminotransferase; AST=aspartate aminotransferase; CTCAE=Common Terminology Criteria for Adverse Events; DRESS=Drug Rash with Eosinophilia and Systemic Symptom; GI=gastrointestinal; IO=immuno-oncology; ir=immune related; IV=intravenous; SJS=Stevens-Johnson Syndrome; T1DM=type 1 diabetes mellitus; TEN=Toxic Epidermal Necrolysis; ULN=upper limit of normal.

Note: Non-irAE will be managed as appropriate, following clinical practice recommendations.

[a] AST/ALT: >3.0 to 5.0 x ULN if baseline normal; >3.0 to 5.0 x baseline, if baseline abnormal; bilirubin:>1.5 to 3.0 x ULN if baseline normal; >1.5 to 3.0 x baseline if baseline abnormal

[b] AST/ALT: >5.0 to 20.0 x ULN, if baseline normal; >5.0 to 20.0 x baseline, if baseline abnormal; bilirubin:>3.0 to 10.0 x ULN if baseline normal; >3.0 to 10.0 x baseline if baseline abnormal

[c] AST/ALT: >20.0 x ULN, if baseline normal; >20.0 x baseline, if baseline abnormal; bilirubin: >10.0 x ULN if baseline normal; >10.0 x baseline if baseline abnormal

[d] The decision to withhold or permanently discontinue pembrolizumab is at the discretion of the investigator or treating physician. If control achieved or ≤ Grade 2, pembrolizumab may be resumed.

[e] Events that require discontinuation include but are not limited to: encephalitis and other clinically important irAEs (eg. vasculitis and sclerosing cholangitis).

6.3.5. Dose Modification and Toxicity Management of Infusion-reactions Related to Pembrolizumab

Pembrolizumab may cause severe or life-threatening infusion-reactions including severe hypersensitivity or anaphylaxis. Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion. The dose of pembrolizumab will remain constant at 200 mg Q3W. However, dose modification (interruption) and toxicity management guidelines on pembrolizumab associated infusion reaction are provided in Table 4.

Table 4. Pembrolizumab Infusion Reaction Dose Modification and Treatment Guidelines

NCI CTCAE Grade	Treatment	Premedication at Subsequent Dosing
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	• Increase monitoring of vital signs as medically indicated until the patients is deemed medically stable in the opinion of the investigator.	None
Grade 2 Requires therapy or infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤ 24 hrs.	• **Stop Infusion.** • Additional appropriate medical therapy may include but is not limited to: • IV fluids • Antihistamines • NSAIDs • Acetaminophen • Narcotics • Increase monitoring of vital signs as medically indicated until the patients is deemed medically stable in the opinion of the investigator. • If symptoms resolve within 1 hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g. from 100 mL/hr. to 50 mL/hr.). Otherwise, dosing will be held until symptoms resolve and the patients should be premedicated for the next scheduled dose. **Patients who develop Grade 2 toxicity despite adequate premedication should be**	Patients may be premedicated 1.5 h (± 30 minutes) prior to infusion of study intervention with: Diphenhydramine 50 mg po (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg po (or equivalent dose of analgesic).

NCI CTCAE Grade	Treatment	Premedication at Subsequent Dosing
	permanently discontinued from further study drug treatment	
Grades 3 or 4 **Grade 3:** Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates) **Grade 4:** Life-threatening; pressor or ventilator support indicated	• **Stop Infusion.** • Additional appropriate medical therapy may include but is not limited to: • Epinephrine** • IV fluids • Antihistamines • NSAIDs • Acetaminophen • Narcotics • Oxygen • Pressors • Corticosteroids • Increase monitoring of vital signs as medically indicated until the patients is deemed medically stable in the opinion of the investigator. • Hospitalization may be indicated. **In cases of anaphylaxis, epinephrine should be used immediately. Patients is permanently discontinued from further study drug treatment.	No subsequent dosing
Appropriate resuscitation equipment should be available at the bedside and a physician readily available during the period of drug administration. For further information, please refer to the Common Terminology Criteria for Adverse Events v5.0 (CTCAE) at http://ctep.cancer.gov.		

6.3.6. Other Allowed Dose Interruption for Pembrolizumab

Pembrolizumab may be interrupted for situations other than treatment-related AEs such as medical or surgical events and/or unforeseen circumstances not related to study intervention. However, study intervention is to be restarted within 3 weeks or 21 days of the originally scheduled dose and within 42 days of the previously administered dose, unless otherwise discussed with the Sponsor.

6.3.7. Dose Interruption for HER-Vaxx

In case of an unexpected immune related Grade 3 and higher AE, the subsequent dose of HER-Vaxx should be held until the AE has returned to Grade 1 or resolved. HER-Vaxx can be restarted with the approval of the Sponsor. Discuss any HER-Vaxx dose interruption due to chemotherapy interruptions with Sponsor.

6.3.8. Dose Interruption for Chemotherapy

Dose adjustments, delays, and discontinuation based on AEs, patient's condition, and cumulative toxicities are permitted for the clinical care of the patient at the discretion of the Investigator.

6.4 Administration

HER-Vaxx will be administered IM into the deltoid region of the upper arm with a 25-38 mm (1-1.5 inches), 21-23G needle as per the Schedule of Activities until treatment discontinuation criterion is met. HER-Vaxx will be administered at least 48 hours prior to initiation of chemotherapy or at least 30-60 minutes prior to the administration of pembrolizumab depending on assigned Arm (when scheduled on the same day).

Arm 1:

Patients will receive intravenous (IV) administration of chemotherapy (ramucirumab 8 mg/kg IV + paclitaxel 80 mg/m^2 IV) as per the Schedule of Activities (Table 1). Chemotherapy will be administered at least 48 hours after the administration of HER-Vaxx (when scheduled on the same day). Premedication and concomitant medications should be administered as per institutional standard practice, with a limit of 24 mg dexamethasone (or equivalent) per chemotherapy cycle with a maximum of 8 mg/d during chemotherapy administration. Dose adjustments and delays, and discontinuation based on AEs, patient's condition, and cumulative toxicities are permitted for the clinical care of the patient at the discretion of the investigator. Patients will receive chemotherapy for as long as clinically indicated. HER-Vaxx may continue after termination of chemotherapy until discontinuation criteria is met.

Body weight will be determined prior to the start of treatment. Body surface area ([BSA]: based on weight and baseline height) will be calculated prior to starting chemotherapy. Dose modification will be required for > 10% change in BSA, unless the investigator considers this not appropriate.

Arm 2:

Patients will receive 200 mg pembrolizumab IV as per the Schedule of Activities (Table 2) at least 30-60 min following the administration of HER-Vaxx (when scheduled on the same day) and will continue treatment until treatment discontinuation criterion is met. Dose modifications for HER-Vaxx are not planned and need to be agreed by the Sponsor. Dose modifications for pembrolizumab are based on immune mediated adverse reactions and/or infusion-related AEs. No dose reduction for pembrolizumab is recommended. In general, withhold pembrolizumab for severe (Grade 3) immune-mediated adverse reactions. Permanently discontinue pembrolizumab for life-threatening (Grade 4) immune-mediated adverse reactions, recurrent severe (Grade 3) immune-mediated reactions that require systemic immunosuppressive

treatment, or an inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks of initiating steroids (see Sections 6.3.4 and 6.3.5 above).

The interventions to be used in Arm 2 of this study are outlined below (Table 5):

Table 5. List of Interventions Arm 2

Intervention Name	Dosage Formulation	Unit Dose Strength(s)	Dosage Level(s)	Route of Administration	Regimen/Treatment Period	Sourcing
Pembrolizumab	Solution for infusion	100 mg/vial	200 mg Q3W	IV infusion	Until end of trial or confirmed PD, unacceptable toxicity, death or discontinuation for any other reason for a maximum of 35 treatment cycles.	Provided by the Sponsor or reimbursed if sourced locally
HER-Vaxx	Solution for injection	See Section 6.2		IM	See Section 6.3	Provided by the Sponsor

Pembrolizumab will be administered as a dose of 200 mg using a 30-minute IV infusion. Sites should make every effort to target infusion timing to be as close to 30 minutes as possible. However, given the variability of infusion pumps from site to site, a window between -5 minutes and +10 minutes is permitted (i.e., infusion time is 30 minutes (-5 min/+10 min).

HER-Vaxx may continue independently until treatment discontinuation criterion is met if pembrolizumab is discontinued.

6.5 Compliance

Study site staff are responsible for administration of HER-Vaxx and chemotherapy or pembrolizumab. To monitor HER-Vaxx compliance, confirmation of successful preparation by droplet test will be documented prior to each administration of HER-Vaxx and the exact volume and dose administered will be recorded in the CRF.

6.6 Treatment of Overdose Arm 2

For this study, an overdose of pembrolizumab will be defined as any dose of 1000 mg or greater.

No specific information is available on the treatment of overdose of pembrolizumab. In the event of overdose, the patients should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

6.7 Meals and Dietary Restrictions

Patients should maintain a normal diet unless modifications are required to manage an AE such as diarrhea, nausea, or vomiting.

6.8 Drug Storage and Drug Accountability

The vaccine and adjuvant must be stored in a safe and locked place with no access for unauthorized personnel.

The peptide antigen P467-CRM197 must be kept frozen until use in a freezer at < -15°C.

The adjuvant Montanide ISA 51 VG must be stored in a refrigerator at + 2 to + 8°C.

Storage conditions stated in the Investigator Brochure (IB) may be superseded by the label storage conditions. Ensure the label is always checked for correct storage conditions.

Storage of chemotherapy (ramucirumab plus paclitaxel) and pembrolizumab is as per SmPC/label for each drug.

IMP's will be disposed of at the study site according to the study site's institutional standard operating procedure or returned to the Sponsor (or Sponsor's delegate) with the appropriate documentation. The site's method of IMP destruction must be agreed upon by the Sponsor. Local or institutional regulations may require immediate destruction of used investigational medicinal product for safety reasons. The site must obtain written authorization from the Sponsor before any IMP is destroyed, and IMP destruction must be documented on the appropriate form. Further guidance and information for the final disposition of unused study treatment is provided in the Pharmacy Manual.

6.9 Concomitant Medications

6.9.1. Permitted Medications

Participants will follow their oncology care plan. All medications required as part of a participant's normal clinical care for support of their medical conditions are permitted during the study, with the exception of prohibited medications listed in Section 6.9.2. All concomitant medications must be recorded in the source documentation and in the CRFs for the duration of patient participation.

Treatment with an oral corticosteroid, such as dexamethasone, up to 8 mg daily (24 mg maximum) during each chemotherapy cycle is allowed if required but may impact the development of HER2/neu antibodies.

Permitted medications include, but are not limited to:

1. Anti-emetics or anti-diarrheal agents as required
2. N-acetyl-para-aminophenol drugs (APAP, [paracetamol/acetaminophen])
3. Nonsteroidal anti-inflammatory drugs (NSAIDs)

The use of APAP and NSAIDs should be assessed on a per-patient basis. Guidelines for the use of paracetamol (acetaminophen) and NSAIDs are as follows:

- Paracetamol
    - Paracetamol may be used for the treatment and first signs of flu-like signs and symptoms, that may be associated with HER-Vaxx vaccination.
    - Dosing of paracetamol: The recommended dose is 500 or 1000 mg every 6 to 8 hours.
    - The MAXIMUM daily (24-hour) dose must NOT exceed 3000 mg and requires adequate hepatic function.
- NSAIDs
    - The decision to use oral NSAID should be made for each individual patient, with attention to the patient's renal and hydration status at the time of HER-Vaxx administration or the time of imaging scans with contrast.
    - Dosing of NSAIDs (e.g., oral ibuprofen, other NSAIDs permitted): The recommended dose is 400 or 600 mg ibuprofen (or an equivalent dose for other NSAIDs) every 8 hours.
    - The MAXIMUM daily (24-hour) dose must NOT exceed 1800 mg ibuprofen (or an equivalent dose for other NSAIDs) and for a total of two days only.

6.9.2. Prohibited Medications

The following medications/treatments are **prohibited** during the study:

- Other investigational drug.
- Continuous systemic treatment with either corticosteroids or other immunosuppressive medications unless required to treat an immune adverse event.
    - Note: inhaled or topical steroids and physiological replacement doses of up to 10 mg daily prednisone equivalents are permitted.
- Total doses greater than 24 mg dexamethasone equivalent of oral corticosteroids per chemotherapy cycle.
- Both treatment Arms: Any vaccination within 30 days prior to any study treatment and during first treatment cycle.
- Arm 2 only: Live or live attenuated vaccines while participating in the study are not allowed.
    - Note: Inactivated vaccines are allowed after the first treatment cycle.
    - Note: Any licensed COVID-19 vaccine (including for Emergency use) in a particular country is allowed in the study as long as they are mRNA vaccines, adenoviral vaccines, or inactivated vaccines. These vaccines will be treated just as any other concomitant therapy.

  - Investigational vaccines (i.e., those not licensed or approved for Emergency Use) are not allowed.

- Other anti-cancer therapy (i.e. chemotherapy; hormonal therapy; extensive, non-palliative radiation therapy, or standard or investigational agents).
- Immunotherapy not specified in this protocol.

If the investigator determines that a patient requires any of the aforementioned treatments for any reason, HER-Vaxx plus chemotherapy or pembrolizumab must be discontinued.

All treatments that the investigator considers necessary for a patient's welfare may be administered at the discretion of the investigator in keeping with the community standards of medical care.

6.10 Method of Assigning Patients to Treatment

Eligible patients (see Section 4) will receive HER-Vaxx plus chemotherapy (Arm 1) or HER-Vaxx plus pembrolizumab (Arm 2) in this study based on their prior treatment as outlined in the inclusion and exclusion criteria in Section 4.

Once patients are assigned to Arm 1 or 2, patients will be assigned to treatment based on order of enrolment.

6.11 Patient Enrollment

All patients will sign the informed consent form (ICF), after being properly informed about the study, and subsequently undergo the screening assessments. Patients who do not meet all inclusion criteria or who meet any of the exclusion criteria are not eligible for study entry (screen failures). As soon as a patient is deemed ineligible during screening, all further study evaluations will be cancelled for this patient.

Each patient will receive a unique number, which is assigned by the site during the screening visit and will be used throughout the study.

All patients, including screening failures, are added to the eCRF by site staff/Sponsor designee.

6.12 End of Study

End of Study in all participating countries is defined as the date the last patient completes the Survival Follow-up Visit.

7. INVESTIGATIONAL PLAN

Study procedures and their timepoints are summarized in the Schedule of Activities for each arm (Table 1 & Table 2).

It is the investigator's responsibility to ensure that the Schedule of Activities is strictly followed. Every attempt should be made to complete all study visits as outlined in the Schedule of Activities. All missed study visits and visits outside the visit window are considered protocol deviations.

7.1 Screening

Patients agreeing to participate in the study will sign the informed consent documents. The reason for all screen failures will be documented. The screening assessments should occur within 21 days prior to starting treatment on Day 1.

Screening can occur across multiple clinic visits within the 21-day screening period. At the first screening visit the patient will be asked to provide consent and the inclusion/exclusion criteria will be checked. All other screening procedures can be conducted at subsequent screening visits.

Patient laboratory results that do not meet the eligibility criteria may be repeated within the Screening Period.

7.2 Re-Screening

Patients may be re-screened in the following situations:

- Drug supply not available at site
- Unable to attend/schedule first dose visit
- Tests or procedures are not completed in screening period (i.e., patients who miss their 21-day screening window).

For any other situation, agreement must be obtained from Imugene Limited before performing re-screening.

A new ICF must be signed before re-screening can commence. Re-screened patients will keep the same screening number. Screening procedures and test results/eligibility checks will be updated as part of re-screening.

7.3 Screen Failures and Replacement of Patients

Screen failures are defined as patients who consent to participate in the clinical study but are not subsequently assigned to the study intervention or entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details and eligibility criteria. These data will be entered into the CRF.

A patient who misses the first administration of HER-Vaxx for reasons other than safety will be replaced.

For the purpose of the primary analysis set for analyses of response-based anti-tumor activity endpoints, in Arm 1 and 2, patients who withdraw before at least one evaluable post-baseline tumor response assessment as per RECIST 1.1 for reasons other than toxicity will be replaced.

In Arm 1, a safety run-in patient may be replaced if the patient does not receive all three HER-Vaxx injections and at least 1 cycle of chemotherapy, for reasons other than toxicity during the DLT observation period.

In Arm 2, a safety run-in patient may be replaced if the patient does not receive all three HER-Vaxx injections and at least 1 dose of pembrolizumab for reasons other than toxicity during the DLT observation period.

No replacement will occur for patients who withdraw later, for both Arms.

7.4 End of Treatment

The End of Treatment (EoT) visit will be completed at least 30 (± 7) days after the last administration of any study treatment.

7.5 Survival Follow-Up

After discontinuation of study treatment and completion of the End of Treatment visit, anti-cancer therapy and survival information will be collected every 12 weeks (± 7 days) for up to 3 years or until death (follow-up via phone call allowed). A blood sample for humoral immunity assessment is planned every 12 weeks for up to 1 year. Anti-cancer therapy and survival information may be collected more frequently than every 12 weeks for quality control and data cleaning purposes. After discontinuation from the study for any reason other than disease progression, radiographic change will be collected every 12 weeks until determination of progressive disease.

All patients will be followed for radiographic change until determination of progressive disease and survival information and anti-cancer treatment until death, unless the patient requests to be withdrawn from radiographic change assessment and survival follow-up contact. This request must be documented in the source documents and signed by the Investigator.

7.6 Unscheduled Visit

Unscheduled visits may be conducted at any time during this study by the Investigator if clinically indicated for the care of the patient.

An unscheduled visit may include any of the protocol required assessments listed in Section 7.3. The exact assessments conducted at the unscheduled visit will be specified by the investigator and recorded in the CRF. Additional tests and procedures may be performed at the unscheduled visit for the clinical care of the patient after discussion with, and agreement of, the medical monitor.

7.6.1. Assessments via Telemedicine

Telemedicine uses advanced telecommunication technologies to exchange health information and provide health care services across geographic, social, and other barriers. Where circumstances allow, and where additional flexibility is required due to restricted patient access to the study clinic or personnel, telemedicine technology may be used to collect study data to supplement study assessments. For example, visits may be conducted over several days within each visit window, with suitable assessments being completed using telemedicine technology with the remaining assessments being completed during a physical clinic visit. Examples of study assessments which may be completed using telemedicine technology include documenting concomitant treatments and adverse events, ECOG performance status, and survival follow-up.

7.6.2. Demographic Data and Medical History

Medical history, including clinically significant diseases, surgeries, cancer history (including prior cancer therapies and procedures), cardiovascular history, reproductive status, smoking history, and use of alcohol and drugs of abuse, will be recorded at baseline. In addition, all medications (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by the patient within 7 days prior to treatment. At the time of each follow-up physical examination, an interval medical history should be obtained and any changes in medications and allergies should be recorded.

Demographic data will include age, sex, and self-reported race/ethnicity.

7.6.3. Physical Examination

A complete physical examination will include an evaluation of body systems (e.g., cardiovascular, gastrointestinal, neurological, head and neck, respiratory, dermatology). After Cycle 1, Day 1 a limited, symptom-directed physical examination is allowed at the investigator's discretion. The physical examination should occur prior to study treatment.

7.6.4. Height, Weight & Vital Signs

Body height (at screening visit only), weight, and vital signs (blood pressure, respiratory rate, heart rate and temperature) will be measured prior to receiving study treatment as per the timepoints in the Schedule of Activities. Temperature to also be recorded 30 min (± 10 mins) after each HER-Vaxx vaccination.

7.6.5. Radiographic Assessment

Computed Tomography (CT) scan of the chest abdomen and pelvis with contrast should be performed. MRI of the abdomen and pelvis with contract and non-contrast CT chest may be done in patients with iodine contrast dye allergy or if lesions cannot be visualized on CT scan. The same radiographic procedure used to assess disease sites at screening should be used throughout the study (e.g., the same contrast protocol for CT scans). Assessments should be performed by the same evaluator, if possible, to ensure internal consistency across visits.

For all patients a radiographic assessment will be performed at Baseline (assessment allowed up to 14 days before Day 1 Visit), followed by every 6 weeks until disease progression. After

discontinuation from the study for any reason other than disease progression, radiographic change will be collected every 12 weeks until determination of progressive disease. Tumor assessments must be performed independently of changes to the study treatment administration schedule (i.e., when treatment is withheld). If a tumor assessment has to be performed early or late, subsequent assessments should be conducted according to the original schedule based on the date of first study treatment administration on Day 1. Objective response (complete response or partial response) must be confirmed by repeat assessment at least 4 weeks after initially documented response. Assessment of the tumor will include evaluation according to RECIST 1.1. Upon PD, a scan may be scheduled 4 to 6 weeks after initial PD scan to confirm progression. If there are clear signs of progression, confirmation scan is not required.

At screening, patient eligibility will require radiographic documentation of at least one lesion that meets the requirements for selection as a target lesion, as defined by RECIST 1.1, prior to patient enrollment. All scheduled scans for patients will be assessed locally and submitted to the central imaging vendor to confirm local assessment, if required. In addition, a scan that is obtained at an unscheduled time point, for any reason (including suspicion of progression or other clinical reason), should also be submitted to the central imaging vendor.

7.6.6. Cardiac Assessment

Cardiac assessment by the study Investigator will be based on assessment of 12-lead ECG results and evaluation of LVEF by echocardiography or MUGA scan as per the Schedule of Activities. Significant abnormal cardiac assessments should be evaluated by a cardiologist.

7.6.7. Laboratory Assessments

Hematology and serum chemistry analyses will be performed by an accredited local laboratory. Serum predication markers of tumor progression and intra-tumor T cell and biomarker analysis including NGS will be performed by an accredited central laboratory. Humoral and cellular immunological analysis will be performed by an accredited specialist central immunology laboratory. Additional details are provided in the study Laboratory Manual.

Unused blood /serum and/or tissue samples collected during the study from patients who have signed an appropriate informed consent form may be stored and used for future research. The coded samples may be used up to 15 years after the clinical study ends. A patient may contact the investigator to have their unused samples destroyed at any time during the storage period. Results from the future use studies will not be shared with patients.

7.6.7.1. Safety Laboratory Assessments

Blood samples of approximately 10 mL per visit for the assessment of hematological and serum chemistry parameters will be collected and processed in accordance with local laboratory procedures and reference ranges. These samples will be collected prior to administration of any study treatment.

Safety laboratory panels are defined as follows:

Human immunodeficiency virus (HIV 1/2 antibodies), hepatitis B (HBsAg reactive) and hepatitis C (HCV ribonucleic acid [RNA] qualitative) assessments are only required at screening if mandated by a local health authority.

Hematology:

Local hematology testing to be collected prior to receiving any study treatment as per the Schedule of Activities. Local labs can be drawn up to 72 hours before any on-study clinic visit.
Hematology to include complete blood count (CBC), including red blood cell (RBC) count, hemoglobin, hematocrit, reticulocyte count, white blood cell (WBC) count with differential (neutrophils, bands, eosinophils, basophils, lymphocytes, monocytes, and other cells), platelet count, and C-reactive protein (CRP).

Serum Chemistry:

Local serum chemistry testing to be collected prior to receiving any study treatment. Local labs can be drawn up to 72 hours before any on-study clinic visit.

Blood urea nitrogen (BUN) or urea, creatinine, sodium, chloride, potassium, magnesium, bicarbonate, calcium, phosphorus, total protein, albumin, alkaline phosphatase, glucose, total bilirubin, direct and indirect bilirubin, lactate dehydrogenase (LDH), cholesterol, uric acid, triglyceride levels, gamma glutamyl transpeptidase (GGT), AST, and ALT.

Thyroid Function Test:

Thyroid stimulating hormone (TSH) and free thyroxine (free T4) to be performed as per the Schedule of Activities. Additional tests may be requested by the investigator in case of abnormal TSH and/or free T4.

7.6.7.2. Exploratory Endpoint Laboratory Assessments

A 10 mL whole blood sample to assess ctDNA and an additional 10 mL whole blood sample to assess NGS (liquid biopsy), vaccine-specific cytokine levels, soluble HER-2, and *in-vitro* inhibition of tumor cell growth will be collected from each patient as per the Schedule of Activities. These samples will be taken prior to administration of any study treatment.

7.6.7.3. Immunologic Assessments

7.6.7.3.1. Humoral Samples

A 10 mL whole blood sample for humoral immunity will be collected from each patient as per the Schedule of Activities. These samples will be taken prior to administration of any study treatment. Additional samples for humoral immunity will be collected every 12 weeks during survival follow up for up to 1 year.

7.6.7.3.2. Cellular Samples

A 40 mL blood sample will be collected for peripheral blood mononuclear cell (PBMC) isolation and analysis of cellular parameters as per the Schedule of Activities. These samples will be taken prior to administration of any study treatment.

7.6.8. HER2/neu Overexpression

Arm 1 only: Documented HER-2 positivity at diagnosis is required. A post-progression tumor biopsy (post-progression fresh or archival tissue) or post-progression pathology report should be provided. A minimum of 5 of 8 patients enrolled in Stage 1 and an additional 5 in Stage 2 must have HER2/neu overexpression as assessed by the central lab or post-progression pathology report.

Arm 2 only: confirmation of HER2/neu overexpression since progression on or after trastuzumab is required for inclusion in this study due to potential HER2+ loss after trastuzumab treatment (Seo, 2009; Takashi, 2020). A previous pathology result confirming HER2/neu overexpression is acceptable as long it has been taken after progression on trastuzumab (Takashi, 2020). If analysis of a tumor biopsy is required for confirmation of HER2/neu overexpression, then this may be achieved via analysis of a fresh or archived tissue sample. HER2/neu analysis will be conducted at each center's local pathology laboratory by IHC and FISH, BDISH, or CISH if IHC result is equivocal.

Using the IHC method an unequivocal result of HER2 overexpression is defined as HER2 +++, an equivocal result is defined as HER2 ++, and a negative result is defined as HER2 +. If equivocal result (IHC HER2 ++) then additional analysis via FISH, BDISH or CISH will be conducted for confirmation of HER2 overexpression. The definition of FISH, BDISH or CISH positivity in gastric or gastro–esophageal junction cancer is a HER2: chromosome 17 ratio of ≥2.0. Sponsor may approve inclusion based on liquid (blood based) biopsy to assess patients' HER2/neu positivity where tumor biopsy is not clinically indicated.

7.6.9. ECOG Performance Status

The ECOG performance status should be determined using the criteria defined in Appendix A: ECOG Performance Status Scale at the time points specified in the Schedule of Activities.

7.6.10. Pregnancy Test

A highly sensitive urine pregnancy test (sensitivity of at least 25 mIU/mL) for all female patients of childbearing potential will be collected once per cycle prior to study treatment. If the urine pregnancy test is positive (or cannot be confirmed as negative), a serum pregnancy test will be required. If the serum pregnancy test is negative, then study treatment may resume.

7.6.11. Tumor Biopsy

A screening visit tumor biopsy (post-progression fresh or archival) or post-progression pathology report should be provided for patients in Arm 1 and must be obtained for all patients in Arm 2. Additional optional tumor biopsies may be collected as per the Schedule of Activities where a patient has consented to the additional tumor biopsies and it is feasible to perform the assessment. All tumor samples will be analyzed for intra-tumor T cells and biochemical markers (including PD-L1 detection by combined positive score [CPS] calculation). The screening visit biopsy sample may also be used to determine HER2/neu overexpression.

8. ADVERSE EVENT REPORTING

All AEs in this study will be collected and processed in accordance with ICH - Good Clinical Practice (GCP) and national and local laws and regulations. In line with these regulations, the Investigator is responsible for reporting Serious adverse events (SAEs) to the Sponsor, within the appropriate timelines (see below). The Investigator is also responsible for notifying the appropriate IRBs/IECs of all unanticipated problems involving risk to human patients or others as per the guidelines of the Institution and in accordance with aforementioned laws and regulations.

All observed or volunteered AEs regardless of treatment Arm or suspected causal relationship to the investigational product(s) will be reported as described in the following sections. All AEs will be collected in response to a general question about the patient's well-being and any possible changes from the baseline or previous visit, but shall not be specifically solicited with respect to particular AEs.

For all AEs, the investigator must pursue and obtain information adequate both to determine the outcome of the AE and to assess whether it meets the criteria for classification as an SAE requiring immediate notification to Imugene Limited or its designated representative.

For all AEs, sufficient information should be obtained by the investigator to determine the causality of the AE. The investigator is required to assess causality. AEs will be followed until resolved, stable, or until the patient's last study visit or lost to follow-up. If an AE is not resolved or stabilized at the patient's last visit, it is up to the discretion of the investigator and the Sponsor's medical monitor to determine if further monitoring of the event is warranted.

As part of ongoing safety reviews conducted by the Sponsor, any non-serious adverse event that is determined by the Sponsor to be serious will be reported by the Sponsor as an SAE.

To assist in the determination of case seriousness further information may be requested from the investigator to provide clarity and understanding of the event in the context of the clinical study.

8.1 Definition

8.1.1. Adverse Event

An AE is defined as any untoward medical occurrence in a clinical study patient administered with a medicinal product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an IMP, whether or not considered related to the IMP used. All AEs reported by the patient or observed by the investigator or site staff will be recorded.

Examples of AEs include but are not limited to:

- Abnormal test findings;
- Clinically significant symptoms and signs;
- Changes in physical examination findings;

- Hypersensitivity;
- Drug abuse;
- Drug dependency.

Additionally, they may include the signs or symptoms resulting from:

- Drug overdose;
- Drug withdrawal;
- Drug misuse;
- Drug interactions;
- Extravasation;
- Exposure during pregnancy;
- Exposure via breastfeeding;
- Medication error.

Worsening of signs and symptoms of the malignancy under study should be reported as AEs in the appropriate section of the CRF. Disease progression assessed by measurement of malignant lesions on radiographs or other methods should not be reported as AEs.

8.1.2. Abnormal Test Findings

The criteria for determining whether an abnormal objective test finding should be reported as an AE are as follows:

- Test result is associated with accompanying symptoms, and/or
- Test result requires additional diagnostic testing or medical/surgical intervention, and/or
- Test result leads discontinuation from the study, significant additional concomitant drug treatment, or other therapy, and/or
- Test result is considered to be an AE by the investigator or sponsor.

Merely repeating an abnormal test, in the absence of any of the above conditions, does not constitute an AE. Any abnormal test result that is determined to be an error does not require reporting as an AE.

8.1.3. Treatment-Emergent Adverse Event (TEAE)

All AEs reported from the start of the study (Day 1) and until 30 days after the last HER-Vaxx dose (for Arm 2 also after last pembrolizumab dose) are considered TEAEs.

8.1.4. Serious Adverse Event (SAE)

Any untoward medicinal occurrence or effect that at any dose:

- Results in death (not due to disease progression);
- Is life-threatening (the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe);
- Requires hospitalization or prolongation of existing hospitalization;
- Results in persistent or significant disability or incapacity;
- Results in a congenital anomaly or birth defect.

Any event or hospitalization which is unequivocally due to disease progression will not be considered an SAE and therefore, does not require reporting as is outlined in this section. These events and hospitalizations will still be reported as an AE.

Hospitalization for elective treatment of a pre-existing condition that has not worsened from its original baseline level will not considered an SAE and therefore, does not require reporting as is outlined in this section.

Any event that does not meet the above criteria may also be considered by the Investigator to be a SAE, based on appropriate medical and scientific judgment. This includes important medical events that may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above.

SAEs will continue to be reported until 90 days after the final dose of study treatment or until initiation of new systemic anti-cancer therapy, whichever occurs first.

8.1.5. Adverse Events of Clinical Interest

Selected non-serious and serious adverse events are also known as Events of Clinical Interest (ECI) also referred to as Adverse Events of Special Interest (AESI) and must be reported to the Sponsor within 24 hours of awareness.

LVEF will be measured by either echocardiogram (ECHO) or MUGA scan. All ECHOs/MUGAs will be evaluated by the investigator or delegated physician for monitoring cardiac function.

8.1.5.1. Potential Drug-Induced Liver Injury

Abnormal values in AST and/or ALT concurrent with abnormal elevations in total bilirubin that meet the criteria outlined below in the absence of other causes of liver injury are considered potential cases of drug-induced liver injury (potential Hy's Law cases) and should always be considered important medical events.

The threshold of laboratory abnormalities for a potential case of drug-induced liver injury depends on the patient's individual baseline values and underlying conditions. Patients who

present with the following laboratory abnormalities should be evaluated further to definitively determine the etiology of the abnormal laboratory values:

- Patients with AST or ALT and total bilirubin baseline values within the normal range who subsequently present with AST or ALT ≥ 3 times the upper limit of normal (X ULN) concurrent with a total bilirubin ≥ 2 X ULN with no evidence of hemolysis and an alkaline phosphatase ≤ 2 X ULN or not available.
- For patients with pre-existing ALT OR AST OR total bilirubin values above the upper limit of normal, the following threshold values should be used in the definition mentioned above:
    - For patients with pre-existing AST or ALT baseline values above the normal range: AST or ALT ≥ 2 times the baseline values and ≥ 3 X ULN, or ≥ 8 X LLN (whichever is smaller).
- Concurrent with
    - For patients with pre-existing values of total bilirubin above the normal range: Total bilirubin increased by one time the upper limit of normal or ≥ 3 times the lower limit of normal (whichever is smaller).

The patient should return to the investigational site and be evaluated as soon as possible, preferably within 48 hours from awareness of the abnormal results.

This evaluation should include laboratory tests, detailed history and physical assessment. For oncology studies, the possibility of hepatic neoplasia (primary or secondary) should be considered. In addition to repeating AST and ALT, laboratory tests should include albumin, creatine kinase, total bilirubin, direct and indirect bilirubin, gamma-glutamyl transferase, prothrombin time (PT)/INR, and alkaline phosphatase. A detailed history, including relevant information, such as review of ethanol, acetaminophen, recreational drug and supplement consumption, family history, occupational exposure, sexual history, travel history, history of contact with a jaundiced patient, surgery, blood transfusion, history of liver or allergic disease, and work exposure, should be collected.

Further testing for acute hepatitis A, B, or C infection and liver imaging (eg, biliary tract) may be warranted.

All cases confirmed on repeat testing as meeting the laboratory criteria defined above, with no other cause for liver function test (LFT) abnormalities identified at the time should be considered potential Hy's Law cases irrespective of availability of all the results of the investigations performed to determine etiology of the abnormal LFTs. Such potential Hy's Law cases should be reported as SAEs.

8.1.5.2. Immune related Adverse Events

If patients experience immune related adverse events (irAEs), then treatment and follow-up of these events should be according to guidance provided in "NCCN Guidelines Insights: Management of Immunotherapy-Related Toxicities, Version 1.2020 (Thompson, 2020) in addition to the specific guidance provided for patients treated with pembrolizumab (Sections

6.3.4 and 6.3.5). Grade 3 or higher irAEs must be reported within 24 hours from when the investigator becomes aware of the event.

8.1.6. Suspected Adverse Reactions (SAR)

Suspected adverse reaction (SAR) means any adverse event for which there is a reasonable possibility that HER-Vaxx caused the adverse event. For the purposes of IND safety reporting, "reasonable possibility" means there is evidence to suggest a causal relationship between the drug and the adverse event. Suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug. Adverse reactions are also referred to as toxicity.

8.1.7. Suspected Unexpected Serious Adverse Reaction (SUSAR)

Any serious adverse reaction where the nature or severity is not consistent with the product information mentioned in the Reference Safety Information in the IB or study protocol.

8.1.8. Toxic Death

Any death to which drug toxicity is thought to have made a contribution should be notified to the Sponsor's designee at once (and maximally within 24 hours). The Sponsor's designee will notify the SRC and Sponsor immediately.

8.1.9. Pregnancy

In this study, pregnancies occurring during participation (including pregnancies of partners of male patients) are ground for immediate and permanent discontinuation. They are not considered as an AE per se, but they must be reported to the Sponsor.

The sites will notify their IRBs/IECs according to the IRB's/IEC's reporting requirements of these pregnancies. The FDA will be notified of pregnancies in the development safety update report (DSUR) and the CSR and as Investigational New Drug Safety Report (INDSRs) if complications or outcomes meet expedited criteria.

Pregnancies must be followed up to determine outcome (including spontaneous miscarriage, elective termination, normal birth, or congenital abnormality) and status of mother and child, even if the patient was discontinued from the study. Pregnancy complications, elective terminations and spontaneous miscarriages must be reported as SAEs.

Patients who become pregnant during the study period must not receive further study treatment but may continue other study procedures at the discretion of the investigator.

Patients should be instructed to notify the investigator if they became pregnant either during the study or within 180 days following cessation of study treatment. If the patient begins a new anticancer therapy, the patient must notify the investigator of a pregnancy 30 days following cessation of study treatment .

If a pregnancy occurs during the study or within 180 days following cessation of study treatment, or if the patient initiates new anticancer therapy, the pregnancy should be followed to term, any premature terminations reported, and the health status of the mother and child

including date of delivery and the child's gender and weight should be reported to Imugene Limited after delivery. The mother may freely choose to terminate the pregnancy as her own decision. Neither the Sponsor nor investigators should influence this decision in any way. Similarly, neither the investigators nor Sponsor have the right to intervene or influence this decision and any ensuing procedures. If this occurs, the termination of pregnancy should be considered an elective surgical procedure and any associated adverse events attributed accordingly.

If the outcome of the pregnancy meets the criteria for an SAE (ie, ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly [in a live born, a terminated fetus, an intrauterine fetal demise, or a neonatal death]), the investigator should follow the procedures for reporting SAEs.

8.1.10. Withdrawal Due to Adverse Events

Withdrawal due to AEs should be distinguished from withdrawal due to other causes (Section 4.3.1), according to the definition of AE noted earlier, and recorded on the appropriate AE CRF page.

When a patient withdraws due to an SAE, the SAE must be reported in accordance with the reporting requirements defined in Section 8.2.5.

8.2 Monitoring, Reporting, and Documentation of SAEs/AEs

8.2.1. Monitoring of AEs

Patients will be monitored for AEs from the time of ICF signature and at all timepoints indicated in Table 1 and Table 2 (Arm 1 and Arm 2). After informed consent has been obtained but prior to initiation of study drug(s), only SAEs caused by a protocol-mandated intervention (e.g., invasive procedures such as biopsies, discontinuation of medications) should be reported. AEs will be assessed using CTCAE v5.0 (Appendix A), including start and stop dates, severity, relationship to study treatment, outcome and action taken.

At every study visit, patients will be asked whether they have experienced or are experiencing any medically related changes in their health. They will also be asked if they have been hospitalized, had any accidents, used any new medications/therapies, or changed concomitant medication regimens (both prescription and over-the-counter medications).

In addition, for all patients with any remaining SAEs at the last follow-up visit after the last treatment administration, regardless of its relationship to study medication, AE information needs to be collected until:

- The symptom subsides or stabilizes;
- Any clinically relevant abnormal laboratory value has returned to baseline;
- There is a satisfactory explanation other than the study medication for the change(s) observed; or
- Death, in which case an autopsy report should be supplied to the Sponsor's designee, if performed.

8.2.2. Documentation of AEs

All AEs are to be evaluated for duration, intensity, and relationship to (associated with) the study treatment or due to other causes including underlying disease.

All AEs, both those observed by study site personnel and those spontaneously reported by the study patients, must be recorded on the AE page in the CRF, as well as in the patient's medical record using standard medical terminology, regardless of causality.

Each event should be recorded as a single diagnosis. Accompanying signs (including abnormal laboratory values, physical examination findings, pulmonary or cardiovascular function tests) or symptoms should not be recorded as additional AEs. However, if the diagnosis is unknown/uncertain, signs and symptoms must be recorded. As soon as the diagnosis causing the signs and symptoms is known, the event terms will be adjusted to the final diagnosis.

For each AE, a minimum required information should be reported, which includes:

- The type of AE;
- An estimate of its severity (using NCI-CTCAE version 5.0, see Appendix A);
- Date and time of occurrence;
- Date of resolution;
- Actions required;
- An assessment of its causal relationship to study medication provided in the Investigator file.

AEs resulting from concomitant illnesses, reactions to concomitant medications, or from disease relapse/progression are also to be recorded. Any medical condition that is present at the screening visit will be considered as baseline and will not be reported as an AE but as medical history. However, if the condition deteriorates at any time during the study, it will be recorded as an AE. Investigators should ensure that the event term recorded captures the change in the condition (e.g., "worsening of...").

8.2.3. Adverse Event Severity Assessment

8.2.3.1. Adverse Event Intensity Grading

Patients will be evaluated for safety if they have received any treatment. Adverse events and other symptoms will be graded according to NCI-CTCAE v5.0. Each AE is to be classified and graded according to CTCAE v5.0 criteria (see Appendix A). Dates of onset and resolution, including dates at which the grade of an AE changes, are to be recorded in the patient file.

If no CTCAE grading is available, the severity of an AE is to be graded as follows:

- **Mild (Grade 1):** the event causes discomfort without disruption of normal daily activities.
- **Moderate (Grade 2):** the event causes discomfort that affects normal daily activities.

- **Severe (Grade 3):** the event makes the patient unable to perform normal daily activities or significantly affects his/her clinical status.
- **Life-threatening (Grade 4):** the patient was at risk of death at the time of the event or the event caused death.
- **Death (Grade 5)**: death related to an AE.

8.2.3.2. Local (injection site) Adverse Event Intensity

Intensity of the following local AEs should be assessed as described in the table (Table 6) below adapted from the *FDA, Center for Biologics Evaluation and Research (CBER), Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials dated September, 2007.*

Injection site AEs will be part of AE reporting as per Schedule of Activities at each study visit and are to be reported if ≥ Grade 1.

Table 6. Grading of Local Adverse Event Intensity

Local Reaction to Injectable Product	Absent (Grade 0)	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Pain	Absent	Does not interfere with activity	Repeated use of non-narcotic pain reliever > 24 hours or interferes with activity	Any use of narcotic pain reliever or prevents daily activity	Emergency room (ER) visit or hospitalization
Tenderness	Absent	Mild discomfort to touch	Discomfort with movement	Significant discomfort at rest	ER visit or hospitalization
Erythema/ Redness *	Absent	2.5 – 5 cm	5.1 – 10 cm	> 10 cm	Necrosis or exfoliative dermatitis
Induration/ Swelling**	Absent	2.5 – 5 cm and does not interfere with activity	5.1 – 10 cm or interferes with activity	> 10 cm or prevents daily activity	Necrosis

* In addition to grading the measured local reaction at the greatest single diameter, the measurement should be recorded as a continuous variable.

** Induration/Swelling should be evaluated and graded using the functional scale as well as the actual measurement.

8.2.4. Causality Assessment to Treatment

The investigator should use medical judgment to determine whether there is a reasonable causal relationship, including all relevant factors such as temporal course and latency, pattern of the reaction, known pharmacological properties of the product, and alternative explanations (e.g., other drugs, medical history, and concomitant diseases). By "reasonable causal relationship" it is understood that there is evidence or argument to suggest a causal relationship. The relationship of an AE to study medication will be recorded on the CRF and defined as follows:

- **Not Related:** An AE that does not follow a reasonable temporal sequence related to the IMP and is likely to have been produced by the patient's clinical state, other modes of therapy or other known ethology.
- **Unlikely Related:** An AE that follows such a temporal sequence from administration of the study medication that a relationship is not likely, and is likely to be due to a cause such as (known characteristics of) the patient's clinical state or other treatment.
- **Possibly Related:** AE that has a reasonable possibility that the event may have been caused by the IMP. The AE has a timely relationship to the IMP; however, the pattern of response is untypical, and an alternative cause seems more likely or there is significant uncertainty about the cause of the event.
- **Probably Related:** An AE that has a reasonable possibility that the event is likely to have been caused by the IMP. The AE has a timely relationship and follows a known pattern of response, but a potential alternative cause may be present.
- **Definitively Related:** There is a reasonable possibility that the event may have been caused by the IMP. A certain event has a strong temporal relationship and an alternative cause is unlikely.

Ultimately, at the time of data analysis, the relationship to the AE will be categorized as either "**unrelated**" (including unlikely or not related) or "**related**" (including definitely, probably or possibly related).

If the investigator does not know whether the investigational product caused the event, then the event will be handled as "related to investigational product" for reporting purposes, as defined by the Sponsor (see Section 8.2.7 Reporting Requirements). If the investigator's causality assessment is "unknown but not related to investigational product", this should be clearly documented on study records.

In addition, if the investigator determines an SAE is associated with study procedures, the investigator must record this causal relationship in the source documents and CRF, as appropriate, and report such an assessment in accordance with the SAE reporting requirements, if applicable.

8.2.5. Reporting of SAEs

If an SAE or ECI occurs, Imugene Limited, or its delegated representative, is to be notified within 24 hours of investigator or designee awareness of the event.

In particular, if the SAE is fatal or life-threatening, notification must be made immediately to Imugene Limited, or its delegated representative, irrespective of the extent of available AE information.

This timeframe also applies to additional new information (follow-up) on previously forwarded SAE or ECI reports as well as to the initial and follow-up reporting of exposure during pregnancy and exposure via breastfeeding cases.

In the rare event that the investigator does not become aware of the occurrence of an SAE or ECI immediately (eg, if an outpatient study patient initially seeks treatment elsewhere), the investigator is to report the event within 24 hours after learning of it and document the time of his/her first awareness of the AE.

Safety Reporting Contact Information:

- By encrypted email to the PPD Pharmacovigilance (PVG) safety inbox EMEAASIASafetyCentral.SM@ppdi.com
- In case of unsuccessful email delivery, the site should report the SAE or ECI to the Safety hotline numbers below:
- By telephone:
  - North America: 1-800-201-8725
  - Asia Pacific: +44 1223 374 240
  - Australia: 1800659318

  When prompted, enter the 5-digit access code: 72338

- By fax:
  - North America: 1-888-488-9697
  - Asia Pacific: +44 1223 374 102
  - Australia: 1800571893

For all SAEs, the investigator is obligated to pursue and provide information to Imugene Limited in accordance with the timeframes for reporting specified above. In addition, an investigator may be requested by Imugene Limited to obtain specific additional follow-up information in an expedited fashion. This information collected for SAEs is more detailed than that captured on the AE CRF. In general, this will include a description of the AE in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Information on other possible causes of the event, such as concomitant medications and illnesses must be provided. In the case of a patient death, a summary of available autopsy findings must be submitted as soon as possible to Imugene Limited or its designated representative.

Serious Adverse Events (SAEs) will be reported from date of first informed consent confirming study participation. After informed consent has been obtained but prior to initiation of study drug(s), only SAEs caused by a protocol-mandated intervention (e.g., invasive procedures such as biopsies, discontinuation of medications) should be reported. After initiation of study drug all adverse events will be reported until 30 days after the last dose of study drug or until initiation of new systemic anti-cancer therapy, whichever occurs first. Serious adverse events and adverse events of special interest will continue to be reported until 90 days after the final

dose of study treatment or until initiation of new systemic anti-cancer therapy, whichever occurs first.

8.2.6. SUSARs

The Sponsor's designee, on behalf of the Sponsor, is required by law to report to the health authorities in a written safety report:

1) all fatal or life-threatening suspected unexpected serious adverse reactions (SUSARs) within seven (7) calendar days of initial notification;

and

2) all other SUSARs within fifteen (15) calendar days of initial notification after the Sponsor determines that the information qualifies for reporting.

All Investigators in the study will be informed about SUSARs that have occurred by the Sponsor's designee, on behalf of the Sponsor by calendar day fifteen (15) for submission to their IRB/IEC.

8.2.7. Sponsor Reporting Requirements to Regulatory Authorities

Adverse event reporting, including suspected serious unexpected adverse reactions, will be carried out in accordance with applicable local regulations.

9. STATISTICAL METHODS

9.1 Statistical Analysis Plan

A statistical analysis plan (SAP) will be written in which the details of the statistical methods will be described. Any deviations from the originally planned statistical analysis or SAP will be described and justified in the clinical study report. Changes known at the time of SAP preparation will also be described in the SAP.

A data review meeting for each Arm separately will be held before database hard lock. Protocol deviations will be reviewed during the data review meeting. Furthermore, assignment of patients to the analysis sets will be performed.

Data of patients who did not meet the entry criteria (screening failures) and data of patients who received no investigational product (e.g. due to withdrawal) entered in the clinical database will only be listed. These data will not be included in any analysis set.

All data will be recorded electronically by the study site. The Investigator is responsible for ensuring the accuracy, completeness, and legibility of the data reported in the CRFs. The monitor will check the accuracy, completeness, and legibility of the data reported in the CRFs.

9.2 Data Sets to be Analyzed

The analysis population sets are defined as follows:

- The safety analysis set (**SAF**) consists of all patients who receive at least one dose of study treatment. All safety and tolerability evaluations will be based on this analysis set.
- The full analysis set (**FAS**), which includes all enrolled participants who receive at least 1 administration of study treatment, will be used for analyses of OS and may be used for additional analyses of selected efficacy and exploratory endpoints.
- The evaluable analysis set (**EAS**), which includes all participants who receive at least 1 administration of study treatment and have an evaluable baseline tumor assessment and who have at least one evaluable post-baseline tumor response assessment as per RECIST v1.1 or were discontinued due to toxicity, will be the primary analysis set for analyses of response-based anti-tumor activity endpoints.

9.3 Statistical Evaluation

Summary statistics for continuous variables will include the number of patients (n), mean, standard deviation, median, minimum, and maximum.

Summary statistics for categorical variables will include the frequency and percentage of patients in each category.

Summary statistics for time to event data will include the number of patients, estimated median and its 95% CI, 25th percentile, 75th percentile, minimum, and maximum times to event, number of events (total and censored).

Results will be summarized by Arm. All data will be listed. Baseline is assumed to be the last observation prior to first dose of study drug. The effects of noncompliance, time to first dose, treatment discontinuations, and premature withdrawal from study will be assessed to determine the impact on the general applicability of results from this study. Further details of the analysis, including the handling of missing data, transformations and other data handling procedures will be provided in the SAP. Exploratory analyses of the data will be conducted as deemed appropriate.

9.3.1. Efficacy Analysis

The ORR is defined as the proportion of patients achieving a confirmed best overall response of CR or PR according to RECIST 1.1 based on local review. The ORR along with the associated 95% CI based on the Clopper-Pearson exact method, will be reported per Arm.

Survival time is defined as the time from first dose of study drug to the date of death due to any cause. Patients who do not die will be censored at the last documented date alive. PFS is defined as the time from first dose of study drug to the date of the first documented progressive disease (PD; that is confirmed by a follow up scan), according to RECIST 1.1, or to death from any cause. Patients who neither progress nor die will be censored at date of last documented response assessment. The DoR measured from the earliest CR or PR until documented PD (confirmed after follow up scan), according to RECIST 1.1, or death due to any cause. Patients with ongoing responses will be censored at last documented response assessment. The Kaplan-Meier method will be used to summarize OS, PFS and DoR. The EAS will be the primary analysis set for analysis of ORR, PFS, and DoR. The FAS will be the primary analysis set for analysis of OS. Each arm will be summarized independently.

9.3.2. Safety Analysis

All safety analyses will be conducted in the SAF.

Adverse events (AEs) will be coded according to the current version of the Medical Dictionary for Regulatory Activities (MedDRA). The severity of AEs will be graded according to NCI CTCAE, v5.0.

Treatment-emergent adverse events (TEAEs) are defined as any AE with onset or worsening of a pre-existing condition after the first dose of study drug through 30 days for AEs and 90 days for SAEs/irAEs following the last dose of study drug. Events including TEAEs, AEs leading to dose reduction/interruption, AEs related to study drug, SAEs, AEs leading to study drug discontinuation, and fatal AEs will be summarized by system organ class (SOC) and preferred term (PT). A summary of AEs of NCI CTCAE Grade 3 or higher, as well as the most frequent AEs (by preferred term), and AEs by relationship to study treatment, will be provided.

A listing of DLTs will be reported for the safety run-in phase of Arm 1 and 2.

Values and changes from baseline in clinical laboratory results will be summarized by visit. Clinical laboratory values will be graded according to the NCI CTCAE, for applicable tests. Shifts in toxicity grades from baseline grade will be summarized. Shifts from baseline in ECOG performance status also will be summarized.

Vital signs, ECG, LVEF and concomitant medication data will be summarized. Graphical displays will be provided where useful to assist in the interpretation of results.

9.3.3. Immunogenicity Analysis

This analysis will be performed on the FAS. The level of HER2-specific antibodies and immune phenotyping will be assessed in peripheral blood at baseline and at the timepoints as per Table 1 & Table 2 while on treatment.

Values and changes from baseline in immunological data will be summarized by visit. Associations between immunologic endpoints with clinical outcomes will be assessed by graphical techniques and measures of association as appropriate.

9.4 Sample Size Determination

The study plans to enroll 15 evaluable patients into each Arm of the study, for a total of approximately 30 evaluable patients.

For each Arm, after 8 evaluable patients are enrolled (Stage 1), an additional 7 evaluable patients will be enrolled in that group (Stage 2) if 1 or more patients respond (i.e., experience CR or PR). If there are no responses in Stage 1, then preliminary anti-tumor activity in the group will not have been identified and no further patients will be enrolled in that Arm. If the Arm continues to Stage 2, a total of 15 evaluable patients will be studied for that Arm. The Arm will be considered successful if ≥ 4 treated patients respond and the Arm may be expanded to enroll 25 patients. This design is applied to each Arm separately and is based on a 2-stage Simon Minimax design for a total of 15 evaluable patients (null hypothesis that ORR $\leq 11\%$ versus the alternative hypothesis that ORR $\geq 40\%$ with alpha=0.07268 and power=90.463%).

9.5 Disposition, Demographic and Other Baseline Characteristics

A patient disposition table will comprise the number of patients included per Arm, exposed to study drug (separately for each agent that is part of the combination), and completing or withdrawing from study (including reason for withdrawal). The number of patients in each analysis set will be included, also per Arm. The patient disposition will be summarized separately by Arm and overall.

Demographic, medical history, baseline disease characteristics, prior treatments for study disease and other baseline data will be presented using summary statistics based on the SAF overall and by Arm.

9.6 Exposure

The number of doses and cumulative total dose of HER-Vaxx will be summarized with descriptive statistics by Arm and overall. Concomitant chemotherapy (ramucirumab plus paclitaxel including use of dexamethasone) and pembrolizumab administered per protocol will also be summarized with descriptive statistics.

9.7 Interim Analysis

Each Arm will be evaluated independently.

After 8 evaluable patients are enrolled (Stage 1) an additional 7 evaluable patients will be enrolled in that Arm (Stage 2) if 1 or more patients respond (i.e., experience CR or PR). If there are no responses in Stage 1, then preliminary anti-tumor activity in the group will not have been identified and no further patients will be enrolled in that Arm. If the Arm continues to Stage 2, a total of 15 evaluable patients will be studied for that Arm. The Arm will be considered successful if ≥ 4 treated patients respond, and the Arm may be expanded to enroll 25 patients. This design is applied to both arms and is based on a 2-Stage Simon Minimax design for a total of 15 evaluable patients (null hypothesis that ORR ≤ 11% versus the alternative hypothesis that ORR ≥ 40% with alpha=0.07268 and power=90.463%).

10. DATA HANDLING AND RECORD KEEPING

10.1 Data Collection

This study will use a 21 CFR Part 11 compliant electronic data capture (EDC) system. An eCRF will be used for data recording. Any data requested on the eCRF must be entered and a reasonable effort should be made to retrieve any missing data.

The data will be checked for completeness and correctness and discrepancy reports will be generated accordingly and transferred to the study center for resolution by the Investigator or his/her designee.

As part of the responsibilities assumed by participating in the study, the Investigator or Sub-Investigator agrees to maintain adequate case histories for the patients treated as part of the research under this protocol. The Investigator or Sub-Investigator agrees to maintain accurate eCRF and source documentation as part of the case histories.

The Investigators or designees must enter all results collected during the clinical study into eCRF. There is a 2-part process to review and collect the eCRF data. Study site personnel will enter the data from each study visit within the timelines outlined in the Clinical Trial Agreement. Investigators are responsible for approval of the entered and/or corrected data. The eCRF responsibilities of the study team members will be documented on the site delegation log, which will be collected at the closeout visits. Investigators can authorize Sub-Investigators to sign and approve the eCRF if they are designated on Form FDA 1572 (where appropriate per local requirements) as Sub-Investigators, have been trained on the EDC system, and have their own username and password. Investigators or designees must review and approve the data before database lock.

The completed original eCRFs are the sole property of Imugene Limited and should not be made available in any form to third parties, except for authorized representatives of Imugene Limited or appropriate regulatory authorities, without written permission from Imugene Limited.

The investigator has ultimate responsibility for the collection and reporting of all clinical, safety and laboratory data entered on the eCRFs and any other data collection forms (source documents) and ensuring that they are accurate, authentic / original, attributable, complete, consistent, legible, timely (contemporaneous), enduring and available when required. In most cases, the source documents are the hospital's or the physician's patient chart. In these cases data collected on the CRFs must match the data in those charts.

10.2 Monitoring

The study will be monitored by a contract research organization (CRO). Its representatives will be allowed access to all information resulting from this study and Imugene Limited will have an unrestricted right to use such information. The study monitor will have access to laboratory test reports and other patient records needed to verify the entries on the CRF. The patients' confidentiality will be respected as required by local law.

10.3 Documentation and Material Supply

All supplies provided to the investigators for the purpose of carrying out the study are supplied only for the purpose of the study and must not be used for any other purpose. The principal investigator or (a) person(s) delegated by the principal investigator is/are responsible for the security and accountability of all supplies. All such supplies, if not used during the course of the study and not forming a part of the documentation required to be retained by the investigator, must be returned to Imugene Limited at the conclusion of the study.

10.4 Record Retention

To enable evaluations and/or audits from regulatory authorities or Imugene Limited, the investigator agrees to keep records, including the identity of all participating patients (sufficient information to link records, e.g., CRFs and hospital records), all original signed informed consent documents, copies of all CRFs, safety reporting forms, source documents, and detailed records of treatment disposition, and adequate documentation of relevant correspondence (e.g., letters, meeting minutes, telephone calls reports). The records should be retained by the investigator according to ICH, local regulations, or as specified in the Clinical Study Agreement (CSA), whichever is longer.

If the investigator becomes unable for any reason to continue to retain study records for the required period (e.g., retirement, relocation), Imugene Limited should be prospectively notified. The study records must be transferred to a designee acceptable to Imugene Limited, such as another investigator, another institution, or to an independent third party arranged by Imugene Limited. Investigator records must be kept for a minimum of 15 years after completion or discontinuation of the study or for longer if required by applicable local regulations.

The investigator must obtain Imugene Limited's written permission before disposing of any records, even if retention requirements have been met.

10.5 Medical Coding

Coding of prior and concomitant medications will be performed using World Health Organization (WHO) Drug Dictionary. AEs and medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA, version to be specified in the data management plan).

10.6 Health Economics Data Collection

Not applicable.

11. ADMINISTRATIVE ASPECTS

11.1 Quality Assurance Audit

This study may be audited by Imugene Limited or its designee to document the authenticity of recorded data and protocol adherence. Patients participating in the study should be informed that their records might be reviewed for this purpose, and also by government health authorities. The patients' confidentiality will be respected as required by local law.

11.2 Investigator Site File

At study initiation, each investigator will be provided with an investigator site file (ISF) containing information as specified in 21CFR312.62 Investigator recordkeeping and record retention. It is the Investigator's responsibility to keep the ISF up to date.

11.3 Protocol Deviations

A protocol deviation is any non-compliance with the clinical study protocol, GCP, or requirements in other procedures. The non-compliance may be either on the part of the participant, the Investigator, or the study site staff. Because of deviations, corrective actions are to be developed by the site and implemented promptly. These practices are consistent with ICH E6:

- 4.5 Compliance with Protocol, Sections 4.5.1, 4.5.2, and 4.5.3
- Quality Assurance and Quality Control, Section 5.1.1
- 5.20 Non-compliance, Sections 5.20.1 and 5.20.2.

Major protocol deviations are any deviations that might significantly affect the completeness, accuracy, and/or reliability of the study data or that might significantly affect a patient's rights, safety, or well-being. This includes deviations related to patient eligibility, informed consent, IMP dosing errors, or failing to perform assessments required to interpret the primary endpoint. Additional categories may be identified as deemed necessary by the Sponsor.

All protocol deviations will be reported by the clinical research associates (CRAs) or other study-involved personnel, such as data manager and statisticians. The protocol deviations will be reviewed by the Sponsor medical monitor. The medical monitor determines whether a deviation is major or not. Major deviations are reported to the Sponsor as part of the regular reporting. Important protocol deviations will be summarized in the clinical study report. In accordance with applicable FDA mandates, the Investigator is responsible for reporting protocol deviations to the IRB/IEC.

In case of a deviation, the Investigator enters a comment in the source documents and the non-compliance will be documented in a Monitoring Visit Report by the CRA. All non-compliance will be followed up and reported to FDA and IRBs/IECs as per regulations. In parallel, corrective and/or preventive actions will be undertaken and documented, including any retraining of the Investigator and site staff. No waivers for inclusion or exclusion criteria will be given.

11.4 Clinical Study Report

A clinical study report according to ICH Guideline "Note for Guidance on Structure and Content of Clinical Trial Reports" will be issued. A summary of the study results will be provided to the IRBs/IECs and the FDA within one year after end of study.

12. ETHICAL AND LEGAL CONSIDERATIONS

The study will be conducted in accordance with legal and regulatory requirements, as well as the general principles set forth in the International Ethical Guidelines for Biomedical Research Involving Human Subjects (Council for International Organizations of Medical Sciences 2002), Guidelines for GCP (ICH 1996), and the Declaration of Helsinki (World Medical Association 1996, 2008).

In addition, the study will be conducted in accordance with the protocol, the ICH guideline on GCP, and applicable local regulatory requirements and laws.

12.1 Institutional Review Boards / Independent Ethics Committees

It is the responsibility of the investigator to have prospective approval of the study protocol, protocol amendments, informed consent documents, and other relevant documents, eg, recruitment advertisements, if applicable, from the IRB/IEC. All correspondence with the IRB/IEC should be retained in the Investigator File. Copies of IRB/IEC approvals should be forwarded to Imugene Limited, or its agent.

The only circumstance in which an amendment may be initiated prior to IRB/IEC approval is where the change is necessary to eliminate apparent immediate hazards to the patients. In that event, the investigator must notify the IRB/IEC and Imugene Limited in writing immediately after the implementation.

12.2 Patient Informed Consent

All parties will ensure protection of patient personal data and will not include patient names on any sponsor forms, reports, publications, or in any other disclosures, except where required by laws.

Patient names, address, birth date and other identifiable data will be replaced by a numerical code consisting of a numbering system provided by Imugene Limited, or its delegate, in order to de-identify the study patient. In case of data transfer, Imugene Limited and its agents will maintain high standards of confidentiality and protection of patient personal data.

The informed consent document must be in compliance with ICH GCP, local regulatory requirements, and legal requirements.

The informed consent document used in this study, and any changes made during the course of the study, must be prospectively approved by both the IRB/IEC and Imugene Limited, or its agent, before use.

The investigator must ensure that each study patient, or his/her legal representative, is fully informed about the nature and objectives of the study and possible risks associated with participation.

The investigator, or a person designated by the investigator, will obtain written informed consent from each patient or the patient's legal representative before any study-specific activity is performed. The investigator will retain the original of each patient's signed consent document.

12.3 Study Discontinuation and Closure

Premature termination of this study may occur because of a regulatory authority decision, change in opinion of the IRB/IEC, drug safety problems, or at the discretion of Imugene. In addition, Imugene retains the right to discontinue development of HER-Vaxx at any time.

If the study is prematurely terminated or discontinued, Imugene will promptly notify the investigator. After notification, the investigator must contact all participating patients and the hospital pharmacy (if applicable) within 7 days. As directed by Imugene, all study materials must be collected and all CRFs completed to the greatest extent possible.

12.4 Confidentiality

Either prior to or during the course of the study, Imugene Limited or their representatives will provide the principal investigator and persons delegated by him/her with confidential information, for example, but not limited to, the protocol and the IB. The information may not be disclosed to anyone else without prior approval from Imugene Limited in writing. This obligation of confidentiality shall survive the completion or early termination of the study.

12.5 Protocol and Investigator Brochure

All study personal must be familiar with the protocol to be able to conduct the study in the manner specified.

Imugene Limited has supplied the investigator with an Investigator's Brochure (IB), which describes the vaccine being tested and its known adverse effects. The investigator must be familiar with this document before the study commences. Imugene Limited will provide additional information requested by the investigator before commencing the study or during its conduct.

This protocol cannot be altered or changed except through a formal protocol amendment, which requires the written approval of Imugene Limited. The protocol amendment must be signed by the investigator and approved by the IRB or IEC before it may be implemented. Protocol amendments will be filed with the appropriate regulatory agencies having jurisdiction over the conduct of the study.

12.6 Reporting of Safety Issues and Serious Breaches of the Protocol or ICH GCP

In the event of any prohibition or restriction imposed (ie, clinical hold) by an applicable Competent Authority in any area of the World, or if the investigator is aware of any new information which might influence the evaluation of the benefits and risks of the investigational product, Imugene Limited should be informed immediately.

In addition, the investigator will inform Imugene Limited immediately of any urgent safety measures taken by the investigator to protect the study patients against any immediate hazard, and of any serious breaches of this protocol or of ICH GCP that the investigator becomes aware of.

12.7 Compensation for Medicine-induced Injury

According to local regulations Imugene Limited will provide insurance coverage to all patients during study period. Imugene Limited assumes liability for and will indemnify all injuries that occur to patients whenever a causal relationship can be established between the event and the clinical study procedure or the study substance under study if the following can be demonstrated:

- The event resulted from a study substance, provided that the substance was administered according to the current protocol and manufacturer's instructions.
- The event occurred as a consequence of diagnostic procedures performed according to the study protocol.
- The event resulted from therapeutic or diagnostic measures legitimately required as a consequence of unexpected events caused by the study substance, by comparative medication, or by diagnostic procedures called for by the study protocol.

Imugene Limited is not liable for events that occur solely as a consequence of the underlying illness of the patient, or for events resulting from diagnostic or therapeutic measures not specifically required by the protocol, or for events resulting from negligence (including failure to act according to accepted medical practice, or to comply strictly with the protocol or the terms of this Agreement) of the investigator or any other involved and/or related clinical staff and facilities.

This indemnity provided by Imugene Limited shall further apply as follows:

- Imugene Limited is to be informed as soon as possible of any complaint, action or suit of proceeding giving rise to the right of indemnification, and the investigator agrees to co-operate fully with Imugene Limited in the defense or disposition of all such cases.
- Imugene Limited will be permitted, at its costs and discretion, to handle and control the defense or disposition of all such cases.

No case will be settled without the prior written consent of Imugene Limited.

12.8 Publication Policy and Protection of Trade Secrets

In accordance with standard editorial and ethical practice, Imugene Limited will support publication of multicenter studies only in their entirety and not as individual center data except for data on sub-studies.

The following rules will apply for determining authorship:

- Authorship credit will be based on the Vancouver statement by the International Committee of Medical Journal Editors, i.e. substantial contribution to the following criteria:
    - Conception and design or analysis and interpretation;
    - Drafting article or critically revising it for intellectual content;

  - Final approval of the version to be published;
- Additional criteria for authorship include:
  - Contributors who register 20% or more of the evaluable cases on the study;
  - Significant contribution to the Cohort Review Committee.

In an appropriate footnote, or at the end of the article, the following statement will be made:

"Participating investigators included: (a list of the individuals who have contributed patients and their institutions)."

Investigator agrees to submit all manuscripts or abstracts to Imugene Limited prior to submission. This allows Imugene Limited to protect proprietary information and to provide comments based on information from other studies that may not yet be available to the authors of the manuscript. Investigator will collaborate with the study statistician for preparation of study data analyses intended to be used in the publication(s) of the study.

Any formal publication of the study in which input of Imugene Limited personnel exceeded that of conventional monitoring will be considered as a joint publication by investigator and Imugene Limited.

Moreover, the following points need to be considered:

- Without investigator's prior written consent, Imugene Limited may not make reference, either directly or indirectly, in a commercial publication, to Investigator's name or institution, or any of its employees in which Investigator performed the present studies, connected with the research and its results.
- Imugene Limited may not use investigator's name or the name of the Medical University Vienna or its employees connected to the research or to the institution in which Investigator performed the present study in its commercial publications as recommendation of quality and/or of the finished product and/or of the drug and the efficacy of its use.
- Should Imugene Limited decide to publish the research results, it must publish them in their entirety and must not quote anything out of context.

Nothing in the aforementioned limitations in clauses will prevent Imugene Limited from quoting from articles, provided that the scientific source of data (scientific conventions, scientific newspapers) is mentioned.

12.9 Conflict of Interest Policy

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this study will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the study.

13. REFERENCE LIST

Alanji AJ, et al. An open-label, multinational, multicenter study of G17DT vaccination combined with cisplatin and 5-fluorouracil in patients with untreated, advanced gastric or gastroesophageal cancer: the GC4 study. Cancer. 2006;106(9):1908-16.

American Cancer Society. Cancer Facts & Figures 2021. Atlanta, Ga: American Cancer Society; 2021. Available at http://www.cancer.org/cancer/stomachcancer/detailedguide/stomach-cancer-survival-rates. Accessed 28 September 2021

Bang Y-J et al. Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-esophageal junction cancer ToGA: a phase 3 open-label, randomized controlled trial, Lancet 2010; 376:687-97

Blank, C., et al., PD-L1/B7H-1 inhibits the effector phase of tumor rejection by T cell receptor (TCR) transgenic CD8+ T cells. Cancer Res, 2004. 64(3): p. 1140-5.

Chemnitz, JM., et al. SHP-1 and SHP-2 Associate with Immunoreceptor Tyrosine-Based Switch Motif of Programmed Death 1 upon Primary Human T Cell Stimulation, but Only Receptor Ligation Prevents T Cell Activation. The Journal of Immunology.2004, 173: 945–954

Curran, M.A., et al., PD-1 and CTLA-4 combination blockade expands infiltrating T cells and reduces regulatory T and myeloid cells within B16 melanoma tumors. Proc Natl Acad Sci U S A, 2010. 107(9): p. 4275-80.

Disis, Mary L. Immune Regulation of Cancer. Journal of Clinical Oncology.2010; 28 (29):4531-4538

Dudley, M E. et al. Adoptive Cell Transfer Therapy Following Non-Myeloablative but Lymphodepleting Chemotherapy for the Treatment of Patients With Refractory Metastatic Melanoma. Journal of Clinical Oncology.2005; 0732-183

Francisco, LM., et al. The PD-1 pathway in tolerance and autoimmunity. Immunological Reviews.2010; 0105-2896

Greenwald, RJ., et al. The B7 Family Revisited. Annual Reviews.2005; 23:515–48

Hirano, F., et al., Blockade of B7-H1 and PD-1 by monoclonal antibodies potentiates cancer therapeutic immunity. Cancer Res, 2005. 65(3): p. 1089-96.

Hofmann M, et al. Assessment of a HER2 scoring system for gastric cancer: results from a validation study. Histopathology. 2008;52(7):797-805.

Hunder NN, et al. Treatment of metastatic melanoma with autologous CD4+ T cells against NY-ESO-1. N Engl J Med 2008;358(25):2698-703

IARC cancer fact sheets: stomach cancer. Available at https://gco.iarc.fr/today/data/factsheets/cancers/7-Stomach-fact-sheet.pdf. Accessed 17 September 2021

Kaumaya PTP, et al. Immunogenicity and antitumor efficacy of a novel human PD-1 B-cell vaccine (PD1-Vaxx) and combination immunotherapy with dual trastuzumab/pertuzumab-like HER-2 B-cell epitope vaccines (B-Vaxx) in a syngeneic mouse model. *Oncoimmunology*. 2020;9(1):1818437.

Maglakelidze M et al. A Phase 2 study of HER-Vaxx (IMU-131), a HER2 targeting peptide vaccine, plus standard of care chemotherapy in patients with HER2 overexpressing metastatic or advanced gastric/GEJ adenocarcinoma. Final Overall Survival Analysis. ASCO GI 2023

Matsushita N, et al. Phase I clinical trial of a peptide vaccine combined with tegafur-uracil plus leucovorin for treatment of advanced or recurrent colorectal cancer. Oncol Rep. 2013;29(3):951-9.

NCCN Clinical Practice Guidelines Oncology Gastric Cancer https://www.nccn.org/professionals/physician_gls/pdf/gastric.pdf (4.2022)
Nomi, T., et al., Clinical significance and therapeutic potential of the programmed death-1 ligand/programmed death-1 pathway in human pancreatic cancer. Clin Cancer Res, 2007. 13(7): p. 2151-7.

Okazaki T, et al. PD-1 immunoreceptor inhibits B cell receptor-mediated signaling by recruiting src homology 2-domain-containing tyrosine phosphatase 2 to phosphotyrosine. Proc Natl Acad Sci U S A 2001;98(24):13866-71.

Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol. 1982;5(6):649-55.

Park DI, et al. HER-2/neu amplification is an independent prognostic factor in gastric cancer. Dig Dis Sci. 2006;51(8):1371-9.

Parry, RV. et al. CTLA-4 and PD-1 Receptors Inhibit T-Cell Activation by Distinct Mechanisms. Molecular and Cellular Biology, 2005; 0270-7306

Pilon-Thomas, S., et al., Blockade of programmed death ligand 1 enhances the therapeutic efficacy of combination immunotherapy against melanoma. J Immunol, 2010. 184(7): p. 3442-9.

Riley, JL., PD-1 signaling in primary T cells. Immunological Reviews. 2009; 0105-2896

Roy V, Perez EA. Beyond trastuzumab: small molecule tyrosine kinase inhibitors in HER-2-positive breast cancer. Oncologist. 2009;14(11):1061-9.

Seo S, et al. Loss of HER2 positivity after anti-HER2 chemotherapy in HER2- positive gastric cancer patients: results of the GASTric cancer HER2 reassessment study 3 (GASTHER3) Gastric Cancer (2019) 22:527–535

Shepard, KA., et al. PD-1 inhibits T-cell receptor induced phosphorylation of the ZAP70/CD3 signalosome and downstream signaling to PKC. FEBS Letters. 2004; 0014-5793

Spranger, S., et al., Mechanism of tumor rejection with doublets of CTLA-4, PD-1/PD-L1, or IDO blockade involves restored IL-2 production and proliferation of CD8(+) T cells directly within the tumor microenvironment. J Immunother Cancer, 2014. 2: p. 3.

Strome, S.E., et al., B7-H1 blockade augments adoptive T-cell immunotherapy for squamous cell carcinoma. Cancer Res, 2003. 63(19): p. 6501-5.

Takashi, K. et al. Comparison of HER2 Status Before and After Trastuzumab-based Chemotherapy in Patients With Advanced Gastric Cancer. Anticancer Research Jan 2020, 40 (1) 75-80.

Thompson, J.A. et al. NCCN Guidelines Insights: Management of Immunotherapy-Related Toxicities, Version 1.2020 in: Journal of the National Comprehensive Cancer Network Volume 18 Issue 3 (2020) (jnccn.org)

Tobias J, et al. Enhanced and long term immunogenicity of a Her-2/neu multi-epitope vaccine conjugated to the carrier CRM197 in conjunction with the adjuvant Montanide. BMC Cancer 2017: 118 (2017)

Wagner S, et al. Delayed tumor onset and reduced tumor growth progression after gastroesophageal adenocarcinoma with fluorouracil, leucovorin plus either oxaliplatin immunization with a Her-2/neu multi-peptide vaccine and IL-12 in c-neu transgenic mice. Breast Cancer Res Treat. 2007;106(1):29-38.

Weber, J., Immune checkpoint proteins: a new therapeutic paradigm for cancer--preclinical background: CTLA-4 and PD-1 blockade. Semin Oncol, 2010. 37(5): p. 430-9.

Weir G, Liwski R, Mansour M. Immune Modulation by Chemotherapy or Immunotherapy to Enhance Cancer Vaccines. Cancers 2011;3: 3114-3142

Wiedermann U, et al. A virosomal formulated Her-2/neu multi-peptide vaccine induces Her 2/neu-specific immune responses in patients with metastatic breast cancer: a phase I study. Breast Cancer Res Treat. 2010;119(3):673-83.

Wiedermann, U., et al. (2021). Clinical and Immunologic Responses to a B-Cell Epitope Vaccine in Patients with HER2/neu-Overexpressing Advanced Gastric Cancer—Results from Phase Ib Trial IMU.ACS.001. Clinical Cancer Research 27(13): 3649-3660.

Wilke H, Muro K, Van Cutsem E, Oh SC, Bodoky G, Shimada Y, Hironaka S, Sugimoto N, Lipatov O, Kim TY, Cunningham D, Rougier P, Komatsu Y, Ajani J, Emig M, Carlesi R, Ferry D, Chandrawansa K, Schwartz JD, Ohtsu A; RAINBOW Study Group. Ramucirumab plus paclitaxel versus placebo plus paclitaxel in patients with previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (RAINBOW): a double-blind, randomised phase 3 trial. Lancet Oncol. 2014 Oct;15(11):1224-35. doi: 10.1016/S1470-2045(14)70420-6. Epub 2014 Sep 17. PMID: 25240821.

Yano T, et al. Comparison of HER2 gene amplification assessed by fluorescence in situ hybridization and HER2 protein expression assessed by immunohistochemistry in gastric cancer. Oncol Rep. 2006;15(1): p. 65-71.

Zhang PD, et al. Structural and Functional Analysis of the Costimulatory Receptor Programmed Death-1. Immunity.2004; 337-347

Zhang XL, et al. Comparative study on overexpression of HER2/neu and HER3 in gastric cancer. World J Surg. 2009;33(10):2112-8.

14. APPENDICES

14.1 Appendix A: Eastern Cooperative Oncology Group (ECOG) Performance Status Scoring (Oken et al, 1982)

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

14.2 Appendix B: Common Terminology Criteria for Adverse Events (CTCAE) version 5.0

CTCAE term (AE description) and grade: The descriptions and grading scales found in the revised NCI-CTCAE version 5.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP web site: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

Quick Reference The NCI-CTCAE is a descriptive terminology, which can be utilized for Adverse Event (AE) reporting. A grading (severity) scale is provided for each AE term.

Components and Organization System Organ Class (SOC), the highest level of the Medical Dictionary for Regulatory Activities (MedDRA) hierarchy, is identified by anatomical or physiological system, etiology, or purpose (e.g. SOC Investigations for laboratory test results). CTCAE terms are grouped by MedDRA Primary SOCs. Within each SOC, AEs are listed and accompanied by descriptions of severity (Grade).

CTCAE Terms An AE is any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medical treatment or procedure that may or may not be considered related to the medical treatment or procedure. An AE is a term that is a unique representation of a specific event used for medical documentation and scientific analyses. Each CTCAE v 5.0 term is a MedDRA Lowest Level Term.

Definitions A brief definition is provided to clarify the meaning of each AE term.

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

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