HERCULES: An Open-label Phase III Three-Arm Noninferiority Trial of HER-Vaxx (IMU-131) Plus Chemotherapy Versus Trastuzumab Plus Chemotherapy Versus Chemotherapy Alone in Chinese Patients with Advanced/Metastatic HER2-positive Gastric Cancer or Gastroesophageal Junction (GEJ) Adenocarcinoma

Sponsored by:

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"There is something better than science, and that is science with a moral compass, science that contributes to social equity, science in the service of humanity."
-Dr. William Foege

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List of abbreviations and acronyms

CEP17: Chromosome 17 Centromere (ISH assay for HER2 status determination)
CORE: Coordinating and Operations Center
CRF: Case Report Form
CTCAE: Common Terminology Criteria for Adverse Events
DOR: Duration of Response
ECOG Score: Eastern Cooperative Oncology Group Performance Scale
FACT-G: Functional Assessment of Cancer Treatment-General
FACT-Ga: Functional Assessment of Cancer Treatment-Gastric Cancer
FISH: Fluorescent *in situ* hybridization
GAD-7: Generalized Anxiety Disorder Scale (measures anxiety)
GEE: Generalized Estimating Equation
GEJ: Gastroesophageal junction adenocarcinoma
HER2+: HER2 positive, refers to cancers with confirmed and substantial surface expression of the HER2/neu receptor
HR: Hazard Ratio
HRQOL: Health-Related Quality of Life
IDMC: Independent Data Monitoring Committee
IHC: Immunohistochemistry
mAb/pAb: monoclonal/polyclonal antibody
ORR: Overall Response Rate
OS: Overall Survival (post-enrollment)
PFS: Progression Free Survival
PHQ-9: Patient Health Questionnaire-9 (measures depression)
PRO: Patient Reported Outcome
SCHARP: Statistical Center for HIV/AIDS Research and Prevention
SMC: Study Monitoring Committee

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Schema

Purpose:

Gastric and esophageal cancers are the fifth and tenth most diagnosed, and fourth and sixth most deadly cancer on a global scale, disproportionately affecting nonwhite racial and ethnic minorities.[1] Thus, gastric cancer is a salient target to ameliorate patient outcomes and promote equity in cancer treatment. A significant fraction of gastric cancers show cell surface expression of HER2/neu, a receptor protein responsible for growth signaling. Trastuzumab (Herceptin, Genentech/Roche), a humanized monoclonal antibody treatment targeting the HER2/neu receptor, was shown in the ToGA trial to significantly prolong overall survival in advanced, HER2-overexpressing gastric cancer patients relative to combination chemotherapy alone (median OS 11.1 versus 13.8 months, p=0.0046).[2] However, innate or acquired tumor resistance to trastuzumab, alongside the treatment's high cost, frequency of administration, and potential side effects, highlight the need for efficacious, alternative anti-HER2 treatments. HER-Vaxx (Imu-131, Imugene) is a B-cell immunotherapy agent designed to stimulate the patient's immune system to produce a polyclonal anti-HER2 antibody response. In preclinical models and early clinical settings, HER-Vaxx has shown potent and durable anti-HER2 immunogenicity, has stimulated cell-mediated vaccine responses such as Th1-biased cytokine ratios, T_{reg} reduction, and B-cell memory responses, and has offered early evidence of clinical activity and safety. HER-Vaxx could benefit patients in need of safe and cost-effective alternatives to trastuzumab since peptide-based vaccines are cheaper to manufacture and administer than monoclonal antibodies. This 3-arm, open-label study aims to investigate whether HER-Vaxx plus chemotherapy is non-inferior in terms of OS to trastuzumab plus chemotherapy in treating locally advanced/metastatic HER2-positive gastric and gastroesophageal cancers in China.

Objectives:

Primary objectives:

1. Assess whether IMU-131 (HER-Vaxx) plus chemotherapy is noninferior to trastuzumab plus chemotherapy in terms of OS.
   Sub-Hypothesis 1 (Assay sensitivity): HER-Vaxx plus chemotherapy is superior to chemotherapy alone in terms of OS.
   Sub-Hypothesis 2 (Retention of Effect): HER-Vaxx plus chemotherapy retains at least 60% of the effect of trastuzumab plus chemotherapy relative to chemotherapy alone in terms of OS.
2. To evaluate the relative safety of IMU-131 (HER-Vaxx) plus chemotherapy to trastuzumab plus chemotherapy and chemotherapy alone.
   Hypothesis 1: HER-Vaxx will have an acceptable safety profile, with similar rates of adverse events across gastrointestinal, blood/lymphatic, and general/metabolic disorders. We anticipate a higher rate of minor local injection site events but a lower rate of infusion-related reactions (allergic reaction, hypersensitivity, chills, arthralgia, and dyspnea) in the experimental arm compared to the active control arms.

Secondary objectives:

1. To compare objective tumor response rates (ORR) in the three study arms in advanced/metastatic HER2 positive gastric cancer/GEJ cancer at months 6 and 12-post enrollment.
2. To compare responses to patient reported outcomes (PROs) to FACT-Ga, FACT-G, PHQ-9, and GAD-7 between patients on HER-Vaxx plus chemotherapy versus trastuzumab plus chemotherapy versus chemotherapy alone arms.

Exploratory objectives:

1. Assess whether HER-Vaxx treatment effect depends on magnitude of anti-HER2 antibody response in the experimental arm.
   Hypothesis 1: higher anti-HER2 antibody titers will be associated with a larger treatment effect in the HER-Vaxx arm.
2. To assess the frequency of HER2-positivity in gastric and gastroesophageal cancer in a large Chinese cohort.

Study Population:

Eligible participants for this study will be adult patients in China with IHC/FISH-confirmed HER2-positive locally advanced (i.e., unresectable), recurrent, or metastatic gastric or gastroesophageal cancer as determined by clinical and pathological criteria by the American Joint Committee on Cancer (AJCC) Classification of Gastric Cancer (8th edition).[3] Participants must have measurable HER2-positive disease per RECIST 1.1, a Karnofsky performance score of ≥60% or EOG score of ≤ 2, and adequate organ function. Exclusion criteria will include non-adenocarcinoma disease, previous chemotherapy/anti-HER therapy for metastatic disease, Karnofsky performance score <60% and ECOG score > 2, CNS metastases, active autoimmune conditions (including history of HIV), immunodeficiency, and history of severe cardiac dysfunction.

We believe that a three-arm trial in HER2-positive gastric cancer with a chemotherapy control is only ethical if the trial enrolls patients who are otherwise unable to receive HER2 testing or trastuzumab treatment. The gastric cancer burden is very high in China; China has the highest raw number of incident gastric cancer cases per GLOBOCAN estimates.[1] A real-world study in China showed only 37% of patients with early-stage breast cancer received HER2 targeted therapies in resource-abundant regions, only 13% received treatment in resource-poor regions,[4] and 49% of patients with advanced disease did not receive first line trastuzumab treatment.[5] Physician surveys in the USA and developing countries cited lack of insurance coverage and drug unavailability as common barriers to anti-HER2 therapies in breast cancer treatment, and 48% of physicians reported instances where anti-HER2 therapy was recommended but not administered.[6,7] Findings from a 2008 survey of 101 hospitals in Beijing showed that basic pathological information was missing for up to 67.2% of newly diagnosed breast cancers.[8] Findings from a nationwide survey of the quality of HER2 testing suggested in 45 Chinese hospitals found that only 62% met acceptable standards.[9] In Beijing, 9% of breast cancer patients had no access to HER2 testing and 10% of breast cancer patients with equivocal IHC results were never tested using ISH methods.[8] In 2008, only 20.6% of patients in Beijing with HER2-positive breast cancer received trastuzumab despite its approval in 2002.[8] A real world study in China between 2010-2015 found that only 40.5% of patients with HER2-positive early breast

cancer received trastuzumab treatment.[5] A study in the early 2010s found that in the Jiangsu province, where trastuzumab has been subsidized for early breast cancer and where trastuzumab use is highest, only 34% received trastuzumab, although health insurance coverage was associated with higher odds of trastuzumab use.[10] A recent cross-sectional study highlighted that availability of HER2 testing for gastric may be the bottleneck for targeted treatment; 72.9% of gastric cancers were not administered HER2 testing in China.[11] By 2013, there were 6 provinces and cities providing public reimbursement for trastuzumab, but only 2 for gastric cancer indication.[12] We focus on Chinese gastric/GEJ cancer due to the high disease burden and limited access to trastuzumab and HER2 testing in China.

Study Design:

The proposed study is an open-label clinical trial with a 5:3:2 block randomization scheme where 50% of patients are assigned to HER-Vaxx plus chemotherapy, 30% are assigned to trastuzumab plus chemotherapy, and 20% are assigned to chemotherapy alone. This allocation ratio was chosen based on the method of Mielke *et al.* 2008. Randomization will be stratified according to clinic, ECOG performance score, chemotherapy regimen, site of primary cancer, and previous gastrectomy status. The primary endpoint for this study will be overall survival post enrollment. The other primary, albeit not alpha-spending, endpoint will be the safety profile of HER-Vaxx plus chemotherapy relative to trastuzumab plus chemotherapy and chemotherapy alone. Secondary endpoints will include objective response rate at months 6 and 12 and responses to patient-reported outcome measures. The main exploratory endpoint will be longitudinal anti-HER2 serology to assess whether experimental treatment effect is mediated by magnitude of the anti-HER2 antibody response. Interim monitoring of all treatment safety profiles and immunogenicity of HER-Vaxx plus chemotherapy will be assessed by the Interim Data Monitoring Committee (IDMC) at regular 6-month intervals or more frequently as needed. The Study Monitoring Committee (SMC), in collaboration with IDMC and sponsors, will evaluate HER2-screening, recruitment, and retention data and will audit and design improvements to study procedures to ensure high quality trial conduct. There are four planned interim efficacy analyses that will follow the three-arm noninferiority trial group-sequential testing algorithm DF-A as described in Ochiai *et al.* 2017.[13]

The planned study will have a 4.5-year (54 month) recruitment period and will have a total planned runtime of 6.75 years (81 months). The planned study has a total Type I error rate of 2.5%, of which 2.5% is allocated to the assay sensitivity and retention of effect tests. Since the non-inferiority hypothesis is the union of assay sensitivity and retention of effect sub-hypotheses, the T1 error rate for the non-inferiority hypothesis is controlled at 2.5% using the principles of union-intersection tests. Based on results from the ToGA & JACOB trials as well as a meta-analysis of survival in advanced gastric cancer under the appropriate chemotherapy regimens, we assume a 10.85-month median survival in the control (chemotherapy alone) arm, and 14.85-month median survival in the trastuzumab plus chemotherapy and HER-Vaxx plus chemotherapy arms. In this setting, we define the minimal acceptable retention fraction to be 0.6, indicating that HER-Vaxx plus chemo is considered noninferior to trastuzumab plus chemo if it retains at least 60% of the active control's effect relative to chemotherapy alone, corresponding to an estimated minimum 2.4-month improvement in survival relative to chemotherapy alone. We estimate the trial will need to enroll 2600 participants to have more than 85% power to demonstrate

noninferiority of HER-Vaxx plus chemotherapy versus trastuzumab plus chemotherapy at the alpha=2.5% level.

Treatment Regimen:

Experimental: HER-Vaxx (P467-CRM197 peptide antigen in PBS buffer and Montanide ISA 51 Sterile adjuvant, 50 micrograms IM injection) administered at baseline, day 14, day 35, day 77, and then every 63 days until disease progression, death, end of study, or cessation of chemotherapy (~18 weeks) plus the following chemotherapy regimen as recommended by 2022 NCCN guidelines.[14]

1. Fluoropyrimidine (5-fluorouracil (750-1000 mg/m^2 IV infusion per 24 hours for 96 hours, repeat cycle every 2 weeks) or capecitabine (1000 mg/m^2 orally twice per day for 28 doses over 3 weeks) plus cisplatin (75-100 mg/m^2 1-2 hour IV every 4 weeks).

Patients will receive a maximum of 6 cycles of chemotherapy.

Patients will be permitted to cease or modify chemotherapy or study drug treatment as directed by clinicians. Use of another anti-HER2 targeted therapy or other experimental treatment that is believed to interfere with the treatment comparison will result in censoring.

Active comparator: trastuzumab (8 mg/kg loading dose IV over 90 minutes, followed by 6 mg/kg IV over 30 minutes every 3 weeks, administered intravenously until disease progression, death, end of study, or cessation of chemotherapy (~18 weeks) plus the following options recommended by the 2022 NCCN guidelines.[14]

1. Fluoropyrimidine (5-fluorouracil (750-1000 mg/m^2 IV infusion per 24 hours for 96 hours, repeat cycle every 2 weeks) or capecitabine (1000 mg/m^2 orally twice per day for 28 doses over 3 weeks) plus cisplatin (75-100 mg/m^2 1-2 hour IV every 4 weeks).

Patients will receive a maximum of 6 cycles of chemotherapy.

Patients will be permitted to cease or modify chemotherapy or study drug treatment as directed by clinicians. Use of another anti-HER2 targeted therapy or other experimental treatment that is believed to interfere with the treatment comparison will result in censoring.

Control: One of the following chemotherapy options recommended by the 2022 NCCN guidelines.[14]

1. Fluoropyrimidine (5-fluorouracil (750-1000 mg/m^2 IV infusion per 24 hours for 96 hours, repeat cycle every 2 weeks) or capecitabine (1000 mg/m^2 orally twice per day for 28 doses over 3 weeks) plus cisplatin (75-100 mg/m^2 1-2 hour IV every 4 weeks).

Patients will receive a maximum of 6 cycles of chemotherapy.

Patients will be permitted to cease or modify chemotherapy treatment as directed by clinicians. Use of another anti-HER2 targeted therapy or other experimental treatment that is believed to interfere with the treatment comparison will result in censoring.

Study Sites:

This study will be coordinated out of the Fred Hutchinson Cancer Research Center, Seattle, WA, USA. We restrict our study to 25 sites in China, the country with the highest raw number of gastric cancer cases and where HER2 testing/trastuzumab treatment is not widely available to all patients. We designate sites that were utilized under the JACOB[15] that successfully recruited patients, meaning most study sites have previous experience participating in a trastuzumab trial and have necessary facilities for diagnosis, imaging, patient care, etc. To safeguard the health of patients, during the informed consent process, clinicians will be instructed to discuss with patients about the benefits and costs of trastuzumab and encourage them to not enroll in the study if they would otherwise have access to trastuzumab treatment.

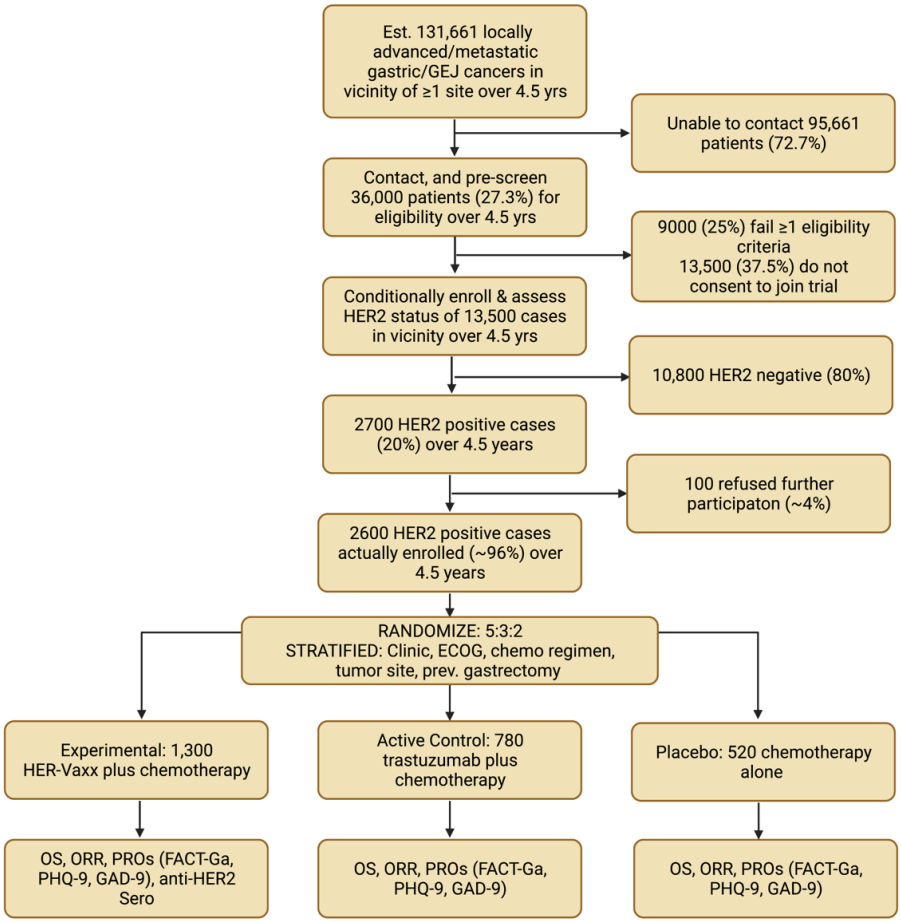
China (478,363 new annual gastric cancer cases per GLOBOCAN) – 25 Sites

JACOB Sites (22)
Beijing Cancer Hospital, Beijing
The First Affiliated Hospital of Zhengzhou University, Zhengzhou
Zhongshan Hospital Fudan University, Shanghai
Fudan University Shanghai Cancer Center, Shanghai
Sun Yet-sen University Cancer Center, Guangzhou
The Affiliated Hospital of Military Medical Science, Beijing
Henan Cancer Hospital, Zhengzhou
The 81st Hospital of P.L.A., Yanggongjing
Changzhou First People's Hospital, Changzhou
Sir Run Run Shaw Hospital, School of Medicine, Shenjiang University, Hangzhou
Cancer Hospital Chinese Academy of Medical Sciences, Beijing
The First Hospital of Jilin University, Changchun
The 1st Affiliated Hospital of Nanchang, Nanchang
Affiliated Hospital of Nontong, Nantong
Jilin Cancer Hospital, Changchun
Fuzhou General Hospital, Fuzhou
General Hospital of Shenyang Military Command of PLA, Shenyang
Harbin Medical University Cancer Hospital, Harbin
Hebei Medical University Fourth Hospital, Shijiazhuang
The Affiliated Hospital of Xuzhou Medical College, Xuzhou
Third Affiliated Hospital of Third Military Medical University, Chong Qing
The First Affiliated Hospital of The Fourth Military Medical University, Xi'an

Novel Sites (3)
Affiliated Hospital of Southwest Medical University, Luzhou
Yanhua Hospital, Beijing
Tianjin Medical University, Tianjin

Schema diagram:

Figure 1: Schema diagram illustrating enrollment and random assignment to the experimental (HER-Vaxx plus chemotherapy), active control (trastuzumab plus chemotherapy), and placebo (chemotherapy alone) study arms.



INTRODUCTION

Background and Prior Research

The Epidemiology of Gastric Cancer

Gastric cancer is the fifth most diagnosed and seventh-most prevalent cancer worldwide.[16] The incidence of gastric cancer varies by region and culture, with the highest incidence in Eastern and Central Asia and Latin America.[16,17] Gastric cancer is the third most deadly cancer among males worldwide. Approximately 8% of all cancer-related deaths are due to gastric cancer.[16] Within the United States, the five-year survival rate of gastric cancer is approximately 33.3%, and gastroesophageal cancer is 20.6%.[18] Low survival rates reflect the fact that most cases of gastric cancer are diagnosed late in the clinical course when the tumors have already metastasized to different parts of the body as early symptoms can be clinically silent.[19] Given low survival rates and few available and feasible treatment options, there is an urgent need to

develop new treatment methods to reduce the incidence, especially among developing nations worldwide. The most common risk factor of gastric cancer is previous *Helicobacter Pylori* infection and its complex interaction between host and bacteria.[17] Additionally, diets high in salt and low in vegetables, along with lifestyle factors such as tobacco, coffee, and alcohol, account for 33- 50% of gastric cancer.[20] Presenting symptoms of gastric cancer are dyspepsia and reflux, but people in later stages often present with dysphagia, weight loss, gastrointestinal bleeding, anemia, and emesis.[21]

Gastric cancer disproportionately affects low and middle-income countries compared to high-income countries. The incidence of gastric cancer in men in developed countries is 173,000 compared to 467,000 in developing countries; thus, 70% of gastric cancer cases worldwide are concentrated in developing countries in East Asia, Central and Eastern Europe, and South America.[22] The mortality rate among men in developed countries is 110,000 compared to 353,000 in developing countries, including Eastern Asia, Central, Eastern Europe, and South America. The fatality-to-case ratio ranges between 63% to 68% in developed nations and 75% to 81% in developing countries, and China alone had almost half of the global gastric cancer cases in 2020 per GLOBOCAN estimates.[1] Unfortunately, in countries where the burden of gastric cancer is high, treatment options are also limited. Many drugs that are standard of care treatment in the United States and other high-income countries are not available or if available, are unaffordable to the public in middle- and low-income countries due to the cost of these drugs.[1]

HER2 Overexpression in Cancers

Human epidermal growth factor receptor 2 (HER2) is a proto-oncogene encoded by ERBB2 on chromosome 17. HER2 is a member of the family of receptors associated with tumor cell proliferation, apoptosis, adhesion, migration, and differentiation.[2] HER2 is overexpressed in many epithelial tumors, including gastroesophageal, breast, ovarian, colorectal, and lung cancers.[23] Overexpression and amplification of HER2/ERBB2 in breast cancer are known to have a worse prognosis compared to HER2-negative breast cancer.[24] An increase in the risk of local tumor growth in addition to metastasis is observed with HER2 positive breast cancer.[24] HER2 is an important biomarker and a key driver of tumorigenesis with amplification and overexpression. Approximately 7-32% of tumors of gastric cancer display HER2 overexpression.[2,23] In gastric cancer, HER2 overexpression is associated with poor outcomes and aggressive disease thus HER2 has been identified as a key therapeutic target for cancer treatment.[23]

Herceptin/Trastuzumab for Gastric Cancer

The ToGA Study (2010), *A Study of Herceptin (Trastuzumab) in Combination With Chemotherapy Compared With Chemotherapy Alone in Patients With HER2-Positive Advanced Gastric Cancer,* was one of the initial studies to target the overexpression of HER2 receptors for cancer treatment. Herceptin, a monoclonal antibody, targets HER2 receptors, induces cellular toxicity, inhibits HER2 mediated signaling and activity, and prevents cleavage of the extracellular domain of HER2.[2] Trastuzumab was evaluated for its effect on overall survival for patients with HER2-positive advanced gastric cancer. Thus, the ToGA trial was conducted in 24 countries in Asia, Central, and South America to assess the clinical efficacy and safety of trastuzumab when added to standard chemotherapy for first-line treatment of advanced gastric or gastroesophageal junction cancers with overexpression of HER2. Findings from the study showed that among participants with advanced gastric and gastroesophageal esophageal junction

cancer, the addition of Trastuzumab to standard chemotherapy improved overall survival time by 2.7 months compared to chemotherapy alone.[25] Further, post-hoc exploratory analysis showed that among participants in the Trastuzumab group, those with HER2 protein overexpression (identified through Immunohistochemistry (IHC)3+ or IHC2+ and Fluorescent *in situ* hybridization (FISH) positive) experienced an overall survival of 16 months in comparison to 11.3 months in the standard chemotherapy group.[25] The trial concluded that for patients with HER2-positive advanced gastric cancer, Trastuzumab with standard chemotherapy should be considered as a new standard treatment option.

The use of monoclonal antibodies targeting HER2 receptors has provided a significant improvement in overall survival of HER2-positive advanced gastric cancer over standard chemotherapy alone. However, there are identified disadvantages associated with Herceptin treatment. Passive antibody administration can lead to primary and secondary resistance.[23] Further, Herceptin intravenous infusion requires a longer period of drug administration, more frequent administration, and high cost.[23] Additionally, in low and middle-income countries where gastric cancer incidence is high, monoclonal antibodies are not available, given the cost, transfer, and feasibility difficulties. These issues could be avoided with vaccine-induced active immunization against the tumor antigen.

HER2/neu vaccine and Chemotherapy for Gastric Cancer

HER-Vaxx (IMU-131) is B-cell immunotherapy designed to treat tumors that overexpress the HER-2/neu receptor, such as gastric, breast, ovarian, lung, and pancreatic cancers.[26] In vitro and in vivo studies of HER-Vaxx show anti-tumor activity for a vaccine-induced antibody against three selected B cell epitope peptides in the HER2/neu extracellular domain.[23] In preclinical models, HER-Vaxx was shown to directly inhibit growth of HER2 overexpressing tumor cells, induce complement-dependent cytotoxicity (CDC), and antibody-dependent cellular cytotoxicity (ADCC).[27,28] A phase I trial was conducted in 10 patients with metastatic, low HER2/neu overexpression breast cancer to assess safety and immunogenicity of a first-generation HER-Vaxx formulation.[29] The formulation was well-tolerated and led to specific immune responses in 8 out of 10 patients. A phase Ib/II clinical trial was conducted among 14 patients with HER2 positive gastroesophageal adenocarcinoma in East Europe and Southeast Asia to assess the safety, tolerability, optimal dose, and clinical effects of active immunization using a new HER-Vaxx formulation intended to improve stability and immunogenicity. Results showed that IMU-131 was well tolerated and safe.[23] Clinical efficacy was assessed as overall survival over approximately 17.5 months after treatment. An interim analysis showed a ~60% reduction in hazard of death, a ~50% reduction in hazard of death/progression, a higher overall response rate, and higher and more durable anti- HER2 antibody responses, and larger reductions in tumor size (with the largest reductions in tumor size associating with higher antibody responses).[30] The induced HER2-specific antibody and cellular responses were dose-dependent and correlated with clinical responses. The highest dose (50 mg) was recommended for further evaluation in a phase II trial, with chemotherapy and IMU-131 or chemotherapy alone.[23]

HER-Vaxx offers several potential advantages relative to trastuzumab. First, HER-Vaxx is polyclonal, meaning it is designed to target multiple HER2 epitopes, or pieces of the HER2 receptor.[31] This may offer a more complete blockade of the HER2 signaling pathway and mitigate or even prevent drug resistance, an outstanding problem with Trastuzumab treatment.

HER-Vaxx is also cheaper to produce and potentially easier and safer to administer.[31] The treatment involves intramuscular injection instead of intravenous transfusion, which is required for Herceptin. Additionally, HER-Vaxx generates natural antibody responses which may be less toxic than synthetic antibodies. The drug can also stimulate continuous antibody production, vaccine-specific cytokine responses, reductions in T_{reg} populations and proliferation of class-switched memory B-lymphocyte populations which may inhibit tumor recurrence.[31] Thus, given the completion of phase I/II trials, we propose a phase III trial to investigate whether (a) HER-Vaxx plus chemotherapy improves overall survival in comparison to chemotherapy alone and (b) whether HER-Vaxx plus chemotherapy is noninferior to trastuzumab plus chemotherapy in patients with HER2 positive gastric and GEJ cancers in a global setting. This study will contribute in the effort to achieve equitable, global access to efficacious targeted cancer therapies.

Rationale

Rationale for Study Population and Phase III Trial

China has the highest raw number of incident gastric cancer cases per GLOBOCAN estimates[1] and is ranked in the second highest tier of per-capita gastric cancer incidence in the world per GLOBOCAN. As highlighted in the schema section, there exists substantial evidence highlighting barriers to HER2-testing and trastuzumab access for various malignancies – including gastric cancer – in China. A recent cross-sectional study highlighted that availability of HER2 testing for gastric cancer may be the bottleneck for targeted treatment; 72.9% of gastric cancers were not provided HER2 testing in China.[11] Conducting our Phase III non-inferiority trial in China targets a population with an acute need for broadened HER2 testing and targeted treatments. We restrict focus to tumors with confirmed IHC3+/IHC2+ and FISH+ HER2 overexpression, as the benefit of trastuzumab treatment was restricted to these patients (4.2 month median improvement in OS, HR=0.65 (95% CI 0.51-0.83)).[2]

The pivotal Phase III ToGA trial[2] demonstrating the clinical efficacy and safety of trastuzumab in patients with advanced and metastatic HER2-positive gastric and gastroesophageal junction cancers was conducted in 2010 and was a landmark achievement in the treatment of gastric cancers. However, 12 years later, trastuzumab plus chemotherapy remains the standard of care first-line therapy for these cancers, and prognosis for patients remains poor due to trastuzumab inaccessibility and the development of trastuzumab resistance. In addition, the high cost of trastuzumab purchase, administration, and safety concerns (especially with respect to infusion reactions and cardiotoxicity) highlight the need for the development of more efficacious, cheaper, and safer alternatives. HER-Vaxx plus chemotherapy may offer an efficacious, cheaper, easier to administer, and potentially safer alternative to trastuzumab in treating HER2-positive malignancies.

Preclinical studies and Phase I/II studies evaluating Her-Vaxx (IMU-131) in gastric and GEJ cancer have demonstrated that HER-Vaxx stimulates a potent polyclonal antibody response to HER-2/neu receptors and has a good indication of clinical response relative to chemotherapy alone. However, given that phase I/II was performed in a small sample size of 14 and 34 participants respectively, a larger sample is needed to rigorously assess the efficacy and safety of

HER-Vaxx in treating gastric and GEJ cancers. Given the ongoing effort to expand the access of trastuzumab and trastuzumab biosimilars to underserved markets, it is of great interest to compare the efficacy of HER-Vaxx plus chemotherapy not just to chemotherapy alone, but also to trastuzumab plus chemotherapy to assess whether HER-Vaxx plus chemotherapy is a non-inferior substitute to trastuzumab plus chemotherapy in settings with limited trastuzumab access.

Rationale for Treatments

Chemotherapy

All treatment arms will receive a fluoropyrimidine-based chemotherapy plus cisplatin chemotherapy regimen, as recommended as preferred, category 1 regimens by the NCCN guidelines for advanced gastric cancer treatment[14]. Consistent with NCCN guidelines, acceptable fluoropyrimidine treatments include 5-fluorouracil infusion (750-1000 mg/m^2 IV infusion per 24 hours for 96 hours, repeat cycle every 2 weeks) or oral capecitabine (1000 mg/m^2 orally twice per day for 28 doses over 3 weeks) plus cisplatin infusion (75-100 mg/m^2 1-2 hour IV every 4 weeks). The choice of fluoropyrimidine regimen must be determined by the clinician prior to randomization.

Trastuzumab

The active control arm will receive an 8 mg/kg loading dose IV of trastuzumab over 90 minutes at baseline, followed by 6 mg/kg IV over 30 minutes every 3 weeks, administered intravenously until disease progression, death, end of study, or cessation of chemotherapy (~18 months) as recommended by 2022 NCCN guidelines for the treatment of advanced HER2-positive gastric cancer.[14] Trastuzumab has been shown to significantly improve OS in advanced gastric cancer patients with HER2-overexpressing gastric cancer.[2]

HER-Vaxx

The experimental treatment arm will receive IM HER-Vaxx doses (P467-CRM197 peptide antigen in PBS buffer and Montanide ISA 51 Sterile adjuvant, in 1:1 ratio, 50 micrograms IM injection) at baseline, day 14, day 35, day 77, and then every 63 days until disease progression, death, end of study, or cessation of chemotherapy (~18 months). HER-Vaxx is composed of three peptides derived from the extracellular domain of the HER2 receptor. This dosing regimen is slightly modified from the Phase I/II HER-Vaxx trials to stop HER-Vaxx treatment with the cessation of chemotherapy for the purposes of cost and real-world feasibility. In the initial formulation of HER-Vaxx, the peptides were coupled to virosomes. While the virosomal vaccine showed good tolerability, it showed poor stability,[29] so it was reformulated with respect to peptide synthesis and conjugation. The CRM197 is frequently used to conjugate licensed vaccines and rapidly induces specific memory T cells and Th1/Th2 cytokine responses.[32] Moreover, CRM197 has biological antitumor effects by binding to its receptor EGF, which is frequently overexpressed in cancer cells.[33] The inclusion of the Montanide as an adjuvant induced high and long-lasting antibody responses and strong Th1-biased cellular responses in preclinical and early clinical models.[23,34] The Phase Ib study dose escalation showed no increase

in adverse safety events and improvements in immunogenicity at the high dose, leading the authors to suggest the high (50 microgram) dose as the optimal dose for further exploration.

It is common practice to administer vaccinations to patients before the onset of chemotherapy, as lymphocyte populations are depleted during the early phase of chemotherapy.[35] Delaying the onset of chemotherapy to afford time for immunological priming was explored in Phase I,[23] and a depletion of B-cells relative to healthy controls was not observed. This practice was abandoned in the Phase II trial, where substantial immunogenicity and clinical activity was demonstrated.[30] For this study, we will not delay chemotherapy onset for immunological priming, consistent with the Phase II trial. At the interim safety & immunogenicity analysis, if there is evidence of substantial depletion of B-cell populations, we will adjust the treatment to include a delayed start of chemotherapy or stagger treatment schedules.

Rationale for Endpoints

Overall Survival

The primary focus of our study will be on the overall survival (OS) endpoint, as it is the purest measure of a therapy's ability to prolong survival. While OS is often eschewed for surrogate endpoints that are faster to ascertain – such as progression free survival (PFS), overall response rate (ORR), and duration of response (DOR) – we believe that focusing on endpoints directly relevant to how a patient feels, functions, survives is critical to understanding the risk/benefit profile of a treatment and ultimately, whether it should be adopted in clinical practice. Especially in patients with a malignancy like gastric cancer that has poor prognosis, achieving longer survival without deterioration of quality of life should be the goal of treatment.

Safety/Toxicity

Understanding the relative safety and toxicity profiles of our treatments is critical to informing critical practice. Phase III trials in trastuzumab plus chemotherapy and Phase I and II trials in HER-Vaxx plus chemotherapy have not revealed any prevailing safety concerns, so we do not designate any safety signals as "Tier 1" safety events of special interest that are subjected to inferential testing. However, we are interested in understanding whether any of the study treatments are associated with increased risks of serious adverse events (especially related to immune reactions or adverse infusion/local injection site reactions) or adverse events that lead to withdrawal from study or treatment/dose modifications. The frequencies of serious adverse events and adverse events that modify study treatment is directly relevant to clinical practice, as less toxic treatments may yield better adherence and better patient outcomes.

Patient Reported Outcomes (PROs)

While overall survival is the primary endpoint of this trial, it is also of great interest to understand how patient quality of life compares between different treatments, capturing the "feels and functions" dimensions of "feels, functions, survives." We firmly believe that quality of life concerns both physical and symptom-related measures as well as social, emotional, and functional measures.

The main patient reported outcome measure for this study will be the Functional Assessment of Cancer Therapy for Gastric Cancer (FACT-Ga), a 19-item questionnaire developed in North America and validated for adults with gastric cancer that quantifies physical, social/family, emotional, functional well-being, and additional concerns related to gastric cancer over the past week. The FACT-Ga is used with the Functional Assessment of Cancer Therapy General (FACT-G) as recommended by the creators. These PRO measures are available in 28 languages and use statements to guide responses. To assess the psychological and emotional dimension of cancer treatment, participants will also be asked to fill out PHQ-9 and GAD-7: Nine and 7-item patient health questionnaires to screen for depression and anxiety.

Longitudinal antibody collection

It is well-established that anti-HER2 therapies like trastuzumab function by binding to HER2 receptors overexpressed cancer cells, thereby inhibiting several mechanisms of tumor growth and directing the host immune system to attack cancer cells. Thus, the levels of anti-HER2 antibodies induced by active immunization with HER-Vaxx may mediate the efficacy of HER-Vaxx treatment. In other words, levels of anti-HER2 antibodies induced by HER-Vaxx seem a very plausible correlate of treatment effect and clinical outcomes. Understanding if levels of anti-HER2 antibodies correlate with clinical outcomes could lead to the development of an immunologic surrogate for survival on HER-Vaxx treatment.

HER2 positivity rate

As part of the HER2 screening procedure, we will assess the frequency of HER2 overexpression in our population patient population. Evaluating the HER2 positivity rate will inform the design of future studies of future anti-HER2 based therapies in the Chinese setting.

Risk/Benefit

Subjects in clinical trials generally cannot expect to receive direct benefit from treatment during participation, as clinical trials are designed to provide information about the safety and effectiveness of an investigational medicine. Especially considering that this trial is in participants with advanced gastric cancer, participants should be hopeful but realistic in terms of benefits to survival and quality of life possible under the experimental treatment.
The active control, cisplatin and capecitabine/5-fluorouracil plus trastuzumab has shown beneficial effects to date with minimal additional toxicity. The ToGA trial[2] found that the addition of trastuzumab to chemotherapy extended median overall survival by 2.7 months (HR=0.74, p=0.0046) and extended progression free survival by 1.2 months (HR=0.71, p=0.0002). Addition of trastuzumab also improved time to progression by 1.5 months (HR=0.70, p=0.0003), and improved the duration of response by 2.1 months (HR=0.54, p<0.0001). Trastuzumab addition improved overall tumor response rate by 12%. A pre-planned exploratory analysis identified a significant interaction between treatment and subgroupings of high and low HER2 expression, with high HER2 expression associated with a 4.2-month improvement in median OS relative to chemotherapy alone.

Trastuzumab, a breakthrough treatment for metastatic and early breast cancer, has been linked to heart failure in 1-4% of participants in clinical trials in breast cancer trials and significant left ventricular fraction decline in 10% of patients.[36] In the ToGA trial, rates of cardiac adverse events were the same between treatment arms (6%), suggesting that trastuzumab did not enhance cardiotoxicity above chemotherapy treatment alone. It is believed that exposure to anthracycline chemotherapies significantly enhances the cardiotoxicity of trastuzumab.[36] However, anthracyclines are not standard of care chemotherapy regimens for the treatment of gastric cancer, and the number of ToGA enrollees with previous anthracycline therapy was less than 1%. The low cardiac toxicity was confirmed in the JACOB trial in metastatic HER2-positive gastric cancer,[15] where 1 out of 388 participants on trastuzumab plus chemotherapy treatment experienced heart failure and only 2% of patients had confirmed LVEF decline.

In the ToGA trial, the most frequently reported adverse events were nausea, vomiting, and neutropenia for the trastuzumab plus chemotherapy group. Rates of overall grade 3 or 4 adverse events did not differ between chemotherapy and chemotherapy plus trastuzumab in the ToGA trial. In the JACOB trial, diarrhea was the most common serious adverse event in the trastuzumab group (5%). The most common grade 3-5 adverse events were neutropenia, anemia, and diarrhea. Treatment related deaths occurred in 7 patients in the control group (organ failure, pulmonary embolism, hemodynamic instability, septic shock, and unexplained death).
While still in early clinical evaluation, the addition of HER-Vaxx to chemotherapy appears to offer survival improvements over standard of care chemotherapy, and potentially above trastuzumab treatment plus chemotherapy. A Phase Ib study[23] demonstrated a dose-response relationship between HER-Vaxx dose and HER2-specific antibody response. Cellular vaccine responses, such as cytokine ratios and reduced regulatory T cell numbers were generated. HER2 and AKT phosphorylation (the mechanism by which HER2 and PI3K/AKT growth pathways are activated) was inhibited by 37% and 13.4% respectively by the addition of the serum from a patient with high antibody levels. One patient on the high dose cohort saw a substantial regression in tumor size. Progression-free survival was prolonged in the highest dose-cohort.

The phase Ib dose-escalation study of HER-Vaxx plus chemotherapy demonstrated that HER-Vaxx was safe without vaccine-related significant local/systemic reactions or serious adverse events in a cohort of 14 patients.[23] No dose limiting toxicities -- defined as unresolvable grade 3 event within 2 weeks, grade 4 toxicity event, serious adverse reaction related to IMU-131 as determined by investigator, anaphylaxis, or two or more patients in a single dose cohort experiencing a serious adverse event related to infection – were observed. All adverse events, including those grades 3 or higher, were deemed not related to HER-Vaxx treatment, and the majority of grade 3 or higher adverse events occurred in the low-dose cohort. Two grade 1 injection site adverse events 3 days after the third vaccination and resolved the next day. Treatment-emergent adverse events possibly related to IMU 131 were hypoalbuminemia (grade 2), hyponatremia (grade 3), decreased appetite (grade 1), and decreased weight (grade 2). 5 patients experienced severe adverse events that were deemed unrelated to HER-Vaxx treatment.[23]

An analysis of the Phase II randomized HERIZON trial[30] in 36 patients provided an indication that HER-Vaxx plus chemotherapy improves overall survival (HR 0.418, p=0.083, Figure 2.A) and improved progression free survival (HR=0.532, p=0.086). While the sample sizes were

small, there was good indication of clinical activity. Rates of treatment-emergent adverse events were equivalent between the HER-Vaxx plus chemotherapy and chemotherapy arms. Out of 14 participants in the experimental arm, no Grade 4 or 5 Treatment-emergent adverse events were observed in the HER-Vaxx plus chemotherapy arm. Four Grade 3 events were observed (two cases of Gamma-GT increased, 1 case of embolism, and one case of acute respiratory failure). Hematological adverse events were consistent between the two arms. Immunogenicity was very robust (Figure 2.B). One patient in the control arm progressed on disease and crossed over to trastuzumab treatment at Week 54 and displayed similar levels of anti-HER2 antibodies to those still alive and with a recorded antibody level on HER-Vaxx treatment (Figure 2.B).

Figure 2.A: Kaplan-Meier curves and logrank test from interim analysis of HERIZON trial, illustrating the overall survival of participants on HER-Vaxx plus chemotherapy and chemotherapy alone.

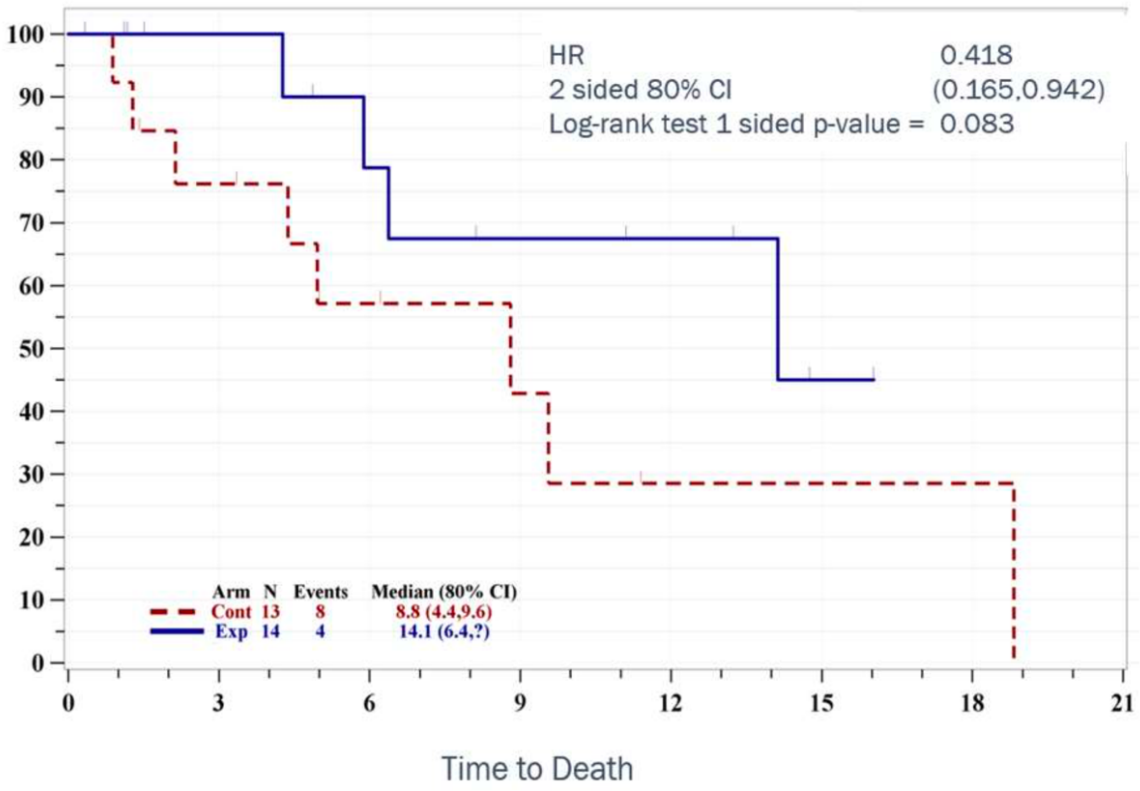
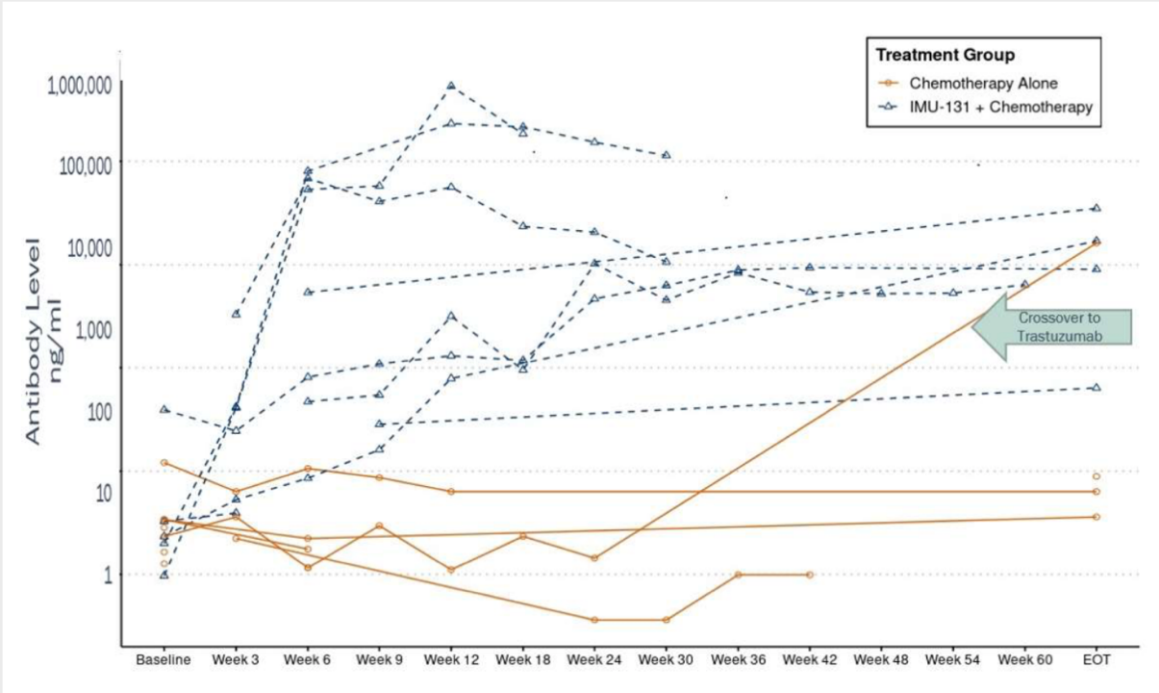


Figure 2.B: Anti-HER2 antibody levels for participants on HER-Vaxx plus chemotherapy and chemotherapy alone treatments.



We believe that HER-Vaxx plus chemotherapy is a good candidate for a non-inferiority trial for several reasons. HER-Vaxx has a well-studied mechanism of action and targets a well-validated cancer pathway that can lead to clinically relevant benefits to patient survival. HER-Vaxx generates a polyclonal antibody response, meaning it is designed to target multiple HER2 epitopes, or pieces of the HER2 receptor.[31] Polyclonal antibody treatments may offer a more complete blockade of the HER2 signaling pathway than mAb treatments like trastuzumab, mitigating drug resistance, an outstanding problem with trastuzumab treatment. HER-Vaxx is also cheaper to produce and potentially easier and safer to administer,[31] given that it is administered by intramuscular injection instead of intravenous infusion, and generates antibodies from the patient's own immune system rather than relying on humanized antibodies. Also, HER-Vaxx stimulates continuous antibody production, offering a potentially superior pharmacokinetic profile to trastuzumab and may benefit patients by providing an anti-HER2 response post-disease progression. HER-Vaxx is also capable of priming the cell-mediated immune response, inducing cytokine proliferation, T cell proliferation, and generating B and T-cell memory responses, which may inhibit tumor recurrence.[31] Thus, given the completion of phase I/II trial, we propose a phase III trial to investigate (a) whether HER-Vaxx plus chemotherapy improves overall survival in comparison to chemotherapy alone and (b) whether HER-Vaxx plus chemotherapy is non-inferior to trastuzumab plus chemotherapy in patients with HER2 positive gastric and GEJ cancers in China.

How results will inform clinical practice

The trial will be considered "positive" if we demonstrate that HER-Vaxx plus chemotherapy is superior to chemotherapy, non-inferior to trastuzumab plus chemotherapy, and has a comparable safety profile to trastuzumab plus chemotherapy. A positive result could expand the availability

and access of anti-HER2 therapies to more patients in China, improving equity in cancer care and improving patient outcomes. If a positive result is achieved, we anticipate future registrational trials in China, other noninferiority trials in other countries where trastuzumab is not widely available, and other uses for HER-Vaxx as a replacement for trastuzumab (e.g., as an adjuvant therapy, for treatment of early-stage cancers, for delaying progression, for preventing metastasis, etc.). If HER-Vaxx plus chemotherapy does not satisfy at least one of these criteria listed above, the trial will be considered "negative." If HER-Vaxx plus chemotherapy shows clinical activity relative to chemotherapy alone but is deemed inferior to trastuzumab plus chemotherapy or has unwanted side effects, next steps would involve considering new formulations of HER-Vaxx and exploring combination regimens that target multiple cancer pathways. If HER-Vaxx plus chemotherapy shows no improvement in OS relative to chemotherapy alone, we suggest abandoning HER-Vaxx as a component of targeted HER2 therapies in China. If HER-Vaxx plus chemotherapy is determined to be superior to both chemotherapy and chemotherapy plus trastuzumab, a "super-positive result," this would represent a paradigm-shift in the treatment of targeted anti-cancer therapies. This would likely contribute to regulatory approval in China and the initiation of international trials to benefit HER2-positive patients world-wide.

Scientifically, the findings of this study will provide a useful assessment on the potential of targeted peptide-based cancer vaccines in treating patients with advanced stage malignancies.

STUDY OBJECTIVES

The following section lists the objectives of the study, ordered according to relative importance. Note that only the first primary objective is designated as alpha-spending. Other endpoints should be interpreted as descriptive/supportive.

Primary Objectives

1. Assess whether IMU-131 (HER-Vaxx) plus chemotherapy is noninferior to trastuzumab plus chemotherapy in terms of OS.

   Sub-Hypothesis 1 (Assay sensitivity): HER-Vaxx plus chemotherapy is superior to chemotherapy alone in terms of OS.
   Sub-Hypothesis 2 (Retention of Effect): HER-Vaxx plus chemotherapy retains at least 60% of the effect of trastuzumab plus chemotherapy relative to chemotherapy alone in terms of OS.

2. To evaluate the relative safety of IMU-131 (HER-Vaxx) plus chemotherapy to trastuzumab plus chemotherapy and chemotherapy alone.

   Hypothesis 1: HER-Vaxx will have an acceptable safety profile, with similar rates of serious adverse events across gastrointestinal, blood/lymphatic, and general/metabolic disorders. We anticipate a higher rate of minor local injection site events but a lower rate of infusion-related reactions (allergic reaction, hypersensitivity, chills, arthralgia, and dyspnea) in the experimental arm compared to the active control arms.

Secondary Objectives

3. To compare objective tumor response rates (ORR) in the three study arms in advanced/metastatic HER2 positive gastric cancer/GEJ cancer at months 6 and 12 post enrollment.

4. To compare responses to patient reported outcomes (PROs) to FACT-Ga, FACT-G, PHQ-9, and GAD-7 differ between patients on HER-Vaxx plus chemotherapy versus trastuzumab plus chemotherapy versus chemotherapy alone arms.

Exploratory Objectives

1. Assess HER-Vaxx immunogenicity and test whether treatment effect depends on magnitude of anti-HER2 antibody response in the experimental arm.

   Hypothesis 1: higher anti-HER2 antibody titers will be associated with a larger treatment effect in the HER-Vaxx plus chemotherapy arm.

2. To assess the frequency of HER2-positive gastric and gastroesophageal cancer in a large Chinese cohort.

   Hypothesis 1: HER2-positivity will lie between 15-20% per previous results.

STUDY POPULATION

The target population for this study will be Chinese adult (18 or over years of age at enrollment) patients with confirmed – via IHC or a FISH – HER2-positive gastroesophageal adenocarcinoma or cancer of the gastroesophageal junction (GEJ) that were locally advanced, recurrent, or metastatic adenocarcinoma of the stomach or gastro-esophageal junction as defined through the clinical and pathological staging criteria developed by the American Joint Committee on Cancer (AJCC) Classification of Gastric Cancer (8th edition).[3] The AJCC pathological criteria may also be used if the tumor has undergone resection. The AJCC classification system employs a "Tumor Node Metastasis" (TNM) classification system that captures characteristics of the primary tumor, lymph node status, and distant metastasis. These clinical criteria are summarized below.

Table 1: AJCC clinical stage groups for gastric adenocarcinoma. Cancers that shaded in orange represent those considered for inclusion in our trial.

Stage grouping	T-category	N-category	M-category
Stage 0	Tis	N0	M0
Stage IA	T1	N0	M0

Stage IB	T1	N1	M0
	T2	N0	M0
Stage II	T1	N2	M0
	T2	N1	M0
	T3	N0	M0
Stage IIIA	T2	N2	M0
	T3	N1	M0
	T4	N0	M0
Stage IIIB	T3	N2	M0
Stage IV	T4	N1, N2, N3	M0
	T1, T2, T3	N3	M0
	Any T	Any N	M1

Where Tis refers to high-grade dysplasia (malignant cells confined to the epithelium by basement membrane), T1 refers to tumor invading the lamina propria, muscularis mucosae, or submucosa, T2 refers to invasion of the muscularis propria, T3 refers to the tumor invading the adventitia, and T4 refers to invasion of adjacent structures (pleura, pericardium, azygous vein, diaphragm, peritoneum, aorta, vertebral body, airway). N0 refers to no regional lymph node metastasis, N1 refers to metastases in 1 or 2 regional lymph nodes, N2 refers to regional metastasis to 3 to 6 lymph nodes, and N3 refers to metastases in 7 or more regional lymph nodes. M0 refers to no distant metastasis, while M1 refers to distant metastasis. It was reported that 80 to 90% of patients present with advanced stage disease, either stage III locally advanced or stage IV metastatic disease.[37,38]

Inclusion Criteria

A patient will be considered for recruitment if:

1. Participant must be willing and able to sign the informed consent. The subject may also provide consent for Future Biomedical Research but need not consent to participate in the main trial.
2. Participants must be adult patients (≥18 years of age on date of signing informed consent) with histologically or cytologically confirmed diagnosis of locally advanced/unresectable, recurrent, or metastatic gastric or GEJ adenocarcinoma.
3. Measurable disease as defined by RECIST 1.1 prior within 21 days prior to randomization.
4. Confirmed HER2 expression status by IHC (3+) or FISH (HER2:CEP17 ratio ≥ 2) per the Rüschoff/Hoffman criteria (shown below). Preferred method of ascertainment will be HER2 expression tests performed and evaluated through the study's central testing location, due to cases of HER2 testing discordance.[39] Previous HER2 testing results will be accepted under adequate documentation of testing procedures. Reassessment of stored tumor samples should be sought in these cases, if possible. Positive HER2 expression is determined by tumors that present with either an IHC score of 3+ or a FISH-positive result. Analysis will consider paraffin-embedded tissue blocks, a partial block, or freshly cut unstained slides. Liquid biopsies may also be accepted.

Table 2: Rüschoff/Hoffman HER2 scoring criteria for IHC performed on surgical and biopsy specimens.

IHC score	Surgical specimen staining pattern	Biopsy specimen staining pattern	HER2 expression assessment
0	No reactivity or membranous reactivity in < 10% of tumor cells	No reactivity or no membranous reactivity in any tumor cell	Negative
1+	Faint or barely perceptible membranous reactivity in ≥ 10% of tumor cells; cells are reactive only in part of their membrane	Tumor cell cluster with a faint or barely perceptible membranous reactivity irrespective of percentage of tumor cells stained	Negative
2+	Weak to moderate complete, basolateral or lateral membranous reactivity in ≥ 10% of tumor cells	Tumor cell cluster with a weak to moderate complete, basolateral or lateral membranous reactivity irrespective of percentage of tumor cells stained	Equivocal (pending FISH testing). If HER2:CEP17 ratio ≥ 2, positive. Else, negative.
3+	Strong complete, basolateral, or lateral membranous reactivity in ≥ 10% of tumor cells	Tumor cell cluster with a strong complete, basolateral or lateral membranous reactivity irrespective of percentage of tumor cells stained	Positive

5. Female participants of childbearing potential must have a negative urine/serum pregnancy test completed within 72 hours of the first study dose.
6. Male and female participants of childbearing potential must be willing to use an adequate method of contraception over the course of study through 120 days after final dose.
7. Patients must have adequate organ function as asses through laboratory values shown in Table 3 below:

Table 3: Adequate Organ Function Laboratory Values.

System	Laboratory Value
Hematological	
Absolute neutrophil count	≥1,500 /mcL
Platelets	≥100,000 / mcL
Hemoglobin	≥9 g/dL – transfusion is acceptable if necessary to increase hemoglobin levels
Renal	
Creatinine OR Measured or calculated creatinine clearance	≤1.5 X upper limit of normal (ULN) OR ≥60 mL/min for subject with creatinine levels > 1.5 X institutional ULN Cisplatin product label should be followed for acceptable creatinine clearance rates

Hepatic	
Total bilirubin AST (SGOT) and ALT (SGPT)	≤2.5 X ULN OR ≤5 X ULN for subjects with liver metastases
Albumin	≥2.5 g/dL
Coagulation	
International Normalized Ratio or Prothrombin Time Activated Partial Thromboplatin Time	≤1.5 X ULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants ≤1.5 X ULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants

Exclusion Criteria

Subject will be excluded from participation if the subject:

1. Has squamous cell gastric/GEJ cancer.
2. Has had therapy for a locally advanced, unresectable, or metastatic gastric/GEJ cancer. Subjects may have received prior neoadjuvant or adjuvant therapy if completed 6 months prior to randomization.
3. Has had major surgery, open biopsy, or significant traumatic injury within 28 days prior to randomization, or anticipation of the need for major surgery while on study.
4. Has had radiotherapy within 14 days of randomization.
5. Has known central nervous system (CNS) metastases and/or carcinomatous meningitis. Subject with previously treated brain metastases may participate provided they are stable, have no evidence of new or enlarging brain metastases,
6. Has tumor Karnofsky performance score <60% and ECOG score > 2 or a life expectancy of less than 3 months.
7. Has an active autoimmune disease that required systemic treatment in the past 2 years: i.e., with use of disease modifying agents, corticosteroids, or immunosuppressive drugs. Replacement therapies (e.g., insulin) is not considered a form of systemic treatment.
8. Has a known history of HIV infection (HIV1/2 antibodies).
9. Has a diagnosis of immunodeficiency of is receiving chronic systemic steroid therapy or any other immunosuppressive therapy within 7 days prior to first dose of trial drug.
10. Has a history of non-infectious pneumonitis that required steroids or current pneumonitis.
11. Has an active infection requiring systemic therapy.
12. Has known psychiatric or substance abuse disorders that would interfere with cooperation with requirements of the trial.
13. Is pregnant or breastfeeding or is expected to conceive or father children within the duration of the trial past 120 days post-final-dose.
14. Has received prior therapy with an anti-HER2 agent.
15. Is currently participating in and receiving or has participated in and received an investigational agent within 4 weeks of first study dose.
16. Has history of severe cardiac dysfunction: history of congestive heart failure, angina pectoris requiring treatment, myocardial infarction within 6 months of the first study dose, clinically

significant valvular heart disease, uncontrollable high-risk cardiac arrhythmia, history or evidence of poorly controlled hypertension, or other serious cardiac conditions will be excluded from the study.

17. Has received a live vaccine within 30 days prior to first dose of trial drug.

STUDY PROCEDURES

Treatment regimens

Experimental: HER-Vaxx (P467-CRM197 peptide antigen in PBS buffer and Montanide ISA 51 Sterile adjuvant, 50 micrograms IM injection administered at baseline, day 14, day 35, day 77, and then every 63 days until disease progression, death, end of study, or cessation of chemotherapy (~18 weeks) plus one of the following chemotherapy regimens as recommended by 2022 NCCN guidelines.[14]

1. Fluoropyrimidine (5-fluorouracil (750-1000 mg/m^2 IV infusion per 24 hours for 96 hours, repeat cycle every 2 weeks) or capecitabine (1000 mg/m^2 orally twice per day for 28 doses over 3 weeks) plus cisplatin (75-100 mg/m^2 1-2 hour IV every 4 weeks).

Patients will receive a maximum of 6 cycles of chemotherapy. Note: it is common practice to administer vaccinations to patients before the onset of chemotherapy, as lymphocyte populations are depleted during the early phase of chemotherapy[35]. Delaying the onset of chemotherapy to afford time for immunological priming was explored in Phase I, and a depletion of B-cells relative to healthy controls was not observed. This practice was abandoned in Phase II. The experimental treatment regimen will not delay chemotherapy onset, consistent with Phase II. At the interim safety & immunogenicity analysis, if there is evidence of substantial depletion of B-cell populations, we will adjust the treatment to include a delay to starting chemotherapy.

Patients will be permitted to cease or modify chemotherapy or study drug treatment as directed by clinicians. Patients will be permitted to use second-line chemotherapy after disease progression, although in many countries this is not standard practice. Use of another anti-HER2 targeted therapy or other experimental treatment that is believed to interfere with the treatment comparison will result in censoring.

Active comparator: trastuzumab (8 mg/kg loading dose IV over 90 minutes, followed by 6 mg/kg IV over 30 minutes every 3 weeks, administered intravenously until disease progression, death, end of study, or cessation of chemotherapy (~18 weeks) plus one of the following options recommended by the NCCN guidelines[14]:

1. Fluoropyrimidine (5-fluorouracil (750-1000 mg/m^2 IV infusion per 24 hours for 96 hours, repeat cycle every 2 weeks) or capecitabine (1000 mg/m^2 orally twice per day for 28 doses over 3 weeks) plus cisplatin (75-100 mg/m^2 1-2 hour IV every 4 weeks).

Patients will receive a maximum of 6 cycles of chemotherapy.

Patients will be permitted to cease or modify chemotherapy or study drug treatment as directed by clinicians. Patients will be permitted to use second-line chemotherapy after disease progression, although in many countries this is not standard practice. Use of another anti-HER2 targeted therapy or other experimental treatment that is believed to interfere with the treatment comparison will result in censoring.

Control: One of the following chemotherapy options recommended by the NCCN guidelines.[14]

1. Fluoropyrimidine (5-fluorouracil (750-1000 mg/m^2 IV infusion per 24 hours for 96 hours, repeat cycle every 2 weeks) or capecitabine (1000 mg/m^2 orally twice per day for 28 doses over 3 weeks) plus cisplatin (75-100 mg/m^2 1-2 hour IV every 4 weeks).

Patients will receive a maximum of 6 cycles of chemotherapy.

Patients will be permitted to cease or modify chemotherapy treatment as directed by clinicians. Patients will be permitted to use second-line chemotherapy after disease progression, although in many countries this is not standard practice. Use of another anti-HER2 targeted therapy or other experimental treatment that is believed to interfere with the treatment comparison will result in censoring.

Note: 5-FU, cisplatin, capecitabine are storable at room temperature, while HER-Vaxx and trastuzumab require standard refrigerator and freezer storage (2-8*C and <15*C respectively).

Adherence assessment

Adherence to infusion-based chemotherapies, trastuzumab infusions, and IM HER-Vaxx administration will be assessed using CRFs. The clinician/nurse providing treatment to the patient at a particular clinic visit will fill out a "Treatment Visit Form" containing participant identifying information, the visit date, whether the participant received treatment, which treatments received and in what quantities, and noting any acute adverse events associated with treatment. At missed or rescheduled treatment visits, the clinician/nurse will indicate a missed visit on the "Treatment Visit Form" along with the participant identifying information, the intended visit date, and any reported reasons for the missed/rescheduled visit.

Capecitabine adherence will be assessed by patient self-reported patient pill count as described in Timmers *et al.* 2016.[40]

Adherence to radiological assessments of disease progression will be recorded using a "Radiology Visit Form" containing the participant identifying information, the scheduled visit date, whether the visit was completed, radiology result if available (particularly the reporting of Complete Response, Partial Response, Stable Disease, or Progressive Disease as indicated by RECIST 1.1 criteria), and any reported reasons for the missed/rescheduled visit.

Data to be collected

Data will be collected at several visits. At the initial screening visit, a patient will be considered for trial eligibility based on personal medical history and disease criteria. If the patient passes the initial screen, they will be referred to HER2 testing, where blocks of tumor tissue will be collected by endoscopy and shipped to the central testing facility for HER2 assessment. If the participant is identified as HER2-positive, they will be eligible for randomization. If they are successfully randomized, various outcome measures will be assessed at baseline and subsequent treatment visits.

Data collected at the screening visit will be as follows:

1. Demographic information (Patient reported): contact information, age, sex, self-reported race or ethnicity
2. Physical examination (Clinician reported): vital signs (pulse rate, blood pressure), physical examination of head, eye, ear, nose, throat, cardiovascular, dermatologic, musculoskeletal, respiratory, GI, genitourinary, and neurologic systems. Any abnormality should be recorded on the General Medical History CRF.
3. Medical history (Patient reported): clinically significant disease, recent or planned traumatic injuries or surgeries, cancer history (including prior cancer therapies and procedures), family history, current or prior tobacco use, all medications, history of cardiovascular ailments, history of autoimmunity/immunodeficiency, HIV infection history, current/recent infection status, recent affiliations with other cancer studies, recent vaccination, and current or planned pregnancy status.
4. Clinically relevant data to inclusion/exclusion (Radiologist/clinician reported): confirmed adenocarcinoma of the stomach or gastroesophageal junction, tumor measurability as assessed by RECIST 1.1, Karnofsky performance score, and ECOG score, whether evidence of CNS metastases, whether patient has had radiotherapy within 14 days.
5. Possession of existing HER2-test result (Patient/Clinician reported): Y/N. If Y, whether the result was positive Y/N.

Data to be collected at biopsy/HER2-testing visit:

1. FFPE tissue blocks to be shipped to central testing location (Surgically collected).
2. HER2 test result (Pathologist reported). See Appendix B for example HER2 test result form.

Data to be collected at enrollment/randomization visit:

1. Informed consent (Patient reported).
2. Randomization assignment (Clinician reported).
3. Participant reported outcomes as assessed by FACT-Ga, FACT-G, PHQ-9, GAD-7 (Patient reported).
4. If assigned to experimental treatment, blood collection for baseline serology results (Clinician collected).
5. Symptom, adverse reaction, and adverse event reporting (Participant reported).
6. Details on treatment administration (Clinician reported): which treatments administered, in what quantities, if any toxicities or treatment-related reactions were observed.

Data to be collected at subsequent treatment visits:

1. Participant reported outcomes as assessed by FACT-GA, PHQ-9, GAD-7 (Patient reported).
2. If assigned to experimental treatment, blood collection for baseline serology results (Clinician collected).
3. Symptom, adverse reaction, and adverse event reporting (Participant reported).
4. Treatment and adherence (Clinician reported): which treatments administered, in what quantities, if any toxicities or treatment-related reactions were observed. Adherence assessed based on whether visit was completed, whether intended treatment was provided, and what, if any, modifications to the treatment regimen were made. If patient is on capecitabine therapy, patient will be asked to provide a pill count.
5. Tumor response assessment (Radiologist reported): every 6/12 months or as needed.

HER2 testing

It is strongly recommended that HER2 assays and scoring be as standardized as possible, including the use of proper antibodies and probes, use of the Ruschoff/Hoffman scoring method, standardized reporting of results using the CAP "Template for Reporting Results of HER2 (ERBB2) Biomarker Testing of Specimens From Patients With Adenocarcinoma of the Stomach or Esophagogastric Junction," and incorporating HER2 testing into laboratory's quality improvement program.[41] In addition, discordance of HER2 testing results between central and local laboratories highlights the need for centralized laboratory HER2 testing.[42] To standardize HER2 testing results, HER2 overexpression assessment will be performed by skilled pathologists at a central laboratory. Study sites will monitor the intake of new gastric cancer patients, and when a new gastric cancer patient is identified who meets screening eligibility criteria, the clinic will collect tumor tissue in FFPE tumor blocks (10% buffered formalin preferred) and ship them to the central laboratory for HER2 testing. If FFPE tissue blocks (or partial block) are unavailable, a minimum of 15 unstained slides should be requested. Patients stand to benefit from this model by receiving streamlined, reliable, state-of-the-art HER2 testing, which can be used to inform treatment choices. If tumor specimen collection is not possible, a well-validated liquid biopsy for HER2 overexpression is also feasible (e.g., Metafer-iFISH Cytelligen system, Li *et al.* 2018).[43]

HER2 testing will be performed by immunohistochemistry (IHC), scored using the Rüschoff/Hoffman scoring system[39] as recommended by clinical experts.[14,41] IHC can be done on formalin-fixed or paraffin-embedded biopsy tissues or surgical specimens and occasionally, cytological samples. In the study, we will use HercepTest IHC (Dako, Denmark). If the IHC result is >= 2+ which is considered equivocal for HER2 overexpression (2+) should be referred for Fluorescent in situ hybridization (FISH) analysis. In the study, we would use the FDA-approved HER2 FISH pharmDx (Dako, Denmark) to test HER2 gene amplification. If the result is HER2/CEP17 >= 2, the HER2 positive case is confirmed. HER2 testing results will be reported in accordance with the CAP "Template for Reporting Results of HER2 (ERBB2) Biomarker Testing of Specimens From Patients With Adenocarcinoma of the Stomach or Esophagogastric Junction."[44] An example of a HER2 testing CRFs is shown in Appendix B.

HER2 testing will be recommended to all participants with suspected or diagnosed metastatic disease or recurrent disease. All patients with locoregional disease that are deemed locoregional non-resectable are also recommended to receive HER2 testing.

Participants with an existing positive HER2 test within the 45 days prior to enrollment will be eligible for inclusion in the trial if they meet all other eligibility criteria, and if there is appropriate documentation supporting the validity of the HER2 testing procedure (method of test, antibodies and probes used, laboratory the test was performed in). Confirmation of HER2 positivity should be sought by reanalysis of stored tumor specimens if possible.

Radiological assessment

Initial baseline tumor imaging must be performed within 21 days prior to the date of randomization. The screening images will be submitted to the central imaging radiologists (at FHCC) for retrospective review. Scans performed as part of routine clinical management are acceptable for use as screening tumor imaging if they are of diagnostic quality and performed within 21 days prior to randomization and can be assessed by the central imaging vendor.

Tumor imaging during the trial will be performed at baseline, and every 6 months for the first two years and then once yearly for 3 years subsequently until disease progression, death, withdrawal of consent, or end of study. Imaging may be conducted upon presentation of new or worsening symptoms. Per RECIST 1.1, partial response and complete response should be confirmed by a repeat tumor imaging assessment obtained 4 weeks or longer form the date the response was first documented. Subjects then will return to regularly scheduled imaging. Imaging should be performed at time of treatment discontinuation (plus or minus 4-week window); if the participant discontinues trial treatment without documented progression, every effort should be made to continue monitoring their disease status via tumor imaging.

Recruitment process

We focus recruitment of participants from China where there is the highest number of raw gastric cancer cases in the world. We chose Fred Hutch as the central trial coordinating site and plan to recruit gastric cancer patients from 25 hospitals/cancer centers in China. Our target is to open the sites in 2023, begin recruitment in 2024 and continue recruitment for a 4.5-year period. Our target is to recruit and randomize 2600 locally advanced/metastatic gastric cancer patients that meet the eligibility criteria described earlier, including: (a) patients with an existing HER2-positive test who consent to joining the trial (who may not have access to trastuzumab treatment) and (b) patients without an existing HER2 test result who receive a HER2-positive test on study.

We will employ several recruitment strategies to identify potential enrollees and obtain the intended number of participants:

1. Create a trial website: develop a landing page to introduce the trial information including the background, risk/benefit, inclusion/exclusion criteria, etc. In addition, there is a list containing contact information for all the sites and investigators, so patients or interested parties can reach out directly.

2. Trial registration: we plan to post our trial to ClinicalTrials.gov and Chinese Clinical Trial Registry (ChiCTR), including a link to the trial website, protocol, and other related info.
3. Local clinical partnerships and medical referrals: establish connections with the oncologists and gastroenterologists at local hospitals, cancer centers, or local clinics. If patients present with locally advanced/metastatic gastric or GEJ cancer, caregivers can refer patients to our trial for HER2 testing and treatment. We may also screen in-patient records to identify good candidates for our trial. We will post information pamphlets about gastric cancer and our trial in these local oncology clinics to inform clinicians and patients about this opportunity to contribute to this study.
4. Direct mail flyer/phone call to patients in population-based cancer registry: by 2018, the registry covered 438 million people (31.5% of China's population). We may consider directly contacting those that match disease criteria.
5. Community involvement: recruit volunteers to set up booths with pamphlets on gastric cancer and information related to our trial at local parks where elderly people exercise frequently. We will establish partnerships with gastric cancer advocacy groups (e.g., Cancer Foundation of China or China Anti-Cancer Association) to promote the trial. We will be active participants in spreading information about the disease and our trial on Gastric Cancer Awareness Day (Nov 29).
6. Establishing a rapport with prospective enrollees: investigators may hold a Tencent Meeting with prospective participants (investigators and clinicians) to answer the questions about their condition, the trial, solicit feedback, etc.

All recruitment and outreach methods and materials for the trial will be submitted to the Internal Review Board (IRB) for approval. We will make sure all outreach materials follow the IRB guidelines before submitting them to the IRB.

Procedures to enhance quality of trial conduct

Screening and recruitment monitoring

Continual analysis of screening and recruitment data will be performed by investigators, sponsors, Study Monitoring Committee (SMC), and Data Monitoring Committee (DMC). These sessions will be co-chaired by the heads of the SMC and DMC and will be designated as "Open sessions" in the DMC charter.

After the conclusion of recruitment, a cross-sectional study of HER2 screening data collected from the trial will be published and disseminated to share insights regarding the frequency of HER2 overexpression in Chinese gastric cancer patients with the broader scientific community.

This trial was designed with a clear-eyed view that recruitment is challenging and often more difficult than anticipated during the design phase. Recruitment in this trial is a particular challenge given the relative dearth of evidence on HER2-positivity and HER2-testing and treatment frequency in Chinese gastric cancer patients. We supply possible protocol amendments that could be explored to enhance recruitment if recruitment is suboptimal.

Investing in community/patient outreach: it is well-known that community participation and developing relationships with patients can have beneficial impacts on recruitment and adherence. In collaboration with the Study Monitoring Committee and participant focus groups, we can receive feedback and develop strategies to collaborate and improve relationships with prospective and enrolled participants. We could also consider renting billboards in metropolitan areas to promote gastric cancer and clinical trial awareness.

Broadening eligibility criteria: we could consider allowing patients with moderate cardiac dysfunction but without recent anthracycline usage to enroll, given the evidence of no increased cardiac toxicity in the ToGA, JACOB, and EVIDENCE trials.

Activating additional sites: if recruitment is suboptimal, we could activate additional study sites used in the open-label La Hoffman-Roche EVIDENCE trial which tested and enrolled 1556 gastric patients over a 5-year period between 2013 and 2018.[45] The previous affiliation of these sites with a trastuzumab trial would allow for a more straightforward integration within the existing network of trial sites. See Appendix D for the list of sites.

Extending the recruitment period: if we have not met recruitment targets, but it is anticipated that the target could be attained in a reasonable timeframe, we could increase the duration of the recruitment period.

Admitting a higher T2 error rate: if necessary, we can admit a higher T2 error rate, up to a maximum of 20%. Admitting T2 error rates beyond 20% runs the risk of failing to obtain a reliable answer to our primary questions.

Dropping a treatment arm: if recruitment is low and patient focus groups highlight concerns with the chemotherapy alone arm, we can consider dropping that treatment arm, and using a combination of contemporary and historical control data (from the ToGA trial) to assess non-inferiority of HER-Vaxx plus chemotherapy to trastuzumab plus chemotherapy.

Interim monitoring of safety, immunogenicity, and efficacy by the IDMC

The independent data monitoring committee (IDMC) will be a collection of independent gastroenterologists, oncologists, statisticians, and ethicists responsible for the interim review of safety and efficacy data during the trial. The IDMC will ideally be composed of Chinese members to ensure familiarity with the cultural, political, and social contexts in which the trial is conducted. The IDMC charter, written exclusively by the IDMC and its members, will outline the procedures by which the committee operates. We stress that the IDMC is completely independent of the sponsors and investigators, although the IDMC may elicit input from the sponsor provided confidentiality is maintained. All IDMC recommendations to the sponsor will be consensus decisions.

The IDMC will interface with the Study Data Management Center, the Statistical Center for HIV/AIDS Research and Prevention (SCHARP), in requesting and receiving interim results. These results will be firewalled off from the sponsor and trial investigators. All sessions

discussing safety and recruitment results will be designated as “closed sessions,” where attendance by only IDMC members is permitted.

Our recommendations for safety monitoring by the IDMC include a safety and toxicity assessment of all interventions every 6 months or more frequently as needed. The IDMC will monitor frequencies of Serious Adverse Events (SAEs), Serious Adverse Reactions (SARs), or Suspected Unexpected Serious Adverse Reactions (SUSARs). Special care should focus on immune-related adverse events: extreme fatigue, skin rashes, pneumonitis, colitis (diarrhea/abdominal pain), swelling of joints and joint pain, liver inflammation (elevated albumin & bilirubin concentrations), and changes in hormone levels associated with inflammation of hormone glands. Special care should be focused on peptide-based immunotherapy reactions such as skin reactions at the injection site, cellulitis around the injection site, edemas of the head and neck, colitis, rectal bleeding, and bladder-vaginal fistulae.[46] If safety concerns arise, the IDMC may recommend a recruitment pause. If safety concerns persist, the IDMC may suggest changes to enrollment criteria, changes to the therapy regimens, dropping a treatment arm, or termination of the trial altogether.

As part of the interim safety monitoring, the IDMC will also monitor unfolding immunogenicity data in the HER-Vaxx plus chemotherapy arm to confirm that the experimental treatment mechanism is operating as intended. If there is poor evidence of immunogenicity, as indicated by an average < 10-fold increase in anti-HER2 antibody titers (ng/ml) frome the baseline measurements, the IDMC may recommend pausing recruitment, modifying eligibility criteria, or terminating the trial for futility.

Our recommendations for efficacy monitoring by the IDMC include using the DF-A group sequential three-arm noninferiority monitoring procedure described by Ochiai *et al.* 2017 with a 4-look O’Brien-Fleming boundary (see Table 4 below).[13] The DF-A algorithm stops the trial if (a) an interim test of assay sensitivity rules out the superiority of the experimental treatment relative to placebo control or (b) an interim test of assay sensitivity proved benefit of experimental arm relative to placebo control arm AND a subsequent interim analysis demonstrated the retention of effect in the experimental treatment relative to the active control. In DF-A, at each analysis point, assay sensitivity is tested first, and retention of effect is only tested after assay sensitivity has been demonstrated. This preserves the alpha used to test retention of effect until after assay sensitivity has been demonstrated. However, we discourage adaptively allocating Type I error rate to the retention of effect test after demonstrating assay sensitivity, as correlation between assay sensitivity and retention of effect test statistics may exist when the allocation ratio is not balanced.

Non-inferiority is only achieved if assay sensitivity and retention of effect are achieved. Since the NI hypothesis is a union hypothesis encompassing assay sensitivity and noninferiority, testing each sub-hypothesis at level alpha controls the overall T1 error rate at level alpha. Thus, each sub-hypothesis may be tested at the alpha=0.025 level while the overall T1 error rate of the whole test procedure is controlled at alpha=0.025.

Table 4: p-values specified under 4-look O’Brien Fleming boundary for interim analyses.

Analysis	Z	Nominal P
1	4.05	2.56×10^{-5}
2	2.86	0.00212
3	2.34	0.00964
4	2.02	0.0215

Reasons for withdrawal from study

The only three reasons for participant discontinuation from the study will be death, withdrawal of consent, or failure to receive one dose of the intended therapy. To prevent loss of information due to high rates of participant discontinuation, the informed consent document will contain a section highlighting the scientific importance of remaining under observation, even if a participant wishes to be taken off treatment. If a participant wishes to terminate from the trial, site administrators will instruct clinicians to encourage participants to consider remaining on the trial but pause study treatment rather than terminating altogether.

Treatment interruptions or stoppages, as requested by participants or as advised by clinicians, will be allowed under this protocol. All analyses will be intention to treat.

Laboratory/Biomarker Assays

Measuring Anti-HER2 antibodies during treatment

Longitudinal anti-HER2 antibody titers will be measured in ng/mL via an anti-HER2 ELISA assay on routinely collected serum derived from blood samples using the abcam Anti-HER2 ELISA Kit (ab237645). Blood will be collected and stored at each treatment visit, including baseline, for participants on the experimental arm. The ELISA assay will only be run on samples from baseline, week 3 visit, week 9 visit, and terminal blood collection visit. Analysis of additional samples may be permitted if anti-HER2 response induction takes longer than 3 weeks or if there is a suspected abnormality in an antibody measurement.

Patient Reported Outcomes

Patient reported outcomes (PROs) comprise standardized data directly reported from the patient to the clinician and research team and commonly include disease symptoms, treatment side effects, various aspects of functioning (e.g., physical, mental, sexual), and quality of life (QoL). PROs can be widely applicable, or they can be disease specific.[47] In addition to individual patient benefits of PROs used in clinical care, using PROs in research in addition to traditional outcome measures such as overall survival (OS) or progression free survival (PFS) can be helpful to understand the nuance of treatment burden, which may be most meaningful when there are negligible differences in OS or PFS. Since disease symptoms and side effects from drugs can negatively impact QoL, it is important to measure these factors, especially for patients with advanced cancer who may have a limited life expectancy, in which case any survival benefits

must be weighed against treatment toxicity and impact on QoL.[15] Given the poor prognosis and debilitating course of the disease, interventions for advanced gastric cancer are typically palliative in nature and thus survival may not be the only significant endpoint. Recently, obtaining "feels and functions" measures via PROs has emerged as an increasingly important outcome to be considered in RCTs alongside traditional oncologic outcomes such as overall survival and tumor control.[20]

In this trial, the following PROs will be used:

Functional Assessment of Cancer Therapy – Gastric (FACT-Ga)
The FACT-Ga is a 46-item questionnaire that combines the 19-item gastric cancer additional concerns domain with the four domains (physical, social, emotional, and functional well-being) measured by the 27 items on the Functional Assessment of Cancer Therapy - General (FACT-G). This PRO was designed concurrently in North America and Asia to ensure cross-cultural validity. The questionnaire takes about 15 minutes to complete and is available in 28 languages. The item format is all statements and responses are provided on a Likert scale, using the past seven days as the recall period. This measure of QoL in patients with gastric cancer has been tested and validated in multiple settings and is one of the mainstays in PROs for gastric cancer research studies.[20]

Patient Health Questionnaire (PHQ-9)
The PHQ-9 is a multipurpose instrument for screening, diagnosing, monitoring, and measuring the severity of depression. This brief measure for depression has 9 items written as statements and responses are provided on a Likert scale, using the past 14 days as the recall period. The questionnaire takes about three minutes to complete and has been tested and validated in many settings for clinical and research purposes.[48]

Generalized Anxiety Disorder (GAD-7)
The GAD-7 is a multipurpose instrument for screening, diagnosing, monitoring, and measuring the severity of anxiety. This brief measure for anxiety has 7 items written as statements and responses are provided on a Likert scale, using the past 14 days as the recall period. The questionnaire takes about three minutes to complete and has been tested and validated in many settings for clinical and research purposes.[49]

Each of these PROs are available in simplified and traditional Chinese.

Adverse Event Definitions and Reporting Requirements

An adverse event is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product or protocol - specified procedure, whether considered related to the medicinal product or protocol-specified procedure. Any worsening (i.e., any clinically significant adverse change in frequency and/or

intensity) of a preexisting condition that is temporally associated with the use of the Sponsor's product, is also an adverse event.

All adverse events that occur after the consent form is signed but before randomization/treatment allocation must be reported by the investigator if they cause the subject to be excluded from the trial or are the result of a protocol-specified intervention.

Adverse events (AE) will be monitored throughout the trial and graded in severity according to the guidelines outlined in the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. AEs will be analyzed including but not limited to all AEs, serious adverse events (SAEs), fatal AEs, and laboratory changes. Toxicities will be characterized in terms regarding seriousness, causality, toxicity grading, and action taken with regard to trial treatment.

A **Serious Adverse Event** is any occurrence of an event during use of a product that results in death, life-threatening health incident, results in persistent or significant disability, results in or prolongs existing hospitalization, is a congenital anomaly, is another important medical event. Any SAE thought by a qualified physician to be related to the Sponsor's product must be reported immediately to investigators and the sponsor.

Adverse events will be graded on the V5.0 CTCAE criteria – Grade 1 adverse events comprise mild/asymptomatic/mild symptoms that do not require intervention, Grade 2 are moderate events require minimal, local, or noninvasive intervention, Grade 3 are severe or medically significant but not immediately life-threatening events, Grade 4 are life threatening consequences that require urgent intervention, and Grade 5 are death related to the adverse event. In accordance with V5.0 CTCAE criteria, the duration of adverse events action taken to address the intervention (was drug administration discontinued), and the physicians' assessment of whether the sponsor's drug caused the adverse event will be included in the assessment.

Adverse event reporting will begin after initiation of study drug. All adverse events, regardless of relationship to study drug, will be reported from first treatment date through end of study. The investigator is not required to actively monitor patients for adverse events; however, the sponsor should be notified if the investigator becomes aware of an adverse event. Serious adverse events should be immediately reported the sponsor.

Information on adverse events should be solicited by non-directive questioning such as "How have you felt since your last clinic visit?" or "Have you had any new or changed health problems since you were last here?"

STUDY DESIGN & STATISTICAL CONSIDERATIONS

Endpoints

The following endpoints will be considered in the analysis of trial data. Note that the target sample size is determined based only on the primary endpoint of overall survival.

Primary

1. Overall Survival (OS) – Time to Event. Assessed via phone call every 12 weeks.

OS is defined as the time from the date of randomization to the date of death due to any cause (in days). Participants will be censored at the date of consent withdrawal or date of last follow-up. Overall survival will be summarized using the median time, in months, from date of randomization to the date of the OS event. OS between groups will be summarized using median OS and the hazard ratio.

Secondary

1. Objective Response Rate (ORR) assessed at month 6 and month 12 tumor response visits.

ORR is defined as the proportion of patients with a complete response or partial response to treatment according to Response Evaluation Criteria in Solid Tumors (RECIST) 1.1, is the most common endpoint used in pivotal trials supporting FDA approval of cancer drugs for solid tumor indications. We will assess ORR at the month 6 and month 12 response visits, or earlier if clinically indicated.

2. Patient reported Outcomes (PROs) to FACT-Ga, FACT-GPHQ-9, and GAD-7 questionnaires – repeated measures at each treatment visit (every 3-4 weeks until death, withdrawal of consent, loss to follow up, or end of study).

FACT-Ga, FACT-G, PHQ-9, and GAD-7 are participant reported outcome questionnaires that assess gastric-cancer-specific measures of physical, social, emotional, and functional well-being as well as general measures of depression and anxiety. These PROs will more fully capture the context of patient well-being as they undergo gastric cancer treatment.

Exploratory endpoints

1. Anti-HER2 antibody levels (ng/ml) measured in serum of experimental participants using ELISA assay at baseline, 3 weeks, 12 weeks, and terminal blood collection date.

2. Assess the frequency of HER2-positive gastric and gastroesophageal cancer in a large Chinese cohort.

Accrual, Follow-up, and Sample Size

Sample Size Parameters

A pre-specified subgroup analysis of the ToGA trial observed that participants with high levels of HER2 expression, i.e., those patients with IHC2+/FISH+ or ICH3+ tumors, survived a median of 16 months on trastuzumab plus chemotherapy (95% CI 15-19 months) relative to a median

survival of 11.8 months on chemotherapy alone (HR=0.65, 95% CI 0.51–0.83). During the ToGA trial, the IDMC encouraged a revision to the design due to a lower-than-expected event rate and the results of the phase III international trial ML17032,[50] demonstrating median overall survival of 10.5 and 9.3 months in advanced gastric cancer patients treated with Capecitabine/cisplatin and 5-FU/cisplatin respectively. The ToGA trial revised its median survival estimates from 7 and 10 months to 10 and 13 months accordingly. In the JACOB trial, chemotherapy and trastuzumab achieved a median overall survival of 14.2 months (95% CI: 12.9- 15.5 months), although the JACOB trial included 5-FU monotherapy instead of cisplatin/5-FU combination therapy as part of its treatment regimen.

As illustrated in the comparison of OS in chemotherapy arms between ToGA and ML17032, there are substantial differences in OS reported from recent phase III trials of chemotherapy for gastric cancer (11.8 versus 9.3/10.5 months). For example, Phase III trials of combination chemotherapies in Japan have achieved median overall survivals exceeding 1 year,[24,51] as compared with around 10 months in Western trials.[52] Two working theories for this discrepancy are (1) the high fraction of Japanese patients (>70%) who receive subsequent chemotherapy after first line therapy[53-55] and (2) Japanese trials inclusion of non-measurable diseases, which may have superior outcomes. However, subgroup analyses in Japanese patients in the ToGA trial still demonstrated efficacy of trastuzumab adjuvanted chemotherapy versus chemotherapy alone.[56] It is important to note that the longer-than-anticipated survivals observed in the chemotherapy arm in the ToGA trial may be due to the inclusion of some non-measurable disease cases (approx. 10% of total cases).

Sample size parameters can have a substantial impact on the sample size estimates. If we assume aggressive survival estimates for the chemotherapy-only arm (11.8 months median OS as observed in ToGA IHC2+/FISH+ or ICH3+ subgroup) and conservative survival estimates for the trastuzumab plus chemotherapy arm (12.9 months as the minimum 95% CI bound for in the JACOB trial), an astronomically large sample size is required, rendering the trial infeasible. However, we eschew this example because these survival estimates come from different trials with potentially different event rates and because it is undesirable to test for noninferiority in a setting with low assay sensitivity, i.e., where the active comparator is not substantially different from the placebo.

A meta-analysis of 5 studies containing 732 patients showed that chemotherapy regimens containing 5-FU and capecitabine treatments showed roughly equivalent median overall survivals of 10.9 and 10.8 months respectively. For our analysis, we will rely on the results of the meta-analysis and assume that the median OS in the chemotherapy only arm will be 10.85 months. This corresponds to a median survival below that seen in the ToGA IHC2+/FISH+ or ICH3+ subgroup but above the OS seen in the ML17032 trial. For the trastuzumab plus chemotherapy arm, we estimate OS to be 14.85 months, corresponding to a weighted average of the median overall survival estimates in the trastuzumab plus chemotherapy arms in the IHC3+/ICH2+ & FISH+ ToGA subgroup and in the JACOB trial.

Target Sample Size Estimates

We consider the target retention fraction, Δ, which represents the minimal acceptable fraction of trastuzumab's effect that should be retained by the addition of HER-Vaxx. We define $\Delta = 0.6$, corresponding to an estimated minimal 2.4-month improvement in median survival relative to chemotherapy and no worse than an estimated 1.6-month reduction in median survival relative to trastuzumab plus chemotherapy. Thus, our margin for non-inferiority is that HER-Vaxx plus chemotherapy retains 60% of the efficacy of trastuzumab plus chemotherapy relative to chemotherapy alone.

Assuming exponential distributions of survival times, the associated relationship between median OS times and hazards: $\lambda = \frac{log(2)}{\text{Median OS}}$, and assuming homogeneous censoring probabilities, we calculate the optimal treatment allocation, 5:3:2 in favor of HER-Vaxx plus chemotherapy, trastuzumab plus chemotherapy, and chemotherapy alone arms using the method of Mielke, Munk, and Schacht (2008).[57]

$$\begin{aligned} n_T^*: n_R^*: n_P^* &= 1: \Delta: (1-\Delta) \\ &= 1: 0.6 : 0.4 \\ &= 5: 3: 2 \end{aligned}$$

Where T, R, and P refer to experimental (HER-Vaxx plus chemo), active control (Trastuzumab plus chemo), and placebo (chemo alone) respectively, and

Using the methods developed by Mielke, Munk, and Schacht (2008),[57] we compute the following sample size estimates per arm using:

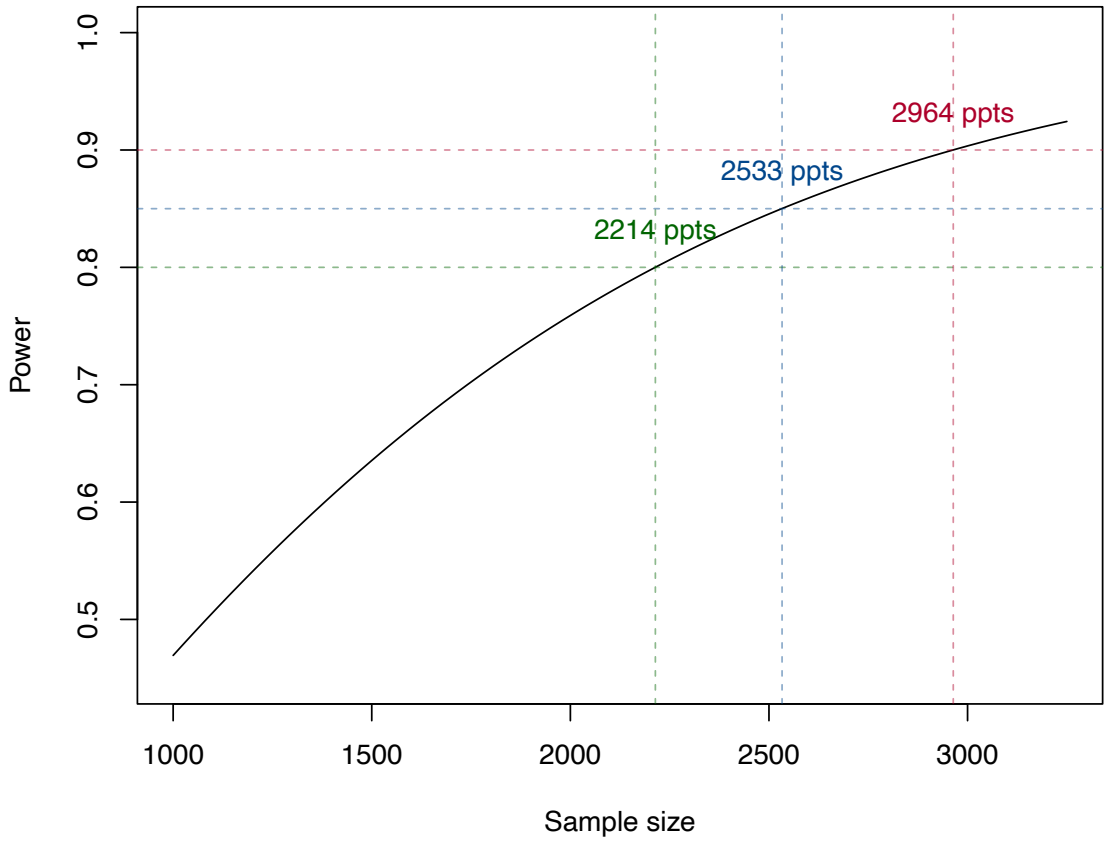
$$(n_T^*, n_R^*, n_P^*) = \frac{2}{p}\left(\frac{z_\alpha - z_{1-\beta}}{\mathrm{h}}\right)^2 (1, \Delta, 1-\Delta)$$

Where p is the probability of being uncensored and $\mathrm{h} = log\left(\widehat{\lambda_T}\right) + \Delta\, log\left(\widehat{\lambda_R}\right) + (\Delta - 1)\, log\left(\widehat{\lambda_P}\right)$. Thus, we calculate the sample size for an idealized trial with $\alpha = 0.025, 1 - \beta = 0.9$, assuming that HER-Vaxx plus chemotherapy is equivalent in hazard to trastuzumab plus chemotherapy and making the conservative assumption that the probability of being uncensored is the probability of being uncensored in the active control group (which should have the longest survival and therefore the lowest event probability). If we design a study with an average follow-up for 54 months (4.5 years), we estimate that 92% of participants will have a recorded OS endpoint by the end of the study. Factoring in a 2% loss of follow-up rate, we estimate that the probability of uncensored event will be 0.9. Thus, the sample size estimates are computed as follows:

$$(n_T^*, n_R^*, n_P^*) = \frac{2}{0.90}\left(\frac{1.96 + 1.282}{\log\left(\frac{\log 2}{14.85}\right) + 0.6\log\left(\frac{\log 2}{14.85}\right) - (1-0.6)\log\left(\frac{\log 2}{10.85}\right)}\right)^2 (1, 0.6, 0.4)$$

Yielding estimated group sample sizes of 1482, 889, and 593 participants respectively, for a total sample size of **2964 patients.** Sample sizes were also confirmed using the `ThreeArmedTrials` R package and a power curve is shown in Figure 3 below for various sample sizes corresponding to different powers to detect non-inferiority. An 85% powered trial would require **2533 patients**, while an 80% powered trial would require **2214 patients**. **We will therefore target enrollment to 2600 patients.**

Figure 3: power curve illustrating statistical power to detect non-inferiority (at least 60% of effect retained) of HER-Vaxx plus chemotherapy relative to trastuzumab plus chemotherapy as a function of total sample size.



As described in Mielke, Munk, and Schacht (2008),[57] the power of the pre-test of superiority comparing the experimental treatment to the placebo is guaranteed in the common situation where $\lambda_T = \lambda_R$ and $\Delta > 1/3$, i.e., the assumed hazards in the experimental and active control groups are equal and the non-inferiority threshold is greater than 1/3 of the active control's effect. Numerical investigations also confirmed that the power of the pre-test was often better than the power for the non-inferiority test, and no sample size adjustment is required for the complete test procedure.

Screening and Recruitment Targets

2020 GLOBOCAN national cancer incidence estimates provide an estimate of 478,363 new cases of gastric cancer each year in China.[1] No GLOBOCAN estimates are available for GEJ cancers, but GEJ cancers are very rare in Asian populations occurring in approximately 0.5 cases per 100,000 population/year.[58] Given the populations of China comprises approximately 1.402 billion persons, the combined incidence would be approximately 7,010 annual cases of GEJ cancer per year. Thus, we estimate that 485,373 gastric/GEJ cancer patients will occur annually in China.

A study by Strong et al. in 2015 examined gastric cancer clinical outcomes in a cohort of 1027 US and 1173 Chinese patients treated at Memorial Sloan Kettering Cancer Center and Beijing Cancer Hospital respectively.[59] In the Chinese cohort, 44% of cancers presented at the Stage IIIa, IIIb, or IV stages. It was reported that 80 to 90% of patients present with advanced stage disease in Western countries, either stage III locally advanced or stage IV metastatic disease, due to a lack of screening programs. In Japan, where routine screening successfully catches many cancers early, many individuals choose not to participate, and approximately 50% of all gastric cancers in Japan are diagnosed at an early stage.[37,38] In accordance with the study by Strong et al., we will assume 44% of gastric and GEJ cancers will present as metastatic or locally advanced disease in China, yielding 213,565 annual advanced cases (210,480 gastric, 3,085 GEJ).

HER-2 positivity rates are highly variable between studies. In the ToGA trial, one of the largest available collections of HER2-screening data in a single clinical trial setting, found 22.1% of patients screened were HER2 positive.[2] Enrollment was completed in Australia, Western and Eastern Europe, East Asia, Central & South America, the Middle East, and South Africa. Rates of HER2 positive between European and Asian populations were consistent (23.6% to 23.9%) but were higher in intestinal versus diffuse type (31.8% vs. 6.1 %) and gastroesophageal cancers versus gastric cancers (32.2% versus 21.4%).[52] However, Kunz *et al.* reported a HER2 positivity rate of 12% for gastric cancers and 10% for GEJ cancers in 169 participants from the US population,[25] while the large international HER-EAGLE trial of nearly 5,000 participants showed IHC positivity in 12.9% of gastric cancer samples and 22.1% of GEJ samples.[60] A large review of a cohort of 8,152 patients sourced from 36 trials showed a range of HER2 positivity between 4 and 53.4%, with an average of 20.2%.[61] A metanalysis of 41 studies and over 17,000 gastric cancer cases showed a HER2 positivity rate of 19.07% (95% CI = (9.16, 28.98)); subgroup analysis concluded that HER2 positivity rates were numerically higher in Asian countries (19.52%) versus European countries (16.91%).[62] We believe a likely range for HER2-positivity rates in China will be between 18-22%. Given the considerable variability in HER2 positivity between studies, we will coordinate a concomitant cross-sectional study of HER2 positivity among advanced gastric cancer patients receiving testing through the trial. Pathologist review of HER2 tests will report the results of each HER2 test in a form described in the CAP "Template for Reporting Results of HER2 (ERBB2) Biomarker Testing of Specimens From Patients With Adenocarcinoma of the Stomach or Esophagogastric Junction"[44] and as shown in Appendix B.

A recent multinational cross-sectional study of molecular testing uptake in various solid tumor types demonstrated that in a collection of 1275 gastric cancer patients in China, only 27.1% of cases received HER2 testing.[11] And out of 42 patients surveyed with HER2-positive gastric cancer, 34 (81%) received trastuzumab, although this estimate is quite imprecise given the small sample size. For the purposes of recruitment target estimation, we will assume that 75% of

gastric cancer patients in China either (a) will not receive HER2 testing or (b) will receive HER2 testing but not trastuzumab treatment.

We estimate that the cities in which our study sites are centered comprise 13.7% of China's total population. If we assume 44% of cases will present as locally advanced/metastatic, 13.7% will reside in the vicinity of one of the study sites, annually 29,304 patients with locally advanced/metastatic disease eligible for screening will be available in the vicinity of at least one site (131,868 over 4.5 years). We intend to contact and screen 8,000 patients for eligibility annually (36,000 over 4.5 years, 27.3% of local cases matching criteria). We estimate 6,000 (75% of those screened) will meet eligibility and 3,000 of those screened (50% of eligible participants) will join the study and be referred for HER2 testing if they have not yet received testing. Assuming a HER2-positivity rate of 20%, we will identify approximately 600 patients annually (2,700 over 4.5 years) with HER2-positive gastric cancer who will be administered treatment. Over 4.5 years, we will cumulatively recruit 2,600 participants. Even with a small loss of patients between enrollment and treatment, a trial with 2600-2700 patients would yield >85% power to detect non-inferiority.

Random Assignment\Blindness

Participants will be randomized (5:3:2) to receive HER-Vaxx plus chemotherapy, trastuzumab plus chemotherapy, or chemotherapy alone. Central randomization will be performed by a block randomization scheme stratified according to clinic, ECOG score, chemotherapy regimen, site of primary cancer, and previous gastrectomy status. Stratification factors were chosen in accordance with stratification factors used in the ToGA[2] and JACOB trials,[15] and randomization will be performed in blocks of size 10.

This trial will be open-label; participants and clinicians will know whether a participant is on HER-Vaxx plus chemo, trastuzumab plus chemo, or chemotherapy alone. The open-label nature of the trial enables the trial to be run more simply and cheaply, since participants would not occupy a hospital chair nor a nurse or clinician's time while receiving a placebo injection or infusion. We believe that the open-label trial will induce minimal bias with respect to the primary outcome, since we do not anticipate that knowledge of treatment assignment will substantially impact overall survival. However, it is plausible that knowledge of treatment assignment could impact participant adherence to treatment and study procedures, PROs/symptom reporting, or participant retention. Retention is the most critical issue, and the informed consent process will stress the critical nature of a participant remaining on study, even if they do not adhere to treatment/clinic visit schedules. Since knowledge of treatment is guaranteed in clinical practice, we anticipate that while knowledge of treatment assignment may impact adherence and PROs/symptom reporting, we anticipate that any impact will be like that reflected in real-world clinical practice.

Critically, secondary clinical endpoints – disease progression and disease response -- will be adjudicated by treatment-blinded radiologists to ensure the objective assessment of these endpoints.

Appropriateness of Control Regimen & Ethical Considerations

We discuss five main ethical considerations for clinical trials which may be challenged in this study.

The major ethical consideration on which this study hinges is the use of a chemotherapy alone control arm. The ToGA study indicates that trastuzumab plus chemotherapy improves the survival rate of HER2-positive gastric cancer patients. Not receiving a more active treatment may expose the patients to higher levels of pain, aggravation of their conditions, or increased risk of death. To safeguard the health of patients, clinicians will be instructed to discuss with patients about the benefits and costs of trastuzumab and encourage them to pursue trastuzumab treatment if it is accessible, affordable, and feasible for them.

We believe this trial is only ethical if it is conducted in a setting where trastuzumab is not universally accessible and where patients are appropriately informed regarding their ability to access trastuzumab treatment. We undertake this trial in China because of known and significant barriers to HER2 testing and trastuzumab access. Findings from a 2008 survey of 101 hospitals in Beijing showed that basic pathological information was missing for up to 67.2% of newly diagnosed breast cancers.[8] Findings from a nationwide survey of the quality of HER2 testing suggested in 45 Chinese hospitals found that only 62% met acceptable standards.[9] In Beijing, 9% of breast cancer patients had no access to HER2 testing and 10% of breast cancer patients with equivocal IHC results were never tested using ISH methods.[8] Only 20.6% of patients in Beijing with HER2-positive breast cancer received trastuzumab despite its approval in 2002.[8] A real world study in China between 2010-2015 found that only 40.5% of patients with HER2-positive early breast cancer received trastuzumab treatment.[5] A study in the early 2010s found that in the Jiangsu province, where trastuzumab has been subsidized for early breast cancer and where trastuzumab use is highest, only 34% received trastuzumab, although health insurance coverage was associated with higher odds of trastuzumab use.[10] It is worth noting that all available research on trastuzumab access focuses on breast cancer; given trastuzumab's more recent approval for gastric cancer, we believe that access for gastric cancer testing and treatment will be even more limited. By 2013, there were more than 6 cities providing public reimbursement for trastuzumab, but only 2 for gastric cancer indication.[12] Citing the numerous pieces of evidence that trastuzumab access is not widely available, we believe that a trial with a chemotherapy alone arm is ethically feasible in China due to the lack of widespread trastuzumab access.

Second, we consider scientific validity. The scientific validity of the trial hinges on enrolling enough participants and achieving the requisite number of events. Inadequate sample size thus could compromise the generous contributions participants are making to advance cancer treatment. Thus, in collaboration with the SMC, we will rigorously analyze screening and recruitment data and exhaust all design and recruitment options to ensure the trial is adequately powered to answer the scientific questions of interest.

Third, we refer to benefits and risks. HER-Vaxx is a B-cell immunotherapy agent designed to stimulate the patient's immune system to produce a polyclonal anti-HER2 antibody response, instead of a monoclonal infusion of anti-HER2 antibodies like trastuzumab. While active immunotherapies like HER-Vaxx offer the benefit of sustained antibody levels after treatment,

HER-Vaxx may take up to 15 days (about 2 weeks) to produce substantial anti-HER2 antibodies and exert an anti-cancerous effect, whereas synthetic monoclonal antibody treatments have an immediate effect. In other words, participants in the HER-Vaxx arm may not receive immediate anti-HER2 therapeutic effects, due to the delay in mounting a humoral immune response. However, we argue that the fight against advanced gastric/GEJ cancer is not won or lost in the first two weeks of treatment, and HER-Vaxx also offers other mechanistic benefits that may offset the delayed mechanism of action. HER-Vaxx's sustained antibody response is favorable to the profile of synthetic monoclonal treatments, which wanes as antibodies degrade or until the patient is re-dosed. In addition, HER-Vaxx may continue to exert therapeutic effects after disease progression, whereas trastuzumab treatment is typically stopped at disease progression. Nevertheless, the lag between treatment and therapeutic effect is an unavoidable challenge of immunotherapies that must be reckoned with and communicated to potential enrollees during the informed consent process.

Fourth, we must consider the global ethical issue in this international clinical trial. Researchers should develop culturally appropriate ways to disclose information that is necessary for adherence to the substantive ethical standard of informed consent, with particular attention to disclosures relating to diagnosis and risk, research design, and possible post-trial benefits. Also, clinicians should provide an optimal care and safety monitoring to every participant in the different countries to ensure patients' safeguard and reduce the bias of this study.

Fifth, we discuss privacy, confidentiality, and autonomy. Privacy relates to the person concerned; confidentiality relates to the information/data about an individual. Participant privacy will be protected by allowing patients to answer questionnaires and comply with study procedures with study procedures to any degree that they feel comfortable. Confidentiality will be protected by assigning unique patient identifiers. The trial must obtain consent from the participants if it is necessary to share the data with other related experts or researchers. All formal statistical analyses will be performed on anonymized data to protect patient privacy. Autonomy will be protected by rigorously ensuring understanding of the trial – its goals, risk/benefit, and expectations – during the informed consent process. We will stress the right of participants to refuse or withdraw without any reason and without affecting their routine treatment at the relevant clinic or hospital. See appendix for the study informed consent form that will be provided to participants at the enrollment visit.

To avoid conflicts of interest, investigators will be required to provide the sponsor with a sufficient, accurate financial information to certify that they do not have competing financial conflicts of interest.

DATA ANALYSIS

Primary Analysis

The primary hypothesis for noninferiority of HER-Vaxx plus chemotherapy to trastuzumab plus chemotherapy will be assessed through a two-stage testing procedure as described in Mielke *et al.* 2008: a pre-test for assay sensitivity – superiority of HER-Vaxx plus chemotherapy versus

chemotherapy alone – and a retention of effect test of HER-Vaxx plus chemotherapy versus chemotherapy alone.[57]

The sub-test for assay sensitivity, i.e., superiority in OS of HER-Vaxx plus chemotherapy versus chemotherapy alone, will be performed using stratified Cox model using Efron's method of tie handling with treatment assignment as the main effect. Stratification will be according to clinic, ECOG performance score, chemotherapy regimen, site of primary cancer, and previous gastrectomy status. The treatment effect will be estimated using a hazard ratio. Inference will be performed using a Wald test with robust/sandwich standard errors. Comparison of OS probabilities over study time between the two groups will be performed using Kaplan-Meier estimates of the survival function. We will allocate a one-sided alpha of 0.025 as the threshold for statistical significance, of which a portion will be spent at interim efficacy analyses using the O'Brien-Fleming boundary.[63]

The retention of effect sub-test will be performed by comparing the following Wald statistic to the critical value of the reference standard normal distribution $Z_{\alpha=0.025}$:

$$T = \frac{\log(HR_{T:P}) - \Delta \log(HR_{R:P})}{\sqrt{\frac{1}{\delta_T} + \frac{\Delta^2}{\delta_R} + \frac{(1-\Delta)^2}{\delta_P}}}$$

Where $HR_{T:P}$ and $HR_{R:P}$ are the hazard ratios between experimental/active control and placebo respectively as estimated from a stratified Cox model using Efron's method of tie handling. δ_T, δ_R, δ_P correspond to number of uncensored observations in the experimental (HER-Vaxx plus chemo), active control (trastuzumab plus chemo), and placebo (chemo alone) arms respectively. $\Delta = 0.6$ refers to the intended retention of effect. We will allocate a one-sided alpha of 0.025 as the threshold for statistical significance, of which a portion will be spent at interim efficacy analyses using the O'Brien-Fleming boundary.[63] However, the DF-A approach described by Ochiai *et al.* will preserve alpha allocated to the retention of effect sub-test until assay sensitivity has been demonstrated.[13]

Non-inferiority in OS of HER-Vaxx plus chemotherapy versus trastuzumab plus chemotherapy will be achieved if and only if the tests for assay sensitivity and retention of effect are deemed significant at the alpha=0.025 level (after adjustment for multiple looks at the data). Given that the test for non-inferiority is a joint test, the Type I error rate of the non-inferiority hypothesis is controlled at the Type I error rates of the assay sensitivity and retention of effect sub-tests.

Analysis of safety results will follow a tiered approach (Table 5). Safety endpoints of special interest specified *a priori* are designated as "Tier 1 events" and are subjected to inferential testing. Given the good safety profiles of trastuzumab (as assessed in the Phase III ToGA and JACOB trials) and early indication of good safety of HER-Vaxx (as assessed in Phase I and II trials), there are no "Tier 1 events" for this study. Other safety parameters will be specified as "Tier 2" and "Tier 3", where Tier 2 endpoints will be assessed via point estimates with 95% confidence intervals and Tier 3 endpoints will just be provided as point estimates. Classification to "Tier 2" or "Tier 3" is in accordance with the number of events observed. Membership in Tier 2 requires at least 5 subjects in any treatment group to experience the event. Since many

confidence intervals may be supplied without adjustment for multiplicity, they should be interpreted as purely exploratory assessments of safety. Continuous measures such as changes in laboratory and vital signs will be designated as Tier 3 safety indications. 95% confidence intervals will be constructed using the Miettinen and Nurminen method.[64]

Table 5: Analysis strategy for safety parameters.

Safety Tier	Safety Endpoint	p-value	95% CI for treatment comparison	Descriptive Statistics
Tier 2	Death		X	X
	Any Grade 3-5 AE		X	X
	Any SAE		X	X
	Any Drug-Related AE		X	X
	Any Serious Drug-Related AE		X	X
	Any Grade 3-5 and Drug-Related AE		X	X
	Dose Modification due to AE		X	X
	Discontinuation due to AE		X	X
	Specific AEs >5 subjects in all treatment groups		X	X
	Infusion-related hypersensitivity reactions (nausea, pyrexia, diarrhea, chills, fatigue, headache, anaphylaxis)		X	X
	Infection-related reactions (pain, itching, swelling, cellulitis, edemas, colitis)		X	X
Tier 3	Specific AE < 5 subjects in all treatment groups			X
	Change from baseline results (Labs, Vital signs)			X

Secondary Analysis

Analysis of ORR at months 6 and 12 will be performed using conditional logistic regression.[65] Treatment arm assignment will be included as a main effect, while clinic, ECOG performance score, chemotherapy regimen, site of primary cancer, and previous gastrectomy status will be included as stratification factors. Point estimates and 95% robust CIs will be constructed to compare the odds ratio of achieving overall response at these two time points between the experimental and placebo/active control arms. No multiplicity adjustment will be made of the number of confidence intervals and number of time points. If the lower bound of the 95% robust confidence interval for the odds ratio of overall response between experimental (Her-Vaxx plus

chemo) and placebo (chemo alone) lies completely above 1, there is a suggestion that HER-Vaxx plus chemotherapy is superior to chemotherapy alone in odds of overall response at 6 or 12 months. If the odds ratio of overall response between experimental (Her-Vaxx plus chemo) and active control (trastuzumab plus chemo alone) lies completely above 0.6, then there is a suggestion that HER-Vaxx plus chemotherapy is non-inferior to chemotherapy alone in odds of overall response at 6 or 12 months.

Responses to the FACT-Ga PRO will be measured as time to deterioration of physical (GP1-7), social/familial (GS1-GS7), emotional (GE1-6), functional well-being (GF1-7), and gastric cancer specific outcomes (all GaCS questions). "Deterioration" will be defined as a consistent (observed twice at consecutive responses) 6-point drop in physical well-being, 4-point drop in emotional well-being, 6-point drop in functional well-being, and 5-point drop in social well-being defined as the upper confidence bound for clinically determined "moderate" differences in FACT-Ga PROs.[66] We define "deterioration" for the gastric cancer specific outcomes as a consistent (observed twice at consecutive responses) ≥10-point decrease in score. We also define time to deterioration of all outcomes as time until a ≥31-point decrease initial FACT-Gastric total score, which is a sum of the margins for category specific scores. We will compare deterioration probabilities using Kaplan-Meier plots along with median time to deterioration and 95% CIs. Item-level responses (abdominal pain (C5, C1, Ga5, Ga6, Ga2) and eating restrictions (C2, Ga1, HN1, Ga12, Ga4, E6, Ga10, Ga9)) may also be reported using line plots and Kaplan-Meier curves.

Similarly, responses to the PHQ-9 PRO, assessing self-reported symptoms of depression, will be analyzed using a "time to deterioration" endpoint, where "deterioration" corresponds to a sustained (twice consecutively observed across responses) 5-point increase in total score.[67] We will compare deterioration probabilities over time using Kaplan-Meier plots along with median time to deterioration and 95% CIs. The GAD-7 PRO, assessing self-reported symptoms generalized anxiety disorder, will be analyzed using a similar "time to deterioration framework", where "deterioration" is defined as a sustained 4-point decrease in GAD-7 total score.[68] We will compare deterioration probabilities over time using Kaplan-Meier plots along with median time to deterioration and 95% CIs.

Exploratory endpoints

Anti-HER2 antibody levels per within the experimental treatment arm will be visualized over time for each participant and based on clinical response characteristics using locally estimated scatterplot smoothing (LOESS) polynomial regression.

To assess heterogeneity of effects with respect to the anti-HER2 response, a Cox regression models will be fit to overall survival with an interaction between treatment arm assignment and log(antibody level) encoded as a time-varying covariate. A descriptive test of heterogeneity of effects will be assessed using a log-likelihood ratio test of the hazard ratio of the experimental arm relative to chemotherapy alone arm using robust/sandwich standard errors. Kaplan-Meier curves along with estimates and 95% CIs of median OS will be generated for experimental participants grouped by quantiles of marginal anti-HER2 antibody responses over time to further profile heterogeneity of effects.

All *post hoc* subgroups analyses of the primary endpoint should report point estimates and CIs and should be considered strictly exploratory.

ORGANIZATION & ADMINISTRATIVE PROCEDURES

Estimated Budget

The budget shown on the next page outlines the estimated cost of this clinical trial. The total cost of the phase III trial is $33.34 million. In order to get a rough estimate of our total study budget, we needed to estimate our site-specific salary budgets in China and in the US. The study intends to have a gastric cancer specialist oncologist (MD) as principal investigator, 2 Co-investigators (MD and Pharmacist), 4 research coordinators (RCs), and 4 research assistants (RAs) in Seattle at the Fred Hutchinson Cancer Center. The biostatistician support for the study will also be based at the Fred Hutch. Additionally, 3 MD co-investigators, 25 RCs and 25 RAs will be paid to coordinate the study sites in China. The budget outlined on the following page consists of salaries and fringe benefits for both study site staffs, with budget spreadsheets available on request.

The estimated cost of six cycles of chemotherapy as well as the trastuzumab and HER-Vaxx calculated based on median expected course, are shown in the table along with various tests needed for the study (Endoscopy, HER2 Screening, CT scan, and echocardiograms). Further, public transportation/parking reimbursement for all participants to and from the clinic for their 6 visits are calculated in this budget. Additionally, estimated costs of computers for the research assistants and research coordinators use and tablets for participants to complete PROs during study visits are calculated into the outline budget. We have also accounted for office supplies and publication costs in this budget.

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6	Year 7	Total
Salaries • Fred Hutch: PI, CO-PI, Biostatistician, Research coordinators, Research Assistants	$667,500	$619,300	$ 642,162	$658, 368	$635,913	$617,961	$681,024	$4,532,228
Fringe Benefits • Fred Hutch: PI, 2 CO-PI, Biostatistician, Research coordinator, Research Assistants	$161,923	$148,013	$153,477	$157, 350	$151,983	$147, 693	$162, 765	$1,083,202
Subcontract in China								
Total Salaries in China with 10% Fringe (7 years) • 3MD CO-PIs, 25 Research coordinators, 25 Research Assistants	~$1,633,500	~$1,633,500	~$1,633,500	~$1,633,500	~$1,633,500	~$1,633,500	~$1,633,501	$11,434,501
HerVaxx + Herceptin + Chemotherapies for sample size of 2600	$4,988,880 **Herceptin** cost + $1,170,000 **HER Vaxx** cost + $7,020,000 **Chemotherapies**							$13,178,880
Screening for HER 2 + Endoscopy + CT scan+ ECHO +Transportation	$3,000,000							~$3,000,000
Computers, IPAD, office supplies	$104,000							$104,000
Publication	$3,000							$3,000
Total								**$33,335,811**

Study Activation

Prior to implementation of this protocol, and any subsequent full version amendments, each site must have the protocol and the protocol consent form(s) approved, as appropriate, by their local institutional review board (IRB)/ethics committee (EC) and any other applicable regulatory entity (RE). Upon receiving final approval, sites will submit all required protocol registration documents to Fred Hutch IRBs and China sites IRBs. Pending successful protocol registration and submission of all required documents, Coordinating and Operations Center (CORE) staff will "activate" the site to begin study operations. Study implementation may not be initiated until a study activation notice is provided to the site.

Study Coordination

Assignment of all sponsor responsibilities for this study will be specified in a Clinical Trials Agreement executed by the NIH and Imugene. Study implementation will be directed by this protocol as well as the CTCAE Version 5.

Study case report forms and other study instruments will be developed by the protocol team, sponsor, and SMC. Data will be transferred to the study data management center (SCHARP) for data entry, cleaning, reporting and analysis, and referral to the IDMC and/or sponsor if the trial has reached completion. Quality control reports and queries will be generated and distributed to the study sites on a routine schedule for verification and resolution. Close coordination between protocol team members will be necessary to track study progress, respond to queries about proper study implementation, and address other issues in a timely manner.

Rates of HER2 positivity, accrual, adherence, and follow-up will be monitored closely by sponsor, study monitoring committee (SMC), as well as the independent data monitoring committee (IDMC). The Protocol Chair, Principal Investigators, Protocol Biostatistician, Project Manager, and CORE Protocol Specialist will address issues related to study eligibility and AE management and reporting as needed to assure consistent case management, documentation, and information-sharing across sites.

Study Documentation

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented, including but not limited to the protocol, protocol amendments, Informed Consent Forms, and documentation of IRB/EC and governmental approval. In addition, at the end of the study, the investigator will receive the patient data, which includes an audit trail containing a complete record of all changes to data.

Study Monitoring

On-site study monitoring will be performed in accordance with FHCC IRB policies. Study monitors will visit the site to verify compliance with human subjects and other research regulations and guidelines; assess adherence to the study protocol, study-specific procedures manual, and local counseling practices; and confirm the quality and accuracy of information collected at the study site and entered in the study database. Site investigators will allow study monitors to inspect study facilities and documentation e.g., informed consent forms, clinic and laboratory records and records of treatment. Investigators will allow inspection of all study-related documentation by authorized representatives of the product manufacturer, and in-country government and regulatory authorities in China. A site visit log will be maintained at the study site to document all visits.

Protocol Compliance

The study will be conducted in full compliance with the protocol. The protocol will not be amended without prior written approval by the Protocol Chair and PI. All protocol amendments must be submitted to and approved by the relevant IRB(s)/EC(s) and prior to implementing the amendment.

Site-specific protocol compliance – proper handling and administration of treatments, reporting of outcomes and adherence on CRFs, follow-up with participants, sufficient attention on recruitment, etc. – will be assessed through semi-frequent audits by the local and central study coordinating centers.

Sites that are non-compliant in a manner deemed significant by a coordinating-center audit will be placed on probation and subjected to more frequent review. A failure of a second compliance audit will result in termination of that study site.

FACILITIES, RESOURCES, & EQUIPMENT

Facilities

The main coordinating site for this trial will be the Fred Hutchinson Cancer Center, under the auspices of its Global Oncology Program. There will be a network of 25 sites in China who were previous participating sites in the Jacob trial (22) or are new sites (3) with existing or new working relationships with the Fred Hutchinson Cancer Center Global Oncology Program.

The Fred Hutchinson Cancer Center (Fred Hutch), home of three Nobel laureates, is an independent, nonprofit research institution dedicated to the development and advancement of biomedical research. Fred Hutch’s organizational mission is the elimination of cancer and related

diseases as a cause of human suffering and death. Fred Hutch is a world leader in advancing the prevention, diagnosis and treatment of cancer, HIV/AIDS, and other life-threatening diseases. The Fred Hutchinson Cancer Center is a member of the National Comprehensive Cancer Network and is organized into five scientific divisions: Basic Sciences, Clinical Research, Public Health Sciences, Human Biology, and Vaccine Infectious Disease. Fred Hutch has more than 2,800 scientists and staff and an annual budget of over $350 million.

Fred Hutch together with its clinical and research partner, the University of Washington (UW), comprises the Fred Hutchinson/University of Washington Cancer Consortium. The Consortium is among 40 National Cancer Institute-designated comprehensive cancer centers nationwide. Supported by 5 P30 CA015704-46 (PI: Lynch), the Fred Hutchinson/University of Washington Cancer Consortium (Consortium) brings together more than 450 members with research interests in basic, clinical, and public health sciences related to cancer. The goal of the Consortium is the elimination of cancer through more effective prevention, diagnostics, and treatment, deriving from fundamental insights into the biology of the disease. The extensive interdisciplinary collaboration between the partner institutions in the cancer research disciplines of basic, clinical, and public health sciences affords new opportunities to reduce suffering and mortality from cancer. The Consortium also supports research infrastructure that enhances collaborative, transdisciplinary research productivity. Consortium grants provide funding for formalized cancer research programs, shared research resources, scientific and administrative management, planning and evaluation activities, development of new scientific opportunities, and centralized clinical trial oversight and functions.

In addition to the local reach of Fred Hutch within the Pacific Northwest and United States, Fred Hutch scientists are actively committed to advancing research to address the burden of cancer in low-resource settings. Scientists at Fred Hutch have long acknowledged that cancer is an increasingly urgent global health issue. By 2030, the global cancer burden is projected to grow by 70 percent, and more than two-thirds of cancer deaths are occurring in low- and middle-income countries. However, only two percent of health funding in these countries is directed toward cancer. Many of the highest-burden cancers in these regions are associated with infectious diseases, including HIV, human papillomavirus, H. Pylori, and viral hepatitis. In answer to these pressing problems, the Fred Hutch Global Oncology program was born in the early 2000s. Since then, partnerships in Africa and China have led to collaborative research that is moving the needle on global cancer incidence.

Fred Hutch has a growing cross-divisional Global Oncology program that investigates globally relevant cancers and seeks to understand the varied genetics and biology of common cancers around the world. The program aims to develop high-impact, low-cost diagnostic tools and therapies that can be used in low-resource settings worldwide. Additionally, the program is an opportunity to collaborate globally to engage scientists and clinicians across the globe using the resources available at Fred Hutch. As part of its Global mission, Fred Hutch has collaborated with Chinese researchers for more than twenty years. With its large population in highly developed urban centers and its growing investments in biomedical research, China provides unique opportunities to gain insights into various health issues that affect millions of people in Asia and around the world. Fred Hutch is sharing scientific data, statistical analysis methods, and clinical research protocol development with Chinese partners in cancer care. One example of

furthering collaboration between Fred Hutch and Chinese researchers through standing partnerships with Chinese institutions is in the gastric cancer setting. Fred Hutch microbiologist Dr. Nina Salaama and Chinese partners are together researching the genetic determinants of multidrug resistance for *H. pylori*, the bacterium associated with increased risk of stomach cancer. In a pilot study published in 2018, Salaama and investigators at Zhengzhou University found that the strain of *H. pylori* may influence cancer risk. It is via continued partnerships such as these that scientific co-discovery with global partners can make a difference for the world's citizens affected by cancer.

The clinical sites in China are as follows (Bolded are centers with existing partnerships with Fred Hutch):

JACOB Sites (22)
Beijing Cancer Hospital, Beijing
The First Affiliated Hospital of Zhengzhou University, Zhengzhou
Zhongshan Hospital Fudan University, Shanghai
Fudan University Shanghai Cancer Center, Shanghai
Sun Yet-sen University Cancer Center, Guangzhou
The Affiliated Hospital of Military Medical Science, Beijing
Henan Cancer Hospital, Zhengzhou
The 81st Hospital of P.L.A., Yanggongjing
Changzhou First People's Hospital, Changzhou
Sir Run Run Shaw Hospital, School of Medicine, Shenjiang University, Hangzhou
Cancer Hospital Chinese Academy of Medical Sciences, Beijing
The First Hospital of Jilin University, Changchun
The 1st Affiliated Hospital of Nanchang, Nanchang
Affiliated Hospital of Nontong, Nantong
Jilin Cancer Hospital, Changchun
Fuzhou General Hospital, Fuzhou
General Hospital of Shenyang Military Command of PLA, Shenyang
Harbin Medical University Cancer Hospital, Harbin
Hebei Medical University Fourth Hospital, Shijiazhuang
The Affiliated Hospital of Xuzhou Medical College, Xuzhou
Third Affiliated Hospital of Third Military Medical University, Chong Qing
The First Affiliated Hospital of The Fourth Military Medical University, Xi'an

Novel Sites (3)
Affiliated Hospital of Southwest Medical University, Luzhou
Yanhua Hospital, Beijing
Tianjin Medical University, Tianjin

Resources

Administrative Support

The Principal Investigator and Co-Investigators have 100 square-foot offices located in the

Arnold Building on the Fred Hutch campus. These office spaces include a Macintosh desktop computer with high-speed internet connection and word processing and statistical software, a telephone, access to a printer, and filing facilities, with a nearby copy/scan/fax machine. The PI has committed research administration support that will assist with any administrative related tasks associated with this proposal. Additionally, all the investigators have access to in-clinic shared office space with computers, phones, fax machines, high-speed internet connection, and conference room space for meetings.

Clinical Trial Operations

Locally, the clinical trial operations for the protocol included in this proposal are supported by a team of clinical research coordinators, data coordinators, and regulatory professionals. These team members are employed by Fred Hutch and have part of their annual salary bought out by this study. The multi-site group has a history of successfully completing investigator-initiated studies in patients with gastric cancer. Meetings will take place remotely using the ZOOM platform. These meetings will be set-up on a regular schedule. Research team members from Fred Hutch are available for local administrative, scientific, and biostatistical support.

Collaborator Support

Our research group includes PIs at each of the following sites. The China-based PIs will serve as regional leads, each responsible for 7-9 sites by geography:
Fred Hutchinson Cancer Center
Tianjin Medical University, Tianjin
Sun Yet-sen University Cancer Center, Guangzhou
Henan Cancer Hospital, Zhengzhou

Laboratory Support

We estimate that the majority of participants will require HER2 testing, since HER2 testing access is highly correlated with trastuzumab access and is limited in the study region. Samples will be collected via local endoscopy or surgery and shipped to Fred Hutch for testing. At Fred Hutch, the Pathology Department provides comprehensive diagnostic pathology services and carries out research study pathologic requirements involving the gastric cancer population of the Seattle Cancer Care Alliance (SCCA). Four pathologists from the Fred Hutch Clinical Division provide the interpretation and review of pathological material from SCCA patients in the ambulatory Clinics at SCCA as well as inpatients from the University of Washington Medical Center (UWMC). In addition, the four pathologists serve as consultants for other institutions worldwide by reviewing outside pathology cases. Services available through this laboratory include surgical pathology, immunofluorescence, immunohistochemistry, special stains, and in-situ hybridization. Her2/neu testing is performed and reported according to CAP/ASCO guidelines. The laboratory's 2007 concordance rate for Her2 IHC and FISH was > 99%.

Imaging and Infusion Support

Each of the sites has imaging capability and can support study required PET/CT scans. Each site has an outpatient infusion area staffed by oncologists and registered nurses trained to deliver chemotherapy and study drugs. Each site additionally has adjacent inpatient beds where the chemotherapy and study drug can be administered should the acuity of the participants demand admission.

Institutional Support

Each of the PIs at the coordinating site has institutional support to work on this study. The PIs are encouraged to pursue investigator-initiated studies, author manuscripts, and take part in multi-institutional studies. Fred Hutch also offers discretionary funds to travel to national meetings for networking, education, and presentation and will fund the Chinese partners to do the same through their Global Oncology program.

Equipment

In addition to the office equipment described above, all centers have the clinical equipment that is needed for drug administration such as infusion chairs, infusion pumps, and clinical monitoring equipment. Each site will use their institution-specific equipment. For the patient-reported outcomes, each institution will have a designated iPad to use in clinic if the patient does not have their own device to use.

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APPENDICES

Appendix A Consent Form

Study Title for Participants: Testing the substitution of an anti-cancer drug, Her-Vaxx, instead of Herceptin, plus the usual chemotherapy treatment compared with chemotherapy alone for advanced stage gastric cancers that are HER2 positive

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Overview and Key Information

What am I being asked to do?

We are asking you to take part in a research study. This study has public funding from the National Cancer Institute (NCI), part of the National Institutes of Health (NIH) in the United States and is being done in partnership with the Fred Hutchinson Cancer Center Global Oncology program. We do research studies to try to answer questions about how to prevent, diagnose, and treat diseases like cancer.

We are asking you to take part in this research study because you have advanced gastric cancer that has spread outside your stomach, and we either know or suspect that your cancer produces a lot of a specific protein called HER2 (often called HER2+ gastric cancer). If you have not had testing for the HER2 marker to see if your gastric cancer is HER2+, we will do this test for you and pay for it to see if you are HER2+ and could participate in this research study.

Taking part in this study is your choice.

You can choose to take part, or you can choose not to take part in this study. You also can change your mind at any time. Whatever choice you make, you will not lose access to your medical care or give up any legal rights or benefits.

This document has essential information to help you make your choice. Take time to read it. Talk to your doctor, family, or friends about the risks and benefits of taking part in the study. Participating in this study will mean that you get treatments for your cancer that are paid for, but

you and your doctor will not get to choose which treatment you take. It is important that you have as much information as you need and that all your questions are answered.

Why is this study being done?

This study is being done to answer the following question:

We are doing this study because we want to find out if this new approach is better or worse than the usual approach for your kind of gastric cancer. The usual approach is defined as care most people get for gastric cancer.

What is the usual approach to my kind of gastric cancer?

The usual approach to treating HER2+ gastric cancer for people not on a research study is to give standard chemotherapy, usually with two different medicines. In parts of the world where it is available, a medicine that targets the HER2+ gene called Trastuzumab (Herceptin) is added to the two chemotherapy drugs. The chemotherapy medicines are given as intravenous infusions or intravenous infusion and pills. Trastuzumab, when it is available, is given as intravenous infusion. These medicines are given together in a schedule that restarts every three weeks (one "cycle") for at least six cycles.

What are my choices if I decide not to take part in this study?

You may choose to have the usual approach described above with chemotherapy alone.
You may choose to have the usual approach described above with chemotherapy and trastuzumab *if it is available to you* (access is limited in China).
You may choose to take part in a different research study, if one is available.
You may choose not to be treated for cancer.
You may choose to get palliative care (comfort care) to help relieve your symptoms and not get treated for your cancer.

What will happen if I decide to take part in this study?

If you decide to take part in this study, you will either get chemotherapy alone, chemotherapy plus Trastuzumab, or chemotherapy plus the study drug (Her-Vaxx). You will be randomly selected to one of the groups. The chemotherapy medicines are the same no matter what group you are randomly selected to join. The difference between the groups is the medicine to treat the HER2 overexpression: one group does not get medicine to treat the high levels of HER2 protein, one group gets the Trastuzumab to treat the high levels of HER2, and one group gets the Her-Vaxx to treat the high levels of HER2. You will receive chemotherapy for six cycles, or until your cancer becomes worse, or until side effects are too severe, or until you decide with your doctor that you no longer wish to take the study medicine. If you are getting Trastuzumab or the Her-Vaxx, you will continue to take this medicine for 18 months, or until your cancer becomes worse, or until side effects are too severe, or until you decide with your doctor that you no longer wish to take the study medicine

After you finish the study medicines, your doctor will continue to follow your condition for at least two years and watch you for side effects and treatment response at least every six months.

What are the risks and benefits of taking part in this study?

There are both risks and benefits to taking part in this study. It is important for you to think carefully about these as you make your decision.

Risks

We want to make sure you know about a few key risks right now. We give you more information in the "What risks can I expect from taking part in this study?" section.

If you choose to take part in this study, there is a risk that the Her-Vaxx may not be as good as Trastuzumab at controlling your cancer. There is also a risk that you will get assigned to the chemotherapy alone group, and therefore you will not get any medicine to treat the high levels of HER2 protein on your tumor.

There is also a risk that you could have side effects from the Her-Vaxx. These side effects may be worse and may be different than you would get with the usual approach for your cancer.

Some of the most common side effects that the study doctors know about are:
Soreness at the Her-Vaxx injection site (this medicine is given as a shot)
Redness at the Her-Vaxx injection site (this medicine is given as a shot)

There may be some risks that the study doctors do not yet know about.

Benefits

There is early evidence that this new medicine, Her-Vaxx is effective in shrinking tumors and improving survival compared to chemotherapy alone. It is not possible to know now if the Her-Vaxx will extend your life or improve your quality of life compared to the usual approach. This study will help the study doctors learn things that will help people in the future.

If I decide to take part in this study, can I stop later?

Yes, you can decide to stop taking part in the study at any time.

If you decide to stop, let your study doctor know as soon as possible. It is important that you stop safely. If you stop, you can decide if you want to keep letting the study doctor know how you are doing. Once you are a part of the research study, we can learn things that may help future patients with gastric cancer, even if you need to stop the study medication, IF you are willing that we continue to check on you and see how you are doing.

Your study doctor will tell you about new information or changes in the study that may affect your health or your willingness to continue in the study.

Are there other reasons why I might stop being in the study?

Yes. The study doctor may take you off the study if:

Your health changes and the study is no longer in your best interest.
New information becomes available, and the study is no longer in your best interest.
You do not follow the study rules.
The study is stopped by the Institutional Review Board (IRB), Food and Drug Administration (FDA), or study sponsor. The study sponsor is the organization who oversees the study.

It is important that you understand the information in the informed consent before making your decision. Please read, or have someone read to you, the rest of this document. If there is anything you don't understand, be sure to ask your study doctor or nurse.

What is the purpose of this study?

The purpose of this study is to compare the usual treatment, chemotherapy plus Trastuzumab to the usual chemotherapy plus a new medicine that targets the HER2 genetic change, called Her-Vaxx. To answer the research question, we also will compare these two treatments with chemotherapy alone. The substitution of the Her-Vaxx for the usual drug Trastuzumab could shrink your cancer. But it could also cause side effects, which are described in the risks section below.

This study will help the study doctors find out if this different approach is better than the usual approach AND make sure that both the HER2 medicines are better than chemotherapy alone. To decide if it the Her-Vaxx is better, the study doctors will be looking to see if the Her-Vaxx works as well as the Trastuzumab, and that both HER2 medicines are better than chemotherapy alone.

There will be about 2600 people taking part in this study.

Another purpose of this study is for the study doctors to learn if the level of anti-HER2 antibody (the response to the HER2 medicines) predict who does best with treatment. An extra tube of blood will be drawn at four different times during the study to test the anti-HER2 antibody levels. The study doctors do not know if using the test is helpful in predicting who does best with treatment. In the future, if we learn how to predict who does best with treatment, it might help doctors know who would most benefit from a certain medicine.

What are the study groups?

This study has three study groups. There will be more people in the Her-Vaxx group than the Trastuzumab group, and more people in the Trastuzumab group than the chemotherapy alone group. That means for every two people who are randomly chosen to be in the chemotherapy alone group, there will be three people randomly chosen to be in the Trastuzumab group, and five people randomly chosen to be in the Her-Vaxx group. You will know what group you are in.

Group 1
If you are in this group, you will get the chemotherapy medicines used to treat this type of cancer. You will get the standard chemotherapy every three weeks for a total of 6 times.

There will be about 520 people in this group.

Group 2

If you are in this group, you will get the usual drugs used to treat this type of cancer. You will get the standard chemotherapy every three weeks for a total of 6 times plus Trastuzumab for up to one year.

There will be about 780 people in this group.

Group 3

If you are in this group, you will get the chemotherapy used to treat this type of cancer plus the study drug. You will get the standard chemotherapy every three weeks for a total of 6 times plus Her-Vaxx for up to one year.

There will be about 1300 people in this group.

We will use a computer to assign you to one of the study groups. This process is called "randomization." It means that your doctor will not choose, and you cannot choose which study group you are in. You will be put into a group by chance.

You will have not have an equal chance of being in the groups because all the groups will have different numbers of people.

You have a 20% chance of being assigned to Group 1 (chemotherapy only)
You have a 30% chance of being assigned to Group 2 (chemotherapy and Trastuzumab)
You have a 50% chance of being assigned to Group 3 (chemotherapy and Her-Vaxx)

What exams, tests, and procedures are involved in this study?

Before you begin the study, your doctor will review the results of your exams, tests, and procedures. This helps your doctor decide if it is safe for you to take part in the study. If you join the study, you will have more exams, tests, and procedures to closely monitor your safety and health. Most of these are included in the usual care you would get even if you were not in a study.

Listed below are exams, tests, and procedures that need to be done as part of this study to monitor your safety and health but may not be included in the usual care. We will use them to carefully follow the effects of the study treatment, including preventing and managing side effects.

These exams, tests, and procedures to monitor your safety and health include:

Heart test (echocardiogram) if there are any new heart symptoms
CT scan every 6 months for the first two years, then once a year for three years

Some exams, tests, and procedures are a necessary part of the research study but would not be included in usual care. Listed below are procedures that will be done for research purposes only.

Use of Existing Tissue Specimen

The research team would like to keep some of the tissue left over from your biopsy when you were diagnosed with cancer. This sample is an optional part of the study. This is not a new biopsy but is only if any leftover tissue samples are available from your gastric cancer biopsies. The purpose would be to do future testing to learn more about gastric cancer. You can say yes or no to providing the study doctor with these samples and still participate in the rest of the study. You and your study doctor will not get the results of this testing.

- ❑ YES, you can use my existing leftover tissue specimens if they are available
- ❑ NO, you can NOT use my existing leftover tissue specimens if they are available

Patient Surveys

If you choose to take part in this study, you will be asked to fill out a form with questions about your physical and mental health and functioning. Researchers will use this information to see if quality of life and problems related to the medicine are different in the three study groups. Since these forms are being used for research, the responses you provide will not be shared with your doctor. If you have any serious health issues or other concerns, please talk with your doctor or nurse right away.

You will be asked to fill out this form 13 times:
After you consent to the trial and before you are randomly put in a group (1)
Every month for the first six months of the trial (6)
Every three months for two years (6)

Each form will take about 20-30 minutes to complete. The forms will ask about things like tiredness, diarrhea, appetite, feeling depressed or anxious, and your ability to work. You don't have to answer any question that makes you feel uncomfortable. The form will be available to do electronically with a secure, confidential program (REDCap). You will be asked if you want to do your form at home or in the clinic. If you do the form at home, you will get a reminder when it is time to click on the secure link and complete your form. You can choose to get a reminder via text or email or both. If you would rather do your form at the clinic, we have an iPad you can use, and we will remind you when it is time for the form.

What risks can I expect from taking part in this study?

General Risks

If you choose to take part in this study, there is a risk that the chemotherapy plus Her-Vaxx may not be as good as chemotherapy plus Trastuzumab at controlling your cancer. There is also the risk that you will be put in the group that gets chemotherapy alone. Even though research has shown already that chemotherapy + Trastuzumab is better than chemotherapy alone, Trastuzumab is not widely available in China.

You also may have the following discomforts:

Spend more time in the clinic or doctor's office.
Be asked sensitive or private questions about things you normally do not discuss.
May not be able to take part in future studies.

The medicines used in this study could be very harmful to an unborn or newborn baby. There may be some risks that doctors do not yet know about. It is very important that you check with your study doctor about what types of birth control or pregnancy prevention to use during the study and after you have completed the study.

Side Effect Risks

The Her-Vaxx used in this study may affect how different parts of your body work such as your liver, kidneys, heart, and blood. In prior studies with Her-Vaxx, there has been no organ damage. The study doctor will test your blood and let you know if changes occur that may affect your health.

There is also a risk that you could have other side effects from the study medication.

Here are important things to know about side effects:

The study doctors do not know who will or will not have side effects.
Some side effects may go away soon, some may last a long time, and some may never go away.
Some side effects may be mild. Other side effects may be very serious and even result in death.

You can ask your study doctor questions about side effects at any time. Here are important ways to make side effects less of a problem:

If you notice or feel anything different, tell your study doctor. They can check to see if it is a side effect.
Your study doctor will work with you to treat your side effects.
Your study doctor may adjust the study drugs to try to reduce side effects.

This study is looking at a combination of the usual drugs used to treat this type of cancer plus a study drug. This different combination of drugs may increase your side effects or may cause new side effects.

Drug Risks

The tables below show the most common and most serious side effects doctors know about. Keep in mind that there might be other side effects doctors do not yet know about. If important new side effects are found, the study doctor will discuss these with you.

Study Group 1, Group 2, and Group 3 – Possible side effects of standard chemotherapy are listed in the tables below. These drugs are part of the usual approach for treating this type of cancer:

Possible Side Effects of Standard Chemotherapy (Cisplatin and Fluorouracil or Capecitabine)
(Table Version Date: May 23, 2022)

COMMON, SOME MAY BE SERIOUS In 100 people receiving standard chemotherapy with cisplatin and fluorouracil or capecitabine, more than 10 and up to 100 may have:
Nausea Vomiting Bruising and bleeding Anemia (low red blood cells) that might cause fatigue Sores in the mouth Hair loss Diarrhea Changes in the way the kidneys work Changes in the heart rhythm Sore hands and feet Hearing changes Infection

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving standard chemotherapy with cisplatin and fluorouracil or capecitabine, from 1 to 10 may have:
Ringing in the ears Taste changes Skin changes and rashes and skin sensitive to sun Nail changes Gritty or sore eyes and blurred vision Numbness or tingling in the hands and feet which may be permanent

RARE, AND SERIOUS In 100 people receiving standard chemotherapy with cisplatin and fluorouracil or capecitabine, 3 or fewer may have:
Damage to the heart which may cause shortness of breath Kidney damage which may require dialysis A new cancer resulting from treatment of a prior cancer

RARE, AND SERIOUS In 100 people receiving standard chemotherapy with cisplatin and fluorouracil or capecitabine, 3 or fewer may have:
Devere redness, pain or peeling of palms and soles

Study Group 2 - In addition to side effects listed above for chemotherapy (Group 1 AND Group 2 AND Group 3), people who are in Group 2 may also have some side effects from Trastuzumab. These side effects are listed below.

Possible Side Effects of Trastuzumab
(Table Version Date: May 16, 2022)

COMMON, SOME MAY BE SERIOUS In 100 people receiving Trastuzumab, more than 25 and up to 100 may have:
Weakness Fever Headache Diarrhea Pain Chills Nausea Cough

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving trastuzumab, from 10 to 24 may have:
Abdominal pain Back pain Loss of appetite Dizziness Shortness of breath Infection Vomiting Trouble sleeping Skin rash Skin sores Allergy-like symptoms such as sneezing, nasal stuffiness, and post-nasal drip

RARE, AND SERIOUS In 100 people receiving trastuzumab, 3-9 may have:
Damage to the heart which may cause a decreased ability for the heart to pump blood Allergic reaction during the infusion which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat Flu-like symptoms Blood tests that show changes in liver function Swelling

RARE, AND SERIOUS In 100 people receiving trastuzumab, 3-9 may have:
Rapid or irregular heartbeat Depression Temporary nerve problems Sore throat Pain in the chest Pain in the muscles, bones, and joints

Study Group 3 - In addition to side effects listed above for chemotherapy (Group 1 AND Group 2 AND Group 3), people who are in Group 3 may also have some side effects from Her-Vaxx.

Possible Side Effects of Her-Vaxx
(Table Version Date: May 16, 2022)

COMMON, SOME MAY BE SERIOUS In 100 people receiving Her-Vaxx, more than 25 and up to 100 may have:
None known at this time

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving Her-Vaxx, from 10 to 24 may have:
Redness at injection site Itching at injection site

RARE, AND SERIOUS In 100 people receiving Her-Vaxx, 3 to 9 or fewer may have:
Blood tests that show low protein Blood test that shows low sodium

What are my responsibilities in this study?

If you choose to take part in this study you will need to:

Keep your study appointments.
Complete the research forms at the right times.
Tell your doctor about:
all medications and supplements you are taking,
any side effects,
any doctors' visits or hospital stays outside of this study, and
if you have been or are currently in another research study.

For women: Do not get pregnant or breastfeed while taking part in this study. **For men:** Do not father a baby while taking part in this study. **For all:** Tell your study doctor right away if you think that you or your partner have become pregnant during the study.

What are the costs of taking part in this study?

The study will pay for the costs of the medicines and tests you get as part of the study. You will not have to pay for exams, tests, and procedures done for research purposes only or that are covered by the study. You will pay for health care that is not related to the study.

Ask your doctor or nurse for help finding the right person to talk to if you are unsure which costs will be billed to you.

Taking part in this study may mean that you need to make more visits to the clinic or hospital than if you were getting the usual approach to treating your cancer. You may:

Have more travel costs.
Need to take more time off work.
Have other additional personal costs.

You will not be paid for taking part in this study. The research may lead to new tests, drugs, or other products for sale. If it does, you will not get any payment. The study staff will make every attempt to schedule study procedures around routine care. If at some point you are asked to come to the clinic for a study activity outside of a regular clinic visit, we will reimburse you for transportation up to 100 CNY/day.

What happens if I am injured because I took part in this study?

If you are injured as a result of taking part in this study and need medical treatment, please talk with your study doctor right away about your treatment options. The study sponsors will not pay for medical treatment for injury.

If you feel this injury was caused by medical error on the part of the study doctors or others involved in the study, you have the legal right to seek payment, even though you are in a study. Agreeing to take part in this study does not mean you give up these rights.

Who will see my medical information?

Your privacy is very important to us. The study team will make every effort to protect it. The study doctors have a privacy permit to help protect your records if there is a court case. However, some of your medical information may be given out if required by law. If this should happen, the study doctors will do their best to make sure that any information that goes out to others will not identify who you are.

Some of your health information, such as your response to cancer treatment, results of study tests, and medicines you took, will be kept by the study sponsor in a central research database. However, your name and contact information will not be put in the database. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used.

There are organizations that may look at or receive copies of some of the information in your study records. Your health information in the research database also may be shared with these organizations. They must keep your information private, unless required by law to give it to another group.

Some of these organizations are:

The study sponsor and any company supporting the study now or in the future.
The Fred Hutchinson IRB, which is a group of people who review the research with the goal of protecting the people who take part in the study.
The FDA and the groups it works with to review research.
The NCI and the groups it works with to review research.

In addition to storing data in the study database, data from studies that are publicly funded may also be shared broadly for future research with protections for your privacy. The goal of this data sharing is to make more research possible that may improve people's health. Your study records may be stored and shared for future use in public databases. However, your name and other personal information will not be used.

Some types of future research may include looking at your information and information from other patients to see who had side effects across many studies or comparing new study data with older study data. However, right now we don't know what research may be done in the future using your information. This means that:
You will not be asked if you agree to take part in the specific future research studies using your health information.
You and your study doctor will not be told when or what type of research will be done.
You will not get reports or other information about any research that is done using your information.

My signature agreeing to take part in the study

I have read this consent form or had it read to me. I have discussed it with the study doctor and my questions have been answered. I will be given a signed and dated copy of this form. I agree to take part in the main study.

Participant's signature

Date of signature

Signature of person(s) conducting the informed consent discussion

Date of signature

Appendix B: CRF HER2 testing form

HEADER: PI NAME, Protocol or IRB Number, SITE CODE, Protocol Short Title

Subject Initials ☐☐☐ **Subject ID** ☐☐☐☐☐ **Date:** ☐☐ ☐☐ ☐☐
Month Day Year

HER2-Testing Result CRF

Select single response unless otherwise indicated.

RESULTS:

HER2 (by immunohistochemistry, using Rüschoff/Hoffman Criteria):

___ Negative (score 0)
___ Negative (score 1þ)
___ Equivocal (score 2þ)
___ Positive (score 3þ)
___ Indeterminate (explain): _____

HER2 (ERBB2) (by in situ hybridization):

___ Negative (not amplified)
___ Positive (amplified)
___ Indeterminate (explain): _____
Number of observers: _____
Number of invasive cancer cells counted: _____
___ Using dual-probe assay
Average number of HER2 (ERBB2) signals per cancer cell: _____
Average number of CEP17 signals per cancer cell: _____
HER2 (ERBB2):CEP17 ratio: _____
___ Using single-probe assay
Average number of HER2 (ERBB2) signals per cancer cell: _____

METHODS CONT. ON NEXT PAGE

HEADER: PI NAME, Protocol or IRB Number, SITE CODE, Protocol Short Title

METHODS:

HER2 (by immunohistochemistry):

___ US FDA cleared (specify test/vendor): _____
___ Laboratory-developed test

Primary Antibody
___ 4B5
___ HerceptTest
___ A0485
___ SP3
___ CB11
___ Other (specify): _____

HER2 (ERBB2) (by in situ hybridization):

___ US FDA cleared (specify test/vendor): _____
___ Laboratory-developed test (specify probe): _____

Form Completed by: _____ Date: _____

Pathologist Signature: _____ Date: _____

Site PI Signature: _____ Date: _____

Appendix C: Case Report Forms

HEADER: PI NAME, Protocol or IRB Number, Protocol Short Title

Clinic No: ☐☐☐ **Patient ID:** ☐☐☐☐☐ **Date:** ☐☐ / ☐☐ / ☐☐
Month Day Year

Demographics

First Name*:
Middle Name (or initial):
Last Name*:

Birthdate*: ☐☐ / ☐☐ / ☐☐☐☐
Month Day Year

Gender*: (check one)
☐ **Male**
☐ **Female**
☐ **Unknown or Not Reported**

Ethnicity*: (check one)
☐ **Hispanic**
☐ **Non-Hispanic**
☐ **Unknown or Not Reported**

Race*: (check all that apply)
☐ **American Indian or Alaska Native**
☐ **Asian**
☐ **Black or African American**
☐ **Native Hawaiian or Other Pacific Islander**
☐ **White or Caucasian**
☐ **Unknown or Not Reported**

Other Medical Record Number(s):

Medical Record Number	Hospital/Care Provider (e.g. VA Hospital, Meriter Hospital, EPIC)

Contact Information:

Address:		**Unit #:**
City:	**State:**	**Zip:**
Phone Number: ☐ Home ☐ Work ☐ Cell ☐ Other	**Alternate Phone Number:** ☐ Home ☐ Work ☐ Cell ☐ Other	**Email address:**
Preferred method of contact:		

Emergency Contact:

Name:		
Address:		**Unit #:**
City:	**State:**	**Zip:**
Phone Number: ☐ Home ☐ Work ☐ Cell ☐ Other	**Alternate Phone Number:** ☐ Home ☐ Work ☐ Cell ☐ Other	**Email address:**
Preferred method of contact:		

*indicates required field

Form Completed By: _____ **Date:** _____

FRED HUTCH

Clinic No: ☐☐☐☐ **Patient ID:** ☐☐☐☐☐☐ **Date:** ☐☐ / ☐☐ / ☐☐
Month Day Year

Eligibility Criteria

Inclusion Criteria

Patients who meet *all* of the following criteria are eligible for enrollment as study participants:

	Yes	No
1. Adult (≥18 years old) patient with stage III/IV gastric/GEJ cancer		
2. Diagnosed with HER2 positive based on IHC (result is 2+ or 3+) and FISH positive (If IHC value is 2+)		
3. Karnovsky Performance Score of ≥60% or an ECOG performance score of ≤ 2		

Exclusion Criteria

Patients who meet *any* of these criteria are *not* eligible for enrollment as study participants:

	Yes	No
4. Previous chemotherapy/anti-HER therapy for metastatic disease		
5. Previous anti-HER treatment		
6. Karnovsky performance score <60% and ECOG score >2		
7. Baseline left ventricular ejection fraction (LVEF) of less than 55%		
8. Life expectancy of less than 3 months		
9. History of congestive heart failure		
10. History of angina pectoris requiring treatment		
11. History of myocardial infarction within 6 months of the first study dose		
12. History of clinically significant valvular heart disease		
13. History of uncontrollable high-risk cardiac arrhythmia		
14. History or evidence of poorly controlled hypertension		
15. History of other serious cardiac conditions		

Form Completed by: _____ Date: _____

Site PI Signature: _____ Date: _____

Clinic No: ☐☐☐☐ **Patient ID:** ☐☐☐☐☐☐ **Date:** ☐☐/☐☐/☐☐

Insert question to ask participant:
Are you currently taking any medications (prescription, over the counter, vitamins, minerals, supplements), or non-drug therapy?

Concomitant Medication Log

#	Medication/ Non-drug Therapy	Indication	Dose (per admin)	Dose Units[1]	Schedule/ Frequency[2]	Dose Form[3]	Route of Administration[4]	Start Date	End Date	Baseline Med (Y/N)	Continuing at end of study (Y/N)

Dose Units[1]
1 - g (gram)
2 - mg (milligram)
3 - µg (microgram)
4 - L (liter)
5 - mL (milliliter)
6 - IU (International Unit)
7 - Other

Schedule (frequency)[2]
1 - QD (once a day)
2 - BID (twice a day)
3 - TID (three times a day)
4 - QID (four times a day)
5 - QOD (every other day)
6 - QM (every month)
7 - QOM (every other mo)
8 - QH (every hour)
9 - AC (before meals)
10 - PC (after meals)
11 - PRN (as needed)
12 - Other

Dose Form[3]
1 - Tablet
2 - Capsule
3 - Ointment
4 - Suppository
5 - Aerosol
6 - Spray
7 - Suspension
8 - Patch
9 - Gas
10 - Gel
11 - Cream
12 - Powder
13 - Implant
14 - Chewable
15 - Liquid
99 - Other

Route of Administration[4]
1 - Oral
2 - Topical
3 - Subcutaneous
4 - Intradermal
5 - Transdermal
6 - Intraocular
7 - Intramuscular
8 - Inhalation
9 - Intravenous
10 - Intraperitoneal
11 - Nasal
12 - Vaginal
13 - Rectal
14 - Other

Clinic No: ☐☐☐☐ **Patient ID:** ☐☐☐☐☐☐ **Date:** ☐☐ / ☐☐ / ☐☐
Month Day Year

Vital Sign Measurements (Standard)

☐ *Vital Sign Measurements not performed*

Visit Number (check one)**:**

☐ Visit # ☐ Visit #
☐ Visit # ☐ Visit #
☐ Visit # ☐ Visit #

Height: ☐☐.☐ inches ☐ *Height not measured*

Weight: ☐☐☐.☐ lbs ☐ *Weight not measured*

Time: ☐☐ : ☐☐ (using 24 hour format of hh:mm)

Temperature: ☐☐☐.☐ Fahrenheit ☐ *Temperature not measured*

Method: (check one) ☐ Oral ☐ Axillary ☐ Tympanic

Respiratory Rate: ☐☐ breaths/min ☐ *Respiratory Rate not measured*

Heart Rate: ☐☐☐ beats/min ☐ *Heart Rate not measured*

Systolic Blood Pressure ☐☐☐ mmHg ☐ *Blood Pressure not measured*

Diastolic Blood Pressure ☐☐☐ mmHg

Method: (check one) ☐ Manual ☐ Automated

Location: (check one) ☐ Left Arm ☐ Right Arm

Position: (check one) ☐ Sitting ☐ Supine ☐ Standing

Additional Notes: _____

_____

_____

Vital Sign Measurements obtained by: _____

FRED HUTCH

HEADER: IRB Number, Title, PI

Clinic No: ☐☐☐☐ **Patient ID:** ☐☐☐☐☐☐ **Date:** ☐☐/☐☐/☐☐

Electrocardiogram Results

Date: ☐☐/☐☐/☐☐ (Month / Day / Year) ☐ *Electrocardiogram not performed*

Time: ☐☐:☐☐ (using 24 hour format) (e.g. hh:mm)

Visit Number (check one)**:**

☐ Visit #	☐ Visit #	☐ Visit #
☐ Visit #	☐ Visit #	☐ Visit #
☐ Visit #	☐ Visit #	☐ Visit #

Position of Subject: ☐ Sitting ☐ Supine

ECG Measurement/Result

			(check one)		(check one)	
Heart Rate	☐☐☐	bpm	☐ Normal ☐ Abnormal	*Clinically significant?*	☐ Yes	☐ No
PR Interval	☐☐☐	msec	☐ Normal ☐ Abnormal	*Clinically significant?*	☐ Yes	☐ No
QRS Duration	☐☐☐	msec	☐ Normal ☐ Abnormal	*Clinically significant?*	☐ Yes	☐ No
QTc Interval	☐☐☐	msec	☐ Normal ☐ Abnormal	*Clinically significant?*	☐ Yes	☐ No

Cardiac Rhythm: (check one or check all that apply)

☐ Normal Sinus Rhythm	☐ Atrial Flutter	☐ Sinus Tachycardia
☐ Atrial Fibrillation	☐ Type I Second Degree AV Block	☐ SupraVentricular Tachycardia
☐ First–degree AV Block	☐ Type II Second Degree AV Block	☐ Third Degree AV Block
☐ Ventricular Tachycardia	☐ Ventricular Fibrillation	☐ Paced Rhythm
☐ Sinus Bradycardia	☐ Other: (specify)	☐ Other: (specify)

Overall assessment ☐ Normal ☐ Abnormal *Clinically significant?* ☐ Yes ☐ No

ECG done by:

ECG read by:

Comment(s):

FRED HUTCH

Clinic No: ☐☐☐ **Patient ID:** ☐☐☐☐☐☐ **Date:** ☐☐/☐☐/☐☐

Drug Dispensation & Accountability Log

		Dispensed to Subject					Returned by Subject				Compliance		
Lot Number(s)	Randomization Number	Number of Containers Dispensed	Number of Units Dispensed	Date Dispensed	Dispensed by (staff initials)	Expected Date of First Dose	Number of Containers Returned	Number of units returned	Date Returned	Verified by (staff initials)	*Actual* number of units used/taken	*Estimated* number of units to be used/taken	% compliance*

#	Date Reported	Adverse Event Description	Adverse Event** *(Select from Safety Profiler)*	Start Date	End Date	Ongoing (Y or N)	Outcome[1]	Severity/ Grade[2]	Serious (Y or N)	AE Treatment[3]	Expected (Y or N)	Study Attribution[5]	Action Taken[4]	Drug/Device Attribution[5^]	PI Initials	Date of PI Initials

- AE number. "1" indicates the first adverse event documented on the form, 2 = the second, etc. If the adverse event changes in severity, enter it as a separate adverse event row on the paper form using the same AE number as the one that ended.

**look up corresponding AE at: https://safetyprofiler-ctep.nci.nih.gov/

Outcome[1]
0 – Fatal
1 – Not recovered/not resolved
2 – Recovered w/sequelae
3 – Recovered w/o sequelae
4 – Recovering/Resolving

Severity/Grade[2]
1 – Mild
2 – Moderate
3 – Severe
4 – Life Threatening
5 – Death (Fatal)

AE Treatment[3]
0 – None
1 – Medication(s)
2 – Non-medication TX

Action Taken[4] with Study Intervention
0 – None
1 – Interrupted
2 – Discontinued
3 – Dose reduced
4 – Dose increased
5 – Not Applicable

Attribution/ Relatedness[5]
0 – Definite
1 – Probable
2 – Possible
3 – Unlikely
4 – Unrelated
^5 – Not Applicable (did not receive intervention)

Clinic No: ☐☐☐ **Patient ID:** ☐☐☐☐☐☐ **Date:** ☐☐ / ☐☐ / ☐☐
Month Day Year

Subject Off Study

Date subject went Off Study: ☐☐ / ☐☐ / ☐☐
Month Day Year

Last Visit Completed:

☐ Visit # ☐ Visit # ☐ Visit #
☐ Visit # ☐ Visit # ☐ Visit #
☐ Visit # ☐ Visit #

INDICATE OFF STUDY REASON: (select only one)

☐ Study Activities Completed

If the subject was withdrawn prior to completing the study (i.e. early withdrawal), select one of the following:

☐ Subject withdrawn – by Subject PRIOR to enrollment**
☐ Subject withdrawn – by Subject AFTER enrollment**
☐ Subject withdrawn – by PI PRIOR to enrollment**
☐ Subject withdrawn – by PI AFTER enrollment**
☐ Death
☐ Other**

If the subject was withdrawn, indicate specific reason(s): (select all that apply)

☐ Subject lost to follow-up
☐ Subject refused follow-up
☐ Due to adverse events or complications
☐ Other**

**Additional explanation required:

_____
_____
_____

FORM COMPLETED BY: _____

HEADER: IRB Number, Title, PI

Note To File

Applicability: *Include subject ID(s) if NTF pertains to a particular subject or subjects*

RE:

Written by: _____

Date: __ __ / __ __ / __ __ __ __

Explanation of Event/Issue:

Description of the issue/process/problem being documented, including (if applicable) how, when, and by whom the issue was identified, cause of issue (if known), corrective and preventive actions taken (when and by whom).

Description of related forms/documents *(if applicable)*:

Author's Signature _____ Date _____

PI's Signature _____ Date _____

Note to File Guidance:

Notes to the Study File are written to acknowledge a discrepancy or problem with the study's conduct, or for other administrative purposes (such as to document where study materials are stored). Notes to the Study File should be written by the individual responsible for its content, and the author should sign and date the note. If the Note to Study File pertains to an item for which the PI is responsible (subject protection, data integrity, etc.), the PI should co-sign and date the note to acknowledge his/her awareness of the issue. Notes to the Study File should be kept on file in the study records and made available to study monitors or auditors reviewing the site's documents and procedures.

Appendix D: Additional Sites to Enroll under Suboptimal Accrual

The following sites have participated in a multi-site gastric cancer trial (EVIDENCE trial) and will be approached to enroll in the study if accrual does not meet thresholds.

EVIDENCE Sites
Anyang Tumor Hospital, Anyang
Cancer Hospital Chinese Academy of Medical Sciences, Beijing
Peking University First Hospital, Beijing
The Affiliated Hospital of Military Medical Sciences (307th Hospital of Chinese PLA), Beijing
Peking University Third Hospital, Beijing
General Hospital of Chinese PLA; Department of Hematology, Beijing
The First Hospital of Jilin University, Changchun
Hu Nan Provincial Cancer Hospital, Changsha
The Second Xiangya Hospital of Central South University, Changsha
Sichuan Provincial Cancer Hospital, Chengdu
West China Medical Center; Center for Gastrointestinal Cancer, Chengdu
Sichuan Provincial People's Hospital, Chengdu
The First People's Hospital of Foshan, Foshan
The First Affiliated Hospital of Fujian Medical University, Fuzhou
Fujian Provincial Hospital, Fuzhou
Fujian Medical University Union Hospital, Fujian
The First Affiliated Hospital, Sun Yat-sen University, Guangzhou
Nanfang Hospital, Southern Medical University, Guangzhou
Guizhou Provincial People's Hospital, Guiyang
Guizhou Cancer Hospital, Guiyang
Hainan provincial people's hospital, Haikou
Cancer Hospital of Hangzhou (Wushan District), Hangzhou
Hangzhou First People's Hospital, Hangzhou
The First Affiliated Hospital of Anhui Medical University, Hefei
Inner Mongolia People's Hospital, Hohhot
Affiliated Hospital of Inner Mongolia Medical College, Hohhot
The First Affilliated Hospital of Kunming Medical College, Kunming
The First People's Hospital of Yunnan Province, Kunming
Yunnan Cancer Hospital, Kunming
The First Affiliated Hospital of Lanzhou University, Lanzhou
Gansu Cancer Hospital, Lanzhou
Taizhou Hospital of Zhejiang Province, Linhai
The First Affiliated Hospital of Henan UN of Science and Technology, Luoyang
The Second Affiliated Hospital to Nanchang University, Nanchang
Jiangxi Cancer Hospital; First department of abdominal surgery, Nanchang
Affiliated Hospital of North Sichuan Medical College, Nanchong
Nanjing 1st Hospital; Endocrinology Dept., Nanjing
Jiangsu Cancer Hospital, Nanjing
Jiangsu Province Hospital, Nanjing
Nan Tong Tumor Hospital, Nantong

The Affiliated Hospital of Medical College Qingdao University, Qingdao
Ruijin Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai
Renji Hospital Affiliated to Shanghai Jiao Tong University School of Medicine, Shanghai
Changhai Hospital of Shanghai, Shanghai
Changhai Hospital; Oncology, Shanghai
Shaoxing People's Hospital, Shaoxing
Liaoning cancer Hospital & Institute, Shenyang
Hebei Medical University Fourth Hospital; (Tumor Hospital of Hebei Province), Shijiazhuang
First Affiliated Hospital of Soochow University, Suzhou
Shanxi Province Cancer Hospital, Taiyuan
The Tumor Hospital of Xinjiang Medical University, Urumqi
The First Teaching Hospital of Xinjiang Medical University, Urumqi
The 2nd Affiliated Hospital & Yuying Children's Hospital of Wenzhou Medical Coll., Wenzhou
Xiehe Hospital, Tongji Medical College Huazhong University of Science & Technology, Wuhan
Tongji Hosp, Tongji Med. Col, Huazhong Univ. of Sci. & Tech, Wuhan
Zhongnan Hospital of Wuhan University, Wuhan
Hubei Cancer Hospital, Wuhan
Wuxi No.4 People's Hospital, Wuxi
The 2nd Affiliated Hospital of The Fourth Military Medical University (Tangdu Hospital), Xi'an
The First Affiliated Hospital of Xiamen University, Xiamen
Zhongshan Hospital Xiamen University, Xiamen
Xinxiang Central Hospital, Xinxiang
Northern Jangsu People's Hospital, Yangzhou
Zhangzhou Municipal Hospital of Fujian Province, Zhangzhou
Henan Provincial People's Hospital, Zhengzhou
Henan Cancer Hospital, Zhengzhou
Affiliated Hospital of Jiangsu University, Zhenjiang