MSK PROTOCOL COVER SHEET

A Phase 2 Trial of ZW25 in HER2 Overexpressed Advanced Endometrial Cancers and Carcinosarcomas (ZW25-IST-2)

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1.0 PROTOCOL SUMMARY AND/OR SCHEMA

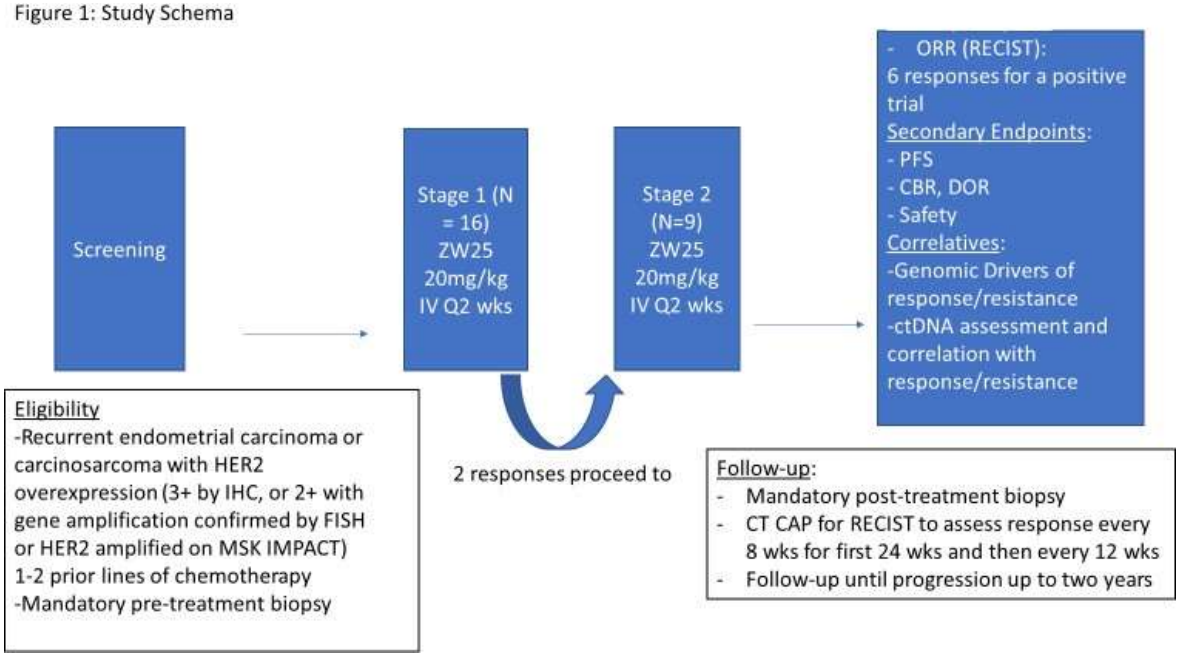
This is a Phase 2, open label study designed to evaluate the efficacy and safety of ZW25 in patients with advanced/recurrent HER2 overexpressed endometrial cancers and carcinosarcomas. Up to 25 patients will be enrolled on this study.

The study will be conducted in two stages. Stage 1 will accrue 16 patients and if two or greater responses are seen, Stage 2 will accrue an additional 9 patients. In this study the recommended ZW25 dose will be 20mg/kg intravenously (IV) every two weeks. Treatment cycles will be 28 days.

Patients will continue to receive study treatment until they present with progressive disease (PD) per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1, develop unacceptable toxicity or withdraw consent, whichever comes first, or until the study is terminated.

Tumor assessments, including radiological assessments by computerized tomography (CT) or magnetic resonance imaging (MRI) scans are performed at Screening and subsequently every eight weeks (from Cycle 1 Day 1) for the first 24 weeks and then every twelve weeks until PD, death or initiation of subsequent anti-cancer therapy, whichever occurs first. All patients who discontinue study treatment for any reason are followed every 3 months until death, lost to follow up, or withdrawal of consent, for survival follow up for up to 2 years.

Figure 1: Study Schema



Abbreviations – IV: intravenous, ORR: Overall response rate, PFS: Progression-free survival, OS: Overall survival, CBR: Clinical benefit rate, DOR: Duration of response

2.0 OBJECTIVES AND SCIENTIFIC AIMS

Primary Objective:

- To determine Overall Response Rate [ORR = Complete Response (CR) + Partial Response (PR)] by RECIST v 1.1 ≤ 24 weeks from the start of treatment

Secondary Objectives:

- To determine Progression Free Survival (PFS) rate at 24 weeks
- To determine Clinical Benefit Rate (CBR) by 24 weeks
- To determine PFS and Overall Survival (OS)
- To determine Duration of Response (DOR)
- To determine the rate of Serious Adverse Events (SAE) of ZW25 by Common Terminology Criteria for Adverse Events version 5 (CTCAE v 5.0)

Exploratory Objectives:

1. Anti-drug antibodies (ADA) will be assessed at baseline (baseline ADA can be collected on C1D1 pre dose) and pre-dose at Cycles 2, 4, 6, 8, 12, 18, 24 Day 1. The immunogenicity testing will be performed using validated assays in 3 steps as follows: screening assay (Tier 1), confirmation assay (Tier 2), and titration (Tier 3). Only samples positive in the screening assay will be tested in confirmation and further titrated to determine the titer of ADA.
2. To explore the molecular associations between the *HER2* biomarkers: gene amplification (by Next Generation Sequencing [NGS] and in situ Hybridization [ISH]), protein overexpression by immunohistochemistry (IHC) and mutational status and/or copy # variations of relevant cancer-related genes using MSK-IMPACT platform in all patients with new research biopsies collected under this protocol, and to determine mechanisms of underlying response and resistance. Mandatory pre-treatment and post-treatment (collected upon progression of disease) tumor biopsies will be obtained on all patients for this purpose. Tissue testing will be performed in the Center for Molecular Oncology.
3. To examine ORR in each cohort by different types of molecular alterations, HER2 amplification (by NGS and ISH separately), mutation and HER2 overexpression, and assess genomic changes with response for potential predictive signatures.
4. To evaluate the predictive value of changes in circulating tumor DNA variant allele frequency during treatment for response to ZW25.

3.0 BACKGROUND AND RATIONALE

HER2 DEPENDENCY

HER2 is a member of the EGFR/ErbB family comprising 4 structurally related receptors: HER1 (EGFR), HER2, HER3, and HER4. HER receptors are normally activated by binding to specific ligands, resulting in a conformational change that allows formation of receptor homodimers and heterodimers. Receptor dimerization triggers autophosphorylation of specific tyrosine residues and activation of intracellular signaling pathways (1). HER2 is unique among HER family members in that it has no known ligand, and maintains a dimerization-ready conformation. HER2 is the preferred dimerization partner for other HER family members. HER2-containing heterodimers, particularly HER2/HER3, deliver the most potent growth signals (2).

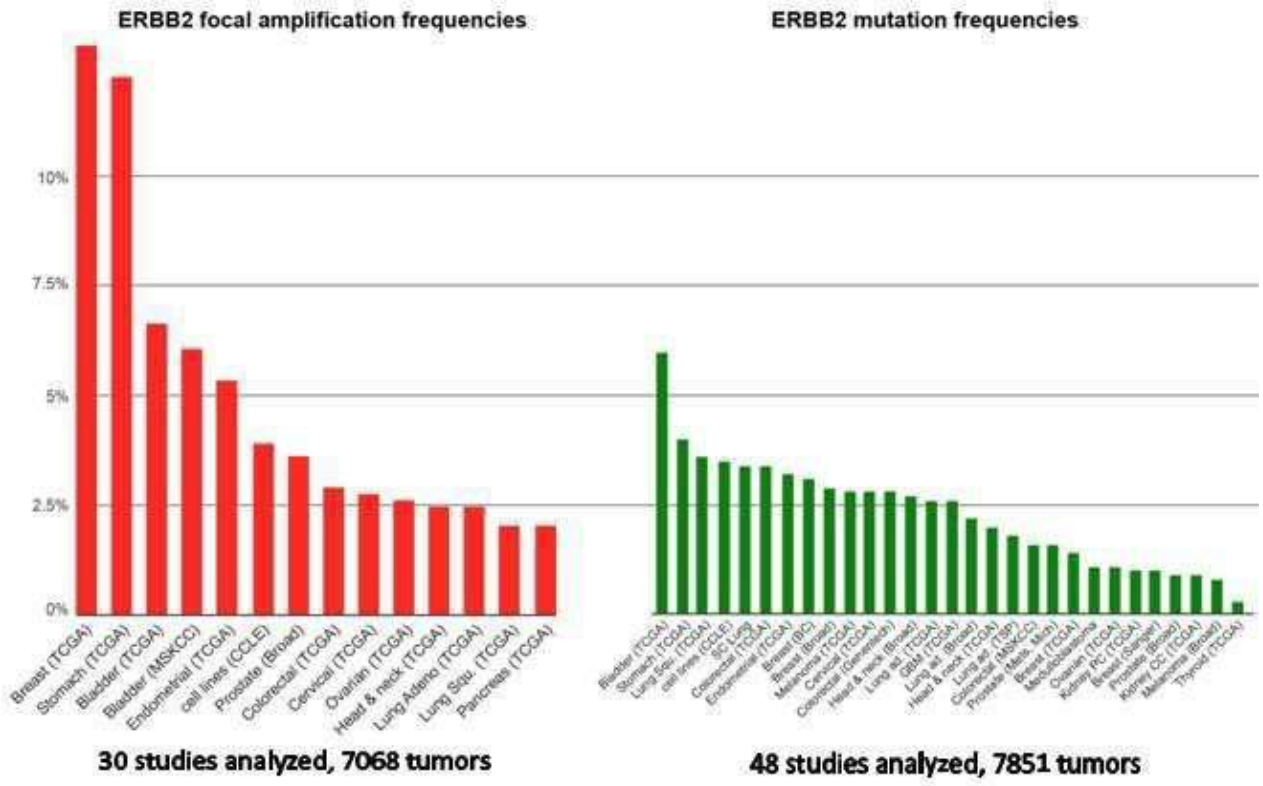
The HER2 gene, which encodes a member of the erbB family of receptor tyrosine kinase, has been described as a key oncogenic driver in numerous malignancies. HER2 amplification is an oncogenic driver event which is found in approximately 20% of breast cancers and the successful application of HER2 targeted therapy in phase 3 randomized controlled trials has revolutionized the care and altered prognosis of these patients (5, 25, 27, 35, 36). Additionally, approximately 15-20% of gastroesophageal cancers are HER2 amplified and the addition of trastuzumab to chemotherapy in these patients was shown to improve overall survival (6). Databases from The Cancer Genome Atlas (TCGA), our institution and others have demonstrated HER2 amplifications in a variety of solid tumor cancers, including lung, bladder, endometrial and other cancers (Figure 1) (7-13 , 37, 38). HER2 amplification occurs in 2-10% of lung cancers, 6% of bladder cancers, 5-12% of endometrial cancers and 2-5% of ovarian and colorectal cancers (7-15). High level HER2 protein overexpression by immunohistochemistry (IHC 3+) is a validated surrogate marker for gene amplification (4-6). HER2 amplification or HER2 overexpression in lung, bladder and endometrial cancers is associated with poor prognosis and these patients are in need of more effective systemic therapy (15-18).

Furthermore, HER2 mutations including insertions/deletions and point mutations in the kinase and extracellular domains occur in 2-3% of lung cancers and have been identified as oncogenic drivers (7, 8, 19, 20). Preclinical models have shown the inhibitory effects of single agent trastuzumab on HER2 mutant lung cancer cell lines (21, 22) and clinical series of patients with HER2 mutant lung cancer have reported high response rates from trastuzumab based therapy (23, 24).

HER2 mutations also occur in approximately 6% of bladder cancer and 2-5% of endometrial, ovarian, breast, gastric and colorectal cancers (7, 8, 9, 10, 12, 14, 19, 39-41). The discovery of HER2 mutations in many solid tumors has led to speculations of their association with HER2 amplification and their clinical significance as an oncogenic driver and independent therapeutic target (7-11, 12, 14, 19-22, 39, 41). Preclinical studies have demonstrated activity of neratinib, afatinib, dacomitinib and trastuzumab in HER2 mutant lung and breast cancer cell lines (21, 22, 42-45). This has led to several phase 2 clinical trials in HER2 mutant lung and breast cancers and the off label use of

HER2 targeted therapies in these patients (23, 24). Despite the availability of a variety of HER2 targeted therapies, the molecular relations between HER2 amplification and mutation, and their true clinical implications remain unknown. This presents an urgent need for translational and clinical research in HER2 biomarkers and HER2 dependent cancers.

Figure 1:



HER2 in Endometrial Carcinomas and Carcinosarcomas

Endometrial cancer (EC) is the most common gynecologic malignancy in the United States. The incidence of endometrial cancer in the United States has been estimated to be 63,230, with approximately 11,350 endometrial cancer related deaths in 2018 (46). ECs are typically defined as Type I and Type II cancers. Type I endometrial cancer accounts for 80% of the cases. This more indolent type is associated with endometrioid histology, retention of hormone receptor status, and younger age of onset (47). Type II tumors are associated with serous, clear cell or grade 3 endometrioid histology, loss of hormone receptor status, black race, and presentation at a later stage. Type II endometrial cancers portend typically poorer prognosis due to their aggressive biology and presentation at an advanced stage (48, 49). Uterine serous carcinoma (USC) accounts for 3-10% of all endometrial cancers; however, it is responsible for 39% of the endometrial cancer-related mortality (50). Uterine carcinosarcomas (UCS) account for

less than 5% of all uterine malignancies and are high grade endometrial carcinomas whose molecular phenotype overlaps with uterine serous carcinomas. (51) UCS accounts for 15% of all deaths caused by uterine corpus malignancy (52).

The mainstay of conventional therapy for USC and UCS is a combination of comprehensive surgical staging, including peritoneal washings, total hysterectomy, bilateral salpingo-oophorectomy, pelvic and para-aortic lymph node dissection, omentectomy, and peritoneal biopsies followed by adjuvant therapy. Both USC and UCS carries a high rate of recurrence of extra-pelvic metastases, even in early-stage disease (48). Thus, adjuvant therapy is routinely administered in both early and advanced USC and UCS in the form of either chemotherapy, radiotherapy, or both (52-54); however, the optimal regimen has yet to be determined in the prospective setting.

Current management of advanced stage endometrial cancer is comprised of platinum and taxane-based chemotherapy.

Based on GOG- 209, a randomized phase III trial designed to compare carboplatin and paclitaxel (CT) to the triplet doxorubicin, cisplatin and paclitaxel (TAP) regimen, CT was not inferior to TAP in terms of PFS (4 months in both arms) and OS (32 vs 38 months, respectively; HR 1.01).(74) The toxicity profile for CT was significantly more favorable, and this regimen serves as the acceptable backbone for future chemotherapy trials in advanced chemotherapy-naïve endometrial carcinomas. This regimen is now the gold standard front-line chemotherapy regimen in advanced endometrial carcinomas.

Following front-line CT chemotherapy, only megestrol acetate for the palliative treatment of advanced (and primarily low grade endometrioid endometrial carcinomas) and pembrolizumab for MSI-H/dMMR recurrent (Based on Phase Ib trial KEYNOTE-028/016/158 evaluating response rates in patients with MSI-H or MMR-d solid tumors where an objective response rate of 46% was seen in the endometrial cancer cohort (76)) endometrial cancers are approved therapies for endometrial carcinomas. However, for serous and serous-like endometrial carcinomas which are known to be MSS and also unresponsive to hormonal therapy, options are quite limited, and novel therapies are needed.

Critical to moving treatment forward for women with advanced uterine serous carcinomas and uterine carcinosarcomas is the identification of actionable opportunities. HER2 over expression is one such target in these highly malignant endometrial cancer subtypes, and this background serves as a basis for this current trial.

ECs harbor specific molecular alterations which make this disease site an attractive ground for targeted therapies (55). Most investigators agree that low-grade (i.e., TCGA copy number low-tumors) and high-grade endometrial cancers (i.e., TCGA copy number high-tumors) are two distinct entities, with significantly different drivers of neoplasia. Along these lines, Type I cancers often have molecular alterations of phosphatase and tensin homolog tumor suppressor (PTEN) (30-80%), beta-catenin (20-50%), and Ras (25%) (56, 57). Oncogenic alterations in the phosphatidylinositol-3-kinase (PI3K)

pathway appear to affect both Type I and Type II cancers (56). PI3K pathway alterations are not only mutual for both types, but are also one of the most frequently detected mutations (30-50%) in endometrial cancers, strongly suggesting that targeted therapies altering this crucial pathway might have significant therapeutic implications (58). Type II cancers, on the other hand, most commonly demonstrate mutations in the TP53 gene (up to 90%) (57). Recent comprehensive whole-exome sequencing studies carried out by TCGA and by our group have reported HER2/PI3K pathway as one of the most altered pathways in USC with HER2/neu gene amplification identified in 27% and 44% of USC and in 11% of UCS (51) , respectively, supporting HER2 as an attractive pathway for novel targeted therapies (55). Importantly, Buza et al. (59) evaluated HER2 overexpression in 108 cases of USC prospectively tested at Yale University by immunohistochemistry (IHC) and fluorescence in-situ hybridization (FISH) assays. This study revealed that over half (i.e., 53%) of the HER2 overexpressing tumors (i.e., overall 35% showed HER2 overexpression at 3+ level by IHC and/or gene amplification) had significant heterogeneity of protein expression by IHC. Furthermore, in contrast to breast carcinomas, USC showed a lateral or basolateral (’U-shaped’) cellular distribution pattern previously observed in gastric/gastroesophageal junction carcinomas.

HER2 as an Oncogenic Target for Advanced/Recurrent USC and UCS Patients

When HER2 is activated by dimerizing with either HER1 (heterodimer), HER2 (homodimer), HER3 (heterodimer), or HER4 (heterodimer), a cascade of responses are set into motion within the cell through the EGF-tyrosine kinase, PI3K/Akt, and Ras/Raf/MAPK pathways (60). These intracellular pathways act to alter angiogenesis, cell proliferation, and metastasis (61). Overexpression and amplification of the HER2 protein and HER2/neu, respectively, play a major role in carcinogenesis, treatment, and outcomes in USC, making HER2 an excellent target for precision medicine (62). Accordingly, precision medicine was recently employed in a randomized phase II trial where a HER2-targeting antibody (trastuzumab) was added to standard chemotherapy in the treatment of 61 USC patients with stage III-IV or recurrent disease overexpressing HER2/neu. Trastuzumab combined with carboplatin and paclitaxel chemotherapy demonstrated a significant improvement in progression-free survival in both advanced and recurrent USC patients while toxicity was not different between treatment arms (54). This practice-changing randomized study represents the first prospective trial in endometrial cancer targeting USC exclusively and the largest randomized trial report to date to describe the activity of trastuzumab in HER2-overexpressing USC (54).

Mechanism of Resistance to HER2-targeted Therapy Active in USC

Despite promising preclinical and clinical results with HER2-targeted therapy in USC, similarly to breast cancer patients treated with trastuzumab, acquired resistance may ultimately develop (54, 63). Primary or secondary resistance to single-agent trastuzumab has been reported in up to 70% of HER2-overexpressing breast cancer patients treated with trastuzumab (64) and several mechanisms of resistance have been described in both breast cancer and USC patients. The main mechanisms of resistance currently identified in USC are: 1) overgrowth of HER2/neu negative cells (i.e., 0-1+ positive by

IHC) under trastuzumab selective pressure in HER2/neu heterogeneous tumors, 2) HER2/neu extracellular domain shedding or alterations in antibody binding site, 3) activation of downstream growth and survival pathways, and 4) overexpression of alternative HER ligands or receptors (65).

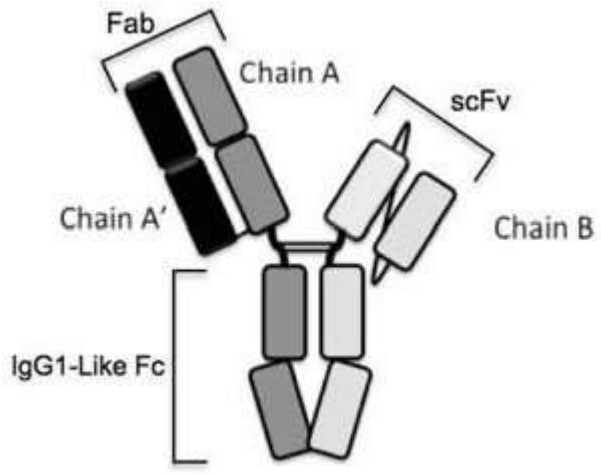
Strategies to Overcome Resistance

As discussed above, heterogeneity in HER2/neu expression in USC patients may represent a major mechanism of primary resistance to trastuzumab. Consistent with this view, single-agent trastuzumab treatment in HER2/neu-overexpressing endometrial cancer patients with recurrent disease was unable to induce any clinical response in patients (68). In contrast, highly encouraging results have recently been reported in advanced/recurrent USC patients treated with a combination of trastuzumab and carboplatin/paclitaxel chemotherapy. These data suggest for the first time that the combination of cytotoxic chemotherapy with a highly targeted agent (i.e., trastuzumab) may have strong synergistic activity in USC patients overexpressing HER2/neu regardless of the high heterogeneity in HER2 expression commonly detected in these rare but highly aggressive tumors (54). Another strategy we can envision to efficiently overcome the obstacle of HER2/neu heterogeneity in USC patients is represented by the use of novel HER2/neu-targeted ADC compounds and agents that target multiple HER2 epitopes. These strategies may potentially overcome the obstacle of high heterogeneity in HER2/neu expression and limit the development/selection of HER2/neu negative clones during trastuzumab-based treatments.

ZW25

ZW25 is a novel, humanized bispecific antibody directed against 2 distinct HER2 epitopes, extracellular domain 4 and 2 of the HER2 receptor (ECD4 and ECD2), the epitopes bound by trastuzumab and pertuzumab, respectively (Figure 2). Simultaneous binding of these two non-overlapping epitopes (known as biparatopic binding) results in dual HER2 signal blockade, including growth-factor mediated signaling, increased binding and removal of HER2 protein from the cell surface relative to trastuzumab, and potent immune effector function. ZW25 therefore has the potential to have greater activity than either trastuzumab or pertuzumab in HER2-expressing tumors.

Figure 2: ZW25 Structure



Fab = fragment antigen-binding arm of antibody;
Fc = fragment crystallizable;
IgG1 = immunoglobulin G antibody isotype 1;
scFv = single-chain variable fragment.

Table 1. Chemical Name and Other Names

Chemical Abstract Service (CAS) Number	2169946-15-8
Chemical Name(s)	ZW25
Company or Laboratory Code	v10000 (variant designation at Zymeworks Inc.)
Generic Name	NA
INN Name	NA
USAN Name	NA

INN = International Nonproprietary Name; NA = not applicable; USAN = United States Adopted Name

Rationale for Studying ZW25 in Endometrial Cancers

Despite the gains obtained with current HER2-directed therapy, medical need remains for patients with all HER2-expressing cancers, particularly with recurrent or metastatic disease that has progressed after standard of care therapy. This includes HER2 overexpressing epithelial uterine malignancies.

HER2-targeted therapies have not been approved for indications other than breast or gastric cancers. Several studies have evaluated HER2-targeted therapies, including trastuzumab or pertuzumab in some of these indications. Many of these studies did not specifically select for patients with HER2 IHC 3+ expression or gene amplification and

have not demonstrated clinical benefit (69, 70; 71, 72,). Challenges to the success of HER2-targeted therapy in non-breast/non-gastric indications include small numbers of patients, criteria for patient selection, increased heterogeneity of HER2 expression compared with breast cancer, and differences in tumor biology, including the relative importance of HER2-mediated signaling in maintaining tumor growth. Notably, in studies with stringent patient selection and dual HER2-targeting, encouraging results have been seen (73). Developing a single multifunctional antibody that has improved capacity and efficiency for binding HER2 compared with available HER2 inhibitors, and that can activate ADCC, block ligand induced heterodimerization of HER2 with other EGFR/ErbB receptors, and down-regulate HER2 may be the key to creating effective HER2-targeted therapies for HER2-expressing tumors.

Trastuzumab combined with chemotherapy is superior to trastuzumab monotherapy and is well tolerated in the treatment of patients with HER2 overexpressing advanced breast cancer (HERCEPTIN®). Similarly, ZW25 may offer better efficacy in combination with other anti-cancer drugs with a favorable safety profile. In preclinical studies, ZW25 was demonstrated to have additive to synergistic anti-tumor activity with a number of different chemotherapeutic agents, including platinum agents, taxanes, receptor tyrosine kinase inhibitors, and DNA synthesis inhibitors in various HER2-expressing tumor cells. In patient-derived and tumor cell line-derived tumor xenograft models, ZW25 demonstrated promising anti-tumor activity that was superior to that observed with trastuzumab in a wide variety of HER2-expressing tumors, including those with low levels of HER2 expression such as in a model of breast or NSCLC cancer. In a GLP repeat-dose toxicology study, ZW25 was well tolerated and no adverse effects were observed at doses up through 150 mg/kg administered as weekly IV infusions for up through 13 weeks. Based on these findings, ZW25 is being evaluated in a first-in-human clinical study in patients with locally advanced (unresectable) and/or metastatic HER2-expressing cancers. Additionally, ZW25 is being explored in combination with standard first-line chemotherapy agents in HER2-expressing gastroesophageal adenocarcinoma (GEA).

Pharmacology studies demonstrated that ZW25 binds HER2 with subnanomolar affinity, induces enhanced tumor cell binding, and blocks growth factor induced tumor growth (likely blocking HER2 heterodimerization with other epidermal growth factor receptor (EGFR)/ErbB family members). ZW25-induced cross-linking of HER2 also results in HER2 clustering and likely enhanced receptor internalization and down-regulation, as well as antibody-dependent cell-mediated cytotoxicity (ADCC). In vitro studies demonstrate that ZW25 is synergistic and/or additive with chemotherapeutic agents in inhibiting the growth of human cancer cell lines that express high to low levels of HER2. In vivo studies demonstrated anti-tumor activity and/or improved host survival against xenografts of human breast, head and neck squamous cell (HNSCC), non-small cell

lung (NSCLC), pancreatic, gastric, and ovarian cancers in nude mice. Further, ZW25 was efficacious in combination with chemotherapeutics in NSCLC, HNSCC and pancreatic cancer xenograft models in nude mice.

Based on the results from the toxicology studies, the nonclinical safety assessment program supported evaluation of ZW25 as an IV infusion in the clinic. Therefore, a first-in-human clinical study was initiated. This ongoing study of ZW25 (ZWI-ZW25-101) is a 3-part Phase 1 study, to evaluate the safety, tolerability, PK, immunogenicity, and preliminary anti-tumor activity of ZW25 as a single agent and in combination with selected chemotherapy agents in patients with locally advanced (unresectable) and/or metastatic HER2-expressing tumors.

Additionally, a Phase 2, open-label, first-line study (ZWI-ZW25-201) has been initiated to investigate the safety, tolerability, and anti-tumor activity of ZW25 plus physician's choice of combination chemotherapy in patients with unresectable, locally advanced, recurrent or metastatic HER2-expressing GEA. Physician's choice of combination chemotherapy includes 3 globally-recognized, multi-agent, first-line treatment regimens: 1) XP, which consists of capecitabine plus cisplatin; 2) 5-FU and leucovorin (FP), which consists of fluorouracil (5-FU) and leucovorin (folinic acid) plus cisplatin; or 3) mFOLFOX6, which consists of 5-FU and leucovorin plus oxaliplatin.

Pharmacology[36]

ZW25 has low nanomolar affinity to recombinant HER2 that was comparable to the binding affinities of trastuzumab and pertuzumab for HER2. It has low nanomolar binding affinity to cultured human cancer cells that express high to low levels of HER2. ZW25 was shown to bind HER2 in a trans-configuration, resulting in clustering of HER2 molecules and likely the enhanced internalization of HER2 observed compared with trastuzumab. In vitro studies demonstrated that ZW25 caused significant inhibition of the growth of human cancer cell lines that express high to low levels of HER2, inhibition of growth factor-mediated tumor cell proliferation, and synergy and additivity with chemotherapeutic agents in inhibiting the growth of human cancer cell lines that express high to low levels of HER2. ZW25 was shown to have affinity to Fcγ receptors equivalent to or greater than wild-type IgG1 and could induce ADCC activity at nanomolar concentrations against cancer cells that express high to low levels of HER2. In vivo studies demonstrated anti-tumor activity and/or improved host survival against xenografts of human breast, HNSCC, NSCLC, pancreatic, gastric, and ovarian cancers in nude mice. Further, ZW25 was efficacious in combination with chemotherapeutics in NSCLC, HNSCC, and pancreatic xenograft models in nude mice.

Results of *in vitro* and *in vivo* nonclinical pharmacodynamic studies as briefly detailed below support the investigational use of ZW25 alone or in combination with chemotherapy.

Pharmacology studies are further detailed in the ZW25 Investigator's Brochure.

Nonclinical studies

Pharmacology studies demonstrated that ZW25 binds HER2 with subnanomolar affinity, induced enhanced tumor cell binding, and blocks growth factor induced tumor growth (likely blocking HER2 heterodimerization with other EGFR/ErbB family members). ZW25-induced cross-linking of HER2 also resulted in HER2 clustering and likely enhanced receptor internalization and down-regulation, as well as ADCC. In vitro studies demonstrated that ZW25 caused significant inhibition of the growth of human cancer cell lines that express high to low levels of HER2, inhibition of growth factor-mediated tumor cell proliferation, and synergy and/or additivity with chemotherapeutic agents in inhibiting the growth of human cancer cell lines that express high to low levels of HER2. ZW25 was shown to have affinity to Fcγ receptors equivalent to or greater than wild-type IgG1 and could induce ADCC activity at nanomolar potency against cancer cells that express high to low levels of HER2. In vivo studies demonstrated anti-tumor activity and/or improved host survival against xenografts of human breast, HNSCC, pancreatic, gastric, and ovarian cancers in nude mice.

The nonclinical testing strategy for ZW25 followed the ICH S9 guidance on nonclinical testing for anti-cancer pharmaceuticals and the ICH S6(R1)1 guidance for biotechnology-derived pharmaceuticals.

Safety pharmacology, including an assessment of its effect on cardiovascular and respiratory function was conducted following dosing as part of the GLP toxicology study, as outlined in ICH S9. ZW25 showed no effect on safety pharmacology parameters. In addition, in vitro studies demonstrated that ZW25 had a similar effect as trastuzumab on human cardiomyocyte viability.

Toxicology

ZW25 has been evaluated in a comprehensive toxicology program (non-GLP and GLP studies). The toxicology program was carried out in cynomolgus macaque monkeys, as it was demonstrated that ZW25 bound both human and monkey HER2 with similar subnanomolar affinity, but did not bind to rodent HER2. Results of these studies supported the first-in-human (FIH) trial exploring the safety and tolerability of ZW25 Toxicology studies are further detailed in the ZW25 Investigator's Brochure.

3.6 Clinical Studies of ZW25

The first-in-human clinical study was initiated on September 2016. This ongoing study of ZW25 (ZWI-ZW25-101) is a 3-part Phase I study, to evaluate the safety, tolerability, PK, immunogenicity, and preliminary anti-tumor activity of ZW25 as a single agent and in combination with selected chemotherapy agents in patients with locally advanced (unresectable) and/or metastatic HER-2 expressing tumors.

Part 1 of the ZWI-ZW25-101 study is using a standard 3+3 dose-escalation design to determine the maximum-tolerated dose (MTD), optimal biological dose (OBD), or recommended dose(s) (RDs) of ZW25 monotherapy administered weekly (QW), once every 2 weeks (Q2W), and/or once every 3 weeks (Q3W) in patients with any HER2-expressing cancer that has progressed after receipt of all therapies known to confer clinical benefit. Part 2 of the study is characterizing the safety, tolerability, and preliminary anti-tumor activity of ZW25 monotherapy administered at the Part 1 MTD, OBD, or RD in patients with selected HER2-expressing locally advanced (unresectable) and/or metastatic cancers in up to 5 disease specific expansion cohorts, including HER2-high breast cancer (immunohistochemistry (IHC) 3+, or IHC 2+/ fluorescent in situ hybridization (FISH+), HER2-intermediate breast cancer (IHC 2+/FISH-negative [FISH-]), HER2-high gastroesophageal adenocarcinoma (GEA), HER2-intermediate GEA, and other HER2-high cancers. The recommended single-agent dose for further study was identified in Part 1 of the study as 20 mg/kg Q2W. Part 3 of the study is evaluating the safety, tolerability and preliminary anti-tumor activity of ZW25 administered in combination with selected chemotherapy agents, including paclitaxel, capecitabine and vinorelbine, in patients with HER2-expressing breast and GEA.

As of 31 October 2018, a total of 67 patients have been enrolled and treated in Parts 1 and 2 of the study (5 mg/kg QW, n=3; 10 mg/kg QW, n=13; 15 mg/kg QW, n=7; and 20 mg/kg Q2W, n=44). Across all dose levels, the median age is 59 years (range, 27–79). More patients are female (74.6%) than male (25.4%), the majority are white (76.1%), and the majority have an Eastern Cooperative Oncology Group (ECOG) performance status of 1 (73.1%). There are no notable differences in demographics or baseline characteristics between dose levels. Most patients have a disease diagnosis of breast cancer (n=39, 58.2%). Additionally, 9 patients (13.4%) have gastric cancer, 4 each (6.0%) have esophageal or colorectal cancer, and 2 (3.0%) have gall bladder cancer. Other disease diagnoses in 1 patient each include adenocarcinoma of the sigmoid colon, cholangiocarcinoma, undifferentiated adnexal carcinoma of the skin, and bladder, cervical, endometrium, fallopian tube, parotid, and rectum cancers. Overall, nearly all the patients have disease with HER2-high expression (IHC 3+ or IHC 2+/FISH+) by local or central review (85.1%). Disease characteristics are generally similar between dose levels. Most patients have received prior HER2-targeted therapies, with 59 (88.1%) receiving trastuzumab (HERCEPTIN®), 36 (53.7%) receiving pertuzumab (PERJETA®), 39 (58.2%) receiving ado-trastuzumab emantasine (KADCYLA®), 18 (26.9%) receiving lapatinib (TYKERB®), and 1 (1.5%) receiving neratinib (NERLYNX®).

Approximately one-third of the response-evaluable patients treated with single-agent ZW25 in Parts 1 and 2 of the study have achieved an objective response (n=15/48 [31.3%]; all partial responses [PRs]) and approximately two-thirds of patients have experienced disease control (n=32/48 [66.7%]; 15 PRs and 17 stable disease). Regardless of dose level of ZW25, 17 patients (60.7%) with breast cancer have experienced disease control, including 8 with a PR and 9 with stable disease. Six patients (66.7%) with GEA have experienced disease control, 4 with PR and 2 with SD. Nine additional patients (81.8%) with other cancers also have experienced disease control, including 2 PRs and 3 SDs in colorectal cancer (CRC), 2 PRs in gall bladder cancer, 1 PR in cholangiocarcinoma, and 1 SD each in fallopian tube cancer, endometrium cancer, and parotid cancer.

The updated data from this study was presented at ESMO 2019, where safety and preliminary anti-tumor activity data on 43 patients was presented (D-Y. Oh et al, ESMO 2019 Annals of Oncology, Volume 30, Issue Supplement_9). In this study a total of 43 patients were treated, including 17 patients with gastroesophageal adenocarcinoma, 6 with biliary cancers, 10 with colorectal cancer, and 10 other cancers, including 3 endometrial cancers. Fifty-nine percent of patients had prior HER2 therapy to include trastuzumab (59%), pertuzumab (10%), TDM-1 (7%), lapatinib (3%) and Neratinib (1%). The median number of prior therapies was 3 (range 1-6) for all patients. The most common treatment-related adverse events (all Grade 1 or 2) were diarrhea (49%) and infusion related reaction (34%). The objective response rate (all partial response (PR)) for response evaluable patients was 41% (14/34), and 38% of patients experienced stable disease (SD). The majority of patients (74%; 25/34) experienced a decrease in the sum of diameters for their target lesions. Compared to FISH, the positive predictive value of HER2 amplification in pre-dose C1D1 ctDNA was 90% (95% CI 79-96%), negative predictive value 45% (25-67%), and diagnostic accuracy 79% (63-90%).

ZW25 Adverse Events

In Parts 1 and 2 of the study, adverse events (AEs) occurring in ≥15% of patients treated with single-agent ZW25 across all dose levels include diarrhea (49.3%), infusion-related reaction (40.3%), fatigue (34.3%), nausea (23.9%), decreased appetite (17.9%), and headache (16.4%). Diarrhea (44.8%) and infusion-related reactions (40.3%) are the most common AEs considered to be related to ZW25 treatment. Other treatment-related AEs occurring in ≥15% of patients include fatigue (17.9%) and nausea (16.4%). Overall, most AEs have been Grade 1 or 2 (>90%). Grade 3 AEs occurring in more than 2 patients include diarrhea, fatigue, and pleural effusion (n=3 each, 4.5% each); 2 of the 3 patients with Grade 3 diarrhea and the 3 patients with Grade 3 fatigue had events that were considered to be related to ZW25. No treatment-related Grade 4 or 5 AEs, no dose-limiting toxicities (DLTs), and no treatment-related serious adverse events (SAEs) have occurred on study. Additionally, no treatment-related cardiac events have occurred thus far on study. Four patients have experienced cardiac events, including bradycardia, tachycardia, sinus tachycardia, and pericardial effusion, all considered unrelated to ZW25 and Grade 1 in severity. The Grade 1 event of worsening pericardial effusion occurred during screening (i.e., before taking any study drug) and was deemed serious

(required hospitalization) and related to pre-existing condition, but subsequently resolved after ECHO guided pericardiocentesis. An SAE of Grade 3 troponin I increased (of unclear etiology but most likely disease progression) was reported in a 36-year-old male patient with metastatic esophageal cancer after the patient discontinued treatment with ZW25. Troponin testing was performed as part of evaluation for inclusion in a different clinical study. The patient was observed in the ER and was asymptomatic. The event was considered recovered with sequelae the same day after serial troponin tests eventually plateaued and the patient was sent home. A stress test on the following day noted normal left ventricular ejection fraction and mild myocardial ischemia with no myocardial injury and no elevation in troponin I.

Preliminary analysis of ADA present in the serum of patients in the dose-escalation phase showed that 9 of 13 patients had pre-existing ADA at baseline, and 2 patients had evidence of ADA by the second dose. Thereafter, no patients had evidence of ADA beyond the second dose of ZW25. One patient death occurred within the 30-day safety reporting period; however, the death was due to disease progression. Nine other patients have died on study, 8 due to disease progression and 1 due to an unrelated event reported as sudden death.

In Parts 1 and 2 of the study, 83.6% of patients have experienced a treatment related TEAE. Similar to TEAEs overall, the most common treatment-related TEAEs include diarrhea (44.8%), infusion-related reaction (40.3%), fatigue (17.9%), and nausea (16.4%).

In Parts 1 and 2 of the study, a total of 25 patients had 33 Grade 3 or higher TEAEs. Events occurring in 2 or more patients treated with ZW25 monotherapy across all dose levels include diarrhea, fatigue, and pleural effusion in 3 patients each (4.5% each), and anemia, decreased appetite, headache, malignant pleural effusion, pneumonia, and small intestinal obstruction in 2 patients each (3.0% each).

Nearly all events were considered to be unrelated to study drug (94.0%). Four patients had events that were considered by the investigator to be related to treatment with ZW25, including fatigue (n=3/67, 4.5%), diarrhea (n=2/67, 3.0%), arthralgia, and hypophosphatemia (n=1/67, 1.5% each). Additionally, all events were Grade 3 in severity with the exception of an unrelated Grade 4 SAE of lung infection and an unrelated Grade 5 SAE of sudden death.

As of the data cut-off date, in Parts 1 and 2 of the ongoing ZWI-ZW25-101 study, 10 patients have died, 9 due to disease progression and 1 due to sudden death considered unrelated to ZW25.

Efficacy analyses are ongoing for study ZWI-ZW25-101. Efficacy assessments are based on investigator assessment of response per response evaluation criteria in solid tumors (RECIST) v1.1. Overall, approximately one-third of the patients on ZW25 monotherapy in Parts 1 and 2 of the study achieved an objective response (n=15/48, 31.3%; all PRs) and approximately two-thirds of patients experienced disease control (n=32/48, 66.7%; 15 PRs and 17 stable disease).

For Parts 1 and 2 of the study regardless of dose level of ZW25, 17 patients (60.7%) with breast cancer experienced disease control, including 8 with a PR and 9 with SD. Six patients (66.7%) with GEA experienced disease control, 4 with PR and 2 with SD. Nine additional patients (81.8%) with other cancers also experienced disease control, including 2 PRs and 3 SDs in colorectal cancer (CRC), 2 PRs in gall bladder cancer, 1 PR in cholangiocarcinoma, and 1 SD each in fallopian tube cancer, endometrium cancer, and parotid cancer.

Please refer to the Investigators' Brochure for detailed safety information.

Rationale for the starting dose of ZW25

Based on ZWI-ZW25-101, the recommended phase II dose of ZW25 was established at 20mg/kg intravenously (IV) every two weeks. This established dose and schedule will be utilized in this study.

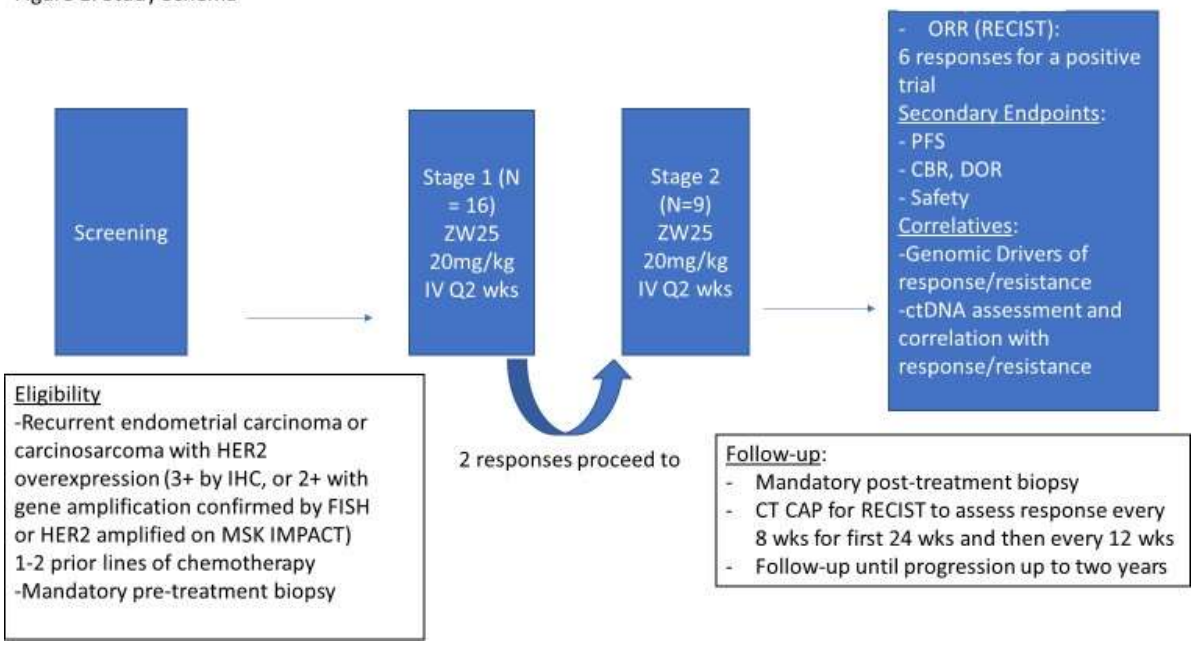
4.0 OVERVIEW OF STUDY DESIGN/INTERVENTION

4.1 Design

This is a MSKCC investigator-initiated, single-center, Phase 2, open label study designed to evaluate the efficacy and safety of ZW25, in patients with HER2 overexpressing endometrial carcinomas and endometrial carcinosarcomas.

HER2 overexpression is defined as 3+ by IHC (immunohistochemistry) or 2+ with gene amplification by FISH (HER2/CEP17 ratio ≥or HER2 amplified (fold change ≥ 2) on MSK IMPACT.

Figure 1: Study Schema



Abbreviations – IV: intravenous ORR: Overall response rate, PFS: Progression-free survival, OS: Overall survival, CBR: Clinical benefit rate, DOR: Duration of response

4.2 Intervention

Up to 25 patients will be enrolled on this study and will receive the RP2D of ZW25 at 20mg/kg intravenously (IV) every two weeks.

The study will be conducted in two stages. Stage 1 will accrue 16 patients; if two or more responses are seen, study will proceed to Stage 2 which will accrue an additional 9 patients. In this study the recommended ZW25 dose will be 20mg/kg intravenously (IV) every two weeks. Treatment cycles will be 28 days long.

Patients will receive study treatment until disease progression, intolerable toxicity, elective withdrawal from the study, study completion, or study termination. Patients will continue to receive study treatment until they present with progressive disease (PD) per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1, develop unacceptable toxicity or withdraw consent, whichever comes first, or until the study is terminated.

Tumor assessments, including radiological assessments by computerized tomography (CT) or magnetic resonance imaging (MRI) scans are performed at Screening and

subsequently every eight weeks for the first 24 weeks and then every twelve weeks until PD, death or initiation of subsequent anti-cancer therapy, whichever occurs first.

Safety will be evaluated in this study through the monitoring of all serious and non-serious AEs, graded according to the current version of the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE v.5).

5.0 THERAPEUTIC/DIAGNOSTIC AGENTS & NON-THERAPEUTIC ASSESSMENTS

5.1 ZW25

ZW25 is supplied by Zymeworks Inc. as a sterile, single-use, preservative-free, colorless to slightly yellow solution in a glass vial. The drug product solution is for IV administration.

MSK will be cross-referencing Zymeworks, Inc.'s IND for ZW25.

ZW25 Formulation
Each vial contains a nominal fill volume of 20 mL (300 mg). The drug product is formulated at 15 mg/mL in 10 mM sodium acetate, 9% (w/v) sucrose, and 0.01% (w/w) polysorbate 20. The pH of the drug product is 4.6. The final container is a 50 mL USP Type I glass vial with a gray Flurotec coated plug and yellow flip-off top seal.

Storage and Handling

Vials containing ZW25 must be stored under refrigeration at −20°C (±5 °C).

Please refer to the Pharmacy Manual for further details on storage and handling. Drug accountability procedures are also provided in the Pharmacy Manual. Refer to the protocol and relevant Pharmacy Manual for specific guidelines regarding the preparation and administration of ZW25.

Upon completion of the study, all study drug dispatched to a site must be accounted for destroyed according to the pharmacy's standard operation procedures (SOP). The pharmacy shall maintain accurate records of all study drugs that have been received, stored, dispensed, destroyed, and used.

Drug accountability will be monitored regularly.

Preparation
Refer to the protocol and relevant Pharmacy Manual for specific guidelines regarding the preparation and administration of ZW25.

Administration

ZW25 will be administered by IV infusion in 0.9% normal saline over 120 to 150 minutes. If for a particular patient the first 2 doses administered are well tolerated, the infusion duration for that patient may be decreased to 90 minutes. If the next 2 doses are well tolerated, the infusion duration may be decreased to 60 minutes. **However, the infusion rate should not exceed 250 mL of 0.9% normal saline/hour** (Example: If a dose of ZW25 is diluted into 250 mL bag of saline, the infusion should be administered over at least 60 minutes. If a dose of ZW25 is diluted into 500 mL bag, the infusion should be administered over at least 120 minutes.) The study drug dosage will be calculated based on patient weight at Screening. Dose will be recalculated only if there is a change in weight by 10% from the assessment at Cycle 1 Day 1. Please refer to the Pharmacy Manual for further instructions and or specific guidelines regarding the preparation and administration of ZW25.

All patients should receive pre-medication as prophylaxis for infusion reaction as described in **Required Therapy** section of the protocol**.**

Overdose
Any overdose or incorrect administration of ZW25 should be noted on the Study Drug Administration Electronic Case Report Form (eCRF). Adverse events associated with an overdose or incorrect administration of ZW25 should be recorded accordingly on the eCRF.

Required Therapy

Prior to dosing with ZW25, all patients should receive prophylactic treatment for infusion reactions that consists of acetaminophen orally, diphenhydramine (or equivalent) orally or IV, and a corticosteroid 30 to 60 minutes prior to infusion of ZW25. The dosage of these pre-medications may be determined by local institutional practice; however, the drug supplier's recommendations are acetaminophen 650 mg orally, diphenhydramine 50 mg orally or IV, and hydrocortisone 100 mg IV or dexamethasone 10 mg IV. All premedication administered should be documented for each infusion. If a patient cannot tolerate one or more of the premedication, please contact the Principal Investigator to discuss alternatives.

Permitted Therapy
Patients are permitted to use the following therapies during the study:

- Oral contraceptives
- Prophylactic or therapeutic anticoagulation therapy (such as warfarin at a stable dose or low-molecular-weight heparin)
- Inactivated influenza vaccinations
- Megestrol administered as an appetite stimulant
- Inhaled corticosteroids (e.g., budesonide)

- Mineralocorticoids (e.g., fludrocortisone)
- Low-dose corticosteroids administered for orthostatic hypotension or adrenocortical insufficiency

G-CSF (i.e., filgrastim or pegfilgrastim) treatment is permitted. The primary prophylaxis should be administered per the ASCO, EORTC, or ESMO guidelines or per local standard practice; namely, in patients who are ≥ 60 years of age and/or with comorbidities (Smith et al. 2006; Crawford et al. 2009; Aapro et al. 2011).

In general, investigators should manage a patient's care with supportive therapies as clinically indicated per local standard practice.

Prohibited Therapy

Use of the following concomitant therapies is prohibited as described below:

- Concomitant therapy intended for the treatment of cancer (including, but not limited to, chemotherapy, hormonal therapy, immunotherapy, radiotherapy, and herbal therapy), whether health authority−approved or experimental, are prohibited for various time periods prior to starting study treatment, depending on the agent and during study treatment until disease recurrence is documented and the patient has discontinued study treatment, except as outlined below or as described elsewhere in the protocol.
- Investigational therapy is prohibited during the study.
- Live, attenuated vaccines (e.g., FluMist) are prohibited within 4 weeks prior to initiation of study treatment, during study treatment, and for 5 months after the last dose of study treatment.
- Systemic immunostimulatory agents (including, but not limited to, interferons and IL-2) are prohibited within 4 weeks or 5 half-lives of the drug, whichever is longer, prior to initiation of study treatment and during study treatment.
- Concomitant use of herbal therapies is not allowed on protocol therapy.

Concomitant Therapy and Additional Restrictions

Concomitant therapy during the study includes any medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient in addition to protocol-mandated study treatment from 7 days prior to initiation of study treatment to the treatment discontinuation visit. All such medications should be reported to the investigator and recorded on the Concomitant Medications eCRF.

Concomitant Medications and Procedures

All concomitant medications and supportive therapy taken within 7 days of Cycle 1 day 1 and through 30 days after last study treatment must be recorded on the appropriate eCRF. The identity of all medications, dosage, and route of administration, frequency, duration of administration, and indication for use will be recorded in the appropriate sections of the eCRF.

Antiemetic and antidiarrheal medications
Antiemetic (e.g. 5-HT3 serotonin receptor antagonists such as palonosetron, granisetron or ondansetron) and antidiarrheal (e.g. loperamide) medications may be used at the discretion of the treating physician.

Hematopoietic Growth Factors
Patients receiving recombinant erythropoietin or darbepoietin-α prior to study start may continue to receive pre-treatment doses.

The use of erythropoietic and granulocyte growth factors in accordance with ASCO guidelines may be implemented at the discretion of the treating physician after Cycle 1.

Other Concomitant Medications
Medications for the treatment of adverse events or cancer symptoms (e.g. packed red blood cells and pain medications), are allowed. Additionally, medications (not addressed above) used to treat underlying medical conditions at study entry, including anti-emetics and anti-diarrheal medications, will be allowed to continue.

Study Treatment Compliance
ZW25 supplied for the study may not be used for any purpose other than the study or administered other than as described in this protocol.

ZW25 from two different drug lots cannot be mixed in a single dose administration.

Study Treatment Administration
ZW25 is an experimental anticancer drug, and, as with other potentially toxic compounds, caution should be exercised when handling these compounds. It is recommended that gloves and protective garments be worn during preparation. Refer to the Pharmacy Manual for more information.

Study Treatment Overview and Schedule
All Cycle visits are allowed a ± 3-day window (see study calendar for details). Note that there must be a minimum of 12 days between doses. If Day 1 of a cycle is delayed for any reason, once the subject reinitiates treatment the next dose delivered will be considered Day 1 of the cycle that was delayed. If a Day 15 dose of a cycle is delayed by ≥ 12 days, then that dose will be considered skipped. The next dose delivered will be considered Day 1 of the subsequent cycle. For logistical reasons such as holidays, delays in the scheduled study treatment please consult with PI.

6.0 CRITERIA FOR PARTICIPANT ELIGIBILITY

6.1 Participant Inclusion Criteria

1. Patients must be enrolled or agree to consent to the companion genomic profiling study MSKCC IRB# 12-245 Part A. Results are not required prior to

initiating treatment on protocol, unless patients do not have other test results by IHC or FISH confirming HER2 overexpression.

2. Patients must have recurrent or persistent HER2 overexpressing endometrial cancer or endometrial carcinosarcoma. HER2 overexpression is defined as 3+ by IHC or 2+ with gene amplification by FISH (HER2/CEP17 ratio ≥ 2) or HER2 amplified (fold change ≥ 2) on MSK IMPACT.
3. Histologic documentation of diagnosis of endometrial carcinoma or carcinosarcoma is required.
4. Age ≥ 18 years
5. Patients must have had at least one but no more than two prior chemotherapeutic regimens for management of endometrial carcinoma (including neo-adjuvant and/or adjuvant chemotherapy). Initial treatment may include chemotherapy, chemotherapy and radiation therapy, and/or consolidation/maintenance therapy. Chemotherapy administered in conjunction with primary radiation as a radio-sensitizer WILL be counted as a systemic chemotherapy regimen. Prior hormonal therapy will **not** count as a prior regimen.
   Prior treatment with trastuzumab is allowed.
6. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.
7. LVEF ≥ 50% on baseline screening ECHO.
8. Resolution of adverse effects of recent surgery, radiotherapy, or chemotherapy to Grade ≤1 prior to first study treatment (with the exception of alopecia or clinically insignificant laboratory values).
9. Patients must have measurable disease. Measurable disease is defined by RECIST (version 1.1). Measurable disease is defined as at least one lesion that can be accurately measured in at least one dimension (longest diameter to be recorded). Each non-nodal lesion must be ≥ 10 mm when measured by CT, MRI or caliper measurement by clinical exam; or ≥ 20 mm when measured by chest x-ray. Lymph nodes must be ≥ 15 mm in short axis when measured by CT or MRI.
10. No active infection requiring antibiotics (with the exception of uncomplicated urinary tract infection).
11. All patients must consent to mandatory pre-treatment and post-treatment core needle biopsies.
12. Patients must have adequate hematological, liver, cardiac and kidney function within 14 days prior to first treatment:
    a. Absolute neutrophil count (ANC) ≥ 1.5 x 10^9/L (> 1500 per mm^3)
    b. Platelet ≥ 100 x 10^9/L (>100,000 per mm^3)
    c. Hemoglobin ≥ 8.0 g/dL

d. Serum bilirubin ≤ 1.5 x institutional upper limit of normal (ULN). (Unless Gilbert's Syndrome, for which Bilirubin ≤ 3 x institutional upper limit of normal (ULN), without concurrent clinically significant liver disease) AST (SGOT)/ALT (SGPT) ≤ 3 x institutional upper limit of normal (ULN) unless liver metastases are present, in which case it must be ≤ 5x ULN.
e. Serum creatinine ≤ 1.5 x institutional upper limit of normal (ULN).

13. For patients of childbearing potential, agreement to use two effective forms of contraception (e.g., surgical sterilization, a reliable barrier method, birth control pills, or contraceptive hormone implants) and to continue its use for the duration of the study and for 12 weeks after the last ZW25 dose.
14. Agree to practice total abstinence when this is in line with the preferred and usual lifestyle of the subject.
    a. A woman is considered to be of childbearing potential unless 1 of the following applies: She is considered to be permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy, tubal ligation, and bilateral oophorectomy.
    b. She is postmenopausal, defined as no menses for 12 months without an alternative medical cause. A high follicle-stimulating hormone (FSH) level consistently in the postmenopausal range (30 mIU/mL or higher) may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy; however, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient to confirm a postmenopausal state.
    c. Female patients of childbearing potential must have a negative serum pregnancy test result less than 3 day prior to administration of the first dose of study treatment.

Patients or their legally authorized representative (LAR) must be willing and able to sign the informed consent form, and to adhere to the study visit schedule and other protocol requirements.

6.2 Participant Exclusion Criteria

1. Women who are pregnant or lactating or women of childbearing potential (WCBP) not protected by highly effective contraceptive methods.
2. > Grade 1 peripheral neuropathy.
3. History of hemorrhagic or ischemic stroke within the prior six months.
4. History of NYHA Class II-IV heart failure, no serious arrhythmia.
5. History of MI or unstable angina within 6 months of study initiation.

6. Patients with a lifetime cumulative dose of anthracycline >300 mg/m2 or who have received anthracycline treatment within 90 days of the expected first dose of ZW25 are not eligible for treatment.
7. Prior hypersensitivity to monoclonal antibodies.
8. Active hepatitis B or hepatitis C infection. Patients with previously resolved hepatitis B infection are eligible. Presence of positive test results for hepatitis B infection who have resolved the infection (defined by positive for HB surface antibody (anti-HBs) and polymerase chain reaction (PCR) assay is negative for HBV DNA are eligible. Patients positive for HCV antibody are eligible only if testing for HCV RNA is negative.
9. Known HIV infection.
10. Current severe, uncontrolled systemic disease (e.g., clinically significant cardiovascular, pulmonary, or metabolic disease).
11. Major surgical procedure or significant traumatic injury within 28 days prior to Day 1 or anticipation of the need for major surgery during the course of study treatment.
12. Known untreated or active central nervous system (CNS) metastases (progressing or requiring anticonvulsants or corticosteroids for symptomatic control) leptomeningeal carcinomatosis.

Patients with a history of treated CNS metastases are eligible, provided that they meet all of the following criteria:

    a. Presence of measurable disease outside the CNS
    b. No radiographic evidence of worsening upon the completion of CNS-directed therapy and no evidence of interim progression between the completion of CNS-directed therapy and the screening radiographic study
    c. No history of intracranial hemorrhage or spinal cord hemorrhage
    d. No ongoing requirement for dexamethasone as therapy for CNS disease (anticonvulsants at a stable dose are allowed)
    e. Absence of leptomeningeal disease

13. Inability to comply with study and follow-up procedures.
14. Known allergy or hypersensitivity to the components of ZW25 formulation.
15. Any other disease, metabolic dysfunction, physical examination finding, or clinical laboratory finding that, in the investigator’s opinion, gives reasonable suspicion of a disease or condition that contraindicates the use of an

investigational drug or that may affect the interpretation of the results or render the patient at high risk from treatment complications.

16. Active or history of inflammatory bowel disease (IBD)
17. Severe infections within 4 weeks prior to initiation of study drug treatment, including but not limited to hospitalization for complications of infection, bacteremia, or severe pneumonia.
18. Treatment with therapeutic oral or IV antibiotics within 2 weeks prior to initiation of study treatment. Patients receiving prophylactic antibiotics (e.g., for prevention of urinary tract infection or to prevent chronic obstructive pulmonary disease exacerbation) are eligible for the study. Patients receiving antibiotic treatment for urinary tract infection are also eligible.
19. Administration of a live attenuated vaccine within 4 weeks prior to initiation of study treatment or anticipated need for such a vaccine during study. Patients must agree not to receive live, attenuated influenza vaccine (e.g., Flumist®) within 4 weeks prior to treatment.)
20. Participation in another clinical study with receipt of an investigational product during the last 4 weeks.
21. History of another primary malignancy except for:
    a. Malignancy treated with curative intent and with no known active disease ≥2 years before the first dose of study drug and of low potential risk for recurrence.
    b. Adequately treated non-melanoma skin cancer or lentigo maligna without evidence of disease.
    c. Adequately treated carcinoma in situ without evidence of disease (e.g., cervical cancer in situ).
    d. Adequately treated stage 1 breast cancer.
22. Receipt of the last dose of anti-cancer therapy (chemotherapy, immunotherapy, targeted therapy, biologic therapy, tumor embolization, monoclonal antibodies) < 21 days prior to the first dose of study drug. Receipt of the last dose of hormonal therapy within < 7 days prior to the first dose of study drug.
23. Any prior radiation therapy must be discontinued at least four weeks prior to registration.
24. QT interval corrected for heart rate (QTc) ≥470 ms on screening electrocardiograms (ECG) using QTC Federica.

25. History of small or large bowel obstruction within 3 months of registration, including subjects with palliative gastric drainage catheters. Subjects with palliative diverting ileostomy or colostomy are allowed if they have been symptom free for more than 3 months.
26. Subjects with refractory ascites, defined as ascites needing drainage catheter or therapeutic paracentesis more often than every 4 weeks.
27. Ongoing bowel perforation or presence of bowel fistula or abscess within 3 months of registration.

7.0 RECRUITMENT PLAN

All eligible patients, regardless of race, will be approached for participation. No additional measures, e.g. advertisement, payment to patients, will be employed to recruit patients.

During the initial conversation between the investigator/research staff and the patient, the patient may be asked to provide certain health information that is necessary to the recruitment and enrollment process. The investigator/research staff may also review portions of their medical records at MSKCC in order to further assess eligibility. They will use the information provided by the patient and/or medical record to confirm that the patient is eligible and to contact the patient regarding study enrollment. If the patient turns out to be ineligible for the research study, the research staff will destroy all information collected on the patient during the initial conversation and medical records review.

Participation in the study is completely voluntary. Patients/LAR will be required to read, agree to, and sign an IRB-approved informed consent form prior to registration on this trial. Patients will not receive payment for their participation on this study. Patients are free to withdraw from the study without consequence at any time.

Potential research subjects will be identified by a member of the patient's treatment team, the protocol investigator, or research team at Memorial Sloan-Kettering Cancer Center (MSKCC). If the investigator is a member of the treatment team, s/he will screen their patient's medical records for suitable research study participants and discuss the study and their potential for enrolling in the research study. Potential subjects contacted by their treating physician will be referred to the investigator/research staff of the study.

Assignment of Patient Number
Patient numbers are assigned in sequential order as patients patient enrolls onto study.

The Investigator will certify that the patient satisfies all eligibility criteria at screening and continues to satisfy all inclusion and exclusion criteria on Cycle 1, Day 1 prior to dosing.

Enrolled Patient Definition
Patients who have consented to the study and have received at least one dose of study treatment will be considered enrolled and evaluable. Those patients who've consented but did not successfully complete the screening process and did not receive a dose of ZW25 will be considered a screen failure. Patient numbers for patients who screen fail will not be re-issued.

7.1 Research Participant Registration

Confirm eligibility as defined in the section entitled Inclusion/Exclusion Criteria. Obtain informed consent, by following procedures defined in section entitled Informed Consent Procedures. During the registration process registering individuals will be required to complete a protocol specific Eligibility Checklist. The individual signing the Eligibility Checklist is confirming whether the participant is eligible to enroll in the study. Study staff are responsible for ensuring that all institutional requirements necessary to enroll a participant to the study have been completed. See related Clinical Research Policy and Procedure #401 (Protocol Participant Registration).

8.0 INFORMED CONSENT PROCEDURES

Before protocol-specified procedures are carried out, consenting professionals will explain full details of the protocol and study procedures as well as the risks involved to participants prior to their inclusion in the study. Participants will also be informed that they are free to withdraw from the study at any time. All participants or their LARs must sign an IRB/PB-approved consent form indicating their consent to participate. This consent form meets the requirements of the Code of Federal Regulations and the Institutional Review Board/Privacy Board of this Center. The consent form will include the following:

1. The nature and objectives, potential risks and benefits of the intended study.
2. The length of study and the likely follow-up required.
3. Alternatives to the proposed study. (This will include available standard and investigational therapies. In addition, patients will be offered an option of supportive care for therapeutic studies.)
4. The name of the investigator(s) responsible for the protocol.
5. The right of the participant to accept or refuse study interventions/interactions and to withdraw from participation at any time.

Before any protocol-specific procedures can be carried out, the consenting professional will fully explain the aspects of patient privacy concerning research specific information. In addition to signing the IRB Informed Consent, all patients must agree to the Research Authorization component of the informed consent form.

Each participant or their LAR and consenting professional will sign the consent form. The participant must receive a copy of the signed informed consent form.

9.0 PRE-TREATMENT/INTERVENTION

Screening Visit
In some cases, clinical assessments performed prior to obtaining informed consent may be used to qualify the patient for the study. These include radiological tumor assessment, physical examinations, hematology, serum chemistry results, coagulation studies, urinalysis, or other assessments which may be considered part of normal standard of care. In these cases, repeat assessments may not be necessary prior to enrollment, unless individual parameters require further study or confirmation and are clinically appropriate.

Within 28 days prior to treatment start:

- Written informed consent
- History and Physical examination
- Review of concomitant medications
- Vital signs (blood pressure, heart rate and temperature), weight and height
- ECOG Performance status
- Toxicity assessment
- 12-lead ECG
- Echocardiogram
- Radiographic tumor measurements (CT C/A/P, MRI)
- Screening Biopsy (3 Cores) if deemed safe and feasible (Refer to: Exploratory Correlative Studies section for details)
- Patients must have documented HER2 overexpression, defined as 3+ by IHC or 2+ with gene amplification by FISH (HER2/CEP17 ratio ≥ 2) or HER2 amplified (fold change ≥ 2) on MSK IMPACT any time prior to starting treatment
- Hepatitis B Testing, if not done previously at MSK to rule out active infection (see exclusion criteria for details)

Within 14 days prior to treatment start:

- Complete Blood Count (CBC) with differential
- Comprehensive profile (BUN, creatinine, sodium, potassium, chloride, CO2, calcium, glucose, total bilirubin, total protein, albumin, alkaline phosphatase, AST, ALT)
- Coagulation tests: Prothrombin time, APTT and INR (PT/PTT)
- Magnesium
- Uric Acid
- Urinalysis
- Pregnancy test (in women of childbearing potential)
    - Women of child bearing potential (WCBP), defined as a sexually mature woman who has not undergone surgical sterilization or who has not been naturally postmenopausal for at least 12 consecutive months (i.e., who has had menses any time in the preceding 12 consecutive months) must agree to use effective

contraceptive methods. Acceptable single methods include intrauterine device, vasectomy of a female patient's male partner, and contraceptive rod implanted into the skin. Abstinence (relative to heterosexual activity) can be used as the sole method of contraception if it is consistently employed as the patient's preferred and usual lifestyle and if considered acceptable by local regulatory agencies and ERCs/IRBs. Periodic abstinence (e.g., ca, ovulation, sympto-thermal, post-ovulation methods, etc.) and withdrawal are not acceptable methods of contraception. Acceptable combination methods (requiring use of two of the following) are acceptable: diaphragm with spermicide (cannot be used in conjunction with cervical cap/spermicide), cervical cap with spermicide (nulliparous women only), contraceptive sponge (nulliparous women only), male condom or female condom (cannot be used together), or hormonal contraceptive such as oral contraceptive pill, estrogen/progestin pill or progestin-only pill), contraceptive skin patch, vaginal contraceptive ring, or subcutaneous contraceptive injection. Acceptable methods of contraception must be used while on study treatment and for at least twelve weeks after the last dose of ZW25.

- All female patients of child-bearing potential will complete a serum beta-human chorionic gonadotropin (β-hCG) or urine pregnancy test (not more than 3 days before the first dose of ZW25); this test must be negative for the patient to be enrolled and to receive the study drug.

ECGs are required during screening, on Cycle 1 Day 1 and Cycle 3 Day 1.
Vital signs will be evaluated according to the Schedule of Assessments listed on section 11 of the protocol.

10.0 TREATMENT/INTERVENTION PLAN

Study treatment will begin on Day 1 of each 4 week dosing cycle (28 days).

In this study the recommended ZW25 dose will be 20mg/kg intravenously (IV) every two weeks on Days 1 and Days 15 a 28-day cycle.

Patients will continue to receive study treatment until they present with progressive disease (PD) per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1, develop unacceptable toxicity or withdraw consent, whichever comes first, or until the study is terminated.

Tumor assessments, including radiological assessments by computerized tomography (CT) or magnetic resonance imaging (MRI) scans are performed at Screening and subsequently every eight weeks for the first 24 weeks and then every twelve weeks until progression of disease, death or initiation of subsequent anti-cancer therapy, whichever occurs first.

Pre- and post-treatment fresh tumor biopsies, blood and serum samples will be collected for biomarker analysis. Post-treatment tumor biopsy will only be performed upon

progression of disease. Results from tissue testing will not be returned to patients. (See Exploratory Correlative Studies section for details)

End of Treatment and Follow-up

End of Treatment Visit
Patients may voluntarily withdraw from the study treatment at any time for any reason, and without prejudice to further treatment. In addition, patients may be withdrawn by the Investigator if they do not feel the patient is deriving clinical benefit or because the patient is experiencing unacceptable toxicity. The reasons for which a patient may be removed from study are listed in Section 12.

Patients who withdraw or is removed from study treatment will have an end of treatment visit within 7 days of the decision to discontinue study treatment. Additionally, these patients will undergo a 30-day follow-up safety visit. The eCRF will capture reasons for withdrawal.

30-Day Safety Follow-up
A safety follow-up visit will occur 30 days (+14 days) after the last treatment.
All serious adverse events, and those adverse events assessed by the Investigator as at least possibly related to study drug should continue to be followed until they resolve or stabilize, whichever comes first. Reporting of SAEs are detailed in Section 15.1.

Survival Follow-up
All patients who discontinue study treatment for any reason will be proceed onto survival follow up. Patients will be followed up for survival status every 3 months (from End of treatment visit) for 2 years until death, lost to follow up or withdrawal of consent.

Exploratory Correlative Studies

1. Anti-drug antibodies (ADA) will be assessed at baseline (baseline ADA can be collected on C1D1 pre dose) and pre-dose at Cycles 2, 4, 6, 8, 12, 18, 24 Day 1. The immunogenicity testing will be performed using validated assays in 3 steps as follows: screening assay (Tier 1), confirmation assay (Tier 2), and titration (Tier 3). Only samples positive in the screening assay will be tested in confirmation and further titrated to determine the titer of ADA.
   At each timepoint, 5mL of blood will be collected into a red top tube and processed as follows:
   - Invert 5x
   - Clot at least for 30 minutes
   - Separate serum within 30-60 minutes of collection
   - Centrifuge 1000-2000 x g at 4c for 15-20min
   - ~1.25mk serum into each 2ml cryovial

   Storage: Store at -70° F/-80°F (storage at -20° F acceptable) for up to 1 month. Ship frozen on dry ice monthly. Blood samples for ADA will be processed and stored at the Immune Monitoring Facility (IMF) until batch shipment to Zymeworks, Inc.

2. To explore the molecular associations between the *HER2* biomarkers: gene amplification (by NGS and ISH), protein overexpression by immunohistochemistry (IHC) and mutational status and/or copy # variations of relevant cancer-related genes using MSK-IMPACT platform in all patients and to determine mechanisms of underlying response and resistance.
3. Mandatory pre-treatment and post-treatment tumor biopsies will be obtained on all patients to assess HER2 expression, its association with treatment response and other genetic changes over time. Attempts will be made to collect 3 cores (Flash Frozen) of tumor material at each time point for research purposes under the current study. Biopsies will only be performed if deemed safe and feasible by the investigator. Post-treatment biopsy will only be done upon progression of disease. Tissue testing will be performed in the CMO. To determine mutational status and/or copy number variations of relevant cancer related genes using MSK-IMPACT platform in patients with response to therapy. MSK-IMPACT tests will be done on new biopsy specimens for research purposes in the context of this protocol. Results from these testing will not be reported to patients.
4. To determine the ability of the laboratory parameters to predict clinical benefit:
    a. All patients will undergo mandatory pre-treatment fresh tumor biopsy (if deemed clinically safe). Post-treatment fresh tumor biopsy will be done upon disease progression.
5. To evaluate the predictive value of changes in circulating tumor DNA variant allele frequency during treatment for response to ZW25. Circulating plasma cell-free DNA will be collected at pre-treatment (any time prior to C1D1), and at End of Treatment. MSK's standard cfDNA workflow will be followed (one streck tube).
    a. Liquid biopsy through the sequencing of plasma ctDNA has the potential to address multiple biologic questions, including global tumor heterogeneity. Targeted deep sequencing of candidate driver oncogenes facilitates analysis of the clonal structure of the tumor, and prioritization of clinically relevant actionable targets. As blood content theoretically integrates mutational data from all sites of disease, deep analysis of plasma ctDNA may offer a solution to the problem of assessing intratumoral heterogeneity with tumor biopsies, and ultimately could define a systemic genomic approach to guide application of targeted therapies. A novel bioinformatics algorithm called FACETS developed at Memorial Sloan Kettering will be applied to interrogate clonality from targeted sequencing of ctDNA.

Whole genome or whole exome sequencing will not be done in this study unless activity is seen after data review, at which point the protocol may be amended to include additional objectives.

Incidental Inherited Genomic Findings:

In the course of this research it is possible that some patients whose tumors are analyzed through investigational "next-generation" profiling in a research (non-CLIA) environment will be found to have somatic or germline mutations in genes that are known to be associated with an increased risk of cancer or other diseases. It will be stated in the consent that the participants will not receive any specific results from

research tests. The consent will tell participants that if they wish to have genetic testing done for personal reasons than they should make an appointment with the MSK Clinical Genetics Service.

If in the course of this research a research finding is obtained that, in the opinion of the investigator, may be critical to the preventive care of the participant or their family, the investigator can communicate that finding to the IRB Genomic Advisory Panel (GAP). The finding will be reviewed by the GAP to determine whether the incidental finding should be discussed with the participant. For MSK, in the event that the GAP determines that the finding should be discussed with the participant, and the participant has consented to be re-contacted, then the treating/consenting physician shall be contacted by the panel and asked to refer the participant to the Clinical Genetics Service for further discussion of the research finding.

The following information must be provided to GAP for review:
• Participant Name/MRN #
• Type of Biospecimen (tissue, blood, saliva)
• Incidental Finding
• Collection Protocol #
• Contact: rtmgapirb@mskcc.org

6. Early changes in clonal variant allele frequency of *HER2* may serve as a powerful predictor of response to targeted therapy. We hypothesize that plasma ctDNA can be used as a non-invasive early predictive biomarker to distinguish between responders and non-responders to targeted therapy, refining precision medicine. Clonal changes of actionable drivers and the emergence of new somatic genetic alterations through serial ctDNA sequencing should offer novel insights into understanding and overcoming drug resistance driven by Darwinian clonal evolution. This may be paradigm changing in the way we select therapy to treat patients and fundamentally change future clinical trials design.
7. To examine ORR in each cohort by different types of molecular alterations, HER2 amplification (by NGS and ISH separately), mutation and HER2 overexpression, and assess their predictive value for response.

11.0 EVALUATION DURING TREATMENT/INTERVENTION

Activity	**Screening**	**Cycle 1** (± 3 days)		**Cycle 2** (± 3 days)		**Cycle 3** (± 3 days)		**Cycles 4+** (± 3 days)		**End of Treatment** (within 7 days of decision to discontinue Treatment)	**30-Day Follow-up** (+ 14 Days)	**Survival Follow-up** (+14 days)
		Day 1	**Day15**	**Day 1**	**Day15**	**Day 1**	**Day15**	**Day 1**	**Day15**			
Informed consent	●[a]											
Demography	●[a]											
Medical History	●[a]											
Confirm Disease Diagnosis from fresh biopsy	●[a]											
Record Baseline Signs and Symptoms	●[a]	●										
Review and document IC/EC	●[a]											
Confirm patient continues to satisfy I/E Criteria		●										
Height	●[a]											
Physical Examination[b]	●[a]	●	●	●	●	●		●		●	●	
Weight	●[a]	●		●		●		●		●	●	
Vital signs[d]	●[a]	●	●	●	●	●		●		●	●	
ECOG PS	●[a]	●[j]		●		●		●		●	●	
Hematology and Chemistry[e]	●[c]	●	●	●	●	●	●	●	●	●	●	

Activity	**Screening**	**Cycle 1** (± 3 days)		**Cycle 2** (± 3 days)		**Cycle 3** (± 3 days)		**Cycles 4+** (± 3 days)		**End of Treatment** (within 7 days of decision to discontinue Treatment)	**30-Day Follow-up** (+ 14 Days)	**Survival Follow-up** (+14 days)
		Day 1	**Day15**	**Day 1**	**Day15**	**Day 1**	**Day15**	**Day 1**	**Day15**			
Magnesium[e]	●[a]	●		●		●		●		●	●	
Coagulation (PT/INR/ aPTT) [e]	●[c]					●				●		
cfDNA [o]	●[o]									●[o]		
Hepatitis B surface antigen [p]	●[a]											
Hepatitis B Core Ab (total) [p]	●[a,h]											
Hepatitis C antibody [h]	●[a,h]											
Urinalysis[e, f]	●[c]	●		●		●		●			●	
Uric Acid	●[c]											
Pregnancy Test (urine or Serum)[f]	●[c]	●[f]		●[f]		●[f]		●[f]			●[f]	
Radiologic tumor assessments [g]	●[a]			Every 8 weeks (from C1D1) until Week 24, then every 12 weeks (± 1 week)[g]						●[h]	●[h]	
12-Lead ECG	●[a]	●				●				●	●	
ECHO	●	Every 12 weeks (from C1D1)								●		
ZW25 Administration		●	●	●	●	●	●	●	●			
AE and SAE assessments[i]	●[k,i]	●[i]	●[i]	●[i]	●[i]	●[i]	●[i]	●[i]	●[i]	●[i]	●[i]	
Record concomitant medications	●[a]	●	●	●	●	●	●	●	●	●	●	
Research blood collection[m]	●[m]	●[m]		●				●[m]				

Activity	Screening	Cycle 1 (± 3 days)		Cycle 2 (± 3 days)		Cycle 3 (± 3 days)		Cycles 4+ (± 3 days)		End of Treatment (within 7 days of decision to discontinue Treatment)	30-Day Follow-up (+ 14 Days)	Survival Follow-up (+14 days)
		Day 1	Day15	Day 1	Day15	Day 1	Day15	Day 1	Day15			
Mandatory biopsy[n]	●									● only upon disease progression		
Survival Status [n]												● [n]

a. Within 28 days prior to the start of Cycle 1, Day 1
b. Directed physical examination is acceptable while on study treatment. Full examination is required at screening and the EOT visit.
c. Within 14 days prior to the start of Cycle 1, Day 1
d. Vital signs (blood pressure, pulse, respiration rate, and temperature) will be measured as outlined in the full protocol.
e. Day 1 laboratory assessments may be performed up to 4 days prior to study agent administration. Laboratory results must be reviewed prior to each scheduled administration of ZW25, with the exception of coagulation testing (PT/INR, aPTT). In the event of severe toxicity, laboratory tests must be repeated as necessary until the toxicity resolves or stabilizes.
f. For WCBP, a urine or serum pregnancy test will be performed at screening, prior to dosing on Day 1 of every cycle (it can be performed up to 14 days prior to Day 1) and at the 30-day Follow-Up visit. Additional testing may be performed in accordance with institutional requirements or local regulation.
g. Patients will complete tumor assessments every 8 weeks (from C1D1) until Week 24, then every 12 weeks (± 1 week). If a patient discontinues prior to documentation of PD, a tumor assessment is to be performed at the End of Study visit or 30-Day Follow up visit, if not performed within the previous 6 weeks. Patients who have discontinued study treatment for reasons other than PD will be followed per RECIST 1.1 every 12 weeks (±3 weeks) until documentation of PD, starting a subsequent anti-cancer therapy or for up to one year from Cycle 1, Day 1, whichever comes first.
h. As clinically indicated.
i. All AEs and SAEs from the time of informed consent should be recorded.
j. ECOG assessment is not necessary on Cycle 1 Day 1 if screening assessment was performed within 3 days prior
k. For logistical reasons such as holidays, a +/- 3 day window applies to all study visits.
l. Mandatory biopsy at screening and EOT (at time of progression of disease) within 14 days of EOT before initiating new treatment regimen.
m. Research bloods include ADA and cfDNA sample collection. Research bloods can be collected at screening or cycle 1 day 1 before initiating treatment for baseline collections.
   ADA will be collected at baseline and pre-dose at cycles 2, 4, 6, 8, 12, 18, 24 Day 1.
n. Survival status' can be documented with a phone call or any clinic visits.
o. CfDNA will be collected at screening or cycle 1 day 1 before initiating treatment for baseline collections and again at End of Treatment
p. Hepatitis B Testing, if not done previously at MSK to rule out active infection (see exclusion criteria for details)

12.0 CRITERIA FOR REMOVAL FROM STUDY

Discontinuation of Study Treatment Due to Adverse Events
If ZW25 is discontinued, the patient must be discontinued from the study. Study treatment should not be resumed in the case of the following treatment-related events.

- ≥ Grade 3 cardiac event
- Other non-hematologic events of Grade 4 severity
- Failure to meet re-treatment criteria within one cycle due to insufficient recovery from a treatment-related toxicity. In such cases, continuation of study treatment may be considered for those patients who have experienced clinical benefit if agreed upon by the Principal Investigator.

Removal of the Patient from the Study or from Study Drug Administration
The patient or legally authorized representative is free to withdraw consent and discontinue participation in the study at any time without prejudice to further treatment.

Patients will be removed from the study treatment when their disease worsens, and there is no clinical benefit. Additionally, a patient's participation in the study may be discontinued at any time at the discretion of the Investigator. The following may be justifiable reasons for the Investigator to remove a patient from the study:

- The patient suffers an intolerable adverse event
- Non-compliance, including failure to appear at one or more study visits
- The patient was erroneously included in the study
- The study is terminated.

If a patient or the patient's legal guardian(s), acting on behalf of the patient, discontinues participation in the study, or the patient is discontinued by the Investigator, the reason for discontinuation must be captured in the eCRF. Any AEs experienced up to the point of discontinuation must be documented on the AE eCRF. All serious adverse events (SAEs), and those AEs assessed by the Investigator as at least possibly related to study drug should continue to be followed until they resolve or stabilize, whichever comes first.

13.0 CRITERIA FOR OUTCOME ASSESSMENT AND ENDPOINT EVALUABILITY

13.1 Criteria for Therapeutic Response/Outcome Assessment

RESPONSE DEFINITION (RECIST 1.1)[48]

DEFINITIONS:

Baseline: Baseline is defined as the most recent assessment performed prior to the first dose of study treatment. Baseline assessments must be performed within the period defined in the protocol eligibility criteria.

Measurable Lesions: Except for lymph nodes (described below), measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥ 10 mm with CT scan (if CT scans have slice thickness greater than 5 mm, the minimum size of a measurable lesion is twice the slice thickness).

- To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and recorded.

- MRI may be substituted for contrast-enhanced CT for lesions at some anatomical sites, but not for lesions in the lungs. The minimum size for measurability is the same as for CT (10 mm) as long as the scans are performed with slice thickness of 5 mm and no gap. If MRI is performed with thicker slices, the size of a measurable lesion at baseline should be twice the slice thickness. In the event there are inter-slice gaps, this also needs to be considered in determining the size of measurable lesions at baseline.

Non-measurable lesion: all other lesions (or sites of disease) including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥ 10 to < 15 mm short axis), are considered non-measurable.

- Lymph nodes that have a short axis < 10mm are considered non-pathological and are not to be recorded or followed.

- Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable.

Target lesions:

All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, are to be identified as target lesions and measured and recorded at baseline.

- Target lesions are to be selected on the basis of their size (lesions with the longest diameter) to represent all involved organs, and to be those that lend themselves to reproducible repeated measurements.

- It may be the case that on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected.

- Target lesions will be measured at each assessment (longest axis for non-nodal lesions, shortest axis for measurable malignant nodal lesions).

  Non-target lesions: All other lesions (or sites of disease) including all non-measurable lesions (including pathological lymph nodes with ≥ 10 to < 15 mm short axis) and all measurable lesions over and above the 5 target lesions are to be identified as non-target lesions and recorded at baseline.

  - Measurements of these lesions are not required, but the presence, absence, unequivocal progression of each is to be recorded throughout follow-up.
  - Lymph nodes that have a short axis < 10 mm are considered non-pathological and are not to be recorded or followed.

  Special Considerations

  Clinical Examination of Lesions: Superficial or visible lesions that cannot be assessed by CT scan or MRI will only be considered for response assessment if these lesions are biopsy-proven metastatic lesions and ≥ 10 mm in diameter. These lesions will be considered non-measurable and thus non-target for response assessment.

  Cystic lesions: Cystic lesions thought to represent cystic metastases can be considered as measurable lesions if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesion.

  Bone lesions: Bone scan, PET scan or plain films are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.

- Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by cross-sectional imaging techniques such as CT or MRI can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above.
- Blastic bone lesions are non-measurable.

  Lesions with prior local treatment: Lesions situated in a previously irradiated area, or in an area subjected to other locoregional therapy, are usually not considered measurable; however, if they meet the following criteria, they may be considered for study:

  - there has been prior documented progression in the lesion by at least 2 sequential CT or MRI scans performed after the completion of radiation, or

- histopathological evidence of progression

Additionally, if such lesions meet the criteria for measurability, they may be considered target lesions.

Imaging Methods:

The same method of assessment and the same technique used to characterize each identified and reported lesion at baseline should be used during each follow-up assessment. Imaging-based evaluation is preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam (referring to biopsy-proven visible lesions(s) at the vaginal apex).

Chest X-ray: Lesions that are identified on chest X-ray must be confirmed and followed by CT scan. If there is/are pre-existing chest lesion(s) before the baseline tumor assessment, a chest X-ray is not necessary to assess those lesions. The pre-existing chest lesion(s) must be assessed at baseline and followed by CT scans.

Conventional CT or MRI: This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion is twice the slice thickness. MRI is also acceptable in certain situations (e.g., for body scan) except for lung.

Other methods of assessment, PET-CT, ultrasound and FDG-PET should not be used for response assessment in this study.

Time Point Assessments:

Patients will have tumor measurements performed within 28 days prior to baseline and every 8 weeks through Week 24 and then every 12 weeks after 24 weeks, per RECIST 1.1 guidelines.

At baseline, tumors and lymph nodes are classified and documented as target or non-target per the definitions provided above. It is possible to record multiple non-target lesions involving the same organ as a single item (e.g., ‘multiple liver metastases’).

At all post-baseline evaluations, the baseline classification (target, non-target) is to be maintained and lesions are to be documented and described in a consistent fashion over time (e.g., recorded in the same order on source documents and CRFs).

For target lesions, measurements should be taken and recorded in metric notation. All tumor measurements must be recorded in millimeters.

At each assessment, a sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported. The baseline sum of the longest diameters (SLD) will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease. The lowest SLD (nadir) since, and including, the baseline value will be used as reference for evaluating progression.

After baseline, the actual size of the target lesion should be documented, if possible, even if the lesions become very small. If in the opinion of the radiologist, the lesion has likely disappeared, 0 mm should be recorded. If the lesion is present but too small to measure, an indicator of "too small to measure" will be provided on the CRF (a default value of 5 mm will be imputed during analysis).

Non-target lesions are to be assessed qualitatively (present, resolved, or unequivocal progression) and new lesion, if any, are to be documented separately.

At each evaluation, a time point response is to be determined for target lesions, non-target lesions, new lesions and overall.

Time Point Response Criteria

Target Lesion Time Point Response (TPR)	
Complete Response (CR)	Disappearance of all target lesions. All pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm.
Partial Response (PR)	At least 30% decrease in the SoD of target lesions, taking as reference the baseline SoD
Progressive Disease (PD)	At least a 20% increase in the SoD of target lesions, taking as reference the smallest (nadir) SoD since and including baseline. In addition to the relative increase of 20%, the SoD must also demonstrate an absolute increase of at least 5 mm.
Stable Disease (SD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD.
Not Applicable (N/A)	No target lesions identified at baseline

Unable to Evaluate (UE)	One or more target lesions are not imaged and the remainder of the SoD compared with the nadir SoD does not meet the criteria for PD
If the target lesion for a patient meets the criteria for both PR and PD at a given time point, the target lesion response is PD. If the nadir SoD is 0 (i.e., the patient had a prior target lesion CR), the re-appearance of any prior target lesions to any degree constitutes PD.	
Non-Target Lesion TPR	
Complete Response (CR)	Disappearance of all non-target lesions and normalization of tumor marker level if tumor marker at baseline is above the upper normal limit. All lymph nodes must be non-pathological in size (< 10 mm short axis)
Progressive Disease (PD)	Unequivocal progression of non-target lesions. Unequivocal progression should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.
Not Applicable (N/A)	No non-target lesions identified at baseline
Unable to Evaluate (UE)	One or more non-target lesions are not imaged and the remaining non-target lesions do not meet the criteria for PD
If the target lesion for a patient meets the criteria for both PR and PD at a given time point, the target lesion response is PD. If the nadir SoD is 0 (i.e., the patient had a prior target lesion CR), the re-appearance of any prior target lesions to any degree constitutes PD.	

New Lesion TPR	
Yes	Lesion present at follow-up visit either for the very first time or re-appearing (i.e., lesion was present at baseline, disappeared at a follow-up visit and re-appeared later).
No	No new lesions present at follow up

Unable to Evaluate (UE)	Patient non-assessed or incompletely assessed for new lesion

Determining Overall TPR

Target Lesion TPR	Non-Target TPR	New Lesions TPR	Overall TPR
CR	CR or NA	No	CR*
CR	Non-CR/non-PD	No	PR*
CR	UE	No	PR*
PR	Non-PD or NA or UE	No	PR*
SD	Non-PD or NA or UE	No	SD
UE	Non-PD	No	UE
PD	Any	No or Yes or UE	PD
Any	PD	No or Yes or UE	PD
Any	Any	Yes	PD
NA	CR	No	CR*
NA	Non-CR/non-PD	No	Non-CR/non-PD
Non-PD	Non-PD	UE	UE

CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; UE, unable to evaluate; NA, not applicable (no such lesions at screening); Any, CR, PR, SD, PD, NA or UE.

The overall response at a given time point does not depend upon the overall response assigned at any prior time point.

*Patients with an overall response of CR or PR must have a repeat tumor assessment performed no less than 4 weeks after the criteria for response are first met

Confirmation - The main goal of confirmation of objective response is to avoid overestimating the observed response rate. For patients with an overall response of PR or CR a given time point, changes in tumor measurements must be confirmed by repeat assessments that should be performed no less than 4 weeks after the criteria for response are first met. However, the presence or absence of confirmation is not considered when assigning a time point response.

Best Overall Response - Best overall response, incorporating confirmation requirements, will be derived during statistical analysis from the series of time point responses and need not be considered when assigning response at any time point.

13.2 Criteria for Study Endpoint Evaluability

Patients who have consented to the study and who have received at least one dose of study treatment will be considered enrolled and evaluable. Those patients who've consented but did not successfully complete the screening process and did not receive a dose of ZW25 will be considered a screen failure. Patient numbers for patients who screen fail will not be re-issued.

14.0 BIOSTATISTICS

14.1 Populations for Analyses

All treated population: all treated patients regardless if they completed cycle 1 or the amount of drug received.

Efficacy population: All treated patients except patients without a post baseline assessment of response will be excluded.

Sample Size
This study aims to assess the activity of ZW25 in advanced HER2 overexpressing endometrial cancers and carcinosarcomas as measured by the best overall response rate as determined by RECIST 1.1. Assuming we use a binary endpoint of response, defined as best overall response of CR or PR versus not (best overall response ≤24 weeks from the start of treatment), a sample size of 25 patients provides 90% power to test the hypothesis that the response rate is promising (defined as 30% or higher) against a non-promising rate of 10% or lower. This calculation is based on historical data from studies with ineffective agents in a similar patient population, which have ORR < 10% and PFS rate at 6 months < 20%,[7,49-51] and uses a two-stage minimax Simon design, with Type I error=10%. Sixteen patients will be enrolled in the first stage and if 1 response is observed among the 16 the study will end for lack of activity. If >=2 responses out of 16 are observed, the study will continue to stage 2, where an additional 9 patients will be enrolled for a total of 25. At the end of the study, if at least 5/25 responses are observed then this will be considered a positive study (i.e. conclude that ORR is >10%).

Based on historical accrual rates in similar populations, and with the increased prior lines of therapy that will not be allowed for eligibility, we anticipate successful enrollment of 2 patients per month yielding a total accrual time of 18 months. Accrual will continue until 25 evaluable for efficacy response patients are treated (i.e. 25 patients in efficacy population as defined above).

Sensitivity analysis for ORR will include in the calculation of ORR patients who do not have post baseline assessment of response as failures.

All statistical analyses will be performed using the most recently released version of SAS statistical software, unless otherwise noted. For categorical variables, the number (n) and percent of each category within a parameter will be presented. For continuous variables, the sample size (n), mean, median, and standard deviation, as well as the minimum and maximum values, will be presented. Missing data will not be imputed unless otherwise stated. There will be a detailed description of patient disposition, patient demographics, and baseline characteristics.

We will report the following statistics for the secondary objectives:

- The clinical benefit rate (CBR) of ZW25 therapy, defined as the percentage of patients with complete response (CR) + partial response (PR) + stable disease (SD) ≤24 weeks from the start of treatment will be reported and the 90% confidence interval will be estimated using exact binomial proportions
- Progression free survival (PFS), defined as the duration of time from start of treatment to time of recurrence, progression, or death due to any cause, whichever occurs first will be reported. Patients will be censored at last follow up date. The Kaplan Meier estimate of median PFS will be reported.
- Overall survival is defined as the duration of time from start of treatment to time of death due to any cause. Patients who are alive will be censored at last follow up date. The Kaplan Meier estimate of median OS will be reported.

- The duration of response (DOR) of ZW25 therapy, defined as the time from which measurement criteria are met for CR or PR (whichever status is recorded first) until the first date of documented disease progression, will be estimated using the Kaplan Meier method. Patients without documented progression will be censored at last follow up.
- Adverse events by the current version of Common Terminology Criteria for Adverse Events version 5 (CTCAE v5) will be tabulated in order to assess the safety profile and tolerability of ZW25therapy in patients with recurrent/persistent endometrial cancer.

ADA titers are a continuous variable and these will be assessed descriptively for changes over time as part of exploratory aims.

All patients will have their tumors molecularly profiled using the MSK-IMPACT platform, to evaluate for genomic alterations defined by MSK-IMPACT. Testing will (looking for presence/absence of genes at baseline and at end of study) be correlated to objective responses outcomes (binary covariates of CR or PR versus not) in an exploratory manner. Chi square of Fishers' exact test will be used to test this association. A subset analysis of patients who respond and then progress and have post progression material for molecular profiling will be performed in order to determine the mechanism(s) underlying acquired resistance. Specifically, we will be looking for presence of genetic alterations (at progression compared to baseline) which based on their understood biological mechanism may explain

acquired resistance. This analysis will be descriptive with the intention of understanding genetic alterations over time (at progression) and the types of mutation alterations among patients who respond and then progress. Patients will be followed up for a minimum of 12 months. Most variables above are binary (presence/absence) or expressed (yes/no) and they will be tested for association with response (yes/no) using Chi square of Fishers' exact test.

Serial pre- and post-treatment blood samples will be collected for cell-free tumor DNA analysis and sequenced using continuous quantitative methods (digital droplet PCR or hybridization capture next-generation sequencing) for the Rb, CD-K, PI3K- pathway alterations identified by pre-treatment and post-treatment tumor testing and descriptively correlated to clinical outcome. Binary covariates (presence/absence) will be tested for association with response (binary: CR or PR vs not) using Chi square of Fishers' exact test. Circulating tumor DNA is a continuous variable and these will be assessed descriptively for changes over time as part of exploratory aims.

15.0 TOXICITIES/RISKS/SIDE EFFECTS

The treating investigator or qualified designee will assess each subject to evaluate for potential new or worsening AEs as specified in the Schedule of Assessments (see Section 10.0) and more frequently if clinically indicated. Adverse experiences will be graded and recorded throughout the study and during the follow-up period according to NCI CTCAE Version 5.0. Toxicities will be characterized in terms regarding seriousness, causality, toxicity grading, and action taken with regard to trial treatment.

ZW25 Monitoring and Management of Adverse Events

Infusion-related Reactions

Some patients treated with IV infusions of therapeutic drugs have experienced concurrent infusion-related reactions (see CTCAE Version 5.0). The signs and symptoms may vary and include for example, headache, fever, facial flushing, pruritus, myalgia, nausea, chest tightness, dyspnea, vomiting, erythema, abdominal discomfort, diaphoresis, shivers, lightheadedness, hypotension, palpitations, and somnolence. Anaphylaxis might occur at any time during an infusion.

While ZW25 is a fully humanized antibody, infusion reactions may occur. Infusion reactions consist of a symptom complex characterized by fever and chills, and may include nausea, vomiting, pain, headache, dizziness, dyspnea, hypotension, rash, and asthenia. Severe and potentially fatal reactions may include bronchospasm, anaphylaxis, angioedema, hypoxia, and severe hypotension. Infusion reactions may occur during or immediately following the initial infusion or at a later time point. While severe reactions usually occur during or immediate after infusion, onset and clinical course can be variable.

Prior to dosing with ZW25, all patients must receive prophylactic treatment for infusion reactions consistent with institutional standards that includes a corticosteroid. The

recommended regimen also includes acetaminophen orally, diphenhydramine (or equivalent) orally or IV 30 minutes through 60 minutes prior to infusion of ZW25 (recommended doses are: acetaminophen 650 mg, diphenhydramine 50 mg), and a corticosteroid (hydrocortisone, dexamethasone, or equivalent). If an alternative premedication regimen is thought to be required, approval from Zymeworks, Inc. should be sought. For patients who experience an infusion reaction despite initial premedication, additional prophylactic treatment may be added prior to subsequent doses, including an H2 blocker such as ranitidine as per institutional guidelines.

In the event of an infusion reaction, ZW25 infusion should be interrupted and medical therapy administered according to institutional standard of care (which, depending upon severity of the event, may include but not be limited to use of H1 and H2 inhibitors, corticosteroids, oxygen, IV fluids, epinephrine, and bronchodilators). Patients should be evaluated and carefully monitored until complete resolution of signs and symptoms. ZW25 should be discontinued in patients who experience a life-threatening (Grade 4) infusion reaction. Patients who experience a Grade 3 infusion reaction may be retreated at the discretion of the investigator at the next scheduled treatment. Such patients should receive additional prophylactic medication that may include a corticosteroid, and the duration of the infusion should be increased.

Infusions should be administered over 120 minutes through 150 minutes for the first 2 doses. If tolerated, infusion time may be reduced to 90 minutes for the next 2 doses, with reduction to 60 minutes for subsequent infusions at the discretion of the treating physician. Patients who experience a Grade 1 or Grade 2 infusion reaction may resume infusion of drug at a reduced infusion rate (30% through 50% slower than initial rate).

Samples will be collected from all treated patients for retrospective analysis to detect the presence of antibodies to ZW25 (i.e., ADA). In the event that an infusion reaction occurs or there is a suspicion of a hypersensitivity event, analysis of available samples collected to date for that patient may be performed.

Potential Cardiotoxicity

HER2 targeted therapies have been associated with cardiotoxicity. Therefore, only patients who have baseline normal left ventricular ejection fraction and no history of significant cardiac disease will be eligible for treatment with ZW25. Patients with a lifetime cumulative dose of anthracycline >300 mg/m2 or who have received anthracycline treatment within 90 days of the expected first dose of ZW25 are not eligible for treatment.

Patients are monitored per the study-specific protocol for changes in cardiac function. Cardiac monitoring includes assessment of ECG (frequency and type of abnormalities using standard 12-lead ECG, including heart rate, PR interval, QRS complex, QTcF), and echocardiogram (estimation of ejection fraction).

Management of decreased left ventricular ejection fraction (LVEF), regardless of relationship to study drug, is described in Table 3 below.

Table 3: Management Guidelines for LVEF Dysfunction

Left Ventricular Dysfunction	Management
Symptomatic cardiac heart failure	● Discontinue ZW25
LVEF <40%	● Do not administer ZW25 ● Repeat LVEF assessment within 4 weeks ● If LVEF <40% is confirmed, discontinue ZW25
LVEF below institutional limits of normal and ≥ 10% points below pre-treatment baseline	● Do not administer ZW25 ● Repeat LVEF assessment within 4 weeks ● If the LVEF has not recovered to within 10% points from baseline, discontinue ZW25
LVEF 40% to ≤ 45% and decrease is < 10% points from baseline	● Continue treatment with ZW25 ● Repeat LVEF assessment within 4 weeks
LVEF > 45%	● Continue treatment with ZW25, as applicable

Gastrointestinal Toxicity

The most common ZW25-related gastrointestinal TEAEs (> 20%) were diarrhea and nausea. Two patients in Part 1/2 developed ZW25-related Grade 3 diarrhea (20 mg/kg), which subsequently resolved with medications. No patients in Part 3 developed ZW25 Grade 3/4 gastrointestinal toxicity.

Table 4: Management Guidelines for Potential Infusion-related Reactions

Infusion Reaction CTCAE v5.0Severity Grade	Management
Grade 1: Mild, transient reaction	Maintain infusion rate unless progression of symptoms to ≥ Grade 2; if symptoms worsen, refer to guidelines below Promethazine (or equivalent) 150 mg PO per day for nausea (or equivalent) Diphenhydramine (or equivalent) 25-50 mg PO or IV prn Methylprednisolone 125 mg (or equivalent) IV prn

Infusion Reaction CTCAE v5.0Severity Grade	Management
Grade 2: Moderate	Interrupt infusion and disconnect infusion tubing from patient Promethazine (or equivalent) 150 mg PO per day for nausea Diphenhydramine (or equivalent) 25-50 mg PO or IV prn Methylprednisolone 125 mg (or equivalent) IV PRN) After recovery from symptoms, resume the infusion at 50% of the previous rate and if no further symptoms appear, gradually increase rate until infusion is completed. For subsequent dosing in future cycles, patients should be pre-medicated with dexamethasone (or equivalent) 8 mg PO BID the day prior to drug administration and acetaminophen (or equivalent) 650 mg PO and diphenhydramine (or equivalent) 25-50 mg PO 30-60 minutes prior to dosing.
Grade 3: Severe, prolonged reaction not rapidly responsive to symptomatic medication and/or brief interruption of infusion; recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae	Immediately stop infusion and disconnect infusion tubing from subject Administer diphenhydramine (25-50 mg) IV (or equivalent) Administer IV steroids (methylprednisolone (or equivalent) up to 0.5mg/kg Q 6h) to treat ongoing reaction and prevent recurrence Administer bronchodilators (nebulized albuterol/salbutamol, 2.5-5 mg in 3 mL of saline or equivalent) as medically indicated Administer normal saline as medically indicated Administer epinephrine (0.2-0.5 mL of a 1:1000 dilution (0.2-0.5 mg) SQ or IM) as medically indicated. Epinephrine should only be used if all other treatment methods fail to manage the infusion-related reaction. Advise patient to seek emergency treatment and notify investigator/clinic if the infusion-related symptoms recur after discharge from clinic. Report as a serious adverse event
Grade 4: Life-threatening consequences, urgent intervention indicated	Management as for Grade 3 reaction and permanently discontinue study medication treatment

Monitoring and Management of Diarrhea Following the Administration of Study Treatment: ZW25-associated Diarrhea

Mild to moderate diarrhea has been frequently reported in patients treated with ZW25. Patients will be prescribed loperamide as a prophylactic measure prior to Cycle 1 Day 1 of treatment and will be instructed on its use. Patient should be advised to contact their treating physician at the first sign of diarrhea and should be treated according to standard institutional practice. One suggested regimen would be the administration of 2-4mg of loperamide at the first sign of loose stool, with repeat dosing every 2 hours until symptoms resolve and up to a maximum of 16mg/day.[46] For Diarrhea that is G3 despite use of optimal anti-diarrheal treatment, hold drug until resolved to ≤ grade 1, then resume at a lower dose level.

Monitoring and Management of Nausea and Vomiting Following the Administration of ZW25

Nausea and vomiting have been reported in patients treated with ZW25. Patients should be advised to contact their treating physician at the first sign of vomiting or worsening nausea. Patients should be treated according to the American Society of Clinical Oncology (ASCO) Clinical Practice Guidelines for the use of antiemetics[47] outlined in Table 5.

Table 5: Management of Nausea and Vomiting

Severity Grade (CTCAE v5.0 Grade)	**Management**
Grade 1	Administer single 8 mg dose of dexamethasone before therapy
Grade 2	Administer a 5- HT_3 receptor antagonist on day 1 (e.g. palonosetron, granisetron, or ondansetron) in combination with dexamethasone on days 1-3 or treat as per institutional guidelines. Aprepitant may be added to the combination.
Grades 3 and 4	Administer a neurokinin 1 receptor antagonist (e.g. aprepitant on days 1-3 or fosaprepitant on day 1), in combination with a 5-HT_3 receptor antagonist on day 1 only, and dexamethasone on days 1-3 or 1-4 or treat as per institutional guidelines. For G3 nausea/vomiting despite optimal use of antiemetics, hold drug until resolved to ≤ grade 1, then resume at a lower dose level.

Other non-hematological toxicities: Except adverse events related to underlying disease, Grade 3 fatigue, isolated symptomatic G3 biochemistry abnormalities that last for < 7 days including electrolyte abnormalities that respond to medical intervention, for a Grade 3 event, hold study drug until resolved to ≤ Grade 1, then resume at lower level. For any grade ≥ 3 cardiac events and for Grade 4, non-hematological toxicities, permanently discontinue ZW25 treatment.

For any Grade 3 hepatic toxicity that does not resolve to baseline within 7 days, an abdominal CT scan must be performed to assess whether it is related to disease progression.

Re-treatment Criteria

To Begin a New Cycle of Treatment or continue treatment within a cycle

For a patient to begin a new cycle or continue a cycle of therapy, the following criteria must be met.

- ANC must be ≥ $1.0x10^9$/L (1,000/μL)
- Platelet count must be ≥ 75 x 10^9/L (75,000/μL)

- All non-hematologic toxicities for which a causal association to study treatment cannot be ruled out, must be ≤ Grade 1 (except alopecia) or returned to baseline.

- If the patient does not meet these criteria, dosing will be delayed and the patient should be re-evaluated within 48-72 hours. Dosing with may resume if these criteria have been met.

If treatment is delayed due to treatment-related toxicity longer than one cycle, then the patient should be removed from study treatment. In such cases, continuation of study treatment may be considered for those patients who have experienced clinical benefit if agreed upon by the principal investigator and Zymeworks.

The use of granulocyte growth factors in accordance with ASCO guidelines may be implemented at the discretion of the treating physician.

Follow-up for AEs Leading to Discontinuation
Patients who discontinue study treatment for an AE or an abnormal laboratory value must be followed at least once a week for 4 weeks, and subsequently at 4-week intervals until resolution or stabilization of the adverse event or laboratory abnormality, whichever occurs first.

Dose Modification Guidelines
ZW25 Dose Reduction Following an AE
ZW25 dose may be reduced at the discretion of the Investigator after discussion with Zymeworks. Patients who develop adverse events requiring an interruption of ZW25 may resume treatment at a reduced dose level as shown in Table 6.

Table 6: ZW25 Dose Modification Guidelines

Regimen	**If the patient was receiving ZW25 at:**
Dose Level 1	20mg/kg intravenously (IV) every two weeks
Dose Level -1	15 mg/kg every two weeks
Dose Level -2	10 mg/kg every two weeks
**Reduction of the ZW25 dose below 10 mg/kg will not be permitted.*	

Overdose and Medication Error

Overdose: There is no known treatment/antidote available for ZW25. Supportive measures should be instituted if an instance arises in which a patient suffers an overdose of any study drug.

Medication Error: Zymeworks must be immediately notified in the event of error in prescribing, dispensing, administering and/or use of ZW25 or of any study drug, and the event must be reported on the eCRF.

If an error resulted in a serious adverse event, a Serious Adverse Event Report Form must be submitted within 24 hours of the event.

15.1 Serious Adverse Event (SAE) Reporting

An adverse event is considered serious if it results in ANY of the following outcomes:

- Death
- A life-threatening adverse event
- An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect
- Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition

Note: Hospital admission for a planned procedure/disease treatment is not considered an SAE.

SAE reporting is required as soon as the participant starts investigational treatment/intervention. SAE reporting is required for 30-days after the participant's last investigational treatment/intervention. Any event that occur after the 30-day period that is unexpected and at least possibly related to protocol treatment must be reported.

Please note: Any SAE that occurs prior to the start of investigational treatment/intervention and is related to a screening test or procedure (i.e., a screening biopsy) must be reported.

All SAEs must be submitted in PIMS. If an SAE requires submission to the HRPP office per IRB SOP RR-408 'Reporting of Serious Adverse Events', the SAE report must be submitted within 5 calendar days of the event. All other SAEs must be submitted within 30 calendar days of the event.

The report should contain the following information:

- The date the adverse event occurred

- The adverse event
- The grade of the event
- Relationship of the adverse event to the treatment(s)
- If the AE was expected
- Detailed text that includes the following
    - An explanation of how the AE was handled
    - A description of the participant's condition
    - Indication if the participant remains on the study
- If an amendment will need to be made to the protocol and/or consent form
- If the SAE is an Unanticipated Problem

15.2. External SAE Reporting

For IND/IDE protocols:
The SAE report should be completed as per above instructions. If appropriate, the report will be forwarded to the FDA by the IND Office

15.2.1 Pharmaceutical Specific Reporting

Recording Adverse Events and Serious Adverse Events
AEs (including SAEs) will be documented on the AE eCRF and monitored continuously throughout the study from the time of informed consent until 30 days after the patient's last study treatment or until the event has resolved or stabilized or becomes chronic, whichever comes first. AEs attributed to study procedures should also be documented on the AE eCRF.

15.2.2 Adverse Events of Special Interest (AESI)
An adverse event of special interest (AESI) (serious or non-serious) is one of scientific and medical concern specific to the Grantor's product for which ongoing monitoring and rapid communication by the investigator to the Grantor could be appropriate. These include infusion-related reactions, non-infectious pulmonary toxicities, and cardiac-events of absolute decrease in LVEF of ≥ 10 percentage points from pretreatment baseline and absolute value <50% and/or grade ≥2 heart failure. These are reportable to the Grantor via monthly listings, unless they are serious and assessed by the investigator as Related to zanidatamab, in which case they are reportable to Zymeworks Drug Safety in an expedited manner using a CIOMS-I form.

The Investigator will promptly supply all information identified and requested by the Grantor regarding the SAE, AESI, or pregnancy.

Reporting to Zymeworks
Any SAE assessed by the Investigator as Related to a zanidatamab or pregnancy that occurs in a study subject between the time of first study drug administration and 30 days after last study drug administration will be reported to Zymeworks Drug Safety

(drugsafety@zymeworks.com) within 24 hours of first awareness of the event. For SAE reporting, including those that are expedited, completed CIOMS-I forms will be provided to Zymeworks. Any SAEs assessed by the Investigator as NOT Related to zanidatamab should be reported to Zymeworks via monthly listings.

Any SAEs deemed related to zanidatamab occurring beyond 30 days after the last study drug administration should be reported to Zymeworks (drugsafety@zymeworks.com).

SADRs
A full report for SAEs that are related to the Product shall be transmitted to Zymeworks on a CIOMS-I form within 24 hours of the awareness date.

Other SAEs
SAEs that are unrelated to the Product shall be transmitted to Zymeworks within thirty (30) calendar days of the awareness date via monthly listings.

AESIs
Non-serious AESIs shall be forwarded to Zymeworks within thirty (30) calendar days of the awareness date via monthly listings.

Pregnancy reports
While such reports are not serious AEs or Adverse Drug Reactions (ADRs) per se, as defined herein, any reports of pregnancy where the fetus may have been exposed to the Product, shall be transmitted to Zymeworks within 24 hours of the awareness date. Pregnancies will be followed up until the outcome of the pregnancy is known, whenever possible, based upon due diligence taken to obtain the follow-up information.

Reporting a Pregnancy
Pregnancy and lactation are exclusion criteria. Zymeworks must be immediately notified in the event of a pregnancy occurring during the course of the study and through 7 months after a patient's last dose of ZW25 whichever is earlier. Pregnancy is not to be reported as an AE; the CIOMS-I form should be used to report a pregnancy. All reported pregnancies must be followed to the completion/termination of the pregnancy. Pregnancy outcomes of spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage and stillbirth must be reported as serious adverse events (Important Medical Events). The reporting procedures will be followed, including pregnancies and pregnancy outcomes listed above are reportable to Zymeworks in the same timeframe as SAEs which are assessed by the investigator as Related to zanidatamab. If the pregnancy continues to term, the outcome (health of infant) must also be reported.

16.0 PROTECTION OF HUMAN PARTICIPANTS

The responsible principal investigator (PI) will ensure that this study is conducted in agreement with the declaration of Helsinki. The study will seek to protect the rights of

human subjects in every way. The potential risks, including adverse drug reactions and potential benefits in terms of pain control will be discussed in detail with the patients.

Potential side effects as outlined above will be discussed with the patients. No patient will be required to participate in the study and participation, or refusal to do so, will not affect the patient's care or treatment.

Participation will be purely voluntary, patient confidentiality will be maintained. No results of the study will be presented or discussed in a fashion that will allow identification of a patient in the study. All adverse events will be fully reported to the IRB in a timely fashion as required.

16.1 Privacy

MSK's Privacy Office may allow the use and disclosure of protected health information pursuant to a completed and signed Research Authorization form. The use and disclosure of protected health information will be limited to the individuals/entities described in the Research Authorization form. A Research Authorization form must be approved by the IRB and Privacy Board (IRB/PB).

The consent indicates that individualized de identified information collected for the purposes of this study may be shared with other qualified researchers. Only researchers who have received approval from MSK will be allowed to access this information which will not include protected health information, such as the participant's name, except for dates. It is also stated in the Research Authorization that their research data may be shared with others at the time of study publication.

16.2 Data Management

A Clinical Research Coordinator (CRC) will be assigned to the study. The responsibilities of the CRC include project compliance, data collection, extraction and data entry, data reporting, coordination of the activities of the protocol study team and, of the flow of regulatory compliance.

The data collected for the study will be entered into a secure database (Medidata RAVE). All routine blood test results required per protocol will be captured in Medidata RAVE in addition to the baseline medical conditions and disease information, response assessments, off-study documentation, and toxicity grade and attribution. Source documentation will be available to support the electronic patient record.

MSKCC will hold the IND and will be responsible for all safety monitoring. All SAEs will be reported to the MSKCC IRB (as applicable). The safety of the study will be monitored by the MSKCC Data and Safety Monitoring Committee.

Weekly registration reports will be generated by the CRC and reviewed by the PI to monitor patient accruals and completeness of registration data. Routine data quality reports will be generated to assess missing data and inconsistencies.

Accrual rates and extent and accuracy of evaluations and follow-up will be monitored periodically throughout the study. Recurrent lapses in data collection, prospective and retrospective deviations will be discussed with the study team and a corrective action plan will be generated and shared with the team. Accrual goals and factors impacting accrual goals will be discussed at the weekly GMO Protocol meetings.

If accrual proceeds more quickly than anticipated, it may be slowed or staggered at the discretion of the Principal Investigator, to account for safety concerns or data management resources.

Final data sets for publication are required to be locked and stored centrally for potential future access requests from outside entities.

16.3 Quality Assurance

Data and project enrollment will be monitored on an ongoing basis by the Principal Investigator. The CRC will inform the PI about the number of patients enrolled, the number of patients in follow-up, and any other outstanding issues protocol related. A log will be maintained of all patients consented and treated. The study data will be assessed for completeness by the PI. Random-sample data quality and protocol compliance audits will be conducted by the study team at minimum of two times per year or more frequently if problems are encountered.

Biweekly registration reports will be generated to monitor patient accruals and completeness of registration data. Routine data quality reports will be generated to assess missing data and inconsistencies. Enrollment logs will be sent to Zymeworks to facilitate drug inventory. These enrollment logs do not contain PHI.

16.4 Data and Safety Monitoring

The Data and Safety Monitoring Plan utilized for this study must align with the MSK DSM Plan, where applicable.

The Data and Safety Monitoring (DSM) Plans at Memorial Sloan Kettering were approved by the National Cancer Institute in August 2018. The plans address the new policies set forth by the NCI in the document entitled “Policy of the National Cancer Institute for Data and Safety Monitoring of Clinical Trials.”

There are several different mechanisms by which clinical studies are monitored for data, safety and quality. At a departmental/PI level there exists procedures for quality control

by the research team(s). Institutional processes in place for quality assurance include protocol monitoring, compliance and data verification audits, staff education on clinical research QA and two institutional committees that are responsible for monitoring the activities of our clinical trials programs. The committees: *Data and Safety Monitoring Committee (DSMC)* for Phase I and II clinical trials, and the *Data and Safety Monitoring Board (DSMB)* for Phase III clinical trials, report to the Deputy Physician-In-Chief, Clinical Research.

During the protocol development and review process, each protocol will be assessed for its level of risk and degree of monitoring required.

The MSK DSMB monitors phase III trials and the DSMC monitors non-phase III trials. The DSMB/C have oversight over the following trials:

- MSK Investigator Initiated Trials (IITs; MSK as sponsor)
- External studies where MSK is the data coordinating center
- Low risk studies identified as requiring DSMB/C review

The DSMC will initiate review following the enrollment of the first participant/or by the end of the year one if no accruals and will continue for the study lifecycle until there are no participants under active therapy and the protocol has closed to accrual. The DSMB will initiate review once the protocol is open to accrual.

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18.0 APPENDICES

Appendix A: Eastern Cooperative Oncology Group (ECOG) Performance Status Scale[52]

GRADE	SCALE
0	Fully active, able to carry out all pre-disease performance without restriction. (Karnofsky 90-100)
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work. (Karnofsky 70-80)

2	Ambulatory and capable of all self-care but unable to carry out work activities. Up and about more than 50% of waking hours. (Karnofsky 50-60)
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours. (Karnofsky 30-40)
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair. (Karnofsky 10-20)

Appendix B: Anaphylaxis Precautions

EQUIPMENT NEEDED

• Tourniquet

• Oxygen

• Epinephrine for subcutaneous, intravenous, and/or endotracheal use in accordance with standard practice

• Antihistamines

• Corticosteroids

• Intravenous infusion solutions, tubing, catheters, and tape

PROCEDURES

In the event of a suspected anaphylactic reaction during study treatment infusion, the following procedures should be performed:

1. Stop the study treatment infusion.

2. Apply a tourniquet proximal to the injection site to slow systemic absorption of study treatment. Do not obstruct arterial flow in the limb.

3. Maintain an adequate airway.

4. Administer antihistamines, epinephrine, or other medications as required by patient status and directed by the physician in charge.

5. Continue to observe the patient and document observation.