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Phase II Trial of Pertuzumab, Trastuzumab, and Hyaluronidase-zzxf (HP) Plus Enzalutamide for the Treatment of Selected Patients With Metastatic Castration-Resistant Prostate Cancer (TraPPer)

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Mayo Clinic Comprehensive Cancer Center

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√Study contributor(s) not responsible for patient care

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Drug Company Supplied: pertuzumab, trastuzumab, hyaluronidase-zzxf

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Protocol Resources

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Lab contact	[redacted]
Serious Adverse Event Reporting	[redacted]

*No waivers of eligibility allowed

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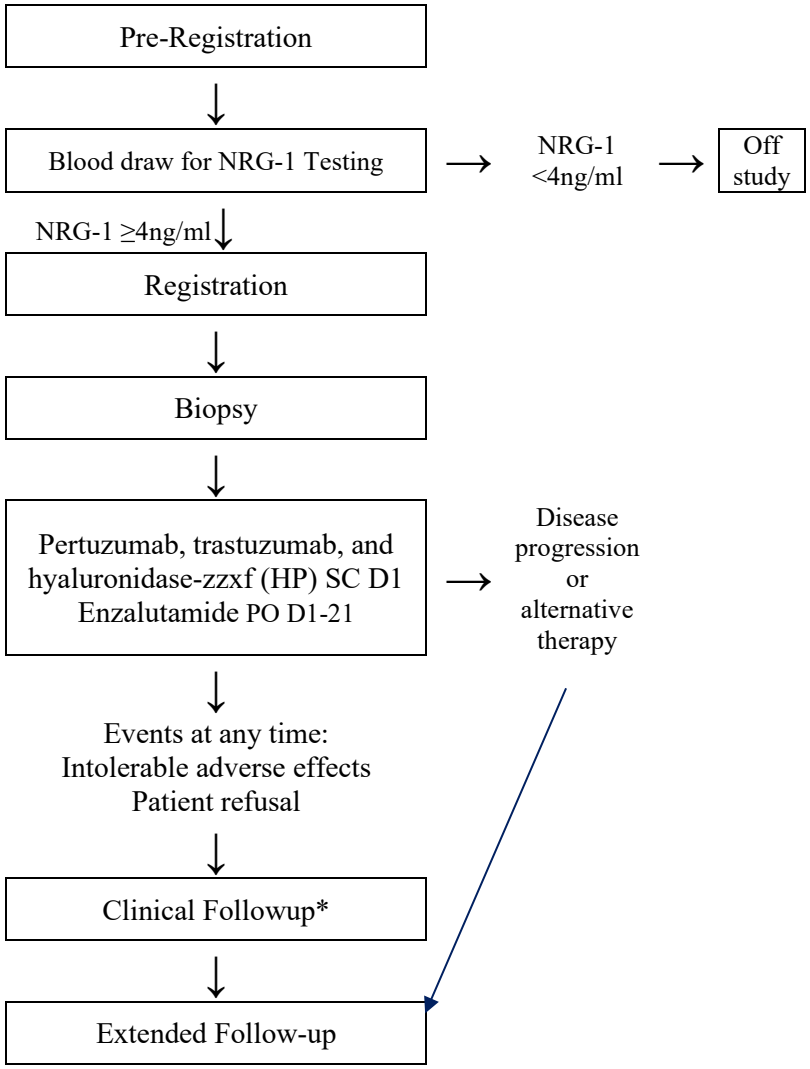
Schema

Safety Run-in Only: Prior to discussing protocol entry with the patient, access the Mayo Clinic Research Registration Application to ensure a place on the protocol is open to the patient and reserve a slot



*CFU approximately every 3 months for up to one year

Cycle = 21 ±3 days

Generic name: pertuzumab, trastuzumab, and hyaluronidase-zzxf (HP) Brand name(s): PHESGO® Availability: Commercial agent supplied by Genentech	Generic name: enzalutamide Brand name(s): XTANDI® Availability: Commercial supply

1.0 Background

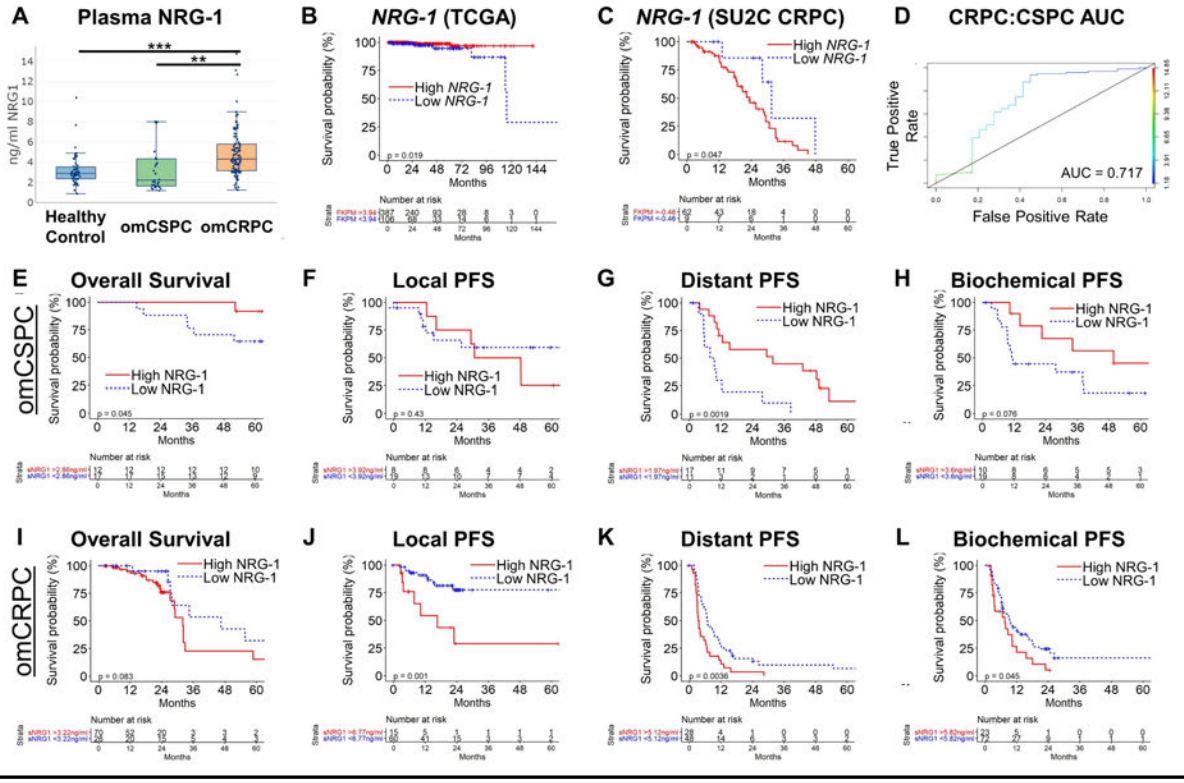
1.1 Prostate Cancer

Treatment resistance is the single most pressing challenge in the treatment of prostate cancer. Castration-resistant prostate cancer (CRPC) kills over 100,000 men each year (Centre 2020; Siegel et al. 2021). Androgen receptor (AR) signaling drives prostate cancer development and is the primary target for prostate cancer treatment (Huggins 1946). Unfortunately, most clinically significant prostate cancer develops resistance to androgen deprivation therapy (ADT) and is termed CRPC. Second-generation antiandrogens like enzalutamide (ENZ) have improved outcomes in CRPC, but this effect usually lasts only about 18 months (Beer et al. 2014; Hussain et al. 2018; Penson et al. 2016). After progression despite chemotherapy and second-generation antiandrogen therapy, additional resistance develops, and treatment becomes difficult. Thus, *there is a critical need to investigate methods to overcome treatment resistance in prostate cancer*.

1.2 NRG-1 as a marker or treatment resistance

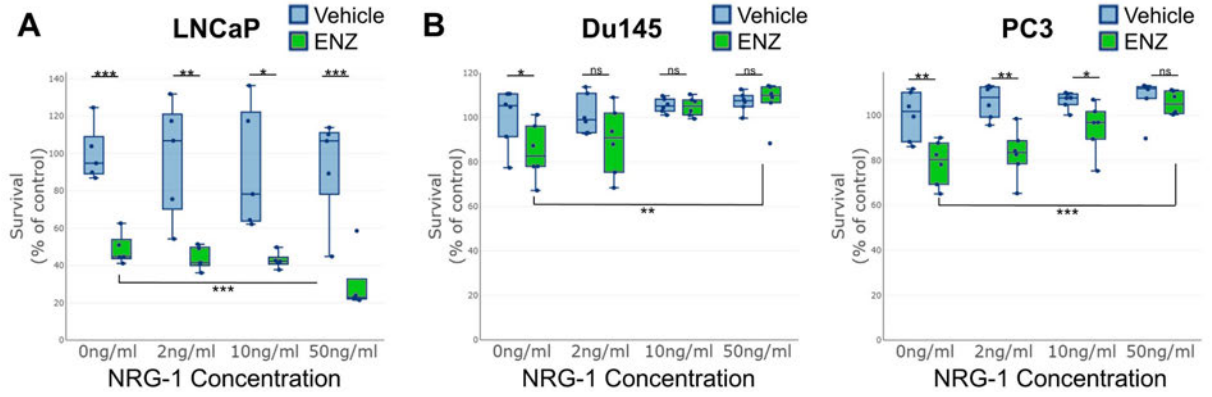
It is known that NRG-1 feeds CRPC cells to induce treatment resistance (Morris et al. 2002; Zhang et al. 2020). However, previous attempts to block NRG-1 signaling with trastuzumab monotherapy have been disappointing in clinical trials (Ziada et al. 2004). We recently discovered that NRG-1 mediates a systemic "switch" between castration-sensitive prostate cancer (CSPC) and CRPC. NRG-1 is elevated in the plasma of patients with metastatic CRPC (*Fig 1A-D*) and is measured by ELISA. Paradoxically, high levels of NRG-1 predict superior outcomes in CSPC (*Fig 1E-H*) but *inferior* outcomes in CRPC (*Fig 1I-L*).

*Fig 1 – **(A)** High NRG-1 transcription predicts poor outcomes in the SU2C dataset. **(B-C)** High systemic NRG-1 readily identifies our CRPC cohort. **(D)** Treatment of CRPC cells with NRG-1 induces enzalutamide resistance. **(E-H)** High systemic NRG-1 predicts superior outcomes in CSPC. **(I-L)** High systemic NRG-1 predicts inferior outcomes in CRPC.*



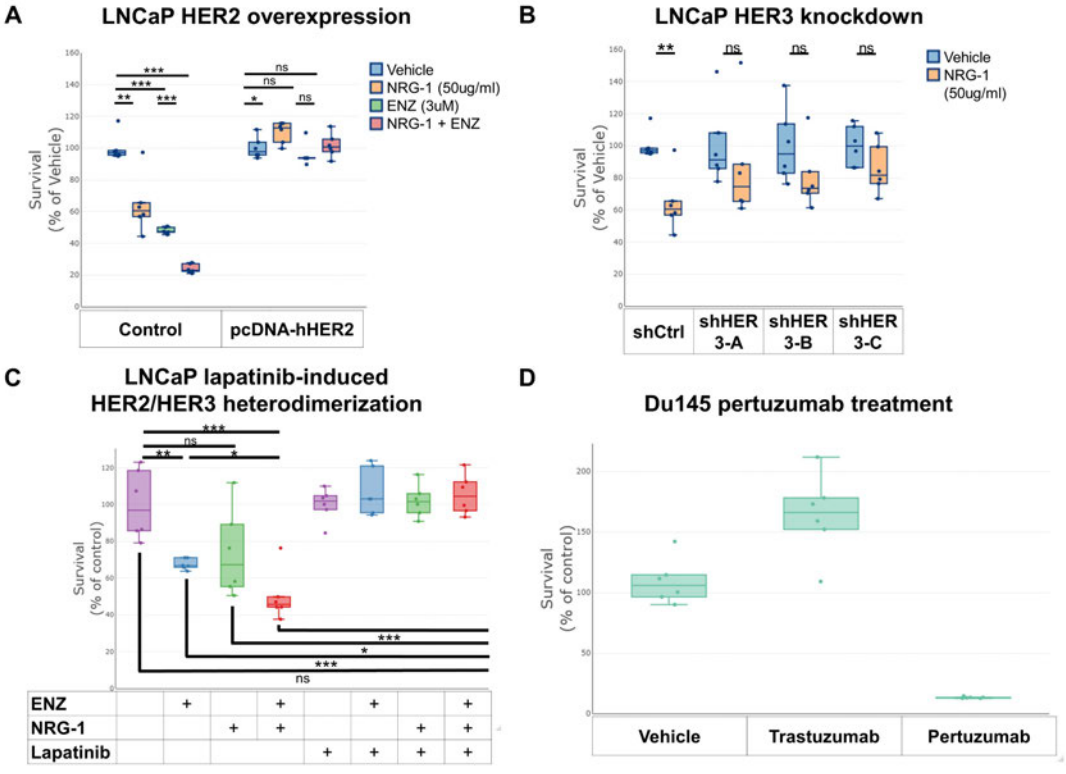
Similarly, treatment of CSPC cell line LNCaP with recombinant NRG-1 sensitizes these tumors to enzalutamide (ENZ)-mediated cell death (*Fig 2A*); conversely, treatment of CRPC cell lines Du145 and PC3 with recombinant NRG-1 induces *resistance* to ENZ (*Fig 2B*).

*Fig 2 – **(A)** Treatment of CSPC (LNCaP) prostate cancer cells with increasing concentrations of NRG-1 leads to cell death and sensitization to enzalutamide (ENZ). **(B)** In contrast, treatment of CRPC (Du145, PC3) prostate cancer cells leads to cell survival and resistance to ENZ.*



This differential response to NRG-1 treatment appears to be through selective HER2/HER3 heterodimerization in CRPC cells. Inducing HER2/HER3 heterodimerization with HER2 overexpression, HER3 suppression, or lapatinib leads to a CRPC phenotype (*Fig 3A-C*). Treatment of Du145 CRPC cells with pertuzumab, in contrast, re-sensitizes these cells to enzalutamide (*Fig 3D*).

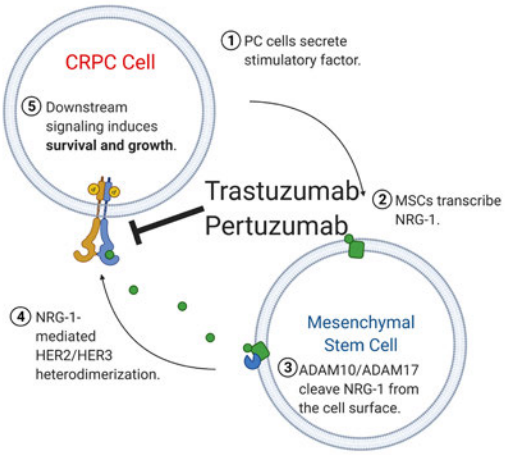
*Fig 3 – Overexpression of HER2 **(A)**, knockdown of HER3 **(B)**, or lapatinib-induced HER2/HER3 heterodimerization **(C)** leads to CSPC (LNCaP) resistance to enzalutamide. In contrast, blockade of HER2/HER3 heterodimerization in CRPC (Du145) cells **(D)** leads to resistant cancer cell death.*



1.3 HER2/HER3 Blockade

In all, these data suggest that blockade of HER2/HER3 heterodimerization may sensitize CRPC cells to enzalutamide, resulting in improved treatment outcomes (*Fig 4*).

Fig 4. NRG-1 supports CRPC cell resistance through HER2/HER3 heterodimerization. Pertuzumab and trastuzumab *prevent this signaling and we hypothesize that combined pertuzumab, trastuzumab, and enzalutamide treatment will overcome NRG-1-mediated CRPC resistance in selected patients with high baseline NRG-1 levels.*



1.4 Trial Goals and Objectives

Our *long-term goal* is to overcome prostate cancer treatment resistance. The *overall objective in this application* is to perform a pilot study of the combination of trastuzumab and pertuzumab, highly effective inhibitors of HER2/HER3 heterodimerization, in overcoming NRG-1-mediated prostate cancer resistance (*Fig 4*). Our *central hypothesis* is that the use of trastuzumab and pertuzumab in selected patients with high NRG-1 will prevent and overcome NRG-1-mediated HER2/HER3 heterodimerization and resultant enzalutamide (ENZ) resistance in a pilot study.

We will objectively test our central hypothesis and thereby attain the objective of this application through the following *specific aims*:

Aim 1. Evaluate the potential for dual HER2/HER3 and AR inhibition in NRG-1-selected castration-resistant prostate cancer progressing despite enzalutamide treatment.

Aim 2. Determine the correlation between the CRPC gene expression signature and tumor response to the dual inhibition of HER2/HER3 and AR in advanced prostate cancer progressing despite enzalutamide treatment.

We will enroll patients on the basis of NRG-1 plasma levels >4ng/ml by ELISA based on ELISA standard curve or comparison patient plasma at this cutoff from our previous cohort. In our previous cohort, 66.2% of patients would be eligible based on this cutoff. This cutoff was determined from the previous cohort with data presented in Figure 1. Receiver operating curve (ROC) analysis identified this cutoff as optimally sensitive and specific for resistant disease.

We will use a commercial ELISA for this testing, which will be done after consent and pre-registration to the study. Historical control plasma at this cutoff or recombinant standard curve calculation will be used to determine which patients qualify. Patients whose NRG-1 levels match our criteria will enter screening for potential enrollment into the treatment phase.

Since there are no data on the safety of this combination in prostate cancer, we will conduct a safety analysis among the initial cohort of patients.

2.0 Goals

2.1 Primary Goal

Evaluate the preliminary efficacy of the combination of pertuzumab, trastuzumab, and hyaluronidase-zzxf plus enzalutamide with regard to objective response rate (PCWG 3.0) in enzalutamide-refractory metastatic castration-resistant prostate cancer .

2.2 Secondary Goals

2.21 Estimate the radiographic progression-free survival for this combination .

2.22 Estimate the overall survival for this combination .

2.3 Exploratory Goals

2.31 Assessment of this combination for adverse events according to clinical judgment and patient-reported outcomes (PRO-CTCAE - Prostate Cancer).

2.32 Assessment of patient quality of life using FACT-P questionnaire.

2.4 Correlative Goals

2.41 Determine the correlation between outcomes as above and systemic NRG-1 levels at baseline and over time.

2.42 Determine the correlation between outcomes as above and change in HER2/HER3/AR gene signatures.

3.0 Patient Eligibility

Safety Run-in Only: Prior to discussing protocol entry with the patient, access the Mayo Clinic Research Registration Application to ensure a place on the protocol is open to the patient and reserve a slot.

3.1 Pre-registration – Inclusion Criteria

3.11 Age ≥18 years

3.12 Clinically or histologically confirmed diagnosis of second-generation antiandrogen-refractory metastatic castration-resistant prostate cancer.

3.13 Measurable disease as defined by the Prostate Cancer Working Group (PCWG3) criteria (See Section 11.0)

3.14 Prior treatment required:
- Second generation anti-androgen (2GAA) therapy (e.g., enzalutamide, abiraterone) at any time prior registration

3.15 Provide written informed consent.

3.16 Willing to return to enrolling institution for follow-up (during the Active Monitoring Phase of the study).

3.17 Ability to complete questionnaire(s) by themselves or with assistance.

3.18 Willingness to provide mandatory blood specimens for correlative research (see Section 14.0).

3.19a Willingness to provide mandatory tissue specimens for correlative research (see Section 17.0).

3.2 Pre-registration - Exclusion criteria

3.21 History of myocardial infarction ≤6 months prior to pre-registration, or congestive heart failure requiring use of ongoing maintenance therapy for life-threatening ventricular arrhythmias.

3.22 Failure to recover from acute, reversible effects of prior therapy regardless of interval since last treatment.
EXCEPTION: Grade 1 peripheral (sensory) neuropathy that has been stable for at least 3 months since completion of prior treatment.

3.23 Uncontrolled intercurrent non-cardiac illness including, but not limited to:
- Ongoing or active infection
- Psychiatric illness/social situations
- Dyspnea at rest due to complications of advanced malignancy or other disease that requires continuous oxygen therapy
- Any other conditions that would limit compliance with study requirements

3.24 Immunocompromised patients and patients known to be HIV positive and currently receiving antiretroviral therapy.
NOTE: Patients known to be HIV positive, but without clinical evidence of an immunocompromised state, are eligible for this trial.

3.25 Receiving any other investigational agent which would be considered as a treatment for the prostate cancer

3.26 Thromboembolic event ≤60 days prior to pre-registration.

3.27 Serious cardiac illness or medical conditions including, but not confined to, the following:

- History of NCI CTCAE v5.0 Grade ≥ 3 symptomatic congestive heart failure (CHF) or New York Heart Association (NYHA) Class ≥ II
- High-risk uncontrolled arrhythmias (i.e., atrial tachycardia with a heart rate ≥ 100/min at rest, significant ventricular arrhythmia [ventricular tachycardia], or higher-grade atrioventricular [AV]-block, such as second-degree AV-block Type 2 [Mobitz II] or third-degree AV-block)
- Serious cardiac arrhythmia or severe conduction abnormality not controlled by adequate medication
- Angina pectoris requiring anti-angina medication
- Clinically significant valvular heart disease
- Evidence of transmural infarction on electrocardiogram (ECG)
- Poorly controlled hypertension (e.g., systolic > 180 mm Hg or diastolic > 100mmHg)

3.28 History of ventricular dysrhythmias or risk factors for ventricular dysrhythmias, such as structural heart disease (e.g., severe left ventricular systolic dysfunction [LVSD], left ventricular hypertrophy), coronary heart disease (symptomatic or with ischemia demonstrated by diagnostic testing), clinically significant electrolyte abnormalities (e.g., hypokalemia, hypomagnesemia, hypocalcemia), or family history of sudden unexplained death or long QT syndrome

3.3 Registration - Inclusion Criteria

3.31 Plasma NRG-1 level ≥4 ng/ml

3.32 ECOG Performance Status (PS) 0, 1 or 2 (Appendix I)

3.33 The following laboratory values obtained ≤15 days prior to registration:

- Hemoglobin ≥9.0 g/dL
- Absolute neutrophil count (ANC) ≥1500/mm^3
- Platelet count ≥100,000/mm^3
- Total bilirubin ≤1.5 x ULN
- Alanine aminotransferase (ALT) **and** aspartate transaminase (AST) ≤3 x ULN (≤5 x ULN for patients with liver involvement)
- PT/INR/aPTT ≤1.5 x ULN OR if patient is receiving anticoagulant therapy and INR or aPTT is within target range of therapy
- Calculated creatinine clearance ≥45 ml/min using the Cockcroft-Gault formula below:

Cockcroft-Gault Equation:

Creatinine clearance for males = $\frac{(140 - \text{age})(\text{weight in kg})}{(72)(\text{serum creatinine in mg/dL})}$

Creatinine clearance for females = $\frac{(140 - \text{age})(\text{weight in kg})(0.85)}{(72)(\text{serum creatinine in mg/dL})}$

3.34 Left ventricular ejection fraction (LVEF) ≥50% ≤15 days prior to registration

3.35 Provide written informed consent.

3.36 Ability to complete questionnaire(s) by themselves or with assistance.

3.37 Willingness to provide mandatory blood specimens for correlative research (see Section 14.0).

3.38 Willingness to provide mandatory tissue specimens for correlative research (see Section 17.0).

3.39a Willing to return to enrolling institution for follow-up (during the Active Monitoring Phase of the study).

3.39b Willing to use birth control during heterosexual intercourse while on treatment and for 7 months after last dose of study treatment.
NOTE: See Section 9.0 for additional information.

3.4 Registration - Exclusion Criteria

3.41 Any of the following because this study involves an agent that has known genotoxic, mutagenic, and teratogenic effects:
- Pregnant persons
- Nursing persons
- Persons of childbearing potential or able to father a child who are unwilling to employ adequate contraception during treatment and for seven months after last dose of study treatment

3.42 Failure to recover from any of the following therapies prior to registration:
- Major surgery
- Chemotherapy
- Infection requiring systemic treatment

3.43 Co-morbid systemic illnesses or other severe concurrent disease which, in the judgment of the investigator, would make the patient inappropriate for entry into this study or interfere significantly with the proper assessment of safety and toxicity of the prescribed regimens.

3.44 Immunocompromised patients and patients known to be HIV positive and currently receiving antiretroviral therapy.

NOTE: Patients known to be HIV positive, but without clinical evidence of an immunocompromised state, are eligible for this trial.

3.45 Uncontrolled intercurrent illness including, but not limited to:
- ongoing or active infection
- symptomatic congestive heart failure
- unstable angina pectoris
- cardiac arrhythmia
- or psychiatric illness/social situations that would limit compliance with study requirements.

3.46 Currently receiving any other investigational agent which would be considered as a treatment for the primary neoplasm.

3.47 Other active malignancy ≤3 years prior to registration.
EXCEPTIONS: Non-melanotic skin cancer or carcinoma-in-situ of the cervix.
NOTE: If there is a history of prior malignancy, they must not be receiving other specific treatment (*e.g.,* other hormonal therapy, chemotherapy) for their cancer.

3.48 History of myocardial infarction ≤6 months, or congestive heart failure requiring use of ongoing maintenance therapy for life-threatening ventricular arrhythmias.

3.49a Known hypersensitivity to pertuzumab, or trastuzumab, or hyaluronidase, or to any of its excipients

3.49b Requirement for drugs or substances which can interfere with the actions of the study drugs (enzalutamide or pertuzumab/trastuzumab/hyaluronidase-zzxf). Consult pharmacist for review.

4.0 Study Schedules

4.1 Test Schedule for Metastatic Castration-Resistant Prostate Cancer

	Screening		Active Monitoring Phase					
Tests and procedures[1]	After Pre-Reg	≤15 days prior to Reg	Prior to Cycle 1 Day 1	Prior to Cycle 2	Prior to each cycle (Cycle 3+)	Every 9 weeks for 27 weeks, then every 12 weeks	End of treatment[2]	Clinical Follow-up[3]
Window				±3 days				
History and exam, weight, PS		X		X	X		X	X
Height		X						
Adverse event assessment		X		X	X	X	X	X
CBC with 5-part diff		X		X	X		X	X
Chemistry group:[4]		X	X[5]	X	X		X	X
Coagulation: PT/INR/aPTT		X						
PSA		X		X			X	X
Echocardiogram for LVEF (ejection fraction only)[6]		X				X		
Biopsy			X[7]	X[8R]			X[9]	
Tumor measurement[10]	X[11]					X		X
Histologic review	X							
Patient questionnaire PRO-CTCAE (Appendix II)			X			X	X	
Patient questionnaire FACT-P (Appendix II)			X			X	X	

Cycle = 21 ±3 days; R=research funded

[1] All tests may be done if clinically needed at any time

[2] End of treatment will be defined as disease progression, patient refusal, or adverse event(s) leading to cessation of therapy

[3] CFU every 3 months for 12 months or until disease progression or start of alternate therapy, whichever occurs first.

[4] CMP (80053) plus magnesium (83735) OR Hepatic Function Panel (80076) plus Renal Function Panel (80069) plus magnesium (83735) -Order additional testing as needed for clinical care

[5] Only repeat if most recent blood draw is ≥21 days prior to C1D1

[6] LVEF ejection fraction should be tested every 12 weeks during treatment with pertuzumab/trastuzumab/hyaluronidase-zzxf

[7] Mandatory biopsy can be done at any time after Registration and prior to treatment on C1D1. A recent (within 60 days) archival sample is also acceptable in lieu of a new biopsy.

[8] Optional research biopsy at end of Cycle 1; Patient may opt out of or delay this biopsy without deviation

[9] Optional clinical/research biopsy at End of Treatment; Patient may opt out of or delay this biopsy without deviation

[10] Tumor assessments per clinical standard of care will be performed every 9 weeks for the first 27 weeks (i.e., Weeks 9, 18, 27), then every 12 weeks (i.e., Weeks 39, 51, etc. ±1 week) from the initiation of treatment regardless of treatment interruptions or holds until the PCWG3 or RECIST 1.1 criteria in Section 11.0 have been met.

[11] Baseline imaging should be ≤29 days prior to Registration

Tests and procedures[1]	Screening		Active Monitoring Phase					
	After Pre-Reg	≤15 days prior to Reg	Prior to Cycle 1 Day 1	Prior to Cycle 2	Prior to each cycle (Cycle 3+)	Every 9 weeks for 27 weeks, then every 12 weeks	End of treatment[2]	Clinical Follow-up[3]
Patient Medication Diary (Appendix III)[12]				X				
Mandatory research tissue specimens (see Section 17.0) [13,R]			X	X			X	
Mandatory research blood specimens (see Section 14.0)[14,R]	X		X	X		X	X	

[12] The diary must begin the day the patient starts taking the medication and must be completed per protocol and returned to the treating institution OR compliance must be documented in the medical record by any member of the care or research teams.
[13] Tissue specimens must be collected and submitted per Section 17.0
[14] Blood specimens will be collected and submitted per Section 14.0. Kits are required

4.2 Extended Follow-up

	Extended Follow-up[1]				
	q. 3 months until PD	At PD	After PD q. 6 months	Death	New Primary
Extended/Survival Follow-up[2]	X	X	X	X	At each occurrence

1. All timelines in this table are approximate and may vary by a month
2. If a patient is still alive 2 years after registration, no further follow-up is required.

5.0 Grouping Factor: None

6.0 Registration Procedures

6.1 Pre-Registration (Step 0)

6.11 Pre-Registering a Patient

To pre-register a patient, access the Mayo Clinic Research Registration Application at www.registration.mayo.edu. The Research Registration Application is available 24 hours a day, 7 days a week. Back up and/or system support contact information is available on the website. If unable to access the website, contact Research Registration Office at (507) 284-2753 or email random01@mayo.edu between the hours of 8 a.m. and 4:30 p.m. Central Time (Monday through Friday).

The instructions for the registration/randomization application are available on the Mayo Clinical Office of Clinical Trials web page (https://www.mayo.edu/research/centers-programs/center-clinical-translational-science/offices/office-of-clinical-trials/research-registration-application) and detail the process for completing and confirming patient registration. Prior to initiation of protocol treatment, this process must be completed in its entirety and an MCCC subject ID number must be available as noted in the instructions. It is the responsibility of the individual registering the patient to confirm the process has been successfully completed prior to release of the study agent. Patient registration via the registration/randomization application can be confirmed in any of the following ways:

- Contact Mayo Clinic Research Registration Office at (507) 284-2753 or email random01@mayo.edu. If the patient was fully registered, the Research Registration Office staff can access the information from the centralized database and confirm the registration.
- Refer to "Instructions for Remote Registration" in section "Finding/Displaying Information about A Registered Subject."

6.12 Verification of information

Prior to accepting the pre-registration, the registration/randomization application will verify the following:

- IRB approval at the registering institution
- Patient pre-registration eligibility
- Existence of a signed consent form
- Existence of a signed authorization for use and disclosure of protected health information.

6.13 Pre-registration tests/procedures

Pre-registration tests/procedures (see Section 4.0) must be completed within the guidelines specified on the test schedule.

6.2 Registration (Step 1)

Safety Run-in Only: Prior to discussing protocol entry with the patient, access the Mayo Clinic Research Registration Application to ensure that a place on the protocol is open to the patient and reserve a slot

To register a patient, access the Mayo Clinic Research Registration Application at www.registration.mayo.edu. The Research Registration Application is available 24 hours a day, 7 days a week. Back up and/or system support contact information is available on the website. If unable to access the website, contact Research Registration by email random01@mayo.edu between the hours of 8 a.m. and 4:30 p.m. Central Time (Monday through Friday).

The instructions for the registration/randomization application are available on the Mayo Clinical Office of Clinical Trials web page (https://www.mayo.edu/research/centers-programs/center-clinical-translational-science/offices/office-of-clinical-trials/research-registration-application) and detail the process for completing and confirming patient registration. Prior to initiation of protocol treatment, this process must be completed in its entirety and an MCCC subject ID number must be available as noted in the instructions. It is the responsibility of the individual registering the patient to confirm the process has been successfully completed prior to release of the study agent. Patient registration via the registration/randomization application can be confirmed in any of the following ways:

- Contact Mayo Clinic Research Registration by email random01@mayo.edu. If the patient was fully registered, the Research Registration Office staff can access the information from the centralized database and confirm the registration.
- Refer to "Instructions for Remote Registration" in section "Finding/Displaying Information about A Registered Subject."

6.3 Verification of materials

Prior to accepting the registration, registration/randomization application will verify the following:

- IRB approval at the registering institution
- Patient eligibility
- Existence of a signed consent form
- Existence of a signed authorization for use and disclosure of protected health information

6.4 Documentation of IRB approval

Documentation of IRB approval must be on file in the Research Registration Office before an investigator may register any patients.

In addition to submitting initial IRB approval documents, ongoing IRB approval documentation must be on file (no less than annually) with Research Registration (email random01@mayo.edu). If the necessary documentation is not submitted in advance of attempting patient registration, the registration will not be accepted, and the patient may not be enrolled in the protocol until the situation is resolved.

When the study has been permanently closed to patient enrollment, submission of annual IRB approvals to the Research Site Management Office is no longer necessary.

6.5 Correlative Research

6.51 Mandatory

A mandatory correlative research component is part of this study, the patient will be automatically registered onto this component (see Sections 3.3, 14.0, 17.0).

6.52 Optional

An optional correlative research component is part of this study, there will be an option to select if the patient is to be registered onto this component (see Sections 14.0 and/or 17.0).

6.6 Patient Permissions

At the time of registration, the following will be recorded:

- Patient has/has not given permission to store and use his/her sample(s) for future research on cancer at Mayo Clinic.
- Patient has/has not given permission to store and use his/her sample(s) for future research to learn, prevent, or treat other health problems.
- Patient has/has not given permission for MCCC to give his/her sample(s) to researchers at other institutions.

6.7 Treatment on protocol

Treatment on this protocol must commence at a Mayo Clinic institution under the supervision of a medical oncologist.

6.8 Treatment start

Treatment cannot begin prior to registration and must begin ≤28 days after registration.

6.9a Pretreatment

Pretreatment tests/procedures (see Section 4.0) must be completed within the guidelines specified on the test schedule.

6.9b Baseline symptoms

All required baseline symptoms (see Section 10.6) must be documented and graded.

6.9c Study drug

Study drug is available on site for this patient.

6.9d Blood draw kits

Blood draw kit is available on site for this patient.

6.9e Study Conduct

The clinical trial will be conducted in compliance with regulations (21 CFR 312, 50, and 56), guidelines for Good Clinical Practice (ICH Guidance E6), and in accordance with general ethical principles outlined in the Declaration of Helsinki; informed consent will be obtained from all participating patients; the protocol and any amendments will be subject to approval by the designated IRB prior to implementation, in accordance with 21 CFR 56.103(a); and subject records will be stored in a secure location and subject confidentiality will be maintained. The investigator will be thoroughly familiar with the appropriate use of the study drug as described in the protocol and Investigator's Brochure. Essential clinical documents will be maintained to demonstrate the validity of the study, and the integrity of the data collected. Master files should be established at the beginning of the study, maintained for the duration of the study and retained according to the appropriate regulations.

7.0 Protocol Treatment

7.1 Treatment Schedule

7.11 Treatment medication table

Agent	Dose Level	Route	Day	ReRx
Pertuzumab/trastuzumab/ hyaluronidase-zzxf [HP] (given as a single dose)	600 mg, 600 mg, and 20,000 units*	Subcutaneous (thigh only)	1	Q3w
Enzalutamide	160 mg	PO once daily	1-21 continuously	Q3w

*Cycle 1 loading dose of 1200 mg pertuzumab/600 mg trastuzumab/30,000 units hyaluronidase-zzxf

Cycle = 21 days ±3 days

7.2 Pertuzumab/Trastuzumab/Hyaluronidase-zzxf (PHESGO™) [HP]

Pertuzumab/trastuzumab/hyaluronidase-zzxf is administered by subcutaneous injection into the thigh once every 3 weeks as a combination injection. Loading dose should be given over approximately 8 minutes. Subsequent doses can be administered over approximately 5 minutes

A loading dose is given Cycle 1, Day 1, and again if it has been more than 6 weeks since most recent previous dose.

Patients must be observed for a minimum of 30 minutes after initial dose and at least 15 minutes for subsequent doses for signs of hypersensitivity symptoms or administration-related reactions

7.3 Enzalutamide

Enzalutamide is taken orally as a single dose once per day at the same time each day.

Enzalutamide can be taken without regard for food.

Enzalutamide is available as tablets or capsules.

Patients should be instructed not to cut, crush, or chew tablets and not to chew, dissolve or open capsules.

If a dose is missed the patient should take it as soon as they remember it.

If an entire day is missed the patient should not make up the lost dose, just resume their normal dose the next day.

7.4 Biopsies

An initial biopsy will be required prior to study treatment.

A second, optional biopsy may be requested at end of Cycle 1 or any time if patient is willing.

A third, required biopsy will be at time patient comes off treatment for any reason (e.g., at the time of disease progression or treatment change) (whichever comes first).

NOTE: Patient may opt out of, or delay second or third biopsies without deviation.

7.5 Safety Analysis

7. 51 Description

Six patients will be enrolled at the planned starting dose level in Section 7.1 and observed for one cycle for evaluation of the safety analysis. See Section 16 for specifics.

7.52 Definitions of Significant Safety Events

7.521 For this protocol, significant safety events will be defined as the following events at least possibly related to treatment, occurring during Cycle 1 only:

Any CTCAE Grade 5 event not definitely related to underlying disease, progression of disease, or intercurrent illness, and at least possibly related to the investigational product

Grade 3 or higher seizure or cardiac disorder event (including heart failure, cardiac arrest, or myocardial infarction)

Neutropenic fever (i.e., febrile neutropenia)

Grade 4+ neutropenia or thrombocytopenia lasting >7 days

Grade 3+ thrombocytopenia with bleeding

Grade 3+ nausea/vomiting or diarrhea lasting >72 hours with adequate antiemetic and other supportive care

Grade 3+ fatigue lasting ≥7 days

Asymptomatic Grade 3+ electrolyte abnormality lasting >72 hours,

Symptomatic Grade 3+ electrolyte abnormality regardless of duration

Exception: Grade 3+ amylase or lipase elevation NOT associated with symptoms or clinical manifestations of pancreatitis does not need to be counted as a significant toxicity

Grade 3+ non-laboratory events

For patients with hepatic metastases: AST or ALT >8×ULN or AST or ALT >5×ULN for ≥14 days

Meets or exceeds Hy's law:

1. The drug causes hepatocellular injury, generally shown by a higher incidence of 3-fold or greater elevations above the ULN of ALT or AST than the (nonhepatotoxic) control drug or placebo
2. Among trial subjects showing such aminotransferase (AT) elevations, often with ATs much greater than 3×ULN, one or more also show elevation of serum total bilirubin (TBL) to >2×ULN, without initial findings of cholestasis (elevated serum alkaline phosphatase [ALP])
3. No other reason can be found to explain the combination of increased AT and TBL, such as viral hepatitis A, B, or C; preexisting or acute liver disease; or another drug capable of causing the observed injury All AEs of the specified grades should count as DLEs except those that are clearly and incontrovertibly due to disease progression or extraneous causes.

7.522 Patients experiencing significant safety events requiring discontinuing study treatment will be monitored and treated as appropriate for these side-effects based on available evidence.

7.6 Return to consenting institution

For this protocol, the patient must return to the consenting institution according to Section 4.0.

7.7 Treatment by local medical doctor (LMD)

Treatment for this clinical trial by a local medical doctor (LMD) is not allowed.

7.8 Safety Follow-up Visit

The mandatory Safety Follow-Up Visit should be conducted approximately 30 days after the last dose of study treatment or before the initiation of a new anti-cancer treatment, whichever comes first. This visit may be done by telephone call or virtual visit as needed. All AEs that occur prior to the Safety Follow-Up Visit should be recorded. Participants with an AE of Grade >1 will be followed until the resolution of the AE to Grade 0-1 or until the beginning of a new anti-cancer therapy, whichever occurs first. SAEs that occur within 90 days of the end of treatment or before initiation of a new anti-cancer treatment should also be followed and recorded.

8.0 Dosage Modification Based on Adverse Events

Strictly follow the modifications in this table for the first **two** cycles, until individual treatment tolerance can be ascertained. Thereafter, these modifications should be regarded as guidelines to produce mild-to-moderate, but not debilitating, side effects. If multiple adverse events are seen, administer dose based on greatest reduction required for any single adverse event observed. Reductions or increases apply to treatment given in the preceding cycle and are based on adverse events observed since the prior dose.

The treating physician may hold, omit, or modify administration at any time based on discussion with Study Investigator or Co-Investigator. This information must be documented in the patient clinical record.

→ ***ALERT:*** ***ADR reporting may be required for some adverse events (See Section 10.0)*** ←

8.1 Dose Levels

Dose Level	Enzalutamide	Pertuzumab/ Trastuzumab/ Hyaluronidase-zzxf (HP)
1*	160mg	600mg/600mg/20kU*
-1	120mg	N/A
-2	80mg	N/A

*Dose level 1 refers to the starting dose

**Loading dose = 1200 mg pertuzumab/600 mg trastuzumab/30,000 units hyaluronidase-zzxf

NOTE: There are no dose reductions for the combination drug trastuzumab/pertuzumab/hyaluronidase-zzxf (HP).

→ → ***Use the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0* unless otherwise specified*** ← ←

* Located at http:/ctep.cancer.gov/protocolDevelopment/electronic_applications.ctc.htm

8.2 Treatment Modification for Enzalutamide

8.21 **Omit**/adjust enzalutamide dose

If a patient experiences a ≥Grade 3 event, withhold dosing for one week or until symptoms improve to ≤Grade 2, then resume at the same or a reduced dose (120 mg or 80 mg), if warranted

- Fatigue
- Falls and fractures
- Lab abnormalities:
  Neutrophil count decreased
  White blood cell decreased
  Hyperglycemia
  Hypermagnesemia
  Hyponatremia
  Hypercalcemia
- Hypertension

8.22 **Discontinue** enzalutamide

Permanently discontinue enzalutamide for any of the following events

- Ischemic heart disease Grade 3-4
- Seizures (any grade)
- Hypersensitivity reactions (any grade)
- Posterior reversible encephalopathy syndrome (PRES)

8.3 Treatment Modification for Pertuzumab, Trastuzumab, Hyaluronidase-xxzf (HP)

8.31 **Hold** pertuzumab, trastuzumab, hyaluronidase-xxzf (HP)

Hold HP dose for up to 4 weeks or until event has resolved to ≤Grade 1, whichever is sooner. If event has not resolved within 4 weeks, patient will end study treatment.

Hold HP until etiology is determined for the following Grade 2 events:

- Left ventricular cardiac dysfunction (See 8.33 below)
- Cardiac arrhythmias
- Hypertension

8.32 **Discontinue** pertuzumab, trastuzumab, hyaluronidase-xxzf (HP)

Discontinue HP for following events (any grade)

- Clinically significant decrease in left ventricular function
- Symptomatic CHF
- Anaphylaxis or hypersensitivity
- Angioedema
- Interstitial pneumonitis or acute respiratory distress syndrome

8.33 HP Dose Modifications for Left Ventricular Dysfunction

Pre-treatment LVEF	Monitor LVEF every	Withhold for at least 3 weeks for LVEF decrease to:		Resume after 3 weeks if LVEF has recovered to:	
		Either		Either	
≥50%	~12 weeks	<40%	40-45% with a fall of ≥10% points below pre-treatment value	>45%	40-45% with a fall of <10%-points below pre-treatment value

8.4 Treatment Discontinuation for Adverse Events

Patients will discontinue all treatment and go to Event Monitoring/Survival/Extended Follow-up if any of the following events occur which meet conditions for Hy's Law:

- ALT or AST >8xULN
- ALT or AST >5xULN for more than 2 weeks
- ALT or AST >3xULN and (TBL >2xULN or INR >1.5)
- ALT or AST >3xULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)

Guidance Document https://www.fda.gov/media/116737/download

9.0 Ancillary Treatment/Supportive Care

9.1 Full supportive care

Patients should receive full supportive care while on this study. This includes blood product support, antibiotic treatment, and treatment of other newly diagnosed or concurrent medical conditions. All blood products and concomitant medications such as antidiarrheals, analgesics, and/or antiemetics received from the first day of study treatment administration until 30 days after the final dose will be recorded in the medical records.

9.2 Blood products and growth factors

Blood products and growth factors should be utilized as clinically warranted and following institutional policies and recommendations. The use of growth factors should follow published guidelines of the Journal of Clinical Oncology, Volume 33, No 28 (October 1), 2015: pp. 3199-3212 (WBC growth factors) AND Journal of Clinical Oncology, Volume 28, No 33 (November 20), 2010: pp. 4955-5010 (darbepoetin/epoetin).

9.3 Antiemetics

Antiemetics may be used at the discretion of the attending physician.

9.4 Diarrhea

Diarrhea could be managed conservatively with loperamide. The recommended dose of loperamide is 4 mg at first onset, followed by 2 mg every 2-4 hours until diarrhea free (maximum 16 mg/day).

In the event of Grade 3 or 4 diarrhea, the following supportive measures are allowed: hydration, octreotide, and antidiarrheals.

If diarrhea is severe (requiring intravenous rehydration) and/or associated with fever or severe neutropenia (Grade 3 or 4), broad-spectrum antibiotics must be prescribed. Patients with severe diarrhea or any diarrhea associated with severe nausea or vomiting **should be hospitalized** for intravenous hydration and correction of electrolyte imbalances.

9.5 Concomitant Medications

Please refer to the enzalutamide package insert for clinically relevant drug interactions. Medications that are listed as a “Risk X: Avoid Combination” are prohibited while patient is on trial unless approved by Principal Investigator. See also Section 15.26.

9.6 Contraception

For biological males: agreement to remain abstinent (refrain from heterosexual intercourse) or use a condom, and agreement to refrain from donating sperm, as defined below:

> With female partners of childbearing potential or pregnant female partners, biological males must remain abstinent or use a condom during the study treatment periods and for seven months after the last dose of study treatment to avoid exposing the embryo. Biological males must refrain from donating sperm during this same period.

10.0 Adverse Event (AE) Monitoring and Reporting

10.1 Definitions

10.11 Roles

Sponsor-Investigator

An individual who both initiates and conducts, alone or with others, a clinical trial and under whose immediate direction the investigational product/study intervention is administered to, dispensed to, or used by a subject. This person holds the IND for the research study.

Investigator

An investigator includes the Site Principal Investigator (PI) or a designated Sub-Investigator.

Sub-Investigator

A Sub-Investigator is a medically qualified delegate who has been identified and confirmed by the Site PI. Medically qualified designations may include, but are not limited to:

- Medical Doctorate (M.D.), or equivalent medical school graduate degree
- Physician Assistant (P.A.)
- Certified Nurse Practitioner (C.N.P.)
- Registered Nurse (R.N.)

10.12 Adverse Event (AE)

An adverse event is defined as any untoward medical occurrence in a clinical trial subject. The event does not necessarily have a causal relationship with study treatment. (FDA, 21 CFR 312.32; ICH E2A and ICH E6)

The definition of AEs includes:

- Worsening of a pre-existing medical condition. Worsening indicates that the pre-existing medical condition or underlying disease (e.g., diabetes, migraine headaches, gout) has increased in severity, frequency, and/or duration more than would be expected and/or has an association with a significantly worse outcome than expected.

  NOTE: A pre-existing condition that has not worsened more than anticipated (i.e., more than usual fluctuation of disease) during the study or involves an intervention such as elective cosmetic surgery or a medical procedure while on study, is not considered an AE.
- Unintended or unfavorable sign or symptom
- A disease temporally associated with participation in the protocol
- An intercurrent illness or injury that impairs the well-being of the subject
- AEs not previously observed in the subject that emerge during the protocol-specified AE reporting period, including signs or symptoms associated with metastatic castration-resistant prostate cancer that were not present prior to the AE reporting period
- Complications that occur as a result of protocol-mandated interventions (e.g., invasive procedures such as cardiac catheterizations)

In general, abnormal laboratory values or diagnostic test results constitute AEs only if they induce clinical signs or symptoms or require treatment or further diagnostic tests.

Hospitalization for elective surgery or routine clinical procedures that are not the result of an AE (e.g., surgical insertion of central line) should not be recorded as an AE.

Disease progression should not be recorded as an AE, unless it is attributable to the study regimen by the site investigator.

The investigator is responsible for ensuring that any AEs observed by the investigator or reported by the subject are recorded in the subject's medical record.

10.13 Serious Adverse Event (SAE)

A serious adverse event is defined as an adverse event that meets ***at least one*** of the following serious criteria (FDA, 21 CFR 312.32; ICH E2A and ICH E6):

- Fatal
- Life threatening (places the subject at immediate risk of death)
- Requires inpatient hospitalization for ≥24 hours or prolongation of existing hospitalization.
  NOTE: Hospitalization for anticipated or protocol specified procedures such as administration of chemotherapy, central line insertion, metastasis interventional therapy, resection of primary tumor, or elective surgery, will not be considered SAEs.
- Results in persistent or significant disability/incapacity. Congenital anomaly/birth defect.
- Is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the subject or may require intervention (e.g., medical, surgical) to prevent one of the other serious outcomes listed in the definition above).

  NOTE: Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions not resulting in hospitalization; or the development of drug dependency or drug abuse. (See Table 10.221)

  If an investigator considers an event to be clinically important, but it does not meet any of the serious criteria, the event could be classified as an SAE under the criterion of "other medically important serious event."
  NOTE: Examples of such events could include allergic bronchospasm, convulsions, blood dyscrasias, drug induced liver injury (DILI), or events that necessitate an emergency room visit, outpatient surgery, or urgent intervention.

10.14 Suspected Adverse Reaction

Any AE for which there is a reasonable possibility that the drug caused the AE.

10.15 Adverse Events of Special Interest (AESI)

Events that would not typically be considered to meet the criteria for expedited reporting, but that for a specific protocol are being reported via expedited means in order to facilitate the review of safety data (may be requested by the FDA and/or the sponsor and/or pharmaceutical partner(s)).

10.16 Protocol Violation/Deviation

Any change, divergence or departure from the study design or research procedures that has not been approved by the IRB.

Major Protocol Violation/Deviation: Any change that affects the rights and welfare of subjects and others, increases risks to subjects and others, decreases potential benefits, compromises the integrity or validity of the research, or represents willful or knowing misconduct.

Minor Protocol Violation/Deviation: Any change that did not increase the risk or decrease the benefit or significantly affect the subject's rights, safety, or welfare and/or the integrity of research data (e.g., a routine lab missed at a visit and re-drawn, shortening the duration between a planned study visit, using an outdated HIPAA form or consent form when there are no differences between the two forms other than the approval date).

10.17 Medication error

A medication error is defined as any accidental incorrect administration or dosing of a medicinal product,

10.18 Expedited Reporting

Events immediately reported to sponsor/investigator and any pharmaceutical partner(s) using the appropriate iMedidata Rave SAE eCRF(s) once study team has become aware of the event.

10.19a Routine Reporting

Events reported to sponsor and any pharmaceutical partner(s) via the appropriate iMedidata Rave AE eCRF(s).

10.19b Expected versus Unexpected Events

Expected events are those described within the Section 15.0 of the protocol, the study specific consent form, package insert (if applicable), and/or the investigator brochure (IB), (if an investigator brochure is not required, otherwise described in the general investigational plan).

Unexpected adverse events or suspected adverse reactions are those not listed in Section 15.0 of the protocol, the study specific consent form, package insert (if applicable), or in the investigator brochure (or are not listed at the specificity or severity that has been observed); if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan.

Unexpected also refers to AEs or suspected adverse reactions that are mentioned in the investigator brochure as occurring with a class of drugs but have not been observed with the drug under investigation.

An investigational agent/intervention might exacerbate the expected AEs associated with a commercial agent. Therefore, if an expected AE (for the commercial agent) occurs with a higher degree of severity or specificity, expedited reporting is required.

NOTE: Refer to protocol or IB for reporting needs.

10.19c Relatedness

A problem or event is "related" if it is possibly related and/or attributed to the research procedures including (but not limited to) investigational product(s), assay process and/or study procedures or activity.

Specifically, they will be categorized using the following terms:

Unrelated	AE is ***not*** *related to study agent(s) or research procedure(s)*
Unlikely	AE is ***doubtfully*** *related to study agent(s) or research procedure(s)*
Possible	AE ***may be*** *related to study agent(s) or research procedure(s)*
Probable	AE is ***likely*** *related to study agent(s) or research procedure(s)*
Definite	AE is ***clearly*** *related to study agent(s) or research procedure(s)*

10.19d Severity Criteria

An assessment of the Adverse Events severity grade will be made by the investigator according to the NCI CTCAE Version 5.0.

A copy of this CTCAE version can be downloaded from the CTEP web site: (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm).

10.2 Site Reporting

Subject data accrued on this study will be reported in accordance with 21CFR 312.32.

All AEs and SAEs will be reported using iMedidata Rave electronic data capture system. Please refer to the "Mayo Clinic Cancer Center Electronic Case Report Form (eCRF) Completion Guidelines" for additional instructions.

All AEs and SAEs must be evaluated, diagnosed, and assessed for safety reporting by an ***investigator***.

The AE grading scale for this study will be Common Terminology Criteria for AEs (CTCAE) version 5.0. All appropriate treatment areas must have access to this CTCAE version.

10.21 Adverse Events

10.211 Site Requirements for Reporting AEs

From the time of registration until ≤ 30 days after the administration of the last dose of study drug/agent or therapy, or until a new anti-cancer treatment starts, whichever occurs first, the Site Principal Investigator (PI) is responsible for ensuring that all AEs (observed by study team, provided by external sources, etc.) are reported to the sponsor/investigator and any pharmaceutical partner(s).

After 30 days from last dose of administration of the last dose of study drug/agent or therapy, only adverse events that are attributed to the study drug (possible, probable, or definite) are required to be recorded on the adverse event forms. Also refer to Section 10.231 for the reporting of any possible SAEs as applicable.

The investigator(s) is responsible for:

- AE diagnosis or syndrome(s), if known (if not known, signs or symptoms),
- Dates of onset and resolution (if resolved),
- Severity,
- Assessment of the relationship to study treatment(s),

- As applicable, identify and clarify if an adjustment in treatment dose occurred due to an AE
- Determine the relationship of the AE with any study mandated activity (e.g., administration of investigational product, protocol-required therapies, and/or procedure (including any screening procedure(s)).
- Reviewing laboratory test results and determining whether an abnormal value in an individual study subject represents a clinically significant change from the subject's baseline values.
  - In general, abnormal laboratory findings without clinical significance (based on the Investigator's judgment) are not to be recorded as AEs. Exceptions may include but are not limited to:
    - AESI (Section 10.212)
    - Baseline and Adverse Events Evaluations (Section 10.213)
  - However, laboratory value changes that require treatment or adjustment in current therapy are considered AEs.
  - Where applicable, clinical sequelae (not the laboratory abnormality) are to be recorded as the AE.
  - Asymptomatic laboratory abnormalities that do not require treatment will not be collected as AEs.
- Following reported AEs until resolution.

The delegated study team member(s) must document and report AEs as follows:

- All AEs must be documented in the subject's medical record and recorded on the appropriate study specific iMedidata Rave "Adverse Events" eCRF. Information documented on the iMedidata Rave "Adverse Events" eCRF must be consistent with that recorded on the source document.
  - AEs will be recorded regardless of whether or not they are considered related to the study drug(s). AEs considered related to study drug(s) will be followed until resolution to ≤ Grade 1 or baseline, deemed clinically insignificant, and/or until a new anti-cancer treatment starts, whichever occurs first. Exceptions may include non-clinically significant labs if they meet non-critical reporting criteria.
- If a subject is permanently withdrawn from protocol-required therapies because of an AE, the subject status must be submitted, via the appropriate iMedidata Rave eCRF.
- If an AE results in adjustment in treatment dose (i.e., dose delay, dose reduction, etc.):
  - the individual AE needs to be documented on iMedidata Rave "Adverse Events" eCRF and,
  - the details of the dose adjustment due to the individual AE need to be documented on the iMedidata Rave "Treatment" (Intervention) eCRF.

10.2111 Additional Reporting per Genentech

Eliciting Adverse Events

A consistent methodology for eliciting AEs at all subject evaluation time points should be adopted. Examples of non-directive questions include:

- "How have you felt since your last clinical visit?"
- "Have you had any new or changed health problems since you were last here?"

Specific Instructions for Recording Adverse Events

Investigators should use correct medical terminology/concepts when reporting AEs or SAEs. Avoid colloquialisms and abbreviations.

Diagnosis vs. Signs and Symptoms

If known at the time of reporting, a diagnosis should be reported rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, it is acceptable to report the information that is currently available. If a diagnosis is subsequently established, it should be reported as follow-up information.

Preexisting Medical Conditions

A preexisting medical condition is one that is present at the start of the study. Such conditions should be reported as medical and surgical history. A preexisting medical condition should be re-assessed throughout the trial and reported as an AE or SAE only if the frequency, severity, or character of the condition worsens during the study. When reporting such events, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., "more frequent headaches").

Adverse Event Reporting Period

The study period during which AEs and SAEs where the patient has been exposed to Genentech product must be reported - reporting period begins after initiation of study treatment and ends 30 days following the last administration of study treatment or study discontinuation/termination, whichever is earlier. After this period, investigators should only report SAEs to Genentech that are attributed to prior study treatment

For patients receiving combination therapy, causality will be assessed individually for each protocol-mandated therapy.

Reporting Requirements for Adverse Events Originating from Patient Reported Outcomes

Although sites are not expected to review the PRO data, if physician/study personnel become aware of a potential adverse event during site review of the PRO questionnaire data, he/she will determine whether the criteria for an adverse event have

been met and, if so, these must be reported using the Adverse Event and Special Situation Reporting Form or MedWatch form.

10.212 Adverse Events of Special Interest (AESIs)

Selected non-serious and serious AEs are also known as Adverse Events of Special Interest (AESI) and must be recorded as such on the "SAE: Event Information" eCRF. AESIs (both non-serious and serious adverse events) identified from the date of first dose through 30 days following cessation of treatment, or 30 days after the initiation of a new anticancer therapy, whichever is earlier, will be reported by the site to Mayo Clinic within one business day.

- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's law:
- Treatment-emergent ALT or AST > 3 × ULN in combination with total bilirubin > 2 × ULN
- Treatment-emergent ALT or AST > 3 × ULN in combination with clinical jaundice
- Data related to a suspected transmission of an infectious agent by the study drug (STIAMP), as defined below:
  Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of the study drug is suspected
- Left ventricular dysfunction (asymptomatic decline in LVEF requiring treatment or leading to discontinuation of pertuzumab and trastuzumab)

The following other Special Situations Reports should be collected even in the absence of an Adverse Event and transmitted to Genentech:

- Data related to the Product usage during breastfeeding
- Data related to overdose, abuse, misuse or medication error (including potentially exposed or intercepted medication errors)
- In addition, reasonable attempts should be made to obtain and submit the age or age group of the patient, in order to be able to identify potential safety signals specific to a particular population
- [This requirement, based on European Medicines Agency's (EMA) Good Pharmacovigilance Practices (GVP) Module VI Section B.3, applies to Genentech because it is part of the larger Roche organization that operates in EU territories]:
  - Batch ID/lot ID for biologics associated with AE/SSR/PC/AESI must be included when submitting the case reports to Genentech.

10.213 Baseline and Adverse Events Evaluations

Pretreatment symptoms/conditions to be graded at baseline and adverse events to be graded at each evaluation.

Grading is per CTCAE v5.0 **unless** alternate grading is indicated in the table below:

CTCAE System/Organ/Class (SOC)	Adverse event/Symptoms	Baseline	Each evaluation
Cardiac disorders	Left ventricular systolic dysfunction	X	X
General disorders and administration site conditions	Fatigue	X	X
Investigations	Neutrophil count decreased	X	X
	White blood cell decreased	X	X
Metabolism and nutrition disorders	Hypercalcemia	X	X
	Hyperglycemia	X	X
	Hypermagnesemia	X	X
	Hyponatremia	X	X
Nervous system disorders	Seizure	X	X
Vascular disorders	Thromboembolic event	X	X

10.22 Serious Adverse Events

10.221 Site Requirements for Reporting SAEs

From the time of registration until ≤ 30 days after the administration of the last dose of study drug/agent or therapy, or until a new anti-cancer treatment starts, whichever occurs first, the Site Principal Investigator (PI) is responsible for ensuring that all SAEs (observed by study team, provided by external sources, etc.) are reported immediately to the sponsor/investigator and any pharmaceutical partner(s).

In addition to reporting to Mayo Clinic, the investigator is responsible for reporting to their appropriate IRB/IEC in accordance with local regulatory requirements and procedures.

10.2211 Initial reporting:

The investigator/study team must report SAEs as follows:

- All SAEs must be immediately submitted to Mayo Clinic following the study team's knowledge of the event via the iMedidata Rave "Adverse Events" eCRF.

NOTES: This eCRF will generate the "SAE: Event Information" eCRF when the event is indicated as "serious." Information documented on the iMedidata Rave "SAE: Event Information" eCRF must be consistent with that recorded on the source document.

Once the SAE information has been captured and submitted in iMedidata Rave, a report can be generated. A copy of this completed report must be kept within the study file at the study site.

- The investigator must assess whether the SAE is possibly related to the investigational product.
- The investigator is expected to follow reported SAEs until stabilization, resolution, or patient death. (See section below on Follow-Up Reporting.)

10.2212 Follow-Up Reporting:

New information relating to a previously reported SAE needs to be submitted to Mayo Clinic:

- Immediately upon site becoming aware of updated information
- Sites may be required to:
  - Provide additional information including but not limited to discharge summaries, medical records, etc.
  - Query external locations for additional information if events occurred outside the participating site (i.e., Hospitalization records)
  - Respond to sponsor/investigator and any pharmaceutical partner(s) query(ies) if additional information is needed
- All SAEs regardless of relation to study drug will be followed until resolution to ≤ Grade 1 or baseline and/or deemed clinically insignificant, until a new anti-cancer treatment starts, or death whichever occurs first.
- Revise the previously documented SAE on the appropriate iMedidata Rave eCRF.

NOTE: Information documented on the iMedidata Rave eCRF must be consistent with that recorded on the source document.

Once the updated SAE information has been captured and submitted in iMedidata Rave, a report can be generated. A copy of this updated report must be kept within the study file at the study site.

NOTE: Refer to Section 10.23 for additional reporting regulatory authorities.

Table 10.222 Expedited Reporting Requirements for Adverse Events/Serious Adverse Events

EXPEDITED REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)

Investigators MUST immediately report to Mayo Clinic **ANY** Serious Adverse Events (SAE), whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64).

Mayo Clinic Sponsor-Investigator will report as applicable

Mayo Clinic will report to FDA, per regulations [21 CFR 312.32(c)(d)].

The definition of a SAE can be found in Section 10.13.

Detailed site requirements for reporting SAEs can be found in Section 10.221.

Initial Reporting		Follow-Up Reporting	
Hospitalization >= 24 hours (any grade and/or attribution)	**IMMEDIATELY,** upon study team's awareness of event. (Not to exceed 24 hours.)	**Hospitalization >= 24 hours** (any grade and/or attribution)	**IMMEDIATELY,** upon receiving any updated information regarding initial event. (Not to exceed 24 hours.)
GRADE 3 Attribution of Possible, Probable, or Definite		**GRADE 3** Attribution of Possible, Probable, or Definite	
GRADES 4 and 5 Regardless of Attribution		**GRADES 4 and 5** Regardless of Attribution	

Refer to Section 10.23 for detailed reporting requirements related to Important Medical Events (IME), Adverse Events of Special Interest (AESI), > 30 days post treatment, Dosing errors, Pregnancy, Fetal Death, Neonatal Death, and Lactation.

Offline reporting when iMedidata Rave is unavailable:

If the iMedidata Rave system is unavailable to the site staff to report the SAE, the information is to be reported to Mayo Clinic by completing, scanning, and submitting a hard copy of the "Adverse Events" CRF and related "SAE: Event Information" CRFs within 24 hours of the investigator's knowledge of the event. See the study forms packet for printable copy of these forms. Completed forms are to be submitted to [redacted].

For studies where the first notification of a SAE is reported to Mayo Clinic using the Offline reporting instructions, the data must be entered into iMedidata Rave when the system is again available. The originally submitted forms and the email correspondence must be kept within the study file at the study site.

10.223 Exceptions for Site(s) Regarding Expedited Reporting Timelines for SAEs

For this protocol only, the following AEs/Grades are expected to occur within this population and do not require Expedited Reporting. These events must still be reported via iMedidata Rave (see Section 10.22):

- Specific protocol exceptions to expedited reporting should be reported immediately by investigators **ONLY** if they exceed the expected grade of the event.

CTCAE System Organ Class (SOC)	Adverse event/ Symptoms	CTCAE Grade at which the event will not be reported in an expedited manner[1]
Blood and lymphatic system disorders	Anemia	Grade 3
General disorders and administration site conditions	Fatigue	Grade 3
	Malaise	Grade 3
Investigations	Neutrophil count decreased	≤Grade 4
	White blood cell decreased	≤Grade 4
Metabolism and nutrition disorders	Hypercalcemia	Grade 3
	Hyperglycemia	Grade 3
	Hypermagnesemia	Grade 3
	Hyponatremia	Grade 3

*These exceptions only apply if the AE does not result in hospitalization. If the AE results in hospitalization, then the standard expedited AEs reporting requirements must be followed.

The following hospitalizations are not considered to be SAEs because there is no "AE" (i.e., there is no untoward medical occurrence) associated with the hospitalization:

- Hospitalizations for respite care.
- Planned hospitalizations required by the protocol.
- Hospitalization planned before informed consent (where the condition requiring the hospitalization has not changed post study drug administration).
- Hospitalization for elective procedures unrelated to the current disease and/or treatment on this trial.
- Hospitalization for administration of study drug or insertion of access for administration of study drug.
- Hospitalization for routine maintenance of a device (e.g., battery replacement) that was in place before study entry.
- Hospitalization or other serious outcomes for signs and symptoms of progression of the cancer.

10.23 Other Reporting

10.231 >30 days post treatment

Immediately, upon study team's awareness of event, submit initial and follow-up (as applicable) reporting as follows:

- SAEs that occur > 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite should be reported to Mayo Clinic (refer to Section 10.22).
- For AEs occurring > 30 days after the last administration of investigational agent/intervention, refer to Section 10.211 for reporting requirements.

10.232 Medication Errors

Medication Error: An error made in prescribing, dispensing, administration, and/or use of the study drug.

The following errors (including but not limited to) are to be reported as a deviation (refer to Section 10.237):

- The dispensing, administration and/or use of the unassigned study drug.
- The administration and/or use of an expired study drug.
- Persistent or sporadic, intentional excessive use of medicinal products, which is accompanied by harmful physical or psychological effects.
- Intentional and inappropriate use of a medicinal product not in accordance with the prescribed or authorized dose, route of administration, and/or the indication(s) or not within the legal status of its supply.
- Administration of a quantity of study drug given per administration or per day, which is above the assigned dose.

For Medication Errors that result in an AE or SAE, the event must be reported via the appropriate iMedidata Rave eCRF (refer to Sections 10.21 and 10.22).

10.233 Pregnancy, Pregnant Partner, Fetal Death, Neonatal Death and Lactation

If a female subject becomes pregnant, or a male subject fathers a child, while the subject is on protocol report the pregnancy to Mayo Clinic as specified below.

NOTES:
Pregnancies and/or lactations that occur after registration but before treatment allocation/randomization must be reported by the investigator if they cause the subject to be ineligible from continued participation on the trial.

Pregnancies and lactations that occur from the time of treatment allocation/randomization through 7 months following cessation of study drug/agent, or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier, must be reported by the investigator.

10.2331 Pregnancy

Immediately, upon the Investigator becoming aware of a pregnancy, the site must contact [redacted] for reporting instructions. Mayo Clinic Cancer Center FDA Coordination Team will follow-up with the investigator regarding additional information that may be required.

If a female subject becomes pregnant during the study, the investigator should attempt

to obtain information regarding the birth outcome and health of the infant. If the outcome of the pregnancy meets a criterion for immediate classification as a Serious Adverse Event (i.e., female subject experiences a spontaneous abortion, stillbirth, or neonatal death or there is a fetal or neonatal congenital anomaly) the investigator will report the event as a Serious Adverse Event.

Pregnancy must be reported in an expedited manner as **Grade 3 "Pregnancy, puerperium, and perinatal conditions - Other (pregnancy)"** under the Pregnancy, puerperium, and perinatal conditions System Organ Class (SOC). Pregnancy should be followed until the outcome is known.

10.2332 Pregnant Partner

If a male subject's female partner becomes pregnant, the investigator should discuss

obtaining information regarding the birth outcome and health of the infant from the pregnant partner. **Prior to obtaining private information about a pregnant woman and her infant, the Investigator must obtain consent from the pregnant woman and the newborn infant's parent or legal guardian before any data collection can occur. A consent form will need to be submitted to the IRB for these subjects if a pregnancy occurs**.

NOTE: If informed consent is not obtained, no information may be collected.

The site must contact [redacted] for reporting instructions. Mayo Clinic Cancer Center FDA Coordination Team will follow-up with the investigator regarding additional information that may be required.

10.2333 Lactation

If a female breastfeeds while taking protocol-required therapies, report the lactation case to Mayo Clinic as specified below.

Immediately upon the Investigator's knowledge of any lactation case, the site must contact [redacted] for reporting instructions. Mayo Clinic Cancer Center FDA Coordination Team will follow-up with the investigator regarding additional information that may be required. Investigators should report lactation cases that occur through 180 days after the last dose of protocol-required therapies.

10.2334 Pregnancy Loss/Fetal Death and Neo-Natal Death

In cases of fetal death, miscarriage or abortion, the mother is the patient. In cases where the child/fetus experiences a SAE other than fetal death, the child/fetus is the patient.

Pregnancy outcomes of: spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage, and stillbirth must be reported as serious events (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported.

Pregnancy loss is defined in CTCAE as "A disorder characterized by death in utero."

Fetal loss at any gestational age must be reported expeditiously, as **Grade 4 "Pregnancy loss" under the SOC**

of "Pregnancy, puerperium and perinatal conditions."

Neonatal death, defined in CTCAE as "Newborn death occurring during the first 28 days after birth" must be reported expeditiously as **Grade 4 "Death neonatal" under the SOC of "General disorders and administration site conditions**."

NOTE: When submitting Mayo Expedited Adverse Event Report reports for "Pregnancy", "Pregnancy loss", or "Neonatal loss", the potential risk of exposure of the fetus to the investigational agent(s) or chemotherapy agent(s) must be documented in the "Description of Event" section. Include any available medical documentation.

In addition to reporting to Mayo Clinic, sites are responsible to report any of the above instances to their IRB per Institutional guidelines.

10.2335 Additional Reporting per Genentech

For pregnancy, per PHESGO protocols, it is recommended that the patients (female and male) use contraceptive methods during the treatment on HER2 products and up to 7 months after receiving the last dose.

If a female subject (or female partner of a male subject) taking investigational product becomes pregnant or within 7 months after the last dose of study drug, or if the female partner of a male study subject becomes pregnant while the study subject is receiving the study drug or within 7 months after the last dose of a study drug a report should be completed and expeditiously submitted to Genentech, Inc, 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. Abortion, whether accidental, therapeutic, or spontaneous, should always be classified as serious, and expeditiously reported as an SAE. Similarly, any congenital anomaly/birth defect in a child born to a female subject exposed to the study drug should be reported as an SAE.

Additional information on any {PHESGO}-exposed pregnancy and infant will be requested by Genentech Patient Safety at specific time points (i.e., According to The Global Enhanced PV Pregnancy Program women exposed to PHESGO during pregnancy or within seven months prior to conception will be monitored and follow-up on the infant will be performed after birth, and at 3, 6, and 12 months of life.)

10.234 Death

A death occurring between the time of registration and ≤30 days after last dose of study treatment requires iMedidata Rave reporting regardless of causality. Attribution to treatment or other cause must be provided.

Reportable categories of Death

- Death Not Otherwise Specified (NOS): A cessation of life that

cannot be attributed to a CTCAE term associated with Grade 5.

- Sudden death NOS: A sudden (defined as instant or within one hour of the onset of symptoms) or an unobserved cessation of life that cannot be attributed to a CTCAE term associated with Grade 5.
- Death due to progressive disease that cannot be attributed to a CTCAE term associated with Grade 5 should be reported as **Grade 5 "Disease progression"** under the SOC of General disorders and administration site conditions. Evidence that the death was a manifestation of underlying disease (e.g., radiological changes suggesting tumor growth or progression: clinical deterioration associated with a disease process) should be submitted.
- All other causes of "Death" must be attributable to a Grade 5 CTCAE term.
- Neonatal and Fetal Death: Refer to Section 10.2334.

10.235 Second*ary* Malignancy

- A ***secondary malignancy*** is a cancer caused by treatment for a previous malignancy (e.g., treatment with investigational agent/intervention, radiation, or chemotherapy). A secondary malignancy is not considered a metastasis of the initial neoplasm.
- All secondary malignancies that occur following treatment with an agent under an IND will be reported. Three options are available to describe the event:
  - Leukemia secondary to oncology chemotherapy (e.g., Acute Myelocytic Leukemia [AML])
  - Myelodysplastic syndrome (MDS)
  - Treatment-related secondary malignancy
- Any malignancy possibly related to cancer treatment (including AML/MDS) should also be reported via iMedidata Rave.

10.236 Second Malignancy

A second malignancy is one unrelated to the treatment of a prior malignancy (and is NOT a metastasis from the initial malignancy). Second malignancies require ONLY routine reporting via iMedidata Rave unless otherwise specified.

10.237 Protocol Violation/Deviation Reporting

The Mayo Clinic [redacted] inbox must be notified immediately, of any Major Deviation (defined in Section 10.16).

Mayo Clinic Sites: All Major and Minor deviations must be entered in PTrax immediately upon the study team becoming aware of the violation/deviation. Mayo Clinic staff are responsible for reporting to the Mayo Clinic IRB per IRB policy.

External NON-Mayo Clinic Sites: All deviations must be entered into the appropriate iMedidata Rave eCRF. Non-Mayo Clinic Sites are responsible to report to their local IRB per IRB policy.

10.3 Sponsor-Investigator Reporting

Per FDA, 21 CFR 312.32, Mayo Clinic will report SAEs and/or suspected unexpected serious adverse reactions as required to regulatory authorities, investigators/institutions, and IRBs/IECs in compliance with all reporting requirements according to local regulations and Good Clinical Practice. Mayo Clinic Cancer Center (MCCC) FDA Coordination Team will assist the sponsor-investigator in the processing of expedited reports (i.e., IND Safety reports, deviations, dosing errors, pregnancy, etc.), as appropriate. The MCCC FDA Coordination Team will report SAEs to the pharma partner(s) per contract.

10.4 Genentech Additional Event Reporting Instructions

All protocol-defined AEs, SAEs, AESIs, Special Situation Reports (including pregnancy reports) and Product Complaints with an AE should be sent to:

Fax: [redacted]
Email: [redacted]

For questions related to safety reporting, please contact Genentech Patient Safety:

Tel: [redacted]
Fax: [redacted]

Product complaints

A Product Complaint is defined as any written or oral information received from a complainant that alleges deficiencies related to identity, quality, safety, strength, purity, reliability, durability, effectiveness, or performance of a product after it has been released and distributed to the commercial market or clinical trial.

Post-Study Adverse Events

For studies involving collection of survival data/ follow up until progression free period/ Extended follow up period the investigator after the end of the adverse event reporting period (defined as 30- days after the last dose of study drug) should report all deaths, (regardless of cause), and any serious adverse event including development of cancer or a congenital anomaly in a subsequently conceived offspring of a female subject [including pregnancy occurring in the partner of a male study subject] who participated in the study that is believed to be related to prior exposure to study drug.

Case Transmission Verification will be performed by both parties during this period (every 3 months for 12 months) to ensure successful transmission of Single case reports

Exchange of Single Case Reports with Genentech

The Investigator will be responsible for collecting all protocol-defined Adverse Events (AEs)/Serious Adverse Events (SAEs), pregnancy reports (including pregnancy occurring in the partner of a male study subject), other Special Situation reports, AESIs and Product Complaints with an AE where the patient has been exposed to the Product. The completed Genentech/Roche approved reporting form should be sent to the Genentech contact specified below. Transmission of these reports (initial and follow-up) will be either electronically via email or by fax and within the timelines specified below:

Fax: [redacted]
Email: [redacted]

All Product Complaints *without* an AE should call via:

PC Hotline Number: [redacted] (M-F: 5 am to 5 pm PST)

Transmission of these reports (initial and follow-up) will be either electronically or by fax and within the timelines specified below:

Type of Report	Timelines
Serious Adverse Events (related and not related to the Product)	30 calendar days from awareness date
Special Situation Reports (With or without AE and pregnancy)	
Product Complaints (With or without AE)	
AESI	

Case Transmission Verification of Single Case Reports (Genentech):

- The parties will verify that all single case reports have been adequately received by Genentech via the investigator emailing Genentech a Quarterly line-listing documenting single case reports sent by the investigator to Genentech in the preceding time period.
- The periodic line-listing will be exchanged within seven (7) calendar days of the end of the agreed time period. Confirmation of receipt should be received within the time period mutually agreed upon.
- If discrepancies are identified, the Sponsor and Genentech will cooperate in resolving the discrepancies. The responsible individuals for each party shall handle the matter on a case-by-case basis until satisfactory resolution. The sponsor shall receive reconciliation guidance documents within the 'Activation Package'.
- Following Case Transmission Verification, single case reports which have not been received by Genentech shall be forwarded by the investigator to Genentech within five (5) calendar days from request by Genentech.

At the end of the study, a final cumulative Case Transmission Verification report will be sent to Genentech

Quarterly line-listings and final CTV should be sent to: [redacted]

Reporting to Regulatory Authorities, Ethics Committees and Investigators

Sponsor-investigator, as the Sponsor of the Study, will be responsible for the expedited reporting of safety reports originating from the Study to the Regulatory Authorities (FDA) where it has filed a clinical trial approval, in compliance with local regulations.

Sponsor-investigator or designee as the Sponsor of the Study, will be responsible for the expedited reporting of safety reports originating from the study to the European Medicine Agency (EMA) through Eudravigilance Clinical Trial Module (EVCTM), where applicable.

Sponsor-investigator or designee will be responsible for the expedited reporting of safety reports originating from the Study to the Independent Ethics Committees/ Institutional Review Boards (IEC/IRB) of the Concerned Member States, where applicable.

Sponsor-investigator or designee as the Sponsor of the Study, will be responsible for the preparation of six-monthly Suspected Unexpected Serious Adverse Reaction (SUSAR) reports and their submission to Investigators, Regulatory Authorities and the Institutional Review Board/Independent Ethics Committee (IRB/IEC), where applicable

Sponsor-investigator or designee will be responsible for the distribution of safety information to its own investigators, where relevant, in accordance with local regulations.

Additional Reporting Requirements for IND Holders (if applicable):
For Investigator-Initiated IND Studies, some additional reporting requirements for the FDA apply in accordance with the guidance set forth in 21 CFR §600.80

Events meeting the following criteria need to be submitted to the Food and Drug Administration (FDA) as expedited IND Safety Reports according to the following guidance and timelines:

7 Calendar Day Telephone or Fax Report:
The Investigator is required to notify the FDA of any fatal or life-threatening adverse event that is unexpected and assessed by the Investigator to be possibly related to the use of Phesgo. An unexpected adverse event is one that is not already described in the Phesgo Investigator Brochure. Such reports are to be telephoned or faxed to the FDA and Genentech within 7 calendar days of first learning of the event.

15 Calendar Day Written Report
The Investigator is also required to notify the FDA and all participating investigators, in a written IND Safety Report, of any serious, unexpected AE that is considered reasonably or possibly related to the use of Phesgo. An unexpected adverse event is one that is not already described in the Phesgo investigator brochure.

Written IND Safety reports should include an Analysis of Similar Events in accordance with regulation 21 CFR§ 312.32. All safety reports previously filed by the investigator with the IND concerning similar events should be analyzed and the significance of the new report in light of the previous, similar reports commented on.

Written IND safety reports with Analysis of Similar Events are to be submitted to the FDA, Genentech, and all participating investigators within 15 calendar days of first learning of the event. The FDA prefers these reports on a MedWatch 3500 form, but alternative formats are acceptable (e.g., summary letter).

FDA fax number for IND Safety Reports:

Fax: 1 (800) FDA 0178

All written IND Safety Reports submitted to the FDA by the Investigator must also be faxed to

Genentech Patient Safety:
Fax: [redacted]
Email: [redacted]

And to the Site IRB:
Submit to Mayo Clinic Cancer Center CRO Safety for submission to Mayo Clinic IRB.

For questions related to safety reporting, please contact Genentech Patient Safety:
Tel: [redacted]
Fax: [redacted]

Aggregate Reports

IND ANNUAL REPORTS

Copies to Genentech:

All IND annual reports submitted to the FDA by the Sponsor-Investigator should be copied to Genentech. Copies of such reports should be emailed to Genentech at:
Genentech Patient Safety CTV mailbox: [redacted]

STUDY CLOSE-OUT

Any study report submitted to the FDA by the Sponsor/Investigator should be copied to Genentech. This includes all IND annual reports and the Clinical Study Report (**final study report**). Additionally, any literature articles that are a result of the study should be sent to Genentech. Copies of such reports should be mailed to the assigned Clinical Operations contact for the study:

[redacted]

And to Genentech Patient Safety CTV oversight mailbox at: [redacted]

QUERIES

Queries related to the Study will be answered by Sponsor-Investigator. However, responses to all safety queries from regulatory authorities, Ethics Committees, and Institutional Review Board, or for publications will be discussed and coordinated between the Parties. The Parties agree that Genentech shall have the final say and control over safety queries relating to the Product. Sponsor-Investigator agrees that it shall not answer such queries from regulatory authorities and other sources relating to the Product independently but shall redirect such queries to Genentech.

Both Parties will use all reasonable effort to ensure that deadlines for responses to urgent requests from Regulatory Authorities and/or IRB/IEC for information or review of data are met. The Parties will clearly indicate on the request the reason for urgency and the date by which a response is required.

SIGNAL MANAGEMENT AND RISK MANAGEMENT

Genentech is responsible for safety signal management (signal detection and/or evaluation) for their own Product. However, it is agreed that the sponsor-investigator as Sponsor of the Study, will be primarily responsible for assessment of the benefit-risk balance of the Study.

If Sponsor-investigator issues a safety communication relevant for Genentech (i.e., a safety issue that notably impacts the benefit-risk balance of the Study and / or triggers any changes to the Study) this will be sent to Roche within five (5) business days of its internal approval.

As needed, Genentech will reasonably assist the sponsor-investigator with signal and risk management activities related to the Product within the Study.

Genentech will also provide the sponsor-investigator with any new relevant information that may modify or supplement known data regarding the Product (e.g., relevant Dear Investigator Letter).

COMPLIANCE WITH PHARMACOVIGILANCE AGREEMENT / AUDIT

The Parties shall follow their own procedures for adherence to AE reporting timelines. Each Party shall monitor and, as applicable, request feedback from the other Party regarding AE report timeliness in accordance with its own procedures. The Parties agree to provide written responses in a timely manner to inquiries from the other Party regarding AE reports received outside the agreed upon Agreement timelines. If there is

any detection of trends of increasing or persistent non-compliance to transmission timelines stipulated in this Agreement, both Parties agree to conduct ad hoc or institute a regular joint meeting to address the issue.

In case of concerns related to non-compliance of processes, other than exchange timelines, with this Agreement, the Parties will jointly discuss and collaborate on clarifying and resolving the issues causing non-compliance. Every effort will be made by the non-compliant Party to solve the non-compliance issues and inform the other Party of the corrective and preventative actions taken.

Upon justified request, given sufficient notice of no less than sixty (60) calendar days, an audit under the provisions of this Agreement can be requested by either Party. The Parties will then discuss and agree in good faith upon the audit scope, agenda and execution of the audit. The requesting Party will bear the cost of the audit.

11.0 Treatment Evaluation/Measurement of Effect

For the purposes of this study, patients should be reevaluated every 9 weeks for the first 27 weeks, then every 12 weeks. The timing of scans should be based off the initiation date of protocol treatment. The restaging schedule should be adhered to regardless of treatment holds or interruptions. In addition to a baseline scan, confirmatory scans should also be obtained at least 6 weeks following initial documentation of objective response.

11.1 Prostate Cancer Working Group 3 (PCWG3) response criteria

This study makes use of the PCWG3 response criteria, which consists of the following three distinct evaluations:

- **Visceral lesions and lymph nodes** will be assessed using a modified form of the RECIST 1.1 criteria as specified in Section 11.2.
- **Bone metastases** will be assessed using the PCWG3 criteria specified below in Section 11.2.

PCWG3 discourages the use of overall response criteria, and in this study, overall response criteria will only apply to soft tissue lesions, will not incorporate bone lesions, and will not incorporate changes in tumor markers.

Tumor markers: Neither PSA nor any other tumor marker will be used in this study for either defining in part or in whole progression or response. PSA will not be used to make treatment decisions either.

Bone lesions: Post-treatment changes will be described as "new lesions" or "no new lesions." There will be no descriptions of post-treatment "responses" for bone metastases. As such, only progression will be defined in regards to bone lesions, using the following table as a descriptor.

Patients are defined as progressing when they meet bone or soft tissue progression (both are not required).

11.11 **Documentation for Radiographic Evidence of Disease Progression**

Date Progression Detected (Visit)[a]	Criteria for Progression	Criteria for Confirmation of Progression (requirement and timing)[b]	Criteria for Documentation of Disease Progression on Confirmatory Scan
Week 9	Bone lesions: Two or more new lesions compared to baseline bone scan by PCWG3 Consider bone flare phenomenon as a possibility[c]	Timing: at least 6 weeks after progression identified or at Week 18 visit[b]	Two or more new bone lesions on bone scan (compared to Week 9 scan)
	Soft tissue lesions: Progressive disease on CT or MRI per Section 11.23	Confirmation required for soft tissue disease (scan of same modality as demonstrated progression)[b]	Confirmation of progressive soft tissue disease per Section 11.23

Date Progression Detected (Visit)[a]	Criteria for Progression	Criteria for Confirmation of Progression (requirement and timing)[b]	Criteria for Documentation of Disease Progression on Confirmatory Scan
Week 18	Bone lesions: Two or more new lesions on bone scan compared to Week 9 bone scan	Timing: at least 6 weeks after progression identified or at Week 27 Visit Required for bone lesions observed on bone scan[b]	Persistent[d] or increase in number of bone lesions on bone scan compared to Week 18 scan
	Soft tissue lesions: Progressive disease on CT or MRI per Section 11.23	No confirmatory scan required for soft tissue disease progression	----------
Week 27 or later	Bone lesions: Two or more new lesions compared to Week 9 bone scan	Timing: at least 6 weeks but no later than 12 weeks after progression identified Required for bone lesions observed on bone scan[b]	Persistent[d] or increase in number of lesions on bone scan compared to prior scan
	Soft tissue lesions: Progressive disease on CT or MRI per Section 11.23	No confirmatory scan required for soft tissue disease	----------

a. Progression detected at an unscheduled visit either prior to Week 9 or between scheduled visits will require a confirmatory scan at least 6 weeks later and should follow confirmation criteria outlined in the table for the next scheduled scan.
b. Confirmation must occur at the next available scan.
c. Bone flare phenomenon can occur early in the course of antiandrogen therapy. If is defined as detection of new bone lesions(s) on first follow-up bone scan occurring due to flare of a pre-existing subclinical metastatic lesion(s) Assuming that the treatment is being tolerated well and there is no clinical or radiographic reason to discontinue it investigators are encouraged to continue treatment and obtain confirmatory imaging studies (including a bone scan) at least 6 weeks later.
d. For confirmation, at least two of the lesions first identified as new must be present at that next available scan (confirmation scan).

Note: For patients with a superscan (confluence of lesions across the axial skeleton such that distinguishing any new lesions is not possible), progression will be defined by clinical progression or progression by RECIST criteria.

11.2 Target Lesions

Soft tissue (non-lymph nodal) lesions ≥10 mm in the longest diameter are considered measurable. Bone metastases are only considered measurable (i.e., target lesion) if they have a soft tissue component ≥10 mm. All other bone metastases are considered inevaluable per modified RECIST 1.1 criteria. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, and should be chosen based on their suitability for accurate repetitive measurements. Record individual sites of spread (lung, liver, adrenal, CNS, etc.) separately, up to 5 lesions per site.

Lymph nodes need to be ≥15 mm in the short axis to be considered target or evaluable lesions to assess changes in size. Record short axis dimensions of pelvic and extrapelvic (retroperitoneal, mediastinal, thoracic, other) nodal disease separately; and up to 5 nodes in total.

Record new lesions versus growth of pre-existing lesions, and sites of new lesions.

It may be the case that, on occasion, the largest lesion does not lend itself to reproducible repeated measurements in which case the next largest lesion that can be measured reproducibly should be selected. A sum of the diameters (longest for all lesions, including nodes) for all target lesions will be calculated and reported as the baseline sum diameters. The baseline sum LD will be used as reference to further characterize the objective tumor response of the measurable dimension of the disease.

11.21 Complete Response

Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in long axis to <10 mm.

11.22 Partial Response (PR)

At least a 30% decrease in the sum of the longest diameters of target lesions, taking as reference the baseline sum diameters.

11.23 Progressive Disease (PD)

At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new non-osseous lesions is also considered progression). Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules, palpable lymph nodes) and at least 10 mm in diameter as assessed using calipers (e.g., skin nodules).

Note: Per PCWG3, visceral (lung, liver adrenal) or extranodal lesions need to be ≥10 mm in one dimension, using spiral CT. However, lymph nodes need to be ≥15 mm in at least one dimension to be considered new.

11.24 Stable Disease (SD)

Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD taking as references the smallest sum diameters while on study.

11.3 Non-target Lesions

All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as non-target lesions and should also be recorded at baseline. Bone metastases without a soft tissue component ≥10 mm (see Section 11.2) are considered inevaluable and should not be designated as non-target lesion(s). Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow-up. Non-target lesions include bone lesions.

11.31 **Complete Response (CR)**

Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm long axis). Note: If

tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

11.32 **Non-complete response (non-CR)/Non-progression (non-PD)**

Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

11.33 **Progressive Disease (PD)**

Appearance of one or more new lesions and/or unequivocal progression of existing 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.

Although a clear progression of non-target lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed later on by the review panel (or Study Chair).

Whether new or pre-existing, lesions must be measurable per Section 11.23 to be used to measure progression. For new bone lesions, adhere to bone progression criteria specified in Section 11.1.

11.4 Evaluation of Best Overall Response

Measurable disease will be evaluated using the PCWG3 criteria in Section 11.1.

11.41 **For Patients with Measurable Disease** (i.e., Target Disease)

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

* In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

Note:

Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as “symptomatic deterioration”. Every effort should be made to document the objective progression even after discontinuation of treatment.

11.42 **For Patients with Non-measurable Disease** (Non-Target) Disease Only

NOTE: This section is included for reference only. See Section 3.0.

Non-target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR / Non-PD	No	Non-CR / Non-PD*
Not all evaluated	No	Not evaluated
Unequivocable PD	Yes or No	PD
Any	Yes	PD

* 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as an endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised

11.5 Guidelines for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. 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.

11.51 Clinical Lesions

Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules, palpable lymph nodes) and ≥ 10 mm diameter as assessed using calipers (e.g., skin nodules). For the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

11.52 **Chest X-ray**

Use of Chest X-ray is not allowed for determination of measurable disease in this study.

11.53 **Conventional CT and 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 should be twice the slice thickness. Visceral (lung, liver, adrenal) or extranodal lesions need to be ≥ 10 mm in one dimension if slice thickness is ≤ 5 mm; however, lymph nodes need to be ≥ 20 mm in at least one dimension to be considered evaluable lesions to assess for changes in size. MRI is also acceptable in certain situations (e.g., for body scans). Use of MRI remains a complex issue. MRI has excellent contrast, spatial, and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion

conspicuity, and measurement. Furthermore, the availability of MRI is variable globally. As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. Furthermore, as with CT, the modality used at follow-up should be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.

11.54 **PET-CT**

The low dose or attenuation correction CT portion of a combined PET- CT is not always of optimal diagnostic CT quality for use with RECIST measurements. At present, there are insufficient data to allow use of PET-CT scans for assessment of measurable disease in this study.

11.55 **Ultrasound (US)**

Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

11.56 **Endoscopy and Laparoscopy**

The utilization of these techniques for objective tumor evaluation is not advised. However, such techniques may be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response (CR) or surgical resection is an endpoint.

11.57 **Tumor Markers alone cannot be used to assess response**

If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

11.6 Confirmation Measurement/Duration of Response

11.61 Confirmation

Confirmatory scans should be performed per Section 11.1 after the initial documentation of disease progression.

11.62 Duration of Overall Response

The duration of overall response is measured from the time measurement criteria are met for CR/PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

The duration of overall complete response is measured from the time measurement criteria are first met for CR until the first date that progressive disease is objectively documented.

11.63 **Duration of Stable Disease**

Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started, including the baseline measurements.

12.0 Descriptive Factors: None

13.0 Treatment/Follow–up Decision at Evaluation of Patient

13.1 Continuation of treatment

Patients who are CR, PR, or SD will continue treatment per protocol.

13.2 Discontinuation of treatment

Per the Schema, patients will discontinue treatment if any of the following occur:
1) Adverse events per Section 8.0
2) Disease progression
3) Alternative therapy
4) Patient refusal

13.3 Progressive disease (PD)

Patients who develop PD while receiving therapy will go to the survival/extended follow-up phase.

13.4 Off protocol treatment

Patients who go off protocol treatment for reasons other than PD or alternative therapy will go to the clinical follow-up phase per Section 4.0.

13.5 Observation/Clinical Follow-up

If the patient has achieved CR, PR, or SD, and stops treatment, the patient will be observed every 3 months for 1 year, and then go to survival/extended followup.

13.6 Unevaluable patients

If a patient fails to complete the first cycle of treatment or does not undergo first post-treatment imaging, the patient will be regarded as unevaluable and will be replaced.

13.7 Ineligible

A patient enrollment is deemed *ineligible* if after registration, it is determined that at the time of registration, the patient did not satisfy each and every eligibility criterion for study entry. If the patient received treatment, the patient may continue treatment at the discretion of the physician as long as there are not safety concerns. The patient will continue in the Active Monitoring/Treatment phase of the study, per Section 4.0 of the protocol.

- If the patient never received treatment, on-study and end of study material must be submitted.

13.8 Major violation

A patient enrollment is deemed a *major violation*, if protocol requirements regarding treatment in cycle 1 of the initial therapy are severely violated that evaluability for primary end point is questionable. If the patient received treatment, the patient may continue treatment at the discretion of the physician as long as there are not safety concerns. The patient will continue in the Active Monitoring/Treatment phase of the study, per Section 4.0 of the protocol.

13.9a Cancel

A patient enrollment is deemed a *cancel* if he/she is removed from the study for any reason before any study treatment is given. On-study material and the End of Active Treatment/Cancel Notification Form must be submitted. The patient will go off study.

13.9b Subsequent Anti-Cancer Therapy Status

The investigator or qualified designee will review all new anti-neoplastic therapy initiated after the last dose of trial treatment. If a participant initiates a new anti-cancer therapy within 30 days after the last dose of trial treatment, the Safety Follow-up visit must occur before the first dose of the new therapy. Once new anti-cancer therapy has been initiated the participant will move into survival follow-up/event monitoring/extended follow-up per Section 4.0.

14.0 Body Fluid Biospecimens

14.1 Summary of the blood biospecimen collection schedule

NOTE: Blood collection is **mandatory** for this study at all timepoints specified.

14.11 Total volume to be collected at each timepoint is provided below

	Timepoint 1 **During Pre-Registration***	Timepoint 2 **Cycle 1, Day 1 prior to start of treatment (Baseline)**	Timepoint 3 **At the end of Cycle 4 and every four cycles****	Timepoint 4 **At end of treatment for any reason†**	**Submit to:**
Total volume	10ml	60ml	50ml	50ml	Dr Jacob Orme Lab

*Eligibility: After consent and prior to registration for determination of NRG-1 level.

**End of Cycle 4, Cycle 8, etc. at same time as imaging

†Or end of Cycle 6 prior to Cycle 7 if patient is still on treatment at that time

14.2 Collection and Processing

Kits will be provided for blood collection outside of Rochester, Minnesota.

Instructions for collection and shipping are in each kit.

See Lab Manual for additional instructions.

In Rochester, Minnesota: Samples should be collected and transported Monday – Friday.

Outside of Rochester, Minnesota: Samples should be collected and shipped **Monday-Thursday**
However, if the subject can only be seen on Fridays, please ensure that Saturday delivery is marked clearly on the shipping boxes and appropriate Mayo Clinic staff are notified.

14.3 Shipping and Handling, see Lab Manual

All samples will be sent to:
Attn: [redacted]
Mayo Clinic
200 First St SW
Rochester MN 55905
Phone: [redacted]
E-mail: [redacted]

15.0 Drug Information

15.1 Pertuzumab, Trastuzumab, and Hyaluronidase-zzxf (PHESGO™) [HP]

15.11 Background

Pertuzumab and trastuzumab are monoclonal antibodies directed against HER2. Pertuzumab targets the extracellular dimerization domain (subdomain II) of HER2 and, thereby, blocks ligand-dependent heterodimerization of HER2 with other HER family members, including EGFR, HER3 and HER4. As a result, pertuzumab inhibits ligand-initiated intracellular signaling through mitogen-activated protein (MAP) kinase and phosphoinositide 3-kinase (PI3K). Trastuzumab binds to subdomain IV of the extracellular domain of the HER2 protein to inhibit the ligand-independent, HER2 mediated cell proliferation and PI3K signaling pathway in human tumor cells that overexpress HER2. Inhibition of these signaling pathways can result in cell growth arrest and apoptosis. Both pertuzumab and trastuzumab-mediated antibody-dependent cell-mediated cytotoxicity (ADCC) have been shown to be preferentially exerted on HER2 overexpressing cancer cells compared with cancer cells that do not overexpress HER2.

Hyaluronidase (recombinant human) is an endoglycosidase used to increase the dispersion and absorption of co-administered drugs when administered subcutaneously. In the doses administered, hyaluronidase acts transiently and locally. The effects of hyaluronidase are reversible, and permeability of the subcutaneous tissue is restored within 24 to 48 hours.

15.12 Formulation

Pertuzumab, trastuzumab, and hyaluronidase-zzxf injection is supplied as two different strengths: a 15 mL single-dose vial containing 1,200 mg of pertuzumab, 600 mg of trastuzumab, and 30,000 units of hyaluronidase; and a 10 mL single-dose vial containing 600 mg of pertuzumab, 600 mg of trastuzumab, and 20,000 units of hyaluronidase. Pertuzumab, trastuzumab, and hyaluronidase-zzxf injection is supplied as a sterile, preservative-free, clear to opalescent, and colorless to slightly brownish solution in single-dose vials for subcutaneous administration. Each carton contains one single-dose vial. Pertuzumab and trastuzumab are produced by recombinant DNA technology in a mammalian cell (Chinese Hamster Ovary) culture. Hyaluronidase (recombinant human) is a glycosylated single-chain protein produced by mammalian (Chinese Hamster Ovary) cells containing a DNA plasmid encoding for a soluble fragment of human hyaluronidase (PH20).

15.13 Preparation and storage

Store vials in the refrigerator at 2°C to 8°C (36°F to 46°F) in the original carton to protect from light. Do not freeze. Do not shake. Do not use vial if particulates or discoloration is present. Discard any unused portion remaining in the vial. For both the initial and maintenance dose, each corresponding vial is ready-to-use for one subcutaneous injection and should not be diluted. To avoid needle clogging, attach the hypodermic injection needle to the syringe immediately prior to administration. If the dose is not to be administered immediately, and the solution has been withdrawn from the vial into the

syringe, replace the transfer needle with a syringe closing cap. Once transferred from the vial to syringe, the syringe may be stored in the refrigerator (2°C to 8°C (36°F to 46°F)) for up to 24 hours and at room temperature (20°C to 25°C (68°F to 77°F)) for up to 4 hours. Pertuzumab, trastuzumab, and hyaluronidase-zzxf injection is compatible with stainless steel, polypropylene, polycarbonate, polyethylene, polyurethane, polyvinyl chloride and fluorinated ethylene polypropylene.

15.14 **Administration**

Pertuzumab, trastuzumab, and hyaluronidase-zzxf injection may be injected using 25G-27G (3/8”-5/8”) hypodermic injection needles. Pertuzumab, trastuzumab, and hyaluronidase-zzxf injection is for subcutaneous use only in the thigh. **Do not administer intravenously.** The subcutaneous injection site should be alternated between the left and right thigh only. New injections should be given at least 1 inch (2.5 cm) from the previous site on healthy skin and never into areas where the skin is red, bruised, tender, or hard. Doses should not be split between two syringes or between two sites of administration. Other medications for subcutaneous administration should preferably be injected at different sites.

Inject 15 mL initial dose of pertuzumab, trastuzumab, and hyaluronidase-zzxf 1,200 mg, 600 mg, 30,000 units subcutaneously over approximately 8 minutes.

Inject 10 mL maintenance dose of pertuzumab, trastuzumab, and hyaluronidase-zzxf 600 mg, 600 mg, 20,000 units subcutaneously over approximately 5 minutes.

Observe patients for a minimum of 30 minutes after initial dose and 15 minutes after each maintenance dose of pertuzumab, trastuzumab, and hyaluronidase-zzxf injection for signs or hypersensitivity symptoms or administration-related reactions. Medications to treat such reactions, as well as emergency equipment, should be available for immediate use.

In patients receiving an anthracycline-based regimen, administer pertuzumab, trastuzumab, and hyaluronidase-zzxf injection following completion of the anthracycline. In patients receiving docetaxel or paclitaxel, administer docetaxel or paclitaxel after pertuzumab, trastuzumab, and hyaluronidase-zzxf injection.

15.15 **Pharmacokinetic information**

Absorption –

Absolute bioavailability – Pertuzumab: 0.7; Trastuzumab: 0.8

T_{max} – Pertuzumab and trastuzumab: 4 days

Distribution – Pertuzumab: 2.8 L; Trastuzumab: 2.9 L

Excretion (Linear Clearance) – Pertuzumab: 0.2 L/day; Trastuzumab: 0.1 L/day

No clinically significant differences in the pharmacokinetics of pertuzumab and trastuzumab were observed based on age, and renal impairment. The effects of hepatic impairment on the pharmacokinetics of pertuzumab and trastuzumab are unknown.

15.16 **Potential drug interactions**

Patients who receive anthracycline after stopping PHESGO may be at increased risk of cardiac dysfunction because of PHESGO's long washout period. If possible, avoid anthracycline-based therapy for up to 7 months after stopping PHESGO. If anthracyclines are used, carefully monitor the patient's cardiac function.

15.17 **Known potential adverse events**

Consult the Investigator's Brochure and package insert for the most current and complete information. Refer to the package insert pertaining to the following boxed warnings: cardiomyopathy, embryo-fetal toxicity, and pulmonary toxicity.

Common known potential adverse events, > 10%:
Dermatologic: alopecia, skin rash, xeroderma
Endocrine & metabolic: decreased serum albumin, decreased serum sodium hot flash, increase serum potassium, weight loss
Gastrointestinal: constipation, decreased appetite, diarrhea, dysgeusia, dyspepsia, nausea, stomatitis, vomiting
Hematologic & oncologic: anemia, decrease absolute lymphocyte count, neutropenia, thrombocytopenia
Hepatic: Increase serum alanine aminotransferase, increase serum aspartate aminotransferase
Local: injection site reaction
Nervous system: asthenia, paresthesia, dizziness, headache, insomnia
Neuromuscular & skeletal: arthralgia, myalgia
Renal: increase serum creatinine
Respiratory: cough, epistaxis, upper respiratory tract infection
Miscellaneous: fatigue, fever, radiation injury

Less common known potential adverse events, 1% - 10%:
Cardiovascular: cardiac failure, peripheral edema, reduced ejection fraction
Dermatologic: dermatitis, erythema of skin, nail discoloration, nail disease, palmar-plantar erythrodysesthesia, pruritus
Endocrine & metabolic: decreased serum glucose, hypokalemia, increase serum sodium
Gastrointestinal: abdominal pain, hemorrhoids, upper abdominal pain
Genitourinary: urinary tract infection
Hematologic & oncologic: febrile neutropenia, leukopenia
Hepatic: increase serum albumin
Hypersensitivity: hypersensitivity reaction
Infection: neutropenic sepsis
Local: pain at injection site
Nervous system: malaise, paresthesia
Neuromuscular & skeletal: back pain, limb pain, muscle spasm, musculoskeletal pain, ostealgia
Ophthalmic: dry eye syndrome, increased lacrimation
Respiratory: dyspnea, flu-like symptoms, nasopharyngitis, rhinorrhea

Frequency not defined:
Cardiovascular: cardiac arrhythmias, cardiomyopathy, hypertension, left ventricular dysfunction
Respiratory: Pulmonary toxicity

15.18 Drug procurement

Genentech will supply PHESGO free of charge for patients on this trial. Genentech will provide each site pharmacy with PHESGO.

15.19 Nursing guidelines

15.191 Injection should only be given SQ in the thigh. Do not administer IV. Alternate between right/left thigh and separate new injections from previous injections by about 1 inch.

15.192 Allergic reactions are possible. Patients should be monitored for at least 30 minutes after initial dose and 15 minutes after subsequent doses. Have emergency medications readily available.

15.193 If patients are receiving anthracycline-based regimen administer the pertuzumab, trastuzumab, hyaluronidase following completion of anthracycline.

15.194 If patients are receiving paclitaxel or docetaxel-injection should be given before chemo.

15.195 GI side effects can be seen, including constipation, diarrhea, nausea, and vomiting. Treat symptomatically and monitor for effectiveness.

15.196 Monitor LFTs

15.197 Monitor electrolytes and correct as needed.

15.198 Patients may experience arthralgias and myalgias. Treat symptomatically and monitor for effectiveness.

15.199a Cardiac side effects can be seen. Monitor EF per study/SOC parameters. Instruct patient to report LE edema, chest pain, or SOB to study team.

15.199b Rash and dermatitis can be seen.

15.2 Enzalutamide

15.21 Background

Enzalutamide competitively inhibits androgen binding to androgen receptors, preventing nuclear translocation of androgen receptors and their interaction with DNA. As a result, prostate cancer cell proliferation decreases, and cell death is induced. N-desmethyl enzalutamide, a major metabolite, exhibits similar in vitro activity.

15.22 Formulation

Enzalutamide is supplied as both 40 mg white to off-white oblong liquid-filled soft gelatin capsules and 40mg and 80mg tablets for oral administration. The capsules also contain caprylocaproyl polyoxylglycerides, butylated hydroxyanisole, butylated hydroxytoluene, gelatin, sorbitol sorbitan solution, glycerin, purified water, titanium dioxide and black iron oxide. The tablet formulation includes hypromellose acetate succinate, microcrystalline cellulose, colloidal silicone dioxide, croscarmellose sodium, and magnesium stearate.

15.23 Preparation and Storage

Store enzalutamide at 20º to 25ºC (68º to 77ºF) in a dry place and keep the container tightly closed. Excursions permitted to 15º to 30ºC (59º to 86º F).

15.24 Administration

Enzalutamide is administered orally once daily with or without food. Swallow capsules whole.

15.25 Pharmacokinetics

Absorption: rapid with time to peak concentration in 1 hour (range 0.5-3 hours). A high-fat meal did not alter the AUC to enzalutamide or N-desmethyl enzalutamide.

Distribution: 110 L; protein binding of parent drug is 97-98% to primarily albumin; protein binding of active metabolite is 95% to plasma proteins

Metabolism: Hepatic via CYP2C8 (formation of active metabolite N-desmethyl enzalutamide) and CYP3A4

Excretion: Primarily eliminated by hepatic metabolism. Following single oral administration of ^{14}C-enzalutamide 160 mg, 85% of the radioactivity is recovered by 77 days post dose: Urine (71%), feces (14%) primarily as inactive metabolite

$T_{1/2}$: Enzalutamide: 5.8 days (range 2.8-10.2 days); N-desmethyl enzalutamide: 7.8-8.6 days

15.26 Drug Interactions

Enzalutamide is metabolized by CYP2C8 and CYP3A4. Co-administration of a strong CYP2C8 inhibitor, gemfibrozil) increased the area under the plasma concentration-time curve (AUC) of enzalutamide and N-desmethyl enzalutamide by 2.2-fold in healthy volunteers. Avoid the administration of strong CYP2C8 inhibitors. If co-administration with a strong CYP2C8 inhibitor cannot be avoided, reduce the dose of enzalutamide. Co-administration of enzalutamide with strong or moderate CYP2C8 inducers (e.g., rifampin) may alter plasma exposure of enzalutamide and should be avoided if possible. Selection of a

concomitant medication with no or minimal CYP2C8 induction potential is recommended.

Co-administration of itraconazole, a strong CYP3A4 inhibitor, increased the AUC of enzalutamide and N-desmethyl enzalutamide by 1.3-fold in healthy volunteers. Co-administration of enzalutamide with strong CYP3A4 inducers (e.g., carbamazepine, phenobarbital, phenytoin, rifabutin, rifampin, rifapentine) may decrease the plasma exposure of enzalutamide and should be avoided if possible. Selection of a concurrent medication with no or minimal CYP3A4 induction potential is recommended. Moderate CYP3A4 inducers (e.g., bosentan, efavirenz, etravirine, modafinil, nafcillin) and St. John's Wort may also reduce the plasma exposure of enzalutamide and should be avoided if possible.

Enzalutamide is a strong CYP3A4 inducer and moderate CYP2C9 and CYP2C19 inducer. Enzalutamide reduced plasma exposure of midazolam (CYP3A4 substrate), warfarin (CYP2C9 substrate), and omeprazole (CYP2C19 substrate). Concomitant use of enzalutamide with narrow therapeutic index drugs that are metabolized by CYP3A4 (e.g., alfentanil, cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, and tacrolimus), CYP2C9 (e.g., phenytoin, warfarin), and CYP2C19 (e.g., S-mephenytoin) should be avoided, as enzalutamide may decrease their exposure. If co-administration with warfarin cannot be avoided, conduct additional INR monitoring.

15.27 Known Potential Adverse Events

Common >10%:
Cardiovascular: Peripheral edema, hypertension
Central Nervous System: Fatigue, falling, headache, dizziness
Endocrine & Metabolic: Hot flash, weight loss
Gastrointestinal: Constipation, diarrhea, decreased appetite
Hematologic & Oncologic: Neutropenia
Neuromuscular & Skeletal: Weakness (falls), back pain, arthralgia, musculoskeletal pain
Respiratory: Upper respiratory tract infection, dyspnea

Less Common 1 to 10%:
Central Nervous System: Myasthenia, insomnia, anxiety, paresthesia, cauda equine syndrome, spinal cord compression, altered mental status, hypoesthesia, hallucination, restless leg syndrome
Dermatologic: Pruritus, xeroderma
Endocrine & Metabolic: Gynecomastia
Gastrointestinal: Dysgeusia
Genitourinary: Hematuria, pollakiuria
Hematologic & Oncologic: Thrombocytopenia
Hepatic: Increased serum bilirubin
Infection: Infection
Neuromuscular & Skeletal: Bone fracture, stiffness
Respiratory: Lower respiratory tract infection, epistaxis

Rare <1%Limited to important or life-threatening: Seizure, ischemic heart disease

Post-Marketing Experience: vomiting, Posterior Reversible Encephalopathy Syndrome, hypersensitivity, skin and subcutaneous tissue disorders (rash, severe cutaneous adverse reactions including Stevens-Johnson syndrome (SJS),

erythema multiforme, toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS) and acute generalized exanthematous pustulosis (AGEP))

15.28 Drug Procurement

Commercial supplies

15.29 Nursing guidelines

15.291 Instruct patients that enzalutamide can be taken either with or without food.

15.292 Assess patient's concurrent medication including over the counter supplements. There are numerous drug-drug interactions as outlined in Section 15.26.

15.293 Patients may experience peripheral edema, instruct patients to report any swelling to the study team.

15.294 Warn patients of myalgias. These can be mild to severe. Treat symptomatically and monitor for effectiveness.

15.295 Rarely patients may experience seizures. Warn patients of this and instruct patients to seek out emergency medical attention if they experience a seizure.

15.296 Patients may experience fatigue. Instruct patient in an energy conserving lifestyle, encourage alternating rest and exercise as tolerated.

16.0 Statistical Considerations and Methodology

16.1 Overview

This is a studyof pertuzumab/trastuzumab/hyaluronidase-zzxf (HP) with enzalutamide in patients with metastatic castration-resistant prostate cancer (mCRPC). The purpose of this study is to determine any preliminary evidence to suggest that a larger scale clinical trial might be recommended. The study will not utilize a formal statistical design but will focus on estimation rather than hypothesis testing. The primary endpoint will be the confirmed overall objective response rate (ORR), defined as any confirmed radiographic complete response plus partial response according to the PCWG3 criteria. In addition to response, this study will also estimate progression-free survival (PFS), overall survival (OS), and adverse event rates as secondary endpoints.

A safety assessment of HP with enzalutamide will be conducted to evaluate the safety of this regimen.

Evaluable Population: The Evaluable Population comprises all patients who are eligible, consented, receive protocol treatment, and undergo first post-treatment imaging scan.

Treated Population: The Treated Population comprises all patients who consent and are registered to the study and receive any protocol treatment.

16.2 Statistical Design

16.21 Sample Size

A maximum of 6 evaluable patients will be enrolled. We anticipate accruing 1-2 additional patients to replace a patient who is ineligible or unevaluable per the definition of Evaluable Population above. Maximum projected accrual is therefore 6-8 patients.

16.22 Accrual Time and Study Duration

The anticipated accrual rate is approximately 1-2 patients per month. Therefore, the accrual period for this study is expected to be between 3 and 6 months. The final analysis can begin approximately 9-12 months after the trial begins, i.e., as soon as the last patient has been observed for 6 months.

16.3 Analysis Plan

The analysis for this trial will commence at the time the patients have become evaluable for the primary endpoint. Such a decision will be made by the Statistician and Study Chair, in accordance with MCCCC Standard Operating Procedures, availability of data for secondary endpoints, and the level of data maturity. It is anticipated that the earliest date in which the results will be made available via manuscript, abstract, or presentation format is when patients have been on study for 6 months (i.e., received at least 8 cycles of treatment).

16.31 Primary Endpoint

16.311 Definition

The primary endpoint of this trial is confirmed overall response rate (ORR). Overall response rate is defined as the proportion of patients who experience either a partial response or complete response as defined by PCWG3 (success). The primary endpoint can be analyzed when data confirms that the necessary number of evaluable patients have reached one of the following trial milestones: 1. Patient has gone

off protocol treatment, or 2. Patient has achieved overall response, or 3. Patient has reached their third re-staging scan (corresponding to ~6 months of treatment). ORR will be estimated, and a 95% confidence interval will be reported.

16.312 Estimation

The proportion of successes will be calculated by the number of successes divided by the total number of evaluable patients. Confidence intervals for the true success proportion will be calculated according to the approach of Clopper and Pearson. The Evaluable Population will be used for this endpoint.

Based on accrual of 6 evaluable patients, two-sided 95% exact binomial confidence intervals for a range of success rates are provided in the following table:

Number of patients with successes	0	1	2	3	4	5	6
Point estimate of success rate:	0.0%	16.7%	33.3%	50.0%	66.7%	83.3%	100.0%
Two-sided 95% confidence interval (exact binomial)	(0.0%, 45.9%)	(0.4%, 64.1%)	(4.3%, 77.7%)	(11.8%, 88.2%)	(22.3%, 95.7%)	(35.9%, 99.6%)	(54.1%, 100.0%)

16.313 Decision Rule

While this study will not utilize formal hypothesis testing, we will consider this regimen promising for a larger scale clinical trial if at least one success is observed out of the six evaluable patients.

16.32 Secondary Endpoints

The following endpoints will be evaluated: progression-free survival, overall survival, adverse events, and quality of life according to the FACT-P.

16.321 Progression-Free Survival

Progression-free survival is defined as the time from study entry to the first of either confirmed radiographic disease progression or death from any cause, where radiographic disease progression will be determined based on PCWG3 criteria. Patients who do not experience disease progression or death while on protocol will be censored at their last disease assessment date. PFS will be estimated using the Kaplan-Meier method. The median PFS and 6-month PFS proportion and corresponding 95% confidence intervals (by Brookmeyer and Crowley) will be reported. The Treated Population will be used for this endpoint.

16.322 Overall Survival (OS)

Overall survival is defined as the time from study entry to death from any cause. Patients will be censored at the date patient was last known

to be alive. OS will be estimated using the Kaplan-Meier method. The median OS and 12-month OS proportion and corresponding 95% confidence intervals (by Brookmeyer and Crowley) will be reported. The Treated Population will be used for this endpoint.

16.323 Adverse events

The rate of patients experiencing any Grade 3 or higher adverse event deemed at least possibly related to treatment will be reported. The maximum grade for each type of adverse event by patient will also be summarized in an exploratory and hypothesis generating fashion by frequencies and percentages using CTCAE version 5.0. Adverse event outcomes assessed via PRO-CTCAE will be descriptively summarized and compared to the physician assessments. The Treated Population will be used for this endpoint.

In addition, the number and proportion of patients experiencing a significant toxicity event in Cycle 1 as described in Section 7.5 will be reported. This proportion will be calculated as the number of patients experiencing a significant toxicity divided by the number of patients who are eligible and receive the expected dose of HP and at least 75% of the expected dose of enzalutamide for the first cycle OR experience a significant safety event in the first cycle of treatment. Confidence intervals for the proportion of patients experiencing a significant toxicity will be calculated according to the approach of Clopper and Pearson.

16.324 Quality of Life

Patient responses to the FACT-P will be summarized descriptively. All patients with responses to one post-baseline survey will be used for this endpoint.

16.4 Data & Safety Monitoring:

16.41 Review

The study chair(s) and the study statistician will review the study at least twice a year to identify accrual, adverse event, and any endpoint problems that might be developing. The Mayo Clinic Cancer Center (MCCC) Data Safety Monitoring Board (DSMB) is responsible for reviewing accrual and safety data for this trial at least twice a year, based on reports provided by the MCCC Statistical Office.

16.42 Adverse Event Stopping Rules

The stopping rules specified below are based on the knowledge available at study development. We note that the Adverse Event Stopping Rule may be adjusted in the event of either (1) the study re-opening to accrual or (2) at any time during the conduct of the trial and in consideration of newly acquired information regarding the adverse event profile of the treatment(s) under investigation. The study team may choose to suspend accrual because of unexpected adverse event profiles that have not crossed the specified rule below.

Accrual will be temporarily suspended to this study if at any time we observe events that satisfy either of the following, regardless of attribution to study treatment:

- if 2 or more treated patients experience a Grade 3 or higher seizure or cardiac disorder event (including heart failure, cardiac arrest, or myocardial infarction).

We note that we will review all other Grade 4 and 5 adverse events to monitor the emergence of a previously unrecognized treatment-related adverse event.

16.5 Subset Analyses for Minorities

16.51 Study availability

This study will be available to all eligible patients, regardless of gender, race, or ethnic origin.

16.52 Statistical analysis by subset

There is no information currently available regarding differential effects of this regimen in subsets defined by race, gender, or ethnicity, and there is no reason to expect such differences to exist. Therefore, although the planned analyses will look for differences in treatment effect based on racial groupings, the sample size is not increased in order to provide additional power for subset analyses.

16.53 Regional population

The geographical region served by MCCC has a population which includes approximately 3% minorities. Expected sizes of racial by gender subsets are shown in the following table:

Accrual Targets			
	Sex/Gender		
Ethnic Category	**Females**	**Males**	**Total**
Hispanic or Latino	0	1	1
Not Hispanic or Latino	0	7	7
Ethnic Category: Total of all subjects	**0**	**8**	**8**
Racial Category			
American Indian or Alaskan Native	0	0	0
Asian	0	0	0
Black or African American	0	1	1
Native Hawaiian or other Pacific Islander	0	0	0
White	0	7	7
Racial Category: Total of all subjects	**0**	**8**	**8**

Ethnic Categories:	**Hispanic or Latino –** a person of Cuban, Mexican, Puerto Rican, South or Central American, or other Spanish culture or origin, regardless of race. The term "Spanish origin" can also be used in addition to "Hispanic or Latino."
	Not Hispanic or Latino
Racial Categories:	**American Indian or Alaskan Native –** a person having origins in any of the original peoples of North, Central, or South America, and who maintains tribal affiliations or community attachment.
	Asian – a person having origins in any of the original peoples of the Far East, Southeast Asia, or the Indian subcontinent including, for example, Cambodia, China, India, Japan, Korea, Malaysia, Pakistan, the Philippine Islands, Thailand, and Vietnam. (Note: Individuals from the Philippine Islands have been recorded as Pacific Islanders in previous data collection strategies.)
	Black or African American – a person having origins in any of the black racial groups of Africa.
	Native Hawaiian or other Pacific Islander – a person having origins in any of the original peoples of Hawaii, Guam, Samoa, or other Pacific Islands.
	White – a person having origins in any of the original peoples of Europe, the Middle East, or North Africa.

17.0 Tissue Biospecimens

17.1 Summary of Tissue Collection

Patients will have clinical biopsies prior to start of treatment and end of treatment/at time of recurrence (or at any time during treatment if clinically indicated). We will request three additional cores for research purposes at each of these timepoints. A recent (within 60 days) archival sample is also acceptable in lieu of a new biopsy.

Patients will be offered the option to have a research biopsy at the end of Cycle 1

Clinical biopsy should be done at end of treatment for any reason (e.g., disease progression or alternative therapy), whichever comes first.

NOTE: Patient may opt out of, or delay research biopsy without deviation.

Three cores will be obtained. Please see Lab Manual for additional information.

	Timepoint 1 (Prior to treatment)	Timepoint 2 End of Cycle 1	Timepoint 3 End of treatment for any reason	Submit to:
Biopsy	3 cores	3 cores	3 cores	Dr Jacob Orme Lab

17.2 Original Diagnostic Tissue - NONE

17.3 Correlative Tissue Collection

17.31 Tissue Kits will not be provided for this protocol.

17.32 Paraffin Embedded Tissue – See Lab Manual

17.33 Frozen Tissue – See Lab Manual

17.34 All samples will be sent to:
Attn: [redacted]
Mayo Clinic
200 First St SW
Rochester MN 55905
Phone: [redacted]
E-mail: [redacted]

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18.0 Records and Data Collection Procedures

18.1 Submission Timetable

Data submission instructions for this study can be found in the Data Submission Schedule.

18.2 Survival Follow-up

See Section 4.

18.3 CRF completion

This study will use Medidata Rave® for remote data capture (rdc) of all study data. Data collection for this study will be done exclusively through the Medidata Rave® clinical data management system. Access to the trial in Rave is granted through the iMedidata application to all persons with the appropriate roles assigned in Regulatory Support System (RSS). To access Rave via iMedidata, the site user must have an active account and the appropriate Rave role (Rave CRA, Read-Only, Site Investigator) on the organization roster at the enrolling site.

18.4 Site responsibilities

Each site will be responsible for ensuring that all materials contain the patient's initials, MCCC registration number, and MCCC protocol number. Patient's name must be removed.

18.5 Supporting documentation

This study requires supporting documentation for diagnosis (e.g., pathology report) and progression (e.g., radiographic evidence) prior to study entry as well as for evidence of response to study therapy, and progression after study therapy. These documents should be uploaded within 14 days of registration (for prior to study entry materials) or within 14 days after the visit at which response or progression is determined.

If patient has genetic testing at any time, please upload to Rave when available.

18.6 Labeling of materials

Each site will be responsible for ensuring that all materials contain the patient's initials, MCCC registration number, and MCCC protocol number. Patient's name must be removed.

18.7 Overdue lists

A list of overdue forms and outstanding queries will be available in Rave through the Rave Task Summary. In addition, the Overdue Materials report will be distributed monthly by the data manager.

19.0 Budget

19.1 Costs charged to patient

Routine clinical care including biopsies, imaging, exams

19.2 Tests to be research funded

- Research biopsy (1 per patient)
- Research testing on blood and tissue specimens

19.3 Other budget concerns:

Mayo Clinic will support the costs of running this study.

Genentech will provide study drug, pertuzumab, trastuzumab, hyaluronidase-zzxf (HP) (PHESGO™), for use in this study.

20.0 References

Beer, Tomasz M. et al. 2014. "Enzalutamide in Metastatic Prostate Cancer before Chemotherapy." *New England Journal of Medicine* 371(5): 424–33. http://www.nejm.org/doi/10.1056/NEJMoa1405095.

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Hussain, Maha et al. 2018. "Enzalutamide in Men with Nonmetastatic, Castration-Resistant Prostate Cancer." *New England Journal of Medicine* 378(26): 2465–74. http://www.nejm.org/doi/10.1056/NEJMoa1800536.

Morris, Michael J. et al. 2002. "HER-2 Profiling and Targeting in Prostate Carcinoma." *Cancer* 94(4): 980–86. http://doi.wiley.com/10.1002/cncr.10339 (April 8, 2020).

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Appendix I ECOG Performance Status

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

*As published in Am. J. Clin. Oncol.:
Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity and Response Criteria of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982.

The ECOG Performance Status is in the public domain therefore available for public use. To duplicate the scale, please cite the reference above and credit the Eastern Cooperative Oncology Group, Robert Comis, M.D., Group Chair.

From http://www.ecog.org/general/perf_stat.html

Appendix II Patient Questionnaire Booklets

Patient booklets and related documents are posted separately as required by the Mayo Clinic IRB.

There are two booklets each with a separate set of questions
Both booklets are completed at the same timepoints: Baseline, End of Every 4th Cycle, End of treatment

1. NCI PRO-CTCAE Questionnaire (11 questions):
2. FACT-P Version 4 (39 questions):

Appendix III MC210504 Patient Medication Diary

NOTE: Patient medication diary will be provided separately and must be approved by the IRB prior to use with a patient.

Appendix IV Guidelines for Contraception

Your study doctor will discuss prohibited and acceptable birth control methods for use during your participation in this study.

You should notify your study doctor if birth control methods other than those specified below are started during the course of this study or if you start any prescription drug or other medication (including herbal and over-the-counter medications) not prescribed by the study doctor.

One of the two forms of birth control must be highly effective, and the second method may also be highly effective or selected from the list of other contraceptive methods.

Highly Effective Methods of Contraception	Progestogen only hormonal contraception associated with inhibition of ovulation (oral, injectable, or implantable)	
	Hormonal methods of contraception including • combined oral contraceptive pills (that is, those that contain both estrogen and progestogen) • vaginal ring • injectables, implants and intrauterine devices (IUDs) Sometimes, hormonal levels of birth control can be affected by the study drug. Your doctor will tell you whether hormonal forms of birth control are allowed for this study.	
	Non-hormonal IUDs	
	Bilateral tubal occlusion	
	Vasectomized partner	
	Complete abstinence	
Less than Highly Effective Methods of Contraception	Diaphragm with spermicide	
	Cervical cap with spermicide	
	Vaginal sponge with spermicide	
	Progestin only pills	
	Male condoms with or without spermicide*	*A male and a female condom must not be used together
	Female Condoms*	
Unacceptable Methods of Contraception	Periodic abstinence (calendar, symptothermal, post-ovulation methods)	
	Withdrawal (coitus interruptus)	
	Spermicide only	
	Lactation amenorrhea method (LAM)	

If you choose abstinence as a method of contraception, your doctor will discuss other methods of contraception with you in the case you choose not to continue abstinence.

Appendix V Genentech Safety Reporting Fax Cover Sheet

Genentech
A Member of the Roche Group

SAFETY REPORTING FAX COVER SHEET

Genentech Supported Research

AE / SAE FAX No: (650) 238-6067

Genentech Study Number	
Principal Investigator	
Site Name	
Reporter name	
Reporter Telephone #	
Reporter Fax #	

Initial Report Date	[DD] / [MON] / [YY]
Follow-up Report Date	[DD] / [MON] / [YY]

Subject Initials (Enter a dash if patient has no middle name)	[ ] - [ ] - [ ]

SAE or Safety Reporting questions, contact Genentech Patient Safety: (888) 835-2555

PLEASE PLACE MEDWATCH REPORT or SAFETY REPORT BEHIND THIS COVER SHEET