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TITLE: Phase II Trial of Paxalisib (GDC-0084) in combination with Trastuzumab for Patients with HER2-Positive Breast Cancer Brain Metastases

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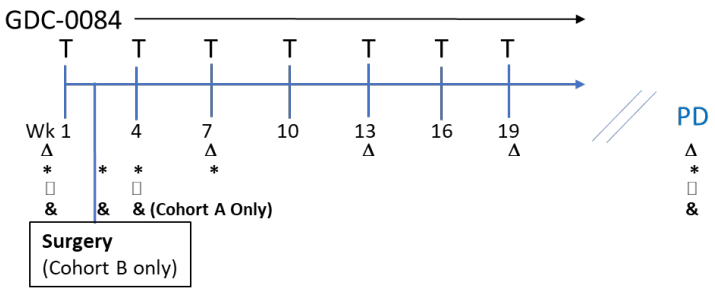
SCHEMA

Inclusion criteria:
- HER2+ breast cancer with active brain met(s)
- Cohort A: Measurable CNS disease (≥ 1 cm)
- Cohort B: Surgical resection indicated
- ECOG PS 0-2
- LVEF ≥ 50%

Exclusion criteria:
- Uncontrolled diabetes
- Unable to tolerate or absorb oral medications



D1 of GDC-0084 will be administered 2-8 days prior to surgery in Cohort B.
T=trastuzumab; PD=progressive disease
Δ Brain MRI and CT of the chest, abdomen, and pelvis will be performed every 6 weeks for the first 24 weeks, then every 9 weeks
***** Research bloods (germline at baseline only, cfDNA for all time points) will be collected at baseline, day of surgery (Cohort B only), C2D1, C3D1, and at time of progression or off protocol therapy, whichever comes first
□ Optional biopsy of extracranial metastasis at baseline, between days 15-29 after start of protocol therapy, and progression in patients with biopsy-accessible disease.
& CSF will be collected at baseline, day of surgery (Cohort B only), cycle 2 day 1 +/- 7 days (Cohort A only) and at time of progression or off protocol therapy, whichever comes first

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1. OBJECTIVES

The hypothesis of this study is that combined PI3K and mTOR inhibition will be efficacious in patients with HER2-positive Breast Cancer Brain Metastases (BCBM).

1.1 Study Design

This is an open-label, single-center, phase II study designed to evaluate the efficacy of the combination of paxalisib (GDC-0084) with trastuzumab for the treatment of central nervous system (CNS) metastases in patients with HER2-positive metastatic breast cancer (MBC), as measured by objective response rate (ORR) in the CNS. Patients will receive the following treatment: paxalisib (GDC-0084) (45 mg orally once daily) and trastuzumab (at a dose of 8 mg/kg intravenously (IV) loading dose; followed by 6 mg/kg IV every 3 weeks thereafter).

The proposed clinical trial will initially enroll a 6-patient safety run-in to assess for DLTs (Cohort A Safety Run-In). Should there be no safety signals, the trial will continue to enroll two expansion cohorts: Cohort A: a single-arm, two-stage, phase II cohort; and Cohort B: a pre-surgical window cohort. Should more than one DLT be observed, a lower dose level may be explored.

Addendum: In April 2019 five participants were enrolled to the 45mg dose level (Dose Level 1) of the Cohort A Safety Run-In. Two DLTs were observed as defined as any toxicity that requires a dose reduction within the first cycle. After detailed discussion within the research team as well as with Kazia Therapeutics, the decision was made to explore a second safety run-in at 30mg (Dose Level -1) to gain additional safety information with 1) more defined DLT definitions and 2) additional safety monitoring and dosing guidance. Participants treated in this cohort will not be required to undergo fresh tissue collections or CSF collections. Upon completion of this 30mg cohort, the PI and team will review the safety data and determine how the study will continue.

Update: Three patients have been enrolled to the Dose Level -1 cohort. The first patient (subject ID 006) had no DLTs. The second patient (subject ID 007) developed a grade 4 cytokine release syndrome / shock. The third patient (subject ID 008) developed grade 3 diarrhea. Subject 008 did not take any antidiarrheals when the diarrhea started, held drug for 4 days, and called the research nurse once the diarrhea was at grade 3. Subject 008 was instructed to take Imodium which improved the diarrhea quickly. The case was reviewed with the study PI and the decision was made to resume treatment at the same dose of 30 mg daily. Since then, subject 008 has taken paxalisib (GDC-0084) and Imodium and has not had any further issues with diarrhea. Given that it is impossible to know whether the diarrhea would have developed to grade 3 had the patient called earlier and started Imodium sooner, subject 008 is being replaced with an additional patient to accurately assess DLTs in this cohort. The quick improvement experienced with the use of Imodium, along with the decision to not reduce subject 008's dose, and the lack of further episodes of diarrhea after starting Imodium may suggest that the grade 3 diarrhea could have been prevented. This toxicity event led to the conclusion that the study team's definition of DLT does not contemplate assessment in the presence of maximum supportive care, nor the duration

of the adverse event for the adverse event to be considered a DLT. Therefore, the definition of DLT has been amended.

Update Two: An additional four patients were enrolled to the Dose Level -1 cohort to complete the safety run-in of 6 patients (with patient 008 being replaced.) All four of these patients completed their first cycle of treatment without incident. There have been no further observed DLTs. Per Section 13, Cohort A has now moved to expansion at the 30mg paxalisib (GDC-0084) dose. Cohort B will be amended to open at the RP2D of 30 mg paxalisib (GDC-0084).

1.2 Primary Objectives

1.2.1 Cohort A

1.2.1.1 To evaluate the efficacy of paxalisib (GDC-0084) in combination with trastuzumab for the treatment of CNS metastases in patients with HER2-positive MBC, as measured by ORR in the CNS according to response assessment in neuro-oncology-brain metastases (RANO-BM) criteria.

1.2.2 Cohort B

1.2.2.1 To evaluate the correlation between inhibition of p-4EBP1 in resected brain tumor tissue of human subjects, with the intracranial response in mouse bearing the corresponding patient-derived xenograft (PDX) models of BCBM and treated with paxalisib (GDC-0084) in combination with trastuzumab.

1.3 Secondary Objectives

1.3.1 Cohort A only

1.3.1.1 To evaluate clinical benefit rate at 18 and 24 weeks, defined as the proportion of participants with stable or responsive disease in both CNS and non-CNS at 18 and 24 weeks per RANO-BM criteria.

1.3.2 Cohort B only

1.3.2.1 To evaluate pharmacodynamic biomarkers associated with exposure to paxalisib (GDC-0084) in resected brain tumor tissue.

1.3.3 Safety objectives

1.3.3.1 To evaluate the safety, and tolerability of the combination of paxalisib (GDC-0084) and trastuzumab.

1.3.4 Efficacy objectives

1.3.4.1 To evaluate the duration of response (DOR) in the CNS (Cohort A only).

1.3.4.2 To evaluate the efficacy of the study combination, as defined by bi-compartmental progression-free survival (PFS) according to RANO-BM criteria[1] (Section 11.1.1).

1.3.4.3 To evaluate the extracranial ORR according RECIST 1.1 criteria[2].

1.3.4.4 To evaluate PFS according to the RECIST 1.1 single-compartmental model.

1.3.4.5 To describe the site of first progression (CNS vs extracranial vs both).

1.3.4.6 To evaluate the overall survival (OS) among patients included in this trial.

1.3.5 Patient-reported outcome objectives

1.3.5.1 To evaluate the impact of the experimental treatment on PROs, as measured by the M.D. Anderson Symptom Inventory-Brain Tumor (MDASI-BT) assessment.

1.3.6 Investigator-Assessed Neurological Evaluation

1.3.6.1 To evaluate the impact of the study treatment, for these same patients, on investigator-assessed neurological evaluation, as measured by the Neurological Assessment in Neuro-Oncology (NANO) scale.

1.3.7 EQ-5D evaluation

1.3.7.1 To evaluate the impact of the study treatment, for these same patients, on general health status assessed by the EQ-5D questionnaire.

1.4 Correlative Objectives

1.4.1 To describe the landscape of somatic mutations and copy number alterations that occur in matched primary tumors, extracranial metastases, and brain metastases, and to trace clonal evolution over time.

1.4.2 To describe a range of tissue-based biomarkers using t-CyCIF for high-dimensional assessment of pAkt, pS6RP, p4EBP1, Ki-67 and cleaved caspase-3, and the immune microenvironment (a variety of 6 color panels will be assessed each incorporating pan-cytokeratin and DAPI [PD-L1, PD-L2, CD3, CD20; CD4, CD8, PD-1, FoxP3; CD4, CD8, TIM-3, LAG3; CD33, CD11b, CD68, Granzyme B]) to quantitate cytotoxic and regulatory T cell populations, T cell activation, checkpoint expression and macrophage populations.

1.4.3 To explore the correlation between Akt/mTOR signature with CNS ORR, PFS, and OS.

1.4.4 To explore whether the number and/or type of somatic mutations (e.g. PIK3CA, AKT1, etc), detected either in archival tumor specimens, fresh tumor specimens, plasma cfDNA, or CSF cfDNA are correlated with patient outcomes (PFS, CNS ORR, CBR, and OS).

1.4.5 To explore whether tumor mutational burden is associated with patient outcomes (PFS, CNS ORR, CBR, and OS).

1.4.6 To collect blood and CSF to study cell-free DNA for quantification of tumor DNA content,copy number variation, targeted sequencing, and/or whole exome sequencing.

1.4.7 To explore whether cfDNA tumor fraction, derived from plasma or CSF, and assessed using ultra low pass whole genome sequencing (ULP-WGS), is associated with patient outcomes (PFS, CNS ORR, CBR, and OS).

1.4.8 To characterize and compare mutations and copy number variation between cfDNA in blood and CSF versus tumor tissue specimens.

1.4.9 To compare mutations, copy number variation, and tumor mutational burden between cfDNA in blood and CSF in baseline versus time-of-progression samples.

1.4.10 To explore the correlation between baseline mutational load (as assessed in cfDNA) with CNS ORR, bi-compartmental PFS, and OS.

1.4.11 To characterize changes in cfDNA tumor fraction in blood and CSF at baseline, on treatment and at time of progression.

1.4.12 To explore whether cfDNA fraction in blood or CSF at baseline is associated with clinical outcomes (PFS, CNS ORR, CBR, and OS).

2. BACKGROUND

2.1 Study Disease

Breast cancer is the most frequently diagnosed cancer and the second cause of cancer death in American women[3,4]. Approximately 15%-20% overexpress human epidermal growth factor receptor 2 (HER2) and are classified as HER2 positive tumors[5-7]. Together with triple negative breast cancer (TNBC), HER-2 positive tumors have the highest rates of brain metastases (BM), with studies reporting up to 50% rate of central nervous system (CNS) involvement among those subtypes[8-12].

Initial treatment for patients with BM typically includes surgery or radiotherapy,

either whole brain radiotherapy (WBRT), stereotactic radiosurgery (SRS), or both, depending on factors such as performance status, expected prognosis, as well the localization and the number of CNS metastases[13]. Although median OS after a diagnosis of brain metastasis now exceeds 2 years in patients with good performance status and HER2-positive disease[14], this outcome has resulted in patients who live long enough to have substantial morbidity from additional CNS progression post-radiation. At this time point, there are currently no systemic therapies approved for use in the treatment of these patients. Clearly, better options for the prevention and treatment of brain metastases in patients with HER2-positive breast cancer are needed.

2.2 The phosphoinositide 3-kinase/Akt/mammalian target of rapamycin (PI3K/Akt/mTOR) pathway in cancer

The PI3K/Akt/mTOR is an intracellular signaling pathway that responds to hormones and growth factors. Its activation leads to numerous cellular processes such as increased cell growth, cell proliferation, and cellular motility, a shift toward glycolytic metabolism, and also increased cell migration and deregulated apoptosis[15].

PI3Ks are grouped into 3 classes (I-III) based on their structure and substrate specificity[16]. The PI3K heterodimer belonging to class IA plays a central role in the signaling pathway[17]. The heterodimer consists of 2 subunits. The regulatory subunit, p85, controls the activation of the catalytic subunit, p110, depending on the stimulation of growth receptor tyrosine kinases[18]. Subunits p110α, p110β, and p110δ are encoded by *PIK3CA*, *PIK3CB*, and *PIK3CD*, while the regulatory subunit is encoded by *PIK3R1*, *PIK3R2*, and *PIK3R3*[19]. p110α and p110β are ubiquitously expressed. Class IB consists of p110γ, which is encoded by *PIK3CG*. Expression of p110δ and p110γ is generally limited to hematopoietic and immunological cells.

Activation takes place through the binding of various extracellular growth factors (e.g., epidermal growth factor (EGF), insulin-like growth factor 1 (IGF-1), and insulin) to their membrane-bound tyrosine kinase receptors[20]. The respective receptor dimerizes, is autophosphorylated and recruits adaptor proteins such as insulin receptor substrate (IRS) 1 and IRS2. Subsequent phosphorylation of phosphatidylinositol-4,5-bisphosphate (PIP_2) into phosphatidylinositol-3,4,4-trisphosphate (PIP_3) leads to the phosphorylation of Akt, a serine/threonine kinase that further influences the tumor cell cycle for growth and survival[21].

PTEN (phosphatase and tensin homolog deleted on chromosome 10) is an important tumor suppressor that has a contrary effect and dephosphorylates PIP_3 to PIP_2. PIP_3 levels are thus directly regulated by the opposing effects of PI3K and PTEN.

mTOR is a serine/threonine kinase that is downstream from PI3K and Akt. Two different complexes involving mTOR, mTORC1 and mTORC2, have different functions. mTORC1 is activated by inhibition of tumor suppressor tuberous sclerosis 1/2 (TSC1/2) and subsequently influences the cell metabolism, leading to anabolic cell growth.

Activation of mTORC1 also leads to a negative feedback loop[20]. Direct inhibition of mTORC1 by an administered treatment can suspend the negative feedback loop, leading to the paradoxical activation of the signaling pathway and expression of multiple receptor tyrosine kinases such as HER2 and the IGF-1 receptor (IGF-1R)[22]. Both this paradoxical activation and the activation of alternative signaling pathways need to be taken into account in the context of therapeutic approaches.

The PI3K/Akt/mTOR pathway in HER2-positive breast cancer:

HER2 belongs to a family of receptor tyrosine kinases which regulates diverse biologic processes, including growth and proliferation[23]. HER2 is a member of the epidermal growth factor receptor (EGFR/HER) family of receptor tyrosine kinases comprising of EGFR (HER1), HER2, HER3, and HER4. Homo- or heterodimerization of these receptors results in the trans-phosphorylation of specific tyrosine residues in their intracellular domain(s) which results in the recruitment of adapter proteins responsible for the initiation of downstream signals[24]. The heterodimer of a ligand-orphan HER2 and a kinase-impaired HER3 is a major activator of PI3K-mTOR signaling. HER3, when phosphorylated can directly couple to the p85 regulatory subunit of PI3K[25]. HER2: HERB3 heterodimers are powerful oncogenic units because of phospho-HER3 augments signaling through the PI3K-mTOR pathway[26]. The p85 subunit of PI3K interacts directly with phospho-HER3 at six consensus phospho-tyrosines at p85-binding motifs (YXXM) within HER3[27]. In contrast, HER2 lacks canonical p85 binding site. But HER2 may activate the PI3K pathway through the adaptor protein GRB2-associated binding protein 1 (GAB1). It has been established that spontaneous formation of HER2: HER3 heterodimer can occur in tumors where HER2 expression on the cell surface is dramatically increased as a consequence of gene amplification and receptor overexpression[28]. Therefore, there are two ways that HER2 can activate the downstream PI3K-AKT-mTOR pathway, 1) by forming heterodimers with HER3 and 2) by directly recruiting adapters (GRB2-GAB1 or GAB2) that couple to p85. The activation of the PI3K pathway in HER2-positive breast cancer represents a critical pathway responsible for the anti-HER2 therapy resistance observed in the clinic.

2.3 Paxalisib (GDC-0084)

Paxalisib (GDC-0084) is a potent, oral, selective, brain-penetrant small molecule inhibitor of class I phosphoinositide 3-kinase (PI3K) and mammalian target of rapamycin (mTOR) kinase being developed by Kazia Therapeutics as an anti-cancer therapeutic agent. Paxalisib (GDC-0084) has shown effectiveness in nonclinical models of tumors driven by activation of the PI3K pathway. Paxalisib (GDC-0084) was designed to efficiently cross the blood-brain barrier to achieve high drug exposure in the brain, thus maximizing its impact on brain cancers such as gliomas or brain metastases.

Genentech Inc., the originator of the product, undertook extensive nonclinical studies and also initiated a Phase 1 clinical study of 47 patients with progressive or recurrent high-grade gliomas. The product was in-licensed by Novogen in October 2016, after the first stage of the Phase 1 study had been completed. On November 2017, Novogen announced that it changed the company name to Kazia Therapeutics.

2.3.1 Summary of Nonclinical Experience

Results from the nonclinical pharmacology studies showed that paxalisib (GDC-0084) is a potent, selective inhibitor of class I PI3K and mTOR kinase with a mean apparent inhibition constant (Ki) for p110α/p85α, p110β/p85α, p110δ/p85α, p110γ of 2.2 nM, 41 nM, 2.7 nM, and 9.7 nM, respectively. Paxalisib (GDC-0084) inhibited human mTOR, with a mean apparent Ki of 70 nM. Paxalisib (GDC-0084) was also potent in inhibiting growth of a panel of human glioma cell lines, with a mean 50% inhibitory concentration (IC50) on cell proliferation ranging from 0.4 to 4.5 μM. Studies of the mechanism of action in U87MG-Luc glioma cells

showed that levels of pAkt and pS6 were markedly reduced following exposure to paxalisib (GDC-0084), leading to cell cycle arrest at the G1 phase and apoptosis. *In vivo* studies in mouse xenograft models of human glioblastoma indicated that paxalisib (GDC-0084) inhibited tumor growth when administered orally. Substantial suppression of the PI3K pathway, evidenced by a marked decrease in pAkt and pS6 levels in the tumor, was also observed. Moreover, paxalisib (GDC-0084) demonstrated its pharmacologic activity without any observed cardiovascular effects.

The absorption, distribution, metabolism, and excretion (ADME) of paxalisib (GDC-0084) were characterized *in vitro* and *in vivo*. Plasma clearance (CL) of paxalisib (GDC-0084) was low in mice, moderate in rats, and high in dogs and monkeys, relative to the known hepatic blood flows in these species. Plasma protein binding was low across all species tested, ranging from 56.9% to 75.5% (bound), and was 75.5 % in human plasma. Paxalisib (GDC-0084) appeared to be primarily metabolized by cytochrome P450 (CYP) 3A4, and *in vitro* CYP inhibition and induction studies suggested a low potential for CYP-related drug-drug interaction at clinically expected exposures.

The toxicology program for paxalisib (GDC-0084) was designed to support once daily oral administration of paxalisib (GDC-0084) for up to 28 days to patients in clinical trials. Paxalisib (GDC-0084) was not genotoxic in a bacterial mutagenesis assay or an *in vitro* human peripheral blood chromosomal aberrations assay. No toxicologically relevant cardiovascular, neurological, or respiratory findings attributed to paxalisib (GDC-0084) were observed in the 29-day repeat-dose toxicity studies, an *in vitro* human ether-à-go-go-related gene (hERG) assay, or *in vivo* telemetry-instrumented dog safety pharmacology study.

With respect to its potential CNS penetration, in normal mouse brain, oral dosing is associated with inhibition of p-Akt and pS6. Levels of paxalisib (GDC-0084) in the CNS vs plasma in rodents is shown below, supporting its use in brain tumor populations.

Compound	PI3Kα K_{iapp}	mTOR K_{iapp}	B-A/A-B (MDR1)	B-A/A-B (Bcrp1)	[Brain]/[Plasma] mouse	[Brain]/[Plasma] rat	[CSF]/[$Plasma_{unbound}$] rat
GDC-0084	2 nM	0.07 μM	0.8	1.6	1.4	1.9-3.3	0.7-1.0

Abbreviations: MDR, multi-drug resistance; Bcrp, breast cancer resistance protein

2.3.2 Summary of Clinical Experience

An open-label, multicenter, dose escalation Phase 1 study (Study GO28070) to evaluate the safety, tolerability, and pharmacokinetics of paxalisib (GDC-0084) administered orally once daily to patients with progressive or recurrent high-grade gliomas has been completed.

Paxalisib (GDC-0084) was rapidly absorbed and demonstrated linear and dose proportional increases in exposure, with a half-life supportive of once daily dosing. The maximum tolerated dose of paxalisib (GDC-0084) was defined as 45 mg when paxalisib (GDC-0084) was administered orally once daily in cycles of 28 days. The reported AEs and other safety findings from this study were generally consistent with the established PI3K-mTOR inhibitor class effects and/or with the disease under study.

Based upon these data, Kazia has initiated a Phase 2a study with paxalisib (GDC-0084) in patients with newly diagnosed GBM with unmethylated MGMT promoter status in the adjuvant setting following surgical resection, and initial treatment with XRT/TMZ. This study will examine the safety, tolerability and pharmacokinetics of once daily. It is anticipated that the

study will also provide information to determine a recommended dose for a subsequent planned Phase 2b study, which will compare paxalisib (GDC-0084) with TMZ as adjuvant therapy in newly diagnosed GBM patients.

2.3.2.1 Clinical Safety

Adverse events

Safety analysis included all 47 patients in Stage 1 who received any amount of paxalisib (GDC-0084). Enrolment for this study was discontinued before expansion to Stage 2 when further clinical development of paxalisib (GDC-0084) was stopped.

Forty-four of 47 patients (93.6%) who received paxalisib (GDC-0084) experienced at least one AE, regardless of causality. The most frequently reported AEs (occurring in ≥ 10% of patients) regardless of causality were fatigue (15 patients [31.9%]), hyperglycemia (14 patients [29.8%]), nausea (13 patients [27.7%]), hypertriglyceridemia (10 patients [21.3%]), headache (9 patients [19.1%]), hypophosphatemia and rash (8 patients each [17.0%]), asthenia and diarrhea (6 patients each [12.8%]), and aphasia, blood cholesterol increased, decreased appetite, dehydration, dizziness, hemiparesis, hyponatremia, mucosal inflammation, stomatitis, and vomiting (5 patients each [10.6%]).

Nine patients (19.1%) experienced Grade 3 AEs related to paxalisib (GDC-0084). There were no AEs related to paxalisib (GDC-0084) that were higher than Grade 3. The most common Grade 3 AEs related to paxalisib (GDC-0084) were hyperglycemia (4 patients [8.5%]) and mucosal inflammation (2 patients [4.3%]). All other Grade ≥ 3 AEs related to paxalisib (GDC-0084) were reported by one patient only.

For further details, see the paxalisib (GDC-0084) Investigator's Brochure.

2.3.2.2 Clinical Activity in Patients with Progressive or Refractory GBM

An objective response rate was estimated only for patients with disease that was measurable by RANO guidelines (Wen, et al. 2010). Objective response was defined as a complete or partial response, as determined by investigator assessment using RANO. Patients with missing or no response assessments were classified as non-responders.

Overall, 26 patients (55.3%) had progressive disease, 19 patients (40.4%) had stable disease, 1 patient was not evaluable, and the data for 1 patient was missing.

Thirty-seven patients (78.7%) were on-study for less than 3 months, 7 patients (14.9%) were on-study for 3-6 months, and 3 patients (6.4%) were on-study for 6-12 months.

For further details, see the paxalisib (GDC-0084) Investigator's Brochure.

2.3.2.3 Clinical Pharmacokinetics and Immunogenicity

Following a single oral dose, paxalisib (GDC-0084) was rapidly absorbed with a median T_{max} of approximately 2 hours (range 1-8 hours). After reaching peak plasma concentrations, concentrations decreased with an apparent terminal phase $t_{1/2}$ of approximately 18.73 hours (range 3.41 – 47.3 hours; calculated across Cohorts 1-6 (2 – 30 mg) following a single dose). The accumulation ratio ($AUC_{0\text{-}24\ hr\ multiple\ dose}/AUC_{0\text{-}24\ hr\ single\ dose}$) ranged from 0.577 – 4.84 with a mean value of 2.12 ± 0.896. Both C_{max} and $AUC_{0\text{-}24}$ appeared to increase in a dose-proportional and dose linear fashion across all cohorts for both single and multiple doses. There have been no clinical immunogenicity studies with paxalisib (GDC-0084).

In two patients who had brain tissue assessed, similar levels of paxalisib (GDC-0084) were achieved in brain tissue/tumor compared to plasma. At doses of 45 mg daily or higher, a

trend towards decreased median standard uptake value (SUV) in normal brain was observed, suggesting global CNS penetration.

2.4 Trastuzumab

Trastuzumab (Herceptin®) is a recombinant monoclonal antibody that binds specifically and with high affinity to the extracellular domain of HER2. Trastuzumab has been shown to inhibit the proliferation of human tumor cells overexpressing HER2 both in vitro and in vivo.

Based on these data, trastuzumab was approved by the U.S. Food and Drug Administration (FDA) for use in HER2-overexpressing MBC in combination with paclitaxel for first-line treatment and as a single agent for patients who have progressed on chemotherapy for metastatic disease. Subsequent randomized studies have demonstrated the value of continued trastuzumab in combination with chemotherapy or targeted therapy, even after prior progression on trastuzumab (von Minckwitz, 2009; Blackwell, 2012). As a result, even after progression on trastuzumab, continuing the blockade of HER-2 pathway, usually with a trastuzumab containing regimen, is considered standard of care[29]. Indeed, the ASCO HER2 guidelines and the ESO-ESMO metastatic breast cancer guidelines both endorse the continuation of trastuzumab as standard of care through multiple lines of therapy in patients with HER2-positive disease. See the trastuzumab package insert (https://www.accessdata.fda.gov/drugsatfda_docs/label/2000/trasgen020900LB.htm) for additional information.

2.5 Rationale for PI3K/mTOR inhibition in patients with HER2-positive breast cancer with brain metastasis

PI3K and mTOR are lipid and protein kinases, respectively, that are involved in tumor cell proliferation, survival, and migration upon activation by growth factor receptors and integrins. PI3K catalyzes the phosphorylation of phosphatidylinositol 4,5 bisphosphate (PIP2) to generate phosphatidylinositol 3,4,5 trisphosphate (PIP3)[18], a second messenger involved in the phosphorylation of Akt and associated proteins in the Akt/mTOR pathway[30]. Activating and transforming mutations, as well as amplification, in the p110α subunit of PI3K are commonly found in solid and hematologic tumors. In addition, the PI3K/Akt pathway is activated in numerous types of cancer by receptor tyrosine kinase signaling or loss of phosphatase and tensin homolog (PTEN) expression or function[18,31-33]. These mechanisms of pathway activation are observed in 39% of HER2-positive breast cancers[34].

Expression of mutant PIK3CA or loss of PTEN in breast cancer cell lines is associated with trastuzumab resistance[35-37]. *In vitro* studies of inhibitors of p110α in breast cancer cell lines demonstrate that HER2 overexpression predicts sensitivity to these agents regardless of PIK3CA mutation status or PTEN expression[38]. Further, we have examined the p110 isoform dependence of HER2-positive/PTEN-deficient tumors and have shown that ablation of p110α, but not p110β, significantly impairs the development of HER2-positive/Pten-null tumors in mice, and that combined HER2 and p110α inhibition effectively reduces PI3K/AKT signaling and growth of cancer cells *in vitro* and of HER2+/PTEN-deficient tumors *in vivo*[39].

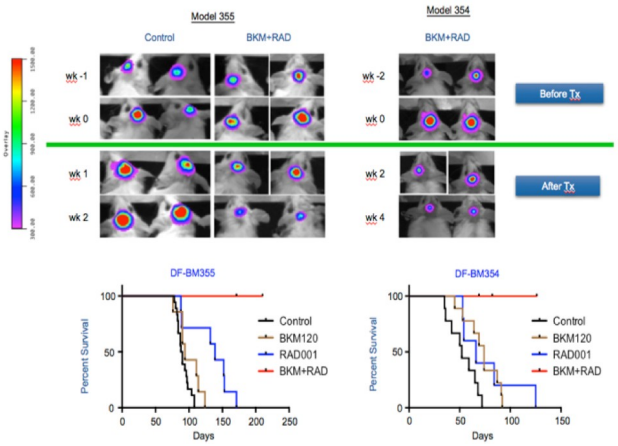
Furthermore, analysis of human tissues suggests that activated signaling through the

PI3K pathway, particularly via PTEN loss, plays an important role in BCBM. Adamo et al analyzed 52 BCBM samples and identified PTEN loss by immunohistochemistry (IHC) in 25%, with concomitant expression of p-AKT and p-S6, indicative of PI3K pathway activation[40]. PTEN loss was correlated with shorter time to brain recurrence. Wikman et al performed array-comparative genetic hybridization on matched primary tumors and BCBM and found more frequent PTEN allelic imbalance in brain metastases (52%) and primary tumors with CNS relapse (59%) compared to primary tumors from patients without relapse (18%, p=0.003) or relapse in other sites (12%, p=0.006)[41]. PTEN mRNA expression was also downregulated in BCBM compared to primary tumors. By contrast, PIK3CA mutation status was not associated with an increased risk of CNS relapse[42]. Moreover, co-culture of MDA-MB-231 BR cells with astrocytes and microglia promoted migration and invasion, and this effect was inhibited upon overexpression of PTEN, suggesting a mechanistic basis by which PTEN loss may mediate the development of BCBM and poorer survival[43].

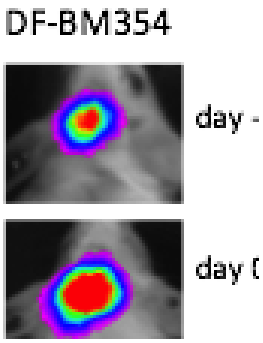
A lack of clinically relevant models has hindered our progress in understanding the pathobiology of this disease. To address this, the Zhao laboratory at Dana-Farber Cancer Institute has invested significant effort into developing orthotopic PDX models of BCBM by implanting BCBM samples from patients directly into mouse brains. To date, 26 models, including 14 HER2+ and 6 ER+ BCBM models have been developed. Histological analyses show that these PDXs resemble the parental BCBMs histologically, including in ER, progesterone receptor (PR) and HER2 expression as well as other epithelial markers. Whole exome sequencing further demonstrates that the PDXs retain excellent conservation of the genetic features of their parental tumors. Therefore, these models provide us with unique systems to study the underlying biology of brain metastasis and to explore new treatment approaches.

Strikingly, nearly all of our HER2+ PDX tumors have lost PTEN protein expression by IHC. Further analysis of 27 clinical specimens of HER2+ BCBMs found that PTEN expression by IHC was lost in 18 (67%), while 9 (30%) had reduced PTEN expression, confirming that loss of PTEN is widespread in BCBM. Genetic analysis revealed that the majority of BCBM PDX models have retained normal copy number of PTEN, suggesting that loss of PTEN occurs at the epigenetic or post-transcription level in metastatic tumor cells.

The above findings provided a rationale to test PI3K-targed agents in the HER2+ BCBM PDX models[44]. Strikingly, little activity was seen when various doublets including HER2-targeted and either alpha-selective or pan-PI3K inhibitors were tested. However, the combination of a PI3K inhibitor and mTOR inhibitor led to dramatic and durable tumor regressions. For example, as shown below, the combination of the pan-PI3K inhibitor BKM120 and the mTOR inhibitor RAD001 resulted in dramatic and durable tumor regressions. Overall, this effect was observed in three of five PDXs tested with associated reductions in p-4EBP1 expression (which lies downstream of PI3K)[44]. The two non-responders were notable for a very high tumor mutational burden and low AKT signature, suggesting potential biomarker predictors of therapeutic response.



BKM120 is no longer being actively developed in breast cancer. However, when either the combination of BYL719 (alpha selective PI3K inhibitor) plus RAD001 (mTOR inhibitor) or single-agent GNE-317 (a tool compound for paxalisib (GDC-0084)) were tested in the PDX models, CNS activity was also observed, suggesting a potential class effect for compounds targeting these key pathways.



As summarized above, paxalisib (GDC-0084) is a potent, selective inhibitor of class I PI3K and mTOR kinase and was designed to efficiently cross the blood-brain barrier to achieve high drug exposure in the brain, thus maximizing its ability to target brain cancers such as glioblastoma or brain metastases from solid tumors. The preclinical findings support a clinical trial testing PI3K/mTOR inhibition for HER2-positive BCBM as a rationally targeted strategy.

2.6 Correlative Studies Background

Tumor Genomic Profile

Intrinsic tumor factors may be associated with response to PI3K/mTOR inhibitors. Although some of the mechanisms related to de novo or acquired resistance to PI3K/mTOR inhibitors have been recently described, including incomplete inhibition of PI3K pathway activity, reactivation of the PI3K pathway, or activation of alternate pro-survival pathways[22,45,46], the knowledge of resistance remains largely unknown. On the other hand, there are data supporting that cells with PIK3CA mutations or PTEN loss are more sensitive to PI3K/Akt

inhibitors[47]. PIK3CA mutant tumors resistant to p110a inhibitors may also be treated with the addition of an mTOR inhibitor to a PI3K inhibitor, since the combination can overcome resistance[48]. Levels of pS6K (S6 kinase) and pAkt may be biomarkers predictive of clinical outcomes and response to inhibitors of the mTOR pathway. In the PDX models that led to the design of the current trial, an Akt/mTOR signature was positively associated with therapeutic response, whereas high mutational burden was inversely associated with response. Finally, HER2-overexpressing tumors seem to be dependent or "addicted" to the PI3K pathway and they are sensitive to mTOR inhibition[49]. Notably, there is no data on genomic mechanisms of de novo resistance to dual PI3K/mTOR inhibitors in patients with breast cancer.

Tumor microenvironment

Clinically, it is not uncommon to observe differing responses to therapeutic agents in the CNS versus extracranially. Although this has historically been attributed simplistically to differences in drug levels between compartments, given the presence of the blood-brain barrier, in fact, the blood tumor barrier is quite leaky, and subtherapeutic drug levels may not be the only or even the most important factor explaining this difference. One hypothesis is that differences in the tumor microenvironment could play a role in differential response to treatment. We will perform t-CyCIF for high-dimensional assessment of biomarker expression in archival and fresh tissue, focusing on the PI3K/mTOR pathway, apoptosis markers, and immune microenvironment.

Circulating free DNA

cfDNA provides a less invasive method by which to characterize tumor genomics. In addition, there is the potential to capture heterogeneity across multiple metastatic sites, in a more practical way than tissue biopsies of multiple sites. In patients with brain metastases, in particular research biopsies of CNS tumors are not feasible—yet given that these tumors have often been exposed to additional therapies (for example, WBRT and/or SRS), their genetic profile may be distinct from that of other metastatic sites. Although there have been some studies describing the genomics of brain metastases, because most resections occur in the setting of a new presentation of a single brain metastasis, they do not truly reflect the patient with progressive brain metastases after local therapy. cfDNA also provides an alternate method by which to quantify tumor burden over time. Finally, the correlation between cfDNA in plasma versus CSF is currently unknown, as is their relationship to patient outcomes in patients with brain metastases.

Our collaborators at the Broad Institute have made a critical technical advance—ultra-low pass whole genome sequencing (ULP-WGS)--that allows cost-effective characterization of genome-wide copy number alterations (CNAs) from plasma[50], without the need for prior knowledge of tumor mutations. We can effectively identify copy number alterations (CNAs) in the context of an admixed normal-tumor DNA input without requiring germline data. Further, the total 'tumor fraction (TFx)' of cfDNA can be estimated based on proportion of DNA with altered ploidy. We have shown that baseline TFx $\geq$ 10% was associated with significantly shorter survival (median 6.4 months versus 15.9 months, log-rank p = 4.51e-5) in patients with metastatic triple-negative breast cancer and remained an independent prognostic factor in a multivariate model. (Stover et al, J Clin Oncol, 2018). Moreover, tumor fraction measurement using ichorCNA has a broad dynamic range, both within individuals and between patients, and changes in TFx appear to track with tumor response status. ULP-WGS

demonstrates high concordance of copy number alterations with standard whole genome sequencing from cfDNA as well as whole exome sequencing of paired metastatic biopsies. Finally, based on extensive benchmarking, greater than 10% 'tumor fraction' can be used as a threshold to identify samples with adequate tumor DNA for high confidence copy number calls and whole exome sequencing.

To date, there is limited data regarding the prevalence and trajectory of cfDNA in patients with brain metastases, either as assessed in plasma, or in the CSF. In addition, there is little to no data regarding correlations between cfDNA in plasma vs CSF in breast cancer brain metastasis patients.

3. PARTICIPANT SELECTION

Eligibility will be assessed as part of the screening procedures for all patients.

3.1 Eligibility Criteria

3.1.1 Cohort A:

3.1.1.1 At least one measurable CNS metastasis, defined as ≥ 10 mm in at least one dimension.

3.1.1.2 Unequivocal evidence of new and/or progressive brain metastases, and at least one of the following scenarios:

- Treated with SRS or surgery with residual un-treated lesions remaining. Such participants are eligible for immediate enrollment on this study providing that at least one untreated lesion is measurable
- Participants who have had prior WBRT and/or SRS and then whose lesions have subsequently progressed or who have new lesions are also eligible. In this case, lesions which have been treated with SRS may be considered as target lesions if there is unequivocal evidence, in the opinion of the treating physician, of progression following SRS.
- Participants who have not previously been treated with cranial radiation (e.g., WBRT or SRS) are eligible to enter the study, but such participants must be asymptomatic from their CNS metastases and not requiring corticosteroids for symptom control.
- Participants who present with systemic stable/absent or progressive disease are eligible to this trial, as long as they fulfill one of the above criteria.

3.1.2 Cohort B:

New and/or progressive brain metastasis(es) with clinical indication for resection.

3.1.3 All Cohorts:

3.1.3.1 Pathologically confirmed HER2-positive MBC by local laboratory with the following requirements: HER2 overexpressed or amplified (immunohistochemistry of 3+ or HER2 gene amplification by in situ hybridization with a ratio of HER2-gene signals to centromere 17 signals ≥ 2.0 or average HER2 copy number ≥ 6.0 signals/cells).

3.1.3.2 Eastern Cooperative Oncology Group (ECOG) Performance Status of ≤ 2.

3.1.3.3 Left ventricular ejection fraction (LVEF) ≥ 50% by echocardiogram (ECHO) or multigated acquisition (MUGA) scan.

3.1.3.4 Stable or decreasing corticosteroid dose for at least 7 days prior to initiation of treatment.

3.1.3.5 Concurrent administration of other anti-cancer therapy during the course of this study is not allowed. Note that concurrent use of supportive care medications (e.g. anti-resorptive agents, pain medications) is allowed.

3.1.3.6 The participant is ≥18 years old.

3.1.3.7 Participants must have normal organ and marrow function as defined below:

- Absolute neutrophil count ≥1,000/µl
- Platelets ≥75,000/µl
- Hemoglobin ≥9 g/dL
- Total bilirubin ≤1.5mg/dL (upper limit of normal) except subject with documented Gilbert's syndrome (≤5 x ULN) or liver metastasis, who must have a baseline total bilirubin ≤3.0 mg/dL;
- AST(SGOT)/ALT(SGPT) ≤ 2.5 × institutional ULN OR ≤ 5.0 × institutional ULN for patients with documented liver metastases.
- Fasting glucose ≤ 140 mg/dL and HbA1c ≤ 7%

3.1.3.8 Serum creatinine ≤ 1.5 mg/dL (or glomerular filtration rate ≥ 30 ml/min as determined by the Cockcroft-Gault equation)Female subjects of childbearing potential must have a negative serum or urine pregnancy test within 8 days of initiating protocol therapy.

3.1.3.9 The effects of paxalisib (GDC-0084) on the developing human fetus are unknown and radiotherapy has known teratogenic effects so women of child-bearing potential and men must agree to use adequate contraception (barrier method of birth control; abstinence) prior to study entry and for the duration of study participation and 7 months after completion of Trastuzumab administration per recommendations from the Trastuzumab package insert.

3.1.3.10 The subject is capable of understanding and complying with the protocol and has signed the informed consent document.

3.1.3.11 Participant must be able to swallow and retain oral medication.

3.2 Exclusion Criteria

3.2.1 Visceral crisis or impending visceral crisis at time of screening.
3.2.2 CNS complications for whom urgent neurosurgical intervention is indicated (e.g., resection, shunt placement).
3.2.3 Known leptomeningeal metastases [Defined as positive CSF cytology and/or unequivocal radiological evidence of clinically significant leptomeningeal involvement. CSF sampling is not required in the absence of suggestive symptoms to exclude leptomeningeal involvement].
3.2.4 Patients with known contraindication to MRI (e.g., due to pacemaker, ferromagnetic implants, claustrophobia, extreme obesity, hypersensitivity, etc.). However, head CT with contrast may be used in place of MRI at baseline and throughout the trial if MRI is contraindicated and a participant's brain metastases are clearly measurable by head CT.
3.2.5 Chemotherapy or targeted therapy within 14 days prior to initiation of protocol therapy. No washout is required for trastuzumab.
3.2.6 Has received prior therapy with a PI3K or mTOR inhibitor.
3.2.7 No washout is required for endocrine therapy. If a patient has been on ovarian suppression for at least 28 days prior to initiation of study treatment, continuation of ovarian suppression is permitted on protocol. Starting a new endocrine therapy during protocol therapy is not permitted.
3.2.8 Current use or history of receiving a non-approved, investigational treatment within 14 days prior to initiation of protocol therapy.
3.2.9 Subjects with a history of hypersensitivity to compounds of similar biologic composition to paxalisib (GDC-0084) or any constituent of the product.
3.2.10 The subject has an uncontrolled intercurrent illness, including, but not limited to, ongoing or active infection, uncontrolled hypertension, unstable angina pectoris, uncontrolled cardiac arrhythmia, congestive heart failure-New York Heart Association Class III or IV, active ischemic heart disease, myocardial infarction within the previous six months, uncontrolled diabetes mellitus (DM), gastric or duodenal ulceration diagnosed within the previous 6 months, chronic liver or renal disease, or severe malnutrition. If a participant has controlled DM but is unable to monitor blood sugars at home, they will be excluded from the trial.
3.2.11 The subject is pregnant or breast-feeding.
3.2.12 No active, second potentially life-threatening cancer.
3.2.13 Has had major surgery within 21 days before initiation of protocol therapy.
3.2.14 Active infection requiring IV antibiotics at the time of protocol therapy initiation.
3.2.15 Symptomatic intrinsic lung disease or extensive tumor involvement of the lungs, resulting in dyspnea at rest.
3.2.16 Known intolerance to trastuzumab that persists after appropriate medical management. Patients who have a history of prior intolerance to trastuzumab that is controlled after medical management and who tolerate trastuzumab thereafter without reactions are eligible to participate.
3.2.17 QTc interval time of $\geq$ 470 msec.
Note: The correction may be made using any method of QTc calculation.

3.2.18 Participants receiving any medications or substances that are strong inhibitors or strong inducers of CYP3A4 are ineligible. Should a participant be taking one of these agents and is able to discontinue the therapy or switch to a different agent, no washout will be required prior to starting study medication. Please see Appendix M for the list of medications. Corticosteroids, which are weak CYP3A4 inducers are allowed. Because the lists of these agents are constantly changing, it is important to regularly consult a frequently-updated list such as http://medicine.iupui.edu/clinpharm/ddis/table.aspx; medical reference texts such as the Physicians' Desk Reference may also provide this information. As part of the enrollment/informed consent procedures, the patient will be counseled on the risk of interactions with other agents, and what to do if new medications need to be prescribed or if the patient is considering a new over-the-counter medicine or herbal product.

3.3 Inclusion of Women and Minorities

Both men and women of all races and ethnic groups are eligible for this trial.

4. REGISTRATION PROCEDURES

4.1 General Guidelines for DF/HCC Institutions

Institutions will register eligible participants in the Clinical Trials Management System (CTMS) OnCore. Registrations must occur prior to the initiation of any protocol-specific therapy or intervention. Any participant not registered to the protocol before protocol-specific therapy or intervention begins will be considered ineligible and registration will be denied.

An investigator will confirm eligibility criteria and a member of the study team will complete the protocol-specific eligibility checklist.

Following registration, participants may begin protocol-specific therapy and/or intervention. Issues that would cause treatment delays should be discussed with the Overall Principal Investigator (PI). If the subject does not receive protocol therapy following registration, the subject must be taken off-study in the CTMS (OnCore) with an appropriate date and reason entered.

4.1 Registration Process for DF/HCC Institutions

Applicable DF/HCC policy (REGIST-101) must be followed.

5. TREATMENT PLAN

5.1 Treatment Regimen

Patients will receive the following treatment: paxalisib (GDC-0084) (orally once daily for a 21-day cycle) and trastuzumab (at a dose of 8 mg/kg intravenously (IV) loading dose;

followed by 6 mg/kg IV every 3 weeks thereafter). Treatment will be administered on an outpatient basis. Reported adverse events and potential risks are described in Section 7. Appropriate dose modifications are described in Section 6. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the participant's malignancy.

Cohort A Safety Run-In Dose Levels			
Dose Level	Paxalisib (GDC-0084)	Trastuzumab (or biosimilar)	Cycle Length
-1	30mg PO daily	8 mg/kg IV loading dose; 6 mg/kg IV thereafter*	21 days (3weeks)
1	45mg PO daily	8 mg/kg IV loading dose; 6 mg/kg IV thereafter*	
*If trastuzumab ≥ 6 mg/kg has been given within 28 days of study entry, then it does not need to be reloaded. If trastuzumab 2 mg/kg has been given within 14 days of study entry, then it does not need to be reloaded.			

Cohort A and B Dose Expansion					
Agent	***Premedications; Precautions***	***Dose***	***Route***	***Schedule***	***Cycle Length***
Paxalisib (GDC-0084)	Not routinely necessary	RP2D from Cohort A Safety Run-In = **30mg PO daily	PO	Once Daily	21 days (3 weeks)
Trastuzumab (or biosimilar)	Not routinely necessary unless prior infusion reaction.	Loading dose of 8 mg/kg followed by standard dose of 6 mg/kg*	IV	Day 1, q3w	21 days (3 weeks)

*If trastuzumab ≥ 6 mg/kg has been given within 28 days of study entry, then it does not need to be reloaded. If trastuzumab 2 mg/kg has been given within 14 days of study entry, then it does not need to be reloaded.
** The RP2D was identified to be 30mg PO daily.

Paxalisib (GDC-0084) is provided in capsule formulations for oral administration. Patients should take the capsules once daily as a single dose one hour before food or two hours after food

on treatment days. The capsules should never be opened and should be swallowed whole, do not chew. Patients should record the time and date that they take each dose in a medication diary. The medication diary should be returned to clinic staff at the end of each cycle.

5.2 Pre-Treatment Criteria

Laboratory results must be reviewed prior to dosing. If screening assessments were completed within 8 days of Cycle 1 Day 1, these assessments do not need to be repeated. Laboratory results do not need to re-meet eligibility criteria but should meet the criteria to treat outlined in section 5.2.1.

5.2.1 All Cycles, Day 1

- absolute neutrophil count ≥1,000/mcL
- platelets ≥75,000/mcL
- AST(SGOT)/ALT(SGPT) ≤ 2.5 × institutional ULN or ≤ 5 × institutional ULN for participants with documented liver metastases
- creatinine ≤ 1.5 mg/dL (or glomerular filtration rate >_ 50 ml/min as determined by the Cockcroft-Gault equation)

5.3 Paxalisib (GDC-0084) Administration

Paxalisib (GDC-0084) will be provided by Kazia Therapeutics. Paxalisib (GDC-0084) will be provided in bottles containing 15 mg capsules. Site personnel must ensure that participants clearly understand the directions for self-medication. Participants should be given a sufficient supply to last until their next study visit. Unused drug and/or empty bottles should be returned to the site at the next study visit. Unused returned medication MUST NOT be re-dispensed to patients. Paxalisib (GDC-0084) is an agent that must be handled and administered with care. Patients should be instructed to keep their medication in the bottles provided and not transfer it to any other container. Due to possible unknown hazards associated with topical and environmental exposure to experimental agents, capsules must not be opened and/or emptied into any vehicle for oral ingestion; capsules must be swallowed intact.

Patients will receive a drug diary to document paxalisib (GDC-0084) intake and information about storage and administration of paxalisib (GDC-0084). The completed diary should be returned to the site at the next study visit.

Patients should be instructed to swallow paxalisib (GDC-0084) capsules whole and not to chew them prior to swallowing. No capsule should be ingested if it is broken, cracked, or otherwise not intact. Patients should be encouraged to take their dose at approximately the same time each day. Patients should be instructed to record daily administration of the study drugs in the patient diary.

Patients should take the capsules once daily as a single dose one hour before food or two hours after food on treatment days. Paxalisib (GDC-0084) will be administered orally once a day for 21 days for each cycle. Paxalisib (GDC-0084) must be dosed in clinic on day 1 of each cycle. On the days of administration of trastuzumab, Paxalisib (GDC-0084) can be administered either before or after trastuzumab administration.

Patients experiencing toxicity related to paxalisib (GDC-0084) may have their dose modified according to the Recommended Dose Modification Section.

General rules for paxalisib (GDC-0084) administration:

- Patients who miss a day's dose entirely will be instructed NOT to "make it up" the next day. Missed or forgotten doses can be taking during the same day the original dose was scheduled.
- Patients who vomit any time after taking a dose will be instructed NOT to "make it up," and to resume treatment the next day as prescribed.
- Patients who inadvertently take 1 extra dose during a day must inform a member of the study team and will be instructed to skip the next day's dose.

5.4 Trastuzumab Administration

The protocol will utilize commercial trastuzumab, as per standard-of-care. Trastuzumab will be administered by trained medical personnel at the investigational site. Treatment compliance will be monitored through documentation of study treatment administration in the subject's medical record.

It is recommended that Trastuzumab will be administered at a loading dose of 8 mg/kg infused intravenously over approximately 90 minutes, followed by standard dose of 6 mg/kg every 3 weeks, infused intravenously over approximately 30 to 90 minutes or per institutional guidelines. If the patient has previously tolerated 30 minute infusions, it may be given over approximately 30 minutes starting at cycle 2 day 1 without a subsequent observation period. If trastuzumab ≥ 6 mg/kg has been given within 4 weeks of study entry, then it does not need to be reloaded. If trastuzumab 2 mg/kg has been given within 2 weeks of study entry, then it does not need to be reloaded. In these cases, the first dose of trastuzumab on protocol may be infused over approximately 30 minutes if previously tolerated, and it may be given without a subsequent observation period.

The dose of trastuzumab will be based on the patient's actual body weight measured on C1D1. Alterations to trastuzumab dosing based on weight changes between cycles should be made based on local institutional standard operating procedures. Every 3-week doses may be administered ± 7 days (no less than 14 days apart) for scheduling or vacation reasons. Patients should not receive more than three, every 3 weeks doses within a 5-week period.

5.4.1 Left Ventricular Ejection Fraction

Assess LVEF as specified in section 6.4 for continuation and discontinuation of trastuzumab based on LVEF assessments in Appendix G.

5.4.2 Infusion-Related Reactions

Like other monoclonal antibodies, trastuzumab has been associated with infusion-related reactions (IRRs), such as chills, diarrhea, fatigue, headache, nausea, and pyrexia. The infusion rate of trastuzumab may be slowed or interrupted and appropriate medical therapies should be administered if the patient develops a significant IRR. Patients should be evaluated and carefully monitored until complete resolution of signs and symptoms.

5.4.3 Hypersensitivity Reactions/Anaphylaxis

The infusion should be discontinued immediately if the patient experiences a serious hypersensitivity reaction.

5.5 Definition of a Dose-Limiting Toxicity (DLT)

A DLT is defined as an AE or clinical significant abnormal laboratory value assessed as having a reasonably possible relationship to the study medication(s) and is unrelated to disease, disease progression, inter-current illness or concomitant medications that occurs within the first cycle (21 days) of treatment with paxalisib (GDC-0084) and Trastuzumab. NCI CTCAE version 5.0 should be used for all grading. Participants that receive less than 75% of their paxalisib (GDC-0084) dose during cycle 1 will be considered unevaluable for DLTs. These subjects do not need to be removed from treatment, but should be replaced by another patient for DLT evaluation. The exception to this rule would be if the missed doses were due to a DLT, in which case, the patient is considered evaluable.
Management and dose modifications associated with adverse events are outlined in Section 6.
All DLTs that occur within the first cycle of the safety run-in will be considered, including those in which the event started in cycle 1 ad the confirmation of the DLT occurs in a subsequent cycle.
The following toxicities would be considered DLTs:

- Grade 4 neutropenia of any duration
- Febrile neutropenia of any duration
- Grade 3 thrombocytopenia associated with significant bleeding or grade 4 thrombocytopenia (platelet count ≤ 25,000 cells/mm3) of any duration
- Grade 3 hematological toxicity > 7 days in duration
- Non-hematologic toxicity Grade ≥ 3 > 7 days in duration (excluding untreated nausea or vomiting, untreated hyperglycemia, untreated rash, or alopecia) determined to be possibly, probably, or definitely attributed to a study agent (as defined in Section 7.2).
- Hyperglycemia, rash, nausea, vomiting, or diarrhea ≥ Grade 3 persisting for > 7 days and/or uncontrolled by aggressive supportive care measures as recommended in Section 6.3.
- Grade ≥ 2 non-hematological toxicity that in the judgment of the Principal Investigator requires dose reduction within the first cycle

5.6 Surgical Resection for Participants on Cohort B

Participants on Cohort B should have a clinical indication for surgical brain resection. This surgery should occur between C1D3 and C1D9. Patients should hold their paxalisib (GDC-0084) the morning of their surgery and they should resume once they are able to swallow oral medication.

5.7 General Concomitant Medication and Supportive Care Guidelines

5.7.1 Concomitant Medication Guidelines

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the ongoing trial. If there is a clinical indication for one of these or other medications or vaccinations specifically prohibited during the trial, discontinuation from trial therapy or vaccination may be required. The investigator should discuss any questions regarding this with the overall PI.

Concomitant Medications

Given the high rate of oral mucositis and stomatitis, all participants must be treated prophylactically at study start using acceptable therapies per local guidelines or institutional standards. An example of an acceptable prophylactic therapy is:

- Dexamethasone 0.5mg/5ml alcohol-free oral solution, 10mL PO QID. Patient should swish solution for 2 minutes and then spit out. Patient should not eat for one hour after mouthwash.

Acceptable Concomitant Medications

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

Prohibited Concomitant Medications

Subjects are prohibited from receiving the following therapies during the Screening and Treatment Phase of this trial:

- Antineoplastic systemic chemotherapy or biological therapy
- Immunotherapy not specified in this protocol
- Radiation therapy
- Any systemically active oral, injected, or implanted hormonal method of contraception except for progesterone coated intrauterine devices (IUDs) that had been previously implanted.
- Estrogen replacement therapy.
- Live vaccines within 28 days prior to the first dose of trial treatment and while participating in the trial. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster, yellow fever, rabies, BCG, and typhoid vaccine.
- If systemic corticosteroids are indicated, the minimum effective dose should be used.
- Subjects may receive other medications that the investigator deems to be medically necessary.

There are no prohibited therapies during the Post-Treatment Follow-up Phase.

Because there is a potential for interaction of paxalisib (GDC-0084) with other concomitantly administered drugs through the cytochrome P3A4 system, medical record must capture the concurrent use of all other drugs, over-the-counter medications, or alternative therapies. Appendix M presents guidelines for identifying medications/substances that could potentially interact with the study agent(s).

5.7.2 Supportive Care Guidelines – general medications

The following treatments are permitted throughout the duration of the study treatment phase and during follow-up:

- Standard therapies for pre-existing medical conditions unless listed as prohibited therapy. Any medication intended solely for supportive care (e.g., analgesics, anti-diarrheal, anti-depressants) may be used at the investigator's discretion.
- Bisphosphonate or denosumab therapy.
- Anticoagulants - Anticoagulation with heparin, heparin derivatives, and/or warfarin may be given at the discretion of the treating physician. Coagulation parameters should be checked at least once monthly, or more frequently at discretion of treating physician.
- Pain medications administered per standard clinical practice are acceptable while the participant is enrolled in the study.
- Hematopoietic growth factors should not be administered prophylactically before initial treatment with study drugs. These agents may be used upon approval of the study PI for treatment-emergent neutropenia and/or for secondary prophylaxis. Clinically significant grade 3/4 neutropenia is not an expected adverse event on protocol.

Patients who experience toxicities should be treated symptomatically as clinically indicated. Medications that are considered necessary for the subject's welfare and that are not expected to interfere with the evaluation of study treatment or be restricted may be given at the discretion of the investigator. Ancillary treatments will be given as medically indicated.

5.8 Criteria for Taking a Participant Off Protocol Therapy

Duration of therapy will depend on individual response, evidence of disease progression and tolerance. In the absence of treatment delays due to adverse event(s), treatment may continue for an indefinite number of cycles, or until one of the following criteria applies:

- Disease progression in CNS by RANO-BM criteria
- Disease progression in extracranial sites by RECIST 1.1 criteria
- Disease progression based on the clinical judgement of the investigator (clinical progression)
- Intercurrent illness that prevents further administration of treatment
- Unacceptable adverse event(s)
- Participant demonstrates an inability or unwillingness to comply with the oral medication regimen and/or documentation requirements
- Participant decides to withdraw from the protocol therapy
- General or specific changes in the participant's condition render the participant unacceptable for further treatment in the judgment of the treating investigator

Participants will be removed from the protocol therapy when any of these criteria apply. The reason for removal from protocol therapy, and the date the participant was removed, must be documented in the case report form (CRF). Alternative care options will be discussed with the participant.

When a participant is removed from protocol therapy and/or is off study, the relevant Off-Treatment/Off-Study information will be updated in OnCore.

5.9 Duration of Follow Up

Participants removed from protocol therapy for unacceptable adverse event(s) will be followed until resolution or stabilization of the adverse event. Participants who are taken off protocol therapy for extracranial progression in the setting of intracranial response or stable disease will be followed for CNS progression and survival until death. It is understood that it may not always be feasible for patients to return for restaging evaluation after coming off protocol therapy, though a strong effort should be made to encourage restaging a minimum of every 12 weeks. In this specific setting, lack of restaging scans at this interval will not constitute a protocol deviation or violation. Participants who are removed from protocol therapy for intracranial disease progression will be followed for survival until death.

5.10 Criteria for Taking a Participant Off Study

Participants will be removed from study when any of the following criteria apply:

- Lost to follow-up
- Withdrawal of consent for data submission
- Death
- Study closure

The reason for taking a participant off study, and the date the participant was removed, must be documented in the case report form (CRF). In addition, the study team will ensure Off Treatment/Off Study information is updated in OnCore in accordance with DF/HCC policy REGIST-101.

6. DOSING DELAYS/DOSE MODIFICATIONS

Dose delays and modifications will be made as indicated in the following table(s). The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for dose delays and dose modifications. A copy of the CTCAE version 5.0 can be downloaded from the CTEP website http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

Dosing interruptions are permitted in the case of medical / surgical events or logistical reasons not related to study therapy (e.g., elective surgery, unrelated medical events, patient vacation, inclement weather, and/or holidays). Participants held for these reasons are required to resume therapy within 3 weeks of the scheduled interruption. The reason for interruption must be documented in the participant's medical record.

If there are dosing delays for any reason, all study assessments are to be delayed in the same fashion, such that that scans and other assessments occur in conjunction with cycles of treatment.

No dose reductions are allowed for trastuzumab in this study. If trastuzumab needs to be permanently discontinued, patients can remain on paxalisib (GDC-0084) at discretion of their physician.

In the event of significant treatment-related toxicity, paxalisib (GDC-0084) dosing may be interrupted or delayed and/or reduced as described below. In the event of multiple toxicities, dose modification should be based on the worst toxicity observed. Patients are to be instructed to notify Investigators at the first occurrence of any adverse sign or symptom.

Dose modifications may occur in three ways:

- Within a cycle: dosing interruption until adequate recovery followed by dose reduction, if required.
- Between cycles: next cycle administration may be delayed due to persisting toxicity when a new cycle is due to start.
- At start of the new cycle: dose reduction may be required in a subsequent cycle based on toxicity experienced in the previous cycle.

Patients discontinuing paxalisib (GDC-0084) treatment due to treatment-related toxicity can continue trastuzumab at the discretion of their physician, off protocol therapy.

6.1 Dosing Interruptions/delays

Patients experiencing the following adverse events will have their treatment with paxalisib (GDC-0084) interrupted/delayed until criteria for retreatment are met:

- Uncomplicated Grade 3 or 4 neutropenia (ANC < 1000/mm^3).
- Grade 3 or 4 neutropenia (ANC < 1000/mm^3) associated with a documented infection or fever ≥ 38.5°C.
- Grade 3 or 4 thrombocytopenia (Platelets < 50,000/mm^3).
- Non-hematologic toxicity persisting despite optimal medical treatment if either Grade 2 lasting more than 3 weeks, or Grade ≥3 (including nausea, vomiting, and diarrhea).
- Concurrent > 3x ULN ALT (or > 5x ULN for participants with liver metastases) and > 2x ULN Total Bilirubin (or > 5x ULN for participants with liver metastases or Gilbert's syndrome). If those occur, the dose needs to be held while the cause is being investigated.

Doses should be held until toxicity resolution. Appropriate follow up assessments, as defined by the investigator, should be undertaken until adequate recovery occurs. Criteria required before treatment can resume are described in the Retreatment Criteria Section.

Depending on when the adverse event resolved, a treatment interruption may lead to the patient missing all subsequent planned doses within that same cycle or even to delay in the initiation of the subsequent cycle.

If the adverse event that led to the treatment interruption recovers within the same cycle, then re-dosing in that cycle is allowed. Doses omitted for toxicity are not replaced within the same cycle. The need for a dose reduction at the time of treatment resumption should be based on the criteria defined in the Dose Reductions Section unless an alternative plan is expressly agreed upon between the investigator and Principal Investigator.

6.2 Retreatment Criteria

Retreatment with paxalisib (GDC-0084) following treatment interruption for treatment-related toxicity or at the start of any new cycle may not occur until all the following parameters have been met:

- Platelet count ≥ 75,000/mm3.
- ANC ≥ 1000/mm3 and no fever.
- Grade ≥ 3 non-hematologic AEs (including nausea, vomiting, diarrhea, and hypertension only if persisting despite optimal medical treatment), have recovered to Grade ≤ 1 or baseline

6.3 Dose Reductions

No specific dose adjustments are required for Grade 1 or short lasting (< 3 weeks) treatment-related Grade 2 toxicity except as noted in the tables below. However, investigators should always manage participants according to their medical judgment and on the individual's clinical circumstances if a dose adjustment for low grade toxicity is in their best interest.

In case of a Grade 2 toxicity lasting for > 3 weeks or a Grade ≥ 3 toxicity (both assessed in the presence of maximum supportive care as judged by the investigator), dose reduction is required for the subsequent cycles. Dose reduction of paxalisib (GDC-0084) by one, and, if needed, by two dose levels (Table below) is recommended depending on type and severity of the toxicity. Patients requiring a dose reduction beyond 15mg daily will be allowed to receive 15 mg/day for 2 weeks on followed by 1 week off study treatment (if, per the investigator's judgment, such a change in schedule is manageable and preferable to permanent paxalisib (GDC-0084) discontinuation). All dose modifications/adjustments must be clearly documented in the participant's medical record.

Once a dose has been reduced for a given patient, all subsequent cycles should be administered at that dose level, unless further dose reduction is required. Dose re-escalation is not allowed.

Dose Level	Paxalisib (GDC-0084) for 21 days (3 weeks)
0	45 mg, daily
-1	30 mg, daily

-2	15 mg, daily*

* Paxalisib (GDC-0084) dose de-escalation below 15 mg/d is not allowed, but the schedule may be changed to 15 mg/day two weeks on followed by one week off (2/1 schedule).

Paxalisib (GDC-0084) recommended dose modifications for treatment related toxicities requiring treatment interruption/delay despite optimal medical treatment are as follows:

Hyperglycemia[a]	**Management/Next Dose for Paxalisib (GDC-0084)**
Grade 1 (>125 to160 mg/dL)	• May educate patients on a diabetic diet • May continue paxalisib (GDC-0084) treatment at the same dose • Consider starting (or increasing) dose of an oral anti-diabetic medication (e.g. metformin)
Grade 2 (>160 to 250 mg/dL)	• Start (or increase dose for) an oral anti-diabetic medication (e.g. metformin) • Start a diabetic diet. Consider endocrinology consult. • Consider paxalisib (GDC-0084) dose interruption until hyperglycemia resolves to Grade ≤ 1. o If interrupted, may resumed paxalisib (GDC-0084) at the same dose.
Asymptomatic Grade 3 (>250 to 500 mg/dL)	• Start or increase dose for an oral anti-diabetic medication (e.g. metformin) • Start a diabetic diet. Consider endocrinology consult. • Interrupt paxalisib (GDC-0084) until hyperglycemia resolves to Grade ≤ 1 o If hyperglycemia resolves to Grade ≤ 1 within less than or equal to 7 days, paxalisib (GDC-0084) may be resumed at the same dose. o If hyperglycemia resolves to Grade ≤ 1 in ≥ 8 days, reduce paxalisib (GDC-0084) by one dose level when treatment resumes. • If Grade ≥ 3 hyperglycemia recurs within 30 days, reduce paxalisib (GDC-0084) by one dose level.
Symptomatic[b] Grade 3 (>250 to 500 mg/dL) or Grade 4 (>500mg/dL)	• Manage per standard of care, including implementation of additional glucose monitoring and initiation or an increase in the dose of anti-diabetic therapy. Consultation to endocrinology is strongly preferred. • Interrupt paxalisib (GDC-0084). • Upon resolving to Grade ≤ 1, reduce paxalisib (GDC-0084) by one dose level when treatment resumes. • If symptomatic Grade 3 or Grade 4 hyperglycemia recurs, discontinue paxalisib (GDC-0084).
a. All grading (CTCAE v 5.0) should be based on ≥ 8 hours fasting. b. Symptomatic hyperglycemia includes hyperglycemia associated with polydipsia, polyuria, polyphagia, blurry vision, or acidosis.	

The anti-hyperglycemic agent metformin should be used first-line for the management of sustained Grade 2 and Grade 3 hyperglycemia. Investigators should exercise caution in the dosing and management of patients receiving metformin in combination with paxalisib (GDC-0084) and must be vigilant for signs of renal impairment and metformin toxicity. In the event metformin is not tolerated or not sufficient, another anti-hyperglycemia medication(s) may be added to or used in place of metformin. Preferred agents include SGLT2 inhibitors, pioglitazone, and DPP4 inhibitors, where available and considered appropriate by investigators.

Rash	**Management/Next Dose for Paxalisib (GDC-0084)**
≤ Grade 1	No change in dose Initiate topical corticosteroid treatment: 3-4 times a day with Triamcinolone or Betamethasone Consider adding oral antihistamine (cetirizine or equivalent) If rash persists after 28 days, consider adding low dose systemic corticosteroid 20-40 mg/day
Grade 2	No change in dose Initiate or intensify topical corticosteroid and oral antihistamine treatment Consider low dose systemic corticosteroid treatment 20-40 mg/day Consider consultation with dermatology
Grade 3	Hold until < Grade 2 Initiate or intensify topical/systemic corticosteroid and oral antihistamine treatment Consider consultation with dermatology Resume at the same dose level for first occurrence of rash, or at next lower dose level in case of second occurrence
Grade 4	Off protocol therapy Consider consultation with dermatology
Recommended management: topical corticosteroids, oral antihistamines, systemic corticosteroids.	

Nausea	**Management/Next Dose for Paxalisib (GDC-0084)**
≤ Grade 1	No change in dose
Grade 2	Hold until ≤ Grade 1. Resume at same dose level.
Grade 3	Hold* until < Grade 2. Resume at one dose level lower, if indicated.**
Grade 4	Off protocol therapy
*Participants requiring a delay of > 2 weeks should stop protocol therapy. **Participants requiring > two dose reductions should stop protocol therapy.	
Recommended management: antiemetics.	

Vomiting	**Management/Next Dose for Paxalisib (GDC-0084)**
≤ Grade 1	No change in dose
Grade 2	Hold until ≤ Grade 1. Resume at same dose level.
Grade 3	Hold* until < Grade 2. Resume at one dose level lower, if indicated.**

Vomiting	**Management/Next Dose for Paxalisib (GDC-0084)**
Grade 4	Off protocol therapy
*Participants requiring a delay of > 2 weeks should stop protocol therapy. **Participants requiring > two dose reductions should stop protocol therapy.	
Recommended management: antiemetics.	
Diarrhea	**Management/Next Dose for Paxalisib (GDC-0084)**
≤ Grade 1	No change in dose
Grade 2	Hold until ≤ Grade 1. Resume at same dose level.
Grade 3	Hold* until < Grade 2. Resume at one dose level lower, if indicated.**
Grade 4	Off protocol therapy
*Participants requiring a delay of > 2 weeks should stop protocol therapy. **Participants requiring > two dose reductions should stop protocol therapy.	
Recommended management: Loperamide antidiarrheal therapy Dosage schedule: 4 mg at first onset, followed by 2 mg with each loose bowel motion until diarrhea-free for 12 hours (maximum dosage: 16 mg/24 hours) Adjunct anti-diarrheal therapy is permitted and should be recorded when used.	

Neutropenia	**Management/Next Dose for Paxalisib (GDC-0084)**
≤ Grade 1	No change in dose
Grade 2	No change in dose
Grade 3	Hold* until ≤ Grade 2. Resume at one dose level lower, if recovery to ≤ Grade 2 takes >1 week.**
Grade 4	Off protocol therapy
*Participants requiring a delay of > 2 weeks should stop protocol therapy. **Participants requiring > two dose reductions should stop protocol therapy.	

Thrombocytopenia	**Management/Next Dose for Paxalisib (GDC-0084)**
≤ Grade 1	No change in dose
Grade 2	Hold until ≤ Grade 1. Resume at same dose level.
Grade 3	Hold* until < Grade 2. Resume at one dose level lower, if indicated.**
Grade 4	Off protocol therapy
*Participants requiring a delay of >2 weeks should go off protocol therapy. **Participants requiring > two dose reductions should go off protocol therapy.	

Other non-hematologic toxicity	**Management/Next Dose for Paxalisib (GDC-0084)**
≤ Grade 1	No change in dose
Grade 2	Hold until ≤ Grade 1. Resume at same dose level.
Grade 3	Hold* until < Grade 2. Resume at one dose level lower, if indicated.**
Grade 4	Off protocol therapy
*Participants requiring a delay of > 2 weeks should stop protocol therapy. **Participants requiring > two dose reductions should stop protocol therapy.	

6.4 Management of toxicities attributable to trastuzumab

Administration of trastuzumab may be delayed to assess or treat adverse events, such as changes in LVEF, as shown in Appendix G.

1. Non-hematological, Grade 1 or 2 (NCI CTCAE v5.0) adverse events, excluding cardiac toxiciy[a]	Continue study treatment.
2. Non-hematological, deemed related grade 3 or 4 (NCI CTCAE v5.0) adverse events, excluding cardiac toxicity[a]	Hold trastuzumab until recovery to Grade ≤ 2. Toxicity resolved to Grade ≤ 1 within a maximum of 6 weeks calculated from **last** administration: resume trastuzumab. Toxicity did **not** resolve to Grade ≤ 2 within a maximum of 6 weeks calculated from last administration: discontinue trastuzumab permanently. Continue treatment as deemed suitable by the local investigator.
3. Recurrence of non-hematological, Grade 3 or 4 (NCI CTCAE v5.0; excluding cardiac toxicity[a]) toxicity upon rechallenge	Discontinue trastuzumab permanently. Continue treatment as deemed suitable by the local investigator.
4. Cardiac toxicity (asymptomatic drop in LVEF or symptomatic CHF)	Trastuzumab to be held, continued, or resumed according to the algorithm in Appendix G Trastuzumab to be discontinued permanently in case of symptomatic CHF.
5. Cardiac toxicity (NCI CTCAE or other cardiac toxicities not covered by the treatment algorithm in Appendix F	Actions must follow rules 2 to 4 for non-hematological toxicities.

CHF = congestive heart failure; LVEF = left ventricular ejection fraction; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; NYHA = New York Heart Association.
a Severity corresponding to NYHA classification (see Appendix G).

6.4.1 Management of Cardiac Safety

All patients must have a baseline evaluation of cardiac function including a measurement of LVEF by either ECHO or MUGA scan prior to study entry. Only patients with LVEF of ≥ 50% should be entered into this study. While receiving trastuzumab, all patients will have regular monitoring of LVEF with ECHO or MUGA (at screening, followed by LVEF evaluations approximately every 3 months or as clinically indicated). During the course of therapy with trastuzumab, participants should be monitored for signs and symptoms of heart failure (i.e., dyspnea, tachycardia, new unexplained cough, neck vein distention, cardiomegaly, hepatomegaly, paroxysmal nocturnal dyspnea, orthopnea, peripheral edema, and rapid unexplained weight gain). The diagnosis must be confirmed using the same method used to measure LVEF at baseline (either ECHO or MUGA).

Patients who develop signs and symptoms of heart failure NCI CTCAE v5.0 Grade 2, 3, or 4 should have trastuzumab held and should receive treatment for heart failure as prescribed by the Heart Failure Society of American (HFSA 2010; e.g., ACE inhibitors, angiotensin-II receptor blockers, β-blockers, diuretics, and cardiac glycosides, as needed).

Consideration should be given to obtaining a cardiac consultation. LVEF should be reassessed after 3 weeks (using the same method of measurement). If the symptoms of heart failure resolve with treatment, and cardiac function (as measured by ECHO or MUGA) improves, trastuzumab may be restarted after discussion with the patient concerning the risks and benefits of continued therapy. If the patient is benefiting clinically from study therapy, the benefit of continued treatment may outweigh the risk of cardiac dysfunction. If trastuzumab is restarted, continued surveillance with noninvasive measures of LVEF (ECHO or MUGA) will continue per protocol.

Study treatment will be adjusted if necessary according to the algorithm described in Appendix G If an investigator is concerned that an adverse event may be related to cardiac dysfunction, an additional LVEF measurement should be performed. Trastuzumab will be discontinued permanently in any patient who develops clinical signs and symptoms suggesting symptomatic CHF, with the diagnosis confirmed by a suggestive chest X-ray and a drop in LVEF by ECHO or MUGA.

CHF should be treated and monitored according to standard medical practice. At present, there are inadequate data available to assess the prognostic significance of asymptomatic drops of LVEF. Trastuzumab must be held in all patients for whom a drop of LVEF to < 40% or 40% −45% with a 10%-point or greater drop below baseline (Appendix G). If this value is confirmed or LVEF has not recovered to > 45% or 40% − 45% and LESS than 10% below baseline with a repeat assessment within 3 weeks of the first assessment, using the same assessment method, trastuzumab must be discontinued (see Appendix G). If the subject was unequivocally deriving clinical benefit, the subject may be able to resume paxalisib (GDC-0084) as determined by the investigator.

Patients who resume therapy will resume trastuzumab at the study dose of 6 mg/kg every 3 weeks (8 mg/kg loading dose of trastuzumab required if study drug is held > 6 weeks). Paxalisib (GDC-0084) will resume at the study dose of 45 mg daily. Patients will be allowed to hold and resume trastuzumab for a maximum of three times, after which trastuzumab must be discontinued.

The incidence of CHF will also be recorded throughout the study. See Appendix H for details of NYHA classification, Appendix I for LVSD according to NCI CTCAE v5.0 grading, and Appendix I for reporting conventions for LVSD/heart failure.

7. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

The safety plan for patients in this study is based on clinical experience with paxalisib (GDC-0084) and trastuzumab in completed and ongoing studies. The anticipated important safety risks are outlined below (see section 7.1).

Measures will be taken to ensure the safety of patients participating in this study, including the use of stringent inclusion and exclusion criteria and close monitoring of patients during the study. Administration of trastuzumab will be performed in a monitored setting in which there is immediate access to trained personnel and adequate equipment and medicine to

manage potentially serious reactions. After initiation of study treatment, all adverse events will be reported until 30 days after the last dose of study treatment or until initiation of new systemic anti-cancer therapy, whichever occurs first, and serious adverse events and adverse events of special interest will continue to be reported until 30 days after the last dose of study treatment or until initiation of new systemic anti-cancer therapy, whichever occurs first.

Guidelines for managing anticipated adverse events, including criteria for dosage modification and treatment interruption or discontinuation, are provided below (see Section 6). Refer to Sections 7.2–7.9 for details on safety reporting during the study.

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. The following list of reported and/or potential AEs (Section 7.1) and the characteristics of an observed AE (Section 7.2) will determine whether the event requires expedited reporting **in addition** to routine reporting.

In the event of an unanticipated problem or life-threatening complications treating investigators must immediately notify the Overall PI.

7.1 Adverse Events Lists

7.1.1 Expected adverse events for Paxalisib (GDC-0084)

Safety analysis included all 47 patients in Stage 1 who received any amount of paxalisib (GDC-0084). Enrolment for this study was discontinued before expansion to Stage 2 when further clinical development of paxalisib (GDC-0084) was stopped.

Forty-four of 47 patients (93.6%) who received paxalisib (GDC-0084) experienced at least one AE, regardless of causality. The most frequently reported AEs (occurring in ≥ 10% of patients) regardless of causality were fatigue (15 patients [31.9%]), hyperglycemia (14 patients [29.8%]), nausea (13 patients [27.7%]), hypertriglyceridemia (10 patients [21.3%]), headache (9 patients [19.1%]), hypophosphatemia and rash (8 patients each [17.0%]), asthenia and diarrhea (6 patients each [12.8%]), and aphasia, blood cholesterol increased, decreased appetite, dehydration, dizziness, hemiparesis, hyponatremia, mucosal inflammation, stomatitis, and vomiting (5 patients each [10.6%]). Refer to Section 5.4.1 of the paxalisib (GDC-0084) Investigator's Brochure for a detailed description of anticipated safety risks for paxalisib (GDC-0084).

1 patient experienced unexpected cytokinase release syndrome (CRS) while enrolled in this trial (DFCI #18-516).

7.1.2 Expected adverse events for Trastuzumab

Trastuzumab has been associated with risks such as the following: cardiac dysfunction, ARRs, pulmonary AEs, neutropenia/febrile neutropenia, diarrhea, fatigue, nausea, vomiting, anddecreased appetite. Please see trastuzumab Investigator’s Brochures for a detailed description of anticipated safety risks for trastuzumab.

7.1.3 Safety Parameters and Definitions

Specification of Safety Variables

Safety assessments will consist of monitoring and reporting adverse events (AEs) and

serious adverse events (SAEs) per protocol. This includes all events of death, and any study specific issue of concern.

Adverse Events

An AE is any unfavorable and unintended sign, symptom, or disease temporally associated with the use of an investigational medicinal product (IMP) or other protocol-imposed intervention, regardless of attribution.

This includes the following:

- AEs not previously observed in the patient that emerge during the protocol-specified AE reporting period, including signs or symptoms 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).
- If applicable, AEs that occur prior to assignment of study treatment associated with medication washout, no treatment run-in, or other protocol-mandated intervention.
- Preexisting medical conditions (other than the condition being studied) judged by the investigator to have worsened in severity or frequency or changed in character during the protocol-specified AE reporting period.

Serious Adverse Events

An AE should be classified as an SAE if the following criteria are met:

- It results in death (i.e., the AE actually causes or leads to death).
- It is life threatening (i.e., the AE, in the view of the investigator, places the subject at immediate risk of death. It does not include an AE that, had it occurred in a more severe form, might have caused death.).
- It requires or prolongs inpatient hospitalization.
- It results in persistent or significant disability/incapacity (i.e., the AE results in substantial disruption of the subject's ability to conduct normal life functions).
- It results in a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to the IMP.
- It is considered a significant medical event by the investigator based on medical judgment (e.g., may jeopardize the subject or may require medical/surgical intervention to prevent one of the outcomes listed above).

7.2 Adverse Event Characteristics

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

- **For expedited reporting purposes only:**

- AEs for the agent(s) that are listed above should be reported only if the adverse event varies in nature, intensity or frequency from the expected toxicity information which is provided.
- Other AEs for the protocol that do not require expedited reporting are outlined in the next section (Expedited Adverse Event Reporting) under the sub-heading of Protocol-Specific Expedited Adverse Event Reporting Exclusions.

- **Attribution** of the AE:
  - Definite – The AE *is clearly related* to the study treatment.
  - Probable – The AE *is likely related* to the study treatment.
  - Possible – The AE *may be related* to the study treatment.
  - Unlikely – The AE *is doubtfully related* to the study treatment.
  - Unrelated – The AE *is clearly NOT related* to the study treatment.

7.3 Methods and Timing for Assessing AND Recording Safety variables

The sponsor is responsible for ensuring that all AEs and SAEs that are observed or reported during the study, are collected and reported to the FDA, appropriate IRB(s), and Kazia Therapeutics in accordance with CFR 312.32 (IND Safety Reports).

7.3.1 Adverse Event Reporting Period

The study period during which all AEs and SAEs must be reported begins after initiation of protocol therapy 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 that are attributed to prior study treatment.

7.3.2 Assessment of Adverse Events

All AEs and SAEs whether volunteered by the participant, discovered by study personnel during questioning, or detected through physical examination, laboratory test, or other means will be reported appropriately. Each reported AE or SAE will be described by its duration (i.e., start and end dates), regulatory seriousness criteria if applicable, suspected relationship to the G paxalisib (GDC-0084) DC-0084 (see following guidance), and actions taken.

To ensure consistency of AE and SAE causality assessments, investigators should apply the following general guideline:

Yes
There is a plausible temporal relationship between the onset of the AE and administration of the paxalisib (GDC-0084), and the AE cannot be readily explained by the subject's clinical state, intercurrent illness, or concomitant therapies; and/or the AE follows a known pattern of response to the paxalisib (GDC-0084); and/or the AE abates or resolves upon discontinuation of the paxalisib (GDC-0084) or dose reduction and, if applicable, reappears upon re-challenge.

No
Evidence exists that the AE has an etiology other than the paxalisib (GDC-0084) (e.g., preexisting medical condition, underlying disease, intercurrent illness, or concomitant

medication); and/or the AE has no plausible temporal relationship to paxalisib (GDC-0084) administration (e.g., cancer diagnosed 2 days after first dose of paxalisib (GDC-0084)).

Expected adverse events are those adverse events that are listed or characterized in the Package Insert (P.I) or current Investigator Brochure (I.B).

Unexpected adverse events are those not listed in the P.I or current I.B or not identified. This includes adverse events for which the specificity or severity is not consistent with the description in the P.I. or I.B. For example, under this definition, hepatic necrosis would be unexpected if the P.I. or I.B. only referred to elevated hepatic enzymes or hepatitis.

7.4 Procedures for Eliciting, Recording, and Reporting Adverse Events

7.4.1 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?"

7.4.2 Specific Instructions for Recording Adverse Events

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

7.4.2.1 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.

7.4.2.2 Deaths

All deaths that occur during the protocol-specified AE reporting period (see Section I), regardless of attribution, will be reported to the appropriate parties. When recording a death, the event or condition that caused or contributed to the fatal outcome should be reported as the single medical concept. If the cause of death is unknown and cannot be ascertained at the time of reporting, report "Unexplained Death".

7.4.2.3 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").

7.4.2.4 Hospitalizations for Medical or Surgical Procedures

Any AE that results in hospitalization or prolonged hospitalization should be documented and reported as an SAE. If a subject is hospitalized to undergo a medical or surgical procedure because of an AE, the event responsible for the procedure, not the procedure itself, should be reported as the SAE. For example, if a subject is hospitalized to undergo coronary bypass surgery, record the heart condition that necessitated the bypass as the SAE. Participants on Cohort B will be undergoing surgical resection of their brain metastases. This is a part of the research and clinical plan and does not require reporting as an AE/SAE.

Hospitalizations for the following reasons do not require reporting:

- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for preexisting conditions
- Hospitalization or prolonged hospitalization required to allow efficacy measurement for the study or
- Hospitalization or prolonged hospitalization for scheduled therapy of the target disease of the study.

7.4.2.5 Pregnancy

If a female subject becomes pregnant while receiving the study drug or within 90 days after the last dose of study drug, a report should be completed and expeditiously submitted to Kazia Therapeutics. Follow-up to obtain the outcome of the pregnancy should also occur. 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 paxalisib (GDC-0084) should be reported as an SAE.

7.4.2.6 Post-Study Adverse Events

The investigator should expeditiously report any SAE occurring after a subject has completed or discontinued study participation if attributed to prior paxalisib (GDC-0084) exposure. If the investigator should become aware of the development of cancer or a congenital anomaly in a subsequently conceived offspring of a female subject who participated in the study, this should be reported as an SAE.

7.4.2.7 Reconciliation

The Sponsor agrees to conduct reconciliation for the product. Kazia Therapeutics and the Sponsor will agree to the reconciliation periodicity and format but agree at minimum to exchange quarterly line listings of cases received by the other party.

If discrepancies are identified, the Sponsor and Kazia Therapeutics 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'.

7.4.2.8 Aggregate reports

The Sponsor will forward a copy of the Final Study Report to Kazia Therapeutics upon completion of the Study.

7.5 Reporting to Principal investigator

Participating investigators must report each serious adverse event to the DF/HCC Overall Principal Investigator within 1 business day of learning of the occurrence. If the participating investigator does not become aware of the serious adverse event immediately (e.g., participant sought treatment elsewhere), the participating investigator is to report the event within 1 business day after learning of it and document his or her first awareness of the adverse event. Report serious adverse events by telephone, email or facsimile to:

Jose Pablo Leone, MD
[redacted]

7.6 Reporting to Kazia Therapeutics

Investigators must report all SAEs (initial and follow-ups) to Kazia Therapeutics within the timelines described below. The completed MedWatch 3500A Form should be emailed to the following contacts at Kazia Therapeutics.

Dr. John Friend
Chief Medical Officer
[redacted]

Dominic Capone
Program Director
[redacted]

- **SADRs**

Serious AE reports that are related to the Product shall be transmitted to Kazia Therapeutics within fifteen (15) calendar days of the awareness date.

- **Other SAEs**

Serious AE reports that are unrelated to the Product shall be transmitted to Kazia Therapeutics within thirty (30) calendar days of the awareness date.

- **Pregnancy reports**

While such reports are not serious AEs or ADRs per se, as defined herein, any reports of pregnancy, where the fetus may have been exposed to the Product, shall be transmitted to Kazia Therapeutics within thirty (30) calendar days of the awareness date. Pregnancies will be followed up until the outcome of the pregnancy is known, whenever possible, based upon due diligence taken to obtain the follow-up information.

7.6.1 Special situation reports

In addition to all AEs and pregnancy reports, the following Special Situations Reports should be collected and transmitted to Kazia Therapeutics even in the absence of an Adverse Event within thirty (30) calendar days:

- Data related to the Product usage during pregnancy or breastfeeding
- Data related to overdose, abuse, off-label use, misuse, inadvertent/erroneous administration, medication error or occupational exposure, with or without association with an AE/SAE unless otherwise specified in the protocol
- Data related to a suspected transmission of an infectious agent via a medicinal product (STIAMP)
- Lack of therapeutic efficacy

In addition, reasonable attempts should be made to obtain and submit the age or age group of the patient, to be able to identify potential safety signals specific to a particular population.

7.6.2 MedWatch 3500A Reporting Guidelines

In addition to completing appropriate patient demographic and suspect medication information, the report should include the following information within the Event Description (section 5) of the MedWatch 3500A form:

- Protocol description (and number, if assigned)
- Description of event, severity, treatment, and outcome if known
- Supportive laboratory results and diagnostics
- Investigator's assessment of the relationship of the adverse event to each investigational product and suspect medication

<u>Follow-up Information</u>

Additional information may be added to a previously submitted report by any of the following methods:

- Adding to the original MedWatch 3500A report and submitting it as follow-up
- Adding supplemental summary information and submitting it as follow-up with the original MedWatch 3500A form
- Summarizing new information and faxing it with a cover letter including patient identifiers (i.e. D.O.B. initial, patient number), protocol description and number, if assigned, brief adverse event description, and notation that additional or follow-up information is being submitted (The patient identifiers are important so that the new information is added to the correct initial report)

Occasionally Kazia Therapeutics may contact the reporter for additional information, clarification, or current status of the patient for whom an adverse event was reported. For questions regarding SAE reporting, you may contact the Kazia Therapeutics Drug Safety representative noted below or the MSL assigned to the study. Relevant follow-up information should be submitted to Kazia Therapeutics Drug Safety as soon as it becomes available and/or upon request.

MedWatch 3500A (Mandatory Reporting) form is available at
http://www.fda.gov/medwatch/getforms.html

For questions related to safety reporting, please contact Kazia Therapeutics Drug Safety:

Dr. John Friend
Chief Medical Officer
[redacted]

Dominic Capone
Program Director
[redacted]

7.7 Reporting to the Institutional Review Board (IRB)

The following adverse events must be reported to the DFCI IRB according to the expedited reporting guidelines:

- **CTCAE Grade 2 and Grade 3 Events** – that are *Unexpected* and there is a *Reasonable Possibility* that the *Adverse Event* is related to the study Intervention.
- **CTCAE Grade 4 Events –** Report all events that are *Unexpected*. Events that are *Expected* and listed within the protocol and/or current consent form do not need to be reported to the DFCI IRB. Please note, an event that presents at a higher severity than what is currently listed within the protocol and/or current consent as expected would be considered unexpected and reportable.
- **ALL CTCAE Grade 5 Events.**

Investigative sites within DF/HCC will report SAEs directly to the DFCI Office for Human Research Studies (OHRS) per the DFCI IRB reporting policy. For all events that meet the expedited reporting criteria, a full written adverse event report must be submitted to the DFCI IRB **within 10 working days** from notification of the event.

7.8 Expedited Reporting to the Food and Drug Administration (FDA)

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:

The Sponsor 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 paxalisib (GDC-0084). An unexpected adverse event is one that is not already described in the paxalisib (GDC-0084) Investigator Brochure. Such reports are to be telephoned or faxed to the FDA and Kazia

Therapeutics within 7 calendar days of first learning of the event.

The Sponsor will also 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 paxalisib (GDC-0084) or Trastuzumab. An unexpected adverse event is one that is not already described in the paxalisib (GDC-0084) or Trastuzumab 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, Kazia Therapeutics, and all participating investigators within 15 calendar days of first learning of the event. The FDA prefers these reports on a MedWatch 3500A form, but alternative formats are acceptable (e.g., summary letter).

[redacted]

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

Dr. John Friend
Chief Medical Officer
[redacted]

Dominic Capone
Program Director
[redacted]

7.9 Expedited Reporting to Hospital Risk Management

Participating investigators will report to their local Risk Management office any participant safety reports or sentinel events that require reporting according to institutional policy.
Immediate Reporting of Adverse Events and Events of Clinical Interest to Kazia Therapeutics.

7.10 Routine Adverse Event Reporting

All Grade 2 or higher Adverse Events **must** be reported in routine study data submissions to the Overall PI on the toxicity case report forms. **AEs reported through expedited processes (e.g., reported to the IRB, FDA, etc.) must <u>also</u> be reported in routine study data submissions.**

8. PHARMACEUTICAL INFORMATION

A list of the adverse events and potential risks associated with the investigational and other agents administered in this study can be found in Section 7.1.

8.1 Paxalisib (GDC-0084)

8.1.1 Description

Paxalisib (GDC-0084) is a potent and selective dual inhibitor of PI3K and mTOR that is being developed as an anti-cancer therapeutic agent. The chemical name is 5-(6,6-dimethyl-4-morpholino-8,9-dihydro-6H-[1,4]oxazino[3,4-e]purin-2-yl)pyrimidin-2-amine. The chemical formula $C_{18}H_{22}N_8O_2$. Molecular weight 382.42 g/mol.

8.1.2 Form

The paxalisib (GDC-0084) Drug Product is provided as GMP manufactured 15 mg capsules. The 15 mg capsules are size 0 and opaque white. Excipients used in the 15 mg capsule formulation are the following: microcrystalline cellulose, lactose monohydrate, croscarmellose sodium, and colloidal silicon dioxide. All excipients used in the formulation are of compendia grade (USP/NF and/or Ph Eur). The paxalisib (GDC-0084) Drug Product is a 15 mg capsule (opaque white size 0) intended for oral administration.

8.1.3 Storage and Stability

Paxalisib (GDC-0084) capsules should be stored at 15°C–30°C (59°F–86°F). Information on the shelf life of the capsules is provided on the label. Solid-state stability studies showed that paxalisib (GDC-0084) is very stable against heat and light. In solution, paxalisib (GDC-0084) is stable under heat conditions and slightly sensitive to oxidative conditions.

8.1.4 Compatibility

The drug will be delivered in compatible bottles.

8.1.5 Handling

Qualified personnel, familiar with procedures that minimize undue exposure to themselves and the environment, should undertake the preparation, handling, and safe disposal of the chemotherapeutic agent in a self-contained and protective environment.

Paxalisib (GDC-0084) is an agent that must be handled and administered with care. Participants should be instructed to keep their medication in the bottles provided and not transfer it to any other container. Due to possible unknown hazards associated with topical and environmental exposure to experimental agents, capsules must not be opened and/or emptied into any vehicle for oral ingestion; capsules must be swallowed intact.

8.1.6 Availability

Paxalisib (GDC-0084) is an investigational agent and will be supplied free of charge from Kazia Therapeutics as paxalisib (GDC-0084) 15mg capsules.

8.1.7 Preparation

Paxalisib (GDC-0084) will be provided in bottles containing 15 mg capsules.
Site personnel must ensure that participants clearly understand the directions for self-medication. Participants should be given a sufficient supply to last until their next study visit. Unused drug and/or empty bottles should be returned to the site at the next study visit. Unused returned medication MUST NOT be re-dispensed to patients.

8.1.8 Administration

Paxalisib (GDC-0084) will be administered orally by the patient once a day and will be swallowed whole (not chewed) with 240 mL (8 oz.) of water on an empty stomach (i.e., approximately 1 hour before or 2 hours after a meal), except on days when administration will be under fasted conditions (i.e., fast overnight for at least 8 hours before dosing and 2 hours after dosing).

8.1.9 Ordering

Orders for paxalisib (GDC-0084) 15mg capsules should be directed to Kazia Therapeutics. The study drug will ship from a US warehouse facility.

8.1.10 Accountability

The investigator, or a responsible party designated by the investigator, should maintain a careful record of the inventory and disposition of the agent using the NCI Drug Accountability Record Form (DARF) or another comparable drug accountability form. (See the NCI Investigator's Handbook for Procedures for Drug Accountability and Storage.)

8.1.11 Destruction and Return

Expired Paxalisib (GDC-0084) will be destroyed per institutional policies. At the end of the study, unused supplies of paxalisib (GDC-0084) should be destroyed according to institutional policies. Destruction will be documented in the Drug Accountability Record Form.

8.2 Trastuzumab

8.2.1 Description

Trastuzumab (Herceptin®) is a recombinant monoclonal antibody that binds specifically

and with high affinity to the extracellular domain of HER2. Trastuzumab has been shown to inhibit the proliferation of human tumor cells overexpressing HER2 both in vitro and in vivo. Commercial trastuzumab (or biosimilar) will be utilized in this study.

8.2.2 **Form, Storage and Stability**

Trastuzumab is supplied for use as a freeze-dried preparation at a nominal content of 150 mg per vial for parenteral administration (may vary upon commercial availability). The drug is formulated in histidine/histidine-HCl, α,α-trehalose dihydrate, and polysorbate 20.

Each 150 mg vial is reconstituted with 7.4 mL of Sterile Water for Injection (SWFI). The reconstituted solution contains 21 mg/mL trastuzumab and will be added to 250 ml of 0.9% Sodium Chloride Injection, USP. Use the Herceptin solution immediately following reconstitution with SWFI, as it contains no preservative. If not used immediately, store the reconstituted Herceptin solution for up to 24 hours at 2ºC-8ºC; discard any unused Herceptin after 24 hours.

8.2.3 **Compatibility**

No incompatibilities between trastuzumab and polyvinylchloride, polyolefin, or polypropylene bags have been observed. Dextrose 5% solution should not be used because it causes aggregation of the protein. Trastuzumab should not be mixed or diluted with other drugs.

8.2.4 **Handling**

Qualified personnel, familiar with procedures that minimize undue exposure to themselves and the environment, should undertake the preparation, handling, and safe disposal of the chemotherapeutic agent in a self-contained and protective environment.

8.2.5 **Availability**

Trastuzumab is commercially available and will not be provided in this study.

8.2.6 **Preparation**

Trastuzumab vials should not be used beyond the expiration date provided by the manufacturer. No preservative is used in the trastuzumab drug product; therefore, each vial is intended for single use only. Discard any unused portion of drug left in a vial. Vial contents should not be frozen or shaken and should be protected from direct sunlight.

8.2.7 **Dosage and Administration**

Trastuzumab will be administered at a loading dose of 8 mg/kg infused intravenously

over approximately 90 minutes, followed by standard dose of 6 mg/kg every 3 weeks, infused intravenously over approximately 30 to 90 minutes. If the patient has previously tolerated 30 minutes infusion, it may be given over approximately 30 minutes starting at cycle 2 day 1 without a subsequent observation period. If trastuzumab ≥ 6 mg/kg has been given within 4 weeks of study entry, then it does not need to be reloaded. If trastuzumab 2 mg/kg has been given within 2 weeks of study entry, then it does not need to be reloaded. In these cases, the first dose of trastuzumab on protocol may be infused over approximately 30 minutes if previously tolerated, and it may be given without a subsequent observation period.

The dose of trastuzumab will be based on the participant's actual body weight measured on C1D1. Alterations to trastuzumab dosing based on weight changes between cycles should be made based on local institutional standard operating procedures. Every 3-week doses may be administered ± 7 days (no less than 14 days apart) for scheduling, inclement weather, or vacation reasons. Participants should not receive more than three, every 3 weeks doses within a 5-week period of time.

8.2.8 **Ordering**

Trastuzumab is commercially available and in stock at the DFCI pharmacy.

8.2.9 **Accountability**

Commercial trastuzumab will be utilized and drug accountability will be performed per institutional guidelines.

8.2.10 **Destruction and Return**

Drug destruction and return will be performed per institutional guidelines.

9. BIOMARKER, CORRELATIVE, AND SPECIAL STUDIES

All participants will be asked to provide archival tumor tissue (both primary and metastatic tissue will be requested if available; either paraffin blocks or 15 unstained slides, ideally 4-micron thickness). However, if archival tissue is not available or not evaluable, this will not be a basis to exclude a participant from any portion of the trial or the planned analysis.

Participants will be asked to consent to optional research biopsies of extracranial metastases at baseline, while on-treatment (C2D1 +/- 7 days [C1D15-C2D8]), and at the time of progression.

Collection of CSF for correlative science is required on this trial unless the procedure is deemed to require general anesthesia, or there is specific contraindication (i.e. significant edema with concern for herniation; use of anticoagulants at therapeutic doses), in which case it will not be performed; CSF will be obtained per the schedule in Table 9-1. Investigators will use their best clinical judgement according to standard of care to evaluate for brain edema.

Serial blood draws for correlative science are required on this trial; blood draws will be obtained per the schedule in Table 9-1.

The Cohort A Safety Run-In cohort at 30mg will only be required to undergo research blood and archival tissue collections consistent with what is required with Cohort A. No CSF or fresh tissue collections will be presented as required or optional tests.

Table 9-1 Summary of Research Tissue and Blood Specimen Collection

Research Sampling	Time point	Contents
Blood	Pre-treatment	2 - Streck Tubes 1 – 10 mL purple top tube
	Day of surgery (Cohort B only)*	2 - Streck Tubes
	Cycle 2 Day 1	2 - Streck Tubes
	Cycle 3 Day 1	2 - Streck Tubes
	At progression or off protocol therapy	2 - Streck Tubes
Fresh Tissue	Pre-treatment (optional)	5-8 cores
	Day of surgery (Cohort B only)	Portion of surgical specimen
	Cycle 2 Day 1 +/- 7 days (optional)	5-8 cores
	At progression (optional)	5-8 cores
Archival Tissue	Any time	1 block or 15, 4-micron thick unstained slides
CSF	Screening	5 to 10 mL total, in Streck Tube
	Day of surgery (Cohort B only)*	5 to 10 mL total, in Streck Tube
	Cycle 2 Day 1 +/- 7 days (Cohort A only)	5 to 10 mL total, in Streck Tube
	At progression or off protocol therapy	5 to 10 mL total, in Streck Tube

* CSF and Blood Collections at the surgery visit may be performed within 1 day prior to surgery. Surgeries should take place C1D3-C1D9, but paxalisib (GDC-0084) should have been taken for two days prior to CSF and blood collection. The earliest CSF and blood collection may take place for this timepoint is on C1D3, which would make the earliest surgery date C1D4.

9.1 Archival Tissue Collection

1 block or 15, 4 microns thick unstained, charged slides will be collected for future research. Samples will be collected from both primary and metastatic sites if available. This tissue can be requested by the study team at any point during the trial.

9.2 Fresh Tissue Collection

9.2.1 Collection

Biopsies of extracranial disease are optional at baseline (pre-treatment) and at C2D1 (+/-7 days [C1D15-C2D8]) after start of protocol therapy. An additional optional biopsy may be collected at the time of progression. If a participant consents to an optional biopsy, but does not complete one for any reason, it is not considered a violation of the protocol. For cohort B only, a portion of the surgical specimen will be collected for research at the day of surgery (required).
For patients who undergo research biopsies of extracranial disease:

Ideally, 5-6 core biopsies will be obtained:

- Core 1: should be frozen in OCT
- Core 2: should be placed in RNAlater
- Core 3: should be frozen in OCT
- Cores 4-6: should be fixed in formalin for FFPE block

If additional cores are obtained, they should be processed as follows:

- Core 7: RNA later
- Core 8: should be fixed in formalin for FFPE block

Guidelines for biopsy from various metastatic sites can be found in Appendix K.

For patients who undergo brain metastases resection between C1D3 and C1D9:

- A portion of the surgical specimen will go for routine pathologic examination and diagnosis per standard of care
- A portion of the surgical specimen will be used for analysis under this protocol
    - This portion should be submitted as fresh tissue.

9.2.2 Handling and Shipping

9.2.2.1 After being obtained, processing of the biopsy cores is as follows:

- All samples should be de-identified and labeled with the Participant initials, Participant Study ID number and date of procedure.

- Cores in RNAlater and OCT should be brought to the DF/HCC Clinical Trial Core Laboratory at the address provided here:

Dana-Farber Cancer Institute
[redacted]

Please email the DF/HCC Clinical Trials Core Laboratory [redacted]) with participant name, study ID, date of collection, approximate time of collection, and study time point the day prior to collection. Any tissue remaining after study-specific protocol testing occurs will be banked in the DF/HCC Clinical Trial Core Laboratory and may be used for additional or future analyses as needed.

Cores in formalin should be fixed for the amount of time required by institutional guidelines and brought to the Standardized Histopathology Lab (SHL) at BWH for paraffin embedding. When complete, they will be stored by the current DFCI CRC.

9.2.2.2 After being obtained, brain metastases resection samples will be submitted in 2 portions:

1) A portion to the pathology department for routine pathologic examination and diagnosis per standard of care

2) A portion of fresh tissue will be collected for correlative studies and will be allocated to:

9.3 Blood Collection

9.3.1 Collection

Research blood collection is mandatory for all patients. The samples will be banked in the DF/HCC Clinical Trial Core Laboratory for these and future research purposes. These specimens will become the property of the DF/HCC.

The DF/HCC Clinical Trials Core Laboratory ([redacted]) should be notified for blood draws performed on Friday afternoons, which will be analyzed on the following Monday.

9.3.2 Handling and Shipping

All samples should be de-identified and labeled with the Participant initials, Participant Study ID number and date of collection and time point (e.g., “Baseline” or “Cycle 1” or “Progressive Disease”).

- **Purple top tubes**:
  Once the tube has been filled with blood, immediately invert the tube 8-10 times to mix and ensure adequate anticoagulation of the specimen. To avoid dilution with EDTA, it is recommended that the tubes contain no less than one-half of the tube volume.
  Tubes must be processed within 3-4 hours of being drawn at ambient temperature.

- **Streck tubes**:

  Fill the Streck tube completely and immediately mix by gentle inversion 8 to 10 times. Inadequate or delayed mixing may result in accurate results. Streck tubes will eventually be processed for plasma and frozen.

  Tube precautions:
  - DO NOT FREEZE OR REFRIGERATE TUBES as this could result in cfDNA breakage. Blood collected in the Streck tube can be stored for 14 days between 6-37 degrees Celsius.
  - Do not use tubes after expiration date.
  - Fill the tube completely; overfilling or underfilling of tubes will result in an incorrect blood-to-additive ratio and may lead to incorrect analytical results.

Blood in Purple top and Streck tubes should be brought to the DF/HCC Clinical Trials Core Laboratory (Dr. Deborah Dillon) in Smith 930 for processing/banking.

9.4 Cerebrospinal fluid (CSF)

9.4.1 Collection

CSF collection is required per protocol unless the procedure is deemed to require general anesthesia, or there is specific contraindication (i.e. significant edema with concern for herniation; use of anticoagulants at therapeutic doses), in which case it will not be performed. We plan to collect CSF at baseline for cytology and potential DNA isolation, the day of surgery (Cohort B only), Cycle 2 Day 1 +/- 7 days (Cohort A only) and at progression or off protocol therapy, whichever comes first. The samples will be banked in the DF/HCC Clinical Trials Core Laboratory for these and future research purposes. These specimens will become the property of the DF/HCC.

Streck Cell-Free DNA BCT tubes should be used to collect samples. After collection, gently invert tubes approximately 10 times to ensure proper mixing of stabilization agent and store at room temperature until processing.

9.4.2 Handling and Shipping

CSF tubes should be brought or shipped to the DF/HCC Clinical Trial Core Laboratory (Dr. Deborah Dillon) provided here:

Dana-Farber Cancer Institute

Please email the DF/HCC Clinical Trials Core Laboratory ( ) with participant name, study ID, date of collection, approximate time of collection, and study time point the day prior to collection.

Note: All liquid transfers should be performed in a sterile laminar flow hood.

1. Samples collected with Streck preservative can be processed within 24 hours.
2. Transfer CSF to a 15mL Falcon tube
3. Spin 15mL tubes containing CSF at 1900g for 10 minutes at room temperature with the brake reduced to 6
    a. A small pellet may be visible after the spin
    b. If also using sample for single cell analysis, reduce speed to 400-700g to pellet cells
4. Carefully remove tubes from centrifuge and transfer 6 mL CSF to a barcoded FluidX 10mL tube
    a. Transfer any additional CSF to a separate FluidX 10mL tube
    b. Note: If FluidX tubes are unavailable, store samples in well-labeled cryotubes
    c. If also using sample for single cell analysis, lyse red blood cells in pellet (after collecting supernatant) using 1X BD Pharm Lyse per the manufacturer's protocol and resuspend in RPMI

Store tube(s) at -80ºC until analysis

9.5 Planned Assays for Correlative Objectives

All the below-mentioned analyses may be altered based on novel developments in the field of cancer molecular and immune profiling at the time of correlative science. Additional markers or alternative technologies (based on scientific developments and/or novel technologies) may also be used, to explore potential prognostic or predictive candidate markers/panels or markers related to treatment benefit and/or safety, to improve diagnostic tests, or to understand breast cancer biology.

9.5.1 Biomarkers

We will conduct t-CyCIF for high-dimensional assessment of biomarker expression in archival and fresh tissue, including pAkt, pS6RP, p4EBP1, Ki-67 and cleaved caspase-3, and the immune microenvironment (a variety of 6 color panels will be assessed each incorporating pan-cytokeratin and DAPI [PD-L1, PD-L2, CD3, CD20; CD4, CD8, PD-1, FoxP3; CD4, CD8, TIM-

3, LAG3; CD33, CD11b, CD68, Granzyme B]) to quantitate cytotoxic and regulatory T cell populations, T cell activation, checkpoint expression and macrophage populations.

9.5.2 Akt/mTOR signature

We will correlate Akt/mTOR signatures with CNS ORR, PFS and OS.

9.5.3 Analysis of cell-free DNA

Blood will be collected at baseline, day of surgery (cohort B only), day 1 of cycles #2, #3, and at the time of progression or off treatment, whichever occurs first for evaluation of cell-free DNA (cfDNA). The cfDNA will be banked in the DF/HCC Clinical Trials Core laboratory for future research purposes. We will describe the trajectory of cfDNA tumor fraction (TFx) in plasma and CNS, correlations between baseline plasma and CSF cfDNA TFx with OS, and correlations between TFx trajectory and clinical outcomes. We will conduct correlations between baseline alterations in the PI3K pathway and in mutational load (as assessed in cfDNA) with CNS ORR, bi-compartmental PFS, and OS. Finally, copy number and mutational changes between baseline and time-of-progression plasma and CSF cfDNA will be evaluated.

9.5.4 Analysis of genomic sequence

We will explore whole exome sequencing (WES) from cfDNA to capture somatic changes over time. RNA sequencing (RNAseq) will be conducted from tissue samples to further characterize molecular changes in brain metastases and extracranial lesions.

9.6 Additional analysis

The above-mentioned analyses may be altered based on novel developments in the field of cancer molecular and immune profiling at the time of correlative science. Additional markers or alternative technologies (based on scientific developments and/or novel technologies) may also be used, to explore potential prognostic or predictive candidate markers/panels or markers related to treatment benefit and/or safety, to improve diagnostic tests, or to understand breast cancer biology.

10. STUDY CALENDAR

Screening evaluations are to be conducted within 28 days prior to start of protocol therapy unless otherwise specified. Screening assessments occurring within 8 days prior to initiating study treatment do not need to be repeated on Cycle 1 Day 1.

Screening laboratory assessments must be done within 8 days prior to initiating protocol therapy. For women of childbearing potential, as defined in the eligibility criteria, a pregnancy test must be completed within 8 days of initiating protocol therapy. If a urine pregnancy test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.

Baseline brain MRI (or head CT with IV contrast may only be performed if a patient has a contraindication to MRI with gadolinium contrast and only if it is determined that target lesions can be adequately assessed using this imaging modality) preferred to be done within 14 days but may be performed up to 28 days prior to start of protocol therapy.

If a participant's condition is deteriorating, laboratory evaluations should be repeated within 48 hours prior to initiation of the next cycle of therapy.

Assessments must be performed prior to administration of any study agent. Study assessments and agents should be administered within $\pm$ 3 days of the protocol-specified date, unless otherwise noted. Research biopsies, research blood collection, and CSF collection should be performed as indicated in the study calendar.

	Screening (Day -28 to C1D1)	C1D1	Surgery (Cohort B only)	C1D8	C1D15	C2D1	C3D1	Cycle 4+ Day 1	EOT[q]	Follow-Up
Informed Consent	X									
Medical History[a]	X									
Physical Exam, ECOG PS, Vital Signs[b,c]	X	X				X	X	X	X	
AE Evaluation	X	X				X	X	X	X	
Concurrent Medications	X	X				X	X	X	X	
Neurological Assessment	X	X				X	X	X	X	
Hematology Panel[d]	X	X				X	X	X	X	
Chemistry Panel[e]	X	X				X	X	X	X	
Fasting Glucose[e]	X	X		X	X	X	X	X	X	
Hemoglobin A1c	X								X	
Pregnancy Test[f]	X									
Single 12-lead EKG	X					X				
LVEF evaluations[g]	X						X	X		
Brain MRI[h]	X						X	X	X	X
CAP CT and/or MRI[i]	X						X	X	X	X
Research Blood[i]	X		X			X[s]	X		X	
Optional Research Biopsy[j]	X					X			X	
Resection / Surgical Tissue Collection[l]			X							
Research CSF collection[m]	X		X[m]			X[m, s]			X	
MDASI-BT, and EQ-5D questionnaires[n]	X						X	X	X	
NANO Scale[n]	X					X	X	X		
General Impression Worksheet[o]	X					X	X	X	X	
Archival Tissue Collection[p]	X									
Paxalisib (GDC-0084) Administration		X		----------X----------						
Trastuzumab Administration		X				X	X	X		
Survival Status[r]										X

a. Medical history includes clinically significant disease, surgeries, and cancer history (including prior cancer therapies and procedures).
b. A complete physical examination, including neurological examination, will be performed at screening. A limited physical exam, to include a neurological exam, will be performed at subsequent Day 1 visits.
c. Vital signs to include: heart rate, systolic and diastolic blood pressures while the patient is in a seated position, and respiratory rate. Vital signs and weight will be assessed before treatment on Day 1 of every 3-week cycle.
d. Hematology: hemoglobin, hematocrit, platelet count, RBC count, WBC count, percent and absolute differential count.
e. Chemistry: sodium, potassium, chloride, bicarbonate, glucose, BUN, creatinine, calcium, total bilirubin, total protein, albumin, ALT, AST, alkaline phosphatase. All glucose testing, whether ordered alone, or as part of a chemistry panel should be performed fasting (≥ 8 hours). If a participant has known diabetes mellitus, it is recommended that they closely monitor their blood sugar levels in between study visits and to notify a member of the study team if a glucose value of >300 mg/dL is observed. Any glucose monitoring occurring in between D1 visits may be performed locally to the patient and faxed to the treating team.
f. In female subjects of child-bearing potential as defined in the eligibility criteria, serum or urine pregnancy test must be performed within **8** days before the first dose of study medication.
g. All patients must have a baseline LVEF ≥ 50%. LVEF evaluations will be assessed at screening, on cycle 3 day 1 and cycle 5 day 1, followed by LVEF evaluation every 3 months during the treatment period. Measurements will be done by either ECHO or MUGA scan (ECHO preferred). The acceptable screening window for LVEF evaluation will be within 3 months before day 1 of study treatment. Patients with a history of LVEF < 50% should have left ventricular ejection fraction (LVEF) ≥ 50% by echocardiogram (echo) or multigated acquisition (MUGA) scan within 30 days before day 1 of study treatment
h. T-1 weighted perfusion MRI will be used. Screening MRI (or head CT with IV contrast may only be performed if a patient has a contraindication to MRI with gadolinium contrast and only if it is determined that target lesions can be adequately assessed) is preferred within 14 days but can be done up to 28 days of C1D1. Subsequent assessments should be performed approximately every 2 cycles (~6 weeks) for the first 4 cycles and then approximately every 3 cycles (~ 9 weeks). The window for these on treatment assessments is +/- 7 from the expected date. If treatment is delayed for any reason, the scans schedule can be adjusted to match the treatment schedule. If progression is suspected, an unscheduled assessment is permitted. For those taken off-study for reasons other than progressive disease in the CNS,

assessments should continue to be repeated every 6-12 weeks until progression or beginning a new cancer therapy regimen. It is understood that it may not always be feasible for patients to return for restaging evaluation after coming off protocol therapy; however, it strongly encouraged. Failure to complete CNS restaging after a patient has been taken off protocol therapy will not constitute a protocol violation.

i. CT and/or MRI should be of the chest, abdomen and pelvis. Additional imaging studies (CT neck, plain films, etc.) are permitted as clinically indicated. The same radiographic procedures and technique must be used throughout the study for each patient. Subsequent assessments should be performed approximately every 2 cycles (~6 weeks) for the first 4 cycles and then approximately every 3 cycles (~ 9 weeks). The window for these on treatment assessments is +/- 7 from the expected date. If treatment is delayed for any reason, the scans schedule can be adjusted to match the treatment schedule. For participants who have not progressed after 1 year on protocol therapy, re-evaluation can be performed approximately every 4 cycles (~2 weeks). For those taken off-treatment for reasons other than progressive disease, tumor measurements should continue to be repeated every 6-12 weeks until progression or beginning a new cancer therapy regimen. Failure to complete restaging after a patient has been taken off protocol therapy will not constitute a protocol violation.
j. For full details on research blood collection timepoints and tube requirements, please see section 9.0.
k. Optional research biopsies to occur at baseline, at C2D1 (+/- 7 days [C1D15-C2D8]) after start of protocol therapy, and at the time of progression. Participants for whom biopsies cannot be performed (e.g. inexistence of extracranial disease, inaccessible or safety concern) must be willing to submit an archival primary and/or metastatic specimen if available. If no archival specimen exists, such patients still eligible for the study. These optional biopsies will not be presented to participants treated at the 30mg dose of the Cohort A Safety Run-In. See Section 9.0 for more information.
l. Participants on Cohort B should plan to undergo this procedure after 2-8 doses of paxalisib (GDC-0084) (between C1D3 and C1D9). At the time of surgery for cohort B, a portion of the surgical specimen will be collected for research. Please see details in Section 9.0.
m. CSF collection will be performed at up to 3-time points per participants: baseline, day of surgery (for cohort B only, - 1 day window), Cycle 2 Day 1 +/- 7 days (Cohort A only) and at progression or off protocol therapy whichever comes first. CSF collection is required, unless the procedure is deemed to require general anesthesia or IV conscious sedation, or there is specific contraindication (i.e. significant edema with concern for herniation; use of anticoagulants at therapeutic doses), in which case it will not be performed. CSF collection is not required for participants treated at the 30mg dose of the Cohort A Safety Run-In. Please see details in Section 9.0
n. MDASI-BT (APPENDIX C) and EQ-5D (APPENDIX E or F) questionnaires will be completed at baseline or C1D1, on day 1 of cycles #3, #5, #9, and off study. NANO Scale (APPENDIX D) should be completed at baseline or C1D1 and day 1 of every cycle thereafter.
o. General Impression Worksheet to be completed at baseline and at the end of each 3-week cycle until participant comes off protocol therapy.
p. Archival tissue may be obtained at any point throughout the study.
q. Off-Treatment visit should occur within 30 days of the last dose of study treatment. Tumor assessments (including brain MRI and CAP CT/MRI do not need to be repeated if done within 28 days of off-treatment visit).
r. Participants will be followed for overall survival every 6 months or until death. This can be a visit to the clinic, medical record review, or a phone call to the patient.
s. Similar to the surgical visit, at least 2 days of paxalisib (GDC-0084) must be taken prior to having research CSF and research blood at the surgical timepoint. The surgical window is C1D3-C1D9. CSF and blood collection may take place up to 1 day prior to surgery. The earliest this may take place is C1D3 (with surgery happening no later than C1D4) and the latest is C1D8 (with surgery happening no later than C1D9). Performing an LP on the day of surgery may be complicated, which is why this window has been included.

11. MEASUREMENT OF EFFECT

In this study, response and progression in the CNS and in non-CNS sites will be evaluated and recorded separately in this trial. For the purposes of this study, participants should be re-evaluated for response every 2 cycles (~ 6 weeks) for the first 4 cycles (~ 24 weeks) and then every 3 cycles (~ 9 weeks) thereafter. For participants who have not progressed after 1 year on protocol therapy, re-evaluation can be performed every 4 cycles (~ 12 weeks). If there are any treatment delays, the scan schedule should also be delayed and continue to align with cycles of treatment.

11.1 Antitumor Effect – CNS disease

Tumor response and progression for CNS disease will be assessed centrally by the DF/HCC Tumor Imaging Metrics Core according to RANO-BM criteria. Please refer to the full publication for additional details.

11.1.1 Response Assessment in Neuro-Oncology-Brain Metastases (RANO-BM) Criteria

11.1.1.1 Definitions

- Definition of Measurable Disease: Measurable disease is defined as a contrast enhancing lesion that can be accurately measured in at least one dimension with a minimum size of 10 mm, visible on two or more axial slices that are preferably ≤ 5 mm apart with 0-mm skip (and ideally ≤ 1.5 mm apart with 0-mm skip). In

addition, although the longest diameter in the plane of measurement is to be recorded, the diameter perpendicular to the longest diameter in the plane of measurement should be at least 5 mm for the lesion to be considered measurable. In the event the MRI is performed with thicker slices, the size of the measurable lesion at baseline should be at least two times the slice thickness. If there are interslice gaps, this also needs to be considered in determining the minimum size of measurable lesions at baseline. Measurement of tumor around a cyst or surgical cavity represents a particularly difficult challenge. In general, such lesions should be considered non-measurable unless there is a nodular component measuring ≥ 10 mm in longest diameter and ≥ 5 mm in the perpendicular plane. The cystic or surgical cavity should not be measured in determining response (Figure 1 in the original publication).

- Definition of Non-measurable Disease: All other lesions, including lesions with longest dimension < 10 mm, lesions with borders that cannot be reproducibly measured, dural metastases, bony skull metastases, cystic-only lesions, and leptomeningeal disease.

11.1.1.2 Specifications of Methods of Measurement

- Method of Assessment: 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. It is important to use imaging techniques that are consistent across all imaging time points in order to ensure that the assessment of interval appearance or disappearance of lesions or of change in size is not affected by scan parameters such as slice thickness. Use of thin section imaging (for example, Appendix A of the original publication) is particularly important when evaluating lesions < 10 mm in LD and/or small changes in lesion size.
- Imaging Modality: Gadolinium-enhanced MRI is the best currently available, sensitive, and reproducible method to measure CNS lesions selected for response assessment. Suggested brain MRI specifications are detailed in Appendix A of the original publication. A sum of the diameters for all target lesions will be calculated and reported as the baseline sum of longest diameters (sum LD). All other CNS lesions should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required and these lesions should be followed as ‘present’, ‘absent’, or ‘unequivocal progression’.

11.1.1.3 Definition of Best Overall CNS Response

Best overall CNS response represents a composite of radiographic CNS target and non-target response (see definitions above), corticosteroid use, and clinical status. In non-randomized trials where CNS response is the primary endpoint, confirmation of PR or CR at least 4 weeks later is required to deem either one the best overall response. At each protocol-specified time point, a response assessment should occur and CNS assessments should be coincident with extra-CNS assessment. Table 1 shows the additional corticosteroid and clinical status requirements to deem a PR or CR.

11.1.1.4 Evaluation of Target Lesions

- **Complete response (CR):** Disappearance of all CNS target lesions sustained for at least 4 weeks; no new lesions; no corticosteroids; stable or improved clinically.
- **Partial response (PR):** At least a 30% decrease in the sum LD of CNS target lesions, taking as reference the baseline sum LD sustained for at least 4 weeks; no new lesions; stable to decreased corticosteroid dose; stable or improved clinically.
- **Progressive disease (PD):** At least a 20% increase in the sum LD of CNS 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 elative increase of 20%, at least one lesion must increase by an absolute value of ≥ 5 mm to be considered progression.
- **Stable disease (SD):** Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD while on study.

11.1.1.5 Evaluation of Non-Target Lesions

Non-target lesions should be assessed qualitatively at each of the time points specified in the protocol.

- **CR:** Requires all of the following: disappearance of all enhancing CNS non-target lesions, no new CNS lesions.
- **Non-CR/Non-PD:** Persistence of one or more non-target CNS lesion(s).
- **PD:** Any of the following: unequivocal progression of existing enhancing non-target CNS lesions, new lesion(s) (except while on immunotherapy-based treatment), or unequivocal progression of existing tumor-related non-enhancing (T2/FLAIR) CNS lesions. In the case of immunotherapy-based treatment, new lesions alone may not constitute progressive disease (see "Guidance in the case of new lesion(s) while on immunotherapy" below).

Special Notes on the Assessment of Target and Non-Target CNS Lesions:

a) *Target lesions that become too small to measure:* While on study, all CNS target lesions should have their actual measurement recorded, even when very small (e.g., 2 mm). If the lesion disappears, the value should be recorded as 0 mm. However, if the lesion is sufficiently small (but still present) that the radiologist does not feel comfortable assigning an exact measure, a default value of 5 mm should be recorded on the case report form.
b) *Lesions that coalesce on treatment*: As lesions coalesce, a plane between them may be maintained that would aid in obtaining maximum LD of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximum LD for the 'coalesced' lesion.
c) *Definition of new lesion(s):* The finding of a new CNS lesion should be unequivocal and not due to technique or slice variation. A new lesion is one that was not present on prior scans. If the MRI is obtained with ≤ 1.5 mm slice thickness, then the new lesion

should also be visible in axial, coronal, and sagittal reconstructions of ≤ 1.5 mm projections. If a new lesion is equivocal, for example because of its small size (i.e., ≤ 5 mm), continued therapy may be considered, and follow up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the initial scan showing the new lesion. In the case of immunotherapy, new lesions alone may not constitute progressive disease (see "Guidance in the case of new lesion(s) while on immunotherapy" below).

d) *Definition of Unequivocal Progression of Non-Target Lesion(s):* When the patient also has measurable disease, to achieve 'unequivocal progression' on the basis of non-target disease alone, there must be an overall level of substantial worsening in non-target disease such that, even in the presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. When the patient has only non-measurable disease, there must be an overall level of substantial worsening to merit discontinuation of therapy.

e) *Guidance in the Case of Uncertain Attribution of Radiographic Findings and/or Equivocal Cases:* If there is evidence of radiographic progression but there is clinical evidence supporting the possibility that the radiological changes are due to treatment effect (and not to progression of cancer), additional evidence is required to distinguish true progression versus treatment effect as standard MRI alone is not sufficient. Per protocol, the scan should be repeated at the next protocol scheduled evaluation or sooner, and generally within ~6 weeks. An investigator may choose a shorter time interval in the case of progressive symptoms or other clinically concerning findings. If there is continued increase in enhancement concerning for tumor growth, then this may be consistent with radiographic progression and the patient should be taken off study. If the lesion is stable or decreased in size, then this may be consistent with treatment effect and the patient may remain on study. For patients with equivocal results even on the next restaging scan, the scan may be repeated again at a subsequent protocol scheduled evaluation or sooner although surgery and/or use of an advanced imaging modality are strongly encouraged. Regardless of the additional testing obtained, if subsequent testing demonstrates that progression has occurred, the date of progression should be recorded as the date of the scan at which this issue was first raised. Patients may also have an equivocal finding on a scan (for example, a small lesion that is not clearly new). It is permissible to continue treatment until the next protocol scheduled evaluation. If the subsequent evaluation demonstrates that progression has indeed occurred, the date of progression should be recorded as the date of the initial scan where progression was suspected.

Notes Regarding Corticosteroid Use and Clinical Deterioration:

a) An increase in corticosteroid dose alone, in the absence of clinical deterioration related to tumor, will not be used as a sole determinant of progression. Patients with stable imaging studies whose corticosteroid dose was increased for reasons other than clinical deterioration related to tumor do not qualify for stable disease or progression. They should be observed closely. If their corticosteroid dose can be reduced back to baseline, they will be considered as having stable disease; if

further clinical deterioration related to tumor becomes apparent, they will be considered to have progression.

b) The definition of clinical deterioration is left to the discretion of the treating physician, but it is recommended that a decline in the KPS from 100 or 90 to 70 or less, a decline in KPS of at least 20 points from 80 or less, or a decline in KPS from any baseline to 50 or less, for at least 7 days, be considered neurologic deterioration unless attributable to comorbid events, treatment-related toxicity, or changes in corticosteroid dose.

Table 1

Summary of the Proposed RANO Response Criteria for CNS Metastases

Criterion	CR	PR	SD
Target lesions	None	≥30% decrease in sum LD relative to baseline	<30% d relative but<20 sum LD nadir
Non-target lesions	None	Stable or improved	Stable c
New lesion(s)**	None	None	None
Corticosteroids	None	Stable or decreased	Stable c

Abbreviations: CNS = central nervous system; CR = complete response; LD= longest dimension; NA = not applicable; PD = progressive disease; PR= partial response; RANO= Response Assessment in Neuro-Oncology; SD = stable disease.

*Progression occurs when this criterion is met.

**New lesion = new lesion not present on prior scans and visible in at least 2 projections. If a new lesion is equivocal, for example because of its small size, continued therapy may be considered, and follow up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the initial scan showing the new lesion. For immunotherapy-based approaches, new lesions alone to

do not define progression (See "Guidance in the Case of New Lesion(s) while on Immunotherapy").

[+]Increase in corticosteroids alone will not be taken into account in determining progression in the absence of persistent clinical deterioration.

11.2 Antitumor Effect – non-CNS disease

Response and progression in extracranial sites of metastases will be evaluated in this study using the international criteria proposed by the RECIST 1.1 criteria[2]. Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria.

11.2.1 RECIST 1.1 Definitions

Evaluable for Target Disease response. Only those participants who have measurable disease outside the field of radiation present at baseline, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for target disease response. These participants will have their response classified according to the definitions stated below. (Note: Participants who exhibit objective disease progression prior to the end of cycle 1 will also be considered evaluable.)

Evaluable Non-Target Disease Response. Participants who have lesions present at baseline that are evaluable but do not meet the definitions of measurable disease, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for non-target disease. The response assessment is based on the presence, absence, or unequivocal progression of the lesions.

11.2.2 Disease Parameters

Measurable disease. Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥ 20 mm by chest x-ray or ≥10 mm with CT scan, MRI, or calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Note: Tumor lesions that are situated in a previously irradiated area are not considered measurable.

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

Non-measurable disease. All other lesions (or sites of disease), including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10 to <15 mm short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease,

abdominal masses (not followed by CT or MRI), and cystic lesions are all considered non-measurable.

Note: Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.

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

Target lesions. All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as **target lesions** and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

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. 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.

11.2.3 Methods for Evaluation of Disease

All measurements should be taken and recorded in metric notation using a ruler, calipers, or a digital measurement tool. 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.

Clinical lesions. Clinical lesions will only be considered measurable when they are superficial (*e.g.*, skin nodules and palpable lymph nodes) and ≥10 mm in diameter as

assessed using calipers (*e.g.*, skin nodules). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

Chest x-ray. Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung; however, CT is preferable.

Conventional CT and MRI. This guideline has defined measurability of lesions on CT scan based on the assumption that CT thickness is 5mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size of a measurable lesion should be twice the slice thickness. 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. It is beyond the scope of the RECIST guidelines to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. 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.

FDG-PET. While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

(a) Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.

(b) No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.

(c) FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease-specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

Note: A 'positive' FDG-PET scan lesion means one which is FDG avid with an uptake greater than twice that of the surrounding tissue on the attenuation corrected image.

PET-CT. At present, 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. However, if the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT in accurately measuring cancer lesions over time. Note, however, that the PET portion of the CT introduces additional data which may bias an investigator if it is not routinely or serially performed.

Ultrasound. 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 data 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 from CT, MRI may be used instead of CT in selected instances.

Endoscopy, 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.

Tumor markers. Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a participant to be considered in complete clinical response. Specific guidelines for both CA-125 response (in recurrent ovarian cancer) and PSA response (in recurrent prostate cancer) have been published [*JNCI* 96:487-488, 2004; *J Clin Oncol* 17, 3461-3467, 1999; *J Clin Oncol* 26:1148-1159, 2008]. In addition, the Gynecologic Cancer Intergroup has developed CA-125 progression criteria which are to be integrated with objective tumor assessment for use in first-line trials in ovarian cancer [*JNCI* 92:1534-1535, 2000].

Cytology, Histology. These techniques can be used to differentiate between partial responses (PR) and complete responses (CR) in rare cases (*e.g.*, residual lesions in tumor types, such as germ cell tumors, where known residual benign tumors can remain).

The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.

11.2.4 Response Criteria

11.2.4.1 Evaluation of Target Lesions

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

Partial Response (PR): At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters.

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 lesions is also considered progressions).

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

11.2.4.2 Evaluation of Non-Target Lesions

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 short 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.

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

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 at a later time by the review panel (or Principal Investigator).

11.2.4.3 Evaluation of New Lesions

The finding of a new lesion should be unequivocal (i.e. not due to difference in

scanning technique, imaging modality, or findings thought to represent something other than tumor (for example, some 'new' bone lesions may be simply healing or flare of pre-existing lesions). However, a lesion identified on a follow-up scan in an anatomical location that was not scanned at baseline is considered new and will indicate PD. If a new lesion is equivocal (because of small size etc.), follow-up evaluation will clarify if it truly represents new disease and if PD is confirmed, progression should be declared using the date of the initial scan on which the lesion was discovered.

11.2.4.4 Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

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

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response when Confirmation is Required*
CR	CR	No	CR	4 wks Confirmation**
CR	Non-CR/Non-PD	No	PR	4 wks Confirmation**
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	no prior SD, PR or CR
Any	PD***	Yes or No	PD	
Any	Any	Yes	PD	

* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.
** Only for non-randomized trials with response as primary endpoint.
*** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

Note: Participants 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.

For Participants with Non-Measurable Disease (*i.e.*, Non-Target Disease)

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
Unequivocal 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		

11.2.5 Duration of Response

Duration of overall response: The duration of overall response is measured from the time measurement criteria are met for CR or 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, or death due to any cause. Participants without events reported are censored at the last disease evaluation).

Duration of overall complete response: The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that progressive disease is objectively documented, or death due to any cause. Participants without events reported are censored at the last disease evaluation.

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.

11.2.6 Clinical Benefit rate

Clinical benefit rate: defined as CR, PR and stable disease (SD) $\geq$ 24 weeks.

11.2.7 Progression-Free Survival

RANO-BM proposes evaluating of progression-free survival according to a bi-compartmental model, i.e. each compartment (CNS and non-CNS) is evaluated separately, CNS according to RANO-BM and non-CNS according to RECIST 1.1. Progression in either compartment is deemed an overall progression event and site of first progression (CNS or non-CNS) is captured as a unique data element in the CRFs.

RECIST 1.1 uses instead a summation approach. With RECIST 1.1, up to 2 target lesions per organ may be assessed and the longest dimension of all target lesions (i.e. CNS and non-CNS) are summed for evaluation of response and progression. As with RANO-BM, unequivocal worsening of target lesions in either CNS or non-CNS compartments also

constitutes a progression event. Unlike RANO-BM, RECIST 1.1 relies primarily on radiographic findings and does not include neurological status or corticosteroid use.

It is unknown what the correlation between RANO-BM and RECIST 1.1 is with respect to PFS and with respect to any relationships between PFS and OS. In this study, data will be collected prospectively to allow calculation of PFS according to both methods.

Overall Survival: Overall Survival (OS) is defined as the time from registration to death due to any cause or censored at date last known alive.

Progression-Free Survival: Progression-Free Survival (PFS) is defined as the time from registration to the earlier of progression or death due to any cause. Participants alive without disease progression are censored at date of last disease evaluation.

Time to Progression: Time to Progression (TTP) is defined as the time from registration to progression or censored at date of last disease evaluation for those without progression reported.

11.3 Antitumor Effect – Hematologic Tumors

N/A

11.4 Other Response Parameters

11.4.1 Patient-Reported Outcome Measure

The PRO outcome measure for this study is as follows: Scores from the MDASI-BT assessment (APPENDIX C).

11.4.2 Investigator-Assessed Neurological Evaluation

In order to standardize the evaluation of key neurological exam components, this study will use the Neurological Assessment in Neuro-Oncology (NANO) scale (APPENDIX D)[51]. The scale was developed by an international group of neuro-oncologists convened bi-weekly between June 2012 and July 2013 as an objective and quantifiable metric of neurologic function evaluable during a routine office examination that will integrate into the existing RANO criteria[1]. The NANO scale is intended to serve as a quick, oncology-friendly, quantifiable, evaluation of eight relevant neurologic domains based on direct examination by clinicians during routine office visits. The scale defines criteria for domain-specific and overall scores of response, progression and stable disease. In addition, a given domain is scored non-assessed if the clinician neglects to examine the domain or non-evaluable if the domain cannot be accurately assessed due to pre-existing conditions, co-morbid events, and/or concurrent medications.

11.4.3 EQ-5D evaluation

In order to evaluate the impact of the study treatment, on general health status assessed by EQ-5D questionnaire (APPENDIX E).

12. DATA REPORTING / REGULATORY REQUIREMENTS

Adverse event lists, guidelines, and instructions for AE reporting can be found in Section 7.0 (Adverse Events: List and Reporting Requirements).

12.1 Data Reporting

12.1.1 Method

The Office of Data Quality (ODQ) will collect, manage, and perform quality checks on the data for this study.

12.1.2 Responsibility for Data Submission

Investigative sites within DF/HCC or DF/PCC are responsible for submitting data and/or data forms to the Office of Data Quality (ODQ) in accordance with DF/HCC policies.

12.2 Data Safety Monitoring

The DF/HCC Data and Safety Monitoring Committee (DSMC) will review and monitor toxicity and accrual data from this study. The committee is composed of medical oncologists, research nurses, pharmacists and biostatisticians with direct experience in cancer clinical research. Information that raises any questions about participant safety will be addressed with the Overall PI and study team.

The DSMC will review each protocol up to four times a year with the frequency determined by the outcome of previous reviews. Information to be provided to the committee may include: up-to-date participant accrual; current dose level information; DLT information; all grade 2 or higher unexpected adverse events that have been reported; summary of all deaths occurring within 30 days of intervention for Phase I or II protocols; for gene therapy protocols, summary of all deaths while being treated and during active follow-up; any response information; audit results, and a summary provided by the study team. Other information (e.g. scans, laboratory values) will be provided upon request.

12.3 Multi-Center Guidelines

N/A

12.4 Reporting to the NCI

As a provision of funding from the NCI under the Dana-Farber Cancer Institute Breast Cancer SPORE, the NCI will be notified should there be any temporary or permanent suspension of the trial. This notification will be inclusive of any actions taken by the FDA, institutional IRB, institutional PI, or commercial sponsor. Additionally, any major changes in the scope or aims of the study that would affect the objectives of the funding grant will be communicated to the NCI.

12.5 Collaborative Research and Future Use of Data and Biospecimens

Tissue, blood, bodily fluids, and other materials derived from these will be collected in this study to analyze genes, DNA, RNA, proteins and cells for the study's correlative endpoints and potential future research, utilizing new types of biomarker testing as it becomes available.

These samples and any data generated as a part of these clinical trials may be used for future research studies and may be provided to collaborating investigators both within and outside of the DF/HCC for either correlative endpoints or secondary use. Samples and data may be shared with outside non-profit academic investigators, as well as with for-profit pharmaceutical investigators or commercial entities, with whom we collaborate. When samples or data are sent to collaborators and when any research is performed on them, all information will be identified with a code, and will not contain any PHI, such as name, birthday, or MRNs.

In order to allow the greatest amount of research to be performed on the specimens and information generated as a part of this trial, researchers in this study may share results of genetic sequencing with other scientists. De-identified specimen or genetic data may be placed into one or more publicly-accessible scientific databases, such as the National Institutes of Health's Database for Genotypes and Phenotypes (dbGaP). The results from the correlative research on this study will be shared with these public databases. Through such databases, researchers from around the world will have access to de-identified samples or data for future research. More detailed information, beyond the public database, may only be accessed by scientists at other research centers who have received special permission to review de-identified data.

12.6 Collaborative Agreements Language

Dana-Farber/Harvard Cancer Center (DF/HCC) follows the International Conference on Harmonisation Guidelines for Good Clinical Practice (ICH GCP) to the extent those guidelines reflect the regulations and guidance set forth by the Food and Drug Administration (FDA) regulations.

13. STATISTICAL CONSIDERATIONS

This is an open-label, single arm, phase II study designed to evaluate the efficacy of the combination of paxalisib (GDC-0084) with trastuzumab for the treatment of CNS metastases in patients with HER2-positive metastatic breast cancer, as measured by ORR in the CNS. Target enrollment is 47 patients. Subjects will be replaced if they register to the study, but do not start treatment. The proposed clinical trial will initially enroll a safety run-in cohort of 6 patients,

followed by two expansion cohorts: Cohort A: a single-arm, two-stage, phase II cohort; and Cohort B: a pre-surgical window cohort.

13.1 Study Design/Endpoints

Primary Endpoint: Cohort A
The primary endpoint is the confirmed ORR in the CNS according to response assessment in neuro-oncology-brain metastases (RANO-BM) criteria (Section 11). All participants treated at the RP2D will be included in the analysis of this endpoint.

Primary Endpoint: Cohort B
The primary endpoint is to evaluate the correlation between inhibition of p-4EBP1 in resected brain tumor tissue of human subjects, with the intracranial response in mouse bearing the corresponding patient-derived xenograft (PDX) models of BCBM and treated with paxalisib (GDC-0084) in combination with trastuzumab.

Secondary endpoints include:
All participants treated on Cohort B and at the RP2D of Cohort A will be assessed for: CBR at 18 and 24 weeks (Cohort A only), pharmacodynamic biomarkers associated with protocol therapy in resected brain tumor tissue (Cohort B only), safety, tolerability, DOR in CNS, PFS according to RANO-BM bi-compartment model, as well according to RECIST 1.1 single compartment model, objective extra-CNS response rates according to RECIST 1.1, site of first progression, OS, and investigator-assessed neurological evaluation, and EQ-5D evaluation.

Correlative science objectives include:

- To describe the landscape of somatic mutations and copy number alterations that occur in matched primary tumors, extracranial metastases, and brain metastases, and to trace clonal evolution over time.
- To explore whether the number and/or type of somatic mutations (e.g. PIK3CA, AKT1, etc), detected either in archival tumor specimens, fresh tumor specimens, plasma cfDNA, or CSF cfDNA are correlated with patient outcomes (PFS, CNS ORR, CBR, and OS).
- To explore whether tumor mutational burden is associated with patient outcomes (PFS, CNS ORR, CBR, and OS).
- To collect blood and CSF to study cell-free DNA for quantification of tumor DNA content, copy number variation, targeted sequencing, and/or whole exome sequencing.
- To explore whether cfDNA tumor fraction, derived from plasma or CSF, and assessed using ultra low pass whole genome sequencing (ULP-WGS), is associated with patient outcomes (PFS, CNS ORR, CBR, and OS).
- To characterize and compare mutations and copy number variation between cfDNA in blood and CSF versus tumor tissue specimens.
- To compare mutations, copy number variation, and tumor mutational burden between cfDNA in blood and CSF in baseline versus time-of-progression samples.
- To characterize changes in cfDNA tumor fraction in blood and CSF at baseline, on treatment and at time of progression.
- To explore whether cfDNA fraction in blood or CSF at baseline is associated with

clinical outcomes (PFS, CNS ORR, CRR, and OS).

13.2 Sample Size, Accrual Rate and Study Duration

Cohort A:

Lapatinib monotherapy produces a CNS ORR of 6% in pre-treated patients with HER2+ BCBM[52]. Anders et al conducted a phase 2 study testing trastuzumab, vinorelbine and the mTOR inhibitor RAD001 in patients with HER2+ BCBM, with a CNS ORR of 4%. Based upon these considerations, paxalisib (GDC-0084) will be considered of interest if the CNS ORR is 20%; the null hypothesis is that the CNS ORR is 5% or less. In the first stage, 12 patients will be enrolled at the RP2D. If there is at least 1 response, accrual will continue to the second stage where an additional 25 patients will be enrolled. If there are at least 4 responses among the 37 patients, the regimen will be considered worthy of further study. If the true ORR is 5%, the chance the regimen is declared worthy of further study is 9.3%; if the true ORR is 20%, the chance that the regimen is declared worthy of further study is 90.2%. The sample size was chosen to have 90% power with a Type I error no more than 10%. The duration of the study will be 36 months.

Cohort B:

For Cohort B, the primary endpoint is to correlate on-treatment p4EBP1 levels in the resected brain tumor tissue collected from patients to intracranial response to paxalisib (GDC-0084) trastuzumab and survival in the PDX model generated from the same patient. Correlation will be assessed using non-parametric Spearman rank coefficients. Under Gaussian assumptions, paired measurement from n=10 patients will provide 80% power to a correlation of 0.8 as significant using a two-sided alpha = 0.05.

We expect around 85% chance of success for the development of PDX models using brain metastases tissue resected from patients in Cohort B. The target enrollment for Cohort B is 10 participants. However, if a PDX model from a participant is unsuccessful, we will enroll up to two additional participants to Cohort B. We will not enroll more than 12 participants to Cohort B.

13.3 Stratification Factors

N/A

13.4 Interim Monitoring Plan

Accrual will be paused, and a formal monitoring of safety will be conducted when the first 6 patients treated on Cohort A have completed at least 1 cycle of treatment to determine if any toxicities requiring a dose de-escalation are observed. If >1 patient develops a dose-limiting toxicity (DLT) during cycle 1, a dose de-escalation to dose level -1 will be opened, and a safety pause will occur after 6 patients have completed at least 1 cycle of dose level -1. If >1 patient develops a DLT to dose level -1 during cycle 1, the study will be discontinued. Once the safety run-in has been completed, we will also begin enrollment into Cohort B (presurgical window). Because we expect that Cohort B will enroll more slowly than Cohort A, there is a chance that insufficient activity may be observed to proceed to the second stage of Cohort A at a time when

there are still available slots on Cohort B. If this occurs, Cohort B will also be closed to accrual.

Addendum: In April 2019 five participants were enrolled to the 45mg dose level (Dose Level 1) of the Cohort A Safety Run-In. Two DLTs were observed as defined as any toxicity that requires a dose reduction within the first cycle and the 6th patient was not enrolled due to safety concerns. A second safety run-in at 30mg (Dose Level -1) will now be explored to gain additional safety information with 1) more defined DLT definitions (section 5.5) and 2) additional safety monitoring and dosing guidance (section 6.0). Participants treated in this cohort will not be required to undergo fresh tissue collections or CSF collections. As per above, if > 1 patient develops a DLT during the first cycle, the trial will not continue. If all participants clear the DLT period, the PI and team will review the safety data and determine how the study will continue.

Update: Three patients have been enrolled to the Dose Level -1 cohort. The first patient (subject ID 006) had no DLTs. The second patient (subject ID 007) developed a grade 4 cytokine release syndrome / shock. The third patient (subject ID 008) developed grade 3 diarrhea. Subject 008 did not take any antidiarrheals when the diarrhea started, held drug for 4 days, and called the research nurse once the diarrhea was at grade 3. Subject 008 was instructed to take Imodium which improved the diarrhea quickly. The case was reviewed with the study PI and the decision was made to resume treatment at the same dose of 30 mg daily. Since then, subject 008 has taken paxalisib (GDC-0084) and Imodium and has not had any further issues with diarrhea. Given that it is impossible to know whether the diarrhea would have developed to grade 3 had the patient called earlier and started Imodium sooner, subject 008 is being replaced with an additional patient to accurately assess DLTs in this cohort. The quick improvement experienced with the use of Imodium, along with the decision to not reduce subject 008's dose, and the lack of further episodes of diarrhea after starting Imodium may suggest that the grade 3 diarrhea could have been prevented. This toxicity event led to the conclusion that the study team's definition of DLT does not contemplate assessment in the presence of maximum supportive care, nor the duration of the adverse event for the adverse event to be considered a DLT. Therefore, the definition of DLT has been amended.

13.5 Analysis of Primary Endpoints

The primary endpoint is ORR in the CNS, which will be assessed among all patients who initiated protocol therapy at the RP2D. CNS response will be assessed using RANO-BM criteria as defined in section 11.

Patients who initiate protocol therapy at the RP2D will be in included in the efficacy analysis population. In the efficacy analysis population, any patient without sufficient data to determine response (e.g., non-evaluable patients) will be classified as a non-responder. The estimate of the ORR with 90% Clopper-Pearson exact CI will be presented.

For Cohort B, the primary endpoint is to correlate on-treatment p4EBP1 levels in the resected brain tumor tissue collected from patients to intracranial response to paxalisib (GDC-0084) /trastuzumab and survival in the PDX model generated from the same patient. Correlation will be assessed using non-parametric Spearman rank coefficients. Under Gaussian assumptions, paired measurement from n = 10 patients will provide 80% power to a correlation of 0.8 as significant using a two-sided α of 0.05.

13.6 Analysis of Secondary Endpoints

Safety Endpoints

The safety population consists of all patients who took at least one dose of any protocol treatment and who have at least one post-baseline safety assessment. Toxicity will be graded according to NCI CTCAE, Version 5.0. Toxicities will be summarized by maximum grade. Incidence rate of each toxicity will be reported.

Efficacy Endpoints

Duration of response (DOR) will be evaluated among patients who had CR or PR. DOR is defined as the time from CR or PR achieved until renewed disease progression is detected in the CNS. DOR will be calculated per RANO-BM criteria, and descriptive statistics will be used to summarize the intervals observed.

Bi-compartmental PFS per RANO-BM criteria, single-compartmental PFS per RECIST 1.1 criteria, and OS will be also analyzed using Kaplan–Meier product-limit estimates and 90% confidence bands. PFS is defined as the time from first dose of paxalisib (GDC-0084) (day 1 cycle 1) to disease progression or death due to any cause, whichever occurred first. Patients alive without disease progression are censored at the date of last disease evaluation. OS is defined as the time from first dose of paxalisib (GDC-0084) (day 1 cycle 1) to death due to any cause. If death was not observed, patients will be censored at the date they were last known alive.

Extracranial ORR per RECIST 1.1 will be reported with 90% exact confidence intervals. For cohort A only, clinical benefit rate at 18 and 24 weeks is defined as CR, PR, SD, respectively, ≥ 18 and 24 weeks. Clinical benefit will be calculated using RANO-BM criteria. Clinical benefit rate will be reported respectively with 90% exact confidence intervals.

The sites of first progression (CNS vs. extracranial vs. both) will be tabulated respectively.

The M.D. Anderson Symptom Inventory-Brain Tumor (MDASI-BT) will be used to assess patient-reported outcomes. The MDASI-BT will assess 13 symptom items and 6 interference items from the core MDAST, as well as 9 symptoms specific to brain tumors. Scores of each item will be calculated following the MDASI-BT scoring guideline.

Patients' provider-rated neurological function will be assessed using the Neurological Assessment in Neuro-Oncology (NANO) scale. Scoring of the NANO scale will follow the NANO scale scoring guideline. The NANO scale should be administered by an M.D., D.O. nurse practitioner, or physicians' assistant (PA).

Global quality of life/health status will be assessed using the EQ-5D questionnaire.

Correlative endpoints

Among the patients who agree to undergo extracranial biopsy, we will describe the landscape of somatic mutations and copy number alterations that occur in matched primary tumors, extracranial metastases, and brain metastases, and will trace clonal evolution over time in a descriptive manner. We will explore whether the number and/or type of somatic mutations (e.g. PIK3CA, AKT1, etc), detected either in archival tumor specimens, fresh tumor specimens, plasma cfDNA, or CSF cfDNA are correlated with patient outcomes (PFS, CNS ORR, CBR, and OS).

We aim to assess cfDNA in the CSF for several purposes; 1) to evaluate the tumor fraction (TFx) using ultra low-pass whole genome sequencing (UL-WGS) and to explore whether baseline or on-study TFx correlates with clinical outcomes; 2) for those patients with CSF TFx $\geq$ 10%, to perform whole exome sequencing (WES) and to compare this with WES results from plasma cfDNA in the same patients; 3) to describe the trajectory of TFx at baseline, on-study, and time of progression; 4) to describe copy number, mutations, and mutational load at baseline and time of progression in the cfDNA derived from CSF.

To explore the relationship between correlative endpoints obtained from cerebrospinal fluid (CSF) to genetic alterations detected in the tumor and plasma, patient and disease characteristics, and clinical outcomes, the following analyses are planned: cell-free DNA (cfDNA) from serial CSF samples and plasma will be quantified using ultra-low pass whole genome sequencing, evaluated as both a continuous factor, and using the pre-defined threshold of TFx > 10% as a dichotomous variable; whole exome sequencing (WES) will be performed to determine copy number and mutation calls. We will describe and compare mutations, copy number variation, and tumor mutational burden between cfDNA in blood and CSF both at baseline, as well as in baseline versus time-of-progression samples.

For paired assessments of WES of circulating tumoral DNA in blood versus CSF at baseline and at time of progression, concordance will be assessed as the proportion of overall agreement using bootstrapped standard error estimates and confidence intervals, and kappa statistics to assess non-zero agreement. The following table shows the true Cohen's Kappa statistic there will be 80% power to detect given the prevalence of the phenotype, number of paired samples, and using a two-sided alpha = 0.05

Prevalence of phenotype	# of paired samples (blood and CSF)	True Cohen's kappa
20%	20	0.63
	30	0.53
	40	0.46
30%	20	0.61
	30	0.51
	40	0.44
40%	20	0.60
	30	0.50
	40	0.43

The association of baseline CSF and blood assessments to PFS and OS will be explored using Kaplan-Meier estimation and Cox proportional hazard models, and the association to ORR and CBR will be assessed using logistic models. Serial assessments will be characterized using descriptive statistics, and the association to clinical outcome will be modeled as post-baseline time-varying covariates (PFS and OS) and longitudinal mixed effects models (ORR and CBR). All analyses will be exploratory, and hypothesis generating and point estimates will be reported with 95% confidence intervals.

13.7 Reporting and Exclusions

13.7.1 Evaluation of Efficacy

For this Phase II trial, the efficacy evaluable population is a modified intent-to-treat (ITT) population. The modified ITT population consists of all patients who initiate protocol therapy, even if there are major protocol therapy deviations.

13.7.2 Evaluation of Safety

The safety population will be used in the safety data summaries. The safety population consists of all patients who took at least one dose of any protocol treatment and who have at least one post-baseline safety assessment. Note that a patient who had no adverse events constitutes a safety assessment. Patients who have received at least one dose of study drug but have no post-treatment safety data of any kind would be excluded.

14. PUBLICATION PLAN

The results should be made public within 24 months of reaching the end of the study. The end of the study is the time point at which the last data items are to be reported, or after the outcome data are sufficiently mature for analysis, as defined in the section on Sample Size, Accrual Rate and Study Duration. If a report is planned to be published in a peer-reviewed journal, then that initial release may be an abstract that meets the requirements of the International Committee of Medical Journal Editors. A full report of the outcomes should be made public no later than three (3) years after the end of the study.

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APPENDIX A PERFORMANCE STATUS CRITERIA

ECOG Performance Status Scale		**Karnofsky Performance Scale**	
Grade	Descriptions	Percent	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (*e.g.*, light housework, office work).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active work.
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.

APPENDIX B ANAPHYLAXIS PRECAUTIONS

EQUIPMENT NEEDED

- Monitoring devices: ECG monitor, blood pressure monitor, oxygen saturation monitor, and thermometer
- Oxygen
- Epinephrine for intravenous, intramuscular, and endotracheal administration in accordance with institutional guidelines
- Antihistamines
- Corticosteroids
- Intravenous infusion solutions, tubing, catheters, and tape

PROCEDURES

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

1. Stop the study treatment infusion.
2. Call for additional medical assistance.
3. Ensure that appropriate monitoring is in place, with continuous ECG and pulse oximetry monitoring, if possible.
4. Administer antihistamines, epinephrine, or other medications as required by participant status and as directed by the physician in charge.
5. Continue to observe the participant and document observations.
6. Draw serum/plasma samples for immunogenicity testing.

Ask participant to return for washout immunogenicity sample if appropriate.

APPENDIX C M.D. ANDERSON SYMPTOM INVENTORY-BRAIN TUMOR (MDASI-BT)

The MDASI-BT consists of 28 items and is a multi-symptom measure of cancer-related symptoms that are sensitive to disease and treatment changes. The MDASI-BT is composed of the symptom severity scale and the symptom interference scale. In the symptom severity scale, patients rate the severity of their symptoms in the last 24 hours on 0 − 10 numeric scales, ranging from “not present” to “as bad as you can imagine.” In the symptom interference scale, patients rate interference with daily activities caused by their symptoms on 0 − 10 numeric scales ranging from “did not interfere” to “interfered completely.” This instrument is brief, takes less than five minutes to complete, is easily understood and validated in the cancer population[53].

The English and Spanish versions of the MDASI-BT are below.

Date: _____ **Institution:** _____

Participant Initials: _____ **Hospital Chart #:** _____

Participant Number: _____

MD Anderson Symptom Inventory - Brain Tumor (MDASI - BT)

Part I. How **severe** are your symptoms?

People with cancer frequently have symptoms that are caused by their disease or by their treatment. We ask you to rate how severe the following symptoms have been ***in the last 24 hours.*** Please select a number from 0 (symptom has not been present) to 10 (the symptom was as bad as you can imagine it could be) for each item.

	Not Present 0	1	2	3	4	5	6	7	8	9	As Bad As You Can Imagine 10
1. Your **pain** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
2. Your **fatigue (tiredness)** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
3. Your **nausea** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
4. Your **disturbed sleep** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
5. Your feelings of being **distressed (upset)** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
6. Your **shortness of breath** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
7. Your problem with **remembering things** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
8. Your problem with **lack of appetite** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
9. Your feeling **drowsy (sleepy)** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
10. Your having a **dry mouth** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
11. Your feeling **sad** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
12. Your **vomiting** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
13. Your **numbness or tingling** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
14. Your **weakness** on one side of the body at its WORST?	○	○	○	○	○	○	○	○	○	○	○
15. Your difficulty **understanding** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
16. Your difficulty **speaking (finding the words)** at its WORST?	○	○	○	○	○	○	○	○	○	○	○

Date: _____ **Institution:** _____

Participant Initials: _____ **Hospital Chart #:** _____

Participant Number: _____

	Not Present 0	1	2	3	4	5	6	7	8	9	As Bad As You Can Imagine 10
17. Your **seizures** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
18. Your difficulty **concentrating** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
19. Your **vision** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
20. Your change in **appearance** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
21. Your change in **bowel pattern (diarrhea or constipation)** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
22. Your **irritability** at its WORST?	○	○	○	○	○	○	○	○	○	○	○

Part II. How have your symptoms **interfered** with your life?

Symptoms frequently interfere with how we feel and function. How much have your symptoms interfered with the following items ***in the last 24 hours***? Please select a number from 0 (symptoms have not interfered) to 10 (symptoms interfered completely) for each item.

	Did Not Interfere 0	1	2	3	4	5	6	7	8	9	Interfered Completely 10
23. **General activity?**	○	○	○	○	○	○	○	○	○	○	○
24. **Mood?**	○	○	○	○	○	○	○	○	○	○	○
25. **Work (including work around the house)?**	○	○	○	○	○	○	○	○	○	○	○
26. **Relations with other people?**	○	○	○	○	○	○	○	○	○	○	○
27. **Walking?**	○	○	○	○	○	○	○	○	○	○	○
28. **Enjoyment of life?**	○	○	○	○	○	○	○	○	○	○	○

Fecha: _____ **Institución:** _____

Iniciales del participante: _____ **Planilla del hospital N.º:** _____

Número del participante: _____

Cuestionario básico de síntomas M D Anderson (Tumor Cerebral) (MDASI-BT)

Parte I: ¿Qué tan **severos (graves)** son sus síntomas?

Las personas con cáncer frecuentemente tienen síntomas causados por la enfermedad o el tratamiento. Le pedimos que califique qué tan severos han sido los siguientes síntomas ***durante las últimas 24 horas***. Para cada pregunta, por favor, llene el círculo que represente qué tan severo fue el síntoma, teniendo en cuenta que 0 representa que el síntoma no estuvo presente y 10 significa que el síntoma fue el peor que pueda imaginar (marque un solo círculo).

	No Estuvo Presente										**El Peor Que Pueda Imaginar**
	0	1	2	3	4	5	6	7	8	9	10
1. ¿Su PEOR **dolor**?	○	○	○	○	○	○	○	○	○	○	○
2. ¿Su PEOR **fatiga (cansancio)**?	○	○	○	○	○	○	○	○	○	○	○
3. ¿Su PEOR **náusea**?	○	○	○	○	○	○	○	○	○	○	○
4. ¿Su PEOR **desvelo**?	○	○	○	○	○	○	○	○	○	○	○
5. ¿Su PEOR **sufrimiento emocional**?	○	○	○	○	○	○	○	○	○	○	○
6. ¿Su PEOR **falta de aire**?	○	○	○	○	○	○	○	○	○	○	○
7. ¿Su PEOR **dificultad para recordar** las cosas?	○	○	○	○	○	○	○	○	○	○	○
8. ¿Su PEOR **falta de apetito**?	○	○	○	○	○	○	○	○	○	○	○
9. ¿Su PEOR **somnolencia (adormilado)**?	○	○	○	○	○	○	○	○	○	○	○
10. ¿Su PEOR **sequedad bucal**?	○	○	○	○	○	○	○	○	○	○	○
11. ¿Su PEOR **tristeza**?	○	○	○	○	○	○	○	○	○	○	○
12. ¿Su peor **vómito**?	○	○	○	○	○	○	○	○	○	○	○
13. ¿Su PEOR **adormecimiento, entumecimiento,** u **hormigueo**?	○	○	○	○	○	○	○	○	○	○	○
14. ¿Su PEOR **debilidad** en un lado del cuerpo?	○	○	○	○	○	○	○	○	○	○	○
15. ¿Su PEOR **dificultad para comprender**?	○	○	○	○	○	○	○	○	○	○	○
16. ¿Su PEOR **dificultad para hablar (encontrar las palabras adecuadas)**?	○	○	○	○	○	○	○	○	○	○	○

Fecha: _____ **Institución:**_____

Iniciales del participante: _____ **Planilla del hospital N.º:**_____

Número del participante: _____

	No Estuvo Presente 0	1	2	3	4	5	6	7	8	9	El Peor Que Pueda Imaginar 10
17. ¿Sus PEORES **ataques o espasmos en su cuerpo**?	○	○	○	○	○	○	○	○	○	○	○
18. ¿Su PEOR **dificultad para concentrarse**?	○	○	○	○	○	○	○	○	○	○	○
19. ¿Su PEOR **dificultad para ver**?	○	○	○	○	○	○	○	○	○	○	○
20. ¿Su PEOR alteración en su **aspecto físico**?	○	○	○	○	○	○	○	○	○	○	○
21. ¿Su PEOR **(diarrea o estreñimiento)**?	○	○	○	○	○	○	○	○	○	○	○
22. ¿Su PEOR **irritabilidad**?	○	○	○	○	○	○	○	○	○	○	○

Parte II. ¿Cómo han **interferido (afectado)** sus síntomas con su estilo de vida?

Los síntomas frecuentemente interfieren con lo que sentimos y con lo que hacemos. ***En las últimas 24 horas***, ¿qué tanto han interferido sus síntomas con lo siguiente? Para cada pregunta, por favor seleccione un número del 0 (sus síntomas no han interferido) al 10 (sus síntomas han interferido completamente).

	No Han Interferido 0	1	2	3	4	5	6	7	8	9	Interfirieron Totalmente 10
23. **¿Actividad en general?**	○	○	○	○	○	○	○	○	○	○	○
24. **¿Estado de ánimo?**	○	○	○	○	○	○	○	○	○	○	○
25. **¿Trabajo normal (incluyendo los que haceres del hogar)?**	○	○	○	○	○	○	○	○	○	○	○
26. **¿Relaciones con otras personas?**	○	○	○	○	○	○	○	○	○	○	○
27. **¿Capacidad para caminar?**	○	○	○	○	○	○	○	○	○	○	○
28. **¿El poder disfrutar de la vida?**	○	○	○	○	○	○	○	○	○	○	○

APPENDIX D NANO SCALE

Neurologic Assessment in Neuro-Oncology (NANO) Scale

Scoring assessment is based on direct observation and testing performed during clinical evaluation and is not based on historical information or reported symptoms. Please check 1 answer per domain. Please check "Not assessed" if testing for that domain is not done. Please check "Not evaluable" if a given domain cannot be scored accurately due to pre-existing conditions, co-morbid events and/or concurrent medications.

Date Assessment Performed (day/month/year): _____
Study time point (i.e. baseline, cycle 1, day 1, etc):_____
Assessment performed by (please print name): _____

Domains	**Key Considerations**
Gait 0 ☐ Normal 1 ☐ Abnormal but walks without assistance 2 ☐ Abnormal and requires assistance (companion, cane, walker, etc.) 3 ☐ Unable to walk ☐ Not assessed ☐ Not evaluable	• Walking is ideally assessed by at least 10 steps
Strength 0 ☐ Normal 1 ☐ Movement present but decreased against resistance 2 ☐ Movement present but none against resistance 3 ☐ No movement ☐ Not assessed ☐ Not evaluable	• Test each limb separately • Recommend assess proximal (above knee or elbow) and distal (below knee or elbow) major muscle groups • Score should reflect worst performing area • Patients with baseline level 3 function in one major muscle group/limb can be scored based on assessment of other major muscle groups/limb
Ataxia (upper extremity) 0 ☐ Able to finger to nose touch without difficulty 1 ☐ Able to finger to nose touch but difficult 2 ☐ Unable to finger to nose touch ☐ Not assessed ☐ Not evaluable	• Non-evaluable if strength is compromised • Trunk/lower extremities assessed by gait domain • Particularly important for patients with brainstem and cerebellar tumors • Score based on best response of at least 3 attempts
Sensation 0 ☐ Normal 1 ☐ Decreased but aware of sensory modality 2 ☐ Unaware of sensory modality ☐ Not assessed ☐ Not evaluable	• Recommend evaluating major body areas separately (face, limbs and trunk) • Score should reflect worst performing area • Sensory modality includes but not limited to light touch, pinprick, temperature and proprioception • Patients with baseline level 2 function in one major body area can be scored based on assessment of other major body areas

Visual Fields

- 0 ☐ Normal
- 1 ☐ Inconsistent or equivocal partial hemianopsia (≥quadrantopsia)
- 2 ☐ Consistent or unequivocal partial hemianopsia (≥quadrantopsia)
- 3 ☐ Complete hemianopsia
- ☐ Not assessed
- ☐ Not evaluable

- Patients who require corrective lenses should be evaluated while wearing corrective lenses
- Each eye should be evaluated and score should reflect the worst performing eye

Facial Strength

- 0 ☐ Normal
- 1 ☐ Mild/moderate weakness
- 2 ☐ Severe facial weakness
- ☐ Not assessed
- ☐ Not evaluable

- Particularly important for brainstem tumors
- Weakness includes nasolabial fold flattening, asymmetric smile and difficulty elevating eyebrows

Language

- 0 ☐ Normal
- 1 ☐ Abnormal but easily conveys meaning to examiner
- 2 ☐ Abnormal and difficulty conveying meaning to examiner
- 3 ☐ Abnormal. If verbal, unable to convey meaning to examiner. OR non-verbal (mute/global aphasia)
- ☐ Not assessed
- ☐ Not evaluable

- Assess based on spoken speech. Non-verbal cues or writing should not be included.
- **Level 1**: Includes word finding difficulty; few paraphasic errors/neologisms/word substitutions; but able to form sentences (full/broken)
- **Level 2**: Includes inability to form sentences (<4 words per phrase/sentence); limited word output; fluent but "empty" speech.

Level of Consciousness

- 0 ☐ Normal
- 1 ☐ Drowsy (easily arousable)
- 2 ☐ Somnolent (difficult to arouse)
- 3 ☐ Unarousable/coma
- ☐ Not assessed
- ☐ Not evaluable

- None

Behavior

- 0 ☐ Normal
- 1 ☐ Mild/moderate alteration
- 2 ☐ Severe alteration
- ☐ Not assessed
- ☐ Not evaluable

- Particularly important for frontal lobe tumors
- Alteration includes but is not limited to apathy, disinhibition and confusion
- Consider subclinical seizures for significant alteration

NANO response criteria:

Definition of Neurologic Response: An overall NANO score will be determined following assessment of each domain and will include one of five possible outcomes: neurologic response; neurologic progression; neurologic stability; not assessed; and non-evaluable.

Neurologic response: ≥ 2 level improvement in at least 1 domain without worsening in other domains from baseline or best level of function.

Neurologic progression: 1) ≥ 2 level worsening from baseline or best level of function within ≥ 1 domain; or 2) worsening to the highest score within ≥ 1 domain.

Neurologic stability: a score of neurologic function that does not meet criteria for neurologic response, neurologic progression, non-evaluable or not assessed.

Non-evaluable (NE): if it is more likely than not that a factor other than underlying tumor activity contributed to an observed change in neurologic function. Such factors may include changes in concurrent medications or a co-morbid event.

Not assessed (NA): if the clinician omits evaluation of that particular domain during their examination. If a particular domain is marked NA at baseline, then that domain cannot be considered for progression or response.

In general, the assessment and scoring of all domains is encouraged.

APPENDIX E EQ-5D ENGLISH QUESTIONARIE

Health Questionnaire

English version for the USA

Under each heading, please check the ONE box that best describes your health TODAY.

MOBILITY

I have no problems walking ❑
I have slight problems walking ❑
I have moderate problems walking ❑
I have severe problems walking ❑
I am unable to walk ❑

SELF-CARE

I have no problems washing or dressing myself ❑
I have slight problems washing or dressing myself ❑
I have moderate problems washing or dressing myself ❑
I have severe problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑
I have slight problems doing my usual activities ❑
I have moderate problems doing my usual activities ❑
I have severe problems doing my usual activities ❑
I am unable to do my usual activities ❑

PAIN / DISCOMFORT

I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

I am not anxious or depressed	❑
I am slightly anxious or depressed	❑
I am moderately anxious or depressed	❑
I am severely anxious or depressed	❑
I am extremely anxious or depressed	❑

We would like to know how good or bad your health is TODAY.

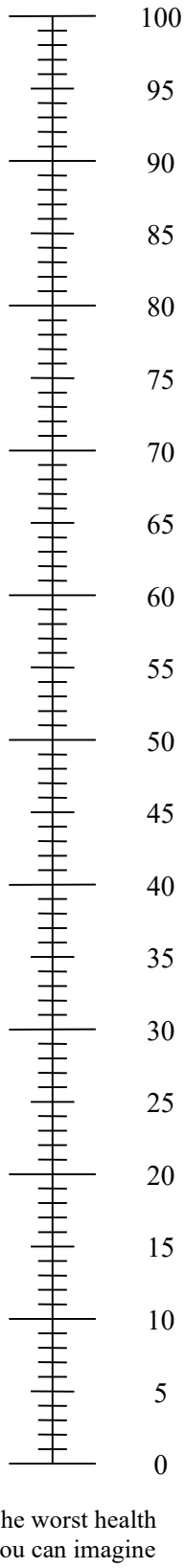
This scale is numbered from 0 to 100.

100 means the best health you can imagine.
0 means the worst health you can imagine.

Mark an X on the scale to indicate how your health is TODAY.

Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



APPENDIX F EQ-5D SPANISH QUESTIONARIE

Cuestionario de Salud

Versión en español para los EE. UU.

(Spanish version for the USA)

Debajo de cada encabezamiento, marque UNA casilla, la que mejor describe su salud HOY.

MOVILIDAD

No tengo problemas para caminar ❑
Tengo problemas leves para caminar ❑
Tengo problemas moderados para caminar ❑
Tengo problemas graves para caminar ❑
No puedo caminar ❑

CUIDADO PERSONAL

No tengo problemas para lavarme o vestirme solo/a ❑
Tengo problemas leves para lavarme o vestirme solo/a ❑
Tengo problemas moderados para lavarme o vestirme solo/a ❑
Tengo problemas graves para lavarme o vestirme solo/a ❑
No puedo lavarme o vestirme solo/a ❑

ACTIVIDADES DE TODOS LOS DÍAS *(Ej.: trabajar, estudiar, hacer las tareas domésticas, actividades familiares o actividades de ocio)*

No tengo problemas para realizar mis actividades de todos los días ❑
Tengo problemas leves para realizar mis actividades de todos los días ❑
Tengo problemas moderados para realizar mis actividades de todos los días ❑
Tengo problemas graves para realizar mis actividades de todos los días ❑
No puedo realizar mis actividades de todos los días ❑

DOLOR / MALESTAR

No tengo dolor ni malestar ❑
Tengo dolor o malestar leve ❑
Tengo dolor o malestar moderado ❑
Tengo dolor o malestar intenso ❑
Tengo dolor o malestar extremo ❑

ANSIEDAD / DEPRESIÓN

No estoy ansioso/a ni deprimido/a	❑
Estoy levemente ansioso/a o deprimido/a	❑
Estoy moderadamente ansioso/a o deprimido/a	❑
Estoy muy ansioso/a o deprimido/a	❑
Estoy extremadamente ansioso/a o deprimido/a	❑

Nos gustaría saber lo buena o mala que es su salud HOY.

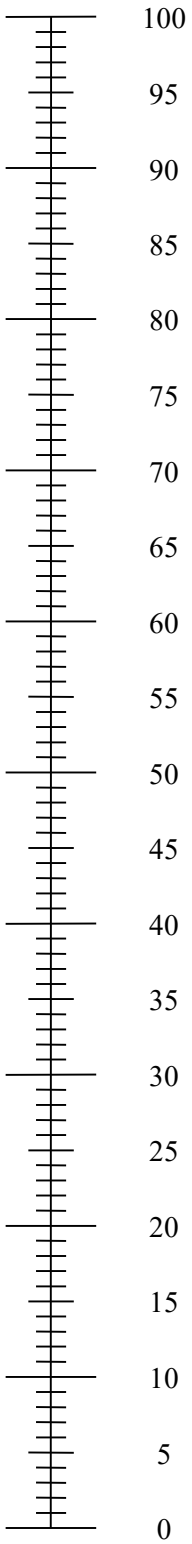
La escala está numerada de 0 a 100.

100 representa la mejor salud que se pueda imaginar.
0 representa la peor salud que se pueda imaginar.

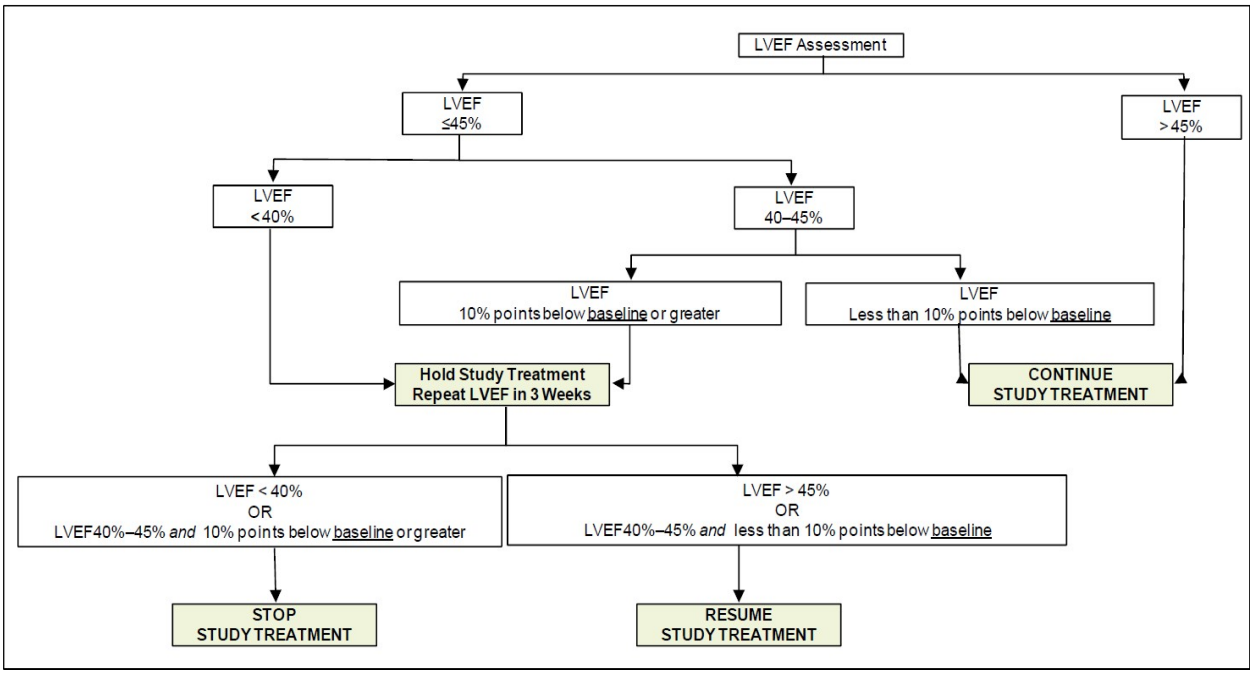
Por favor haga una X en la escala para indicar cuál es su estado de salud HOY.

Ahora, por favor escriba en la casilla que encontrará a continuación el número que ha marcado en la escala.

SU SALUD HOY = ☐



APPENDIX G ASYMPTOMATIC DECLINE IN LVEF: ALGORITHM FOR CONTINUATION AND DISCONTINUATION OF TRASTUZUMAB BASED ON LVEF ASSESSMENTS



APPENDIX H NEW YORK HEART ASSOCIATION CLASSIFICATION OF FUNCTIONAL CARDIAC CAPACITY

Class	
I	No limitation: Ordinary physical activity does not cause undue fatigue, dyspnea, or palpitation.
II	Slight limitation of physical activity: Such patients are comfortable at rest. Ordinary physical activity results in fatigue, palpitations, dyspnea, or angina.
III	Marked limitation of physical activity: Although patients are comfortable at rest, less than ordinary physical activity will lead to symptoms.
IV	Inability to carry on physical activity without discomfort: Symptoms of congestive heart failure are present even at rest. With any physical activity, increased discomfort is experienced.

From: Criteria Committee, New York Heart Association, Inc. Diseases of the heart and blood vessels. Nomenclature and criteria for diagnosis. 6th ed. Boston, Little, Brown and Co, 1964:114.

APPENDIX I LEFT VENTRICULAR SYSTOLIC DYSFUNCTION GRADING

NCI CTCAE Grade	Left Ventricular Systolic Dysfunction Severity
1 –	
2 –	
3	Symptomatic due to drop in ejection fraction responsive to intervention
4	Refractory or poorly controlled heart failure due to drop in ejection fraction; intervention such as ventricular assist device, intravenous vasopressor support, or heart transplant indicated
5	Death

NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events.
Note: Based on the most recent version of NCI CTCAE (v 5.0), which can be found at:
http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm
LVSD Definition: A disorder characterized by failure of the left ventricle to produce adequate output despite an increase in distending pressure and in end-diastolic volume. Clinical manifestations may include dyspnea, orthopnea, and other signs and symptoms of pulmonary congestion and edema.

APPENDIX J REPORTING CONVENTIONS FOR LEFT VENTRICULAR SYSTOLIC DYSFUNCTION/HEART FAILURE

Observation	How to Report	Term to be Reported	Grading
Asymptomatic decline in LVEF $<$10% points from baseline or tan an LVEF $\geq$45%	No additional reporting required, LVEF results to be reported on eCRF	N/A	N/A
Asymptomatic decline in LVEF $\geq$10% points from baseline or tan an LVEF $<$45%	AE (eCRF)	"Ejection fraction decreased" [a]	NCI CTCAE for "ejection fraction decreased"
Asymptomatic decline in LVEF requiring treatment or leading to discontinuation of pertuzumab and trastuzumab	AE (eCRF) and on-serious AESI (reported on an SAE form)	"Ejection fraction decreased" [a]	NCI CTCAE for "ejection fraction decreased"
Heart failure/CHF (symptomatic LVSD)	AE (eCRF) and SAE (SAE form)	"Heart failure"	NCI CTCAE for "heart failure" and NYHA Class

AE = adverse event; CHF = congestive heart failure; eCRF = electronic Case Report Form; LVEF = left ventricular ejection fraction; LVSD = left ventricular systolic dysfunction; N/A = not applicable; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; NYHA = New York Heart Association; SAE = serious adverse event.
Note: Any symptomatic LVSD event must be reported as "heart failure."
[a] Report the status "asymptomatic" and the LVEF value in the comments field as appropriate.

15. APPENDIX K GENERAL IMPRESSION WORKSHEET (TO BE COMPLETED AT BASELINE AND AT THE END OF EACH 3-WEEK CYCLE)

Patient_____Examiner_____Date_____

In the opinion of the treating physician, overall, has the patient had clinical deterioration since baseline?

( ) YES

( ) NO

In the opinion of the treating physician, overall, has the patient had clinical deterioration since his/her last visit

( ) YES

( ) NO

Is the patient currently taking corticosteroids?

( ) YES

( ) NO

If yes, please list name of medication and dose (e.g. decadron, 4 mg QD):
drug: _____
dose:_____
frequency:_____

Please indicate the patient's ECOG Performance Status (see Appendix A for definitions): _____

Please indicate the patient's Karnofsky Performance Status (see Appendix A for definitions): _____

APPENDIX L GUIDELINES FOR COLLECTING RESEARCH BIOPSY TISSUE

Tissue specimens will be collected from metastatic lesions using standard institutional procedures. The amount of tissue collected may follow the guidelines listed below:

Skin/chest wall: A goal of 2 4-mm punch biopsies will be obtained.

Lymph node: A goal of 3-6 core biopsy specimens will be obtained using an 18-gauge needle.

Liver: A goal of 3-6 core biopsy specimens will be obtained using an 18-gauge needle.

Lung: Because of the risk of pneumothorax associated with core needle biopsies of lung nodules, no core biopsies of lung nodules are mandated on this protocol, unless they are clinically indicated.

Bone: Because the yield of malignant tissue from bone biopsies tends to be relatively low, if a patient has another accessible site of disease (i.e. skin, lymph node, liver), that site should be biopsied preferentially. If bone is the only biopsy-accessible site, then a goal of 3-6 core biopsy specimens will be obtained using an 11-13 gauge needle.

Please note that the above are guidelines for the amount of tissue to be obtained, and are not meant to replace clinical judgment at the time the procedure is performed. Less than the goal quantity of tissue is accepted for each type of biopsy, and will be left to the clinical judgment of the physician performing the procedure.

Coded laboratory specimens will be stored in the Tumor Bank of the DFCI. These specimens will become the property of DFCI. Patients will be informed that their specimens may be used for research by investigators at DF/HCC and other approved collaborators. Shared specimens will be identified with a sample ID number; all patient identifying material will be removed.

Risks of Research Biopsy and Procedures for Minimizing Risk

Potential risks according to site are:
Skin/chest wall (punch biopsy):

- Likely: local discomfort and minor bleeding
- Less likely: moderate or major bleeding, or infection

Lymph node, liver, or bone (core needle biopsy):

- Likely: local discomfort and minor bleeding
- Less likely: moderate or major bleeding, need for blood transfusion, hospitalization due

to bleeding or other complications, infection, damage to adjacent organs. Additional risks may be present if intravenous conscious sedation is required

Breast (core biopsy):

- Likely: local discomfort and minor bleeding.
- Less likely: moderate or major bleeding, need for blood transfusion, hospitalization due

to bleeding or other complications, infection, pneumothorax, damage to adjacent organs.

Pleural fluid (thoracentesis):

- Likely: local discomfort and minor bleeding
- Less likely: moderate or major bleeding, need for blood transfusion, hospitalization due to bleeding or other complications, infection, pneumothorax, damage to adjacent organs

Ascites fluid (paracentesis):

- Likely: local discomfort and minor bleeding
- Less likely: moderate or major bleeding, need for blood transfusion, hospitalization due to bleeding or other complications, infection, bowel perforation or damage to adjacent organs. In order to minimize the risk of a biopsy, only qualified personnel will perform these procedures.

Prior to the procedure, the physician performing the procedure will discuss the risks with each study participant, answer any questions, and obtain separate procedure consent. Patients will be evaluated for comorbidities or concomitant medications that may increase the risk of potential complications. For biopsies of lesions that are not superficial and clearly palpable, imaging studies such as CT or ultrasound will be used to guide the biopsy in order to minimize the risk of damage to adjacent structures. After lymph node biopsies, patients will be observed after the procedure, or according to standard institutional guidelines. After liver biopsies, patients will be observed a minimum of 4 hours (range 4-6 hours) after the procedure, or according to standard institutional guidelines. Less than the goal quantity of tissue is accepted for each type of biopsy, and will be left to the clinical judgment of the physician performing the procedure.

Risks of Anesthesia

Local Anesthesia

All biopsy procedures require local anesthesia using lidocaine, xylocaine, or related compounds. There is a small risk of an allergic reaction associated with these drugs. In order to minimize the risk of local anesthesia, only qualified personnel will perform the biopsy procedure. Patients will be queried if they have had previous allergic reactions to local anesthetics.

Intravenous Conscious Sedation

Certain biopsy procedures, such as lymph node, liver, or bone biopsies, may require intravenous conscious sedation (IVCS). IVCS is a minimally depressed level of consciousness that retains the patient's ability to maintain a patent airway independently and continuously and respond appropriately to physical stimulation and verbal commands.
The risks of intravenous conscious sedation include: inhibition of the gag reflex and concomitant

risk of aspiration, cardiopulmonary complications (myocardial infarction, cardiac arrhythmias, hypoxemia), and allergic reactions to the sedative or analgesic medications. These risks are small but real; for example, in a prospective study of 14,149 patients undergoing IVCS during upper gastrointestinal endoscopies, the rate of immediate cardiopulmonary events was 2 in 1000[54]. The 30-day mortality was 1 per 2,000 cases. In this study, there was a strong association between lack of monitoring and use of high-dose benzodiazepines with adverse outcomes. There was also an association between the use of local anesthetic sprays to the oropharynx and the development of pneumonia. In order to minimize the risk of intravenous conscious sedation, only qualified personnel will be responsible for conscious sedation. A minimum of two individuals will be involved in the care of patients undergoing conscious sedation—the physician performing the biopsy procedure, and the individual (M.D. or R.N.) who monitors the patients and his/her response to both the sedation and the procedure, and who is capable of assisting with any supportive or resuscitative measures. The room where the procedure utilizing IVCS takes place will have adequate equipment to provide supplemental oxygen, monitor vital signs, and maintain an airway should this be necessary. An emergency cart will also be immediately accessible to the room where the procedure is to take place, and emergency support services will be available on page. Patients will be screened and evaluated for their fitness to undergo conscious sedation by a trained physician. Patients with active cardiac disease are excluded from this study. No local anesthetic spray to the oropharynx will be necessary, given that endoscopy is not a planned procedure. Following the procedure, patients will be observed closely in the recovery room for a minimum of 2 hours.

General Anesthesia

Because of the higher risk of general anesthesia compared with local anesthesia or intravenous conscious sedation, biopsies that would require general anesthesia in order to be performed *are not permitted* on this protocol.

For Biopsies of Soft Tissue, Liver, Bone, Breast, Etc.:

1. After biopsy is performed, the tissue mass is placed on a sterile gauze
2. Using forceps, separate the tumor tissue
3. Place 2 pieces (cores) of tumor tissue in each cassette (typically end up with 3 cassettes per biopsy); the last cassette will contain many small pieces of tumor tissue
4. Fill cassettes with OCT
    a. Completely cover tissue
    b. Limit the amount of bubbles
5. Place cassettes on dry ice and prepare for transport by limiting OCT leakage
6. Return samples to the lab and complete freezing of samples in OCT with dry ice (about 10 minutes freezing time)
7. Once samples are frozen, place in plastic bag; label bag with date, protocol number, patient number, and number of initials included
8. Store in –80C freezer

For Effusions and Ascites

1. Fluid sample should be split into two equal aliquots
2. One aliquot should be spun down into a pellet and snap frozen in an ETOH/dry ice bath or in liquid N2
3. One aliquot should be fixed and processed as a standard cell block.

Note: if the sample preparation is done by a clinical cytopathology laboratory, it is important to explain that the sample is for research purposes only and that no thin prep should be performed as this uses up a significant portion of the sample.

For Fine Needle Aspiration Samples

A goal of 3 passes:

1. One pass should be evacuated and rinsed directly into 2mL of room temperature Trizol for RNA analysis.
2. One pass should be evacuated and rinsed directly into 2mL of room temperature Trizol for DNA analysis.
3. One pass should be evacuated and rinsed directly into 10-20mL of RPMI to prepare a cell block.

APPENDIX M PROHIBITED STRONG INHIBITORS AND STRONG INDUCERS OF CYP3A4

Inhibitors:
indinavir
nelfinavir
ritonavir
clarithromycin
itraconazole1
ketoconazole
nefazodone
saquinavir
suboxone
telithromycin

Inducers:
efavirenz
nevirapine
barbiturates
modafinil