MD Anderson IND Sponsor Cover Sheet

Protocol ID	2020-0198
Protocol Title	Neratinib and Capmatinib combination (phase Ib/II) in metastatic breast cancer and inflammatory breast cancer patients with abnormal HER-family and c-Met pathway activity as measured by the CELsignia Signaling Analysis Test
Protocol Version	06
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Protocol PI	Rachel M. Layman
Department	Breast Medical Oncology
IND Sponsor	MD Anderson Cancer Center
IND #	159611

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STUDY NUMBER:	2020-0198
VERSION NUMBER:	06
TEST PRODUCTS:	Capmatinib and Neratinib
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SUPPORT PROVIDED BY:	Celcuity Novartis (study drug, capmatinib) Puma Biotechnology (study drug, neratinib)

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Study Synopsis

Title	Neratinib and Capmatinib combination (phase Ib/II) in metastatic breast cancer and inflammatory breast cancer patients with abnormal HER-family and c-Met pathway activity as measured by the CELsignia Signaling Analysis Test
Protocol No.	2020-0198
Phase	Ib/II
IND Number:	159611
IND Sponsor	MD Anderson Cancer Center
Primary Objectives	• Phase Ib: To determine maximum tolerated dose for use in the Phase II portion of the trial • Phase II: To determine overall response rate (ORR: CR+PR)
Secondary Objectives	• To further characterize the safety and tolerability of neratinib + capmatinib and of neratinib + capmatinib in combination with an aromatase inhibitor in ER+ MBC • To determine clinical benefit rate: (CBR: CR + PR + SD ≥ 24 weeks) • To determine the duration of response • To determine progression free survival (PFS) • To determine 2 years overall survival (OS)
Exploratory Objectives	• To determine the functional status of the HER2, c-Met, and EGFR pathways using the CELsignia test • To determine the ORR, CBR, DOR, PFS, and OS for the sub-group of patients with metastatic inflammatory breast cancer and for the sub-group of patients with metastatic non-inflammatory breast cancer • Assess response per molecular subtype, Hormone Receptor positive (ER and/or PR, HER2 negative) and Triple Negative Breast Cancer • Assess genomic profile of cancers treated on study to explore potential mechanisms of response and resistance.
Treatment Regimen	Neratinib PO once daily and Capmatinib PO twice daily (all patients). Aromatase inhibitor PO daily +/- ovarian suppression for patients with ER+ breast cancer.

Study Design	This is an open-label, phase Ib/II study of neratinib plus Capmatinib in patients with metastatic breast cancer and patients with metastatic IBC. **Phase 1b – Dose Escalation of Neratinib with Capmatinib** This phase of the study will employ the Bayesian optimal interval (BOIN) design with the 3+3 design run-in, to find the MTD. The BOIN design is implemented in a simple way similar to the traditional 3+3 design, but is more flexible and possesses superior operating characteristics that are comparable to those of the more complex model-based designs, such as the continual reassessment method (CRM). The maximum sample size for dose escalation is 18. Patients are treated in cohorts of 3, beginning with Neratinib PO dose level 1 (120 mg, Dose 1-7, 160 mg, through end of treatment, see Table 2) in combination with Capmatinib PO level 1 (400 mg, see Table 3), with a maximum of 12 patients per dose. The target toxicity rate for the maximum tolerable dose (MTD) is 25%. **Phase II** Phase II will be a prospective, open label, interventional study for patients with previously treated HER2-negative metastatic breast cancer or metastatic inflammatory breast cancer. Subjects receive Capmatinib in combination with Neratinib (including an AI for patients with ER+/HER2- breast cancer). The MTD determined during Phase 1b will be used. This portion of the trial will be conducted to assess the overall response rate (ORR) for patients treated at the MTD. The target ORR will be 25%, with unacceptable ORR as 5%. We assess the ORR using the Bayesian optimal phase 2 (BOP2) design (Zhou, Lee and Yuan, 2017). Up to an additional 29 evaluable subjects with measurable disease will be enrolled. An interim analysis will be performed when the number of enrolled patients reaches 15.
Number of Patients	Total: 47 patients
Number of Sites	1 site
Study Population	Phase 1b: previously treated HER2-positive and HER2-negative, ER-positive and ER-negative metastatic and inflammatory breast cancer patients. Phase II: previously treated HER2-negative, ER-positive and ER-negative metastatic and inflammatory breast cancer patients with abnormal HER-family and c-Met signaling tumors. The CELsignia Multi-Pathway (CELsignia MP) Test will characterize the subjects' HER-family and c-Met-driven signaling pathways as either hyperactive or normally active.

Study Endpoints	**Primary Endpoints:** • **Safety** The primary safety endpoint is to determine the safety, tolerability, and dose limiting toxicities (DLT) (Phase 1b) of the combination of Neratinib + Capmatinib in ER- MBC and of Neratinib + Capmatinib in combination with an aromatase inhibitor for ER+ MBC. • **Efficacy** For the Phase 2 portion of the study, the primary efficacy endpoint is overall response rate (ORR), defined as the rate of patients who achieved partial response or complete response as the best response. All tumor response will be evaluated by RECIST 1.1 and measured by QIAC system, via research collaboration. **Secondary Endpoint(s):** • **Clinical benefit rate (CBR)** Defined as the rate of patients who achieved complete response, partial response and stable disease for ≥ 24 weeks as the best response of treatment. • **Duration of response (DOR)** DOR is defined as the period measured from the date of the first occurrence of a CR or PR (whichever status is recorded first) until the first date that progressive disease or death is documented. Patients who have not progressed and who have not died by the date of data cutoff for analysis will be censored at the time of last tumor assessment date. If tumor assessments were performed after the date of the first occurrence of a CR or PR showed different response, DOR will be censored at the date of the first occurrence of a CR or PR plus remaining stable response from that time point. • **Progression free survival (PFS)** PFS is defined as the time between date of treatment start to the date of documented disease progression or death, whichever occurs first. Data from patients who have not experienced disease progression or death will be censored at the last tumor assessment date and known to be free of disease progression. Data from patients with no post-baseline tumor assessment will be censored at the treatment start date plus 1 day. • **2 year overall survival (OS)** 2 year OS definition: the proportion of patients in the study who are alive 2 years after enrollment on to the study **Exploratory Endpoints:** • For exploratory purposes, ORR, CBR, DOR, PFS, and OS will also be analyzed separately for the sub-group of IBC patients and for the sub-group of advanced or metastatic non-IBC breast cancer patients. • Assess response per molecular subtype, Hormone Receptor positive (ER and/or PR) and Triple Negative Breast Cancer • Assess genomic profile of cancers treated on study to explore potential mechanisms of response and resistance.

1.0 Background Information

1.1 Metastatic and Inflammatory Breast Cancer and Clinical Unmet Need

Targeting the HER family receptor tyrosine kinases (RTKs) with small molecule inhibitors or monoclonal antibodies has been a common therapeutic strategy against multiple cancers. In particular, over expression of HER2 in breast cancer has been targeted successfully by anti-HER2 agents like neratinib, trastuzumab, and pertuzumab (1-3). The use of these agents led to remarkable improvements in outcomes for patients with HER2 overexpressing breast cancer. However, HER2 overexpression as detected by IHC or FISH is limited to 15-20% of all breast cancers and to 40% of inflammatory breast cancer (IBC). Moreover, some clinical trials have also indicated a weak correlation between HER2 expression or amplification levels and HER2 targeted therapy benefit (4-5). In addition to HER2 expression and amplification, somatic mutations in HER2 have been identified in 1-4% of breast cancers, mostly in HER2 amplification-negative breast cancer (6). Bose et al. have shown that some of these HER2 mutations conferred resistance to the reversible HER2/EGFR TKI lapatinib, but were sensitive to the irreversible HER2/RGFR TKI neratinib when tested in breast cancer cell lines (7). They also examined the location of these mutations and found that majority of these mutations (68%) mapped to the kinase domain. Seven of the 13 HER2 somatic mutations they characterized were activating mutations that are likely true driver mutations. These findings by Bose and his colleagues indicate that breast tumors considered to be HER2-negative may still be "addicted" to HER2 signaling as a consequence of harboring HER2 activating mutations, and hence may be susceptible to select anti-HER2 agents.

Preclinical data have also shown that c-Met and other HER family signaling pathways also participate in extensive crosstalk that can drive cancer progression (8,9). c-Met is the cognate receptor for Hepatocyte Growth Factor (HGF). In breast cancer, c-Met and HGF overexpression correlates with poor outcomes (10). Lindemann et al reported c-Met overexpression in 25% of HER2-positive breast tumors, supporting the hypothesis that both HER2 and c-Met receptors could synergize in promoting tumor growth (11). Shattuck et al showed that c-Met contributes to trastuzumab resistance, and a subset of HER2-positive breast cancer patients may benefit from combined inhibition of both HER2 and MET (12).

Phase II trials with c-Met targeting therapeutics in combination with the HER1 (EGFR) inhibitor erlotinib showed promising results in progression-free survival (13). However, Phase III clinical trials in NSCLC using MET overexpression as an indicator for c-Met targeted therapy and trials enrolling unselected patients to receive combination c-Met/HER targeting treatment failed to demonstrate clinical efficacy (14). These disappointing results suggest that the current methodologies to identify patients likely to respond to these therapies are not effective. Hence an alternative approach may be to identify patients with dysfunctional c-Met signaling who may respond to existing therapies.

1.2 A need to develop a HER2 and c-Met Signaling Activity Test in the Clinic

To address this unmet need, Celcuity developed a functional cellular analysis diagnostic platform, 'CELsignia,' to measure real-time cell signal transduction activity in living tumor cells

of individual cancer patients (15,16). This approach overcomes the limitations of static genetic analyses of fixed cells by determining whether the dynamic signaling activity of certain known oncogenic pathways is normal or abnormal and can be inhibited by a matching targeted therapy. The CELsignia platform quantifies specific dynamic signal transduction activities in a patient's tumor cells.

To elucidate the role of HER-family signaling and the involvement of c-Met signaling as a cancer driver, the CELsignia Multi-Pathway (MP) test was developed using an impedance biosensor and live cells derived from each patient's tumor. The CELsignia MP test measures ex vivo real-time live cell response to specific HER-family and c-Met agonists to diagnose breast tumors with hyperactive HER1, HER2, HER3, HER4, and c-Met signaling activity. This functional assay is being utilized to select HER2-negative breast cancer patients with abnormal HER2-driven signaling activity in their tumor specimens for treatment with neoadjuvant HER2 therapies in two trials. These early stage breast cancer patients will be treated with HER2 inhibitors in combination with chemotherapy cycles followed by surgery and then assessed for pathological complete response (17,18).

To determine the prevalence of abnormal HER-family and c-Met signaling in HER2-negative breast cancer patients, the CELsignia MP test evaluated fresh tumor samples from 79 HER2-negative breast cancer patients (19). Of these, 19 of 79 samples had both hyperactive c-Met signaling and at least one hyperactive signaling HER-family receptor. Using 6 of these tumor samples, the IC50 values of multiple pan-HER inhibitors and c-Met inhibitors was determined along with the efficacy of the combinations of each pan-HER inhibitor with each c-Met inhibitor (20). The IC50 values for these inhibitors obtained using the CELsignia MP test were comparable to those derived using cell-free methods. In drug efficacy studies, every combination of pan-HER and c-Met inhibitors provided comparably high (at least 80%) of inhibitory activity effect ex vivo (22). These results suggest the sub-group of HER2-negative breast cancer patients diagnosed with coincident hyperactive c-Met and ErbB signaling by the CELsignia MP test may respond to a pan-HER and c-MET inhibitor combination. Chou and Talalay analyses using the CELsignia MP test were performed to characterize the linkage between c-MET and HER-family dysfunctional signaling in order to determine whether combined c-Met and pan-HER inhibitors would act additively, synergistically, or antagonistically. The analysis revealed that the mechanism of pan-HER inhibitors and c-MET inhibitors are not mutually exclusive and that this inhibitor combination is synergistic. The synergistic activity of these two classes of drugs suggests that the threshold drug concentrations for efficacy when the drug combination is used is less than what is required when these inhibitors are used as single agents. Thus, lower doses of these inhibitors can likely be used in combination than when used as single agents without affecting efficacy.

Hence, we propose a trial wherein we will identify HER2-negative advanced breast cancer and inflammatory breast cancer patients with hyperactive c-Met/HER-family activation in the tumor using the CELx MP test and treating them with a combination of neratinib, an irreversible tyrosine kinase inhibitor of the ErbB family of receptors (epidermal growth factor receptor (EGFR)/HER1, HER2, and HER4) and Capmatinib, a tyrosine kinase inhibitor of c-Met.

CELsignia Platform

Patient cancer cells are first isolated from tumor tissue using Celcuity's proprietary cell microenvironment technology. Dynamic cell signaling activity is then measured using these patient tumor cells with an impedance biosensor instrument. An impedance biosensor is an analytical platform that converts changes in cellular activity to a measurable electrical signal. This instrument measures dynamic changes in cell adhesion and morphology initiated by signal pathway activation or inhibition in live patient tumor cells.

To determine the activity of a specific signaling pathway, an activating agent specific to a pathway receptor is used to turn on the pathway and a corresponding inhibitory agent specific to the pathway receptor is used to turn signaling off. When signaling pathways are stimulated in this manner, adhesion molecules are affected and cause a change in the impedance measured in a well. By relying on the principle of detecting signaling pathway activity, tests can be developed for a range of disease types and targeted therapies that affect various cellular pathways.

CELsignia Multi-Pathway Signaling Activity Test

The CELsignia Multi-Pathway Test (MP) is a qualitative Laboratory Developed Test (LDT) that measures HER1/EGFR, HER2, HER3 and c-Met signaling activity in tumor cells obtained from patients previously diagnosed with HER2-negative breast cancer. Fresh tissue specimens obtained from a biopsy procedure are collected in a Celcuity provided specimen collection kit at the clinical site and then delivered directly to Celcuity's CLIA-certified and CAP-accredited laboratory where the test is performed, and the test report is issued.

The CELsignia MP Test incorporates the following steps:

1) Measures signaling driven by HER2 dimerization with HER1 and HER3 and by HER1, HER3, and c-Met homodimerization:

A. Contacts cells with HER3 ligand (NRG1), HER1 ligand (EGF), and c-Met ligand (HGF) to activate corresponding pathways.

B. Contacts cells with HER2 dimer-blocker

2) Quantifies amount of HER1, HER2, HER3, and c-Met signaling

3) Transforms quantitative result into a final qualitative result that characterizes the activity level of HER-family and c-Met signaling in the tested patient tumor cells as either normally active or hyperactive.

Celcuity has completed analytical validation studies in accordance with applicable FDA guidance and Clinical and Laboratory Standards Institute (CLSI) standards in its CLIA/CAP certified laboratory to characterize the performance of the CELsignia MP test. A summary of the results is below:

Table 1. Results of Analytical Validation Studies for CELsignia MP Test

Performance Characteristics	Results
Analytical Precision (Qualitative)	
Analytical Sensitivity (95% CI)	95.8% - 100% (88/88)
Analytical Specificity (95% CI)	95.8% - 100% (88/88)
Detection Limits	
Limit of Blank	0.0020 cell attachment units
Limit of Detection	0.0099 cell attachment units
Limit of Quantification	0.1000 cell attachment units
Cut-Off Characterization	
HER2	250 signaling units
c-Met	

1.3 Co-activation of ER and HER2 pathway and need of co-inhibit.

Preclinical and clinical data suggest the possibility that tumors can alternate between ER and HER2 as the dominant pathway, with targeted therapy against one pathway causing reactivation of the other growth factor pathways. For example, more than 20% of ER positive breast cancers activate HER2 pathways by many ways including ERBB2 mutation, amplification, or biological activation noted in both pre-clinical and clinical settings (20-22). While the data on whether the HER2 inhibition will re-activate the ER dependency of cancers may not be well established, enough accumulated data supports the additional inhibition of ER to the proposed combination of HER2 and c-MET inhibition. Therefore, we will add aromatase inhibitor therapy to the proposed study combination for patients with ER positive breast cancer in our study.

2.0 Scientific/Medical Rationale

For previously treated metastatic breast cancer or IBC patients, the prognosis is poor, which may be due to untreated dysregulated pathways, such as HER2 and c-Met. For HER2-negative breast cancer patients diagnosed with dysregulated HER-family and c-Met signaling by the CELsignia MP test, there is a strong scientific basis for treating these patients with neratinib and capmatinib, which are designed to inhibit this dysregulated signaling activity. Of note, metastatic IBC harbors the worst clinical prognosis compared to any other breast cancers. Moreover, once it becomes resistant to first line therapy – the response rate to second or above lines of therapy is poor (5-10% by history).

The primary study endpoints are the safety and efficacy of the combination of capmatinib and neratinib. Overall Response Rate (ORR) is the primary efficacy endpoint. This endpoint is typically used to assess the activity of a drug or drug combination when treating a patient population believed to have a disease mechanism corresponding to the therapy's mechanism of action.

2.1 Rationale for Open-Label Study

Once there is clear response rate observed here, we will further conduct confirmatory phase II or phase III studies. However, given the rarity of advanced breast cancer with HER2 activity while not called as HER2 positive, IBC, and their well-established poor outcomes, we believe a single arm phase II is sufficient to offer a clinical signal of this novel combination therapy that will possibly offer new options to patients who are in desperate need of better treatment.

2.2 Rationale to Combine the Neratinib and Capmatinib in IBC with HER2 and c-Met Pathway Activity

We believe that utilizing the CELsignia MP test to identify patients with hyperactive HER-family/c-MET signaling pathways can identify the cancer driver in HER2-negative breast cancer patients that traditional IHC methodology may not detect. The linkage between c-MET and HER-family dysfunctional signaling has been established both by Celcuity and other researchers and further analysis by Celcuity revealed that the mechanism of pan-HER inhibitors and c-MET inhibitors are not mutually exclusive and that this inhibitor combination is synergistic.

Furthermore, the synergistic activity of these two classes of drugs suggests that the threshold drug concentrations for efficacy when the drug combination is used is less than what is required when these inhibitors are used as single agents. Thus, lower doses of these inhibitors can likely be used in combination than when used as single agents without affecting efficacy, as is proposed here. Therefore, we propose a phase Ib/II trial to study the combination of Neratinib and Capmatinib in HER2-negative advanced recurrent or metastatic breast cancer and inflammatory breast cancer patients whose tumors have hyperactive HER-family and c-Met signaling activity as determined by the CELx MP Test.

3.0 Objectives

3.1 Primary objective

- Phase Ib: To determine maximum tolerated dose for use in the Phase II portion of the trial
- Phase II: To determine overall response rate (ORR: CR+PR)

3.2 Secondary objectives

- To further characterize the safety and tolerability of neratinib + capmatinib in ER- MBC and of neratinib + capmatinib with Aromatase Inhibitor in ER+ MBC
- To determine clinical benefit rate: (CBR: CR + PR + SD ≥ 24 weeks)
- To determine the duration of response
- To determine progression free survival (PFS)
- To determine 2 year overall survival (OS)

3.3 Exploratory Objectives

- To determine the functional status of the HER2, c-Met, and EGFR pathways using the CELsignia test

- To determine the ORR, CBR, DOR, PFS, and OS for the sub-group of patients with metastatic inflammatory breast cancer and for the sub-group of patients with metastatic non-inflammatory breast cancer
- Assess response per molecular subtype, Hormone Receptor (HR) positive (ER and/or PR), HER2 negative and Triple Negative Breast Cancer
- Assess genomic profile of cancers treated on study to explore potential mechanisms of response and resistance.

4.0 Study design

This is an open-label, phase Ib/II study of Neratinib plus Capmatinib in patients with metastatic breast cancer and metastatic IBC. In both phase Ib/II, patients with ER positive, breast cancer will also receive an aromatase inhibitor +/- ovarian suppression (for pre/peri menopausal patients).

4.1 Phase 1b – Dose Escalation of Neratinib with Capmatinib

This phase of the study will employ the Bayesian optimal interval (BOIN) design (Liu and Yuan, 2015 Yuan et al., 2016) (24, 25), with the 3+3 design run-in, to find the MTD. The BOIN design is implemented in a simple way similar to the traditional 3+3 design, but is more flexible and possesses superior operating characteristics that are comparable to those of the more complex model-based designs, such as the continual reassessment method (CRM) (Zhou et al., 2018) (26). The maximum sample size for dose escalation is 18. Patients are treated in cohorts of 3, beginning with Neratinib PO dose level 1 (120 mg, Dose 1-7 , 160 mg, through end of treatment, see Table 2) in combination with Capmatinib PO level 1 (400 mg, see Table 3), with a maximum of 12 patients per dose. The target toxicity rate for the maximum tolerable dose (MTD) is 25%.

This trial was designed and will be conducted using the shiny app "BOIN" (BOIN V2.6.3.0) available at http://www.trialdesign.org.. Further information about the design can be found in Section 13.

Table 2. Phase Ib Neratinib PO dose levels, in combination of Capmatinib PO.

Dose Level	1	2	3
Neratinib PO	120 mg, Dose 1-7 , 160 mg, through end	120 mg, Dose 1-7, 160 mg, Dose 8-14, 200 mg, through end	120 mg, Dose 1-7, 160 mg, Dose 8-14, 240 mg, through end
Capmatinib PO	400 mg b.i.d.	400 mg b.i.d.	400 mg b.i.d.

Table 3 : Fallback Dose levels.

	Dose level -1	Dose level -2
Neratinib PO	120 mg, Dose 1-7, 160 mg, through end	120 mg, Dose 1-7, through end
Capmatinib PO	300 mg b.i.d.	200 mg b.i.d.

Note: dose reduction should be based on the worst toxicity demonstrated at the last dose.
Dose reduction below 200 mg is not allowed

This protocol will be monitored by IND Office and safety data will be reviewed by IND Office after all subjects in a given cohort have completed the DLT assessement period (Cycle 1 and 2, total 56 days) and the dose level for next cohort will be determined based on the results.

Prior to advancing/changing dose levels, a cohort summary will be completed and submitted to the IND Medical Monitor for review and approval.

4.2 Phase II

Phase II will be a prospective, open label, interventional study with previously treated HER2-negative metastatic breast cancer and metastatic inflammatory breast cancer patients. Subjects receive capmatinib in combination with neratinib. The MTD determined during Phase 1b will be used.

This portion of the trial will be conducted to assess the overall response rate (ORR) for patients treated at the MTD. The target ORR will be 25%, with unacceptable ORR as 5%. We will assess the ORR using the Bayesian optimal phase 2 (BOP2) design (Zhou, Lee and Yuan, 2017).

Up to an additional 29 evaluable subjects with measurable disease will be enrolled. An interim analysis will be performed when the number of enrolled patients reaches 15.

The study Phase II portion safety and efficacy data will be monitored by the IND Office.

Treatment response will be evaluated per RECIST tumor response through QIAC.

4.3. Subject Population to be included:

In the Phase 1b portion of the study, previously treated HER2-positive and HER2-negative, HR-positive and HR-negative metastatic and inflammatory breast cancer patients will be enrolled.

In the Phase II portion of the study, previously treated HER2-negative, HR-positive and HR-negative metastatic and inflammatory breast cancer patients with abnormal HER-family and c-Met signaling tumors will be enrolled. The CELsignia Multi-Pathway (CELsignia MP) Test will characterize the subjects' HER-family and c-Met-driven signaling pathways as either hyperactive or normally active.

4.4 Number of Subjects per Study Group:

Phase Ib

This portion of the study will enroll a maximum of 18patients in the dose-finding trial including the possibility of adding up to 6 additional ER+ HER2 negative patients in a safety assessment of aromatase inhibitor treatment. The statistical considerations used to derive this sample size are presented in Section 13.1.

Phase II

This portion of the study will enroll a maximum of 29 patients. The statistical considerations used to derive this sample size are presented in Section 13.2.

Total accrual of this study will be up to 47 patients. We plan the enrollment for Phase Ib dose escalation to be 1-3 per 2 months since the DLT observation period is 2 months; and for Phase II to be 0-2 per month for each open site.

5.0 Study Endpoints

5.1 Primary Endpoints

- **Safety**

The primary safety endpoint is to determine the safety, tolerability, and dose limiting toxicities (DLT) (Phase 1b) of the combination of capmatinib and neratinib, and of neratinib + capmatinib in combination with an aromatase inhibitor in ER+ MBC.

- **Efficacy**

For the Phase 2 portion of the study, the primary efficacy endpoint is overall response rate (ORR), defined as the rate of patients who achieve partial response or complete response as the best response.

All tumor response will be evaluated by RECIST 1.1 and measured by QIAC system, via research collaboration.

5.2 Secondary Endpoint(s):

- **Clinical benefit rate (CBR)**

Defined as the rate of patients who achieved complete response, partial response and stable disease for ≥ 24 weeks as the best response of treatment.

- **Duration of response (DOR)**

DOR is defined as the period measured from the date of the first occurrence of a CR or PR (whichever status is recorded first) until the first date that progressive disease or death is documented. Patients who have not progressed and who have not died by the date of data cutoff for analysis will be censored at the time of last tumor assessment date. If tumor assessments performed after the date of the first occurrence of a CR or PR showed a different response, DOR will be censored at the date of the first occurrence of a CR or PR plus remaining stable response from that time point.

- **Progression free survival (PFS)**

PFS is defined as the time between date of treatment start to the date of documented disease progression or death, whichever occurs first. Data from patients who have not experienced disease progression or death will be censored at the last tumor assessment date known to be free of disease progression. Data from patients with no post-baseline tumor assessment will be censored at the treatment start date plus 1 day.

- **2 year overall survival (OS)**

2 year OS definition: the proportion of patients in the study who are alive 2 years after enrollment on to the study.

5.3 Exploratory Endpoints:

- For exploratory purposes, ORR, CBR, DOR, PFS, and OS will also be analyzed separately for the sub-group of IBC patients and for the sub-group of advanced or metastatic non-IBC breast cancer patients.
- Assess response per molecular subtype, Hormone Receptor positive (ER and/or PR), HER2 negative and Triple Negative Breast Cancer
- Assess genomic profile of cancers treated on study to explore potential mechanisms of response and resistance.

6.0 Eligibility Criteria

6.1 Inclusion Criteria

1. Signed Informed Consent Form (ICF) and comply with the requirements of the study protocol

2. Age ≥ 18 years.

3. ECOG performance status 0-1

4. Confirmed diagnosis of metastatic breast cancer or inflammatory breast cancer according to international consensus criteria[30]:

-Onset: Rapid onset of breast erythema, edema, and/or peau d'orange, and/or warm breast, with or without an underlying breast mass

-Duration: History of such findings no more than 6 months

-Extent: Erythema occupying at least 1/3 of whole breast

-Pathology: Pathologic confirmation of invasive carcinoma

5. Patients who have metastatic disease which is not amenable to curative treatment with available local and systemic therapy. Patients must have received at least 1 line or up to 6 lines of therapy in the metastatic setting with at least 2 weeks washout period before the initiation of study treatment.

i. Unless a contraindication to therapy exists, patients with ER+ breast cancer must have received prior endocrine therapy combined with a CDK4/6 inhibitor, patients with *BRCA1* or *BRCA2* mutations must have received prior PARP inhibitor, and patients with PD-L1+ triple negative breast cancer must have received prior immunotherapy.

ii. Patients with HER2-positive disease must have received at least 2 regimens of anti-HER2 therapy in metastatic setting.

6. For Phase Ib, any ER, PR, and HER2 status, For Phase 2, HER2-negative per ASCO/CAP guidelines and any ER and PR status.

7. For Phase II only, Patients with measurable disease according to the Response Evaluation Criteria in Solid Tumor (RECIST, v1.1) (local or distant) and at least one metastatic lesion amenable for biopsy (core or punch)

NOTE:

Measurable disease: Measurable lesions are defined as those that can be accurately measured in at least one-dimension (longest diameter to be recorded) as ≥ 20mm by chest X-ray, ≥ 10mm by computed tomography (CT) scan, ≥ 10mm with calipers by clinical exam.

Measurable malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15mm in short axis when assessed by CT scan.

Non-measurable disease: All other lesions (or sites of disease), including small lesions, are considered non-measurable. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis, cutis/pulmonitis, inflammatory breast disease, and abdominal masses [not followed by CT or magnetic resonance imaging (MRI)] are considered non-measurable.

8. Left Ventricular Ejection Fraction ≥ 50% measured by MUGA scan or Echocardiogram.

9. Abnormal HER-family and c-Met signaling activity based on CELsignia MP Test results (for phase II patients only).

10. Participants must have adequate organ function including the following laboratory values at the screening visit. Screening must occur within 28 days prior to the first dose of study drug. Screening samples for hematology and serum chemistries must be drawn within 14 days prior to the first dose of study drug:

- Absolute neutrophil count (ANC) ≥ 1.5 x 10^9/L without growth factor support
- Platelets (PLT) ≥ 75 x 10^9/L
- Hemoglobin (Hgb) ≥ 9 g/dL
- Calculated creatinine clearance (using Cockcroft-Gault formula) ≥ 45 mL/min
- Total bilirubin (TBIL) ≤ ULN (upper limit of normal) with the following exception: Patients with known Gilbert disease who have serum bilirubin level ≤ 3 x ULN may be enrolled.
- Aspartate transaminase (AST) ≤ 3 x ULN, except for participants with liver metastasis, who may only be included if AST ≤ 5 x ULN
- Alanine transaminase (ALT) ≤ 3 x ULN, except for participants with liver metastasis, who may only be included if ALT ≤ 5 x ULN
- Alkaline phosphatase (ALP) ≤ 5.0 x ULN

- Asymptomatic serum amylase ≤ grade 2. Participants with grade 1 or grade 2 serum amylase at the beginning of the study must be confirmed to have no signs and/or symptoms suggesting pancreatitis or pancreatic injury (e.g., elevated P-amylase, abnormal imaging findings of pancreas, etc.)
- Serum lipase ≤ ULN

11. Willing and able to comply with scheduled visits, treatment plan and laboratory tests. Patients who are cognitively impaired who may not be able to comply with the oral study medication schedule are excluded.

i) Patients with ER positive (defined at ER>/=10%)breast cancer, must start (or continue) an aromatase inhibitor of physician choice during the study duration. In addition, pre-/peri-menopausal women with ER+ breast cancer will also require ovarian suppression therapy.

12. Non-English speaking subjects are eligible as long as a translator is available at the treating site.

6.2 Exclusion Criteria

1. Concurrent anticancer therapy within 2 weeks of initiation of study treatment; except:

i. Endocrine therapy (SERM, aromatase inhibitor, fulvestrant, medical ovarian suppression therapy)

ii. Palliative radiotherapy for bone metastases < 1 week prior to study treatment

2. Unstable and symptomatic brain metastasis (Stable disease is defined as CNS radiographic study ≥ 4 weeks from completion of radiotherapy and ≥ 2 weeks from discontinuation of corticosteroids)

3. Non-hematologic adverse events from prior anticancer therapy that have not resolved to Grade ≤ 1 (CTCAE v 5.0), except for alopecia, vitiligo, pain, constipation if these symptoms existed during screening baseline.

i. Grade 3 or above neuropathy induced from prior treatment, that is not resolved to grade 2 or below despite best supportive care

4. Known clinically significant liver disease, including active viral, alcoholic, or other hepatitis; cirrhosis

5. Acute exacerbations of underlying condition within the last 12 months (requiring psoralen plus ultraviolet A radiation [PUVA], methotrexate, retinoids, biologic agents, oral calcineurin inhibitors; high potency or oral steroids)

6. Patients with known HIV infection. Testing for HIV is not required for study screening: 1) CD4+ count<350 cells/uL; or 2) had AIDS-defining opportunistic infections < 12 months

7. Known active hepatitis B (chronic or acute) or hepatitis C infection. Testing for hepatitis is not required for study screening:

i) Patients with past or resolved hepatitis B infection (defined as having a negative hepatitis B surface antigen [HbsAg] test and a NEGATIVE anti-HBc [antibody to hepatitis B core antigen] antibody test). Patient is eligible if anti-HBc is POSITIVE, but should sample for HBV DNA and referral to virologist to monitor for HBV reactivation

ii) Patients with positive for hepatitis C virus (HCV) antibody and have positive polymerase chain reaction (PCR) for HCV RNA.

8. Severe infections within 4 weeks prior to study treatment, including but not limited to hospitalization for complications of infection, bacteremia, or severe pneumonia

9. Signs or symptoms of infection within 2 weeks prior to study treatment per treating physician and PI judgement.

10. Concurrent oral or IV antibiotics within 5 days prior to study treatment

* Patients receiving prophylactic antibiotics (e.g., for prevention of a urinary tract infection or chronic obstructive pulmonary disease) are allowed and eligible so long as the antibiotic is not prohibited with the study medication (See Tables 8).

11. Major surgical procedure within 28 days prior to study treatment or anticipation of need for a major surgical procedure during the course of the study.

12. Presence or history of interstitial lung disease or interstitial pneumonitis, including clinically significant radiation pneumonitis (i.e., affecting activities of daily living or requiring therapeutic intervention).

13. Long QT syndrome, family history of idiopathic sudden death or congenital long QT syndrome.

14. Clinically significant, uncontrolled heart diseases.

- Unstable angina within 6 months prior to screening
- Myocardial infarction within 6 months prior to screening
- History of documented congestive heart failure (New York Heart Association functional classification III-IV)
- Uncontrolled hypertension defined by a Systolic Blood Pressure (SBP) ≥ 160 mm Hg and/or Diastolic Blood Pressure (DBP) ≥ 100 mm Hg, with or without antihypertensive medication. Initiation or adjustment of antihypertensive medication(s) is allowed prior to screening
- Ventricular arrhythmias
- Supraventricular and nodal arrhythmias not controlled with medication
- Other cardiac arrhythmia not controlled with medication
- QTcF (QT interval corrected by Fridericia's formula) ≥ 470 ms on the screening ECG (as mean of triplicate ECG)

15. Major surgery (e.g., intra-thoracic, intra-abdominal or intra-pelvic) within 4 weeks prior (2 weeks for resection of brain metastases) to starting study therapy or who have not recovered from side effects of such procedure.

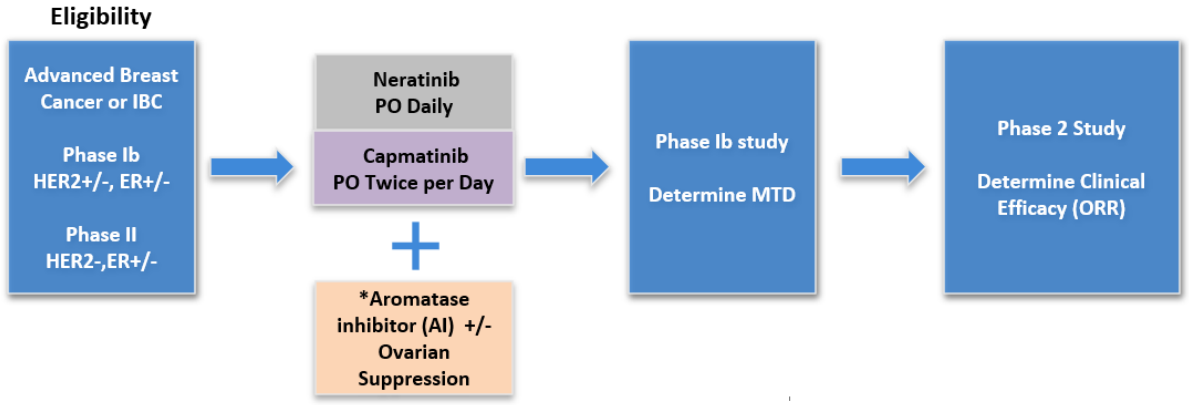
16. Unable to swallow or absorb study drugs due to impairment of GI function or GI disease e.g., ulcerative diseases, uncontrolled nausea, vomiting, diarrhea, or malabsorption syndrome
17. Participants receiving treatment with any enzyme-inducing anticonvulsant that cannot be discontinued at least 1 week before first dose of capmatinib, and for the duration of the study.
18. Other severe, acute, or chronic medical or psychotic conditions, substance abuse or laboratory abnormalities that in the opinion of the investigator may increase the risk associated with study participation, or that may interfere with the interpretation of study results.
19. Pregnant or nursing (lactating) women
20. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception during dosing and for one month after stopping treatment. Highly effective contraception methods include:
    - Total abstinence (when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception
    - Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy) total hysterectomy, or tubal ligation at least six weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment
    - Male sterilization (at least 6 months prior to screening). For female subjects on the study, the vasectomized male partner should be the sole partner for that subject
    - Use of injected or implanted hormonal methods of contraception or placement of an intrauterine device (IUD) or intrauterine system (IUS), or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception. Women are considered post-menopausal and not of childbearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g., age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy) or tubal ligation at least six weeks before study entry. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of child-bearing potential.
21. Sexually active males will not be eligible unless they use a condom during intercourse while taking drug and for 3 months after stopping treatment and should not father a child in this period. A condom is required for all sexually active male to prevent them from fathering a child AND to prevent delivery of study treatment via seminal fluid to partner. In addition, male participants must not donate sperm for the time period specified above.
22. Participants receiving treatment with the following medications that cannot be discontinued at least 1 week prior to the start of treatment with study therapy and for the duration of the study:
    a. strong inducers of CYP3A

b. moderate inducer of CYP3A4
c. strong CYP3A4 inhibitor
d. concomitant use of a moderate CYP3A4 and P-gp dual inhibitor (verapamil).
e. proton pump inhibitor. Neratinib may be taken at least 2 hours before or 10 hours after an H2-receptor antagonist, and 3 hours after antacids.
f. P-gp substrates (such as digoxin, dabigatran, fexofenadine) or strong P-gp inducers (such as carbamazepine, phenytoin, rifampicin, and St. John's wort).
g. Chronic immunosuppressive therapies including systemic corticosteroids. Steroids given for physiological replacement, as anti-emetics or inhaled as well as short course of oral/topical steroids given for allergic reactions or asthma flares are allowed.

23. No prior treatment with Capmatinib, Neratinib, or other HER2 directed tyrosine kinase inhibitor (for phase II patients only).

7.0 Study Procedures

7.1 Schema



***All patients with ER + breast cancer will start taking (or continue if they were already on) an aromatase inhibitor. Pre/peri-menopausal patients with ER + breast cancer will also receive ovarian suppression. The treating physician will choose the AI and ovarian suppression the patient will receive during the study duration.**

Figure 1. Study Schema

7.2 Dosing level and Drug Administration

All participants will receive two drugs (neratinib and capmatinib) during the study as scheduled per Schema. Capmatinib and neratinib will be provided by Novartis and Puma respectively, and not billed to the patient. Additionally, patients with ER+ breast cancer will receive endocrine therapy (AI +/- ovarian suppression). Endocrine therapy is standard of care (SOC), not provided by the study.

The Phase Ib portion of the trial will determine the Maximum Tolerated Dose (MTD) from the combination of dosing levels listed in Tables 2 and 3, starting at Dose Level (1,1) (capmatinib PO 400 mg twice per day and neratinib PO 120 mg on days 1-7, then 160 mg through end of treatment). The maximum accrual for phase Ib is 18 patients (including the possibility of adding up to 6 additional ER+/HER2 negative patients in a safety assessment of aromatase inhibitor treatment).

The Phase II portion of the trial will enroll 29 patients treated at the MTD determined from the phase Ib portion of the study.

Total accrual of this study will be up to 47 patients

Both drugs are oral agents and each study cycle will be 28 days.

Patient will take study drugs by mouth with or without food per cohort dosing. Neratinib will be taken once daily with food. Capmatinib will be taken twice daily about 12 hours apart (+/-2 hours)with or without food. Patients will have a medication diary to record daily study drug intake information for each cycle. The study manager will collect it at each clinic visit as source document.

Neratinib

Nertatinib will be supplied as 40 mg tablets, equivalent to 48.31 mg neratinib maleate. Tablets are film-coated, red, oval shaped and debossed with 'W104' on one side and plain on the other side. 3 – 6 tablets daily will be prescribed based on patient's dose level. Tablets should be swallowed whole (tablets should not be chewed, crushed, or split prior to swallowing).

If a patient misses a dose, it should not be replaced, and the patient should be instructed to resume neratinib with the next scheduled daily dose.

Neratininb should be stored at controlled room temperature, 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F).

Capmatinib

Capmatinib will be supplied at 200 mg and 150 mg tablets. Capmatinib should be taken twice daily with or without food. Tablets should be swallowed whole. Do not break, crush or chew the tablets.

If a patient misses or vomits a dose, instruct the patient not to make up the dose, but to take the next dose at its scheduled time.

Capmatinib should be stored at 20 – 25ºC (68 – 77ºF), excursions permitted between 15ºC and 30ºC (59 - 86ºF). Protect from moisture.

Endocrine Therapy (for patients with ER+ breast cancer in Phase 1b and Phase II)

Patients with ER+ (defined at ER ≥10%)breast cancer will receive (start or continue) continuous aromatase inhibitor therapy by mouth dosed once daily. The aromatase inhibitor drug administered will be of physician's choice during the study duration. For pre-/peri-menopausal

women with ER+ breast cancer, ovarian suppression therapy of physician's choice will also be administered.

7.3 General Treatment Guidelines

If a toxicity is attributed to one of the study drugs, it may be held and the other drug(s) will still be given as scheduled. If a toxicity is not clearly linked to a single drug, then both neratinib and capmatinib may be held. The treating physician may withhold any of the drugs per their discretion and discussion with the principal investigator as needed to maintain patient safety while a toxicity is evaluated and treated. The drug should be resumed after appropriate toxicity management and dose reduced, if indicated as per Section 10 of the protocol.

Patients must receive at least 80% of the scheduled doses of each study medication to be considered evaluable for DLT. Patients with ER+ breast cancer must receive at least 80% of the scheduled dose of AI to be considered evaluable for DLT. However, any patient who experiences DLT, will be counted as a DLT regardless of how many doses received.

As study therapy is given continuously, missed days of treatment will not be made up. A cycle is defined as 28 days regardless of the number of days of treatment received.

In the event the patient experiences intolerable side effect(s) attributed to the endocrine therapy agent(s), the treating physician may withhold the agent per their discretion and discussion with the principal investigator as needed to maintain patient safety while a toxicity is evaluated and treated. The treating physician may change the AI agent administered and prescribe treatment for symptom control, as clinically indicated.

The following delays are allowed except during the DLT assessment period:

1) Up to 4 weeks due to study related AEs
2) Up to 8 weeks due to non-study related AEs

Unanticipated Dose Interruptions:

Interruptions due to non-study related issues (logistical, natural disaster, etc) are permitted in the case of logistical reasons not related to study therapy, up to 2 cycles of study.

7.4 Dose Limiting Toxicity (DLT)

DLT is defined as any of the following possibly, probably, or definitely due to study therapy, assessed during the first 2 cycles [56 days]:

- Any death not clearly due to the underlying disease or extraneous causes
- Non- hematologic toxicity
    - Grade 3 or higher non-hematologic toxicity, Grade 3 diarrhea will be considered a DLT only if it lasts ≥ 2 days despite prophylaxis and optimal standard medication and medical management.

- Grade 2 diarrhea lasting ≥ 5 days despite prophylaxis and optimal standard medical management
- Pulmonary toxicity
    - Any grade of pneumonitis or ILD confirmed not attributable to infection or another etiology.
- Hy's Law case, defined as a patient meeting all of the following criteria:
    - ALT or AST ≥ 3 x Upper Limit of Normal (ULN)
    - Total bilirubin >2 x ULN
    - Little or no evidence of cholestasis (alkaline phosphatase <2 x ULN)
    - No other identified explanation for the injury (such as hepatitis A, B, C, or other viral hepatic injury, alcohol ingestion, congestive heart failure).
- Neutropenic fever, defined as per CTCAE version 5.0:
  ANC <1000/mm3 and a single temperature of >38.3 degrees C (101 degrees F) or a sustained temperature of >=38 degrees C (100.4 degrees F) for more than one hour.
- Hematologic toxicity
    - Grade 4 neutropenia or thrombocytopenia >7 days
    - Grade 3 thrombocytopenia with bleeding
    - Grade 4 anemia

The targeted maximum DLT rate is 25%, and we will enroll patients in cohorts of size 3.

Table 4. Capmatinib and Neratinib overlapping toxicities

SOC	**Capmatinib toxicity** (Ref: CDS)	**Neratinib toxicity** (Ref: USPI and SmPC)
Congenital, familial and genetic disorders	***Embryo-Fetal Toxicity***	***Embryo-Fetal Toxicity***
Gastrointestinal disorders	***Diarrhoea***	***Diarrhoea***
	Vomiting	***Vomiting***
	Nausea	***Nausea***
	Constipation	Abdominal pain*
	Amylase increased	Stomatitis**
	Lipase increased	Dyspepsia
	Acute pancreatitis	Abdominal distension
		Dry mouth

General disorders and *administration site conditions*	***Fatigue*[1]**	***Fatigue***
	Weight decreased	***Weight decreased***
	Back pain	
	Oedema peripheral[2]	
	Non-cardiac chest pain[3]	
	Pyrexia[4]	
Hepatobiliary disorders	***Alanine aminotransferase increased***	***Alanine aminotransferase increased***
	Aspartate aminotransferase increased	***Aspartate aminotransferase increased***
	Blood bilirubin increased	**Blood bilirubin increased**
	Hypoalbuminemia	
Infections and infestations	Cellulitis	Urinary tract infection
Metabolism and nutrition disorders	***Decreased appetite***	***Decreased appetite***
	Hyponatremia	Dehydration
	Hypophosphataemia	
Respiratory, thoracic and mediastinal disorders	Pneumonitis/ILD	Epistaxis
	Dyspnoea	
	Cough	
Skin and subcutaneous tissue disorders	***Urticaria***	***Rash******
	***Pruritus*[5]**	***Dry skin***
		Nail Disorder********
		Skin fissures
Renal and urinary disorders	***Blood creatinine increased***	***Blood creatinine increased***
	***Acute kidney injury*[6]**	**Renal failure**
Musculoskeletal and Connective Tissue Disorders		Muscle spasms

[1] *Includes fatigue and asthenia*

[2] *Includes peripheral swelling, oedema peripheral, and fluid overload*

[3] *Includes chest discomfort, musculoskeletal chest pain, non-cardiac chest pain, and chest pain*

[4] *Includes pyrexia and body temperature increased*

[5] *Includes pruritus, pruritus allergic, and pruritus generalized*

[6] *Includes acute kidney injury and renal failure.*

** Includes abdominal pain, abdominal pain upper, and abdominal pain lower*

*** Includes stomatitis, aphthous stomatitis, mouth ulceration, oral mucosal blistering, mucosal inflammation, oropharyngeal pain, oral pain, glossodynia, glossitis, and cheilitis*

**** Includes rash, rash erythematous, rash follicular, rash generalized, rash pruritic, rash pustular, rash maculo-papular, rash papular, dermatitis, dermatitis acneiform, and toxic skin eruption*

***** Includes nail disorder, paronychia, onychoclasis, nail discoloration, nail toxicity, nail growth abnormal, and nail dystrophy*

7.5 Duration of therapy

In the absence of treatment delays due to AEs, the treatment will continue up to 3 years or until disease progression, death of patient for any cause or meeting the treatment discontinuation criteria, whichever comes first.

7.6 Study Discontinuation

Patient will stop receiving the study treatment if any of the following criteria are met:

1) Disease progression

Disease progression is defined as rapid growth of multiple measurable, non-measurable, or new lesions, or at least a 20% increase in the sum of diameters of target (measurable) 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 progression).

2) Noncompliance

If the patient is not able to be compliant with the treatment schedule in the absence of toxicity, missing medications by non-medical reasons that are reported to the research staff more than 14 days, the study treatment should be discontinued for the patient.

3) Sustained toxic effects

Study treatment will be discontinued for patients who have sustained toxic effects that are attributed to the study drug and require a dose interruption lasting more than 8 weeks.

4) Initiation of new anticancer treatment

In patients for whom the investigator, in his or her judgment, determines new treatment for breast cancer is warranted, the study treatment may be discontinued.

5) Patient withdraws consent

Patients have the right to voluntarily withdraw from the study at any time for any reason. Every effort should be made to obtain information on patients who withdraw from the study. The primary reason for withdrawal from the study should be documented on the appropriate Case Report Form (CRF) in the RedCap database. However, patients will not be followed for any reason after consent has been withdrawn

6) Any medical condition that the investigator, IND medical monitor or Novartis and PUMA determines may jeopardize the patient's safety if he or she continues in the study

7) Intolerable toxicity related to study treatment determined by the investigator to be unacceptable given the individual patient's potential response to therapy and severity of the event

8) Pregnancy

9) Symptomatic deterioration attributed to disease progression

7.7 Follow up

Patients will be followed for safety for 30 days following the last dose of study drug, or until receipt of another anticancer therapy, whichever comes first.

Patients who have an ongoing major study treatment related AE upon study completion or at discontinuation from the study will be followed up to 6 weeks until the event has resolved to baseline grade, the event is assessed by the investigator as stable, new anticancer treatment is initiated, the patient is lost to follow-up, the patient withdraws consent, or until it has been determined that study treatment or participation is not the cause of the AE.

After treatment discontinuation, information on survival follow-up and new anti-cancer therapy will be collected via telephone calls, patient medical records, and/or clinic visits approximately every 6 months for 2 years (unless the patient withdraws consent or study is terminated).

7.8 End of Study

The end of this study is defined as the date when the last patient, last visit (LPLV) occurs or the date at which the last data point required for statistical analysis (i.e., OS) or safety follow-up is received from the last patient, whichever occurs later. LPLV is expected to occur 3 years after the first patient is enrolled.

7.9 Correlative Research

Blood: Research blood, approximately 30 ml, will be collected at baseline and then every 2 cycles until the end of study treatment. Each blood collection will consist of 1x10mL red top tube (for serum) and 2x10mL EDTA tubes (for plasma and PBMC isolation). Samples will be processed and aliquots banked in the MDA IBC translational lab for future research. Samples will be stored in the short term at -80C (serum and plasma, Z12.4041) and LN2 dewar (for PBMCs) in the Zayed laboratory and transferred to off-site storage at Cryogene per routine laboratory procedures. Samples will be coded by a de-identification number and a key will be maintained by the research staff to associate each sample with the related clinical data. For any visits performed outside of MD Anderson, research blood will not be collected.

Tissue: Fresh tissue samples from breast/chest wall, or a metastatic site including lung, liver or lytic lesions of the bone that may be safely accessed, will be collected via image-guided core biopsy. Tissue should be from a viable section of the tumor. Core needle biopsy specimen diameter should not be smaller than 16 gauge with 2 or more cores preferred. Viable tumor resection biopsies should not be less than 25 mg. Fine needle aspirates are not acceptable. Samples will be collected using a Celcuity provided specimen collection kit and then delivered directly to Celcuity's CLIA-certified and CAP-accredited laboratory where the CELsignia MP test (HER2, EGFR, HER3, c-MET etc.) is performed. Additional details regarding sample collection and processing are included in Appendix 2, "CELsignia Collection Kit User Instructions Card". Please also see Appendix 3 for the "CELsignia Specimen Collection Requisition" form.

In addition to the CELsignia MP test, remaining tissue will be banked inthe MDA IBC Lab for future research and to perform companion genomic testing to include major relevant pathways affected by the combination treatment. A total of 4-6 cores will be obtained from each patient, 2-4 of which will be sent to Celcuity for the CELsignia assay. The remaining cores will be preserved in OCT in order to preserve morphology, for further research on biomarkers of response/resistance to the therapy. IHC for c-MET will not be used for patient selection for the clinical trial given lack of validated clinical data.

Future studies performed on tissue and/or blood may include, but will not be limited to analysis of genomics, RNA, protein expression, or other analytes to study biomarkers, mechanisms of action, mechanisms of response/resistance, and pathways of interest.

In addition, we will perform mandatory collection of available data on cancer genomics that has been performed on the cancers of study participants for purposes outside of this study.

7.10. Study Calendar

Trial Period:	**Screening Phase**	**Treatment Cycles 1 cycle=28 days [a]**								**End of Treatment**	**Post-Treatment**	
	Screening /Baseline	1	2	3	4	5	6	7	8+		Safety F/U [f]	F/U [g]
Scheduling Window (Days):	Within 28 days +/- 3 days	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3		1 month	2 years
Informed Consent	x											
Inclusion/Exclusion Criteria	x											
Physical Exam [b], V/S, concomittent medications, ECOG[b]	x	x	x	x	x	x	x	x	x	x[l]		
Adverse Events [b]	x	x	x	x	x	x	x	x	x	x[l]	x	x
Pregnancy Test – Urine or Serum β-HCG (for women with childbearing potential)	x	x	x	x	x	x	x	x	x	x[l]		
CBC and Biochemical Profiles [c]	x	x	x	x	x	x	x	x	x	x[l]		
Urine analysis [c]	x	x	x	x	x	x	x	x	x	x[l]		
EKG, MUGA or ECHO as SOC [i]	x				x			x				
Radiological Evaluation as clinically indicated and as SOC [d]	x			x		x		x		x[l]		
Correlative Studies Blood Collection [e]	x			x		x		x				
Biopsy [h]	x											
Survival Status												x
Neratinib j		x	x	x	x	x	x	x	x			
Capmatinib [j]		x	x	x	x	x	x	x	x			
Endocrine Therapy [K]		x	x	x	x	x	x	x	x	x		

a. Study treatment can be up to 3 years until the treatment is discontinued.
b. Complete physical exam during the screening period. This will not be repeated if done within 8 (+/- 3 days) days before the start of treatment. During treatment Physical Exam as clinically indicated prior to trial treatment administration. Adverse events and ECOG performance status assessment can be done within 8 (+/- 3 days) days before the start of treatment. If a virtual visit is required, then physical exam and VS will not be obtained.
c. Hematologic and biochemical profiles (CBC, albumin, alkaline phosphatase, ALT, AST, LDH, amylase, lipase, uric acid, calcium, glucose, phosphorus, potassium, sodium, magnesium, total bilirubin, total protein, BUN, creatinine, as standard of care (will not be repeated if done within 8 (+/- 3 days) days before the start of treatment). During treatment, an earlier evaluation will be performed if clinically indicated.
d. Radiological evaluation will be performed every 2 cycles as standard of care and may include CT of the chest and abdomen, Ultrasound, bone Scan and X-Rays, brain MRI as clinically indicated for standard of care. PET/CT, Chest wall/breast photos may also be performed as indicated for standard of care. During treatment, an earlier evaluation will be performed if clinically indicated. The same method of evaluation, specific to the subject's condition, will be performed according to the time points.
e. Blood (EDTA tube) and serum (red tube) for correlative studies. Approximately 30cc of blood will be drawn at baseline, and every 2 cycles (i.e. 3th, 5th, 7th, etc.). For any visits performed outside of MD Anderson, research blood will not be collected. Correlative research blood is mandatory.
f. The Safety Follow-Up Visit should be conducted approximately 30 days after the last dose of trial treatment or before the initiation of a new anti-cancer treatment, whichever comes first. All AEs that occur prior to the Safety Follow-Up Visit should be recorded. Safety Follow-Up Visit can be done in the clinic, or by phone/video if patient is not willing to come to the clinic for follow up.
g. 2 years follow up can be performed every 6 months in the clinic, or by phone/video if patient is not willing to come to the clinic for follow up.
h. Mandatory to Phase II patients only. Biopsy at baseline can be combined with the primary diagnosis biopsy, or any time before the initiation of this trial to confirm the Celcuity assay score.
i. EKG, MUGA or ECHO will be performed every 3 cycles as standard of care.
j. Participants may follow Study Medication Disposal Guide of MDA to dispose of study medications locally when participants cannot come back to study site to return remaining study medications and medication bottles. Participants may also capture pictures of the pill diaries and send them to research staff, if needed.
k. ER+ breast cancer patients only (defined at ER ≥10%) will receive continuous aromatase inhibitor therapy (of physician's choice) by mouth dosed once daily. In addition, for pre-/peri-menopausal women with ER+ breast cancer, ovarian suppression therapy will also be administered.
l. If applicable; can be combined with post 1 month follow up.

7.11. Remote Procedures

In case of any unexpected incidents resulting in the inability to return to MD Anderson Cancer Center for study treatment and assessments, remote procedures can be applied for this trial conduction, including remote consent, remote toxicity assessment via phone calls, virtual visit, etc., with compliance with institutional policies. Patients may have routine lab work and additional labs performed at a local facility for toxicity management as needed. Lab certificates (CLIA/CAP) of the local lab will be obtained for regulatory compliance. Laboratory work done at an outside facility is to be forwarded to the subject's attending physician at MDACC or the PI of the study, who will date and sign off on the labs to verify the results were reviewed. If the patient's outside records are available to review in MDACC's EMR (i.e. EPIC 'Care Everywhere'), then it will be documented in either the physician's note and/or the study coordinator's note (attested by the physician) that the outside labs were reviewed by the MDA attending physician. Remote monitoring (virtual video or telephone visit) can be applied as needed. Study drug may be mailed to the patient per institutional guidelines/approval. Physician exam and VS assessment may be omitted if a virtual visit is necessary.

7.12. Drug Accountibility and Reconcilation

At completion of the study, to satisfy regulatory requirements regarding drug accountability, accurate records of of the amount dispensed to and returned by the subjects and the amount

remaining at the conclusion of the trial will be documentated, all unused and/or partially used investigational products Neratinib and Capmatinib will be reconciled and destroyed in accordance with applicable state and federal regulations and in accordance to MD Anderson institutional policies and procedures for drug destruction, and appropriate records of disposal are kept.

8.0 Clinical Safety Information for Study Drugs

8.1 Neratinib:

As of 01-MAY-2019, the total safety population from 37 completed and ongoing neratinib clinical studies consist of 6574 subjects; out of these, 2686 subjects with early-stage HER2-positive, or locally advanced, or metastatic solid malignancies have received at least 1 dose of single-agent neratinib administered subjects with cancer are known to have received neratinib in combination with other drugs. once a day; and 1317 subjects with cancer are known to have received neratinib in combination with other drugs.

Safety results from the completed and ongoing studies show that neratinib is generally well tolerated and with a consistent safety profile for subjects with breast cancer or other solid tumors. GI disorders accounted for the most frequently reported TEAEs. An updated prophylactic diarrhea management plan has shown promise in reducing the incidence and severity of diarrhea resulting from neratinib treatment. Please see details in the Investigator's Brochure.

8.1.1 Incidence of Treatment-emergent Adverse Events of Single-agent Studies

Safety data is available for 2686 subjects with early-stage HER2-positive, or locally advanced, or metastatic solid malignancies who received at least 1 dose of single-agent neratinib administered once a day in 9 studies. Six (6) of these studies have been completed. The most frequently reported SAEs in neratinib monotherapy studies were diarrhea, vomiting, anddehydration.

Table 5: Incidence of Treatment-emergent Adverse Events Reported in ≥10% of Subjects, by Treatment Arm, Maximum CTCAE Grades 1-4 by System Organ Class and Preferred Term (Safety Population); Study 3144A2-3004-WW/B1891004

MedDRA System Organ Class Preferred Term	Neratinib (N=1408) Grade 1-4 n (%)	 Grade 3 n (%)	 Grade 4 n (%)	Placebo (N=1408) Grade 1-4 n (%)	 Grade 3 n (%)	 Grade 4 n (%)
Any Adverse Event	**1385 (98.4)**	**684 (48.6)**	**15 (1.1)[a]**	**1239 (88.0)**	**169 (12.0)[a]**	**14 (1.0)**
Gastrointestinal Disorders	**1355 (96.2)**	**599 (42.5)**	**2 (0.1)**	**793 (56.3)**	**38 (2.7)**	**0**
Diarrhoea	1343 (95.4)	561 (39.8)	1 (0.1)	499 (35.4)	23 (1.6)	0
Nausea	605 (43.0)	26 (1.8)	0	303 (21.5)	2 (0.1)	0
Vomiting	369 (26.2)	47 (3.3)	0	112 (8.0)	5 (0.4)	0
Abdominal Pain	338 (24.0)	24 (1.7)	0	144 (10.2)	3 (0.2)	0
Abdominal Pain Upper	212 (15.1)	11 (0.8)	0	96 (6.8)	3 (0.2)	0
General Disorders And Administration Site Conditions	**639 (45.4)**	**40 (2.8)**	**0**	**546 (38.8)**	**8 (0.6)**	**0**
Fatigue	382 (27.1)	23 (1.6)	0	282 (20.0)	6 (0.4)	0
Skin And Subcutaneous Tissue Disorders	**517 (36.7)**	**16 (1.1)**	**0**	**313 (22.2)**	**5 (0.4)**	**0**
Rash	210 (14.9)	5 (0.4)	0	100 (7.1)	0	0
Nervous System Disorders	**463 (32.9)**	**29 (2.1)**	**0**	**445 (31.6)**	**20 (1.4)**	**2 (0.1)**
Headache	277 (19.7)	8 (0.6)	0	275 (19.5)	6 (0.4)	0
Dizziness	146 (10.4)	3 (0.2)	0	128 (9.1)	3 (0.2)	0
Musculoskeletal And Connective Tissue Disorders	**411 (29.2)**	**7 (0.5)**	**0**	**493 (35.0)**	**18 (1.3)**	**0**
Muscle Spasms	158 (11.2)	1 (0.1)	0	45 (3.2)	1 (0.1)	0
Arthralgia	86 (6.1)	2 (0.1)	0	162 (11.5)	4 (0.3)	0
Metabolism And Nutrition Disorders	**292 (20.7)**	**35 (2.5)**	**3 (0.2)**	**163 (11.6)**	**23 (1.6)**	**3 (0.2)**
Decreased Appetite	169 (12.0)	3 (0.2)	0	40 (2.8)	0	0

[a] In the neratinib arm, 1 subject with Grade 4 also experienced Grade 5; in the placebo arm, 1 subject with Grade 3 also experienced Grade 5.
Table grades are based on the highest grade reported; subjects with Grade 5 are not included.
MedDRA (Version 17) coding dictionary applied.

8.1.2 Adverse Drug Reactions with Neratinib Monotherapy

The ADRs occurring in subjects receiving neratinib monotherapy is based on the safety data from Study 3144A2-3004-WW/B1891004, a large randomized, double-blind, placebo-controlled Phase 3 study in women with early-stage HER2-positive breast cancer who received neratinib 240 mg monotherapy in the extended adjuvant setting (Table 6). In this study, 1408 subjects received neratinib monotherapy; diarrhea management with prophylactic use of loperamide was not implemented.

Table 6: Adverse Drug Reactions Occurring in Subjects Receiving Neratinib Monotherapy (N=1408)

System Organ Class	Adverse Reactions	All Adverse Reactions n (%)	All Fatal Adverse Reactions n (%)	All Life-threatening Adverse Reactions n (%)
Infections and infestations	Urinary tract infection	72 (5.1)	0 (0.0)	0 (0.0)
Metabolism and nutrition disorders	Decreased appetite	169 (12.0)	0 (0.0)	0 (0.0)
	Dehydration	51 (3.6)	0 (0.0)	1 (0.1)
Respiratory, thoracic and mediastinal disorders	Epistaxis	71 (5.0)	0 (0.0)	0 (0.0)
Gastrointestinal disorders	Diarrhoea	1343 (95.4)	0 (0.0)	1 (0.1)
	Nausea	605 (43.0)	0 (0.0)	0 (0.0)
	Vomiting	369 (26.2)	0 (0.0)	0 (0.0)
	Abdominal pain	338 (24.0)	0 (0.0)	0 (0.0)
	Abdominal pain upper	212 (15.1)	0 (0.0)	0 (0.0)
	Stomatitis[a]	143 (10.2)	0 (0.0)	0 (0.0)
	Dyspepsia	137 (9.7)	0 (0.0)	0 (0.0)
	Abdominal distension	68 (4.8)	0 (0.0)	0 (0.0)
	Dry mouth	47 (3.3)	0 (0.0)	0 (0.0)
Hepatobiliary disorders	Alanine aminotransferase increased	120 (8.5)	0 (0.0)	3 (0.2)
	Aspartate aminotransferase increased	104 (7.4)	0 (0.0)	3 (0.2)
	Blood bilirubin increased	4 (0.3)	0 (0.0)	0 (0.0)
Skin and subcutaneous tissue disorders	Rash[b]	223 (15.8)	0 (0.0)	0 (0.0)
	Nail disorder[c]	113 (8.0)	0 (0.0)	0 (0.0)
	Dry skin	85 (6.0)	0 (0.0)	0 (0.0)
	Skin fissures	28 (2.0)	0 (0.0)	0 (0.0)
Musculoskeletal and connective tissue disorders	Muscle spasms	158 (11.2)	0 (0.0)	1 (0.1)
Renal and urinary disorders	Blood creatinine increased	14 (1.0)	0 (0.0)	1 (0.1)
	Renal failure	4 (0.3)	0 (0.0)	0 (0.0)
General disorders and administration site conditions	Fatigue	382 (27.1)	0 (0.0)	0 (0.0)
Investigations	Weight decreased	68 (4.8)	0 (0.0)	0 (0.0)

8.1.3 Reference Safety Information for Assessment of Expectedness of Serious Adverse

Table 6 is based on data from n=1408 subjects who received neratinib monotherapy in Study 3144A2-3004-WW/B1891004. Diarrhea management with prophylactic use of loperamide

was not implemented in this study. For the purpose of safety reporting in clinical trials, only SARs listed in Table 7. should be considered expected in subjects receiving neratinib monotherapy.

Table 7: Serious Adverse Reactions for Neratinib Monotherapy Considered Expected for Safety Reporting Purposes (N=1408 Subjects Exposed)

		Number of Subjects Exposed (N) = 1408		
System Organ Class	SARs	All SARs n (%)	All Fatal SARs n (%)	All Life-threatening SARs n (%)
Metabolism and nutrition disorders	Dehydration	9 (0.6)	0 (0.0)	0 (0.0)
Gastrointestinal disorders	Diarrhoea	22 (1.6)	0 (0.0)	0 (0.0)
	Vomiting	12 (0.9)	0 (0.0)	0 (0.0)
	Nausea	4 (0.3)	0 (0.0)	0 (0.0)
	Abdominal pain	2 (0.1)	0 (0.0)	0 (0.0)
Hepatobiliary disorders	Alanine amino-transferase increased	4 (0.3)	0 (0.0)	0 (0.0)
	Aspartate amino-transferase increased	4 (0.3)	0 (0.0)	0 (0.0)
Renal and urinary disorders	Renal failure	2 (0.1)	0 (0.0)	0 (0.0)
General disorders and administration site conditions	Fatigue	3 (0.2)	0 (0.0)	0 (0.0)

MedDRA (Version 20) coding dictionary applied. Toxicity graded using NCI CTCAE version 3.0; each patient counted only once in the worst grade category.

8.1.4 Interaction With Other Medicinal Products and Other Forms of Interaction

Table 8: Drug Interactions That Affect Neratinib (NERLYNX)

Gastric Acid Reducing Agents	
Clinical Impact	Concomitant use of NERLYNX with a proton pump inhibitor (PPI), H_2-receptor antagonist, or antacid may decrease neratinib AUC *[see Clinical Pharmacology (12.3)]*, which may reduce NERLYNX activity.
Prevention or Management [see Dosage and Administration (2.5)]	Avoid concomitant use of PPIs.
	Separate administration of NERLYNX at least 2 hours before or 10 hours after the H_2-receptor antagonist dose.
	Separate administration of NERLYNX by at least 3 hours after antacids.
Strong CYP3A4 Inhibitors	
Clinical Impact	Concomitant use of NERLYNX with a strong CYP3A4 inhibitor increased neratinib C_{max} and AUC *[see Clinical Pharmacology (12.3)]*, which may increase the risk of NERLYNX toxicity.
Prevention or Management	Avoid concomitant use of NERLYNX with strong CYP3A4 inhibitors.
P-gp and Moderate CYP3A4 Dual Inhibitors	
Clinical Impact	Concomitant use of NERLYNX with a P-gp and moderate CYP3A4 dual inhibitor may increase neratinib C_{max} and AUC *[see Clinical Pharmacology (12.3)]*, which may increase the risk of NERLYNX toxicity.
Prevention or Management	Avoid concomitant use of NERLYNX with P-gp and moderate CYP3A4 dual inhibitors.
Strong or Moderate CYP3A4 Inducers	
Clinical Impact	Concomitant use of NERLYNX with a strong CYP3A4 inducer reduced neratinib C_{max} and AUC *[see Clinical Pharmacology (12.3)]*, which may reduce NERLYNX activity.
Prevention or Management	Avoid concomitant use of NERLYNX with strong or moderate CYP3A4 inducers.

AUC=Area Under Curve; C_{max}=Maximum Concentration

Certain P-glycoprotein (P-gp) Substrates

Concomitant use of NERLYNX increased concentrations of a P-gp substrate, which may increase the risk of adverse reactions of these substrates. Monitor for adverse reactions of certain P-gp substrates for which minimal concentration changes may lead to serious adverse reactions.

8.1.5. Adverse Events of Special Interest

- Pulmonary Toxicity:
  Interstitial lung disease (ILD) or pneumonitis, a diffuse parenchymal lung disease, is a group of fibrotic lung disorders that affect the alveoli of the lung. In theory, neratinib may induce interstitial lung disease as this risk was identified for similar compound(class effect).
- Cardiac Toxicity (Left Ventricular Ejection Fraction Decreased):

Small-molecule TKIs have been shown to be associated with a certain degree of cardiovascular side effects that are often reversible. In theory, neratinib may decrease left ventricular ejection fraction (LVEF) as this risk was identified for similar compounds (class effect).

8.1.6. Special Precautions

- Pregnancy and Lactation
  The potential effects of neratinib on pregnancy and lactation have not been investigated in humans. Safety for women of childbearing capacity cannot be implied from the existing data. If a woman becomes pregnant within 1 month of her being exposed to neratinib or within 3 months of her partner's being exposed to neratinib, the pregnancy should be followed to its outcome.
- Risk to Unborn Children
  It is not known whether neratinib may cause side effects to pregnant women, to an unborn child (an embryo or a fetus), or to children of nursing women. In a study with pregnant animals, administration of neratinib caused harm, including birth defects and death, to the fetuses.
- Effects on Ability to Drive and Use Machines
  In Study 3144A2-3004-WW/B1891004, the incidence of dizziness was similar between the neratinib arm and placebo arm, and the incidence of hypotension was <1% in both arms. Subjects should be instructed that if they experience dizziness, they should avoid potentially hazardous tasks such as driving or operating machinery.
- Overdose
  No specific antidotes exist for the treatment of neratinib overdoses, and the benefit of hemodialysis in the treatment of neratinib overdose is unknown. General supportive care is recommended.

8.2 Capmatinib

Capmatinib has been extensively tested in both healthy volunteers and cancer patients (majority with NSCLC). As of the safety cut-off date of 28-Sep-2023, more than 800 participants with solid tumors have been treated with capmatinib as a single agent, and 845 participants have received capmatinib in combination with other therapies. The recommended phase II dose (RP2D) for capmatinib as a single agent has been determined to be 400 mg b.i.d. in tablet formulation. See detailed data in Investigator Brochure (IB).

8.2.1 Reference Safety Information for Capmatinib

The reference safety information (RSI) tables are based upon evaluation of the available clinical safety information, including data from all capmatinib global clinical trials sponsored by Novartis (and the Novartis safety database Argus (cut-off date: 28-Sep-2023). Only suspected serious adverse reactions (SARs) are included into the RSI tables, and are used for determination of "expectedness" for single case SAE reporting. Table 9 constitutes the Reference Safety Information used for determination of "expectedness" for single case SAE reporting. For the purpose of individual case safety reporting in clinical trials, fatal and life-threatening SARs will always be considered unexpected. The safety profile may change as more data becomes available

Capmatinib monotherapy reference safety information

Serious suspected adverse reactions considered expected for reporting purposes in the capmatinib trials were identified based on the review of the capmatinib monotherapy data from the pooled safety data from six studies (CINC280A2201, CINC280X1101, CINC280X2102, CINC280A2103, CINC280A2105 and CINC280A2108) which includes a total of 580 patients treated at the recommended capmatinib dose.

Table 9: Serious Adverse Drug Reactions for Treatment With Capmatinib As Single Agent Considered Expected for Safety Reporting Purposes

System Organ Class	Serious Adverse Reactions	Number of subjects exposed to INC280 monotherapy safety pooled data set (N)=580			
		Occurrence of suspected SARs n* (%)	Frequency category of suspected SARs	Occurrence of fatal SARs n* (%)	Occurrence of life-threatening SARs n* (%)
Gastrointestinal disorders	Vomiting	12 (2.1)	Common	0	0
	Nausea	7 (1.2)	Common	0	0
	Diarrhea	4 (0.7)	Uncommon	0	0
	Amylase increased	2 (0.3)	Uncommon	0	0
General disorders and administration site conditions	Edema peripheral	4 (0.7)	Uncommon	0	0
	Peripheral swelling	3 (0.5)	Uncommon	0	0
Immune system disorders	Hypersensitivity	2 (0.3)	Uncommon	0	0
Infections and infestations	Cellulitis	2 (0.3)	Uncommon	0	0
Metabolism and nutrition disorders	Decreased appetite	2 (0.3)	Uncommon	0	0
Renal and urinary disorders	Renal failure	2 (0.3)	Uncommon	0	0
	Blood creatinine increased	2 (0.3)	Uncommon	0	0
Respiratory, thoracic and mediastinal disorders	Pneumonitis	3 (0.5)	Uncommon	1 (0.2)	0
	Interstitial lung disease	2 (0.3)	Uncommon	0	0
	Dyspnoea	2 (0.3)	Uncommon	0	0

n* = number of subjects who have experienced the SAR
Frequency category is based on the clinical trial database (N) according to the CIOMS III convention: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000)
Frequency is based on INC280 monotherapy data from the pooled safety data from six pooled studies: (Studies CINC280A2201, CINC280X1101, CINC280X2102, CINC280A2103, CINC280A2105, CINC280A2108), which includes a total of 580 patients.
Cut-off date: 30-Aug-2021

Capmatinib combination trials reference safety information

Based on a review of the available safety data at the time of capmatinib IB data cut-off, no SAR expected for reporting purposes has been identified for capmatinib administered in combination with EGF816, nivolumab, PDR001 and pembrolizumab. Therefore, no combination therapy RSI table was generated. Please refer to the respective IBs for single agent RSI of compounds used in combination studies.

8.2.2 Summary of clinical safety for capmatinib administered as single agent

As of 28-Sep-2023, a total of 1731 cancer patients and 236 non-cancer subjects have received capmatinib. A total of 1122 subjects, including healthy volunteers, have been treated with capmatinib as a single agent at different doses. The MTD for capmatinib as single agent was not reached. The RP2D for capmatinib as a single agent has been determined to be 400 mg BID in tablet formulation.

Overall, capmatinib has been well tolerated by patients and the majority of the adverse events (AEs) reported with capmatinib single agent have been of mild or moderate severity. See detailed data in current version of Investigator's Brochure.

Clinical safety monitoring

Clinical safety findings while on treatment with capmatinib may vary. The more frequent adverse events could include peripheral edema, nausea, blood creatinine increased, vomiting, decreased appetite, fatigue and diarrhoea. Onset or worsening of any of these events should be reported to the treating physician.

Precautions and management of potential risks

While the available clinical experience with capmatinib is increasing, the sponsor strongly suggests that the treating physician continues to inform the Novartis medical monitor if, during the treatment period, any signs or symptoms are observed that are not consistent with the toxicities discussed within IB. The potential risks associated with capmatinib will be carefully assessed and monitored following the procedure defined in the protocol.

Hepatic effects

Capmatinib is primarily metabolized by liver enzymes. Liver function test alterations (ALT and/or AST and/or bilirubin increase) have been observed in a number of patients. Overall, when capmatinib is administered as a single agent, liver function test alterations appear to be limited. Progressive liver disease or underlying primary malignancies could not be fully ruled out as causally related to the liver function test alterations in a number of patients. Caution is recommended when capmatinib is administered in combination with other anticancer drugs with known risk of hepatotoxicity.

Renal dysfunction

Capmatinib inhibits renal transporter MATE1 and MATE2K with a Ki of 0.28 μM *in vitro*. It has been reported that a small portion of creatinine could be cleared via active tubular secretion by these renal transporters such as MATE and OAT.

In HV DDI study (A2102), both creatinine and cystatin C levels were evaluated following single dose of capmatinib. The results showed that cystatin C levels did not change while serum creatinine levels increased slightly. Creatinine mainly cleared by passive glomerular filtration, but 10-40% could be active tubular secretion. Cystatin C is 100% through glomerular filtration. So it is likely that the transient increase of creatinine is caused by transporter inhibition.

In the [CINC280A2201] study, 101 patients (27.1%) experienced events of blood creatinine increased of which except for 1 patient with Grade 3 blood creatinine increased all other patients had Grade 1/2 events. Three Grade 1/2 events of renal failure (0.8%) suspected to be related to capmatinib were reported (with no Grade 3/4 events of renal failure). There was one Grade 3 event of acute kidney injury reported as suspected to be related to capmatinib. None of the events were fatal.

Effects on pancreas
When capmatinib is administered as a single agent, pancreatic events are reported in a number of patients; in [CINC280A2201] study 52 patients (13.9%) experienced amylase increase and lipase increase, respectively, of any grade suspected to be related to capmatinib. Grade 3/4 AEs of increased amylase/lipase suspected to be related to study treatment have been reported in 32 patients (8.6%), and one patient experienced acute pancreatitis (0.3%) suspected to be related to the study treatment. Based on the current available data, a direct toxic effect of capmatinib on pancreas cannot be definitively identified.

Pneumonitis/ILD
In preclinical studies, capmatinib did not show any toxic effect on lung tissue.
In capmatinib single agent study [CINC280A2201], any grade ILD/pneumonitis was reported in 17 of 373 patients (4.6%) treated with capmatinib. Grade 3 ILD/pneumonitis was reported in 7 patients (1.9%), with a fatal event of pneumonitis reported in 1 patient (0.3%).
Most of these subjects had previous treatment with immunotherapy (nivolumab and pembrolizumab) or radiotherapy to the lung as confounding factors and had progressive disease at the onset of ILD/pneumonitis.

Eight patients (2.1%) discontinued capmatinib due to ILD/pneumonitis. ILD/pneumonitis mostly occurred within approximately the first 3 months of treatment. The median time-to-onset of Grade 3 or higher ILD/pneumonitis was 7.9 weeks (range: 0.7 to 88.4 weeks).
Investigators are advised to carefully monitor patients for signs and symptoms of pneumonitis in all capmatinib studies, both single agent and especially in combination studies with EGFR TKIs.

Hypersensitivity reactions

No cases of serious hypersensitivity have been reported in patients treated with capmatinib in capmatinib single-agent study [CIN280A2201]. In other clinical studies, cases of serious hypersensitivity (Uncommon frequency) were reported in patients treated with capmatinib. Clinical symptoms included pyrexia, chills, pruritus, rash, blood pressure decreased, nausea and vomiting.

Based on the severity of the hypersensitivity reaction, investigators are advised to temporarily withhold or permanently discontinue capmatinib and institute appropriate treatment for hypersensitivity reactions.

Photosensitivity
Capmatinib has shown photosensitization potential in *in vitro* and *in vivo* assays. Clinical protocol provisions advise against ultraviolet exposure while taking capmatinib.
In capmatinib single agent study [CINC280A2201], there was only 1 subject (0.3%) who experienced an event of phototoxicity (Grade 1) and did not lead to discontinuation of treatment. The subject had psoriasis at baseline which was a confounding factor.

Teratogenicity
Capmatinib should be considered potentially teratogenic to humans. Male patients must be willing to abide by protocol permitted methods to avoid fathering a child from the time of creening through follow-up. Women of child-bearing potential who agree to participate in initial clinical studies must agree to abide by permitted methods defined in the clinical protocol to avoid pregnancy and lactation from screening through follow-up.

Pregnancy testing
The pregnancy status of females of reproductive potential should be verified prior to starting treatment with capmatinib.

Contraception
Females
Sexually-active females of reproductive potential should use effective contraception (methods that result in less than 1% pregnancy rates) during treatment with capmatinib and for at least one month after the last dose.
Males
Male patients with sexual partners who are pregnant, possibly pregnant, or who could become pregnant should use condoms during treatment with capmatinib and for at least 3 months after the last dose.

Safety assessments
Safety will be monitored using the following assessments: hematology, chemistry, coagulation parameters, urinalysis, 12-lead ECG, physical (including neurological) exam, vital signs, height, weight, performance status, radiology examinations, and cardiac assessment. In addition, AEs,

pregnancy tests and concomitant medications will also be collected at every visit. Pregnancy tests will be obtained in women of childbearing potential prior to each cycle of therapy.

9.0 Concomitant and Prohibited Therapy

Concomitant therapy includes any prescription medications or over the counter preparations used by a patient between the 7 days preceding the screening evaluation and the treatment discontinuation visit. If the patient is taking any prohibited medications as of the day of consent, alternatives will be discussed with the patients prior to initiating treatment on study. For agents known to prolong QT interval, if the principal investigator and/or attending physician deems the risk for QT prolongation to be low, continuation may be allowed if it is considered in the patient's best interest. Increased cardiac monitoring may be done in these circumstances for patient safety per physician's discretion as standard of care.

Patients who use hormone-replacement therapy, prophylactic or therapeutic anticoagulation therapy (such as low-molecular-weight heparin or warfarin at a stable dose level) should continue their use. However, hormone-replacement therapy should be discontinued if the patient is HR-positive.

All concomitant medications will be documented in medical record as standard of care only, and will not be collected for this study.

Any other anti-cancer agents and agents listed below are prohibited.

9.1 Prohibited Concomitant Therapy and Cautions for Capmatinib Use:

There is no contraindication for the use of Capmatinib. But there are some drug interactions identified:

- **P-gp Inducers**
  Capmatinib is a substrate for P-gp. Strong P-gp inducers may have the potential to decrease Capmatinib exposure. Concomitant use of strong P-gp inducers (e.g., carbamazepine, phenytoin, rifampicin, and St. John's wort) should be avoided.
- **P-gp Substrates**
  Multiple administrations of Capmatinib HCl hydrate 500 mg once daily for 8 days had a mild effect on the PK of the sensitive P-gp substrate dabigatran etexilate, increasing its exposure by approximately 50% based on the AUC. Monitoring the clinical effects of P gp-dependent substances with a narrow therapeutic index (e.g., digoxin) is recommended during co-administration with Capmatinib.
- **BCRP Substrates**
  Capmatinib can inhibit the transport of sensitive substrates of BCRP. Monitoring the clinical effects of sensitive BCRP substrates is recommended during co-administration with Capmatinib.
- **Metformin**
  Based on in vitro data, Capmatinib and its metabolite may have the potential to increase the AUC of co-administered metformin in humans, through inhibition of its renal excretion mediated via OCT1 and OCT2, and MATE1 and MATE2. Monitoring of the

effect of metformin is recommended during co-administration with Capmatinib, which not contraindicated.

- **Proton Pump Inhibitor**
  The solubility of capmatinib is pH-dependent. The [CINC280A2101] study was a clinical drug-drug interaction study investigating the effect of the proton pump inhibitor, rabeprazole, on a single dose of 600 mg capmatinib tablet in healthy subjects. Rabeprazole treatment resulted in a modest reduction in the extent of capmatinib absorption with a 37.5% decrease in Cmax and a 25.2% decrease in AUCinf.

9.2 Prohibited Concomitant Therapy for Neratinib use:

1. Agents known to be strong cytochrome P450 (CYP) 3A4 inducers or inhibitors, such as: phenobarbital, phenytoin, primidone, rifampin, dexamethasone, and oral contraceptives.

Patients should also avoid grapefruit and herbal remedies, including, but not limited to St. John's Wort.

2. Chronic immunosuppressive therapies including systemic corticosteroids. Steroids given for physiological replacement, as anti-emetics or inhaled as well as short course of oral/topical steroids given for allergic reactions or asthma flares are allowed.
3. P-glycoprotein (P-gp) Substrates: Concomitant use of neratinib with digoxin, a P-gp substrate, increased digoxin concentrations. Increased concentrations of digoxin may lead to increased risk of adverse reactions including cardiac toxicity. Refer to the digoxin prescribing information for dosage adjustment recommendations due to drug interactions. Neratinib may inhibit the transport of other P-gp substrates (e.g., dabigatran, fexofenadine).
4. Drugs that have interactions that affect neratinib (see Table 8 Drug Interactions That Affect Neratinib).

10.0 Common Toxicity and Dose Modification

10.1 Neratinib Dose Modifications and Management – General Toxicities

For toxicities deemed to be related to neratinib, follow Table 10.

Table 10: Neratinib Dose Modifications and Management – General Toxicities*

Severity of Toxicity†	Action
Grade 3	Hold NERLYNX until recovery to Grade ≤1 or baseline within 3 weeks of stopping treatment. Then resume NERLYNX at the next lower dose level.
Grade 4	Discontinue NERLYNX permanently.

* Refer to Tables 13, 14 below for management of diarrhea and hepatotoxicity
† Per CTCAE v5.0

10.2 Management of Diarrhea

Diarrhea is a commonly occurring toxicity. Monotherapy with neratinib has a median time of 3 days to onset of diarrhea. With combination therapy, it is anticipated that diarrhea may occur

earlier. For the majority of patients, diarrhea subsides after about 2 weeks. Therefore, intensive prophylactic measures begin at the start of therapy. If diarrhea occurs despite prophylaxis, treat with additional antidiarrheals, fluids and electrolytes as clinically indicated. Additionally, based on results from the CONTROL clinical trial, the neratinib dose will be escalated to the assigned target dose during the 1st cycle of treatment (29).

Patients **must** be instructed to:

- start prophylactic antidiarrheal therapy (see below) on day 1, with the first dose of neratinib
- continue prophylactic therapy as directed
- promptly report diarrhea symptoms
- record the number of stools per day
- record each dose of antidiarrheal medicine taken each day
- report constipation *before* taking any laxatives or stopping antidiarrheal medication. Anti-diarrheal medication may be held for constipation at the discretion of the treating physician, but should be resumed if diarrhea recurs.

Intensive primary prophylaxis

Antidiarrheal medication **(**loperamide**)** must begin with the first dose of neratinib. Patients must take an initial dose of loperamide 4 mg p.o. with the first dose of neratinib, then followed by 4 mg TID for the first 14 days. After two weeks on study, patients will take loperamide PO 4 mg twice a day (BID) for the remainder of the first two cycle of neratinib. Thereafter, loperamide will be administered as needed throughout neratinib treatment, not to exceed 16 mg per day.

Table 11: Suggested Dosing Time

	7am	**2pm**	**7pm**	**9pm**
C1D1 through 28 days	Neratinib & Capmatinib with food**		Capmatinib	
	Loperamide 4mg***	Loperamide 4mg***		Loperamide 4mg***

****** Neratinib and Capmatinib dose will be as assigned

******* After the first 14 days, loperamide 4 mg is to be taken twice a day through the first two cycle only of therapy (Day 56). Daily dose as needed (not to exceed 16 mg per day) for Days 56+ (Cycle 3 and beyond).

For Grade 2 diarrhea lasting ≥ 5 days despite prophylactic medication, and higher grade (Grade 3 and 4), we recommend following the guideline as noted in below Table 12.

Table 12: Management Guideline for Neratinib-related Diarrhea

Severity of Diarrhea*	Action
• Grade 1 diarrhea [increase of <4 stools per day over baseline] • Grade 2 diarrhea [increase of 4–6 stools per day over baseline] lasting ≤5 days • Grade 3 diarrhea [increase of ≥7 stools per day over baseline; incontinence; hospitalization indicated; limiting self-care activities of daily living] lasting ≤2 days	• Adjust antidiarrheal treatment • Diet modifications • Fluid intake of ~2 L should be maintained to avoid dehydration • Once event resolves to ≤Grade 1 or baseline, start loperamide 4 mg with each subsequent NERLYNX administration
• Any grade with complicated features† • Grade 2 diarrhea lasting longer than 5 days‡ • Grade 3 diarrhea lasting longer than 2 days‡	• Interrupt NERLYNX treatment • Diet modifications • Fluid intake of ~2 L should be maintained to avoid dehydration • If diarrhea resolves to Grade 0–1 in one week or less, then resume NERLYNX treatment at the same dose. • If diarrhea resolves to Grade 0–1 in longer than one week, then resume NERLYNX treatment at reduced dose (see Table 2) • Once event resolves to ≤Grade 1 or baseline, start loperamide 4 mg with each subsequent NERLYNX administration
• Grade 4 diarrhea [life-threatening consequences; urgent intervention indicated]	• Permanently discontinue NERLYNX treatment
• Diarrhea recurs to Grade 2 or higher at 120 mg per day	• Permanently discontinue NERLYNX treatment

Note: Antidiarrheal treatment adjustment will be per physician's discretion. Examples of antidiarrheal treatment include but not limited to:

- Diphenoxylate 5 mg/Atropine Sulfate 0.05 mg (Lomotil): 2 tablets or 10 mL by mouth, 4 times per day, as needed. Maximum 8 tablets, or 40 mL per day.
- Colestipol: 2 grams by mouth twice per day. Colestipol should be taken at least 1 hour after and at least 4 hours before other oral medications.
- Tincture of Opium, 10 mg/mL: 6 mg (0.6 mL) 4 times per day, as needed.

Note: If grade 3 diarrhea reoccurs, the patient patient maymaintain the same dose level of Neratinib or have dose reduced to the next lower dose(120 mg is the lowest dose level of Neratinib), per physician discretion. The patient may voluntarly come off the study at any time.

* Per CTCAE v5.0
† Complicated features include dehydration, fever, hypotension, renal failure, or Grade 3 or 4 neutropenia
‡ Despite being treated with optimal medical therapy

Stop Loperamide if no bowel movement for >/= 2 days per attending physician's discretion and resume the Loperamide as instructed if any signs and symptoms of abdominal cramping, loose stool and diarrhea occurs: take 2 pills of Loperamide immediately, then 1 pill of Loperamide with each subsequent episode of diarrhea, which is not to exceed 8 pills of Loperamide in 24

hours. If diarrhea persists, take Lomotil and/or other antidiarrheal medications as needed per standard of care per attending physician's discretion. Resume adjusted dosage of Loperamide as per attending physician's discretion to manage the diarrhea and Loperamide induced constipation.

10.3 Management of Cardiac Left Ventricular Dysfunction

Neratinib must be discontinued for patients who have a symptomatic decrease in LVEF.

- Congestive heart failure (grade 3):

Patients should be monitored for signs and symptoms of CHF (e.g., dyspnea, tachycardia, cough, neck vein distention, cardiomegaly, hepatomegaly, paroxysmal nocturnal dyspnea, orthopnea, peripheral edema). If the patient develops any of these signs and symptoms, neratinib must be held. The investigator must confirm the diagnosis of CHF with either an echocardiogram or a MUGA scan. Once the diagnosis of CHF is confirmed, neratinib must be permanently discontinued.

- Severe refractory/poorly controlled CHF (grade 4):

Neratinib should be discontinued if the patient develops severe refractory/poorly controlled CHF.

For asymptomatic patients, the decision to continue or stop neratinib is based on two factors, the value of the measured ejection fraction and the change in ejection fraction from baseline, which was performed at the time of registration.

10.4 Neratinib Dose Modifications for Hepatic Impairment

Guidelines for dose adjustment of neratinib in the event of liver toxicity are shown in Table 13. Patients who experience ≥Grade 3 diarrhea requiring IV fluid treatment or any signs or symptoms of hepatotoxicity, such as worsening of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, or eosinophilia, should be evaluated for changes in liver function tests. Fractionated bilirubin and prothrombin time should also be collected during hepatotoxicity evaluation.

Table 13: Dose Modifications for Hepatotoxicity

Severity of Hepatotoxicity*	Action
• Grade 3 ALT or AST (>5–20× ULN) OR • Grade 3 bilirubin (>3–10× ULN)	• Hold NERLYNX until recovery to ≤Grade 1 • Evaluate alternative causes • Resume NERLYNX at the next lower dose level if recovery to ≤Grade 1 occurs within 3 weeks. If Grade 3 ALT or AST, or bilirubin occurs again despite one dose reduction, permanently discontinue NERLYNX
• Grade 4 ALT or AST (>20× ULN) OR • Grade 4 bilirubin (>10× ULN)	• Permanently discontinue NERLYNX • Evaluate alternative causes

ALT=Alanine Aminotransferase; AST=Aspartate Aminotransferase; ULN=Upper Limit Normal
* Per CTCAE v5.0

10.5 Capmatinib Dose Reduction and Toxicity Management

10.5.1 Capmatinib Dose Reduction Levels

Table 14: Dose Reduction Steps for Capmatinib PO

	Starting dose level 1	Dose level -1	Dose level -2
capmatinib	400 mg b.i.d.	300 mg b.i.d.	200 mg b.i.d.

Note: dose reduction should be based on the worst toxicity demonstrated at the last dose.
Dose reduction below 200 mg is not allowed

10.5.2 Capmatinib Treatment Interrruption and Dose Reduction Guidance

Table 15. Criteria for Dose Reduction/Interruption And Re-initiation of Capmatinib Treatment for Adverse Drug Reactions

To be considered recommended dose modifications, unless otherwise specified as mandatory in this Table 15. Refer to Table 16 for follow-up evaluations as applicable.

Worst toxicity CTCAE Grade[a] during a cycle of therapy	
No toxicity	Maintain dose level
HEMATOLOGICAL	
Neutrophil count decreased (ANC) Neutropenia	
Grade 1 (ANC < LLN - 1500/mm^3; < LLN - 1.5 x 10^9/L)	Maintain dose level
Grade 2 (ANC < 1500 - 1000/mm^3; < 1.5 - 1.0 x 10^9/L)	Maintain dose level
Grade 3 (ANC < 1000 - 500/mm3; < 1.0 - 0.5 x 109/L)	Omit dose until resolved to ≤ grade 2, then: If resolved in ≤ 7 days, resume treatment at the same dose level If resolved in > 7 days, then ↓ 1 dose level
Grade 4 (ANC < 500/mm^3; < 0.5 x 10^9/L)	Omit dose until resolved to ≤ grade 2 and then ↓ 1 dose level

Febrile neutropenia	
(ANC < 1000/mm3 (< 1.0 x 109/L), fever > 38.3°C)	Omit dose, then: If resolved in ≤ 7 days, resume treatment at ↓ 1 dose level If resolved in > 7 days, permanently discontinue participant from capmatinib treatment
Platelet count decreased (Thrombocytopenia)	
Grade 1 (PLT < LLN - 75,000/mm^3; < LLN - 75 x 10^9/L)	Maintain dose level
Grade 2 (PLT < 75,000 - 50,000/mm^3; < 75 - 50 x 10^9/L)	Maintain dose level
Grade 3 (PLT < 50,000 - 25,000/mm3; < 50 - 25 x 109/L)	Omit dose until resolved to ≤ grade 2, then: If resolved in ≤ 7 days, then maintain dose level If resolved in > 7 days, then ↓ 1 dose level
Grade 4 (PLT < 25,000/mm^3; < 25 x 10^9/L)	Omit dose until resolved to ≤ grade 2, then ↓ 1 dose level
Hemoglobin decreased (Anemia)	
Grade 1 (Hemoglobin [Hgb] < LLN - 10.0 g/dL; < LLN - 6.2 mmol/L; < LLN - 100 g/L)	Maintain dose level
Grade 2 (Hgb < 10.0 - 8.0 g/dL; < 6.2 – 4.9 mmol/L; < 100 - 80 g/L)	Maintain dose level
Grade 3 (Hgb < 8.0 g/dL; < 4.9 mmol/L; < 80 g/L; transfusion indicated)	Omit dose until resolved to ≤ grade 2, then: If resolved in ≤ 7 days, resume treatment at the same dose level If resolved in > 7 days, then ↓ 1 dose level
Grade 4 (Life-threatening consequences; urgent intervention indicated)	Omit dose until resolved to ≤ grade 2 and then ↓ 1 dose level If toxicity recurs, permanently discontinue participant from capmatinib treatment.
RENAL	
Serum creatinine	
Grade 1 (> ULN - 1.5 x ULN)	Maintain dose level
Grade 2 (> 1.5 - 3.0 x ULN)	Omit dose until resolved to ≤ grade 1 or baseline, then resume treatment at the same dose level.
Grade 3 (> 3.0 - 6.0 x ULN)	Omit dose until resolved to ≤ grade 1 or baseline, then resume treatment at ↓ 1 dose level.
Grade 4 (> 6.0 x ULN)	Permanently discontinue participant from capmatinib treatment
HEPATIC	
Isolated Total Bilirubin elevation*	
Grade 1 (> ULN - 1.5 x ULN)	Maintain dose level

Grade 2 (> 1.5 - 3.0 x ULN)	Omit dose until resolved to ≤ grade 1, then If resolved in ≤ 7 days, maintain dose level. If resolved in > 7 days, ↓1 dose level
Grade 3 (> 3.0 - 10.0 x ULN)	Omit dose until resolved to ≤ grade 1, then If resolved in ≤ 7 days, ↓ 1 dose level If resolved in > 7 days, permanently discontinue participant from capmatinib treatment
Grade 4 (> 10.0 x ULN)	Mandatory: Permanently discontinue participant from capmatinib treatment
Isolated AST or ALT elevation	
Grade 1 (> ULN - 3 x ULN)	Maintain dose level
Grade 2 (> 3.0 - 5.0 x ULN)	Maintain dose level
Grade 3 (> 5.0 - 20.0 x ULN)	Omit dose until resolved to ≤ grade 1 (or ≤ grade 2 if grade 2 elevation at baseline) then If resolved in ≤ 7 days, then resume treatment at the same dose level If resolved in > 7 days, resume treatment at ↓ 1 dose level
Grade 4 (> 20.0 x ULN)	Mandatory: Permanently discontinue participant from capmatinib treatment
Combined elevations of AST or ALT and Total Bilirubin [b,c,d]	
For participants with normal baseline ALT and AST and total bilirubin value: AST or ALT > 3.0 x ULN combined with total bilirubin > 2.0 x ULN without evidence of cholestasis or hemolysis OR For participants with elevated baseline AST or ALT or total bilirubin value: [AST or ALT > 3 x baseline] OR [AST or ALT > 8.0 x ULN], whichever is lower, combined with [total bilirubin > 2 x baseline AND > 2.0 x ULN] without evidence of cholestasis or hemolysis	Mandatory: Permanently discontinue participant from capmatinib treatment
METABOLIC	
Amylase and/or lipase elevation	
Grade 1 (> ULN - 1.5 x ULN)	Maintain dose level
Grade 2 (> 1.5 - 2.0 x ULN; > 2.0 - 5.0 x ULN and asymptomatic)	Maintain dose level
Grade 3 (> 2.0 - 5.0 x ULN with signs or symptoms; > 5.0 x ULN and asymptomatic)	Omit the dose until resolved to ≤ grade 2, then If resolved in ≤ 14 days, resume treatment at the same dose level

	If resolved in > 14 days, then ↓ 1 dose level
Grade 4 (> 5.0 x ULN with signs or symptoms)	Permanently discontinue participant from capmatinib treatment
CARDIAC	
Electrocardiogram QT corrected (QTc) interval prolonged	
Grade 1 (QTcF 450-480 ms)	Maintain dose level
Grade 2 (QTcF 481-500 ms)	Maintain dose level
Grade 3 (QTcF ≥ 501 ms on at least two separate ECGs)	Omit dose until resolved to ≤ grade 2, then: If resolved in ≤ 7 days, resume treatment at the same dose level If resolved in > 7 days, then ↓ 1 dose level
Grade 4 (QTcF ≥ 501 or > 60 ms change from baseline and Torsades de pointes or polymorphic ventricular tachycardia or signs/symptoms of serious arrhythmia)	Permanently discontinue participant from capmatinib treatment
GASTROINTESTINAL	
Pancreatitis	
Grade 2	Maintain dose level
Grade ≥ 3	Mandatory: Permanently discontinue participant from capmatinib treatment
Diarrhea**	
Grade 1 (despite appropriate anti-diarrheal medication)	Maintain dose level
Grade 2 (despite maximal anti-diarrheal medication)	Omit dose until resolved to ≤ grade 1, then maintain dose level. If diarrhea returns as ≥ grade 2, then omit dose until resolved to ≤ grade 1, then resume treatment at ↓ 1 dose level
Grade 3 or 4 (despite appropriate anti-diarrheal medication)	Omit dose until resolved to ≤ grade 1, then resume treatment at ↓ 1 dose level
Vomiting	
Grade 1 (despite appropriate anti-emetics)	Maintain dose level
Grade 2 (despite appropriate anti-emetics)	Omit dose until resolved to ≤ grade 1, then maintain dose level. If vomiting returns as ≥ grade 2, then omit dose until resolved to ≤ grade 1, then ↓ 1 dose level.
Grade 3 (despite appropriate anti-emetics)	Omit dose until resolved to ≤ grade 1, then ↓ 1 dose level
Grade 4 (despite appropriate anti-emetics)	Omit dose until resolved to ≤ grade 1, then ↓ 1 dose level
Nausea	
Grade 1 or 2 (despite appropriate anti-emetics)	Maintain dose level

Grade 3 (despite appropriate anti-emetics)	Omit dose until resolved to ≤ grade 1, then ↓ 1 dose level
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	
Rash/photosensitivity* **	
Grade 1	Maintain dose level
Grade 2	Maintain dose level
Grade 3, despite skin toxicity therapy	Omit dose until resolved to grade ≤ 1, then: If resolved in ≤ 7 days, then resume treatment at ↓ 1 dose level If resolved in > 7 days (despite appropriate skin toxicity therapy), then permanently discontinue participant from capmatinib treatment
Grade 4, despite skin toxicity therapy	Omit dose and permanently discontinue participant from capmatinib treatment
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	
ILD /Pneumonitis	
Monitor participants for pulmonary symptoms indicative of ILD/pneumonitis. In addition, withhold capmatinib for acute onset of new or progressive unexplained pulmonary symptoms, such as dyspnea, cough and fever and during diagnostic workup for ILD/pneumonitis to exclude alternative causes such as, but not limited to infections, lymphangitic carcinomatosis, cardiogenic edema, or pulmonary hemorrhage.	
Grade 1	Interrupt capmatinib during diagnostic workup for ILD/Pneumonitis. Exclude infections and other etiologies. In presence of diagnosis of ILD/Pneumonitis after diagnostic workup, it is mandatory to permanently discontinue capmatinib. Only in the absence of a diagnosis of ILD/Pneumonitis, capmatinib may be restarted at the same dose. If it recurs after resumption of study drug, permanently discontinue capmatinib.
Grade 2	Mandatory: Interrupt capmatinib dose during diagnostic workup for ILD/pneumonitis until improvement to ≤ Grade 1. Exclude infections and other etiologies. In presence of diagnosis of ILD/Pneumonitis after diagnostic workup, it is mandatory to permanently discontinue capmatinib. Only in the absence of a diagnosis of ILD/Pneumonitis, capmatinib may be restarted following these guidelines: · If resolves to ≤ Grade 1 in ≤ 7 days reduce study drug by 1 dose level

	· If fails to resolve to ≤ Grade 1 within 7 days or recur after resumption of study drug at decreased dose, permanently discontinue capmatinib
Grade 3 and Grade 4	Mandatory: Permanently discontinue capmatinib. Treat with IV steroids as clinically indicated. Oxygen therapy as indicated
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	
Fatigue/ Asthenia	
Grade 1 or 2	Maintain dose level
Grade 3	Omit dose until resolved to ≤ grade 1, then: If resolved in ≤ 7 days, resume treatment at same dose level If resolved in > 7 days, resume treatment at ↓ 1 dose level
Peripheral edema	
Grade 1 or 2	Maintain dose level.
Grade 3	Omit dose until resolved to ≤ Grade 1, then ↓1 dose level
Grade 4	Permanently discontinue capmatinib
Other adverse events	
Grade 1 or 2	Maintain dose level, consider to initiate appropriate support medication. For any intolerable grade 2 (e.g. limiting instrumental ADL), consider omitting the dose until resolved to ≤ grade 1, then then restart either at same dose or ↓ 1 dose level.
Grade 3	Omit dose until resolved to ≤ grade 1, then↓ 1 dose level
Grade 4	Permanently discontinue capmatinib

All dose modifications should be based on the worst preceding toxicity.

a Common Toxicity Criteria for Adverse Events (CTCAE version 5.0).

b "Combined" defined as: total bilirubin increase to the defined threshold concurrently with ALT/AST increase to the defined threshold

c "Cholestasis" defined as: ALP elevation (> 2.0 x ULN and R value (ALT/ALP in x ULN) < 2.0) in participants without bone metastases, or elevation of ALP liver fraction in participants with bone metastases

d If combined elevations of AST or ALT and total bilirubin do not meet the defined thresholds, please follow the instructions for isolated elevation of total bilirubin and isolated elevation of AST/ALT, and take a conservative action based on the degree of the elevations (e.g. discontinue treatment at the situation when omit dose is needed for one parameter and discontinue treatment is required for another parameter). After all elevations resolve to the defined thresholds that allow treatment re-initiation, re-start the treatment either at the same dose or at one dose lower if meeting a criterion for dose reduction

* Note: If total bilirubin > 3.0 x ULN is due to the indirect (non-conjugated) component only, and hemolysis as the etiology has been ruled out as per institutional guidelines (e.g., review of peripheral blood smear and haptoglobin determination), then ↓ 1 dose level and continue treatment at the discretion of the investigator.

** Note: antidiarrheal medication is recommended at the first sign of abdominal cramping, loose stools or overt diarrhea

*** During the whole duration of treatment with capmatinib, the participant is recommended to use precautionary measures against ultraviolet exposure (e.g., use of sunscreen, protective clothing and avoid sunbathing or using a solarium intensively).

These dose changes must be recorded on the appropriate eCRF.

10.5.3 Toxicity Follow-up

Follow-up for toxicities

All participants will be followed for safety until 30 days after the last dose of neratinib and capmatinib . Participants whose treatment is temporarily interrupted or permanently discontinued due to an AE or abnormal laboratory value must be followed until resolution or stabilization of the event, whichever comes first, including all study assessments appropriate to monitor the event.

An unscheduled assessment should be performed in all cases below where toxicity monitoring is recommended more frequently than defined by the schedule of assessments. Subsequent monitoring must be performed as per the regular visit schedule.

Table 16. Follow-up Evaluations for Selected Toxicities*

TOXICITY	FOLLOW-UP EVALUATION
HEMATOLOGICAL	
Febrile neutropenia, Neutropenia ≥ CTCAE grade 3 Thrombocytopenia ≥ CTCAE grade 3 Anemia ≥ CTCAE grade 3	Test weekly (or more frequently if clinically indicated) until ≤ CTCAE grade 2. Perform physical exam for check on bruising in case of major thrombocytopenia.
RENAL	
Serum creatinine ≥ CTCAE grade 2	Test weekly (or more frequently if clinically indicated) until ≤ CTCAE grade 1 or baseline. Participants will be instructed to increase hydration until resolution to ≤ CTCAE grade 1 or baseline.
HEPATIC	
Isolated total bilirubin elevation	**Total bilirubin CTCAE Grade 1:** Monitor LFTs per protocol or more frequently if clinically indicated **Total bilirubin CTCAE Grade 2:**

TOXICITY	FOLLOW-UP EVALUATION
	Weekly monitoring of LFTs, or more frequently if clinically indicated, until resolved to ≤ 1.5 x ULN **Total bilirubin CTCAE Grade 3:** Weekly monitoring of LFTs, or more frequently if clinically indicated, until resolved to ≤ 1.5 x ULN. If resolved in > 7 days, after discontinuing the participant from capmatinib permanently, the participant should be monitored weekly (including LFTs), or more frequently if clinically indicated, until total bilirubin have resolved to baseline or stabilization over 4 weeks **Total bilirubin CTCAE Grade 4:** After discontinuing the participant from capmatinib permanently, the participant should be monitored weekly (including LFTs), or more frequently if clinically indicated, until total bilirubin have resolved to baseline or stabilization over 4 weeks
Isolated AST/ALT elevation	**AST/ALT CTCAE Grade 2 elevation:** For participants with baseline value ≤ 3.0 x ULN: repeat LFTs as soon as possible, preferably within 48-72 hr from awareness of the abnormal results; if abnormal lab values are confirmed upon the repeat test, then monitor LFTs weekly, or more frequently if clinically indicated, until resolved to ≤ 3.0 x ULN For participants with baseline value > 3.0 x ULN: monitor LFTs per protocol or more frequently if clinically indicated **AST/ALT CTCAE Grade 3 elevation:** For AST/ALT elevation > 5.0 - 10.0 x ULN: • For participants with baseline value ≤ 3.0 x ULN: repeat LFTs as soon as possible, preferably within 48-72 hr from awareness of the abnormal results; monitor LFTs weekly, or more frequently if clinically indicated, until resolved to ≤ 3.0 x ULN • For participants with baseline value > 3.0 x ULN: repeat LFTs as soon as possible, preferably within 48-72 hr from awareness of the abnormal results; if abnormal lab values are confirmed upon the repeat test, then monitor LFTs, weekly, or more frequently if clinically indicated, until resolved to ≤ 5.0 x ULN For AST/ALT elevation > 10.0 - 20.0 x ULN: • Repeat LFTs as soon as possible, preferably within 48-72 hr from awareness of the abnormal results; monitor LFTs weekly, or more frequently if clinically indicated, until resolved to ≤ baseline

TOXICITY	FOLLOW-UP EVALUATION
	AST/ALT CTCAE Grade 4 elevation: Repeat LFTs as soon as possible, preferably within 48-72 hr from awareness of the abnormal results; monitor LFTs weekly, or more frequently if clinically indicated, until resolved to baseline or stabilization over 4 weeks.
Combined elevations in ALT and/or AST with concurrent total bilirubin increase, in the absence of cholestasis or hemolysis	Combined elevations of AST or ALT and total bilirubin: After discontinuing the participant from capmatinib permanently, repeat LFTs as soon as possible, preferably within 48 hr from awareness of the abnormal results, then with weekly monitoring of LFTs, or more frequently if clinically indicated, until AST, ALT, or bilirubin have resolved to baseline or stabilization over 4 weeks. Core LFTs consist of ALT, AST, GGT, total bilirubin (fractionated [direct and indirect], if total bilirubin > 2.0 x ULN), and alkaline phosphatase (fractionated [quantification of isoforms], if alkaline phosphatase > 2.0 x ULN.)
METABOLIC	
Asymptomatic amylase or lipase ≥ CTCAE grade 3	Test weekly (or more frequently) until ≤ CTCAE grade 2. A CT scan or equivalent imaging procedure to assess the pancreas, liver, and gallbladder is recommended within 7 days of the first occurrence of any ≥ CTCAE grade 3 result, to exclude disease progression or potential other liver or pancreatic disease.
CARDIAC	
≥ CTCAE grade 3	Test weekly (or more frequently) until ≤ CTCAE grade 2.
QTcF ≥ 501 ms (CTCAE grade 3)	When QTcF ≥ 501 ms (CTCAE grade 3), perform the following: Perform an analysis of serum potassium, calcium, phosphorus, and magnesium, and if below lower limit of normal, correct with supplements to within normal limits. Review concomitant medication usage for the potential to prolong the QT-interval. Check compliance with correct dose and administration of capmatinib. Perform a repeat ECG within one hour of the first QTcF of ≥501 ms. If QTcF remains ≥ 501 ms, repeat ECG as clinically indicated, but at least once daily until the QTcF returns to < 501 ms. Repeat ECGs 7 days and 14 days (and then every 21 days) after dose resumption for all participants who had therapy interrupted due to QTcF ≥ 501 ms. If QTcF of ≥ 501 ms recurs, repeat ECGs as described above. Notes: *Call the study's central ECG review laboratory immediately and request an immediate manual read of the ECG"*

TOXICITY	FOLLOW-UP EVALUATION
	The investigator should contact the Novartis Medical Lead or designee regarding any questions that arise if a participant with QTcF prolongation should be maintained on study.
GASTROINTESTINAL	
Diarrhea	Investigate potential concomitant medication, food or comorbidity driven causes of diarrhea (including infectious causes) and remedy these causes if possible (e.g. discontinuation of concomitant medication, dietary modification, treatment of comorbidity). The participant should be monitored for signs of dehydration and instructed to take preventive measures against dehydration as soon as diarrhea occurs. Antidiarrheal medication must be initiated at the first sign of abdominal cramping, loose stools or overt diarrhea. Concomitant medication for the treatment of diarrhea should follow local practice and the investigator's best judgment and may follow "the recommended guidelines for the treatment of cancer treatment-induced diarrhea" (Benson et al 2004). For example: For uncomplicated diarrhea (grade 1 or 2 without complicating signs or symptoms), loperamide given at a standard dose (e.g. initial administration of 4 mg, then 2 mg every 2-4 hr, maximum of 16 mg/day), along with oral hydration and dietetic measures should be considered. Note: complicating signs or symptoms include moderate to severe cramping, decreased performance status, fever, neutropenia, frank bleeding or dehydration. For complicated diarrhea (all grade 3 or 4, grade 1-2 with complicating signs or symptoms), management should involve intravenous (IV) fluids, and consider treatment with octreotide (at starting dose of 100 to 150 µg sub-cutaneous tid or 25 to 50 µg IV) and antibiotics (e.g. fluoroquinolone) should be given
Nausea and Vomiting	The investigator should consider/investigate potential concomitant medication, food or comorbidity driven causes of nausea and/or vomiting and remedy these causes if possible (e.g. discontinuation of concomitant medication, dietary modification, treatment of comorbidity). Individualized supportive and anti-emetic treatment should be initiated, as appropriate, at the first signs and/or symptoms of these AEs. In participants with vomiting, the participant should be monitored for signs of dehydration and instructed to take preventive measures against dehydration. Concomitant medication for the treatment of nausea and/or vomiting should follow local practice and the investigator's best judgment.
SKIN TOXICITY	
Rash and Photosensitivity	

TOXICITY	FOLLOW-UP EVALUATION
CTCAE grade 1	Consider to initiate institute appropriate skin toxicity therapy (such as antihistamines, topical corticosteroids and low-dose systemic corticosteroids)
CTCAE grade 2	Initiate/intensify appropriate skin toxicity therapy (such as antihistamines, topical corticosteroids and low-dose systemic corticosteroids).
≥ CTCAE grade 3	Intensify appropriate skin toxicity therapy and monitor weekly or more frequently until resolved to grade ≤ 2
Peripheral edema	
CTCAE grade≤2	Consider to initiate conservative measures such as leg elevation, compression stockings, and dietary salt modification as clinically indicated.
CTCAE grade≥3	Initiate/intensify conservative measures
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	
ILD/Pneumonitis	
CTCAE Grade 1	CT scan (high-resolution with lung windows) recommended, with serial imaging to monitor for resolution or progression- re-image at least every 3 weeks Monitor for symptoms every 2-3 days - Clinical evaluation and laboratory work-up for infection Monitoring of oxygenation via pulse oximetry recommended Consultation of pulmonologist recommended
CTCAE Grade 2	CT scan (high-resolution with lung windows) • Monitor symptoms daily, consider hospitalization • Clinical evaluation and laboratory work up for infection • Consult pulmonologist • Pulmonary function tests a - if normal at baseline, repeat every 8 weeks • Bronchoscopy with biopsy and/or BAL recommended [c] Symptomatic therapy including corticosteroids if clinically indicated (1 to 2 mg/kg/day prednisone or equivalent as clinically indicated) b
CTCAE Grade 3 and Grade 4	CT scan (high-resolution with lung windows) Clinical evaluation and laboratory work-up for infection Consult pulmonologist Pulmonary function testsa-if < normal, repeat every 8 weeks until ≥ normal Bronchoscopy with biopsy and/or BAL if possiblec Treat with IV steroids (methylprednisolone 125 mg) as indicated. When symptoms improve to ≤ Grade 1, a high dose oral steroid

TOXICITY	FOLLOW-UP EVALUATION
	(prednisone 1 to 2 mg/kg once per day or dexamethasone 4 mg every 4 hr)b. If IV steroids followed by high dose oral steroids does not reduce initial symptoms within 48 to 72 hours, consider non-corticosteroid immunosuppressive medication

[a] PFT (Pulmonary function tests) to include: diffusing capacity corrected for hemoglobin (DLCO); spirometry; resting oxygen saturation

Guideline for significant deterioration in lung function: Decrease in spirometry and/or DLCO of 30% and/or O2 saturation ≤ 88% at rest on room air.

b Duration and dose of course of corticosteroids will vary according to circumstances but should be as limited as possible. Consider tapering dosage at end.

c If bronchoscopy is performed, bronchoalveolar lavage (BAL) should be done where possible to exclude alveolar hemorrhage, opportunistic infections, cell count + determination lymphocyte CD4/8 count where possible.

Follow-up on potential drug-induced liver injury (DILI) cases

Participants with transaminase increase combined with total bilirubin increase may be indicative of potentially severe drug- induced liver injury (DILI) and should be considered as clinically important events and assessed appropriately to establish the diagnosis. The required clinical information, as detailed below, should be sought to obtain the medical diagnosis of the most likely cause of the observed laboratory abnormalities.

The threshold for potential DILI may depend on the participant's baseline AST/ALT and total bilirubin value; participants meeting any of the following criteria will require further follow-up as outlined below:

- For participants with normal ALT and AST and total bilirubin value at baseline: AST or ALT > 3.0 x ULN combined with total bilirubin > 2.0 x ULN
- For participants with elevated AST or ALT or total bilirubin value at baseline: [AST or ALT >3.0 x baseline] OR [ALT or AST > 8.0 x ULN], whichever is lower, combined with [total bilirubin > 2.0 x baseline AND > 2.0 x ULN]

As DILI is essentially a diagnosis of exclusion, other causes of abnormal liver tests should be considered and their role clarified before DILI is assumed as the cause of liver injury.

A detailed history, including relevant information such as review of ethanol consumption, concomitant medications, herbal remedies, supplement consumption, history of any pre-existing liver conditions or risk factors, should be collected.

Laboratory tests should include ALT, AST, total bilirubin, direct and indirect bilirubin, GGT, GLDH, prothrombin time (PT)/ International normalized ratio (INR), alkaline phosphatase, albumin, and creatine kinase.

Evaluate status of liver metastases (new or exacerbation) or vascular occlusion – e.g. using CT, MRI, or duplex sonography.

Perform relevant examinations (Ultrasound or MRI, ERCP) as appropriate, to rule out an extrahepatic cause of cholestasis. Cholestasis (is defined as an ALP elevation > 2.0 x ULN with R value < 2 in participants without bone metastases, or elevation of the liver-specific ALP isoenzyme in participants with bone metastases).

Note: The R value is calculated by dividing the ALT by the ALP, using multiples of the ULN for both values. It denotes whether the relative pattern of ALT and/or ALP elevation is due to cholestatic (R ≤ 2), hepatocellular (R ≥ 5), or mixed (R >2 and < 5) liver injury. In clinical situations where it is suspected that ALP elevations are from an extrahepatic source, the GGT can be used if available. GGT may be less specific than ALP as a marker of cholestatic injury, since GGT can also be elevated by enzyme induction or by ethanol consumption. It is more sensitive than ALP for detecting bile duct injury (livertox.nih.gov/rucam.html).

Table 17 provides guidance on specific clinical and diagnostic assessments which can be performed to rule out possible alternative causes of observed LFT abnormalities.

Table 17. Clinical And Diagnostic Assessments for LFT Abnormalities

Disease	Assessment
Hepatitis A, B, C, E	IgM anti-HAV; HBsAg, IgM & IgG anti-HBc, HBV DNA; anti-HCV, HCV RNA, IgM & IgG anti-HEV, HEV RNA
CMV, HSV, EBV infection	IgM & IgG anti-CMV, IgM & IgG anti-HSV; IgM & IgG anti-EBV
Autoimmune hepatitis	ANA & ASMA titers, total IgM, IgG, IgE, IgA
Alcoholic hepatitis	Ethanol history, GGT, MCV, CD-transferrin
Nonalcoholic steatohepatitis	Ultrasound or MRI
Hypoxic/ischemic hepatopathy	Medical history: acute or chronic CHF, hypotension, hypoxia, hepatic venous occlusion. Ultrasound or MRI.
Biliary tract disease	Ultrasound or MRI, ERCP as appropriate.
Wilson disease (if <40 yrs old)	Ceruloplasmin
Hemochromatosis	Ferritin, transferrin
Alpha-1-antitrypsin deficiency	Alpha-1-antitrypsin

Other causes should also be considered based upon participants' medical history (hyperthyroidism / thyrotoxic hepatitis – T3, T4, TSH; CVD / ischemic hepatitis – ECG, prior hypotensive episodes; T1D / glycogenic hepatitis).

Obtain PK sample to determine exposure to study treatment and metabolites.

Following appropriate causality assessments, as outlined above, the causality of the treatment is estimated as "probable" i.e. >50% likely, if it appears greater than all other possible causes of liver injury combined. The term "treatment-induced" indicates *probably caused* by the treatment, not by something else, and only such a case can be considered a DILI case and should be reported as an SAE.

All cases confirmed on repeat testing meeting the laboratory criteria defined above, with no other alternative cause for LFT abnormalities identified, should be considered as "medically significant," and thus, meet the definition of SAE and should be reported as SAE using the term "potential treatment-induced liver injury." All events should be followed up with the outcome clearly documented.

11.0 Tumor Response Evaluation Criteria

11.1 Evaluation of Target Lesions

This section provides the definitions of the criteria used to determine objective tumor response for 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 diameters of target lesions, taking as reference the baseline sum of diameters
- Progressive disease (PD): at least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (nadir), including baseline
  In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm.
  The appearance of one or more new lesions is also 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 on study

11.2 Evaluation of Non-Target Lesions

This section provides the definitions of the criteria used to determine the tumor response for the group of non-target lesions. While some non-target lesions may actually be measurable, they need not be measured and, instead, should be assessed only qualitatively at the time points specified in the protocol.

- CR: disappearance of all non-target lesions and (if applicable) normalization of tumor marker level)
  All lymph nodes must be non-pathological in size (< 10 mm short axis).
- Non-CR/Non-PD: persistence of one or more non-target lesion(s) and/or (if applicable) maintenance of tumor marker level above the normal limits
- PD: unequivocal the appearance of one or more new lesions is also considered progression.

12.0 Safety Monitoring and Reporting

All study patients who have received neratinib and capmatinib as combination therapy will be evaluable for safety. The ongoing review of safety data will include review of clinical AEs and SAEs.

12.1 Adverse Event

12.1.1 Adverse Event Definition

An Adverse Event is defined as any untoward medical occurrence in a patient regardless of its causal relationship to study treatment. An AE can be any unfavorable and unintended sign

(including any clinically significant abnormal laboratory test result), symptom, or disease temporally associated with the use of the study treatment, whether or not it is considered to be study drug(s) related. Included in this definition are any newly occurring events and any previous condition that has increased in severity or frequency since the administration of study

12.1.2 Adverse Event Attribution

Attribution is the determination of whether an adverse event is related to a medical treatment or procedure.

Definite - the adverse event is clearly related to the investigational agent(s).

Probable - the adverse event is likely related to the investigational agent(s).

Possible - the adverse event may be related to the investigational agent(s).

Unlikely - The adverse event is doubtfully related to the investigational agent(s).

Unrelated - The adverse event is clearly NOT related to the investigational agent(s).

The Study PI or designee will be responsible for assigning attribution of adverse events to the study agent and signing the case report form.

12.1.3 Adverse Event Severity

The severity of the adverse events (AEs) will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) 5.0. Events not included in the NCI CTCAE will be scored as follows:

General grading:

Grade 1: Mild: discomfort present with no disruption of daily activity, no treatment required beyond prophylaxis.

Grade 2: Moderate: discomfort present with some disruption of daily activity, require treatment.

Grade 3: Severe: discomfort that interrupts normal daily activity, not responding to first line treatment.

Grade 4: Life Threatening: discomfort that represents immediate risk of death

Grade 5: Fatal

12.1.4 Adverse Event Recording

Adverse events and Serious Adverse Events will be captured in the study database REDCap.

All AEs and SAEs will be captured during the study Phase 1b portion. For the Phase II portion of the study, only AEs >/= grade 2 non-hematological and >/= grade 3 hematological AEs, occurring after first protocol intervention observed by the investigator or reported by the subject (whether or not attributed to investigational product), will be documented in the medical record and recorded in RedCap. Baseline toxicities will be documented in the patients' medical record.

Abnormal laboratory values will not be reported as AEs; however, the abnormal laboratory value is considered to be an AE if the abnormality:

- Results in discontinuation from the study
- Requires treatment, modification/interruption of study treatment dose, or any other therapeutic intervention
- Is judged to be of significant clinical importance
- If a laboratory abnormality is one component of a diagnosis or syndrome, then only the diagnosis or syndrome should be recorded on the AE page of the eCRF. If the abnormality was not a part of a diagnosis or syndrome, then the laboratory abnormality should be recorded as the AE.

12.2 Serious Adverse Event Reporting (SAE)

12.2.1 Internal SAE reporting to Investigational New Drug (IND) Office

Serious Adverse Event (SAE) Reporting Requirements for M D Anderson Sponsor Single Site IND Protocols

An adverse event or suspected adverse reaction is considered "serious" if, in the view of either the investigator or the sponsor, it results in any of the following outcomes:

- Death
- A life-threatening adverse event
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- A congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse (21 CFR 312.32).

- Important medical events as defined above, may also be considered serious adverse events. Any important medical event can and should be reported as an SAE if deemed appropriate by the Principal Investigator or the IND Sponsor, IND Office.
- All events occurring during the conduct of a protocol and meeting the definition of a SAE must be reported to the IRB in accordance with the timeframes and procedures outlined in "The University of Texas M. D. Anderson Cancer Center Institutional Review Board Policy on Reporting Adverse Events for Drugs and Devices".

- Serious adverse events will be captured from the time of the first protocol-specific intervention, until 30 days after the last dose, unless the participant withdraws consent.
- Serious adverse events must be followed until clinical recovery is complete and laboratory tests have returned to baseline, progression of the event has stabilized, or there has been acceptable resolution of the event.
- All SAEs, expected or unexpected/ initial or follow up, must be reported to the IND Office **within 5 working days of knowledge of the event** regardless of the attribution**.**
- Death or life-threatening events that are unexpected, possibly, probably or definitely related to drug must be reported (initial or follow up) to the IND Office **within 24 hours of knowledge of the event**
- Additionally, any serious adverse events that occur after the 30-day time period that are related to the study treatment must be reported to the IND Office. This may include the development of a secondary malignancy.
- The electronic SAE application (eSAE) will be utilized for safety reporting to the IND Office and MD Anderson IRB.
- All events reported to the supporting company must also be reported to the IND Office

Reporting to FDA:

- Serious adverse events will be forwarded to FDA by the IND Sponsor according to 21 CFR 312.32.

It is the responsibility of the PI and the research team to ensure serious adverse events are reported according to the Code of Federal Regulations, Good Clinical Practices, the protocol guidelines, the sponsor's guidelines, and Institutional Review Board policy.

12.2.3 Investigator Communication with Supporting Company

The MDACC Internal SAE Report Form will be used for reporting to Puma Biotechnology Inc. and Novartis and reporting timeline is as below:

- Death that is unanticipated and definitely, probably or possibly related to study intervention that occur any time from the first protocol-specific intervention, until 30-days after the last day of active study intervention will be reported to Puma Biotechnology Inc. and Novartis within 24 working hours, not including holidays.
- All other SAEs regardless of suspected causality (unanticipated, and definitely, probably or possibly related to study drugs) will be reported to Puma Biotechnology Inc. and Novartis within 24 working hours, not including holidays. The investigator must assess and record the relationship of each SAE to each specific study treatment (if there is more than one study treatment), and submit the completed form to Puma via email to PumaSAE@parexel.com and to Novartis via email to clinicalsafetyop.phuseh@novartis.com (Fax: + 1 877 778 9739).

- Any additional information for the SAE including complications, progression of the initial SAE, and recurrent episodes must be reported as follow-up to the original episode within 24 hours of the investigator receiving the follow-up information. An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one should be reported separately as a new event.
- Any SAEs experienced after the 30-day safety follow-up period should only be reported to Novartis if the investigator suspects a causal relationship to the study treatment.
- Follow-up information is submitted in the same way as the original SAE Report. Each re-occurrence, complication, or progression of the original event should be reported as a follow-up to that event regardless of when it occurs. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, whether the blind was broken or not, and whether the subject continued or withdrew from study participation.
- If the SAE is not previously documented in the Investigator's Brochure or Package Insert (new occurrence) and is thought to be related to the Novartis study treatment, an oncology Novartis Chief Medical Office and Patient Safety (CMO&PS) department associate may urgently require further information from the investigator for Health Authority reporting. Novartis may need to issue an Investigator Notification (IN), to inform all investigators involved in any study with the same drug that this SAE has been reported. Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with Directive 2001/20/EC or as per national regulatory requirements in participating countries.
- Other events requiring reporting - Pregnancy

  To ensure subject safety, each pregnancy occurring while the subject is on study treatment must be reported to Novartis within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

13.0 Statistical Consideration

Safety will be evaluated in this study through the monitoring of adverse events and serious adverse events defined as Section 12.1. This is an IND study and will be monitored by MD Anderson IND office.

13.1 Phase 1b Dose-Finding Design

We will employ the Bayesian optimal interval (BOIN) design (Liu and Yuan, 2015; Yuan et al., 2016) (24, 25), with the 3+3 design run-in, to find the MTD (see Appendix 1 for design parameters). The BOIN design is implemented in a simple way similar to the traditional 3+3 design, but is more flexible and possesses superior operating characteristics that are comparable to those of the more complex model-based designs, such as the continual reassessment method (CRM) (Zhou et al., 2018)(26).

The target toxicity rate for the MTD is $\phi = 0.25$ and the maximum sample size for dose escalation is 18. We will enroll and treat patients in cohorts of size 3. DLTs are defined in **Section 7.4** and only those DLTs that occur within **the first 2 cycles (56 days)** will be used for dose finding. As shown in Figure 2, the BOIN design uses the following rule, optimized to minimize the probability of incorrect dose assignment, to guide dose escalation/de-escalation:

- if the observed DLT rate at the current dose is ≤ 0.197, escalate the dose to the next higher dose level;
- if the observed DLT rate at the current dose is > 0.298, de-escalate the dose to the next lower dose level;
- otherwise, stay at the current dose.

The 3+3 design run-in will be applied to override the above decision rule when the number of patients treated at the current dose is 3. That is, we will escalate the dose if 0/3 DLT, stay at the current dose if 1/3 DLT, and de-escalate the dose if >= 2/3 DLTs. For the purpose of overdose control, doses j and higher levels will be eliminated from further examination if $\Pr(p_j > 0.25 \mid \text{data}) > 0.95$ and at least 3 evaluable patients have been treated at dose level j, where p_j is the true DLT rate of dose level $j, j = 1,\cdots, 3$. This posterior probability is evaluated based on the beta-binomial model $y_j \mid p_j \sim \text{binomial}(p_j)$ with $p_j \sim \text{uniform}(0,1)$, where y_j is the number of patients experienced DLT at dose level j. When the lowest dose is eliminated, stop the trial for safety. The probability cutoff 0.95 is chosen to be consistent with the common practice that when the target DLT rate <=1/6, a dose with 2/3 patients experienced DLT is eliminated. The above dose escalation/de-escalation and elimination rule can be equivalently presented in Table 18, which will be used to conduct the trial.

The steps to implement the BOIN design are described as follows:

1. Patients in the first cohort are treated at dose level 1.
2. To assign a dose to the next cohort of patients, conduct dose escalation/de-escalation according to the rule displayed in Table 18. When using Table 18, please note the following:
    a. “Eliminate” means eliminate the current and higher doses from the trial to prevent treating any future patients at these doses because they are overly toxic.
    b. When we eliminate a dose, automatically de-escalate the dose to the next lower level. When the lowest dose is eliminated, stop the trial for safety. In this case, no dose should be selected as the MTD.
    c. If none of the actions (i.e., escalation, de-escalation or elimination) is triggered, treat the new patients at the current dose.
    d. If the current dose is the lowest dose and the rule indicates dose de-escalation, treat the new patients at the lowest dose unless the number of DLTs reaches the elimination boundary, at which point terminate the trial for safety.

e. If the current dose is the highest dose and the rule indicates dose escalation, treat the new patients at the highest dose.

3. Repeat step 2 until the maximum sample size of 18 is reached, or stop the trial if the number of evaluable patients treated at the current dose reaches 9.

Table 18. Dose Escalation/Deescalation Rule for the BOIN Design

	Number of evaluable patients treated at current dose											
	1	2	3	4	5	6	7	8	9	10	11	12
Escalate if # of DLT <=	0	0	0	0	0	1	1	1	1	1	2	2
Deescalate if # of DLT >=	1	1	2*	2	2	2	3	3	3	3	4	4
Eliminate if # of DLT >=	NA	NA	3	3	3	4	4	4	5	5	6	6

Note. “# of DLT” is the number of patients with at least 1 DLT. When none of the actions (i.e., escalate, de-escalate or eliminate) is triggered, stay at the current dose for treating the next cohort of patients. “NA” means that a dose cannot be eliminated before treating 3 evaluable patients. “*" indicates the 3+3 design run-in.

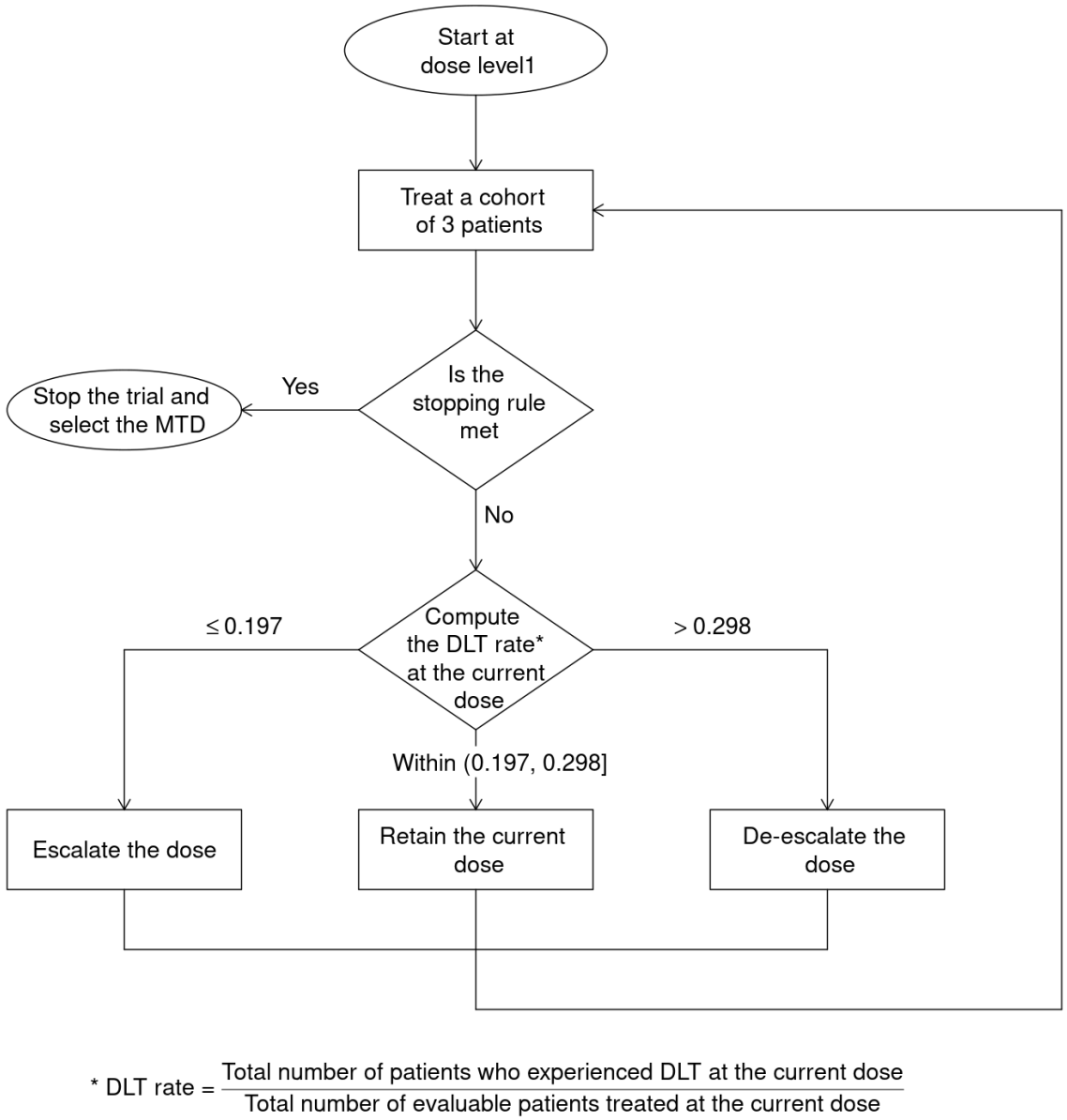


Figure 2. Flowchart for trial conduct using the BOIN design

After the trial is completed, select the MTD based on isotonic regression as specified in Liu and Yuan (2015) (24). This computation is implemented by the shiny app "BOIN" (Zhou et al., 2020) (27) available at http://www.trialdesign.org. Specifically, select as the MTD the dose for which the isotonic estimate of the toxicity rate is closest to the target toxicity rate. If there are ties, select the higher dose level when the isotonic estimate is lower than the target toxicity rate and select the lower dose level when the isotonic estimate is greater than or equal to the target toxicity rate.

Operating Characteristics

Table 19 shows the operating characteristics of the trial design based on 1000 simulations of the trial using shiny app "BOIN" (BOIN V2.6.3.0) available at http://www.trialdesign.org. The operating characteristics show that the design selects the true MTD, if any, with high probability and allocates more patients to the dose levels with the DLT rate closest to the target of 0.25.

Table 19. Operating Characteristics of the BOIN Design

	Dose Level -2	Dose Level -1	Dose Level 1	Dose Level 2	Dose Level 3	Number of Patients	% Early Stopping
Scenario 1							
True DLT Rate	0.25	0.41	0.45	0.49	0.53		
Selection %	50.1	29	13.2	2.4	0.7		4.6
% Pts Treated	24.7	32.2	34	7.6	1.4	17.2	
Scenario 2							
True DLT Rate	0.12	0.25	0.42	0.49	0.55		
Selection %	19	52.1	24.1	4	0.6		0.2
% Pts Treated	12.2	35.7	41.4	9.2	1.5	17.1	
Scenario 3							
True DLT Rate	0.04	0.12	0.25	0.43	0.63		
Selection %	0.7	18.4	62.8	17.4	0.7		0
% Pts Treated	1.7	19	50.6	24.6	4	16.6	
Scenario 4							
True DLT Rate	0.02	0.06	0.1	0.25	0.4		
Selection %	0	0.5	25.3	54.2	20		0
% Pts Treated	0	2.6	35.9	39.2	22.2	17.1	

Note: "% Early Stopping"" refers to early stopping due to excessive DLT.

13.2 Phase II Single-Arm Toxicity Monitoring and Efficacy Trial

Phase II single-arm trial will be conducted to assess the overall response rate (ORR) for patients treated at the MTD. Only patients with abnormal HER-family and c-Met signaling activity based on CELsignia MP Test results will be included in the efficacy analysis. The target ORR will be 25%, with unacceptable ORR as 5%.

We will monitor the ORR using the Bayesian optimal phase 2 (BOP2) design (Zhou, Lee and Yuan, 2017)[28]. The assessment window for ORR monitoring is 4 cycles. Specifically, let n

denote the interim sample size and N denote the maximum sample size. Let p_{eff} denote the ORR and define the null hypothesis $H_0: p_{eff} \leq 0.05$, under which the treatment is deemed as unacceptable. We will stop enrolling patients and claim that the treatment is unacceptable if

$$Pr(p_{eff} > 0.05|data) < \lambda \left(\frac{n}{N}\right)^{\alpha},$$

where λ=0.84 and α=0.86 are design parameters optimized to maximize power under the alternative hypothesis $H_1: p_{eff} = 0.25$, (i.e., the probability of correctly claiming that the treatment is acceptable under H_1), while controlling the type I error rate (i.e., the probability of incorrectly claiming that the treatment is acceptable under H_0) at 0.05. This optimization is performed assuming a vague prior Beta(0.05,0.95) for p_{eff}. The above decision rule leads to the following stopping boundaries and yields a statistical power of 0.95 under H_1:

Table 20. Optimized Stopping Boundaries

# patients treated	Stop if # responses <=
15	0
29	3

Based on Table 20, we perform the interim analysis when the number of enrolled patients reaches 15. When the total number of patients reaches the maximum sample size of 29, we reject the null hypothesis and conclude that the treatment is acceptable if the number of responses is greater than 3; otherwise we conclude that the treatment is unacceptable. The go/no-go criteria in Table 20 are non-binding and final decision will be based on the total evidence of efficacy.

Below are the operating characteristics of the design based on 10000 simulations using the BOP2 web application, which is available at http://www.trialdesign.org.

Table 21. Operating Characteristics

Response rate	Early stopping (%)	Claim promising (%)	Sample size
0.05	46.3	5.3	22.5
0.15	8.7	63.9	27.8
0.25	1.3	94.8	28.8
0.35	0.2	99.6	29.0

Toxicity monitoring

We will monitor the Grade 3+ toxicity rate over 2 treatment cycles (28 days/cycle). Patients treated on Phase 1b at the MTD will be included for Phase II toxicity monitoring. Assuming 9

patients from phase 1b, the total sample size for toxicity monitoring will be 29+9=38. Formally, we will stop accrual if at any time: Pr (Grade 3+ toxicity > 0.20 | Data) > 0.90, with a prior beta(0.1, 0.4). Stopping boundaries given an initial cohort of 6 followed by cohorts of 6 patients and with a total of up to 38 patients are:

Table 22. Safety Stopping Boundaries for Phase II

Number of Total Patients (Cohorts of 6)	Discontinuation of arm if Grade 3+ toxicity >=
6	3
12	5
18	7
24	8
30	10
38	12

Below shows the operating characteristics of toxicity monitoring rule:

Table 23. Operating Characteristics of Toxicity Monitoring

True Toxicity	Probability of Early Stop	Avg. N Patients*
.1	.02	37.4
.2	.19	33.0
.3	.57	23.9
.4	.89	14.7
.5	.99	9.7

*include assumed 9 patients in phase I

Considering that patients with ER+ breast cancer will receive additional treatment with an aromatase inhibitor, in addition to the above overall toxicity monitoring rule, we will perform additional safety monitoring for the first 3 and 6 patients of ER+ breast cancer patients using the BOIN de-escalation boundaries provided in Table 18. That is, ≥ 2 out of 3 or 6 ER+ breast cancer patients experience a DLT after receiving additional treatment with an aromatase inhibitor, the enrollment of ER+ breast cancer will be paused and dose reduction may be performed for ER+ breast cancer patients based on the totality of the data.

Analyses of secondary outcomes will occur after all subjects have completed the study or completed at least 3 treatment cycles, each spanning 28 days, for a total of 84 days. A 95% level of confidence will be assumed.

Incidence of adverse events will be summarized by CTCAE level as counts with percentages.

Clinical benefit rate (CBR) is defined as the rate of patients who achieved complete response, partial response and stable disease for ≥ 24 weeks. The CBR proportion will be reported together with 95% confidence interval.

Duration of response (DOR) is defined as the period from the date of the first occurrence of a CR or PR until the first date that progressive disease or death is documented. Progression-Free survival (PFS) is defined as the time from treatment onset to either disease progression or death from any cause. 2 year overall survival (OS) is defined as the time from treatment onset to death over 2 years. For events that have not occurred by the time of data analysis, times will be censored at the last contact at which the patient was known to be progression-free for DOR and PFS, or the last time the patient was known to be alive for OS. DOR, PFS and OS will be summarized by the Kaplan-Meier method, including estimates of median and mean survival along with 95% CI.

IND Office Safety and Efficacy Stopping Rule Monitoring:

The Investigator is responsible for completing toxicity summary reports and submitting them to the IND office Medical Monitor for review. These should be submitted as follows:

- **Phase 1b Dose-Finding:**
    - A toxicity summary will be submitted after the first 3 evaluable patients complete 2 cycles (56 days) of study treatment, and every 3 evaluable patients thereafter, prior to changing dose levels or moving to the study Phase II portion. IND Sponsor approval will be obtained after each submission, prior to enrolling additional subjects.

- **Phase II – Toxicity Monitoring:**

    A toxicity summary will be submitted after every 6 evaluable subjects complete 2 cycles (56 days) of study treatment until enrollment is complete. Patients treated at the MTD in the phase I portion will be included for phase II toxicity monitoring evaluation.
    - An additional toxicity summary will be submitted for the subjects with ER+ breast cancer treated at the MTD with AI therapy, after the first 3, and first 6 evaluable patients with ER+ breast cancer treated at the MTD with AI therapy complete 2 cycles (56 days) of study treatment. This toxicity summary may include patients with ER+/HER2- breast cancer treated at the MTD in phase 1b and phase 2. If ≥ 2 out of 3 or 6 patients with ER+ breast cancer experience a DLT at the MTD, the MTD may be decreased to a lower dose level and used for patients with ER+ HER2 negative breast cancer in phase 2.

- **Phase II – Efficacy Monitoring:**

    An efficacy summary will be submitted after 15 evaluable subjects complete 4 cycles of study treatment. Final efficacy summary will be submitted when enrollment is complete. Only patients with abnormal HER-family and c-Met

signaling activity based on CELsignia MP Test results will be included in the efficacy analysis.

A copy of each safety summary report should be placed in the Investigator's Regulatory Binder under "Protocol Summary".

14.0 Data Management

The Principal Investigator is responsible for assuring that the data entered into the database is complete and accurate and that data entry is performed in a timely manner. RedCap will be used as the electronic case report form for this protocol and protocol specific data will be entered into RedCap.

CORe (Clinical Oncology Research system) will be utilized for subject enrollment/registration.

14.1 Data collection

Data collection for this study including:

- Demographic information (sex, race, and date of birth)
- Date of initial breast cancer diagnosis, pathology report of primary breast cancer, biomarker status, and date and location of distant metastases at disease progression
- History of breast cancer surgery, and radiation therapy, if applicable
- Date and type of chemotherapy and/or hormonal therapy for metastatic disease

All AEs will be collected. See details at 12.1.4.

Concomitant medication will be recorded per standard of care in clinic database and will not be recorded in the study database.

14.2 Data confidentiality plan

Participant confidentiality and privacy is strictly held in trust by the participating investigator, their staff, the safety and oversight monitor(s), and the sponsor(s) and funding agency. This confidentiality is extended to the data being collected as part of this study. Data that could be used to identify a specific study participant will be held in strict confidence within the research team. No personally identifiable information from the study will be released to any unauthorized third party without prior written approval of the sponsor/funding agency, as applicable.

All research activities will be conducted in as private a setting as possible.

All laboratory and clinical data gathered in this protocol will be stored in a password-protected database. All patient information will be handled using anonymous identifiers. Linkage to patient identity will be possible only after accessing a password-protected database. Access to the database will be available only to individuals directly involved in the study.

Access to Study Records

Study records may be accessed by IRB approved study personnel, or authorized inspectors. The study monitor, other authorized representatives of the sponsor or funding agency, representatives of the Institutional Review Board (IRB), regulatory agencies or representatives from companies or organizations supplying the product, may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

Methods of Storage of Study Records

All data collected from MD Anderson Cancer Center (MDACC) sources will be maintained on a password protected server compliant with HIPAA. Study staff will have role based restricted access to directories and files on the server, according to project responsibilities. Only those with data entry permissions can add records. The PI or a delegate will review the conditions under which data will be released to recipient- investigators. Each application for use will need IRB approval and consents, if appropriate. The level of identifiability will determine the process for review and approval as well as the way information is shared.

Any study data or records maintained in paper documents will be stored in the offices of the PI or other delegated study staff, in a locked cabinet or other comparable controlled environment, and will be accessible only to authorized study team members or authorized inspectors.

Information gathered for this study will be banked for future research with IRB approval. Once the research has been completed, identifiers will be retained for as long as is required by law and by institutional regulations, and at that point will be destroyed.

Sharing of Study Records

There are no plans to share study data with entities external to MD Anderson Cancer Center, aside from authorized inspectors as applicable (i.e. authorized representatives of the sponsor or funding agency, representatives of the Institutional Review Board (IRB), regulatory agencies or representatives from companies or organizations supplying the product). If data will be shared, IRB approval will be sought, and applicable inter-institutional agreements executed, prior to data sharing.

14.3 Data and Safety Monitoring

Data and Safety Monitoring is the process for reviewing data collected as research progresses to ensure the continued safety of current and future participants as well as the scientific validity and integrity of the research. Studies conducted at MD Anderson will follow the DSMP that has been approved by the NCI.

The Principal Investigator is ultimately responsible for the conduct and monitoring of all aspects of the study on an ongoing basis. The Principal Investigator will provide an annual review and report of the study, including all adverse events, accrual information, efficacy and response data, along with overall study progress and continuation plans to MD Anderson's Data and Safety Monitoring Committees (DSMC) responsible for study oversight.

14.4 Clinical Trial Monitoring

Regular monitoring of trial conduct will be conducted to ensure that the rights and well-being of trial participants are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol/amendment(s), with ICH GCP, and with applicable regulatory requirement(s).

15. Consent Process and Documentation

This protocol will follow the SOP 04_Informed Consent Process. SOP 04 has been read by the research staff and investigators. Informed consent may be obtained using in-person consent and/or remote consent.

16.0 References

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18. NCT03812393 Phase II Trial to Evaluate the Efficacy and Safety of Neoadjuvant Neratinib Followed by Weekly Paclitaxel and Carboplatin Plus Neratinib in Early Stage Triple-Negative Breast Cancer Patients Who Exhibit Enhanced HER2 Signaling by Live Cell HER2 Signaling Transduction Analysis.

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Appendix 1: Phase Ib Trial and Design Specifications

Parameter	Value
Number of doses	5
Starting dose	3
Max sample size	18
Cohort size	3
Stop trial if # patients assigned to single dose reaches	9
Apply the 3+3 design run-in	TRUE
Use accelerated titration	FALSE
Target toxicity probability	0.25
Use the default alternatives to minimize decision errors	TRUE
Alternative (unacceptable high toxicity) for optimization	Default
Alternative (unacceptable low toxicity) for optimization	Default
Eliminate dose threshold	0.95
Impose a more stringent safety stopping rule	FALSE
Require the isotonic estimate of the DLT probability for the dose selected as the MTD less than the de-escalation boundary	FALSE
Number of repetitions per scenario	1000
Random number generator seed	6

Appendix 2: CELsignia Collection Kit User Instructions Card

CELsignia breast

Collection Kit User Instructions Card

This Collection kit includes:

QTY.	ITEM
1	**Instruction Card** (this document)
1	**Kit Box with FedEx Return Service Label** *(**DO NOT DISCARD**: use this same box to ship specimen to Celcuity)*
1	**Internal Styrofoam Container**
1	**2-part Specimen Collection Requisition** with Labels
1	**6" x 9" Specimen Bag** with 3" x 4" Absorbent Sheet
1	**6.5" x 5" Foil Bubble Pouch**
1	**Ambient 3oz Gel Pack**
1	**10mL Vial** (filled)
1	**7.5oz Polar Pack Brick** *(Place flat in freezer)*
1	**15oz Polar Pack Brick** *(Place flat in freezer)*
1	**Red Security Seal**

Note: The 6" x 9" Specimen Bag will include a 3" x 4" absorbent sheet and a Foil Bubble Pouch with the 10mL vial, 3oz ambient gel pack inside.

Contact Information

If you have any questions regarding the tumor sampling procedure, or if you require additional CELsignia Specimen Collection Kits, please contact Celcuity.

Email: http://celcuity.com/contact/
Phone: 844-310-3900

The Day of the Biopsy Procedure

IMPORTANT: Do not discard this Kit Box or Internal Styrofoam Container! These will be used to ship the biopsy specimen.

1. Open the Specimen Collection Kit box and remove this Instruction Card and the 2-part Specimen Collection Requisition form.
2. Remove the lid from the Styrofoam Container, leaving the Styrofoam Container inside the kit/shipping box.
3. Remove the (2) Polar Pack Bricks – 1 large and 1 small found in the Styrofoam Container and place them in the storage freezer taking care to lay them flat.

   These 2 Polar Pack Bricks will be used as replacements to the ones in the "Celcuity Polar Pack Brick Bag." The **Polar Pack Bricks must be frozen for at least 24 hours** before use in order to maintain the integrity of the biopsy specimen.
4. Pull 2 frozen Polar Pack Bricks (1 large and 1 small) that are in the "Celcuity Polar Pack Brick Bag" from the freezer and place in Styrofoam Container. ***The biopsy specimen must be packaged and shipped with 1 large and 1 small frozen Polar Pack Bricks in order to maintain the integrity of the biopsy specimen.***
5. Replace Styrofoam lid and place this Instruction Card and the 2-part Specimen Collection Requisition form back into the box until the biopsy procedure.

Kit instructions are continued on the back of this card.

During the Biopsy Procedure

IMPORTANT FOR BIOPSY PROCEDURE:

- ***2 core biopsy specimens are preferred, 1 is acceptable.***
- ***Minimum 14 gauge needle required.***
- ***Specimen must be placed in the 10mL vial that contains the tissue preservative within 1 hour of removal.***

1. Remove 2-part Specimen Collection Requisition form and set aside.
2. Remove the Foil Bubble Pouch from 6" x 9" Specimen Bag. Ensure that the 3" x 4" absorbent sheet remains inside the 6" x 9" Specimen Bag.
3. Remove **ONLY** the 10mL vial from the Foil Bubble Pouch. This bag also includes an ambient gel pack DO NOT REMOVE THIS, leave it in the foil pouch.
4. Remove the biopsy specimen from the biopsy tool and place the tissue specimen in the 10mL vial, and then close the 10mL vial, ensuring cap is snug.
5. Place one of the bar code labels from the Specimen Collection Requisition on the 10mL specimen vial, along with a second subject identifier (DOB).
6. Place the labeled 10mL vial that contains the specimen back into the Foil Bubble Pouch with the ambient gel pack and peel off the closure tape, fold and seal it.
7. Place the Foil Bubble Pouch now containing the biopsy specimen vial and ambient gel pack back into the 6" x 9" Specimen Bag with absorbent sheet and seal the bag.
8. Place the (1) large frozen Polar Pack Brick on the bottom of the Styrofoam Container, place the Specimen Bag directly on top of it, and:
9. Place the remaining smaller frozen Polar Pack Brick on top of the sealed Specimen Bag.

IMPORTANT: It's critical the prior instructions are followed as outlined in order to maintain the integrity of the biopsy specimen. This process will ensure the biopsy specimen temperature maintains between 0° and 8°C during shipment.

10. Place the lid on top of the Styrofoam Container. The lid should fit snuggly.
11. Complete the 2-part Specimen Collection Requisition. Note, the remaining 3 bar code labels are for your use (on patient's records).

    Please place the completed top copy of the requisition inside the shipping box, on top of the Styrofoam lid.
12. Close and secure the kit box flap with Styrofoam Container inside. Place the Red Security Seal over flap to secure it.

IMPORTANT: The Specimen Collection Kit must be picked-up for shipment the same day the specimen is obtained.

Shipping the Specimen Kit

1. **Call FedEx for pick-up that day** and ensure that the FedEx Shipping Label is still affixed to the kit/shipping Box. FedEx Shipping label was already affixed to the kit box when it was received.
2. **Send an Email the day of the procedure to http://celcuity.com/contact/ to alert Celcuity that a tissue specimen has been shipped.**

A MATERIAL SAFETY DATA SHEET IS NOT REQUIRED:

CELx Retain (Tissue Preservative) MSDS: Per OSHA 29CFR1910.1200 and the latest amendments to the European Union Directives 67/548/EC and 1999/45/EC, CELx Retain does not require a Material Safety Data Sheet (MSDS). Therefore, Celcuity does not provide an MSDS for this product. CELx Retain does not contain more than 1% of a component classified as hazardous and does not contain more than 0.1% of a component classified as carcinogenic. However, when working with this or any chemical reagent, we recommend the use of gloves, laboratory coats, and eye protection. Celcuity assumes no liability for damage resulting from handling or contact with this product.
For *in vitro* diagnostic use.

celcuity
EXPANDING TREATMENT OPTIONS
844-310-3900

Appendix 3: CELsignia Specimen Collection Requisition

CELsignia breast

Specimen Collection Requisition

Place Bar Code from below in this area.

Please complete this form and place the top copy back into the CELsignia Specimen Collection Kit. This form is to be returned with the biopsy specimen to Celcuity.

PATIENT INFORMATION		
Celcuity Specimen ID		
Date of Birth (mm/dd/yy)	Gender ☐ Female ☐ Male	Ethnicity ☐ Hispanic ☐ Non-Hispanic
Race ☐ White ☐ Black or African American ☐ American Indian ☐ Asian ☐ Ashkenazi Jewish ☐ Native Hawaiian/Other Pacific Islander ☐ Other: _____		

SPECIMEN COLLECTION INFORMATION		
☐ Pathology Report is attached ☐ Pathology Report will be sent later		
Date of Procedure/Specimen Removal (mm/dd/yy)	Time of Procedure AM / PM	Time Placed in Vial AM / PM
Core Biopsy Information: Gauge of needle Used (Minimum 14 gauge needle required)	Number of Cores Submitted (2 cores preferred, 1 accepted)	
Name of Sending Facility	Contact Name	
Department	Daytime Phone and Ext.	
Email	Additional Comments: *Record tissue removal site, ex. Breast, Lung, etc.*	

TEST ORDER INFORMATION
Name of Clinical Trial (ex. FACT-3, etc.):

REPORTS WILL BE SUBMITTED TO	
Physician Name	Clinical Research Coordinator Name
Physician Email	Clinical Research Coordinator Email
Physician Daytime Phone and Ext. *(optional)*	Clinical Research Coordinator Daytime Phone and Ext.

Specimen Submitted By (Printed Name)	Department or Title	Date (mm/dd/yy)

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Bar Code for Requisition | Bar Code for 10mL Vial | Bar Code for Patient File | Bar Code for Patient File