NCCN Request for Proposals (RFP): Phase I/II Clinical and/or Correlative Studies of the panHER Inhibitor Neratinib in the Treatment of Breast, Gastrointestinal, Lung, and Neurological Cancers

1.0 Purpose

The National Comprehensive Cancer Network (NCCN) has received a $2 Million Dollar research grant from Puma Biotechnology (hereafter, "Grantor") to support NCCN Member Institution faculty for the performance of clinical and correlative studies to further evaluate the effectiveness of neratinib in the treatment of breast, gastrointestinal (GI), lung and neurological cancers. NCCN will serve as the funding organization. Grants are available only to investigators from NCCN Member Institutions.

2.0 Background

NCCN has received a grant from the Grantor for the design and performance of clinical studies using neratinib for breast, GI, lung and neurological cancers.

Mechanism of Action

Neratinib is an anilinoquinoline derivative intracellular oral kinase inhibitor that irreversibly binds to epidermal growth factor receptor (EGFR), HER2, and HER4. In vitro, neratinib reduces EGFR and HER2 autophosphorylation, downstream MAPK and AKT signaling pathways, and showed antitumor activity in EGFR and/or HER2 expressing carcinoma cell lines. Neratinib human metabolites M3, M6, M7, and M11 inhibited the activity of EGFR, HER2, and HER4 in vitro. In vivo, oral administration of neratinib inhibited tumor growth in mouse xenograft models with tumor cell lines expressing HER2 and EGFR. A comprehensive review article has been published that investigators can review for additional preclinical information on neratinib.[1]

Preclinical Data

Single Agent Activity

In vitro assays demonstrated that neratinib inhibited HER2 and EGFR activity at nanomolar concentrations (mean IC_{50} ± standard error [SE]: 59 ± 13 nM and 92 ± 17 nM, respectively). It had no significant effect on a panel of other assorted serine/threonine kinases. Neratinib inhibits HER4 activity at a mean IC_{50} of 19 nM. Neratinib inhibited ligand-dependent and -independent phosphorylated HER2 and EGFR activity and downstream MAPK and AKT signaling. Neratinib binds covalently based on its antiproliferative effect in cell lines despite withdrawal of the drug and was shown to have a concentration-dependent impact on cyclin D1, p27, and Rb cell cycle proteins. Finally, neratinib significantly inhibited tumor growth in vivo in xenograft models overexpressing HER2 (3T3/neu and BT474) and EGFR (SKOV-3 and A431).[1]

Neratinib is more potent than lapatinib or afatinib in cell line models of HER2+ breast cancer and can potentiate the effects of trastuzumab in trastuzumab-sensitive HER2+ breast cancer cell lines. Cell line models with trastuzumab resistance are sensitive to neratinib, whereas neratinib-resistant cell line models are cross-resistant to trastuzumab, lapatinib, and afatinib. This may be due to neratinib's ability to inhibit HER1-4 signaling compared to the activity of other TKIs. The

addition of lapatinib and neratinib to trastuzumab is beneficial in trastuzumab-sensitive HER2+ cells; the addition of pertuzumab does not enhance this effect. The triple combination of trastuzumab, pertuzumab, and neratinib was more effective than the lapatinib triplet in innately HER2-targeted therapy-resistant cell line models.

A patient population that may benefit from HER2 inhibitors are those whose tumors harbor activating HER2 mutations without gene amplification. Multiple studies have reported that oncogenic HER2 mutations occur primarily in the kinase domain of HER2.[2] Screening of 22 HER2 exons in 1248 primary breast cancers identified HER2 mutation in 2.24% of tumors (28 of 1248). In certain populations this percentage may be higher such as metastatic tumors (up to 5%) and lobular cancers (7.8%).[3,4] Mouse xenografts established from a patient with a HER2+ tumor with an acquired D769Y mutation in HER2 were resistant to trastuzumab and lapatinib but sensitive to neratinib.

Combination Data

The cytotoxicity of neratinib can be enhanced by HDAC inhibitors and checkpoint inhibitors in murine breast cancer models as well.[5] Neratinib has potential to synergize with a variety of molecular targeted therapies, such as trastuzumab, T-DM1, anti-estrogens, Src inhibitors, CDK4/6 inhibitors, HSP90 inhibitors, and HDAC inhibitors, in the treatment-naive or treatment-refractory settings. Neratinib has also been shown to significantly increase cellular internalization of trastuzumab emtansine (TDM1) and trastuzumab deruxtecan (TDxD) in HER2+ cell lines. The increased internalization leads to greater release of cytotoxic payload and tumor growth inhibition in preclinical models.[6]

Data on Resistance Mechanisms

Next gen sequencing of DNA from breast tumors or circulating tumor DNA (ctDNA) from plasma in patients progressing on neratinib has identified acquired drug-resistant gatekeeper mutations in HER2.[7, 8] A more recent report also identified multiple HER2 mutations at disease progression in patients with ER+ breast cancer who had derived clinical benefit from neratinib.[9] These mutations may also be causal to drug resistance. These results validate mutant HER2 as a therapeutic target and an oncogenic driver in these cancers and also imply that DNA profiling of tumors that progress on neratinib may inform future therapies in these patients.

Several mechanisms of resistance to neratinib have been proposed, including decreased pro-apoptotic BCL2 family member expression.[10] Resistant cell lines exhibited downstream activation of ERK-1/2 while on neratinib therapy. These neratinib-resistant cell lines were treated using the specific ERK1/2 inhibitor SCH772984 and the pan-BCL2 inhibitor ABT-737. Although the combination of neratinib and SCH772984 induced apoptosis in SKBR3-NR and ZR75-30-NR, the triple combination of neratinib, SCH772984, and ABT-737 was required to overcome neratinib resistance in BT474-NR cells. Sudhan et al. demonstrated that neratinib-resistant 5637 and OVCAR8 cell lines with activating HER2 mutations had S6 kinase activity and S6 activation was primarily mediated by mammalian target of rapamycin (mTOR) complex 1 (mTORC1) pathway activation.[11] The combination of neratinib and everolimus overcame neratinib resistance in vitro and in vivo. Also, patients with concurrent mTOR-activating alterations and HER2 mutations were resistant to neratinib in the SUMMIT study.

Summary of Clinical Data

Breast cancer:

- Extended adjuvant: reduced risk of recurrence; early recurrences prevented
    - ExteNET: extended adjuvant approved by FDA, EMA.
    - Descriptive analyses show OS improvements in estrogen receptor positive patients with residual disease following neoadjuvant therapy.[12]

- Neoadjuvant: improved pCR rates in combination with chemo, and trastuzumab and chemo
    - I-SPY2: higher estimated pCR rates with neratinib + chemo vs. trastuzumab + chemo.[13]
    - NSABP FB-7: highest pCR rates with neratinib + trastuzumab + chemo; lower pCR rates with neratinib + chemo vs. trastuzumab + chemo.[14]

- Metastatic disease
    - NSABP FB-10: neratinib 160 mg + T-DM1 active in trastuzumab + pertuzumab pretreated subjects.[15]
    - NEfERT-T: 1st line neratinib + paclitaxel delayed CNS progression vs. trastuzumab + paclitaxel.[16]
    - TBCRC 022: neratinib + capecitabine active against refractory HER2+ brain metastases.[17]
    - NALA: Improved PFS for neratinib + capecitabine vs. lapatinib + capecitabine, delayed time to CNS intervention.[18]
    - The combination of neratinib + fulvestrant + trastuzumab demonstrated encouraging clinical activity in heavily pre-treated HER2-mutant, HR+, HER2-non-amplified MBC (ORR 45.9% and median PFS 8.3 months), including patients who had previously received either fulvestrant and/or CDK4/6 inhibitor-based therapies.[19]
    - The combination of navelbine 25mg/m2 weekly plus neratinib 240mg daily was feasible and had activity in lapatinib naïve (ORR 41%) but modest response in lapatinib treated patients (ORR 8%).[20]

HER2 activated and EGFR exon 18 mutated lung adenocarcinoma:

- Neratinib, as monotherapy, has limited activity in HER2-mutated NSCLC
- Neratinib combined with either the mTOR inhibitor temsirolimus (19% ORR)[21], or trastuzumab (17% ORR) produced numerically greater efficacy including durable responses in a subset of pre-treated patients.
- Single-arm phase 2 SUMMIT trial cohort showing early clinical efficacy of single-agent neratinib in TKI-refractory *EGFR* exon 18-mutant NSCLC demonstrated ORR 40%, CBR 80%, and median PFS of 9.1 months.
- Neratinib increased the uptake of TDM-1 and had preclinical evidence of increasing the efficacy of this antibody drug conjugate in HER2 mutant NSCLC.[19]

Colorectal cancer:

Neratinib-plus-cetuximab in Quadruple WT (KRAS, NRAS, BRAF, PIK3CA) Metastatic Colorectal Cancer Resistant to Cetuximab or Panitumumab: NSABP FC-7, A Phase Ib Study evaluated weekly fixed-dose cetuximab plus daily neratinib with dose escalation using a 3+3 design. Sixteen patients were evaluable for dose-limiting toxicity. The RP2D for neratinib monotherapy and in combination with cetuximab (400mg/kg loading followed by 250mg/kg weekly) was 240mg. Best response was stable disease (SD) in 7/16 (44%).[22]

A phase 2 trial in quadruple wild type colorectal cancer with neratinib plus trastuzumab or neratinib plus cetuximab is ongoing. [23]

Biliary tract cancers:

A biliary tract cancer cohort (N=25) of the SUMMIT phase 2 study demonstrated preliminary neratinib monotherapy activity in pretreated patients. The confirmed ORR was 16% (95% CI 5–36) and CBR was 28% (95% CI, 12.–49), including 4 confirmed PRs and 3 patients achieving stable disease. Median PFS was 2.8 months (95% CI, 1.1–3.7)[22]

Primary nervous system tumors:

While there is no data to date with neratinib, data from a small phase 2 study in neurofibromatosis type 2 vestibular schwannomas (VS) demonstrated volumetric responses in 23.5% patients treated with lapatinib.[25] A follow up retrospective analysis further suggested that treatment with lapatinib may have the potential to arrest or reduce the growth of NF2 related meningiomas.[24] In another study, despite lack of radiographic response, 27% of patients treated with erlotinib for progressive NF2 associated VS experienced prolonged stable disease during treatment.[26]

3.0 Scope and Aims

The overall aim is to develop innovative studies to help determine the role of neratinib for breast, GI, lung and certain neurological cancers. It is hoped proposals submitted in response to this RFP should be useful in guiding further clinical development of neratinib. Clinical studies with correlative endpoints are encouraged.

Collaboration between NCCN Member Institutions is strongly encouraged in order to foster the interactive sharing of knowledge and expertise, and to utilize the combined clinical strengths of members, particularly in the case of uncommon tumors. Although the submitting investigator must be from an NCCN Member Institution, participating institutions do not need to be an NCCN Member Institution. This can also include cross-institutional collaboration for the conduct of correlative studies.

The NCCN Request for Proposals Development Team (RFPDT) has developed a Request for Proposals (RFP) with a formalized review procedure to accept applications and select the proposals of highest scientific merit. The NCCN RFPDT has overseen the development of the RFP and a NCCN Scientific Review Committee composed of members of this group will perform the review of applications.

The areas of research emphasis identified for this RFP include:

- Phase I/II and/or correlative studies of neratinib in the identified tumor types:
    - Breast cancer:
        - Neoadjuvant therapy utilizing combination systemic therapy with neratinib in HER2 amplified, overexpressing, or HER2 mutated breast cancers of any receptor subtype.
        - Proposals including populations of HER2 driven breast cancers identified using emerging predictive biomarkers other than HER2 IHC and ISH that could be suitable for prospective use in clinical trials.
        - Novel strategies for the treatment of patients with HER2+ (ASCO/CAP criteria) brain metastases and leptomeningeal disease.
        - Additional predictive biomarker studies in HER2 mutated breast cancers treated with neratinib.
        - Novel combinations in metastatic HER2+ breast cancer, particularly combinations with antibody drug conjugates (ADCs) and/or immunotherapy.
    - NSCLC with HER2 activating mutations or exon 18 EGFR mutations:
        - Patients with CNS disease can be included.
        - Novel combinations with neratinib, particularly ADCs.
        - Due to the rarity of these subtypes, multicenter proposals are strongly encouraged.
    - GI:
        - HER2 mutated or activated biliary tract, gastric and colon malignancies, evaluating either neratinib single agent or in combination with other therapies.
    - Certain primary nervous system tumors including:
        - NF2-associated schwannomas, ependymomas, and meningiomas.
        - Primary CNS tumors, such as Glioblastoma:
            - Treatment (neoadjuvant included) to understand the effects of neratinib on CNS penetration, pharmacodynamic targets, the tumor microenvironment, and imaging during treatment.
        - Due to the rarity of these tumor types, multicenter proposals are encouraged.
- Drug combination studies in any of the aforementioned tumor types are acceptable if:
    - The toxicity profile of the agent allows combination with neratinib.
    - There is sufficient data regarding the single agent activity of the combining drug so that the contribution of neratinib can be determined.

  Supportive care studies evaluating new methods to enhance tolerability and treatment delivery with neratinib in standard of care setting.

Specific exclusions from this RFP include:

- Proposals not involving patients or patient samples for translational research (i.e. purely preclinical/basic science proposals).
- Adjuvant studies with long term efficacy primary endpoints beyond the performance period of the grant.

Studies should not utilize doses outside of the range for which safety data is available (i.e., no dose greater than 240mg/day) or a mode of administration other than oral. Also, it is strongly recommended that, when applicable, a weekly dose escalation over 3-4 weeks with loperamide as needed is utilized when initiating neratinib therapy, if full dose treatment is planned.

Proposals duplicative of completed, ongoing, or planned studies will not be considered. **A listing of ongoing and planned IST studies utilizing neratinib can be found as Attachment A to this RFP.** A listing of ongoing and previously completed clinical studies utilizing neratinib can be found on the NCCN website at https://www.nccn.org/clinical_trials/clinicians.aspx. If you wish additional information or have questions, please contact Nicole Kamienski at kamienski@nccn.org with the subject line, "2021 Neratinib Project".

4.0 Study Time Frames

All approved clinical studies are expected to commence, which is defined as the first patient receiving the first dose of study drug(s), no later than ten (10) months of notice of study approval and are to complete accrual within two (2) years of commencement. A manuscript must be submitted to NCCN for review no later than nine (9) months after study endpoint achieved. Studies will be funded as described in Section 9.0 and should be designed with subject number commensurate with study time frames and funding.

Studies for rarer cancers or those that require large numbers of patients for statistical power must be multi-institutional. Network appropriate studies will be considered as long as submitting PI is from an NCCN Member Institution.

Accepted studies will be held to the following time frames:

Phase I studies are expected to meet primary objective within two years of commencement.

Single-arm Phase II studies are expected to explore new approaches that can be tested in larger confirmatory studies if positive results are obtained. It is expected that these studies will meet the primary objective within two years of commencement. To meet this goal, single-arm Phase II trials are encouraged to be multi-institutional. Data management and monitoring of studies should be coordinated by the applying institution. Additional funding for the applying institution may be requested to support the additional resources required for this activity, if the study involves multi-institutional participation.

Correlative laboratory studies are expected to be completed within the same time frame as the corresponding clinical trial. Correlative laboratory studies within clinical trials already supported through other mechanisms must be completed within 2 years.

Larger randomized Phase II studies already supported through other mechanisms which will be completed within two years (i.e. cooperative group) will be considered for support where the support requested will be for correlative laboratory studies that are unfunded and enhance the evaluation of the patient data.

Randomized Phase II multi-institutional studies are expected to be completed within a two-year time frame. Multi-institutional data management and monitoring of these studies should be coordinated by the applying institution. Additional funding for the applying institution may be requested to support the additional resources required for this activity.

All studies will require documentation of the feasibility of accruing the targeted study population; studies may be multi-institutional.

5.0 Proposals

In order to respond to the RFP, investigators will submit a proposal in the format delineated below to NCCN, which will be evaluated by the NCCN Scientific Review Committee (SRC).

Proposals are required to be submitted electronically to the NCCN research portal at https://nccn.envisionpharma.com/ienv_nccn **and include a letter of support from the governing groups of the institution verifying:**

1) Office of Sponsored Research approval
2) Department Chair/Division approval
3) Institutional budgetary review and approval
4) For clinical trials, the priority status of the research stating if there are competing trials. If there are competing trials, please verify that this trial will have a higher priority.
5) Documentation to support feasibility of clinical trials with at least one of the following:
    - Letter from institution's Feasibility Committee if applicable
    - Documentation by previous studies and accrual (if available, publications and abstracts)
6) Letter(s) of support from participating institutions including name of PI at participating institution and their feasibility

Letters should be addressed to Wui-Jin Koh, MD, CMO, National Comprehensive Cancer Network, 3025 Chemical Road, Suite 100, Plymouth Meeting, PA 19462.

Proposals will provide concise documentation of the research plan. The proposal is expected to contain sufficient information to allow the reviewers to fully assess the scientific rigor of the proposed study. A full research project plan may be submitted as an attachment. A robust review of the statistical plan will be conducted.

Proposals should contain detailed information regarding the following areas:

5.1 Clinical Trials

A. General Information: Title/Type of Support/Subsite(s)
B. Investigators and institutional affiliations
C. Concept information

i. Enrollment/Design/Phase
ii. Estimated time of completion
iii. Overview/Hypothesis
iv. Background/Rationale

D. Scientific summary
i. Primary/Secondary objectives
ii. Inclusion/Exclusion criteria
iii. Study population
iv. Statistical analysis
v. Treatment plan
vi. References

E. Oncology analysis
i. Tumor Type/Stage
ii. Correlative study information
iii. Outcome measures
iv. Feasibility documentation

F. Request for product: Formulation Dosage/Quantity
G. Planned publications: Journal/Congress/Anticipated Dates

5.2 Budget using NCCN (within iEnvision) template (Exhibit A)

A. Breakdown by major cost categories
B. Justification of major costs with enough detail to demonstrate how funding for major elements in the study will be allocated
C. Salaries are capped at the current NIH salary cap
D. No travel or publication costs will be covered

5.3 Required Documentation for Combination Treatment

This documentation must be provided to NCCN along with the proposal or it will not be considered for funding.

A. Investigators must document the source for any drug(s) used in combination with neratinib. Documentation within the proposal will be accepted for any drug(s) obtained as standard of care.
B. A letter of support from the pharmaceutical company is needed if neratinib is to be studied in combination with an approved agent(s) used outside of its indication.
C. If neratinib will be studied in combination with an investigational agent(s) obtained from a pharmaceutical company, the investigator must provide letter stating the following:
i. The company's commitment to provide drug for the investigation;
ii. The agreement of that company to allow presentation and publication of results, and
iii. The agreement of that company to allow cross-filing or filing of a new IND.
D. If pharmacokinetic studies (PK) of investigational agents other than neratinib are planned, the investigator must provide documentation of that company's commitment to provide support or alternative mechanism for performing PK studies for that agent.

5.4 Ancillary Documentation

A. NCI format BioSketch of the Principal Investigator
B. An appendix of supportive literature may be provided
C. Any additional information to support proposal submission

6.0 Proposal Requirements

6.1 Submission

All proposals must be submitted electronically using the directions below and are due by **5:00 PM (EDT) on April 19, 2021.** No exceptions will be granted.

A. Please use the link below to register in the system:
    i. https://nccn.envisionpharma.com/ienv_nccn
B. Select "Register for New Account" in the upper right corner of the page, above the "Log In" button
C. Complete all fields (Note: Fields with an asterisk are required)
D. You will receive a confirmation email. Click on the link in the email to activate your account.
E. Enter your username and password (Note: Your user name is your email address. Do not copy and paste.)
F. Set up your security questions
G. Submit your study

For technical assistance with the iEnvision system, please contact iEnvision_general_request@envisionpharmagroup.com.

Studies that have safety issues, are already well-funded concepts, or are not consistent with the strategy for investigation as written in this RFP will not be reviewed by the SRC.

For questions or issues, please contact Nicole Kamienski at kamienski@nccn.org or (215) 690-0230. NCCN will seek to provide information to potential investigators regarding ongoing or completed studies of neratinib in order to avoid the submission of a proposal that is already a well-studied concept.

6.2 Requirements

6.2.1 Human Biological Specimens: All specimens must be obtained under informed consent and IRB approval appropriate for the study. Compliance with all federal regulations is required.

6.2.2 IRB:

6.2.2(a) Draft protocols will be reviewed by NCCN and the Grantor **prior** to IRB review. **A copy of the draft protocol must be submitted to NCCN within 4 weeks after the study approval letter.** The protocol must be consistent with the approved proposal and all reviewer comments must be addressed.

6.2.2(b) All investigators will submit protocols for IRB review and document approval to NCCN prior to study activation and all collaborators will furnish evidence of IRB approval. It is expected that IRB review and approval be completed **within 150 days** following NCCN notification of funding for the project.

6.2.3 IACUC review and approval: All investigators conducting animal experiments will submit research project plans for IACUC review and document approval to NCCN prior to study activation. It is expected that IACUC review and approval be completed **within 90 days** following NCCN notification of funding for the project.

6.2.4 Serious Adverse Event Reporting: All serious adverse events will be reported to NCCN and the Grantor in addition to local regulatory authorities.

6.2.5 Institutional Monitoring: All studies will be internally monitored in accordance with appropriate committees (e.g. institutional Data Safety and Monitoring Plan in the case of human studies). A copy of the Data Monitoring Plan for the study must be submitted to NCCN prior to NCCN approval of study activation.

6.2.6 IND:

6.2.6(a) Investigators are required to hold INDs for studies but will be allowed to cross-reference a filing to Grantor's IND. Investigators are encouraged to apply to the FDA for IND exemption if studies meet all criteria according to 21 CFR 312.2(b). A copy of the FDA approval letter for IND exemption must be submitted to NCCN before study drug will be released.

6.2.6(b) Proposals using an experimental diagnostic imaging agent that will require an IND must outline how regulatory issues will be handled in order to meet the required study time frame.

6.2.7 Progress Reports: Investigators will provide interim progress reports to NCCN detailing the progress of studies quarterly, and upon study completion. These reports will be used administratively for funding purposes. If study progress or accrual lags behind the expected rate, the SRC may be asked for suggestions to improve study progress, or alternatively, to terminate the study and any further funding.

6.2.8 Specimen Transmittal: If specimens are to be transported extramurally for collaborative laboratory studies, all institutional requirements for safety and confidentiality will be met.

6.2.9 Abstracts and Publications: Abstracts for presentation at scientific meetings and all publications of study results will be submitted to NCCN and Grantor for review related to protection of company's intellectual property and confidential information **prior to any submission**. Abstracts must be submitted at least 10 days prior to submission and manuscripts at least 30 days prior to

submission. Grantor may delay publication and disclosure of the manuscript or abstract for up to an additional sixty (60) days so as to seek patent protection of intellectual property rights.

6.2.10 NCCN Multi-Institutional Studies: Collaborative studies between NCCN Member Institutions are encouraged. For these studies, the proposal feasibility section should provide information about data management, statistical analysis, and specimen handling issues. Additional funding may be provided for centralized data management and monitoring by the applying institution.

6.2.11 NCCN institutions and investigators will be responsible for conducting all studies in accordance with the applicable research plan, GCP Guidelines, and all applicable laws and regulations. NCCN institutions and investigators will be responsible for all data collection, statistical analysis and safety reporting.

6.2.12 Investigators must provide reasonable assurance that submitted studies will be able to reach completion within the time frames specified in Section 4.0.

6.2.13 Final protocols must be consistent with approved proposals. Funds will be rescinded if there are significant changes without prior NCCN approval. There will be no exceptions.

6.2.14 The Principal Investigator (PI) listed on the protocol must be the same PI listed on the proposal submission unless approved by NCCN.

7.0 Drug Supply

Neratinib will be supplied for all approved and funded studies by Grantor.

8.0 Selection Criteria

Proposals will be judged based on the following criteria:

- Scientific value
- Research experience of the Principal Investigator
- Soundness of study design
- Feasibility including reasonable assurance of achieving intended and full accrual
- Budgetary reasonableness
- Statistics

The GRANTOR has the ability to reject any study with safety issues or if it is an already studied concept.

9.0 Funding

NCCN and its member institutions have an agreement to include a maximum of 25% indirect costs for trials funded by the NCCN. Direct funding will include all costs including investigators' salaries. For example, $80,000 direct costs and $20,000 indirect costs for a total grant of

$100,000. Any funds in excess of the limits stipulated in this section for direct funding will require detailed justification and review.

Phase I and Single-arm Phase II clinical trials will be funded at a cost of up to $300,000 (total costs including direct costs and 25% indirect costs) per trial. Multi-institutional data management and monitoring of these studies should be coordinated by the applying institution. Additional funding for the applying institution may be requested to support the additional resources required for this activity.

The Correlative Laboratory studies section of the clinical trial will be funded up to a total cost of $100,000, including up to 25% indirect costs.

Larger Randomized Phase II trials already supported through other mechanisms (i.e. cooperative group) will be considered for support where the support requested will be for correlative laboratory studies that are unfunded and enhance the evaluation of the patient data. Correlative studies for larger randomized trials will be funded up to $100,000.

Funding should not exceed $500,000. Clinical study maximum $300,000 + correlative study maximum $100,000 + multi-institutional funding maximum $100,000 = $500,000 MAXIMUM funding

Funding will be disbursed to approved studies as follows:

Phase I trials:

- 15% of total award for such Study after IRB approval and dosing of first study subject;
- Based on the per Study Subject costs, after the initial 15% of funding has been accounted for based on Study Subject accrual, funds will be awarded on a quarterly basis for eligible Study Subjects enrolled in a Study, based on the per Study Subject rate up to a maximum of an additional 65% of the funding; and
- 20% of funds will be awarded after submission of a manuscript for publication

Phase II trials and correlative Study(ies):

- 15% after IRB approval and dosing of first Study Subject;
- Based on the per Study Subject costs, after the initial 15% of funding has been accounted for based on Study Subject accrual, funds will be awarded on a quarterly basis for eligible Study Subjects enrolled in a Study, based on the per Study Subject rate up to a maximum of an additional 65% of the funding; and
- 20% after submission of a manuscript for publication.

Phase II trials with 2-Stage Design with Early Stopping Rules:

- 15% of total requested funding (based on maximum number of anticipated Study Subjects) after IRB approval and dosing of first Study Subject;
- Remainder of per Study Subject funding for the number of Study Subjects in the first stage after all Study Subjects are accrued to the first stage of a Study (total funding for the number of Study Subjects in first stage less the initial payment) up to a maximum of an additional 65% of the funding;

- Total per Study Subject funding for the number of Study Subjects in the second stage less final payment after all Study Subjects are accrued to the second stage; and
- 20% of total requested funding (based on maximum number of anticipated Study Subjects) after submission of a final report or manuscript for publication.

Multi-center Randomized Phase II Study(ies):

- 15% after IRB approval and dosing of first Study Subject;
- Based on the per Study Subject costs, after the initial 15% of funding has been accounted for based on Study Subject accrual, funds will be awarded on a quarterly basis for eligible Study Subjects enrolled in a Study, based on the per Study Subject rate up to a maximum of an additional 65% of the funding;
- 20% after submission of publication; and
- Any additional funding will be disbursed to the coordinating center for data management and monitoring. These funds will be delegated at the discretion of the lead Principal Investigator and may include outsourcing of data management and/or monitoring to an independent research organization.

The goal is to have rapid submission of a manuscript so as to have the data available to the wider scientific community.

Studies that do not meet the time frame requirements as stipulated in Section 4.0 will have funds rescinded and will be required to return any and all unused funds previously disbursed.

10.0 Study Agreement

A study agreement will be signed between NCCN and each participating institution.

If an institution requires a separate contract with another pharmaceutical company for a study, that contract must be fully executed by the time of study activation.

All aforementioned points between NCCN and the participating institution must be strictly adhered to.

11.0 References

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2. Wen W, Chen WS, Xiao N, et al. Mutations in the Kinase Domain of the HER2/ERBB2 Gene Identified in a Wide Variety of Human Cancers. *J Mol Diagn.* 2015;17(5):487-495.
3. Ma CX, Bose R, Gao F, et al. Neratinib Efficacy and Circulating Tumor DNA Detection of HER2 Mutations in HER2 Nonamplified Metastatic Breast Cancer. *Clinical Cancer Research.* 2017;23(19):5687-5695.
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8. Ma CX, et al.. Neratinib Efficacy and Circulating Tumor DNA Detection of HER2 Mutations in HER2 Nonamplified Metastatic Breast Cancer. Clin Cancer Res. 2017 Oct 1;23(19):5687-5695.
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ATTACHMENT A

Ongoing IST Research:

1. A Phase II Trial of HKI-272 (Neratinib), Neratinib and Capecitabine, and Neratinib and Ado-Trastuzumab Emtansine (T-DM1) for Patients with Human Epidermal Growth Factor Receptor 2 (HER2)-Positive Breast cancer and Brain Metastases (TBCRC-022)
2. A phase 1b study of neratinib, pertuzumab and trastuzumab with taxol (3HT) in metastatic and locally advanced breast cancer, and phase II study of 3HT followed by AC in HER2 + primary IBC, and neratinib with taxol (NT) followed by AC in HR+ /HER2- primary IBC
3. Phase Ib/II Study of Capecitabine 7/7 Schedule with Neratinib in Patients with Metastatic HER2-Positive Breast Cancer
4. An open label study to characterize the incidence and severity of diarrhea in patients with early stage HER2+ breast cancer treated with adjuvant trastuzumab and neratinib followed by neratinib monotherapy, and intensive anti-diarrhea prophylaxis
5. FB-10: A Phase Ib/II Dose-Escalation Study Evaluating the Combination of Trastuzumab Emtansine (T-DM1) with Neratinib in Women with Metastatic HER2-Positive Breast Cancer
6. Targeting EGFR/ERBB2 with Neratinib in hormone receptor (HR)-positive/HER2-negative HER2-enriched advanced/ m-breast cancer
7. Individualized screening trial of Innovative Glioblastoma therapy (INSIGhT)
8. Phase I Study of the Pan-ERBB Inhibitor Neratinib Given in Combination with Everolimus, Palbociclib or Trametinib in Advanced Cancer Subjects with EGFR Mutation/Amplification, HER2 Mutation/Amplification, or HER3/4 Mutation or KRAS mutation
9. A Phase I/II study of Neratinib in pediatric patients with R/R solid tumors.
10. A Phase II Study Evaluating the Combination of Neratinib Plus Trastuzumab or Neratinib Plus Cetuximab in Patients with "Quadruple Wild-Type" (KRAS/NRAS/BRAF/PIK3CA Wild-Type) Metastatic Colorectal Cancer Based onHER2 Status: Amplified, Non-Amplified (Wild-Type) or Mutated
11. Phase 1/2 Study of Neratinib and Divalproex Sodium (Valproate) in Advanced Solid Tumors, with an Expansion Cohort in RAS-Mutated Cancer
12. A phase 1/1b clinical trial of Niraparib and Neratinib in advanced solid tumors with an expansion cohort in platinum-resistant ovarian cancer
13. (MutHER): Neratinib ± Fulvestrant in Metastatic HER2 Non-amplified But HER2 Mutant Breast Cancer

Planned Research:

Indication	Drug Combination
Neoadjuvant EBC	Neratinib + Trastuzumab + Endocrine therapy
CNS metastases mBC	Neratinib + SOC systemic therapy
mCRPC	Neratinib monotherapy
Gastric cancer with HER mutation	Neratinib + Paclitaxel + Pembrolizumab
HER2+ cancer /w CNS metastasis	Neratinib + Capecitabine

HER2+ mBC	Neratinib + Nivolumab + Radiation therapy
HER2 mutant advanced solid cancers	Neratinib + Trastuzumab
HR+/HER- BC neoadjuvant	Neratinib + Paclitaxel
HER-mBC (HER2 signaling)	Neratinib + Fulvestrant
HER-mBC (HER2 signaling)	Neratinib + Capecitabine
HER2 mBC & IBC (HER2 signaling)	Neratinib + Capmatinib
Neoadjuvant EBC	Neratinib + Trastuzumab + Endocrine therapy