NCCN Request for Proposals (RFP): Preclinical and Clinical Studies of CDK4 and 6 Inhibition with Abemaciclib for Breast Cancers

1.0 Purpose

The National Comprehensive Cancer Network (NCCN) has received a Two Million Dollar research grant from Eli Lilly and Company (hereafter, "Grantor") to support the performance of preclinical, clinical and correlative studies of abemaciclib in the treatment of breast cancer. NCCN will serve as the funding organization. Grants are available only to investigators from NCCN Member Institutions.

2.0 Scope and Aims

NCCN has received a grant from the Grantor for the design and performance of preclinical, clinical, and correlative studies using abemaciclib to treat breast cancer.

The overall aim is to develop innovative studies to help determine the role of abemaciclib in the treatment of breast cancer. Proposals (which can be preclinical, phase I/II clinical trials or correlative trials) submitted in response to this RFP will be useful in guiding further development of abemaciclib.

For clinical trial proposals:

- All proposed clinical trials (phase I or II; please note that phase III trial proposals are not allowed) must contain abemaciclib.
- Abemaciclib can be combined with investigational and FDA-approved drugs from other pharmaceutical companies or FDA-approved drugs from Lilly (non-FDA approved drugs from Lilly's pipeline will not be allowed).
- Clinical trials must utilize dosages and dosing schedule based on already known safety data for the drug. Specifically, as a single agent, the starting dose of abemaciclib should be the approved dose of 200 mg PO BID. In combination, the starting dose of 150 mg PO BID abemaciclib should be used and dose reduction per the label, if necessary. Of note, abemaciclib should not be crushed and proposals should focus on patient populations that are able to reliably swallow pills.

For preclinical proposals:

- Lilly will provide drugs in their pipeline (including non-FDA approved drugs) based on material availability. The potential drugs are listed below and may be expanded or retracted based on decisions at Lilly:

Early Phase	merestinib, prexasertib, TFGb Inhibitor II, Aur A Kinase inhibitor, ERKi, IDO1i
Late Phase	ramucirumab, abemaciclib, pegilodecakin

For translational/ correlative trial proposals:

- May be added to an ongoing project or clinical trial

While a wide variety of proposals are welcome, the areas of research emphasis for this RFP include:

- Mechanisms of resistance to CDK4 and 6 inhibitors (CDK4 and 6i). For example (but not restricted to):
    - Resistance to CDK4 and 6i in Rb proficient tumors
    - In HR+ breast cancers, is tumor progression post endocrine therapy + CDK4 and 6i related to endocrine therapy, CDK4 and 6i or both?
    - Difference between acquired and *de novo* resistance
    - Resistance signatures
    - Novel models for CDK4 and 6i resistance
- Therapy optimization. For example (but not restricted to):
    - Is single agent abemaciclib as effective as abemaciclib in combination with endocrine or other therapies?
    - Are there differences between CDK4/6 inhibitors in preclinical models?
    - Biomarkers of response and resistance (better patient selection; analysis of extreme responders and progressors; etc.)
    - Novel combinations (synergy/ sequencing with PARP inhibitors in BRCA-mutated patients; combinations targeting improvement of apoptotic effect; testing of novel combinations in preclinical models; etc.)
    - Leveraging the immune effects of CDK4 and 6i
    - Combination/ models in CNS metastasis
- Characterization of mechanisms of toxicity. For example (but not restricted to):
    - Analysis of microbiome and its modulation in GI toxicity from abemaciclib
- Race/ ethnic disparities in CDK4 and 6i treatment

Specific <u>exclusions</u> from this RFP include:

- No studies will utilize doses outside the range for which safety data is available
- Phase III clinical trial proposals
- Non-FDA approved drugs from Lilly's pipeline will not be allowed in phase I or II clinical trial proposals (but will be allowed in preclinical proposals)
- Use of other CDK4 and 6i in clinical trial proposals

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

The goal of the RFP is to generate innovative projects that are not duplicative of completed, ongoing or planned studies. **A listing of ongoing studies is at the end of the RFP.** If there are any questions about what constitutes duplicative versus complementary research please email Patricia Esposito at esposito@nccn.org with the subject line, "2019 Abemaciclib Project".

3.0 Background

Mechanism of Action

Abemaciclib is an inhibitor of cyclin-dependent kinases 4 and 6 (CDK4 and CDK6). These kinases are activated upon binding to D-cyclins. In estrogen receptor-positive (ER+) breast cancer cell lines, cyclin D1 and CDK4/6 promote phosphorylation of the retinoblastoma protein (Rb), cell cycle progression, and cell proliferation. In vitro, continuous exposure to abemaciclib inhibited Rb phosphorylation and blocked progression from G1 into S phase of the cell cycle, resulting in senescence and apoptosis. In breast cancer xenograft models, abemaciclib dosed daily without interruption as a single agent or in combination with antiestrogens resulted in reduction of tumor size.

Preclinical Data

Abemaciclib is most active against CDK4/cyclin in enzymatic assays, exhibiting 14-fold higher potency for CDK4/cyclin D1 than CDK6/cyclin D3. Consistent with the mechanism of action, preclinical evidence demonstrates that Rb expression is necessary but not sufficient to confer high sensitivity to abemaciclib. In an effort to identify genetic features associated with sensitivity to abemaciclib, 560 cancer cell lines were treated with abemaciclib for two cell doubling times. The majority of these cell lines expressed *RB1*, but only ~15% of cell lines were highly sensitive to abemaciclib (IC50 below 1 μM), suggesting that in the remaining *RB1*-proficient cell lines, other compensatory mechanisms result in reduced abemaciclib sensitivity. Recent evidence also suggests abemaciclib may promote anti-tumor immunity by increasing antigen presentation and T cell activation. As a result of its brain exposure, treatment with abemaciclib produces a statistically significant and dose-dependent improvement in survival when assessed in a rat orthotropic brain tumor model.

Clinical Data

<u>Abemaciclib in Combination with a Non-steroidal Aromatase Inhibitor (MONARCH 3)</u>

Postmenopausal women with HR-positive, HER2-negative advanced or metastatic breast cancer with no prior systemic therapy in this disease setting

MONARCH 3[1] was a randomized (2:1), double-blinded, placebo-controlled, multicenter study in postmenopausal women with HR-positive, HER2-negative advanced or metastatic breast cancer in combination with a nonsteroidal aromatase inhibitor as initial endocrine-based therapy, including patients not previously treated with systemic therapy for breast cancer.

Randomization was stratified by disease site (visceral, bone only, or other) and by prior (neo)adjuvant endocrine therapy (aromatase inhibitor versus other versus no prior endocrine therapy). A total of 493 patients were randomized to receive 150 mg Abemaciclib or placebo orally twice daily, plus physician's choice of letrozole (80% of patients) or anastrozole (20% of patients). Patient median age was 63 years (range, 32-88 years) and the majority were White (58%) or Asian (30%). A total of 51% had received prior systemic therapy and 39% of patients had received chemotherapy, 53% had visceral disease, and 22% had bone-only disease.

Efficacy results are summarized in Table 1. PFS was evaluated according to RECIST version 1.1 and PFS assessment based on a blinded independent radiologic review was consistent with the investigator assessment. Consistent results were observed across

patient stratification subgroups of disease site and prior (neo)adjuvant endocrine therapy. At the time of the PFS analysis, 19% of patients had died, and overall survival data were immature.

Table 1: Efficacy Results in MONARCH 3 (Investigator Assessment, Intent-to-Treat Population)

	Abemaciclib plus Anastrozole or Letrozole	**Placebo plus Anastrozole or Letrozole**
Progression-Free Survival	**N=328**	**N=165**
Number of patients with an event (n, %)	138 (42.1)	108 (65.5)
Median (months, 95% CI)	28.2 (23.5, NR)	14.8 (11.2, 19.2)
Hazard ratio (95% CI)	0.540 (0.418, 0.698)	
p-value	<0.0001	
Objective Response for Patients with Measurable Disease	**N=267**	**N=132**
Objective response rate[a,b] (n, %)	148 (55.4)	53 (40.2)
95% CI	49.5, 61.4	31.8, 48.5

Abbreviations: CI = confidence interval, NR = not reached.
[a] Complete response + partial response.
[b] Based upon confirmed responses.

Dose reductions due to an adverse reaction occurred in 43% of patients receiving Abemaciclib plus anastrozole or letrozole. Adverse reactions leading to dose reductions in ≥5% of patients were diarrhea and neutropenia. Abemaciclib dose reductions due to diarrhea of any grade occurred in 13% of patients receiving Abemaciclib plus an aromatase inhibitor compared to 2% of patients receiving placebo plus an aromatase inhibitor. Abemaciclib dose reductions due to neutropenia of any grade occurred in 11% of patients receiving Abemaciclib plus an aromatase inhibitor compared to 0.6% of patients receiving placebo plus an aromatase inhibitor.

Permanent treatment discontinuation due to an adverse event was reported in 13% of patients receiving Abemaciclib plus an aromatase inhibitor and in 3% of patients receiving placebo plus an aromatase inhibitor. Adverse reactions leading to permanent discontinuation for patients receiving Abemaciclib plus an aromatase inhibitor were diarrhea (2%), ALT increased (2%), infection (1%), venous thromboembolic events (VTE) (1%), neutropenia (0.9%), renal impairment (0.9%), AST increased (0.6%), dyspnea (0.6%), pulmonary fibrosis (0.6%) and anemia, rash, weight decreased and thrombocytopenia (each 0.3%).

Deaths during treatment or during the 30-day follow up, regardless of causality, were reported in 11 cases (3%) of Abemaciclib plus an aromatase inhibitor treated patients versus 3 cases (2%) of placebo plus an aromatase inhibitor treated patients. Causes of death for patients receiving Abemaciclib plus an aromatase inhibitor included: 3 (0.9%) patient deaths due to underlying disease, 3 (0.9%) due to lung infection, 3 (0.9%) due to VTE event, 1 (0.3%) due to pneumonitis, and 1 (0.3%) due to cerebral infarction.

The most common adverse reactions reported (≥20%) in the Abemaciclib arm and ≥2% than the placebo arm were diarrhea, neutropenia, fatigue, infections, nausea, abdominal pain, anemia, vomiting, alopecia, decreased appetite, and leukopenia (Table 2). The most frequently reported (≥5%) Grade 3 or 4 adverse reactions were neutropenia, diarrhea, leukopenia, increased ALT, and anemia. Diarrhea incidence was greatest during the first month of Abemaciclib dosing. The median time to onset of the first diarrhea event was 8

days, and the median durations of diarrhea for Grades 2 and for Grade 3 were 11 days and 8 days, respectively. Most diarrhea events recovered or resolved (88%) with supportive treatment and/or dose reductions. Nineteen percent of patients with diarrhea required a dose omission and 13% required a dose reduction. The median time to the first dose reduction due to diarrhea was 38 days.

Table 2: Adverse Reactions ≥10% of Patients Receiving Abemaciclib Plus Anastrozole or Letrozole and ≥2% Higher Than Placebo Plus Anastrozole or Letrozole in MONARCH 3

	Abemaciclib plus Anastrozole or Letrozole N=327			**Placebo plus Anastrozole or Letrozole N=161**		
	All Grades %	**Grade 3 %**	**Grade 4 %**	**All Grades %**	**Grade 3 %**	**Grade 4 %**
Gastrointestinal Disorders						
Diarrhea	81	9	0	30	1	0
Nausea	39	<1	0	20	1	0
Abdominal pain	29	1	0	12	1	0
Vomiting	28	1	0	12	2	0
Constipation	16	<1	0	12	0	0
Infections and Infestations						
Infections[a]	39	4	<1	29	2	<1
Blood and Lymphatic System Disorders						
Neutropenia	41	20	2	2	<1	<1
Anemia	28	6	0	5	1	0
Leukopenia	21	7	<1	2	0	<1
Thrombocytopenia	10	2	<1	2	<1	0
General Disorders and Administration Site Conditions						
Fatigue	40	2	0	32	0	0
Influenza like illness	10	0	0	8	0	0
Skin and Subcutaneous Tissue Disorders						
Alopecia	27	0	0	11	0	0
Rash	14	<1	0	5	0	0
Pruritus	13	0	0	9	0	0
Metabolism and Nutrition Disorders						
Decreased appetite	24	1	0	9	<1	0
Investigations						
Blood creatinine increased	19	2	0	4	0	0
Alanine aminotransferase increased	16	6	<1	7	2	0
Aspartate aminotransferase increased	15	3	0	7	1	0
Weight decreased	10	<1	0	3	<1	0
Respiratory, Thoracic, and Mediastinal Disorders						
Cough	13	0	0	9	0	0
Dyspnea	12	<1	<1	6	<1	0
Nervous System Disorders						
Dizziness	11	<1	0	9	0	0

[a] Includes all reported preferred terms that are part of the Infections and Infestations system organ class. Most common infections (>1%) include upper respiratory tract infection, lung infection, and pharyngitis.

Additional adverse reactions in MONARCH 3 include venous thromboembolic events (deep vein thrombosis, pulmonary embolism, and pelvic venous thrombosis), which were reported in 5% of patients treated with Abemaciclib plus anastrozole or letrozole as compared to 0.6% of patients treated with anastrozole or letrozole plus placebo.

Table 3: Laboratory Abnormalities ≥10% in Patients Receiving Abemaciclib Plus Anastrozole or Letrozole and ≥2% Higher Than Placebo Plus Anastrozole or Letrozole in MONARCH 3

	Abemaciclib plus Anastrozole or Letrozole N=327			**Placebo plus Anastrozole or Letrozole N=161**		
Laboratory Abnormality	**All Grades %**	**Grade 3 %**	**Grade 4 %**	**All Grades %**	**Grade 3 %**	**Grade 4 %**
Creatinine increased	98	2	0	84	0	0
White blood cell decreased	82	13	0	27	<1	0
Anemia	82	2	0	28	0	0
Neutrophil count decreased	80	19	3	21	3	0
Lymphocyte count decreased	53	7	<1	26	2	0
Platelet count decreased	36	1	<1	12	<1	0
Alanine aminotransferase increased	48	6	<1	25	2	0
Aspartate aminotransferase increased	37	4	0	23	<1	0

Creatinine Increased

Abemaciclib has been shown to increase serum creatinine due to inhibition of renal tubular secretion transporters, without affecting glomerular function. Across the clinical studies, increases in serum creatinine (mean increase, 0.2-0.3 mg/dL) occurred within the first 28-day cycle of Abemaciclib dosing, remained elevated but stable through the treatment period, and were reversible upon treatment discontinuation. Alternative markers such as BUN, cystatin C, or calculated GFR, which are not based on creatinine, may be considered to determine whether renal function is impaired.

<u>Abemaciclib in Combination with Fulvestrant (MONARCH 2)</u>

Patients with HR-positive, HER2-negative advanced or metastatic breast cancer with disease progression on or after prior adjuvant or metastatic endocrine therapy

MONARCH 2 (NCT02107703)[2] was a randomized, placebo-controlled, multicenter study in women with HR-positive, HER2-negative metastatic breast cancer in combination with fulvestrant in patients with disease progression following endocrine therapy who had not received chemotherapy in the metastatic setting. Randomization was stratified by disease site (visceral, bone only, or other) and by sensitivity to prior endocrine therapy (primary or secondary resistance). Primary endocrine therapy resistance was defined as relapse while on the first 2 years of adjuvant endocrine therapy or progressive disease within the first 6 months of first line endocrine therapy for metastatic breast cancer. A total of 669 patients were randomized to receive Abemaciclib or placebo orally twice daily plus intramuscular injection of 500 mg fulvestrant on days 1 and 15 of cycle 1 and then on day 1 of cycle 2 and beyond (28-day cycles). Pre/perimenopausal women were enrolled in the study and received the gonadotropin-releasing hormone agonist goserelin for at least 4 weeks prior

to and for the duration of MONARCH 2. Patients remained on continuous treatment until development of progressive disease or unmanageable toxicity.

Patient median age was 60 years (range, 32-91 years), and 37% of patients were older than 65. The majority were White (56%), and 99% of patients had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. Twenty percent (20%) of patients had de novo metastatic disease, 27% had bone-only disease, and 56% had visceral disease. Twenty-five percent (25%) of patients had primary endocrine therapy resistance. Seventeen percent (17%) of patients were pre- or perimenopausal.

The efficacy results from the MONARCH 2 study are summarized in Table 4. Median PFS assessment based on a blinded independent radiologic review was consistent with the investigator assessment. Consistent results were observed across patient stratification subgroups of disease site and endocrine therapy resistance. At the time of primary analysis of PFS, overall survival data were not mature (20% of patients had died).

Table 4: Efficacy Results in MONARCH 2 (Investigator Assessment, Intent-to-Treat Population)

	Abemaciclib plus Fulvestrant	**Placebo plus Fulvestrant**
Progression-Free Survival	**N=446**	**N=223**
Number of patients with an event (n, %)	222 (49.8)	157 (70.4)
Median (months, 95% CI)	16.4 (14.4, 19.3)	9.3 (7.4, 12.7)
Hazard ratio (95% CI)	0.553 (0.449, 0.681)	
p-value	p<.0001	
Objective Response for Patients with Measurable Disease	**N=318**	**N=164**
Objective response rate[a] (n, %)	153 (48.1)	35 (21.3)
95% CI	42.6, 53.6	15.1, 27.6

Abbreviation: CI = confidence interval.
[a] Complete response + partial response.

Dose reductions due to an adverse reaction occurred in 43% of patients receiving Abemaciclib plus fulvestrant. Adverse reactions leading to dose reductions in ≥5% of patients were diarrhea and neutropenia. Abemaciclib dose reductions due to diarrhea of any grade occurred in 19% of patients receiving Abemaciclib plus fulvestrant compared to 0.4% of patients receiving placebo and fulvestrant. Abemaciclib dose reductions due to neutropenia of any grade occurred in 10% of patients receiving Abemaciclib plus fulvestrant compared to no patients receiving placebo plus fulvestrant.

Permanent study treatment discontinuation due to an adverse event were reported in 9% of patients receiving Abemaciclib plus fulvestrant and in 3% of patients receiving placebo plus fulvestrant. Adverse reactions leading to permanent discontinuation for patients receiving Abemaciclib plus fulvestrant were infection (2%), diarrhea (1%), hepatotoxicity (1%), fatigue (0.7%), nausea (0.2%), abdominal pain (0.2%), acute kidney injury (0.2%), and cerebral infarction (0.2%).

Deaths during treatment or during the 30-day follow up, regardless of causality, were reported in 18 cases (4%) of Abemaciclib plus fulvestrant treated patients versus 10 cases (5%) of placebo plus fulvestrant treated patients. Causes of death for patients receiving Abemaciclib plus fulvestrant included: 7 (2%) patient deaths due to underlying disease, 4

(0.9%) due to sepsis, 2 (0.5%) due to pneumonitis, 2 (0.5%) due to hepatotoxicity, and one (0.2%) due to cerebral infarction.

The most common adverse reactions reported (≥20%) in the Abemaciclib arm were diarrhea, fatigue, neutropenia, nausea, infections, abdominal pain, anemia, leukopenia, decreased appetite, vomiting, and headache (Table 5). The most frequently reported (≥5%) Grade 3 or 4 adverse reactions were neutropenia, diarrhea, leukopenia, anemia, and infections.

Table 5: Adverse Reactions ≥10% in Patients Receiving Abemaciclib Plus Fulvestrant and ≥2% Higher Than Placebo Plus Fulvestrant in MONARCH 2

	Abemaciclib plus Fulvestrant N=441			**Placebo plus Fulvestrant N=223**		
	All Grades %	**Grade 3 %**	**Grade 4 %**	**All Grades %**	**Grade 3 %**	**Grade 4 %**
Gastrointestinal Disorders						
Diarrhea	86	13	0	25	<1	0
Nausea	45	3	0	23	1	0
Abdominal pain[a]	35	2	0	16	1	0
Vomiting	26	<1	0	10	2	0
Stomatitis	15	<1	0	10	0	0
Infections and Infestations						
Infections[b]	43	5	<1	25	3	<1
Blood and Lymphatic System Disorders						
Neutropenia[c]	46	24	3	4	1	<1
Anemia[d]	29	7	<1	4	1	0
Leukopenia[e]	28	9	<1	2	0	0
Thrombocytopenia[f]	16	2	1	3	0	<1
General Disorders and Administration Site Conditions						
Fatigue[g]	46	3	0	32	<1	0
Edema peripheral	12	0	0	7	0	0
Pyrexia	11	<1	<1	6	<1	0
Metabolism and Nutrition Disorders						
Decreased appetite	27	1	0	12	<1	0
Respiratory, Thoracic and Mediastinal Disorders						
Cough	13	0	0	11	0	0
Skin and Subcutaneous Tissue Disorders						
Alopecia	16	0	0	2	0	0
Pruritus	13	0	0	6	0	0
Rash	11	1	0	4	0	0
Nervous System Disorders						
Headache	20	1	0	15	<1	0
Dysgeusia	18	0	0	3	0	0
Dizziness	12	1	0	6	0	0
Investigations						
Alanine aminotransferase increased	13	4	<1	5	2	0
Aspartate aminotransferase increased	12	2	0	7	3	0
Creatinine increased	12	<1	0	<1	0	0
Weight decreased	10	<1	0	2	<1	0

[a] Includes abdominal pain, abdominal pain upper, abdominal pain lower, abdominal discomfort, abdominal tenderness.
[b] Includes upper respiratory tract infection, urinary tract infection, lung infection, pharyngitis, conjunctivitis, sinusitis, vaginal infection, sepsis.
[c] Includes neutropenia, neutrophil count decreased.
[d] Includes anemia, hematocrit decreased, hemoglobin decreased, red blood cell count decreased.
[e] Includes leukopenia, white blood cell count decreased.
[f] Includes platelet count decreased, thrombocytopenia.
[g] Includes asthenia, fatigue.

Additional adverse reactions in MONARCH 2 include venous thromboembolic events (deep vein thrombosis, pulmonary embolism, cerebral venous sinus thrombosis, subclavian vein thrombosis, axillary vein thrombosis, and DVT inferior vena cava), which were reported in 5% of patients treated with Abemaciclib plus fulvestrant as compared to 0.9% of patients treated with fulvestrant plus placebo.

Table 6: Laboratory Abnormalities ≥10% in Patients Receiving Abemaciclib Plus Fulvestrant and ≥2% Higher Than Placebo Plus Fulvestrant in MONARCH 2

	Abemaciclib plus Fulvestrant N=441			**Placebo plus Fulvestrant N=223**		
	All Grades %	**Grade 3 %**	**Grade 4 %**	**All Grades %**	**Grade 3 %**	**Grade 4 %**
Creatinine increased	98	1	0	74	0	0
White blood cell decreased	90	23	<1	33	<1	0
Neutrophil count decreased	87	29	4	30	4	<1
Anemia	84	3	0	33	<1	0
Lymphocyte count decreased	63	12	<1	32	2	0
Platelet count decreased	53	<1	1	15	0	0
Alanine aminotransferase increased	41	4	<1	32	1	0
Aspartate aminotransferase increased	37	4	0	25	4	<1

Abemaciclib Administered as a Monotherapy in Metastatic Breast Cancer (MONARCH 1)

Patients with HR-positive, HER2-negative breast cancer who received prior endocrine therapy and 1-2 chemotherapy regimens in the metastatic setting

MONARCH 1 (NCT02102490)[3] was a single-arm, open-label, multicenter study in women with measurable HR-positive, HER2-negative metastatic breast cancer whose disease progressed during or after endocrine therapy, had received a taxane in any setting, and who received 1 or 2 prior chemotherapy regimens in the metastatic setting. A total of 132 patients received 200 mg Abemaciclib orally twice daily on a continuous schedule until development of progressive disease or unmanageable toxicity.

Patient median age was 58 years (range, 36-89 years), and the majority of patients were White (85%). Patients had an Eastern Cooperative Oncology Group performance status of 0 (55% of patients) or 1 (45%). The median duration of metastatic disease was 27.6 months. Ninety percent (90%) of patients had visceral metastases, and 51% of patients had 3 or more sites of metastatic disease. Fifty-one percent (51%) of patients had had one line of chemotherapy in the metastatic setting. Sixty-nine percent (69%) of patients had received a taxane-based regimen in the metastatic setting and 55% had received

capecitabine in the metastatic setting. Table 7 provides the efficacy results from MONARCH 1.

Table 7: Efficacy Results in MONARCH 1 (Intent-to-Treat Population)

	Abemaciclib 200 mg N=132	
	Investigator Assessed	**Independent Review**
Objective Response Rate[a,b], n (%)	26 (19.7)	23 (17.4)
95% CI (%)	13.3, 27.5	11.4, 25.0
Median Duration of Response	8.6 months	7.2 months
95% CI (%)	5.8, 10.2	5.6, NR

Abbreviations: CI = confidence interval, NR = not reached.
[a] All responses were partial responses.
[b] Based upon confirmed responses.

Safety data below are based on MONARCH 1, a single-arm, open-label, multicenter study in 132 women with measurable HR-positive, HER2-negative metastatic breast cancer. Patients received 200 mg Abemaciclib orally twice daily until development of progressive disease or unmanageable toxicity. Median duration of treatment was 4.5 months.

Ten patients (8%) discontinued study treatment from adverse reactions due to (1 patient each) abdominal pain, arterial thrombosis, aspartate aminotransferase (AST) increased, blood creatinine increased, chronic kidney disease, diarrhea, ECG QT prolonged, fatigue, hip fracture, and lymphopenia. Forty-nine percent of patients had dose reductions due to an adverse reaction. The most frequent adverse reactions that led to dose reductions were diarrhea (20%), neutropenia (11%), and fatigue (9%).

Deaths during treatment or during the 30-day follow up were reported in 2% of patients. Cause of death in these patients was due to infection.

The most common reported adverse reactions (≥20%) were diarrhea, fatigue, nausea, decreased appetite, abdominal pain, neutropenia, vomiting, infections, anemia, headache, and thrombocytopenia (Table 8). Severe (Grade 3 and 4) neutropenia was observed in patients receiving abemaciclib.

Table 8: Adverse Reactions (≥10% of Patients) in MONARCH 1

	Abemaciclib N=132		
	All Grades %	**Grade 3 %**	**Grade 4 %**
Gastrointestinal Disorders			
Diarrhea	90	20	0
Nausea	64	5	0
Abdominal pain	39	2	0
Vomiting	35	2	0
Constipation	17	<1	0
Dry mouth	14	0	0
Stomatitis	14	0	0
Infections and Infestations			
Infections	31	5	2
General Disorders and Administration Site Conditions			
Fatigue[a]	65	13	0
Pyrexia	11	0	0

Blood and Lymphatic System Disorders			
Neutropenia[b]	37	19	5
Anemia[c]	25	5	0
Thrombocytopenia[d]	20	4	0
Leukopenia[e]	17	5	<1
Metabolism and Nutrition Disorders			
Decreased appetite	45	3	0
Dehydration	10	2	0
Respiratory, Thoracic and Mediastinal Disorders			
Cough	19	0	0
Musculoskeletal and Connective Tissue Disorders			
Arthralgia	15	0	0
Nervous System Disorders			
Headache	20	0	0
Dysgeusia	12	0	0
Dizziness	11	0	0
Skin and Subcutaneous Tissue Disorders			
Alopecia	12	0	0
Investigations			
Creatinine increased	13	<1	0
Weight decreased	14	0	0

[a] Includes asthenia, fatigue.
[b] Includes neutropenia, neutrophil count decreased.
[c] Includes anemia, hematocrit decreased, hemoglobin decreased, red blood cell count decreased.
[d] Includes platelet count decreased, thrombocytopenia.
[e] Includes leukopenia, white blood cell count decreased.

Table 9: Laboratory Abnormalities for Patients Receiving Abemaciclib in MONARCH 1

	Abemaciclib N=132		
	All Grades %	**Grade 3 %**	**Grade 4 %**
Creatinine increased	98	<1	0
White blood cell decreased	91	28	0
Neutrophil count decreased	88	22	5
Anemia	68	0	0
Lymphocyte count decreased	42	13	<1
Platelet count decreased	41	2	0
ALT increased	31	3	0
AST increased	30	4	0

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 nine (9) 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 a 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:

Preclinical studies are expected to be completed within a 2-year time frame.

Phase I studies are expected to meet primary objective within 2 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 2 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.

Randomized Phase II multi-institutional studies are expected to be completed within a 2-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.

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 will be completed within 2 years.

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 must submit a proposal to NCCN in the format delineated below, 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 letters 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) 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

5) 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 a supplemental attachment. A robust review of the statistical plan will be conducted.

Proposals should contain detailed information regarding the following areas:

5.1 Clinical/Non-Clinical Research
- 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 template (within iEnvision)
- 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 Ancillary Documentation
- A. An NCI format BioSketch of the Principal Investigator
- B. An appendix of supportive literature may be provided

6.0 Proposal Requirements

6.1 Submission

All proposals must be submitted electronically using the directions below and are due on **March 22, 2019 by 11:59 PM (ET).** No exceptions will be granted.

1. Please use the link below to register in the system: https://nccn.envisionpharma.com/ienv_nccn
2. Select "Register for New Account" in the upper right corner of the page, above the "Log In" button
3. Complete all fields (Note: Fields with an asterisk are required)
4. You will receive a confirmation email. Click on the link in the email to activate your account.
5. Enter your name and password (Note: Your user name is your email address. Do not copy and paste.)
6. Set up your security questions
7. Submit your study
   i. RFP ID: ABEM
   ii. Primary compound: Abemaciclib
8. Refer to "Requestor User Manual" located under the question mark on the upper right side of the screen for additional instructions

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

Studies that have safety issues, are already 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 call Patricia Esposito at (215) 690-0560. NCCN will seek to provide information to potential investigators regarding ongoing or completed studies of abemaciclib in order to avoid the submission of a proposal that is already a 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) If abemaciclib is studied in combination with an investigational agent from another pharmaceutical company, or an agent used outside of its indication, the investigator must provide documentation of that company's commitment to provide drug for the investigation as well as the agreement of that company to allow presentation and publication of results and allow cross-filing or filing of a new IND. **This documentation must be provided to NCCN along with the proposal.**

6.2.6(c) 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 15 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

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

If abemaciclib is studied in combination with an investigational agent from another pharmaceutical company, or an agent is used outside of its indication, the investigator must provide documentation of that company's commitment to provide drug for the investigation as well as the agreement of that company to allow presentation and publication of results, and allow cross-filing or filing of a new IND.

If pharmacokinetic studies of investigational agents other than abemaciclib are planned, the investigator must provide documentation of that company's commitment to or alternative mechanism for performing PK studies for that agent. This documentation must be provided to NCCN along with the proposal.

8.0 Selection Criteria

Proposals will be judged based on the following criteria:

1. Scientific value
2. Research experience of the Principal Investigator
3. Soundness of study design
4. Feasibility including reasonable assurance of achieving intended and full Accrual
5. Budgetary reasonableness
6. 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 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.

Preclinical studies will be funded up to a total cost of $100,000, including up to 25% indirect costs.

Phase I and 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. Up to $100,000 in 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. Unfunded correlative laboratory studies within clinical trials already supported through other mechanisms will also be considered for support.

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:

(a) Research Projects (Basic Research):

- 50% upon approval of Protocol;
- 35% upon completion of research and receipt of final report by NCCN; and
- 15% upon submission of article for publication.

(b) Phase I trials:

- 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% of funds will be awarded after submission of a manuscript for publication.

(c) 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 for publication.

(d) 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 manuscript for publication or of a final report.

(e) 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 for 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 final contract execution with NCCN.

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

11.0 References

1. Goetz MP, Toi M, Campone M, et al. MONARCH 3: Abemaciclib As Initial Therapy for Advanced Breast Cancer. J Clin Oncol 2017;35:3638-46.
2. Sledge GW, Jr., Toi M, Neven P, et al. MONARCH 2: Abemaciclib in Combination With Fulvestrant in Women With HR+/HER2- Advanced Breast Cancer Who Had Progressed While Receiving Endocrine Therapy. J Clin Oncol 2017;35:2875-84.
3. Dickler MN, Tolaney SM, Rugo HS, et al. MONARCH 1, A Phase II Study of Abemaciclib, a CDK4 and CDK6 Inhibitor, as a Single Agent, in Patients with Refractory HR(+)/HER2(-) Metastatic Breast Cancer. Clin Cancer Res 2017;23:5218-24.

12.0 Ongoing Research Projects

TREATMENT	TUMOR TYPE
Neo-Adjuvant	
Abema	Surgically Resectable, Chemo Resistant TNBC
Abema + Tr + Per + F	ER+, HER2+ BC
Abema + AI + durva	HR+ BC
Abema	HR+, any HER2 status
Abema + Fulv	HR+, recurrence on adjuvant Endo tx. Salvage Surgery.
Adjuvant	
Abema+ HCQ	
Metastatic	
Abema + tucatinib	HER2+ MBC
Abema + Fulv vs Abema	HR+, HER2- MBC
Abema + T-DM1	HER2+ MBC
Abema + trastuzumab + pembro	Advanced HER2+ BC
Abema	RB+ TNBC
Abema + AI	HR+ HER2– second line; MBC– post Fulvestrant
Abema + HCQ	HR ER+
Abema + Bicalutamide	HR+, HER2-, MBC
Abema + pembro	Rb+ TNBC
Abema + ET	HR+ Her2- First line MBC (visceral met) vs Chemo
Label indication– treatment management	HR+ Her2
Abema + Endocrine	Symptomatic MBC
Abema + probiotics+ SOC (diarrhea study)	ER+/HER2- MBC