Abemaciclib in metastatic or locally advanced Anaplastic/Undifferentiated Thyroid Cancer

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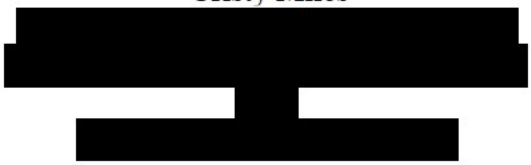

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PROTOCOL SYNOPSIS

TITLE	Abemaciclib in metastatic or locally advanced Anaplastic/Undifferentiated Thyroid Cancer
STUDY PHASE	Phase 2
INDICATION	Anaplastic/Undifferentiated Thyroid Cancer without curative option
INVESTIGATIONAL PRODUCT OR PROCEDURE	Abemaciclib
PRIMARY OBJECTIVE(S)	Overall response rate
SECONDARY OBJECTIVE(S)	Overall Survival

	Progression Free Survival Safety Analysis
TREATMENT SUMMARY	Until progression/intolerance of therapy. Projected 2 to 6 months per patient
SAMPLE SIZE	Simon's Stage 1 (n=9): at least 1 response required to continue to Stage 2 Simon's Stage 2 (additional 8 patients, total n=17)
STATISTICAL CONSIDERATIONS	Simon's optimal two-stage design (Simon, 1989) will be used.

SCHEMA

Pre-Screening portion: molecular analysis will be performed to determine if patients have *BRAF V600E* negative ATC/UTC. These will be treated with Abemaciclib

Therapeutic portion:

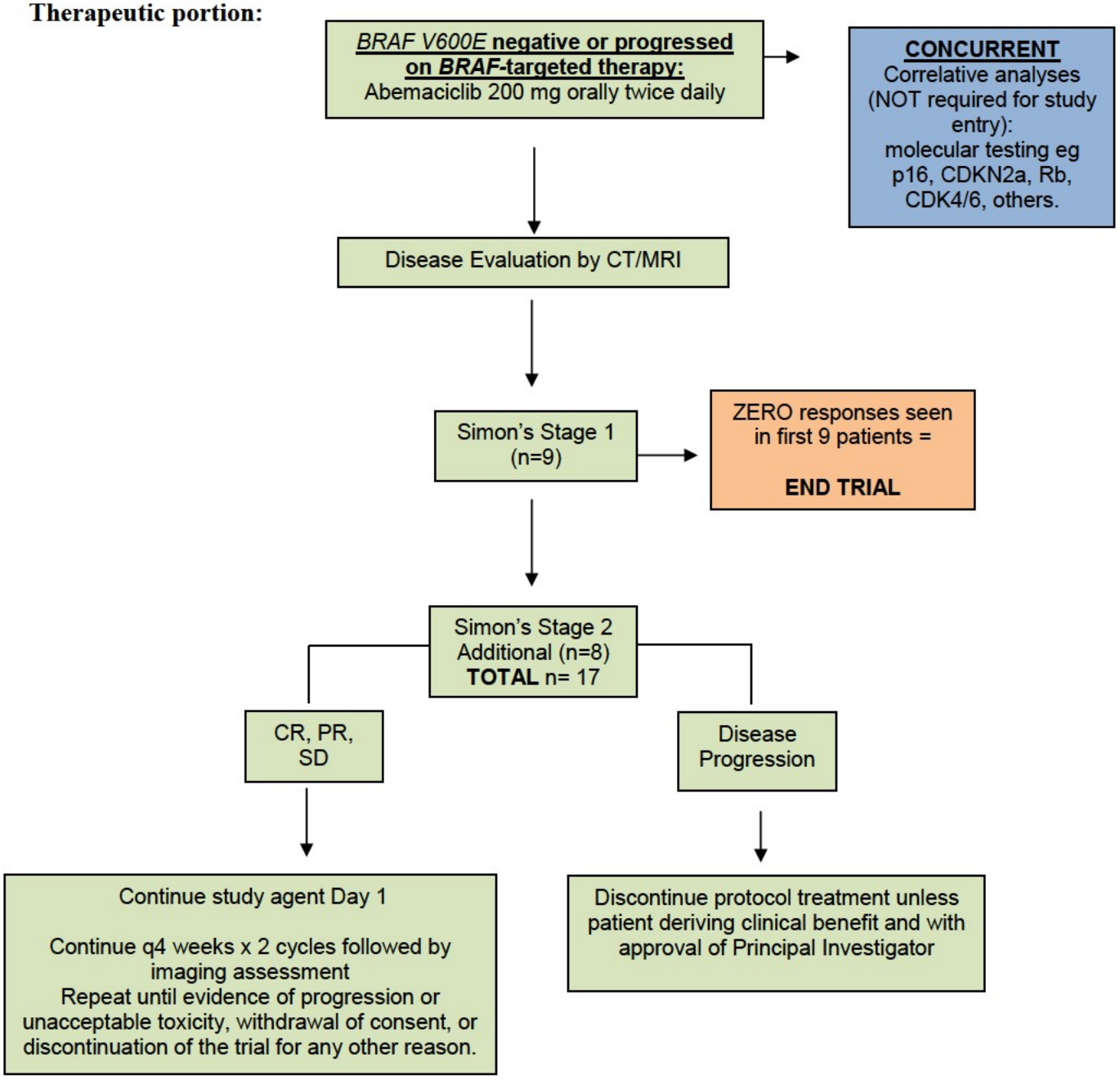

Fig 1-1 Trial schema

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

AE	Adverse Event
ALCL	Anaplastic large cell lymphomas
ALK	Anaplastic lymphoma kinase
ALT	Alanine aminotransferase/glutamic pyruvic transaminase/GPT
AST	Aspartate aminotransferase/glutamic oxaloacetic transaminase/GOT
ATC	Anaplastic Thyroid Cancer
BCRP	multidrug transporter ABCG2
b.i.d.	bis in diem/twice a day
CNS	Central nervous system
CR	Complete Response
CrCl	creatinine clearance
CRO	Contract Research Organization
DLT	Dose Limiting Toxicity
DS&E	Drug Safety and Epidemiology
ECG	Electrocardiogram
EIAED	enzyme inducing anti-epileptic medication
EGFR	epidermal growth factor receptor
EOT	End of treatment
FAS	Full Analysis Set
GI	Gastric intestinal
hERG	human Ether-à-go-go-Related Gene
IUD	intrauterine device
IUS	intrauterine system
i.v.	intravenous (lv)
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IHC	immunohistochemistry
IRB	Institutional Review Board
LLN	Lower limit of normal
LLNA	local lymph node assay
MTD	Maximum Tolerated Dose NSCLC non-small cell lung cancer
o.d.	omnia die/once a day

OS	Overall survival
OTC	over-the counter
QD	once daily
PD	Progressive disease
p.o.	per os/by mouth/orally
PFS	Progression free survival
PHI	Protected Health Information
PK	Pharmacokinetics
PPI	proton pump inhibitors
PR	Partial response
Racc	accumulation ratio
RAP	The Report and Analysis Plan (RAP) is a regulatory document which provides evidence of preplanned analyses
RDE	Recommended dose for expansion
REB	Research Ethics Board
RECIST	Response Evaluation Criteria In Solid Tumors
RR	Response Rate
SAE	Serious Adverse Event
SOP	Standard Operating Procedure
TDI	time-dependent inhibition
TKI	tyrosine kinase inhibitors
ULN	upper limit of normal
UTC	Undifferentiated thyroid cancer
UV	Ultraviolet radiation
VATS	Video-assisted thoracic surgery
VEGF	vascular endothelial growth factor
WHO	World Health Organization

1. OBJECTIVES

1.1. Primary Objective

The primary objective is to determine the overall response rate after treatment with abemaciclib in patients with anaplastic thyroid/undifferentiated thyroid cancer.

1.2. Secondary Objectives

The secondary objectives are to describe the overall survival (OS) and progression-free survival (PFS) after treatment with abemaciclib in patients with anaplastic thyroid/undifferentiated thyroid cancer. Safety assessments of AE's will also be analysed.

2. BACKGROUND

2.1 Study Disease

2.1.1 Anaplastic Thyroid Cancer

Anaplastic thyroid cancer (ATC) is an undifferentiated tumor of thyroidal follicular epithelium. Although not as common as differentiated thyroid cancers, ATC has much higher disease specific mortality, approaching 100% (Are and Shaha 2006).). In fact, despite accounting for less than 5% of all thyroid cancer diagnoses, ATC leads to more than half of the 1200 deaths from thyroid cancer every year in the United States (Hundahl, Fleming et al. 1998, McIver, Hay et al. 2001).

Forty six percent of patients present with distant metastases, and almost 70% demonstrate metastases at some stage of the disease (McIver, Hay et al. 2001). All staging for anaplastic thyroid cancer is as stage IV (McIver, Hay et al. 2001), given its aggressive nature and propensity for metastasis. Even with the most aggressive existing multimodality therapy involving surgery, radiation and chemotherapy, most patients do not derive consistent, sustained benefit in outcomes and survival. Median overall survival remains 3-4 months, with 90% of patients dead at 1 year from diagnosis (McIver, Hay et al. 2001). Patients often suffer from distant metastases even after local therapy is completed, demonstrating the inadequacy of treatment. Lung, brain and bone metastases are common as well as significant airway compromise and suffocation even after tracheostomy.

2.1.2 Treatment for Anaplastic Thyroid Cancer-Chemotherapy

Doxorubicin is the only approved chemotherapy for anaplastic thyroid cancer (Smallridge, Ain et al. 2012), and is often combined with radiation or surgery as part of multi-modality therapy. No randomized trial has demonstrated improved statistically significant survival or better quality of life in patients treated with any current therapy (Smallridge, Ain et al. 2012).

Given the poor prognosis, guidelines from the American Thyroid Association as well as the National Comprehensive Cancer Network recommend all patients should be treated as part of a clinical trial regardless of stage (NCCN clinical practice guidelines in Oncology , Smallridge, Ain et al. 2012).

This treatment protocol aims to offer targeted, mutation and oncogene driven therapy for patients with anaplastic thyroid cancer who would otherwise have very poor treatment options and outcome.

As new biomarkers and drug combinations are identified, additional arms will be added to the therapeutic portion of the study based on that knowledge.

2.1.3 Treatment for Anaplastic Thyroid Cancer-Targeted Therapy and Clinical Trials

There are currently no approved and no commonly employed targeted therapies in anaplastic thyroid cancer. This is an area of urgent need for patients, not just for approved treatments but also rationally-designed clinical trials designed specifically for ATC.

Newer agents have been tested in patients with ATC, but currently none have been approved for any stage of therapy for patients in the US. Fosbretabulin is a novel tubulin binding compound that demonstrated activity in ATC (Mooney, Nagaiah et al. 2009). A Phase III trial randomized ATC patients to fosbretabulin or placebo, these patients had previously been treated with carboplatin and paclitaxel and 55% of them had undergone surgical resection (Sosa, Balkissoon et al. 2012). The arm containing the experimental drug had 33.3% survival at one year vs 7% for the carboplatin and paclitaxel alone arm. Although not powered to detect differences in survival, the median survival for the standard arm was reported as 4 months for the control arm versus 8.4 months for the fosbretabulin arm.

Sorafenib has demonstrated some activity in multi-institution, small studies. In 20 patients treated with sorafenib, 2 patients demonstrated a partial response (Savvides, Nagaiah et al. 2013). Sorafenib is currently not listed as a recommended regimen in the NCCN guidelines for anaplastic thyroid cancer, nor in the ATA guidelines for Anaplastic Thyroid Cancer.

A minority of ATC patients have a BRAF V600E mutation are offered dabrafenib and trametinib as treatment. These drugs are not curative, and they then require further therapy. These patients often need to start subsequent therapy quickly because they have rapidly growing tumors.

Patients whose most recent treatment has been with only dabrafenib and trametinib may be enrolled on to the study and start abemaciclib 1 week after discontinuation of dabrafenib and trametinib, instead of 3 weeks as is required for cytotoxic chemotherapies. Dabrafenib and trametinib have short half lives and upon discontinuation there is rapid clearance of these drugs and resolution of their toxicities.

Additionally some patients are treated with lenvatinib, though the FDA label limits the indication to differentiated thyroid cancer. Lenvatinib has a half-life of 28 hours per the package insert. https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/206947s007lbl.pdf. Due to this short half life a washout period of 1 week is sufficient to reach a point where there is minimal lenvatinib.

Clinical trials for this disease are also extremely rare, leaving patients with very limited treatment options. Patients diagnosed with anaplastic thyroid cancer have a very high likelihood of dying because of their disease. As such there is a clear need for improving therapy for anaplastic thyroid cancer in a rational, patient selective manner.

2.2 Study Agent/Device/Procedure

In the mammalian cell cycle, entry into S phase is achieved by CDK4/6. Abemaciclib is a small molecule inhibitor that is selective for CDK4 and 6. It blocks phosphorylation of the retinoblastoma tumor suppressor protein. This leads to impaired progression through the cell cycle and arrest in the G1 phase(Sledge, Toi et al. 2017). Currently, Abemaciclib is FDA-approved for use in breast cancer, with the package insert providing further information about pharmacology, dosage and administration, drug interactions and use in special populations:
https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/208716s000lbl.pdf

For clinicaltrials.gov compliance
Abemaciclib is FDA approved for use in breast cancer. This clinical trial will not be seeking a new indication. An IND is not required in conjunction with this clinical trial.

2.3 Rationale

Experimental Therapy: Abemaciclib

2.3.1 Evidence suggesting benefit of abemaciclib in ATC/UTC

Retinoblastoma,CDNK2A/p16 in ATC/UTC

Retinoblastoma (Rb) is a critical negative regulator of the cell cycle which prevents premature cell division(Schwartz and Shah 2005). Rb inactivation leads to uncontrolled cell division, and has been detected in many cancers, for example breast (20-30%)(Bosco and Knudsen 2007). In tumors with functional Rb, CDK 4/6 inhibitors inhibit cell growth and suppress DNA replication(Fry, Harvey et al. 2004). In Rb-deficient tumors, CDK 4/6 inhibitors have limited efficacy(Dean, Thangavel et al. 2010). Rb mutations have been reported in thyroid

cancer cases, but there is a dichotomy based on histologic sub-type, as differentiated thyroid cancers often lose Rb but more aggressive variants such as ATC almost always have intact Rb(Anwar, Emond et al. 2000).

In an analysis of Rb staining in thyroid cancers, 4 anaplastic thyroid cancer samples all showed strong positive Rb expression(Anwar, Emond et al. 2000) .By contrast, all of the more common papillary thyroid cancers and follicular variant of papillary showed entirely negative staining for Rb (table). Other subtypes showed a varied staining pattern, such as medullary thyroid cancer (50% Rb positive) and Hurthle cell (20% Rb positive). This shows that anaplastic is unique amongst thyroid cancers in expressing intact Rb, suggesting a role for CDK 4/6 inhibition.

The p16 mutation inhibits CDK4/6 which phosophorylates Rb, resulting in cell cycle progression. High p16 levels are seen in some cancers, such as human papilloma virus (HPV) associated head and neck squamous cell cancer. The true value of p16 as a predictive biomarker for CDK4/6 inhibition is still being analyzed. However current thinking suggests that if p16 levels are high, it is likely that pharmacological inhibition of CDK4/6 would be less effective.

In anaplastic thyroid cancer p16 levels were undetectable in 24 out of 27 (89%) cancer specimens (Lee, Foukakis et al. 2007).

CDKN2A encodes the cell cycle regulator p16. There was deletion or LOH in 3/5 anaplastic thyroid cancer specimens (Tung, Shevlin et al. 1996). Using 90 ATC patient samples, we performed comprehensive genomic profiling to determine the frequency of CDKN2A loss. These data were presented at ASCO 2016 and published results (Khan, Ci et al. 2019) showed more than 30% of ATC patients demonstrate loss of CDKN2A. Rb1 loss was seen in 2/90 patients.

2.4 Study Design

This study will be an open-label, single cohort study for the purpose of evaluating the efficacy of treatment with abemaciclib in patients with analplastic thyroid/undifferentiated thyroid cancer. There will be no randomization. An optimal Simon 2 stage design will be utilized to address the primary objective.

2.5 Correlative Studies Background

See above; no correlative studies will be done in this study.

3. PARTICIPANT SELECTION AND ENROLLMENT PROCEDURES

Patient population

Subjects from this study will be selected from those with anaplastic or undifferentiated thyroid cancer. Patients with a histologically confirmed diagnosis of anaplastic or undifferentiated thyroid cancer will be eligible to be enrolled on to the pre-screening portion of the trial. Molecular testing is considered standard for these patients using next generation sequencing platforms that have broad coverage of many genes.

Patients enrolled to the therapeutic portion of the study will have histologically proven anaplastic or undifferentiated anaplastic thyroid cancer that is BRAF V600E negative.

Patients that have a documented BRAF V600E positive ATC/UTC will be treated first with BRAF targeted therapy, currently the FDA approved regimen is combination of dabrafenib and trametinib. Patients will be eligible for abemaciclib therapy after they have progressed on this combination or become intolerant.

3.1 Inclusion Criteria

Patients eligible for inclusion in this early treatment protocol have to meet **all** of the following criteria:

1. Histologically or cytologically confirmed diagnosis of anaplastic thyroid cancer or undifferentiated thyroid cancer that does not have a known BRAF V600E positive on tissue/blood testing. BRAF V600E positive patients are eligible if they have previously received FDA approved therapy for this genetic abnormality and progressed or become intolerant.
2. Patients will be eligible if they meet either criteria:
    a. Unresectable anaplastic thyroid cancer limited to the neck: Patients must have received radiation therapy or surgery to primary tumor and have subsequent evidence of ATC.

    b. Metastatic anaplastic thyroid cancer: either with entirely surgically removed cancer/metastatic only disease, or with disease in the neck not requiring radiation or surgery to the neck mass.
3. Patients with a bulky thyroid/neck mass and those in whom airway obstruction is suspected should undergo an evaluation via indirect or direct laryngoscopy to ensure patency of the trachea/airway prior to enrollment
4. Patients will not have any other curative therapeutic option, such as radiation or surgery.
5. ECOG performance status 0-1.

6. Have measurable disease based on RECIST 1.1
7. Be willing to provide tissue from a newly obtained core or excisional biopsy of a tumor lesion. Newly-obtained is defined as a specimen obtained up to 6 weeks (42 days) prior to initiation of treatment on Day 1. Subjects for whom newly-obtained samples cannot be provided (e.g. inaccessible or subject safety concern) may submit an archived sample.
8. Be ≥ 18 years of age on day of signing informed consent.
9. Patients who received chemotherapy must have recovered (Common Terminology Criteria for Adverse Events [CTCAE] Grade ≤1) from the acute effects of chemotherapy except for residual alopecia or Grade 2 peripheral neuropathy prior to study treatment start. A washout period of at least 21 days is required between last chemotherapy dose and study treatment start (provided the patient did not receive radiotherapy). Note: Patients who have most recently been treated with dabrafenib and/or trametinib and/or lenvatinib require a washout period of 1 week from their last dose
10. Patients who received radiotherapy must have completed and fully recovered from the acute effects of radiotherapy. A washout period of at least 14 days is required between end of radiotherapy and study treatment start.
11. The patient is able to swallow oral medications.
12. The patient has adequate organ function for all of the following criteria, as defined in Table 3-1 below:

Table 3-1: Laboratory Value Guidance to Establish Adequate Organ Function

System	Laboratory Value
Hematologic	
ANC	≥1.5 × 10^9/L
Platelets	≥100 × 10^9/L
Hemoglobin	≥8 g/dL
	Patients may receive erythrocyte transfusions to achieve this hemoglobin level at the discretion of the investigator. Initial treatment must not begin earlier than the day after the erythrocyte transfusion.
Hepatic	
Total bilirubin	≤1.5 × ULN Patients with Gilbert's syndrome with a total bilirubin ≤2.0 times ULN and direct bilirubin within normal limits are permitted.
ALT and AST	≤3 × ULN

Abbreviations: ALT = alanine aminotransferase; ANC = absolute neutrophil count; AST = aspartate aminotransferase; ULN = upper limit of normal.

13. Women of childbearing potential and all men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) while taking drug and agree to continue for 3 months after the last dose of study treatment. Women of child bearing potential and male patients for 3 months should not mother or father a child in this period. A condom is required to be used also by vasectomized men in order to prevent delivery of the drug via seminal fluid.
14. Patient has the ability to understand and provide signed informed consent.
15. Willingness and ability to comply with scheduled visits, treatment plans, laboratory tests and other procedures.

3.2 Exclusion criteria

Patients eligible must not meet **any** of the following criteria:

1. Patients with known hypersensitivity to any of the excipients of abemaciclib
2. History of carcinomatous meningitis
3. Prior therapy with abemaciclib.
4. The patient has serious and/or uncontrolled preexisting medical condition(s) that, in the judgment of the investigator, would preclude participation in this study (for example, interstitial lung disease, severe dyspnea at rest or requiring oxygen therapy, severe renal impairment [e.g. estimated creatinine clearance <30ml/min], history of major surgical resection involving the stomach or small bowel, or preexisting Crohn's disease or ulcerative colitis or a preexisting chronic condition resulting in baseline Grade 2 or higher diarrhea).
5. Females who are pregnant or lactating.
6. The patient has active systemic bacterial infection (requiring intravenous [IV] antibiotics at time of initiating study treatment), fungal infection, or detectable viral infection (such as known human immunodeficiency virus positivity or with known active hepatitis B or C [for example, hepatitis B surface antigen positive]. Screening is not required for enrollment.
7. The patient has a personal history of any of the following conditions: syncope of cardiovascular etiology, ventricular arrhythmia of pathological origin (including, but not limited to, ventricular tachycardia and ventricular fibrillation), or sudden cardiac arrest.
8. Presence or history of a malignant disease other than thyroid cancer that has been diagnosed and/or required therapy within the past year and is undergoing active anticancer treatment. Exceptions to this exclusion include the following: completely resected basal cell and squamous cell skin cancers, and completely resected carcinoma in situ of any type.

3.3 Informed Consent Process

All participants must be provided a consent form describing the study with sufficient information for participants to make an informed decision regarding their participation. Participants must sign the IRB approved informed consent prior to participation in any study specific procedure. The participant must receive a copy of the signed and dated consent document. The original signed copy of the consent document must be retained in the medical record or research file. A high definition electronic copy such as PDF scan or electronic photograph of entire signed consent form is acceptable for documentation of consent.

3.4 Registration Process

The sites will register the subject on OnCore within 5 business days and immediately notify the Stanford Study Coordinators, Monday through Friday, between 9:00 a.m. and 5:00 p.m. (Pacific Time). The individual notifying the Stanford study team will also provide the subject's eligibility information when eligibility checklist is complete, with the secondary reviewer to be signed off by a designated Stanford Research Staff member. No subject may begin study treatment until registration, eligibility confirmation, and assignment of a subject identification number is completed.

At registration, Stanford will sequentially assign eligible subjects an identification number. As confirmation, Stanford will provide the Investigator with written verification of the subject's registration by e-mail or fax. The subject's identification number will be used on all subject-specific Case Report Forms (CRFs) and serious adverse event (SAE) forms. Participant information should be entered into Oncore® within 5 business days.

3.5 Randomization Procedures

There is no randomization.

3.6 Study Timeline

Primary Completion:
The study will reach primary completion 24 months from the time the study opens to accrual.

Study Completion:
The study will reach study completion 36 months from the time the study opens to accrual.

Definition of end of the Study

The arm will be completed when 17 patients have evidence of disease progression by RECIST, unacceptable toxicity, withdrawal of consent, or discontinuation of the trial for any other reason. Patients who have RECIST-defined PD as assessed by the investigator but who, in the opinion of the investigator, have evidence of continued clinical benefit from study drug may continue to receive the study medication. In such cases, these patients must continue to be followed for safety and efficacy assessments as per the schedule of assessments.

At the completion or discontinuation of study medication, all patients will be seen within 30 days for an end of therapy evaluation. This will include a safety assessment for AE's SAE's. Any unused medication will be destroyed

4. TREATMENT PLAN

For this study, the term "treatment" refers to abemaciclib. The dose and schedule are listed under table 4-1.

Each cycle of therapy will be 28 days long. A completed cycle will be twice daily abemaciclib. Day 1 will be the first day that abemaciclib is taken, and the last day of a completed treatment cycle will be day 28. All doses prescribed to and taken by patients, any dose adjustments and interruption or discontinuations will be recorded in the clinical trial record.

Table 4-1 Dose and treatment schedule

Study treatments	**Pharmaceutical form and route of administration**	**Dose**	**Frequency and/or Regimen**
Abemaciclib	Tablet for oral intake	200 mg orally	Twice daily (28 day cycle)

Dosing regimen

Patients on the therapeutic portion of this trial will begin therapy on day 1 of Cycle 1 with the first administration of abemaciclib.

Administration of abemaciclib

The investigational pharmacist or designee will dispense abemaciclib to the patient at the beginning of each cycle. Patients will self-administer the doses of abemaciclib for the 28-day cycle.

- The institution will be supplied with abemaciclib by Lilly. Treatment will be administered orally daily at the doses noted on a continuous dosing schedule. The investigator must instruct the patient to take the treatment exactly as prescribed. Patients should take

treatment daily at approximately the same time each day, in the morning, afternoon, or evening.

- If vomiting occurs during the course of treatment, do not take another tablet before the next scheduled dose.
- Do not make up missed doses or partial doses (i.e., when the entire dose is not taken as instructed). A missed or partial dose will be defined as a case when the full dose is not taken within 8 hours after the approximate time of the usual daily dosing. That day's dose (or partial remaining dose) should be omitted, and continue treatment with the next scheduled dose on the following day.

Treatment duration

Patients will continue abemaciclib treatment until they experience any of the following:

-Disease progression determined by the local investigator.
-Unacceptable toxicity that precludes further treatment.
-Start of a new anti-cancer therapy.
-Pregnancy.
-Treatment is discontinued at the discretion of the investigator or patient.
-Lost to follow-up.
-Death.
-Completed.

4.1 General Concomitant Medication and Supportive Care Guidelines

Abemaciclib is predominantly cleared by oxidative metabolism via CYP3A4. Clinical drug interaction studies with a CYP3A inhibitor and CYP3A inducer significantly altered the PK of abemaciclib and its circulating major metabolites.

CYP3A inducers

Avoid concomitant use of CYP3A inducers and consider alternative agents.

CYP3A inhibitors

Avoid concomitant use of strong CYP3A inhibitors (for example, voriconazole) and use caution with coadministered moderate (for example, ciprofloxacin) or weak (for

example, ranitidine) CYP3A inhibitors. If coadministration with a strong CYP3A inhibitor is unavoidable, reduce the abemaciclib dose to 100 mg twice daily or, in the case of ketoconazole, reduce the abemaciclib dose to 50 mg twice daily. In patients who have had a dose reduction to 100 mg twice daily due to adverse reactions, further reduce the abemaciclib dose to 50 mg twice daily. Avoid grapefruit or grapefruit juice. If a CYP3A inhibitor is discontinued, increase the abemaciclib dose (after 3-5 half-lives of the inhibitor) to the dose that was used before starting the inhibitor.

4.2 Criteria for Removal from Study

Patients may voluntarily withdraw from the study (no further study data to be collected) at any time.

Patient death will be considered as a withdrawal from the study. Patients may also be withdrawn (the physician may decide to remove the patient from any further study activity) if any of the following occur:

1. Adverse event(s) (see section 7)
2. Disease progression
3. Major protocol deviation
4. Technical problems
5. Physician decision
6. Non-compliance with study treatment.
7. Death
8. Completed

Patients must be withdrawn if any of the following occur:

1. Lost to follow-up
2. Subject/guardian decision
3. Pregnancy (Pregnancy will be followed for outcome)

Patients lost to follow up should be recorded as such in the clinical trial record. For patients who are lost to follow-up, the investigator will record the attempts at “due diligence” by documenting in the source documents steps taken to contact the patient, e.g. dates of telephone calls, registered letters, etc.

4.3 Alternatives

The study agent is FDA approved and therefore has a well established safety and toxicity profile. The treatment options available to this study population are not existent. Therefore, minimal risk to the patient is expected. In the event that a patient is deemed to be at risk sufficiently great to preclude further study participation as outlined in this study protocol they may removed from the study.

5. INVESTIGATIONAL AGENT/DEVICE/PROCEDURE INFORMATION

5.1 Investigational Agent/Device/Procedure

Abemaciclib is FDA approved and in regular use for clinical practice. For further details please refer to the abemaciclib investigator brochure.

For clinicaltrials.gov and Stanford Clinical Trials Directory compliance

Intervention Description

1. Abemaciclib 200 mg orally twice daily
2. Number of Cycles: until progression or unacceptable toxicity develops.

Arms/Groups

1. single arm study

5.2 Availability

The drug will be provided by the manufacturer Lilly, pharmaceutical company.

5.3 Agent Ordering

The Stanford University designated Investigational Drug Services (IDS) pharmacy will handle agent ordering and compounding at their SOP level.

5.4 Agent Accountability

5.4.1 Study drug preparation and dispensation

The investigator and delegates, as well as other study personnel will instruct the patient to take abemaciclib according to protocol. Abemaciclib will be dispensed by authorized site personnel, and all doses recorded in the clinical trial record.

Abemaciclib received from the manufacturer will be stored in our investigational pharmacy and dispensed at the beginning of each cycle. This will only be after confirmation from the investigator or co-investigator that the patient is to continue and has received instructions on how to take the medicine per protocol.

5.4.2 Study drug packaging and labeling

The manufacturer will provide abemaciclib in clearly labeled packaging. Immediately before dispensing the medicine to the patient, the patient's Drug Label Form will be updated to link the medication to the patient.

5.4.3 Drug supply and storage

Abemaciclib will be stored according to the instructions specified on the drug labels and in the Investigator's Brochure. The drug supply will be in a secure location that only the investigator and authorized personnel may have access to.

5.5 Study drug compliance and accountability

5.5.1 Study drug compliance

The patient will be asked to keep a diary of taking the medication, as well as bringing pill bottles to each clinic visit. At each visit, the patient's compliance in study medication according to protocol will be assessed by the investigator and/or study personnel. This information will be entered into the Drug Accountability Form and captured into the source document at each visit, in their medication diary.

5.5.2 Study drug accountability

The IDS will maintain an accurate record of the shipment and dispensation of study drug in the drug accountability log. This will be made available to the appropriate regulatory authority upon request.

During therapy, the patient will be asked to regularly return all unused drug and packaging. All unused medication and packaging will be destroyed. At the completion of the therapeutic portion of the protocol, all stored medication and packaging will be destroyed.

6. DOSE MODIFICATIONS

Dose escalation guidelines

No doses escalation will be permitted on this study.

Dose modifications

For patients who do not tolerate the protocol-specified dosing schedule, dose adjustments are permitted in order to allow the patients to continue the abemaciclib treatment. Any changes in drug administration will be recorded in the clinical trial record.

For patients who do not tolerate the protocol-specified dosing schedule, adjustments are recommended in order to allow the patient to continue the study treatment. Refer to Section 7.3.1 for dose level reductions**.**For purposes of EDC entry, dose modification is defined as dose reductions and dose holds.

General guidelines for dose modifications

- For grade 1 and tolerable grade 2 treatment-related toxicities, with the exception of pneumonitis, patients may continue at the current dose of abemaciclib.
- For intolerable grade 2 treatment-related toxicities, with the exception of pneumonitis, dosing should be interrupted until resolution to grade 1 or lower followed by dose reduction to the next dose level.
- For grade 3 or grade 4 treatment-related toxicity, that is not considered by the investigator to be life-threatening, dosing should be interrupted and the patients should be followed until the toxicity resolution to grade 1 or lower. Following recovery from grade 3 or grade 4 events, study treatment may continue following a dose reduction to the next dose level, if, in the opinion of the Investigator, the patient continues to experience clinical benefit. For any grade 3 or grade 4 treatment-related toxicity that is considered by the investigator to be life-threatening, permanently discontinue study treatment.

All dose modifications, interruptions or discontinuations must be based on the worst preceding toxicity as graded by the NCI Clinical Toxicity Criteria version 5

Patients whose treatment is interrupted or permanently discontinued due to an AE must be followed until resolution or stabilization of the event. Patients requiring interruptions greater than 2 cycle (56 days) should be discontinued from abemaciclib treatment. All patients will be followed for safety until 30 days after the last dose of abemaciclib.

7. ADVERSE EVENTS AND REPORTING PROCEDURES

7.1 Potential Adverse Events

7.1.1 Follow-up for toxicities

An unscheduled visit should be performed in all cases below where toxicity monitoring is recommended more frequently than defined by the schedule of assessments (Section 9).

Ongoing SAEs at the final safety evaluation visit or the end of study treatment visit (whichever is later) should be followed until they improve becoming non serious events, stabilize, or return to baseline levels. Refer to Section 7 for SAE.

A summary of selected toxicity follow-up recommendations is listed below.

7.2 Abemaciclib dose modification for toxicities

Management of severe or intolerable adverse reactions requires dose reduction, temporary interruption, and/or discontinuation of abemaciclib therapy.

7.3 Guidelines for on-study patient management

7.3.1 Guidelines for Diarrhea Management

Clinical trial data indicates the majority of patients who receive abemaciclib will develop diarrhea. Our experience indicates early identification and intervention for the management of diarrhea has been helpful to patients.

At enrollment, patients should receive instructions on the prompt management of diarrhea. In the event of diarrhea, supportive care measures should be initiated as early as possible. These include the following:

- At the first sign of loose stools, the patient should initiate antidiarrheal therapy (e.g. loperamide) and notify the investigator for further instructions and appropriate follow-up.
- Patients should also be encouraged to drink fluids (e.g., 8 to 10 glasses of clear liquids per day).
- Site personnel should assess response within 24 hours.
- Refer to Table 7-1 for additional information for diarrhea management and dose modification.

Table 7-1: Dose Modification and Management- Diarrhea

At the first sign of loose stools, start treatment with antidiarrheal agents, such as loperamide.

CTCAE Grade	Abemaciclib Dose Modifications
Grade 1	No dose modification is required.
Grade 2	If toxicity does not resolve within 24 hours to ≤Grade 1, suspend dose until resolution. Dose reduction is not required.
Grade 2 that persists or recurs after resuming the same dose despite maximal supportive measures	Suspend dose until toxicity resolves to ≤Grade 1. Resume at next lower dose.
Grade 3 or 4 or requires hospitalization	

Dose level reductions should be made in 50 mg increments. For example, if the starting dose of abemaciclib is 200 mg twice daily, dose reduction 1 would be 150 mg twice daily, dose reduction 2 would be 100 mg twice daily.

7.3.2 General Guidance for Increases in Serum Creatinine and Assessment of Renal Insufficiency

Abemaciclib has been shown to increase serum creatinine due to inhibition of renal tubular transporters without affecting glomerular function (as measured by iohexol clearance). In clinical studies, increases in serum creatinine occurred within the first month of abemaciclib dosing, remained elevated but stable through the treatment period, were reversible upon treatment discontinuation, and were not accompanied by changes in markers of renal function, such as blood urea nitrogen (BUN), cystatin C, or calculated glomerular filtration rate based on cystatin C.

7.3.3 General Guidance for Interstitial lung disease (ILD)/Pneumonitis events

Interstitial lung disease (ILD) /pneumonitis has been identified as an adverse drug reaction for abemaciclib. The majority of events observed in clinical trials were Grade 1 or Grade 2 with serious cases and fatal events reported. Additional information is available in the IB. Monitor for clinical symptoms or radiological changes indicative of ILD/pneumonitis and ask your patients to report any new or worsening pulmonary symptoms such as dyspnea, cough, and fever, and investigate and treat as per your local clinical practice (including corticosteroids as appropriate). If ILD/pneumonitis is suspected, investigations may include imaging, such as high resolution computed tomography, broncheoalveolar lavage, and biopsy as clinically indicated. Discontinue abemaciclib in cases of severe (Grade 3 or 4) ILD/pneumonitis (see also Table 7-2: *refer to dose adjustment table for interstitial lung*

disease/pneumonitis).

Table 7-2: Dose Modification and Management — Interstitial Lung Disease/Pneumonitis

CTCAE Grade	Abemaciclib Dose Modifications
Grade 1 or 2	No dose modification is required.
Persistent or recurrent Grade 2 toxicity that does not resolve with maximal supportive measures within 7 days to baseline or Grade 1	Suspend dose until toxicity resolves to baseline or Grade 1. Resume at next lower dose.
Grade 3 or 4	Discontinue abemaciclib.

7.3.4 General Guidance for Hepatic Monitoring

Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) elevation are considered as ADR with the use of abemaciclb. **The following information in Table 7-3 is to be followed for hepatic monitoring:**

Table 7-3: Dose Modification and Management — Increased ALT/AST

Monitor ALT/AST prior to the start of abemaciclib therapy, every 2 weeks for the first 2 months, monthly for the next 2 months, and as clinically indicated.	
CTCAE Grade	**Abemaciclib Dose Modifications**
Grade 1 (>ULN-3.0 x ULN) Grade 2 (>3.0-5.0 x ULN)	No dose modification is required.
Persistent or Recurrent Grade 2, or Grade 3 (>5.0-20.0 x ULN) that does not resolve with maximal supportive measures within 7 days to baseline or Grade 1	Suspend dose until toxicity resolves to baseline or Grade 1. Resume at next lower dose.
≥Grade 2 (>3.0 x ULN) with **total bilirubin >2 x** ULN, in the absence of cholestasis	Discontinue abemaciclib.
Grade 4 (>20.0 x ULN)	Discontinue abemaciclib.

To ensure patient safety the investigator should collect specific recommended clinical information and follow-up laboratory tests as shown below in Table 7-4.

Details for hepatic monitoring depend upon the severity and persistence of observed laboratory test abnormalities. If a study patient experiences elevated ALT/AST 5×ULN and elevated TBL 2×ULN, or ALT/AST 8×ULN, liver tests, including ALT, AST, TBL, direct bilirubin, gamma-glutamyl transferase (GGT), and creatine phosphokinase (CPK), should be repeated within 3 to 5 days to confirm the abnormality and to determine if it is increasing or decreasing. If the abnormality persists or worsens, clinical and laboratory monitoring should be initiated by the investigator, based on the hepatic monitoring tests below.

Table 7-4: Hepatic Monitoring Tests for a Hepatic Treatment Emergent Abnormality.

Hematology	**Clinical Chemistry**
Hemoglobin	Total bilirubin
Hematocrit	Direct bilirubin
Erythrocytes (RBCs - red blood cells)	Alkaline phosphatase (ALP)
Leukocytes (WBCs - white blood cells)	Alanine aminotransferase (ALT)
Differential:	Aspartate aminotransferase (AST)
Neutrophils, segmented	Gamma-glutamyl transferase (GGT)
Lymphocytes	Creatine kinase (CK)
Monocytes	**Other Chemistry**
Basophils	Acetaminophen
Eosinophils	Acetaminophen protein adducts
Platelets	Alkaline phosphatase isoenzymes
Cell morphology (RBC and WBC)	Ceruloplasmin
	Copper
Coagulation	Ethyl alcohol (EtOH)
Prothrombin time, INR (PT-INR)	Haptoglobin
	Immunoglobulin IgA (quantitative)
Serology	
Hepatitis A virus (HAV) testing:	Immunoglobulin IgG (quantitative)
HAV total antibody	Immunoglobulin IgM (quantitative)

HAV IgM antibody	Phosphatidylethanol (PEth)
Hepatis B virus (HBV) testing:	**Urine Chemistry**
Hepatitis B surface antigen (HBsAg)	Drug screen
Hepatitis B surface antibody (anti-HBs)	Ethyl glucuronide (EtG)
Hepatitis B core total antibody (anti-HBc)	**Other Serology**
Hepatitis B core IgM antibody	Anti-nuclear antibody (ANA)
Hepatitis B core IgG antibody	Anti-smooth muscle antibody (ASMA) [a]
HBV DNA [c]	Anti-actin antibody [b]
Hepatis C virus (HCV) testing:	Epstein-Barr virus (EBV) testing:
HCV antibody	EBV antibody
HCV RNA [c]	EBV DNA [c]
Hepatitis D virus (HDV) testing:	Cytomegalovirus (CMV) testing:
HDV antibody	CMV antibody
Hepatitis E virus (HEV) testing:	CMV DNA [c]
HEV IgG antibody	Herpes simplex virus (HSV) testing:
HEV IgM antibody	HSV (Type 1 and 2) antibody
HEV RNA [c]	HSV (Type 1 and 2) DNA [c]
	Liver kidney microsomal type 1 (LKM-1) antibody
Microbiology	
Culture:	
Blood	
Urine	

[a] Not required if anti-actin antibody is tested.
[b] Not required if anti-smooth muscle antibody (ASMA) is tested.
[c] Reflex/confirmation dependent on regulatory requirements, testing availability, or both.

General Guidance for Venous Thromboembolic Events

VTE has been identified as an ADR for abemaciclib in combination with endocrine therapy. However, in studies with single-agent abemaciclib use in the metastatic breast cancer or other tumor types, including NSCLC, no increased rates of VTEs were observed as compared to the incidence of VTEs for these particular patient populations who were treated with other

anticancer agents. At this time, the mechanism underlying the association between abemaciclib and the occurrence of VTEs is not known. Venous thromboembolic events have been reported with other CDK4 and 6 inhibitors, and ET is known to be associated with the occurrence of VTEs. Monitor patients for signs and symptoms of deep vein thrombosis and pulmonary embolism and treat as medically appropriate.

Table 7: Dose Modification and Management — Venous Thromboembolic Events

CTCAE Grade	Abemaciclib Dose Modifications
Grade 1 or 2	No dose modification is required.
Grade 3 or 4	Suspend dose and treat as clinically indicated. Abemaciclib may be resumed when the patient is clinically stable.

7.3.5 General Guidance for Hematology Toxicity and Dose Modification

Hematologic toxicities including neutropenia, leukopenia, anemia, and thrombocytopenia have been observed in patients treated with abemaciclib, and causality has been established. Severe (Grade 3 and 4) neutropenia was observed in patients receiving abemaciclib. Patients should be monitored closely for signs of infection, anemia, and bleeding. **The following instructions from Table 7-5 must be used to manage hematologic toxicities.**

Table 7-5: Dose Modification and Management — Hematologic Toxicities

Monitor complete blood counts prior to the start of abemaciclib therapy, every 2 weeks for the first 2 months, monthly for the next 2 months, and as clinically indicated.	
CTCAE Grade	**Abemaciclib Dose Modifications**
Grade 1 or 2	No dose modification is required.
Grade 3	Suspend dose until toxicity resolves to ≤Grade 2. Dose reduction is not required.
Grade 3, recurrent, or Grade 4	Suspend dose until toxicity resolves to ≤Grade 2. Resume at next lower dose.
Patient requires administration of a blood cell growth factor	Suspend abemaciclib dose for at least 48 hours after the last dose of blood cell growth factor and until toxicity resolves to ≤Grade 2. Resume abemaciclib at next lower dose unless the dose was already reduced for the toxicity that led to the use of the growth factor.

7.3.6 General Guidance for Nonhematologic Toxicities (excluding diarrhea, increased ALT and ILD/Pneumonitis) Monitoring

Nonhematologic toxicities excluding diarrhea

• Grade 1 or 2: No dose modification is required.

• Persistent or recurrent Grade 2 toxicity that does not resolve with maximal supportive measures within 7 days to baseline or Grade 1: suspend dose until toxicity resolves to baseline or Grade 1. Resume at next lower dose.

• Grade 3 or 4: suspend dose until toxicity resolves to baseline or Grade 1. Resume at next lower dose.

Table 7-6: Dose Modification and Management — Nonhematologic Toxicities Excluding Diarrhea, ALT/AST Increased, and ILD/Pneumonitis

CTCAE Grade	Abemaciclib Dose Modifications
Grade 1 or 2	No dose modification is required.
Persistent or recurrent Grade 2 toxicity that does not resolve with maximal supportive measures within 7 days to baseline or Grade 1	Suspend dose until toxicity resolves to baseline or Grade 1. Resume at next lower dose.
Grade 3 or 4	

7.3.7 Guidelines for monitoring pneumonitis

Monitor patients for pulmonary symptoms indicative of pneumonitis. In addition, withhold study therapy for acute onset of new or progressive unexplained pulmonary symptoms, such as dyspnea, cough and fever and during diagnostic workup for pneumonitis/ILD.

7.4 Adverse Event Reporting

For guidance on reporting adverse events, refer to the Adverse Event SOP. Please modify the below template language as needed.

Adverse events will be graded according to CTCAE v5. Both Serious and Non-Serious Adverse Events will be clearly noted in source documentation and listed on study specific Case Report Forms (CRFs). The Protocol Director (PD) or designee will assess each Adverse Event (AE) to determine whether it is unexpected according to the Informed Consent, Protocol Document, or Investigator's Brochure, and related to the investigation. All Serious Adverse Events (SAEs) will be tracked until resolution, or until 30 after the last dose of the

study treatment.

SAEs CTCAE Grade 3 and above, and all subsequent follow-up reports will be reported to the Stanford Cancer Institute Data and Safety Monitoring Committee (DSMC) using the study specific CRF regardless of the event's relatedness to the investigation. It is the Investigator and study team's responsibility to report events meeting the IRB definition of 'Unanticipated Problem' to the IRB using eProtocol within 10 working days, or within 5 working days for deaths or life-threatening experiences.

No specific safety precautions or adverse event reporting guidance is required to the manufacturer. Follow standard precautions and reporting as below. Additional information is available in the Package Insert: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/208716s000lbl.pdf

For other participating sub-sites, non-serious grade 1 and 2 adverse events will be reported to the participating sites in regular conference calls. All adverse and serious adverse events should be recorded into the RedCap eCRF. All Serious Adverse Events (Grade 3 or above as graded by CTCAE v 5) will additionally be reported to the overall PI of the study at Stanford in writing within 24 hours of learning the event and to CCTO-Safety@stanford,edu. The participating sub-site will also report to Eli Lilly as described at the end of this section. Stanford will promptly report SAEs to CCTO for forwarding as necessary to the Stanford IRB and DSMC; the participating sub-site will notify their IRB per their SOP. Any death associated with the use of investigational agents or devices will prompt suspension of further patient enrollment into the trial from all sites until the cause of death is investigated by the principal investigator from the respective site and the overall PI of the study at Stanford.

Regulatory and reporting requirements

It is the responsibility of the investigator to document all adverse events which occur during the investigation. An adverse event is any untoward medical occurrence in a patient or clinical investigation subject, temporally associated with the use of the medicinal product, whether or not considered related to the medicinal product. *An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product.* Anticipated day-to-day fluctuations of the disease under study that do not represent a clinically significant exacerbation or worsening need not be considered an adverse event.

In addition, any SAEs which occur as a result of protocol specific diagnostic procedures or interventions must also be reported.

(a) Definition of Serious Adverse Events

A serious adverse experience is any event which is fatal, life threatening, disabling or incapacitating or results in hospitalization, prolongs a hospital stay or is associated with congenital abnormality. In addition, any experience which the investigator regards as serious or which would suggest any significant hazard, contraindication, side effect or precaution that may be associated with the use of the drug should be reported as a serious adverse event. Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

Abnormal laboratory findings (e.g., clinical chemistry, hematology) or other abnormal assessments (e.g., x-rays, scans, vital signs, etc.) that are judged by the investigator as **clinically significant** will be recorded as AEs or SAEs if they meet the definition of an AE or SAE.

***Life threatening definition*:**

An adverse event is life threatening if the patient was at immediate risk of death from the event as it occurred (i.e. it does not include a reaction that if it had occurred in a more serious form might have caused death). For example, drug-induced hepatitis that resolved without evidence of hepatic failure would not be considered life threatening even though drug-induced hepatitis could be fatal.

Disability/incapacitating definition:

An adverse experience is incapacitating or disabling if the experience results in a substantial and/or permanent disruption of the patient's ability to carry out normal life functions.

Hospitalization definition:

An adverse event that results in emergency department admission greater than 24 hours or requires general in-patient hospitalization. Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

Reporting Serious Adverse Events

Any serious adverse events that occur during the clinical study and up to 30 days after completion of all study treatments must be reported by the investigators as study-related SAE. Attribution of SAE to study drug should follow the standard attribution and grading system as specified by CTEP (http://ctep.cancer.gov/reporting/adeers.html, see table below).

Note: During the screening period, only protocol-related SAE's will be reported. Documentation for non-protocol related events will be provided in patient chart.

Attribution of Adverse Events:

Code	Descriptor	Definition
1	Unrelated	The Adverse Event is clearly not related to the investigational agent(s)
2	Unlikely	The Adverse Event is doubtfully related to the investigational agent(s)
3	Possible	The Adverse Event may be related to the investigational agent(s)
4	Probable	The Adverse Event is likely related to the investigational agent(s)
5	Definite	The Adverse Event is clearly related to the investigational agent(s)

In addition, any SAEs which occur as a result of protocol specific diagnostic procedures or interventions must also be reported to the local DSMB and local IRB (using the formed attached or an allowable local form), the coordinating site (Stanford University).

SAEs

Serious Adverse Event Reporting to Lilly:

• To comply with applicable laws, regulations and standards regarding Investigators' and Institution's obligations, as the sponsor of the Study, to collect and report adverse events to regulatory authorities, IRBs, Ethics Committees or other third parties. In addition to the obligations set forth below, Investigators and Institutions agree to provide Lilly with a copy of all information Investigator and/or Institution submit to regulators related to any adverse events for the Study Drug that occur during the Study that Investigator and/or Institution have not otherwise provided Lilly;

• To notify Lilly, sub-investigators, and the IRB of any problems involving risk to Study patients and report new safety information to IRBs in accordance with applicable requirements;

• to notify Lilly within fifteen (15) business days of Investigator and/or Institution receiving notification of any "serious" adverse event experienced by a patient participating in the Study and receiving Study Drug. For purposes of this requirement, "serious" means: (1) death; (2) in-patient hospitalization or prolonged hospitalization; (3) life-threatening; (4) persistent or significant disability or incapacity; (5) congenital anomaly or birth defect; or (6) other serious events that may jeopardize the patient and may require medical or surgical intervention to prevent one of the other five listed outcomes. Serious adverse events should be reported to Lilly using a CIOMS Form or other form acceptable to Lilly. Investigator and Institution further agree to make available promptly to Lilly such records as may be necessary and pertinent for Lilly to further investigate an adverse event in the Study that is possibly associated with the Study Drug.

8. CORRELATIVE/SPECIAL STUDIES

No study specific correlative procedures are planned. Analysis of exploratory biomarkers will utilize data derived from standard of care testing platforms.

9. STUDY CALENDAR

Table 9-1 Visit evaluation Schedule		**Screening / Baseline**	**Day 1 of Cycle 1 (28d) +/- 3**	**Day 1 of Cycle 2 (28d) +/-3**	**Day 1 of Subsequent cycles (28d) +/-3**	**End of study treatment (EoT) (at last visit, or up to 30 days from last dose)**
Visit Number		**1**	**2**	**3**	**4, 5..**	**Last**
Day of cycle		**D-30 to -1**	**D1**	**D29**	**D57, D85..**	**Last**
Obtain Informed Consent		X				
Patient history						
Inclusion/exclusion criteria		X				
Diagnosis and extent of cancer		X				
Demography		X				
Relevant medical history/current medical conditions		X				
Prior antineoplastic therapy (meds, surgery, radiation)		X				
Prior/concomitant medications		X	X	X	X	X
Surgical and Medical Procedures		X	X	X	X	X
Physical examination		**X**	X	**X**	**X**	**X**
Performance status (WHO)		X	X	X	X	X
Height		X				
Weight		X	X	X	X	X
Vital signs		X	X	X	X	X

Table 9-1. Visit evaluation Schedule (continued)	**Screening / Baseline**	**Day 1 of Cycle 1 (28d) +/- 3**	**Day 1 of Cycle 2 (28d) +/- 3**	**Day 1 of Subsequent cycles (28d) +/- 3**	**End of study treatment (EoT) (at last visit, or up to 30 days from last dose)**
Visit Number	**1**	**2**	**3**	**4, 5,…**	**Last**
Day of cycle	**D-30 to-1**	**D1**	**D29**	**D57, D85..**	**Last**
Lab assessments*	X	X	X	X	X
CBC	X	X and at cycle 1 d14	X and at cycle 2 d14	X	X
Chemistry	X	X and at cycle 1 d14	X and at cycle 2 d14	X	X
Creatinine clearance	X				
Serum Pregnancy test for women of childbearing potential	X (-7 to -1 days)				
Imaging					
Standard of care imaging of neck/chest/abdomen/pelvis (CT, MRI) as indicated to areas of known/ suspected disease	X			X (within 0-7d prior to every odd cycle)	
Standard of Care Imaging of the brain at baseline and then as clinically indicated (MRI/CT)	X			X (if known or suspected brain metastases)	
Safety					
Adverse Events	X	X	X	X	X
ECG	X				
Drug administration		**Continuous**			

*Please refer to Table 9-3 for local Clinical laboratory parameters

9.1 Visit schedule and assessments

Table 9-1 lists the protocol schedule and assessments and indicates when particular assessments will be performed with an "X". The cycle length is fixed at 28 days, and will be maintained regardless of whether there were dose modifications or interruptions in therapy. If treatment with abemaciclib is interrupted, future visits and assessments will continue as listed from Cycle 1 day as Day#1 for the purpose of scheduling.

Visit windows of ± 3 days from scheduled study assessments will apply during and beyond Cycle 1.

9.1.1 Screening/Baseline Procedures

Assessments performed exclusively to determine eligibility for therapy on this study will be done only after obtaining informed consent. Assessments performed for clinical indications (not exclusively to determine study eligibility) may be used for baseline values even if the studies were done before informed consent was obtained.

All screening procedures must be performed within 30 days prior to day of initiating therapy unless otherwise stated. Screening and C1D1 procedures may be done on the same day, so long as patient completes screening procedures and is eligible prior to dosing. Re-screening of patients will be allowed, if all entry criteria are met during the re-screening phase time period (-30 days to -1 day). The screening procedures include:

9.1.1.1 Informed Consent

Screening assessments to confirm eligibility will be performed as per the schedule of assessments. Documented Informed consent must be obtained before any study specific procedure will be performed. We recognize that some patients travel from great distances to receive their care at Stanford. Therefore patients who have met with investigators and had an opportunity to hear about the trial and have had their questions answered, may submit a signed consent form from home at a later date via a high fidelity electronic means such as facsimile, computer scan, or smartphone camera image of the relevant signed pages of the consent form, as long as those images contain all relevant data on the signature page of the consent form, including dated signature of the subject and version date of the consent, and are legible. The Investigator may sign the consent form at a date different from the subject, but not prior to the subject signature date.

9.1.1.2 Medical history

Complete medical and surgical history, history of infections

9.1.1.3 Demographics

Data to be collected on patient characteristics at screening include:

-Demography (including: date of birth, age, patient initials, gender, childbearing potential,
race and ethnicity, or as allowed by local regulations)

-ATC diagnosis and extent of disease, including:

- Date of diagnosis (collection date of the first path report confirming ATC/UTC)
- Site of active disease
- Prior antineoplastic therapies (medications, radiation, surgeries)
- Prior and Concomitant Medications, surgical and medical procedures

9.1.1.4 Review subject eligibility criteria

9.1.1.5 Review previous and concomitant medications

All other medications taken within 28 days before the first dose of treatment is administered will be noted in the clinical trial medication record and any changes to medications will be updated at the appropriate study visit.

9.1.1.6 Physical exam including vital signs, height and weight

Vital signs (temperature, pulse, respirations, blood pressure), height, weight

9.1.1.7 Performance status

Performance status evaluated prior to study entry

9.1.1.8 Adverse event assessment

Baseline adverse events will be assessed. See Section 7.4 for Adverse Event monitoring and reporting.

9.1.1.9 Hematology

Hgb, platelets, white blood cells (WBC), red blood cells (RBC), differential (basophils, eosinophils, lymphocytes, monocytes, neutrophils (% or absolute))

9.1.1.10 Serum chemistries

Albumin, ALT, AST, calcium, creatinine, total bilirubin, blood urea nitrogen (BUN) or urea , potassium, sodium, glucose. Creatinine clearance will be calculated using the serum creatinine value.

9.1.1.11 Pregnancy test (for females of child bearing potential)

At screening visit, serum pregnancy test will be performed. Following the screening assessment, urine pregnancy tests should be performed. Pregnancy test must be performed according to the date windows listed under schedule of assessments.

9.1.1.12 Tumor assessment

To be performed using radiographic imaging according to Section 9.1.4.1.

9.1.1.13 Information to be collected on screening failures

A patient who signs an informed consent but fails to satisfy all eligibility criteria for any reason will be considered a screen failure. The demographic information, informed consent, and documentation supporting the reason for screenfail will be completed for Screen Failure patients. No other data will be entered into the clinical database for patients who are screen failures, unless the patient experienced a Serious Adverse Event during the Screening Phase (see SAE Section 7.4 reporting details).

9.1.1.14 Replacement policy

If an eligible patient is unable to start therapy with study treatment, they may be replaced with another eligible patient if they have not received any study drug.

Apart from the above, patients will not be replaced on this study.

9.1.2 Treatment period

Following completion of screening procedures and verifying patient eligibility, the patient will be approved for treatment per protocol.

The study treatment phase begins on Cycle 1, Day 1 with the first administration of abemaciclib and will continue to receive treatment until disease progression by RECIST, unacceptable toxicity, withdrawal of consent, or discontinuation of the trial for any other reason whichever occurs first. Patients who have RECIST-defined PD as assessed by the investigator but who, in the opinion of the investigator, have evidence of continued clinical benefit from abemaciclib may continue to receive the study medication upon approval by the principal investigator. In such cases, these patients must continue to be followed for safety and efficacy assessments as per the schedule of assessments. Patients will be assessed as per visit schedule in Table 9-1.

9.1.3 End of treatment visit including study completion and premature withdrawal

Patients will be evaluated upon discontinuation of the study treatment by a clinic visit. At that time all assessments listed for End Of Treatment will be performed. A note will be entered into the clinical trial record will be completed, giving the date and reason for stopping the study treatment.

At a minimum, all patients who discontinue study treatment, including those who refuse to return for a final visit, will be contacted for safety evaluations during the 30 days following the last dose of treatment.

9.1.3.1 Criteria for patient withdrawal

Refer to Section 4.2 for details.

9.1.4 Assessment types

9.1.4.1 Efficacy assessments

Efficacy evaluations will be via revised RECIST 1.1 criteria on imaging performed at the conclusion of every 2 cycles. Target lesions will be identified prior to initiation of therapy on imaging and will be followed on subsequent imaging.

Physical exam findings of progressive disease will be considered as sufficient for documented progression if the record records biopsy proven tumor measurements in 2 dimensions and shows an increase in both dimensions of 20%.

Imaging exams will be according to standard of care guidelines to areas of known/suspected disease. These will include CT of the neck, chest, abdomen and pelvis as well as MRI of the brain. Other tests may be clinically indicated, these will be ordered according to disease and patient specific guidelines. Imaging of the brain will be required at baseline by CT or MRI per standard of care for Anaplastic Thyroid Cancer.

9.1.4.2 Safety and tolerability assessments

Safety will be monitored by the assessments described below as well as the collection of AEs at every visit. For details on AE collection and reporting, refer to Section 7. Significant
findings that were present prior to the signing of informed consent must be included in the
relevant medical history/current medical conditions in the clinical trial record. Significant new findings that begin or worsen after informed consent must be recorded in the clinical trial record.

9.1.4.3 Physical examination

Physical examinations will include an examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, and a basic nervous system evaluation. Information about the physical examination will be present in the source documentation. For the assessment schedule refer to Table 9-1.

Significant findings that were present prior to the signing of informed consent must be included in the clinical trial record. Significant new findings that begin or worsen after informed consent must be recorded in the clinical trial record. Findings related to tumor do not need to be reported.

9.1.4.4 Vital signs

Vital signs include body temperature, blood pressure and pulse measurements. Blood pressure (systolic and diastolic) and pulse should be measured.

For the assessment schedule refer to Table 9-1.

9.1.4.5 Height and weight

Height in centimeters (cm) and body weight (to the nearest 0.1 kilogram [kg] in indoor clothing, but without shoes) will be measured. Height will be measured at screening only. For the assessment schedule for weight refer to Table 9-1.

9.1.4.6 Performance status

ECOG performance status will be assessed as per the assessment schedule (refer to Table 9-1).

Assessment of ECOG performance status (Table 9-2) will be performed within the time windows described above of the scheduled assessment, even if study medication is being held. More frequent examinations may be performed at the investigator's discretion, if medically indicated.

Table 9-2 ECOG Performance status scale

Score	Performance Status
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g. light housework, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

9.1.4.7 Laboratory evaluations

Local site laboratories will be used for the analysis of scheduled hematology, biochemistry, urine, and other blood specimens collected as part of safety monitoring. All unscheduled blood testing will be performed locally, with exceptions for emergency conditions. The time windows granted for laboratory evaluations are identical to the corresponding visit time windows for each visit (refer to Section 9.1).

Laboratory abnormalities that are considered clinically significant, induce clinical signs or symptoms, require concomitant therapy or require changes in study treatment constitute an adverse event (AE) and must be reported as an AE in the clinical trial record.

Laboratory values obtained at the screening visit will be used to assess eligibility to meet

inclusion criteria. In addition, eligible patients must have baseline laboratory assessments performed on Cycle 1 Day 1 or within 24 hours prior to dosing.

Table 9-3 Local Clinical laboratory parameters collection plan

Test Category	**Data Results**	**Test Name**
Hematology		Hgb, platelets, white blood cells (WBC), red blood cells (RBC), differential (basophils, eosinophils, lymphocytes, monocytes, neutrophils (% or absolute))
Chemistry		Albumin, ALT, AST, calcium, creatinine, total bilirubin, blood urea nitrogen (BUN) or urea , potassium, sodium, glucose.
Creatinine clearance		Creatinine clearance will be calculated using the serum creatinine value.
Pregnancy test		At screening visit, serum pregnancy test will be performed. Following the screening assessment, urine pregnancy tests should be performed. Pregnancy test must be performed according to the date windows listed under schedule of assessments. If local requirements dictate otherwise, local regulations should be followed

9.1.4.8 Hematology

Hematology assessments of the parameters listed in Table 9-3 will be tested as per the schedule of assessments (Table 9-1).

9.1.4.9 Clinical chemistry and Creatinine clearance

Clinical chemistry and Creatinine clearance assessments of the parameters listed in Table 9-3 will be tested as per the schedule of assessments (Table 9-1).

9.1.4.10 Pregnancy and assessments of fertility

Women who are determined not to be of child bearing potential before the study will only be tested at screening. When non-child bearing potential status is determined during the study, further pregnancy testing will not be continued. Women are considered post-menopausal if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms), and otherwise not of child bearing potential if they have had surgical bilateral oophorectomy (with or without hysterectomy) or tubal ligation at least six weeks ago. 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.

The time windows granted for pregnancy testing are identical to the corresponding visit time windows for each visit.

If a positive pregnancy test is performed in between study visits, the patients must immediately notify the investigator.

9.1.4.11 General Guidance for Women of Child Bearing Potential and/or Use of Contraceptive Methods

Based on findings in animals, abemaciclib can cause fetal harm when administered to a pregnant woman. In animal studies, abemaciclib was teratogenic and caused decreased fetal weight at maternal exposures that were similar to human clinical exposure based on the area under the plasma concentration versus time curve (AUC) at the recommended human dose. Therefore, teratogenicity is considered an important potential risk for abemaciclib. There are no available human data informing the drug-associated risk. Advise pregnant women of the potential risk to a fetus. Additionally, there are no available data on effects of breastfeeding. Advise a nursing woman to discontinue breastfeeding during treatment with abemaciclib.

- A female of childbearing potential, must have a negative serum pregnancy test within 7 days of the first dose of abemaciclib and agree to use a highly effective contraception method during the treatment period and for 3 weeks following the last dose of abemaciclib.
- Contraceptive methods may include an intrauterine device [IUD] or barrier method. If condoms are used as a barrier method, a spermicidal agent should be added as a double barrier protection.
- Cases of pregnancy that occur during maternal exposures to abemaciclib should be reported. If a patient or spouse/partner is determined to be pregnant following abemaciclib initiation, she must discontinue treatment immediately. Data on fetal outcome and breast-feeding are to be collected for regulatory reporting and drug safety evaluation.

10. MEASUREMENTS

Primary Outcome Measure

Definition: Overall response defined as either complete response or partial response assessed using RECIST v1.1 criteria. This measure will be reported as a number without dispersion.

- Title: overall response
- Time Frame: 8 (+/-4) weeks from start of treatment.
- Safety Issue: No

10.1 Primary outcome measure

The primary endpoint will be overall response assessed 8 (+/-4) weeks from start of treatment using RECIST v1.1 criteria (please see details below for how this will be measured and defined).

10.1.1 Relevant Subset

Overall response rate will be reported for all patients who receive at least 1 dose of the study agent. Subjects receiving less than that or no study agent will be determined as inevaluable for the primary outcome though their data will still be collected for safety and survival purposes.

10.1.2 Measurement Definition- Antitumor Effect- Solid Tumors

Response and progression will be evaluated in this study using the international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) Committee [*JNCI* 92(3):205-216, 2000]. Changes in only the largest diameter (unidimensional measurement) of the tumor lesions are used in the RECIST v1.1 criteria.

Definitions

Evaluable for toxicity. All subjects will be evaluable for toxicity from the time of their first treatment with study drug.

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

Disease Parameters

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

Note: Previously irradiated lesions are non-measurable except in cases of documented progression of the lesion since the completion of radiation therapy.

Non-measurable disease. All other lesions (or sites of disease), including small lesions (longest diameter <20 mm with conventional techniques or <10 mm using spiral CT scan), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonis, inflammatory breast disease, abdominal masses (not followed by CT or MRI), and cystic lesions are all non-measurable.

Target lesions. All measurable lesions up to a maximum of 3 lesions per organ and 6 lesions in total, representative of all involved organs, should be identified as **target lesions** and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinically). A sum of the longest diameter (LD) for all target lesions will

be calculated and reported as the baseline sum LD. The baseline sum LD will be used as reference by which to characterize the objective tumor response.

Non-target lesions. All other lesions (or sites of disease) including any measurable lesions over and above the 6 target lesions should be identified as **non-target lesions** and should also be recorded at baseline. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow-up.

10.1.3 Measurement Methods

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 30 days before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used to assess the antitumor effect of a treatment.

Conventional CT and MRI. These should be performed with cuts of 10 mm or less in slice thickness contiguously. Spiral CT should be performed using a 5 mm contiguous reconstruction algorithm.

CT scans of the neck, chest, abdomen and pelvis will be performed at baseline and every two cycles according to standard of care. Other imaging of these areas such as PET/MRI will be allowed if CT cannot be performed.
MRI of the brain will be performed at baseline and as clinically indicated. Wherever it can be safely given, radiographic contrast agents should be given for the imaging studies.

Response Criteria

(i) Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions, determined by two separate observations conducted not less than 4 weeks apart. There can be no appearance of new lesions.

Partial Response (PR): At least a 30% decrease in the sum of the longest diameter (LD) of target

lesions, taking as reference the baseline sum LD. There can be no appearance of new lesions.

Progressive Disease (PD): At least a 20% increase in the sum of the LD of target lesions, taking as reference the smallest sum LD recorded since the treatment started, or the appearance of one or more new lesions.

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started.

(ii) Evaluation of Non-Target Lesions

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level.

Incomplete Response/Stable Disease (SD): Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

Progressive Disease (PD): Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions

(iii) Evaluation of Best Overall Response

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

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Response for this

				Category Also Requires:
CR	CR	No	CR	n/a
CR	Non-CR/Non-PD	No	PR	N/a
PR	Non-PD	No	PR	
SD	Non-PD	No	SD	Documented at least once ≥4 wks. from baseline
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD*	Yes or No	PD	
Any	Any	Yes	PD	
In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression. Subjects with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "*symptomatic deterioration"*. Every effort should be made to document the objective progression even after discontinuation of treatment.				

Note: If subjects respond to treatment and are able to have their disease resected, the patient's response will be assessed prior to the surgery.

Duration of Response

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

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

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

10.1.4 Measurement Time Points

The outcome will be measured as long as the patient remains without progression and getting scans for assessment. Patients will be followed for survival as long as they remain consented.

10.1.5 Response Review

Response will be independently reviewed by a radiologist, though primary assessment will remain with the treating physician.

10.2 Secondary Outcome Measures

1) Overall survival defined as duration of time from start of treatment to death from any cause. This will be reported as median survival time with interquartile range.
2) Progression-free survival (PFS) defined as the duration of time from start of treatment to time of progression or death from any cause. This will be reported as median time with interquartile range.
3) Safety analysis of AEs.

11. MULTISITE REGULATORY CONSIDERATIONS

11.1 Monitoring plan

The Stanford Cancer Institute Data and Safety Monitoring Committee (DSMC) will be the monitoring entity for this study. The DSMC will audit study-related activities approximately once per year to determine whether the study has been conducted in accordance with the protocol, local standard operating procedures, FDA regulations, and Good Clinical Practice (GCP). This may include review of the following types of documents participating in the study: regulatory binders, case report forms, eligibility checklists, and source documents. In addition, the DSMC will regularly review serious adverse events and protocol deviations from all sites associated with the research to ensure the protection of human subjects. Results of the DSMC audit will be communicated to the IRB and the appropriate regulatory authorities at the time of continuing review, or in an expedited fashion, as needed.

11.2 Protocol Review and Amendments

The protocol, the proposed informed consent and all forms of participant information related to the study (e.g. advertisements used to recruit participants) will be reviewed and approved by the Stanford IRB and Stanford Cancer Institute Scientific Review Committee (SRC). Any changes made to the protocol will be submitted as a modification and will be approved by the IRB prior to implementation. The Protocol Director and/or study team will disseminate the protocol amendment to all participating investigators. Investigators will be expected to obtain IRB approval within 90 days for all amendments.

11.3 Data management

The Protocol Director, or his/her designee, will prepare and maintain adequate and accurate participant case histories with observations and data pertinent to the study. Study specific Case Report Forms (CRFs) will document treatment outcomes for data analysis. Case report forms will be developed using the REDcap database system and will be maintained by the clinical trial coordinators. CRFs will be kept in a locked office, only accessible to the research team.

Registration and deviations will be recorded on OnCore. Refer to sections 3.4 and 7.4 for additional details on reporting and data management.

11.4 Study Documentation

The Protocol Director and participating site investigators must maintain adequate and accurate participant case histories with observations and other data pertinent to the study. Original source documents should be transcribed to Case Report Forms (CRFs) and used to communicate study data to the lead site. Source documents include hospital records, clinical charts, laboratory and pharmacy records, and recorded electronic data.

Participating Center's PIs will be responsible for maintaining the clinical protocol and subjects' study charts, reporting adverse events, assuring that consent is obtained and documented, and reporting the status of the trial in continuing renewals submitted to their IRB and trial monitoring group(s) as per their facility protocol.

11.5 Site Communication

When all participating institutions have successfully received IRB approval *and* have started enrolling patients, teleconferences to discuss participants and study-related matters will be held at a mutually agreed time, although calls may occur more frequently if needed.

Teleconferences will be coordinated by Research staff at a participating institution; PIs, Research Coordinators, Nurses, and Co-Investigators if needed will participate. Any issues with patient compliance, database entry, or other items will also be discussed in these calls. Calls will include review by PIs of subject data to assure validity as well as the safety of subjects; and the progress of the trial may also be discussed. At times of study renewal or more frequently if needed, PIs will review safety reports and clinical trial efficacy endpoints and confirm that the safety outcomes favor continuation of the study.

12. STATISTICAL CONSIDERATIONS

12.1 Statistical Design

This is an open-label, single cohort study designed to evaluate the activity of targeted therapy in anaplastic/undifferentiated thyroid cancer. There will be no randomization. An optimal Simon 2 stage design will be utilized to address the primary objective.

Anaplastic or Undifferentiated thyroid cancer patients without curative option will be considered eligible for this trial. Due to the rarity of the disease and difficulty in establishing the diagnosis

of anaplastic thyroid cancer, cases of anaplastic thyroid cancer can be classified as undifferentiated thyroid cancer. For this purpose, both undifferentiated and anaplastic thyroid cancer cases will be eligible.

There is no effective treatment for anaplastic thyroid cancer in the locally recurrent or metastatic setting for untreated *BRAF V600E* negative or *BRAF V600E* positive ATC/UTC AFTER da*braf*enib and trametinib. Abemaciclib will be administered to the patient until disease progression by RECIST, unacceptable toxicity, withdrawal of consent, or discontinuation of the trial for any other reason. Patients who have RECIST-defined PD as assessed by the investigator but who, in the opinion of the investigator, have evidence of continued clinical benefit from abemaciclib may continue to receive the study medication. In such cases, these patients must continue to be followed for safety and efficacy assessments as per the schedule of assessments.

12.1.1 Randomization

There is no randomization.

12.2 Interim analyses

We plan to conduct one interim analysis for futility. Following an optimal Simon 2 stage design, we will enroll 9 patients and assess overall response. If 0 patients have overall response, we will stop the study for futility. Otherwise, we will continue the study and enroll 8 more patients. At the end of the study, if 3 or more patients have overall response, we will deem this treatment strategy acceptable.

12.3 Descriptive Statistics and Exploratory Data Analysis

Demographic, disease characteristics and other baseline data will be summarized descriptively for the full analysis set. Treatment compliance and duration of treatment exposure will also be summarized for both the full analysis and safety set. Categorical data will be presented as frequencies and percentages. For continuous data, mean, standard deviation, median, 25th and 75th percentiles will be presented.

12.4 Primary Analysis

12.4.1 Analysis Population

The Full Analysis Set (FAS) comprises all consented patients who receive at least one dose of abemaciclib.
The Safety Set includes all patients who received at least one dose of abemaciclib medication.

12.4.2. Analysis Plan

Our primary analysis will be the calculation of the overall response rate, defined as the percentage of patients who have overall response in the full analysis set. The rate of overall response and its 95% confidence interval in the full analysis set will be estimated using exact binomial method.

12.5 Secondary Analysis

12.5.1 Analysis Population

The analysis population will include all consented patients who receive at least one dose of abemaciclib.

12.5.2 Analysis Plan

Overall survival (OS) is defined as the time from start of treatment to death due to any cause. If a subject is not known to have died, then OS will be censored at the latest date the subject was known to be alive. The OS distribution will be estimated using the Kaplan-Meier method, and the Kaplan-Meier curves, medians and 95% confidence intervals of the medians will be presented.

Progression-free survival is defined as the time from start of treatment to date of progression or death due to any cause. If a subject is not known to have progressed or died, then PFS will be censored at the latest date the subject was known to be alive or disease-free. The PFS distribution will be estimated using the Kaplan-Meier method, and the Kaplan-Meier curves, medians and 95% confidence intervals of the medians will be presented.

In addition, we will estimate response duration using Kaplan-Meier methods.

For all safety analyses, the safety set will be used. Toxicities will be dichotomized as none versus any adverse event, or none and mild versus moderate to severe adverse event.

Summary tables for adverse events (AEs) will include only AEs that started or worsened during the on-treatment period, the treatment-emergent AEs, unless otherwise specified.

All safety data collected in the study will be listed regardless of the study period with data collected during the pre-treatment and post-treatment period flagged. The incidence of treatment-emergent adverse events (new or worsening from baseline) will be summarized by system organ class and or preferred term, severity (based on CTCAE grades), type of adverse event, relation to study treatment by the Principal Investigator and/or research team.

Deaths reportable as SAEs and non-fatal serious adverse events will be listed by patient and tabulated by type of adverse event.

Specific safety event categories (SEC) will be considered. Such categories consist of one or more well-defined safety events which are similar in nature and for which there is a specific clinical interest in connection with the study treatment(s).

For each specified category, number and percentage of patients with at least one event per category will be summarized.

Handling of missing values/censoring/discontinuations

All attempts will be made to ensure that the database contains complete information. No imputation will be applied for missing data.

12.6 Sample Size

12.6.1 Accrual estimates

As a rare cancer, ATC patients are seen at <10/year at SCI. However, because treatment options are so uncommon it is expected the patients in the region will be attracted to come to SCI specifically to participate in this study.

12.6.2 Sample size justification

The sample size calculation is based on Simon's two-stage design (Simon, 1989). Simon's optimal two-stage design will be used for conducting the trial. The null hypothesis is that the true response rate is 0.05 (5%), and the alternative hypothesis is that the true response rate is 0.3 (30%). The trial is carried out in two stages.

In stage I, a total number of 9 patients is accrued. If there are 0 response among these 9 patients, the study will be early stopped.

Otherwise, additional 8 patients will be accrued in stage II, resulting in a total number sample size of 17. If there are 3 or more responses among these 17 patients, we reject the null hypothesis and claim that the treatment is promising. The design controls the type I error rate at 0.05 and yields the power of 0.9.

12.6.3 Effect size justification

There are limited data describing the efficacy of drugs targeting CDK4/6 in ATC. This protocol is designed to determine their efficacy in a patient population for whom there are limited data currently.

12.7 Criteria for future studies

If the overall response rate criteria is met, then a larger study in more patients will be undertaken to confirm the overall response rate and any potential benefit in improving survival outcomes.

Ethical considerations and administrative procedures

Regulatory and ethical compliance

This clinical study was designed, shall be implemented and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/20/EC and US Code of Federal Regulations Title 21), and with the ethical principles laid down in the Declaration of Helsinki.

Informed consent procedures

Eligible patients will only be included on this after providing written (witnessed, where required by law or regulation), IRB/IEC/REB-approved informed consent.

Informed consent must be obtained before conducting any protocol-specific procedures (i.e. all of the procedures described in the protocol). The process of obtaining informed consent should be documented in the patient source documents. The date when a subject's Informed Consent was actually obtained will be captured in the clinical trial record. The informed consent document will be approved by the IRB.

Discontinuation of the study

This study will discontinue if terminated by the Institutional Review Board or at the discretion of the Principal Investigator.

Publication of the study and results

The results of this study will be updated and posted per regulatory requirements, including (but not limited) to databases such as clinicaltrials.gov.

(b) Communication and Publication of Clinical Trial Results

All submitted manuscripts will comply with institutional guidelines and with authorship guidelines of the International Committee of Medical Journal Editors.

Study documentation, record keeping and retention of documents

The investigator/institution should maintain the trial documents as specified in Essential Documents for the Conduct of a Clinical Trial (ICH E6 Section 8) and as required by applicable regulations and/or guidelines. The investigator/institution should take measures to prevent accidental or premature destruction of these documents.

Confidentiality of study documents and patient records

The investigator must ensure anonymity of the patients; patients must not be identified by names in any trial documents. Signed informed consent forms and patient enrollment log must be kept strictly confidential to enable patient identification.

Audits and inspections

Source data/documents must be available to inspections by Health Authorities.

13. References (available upon request)

Anwar, F., M. J. Emond, R. A. Schmidt, H. C. Hwang and M. P. Bronner (2000). "Retinoblastoma expression in thyroid neoplasms." Mod Pathol **13**(5): 562-569.

Are, C. and A. R. Shaha (2006). "Anaplastic thyroid carcinoma: biology, pathogenesis, prognostic factors, and treatment approaches." Ann Surg Oncol **13**(4): 453-464.

Bosco, E. E. and E. S. Knudsen (2007). "RB in breast cancer: at the crossroads of tumorigenesis and treatment." Cell Cycle **6**(6): 667-671.

Dean, J. L., C. Thangavel, A. K. McClendon, C. A. Reed and E. S. Knudsen (2010). "Therapeutic CDK4/6 inhibition in breast cancer: key mechanisms of response and failure." Oncogene **29**(28): 4018-4032.

Fry, D. W., P. J. Harvey, P. R. Keller, W. L. Elliott, M. Meade, E. Trachet, M. Albassam, X. Zheng, W. R. Leopold, N. K. Pryer and P. L. Toogood (2004). "Specific inhibition of cyclin-dependent kinase 4/6 by PD 0332991 and associated antitumor activity in human tumor xenografts." Mol Cancer Ther **3**(11): 1427-1438.

Hundahl, S. A., I. D. Fleming, A. M. Fremgen and H. R. Menck (1998). "A National Cancer Data Base report on 53,856 cases of thyroid carcinoma treated in the U.S., 1985-1995 [see comments]." Cancer **83**(12): 2638-2648.

Khan, S. A., B. Ci, Y. Xie, D. E. Gerber, M. S. Beg, S. I. Sherman, M. E. Cabanillas, N. L. Busaidy, B. A. Burtness, A. M. Heilmann, M. Bailey, J. S. Ross, D. J. Sher and S. M. Ali (2019). "Unique mutation patterns in anaplastic thyroid cancer identified by comprehensive genomic profiling." Head Neck **41**(6): 1928-1934.

Lee, J. J., T. Foukakis, J. Hashemi, L. Grimelius, N. E. Heldin, G. Wallin, C. Rudduck, W. O. Lui, A. Hoog and C. Larsson (2007). "Molecular cytogenetic profiles of novel and established human anaplastic thyroid carcinoma models." Thyroid **17**(4): 289-301.

McIver, B., I. D. Hay, D. F. Giuffrida, C. E. Dvorak, C. S. Grant, G. B. Thompson, J. A. van Heerden and J. R. Goellner (2001). "Anaplastic thyroid carcinoma: a 50-year experience at a single institution." Surgery **130**(6): 1028-1034.

Mooney, C. J., G. Nagaiah, P. Fu, J. K. Wasman, M. M. Cooney, P. S. Savvides, J. A. Bokar, A. Dowlati, D. Wang, S. S. Agarwala, S. M. Flick, P. H. Hartman, J. D. Ortiz, P. N. Lavertu and S. C. Remick (2009). "A phase II trial of fosbretabulin in advanced anaplastic thyroid carcinoma and correlation of baseline serum-soluble intracellular adhesion molecule-1 with outcome." Thyroid **19**(3): 233-240.

NCCN clinical practice guidelines in Oncology, D. **http://www.nccn.org/professionals/physician_gls/pdf/thyroid.pdf**.

Savvides, P., G. Nagaiah, P. Lavertu, P. Fu, J. J. Wright, R. Chapman, J. Wasman, A. Dowlati and S. C. Remick (2013). "Phase II trial of sorafenib in patients with advanced anaplastic carcinoma of the thyroid." Thyroid **23**(5): 600-604.

Schwartz, G. K. and M. A. Shah (2005). "Targeting the cell cycle: a new approach to cancer therapy." J Clin Oncol **23**(36): 9408-9421.

Sledge, G. W., Jr., M. Toi, P. Neven, J. Sohn, K. Inoue, X. Pivot, O. Burdaeva, M. Okera, N. Masuda, P. A. Kaufman, H. Koh, E. M. Grischke, M. Frenzel, Y. Lin, S. Barriga, I. C. Smith, N. Bourayou and A. Llombart-Cussac (2017). "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 **35**(25): 2875-2884.

Smallridge, R. C., K. B. Ain, S. L. Asa, K. C. Bible, J. D. Brierley, K. D. Burman, E. Kebebew, N. Y. Lee, Y. E. Nikiforov, M. S. Rosenthal, M. H. Shah, A. R. Shaha, R. M. Tuttle and T. American Thyroid Association Anaplastic Thyroid Cancer Guidelines (2012). "American Thyroid Association guidelines for management of patients with anaplastic thyroid cancer." Thyroid **22**(11): 1104-1139.

Sosa, J. A., J. Balkissoon, S. P. Lu, P. Langecker, R. Elisei, B. Jarzab, C. S. Bal, S. Marur, A. Gramza and F. Ondrey (2012). "Thyroidectomy followed by fosbretabulin (CA4P) combination regimen appears to suggest improvement in patient survival in anaplastic thyroid cancer." Surgery **152**(6): 1078-1087.

Tung, W. S., D. W. Shevlin, D. Bartsch, J. A. Norton, S. A. Wells, Jr. and P. J. Goodfellow (1996). "Infrequent CDKN2 mutation in human differentiated thyroid cancers." Mol Carcinog **15**(1): 5-10.

APPENDICES

APPENDIX A**: Participant Eligibility Checklist**

A Participant Eligibility Checklist must be completed in its entirety for each subject prior to registration. The completed, signed, and dated checklist must be retained in the patient's study file and the study's Regulatory Binder.

The study coordinator, treating physician and an independent reviewer must verify that the participant's eligibility is accurate, complete, and legible in source records. A description of the eligibility verification process should be included in the EPIC or other Electronic Medical Record progress note.

The following is an **example** of a Participant Eligibility checklist template. Modify this checklist to fit your study and include it in the appendix section of your protocol document. The protocol-specific checklist is **required** by the SRC and must be approved by the IRB.

Protocol Title:	**Abemaciclib in metastatic or locally advanced Anaplastic/Undifferentiated Thyroid Cancer**
Protocol Number:	**Stanford IRB: 57905** **Sub-Site IRB:**
Principal Investigator:	**Stanford: Saad Khan, MD** **Sub-Site PI:**

II. Subject Information:

Subject Name/ID:
Gender: ☐ Male ☐ Female

III. Study Information:

SRC Approved ☒ IRB Approved ☒ Contract signed ☒

IV. Inclusion/Exclusion Criteria

Inclusion Criteria	**Yes**	**No**	**Supporting Documentation***
1. Histologically or cytologically confirmed diagnosis of anaplastic thyroid cancer or undifferentiated thyroid cancer that does not have a known BRAF V600E positive on tissue/blood testing. BRAF V600E positive patients are eligible if they have previously received FDA	☐	☐	

approved therapy for this genetic abnormality and progressed or become intolerant.			
2. Patients will be eligible if they meet either criteria: 2a. Unresectable anaplastic thyroid cancer limited to the neck: Patients must have received radiation therapy or surgery to primary tumor and have subsequent evidence of ATC. 2b. Metastatic anaplastic thyroid cancer: either with entirely surgically removed cancer/metastatic only disease, or with disease in the neck not requiring radiation or surgery to the neck mass.	☐	☐	
3. Patients with a bulky thyroid/neck mass and those in whom airway obstruction is suspected should undergo an evaluation via indirect or direct laryngoscopy to ensure patency of the trachea/airway prior to enrollment	☐	☐	
4. Patients will not have any other curative therapeutic option, such as radiation or surgery.	☐	☐	
5. ECOG performance status 0-1.	☐	☐	
6. Have measurable disease based on RECIST 1.1.	☐	☐	
7. Be willing to provide tissue from a newly obtained core or excisional biopsy of a tumor lesion. Newly-obtained is defined as a specimen obtained up to 6 weeks (42 days) prior to initiation of treatment on Day 1. Subjects for whom newly-obtained samples cannot be provided (e.g. inaccessible or subject safety concern) may submit an archived sample.	☐	☐	

8. Be ≥ 18 years of age on day of signing informed consent.	☐	☐	
9. Patients who received chemotherapy must have recovered (Common Terminology Criteria for Adverse Events [CTCAE] Grade ≤1) from the acute effects of chemotherapy except for residual alopecia or Grade 2 peripheral neuropathy prior to study treatment start. A washout period of at least 21 days is required between last chemotherapy dose and study treatment start (provided the patient did not receive radiotherapy). Note: Patients who have most recently been treated with dabrafenib and/or trametinib and/or lenvatinib require a washout period of 1 week from their last dose	☐	☐	
10. Patients who received radiotherapy must have completed and fully recovered from the acute effects of radiotherapy. A washout period of at least 14 days is required between end of radiotherapy and study treatment start.	☐	☐	
11. The patient is able to swallow oral medications.	☐	☐	
12. The patient has adequate organ function for all of the following criteria:	☐	☐	
12a. Absolute neutrophil count (ANC) ≥1.5 × 10^9/L	☐	☐	
12b. Platelets ≥100 × 10^9/L	☐	☐	
12c. Hemoglobin ≥8 g/dL Note: Patients may receive erythrocyte transfusions to achieve this hemoglobin level at the discretion of the investigator. Initial treatment must not begin earlier than the day after the erythrocyte transfusion.	☐	☐	

12d. Total bilirubin ≤ 1.5 × ULN Note: Patients with Gilbert's syndrome with a total bilirubin ≤2.0 times ULN and direct bilirubin within normal limits are permitted.	☐	☐	
12e. ALT and AST ≤3 × ULN	☐	☐	
13. Women of childbearing potential and all men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) while taking drug and agree to continue for 3 months after the last dose of study treatment. Women of child bearing potential and male patients for 3 months should not mother or father a child in this period. A condom is required to be used also by vasectomized men in order to prevent delivery of the drug via seminal fluid.	☐	☐	
14. Patient has the ability to understand and provide signed informed consent.	☐	☐	
15. Willingness and ability to comply with scheduled visits, treatment plans, laboratory tests and other procedures.	☐	☐	
Exclusion Criteria	**Yes**	**No**	**Supporting Documentation***
1. Patients with known hypersensitivity to any of the excipients of abemaciclib	☐	☐	
2. History of carcinomatous meningitis	☐	☐	
3. Prior therapy with abemaciclib	☐	☐	
4. The patient has serious and/or uncontrolled preexisting medical condition(s) that, in the judgment of the investigator, would preclude participation in this study (for example, interstitial lung disease,	☐	☐	

severe dyspnea at rest or requiring oxygen therapy, severe renal impairment [e.g. estimated creatinine clearance <30ml/min], history of major surgical resection involving the stomach or small bowel, or preexisting Crohn's disease or ulcerative colitis or a preexisting chronic condition resulting in baseline Grade 2 or higher diarrhea).			
5. Females who are pregnant or lactating	☐	☐	
6. The patient has active systemic bacterial infection (requiring intravenous [IV] antibiotics at time of initiating study treatment), fungal infection, or detectable viral infection (such as known human immunodeficiency virus positivity or with known active hepatitis B or C [for example, hepatitis B surface antigen positive]. Screening is not required for enrollment.	☐	☐	
7. The patient has a personal history of any of the following conditions: syncope of cardiovascular etiology, ventricular arrhythmia of pathological origin (including, but not limited to, ventricular tachycardia and ventricular fibrillation), or sudden cardiac arrest.	☐	☐	
8. Presence or history of a malignant disease other than thyroid cancer that has been diagnosed and/or required therapy within the past year and is undergoing active anticancer treatment. Exceptions to this exclusion include the following: completely resected basal cell and squamous cell skin cancers, and completely resected carcinoma in situ of any type.	☐	☐	

*All subject files must include supporting documentation to confirm subject eligibility. The method of confirmation can include, but is not limited to, laboratory test results, radiology test results, subject self-report, and medical record review.

IV. Statement of Eligibility

By signing this form of this trial I verify that this subject is [☐ **eligible** / ☐ **ineligible**] for participation in the study. This study is approved by the Stanford Cancer Institute Scientific Review Committee, the Stanford IRB, and has finalized financial and contractual agreements as required by Stanford School of Medicine's Research Management Group.

Treating Physician Signature:	Date:
Printed Name:	

Secondary Reviewer Signature:	Date:
Printed Name:	

Study Coordinator Signature:	Date:
Printed Name:	