Official Protocol Title:	A Phase 1b Study of ARQ 751 as a Single Agent or in Combination with Other Anti-cancer Agents in Adult Subjects with Advanced Solid Tumors with PIK3CA/AKT/ PTEN Mutations
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Title:	A Phase 1b Study of ARQ 751 as a Single Agent or in Combination with Other Anti-cancer Agents in Adult Subjects with Advanced Solid Tumors with PIK3CA/AKT/PTEN Mutations
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Study Drug:	ARQ 751
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Confidentiality Statement

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SYNOPSIS

Study Title:	A Phase 1b Study of ARQ 751 as a Single Agent or in Combination with Other Anti-cancer Agents in Adult Subjects with Advanced Solid Tumors with *PIK3CA/AKT/PTEN* Mutations
Study Number:	ARQ 751-101
Study Phase:	1b
Rationale for the Study	Multiple genetic alterations in the phosphatidylinositol-3-kinase (*PI3K*)/ v-Akt murine thymoma viral oncogene homolog (*AKT*)/ mammalian target of rapamycin (*mTOR*) signaling pathway have been identified in solid tumors and hematologic malignancies. Under normal condition, PI3K pathway regulates cell growth, survival, and proliferation with *PI3K* and tensin homolog (*PTEN*) being positive and negative regulators of PI3K pathway, respectively. Both genes depend on AKT signaling. Thus, *AKT* is an attractive target for drug development. Currently, a number of inhibitors, targeting key nodes of this pathway, including AKT inhibitors, are in various stages of clinical development. In general, some clinical activity with targeted agents has been reported in monotherapy trials, however, the combination therapy of drugs with different mechanism of action has shown more promising clinical outcomes, such as improvement on efficacy and overcoming resistance or recurrence. Thus, combination of PI3K/AKT pathway inhibitors with other anti-cancer agents (e.g., cytotoxic, endocrine, or other targeted agents) may enhance the growth inhibition effect of a single agent, allow to overcome resistance to a single agent therapy, restore sensitivity to chemotherapy or targeted/endocrine therapy, and therefore afford a durable response, particularly in tumors with *PIK3CA/AKT/PTEN* genetic alterations. This study consists of two parts; Part 1, that was originally designed as a dose escalation and expansion study of ARQ 751 as a single agent, and Part 2,that is designed primarily to determine recommended phase 2 dose (RP2D) of ARQ 751 in combination with other anti-cancer agents. Originally, the ARQ 751-101 study was named "A Phase 1 Dose Escalation Study of ARQ 751 in Adult Subjects with

	Advanced Solid Tumors with AKT1, 2, 3 Genetic Alterations, Activating PI3K Mutations or PTEN-null" and was initiated as a single agent dose-escalation, safety, and tolerability trial. Subsequently, this study was amended to also include subjects with other known actionable PTEN mutations ("A Phase 1 Dose Escalation Study of ARQ 751 in Adult Subjects with Advanced Solid Tumors with AKT1, 2, 3 Genetic Alterations, Activating PI3K Mutations, PTEN-null, or other known actionable PTEN mutations"). The dose escalation cohorts of ARQ 751 as a single agent were completed and the RP2D of ARQ 751 as a single agent has been determined to be 75 mg QD. To further evaluate safety and tolerability, and to assess preliminary efficacy of ARQ 751 as a single agent, up to 30 subjects are planned to be enrolled and treated with ARQ 751 at the RP2D level in Arm A (expansion cohort). It is planned to enroll up to 15 subjects with solid tumors with PIK3CA or PTEN actionable mutations and up to 15 subjects with AKT genetic alterations. As discussed above, a single drug approach may not be sufficient to inhibit tumor growth, a simultaneous inhibition of the multiple pathways may be needed to generate durable anti-neoplastic effect. Part 2 is designed to determine RP2D and to assess safety, tolerability, and preliminary efficacy of ARQ 751 in combination with other anti-cancer agents. Thus, the protocol has been re-named as "A Phase 1b Study of ARQ 751 as a Single Agent or in Combination with Other Anti-cancer Agents in Adult Subjects with Advanced Solid Tumors with PIK3CA/AKT/PTEN Mutations" Part 2 consists of two combination therapy arms, Arm B (paclitaxel) and Arm C (fulvestrant).

Study Design and Treatment:	ARQ 751-101 is a multi-center, open label, study of a second-generation pan-AKT inhibitor ARQ 751 administered orally as a single agent or in combination with paclitaxel or fulvestrant in subjects with advanced, inoperable, metastatic and/or recurrent solid tumors with *PIK3CA/AKT/PTEN* mutations. **Part 1:** The dose escalation of ARQ 751 as single agent is completed . The study was initiated in August 2016 as an open-label, phase 1, first-in-human, dose escalation study. Seven dose levels of ARQ 751 (from 5 mg QD to 100 mg QD) were evaluated and RP2D was determined to be 75 mg QD. All enrolled subjects had advanced or inoperable solid tumors with *PI3K/AKT/PTEN* genetic alterations. Twenty two of the 34 subjects in single agent dose escalation were evaluable for response, in two subjects the best response was PR (both with HR+/HER2- breast cancer with *PTEN C296fs*2* and *PIK3CA H1047R,* respectively), in eight SD, and in twelve PD. A durable stable disease of >40 weeks was achieved in two subjects, one with endometrial cancer and one with breast cancer, with *AKT1 E17K* and *PIK3CA* mutations, respectively. Enrollment is ongoing in the single agent dose expansion cohort (Arm A). Subjects enrolled in Arm A receive ARQ 751 at 75 mg QD, continuously. **Part 2** is designed to determine RP2D and to assess safety, tolerability, and preliminary efficacy of ARQ 751 in combination with paclitaxel (Arm B) and fulvestrant (Arm C). Enrollment in each arm will be initiated per Sponsor discretion. The choice of treatment Arm will be made at the discretion of the Investigator, provided that the combination therapy with paclitaxel or fulvestrant rather than a monotherapy (Arm A, ARQ 751) would be appropriate for their patients' disease. Depending on the study safety and efficacy data, the Sponsor may limit the number of subjects with a specific tumor type(s) or *PIK3CA/AKT/PTEN* mutation status to be enrolled. Mutation status must be documented prior to the first dose of ARQ 751. If the status is unknown, archival or fresh tumor biopsy must be collected and tested to verify

eligibility; redacted copies of all genetic testing reports will be collected.

To determine RP2D of ARQ 751 in combination with paclitaxel (Arm B) or fulvestrant (Arm C), standard 3+3 dose finding design will be used. Assessment of the safety and tolerability of combination regimens will include all subjects treated in Arm B and Arm C independent of the ARQ 751 dose level subjects may receive. Additional arms may be added to assess ARQ 751 in combination with other anti-cancer agents.

In Arms B and C, dose determination will be done as follows:

Cohort	**ARQ 751 (orally, PO)**	**Paclitaxel (Arm B)**	**Fulvestrant (Arm C)**
-1	25 mg QD	80 mg/m^2 (IV) Days 1,8,15 followed by a week of rest	500 mg (IM) Days 1 &15 of Cycle 1, and Day 1 of all subsequent cycles
1	50 mg QD		
2	75 mg QD		
Expansion	RP2D		

Dose escalation will proceed to 75 mg QD, the dose that was defined to be the ARQ 751 RP2D as a single agent. Once MTD/RP2D for each combination therapy Arm is determined, approximately 6-9 subjects will be enrolled in each arm (expansion cohort). Intra-subject dose escalation will be permitted if the next higher dose of ARQ 751 for that regimen is determined to be safe.

Approximately 94 subjects will be enrolled in this study at 4-10 sites in the USA; 64 subjects in Part 1 (Dose escalation cohorts and Arm A) and 30 in Part 2 (Arm B and Arm C). Thirty four subjects were enrolled in dose escalation cohorts. It is planned that up to 30 subjects with advanced, inoperable, metastatic, or recurrent solid tumors will be enrolled in Arm A, up to 15 subjects with PIK3CA/PTEN activating mutations and up to 15 subjects with AKT genetic alterations. In Part 2, approximately 15 subjects will be enrolled in each combination therapy arm (Arm B, ARQ 751+paclitaxel and Arm C, ARQ 751+fulvestrant).

Assessment of safety and tolerability of ARQ 751 as a single agent and in combination with paclitaxel or

	fulvestrant will be based on continuous evaluation of adverse events, physical examination findings and laboratory tests. All clinical assessments and laboratory tests will be performed according to the protocol-defined timepoints. If clinically indicated, unscheduled laboratory tests and any clinical assessments or evaluations may be performed per discretion of the Investigator. Tumor assessments (CT or MRI) will be performed according to protocol-defined timepoints, or as otherwise clinically indicated. Tumor response will be evaluated according to RECIST 1.1 guidelines. Pharmacokinetic (PK) samples will be collected pre-dose and at different timepoints post-dose as defined in the protocol (See Appendix 3). Additional unscheduled blood sample(s) for PK may be collected on any study day(s) upon agreement between the Investigator and the Sponsor. Two baseline single blood samples to determine CYP2D6 genotype and *PIK3CA/AKT/PTEN* mutation in circulating tumor (ct)DNA will be collected. Treatment will continue until disease progression, unacceptable toxicity or other treatment discontinuation criterion is met.
Primary Objective:	**Part 1:** The primary objective is to assess the safety and tolerability of ARQ 751 in subjects with advanced solid tumors with AKT1, 2, 3 genetic alterations, activating PI3K mutations, PTEN-null, or other known actionable PTEN mutations. **Part 2:** The primary objective is to assess the safety and tolerability of ARQ 751 in combination with paclitaxel or fulvestrant in subjects with advanced, inoperable, metastatic and/or recurrent solid tumors with *PIK3CA/PTEN* actionable mutations and/or AKT genetic alterations
Secondary Objectives:	**Part 1:** • To assess the pharmacokinetic (PK) profile of ARQ 751 • To assess the pharmacodynamic activity of ARQ 751 in blood specimens obtained from subjects with advanced solid tumors with AKT1, 2, 3 genetic alterations, activating PI3K mutations, PTEN-null, or other known actionable PTEN mutations

	• To determine the maximum tolerated dose (MTD) and/or the recommended Phase 2 dose (RP2D) of ARQ 751 as single agent • To generate preliminary evidence of anti-tumor activity **Part 2:** • To determine MTD/RP2D dose of ARQ 751 in combination with paclitaxel or fulvestrant • To assess the PK profile of ARQ 751 in combination with paclitaxel or fulvestrant • To generate preliminary evidence of anti-tumor activity of ARQ 751 in combination with paclitaxel or fulvestrant in subjects with advanced, inoperable, metastatic and/or recurrent solid tumors with PIK3CA/PTEN actionable mutations and/or AKT genetic alterations
Study Endpoints:	**Part 1:** The primary endpoint is safety and tolerability and is measured by safety variables which include the reported AEs, laboratory tests, vital signs, ECOG performance status, and physical examination. Secondary and exploratory endpoints include the following: • Pharmacokinetics which are measured by maximum plasma drug concentration (C_{max}), area under the curve (AUC), and elimination half-life ($t_{1/2}$) • Pharmacodynamic activity will be evaluated by changes in serum glucose and insulin levels, and by changes in cell-free ctDNA. • RP2D will be determined following review of all safety, pharmacodynamic data and anti-tumor activity generated in the dose escalation portion of the study. Together with the Investigators, the RP2D will be set at or below the MTD and at a dose at which pharmacodynamic activity or anti-tumor activity is demonstrated. • Preliminary evidence of anti-tumor activity will be evaluated by RECIST v1.1 Response Criteria. **Part 2:** Primary endpoint:

	Safety and tolerability as assessed by the frequency, duration, and severity of adverse events (AEs) from the first dose of study treatment through 30 days after the last dose of therapy. Secondary endpoints include the following: • Pharmacokinetics as measured by maximum plasma drug(s) concentration (C_{max}), time to maximum plasma drug concentration [T_{max}], area under the curve (AUC), and elimination half-life ($t_{1/2}$) • RP2D as determined following review of all safety data generated in the dose escalation cohort(s) for each combination therapy Arm. The RP2D will be set at or below the MTD. • Preliminary evidence of anti-tumor activity as assessed by RECIST v. 1.1.
Study Population:	Adult subjects with advanced solid tumors with documented *AKT genetic alterations*, *PIK3CA* or *PTEN* actionable mutations whose cancer has progressed following standard therapy, or for whom standard therapy is not available or is not tolerable will be enrolled. . To be enrolled, subjects must meet all eligibility criteria. **Inclusion Criteria** 1. Signed written informed consent granted prior to initiation of any study-specific procedures 2. 18 years of age and older 3. Histologically and/or cytologically documented diagnosis of a selected tumor type that is locally advanced, inoperable, metastatic or recurrent (including but not restricted to breast cancer, TNBC [triple negative]; HR-positive [HR+]/HER2-negative [HER2-] or endometrial cancer) 4. Documented *AKT* genetic alterations or known actionable *PIK3CA*/*PTEN* mutations by genetic testing • subjects with tumors with PTEN null/PTEN loss-of-function mutations are not eligible 5. For Arms B or C, subjects should be eligible for paclitaxel or fulvestrant therapy as per Investigator assessment 6. Failure to respond to standard systemic therapy, or for whom standard or curative systemic therapy does not exist or is not tolerable. • Subjects in Arm A (with *AKT* genetic alterations) and subjects in dose escalation cohorts of Arms B

	and C should have at least one line of standard systemic therapy • Subjects in Arm A (with *PIK3CA/PTEN* actionable mutations) and subjects in the expansion cohorts of Arms B and C should have no more than 3 prior systemic regimens for the advanced disease • Neoadjuvant and adjuvant chemotherapy are considered one regimen if they are a continuation of the same regimen with interval debulking surgery • If the subject is refractory or has disease progression within 6 months after completion of the adjuvant treatment, then the adjuvant treatment should be considered as the line of treatment rather than an adjuvant therapy. • Endocrine (hormonal) therapy does not count toward total lines of therapy • Maintenance therapy is considered part of the preceding regimen if one or more of the same drugs are continued 7. Has at least one measurable target lesion according to RECIST v. 1.1 8. Eastern Cooperative Oncology Group (ECOG) performance status (PS) ≤ 1 9. Adequate organ function as indicated by the following laboratory values. (All laboratory tests must be obtained within 14 days prior to the first dose of study treatment): a. Hematological • Absolute neutrophil count (ANC) $\geq 1.5 \times 10^9$/L • Platelet count (Plt) $\geq 100 \times 10^9$/L • Hemoglobin (Hb) ≥ 9 g/dL • International normalized ratio (INR) 0.8 to upper limit of normal (ULN) or ≤ 3 for subjects receiving anticoagulant therapy such as Coumadin or heparin b. Renal • Serum creatinine ≤ 1.5 x ULN or calculated creatinine clearance ≥ 60 mL/min/1.73 m^2 for subjects with serum creatinine levels > 1.5 x institutional ULN c. Hepatic • Total bilirubin ≤ 1.5 x ULN

	• Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 3 x ULN or ≤ 5 x ULN for subjects with known liver metastases d. Metabolic • Glycated hemoglobin (HbA1c) ≤ 8% (≤ 64 mmol/mol) 10. If a subject is currently receiving bisphosphonates or any other drug for treatment of osteoporosis, treatment-induced bone loss and metastases to bone, the subject must have received the bisphosphonates for at least four weeks prior to the first dose of study treatment. • Initiation of bisphosphonates or similar agents during the study may be allowed provided the subject completes the first cycle of treatment without any dose limiting toxicity (DLT) and the Investigator rules out tumor progression. 11. Male or female subjects of child-producing potential must agree to use adequate contraception, including double-barrier contraceptive measures, oral contraception, or avoidance of intercourse during the study and for 90 days after the last dose of study treatment. 12. Women of childbearing potential must have a negative serum pregnancy test during Screening Period and within 48 hours of the first dose of study treatment. "Women of childbearing potential" is defined as sexually mature women who have not undergone a hysterectomy or who have not been naturally postmenopausal for at least 12 consecutive months prior to the first dose of study treatment. **Exclusion Criteria** 1. Anti-cancer therapy, such as chemotherapy, immunotherapy, hormonal therapy, targeted therapy, or investigational agents within five half-lives or four weeks, whichever is shorter, prior to administration of the first dose of study treatment • To be eligible for study treatment, toxicity from prior treatment(s) must recover to Grade ≤ 1, except for alopecia • Concurrent systemic high-dose corticosteroids (in dosing exceeding 10 mg QD of prednisone equivalent) when used intermittently in an antiemetic regimen, for central nervous system

	(CNS) metastases management, or as a part of the premedication regimen are allowed 2. Radiation therapy within four weeks, or palliative radiation therapy within two weeks, prior to administration of the first dose of study treatment • To be eligible for study treatment, radiation therapy-related toxicity must recover to Grade ≤ 1 prior to administration of the first dose of study treatment • Concurrent palliative radiotherapy for local pain-control or prevention of fracture (for known bone metastases) may be allowed provided the subject completes the first cycle of treatment, does not meet criteria of progressive disease, and treated lesions will not be included in the target/non-target lesion assessment. 3. Major surgical procedure within four weeks prior to administration of the first dose of study treatment • To be eligible for the study treatment, all surgical wounds must be fully healed, and any surgery-related adverse events must recover to Grade ≤ 1. 4. Unable or unwilling to swallow the complete daily dose of ARQ 751 5. Previous treatment with • AKT inhibitors (e.g., ARQ 092, MK-2206, GSK2141795, AZD5363; prior treatment with PI3K or mTOR inhibitor are allowed) • Prior taxane therapy for the advanced, metastatic disease (for subjects considered for Arm B, ARQ 751+paclitaxel, only) 6. Known prior allergic reaction to or severe intolerance of paclitaxel or fulvestrant. Intolerance is defined as a serious adverse event, a grade 3 or 4 AE per CTCAE v.4.03, or permanent treatment discontinuation 7. History of Type 1 diabetes mellitus or Type 2 diabetes mellitus requiring regular medication (other than oral hypoglycemic agents) or fasting glucose ≥ 160 mg/dL at Screening visit. 8. Significant gastrointestinal disorder(s) that could, in the opinion of the Investigator, interfere with the absorption, metabolism, or excretion of ARQ 751 (e.g., inflammatory bowel disease, Crohn's disease, ulcerative colitis, extensive gastric resection)

	9. Known untreated or active CNS metastases and/or carcinomatous meningitis • To be eligible for the study treatment, subjects must have stable disease ≥ 1 month, confirmed by magnetic resonance imaging (MRI) or computed tomography (CT) scan, and have CNS metastases well controlled by low-dose steroids, anti-epileptics, or other symptom-relieving medications. 10. History of myocardial infarction (MI) or New York Heart Association (NYHA) Class II-IV congestive heart failure within 6 months of the administration of the first dose of study treatment (MI occurring > 6 months of the first dose of study treatment will be permitted); Grade 2 or worse conduction defect (e.g., right or left bundle branch block). 11. A heart rate corrected QT (QTc) interval ≥ 480 msec, using the Fridericia's formula QTcF 12. Left ventricular ejection fraction (LVEF) <50% as determined by Multiple Gated Acquisition (MUGA) scan or echocardiogram (ECHO) in subjects who received prior treatment with anthracyclines 13. Concurrent severe and/or uncontrolled illness not related to cancer and/or social situation that would limit compliance with study requirements, including but not limited to: • Psychiatric illness, substance abuse • Ongoing or active known infection, including human immunodeficiency virus (HIV) infection, hepatitis B or C virus • Significant pulmonary dysfunction, including pneumonitis, interstitial lung disease (ILD), idiopathic pulmonary fibrosis, cystic fibrosis, severe COPD • Peripheral neuropathy grade ≥2 (Arm B, ARQ 751+paclitaxel) • Bleeding diathesis, thrombocytopenia or coagulation disorders (Arm C, ARQ 751+fulvestrant) • Thrombotic/coagulation disorders within 6 months prior to the first dose of study treatment unless stable on anticoagulation for > 3 months 14. Active or history of other malignancy other than the current cancer within 2 years of the first dose of study treatment, with the exception of carcinoma in-situ of

	the cervix, basal cell carcinoma, and superficial bladder tumors curatively treated 15. Blood transfusion or administration of growth factors within 5 days prior to a blood draw being used to confirm eligibility 16. Pregnant or breastfeeding
Study Drugs, Doses, and Administration:	**Part 1:** The investigational drug ARQ 751 is supplied as capsules for oral administration. ARQ 751 is packaged in multiple strengths of 5 mg and 25 mg and is supplied directly to the pharmacy at the clinical site. ARQ 751 must be administered under fasted conditions (one hour prior to or two hours after the meal). The dosing began at 5 mg once a day (QD) and escalated until the MTD and/or RP2D was determined. Subjects receive ARQ 751 at dose levels specified for their respective dose cohorts. Treatment continues until unacceptable toxicity, documented disease progression (clinical or radiological), or another discontinuation criterion is met. **Part 2:** The investigational drug ARQ 751 is supplied as capsules for oral administration. ARQ 751 is packaged in strength of 25 mg and is supplied directly to the pharmacy at the clinical site. ARQ 751 must be administered under fasted conditions (one hour prior to or two hours after the meal), subjects will receive ARQ 751 at dose levels specified for their respective Arm/cohort dose. In general, administration of paclitaxel and fulvestrant should follow the FDA approved label, NCCN guidelines, or institutional practice. • Paclitaxel: 80 mg/m2 (IV), Days 1,8,15 followed by a week of rest of each cycle • Fulvestrant: 500 mg (IM), Days 1, 15 of Cycle 1 & Day 1 of each cycle thereafter Paclitaxel and fulvestrant will be obtained from commercial sources.
Criteria for Determination of Dose-Limiting Toxicity:	**Part 1:** Dose-limiting toxicities (DLT) were determined during the first cycle (four weeks/28 days) of treatment. A DLT was defined by the occurrence of any of the following toxicities related, probably related, or possibly related to ARQ 751 within the first cycle of treatment and graded according to

	Common Terminology Criteria for Adverse Events (CTCAE) version 4.03:
	• Grade 4 anemia
	• Grade 4 neutropenia
	• Grade 4 thrombocytopenia
	• Grade 3 neutropenia lasting longer than 7 days despite optimal treatment
	• Grade 3 thrombocytopenia in the presence of bleeding
	• ≥ Grade 3 hyperglycemia (fasting blood glucose > 250 mg/dL or non-fasting > 500 mg/dL) requiring insulin (uncontrolled with oral hypoglycemic agents)
	• ≥ Grade 3 non-hematological toxicity of any duration, except for the following:
	  ○ Nausea, vomiting, or diarrhea responding to optimal medical management within 48 hours
	  ○ Alopecia
	• Any other toxicity that in the view of the Investigator represents a clinically significant hazard to the subject
	
	Part 2:
	Dose-limiting toxicities will be determined during the first cycle (28 days) of combination therapy. A DLT is defined by the occurrence of any of the following toxicities related, probably related, or possibly related to ARQ 751 when administered in combination with paclitaxel or fulvestrant within the first cycle of treatment and graded according to Common Terminology Criteria for Adverse Events (CTCAE) version 4.03:
	• Grade 4 anemia
	• Grade 4 neutropenia
	• Grade 4 thrombocytopenia
	• Grade 3 neutropenia lasting longer than 7 days despite optimal treatment
	• Grade 3 thrombocytopenia in the presence of bleeding
	• ≥ Grade 3 hyperglycemia (fasting blood glucose > 250 mg/dL or non-fasting > 500 mg/dL) requiring insulin (uncontrolled with oral hypoglycemic agents)
	• ≥ Grade 3 non-hematological toxicity of any duration, except for the following:

	○ Nausea, vomiting, or diarrhea responding to optimal medical management within 48 hours ○ Alopecia • The Investigator to assess ALT and AST changes to determine if these changes may be a DLT • ≥ Grade 3 ALT or AST elevation for subjects with ALT/AST ≤ 3 ULN at Baseline • ALT/AST levels for subjects with known liver metastases and ALT/AST ≤ 5 x ULN at Baseline • Grade 2 ALT/AST elevation accompanied by ≥ Grade 2 elevation in bilirubin • Any other toxicity that in the view of the Investigator represents a clinically significant hazard to the subject

Part 1 - Criteria for Dose Escalation:	Enrollment at the next dose level and/or enrollment of additional subjects into the ongoing cohort occurred according to the following criteria: • If zero of three initially treated subjects experience a DLT (ARQ 751-related, probably related, or possibly related) by Day 29 of dosing, then dose escalation will occur • If one of three initially treated subjects experiences a DLT by Day 29 of dosing, then an additional three subjects will be enrolled for a total of six subjects treated at the same dose level. Escalation will occur if no additional DLTs are seen in that cohort (DLT in one of six subjects). • If two or more treated subjects at a dose level experience a DLT by Day 29 of continuous dosing, dose escalation will stop and the prior dose level and/or a less frequent drug administration schedule will be considered the MTD. If the first dose results in 2 or more subjects experiencing DLT, subsequent subjects will be enrolled at a less frequent drug administration schedule (e.g., 5 mg QOD). • If a subject withdraws from the study treatment for any reason other than a DLT during the first cycle (4 weeks/28 days), that subject will be replaced. The MTD was defined as the dose level at which no more than one out of six subjects has an observable DLT. ArQule's Medical Monitor and the Investigator(s) reviewed all significant ARQ 751-related toxicities to determine if the dose escalation schedule requires modification. Intermediate doses and alternative dosing schedules could be assigned to a cohort after agreement between the Medical Monitor and the Investigator(s). During the dose escalation period, intra-subject dose escalation was only permitted if the following criteria were met: 1. The next higher dose for this regimen has demonstrated to be safe by at least 3 subjects and the last subject completed one cycle without exceeding a DLT. 2. The subject in question has not experienced a DLT.

	Once the MTD ws determined, intra-subject dose escalation to the MTD was considered to optimize the treatment in subjects enrolled at lower dose levels. Multiple intra-subject dose escalations per subject was considered.

Part 2 - Criteria for Determination of RP2D of ARQ 751 in combination with other anti-cancer agents:	To determine RP2D of ARQ 751 in combination with paclitaxel and fulvestrant, a minimum of two dose levels will be tested. Enrolled subjects will initially be treated with 50 mg QD of ARQ 751 (Cohort 1 of Arms B and C). Enrollment at the next dose level and/or enrollment of additional subjects into the ongoing cohort will occur according to the following criteria: • If zero of three initially treated subjects experience a DLT (ARQ 751-related, probably related, or possibly related) by Day 29 of dosing, then dose escalation will occur (i.e., Cohort 2) • If one of three initially treated subjects experience a DLT by Day 29 of dosing, then an additional three subjects will be enrolled for a total of six subjects treated at the same dose level. Escalation will occur if no additional DLTs are seen in that cohort (DLT in one of six subjects). • If two or more treated subjects at a dose level experience a DLT by Day 29 of continuous dosing, further dose escalation will not be initiated, and the prior dose level and/or a less frequent drug administration schedule will be considered the MTD. If the first dose level of study treatment results in 2 or more subjects experiencing a DLT, subsequent subjects will be enrolled at 25 mg QD (i.e., Cohort -1). • If a subject withdraws from the study treatment for any reason other than a DLT during the first cycle (28 days), that subject will be replaced. The MTD is defined as the dose level at which no more than one out of six subjects have an observable DLT. The dose levels for paclitaxel and fulvestrant will stay the same for all cohorts. ArQule's Medical Monitor and the Investigator(s) will review all significant treatment-related toxicities to determine if the dose escalation schedule requires modification. Intermediate doses and alternative dosing schedules may be assigned to a cohort after agreement between the Medical Monitor and the Investigator(s). During regular calls, the Sponsor and the Investigator(s) will also monitor subjects' safety by reviewing and evaluating

	study data and any emerging safety data/signals on an ongoing basis.
Duration of Treatment:	For an individual subject, treatment with ARQ 751 as a single agent or in combination with paclitaxel or fulvestrant will continue until unacceptable toxicity, disease progression (clinical or radiological), or another discontinuation criterion is met. It is expected that most subjects will receive between one (4 weeks) and six cycles (24 weeks) of treatment with ARQ 751 as a single agent or in combination with other anti-cancer agents. A treatment cycle is defined as 28 days.
Pharmacokinetic Variables:	PK variables will include C_{max}, AUC, and $t_{1/2}$. Blood samples for PK analysis will be drawn at timepoints defined in the protocol. Additional unscheduled blood sample(s) for PK may be collected on any study day(s) upon agreement between the Investigator and Sponsor.
Concomitant Medications:	**Permitted Treatments** • Standard therapies for concurrent medical conditions • Erythropoietin Stimulating Agents (ESA): Please follow American Society of Clinical Oncology (ASCO) or MEDICARE guidelines for the use of ESA in patients diagnosed with cancer, drug labels, and the Food and Drug Administration (FDA) • Hematopoietic growth factors including filgrastim (Neupogen®) or other colony-stimulating factors. ASCO guidelines should be followed for the use of white blood cell (WBC) growth factors • Prophylactic and supportive anti-emetics or low-dose corticosteroids may be administered according to standard practice • Hypoglycemic agents for elevated blood glucose may be administered according to standard practice (administration of insulin is not allowed at baseline but may be administered during the study) • Bisphosphonates or any other drug for treatment of osteoporosis, treatment-induced bone loss and metastases to bone if started at least four weeks before the first dose of study treatment, or upon completion of the first cycle of treatment without any DLT, and if the Investigator rules out tumor progression. • Palliative radiotherapy for local pain control or prevention of fracture (for known bone metastases) may be allowed, provided the subject completes the first cycle of treatment, does not meet criteria of progressive

	disease and treated lesions will not be included in the target/non-target lesion assessment. **Prohibited Treatment** The following treatments are <u>not allowed</u> during the study: • Any concurrent anticancer therapy including, but not limited to, chemotherapy, radiotherapy (except palliative radiotherapy for local pain control), hormonal therapy, immunotherapy, or locoregional therapy • Immunosuppressive therapies including continuous high-dose corticosteroids (except when used intermittently in an antiemetic regimen, for CNS metastases management or as a part of the premedication regimen) • Other investigational agents **Treatment to Be Avoided or Used with Caution** ARQ 751 demonstrated substantial inhibition of CYP2C19 and CYP2D6 and slight metabolism-dependent inhibition of CYP3A4/3A5 enzyme activity. Sensitive substrates for these cytochrome P450 (CYP) isoenzymes should be avoided or used with caution during enrollment in the trial. ARQ 751 was determined to be both a substrate and inhibitor of P-glycoprotein (P-gp), therefore co-administration of ARQ 751 with drugs known to be P-gp substrates with narrow therapeutic index should be avoided or used with caution. The following treatments should be avoided, if possible, or used with caution during the study: • CYP2C19 substrates and inducers • CYP2D6 inhibitors and inducers • CYP3A4/3A5 inhibitors and inducers • P-gp substrates, inhibitors, and inducers • Grapefruit juice **Potential Drug Drug Interaction (DDI)** The potential for DDI reported here are preliminary and based on in vitro ARQ 751 data and available published data on paclitaxel and fulvestrant. The human in vivo metabolism and associated contributions of important metabolic pathways of ARQ 751 have not yet been fully investigated. Further, no clinical DDI studies with ARQ 751 have been performed.

Combination Therapy: potential effect with ARQ 751 (ARQ 751 as a victim)

Combination drug	**Inhibited by CYPs**	**ARQ 751 metabolized by CYPs**	**DDI**
paclitaxel	not reported	2D6, 3A4	unknown
fulvestrant	1A2, 2C9, and 3A4	2D6, 3A4	low/possible*

* Possible if CYP3A4 metabolism is the primary route of elimination of ARQ 751

Combination Therapy: potential effect on ARQ 751 (ARQ 751 as a perpetrator)

Combination drug	**Metabolized by CYPs**	**ARQ 751 inhibited by CYPs**	**DDI**
paclitaxel	2C8 and 3A4	2D6, 2C19	low
fulvestrant	3A4	2D6, 2C19	low

Statistical Methods:	All subjects (Part 1 and Part 2) who have received at least one dose of ARQ 751 will be included in the safety analysis (safety population). Also, the safety analysis for ARQ 751 as a single agent or in combination with other anti-cancer agents will be performed. In addition to the evaluation and categorization of adverse events, listings of laboratory test results collected at Baseline and during the study will be generated. Descriptive statistics summarizing the changes in those laboratory tests over time will be presented. The total number of subjects expected to enroll in Part 1 is approximately 64 subjects, including 34 subjects in single agent dose escalation cohorts and up to 30 subjects in Arm A (expansion cohort of ARQ 751 single agent); Arm A will consist of up to 15 subjects with locally advanced, inoperable, metastatic or recurrent solid tumors with PIK3CA/ PTEN actionable mutations and up to 15 subjects with AKT genetic alterations who will be treated with ARQ 751 as a single agent at the RP2D level. • The total number of subjects expected to enroll in Part 2 is approximately 30 subjects: up to 15 subjects in combination therapy arms, each: o Arm B (ARQ 751+paclitaxel) – dose escalation cohorts (3+3 design) and 6-9 subjects at the RP2D (expansion cohort) o Arm C (ARQ 751+fulvestrant) – dose escalation cohorts (3+3 design) and 6-9 subjects at the RP2D (expansion cohort) Since the sample size is limited (approximately 15 subjects per subgroup), formal sample size justification is not feasible, therefore the descriptive statistics will be used. However, in addition to overall assessment of safety population, each arm will be analyzed separately for safety/tolerability and preliminary efficacy. • H1 – ARQ 751 as a single agent therapy or in combination with paclitaxel or in combination withfulvestrant is sufficiently well tolerated to permit further clinical investigation • H0 – ARQ 751 as a single agent therapy or in combination with paclitaxel or in combination withfulvestrant is not tolerated.

	Subjects who have received at least one cycle of ARQ 751 and have had at least one disease assessment following the initiation of therapy will be considered evaluable for response. The anti-tumor activity will be evaluated on an exploratory basis and will be summarized using descriptive statistics or graphics.

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LIST OF ABBREVIATIONS

AC	before meals
AE	adverse event
AKT	v-Akt murine thymoma viral oncogene homolog
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AN3CA	human endometrial cancer cell line
ANC	absolute neutrophil count
ARQ 751	N-[1-(3-{3-[4-(1-aminocyclobutyl)phenyl]-2-(2-aminopyridin-3-yl)-3H-imidazo[4,5-b]pyridin-5-yl}phenyl)piperidin-4-yl]-N-methylacetamide (2*R*,3*R*)-tartrate
ASCO	American Society of Clinical Oncology
AST	aspartate aminotransferase
AUC	area under the curve
AUC_{0-24}	area under the concentration-time curve from time 0 to 24 hours after dose administration
BCRP	breast cancer resistant protein
BID	twice a day
BSA	body surface area
BUN	blood urea nitrogen
CBC	complete blood count
CFR	Code of Federal Regulations
C_{max}	maximum plasma drug concentration
CNS	central nervous system
CR	complete response
CT	computed tomography
CTC	circulating tumor cells
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	circulating tumor deoxyribonucleic acid
CYP	cytochrome P450
DLT	dose limiting toxicity
EC_{50}	half maximal effective concentration

ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
EOT	end of treatment
ESA	Erythropoietin Stimulating Agents
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GI	gastrointestinal
GI_{50}	concentration for 50% of maximal inhibition of cell proliferation
GnRH	Gonadotropin-releasing hormone
GSK3	glycogen synthase kinase 3
Hb	hemoglobin
HbA1c	glycated hemoglobin
HDL	high-density lipoprotein
HER2	human epidermal growth factor receptor 2
hERG	human ether-a-go-go-related gene
HIPAA	Health Information Portability and Accountability Act
HIV	human immunodeficiency virus
HNSTD	highest non-severely toxic dose
IB	Investigator's Brochure
IC_{50}	inhibitor concentration required for 50% inhibition
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	independent ethics committee
INR	international normalized ratio
IRB	institutional review board
ITT	intent to treat
IV	intravenous

IVF	intravenous fluids
K_i	inhibitory constant
LDH	lactate dehydrogenase
LDL	low-density lipoprotein
LFT	liver function tests
MedDRA	Medical Dictionary for Regulatory Activities
MI	myocardial infarction
min	minute
MNBW	mean net body weight
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
mTOR	mammalian target of rapamycin
mTORC2	mammalian target of rapamycin complex 2
MUGA	Multiple Gated Acquisition
NE	not evaluable
NOAEL	no observed adverse effect level
NYHA	New York Heart Association
ORR	overall response rate
p-	phosphorylated-
PD	progressive disease, pharmacodynamic
PET	positron emission tomography
P-gp	P-glycoprotein
PH	pleckstrin homology
PI3K	phosphatidylinositol 3-kinase
PIK3CA	Phosphatidylinositol-4,5-Bisphosphate 3-Kinase, Catalytic Subunit Alpha
PK	pharmacokinetics
Plt	platelet
PO	by mouth, per os
PR	partial response

PRAS40	proline-rich Akt substrate of 40 kilodaltons
PS	performance status
PT	prothrombin time
PTEN	phosphatase and tensin homolog deleted on chromosome ten
PTT	partial prothrombin time
QD	daily
QHS	before every bedtime
QOD	every other day
QTc	heart rate corrected QT
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	recommended Phase 2 dose
SAE	serious adverse event
SD	stable disease
Ser473	serine 473
STD_{10}	severely toxic dose in 10% of animals
SUSAR	suspected unexpected serious adverse reactions
$t_{1/2}$	elimination half-life
TBD	to be determined
TEAE	treatment-emergent adverse event
TGI	tumor growth inhibition
Thr308	threonine 308
TID	three times daily
T_{max}	time to maximum plasma concentration
ULN	upper limit of normal
WBC	white blood cells

1 INTRODUCTION

The phosphatidylinositol-3-kinase (PI3K)/ v-Akt murine thymoma viral oncogene homolog (AKT)/ mammalian target of rapamycin (mTOR) signaling pathway plays a major role in physiological processes regulating cellular growth, proliferation, angiogenesis, survival, and metabolism (Brazil, 2004; Bellacosa, 2005; Engelman, 2006). The PI3K/AKT/mTOR (PI3K) pathway is frequently altered in solid malignancies, promoting tumor growth, proliferation and survival. The pathway's three critical nodes, PI3K, AKT and mTOR, have been recognized as important therapeutic targets. Recently, a number of PI3K pathway inhibitors has been tested in clinical trials (Dienstmann, 2014; LoRusso, 2016; Li, 2018). Unfortunately, the single-agent activity of these inhibitors has been limited by compensatory activation of other pathways, e.g., growth factor receptor signaling that allows bypassing the targeted inhibition. (Fruman, 2014; LoRusso, 2016). Thus, it seems reasonable to suggest that combination therapies may improve clinical response by targeting multiple tumor-specific pathways by simultaneous inhibition of the crosstalk between these activated pathways.

In vitro and in vivo studies showed that PI3K pathway inhibitors might sensitize tumors to chemotherapy by altering surrounding vasculature and tumor perfusion (Fokas, 2012), thus increasing exposure to systemic therapies and synergistically inducing apoptosis (Bender, 2011, Kilic-Eren, 2013). In clinical trials, antitumor activity was observed in NSCLC subjects treated with pictilisib, carboplatin and paclitaxel, with or without bevacizumab (Soria, 2017) and in HER2-negative gastric cancer subjects treated with ipatasertib plus mFOLFOX6 (Bang, 2014) study. Also, paclitaxel, as a single agent or in combination with other agents, is the standard chemotherapeutic agent for patients with other advanced solid tumors, including ovarian, endometrial, cervical, and triple-negative breast cancer. PI3K pathway has been implicated in the development of a number of gynecological cancers, e.g., it is activated in approximately 35% of HR-positive breast cancers (Stemke-Hale, 2008) and is associated with development of resistance to endocrine therapy (Miller, 2011). Thus, combination of PI3K/AKT/mTOR inhibitors with chemotherapeutic agents, and endocrine therapy may restore sensitivity to and improve efficacy of these therapies compared to a single agent therapy.

ARQ 751

A novel class of AKT inhibitors have been discovered and developed at ArQule, Inc. One of these inhibitors, ARQ 751, is a potent allosteric pan-AKT inhibitor with biochemical IC_{50} values of 0.55, 0.81, and 1.31 nM against AKT1, AKT2, and AKT3, respectively and is highly selective among the kinome. Out of 245 kinases screened, ARQ 751 did not inhibit any kinase other than AKT1 by more than 50% at a concentration of 5 µM.

ARQ 751 effectively inhibits the phosphorylation of AKT1 and its downstream target PRAS40 as well as the growth of cancer cell lines with elevated AKT signaling. The ability of ARQ 751 to inhibit the AKT pathway was assessed in a human endometrial cancer cell line (AN3CA). AN3CA cells do not express PTEN and exhibit constitutive activation of AKT (Byron, 2008). ARQ 751 was able to inhibit the phosphorylation of AKT (Thr308) and AKT(Ser473) as well as the phosphorylation of the downstream substrate PRAS40(Thr246). The half maximal effective concentration (EC_{50}) values for inhibition of phosphorylated-AKT(Thr308) (p-AKT[Thr308]), p-AKT(Ser473), and p-PRAS40(Thr246) were 5.10, 10.20, and 48.55 nM, respectively, in

AN3CA cells. These results suggest that ARQ 751 effectively inhibits the AKT pathway in human cancer cells.

The anti-proliferative activity of ARQ 751 was evaluated in 239 human cancer cell lines using OncoPanel™ 240. The concentration for 50% of maximal inhibition of cell proliferation (GI_{50}) values for breast T47D, MCF7, BT474, endometrial AN3CA, ovarian OVCAR3, and prostate LNCaP cancer cell lines were 1.05, 2.20, 3.25, 11.09, 13.00, and 15.00 nM, respectively. AN3CA and LNCaP cells are PTEN-deficient; (Byron, 2008) while BT474 cells, MCF7, and T47D cells harbor actionable mutations of PIK3CA (Brugge, 2007). All of the aforementioned cell lines have constitutive activation of AKT. Furthermore, 73% of cancer cells bearing PIK3CA/R1 mutations were sensitive to ARQ 751, whereas only 42% cells with wild type PIK3CA/R1, suggesting that cancer cells with PIK3CA/R1 mutations are more responsive to ARQ 751 (Yu, 2015). These data suggest that ARQ 751 is effective in inhibiting the growth of cancer cell lines with dysregulated AKT signaling.

The AN3CA human endometrial cell line was extensively used for the development of the cell proliferation assays and the *in vivo* pharmacodynamic assay in the study of ARQ 751. Additionally, the anti-tumor *in vivo* activity of ARQ 751 was tested in an athymic mouse xenograft model explanted with the AN3CA cells. Tumor growth inhibition (TGI) of ARQ 751 after ten days oral treatment at 120 mg/kg daily to 5 mg/kg ranged from 92% to 29%. This was accompanied by a mean net body weight (MNBW) of not more than 10%. In an endometrial PDX model driven by actionable mutation of AKT1 (AKT1 E17K), ARQ 751 treatment resulted in TGI of 68, 78 and 98% (Yu et al 2015). These data indicate that ARQ 751 has the potential to exert significant anti-tumor effects on human tumors with dysregulated AKT signaling.

The pharmacodynamic effect of ARQ 751 was demonstrated in AN3CA xenograft models. In AN3CA tumors, phospho-AKT(Thr308), phospho-AKT(Ser473), and phospho-PRAS40(Thr246) levels were reduced 63.9-99.7%, , by Western blotting analysis, 6 hours after 10 to 120 mg/kg dosing. At 24 hours post-dose, AKT phosphorylation and PRAS40 phosphorylation had decreased at all doses levels in the range of 32.3-98.1% for phospho-AKT(Thr308), 0-99.2% for phospho-AKT(Ser473), and 8.6-66% for phospho-PRAS40(Thr246). At oral dose levels of ARQ 751 $\geq$ 20 mg/kg, maximum plasma drug concentrations (C_{max}) of ARQ 751 were $\geq$ 1.6 µM. In summary, ARQ 751 showed a marked inhibition of the AKT pathway as determined by Western blotting in an AN3CA xenograft model.

An *in vitro* combination study of ARQ 751 with aromatase inhibitor, anastrozole or ER antagonist, fulvestrant was performed in ER positive endometrial cancer cells with dysregulated PI3K/AKT pathway. Combination of ARQ 751 at defined concentrations with fulvestrant (10 µM) or anastrozole (200 µ M) showed significant enhancement in anti-proliferative activity in MFE-280 (ER+, PIK3CAH1047R), HEC-1B (ER+, PIK3CAG1049R), and Ishkawa (ER+, PIK3R1T319fs*1&V290fs*1), compared to single agents (Data on file). Furthermore, *in vivo* efficacy study of ARQ 751 in combination with anti-PD1 antibody was performed in a syngeneic mouse CT26 colon tumor model. Combination of ARQ 751 with anti-PD1 antibody exerted TGI (%Treated/vehicle) of 51%, whereas ARQ 751 and anti-PD1 antibody as single agents showed little or no TGI (102% and 89% respectively). (Data on file.)

1.1 Pharmacokinetic Characteristics

The pharmacokinetics (PK) of ARQ 751 following oral administration to rats and monkeys were evaluated. The mean oral bioavailability of ARQ 751 was 33.1% in rats, and was 16.1% or 13.7% in monkeys dosed with a solution formulation or powder filled capsule, respectively. In a 4-week repeat-dose rat study after oral administration, ARQ 751 was readily absorbed, with time to maximum plasma concentration (T_{max}) values ranging from 4.00 to 8.00 hours on Day 1 and from 4.00 to 6.00 hours on Day 28. After reaching C_{max}, ARQ 751 concentrations steadily declined, with the elimination half-life ($t_{1/2}$) values ranging from 3.81 to 6.24 hours on Day 1 and from 3.51 to 7.56 hours on Day 28. Exposure to ARQ 751 increased with the increase in ARQ 751 dose level from 2.5 to 40 mg/kg/day on Day 1 and from 2.5 to 10 mg/kg/day on Day 28. Sex differences in C_{max} and area under the concentration-time curve from time 0 to 24 hours after dose administration (AUC_{0-24}) values were less than 2-fold. Values for C_{max} and AUC_{0-24} were similar to slightly lower on Day 28 than on Day 1 at the 2.5 and 10 mg/kg/day dose levels, indicating no accumulation of ARQ 751 after multiple dosing of rats at these doses. The increases in C_{max} and AUC_{0-24} for males and females were greater than dose proportional. Similar findings were noted in the 14-day repeat-dose rat study.

In the 4-week repeat-dose monkey study, after oral gavage administration, ARQ 751 was readily absorbed, with mean T_{max} values ranging from 2.00 to 4.40 hours on Day 1 and from 2.00 to 2.02 hours during Week 4. After reaching C_{max}, ARQ 751 concentrations readily declined, with mean $t_{1/2}$ values ranging from 4.52 to 6.59 hours on Day 1 and from 3.56 to 6.95 hours during Week 4. Exposure to ARQ 751 increased with the increase in ARQ 751 dose level from 2.5 to 40 mg/kg/day on Day 1 and from 2.5 to 10 mg/kg/day during Week 4. No consistent sex differences in mean C_{max} and AUC_{0-24} values were observed, and any differences were generally less than 2-fold. There were no consistent changes in mean C_{max} and AUC_{0-24} values after multiple dosing at the 2.5 and 10 mg/kg dose levels but the results, in general, indicate no accumulation of ARQ 751 after multiple dosing of ARQ 751 in monkeys at these levels. The increases in mean C_{max} and AUC_{0-24} for males and females were greater than dose proportional. Similar findings were noted in the 14-day repeat-dose monkey study.

1.2 Metabolism of ARQ 751

Data from *in vitro* metabolism studies in primary hepatocytes suggested that [^{3}H]-ARQ 751 was metabolized to a small extent, 16.4 to 31.5% (83.6 to 68.5% parent remaining) in incubations containing rat, monkey, and human hepatocytes with the highest level of metabolism observed in monkey hepatocyte incubations, followed by human hepatocyte incubations, and the lowest in rat hepatocyte incubations. A total of four metabolite peaks (M2, M3, M4, and M5) were observed in rat hepatocyte incubations, three metabolite peaks (M1, M2, and M4) were observed in monkey hepatocyte incubations, and six metabolite peaks (M1, M2, M3, M4, M6, and M7) were observed in human hepatocyte incubations.

Incubations with individually expressed human recombinant cytochrome P450 (CYP) isoenzymes, indicated that CYP2D6, CYP3A4, and CYP3A5 were the major enzymes involved in the metabolism of [^{3}H]-ARQ 751. [^{3}H]-ARQ 751 was metabolized to a small extent, approximately 30% in incubations containing 1 mg/mL microsomal protein and an incubation time of 60 minutes, in pooled human liver microsomal incubations. A total of four distinct metabolites (M1, M2, M3, and M4) were observed in pooled liver microsomal incubations. Based on the 1 mg/mL human

liver microsomal protein incubations conducted for 60 minutes, metabolite formation was rank ordered as M2~M3>M1>M4. Metabolite M1 was mainly formed by CYP2D6, whereas metabolites M2, M3, M4 appeared to be formed mainly by CYP3A4 and CYP3A5. An additional metabolite, M5, was observed in incubations with recombinant CYP3A4 and CYP3A5, but not in pooled liver microsomal incubations.

Based on the fact that the IC_{50} values were all greater than 30 µM, ARQ 751 is not likely to cause drug-drug interactions due to inhibition of CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2E1, and CYP3A4/5 enzyme activities *in vivo* in humans. However, ARQ 751 showed substantial inhibition of CYP2C19 and CYP2D6 enzyme activities. The IC_{50} values were calculated to be 16.5 and 14.5 µM, respectively. Additional experiments were conducted to evaluate the kinetics of inhibition. ARQ 751 showed competitive-full inhibition towards CYP2C19 and the inhibitory constant (K_i) was calculated to be 6.8 µM. ARQ 751 showed mixed-partial inhibition towards CYP2D6 and the K_i was calculated to be 3.1 µM. Therefore, ARQ 751 may cause drug-drug interactions by inhibition of CYP2C19 and CYP2D6. ARQ 751 did not show metabolism-dependent inhibition of CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP2E1 enzyme activities in pooled human liver microsomes. Slight metabolism-dependent inhibition of CYP3A4/5 enzyme activities was observed. Based on these data, ARQ 751 is not likely to cause drug-drug interactions due to metabolism-dependent inhibition of CYP enzyme activities *in vivo*, in humans. ARQ 751 was determined to be both a substrate and inhibitor of P-glycoprotein (P-gp), but not a substrate of breast cancer resistant protein (BCRP). ARQ 751 did not induce CYP1A2, CYP2B6, or CYP3A4 enzyme activity. ARQ 751 was found to be highly bound to proteins in human plasma (95.3 to 96.9%).

1.3 Nonclinical Toxicology

The toxicity profile of orally administered ARQ 751 in both rats and monkeys was characterized principally by findings in the immune system and kidney (rats, high dose only). In rats at the high dose (40/30 mg/kg), notable clinical pathology findings were consistent with renal dysfunction/toxicity, dehydration, and poor health. Moderately to markedly increased urea nitrogen and creatinine observed in most of these animals were consistent with renal damage and correlated with kidney microscopic findings (renal tubule degeneration/necrosis, tubule cell vacuolation, and proteinaceous casts). Additional notable clinical pathology findings in these animals included mildly to markedly increased glucose and insulin, minimally to mildly increased white blood cell (WBC) and absolute neutrophil counts, and minimally to moderately increased red cell mass (e.g., red blood cell count, hemoglobin, and hematocrit). It should be noted that the myelosuppressive effects of ARQ 751 noted at 40/30 mg/kg/day resulted in increased red cell mass and WBC, which are considered secondary effects of ARQ 751 due to dehydration and/or poor health. In rats, all observations reversed at 2.5 and 10 mg/kg during the recovery phase. In monkeys, ARQ 751-related microscopic findings were restricted to decreased lymphocytes in the thymus, spleen, and lymph nodes. Decreased lymphocytes were noted in males given 40/30 mg/kg/day and females given > 10 mg/kg/day, with recovery of lymphocytes at the recovery sacrifice.

In rats, no ARQ 751-related effects occurred on functional observation battery tests or locomotor activity, no ARQ 751-related lesions were noted during ophthalmic examinations for animals

administered 2.5 or 10 mg/kg/day, and ARQ 751-related plethysmography findings were limited to decreased respiration rate (16%) for animals administered 40 mg/kg.

Increased plasma glucose and insulin levels which were observed in both species have been reported for other AKT inhibitors and may be a characteristic of this class of kinase inhibitors. (Tan, 2011).

ARQ 751 showed potential to inhibit human ether-a-go-go-related gene (hERG) in *in vitro* studies (IC_{50} = 14.9 µM). Additionally, in the 4-week repeat-dose monkey study, administration of ARQ 751 was associated with longer heart rate-corrected QT (QTc) intervals in animals given 10 or 40/30 mg/kg/day. Mean QTc intervals on Day 21 of the dosing phase were 25 msec (7%) longer in males and 51 msec (15%) longer in females given 40/30 mg/kg/day compared with their respective pre-dose phase values. Mean QTc intervals 3 hours post-dose on Day 22 of the dosing phase were 12 msec (4%) longer in males and 31 msec (9%) longer in females given 10 mg/kg/day compared with controls. Longer QTc intervals were reversed in animals given 10 mg/kg/day by 24 hours post-dose on Day 22 of the dosing phase and Day 22 of the recovery phase. No ARQ 751-related changes in QTc interval were observed in animals given 2.5 mg/kg/day. However, in monkey telemetry studies, cardiovascular function was assessed in four male cynomolgus monkeys given a single oral gavage dose of vehicle control article or 2.5, 10, or 40 mg/kg of ARQ 751 and no abnormal electrocardiogram (ECG) waveforms or arrhythmias were attributed to ARQ 751. Additionally, administration of ARQ 751 had no effect on QRS duration or PR or QTc interval, diastolic or pulse pressure, or body temperature. The only ARQ 751-related effects were observed at 40 mg/kg and consisted of higher heart rate and higher systolic and mean arterial pressures. Inhibition of hERG and QT prolongation have been reported for other AKT inhibitors and may be an on-target toxicity associated with this class of kinase inhibitors. (Konopleva, 2014) (Zhang Y., 2006).

ARQ 751 was evaluated for phototoxic potential on Balb/c 3T3 fibroblasts using the Neutral Red Uptake assay and is considered to have phototoxic potential.

Based on the 4-week rat study, the severely toxic dose in 10% of rats (STD_{10}) of ARQ 751 was determined to be greater than 10 mg/kg/day but less than 30 mg/kg/day when given via oral gavage daily. Conservatively, the 10 mg/kg/day dose level will be used as the STD_{10} in rats. This correlates to a human equivalent dose of 60 mg/m^2/day. Based on the 4-week monkey study, both the NOAEL and the highest non-severely toxic dose (HNSTD) of ARQ 751 were determined in males and females to be 10 mg/kg/day and 2.5 mg/kg/day, respectively. Therefore, the NOAEL/HNSTD dose of 2.5 mg/kg/day from females will be used. This correlates to a human equivalent dose of 30 mg/m^2/day. Based on this information, the monkey is considered to be the more sensitive species for purposes of calculating a safe starting dose for the First in Human study in subjects with advanced malignancies. As described in the International Council for Harmonisation (ICH) guidance document: *S9 Nonclinical Evaluation for Anticancer Pharmaceuticals,* a safe human starting dose based on assessment of toxicity in monkey species is 1/6th of the HNSTD. Therefore, the Phase 1 starting dose iwas calculated to be 5 mg/m^2/day or 8.1 mg/day (based on a body surface area [BSA] of 1.62 m^2). Hence, the initial starting dose of ARQ 751 in humans was 5 mg daily (QD).

In summary, the nonclinical pharmacology data support that ARQ 751 has the potential to exert significant anti-tumor effects on human tumors with dysregulated AKT signaling.

Detailed non-clinical and clinical data can be found in the ARQ 751 Investigator's Brochure (IB).

2 INVESTIGATIONAL PLAN

As discussed in the Introduction section of the protocol and in the IB, the current understanding of the tumor biology, specifically the PI3K/AKT/mTOR pathway in breast and gynecological cancers, has provided rationale for combination of targeted, endocrine and chemotherapeutic agents.
Such combination regimens may enhance the growth inhibition effect of a single agent, allow to overcome resistance to a single agent therapy, restore sensitivity to chemotherapy or targeted/endocrine therapy, and/or afford a durable response, particularly in molecularly selected tumors.

This study consists of two parts: Part 1 that includes all subjects enrolled in the single agent dose escalation cohorts and single agent expansion cohort (Arm A) and Part 2 that includes all subjects in the combination treatment arms (Arms B and C).

ARQ 751-101 study was initiated in August 2016 as an open-label, phase 1, first-in-human, dose escalation study. The proposed ARQ 751 dose levels and administration schedule for the combination therapy arms have been initially tested in the monotherapy single agent Dose Escalation cohorts of this trial. Thirty-four subjects with advanced solid tumors with documented *PIK3CA/AKT/PTEN* genetic alterations were enrolled in the single agent dose escalation cohorts. Dose escalation followed the traditional escalation design (3+3 subjects) with the initial dose of 5 mg QD and the highest tested dose of 100 mg QD, continuously. Dose limiting toxicities (DLTs) were assessed during the first cycle (28 days) of treatment with ARQ 751.

Overall, ARQ 751 as a single agent demonstrated manageable safety profile. Reversible grade 3 pruritic rash was the only DLT observed in the study. The dose of 100 mg QD was deemed to be intolerable and an intermediate dose cohort was introduced. Eight subjects were treated at the intermediate dose level of 75 mg QD, seven completed the first cycle without any DLT, one subject was discontinued due to clinical disease progression. Based on the tolerability and safety of ARQ 751, RP2D of ARQ 751 as a single agent has been defined as 75 mg QD, continuously under fasting conditions.

To further evaluate safety and tolerability, and to assess preliminary efficacy of ARQ 751 as a single agent, up to 30 subjects are planned to be enrolled and treated with ARQ 751 at the RP2D level in Arm A (expansion cohort). It is planned to enroll up to 15 subjects with solid tumors with PIK3CA or PTEN actionable mutations and up to 15 subjects with AKT genetic alterations. Subjects enrolled in Arm A will receive ARQ 751 at 75 mg QD, continuously.

Since a single drug approach may not be sufficient to inhibit tumor growth, a simultaneous inhibition of the multiple pathways may be needed to generate durable anti-neoplastic effect. Part 2 is designed to determine RP2D and to assess safety, tolerability, and preliminary efficacy of ARQ 751 in combination with other anti-cancer agents. Part 2 consists of two combination therapy arms, Arm B (paclitaxel) and Arm C (fulvestrant).

This protocol is a multi-center, open label, study of oral ARQ 751 in subjects with advanced, inoperable, metastatic and/or recurrent solid tumors with, *AKT* genetic alterations, and *PIK3CA* and *PTEN* actionable mutations.

Enrollment in each arm will be initiated per Sponsor discretion. The choice of treatment Arm will be made at the discretion of the Investigator, provided combination therapy with paclitaxel or fulvestrant would be appropriate for their patients' disease for Arms B and C. Depending on the study safety and efficacy data, the Sponsor may limit the number of subjects with a specific tumor type(s) or *PIK3CA/AKT/PTEN* mutation status to be enrolled.

To determine RP2D of ARQ 751 in combination with paclitaxel (Arm B) or fulvestrant (Arm C) in Part 2, standard 3+3 dose finding design will be used. Assessment of the safety and tolerability of combination regimens will include all subjects treated in Arm B and Arm C independent of the ARQ 751dose level subjects may receive. Additional arms may be added to assess ARQ 751 in combination with other anti-cancer agents.

In Arms B and C, dose determination will be done as follows:

Cohort	ARQ 751 (orally, PO)	Paclitaxel (Arm B)	Fulvestrant (Arm C)
-1	25 mg QD	80 mg/m^2 (IV) Days 1,8,15 followed by a week of rest	500 mg (IM) Days 1 &15 of Cycle 1, and Day 1 of all subsequent cycles
1	50 mg QD		
2	75 mg QD		
Expansion	RP2D		

Dose escalation will proceed to 75 mg QD, the dose that was defined to be the ARQ 751 RP2D as a single agent. Once MTD/RP2D for each combination therapy Arm is determined, additional six subjects will be enrolled. Intra-subject dose escalation will be permitted if the next higher dose of ARQ 751 for that regimen is determined to be safe. Paclitaxel and fulvestrant administration and premedication therapy if required should follow the FDA approved regimens (see drug labels), NCCN guidelines, or institutional SOC.

Approximately 94 subjects will be enrolled in this study at 4-10 sites in the USA; 64 subjects in Part 1 (Dose escalation cohorts and Arm A) and 30 in Part 2 (Arm B and Arm C). Thirty four subjects were enrolled in dose escalation cohorts. It is planned that up to 30 subjects with advanced, inoperable, metastatic, or recurrent solid tumors will be enrolled in Arm A, up to 15 subjects with PIK3CA/PTEN activating mutations and up to 15 subjects with AKT genetic alterations. In Part 2, approximately 15 subjects will be enrolled in each combination therapy arm (Arm B, ARQ 751+paclitaxel and Arm C, ARQ 751+fulvestrant).

Assessment of safety and tolerability of ARQ 751 as a single agent and in combination with paclitaxel or fulvestrant will be based on continuous evaluation of adverse events, physical examination findings and laboratory tests. All clinical assessments and laboratory tests will be performed according to the protocol-defined timepoints. If clinically indicated, unscheduled

laboratory tests and any clinical assessments or evaluations may be performed per discretion of the Investigator.

Tumor assessments (CT or MRI) will be performed according to protocol-defined timepoints, or as otherwise clinically indicated. Tumor response will be evaluated according to RECIST 1.1 guidelines.

Pharmacokinetic (PK) samples will be collected pre-dose and at different timepoints post-dose as defined in the protocol. Additional unscheduled blood sample(s) for PK may be collected on any study day(s) upon agreement between the Investigator and the Sponsor. Two single blood samples to determine CYP2D6 genotype and PIK3CA/AKT/PTEN mutation in ctDNA will be collected.

For an individual subject, treatment will continue until unacceptable toxicity, disease progression (clinical or radiological), or another discontinuation criterion is met. It is expected that most subjects will receive between one and six cycles (four to 24 weeks). A treatment cycle is defined as 28 days.

Study Objectives

The study objectives for Part 1 are

The **primary objective** is to assess the safety and tolerability of ARQ 751 in subjects with advanced solid tumors with AKT1, 2, 3 genetic alterations, activating PI3K mutations, PTEN-null, or other known actionable PTEN mutations.

Secondary and exploratory objectives include the following:

- To assess the pharmacokinetic (PK) profile of ARQ 751
- To assess the pharmacodynamic activity of ARQ 751 in blood specimens obtained from subjects with advanced solid tumors with AKT1, 2, 3 genetic alterations, activating PI3K mutations, PTEN-null, or other known actionable PTEN mutations
- To determine the maximum tolerated dose (MTD) and/or the recommended Phase 2 dose (RP2D) of ARQ 751 as single agent
- To generate preliminary evidence of anti-tumor activity

The study objectives for Part 2 are:

The **primary objective** is to assess the safety and tolerability of ARQ 751 in combination with paclitaxel or fulvestrant in subjects with advanced, inoperable, metastatic and/or recurrent solid tumors with *PIK3CA /PTEN* actionable mutations and/or AKT genetic alterations.

Secondary and exploratory objectives include the following:

- To determine MTD/RP2D dose of ARQ 751 in combination with paclitaxel or fulvestrant
- To assess the PK profile of ARQ in combination with paclitaxel or fulvestrant
- To generate preliminary evidence of anti-tumor activity of ARQ 751 in combination with paclitaxel or fulvestrant in subjects with advanced, inoperable, metastatic and/or recurrent solid tumors with PIK3CA/PTEN actionable mutations and/or AKT genetic alterations
- To determine CYP2D6 genotype
- To determine PIK3CA/AKT/PTEN mutation status by ctDNA

Study Endpoints for Part 1

Primary endpoint:

The primary endpoint of the study is safety and tolerability and is measured by safety variables which include the reported AEs, laboratory tests, vital signs, ECOG performance status, and physical examination.

Secondary and exploratory endpoints include the following:

- Pharmacokinetics which are measured by maximum plasma drug concentration (C_{max}), area under the curve (AUC), and elimination half-life ($t_{1/2}$)
- Pharmacodynamic pharmacodynamics will be evaluated by changes in serum glucose and insulin levels, and by changes in cell-free ctDNA.
- RP2D will be determined following review of all safety, pharmacodynamic data and anti-tumor activity generated in the dose escalation portion of the study. Together with the Investigators, the RP2D will be set at or below the MTD and at a dose at which pharmacodynamic activity or anti-tumor activity is demonstrated.
- Preliminary evidence of anti-tumor activity will be evaluated by RECIST v1.1 Response Criteria
-

Study Endpoints for Part 2

Primary endpoint:

Safety and tolerability as assessed by the frequency, duration, and severity of adverse events (AEs) from the first dose of study treatment through 30 days after the last dose of therapy.

Secondary endpoints include the following:

- Pharmacokinetics as measured by maximum plasma drug(s) concentration (Cmax), time to maximum plasma drug concentration [Tmax], area under the curve (AUC), and elimination half-life (t1/2)
- RP2D as determined following review of all safety generated in the dose escalation cohort(s) for each combination therapy Arm. The RP2D will be set at or below the MTD.
- Preliminary evidence of anti-tumor activity as assessed by RECIST v. 1.1

Exploratory endpoints are as follows:

- To evaluate the effect of CYP2D6 polymorphism on ARQ 751 exposure
- To determine presence of PIK3CA/AKT/PTEN mutation(s) by ctDNA in blood

2.1 Criteria for ARQ 751 Dose Escalation and Determination of Dose-Limiting Toxicity for Part 1

Enrollment at the next dose level and/or enrollment of additional subjects into the ongoing cohort occurred according to the following criteria:

- If zero of three initially treated subjects experience a DLT (ARQ 751-related, probably related, or possibly related) by Day 29 of dosing, then dose escalation will occur
- If one of three initially treated subjects experiences a DLT by Day 29 of dosing, then an additional three subjects will be enrolled for a total of six subjects treated at the same dose level. Escalation will occur if no additional DLTs are seen in that cohort (DLT in one of six subjects).
- If two or more treated subjects at a dose level experience a DLT by Day 29 of continuous dosing, dose escalation will stop and the prior dose level and/or a less frequent drug administration schedule will be considered the MTD. If the first dose results in 2 or more subjects experiencing DLT, subsequent subjects will be enrolled at a less frequent drug administration schedule (e.g., 5 mg QOD).
- If a subject withdraws from the study treatment for any reason other than a DLT during the first cycle (4 weeks/28 days), that subject will be replaced.

The MTD was defined as the dose level at which no more than one out of six subjects has an observable DLT.

ArQule's Medical Monitor and the Investigator(s) reviewed all significant ARQ 751-related toxicities to determine if the dose escalation schedule requires modification. Intermediate doses and alternative dosing schedules could be assigned to a cohort after agreement between the Medical Monitor and the Investigator(s).

During the dose escalation period, intra-subject dose escalation was only permitted if the following criteria were met:

1. The next higher dose for this regimen has demonstrated to be safe by at least 3 subjects and the last subject completed one cycle without exceeding a DLT.
2. The subject in question has not experienced a DLT.

Once the MTD was determined, intra-subject dose escalation to the MTD was considered to optimize the treatment in subjects enrolled at lower dose levels. Multiple intra-subject dose escalations per subject was considered.

2.2 Criteria for ARQ 751 Dose Escalation and Determination of Dose-Limiting Toxicity for Part 2

To determine RP2D of ARQ 751 in combination with paclitaxel and fulvestrant, a minimum of two dose levels will be tested. Enrolled subjects will initially be treated with 50 mg QD of ARQ 751 (Cohort 1 of Arms B and C). Evaluable subjects are defined as having been exposed to ARQ 751 for 28 days (one cycle/first cycle of treatment). Enrollment at the next dose level and/or enrollment of additional subjects into the ongoing cohort will occur according to the following criteria:

- If zero of three initially treated subjects experience a DLT (ARQ 751-related, probably related, or possibly related) by Day 29 of dosing, then dose escalation will occur (i.e., Cohort 2)
- If one of three initially treated subjects experience a DLT by Day 29 of dosing, then an additional three subjects will be enrolled for a total of six subjects treated at the same dose level. Escalation will occur if no additional DLTs are seen in that cohort (DLT in one of six subjects).
- If two or more treated subjects at a dose level experience a DLT by Day 29 of continuous dosing, further dose escalation will not be initiated, and the prior dose level and/or a less frequent drug administration schedule will be considered the MTD. If the first dose level of study treatment results in 2 or more subjects experiencing a DLT, subsequent subjects will be enrolled at 25 mg QD (i.e., Cohort -1).
- If a subject withdraws from the study treatment for any reason other than a DLT during the first cycle (28 days), that subject will be replaced.

The MTD is defined as the dose level at which no more than one out of six subjects have an observable DLT.

The dose levels for paclitaxel and fulvestrant will stay the same for all cohorts.

ArQule's Medical Monitor and the Investigator(s) will review all significant treatment-related toxicities to determine if the dose escalation schedule requires modification. Intermediate doses and alternative dosing schedules may be assigned to a cohort after agreement between the Medical Monitor and the Investigator(s).

During regular calls, the Sponsor and the Investigator(s) will also monitor patients' safety by reviewing and evaluating study data and any emerging safety data/signals on an ongoing basis.

2.3 ARQ 751 Dose Limiting Toxicity – Part 1

Dose-limiting toxicities (DLT) were determined during the first cycle (four weeks/28 days) of treatment. A DLT was defined by the occurrence of any of the following toxicities related, probably related, or possibly related to ARQ 751 within the first cycle of treatment and graded according to Common Terminology Criteria for Adverse Events (CTCAE) version 4.03:

- Grade 4 anemia
- Grade 4 neutropenia
- Grade 4 thrombocytopenia
- Grade 3 neutropenia lasting longer than 7 days despite optimal treatment
- Grade 3 thrombocytopenia in the presence of bleeding
- ≥ Grade 3 hyperglycemia (fasting blood glucose > 250 mg/dL or non-fasting > 500 mg/dL) requiring insulin (uncontrolled with oral hypoglycemic agents)
- ≥ Grade 3 non-hematological toxicity of any duration, except for the following:
    - Nausea, vomiting, or diarrhea responding to optimal medical management within 48 hours
    - Alopecia
- Any other toxicity that in the view of the Investigator represents a clinically significant hazard to the subject

2.4 ARQ 751 Dose Limiting Toxicity (Arms B and C) – Part 2

Dose-limiting toxicities will be determined during the first cycle (28 days) of combination therapy. A DLT is defined by the occurrence of any of the following toxicities related, probably related, or possibly related to ARQ 751 when administered in combination with paclitaxel or fulvestrant within the first cycle of treatment and graded according to Common Terminology Criteria for Adverse Events (CTCAE) version 4.03:

- Grade 4 anemia

- Grade 4 neutropenia
- Grade 4 thrombocytopenia
- Grade 3 neutropenia lasting longer than 7 days despite optimal treatment
- Grade 3 thrombocytopenia in the presence of bleeding
- ≥ Grade 3 hyperglycemia (fasting blood glucose > 250 mg/dL or non-fasting > 500 mg/dL) requiring insulin (uncontrolled with oral hypoglycemic agents)
- ≥ Grade 3 non-hematological toxicity of any duration, except for the following:
    - Nausea, vomiting, or diarrhea responding to optimal medical management within 48 hours
    - Alopecia
- The Investigator to assess ALT and AST changes to determine if these changes may be a DLT
    - ≥ Grade 3 ALT or AST elevation for subjects with ALT/AST ≤ 3 ULN at Baseline
    - ALT/AST levels for subjects with known liver metastases and ALT/AST ≤ 5 x ULN at Baseline
    - Grade 2 ALT/AST elevation accompanied by ≥ Grade 2 elevation in bilirubin
- Any other toxicity that in the view of the Investigator represents a clinically significant hazard to the subject

3 SELECTION OF STUDY POPULATION

Adult subjects with advanced solid tumors with documented *AKT* genetic alterations, *PIK3CA* or *PTEN* actionable mutations whose cancer has progressed following standard therapy, or for whom standard therapy is not available or is not tolerable will be enrolled.

Part 1 of this study includes all subjects enrolled in the single agent dose escalation cohorts and expansion cohort (Arm A) and Part 2 includes all subjects in the combination treatments arms (Arms B and C).

See Annex 1 for inclusion/exclusion criteria for subjects enrolled under Amendment 5.

To be enrolled, subjects must meet all eligibility criteria.

3.1 Inclusion Criteria

1. Signed written informed consent granted prior to initiation of any study-specific procedures
2. 18 years of age and older
3. Histologically and/or cytologically documented diagnosis of a selected tumor type that is locally advanced, inoperable, metastatic or recurrent (including but not restricted to breast cancer, TNBC [triple negative]; HR-positive [HR+]/HER2-negative [HER2-] or endometrial cancer)
4. Documented *AKT* genetic alterations or known actionable *PIK3CA*/*PTEN* mutations by genetic testing
   - subjects with tumors with PTEN null/PTEN loss-of-function mutations are not eligible
5. For Arms B or C, subjects should be eligible for paclitaxel or fulvestrant therapy as per Investigator assessment
6. Failure to respond to standard systemic therapy, or for whom standard or curative systemic therapy does not exist or is not tolerable.
   - Subjects in Arm A (with *AKT* genetic alterations) and subjects in dose escalation cohorts of Arms B and C should have at least one line of standard systemic therapy
   - Subjects in Arm A (with *PIK3CA/PTEN* actionable mutations) and subjects in the expansion cohorts of Arms B and C should have no more than 3 prior systemic regimens for the advanced disease
   - Neoadjuvant and adjuvant chemotherapy are considered one regimen if they are a continuation of the same regimen with interval debulking surgery
   - If the subject is refractory or has disease progression within 6 months after completion of the adjuvant treatment, then the adjuvant treatment should be considered as the line of treatment rather than an adjuvant therapy.
   - Endocrine (hormonal) therapy does not count toward total lines of therapy
   - Maintenance therapy is considered part of the preceding regimen if one or more of the same drugs are continued
7. Has at least one measurable target lesion according to RECIST v. 1.1
8. Eastern Cooperative Oncology Group (ECOG) performance status (PS) ≤ 1

9. Adequate organ function as indicated by the following laboratory values. (All laboratory tests must be obtained within 14 days prior to the first dose of study treatment):

   a. Hematological
      - Absolute neutrophil count (ANC) ≥ 1.5 x 109/L
      - Platelet count (Plt) ≥ 100 x 109/L
      - Hemoglobin (Hb) ≥ 9 g/dL
      - International normalized ratio (INR) 0.8 to upper limit of normal (ULN) or ≤ 3 for subjects receiving anticoagulant therapy such as Coumadin or heparin

   b. Renal
      - Serum creatinine ≤ 1.5 x ULN or calculated creatinine clearance ≥ 60 mL/min/1.73 m2 for subjects with serum creatinine levels > 1.5 x institutional ULN
      - Hepatic
      - Total bilirubin ≤ 1.5 x ULN
      - Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 3 x ULN or ≤ 5 x ULN for subjects with known liver metastases
      - Metabolic
      - Glycated hemoglobin (HbA1c) ≤ 8% (≤ 64 mmol/mol)

10. If a subject is currently receiving bisphosphonates or any other drug for treatment of osteoporosis, treatment-induced bone loss and metastases to bone, the subject must have received the bisphosphonates for at least four weeks prior to the first dose of study treatment.

    - Initiation of bisphosphonates or similar agents during the study may be allowed provided the subject completes the first cycle of treatment without any dose limiting toxicity (DLT) and the Investigator rules out tumor progression.

11. Male or female subjects of child-producing potential must agree to use adequate contraception, including double-barrier contraceptive measures, oral contraception, or avoidance of intercourse during the study and for 90 days after the last dose of study treatment.

12. Women of childbearing potential must have a negative serum pregnancy test during Screening Period and within 48 hours of the first dose of study treatment. "Women of childbearing potential" is defined as sexually mature women who have not undergone a hysterectomy or who have not been naturally postmenopausal for at least 12 consecutive months prior to the first dose of study treatment

3.2 Exclusion Criteria

1. Anti-cancer therapy, such as chemotherapy, immunotherapy, hormonal therapy, targeted therapy, or investigational agents within five half-lives or four weeks, whichever is shorter, prior to administration of the first dose of study treatment

- To be eligible for study treatment, toxicity from prior treatment(s) must recover to Grade ≤ 1, except for alopecia
- Concurrent systemic high-dose corticosteroids (in dosing exceeding 10 mg QD of prednisone equivalent) when used intermittently in an antiemetic regimen, for central nervous system (CNS) metastases management, or as a part of the premedication regimen are allowed

2. Radiation therapy within four weeks, or palliative radiation therapy within two weeks, prior to administration of the first dose of study treatment
    - To be eligible for study treatment, radiation therapy-related toxicity must recover to Grade ≤ 1 prior to administration of the first dose of study treatment
    - Concurrent palliative radiotherapy for local pain-control or prevention of fracture (for known bone metastases) may be allowed provided the subject completes the first cycle of treatment, does not meet criteria of progressive disease, and treated lesions will not be included in the target/non-target lesion assessment.
3. Major surgical procedure within four weeks prior to administration of the first dose of study treatment
    - To be eligible for the study treatment, all surgical wounds must be fully healed, and any surgery-related adverse events must recover to Grade ≤ 1.
4. Unable or unwilling to swallow the complete daily dose of ARQ 751
5. Previous treatment with
    - AKT inhibitors (e.g., ARQ 092, MK-2206, GSK2141795, AZD5363; prior treatment with PI3K or mTOR inhibitor are allowed)
    - Prior taxane therapy for the advanced, metastatic disease (for subjects considered for Arm B, ARQ 751+paclitaxel, only)
6. Known prior allergic reaction to or severe intolerance of paclitaxel or fulvestrant. Intolerance is defined as a serious adverse event, a grade 3 or 4 AE per CTCAE v.4.03, or permanent treatment discontinuation
7. History of Type 1 diabetes mellitus or Type 2 diabetes mellitus requiring regular medication (other than oral hypoglycemic agents) or fasting glucose ≥ 160 mg/dL at Screening visit.
8. Significant gastrointestinal disorder(s) that could, in the opinion of the Investigator, interfere with the absorption, metabolism, or excretion of ARQ 751 (e.g., inflammatory bowel disease, Crohn's disease, ulcerative colitis, extensive gastric resection)
9. Known untreated or active CNS metastases and/or carcinomatous meningitis
    - To be eligible for the study treatment, subjects must have stable disease ≥ 1 month, confirmed by magnetic resonance imaging (MRI) or computed tomography (CT) scan, and have CNS metastases well controlled by low-dose steroids, anti-epileptics, or other symptom-relieving medications.

10. History of myocardial infarction (MI) or New York Heart Association (NYHA) Class II-IV congestive heart failure within 6 months of the administration of the first dose of study treatment (MI occurring > 6 months of the first dose of study treatment will be permitted); Grade 2 or worse conduction defect (e.g., right or left bundle branch block).
11. A heart rate corrected QT (QTc) interval ≥ 480 msec, using the Fridericia's formula QTcF
12. Left ventricular ejection fraction (LVEF) <50% as determined by Multiple Gated Acquisition (MUGA) scan or echocardiogram (ECHO) in subjects who received prior treatment with anthracyclines
13. Concurrent severe and/or uncontrolled illness not related to cancer and/or social situation that would limit compliance with study requirements, including but not limited to:
    - Psychiatric illness, substance abuse
    - Ongoing or active known infection, including human immunodeficiency virus (HIV) infection, hepatitis B or C virus
    - Significant pulmonary dysfunction, including pneumonitis, interstitial lung disease (ILD), idiopathic pulmonary fibrosis, cystic fibrosis, severe COPD
    - Peripheral neuropathy grade ≥2 (Arm B, ARQ 751+paclitaxel)
    - Bleeding diathesis, thrombocytopenia or coagulation disorders (Arm C, ARQ 751+fulvestrant)
    - Thrombotic/coagulation disorders within 6 months prior to the first dose of study treatment unless stable on anticoagulation for > 3 months
14. Active or history of other malignancy other than the current cancer within 2 years of the first dose of study treatment, with the exception of carcinoma in-situ of the cervix, basal cell carcinoma, and superficial bladder tumors curatively treated
15. Blood transfusion or administration of growth factors within 5 days prior to a blood draw being used to confirm eligibility
16. Pregnant or breastfeeding

4 STUDY VISITS

Before the start of any study required procedures, the Investigator or designee must obtain a signed written informed consent form (ICF) for the study from each prospective study subject or his/her legal representative.

For Part 1, all ongoing subjects enrolled in the single dose escalation cohort will continue treatment per Schedule of Events (see Annex 1). All ongoing subjects enrolled in the single agent dose expansion cohort (Arm A) will follow the revised visit schedule outlined below once reconsented.

For Part 2, study visits will consist of a Screening Visit, during which the subject's eligibility for the study and baseline disease state will be evaluated; on-treatment (weekly, bi-weekly or monthly) visits depending on the cycle and treatment Arm the subject is enrolled, the End of Treatment Visit, and a 30-Day Safety Follow-up.

Following the Screening Visit and a determination by the Investigator that the subject meets all eligibility criteria, the subject will be considered entered into the study.

4.1 Informed Consent

A sample ICF with core information will be provided to each study site. Prior to study initiation at a given study site, each site/Investigator must obtain a written approval/favorable opinion from its respective institutional review board (IRB)/ independent ethics committee (IEC) for the ICF and any other written information to be provided to subjects. All ICFs must be compliant with ICH Good Clinical Practice (GCP) guidelines and local regulations and must be approved by the Sponsor or designee prior to submission to the IRB/IEC. The written approval of the IRB/IEC, together with the approved subject information/ICF, must be maintained in the study master files.

Written informed consent must be obtained from a prospective subject before any study-specific procedures are performed on that individual. Subjects who agree to participate in the study will sign the most recently approved ICF and will be provided with a copy of the fully executed document. The original, executed ICF will be maintained in the respective subject's clinical study file. The ICF can be signed greater than 14 days prior to dosing, and does not need to be re-signed prior to dosing unless specific reasons apply (e.g., a new consent version has been issued and approved by the IRB/IEC).

4.2 Study Visits

4.2.1 Arm A (ARQ 751 as a single agent)

Screening	**Cycle 1**		**Cycle 2+**	**EOT**	**30-day Safety Follow up**
(-14 to -1 days)	**Day 1** (-1 to 0 days)	**Day 15** (±3 days)	**Day 1** (±3 days)	(within 7 days of decision to permanently discontinue)	(30 days+ after last dose)
☐ Signed ICF ☐ Medical history ☐ Physical exam, incl. skin ☐ Vital signs (temperature, blood pressure, respiration rate, pulse) & height, weight ☐ ECOG PS ☐ Fasting clinical blood tests ☐ Tumor markers[5] ☐ Urinalysis ☐ 12-lead ECG[2] ☐ Record concomitant medications (conmeds) ☐ Tumor measurement and staging ☐ Echocardiogram or MUGA scan to assess LVEF[3] ☐ Bone scan ☐ Serum pregnancy test ☐ Collect redacted copy of tumor gene sequencing report	☐ Physical exam, incl. skin ☐ Vital signs (temperature, blood pressure, respiration rate, pulse) & weight ☐ ECOG PS ☐ Fasting clinical blood tests[1] ☐ Tumor markers[5] ☐ Blood samples for PK[4] ☐ Triplicate 12-lead ECG[2] ☐ Administer ARQ 751 ☐ Dispense ARQ 751 ☐ Record conmeds ☐ Assess AEs ☐ Blood sample for CYP2D6 ☐ Blood sample for ctDNA	☐ Physical exam, incl. skin ☐ Vital signs (temperature, blood pressure, respiration rate, pulse) ☐ ECOG PS ☐ Fasting clinical blood tests[1] ☐ Tumor markers[5] ☐ Blood samples for PK[4] ☐ Triplicate 12-lead ECG[2] ☐ Administer ARQ 751 ☐ Record conmeds ☐ Assess AEs	☐ Physical exam, incl. skin ☐ Vital signs (temperature, blood pressure, respiration rate, pulse) & weight ☐ ECOG PS ☐ Fasting clinical blood tests[1] ☐ Tumor markers[5] ☐ Blood samples for PK[4] (ONLY at Cycles 2, 3 and 4) ☐ Triplicate 12-lead ECG[2] (ONLY at Cycles 2, 3 and 4 and if clinically indicated) ☐ Radiographic tumor assessment (per Section 5.8) ☐ Administer ARQ 751 ☐ Dispense ARQ 751 ☐ Record conmeds ☐ Assess AEs	☐ Physical exam, incl. skin ☐ Vital signs (temperature, blood pressure, respiration rate, pulse) & weight ☐ ECOG PS ☐ Fasting clinical blood tests [1] ☐ Tumor markers[5] ☐ Urinalysis ☐ Serum pregnancy test ☐ 12-lead ECG[2] ☐ Radiographic tumor assessment (if PD not seen on prior scan) ☐ Record conmeds ☐ Assess AEs	☐ Record conmeds ☐ Record AEs

1 Fasting clinical blood tests (see Section 5.4) may be obtained within 24 hours of the visit (except for timepoints where insulin and glucose samples that are collected serially– see Appendix 3)
2 Collect redacted copies of all ECG tracings. See Appendix 3 for details on ECG timepoints.
3 Only for subjects who received prior therapy with anthracyclines 4 See Appendix 3 for details on PK timepoints.
5 Tumor markers (if applicable) - at Screening and frequency of testing while on treatment as per FDA/NCCN guidelines, or institutional standards

4.2.2 Arm B (ARQ 751+paclitaxel)

Screening	**Cycle 1**		**Cycle 2+**	**Cycle 2+**	**EOT**	**30-day Safety Follow up**
(-14 to -1 days)	**Day 1** (-1 to 0 days)	**Day 8 and Day 15** (±2 days)	**Day 1** (±2 days)	**Day 8 and Day 15** (±2 days)	(within 7 days of decision to permanently discontinue)	(30 days+ after last dose)
☐ Signed ICF ☐ Medical history ☐ Physical exam, incl. skin ☐ Vital signs (temperature, blood pressure, respiration rate, pulse) & height, weight ☐ ECOG PS ☐ Fasting clinical blood tests ☐ Tumor markers[5] ☐ Urinalysis ☐ 12-lead ECG[2] ☐ Record concomitant medications (conmeds) ☐ Tumor measurement and staging ☐ Echocardiogram or MUGA scan to assess LVEF[3] ☐ Bone scan ☐ Serum pregnancy test ☐ Collect redacted copy of tumor gene sequencing report	☐ Physical exam, incl. skin ☐ Vital signs (temperature, blood pressure, respiration rate, pulse) & weight ☐ ECOG PS ☐ Fasting clinical blood tests[1] ☐ Tumor markers[5] ☐ Blood samples for PK[4] ☐ Triplicate 12-lead ECG[2] ☐ Administer ARQ 751 ☐ Administer paclitaxel ☐ Dispense ARQ 751 ☐ Record conmeds ☐ Assess AEs ☐ Blood sample for CYP2D6 ☐ Blood sample for ctDNA	☐ Physical exam, incl. skin ☐ Vital signs (temperature, blood pressure, respiration rate, a pulse) & weight ☐ ECOG PS ☐ Fasting clinical blood tests[1] ☐ Tumor markers[5] ☐ Blood samples for PK[4] (Day 15 ONLY) ☐ Triplicate 12-lead ECG[2] (Day 15 ONLY) ☐ Administer ARQ 751 ☐ Administer paclitaxel ☐ Record conmeds ☐ Assess AEs	☐ Physical exam, incl. skin ☐ Vital signs (temperature, blood pressure, respiration rate, a pulse) & weight ☐ ECOG PS ☐ Fasting clinical blood tests[1] ☐ Tumor markers[5] ☐ Blood samples for PK[4] (ONLY at Cycles 2, 3 and 4) ☐ Triplicate 12-lead ECG[2] (ONLY at Cycles 2, 3 and 4 and if clinically indicated) ☐ Radiographic tumor assessment (per Section 5.8) ☐ Administer ARQ 751 ☐ Administer paclitaxel ☐ Dispense ARQ 751 ☐ Record conmeds ☐ Assess AEs	☐ Physical exam, incl. skin ☐ Vital signs (temperature, blood pressure, respiration rate, pulse) & weight ☐ ECOG PS ☐ Fasting clinical blood tests[1] ☐ Tumor markers[5] ☐ Administer ARQ 751 ☐ Administer paclitaxel ☐ Record conmeds ☐ Assess AEs	☐ Physical exam, incl. skin ☐ Vital signs (temperature, blood pressure, respiration rate, pulse) & weight ☐ ECOG PS ☐ Fasting clinical blood tests[1] ☐ Tumor markers[5] ☐ Urinalysis ☐ Serum pregnancy test ☐ 12-lead ECG[2] ☐ Radiographic tumor assessment (if PD not seen on prior scan) ☐ Record conmeds ☐ Assess AEs	☐ Record conmeds ☐ Record AEs

1 Fasting clinical blood tests (see Section 5.4) may be obtained within 24 hours of the visit (except for timepoints where insulin and glucose samples that are collected serially– see Appendix 3)
2 Collect redacted copies of all ECG tracings. See Appendix 3 for details on ECG timepoints.
3 Only for subjects who received prior therapy with anthracyclines
4 See Appendix 3 for details on PK timepoints
5 Tumor markers (if applicable) - at Screening and frequency of testing while on treatment as per FDA/NCCN guidelines, or institutional standards

4.2.3 Arm C (ARQ 751+fulvestrant)

Screening	**Cycle 1**		**Cycle 2+**	**Cycle 2 (only)**	**EOT**	**30-day Safety Follow up**
(-14 to -1 days)	**Day 1** (-1 to 0 days)	**Day 15** (±3 days)	**Day 1** (±3 days)	**Day 15** (±3 days)	(within 7 days of decision to permanently discontinue)	(30 days+ after last dose)
☐ Signed ICF ☐ Medical history ☐ Physical exam, incl. skin ☐ Vital signs (temperature, blood pressure, respiration rate, pulse) & height, weight ☐ ECOG PS ☐ Fasting clinical blood tests ☐ Tumor markers[5] ☐ Urinalysis ☐ 12-lead ECG[2] ☐ Record concomitant medications (conmeds) ☐ Tumor measurement and staging ☐ Echocardiogram or MUGA scan to assess LVEF[3] ☐ Bone scan ☐ Serum pregnancy test ☐ Collect redacted copy of tumor gene sequencing report	☐ Physical exam, incl. skin ☐ Vital signs (temperature, blood pressure, respiration rate, pulse) & weight ☐ ECOG PS ☐ Fasting clinical blood tests[1] ☐ Tumor markers[5] ☐ Blood samples for PK[4] ☐ Triplicate 12-lead ECG[2] ☐ Administer ARQ 751 ☐ Administer fulvestrant ☐ Dispense ARQ 751 ☐ Record conmeds ☐ Assess AEs ☐ Blood sample for CYP2D6 ☐ Blood sample for ctDNA	☐ Physical exam, incl. skin ☐ Vital signs (temperature, blood pressure, respiration rate, pulse) ☐ ECOG PS ☐ Fasting clinical blood tests[1] ☐ Tumor markers[5] ☐ Blood samples for PK[4] ☐ Triplicate 12-lead ECG[2] ☐ Administer ARQ 751 ☐ Administer fulvestrant ☐ Record conmeds ☐ Assess AEs	☐ Physical exam, incl. skin ☐ Vital signs (temperature, blood pressure, respiration rate, pulse) & weight ☐ ECOG PS ☐ Fasting clinical blood tests[1] ☐ Tumor markers[5] ☐ Blood samples for PK[4] (ONLY at Cycles 2, 3 and 4) ☐ Triplicate 12-lead ECG[2] (ONLY at Cycles 2, 3 and 4 and if clinically indicated) ☐ Radiographic tumor assessment (per Section 5.8 ☐ Administer ARQ 751 ☐ Administer fulvestrant ☐ Dispense ARQ 751 ☐ Record conmeds ☐ Assess AEs	☐ Physical exam, incl. skin ☐ Vital signs (temperature, blood pressure, respiration rate, pulse) ☐ ECOG PS ☐ Fasting clinical blood tests[1] ☐ Tumor markers[5] ☐ Administer ARQ 751 ☐ Record conmeds ☐ Assess AEs	☐ Physical exam, incl. skin ☐ Vital signs (temperature, blood pressure, respiration rate, pulse) & weight ☐ ECOG PS ☐ Fasting clinical blood tests[1] ☐ Tumor markers[5] ☐ Urinalysis ☐ Serum pregnancy test ☐ 12-lead ECG[2] ☐ Radiographic tumor assessment (if PD not seen on prior scan) ☐ Record conmeds ☐ Assess AEs	☐ Record conmeds ☐ Record AEs

1 Fasting clinical blood tests (see Section 5.4) may be obtained within 24 hours of the visit (except for timepoints where insulin and glucose samples that are collected serially– see Appendix 3)
2 Collect redacted copies of all ECG tracings. See Appendix 3 for details on ECG timepoints.
3 Only for subjects who received prior therapy with anthracyclines
4 See Appendix 3 for details on PK timepoints
5 Tumor markers (if applicable) - at Screening and frequency of testing while on treatment as per FDA/NCCN guidelines, or institutional standards

4.3 Subject Discontinuation

Subjects will be removed from the **treatment** or the **study** at any time if they meet any of the following criteria:

4.3.1 Subject Discontinuation from Treatment

- Documented radiographic progression of disease
  - Subjects may remain on study treatment if, in the opinion of the Investigator and with the agreement of the Medical Monitor, they continue to derive benefit from the study drug (ARQ 751)
- Documented clinical progression of disease
- Clinically unacceptable toxicities despite optimal treatment or dose reduction
- Withdrawal of consent
- Noncompliance with any part of the study, as assessed by the Investigator or Medical Monitor
- Investigator's decision (with the agreement with the Sponsor/Medical Monitor or designee)
- Death

4.3.2 Subject Discontinuation from the Study

- Safety follow-up visit is completed per the protocol and drug-related AEs have resolved to baseline, NCI CTCAE Grade 1, stabilized, or are deemed irreversible
- Withdrawal of consent
- Lost to follow-up
- Death

4.4 Study Discontinuation

The Sponsor reserves the right to temporarily or permanently discontinue the study at any site and at any time. Reasons for study discontinuation may include, but are not limited to, the following:

- Safety concerns
- Poor enrollment
- Non-compliance with the protocol, GCP guidelines, or other regulatory requirements by the Investigator(s)
- Request to discontinue the trial by a regulatory or health authority
- Discontinuation of product development
- Manufacturing difficulties/concerns

The Sponsor and/or designee will promptly inform all Investigators and the appropriate regulatory authorities if the study is suspended or terminated for safety reasons. In the case of such termination, the Investigator will notify the IRB or IEC, as appropriate.

If any subject in Arms B or C permanently discontinues ARQ 751, they will at that time discontinue from the study. If any subject in Arms B or C permanently discontinues the combination therapy (paclitaxel or fulvestrant) the subject will be allowed continue in the study taking ARQ 751 until one of the discontinuation criteria is met.

5 STUDY PROCEDURES

Detailed information on schedule of assessments, and instructions on collection and shipment of study-related samples and laboratory/testing reports can be found in section 4.2 (Study Visits) and Appendices (1 and 3).

All collected biological samples, clinical reports and CT/MRI scans will be labeled by personnel from the institution with subjects' study ID and their identity will not be made known to employees from the Sponsor, additional collaborators, or other Investigators. Samples will only be used for the purposes of the protocol and will only be used by the Sponsor's personnel or by an external laboratory chosen by the Sponsor to outsource the analysis according to internal guidelines. Samples will be kept until all protocol-related analyses are completed, for a period not exceeding 10 years or as required by local law.

5.1 Medical History

Medical history will include, but is not limited to the following:

- Demography: date of birth, sex, race, ethnic origin
- Clinically significant prior diagnoses, surgeries, and concomitant medications
    - Medications used within 30 days prior to the first dose of ARQ 751 should be reported
- Current cancer history: diagnosis, tumor stage at time of diagnosis and study enrolment; tumor markers; previous anti-cancer therap(ies) for advanced disease, including dates, duration and outcome of treatment; previous radiation therapy, including anatomic site, dose and dates of treatment; previous neoadjuvant, adjuvant and maintenance therap(ies), including dates, duration and outcome of treatment; previous cancer-related surgical procedures, including type of the procedures and dates.

5.2 Physical Examination

Complete physical examination of the major body systems, including skin, height, weight, vital signs (to include blood pressure, heart rate, respiratory rate, temperature [oral, axillary or tympanic]), and ECOG PS (see Appendix 2).

5.3 12-lead ECG and Echocardiogram/MUGA Scan

An echocardiogram/MUGA should be conducted at the screening visit ONLY for Subjects who received prior therapy with anthracyclines. 12-lead ECGs (either single or triplicate) should be conducted at the protocol defined timepoints (see Appendix 3). Additional ECG(s) and echocardiogram/MUGA scan(s) may be conducted if clinically indicated. Copies of ECG tracings should be provided to the Sponsor.

5.4 Clinical Laboratory Tests

Safety laboratory determinations will include hematology, blood chemistry, and urinalyses. All laboratory tests required during the study must be obtained at the local laboratory at the investigational site. Chemistry samples should be taken in a fasting state (fasting for at least

8 hours) and prior to administration of study treatment (except for timepoints where insulin and glucose samples that are collected serially, see Appendix 3). If, in error, subject has eaten ahead of testing, this should be documented as a fed rather than as a fasting sample in the electronic case report form (eCRF) and on the requisition form.

- Hematology: complete blood count (CBC) including hemoglobin, hematocrit, white blood cell count with 5-part differential, red blood cell, and platelet count
- Coagulation tests: (at Screening and End of Treatment visits, and if clinically indicated): prothrombin time (PT), INR, and partial prothrombin time (PTT)
- Blood chemistry: HbA1c (at Screening visit only), bicarbonate, blood urea nitrogen (BUN), calcium, chloride, creatinine, glucose, insulin, magnesium, potassium, total protein, sodium, uric acid
- Liver function tests: albumin, ALT, AST, alkaline phosphatase (ALP), total and direct bilirubin, lactate dehydrogenase (LDH)
- Lipids: cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL), and triglycerides
- Tumor markers (if applicable) to monitor disease status (at screening and during the treatment). Frequency of testing will be as per the FDA/NCCN guidelines, or institutional standard of care
- Routine urinalysis (at Screening and End of Treatment visits, and if clinically indicated): dipstick and microscopy (only if clinically indicated or dipstick is not done)
- Serum pregnancy test (at Screening and End of Treatment visits only): for female subjects of childbearing potential

Note: Fasting clinical blood tests may be obtained within 24 hours of the visit (except for timepoints where insulin and glucose samples that are collected serially, see Appendix 3)

5.5 Pharmacokinetic/Pharmacodynamic Assessments

PK variables measured will include C_{max}, AUC, and $t_{1/2}$.

For subjects enrolled in the single dose escalation cohorts and subjects enrolled in single agent dose expansion (Arm A) under Amendment 5, blood samples for PK analysis were collected during Cycle 1 Day 1 (24-hour full assessment, including the 24-hour collection on the morning of Day 2), Day 8, Day 15, Day 22 (Day 21 for subjects receiving ARQ 751 QOD) (24-hour full assessment, including the 24 hour collection on the morning of Day 23 [Day 22 for subjects receiving ARQ 751 QOD]) and on Cycle 2 Day 1 and Day 15.

For subjects in Arm A (enrolled and/or reconsented under Amendments 6 or later) and subjects in Arms B and C, blood samples for PK analysis will be collected according to protocol defined timepoints (see Appendix 3).

The blood sample collection date and time, and the time of dosing of ARQ 751, paclitaxel and fulvestrant administration on the days of PK must be recorded on the eCRF.

Additional unscheduled blood sample(s) for PK may be collected on any study day(s) upon agreement between the Investigator and the Sponsor.

Detailed instructions for collection and shipment of plasma PK samples will be provided in the laboratory manual.

A blood sample to determine CYP2D6 genotype will be collected. Patient CYP2D6 status will be determined and the effect on PK exposure will be evaluated.

A blood sample to determine mutation status by liquid biopsy (ctDNA) will be collected.

Detailed instructions for collection and shipment of biological samples is provided in the laboratory manual.

5.6 Home Blood Glucose Monitoring

Subjects should perform a home fasting blood glucose test at least once per day (before breakfast) for the first four weeks except for days where the subject has glucose tested at the site. If the fasting glucose level is > 160 mg/dL but ≤ 250 mg/dL, subjects are to test again before dinner. If the fasting glucose level is > 250 mg/dL, subjects are to call their Investigator. After the first four weeks of treatment, the Investigator will determine if a subject should continue home glucose testing and the testing frequency.

5.7 Tumor Evaluation

Standard imaging studies (CT scan or MRI) should be performed according to institutional procedures and/or standard of care. Tumor response will be evaluated using the guidelines for Response Evaluation Criteria in Solid Tumors (RECIST) v. 1.1 outlined in Appendix 5.

For all subjects, a bone scan should be performed during Screening period and if clinically indicated thereafter.

Imaging studies can be used as the baseline assessment if they were performed within four weeks (28 days) prior to the first dose of ARQ 751.

While on study, tumor evaluations will be performed every 2 cycles during first 12 cycles. For subjects who do not experience disease progression and continue to benefit from the treatment after 12 cycles, tumor evaluation may be performed every 3 cycles upon agreement between the Investigator and the Medical Monitor. Tumor evaluation will also be performed at the End of Treatment visit unless the prior scan showed radiographic disease progression.

6 TREATMENT

ARQ 751, Paclitaxel and Fulvestrant Administration

The Sponsor will provide ARQ 751 required for this study. Paclitaxel and fulvestrant will be obtained by the subject from commercial sources. For administrative reasons, the treatment period is divided into 4-week cycles (28 days).

Subjects enrolled in Arm A will receive ARQ 751 at 75 mg QD, continuously.

In Arms B and C, dose determination will begin with cohort 1 (50 mg ARQ 751) and will be done as follows:

Cohort	**ARQ 751 (orally, PO)**	**Paclitaxel (Arm B)**	**Fulvestrant (Arm C)**
-1	25 mg QD	80 mg/m^2 (IV) Days 1,8,15 followed by a week of rest	500 mg (IM) Days 1 &15 of Cycle 1, and Day 1 of all subsequent cycles
1	50 mg QD		
2	75 mg QD		
Expansion	RP2D		

ARQ 751 will be administered by mouth under fasted condition (one hour prior to or two hours after the meal). The dose of ARQ 751 to be administered depends on the dose level cohort to which the subject is enrolled. ARQ 751 should be taken at approximately the same time each day, especially on PK sampling days. On non-PK sampling days, ARQ should be taken within 4-6 hours of the scheduled dosing time.

It is expected that most subjects will receive ARQ 751 as a single agent or in combination with paclitaxel or fulvestrant for four to 24 weeks.

Paclitaxel and fulvestrant administration and administration of premedication therapy if required should follow the FDA approved regimens, NCCN guidelines, or institutional SOC.

6.1 ARQ 751

The investigational drug ARQ 751 is supplied as capsules for oral administration. ARQ 751 is packaged in strength of 25 mg and is supplied to the pharmacy at the clinical site. ARQ 751 is labeled as an investigational agent, limited by federal and other applicable laws. The appropriate quantity of capsules should be dispensed to the subject according to the cohort dosing level and schedule of administration the subject is enrolled to. ARQ 751 should be stored according to the instructions provided on the drug label.

6.2 Investigational Product Accountability

The recipient will acknowledge receipt of ARQ 751 by indicating shipment content and condition. Damaged supplies will be replaced. Until dispensed to the subjects, the study drug will be stored in a secure area, accessible to authorized personnel only.

Drug accountability records will be maintained for ARQ 751. These records should record quantities of study drug received and quantities dispensed to subjects, including lot number, date received and dispensed, subject identifier number, subject initials, protocol number, dose, quantity returned, balance remaining, and the initials of the person dispensing the drug. Accurate records of all study drug dispensed from and returned to the study site are to be maintained. The study site must supply a copy of their drug destruction policy to the Sponsor before authorization for destruction will be granted. Product accountability will be monitored throughout the study. Upon completion or termination of the study and after inventory verification by an ArQule monitor or designated representative, all unopened, undispensed investigational product is to be returned to ArQule in the original containers unless approval has been granted to destroy unused investigational product at the site or local destruction facility.

6.3 Storage and Handling

At a study site, ARQ 751 should be stored at controlled room temperature (20°C-25°C; 68°F-77°F) according to the storage instructions provided on the label, until dispensed to the subject.

At a study site, storage and handling of paclitaxel and fulvestrant should follow the FDA approved label or institutional pharmacy guidelines.

6.4 Missed or Vomited Dose

A missed dose may be taken within a 4-6 hour window of the regular, scheduled dose. A vomited dose should not be replaced. The subject should be instructed to take the next scheduled dose at the regularly scheduled time. If the subject vomited the very first dose of study drug (ARQ 751), the subject may be re-challenged at the discretion of the Investigator.

6.5 Dose Modifications

In general, once the dose of ARQ 751 has been modified for a subject, all subsequent doses should be administered to that subject at the modified dose level and dose administration schedule.

When a ARQ 751-related toxicity (any toxicity considered to be related, probably related, or possibly related to ARQ 751) is observed, dose delays and/or reductions in ARQ 751 administration are allowed. If dose reduction is indicated, the subject should be assigned to the previous (lower) cohort dose and schedule (dose re-escalation is not permitted) or to a dose and schedule agreed upon by the Sponsor and the Investigator. In the event of a dose modification, the dose change(s) must be captured in the electronic data capture (EDC) system.

Once the RP2D ARQ 751 dose in combination with paclitaxel or fulvestrant is determined, intra-subject dose escalation of ARQ 751 may be considered to optimize the treatment in subjects enrolled at lower dose levels.

The dose level for paclitaxel and fulvestrant will stay the same for all cohorts. Paclitaxel and fulvestrant dose modifications or delays should follow the FDA approved label, NCCN guidelines, or institutional standard of practice.

In case of non-ARQ 751-related toxicity and if treatment with paclitaxel or fulvestrant is interrupted, the subject may continue taking ARQ 751 upon agreement between the Investigator and the Sponsor's Medical Monitor. In case of ARQ 751-related toxicity that required ARQ 751-

treatment interruption, the subject may continue treatment with paclitaxel or fulvestrant upon agreement between the Investigator and the Sponsor's Medical Monitor.

Table 1 Dose Delays/Reductions for ARQ 751-Related Toxicity Except Hyperglycemia

Event Grade	Action
Alopecia	Continue current dose level
Grade 1 or 2	Continue current dose level, however, at the discretion of the Investigator, dose interruption/modification may be implemented (e.g., rash). If recovery occurs after more than 21 days on drug hold, permanently discontinue ARQ 751.
Grade 3-4 (except Grade 3 nausea, vomiting, or diarrhea lasting less than 24 hours)	Withhold ARQ 751 until recovery to Grade 1 or baseline. If recovery occurs within 21 days, restart ARQ 751 at the dose and schedule of the previous cohort for subsequent doses, unless further dose reduction is required. If recovery occurs after more than 21 days on drug hold, permanently discontinue ARQ 751.
Grade 3 nausea, vomiting, or diarrhea lasting less than 24 hours	Withhold ARQ 751 until recovery to Grade 1 or baseline. If recovery occurs within 24 hours, restart ARQ 751 at the current dose level. If recovery occurs after 24 hours and within 21 days, restart ARQ 751 at the dose and schedule of the previous cohort for subsequent doses, unless further dose reduction is required. If recovery occurs after more than 21 days on drug hold, permanently discontinue ARQ 751.

Table 2 Dose Modification for ARQ 751-related Hyperglycemia and Suggested Clinical Treatment and Management of Hyperglycemia

Event Grade	ARQ 751 Dose Modification	Suggested Clinical Treatment and Management of Hyperglycemia
Grade 1	Continue treatment with current dose level and schedule	Start once per day home glucose monitoring (alternate between before breakfast and before dinner; preferably fasting) No treatment needed
Grade 2	Continue treatment with the current dose level and schedule	Start home glucose monitoring twice per day (before breakfast and dinner; preferably fasting). Treat hyperglycemia following the algorithm in Section A of Table 3 or per the Investigator's discretion.
Grade 3 (Asymptomatic)	Continue treatment with current dose level and schedule	Start home glucose monitoring twice per day (before breakfast and dinner; preferably fasting) Treat hyperglycemia following the algorithm in Section B of Table 3 or per the Investigator's discretion.
Grade 3 (Symptomatic) or Grade 4 (Asymptomatic)	If improved (glucose < 250 mg/dL) within one week, continue ARQ 751 treatment at the current dose level until dose reduction is required. If not improved (glucose ≥ 250 mg/dL) within one week, withhold study drug and restart ARQ 751 treatment at the next lower dose level when glucose is <250 mg/dL and there are no symptoms.	Start home glucose monitoring three times per day and before every bed time; preferably fasting Treat hyperglycemia following the algorithm in Section C of Table 3 or per the Investigator's discretion.
Grade 4 (Symptomatic)	Withhold study drug. If improved (glucose < 250 mg/dL) within 7 days, restart ARQ 751 at the next lower dose level until further dose reduction is required. If not improved (glucose ≥ 250 mg/dL) within 7 days, discontinue study treatment permanently	Refer to an endocrinology or diabetes treating specialist

Source: Busaidy NL, Farooki A, Dowlati A, et al. Management of metabolic effects associated with anticancer agent targeting the PI3K-Akt-mTOR pathway. *J Clin Oncol*. 2012;30(23):2919-28.

Table 3 Suggested Clinical Treatment and Management of Hyperglycemia

A

Management for Grade 2 hyperglycemia
(161-250 mg/dL)
Check home blood glucoses AC BID

Lifestyle change (TLC) | Metformin*

↓

After 2 weeks: If the fasting glucose is Grade 2 or random glucose is > 200 mg/dL

Continue metformin* | Add sulfonylurea and titrate

↓

After an additional 1 week: If fasting glucose is > 160 mg/dL or random glucose is > 200 mg/dL

Continue two oral agents | Add basal insulin

↓

Stop oral agents. Begin basal bolus insulin four injections/day.

B

Management for asymptomatic Grade 3 hyperglycemia
(250-500 mg/dL)
Begin metformin* and sulfonylurea

Check home blood glucose AC BID | Rapidly titrate oral agents

↓

After 1 week: If fasting glucose is > 160 mg/dL or random glucose is > 200 mg/dL

Add basal insulin to oral agents | Titrate basal insulin to fasting glucose

↓

After an additional 1 week: If fasting glucose is > 160 mg/dL or random glucose is > 200 mg/dL

Stop oral agents; add pre-meal insulin | Check glucose AC TID and QHS

C

Management for symptomatic Grade 3 hyperglycemia (250-500 mg/dL)
or Grade 4 hyperglycemia (> 500 mg/dL)
Consider IVF and/or admit if hypovolemic signs/symptoms

Diabetes consultation | Four-injection basal bolus insulin regimen

↓

Check home glucose AC TID and QHS
After 1 week: If fasting or random glucose > 250 mg/dL

DLT and hold ARQ 751 | Restart when glucose < 250 mg/dL and no symptoms

Management of (A) Grade 2 hyperglycemia (161 to 250 mg/dL), (B) asymptomatic Grade 3 hyperglycemia (250 to 500 mg/dL), (C) symptomatic Grade 3 hyperglycemia (250 to 500 mg/dL) or asymptomatic Grade 4 hyperglycemia (> 500 mg/dL).
Abbreviations: AC: before meals, DLT: dose-limiting toxicity, IVF: intravenous fluids, QHS: before every bedtime, TID: three times daily
(*) Do not use metformin if creatine is 1.3 mg/dL (women) or 1.4 mg/dL (men) or if any state of decreased tissue perfusion or hemodynamic instability is present (e.g., heart failure); hold metformin for CT scans; GI symptoms may occur with initiation but usually subside after the first week.
Source: Busaidy NL, Farooki A, Dowlati A, et al. Management of metabolic effects associated with anticancer agent targeting the PI3K-Akt-mTOR pathway. *J Clin Oncol*. 2012;30(23):2919-28.

6.6 Treatment Compliance with ARQ 751

A subject is considered compliant with the study protocol when study medication is administered at a compliance level of ≥ 80%. In order to evaluate the safety of ARQ 751, replacement of non-compliant subjects will be allowed during the first 28 days of dosing.

Compliance will be calculated using the following equation:

(Number of capsules actually ingested /number of capsules that should have been ingested per dose level) x 100 = % compliance

6.7 Blinding

This is an open-label study. Neither the subject nor the Investigator or site staff will be blinded to the treatment administered.

6.8 Concomitant Medication

6.8.1 Permitted Treatment

All information regarding concomitant treatments (medications, blood transfusions, or procedures) must be recorded on the subject's eCRF (including the name of the medication or procedure and duration of treatment). Palliative and supportive care for disease-related symptoms will be offered to all subjects in this study.

The following treatments are allowed:

- Standard therapies for concurrent medical conditions
- Erythropoietin Stimulating Agents (ESA): Please follow American Society of Clinical Oncology (ASCO) or MEDICARE guidelines for the use of ESA in patients diagnosed with cancer, drug labels, and the Food and Drug Administration (FDA)
- Hematopoietic growth factors including filgrastim (Neupogen®) or other colony-stimulating factors. ASCO guidelines should be followed for the use of WBC growth factors
- Prophylactic and supportive anti-emetics or low-dose corticosteroids may be administered according to standard practice
- Hypoglycemic agents for elevated blood glucose may be administered according to standard practice (administration of insulin is not allowed at baseline but may be administered during the study)
- Bisphosphonates or any other drug for treatment of osteoporosis, treatment-induced bone loss and metastases to bone if started at least four weeks before the first dose of ARQ 751, or upon completion of the first cycle of treatment without any DLT, and if the Investigator rules out tumor progression.
- Palliative radiotherapy for local pain control may be allowed, provided the subject completes the first cycle of treatment, does not meet criteria of progressive disease and treated lesions will not be included in the target/non-target lesion assessment.

6.8.2 Prohibited Treatment

The following treatments are not allowed during the study:

- Any concurrent anticancer therapy including, but not limited to, chemotherapy, radiotherapy (except palliative radiotherapy for local pain control), hormonal therapy, immunotherapy, or locoregional therapy
- Immunosuppressive therapies including continuous high-dose corticosteroids (except when used intermittently in an antiemetic regimen, for CNS metastases management or as a part of the premedication regimen)
- Other investigational agents

6.8.3 Treatment to be Avoided or Used with Caution While on Study

ARQ 751 demonstrated substantial inhibition of CYP2C19 and CYP2D6, and slight metabolism-dependent inhibition of CYP3A4/3A5 enzyme activity. Sensitive substrates for these CYP isoenzymes should be avoided or used with caution during enrollment in the trial.

ARQ 751 was determined to be both a substrate and inhibitor of P-gp, therefore co-administration of ARQ 751 with drugs known to be P-gp substrates with narrow therapeutic index should be avoided or used with caution.

The following treatments should be avoided, if possible, or used with caution during the study:

- CYP2C19 substrates and inducers (see Appendix 4 for details)
- CYP2D6 inhibitors and inducers (see Appendix 4 for details)
- CYP3A4/3A5 inhibitors and inducers (see Appendix 4 for details)
- P-gp substrates, inhibitors, and inducers (see Appendix 4 for details)
- Grapefruit juice

6.9 Potential Benefit and Risks for Study Subjects

Detailed non-clinical and clinical data can be found in the ARQ 751 IB.

Preliminary efficacy data suggest that ARQ 751 may be clinically active in cancer subjects whose tumors harbor *PIK3CA*, *AKT* and *PTEN* mutations. The current protocol amendment seeks to test a number of combination regimens in tumor types with specific molecular characteristics that may identify specific patient population(s) most likely to derive benefit from these therapies.

In animal models, the toxicity profile of orally administered ARQ 751 was characterized principally by findings in the hematopoietic system, GI tract, and kidney, some of which were secondary to reduced food consumption, weight loss, and/or dehydration. Also, based on nonclinical data, it has been suggested that ARQ 751 may cause a phototoxic reaction in some subjects exposed to the drug and sunlight. The amount of ARQ 751 that may be required to cause such a reaction is unknown. All subjects should be instructed to avoid the exposure to sunlight, to use sunscreen to protect exposed areas of the body (e.g., forehead, nose, lips, and hands), and to report symptoms that may be associated with phototoxic reaction (e.g., redness, pruritus, swelling, and blister formation).

A number of AKT inhibitors (e.g., MK-2206, GSK690693, ipatasertib) have been tested in clinical trials (Nitulescu, 2016) and class-related, on-target toxicities have been reported. The most commonly reported adverse events that may be associated with this class of kinase inhibitors are hyperglycemia, skin rash, pruritus, nausea and diarrhea. (Tan, 2011) (Yap, 2011) Cardiovascular toxicity has not been observed in non-clinical ARQ 751 studies, however, inhibition of hERG and QT prolongation have been reported for other AKT inhibitors and may be an on-target toxicity specific for this class of kinase inhibitors. (Konopleva, 2014) (Zhang Y., 2006)

In the Part 1, Dose Escalation Cohorts of ARQ 751 administered as a single agent, 33 out of 34 subjects experienced TEAEs, including 24 events assessed as ARQ 751-related. In one subject treatment was interrupted, and in three subjects' treatment was interrupted and subsequently dose was modified due to ARQ 751-related AEs, and one subjects with ARQ 751-related grade 1 hot flush and nausea was discontinued from the study treatment. The most common AEs (≥10%) of all grades were GI disorders (diarrhea, constipation, nausea, vomiting and abdominal pain), fatigue, peripheral edema, urinary tract infection, AST increase, decrease appetite, hyponatremia, headache, cough, dyspnea, and rash. The most common grade 3 AEs (≥10%) were constipation and AST increase, there was only one reported grade 4 AE of thrombocytopenia. The most common ARQ 751-related AEs (≥5%) of all grades included GI disorders (diarrhea, nausea, vomiting and stomatitis), fatigue, mucosal inflammation, hyperglycemia, and rash. The most common grade 3 ARQ 751-related AEs (≥5%) were diarrhea and hyperglycemia, there were no reported grade 4 events. There were 32 SAE reports in 17 subjects, including 8 deaths that were all due to disease progression; in three subjects, the SAEs were reported as ARQ 751-related (hyperglycemia, diarrhea, and diarrhea/vomiting), these events were managed with dose interruption and in one subject also with dose modification.

In summary, all subjects enrolled in the ARQ 751-101 study should be closely monitored for ARQ 751-related AEs such as hyperglycemia, rash, stomatitis/mucositis, and gastrointestinal toxicity (diarrhea, nausea, vomiting).

7 SAFETY ASSESSMENTS

7.1 Definitions

7.1.1 Adverse Event

An AE is defined as any untoward medical occurrence in a subject or clinical investigational subject administered a pharmaceutical product that does not necessarily have a causal relationship with study-drug treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

7.1.2 Adverse Reaction

An adverse reaction is defined as any event for which there is a reasonable possibility that the drug caused the event.

7.1.3 Suspected Adverse Reaction

A suspected adverse reaction is defined as any adverse event for which there is a reasonable possibility that the drug caused the adverse event. Reasonable possibility means that there is evidence to suggest a causal relationship between the drug and the adverse event.

7.1.4 Unexpected Adverse Event or Unexpected Suspected Adverse Reaction

An adverse event or suspected adverse reaction is considered "unexpected" if it is not listed in the Investigator's Brochure or is not listed at the specificity or severity that has been observed. "Unexpected" also refers to adverse events or suspected adverse reactions that are mentioned in the Investigator's Brochure as occurring with the class of drugs or as anticipated from the pharmacological properties of the drug but are not specifically mentioned as occurring with the particular drug under investigation.

7.1.5 Serious Adverse Event or Unexpected Suspected Adverse Reaction

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

- Death
- Life-threatening
- Requires new inpatient hospitalization defined as a hospital admission lasting $\geq$ 24 hours (not including emergency room visit without hospital admission), or prolongation of existing hospitalization
- Persistent or significant disability/incapacity
- Congenital anomaly/birth defect
- Other important medical events that may not result in death, be life-threatening, or require hospitalization, but may be considered serious when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed. An important medical event may be considered a serious adverse event (SAE) based upon appropriate medical judgment.

7.1.6 Suspected Unexpected Serious Adverse Reaction

All adverse events that are determined by the Investigator or by the Sponsor as having a reasonable suspected causal relationship (possibly, probably, or definitely related) to a study drug including placebo and that are both unexpected and serious are considered to be suspected unexpected serious adverse reactions (SUSAR) and are subject to expedited regulatory reporting.

7.1.7 Inpatient Hospitalization

An inpatient hospitalization is a hospital admission that lasts more than 24 hours.

7.1.8 Study Drug-related Adverse Event or Serious Adverse Event

Study drug-related AE or SAE is defined as an AE or SAE that is related, probably related, or possibly related to the treatment with ARQ 751 and/or with one of the combination drugs.

7.1.9 Adverse Events of Potential Risk

Adverse events of potential risk include hyperglycemia, rash, diarrhea, LFTs increase and QTc prolongation. These AEs should be closely monitored and recorded in the EDC system of this study and discussed with the sponsor during the sponsor/investigator calls.

7.1.10 Further Instructions on Reporting Adverse Events or Serious Adverse Events

Wherever possible, a specific disease or syndrome rather than individual associated signs and symptoms should be identified. However, if an observed or reported sign or symptom is not considered a component of a specific disease or syndrome by the Investigator, it should be recorded as a separate AE.

Laboratory data are to be collected as stipulated in this protocol. Clinical syndromes associated with laboratory abnormalities are to be recorded as appropriate (e.g., diabetes mellitus instead of hyperglycemia).

Scheduled hospitalizations or elective surgical procedures will not be considered as AEs or SAEs.

Prolongation of a scheduled hospitalization can be considered an SAE.

Complications associated with scheduled procedures are considered AEs or SAEs.

Progression of disease is considered an efficacy outcome parameter and should not be captured as an AE or a SAE unless its outcome is death.

Exposure *in utero* during clinical studies: Although pregnancy is not technically an AE, all pregnancies while receiving the study treatment or within 30 days after the last dose of the study treatment must be reported as a SAE and must be followed to conclusion to determine their outcome. The Investigator should make every effort to follow the subject until completion of the pregnancy. If the outcome of the pregnancy meets the criteria for immediate classification as a SAE (e.g., post-partum complications, spontaneous abortion, stillbirth, neonatal death, or congenital anomaly, including that in an aborted fetus), the Investigator should follow the procedures for SAE reporting.

Adverse events, including SAEs that occur following the execution of the ICF but prior to dosing will not be recorded as AEs or SAEs, they have to be reported as part of Medical History.

Adverse events including SAEs that occur after subjects receive any anticancer therapy other than the study-defined treatment(s) will not be recorded as AEs or SAEs.

7.2 Responsibilities and Procedures

The responsibility for the safety of an individual subject lies in all cases with the Investigator. This includes the timely review of all safety data obtained during the course of the study.

An Investigator must instruct his/her subjects to report any AE and SAEs they experience.

Investigators capture, evaluate and document all AEs and SAEs occurring during a subject's enrollment in the trial, commencing with the first day of treatment and including the protocol-defined 30-day post-treatment follow-up period (Code of Federal Regulations [CFR] 21 §312.64[b]) as source documents and on designated eCRF pages. These AEs/SAEs must be recorded in the EDC system of this study.

Investigators should assess AEs at each scheduled and non-scheduled visit, by the use of open-ended questioning, physical examination, and review of laboratory results.

Note: It is important to record all AEs and SAEs that result in temporary and permanent discontinuation of study treatment, regardless of severity.

Investigators must report all SAEs, whether or not they are considered study-drug related, to the Sponsor or designee within 24 hours from knowledge of the event (see Section 7.4).

In cases of SUSAR, Investigators are responsible for reporting to their local IRB/IEC. The Sponsor or designee(s) is responsible for notifying regulatory authorities and all relevant Investigators of SUSARs.

7.3 Adverse Event or Serious Adverse Event Assessment Criteria

Adverse events and SAEs are evaluated and graded using NCI CTCAE guidelines, version 4.03.

7.4 Serious Adverse Event Reporting

The Investigators are obligated to immediately report to the Sponsor (or the drug safety designee of the Sponsor), each SAE that occurs during this investigation, within 24 hours from knowledge of the event, whether or not it is considered study-drug related. All new and/or updated information must be forwarded to the Sponsor or designee as soon as it becomes available. If any questions or considerations regarding a SAE arise, the Medical Monitor or designee should be consulted.

C3i Solutions SAE Report	Sponsor's Medical Monitor
Email: PPD Fax for North America: PPD For fax or email issues, email PPD or call PPD.	PPD Telephone: PPD email: PPD

The information provided in a SAE report should be as complete as possible but contain a minimum of:

- A short description of the AE (diagnosis) and the reason why the AE was categorized as serious
- Subject identification and treatment (if applicable)
- Investigator's name and phone number (if applicable)
- Name of the suspect medicinal product and dates of administration
- Assessment of causality

If all information about the SAE is not yet known, the Investigator will be required to report any additional information within 24 hours as it becomes available.

All SAEs will be evaluated by the Medical Monitor or designee. The Sponsor will determine reportability regardless of the Investigator's assessment. In the case of a SUSAR, the Sponsor or designee will report the event to all pertinent regulatory authorities having jurisdiction over ongoing ARQ 751 trials in an expedited manner (within 7 days or 15 days of knowledge) and to all Investigators involved in ARQ 751 clinical trials.[1]

The Investigators must in turn notify their governing IRB/IEC in accordance with their bylaws.

7.5 Post-treatment Safety Follow-up

In this study, the post-treatment safety follow-up period is defined as 30 days after the last dose of assigned treatment. All AEs occurring during the study period from the time of the first dose of ARQ 751 administration to the last day of the 30-day post-treatment Safety Follow-up period will be captured.

All subjects will be followed for a minimum of 30 days after discontinuation of ARQ 751. All subjects should be instructed to report AEs or SAEs occurring during the 30-day post-treatment Safety Follow-up period.

Unresolved study drug-related (see Section 7.1.8 for definition) AEs and SAEs at the time of treatment discontinuation or new study drug-related AEs and SAEs that occur during the 30-day safety follow-up period will be followed until they have, in the opinion of the Investigator, resolved to baseline, stabilized, or are deemed to be irreversible.

If a subject receives other anticancer therapy within the 30-day Safety Follow-up period, the follow-up for AEs will cease, beginning on the first day of the new therapy.

7.6 Grading of Severity

Each AE or SAE will be graded for severity according to NCI CTCAE version 4.03.

For AEs not listed in the NCI CTCAE version 4.03, a similar grading system should be used as follows:

- Grade 1 Mild AE
- Grade 2 Moderate AE
- Grade 3 Severe AE
- Grade 4 Life-threatening or disabling AE
- Grade 5 Death related to AE

For AEs that can be described by the NCI CTCAE guidelines, the NCI CTCAE Grade (life-threatening or disabling AE) is assessed based on unique clinical descriptions of severity for

[1] An adverse event or suspected adverse reaction is considered "unexpected" if it is not listed in the Investigator's Brochure or is not listed at the specificity or severity that has been observed; or, if an Investigator's Brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended. Source: 21CFR312.32 (a)

each AE, and these criteria may be different from those used for the assessment of AE seriousness. An AE assessed as Grade 4 based on the NCI CTCAE grades may or may not be assessed as serious based on the seriousness criteria.

7.7 Assessment of Causality

The Investigator will provide the Sponsor with an assessment of causality for an adverse event and study treatment (ARQ 751, paclitaxel and fulvestrant) based on his/her clinical judgment and the definitions described below.

7.7.1 Related Adverse Events

- The AE follows a reasonable temporal sequence from study treatment administration, and cannot be reasonably explained by the subject's clinical state or other factors (e.g., disease under study, concurrent diseases, concomitant medications)
- The AE follows a reasonable temporal sequence from study drug administration and is a known reaction to the drug(s) under study or its chemical group or is predicted by known pharmacology or a known reaction to agent or chemical group.

7.7.2 Not Related Adverse Events

- The AE does not follow a reasonable sequence from study treatment administration or can be reasonably explained by the subject's clinical state or other factors (e.g., disease under study, concurrent diseases, and concomitant medications).

8 QUALITY CONTROL AND ASSURANCE

The study will be initiated and conducted under the sponsorship of ArQule. Study drugs ARQ 751, clinical supplies, and eCRFs will be supplied by the Sponsor or its representative. Representatives of the Sponsor will monitor the study to verify study data, medical records, and eCRFs in accordance with current ICH GCP and other applicable regulations and guidelines.

9 PLANNED STATISTICAL METHODS

The material presented in this section will serve as the basis for the statistical analysis plan. This plan may be revised during the study to accommodate protocol amendments. Because of the nature of this study, no formal statistical analysis is planned. Evaluation of the data will consist primarily of summary displays (e.g., descriptive statistics and graphs).

9.1 Determination of Sample Size

The exact number of subjects estimated for this study is dependent on the number of subject cohorts investigated based on the toxicity encountered. Approximately 94 subjects will be enrolled in this study at 4-10 sites in the USA; 64 subjects in Part 1 (Dose escalation cohorts and Arm A) and 30 in Part 2 (Arm B and Arm C). Thirty four subjects were enrolled in dose escalation cohorts. It is planned that up to 30 subjects with advanced, inoperable, metastatic, or recurrent solid tumors will be enrolled in Arm A, up to 15 subjects with PIK3CA/PTEN activating mutations and up to 15 subjects with AKT genetic alterations. In Part 2, approximately 15 subjects will be enrolled in each combination therapy arm (Arm B, ARQ 751+paclitaxel and Arm C, ARQ 751+fulvestrant).

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9.2 Analysis Variables

9.2.1 Demographics and Baseline Characteristics

Subject demographics and baseline characteristics will include:

- Demographics (age, gender, race)
- Baseline disease characteristics (stage, date of diagnosis, tumor biomarker status, and other prognostic factors)
- Clinically significant medical history, including surgeries
- Prior therapies
- Baseline concomitant medications and treatments

9.2.2 Safety

The safety analysis will be based on the safety population. The safety population includes all subjects who receive at least one dose of ARQ 751. Safety variables include the reported AEs, laboratory tests, vital signs, ECOG performance status, and physical examination.

9.2.3 Pharmacokinetics

PK parameters include C_{max}, AUC, and where possible $t_{1/2}$.

9.3 Statistical Methods

9.3.1 Demographic and Baseline Characteristics

All demographic and baseline characteristics will be descriptively summarized. Categorical variables will be summarized as the number and percentage of subjects in each category.

Continuous variables will be summarized as mean, standard deviation, median, minimum, and maximum.

9.3.2 Extent of Treatment Exposure

Duration of exposure is defined as the total number of days of study drug administration, ignoring any temporary drug discontinuation. For intermittent and weekly dosing schedules, the duration of exposure is defined as the duration from the date of the first dose (including first dose date) to the date of the last dose, ignoring any temporary drug discontinuations and planned drug breaks. If the date of last administration is unknown, the date until which the dispensed drug would have lasted without counting the extra drug provided should be used.

9.3.3 Analyses of Safety Variables

9.3.3.1 Adverse Events

Adverse events will be evaluated for severity using NCI CTCAE, version 4.03. AE summaries will include the incidence of treatment emergent AEs (TEAE). All TEAEs will be coded using Medical Dictionary for Regulatory Activities (MedDRA®) and summaries will present data by system organ class and preferred term. Separate TEAE summaries will be generated for the following:

- All TEAEs
- Severe TEAEs (Grade 3 or higher)
- SAEs
- TEAEs related to ARQ 751
- TEAE related to combination drugs (paclitaxel or fulvestrant)
- TEAEs leading to treatment discontinuation
- TEAEs resulting in death
- TEAEs listed according to maximum severity
- TEAEs listed by dosing schedule/regimen
- TEAEs related to ARQ 751 by treatment Arm

9.3.3.2 Laboratory Tests

Summary statistics for baseline, each post-baseline measurement, and change from baseline for each post-baseline measurement will be presented for each hematology, serum chemistry, liver function test, electrolyte, and urinalysis parameter.

9.3.3.3 Vital Signs

Summary statistics for baseline, each post-baseline measurement, and change from baseline for each post-baseline measurement will be presented for each vital sign parameter.

9.3.3.4 ECOG Performance Status

Number and percent of subjects having each ECOG performance status level will be presented for baseline and each post-baseline measurement.

9.3.3.5 Physical Examinations

Data from physical examinations will be presented in the data listings.

9.3.3.6 Response Rate

Analyses on the Overall Response Rate (ORR) will be performed in the Intent to Treat (ITT) and Evaluable subject populations. The evaluable subject population is defined as the subjects who have received at least one cycle of ARQ 751 and have had at least one disease assessment following the initiation of therapy. The 95% confidence interval will be estimated.

The 95% confidence interval for percent of subjects in each RECIST response category (e.g., complete response [CR], partial response [PR], stable disease [SD], and progressive disease [PD]) and disease control rate [DCR] will also be estimated.

9.3.4 Pharmacokinetics and Pharmacodynamics

PK parameters include C_{max}, AUC, and $t_{1/2}$ (where possible) summary statistics will be performed.

Summary statistics including mean, standard deviation, median, coefficient of variation, minimum and maximum for baseline, each post-baseline measurement, and change from baseline will be performed on specified biomarkers.

To explore the association of blood concentration with clinical outcome, the above descriptive statistics will also be presented separately for each response category (CR, PR, and SD combined vs. PD). Logistic regression will also be utilized if appropriate.

9.3.5 Interim Analysis

There will be no interim analysis for this Phase 1, single arm, open-label study.

10 COMPLIANCE WITH GOOD CLINICAL PRACTICE AND ETHICAL CONSIDERATIONS

10.1 Institutional Review Board or Independent Ethics Committee Approval

The protocol, any protocol modifications, the ICF, and, if applicable, permission to use private health information must be approved by the Investigator's IRB/IEC in compliance with Federal regulations 21 CFR §56 prior to study initiation. Documentation of this approval must be provided to the Sponsor or its designee and made available during an inspection by the FDA or other regulatory agency inspectors. The Investigator will also provide the Sponsor with the General Assurance Number documenting that the IRB/IEC is duly constituted, as well as a list of the names, occupations, and affiliations of the members of the IRB/IEC when available.

Before initiating a trial, the Investigator/Institution should have written and dated approval/favorable opinion from the IRB/IEC and where applicable, competent authorities/regulatory bodies for the trial protocol/amendment(s), written ICF subject recruitment procedures (e.g., advertisements), and written information to be provided to subjects.

10.2 Compliance with Good Clinical Practice and Ethical Considerations

This study must be conducted in compliance with IRB/IEC informed consent regulation and the ICH GCP Guidelines. In addition, all local regulatory requirements will be adhered to, in particular those affording greater protection to the safety of the trial participants.

This study will also be conducted according to the current revision of the Declaration of Helsinki Revised Edinburgh, Scotland, 2000, with all subsequent revisions, and with local laws and regulations relevant to the use of new therapeutic agents in the country of conduct.

Changes to the protocol will require written IRB/IEC and, where applicable, competent authorities/regulatory bodies approval/favorable opinion prior to implementation, except when the modification is needed to eliminate an immediate hazard(s) to subjects.

10.3 Subject Information and Consent

The Investigator, or designee, is responsible for the content of the ICF, but the original and any updated versions must be approved by the Sponsor prior to submission to the IRB/IEC. The ICF should also include any additional information required by local laws relating to institutional review.

Before the start of any study-related procedures are undertaken, the Investigator or authorized designee must obtain written, informed consent from each study participant (or his/her legal representative) in accordance with US federal regulations (21 CFR §50) and the ICH document "Guidance for Industry – E6 Good Clinical Practice: Consolidated Guidance". Informed consent will be obtained by discussing with the subject the purpose of the study, the risks and benefits, the study procedures, and any other information relevant to the subject.

The Investigator or designee must explain to the subject that for purposes of evaluating the study results, the subject's private health information obtained during the study may be shared with the study Sponsor, regulatory agencies, and IRBs/IECs, before enrolling that subject into the study.

It is the Investigator's (or designee's) responsibility to obtain permission to use private health information per the Health Information Portability and Accountability Act (HIPAA) from each subject, or if appropriate, the subject's legal representative.

The subject or his/her legal representative will document his/her informed consent by signing the current version of the written, IRB-approved ICF. The person who conducted the informed consent discussion with the subject and/or subject's legal representative must also sign the ICF. The subject is given a fully executed copy of the ICF bearing all appropriate signatures, and the original must be maintained in the clinical master files at the site.

All active subjects participating on the protocol must be re-consented each time the ICF is updated and re-approved by the IRB/IEC.

11 STUDY MANAGEMENT AND MATERIALS

11.1 Monitoring, Verification of Data, Audit, and Inspection

A Sponsor monitor or designee will periodically visit each clinical study site to discuss the progress of the clinical trial and to review eCRFs and original source documents for accuracy of data recording, study drug accountability, and correspondence. When requested, the Investigator must be available to the study monitor for personal, one-to-one consultation.

Periodically, some or all of the facilities used in the trial may be reviewed or inspected by the IRB/IEC and/or regulatory authorities. An audit or inspection may include, for example, a review of all source documents, drug records, and original clinical medical notes.

The Investigator is to ensure that the trial participants are aware of and consent to the review of personal information during the data verification process, as part of the monitoring/auditing process conducted by properly authorized agents of the Sponsor or be subject to inspection by regulatory authorities. In addition, participation and personal information is treated as strictly confidential to the extent of applicable law and is not publicly available.

11.2 Data Recording and Retention of Study Data

In compliance with GCP, the medical records/medical notes, and other study-related materials should be clearly marked and permit easy identification of participation by an individual in a specified clinical trial.

The Investigator is to record all data with respect to protocol procedures, drug administration, laboratory data, safety data, and efficacy ratings on the eCRFs.

If the Investigator relocates or retires, or otherwise withdraws his/her responsibility for maintenance and retention of the master clinical study records, the Sponsor must be notified in writing so that adequate provision can be made with regard to the trial documents.

Trial documents should be retained for at least two years after the approval of a marketing application in an ICH region and until there are no pending or planned marketing applications in an ICH region, or until at least two years have elapsed since the formal discontinuation of clinical development of ARQ 751 by the Sponsor. The documents should be retained for a longer period, however, if required by the applicable regulatory requirements or by an agreement with the Sponsor that it will inform the Investigator, in writing, as to when the retention of these documents is no longer necessary.

11.3 Electronic Case Report Forms

An EDC system will be used to collect the data in this study. The EDC system provides functionality for the clinical sites to enter the data directly into the eCRFs and respond to data discrepancies. Once the data are entered, the information is encrypted and transmitted over the Internet to a clinical trial server where it is electronically reviewed. Any resulting data queries are immediately sent back to the site for resolution. The system automatically keeps a full audit trail of all data changes that occur. The clinical team will undertake additional manual review of the data, but all resulting data queries or clarifications will be entered into the EDC system for

resolution. All eCRFs will be completed according to instructions provided in the eCRF Completion Guidelines and ICH/GCP guidelines.

11.4 Confidentiality, Publication, and Disclosure Policy

The Investigator understands that the Sponsor will use the information developed in the clinical study in connection with the development of ARQ 751. This information may be disclosed to other clinical Investigators, the FDA, and other government agencies.

All information disclosed to the Investigator by the Sponsor for the purpose of having the Investigator conduct the clinical trial described in this protocol, or information generated by the Investigator as results in the clinical trial shall be treated by the Investigator as strictly confidential. The Investigator shall not use such information other than for the purpose of conducting the clinical trial and may not disclose such information to others, except when such disclosure is made to colleagues and/or employees who reasonably require the information in order to assist in carrying out the clinical trial and who are bound by like-obligations of confidentiality. Notwithstanding, the Investigator may use or disclose to others any information which: (i) was known to the Investigator prior to the date of its disclosure; (ii) is now, or becomes in the future, publicly available; or (iii) is lawfully disclosed to the Investigator on a non-confidential basis by a third party who is not obligated to the Sponsor or any other party to retain such information in confidence.

The Sponsor acknowledges that the Investigator has certain professional responsibilities to report to the scientific community on findings made in the clinical investigations they conduct. The Investigator shall have the right to publish the results of research performed under this protocol, provided that such publication does not disclose any Confidential Information or trade secrets of the Sponsor (other than the Data). If the study is conducted as part of a multi-center protocol, the Investigator agrees not to independently publish the findings except as part of an overall multi-center publication, unless specifically approved in writing by the Sponsor or unless more than 12 months have elapsed since the last subject in the study has completed his/her study designed treatment.

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Appendix 1 Schedule of Assessments

Tests & Procedures	Screening	Treatment Visits								End of Treatment	30-day Safety Follow-up
Cycle	**Baseline**	**1**				**2+**				Within 7 days of decision to permanently discontinue	30+ days after the last dose of ARQ 751
Day	**0**	**1**	**2**	**8[1]**	**15**	**1**	**2**	**8[1]**	**15[2]**		
Window (in days)	-14 - 0	-1	0	±2	±3[3]	±3 [3]	0	±2	±3 [3]		
Written Informed Consent[4]	X										
Medical History	X										
Physical Examination (including skin)	X	X		X	X	X		X	X	X	
ECOG PS	X	X		X	X	X		X	X	X	
Vital Signs[5]	X	X		X	X	X		X	X	X	
Fasting Clinical Blood Tests[6]	X	X		X	X	X		X	X	X	
Urinalysis	X									X	
Serum Pregnancy Test, if applicable	X									X	
CYP2D6 Sample		X									
ctDNA Sample		X									
Glucose Metabolism Blood Samples[7]		X	X		X	X	X				
PK Blood Samples[7]		X	X		X	X	X				
Home Blood Glucose Monitoring[8]			X	X	X						
Blood Tumor Markers, (if applicable)[9]	X	X	X	X	X	X	X	X	X	X	
12-Lead ECG[10]	X	X			X	X				X	
Bone Scan	X										
Echocardiography/MUGA (if applicable)[11]	X										
Tumor Assessment and Re-staging[12]	X					X				X	
Concomitant Medications	X	X		X	X	X		X	X	X	X
Adverse Events Assessment		X		X	X	X		X	X	X	X
ARQ 751 Dispensation		X				X					

[1] Day 8 visits are only required for Arm B (ARQ 751+paclitaxel)

[2] Cycle 2 Day 15 visit is only required for Arm B (ARQ 751+paclitaxel) and Arm C (ARQ 751+fulvestrant). Day 15 visits in cycle 3 are higher are required only for Arm B (ARQ 751+paclitaxel)

[3] Window of ±3 days is allowed for Arms A (ARQ 751 single agent) and Arm C (ARQ 751+fulvestrant), but window of ±2 days is required for Arm B (ARQ 751+paclitaxel).

[4] ICF can be signed greater than 14 days prior to first dose.

[5] Temperature, BP, HR and RR at every visit. Height only at Screening. Weight at Screening, Day 1 of each cycle and at End of Treatment visit.

[6] Refer to Section 5.4 for detailed description of clinical laboratory tests

[7] Refer to Section 5.5 and Appendix 3 for details on PK and Glucose Metabolism (insulin and glucose) timepoints.

[8] Refer to Section 5.6. Home blood glucose monitoring should be performed by the subjects at least once per day (before breakfast) for the first 4 weeks. Not necessary on days where glucose will be tested at the study site. After the first four weeks of treatment, the Investigator will determine if a subject should continue home glucose testing and the testing frequency.

[9] Tumor markers testing (if applicable) will be done at the study site. Tumor markers will be tested at Screening and frequency of testing while on treatment will be as per FDA/NCCN guidelines, or institutional standards.

[10] Refer to Section 5.3. Single 12-lead ECG to be performed at Screening and at End of Treatment visit. Repeat triplicate ECGs to be performed at C1D1, C1D15, C2D1, C3D1 and C4D1. See Appendix 3 for details for scheduled visits. Additional ECGs may be conducted if clinically indicated.

[11] Echo/MUGA only required for subjects who received prior therapy with anthracyclines

[12] Refer to Section 5.7. Tumor assessment (CT and/or MRI) at Screening can be done up to 28 days prior to the 1st dose of ARQ 751). Post treatment, tumor assessment must be done at the beginning of every other cycle, starting at Cycle 3 Day 1. Tumor assessment required at the End of Treatment (EOT) visit unless disease progression was seen on the prior scan.

Appendix 2 Performance Status

ECOG Performance Status Scale	
Grade	**Descriptions**
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).
2	In bed < 50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed > 50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

Appendix 3 Pharmacokinetic, Pharmacodynamic, Glucose Metabolism (GM) Sampling and ECG Schedule

A. Blood Collection Schedule for PK and GM (insulin & glucose) and ECG schedule

Day	Blood Samples		Desired Time	ECG (within 30 minutes prior to time-matched PK collection)
SCREENING				
14 - -1	NA		NA	12-lead single ECG, any time
CYCLE 1 DAY 1				
C1D1	PK	GM	0 hour (prior to the 1st dose of ARQ 751)	Triplicate 12-lead ECG
C1D1	PK	GM	1 hour (± 15 minutes)	
C1D1	PK	GM	2 hour (± 20 minutes)	Triplicate 12-lead ECG
C1D1	PK	GM	4 hours (± 30 minutes)	Triplicate 12-lead ECG
C1D1	PK	GM	6 hours (± 30 minutes)	
C1D1	PK	GM	8 hours (± 30 minutes)	
CYCLE 1 DAY 2				
C1D2	PK	GM	24 hours (± 2 hours) (prior to the morning dose)	
CYCLE 1 DAY 15				
C1D15	PK	GM	0 hour (prior to the morning dose)	Triplicate 12-lead ECG
C1D15	PK	GM	1 hour (± 15 minutes)	
C1D15	PK	GM	2 hour (± 20 minutes)	Triplicate 12-lead ECG
CYCLE 2 DAY 1				
C2D1	PK	GM	0 hour (prior to the morning dose)	
C2D1	PK	GM	1 hour (± 15 minutes)	
C2D1	PK	GM	2 hour (± 20 minutes)	Triplicate 12-lead ECG
C2D1	PK	GM	4 hours (± 30 minutes)	Triplicate 12-lead ECG
C2D1	PK	GM	6 hours (± 30 minutes)	
C2D1	PK	GM	8 hours (± 30 minutes)	
CYCLE 2 DAY 2				
C2D2	PK	GM	24 hours (± 2 hours) (prior to the morning dose)	
CYCLE 3 DAY 1				
C3D1	PK	GM	0 hour (prior to the morning dose)	Triplicate 12-lead ECG
C3D1	PK		1 hour (± 15 minutes)	
C3D1	PK		2 hour (± 20 minutes)	Triplicate 12-lead ECG
CYCLE 4 DAY 1				

C4D1	PK	GM	0 hour (prior to the morning dose)	Triplicate 12-lead ECG
C4D1	PK		1 hour (± 15 minutes)	
C4D1	PK		2 hour (± 20 minutes)	Triplicate 12-lead ECG
End of Treatment				
EOT	NA	NA	NA	12-lead single ECG, any time

*The exact time of co-drug administration, including start/stop time of infusion if applicable, has to be recorded in eCRF and sample collection/requisition form.

B. Blood Sample Collection for CYP2D6 and ctDNA

DAY	PROCEDURE	SAMPLE	DESIRED TIME
CYCLE 1 DAY 1			
C1D1	Draw blood sample	CYP2D6	0 hour (prior to the dose of ARQ 751)
C1D1	Draw blood sample	ctDNA	0 hour (prior to the dose of ARQ 751)

Appendix 4 Examples of *In Vivo* Substrates, Inhibitors, and Inducers for Specific CYP Enzymes and P-glycoproteins

Examples of *In Vivo* Substrates, Inhibitors, and Inducers for Specific CYP Enzymes[1]

CYP	Substrate	Inhibitor	Inducer
2D6	atomoxetine, desipramine, dextromethorphan , eliglustat, nebivolol, nortriptyline, perphenazine, tolterodine, venlafaxine	bupropion, fluoxetine, paroxetine, quinidine, terbinafine	none identified
2C19	S-mephenytoin, omeprazole	fluconazole, fluoxetine, fluvoxamine, ticlopidine	Rifampin, ritonavir
3A4/3A5	alfentanil, avanafil, buspirone, conivaptan, darifenacin, darunavir, ebastine, everolimus, ibrutinib, lomitapide, lovastatin, midazolam, naloxegol, nisoldipine, saquinavir, simvastatin, sirolimus, tacrolimus, tipranavir, triazolam, vardenafil	boceprevir, cobicistat, conivaptan, danoprevir and ritonavir, elvitegravir and ritonavir, grapefruit juice, indinavir and ritonavir, itraconazole, ketoconazole, lopinavir and ritonavir, paritaprevir and ritonavir and (ombitasvir and/or dasabuvir, posaconazole, ritonavir, saquinavir and ritonavir, telaprevir, tipranavir and ritonavir, troleandomycin, voriconazole	carbamazepine, enzalutamide, mitotane, phenytoin, rifampin, St. John's wort

Source: www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm093664.htm (extracted on 4/3/2019)

[1] This is not an exhaustive list

Substrates for any particular CYP enzyme listed in this table are those with plasma AUC values increased by 2-fold or higher when co-administered with inhibitors of that CYP enzyme; for CYP3A, only those with plasma AUC increased by 5-fold or higher are listed.

Inhibitors listed are those that increase plasma AUC values of substrates for that CYP enzyme by 2-fold or higher. For CYP3A inhibitors, only those that increase AUC of CYP3A substrates by 5-fold or higher are listed.

Inducers listed are those that decrease plasma AUC values of substrates for that CYP enzyme by 30% or higher.

Examples of *In Vivo* Substrates, Inhibitors, and Inducers of P-glycoprotein[1]

Transporter	Substrates	Inhibitors[2]	Inducers[3]
P-gp (Gene *ABCB1*)	dabigatran, digoxin, fexofenadine	Cyclosporine Elacridar (GF120918) Ketoconazole Quinidine Reserpine Ritonavir Tacrolimus Valspodar (PSC833) Verapamil Zosuquidar (LY335979)	Avasimibe[4] Carbamazepine phenytoin rifampin St John's wort[5] tipranavir/ritonavir

Source: Guidance for Industry: Drug Interaction Studies – Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations.

1 Not an exhaustive list. For an updated list, see the following link: https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm093664

2 Inhibitors listed for P-gp are those that showed (1) AUC fold-increase of digoxin ≥2 with co-administration and (2) in vitro inhibitor.

3 Inducers listed for P-gp are those that showed >20% decrease in digoxin AUC or otherwise indicated if substrate is other than digoxin.

4 Not a marketed drug

5 Herbal product

Appendix 5 Assessment of Anti-tumor Activity

Assessment of tumor response should be performed following the revised RECIST guidelines, version 1.1. Some of these definitions and criteria are highlighted below.

Tumor evaluations will be performed at the Screening Visit (Baseline), every 2 cycles during first 12 months of treatment. For subjects who do not experience disease progression and continue to benefit from the treatment after 12 months of treatment, tumor evaluation may be performed every 3 cycles upon agreement between the Investigator and the Medical Monitor. Tumor evaluation will also be performed at the End of Treatment visit if radiographic disease progression was not seen on the prior scan.

Screening	**On-treatment ≤12 months of tx**	**On-treatment >12 months of tx**	**EOT**
within 28 days prior the 1st dose of ARQ 751	C3D1, C5D1, C7D1, C9D1, C11D1 C13D1	C16D1, C19D1, etc.	If no PD seen at prior scan

Measurability of Tumor Baseline

CT with intravenous (IV) contrast and MRI are the best currently available and reproducible methods to measure target lesions selected for response assessment. Conventional CT and MRI 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.

All imaging methods should be performed according to institutional standards with each subject having consistency of methods beginning from baseline through the course of the study.

Definitions

At baseline, tumor lesions/lymph nodes will be categorized measurable or non-measurable as follows:

Measurable

Tumor lesions: Must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:

- 10 mm by CT scan (CT scan slice thickness no greater than 5 mm)
- 10 mm caliper measurement by clinical examination (lesions which cannot be accurately measured with calipers should be recorded as non-measurable)
- 20 mm by chest X-ray

Measurable malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed. See also notes below on 'Baseline documentation of target and non-target lesions' for information on lymph node measurement.

Non-Measurable

All other lesions, including small lesions (longest diameter < 10 mm or pathological lymph nodes with ≥ 10 to < 15 mm short axis) as well as truly non-measurable lesions. Lesions considered truly non-measurable include: leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin (nevi) or lung, and abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

Special Considerations Regarding Lesion Measurability

Bone lesions, cystic lesions, and lesions previously treated with local therapy require particular comment:

Bone lesions

Bone scan, PET scan, or plain films are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.

Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by cross sectional imaging techniques such as CT or MRI can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above.

Blastic bone lesions are non-measurable.

Cystic lesions

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

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

Lesions with prior local treatment

Tumor lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are not considered measurable unless there has been demonstrated progression in the lesion.

Specifications by Methods of Measurements

Measurement of Lesions

All measurements should be recorded in metric notation, using calipers if clinically assessed. All baseline evaluations should be performed as close as possible to the treatment start and NEVER more than 4 weeks before the beginning of the treatment.

Method of Assessment

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation should always be done rather than clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

Clinical lesions: Clinical lesions will only be considered measurable when they are superficial and ≥ 10 mm diameter as assessed using calipers (e.g., skin [nevi] nodules). For the case of skin (nevi) lesions, documentation by color photography including a ruler to estimate the size of the lesion is suggested. As noted above, when lesions can be evaluated by both clinical exam and imaging, imaging evaluation should be undertaken since it is more objective and may also be reviewed at the end of the study.

Chest X-ray: Chest CT is preferred over chest X-ray, particularly when progression is an important endpoint, since CT is more sensitive than X-ray, particularly in identifying new lesions. However, lesions on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.

CT, MRI: CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. When CT scans have a slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g., for body scans).

Tumor Response Evaluation

Assessment of Overall Tumor Burden and Measurable Disease

To assess objective response or future progression, it is necessary to estimate the overall tumor burden at baseline and use this as a comparator for subsequent measurements. In this study, only subjects with measurable disease at baseline should be included in the study.

Baseline Documentation of 'Target' and 'Non-Target' Lesions

When more than one measurable lesion is present at baseline, all lesions up to a maximum of five lesions total (and a *maximum* of two lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline (this means in instances where subjects have only one or two organ sites involved, a maximum of two and four lesions respectively will be recorded).

Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected.

Lymph nodes merit special mention since they are normal anatomical structures which may be visible by imaging even if not involved by tumor. As noted above, pathological nodes which are defined as measurable and may be identified as target lesions must meet the criterion of a short

axis of ≥ 15 mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumor. Nodal size is normally reported as two dimensions in the plane in which the image is obtained (for CT scan this is almost always the axial plane; for MRI the plane of acquisition may be axial, sagittal, or coronal). The smaller of these measures is the short axis. For example, an abdominal node which is reported as being 20 mm x 30 mm has a short axis of 20 mm and qualifies as a malignant, measurable node. In this example, 20 mm should be recorded as the node measurement. All other pathological nodes (those with short axis ≥ 10 mm but < 15 mm) should be considered non-target lesions. Nodes that have a short axis < 10 mm are considered non-pathological and should not be recorded or followed.

A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum of the diameters. If lymph nodes are to be included in the sum, then as noted above, only the short axis is added into the sum. The baseline sum of the diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

All other lesions (or sites of disease) including pathological lymph nodes should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required, and these lesions should be followed as 'present', 'absent', or in rare cases 'unequivocal progression' (more details to follow). In addition, it is possible to record multiple non-target lesions involving the same organ as a single item on the case record form (e.g. 'multiple enlarged pelvic lymph nodes' or 'multiple liver metastases').

Response Criteria

This section provides the definitions of the criteria used to determine objective tumor response for target lesions.

Evaluation of Target Lesions

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

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

Progressive Disease (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression).

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study. In this study, the minimum duration for SD is defined as 8 weeks (± 3 days).

Special Notes on the Assessment of Target Lesions

Lymph nodes. Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the nodes regress to below 10 mm on study. This means that when lymph nodes are included as target lesions, the 'sum' of lesions may not be zero even if complete response criteria are met, since a normal lymph node is defined as having a short axis of < 10 mm. For PR, SD, and PD, the actual short axis measurement of the nodes is to be included in the sum of target lesions.

Target lesions that become 'too small to measure'. While on study, all lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each Response Criteria subsequent evaluation, even when very small (e.g. 2 mm). However, sometimes lesions or lymph nodes which are recorded as target lesions at baseline become so faint on CT scan that the radiologist may not feel comfortable assigning an exact measure and may report them as being 'too small to measure'. When this occurs, it is important that a value be recorded on the case report form. If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm. If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned (Note: It is less likely that this rule will be used for lymph nodes since they usually have a definable size when normal and are frequently surrounded by fat such as in the retroperitoneum; however, if a lymph node is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned in this circumstance as well). This default value is derived from the 5 mm CT slice thickness (but should not be changed with varying CT slice thickness). The measurement of these lesions is potentially non-reproducible, therefore providing this default value will prevent false responses or progressions based upon measurement error. To reiterate, however, if the radiologist is able to provide an actual measure, that should be recorded, even if it is below 5 mm.

Lesions that split or coalesce on treatment. When non-nodal lesions 'fragment', the longest diameters of the fragmented portions should be added together to calculate the target lesion sum. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximal longest diameter for the 'coalesced lesion'.

Evaluation of Non-Target Lesions

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

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (< 10 mm short axis).

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

Progressive Disease (PD): Unequivocal progression (see comments below) of existing non-target lesions. (Note: the appearance of one or more new lesions is also considered progression).

Special Notes on the Assessment of Progression of Non-target Disease

The concept of progression of non-target disease requires additional explanation as follows:

When the subject also has measurable disease. In this setting, to achieve 'unequivocal progression' on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in the presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy (see further details below). A modest 'increase' in the size of one or more non-target lesions is usually not sufficient to quality for unequivocal progression status. The designation of overall progression solely on the basis of change in non-target disease in the face of SD or PR of target disease will therefore be extremely rare.

Evaluation of New Lesions

The appearance of new malignant lesions denotes disease progression; therefore, some comments on detection of new lesions are important. There are no specific criteria for the identification of new radiographic lesions; however, the finding of a new lesion should be unequivocal: e.g., not attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumor (for example, some 'new' bone lesions may be simply healing or flare of pre-existing lesions). This is particularly important when the subject's baseline lesions show partial or complete response. For example, necrosis of a liver lesion may be reported on a CT scan report as a 'new' cystic lesion, which it is not.

A lesion identified on a follow-up study in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression. An example of this is the subject who has visceral disease at Baseline and while on study has a CT or MRI of the brain ordered which reveals metastases. The subject's brain metastases are considered to be evidence of PD even if he/she did not have brain imaging at baseline.

If a new lesion is equivocal, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the initial scan.

Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the study treatment until the end of treatment. No confirmatory measurement for CR or PR is required in this study.

The subject's best overall response assignment will depend on the findings of both target and non-target disease and will also take into consideration the appearance of new lesions.

Time Point Response

It is assumed that at each protocol specified time point, a response assessment occurs. The table below provides a summary of the overall response status calculation at each time point for subjects who have measurable disease at baseline.

Time Point Response: Subjects with Target (± non-target) Disease			
Target Lesions	**Non-Target Lesions**	**New Lesions**	**Overall Response**
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, and NE = not evaluable.

Missing Assessments and Inevaluable Designation

When no imaging/measurement is done at all at a particular time point, the subject is not evaluable (NE) at that time point. If only a subset of lesion measurements are made at an assessment, usually the case is also considered NE at that time point, unless a convincing argument can be made that the contribution of the individual missing lesion(s) would not change the assigned time point response. This would be most likely to happen in the case of PD. For example, if a subject had a baseline sum of 50 mm with three measured lesions and at follow-up only two lesions were assessed, but those gave a sum of 80 mm, the subject will have achieved PD status, regardless of the contribution of the missing lesion.

Best Overall Response: All Time Points

The best overall response is determined once all the data for the subject is known.

Best response determination in trials where confirmation of complete or partial response IS NOT required: Best response in these trials is defined as the best response across all time points (for example, a subject who has SD at first assessment, PR at second assessment, and PD on last assessment has a best overall response of PR). When SD is believed to be the best response, it must also meet the protocol specified minimum time from Baseline of 8 weeks. If the minimum time is not met when SD is otherwise the best time point response, the subject's best response depends on the subsequent assessments. For example, a subject who has SD at the first assessment, PD at second the assessment, and does not meet the minimum duration for SD, the subject will have a best response of PD. The same subject lost to follow-up after the first SD assessment would be considered inevaluable.

Special Notes on Response Assessment

When nodal disease is included in the sum of target lesions and the nodes decrease to 'normal' size (< 10 mm), they may still have a measurement reported on scans. This measurement should be recorded even though the nodes are normal in order not to overstate progression should it be based on increase in the size of the nodes. As noted earlier, this means that subjects with CR may not have a total sum of 'zero' on the eCRF.

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 objective progression even after discontinuation of treatment. Symptomatic deterioration is not a descriptor of an objective response: it is a reason for stopping study therapy. The objective response status of such subjects is to be determined by evaluation of target and non-target disease.

For equivocal findings of progression (e.g., very small and uncertain new lesions; cystic changes or necrosis in existing lesions), treatment may continue until the next scheduled assessment. If at the next scheduled assessment, progression is confirmed, the date of progression should be the earlier date when progression was suspected.

Frequency of Tumor Re-evaluation

In this study, tumor measurement will be conducted at the Baseline visit, and then in 8-week intervals (every two cycles) during the first 32 weeks (8 cycles) and then in 12-week intervals (every 3 cycles) while the subject is on treatment or as clinically indicated until progression of disease, withdrawal of consent, death, or loss to follow-up. Tumor measurement will also be performed during the End of Treatment visit if it is not done within 28 days of the visit date.

Baseline tumor assessments must be performed within four weeks (28 days) of the first dose of treatment.

All efforts should be made to ensure consistency between the baseline measurements and all subsequent measurements in reference to utilization of scanning methods, equipment, technique (including slice thickness and field of view), and the radiographic interpreter.

The radiological evaluation must include CT or MRI scanning of the chest, abdomen, and pelvis. Any additional suspected sites of disease should also be imaged. All evaluations should meet the standard of care for imaging of lesions in the respective organ(s).

All target and non-target sites are evaluated at each time point of tumor assessment.

Confirmatory Measurement/Duration of Response

Confirmation

Confirmation of PR and CR is NOT required in this study.

Duration of Overall Response

The duration of overall response is measured from the time measurement criteria are first met for CR/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 on study).

The duration of overall complete response is measured from the time measurement criteria that 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 sum on study (if the baseline sum is the smallest, this is the reference for calculation of PD). In this study, the minimum duration for SD is defined as 8 weeks (±3 days).

ANNEX 1

ELIGIBILITY FOR PART 1 SUBJECTS ENROLLED UNDER AMENDMENT 5

Adult subjects with advanced solid tumors with known/documented AKT1, 2, 3 genetic alterations, activating PI3K mutations, PTEN-null, or other known actionable PTEN mutations whose cancer has progressed following standard therapy, or for whom standard therapy is not available or is not tolerable will be enrolled.

Subject accrual will occur over a period of time dependent upon the number of cohorts enrolled.

Inclusion Criteria

Each prospective subject must meet ALL of the following inclusion criteria in order to be eligible for this study:

1. Signed written informed consent granted prior to initiation of any study-specific procedures
2. 18 years of age and older
3. Histologically or cytologically documented locally advanced, inoperable or metastatic solid tumors with documented AKT1, 2, 3 genetic alterations, activating PI3K mutations, PTEN-null, or other known actionable PTEN mutations
4. Failure to respond to standard therapy, or for whom standard or curative therapy does not exist, or is not tolerable.
    a. Subjects enrolled in the Expanded Cohort should have no more than 3 prior systemic regimens with confirmed disease progression. If the subject is refractory or has disease progression within 6 months of the adjuvant treatment, then the previous treatment should be considered as the line of treatment rather than an adjuvant therapy.
5. Measurable disease
6. Eastern Cooperative Oncology Group (ECOG) performance status (PS) ≤ 2
7. Archival tissue samples and/or fresh tumor biopsy samples:
    a. Subjects should agree to provide archival and/or fresh tumor biopsy samples
    b. Archival tumor samples should be collected for all enrolled subjects; if archival tissue samples are not available, a recent core needle biopsy should be collected
    c. Paired, pre- and post-treatment, tumor biopsy is optional for subjects enrolled in the Dose Escalation and Food-effect cohorts
    d. Paired tumor biopsy is mandatory for all subjects enrolled in the Expanded cohort; subjects should agree to and be eligible for paired tumor biopsy
8. Adequate organ function as indicated by the following laboratory values. All laboratory tests must be obtained within 7 days prior to the first dose of ARQ 751:
    a. Hematological
        i. Absolute neutrophil count (ANC) $\geq 1.5 \times 10^9$/L
        ii. Platelet count (Plt) $\geq 100 \times 10^9$/L
        iii. Hemoglobin (Hb) ≥ 9 g/dL
        iv. International normalized ratio (INR) 0.8 to upper limit of normal (ULN) or ≤ 3 for subjects receiving anticoagulant therapy such as Coumadin or heparin

b. Renal
    i. Serum creatinine ≤ 1.5 x ULN or calculated creatinine clearance ≥ 60 mL/min/1.73 m^2 for subjects with serum creatinine levels > 1.5 x institutional ULN
c. Hepatic
    i. Total bilirubin ≤ 1.5 x ULN
    ii. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 3 x ULN or ≤ 5 x ULN for subjects with known liver metastases
d. Metabolic
    i. Glycated hemoglobin (HbA1c) ≤ 8%

9. If a subject is currently receiving bisphosphonates, the subject must have received the bisphosphonates for at least four weeks prior to the first dose of ARQ 751.
    a. Initiation of bisphosphonates during the study may be allowed provided the subject completes the first cycle of treatment without any dose limiting toxicity (DLT) and the Investigator rules out tumor progression.
10. Male or female subjects of child-producing potential must agree to use double-barrier contraceptive measures, oral contraception, or avoidance of intercourse during the study and for 90 days after the last dose of ARQ 751.
11. Women of childbearing potential must have a negative serum pregnancy test during the Screening Period and within 48 hours of the first dose of ARQ 751. "Women of childbearing potential" is defined as sexually mature women who have not undergone a hysterectomy or who have not been naturally postmenopausal for at least 12 consecutive months prior to the first dose of ARQ 751.

Exclusion Criteria

Potential subjects who meet ANY of the following exclusion criteria are not eligible for enrollment into this study:

1. Anti-cancer therapy, such as chemotherapy, immunotherapy, targeted, and hormonal/endocrine therapy, or investigational agents within five half-lives or four weeks, whichever is shorter, prior to administration of the first dose of study drug (five half-lives or two weeks, whichever is shorter, for orally administered drugs and six weeks for nitrosoureas, mitomycin C, or bevacizumab)
    a. To be eligible for study treatment, toxicity from prior treatment must recover to Grade ≤ 1, except for alopecia
    b. Concurrent systemic high-dose corticosteroids when used intermittently in an antiemetic regimen, for central nervous system (CNS) metastases management, or as a part of the premedication regimen are allowed
    c. Concurrent standard long-term anticancer hormonal therapy with drugs including, but not limited to, selective estrogen receptor modulators or Gonadotropin-releasing hormone (GnRH) analogs if started at least six months before the first dose of ARQ 751 is allowed
2. Radiation therapy within four weeks prior to administration of the first dose of ARQ 751

a. To be eligible for study treatment, radiation therapy-related toxicity must recover to Grade ≤ 1 prior to administration of the first dose of ARQ 751.

b. Concurrent palliative radiotherapy for local pain-control may be allowed provided the subject completes the first cycle of treatment, does not meet criteria of progressive disease, and treated lesions will not be included in the target/non-target lesion assessment.

3. Major surgical procedure within four weeks prior to administration of the first dose of ARQ 751

    a. To be eligible for the study treatment, all surgical wounds must be fully healed and any surgery-related adverse events must recover to Grade ≤ 1.

4. Previous treatment with AKT inhibitors (e.g., ARQ 092, MK-2206, GSK2141795, AZD5363)

5. Unable or unwilling to swallow the complete daily dose of ARQ 751

6. A QTc interval ≥ 480 msec using the Fridericia's formula QTcF

7. History of Type 1 or 2 diabetes mellitus requiring regular medication (other than oral hypoglycemic agents) or fasting glucose ≥ 160 mg/dL at the Pre-Study visit

8. Significant gastrointestinal (GI) disorder(s) that could, in the opinion of the Investigator, interfere with the absorption, metabolism, or excretion of ARQ 751 (e.g., Crohn's disease, ulcerative colitis, extensive gastric resection)

9. Known active CNS metastases and/or carcinomatous meningitis

    a. To be eligible for the study treatment, subjects must have stable disease ≥ 1 month, confirmed by magnetic resonance imaging (MRI) or computed tomography (CT) scan, and have CNS metastases well controlled by low-dose steroids, anti-epileptics, or other symptom-relieving medications.

10. History of myocardial infarction (MI) or New York Heart Association (NYHA) Class II-IV congestive heart failure within 6 months of the administration of the first dose of ARQ 751 (MI occurring > 6 months of the first dose of ARQ 751 will be permitted); Grade 2 or worse conduction defect (e.g., right or left bundle branch block)

11. Concurrent severe uncontrolled illness not related to cancer and social situation that would limit compliance with study requirements, including but not limited to:

    a. Psychiatric illness, substance abuse

    b. Ongoing or active known infection, including human immunodeficiency virus (HIV) infection

12. Active or history of other malignancy other than the current cancer within 2 years of the first dose of ARQ 751, with the exception of carcinoma in-situ of the cervix, basal cell carcinoma, and superficial bladder tumors curatively treated

13. Blood transfusion or administration of growth factors within 5 days prior to a blood draw being used to confirm eligibility
14. Pregnant or breastfeeding

SCHEDULE OF EVENTS FOR PART 1 SUBJECTS ENROLLED UNDER AMENDMENT 5

Tests & Procedures	Pre-Study	Treatment Visits								End of Treatment	30-day Safety Follow-up
Cycle	Baseline	Cycle 1						Cycle 2+		7 days after the last dose of ARQ 751	30 days after the last dose of ARQ 751
Week		1		2	3	4		1	3		
Day	0	1	2	8	15	22	23	1	15		
Window	-14 - 0	-1	0	± 3 days			0	± 3 days		+ 3 days	± 3 days
Written Informed Consent	X										
Medical History	X										
Physical Examination (including skin)	X	X		X	X	X		X	X	X	
ECOG PS	X	X		X	X	X		X	X	X	
Vital Signs (T°, BP, RR, HR)	X	X	X	X	X	X	X	X	X	X	
• height	X										
• weight	X	X						X		X	
Fasting Clinical Blood Tests[0]	X	X		X	X	X		X	X	X	
Urinalysis[0]	X	X		X	X	X		X		X	
Serum Pregnancy Test, if applicable[0]	X									X	
CYP2D6 Sample		X									
Glucose Metabolism Blood Samples[7]		X[10]	X	X	X	X	X	X	X		
PK Blood Samples[7]		X[10]	X	X	X	X	X	X	X		
PD Blood Samples[Error! Reference source not found.]		X[10]						X		X	
Home Blood Glucose Monitoring[8]		X	X	X	X	X		X	X		
Tumor Markers Blood Samples, if applicable[9]	X	X						X		X	
12-Lead ECG[10]	X	X						X		X	
• in triplicate, pre- and post-dose		X						X			

Tests & Procedures	Pre-Study	Treatment Visits								End of Treatment	30-day Safety Follow-up
Cycle	Baseline	Cycle 1						Cycle 2+		7 days after the last dose of ARQ 751	30 days after the last dose of ARQ 751
Week		1		2	3	4		1	3		
Day	0	1	2	8	15	22	23	1	15		
Window	-14 - 0	-1	0	± 3 days			0	± 3 days		+ 3 days	± 3 days
Echocardiography/MUGA, if applicable[10]	X							X		X	
Archival and/or Fresh Tumor Biopsy[7]	X				X						
Tumor Assessment and Re-staging[11]	X							X		X	
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X
Adverse Events Assessment[9]		X[10]	X	X	X	X	X	X	X	X	X
ARQ 751 Dispensation		X[10]	X	X	X	X	X	X	X		

1 Detailed description of clinical laboratory tests recorded in Protocol Section 5.4

2 Refer to Annex 1 for timepoints. Day 22 and Day 23 PK and glucose metabolism blood samples should be collected on Day 21 and Day 22 for subjects receiving ARQ 751 QOD.

3 PD blood samples should be collected on Day 1 of Cycle 1, 2, 3 and End of treatment visit.

4 Refer to Annex 1 for timepoints. Home blood glucose monitoring should be performed at least once per day (before breakfast) for the first 4 weeks except for PK days (Cycle 1 Days 1, 2, 8, 15, 22 [Day 21 for subjects receiving ARQ 751 QOD], and 23 [Day 22 for subjects receiving ARQ 751 QOD]). After the first four weeks of treatment, the Investigator will determine if a subject should continue home glucose testing and the testing frequency.

5 Tumor markers testing will be done at the study site

6 12-lead ECG should be performed at Baseline and on Day 1 of the first six cycles; and in triplicate pre- and post-dose on Day 1 of Cycle 1 and Cycle 2. If applicable (previous treatment with anthracyclines), echocardiography or MUGA scan should be done at Baseline, every eight weeks for the first 24 weeks (six cycles) of treatment and every 12 weeks thereafter.

7 Archival tumor samples should be collected for all enrolled subjects; paired, pre- and post-treatment biopsy is optional for subjects enrolled in the Dose Escalation and Food-effect cohorts and mandatory for subjects enrolled in the Expanded cohort. Post-treatment biopsy can be performed Day 15 of Cycle 1 and Day 1 of Cycle 2.

8 Tumor assessment should be done at Baseline (if done within 28 days prior to the 1st dose of ARQ 751), every eight weeks during treatment, and at End of Treatment (EOT) unless it was done within 28 days prior to the EOT visit.

9 Only AEs that occurred after the administration of the first dose of ARQ 751 and within 30 days of the Safety Follow-up period should be reported as an AE, any AE that occurred prior to the administration of the first dose of ARQ 751 should be reported as Medical history.

10 These tests and procedures must be performed on C1D1. ARQ 751 must be dispensed on C1D1.

STUDY VISITS FOR PART 1 SUBJECTS ENROLLED UNDER AMENDMENT 5

Pre-Study Visit

After written informed consent is obtained, subject's eligibility for the study and baseline disease status will be assessed.

The following will be evaluated and documented within 14 days prior to first dose of ARQ 751:

- Medical history
- Physical examination, including skin
- ECOG PS
- Vital signs (height, weight, temperature, blood pressure, respiration rate, and heart rate)
- Fasting clinical blood tests
- Urinalysis
- Serum pregnancy test, if applicable
- 12-lead electrocardiogram (ECG)
- Echocardiography or Multiple Gated Acquisition (MUGA) scan, if applicable
- Archival and/or fresh tumor samples should be collected and available to be shipped to the Sponsor or designee
    - Tumor biopsy is optional for subjects enrolled in the Dose Escalation and Food-effect cohorts and is mandatory for subjects enrolled in the Expanded cohort
- Blood sample for tumor markers, if applicable (to be tested at the study site)
- Record prior and concomitant medications (medications used within 30 days prior to the first dose of ARQ 751)
- Tumor measurement and staging

Note: CT, MRI, and PET scans can be used as Baseline assessment if they were performed within four weeks (28 days) prior to the first dose of ARQ 751. For subjects with known or suspected bone metastases, a bone scan should be performed within four weeks (28 days) prior to the first dose of ARQ 751.

Subjects who satisfy all inclusion and exclusion criteria may be enrolled in the study.

Cycle 1, Weekly Evaluations

Cycle 1, Day 1 (- 1 Day)

The following assessments will be made during this visit:

- Physical examination, including skin
- ECOG PS
- Vital signs (weight, temperature, blood pressure, respiration rate, and heart rate)
- CYP2D6 samples
- Fasting clinical blood tests
- Urinalysis
- Blood sample for tumor markers, if applicable (to be tested at the study site)
- Blood samples for PK and glucose metabolism; must be performed on C1D1
- Blood samples for pharmacodynamics (cell-free ctDNA and CTCs); must be performed on C1D1
- 12-lead ECG in triplicate at pre-dose and post-dose
- Record concomitant medication
- Dispense and administer the first dose of ARQ 751 after all assessments listed above are completed (other than post-dose PK and post-dose glucose/insulin blood samples and post-dose ECG); must be performed on C1D1
- Assess adverse events (AE) (after administration of the first dose); must be performed on C1D1

Note: Blood samples for PK will be collected immediately prior to the first dose of ARQ 751 and will continue through 24 hours after administration of the first dose of ARQ 751.

Cycle 1, Day 2

The following assessments will be made during this visit:

- Vital signs (temperature, blood pressure, respiration rate, and heart rate)
- Blood samples for PK and glucose metabolism, prior to administration of the daily dose of ARQ 751
- Record concomitant medication
- Assess AEs
- Dispense ARQ 751

Cycle 1, Day 8 (± 3 days)

The following assessments will be made during this visit:

- Physical examination, including skin
- ECOG PS

- Vital signs (temperature, blood pressure, respiration rate, and heart rate)
- Fasting clinical blood tests
- Urinalysis
- Blood samples for PK and glucose metabolism, prior to administration of the daily dose of ARQ 751
- Record concomitant medication
- Assess AEs
- Dispense ARQ 751

Cycle 1, Day 15 (± 3 days)

The following assessments will be made during this visit:

- Physical examination, including skin
- ECOG PS
- Vital signs (temperature, blood pressure, respiration rate, and heart rate)
- Fasting clinical blood tests
- Urinalysis
- Blood samples for PK and glucose metabolism, prior to administration of the daily dose of ARQ 751
- Tumor biopsy, if applicable
- Record concomitant medication
- Assess AEs
- Dispense ARQ 751

Cycle 1, Day 22 (± 3 days)

The following assessments will be made during this visit:

- Physical examination, including skin
- ECOG PS
- Vital signs (temperature, blood pressure, respiration rate, and heart rate)
- Fasting clinical blood tests
- Urinalysis
- Blood samples for PK and glucose metabolism (Day 21 for subjects receiving ARQ 751 QOD)
- Record concomitant medication

- Assess AEs
- Dispense ARQ 751

Cycle 1, Day 23

The following assessments will be made during this visit:

- Vital signs (temperature, blood pressure, respiration rate, and heart rate)
- Blood samples for PK and glucose metabolism, prior to administration of the daily dose of ARQ 751 (Day 22 for subjects receiving ARQ 751 QOD)
- Record concomitant medication
- Assess AEs
- Dispense ARQ 751

Note: Home blood glucose monitoring should be performed at least once per day (before breakfast) for the first 4 weeks except for PK days (Cycle 1 Days 1, 2, 8, 15, 22 (Day 21 for subjects receiving ARQ 751 QOD), and 23 (Day 22 for subjects receiving ARQ 751 QOD), and Cycle 2 Day 1 and Day 15). If the fasting glucose level is > 160 mg/dL but ≤ 250 mg/dL, subjects are to test again before dinner. If the fasting glucose level is > 250 mg/dL, subjects are to call their Investigator. After the first 4 weeks, the Investigator will determine if a subject should continue home glucose testing and the testing frequency.

Cycle 2 and All Subsequent Cycles, Bi-Weekly Evaluations

Cycle 2 and All Subsequent Cycles, Day 1 (± 3 days)

The following assessments will be made during this visit:

- Physical examination, including skin
- ECOG PS
- Vital signs (weight, temperature, blood pressure, respiration rate, and heart rate)
- Fasting clinical blood tests
- Urinalysis, Cycles 2 - 6 and if clinically indicated
- Blood sample for tumor markers, if applicable (to be tested at the study site)
- Blood samples for PK and glucose metabolism, prior to administration of the daily dose of ARQ 751; only on Cycle 2 Day 1
- Blood samples for pharmacodynamics (cell-free ctDNA and CTCs), prior to administration of the daily dose of ARQ 751; only on Cycle 2 Day 1 and Cycle 3 Day 1
- 12-lead ECG monthly for the first 6 months on study and thereafter once every 3 months. ECG should be done in triplicate at pre-dose and post-dose on Cycle 2 Day 1. During

subsequent monthly visits, it should be done once at pre-dose. If clinically indicated, 12-lead ECG will continue to be done monthly.

- Echocardiography or MUGA scan, if applicable
- Tumor assessment and staging
- Record concomitant medication
- Assess AEs
- Dispense ARQ 751

Cycle 2 and all Subsequent Cycles, Day 15 (± 3 days)

The following assessments will be made during this visit:

- Physical examination, including skin
- ECOG PS
- Vital signs (temperature, blood pressure, respiration rate, and heart rate)
- Fasting clinical blood tests
- Blood samples for PK and glucose metabolism, prior to administration of the daily dose of ARQ 751; only on Cycle 2 Day 15
- Record concomitant medication
- Assess AEs
- Dispense ARQ 751

Notes:

1) Subjects who do not experience Grade 3/4 toxicity after 4 months/cycles (16 weeks) at the same dose level can be evaluated every 4 weeks (and skip the mid-month/cycle visits) upon agreement between the Investigator and the Medical Monitor.

2) For subjects who do not experience disease progression and continue to benefit from the treatment after 11 cycles, tumor evaluation may be performed every 3 months upon agreement between the Investigator and the Medical Monitor.

End of Treatment Visit

If possible, the End of Treatment visit should be performed 7 (+3) days after the decision to permanently discontinue ARQ 751 is made. The following assessments will be made during the End of Treatment visit:

- Physical examination, including skin
- ECOG PS
- Vital signs (weight, temperature, blood pressure, respiration rate, and heart rate)

- Fasting clinical blood tests
- Urinalysis
- Serum pregnancy test, if applicable
- Blood sample for tumor markers, if applicable (to be tested at the study site)
- Blood samples for pharmacodynamics (cell-free ctDNA and CTCs)
- 12-lead ECG
- Echocardiography or MUGA scan, if applicable
- Tumor assessment and staging, if not done within four weeks (28 days) prior to the End of Treatment visit
- Record concomitant medication
- Assess AEs

30-Day Safety Follow-up Visit (± 3 days)

All subjects will be followed for a minimum of 30 days after the last dose of ARQ 751. If a subject is removed from the study treatment due to drug-related AEs, the subject will be followed until drug-related AEs, occurring during the study or within 30 days after the last dose of ARQ 751, have resolved to baseline, NCI CTCAE Grade 1, are stabilized, or deemed irreversible. If a subject receives other anticancer therapy within the 30-day follow-up period, the follow-up for AEs will cease, beginning on the first day of the new therapy.

Note: The visit can occur either as an office visit or by telephone.

PK, PD, AND GLUCOSE METABOLISM SAMPLING SCHEDULES FOR PART 1 SUBJECTS ENROLLED UNDER AMENDMENT 5

A. Blood Collection Schedule for PK and GM[1,2]

Day	Procedure			Desired Time
CYCLE 1 DAY 1				
C1D1	Draw blood sample	PK	GM	0 hour (prior to the 1st dose of ARQ 751)
C1D1	Draw blood sample	PK	GM	1 hour (± 10 minutes)
C1D1	Draw blood sample	PK	GM	2 hours (± 10 minutes)
C1D1	Draw blood sample	PK	GM	4 hours (± 10 minutes)
C1D1	Draw blood sample	PK	GM	6 hours (± 10 minutes)
C1D1	Draw blood sample	PK	GM	8 hours (± 10 minutes)
C1D1	Draw blood sample	PK	GM	10 hours (± 10 minutes)
C1D1	Draw blood sample	PK	GM	12 hours (± 10 minutes)
CYCLE 1 DAY 2				
C1D2	Draw blood sample	PK	GM	24 hours (± 2 hours) (prior to the morning dose)
CYCLE 1 DAY 8				
C1D8	Draw blood sample	PK	GM	0 hour (prior to the morning dose)
CYCLE 1 DAY 15				
C1D15	Draw blood sample	PK	GM	0 hour (prior to the morning dose)
CYCLE 1 DAY 22[3]				
C1D22	Draw blood sample	PK	GM	0 hour (prior to the morning dose)
C1D22	Draw blood sample	PK	GM	1 hour (± 10 minutes)
C1D22	Draw blood sample	PK	GM	2 hours (± 10 minutes)
C1D22	Draw blood sample	PK	GM	4 hours (± 10 minutes)
C1D22	Draw blood sample	PK	GM	6 hours (± 10 minutes)
C1D22	Draw blood sample	PK	GM	8 hours (± 10 minutes)
C1D22	Draw blood sample	PK	GM	10 hours (± 10 minutes)
C1D22	Draw blood sample	PK	GM	12 hours (± 10 minutes)
CYCLE 1 DAY 23[4]				
C1D23	Draw blood sample	PK	GM	24 hours (± 2 hours) (prior to the morning dose)
CYCLE 2 DAY 1				
C2D1	Draw blood sample	PK	GM	0 hour (prior to the morning dose)
CYCLE 2 DAY 15				
C2D15	Draw blood sample	PK	GM	0 hour (prior to the morning dose)

1 Based on PK modeling data and/or the dosing regimen, the PK Blood Collection Schedule may be modified, as appropriate. Change will be incorporated into the laboratory manual.

2 Glucose metabolism includes plasma glucose and insulin metabolism

3 Cycle 1 Day 21 for subjects treated with ARQ 751 QOD

4 Cycle 1 Day 22 for subjects treated with ARQ 751 QOD

B. Tumor Tissue Biopsy Schedule for Pharmacodynamic Assessment

DAY	PROCEDURE	DESIRED TIME
BASELINE (Required)		
-14 – 0 days	Tumor biopsy (if archival tissue is not or paired biopsy is planned)	0 (prior to the 1st dose of ARQ 751)
ON STUDY: post-treatment biopsy		
Any day between C1D15 and C2D1	Dose Escalation cohorts: optional Expanded Cohort: required	prior to the dose

C. Blood Sample Collection Schedule for Pharmacodynamic Assessment

DAY	PROCEDURE	SAMPLE	DESIRED TIME
CYCLE 1 DAY 1			
C1D1	Draw blood sample	PD	0 hour (prior to the dose of ARQ 751)
C1D1	Draw blood sample	CYP2D6	0 hour (prior to the dose of ARQ 751)
CYCLE 2 DAY 1			
C2D1	Draw blood sample	PD	0 hour (prior to the dose of ARQ 751)
CYCLE 3 DAY 1			
C3D1	Draw blood sample	PD	0 hour (prior to the dose of ARQ 751)
END OF TREATMENT			
EOT	Draw blood sample	PD	--

Sponsor's Signature

Study Title:	A Phase 1b Study of ARQ 751 as a Single Agent or in Combination with Other Anti-cancer Agents in Adult Subjects with Advanced Solid Tumors with PIK3CA/AKT/PTEN Mutations
Study Number:	ARQ 751-101

This clinical study protocol was subject to critical review and has been approved by the Sponsor.

Signed: PPD _____ Date: 09April2019

PPD
Chief Medical Officer
ArQule, Inc.

Investigator's Signature

Study Title:	A Phase 1b Study of ARQ 751 as a Single Agent or in Combination with Other Anti-cancer Agents in Adult Subjects with Advanced Solid Tumors with PIK3CA/AKT/PTEN Mutations
Study Number:	ARQ 751-101

I have received and read the protocol described above. I agree to comply with all applicable regulations and to conduct the study as described in the protocol. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.

Printed Name:_____

Signed:_____ Date:_____