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PROTOCOL SYNOPSIS

EudraCT/IND Number:	2009-016025-34/71,073
Protocol Number:	ARQ 197-A-U252
Investigational Product:	ARQ 197
Active Ingredient(s)/International Nonproprietary Name:	(3*R*,4*R*)-3-(5,6-Dihydro-4*H*-pyrrolo[3,2,1-*ij*]quinolin-1-yl)-4-(1*H*-indol-3-yl)pyrrolidine-2,5-dione
Study Title:	A Randomized, Placebo-Controlled, Phase 1/2 Study of ARQ 197 in Combination with Irinotecan and Cetuximab in Subjects with Metastatic Colorectal Cancer with Wild-Type KRAS Who Have Received Front-Line Systemic Therapy
Study Phase:	Phase 1 and Phase 2 (Phase 1/2)
Indication Under Investigation:	Treatment for metastatic colorectal cancer (CRC) in combination with irinotecan and cetuximab after failure of front-line systemic therapy in subjects with wild-type KRAS alleles.
Study Objectives:	**Phase 1:** **Primary Objectives:** • To evaluate the safety and tolerability of ARQ 197 when administered with irinotecan and cetuximab in subjects who have received front-line systemic therapy. • To define the recommended dose for Phase 2 study in combination with irinotecan and cetuximab. **Phase 2:** **Primary Objective:** • To estimate the difference in progression-free survival (PFS) between the study and control arms in subjects with CRC with wild-type KRAS who have received front-line systemic therapy.

Study Objectives: (continued)

Secondary Objectives:

- To estimate the difference between control and study arms in overall survival (OS) and objective response rate (ORR).
- To evaluate the safety profile of ARQ 197 in combination with irinotecan and cetuximab.

Exploratory Objectives:

- To evaluate the changes in epidermal growth factor (EGFR) mutations, BRAF mutations, EGFR fluorescence in-situ hybridization (FISH), mesenchymal-epithelial transition factor (c-MET) FISH, immunohistochemistry (IHC) for total c-MET, phosphatase and tensin homolog (PTEN) in tumors and explore their correlation with the effects of study treatment.
- To evaluate the changes in hepatocyte growth factor (HGF), vascular endothelial growth factor (VEGF), soluble c-MET, and sVEGF receptor (VEGFR) in plasma.
- To evaluate additional biomarkers, using these tumor and blood samples, as new data suggest.
- To explore the relationship between common genetic variants in CYP2C19 and UGT1A1 on primary and secondary endpoints as well as pharmacokinetic (PK) and pharmacodynamic measurements.
- To evaluate the PK/pharmacodynamic relationship of ARQ 197. Population PK/pharmacodynamic analysis will be conducted separately with possible pooling of data from other clinical studies of ARQ 197. This analysis will not be part of the statistical analysis plan for this study.
- To evaluate the population PK of irinotecan and the active metabolite SN-38. This will be conducted separately. This analysis will not be part of the statistical analysis plan for this study.
- To evaluate health-related quality of life (HRQOL), based on the Functional Assessment of Cancer Therapy-Colorectal (FACT-C) scale, in the control and study arms.

Study Design:	This is a phase 1/2 multicenter study. **Phase 1:** The Phase 1 portion is designed as an open-label study to evaluate the safety of ARQ 197 administered in combination with irinotecan and cetuximab. **Phase 2:** The Phase 2 portion is designed as a randomized, double-blind, placebo-controlled study to assess the efficacy and safety of ARQ 197 or matching placebo administered in combination with irinotecan and cetuximab. **Follow-up:** Follow-up information on overall survival and disease progression will be obtained, as appropriate, from all subjects for up to 12 months after the end of therapy visit.
Study Duration:	**Phase 1**: The estimated duration of the Phase 1 portion of the study is 24 weeks. **Phase 2**: All subjects will be followed until death, loss to follow-up, withdrawal of consent, start of a new therapy, or for 12 months after the end of treatment visit for the last subject on the study whichever comes first.
Study Sites and Location:	**Phase 1**: Approximately 3 sites in the United States (US). **Phase 2**: Approximately 40 sites in the US and Europe.
Planned Sample Size:	**Phase 1**: Approximately 6 to 18 eligible subjects will be enrolled.

Planned Sample Size: (continued)	**Phase 2**: For the Phase 2 portion of the study, a total of 150 subjects will be randomized equally to 2 treatment groups (1:1 randomization ratio), resulting in 134 evaluable subjects (if they receive study treatment, have measurable disease at baseline, have at least one post-baseline assessment for the primary efficacy variable and do not drop out prior to event [progression or death] or maximum follow-up time) assuming a 10% drop out rate. Assuming that the median PFS is 4.1 months for the placebo plus irinotecan and cetuximab group[1] and the ARQ 197 plus irinotecan and cetuximab group increases median PFS by 50% (ie, hazard ratio of 0.667), accrual of subjects is over 12 months, and the maximum treatment plus follow-up period for any subject is 20 months, then a total of 110 events are required to yield at least 80% power to detect a difference of 50% improvement in median PFS at a significance level of 0.10 (1-sided). The sample size computation is performed using the test based on exponential survival, accrual period procedure in the nQuery Advisor 7.0.
Subject Eligibility Criteria:	**Inclusion Criteria** Subjects must satisfy all of the following criteria to be included in the study: 1. Subjects with surgically unresectable locally advanced or metastatic disease who have received one prior line of chemotherapy, including irinotecan-based chemotherapy. Subjects who received only adjuvant treatment will be eligible if disease progressed less than 6 months after completion of adjuvant therapy (The Phase 1 portion of the study will be open for enrollment for subjects who received 1 or more prior therapies). Both relapsed and refractory CRC are allowed. Subjects must have radiologically documented disease progression prior to enrollment. 2. All subjects must express the wild-type form of the gene KRAS. 3. Measurable disease according to Response Evaluation Criteria in Solid Tumors [RECIST], Version 1.1 criteria. 4. Male or female ≥ 18 years of age. 5. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.

Subject Eligibility Criteria: (continued)	6. Resolution of any toxic effects of prior therapy (except alopecia) to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), Version 4.0, grade ≤ 1. 7. Adequate bone marrow, liver, and renal functions, defined as: • Hemoglobin ≥ 9.0 g/dL (transfusion and/or growth factor support allowed). • Absolute neutrophil count (ANC) $\geq 1.5 \times 10^9$/L. • Platelet count $\geq 75 \times 10^9$/L. • Serum creatinine $\leq 1.5 \times$ ULN or creatinine clearance ≥ 60 mL/min. • Alanine transaminase (ALT), aspartate transaminase (AST), and alkaline phosphatase $\leq 2.5 \times$ upper limit of normal (ULN) in subjects with no liver metastasis and ≤ 5.0 x ULN in subjects with liver metastasis. • Total bilirubin ≤ 1.5 x ULN (≤ 4 x ULN and direct bilirubin ≤ 1.5 x ULN is acceptable for subjects with Gilbert's syndrome). 8. Male and female subjects of child-bearing potential must agree to use double-barrier contraceptive measures, oral contraception, or avoidance of intercourse during the study and for 90 days after last investigational drug dose received. 9. All female subjects of childbearing potential must each have a negative pregnancy test (serum or urine) result before initiating study treatment. 10. Subjects must be fully informed about their illness and the investigational nature of the study protocol (including foreseeable risks and possible side effects) and must sign and date an Independent Ethics Committee (IEC) or Institutional Review Board (IRB)-approved informed consent form (ICF) (including Health Insurance Portability and Accountability Act [HIPAA] authorization, if applicable) before performance of any study-specific procedures or tests.

Subject Eligibility Criteria: **Exclusion Criteria**

(continued) Subjects who meet any of the following criteria will be disqualified from entering the study:

1. Prior therapy with an EGFR inhibitor.
2. History of malignancy other than CRC, unless there is an exception that the malignancy has been cured and no tumor-specific treatment for the malignancy has been administered within the 5 years prior to initiation of study treatment (subjects with a history of basal cell carcinoma or benign tumor of cervix can be enrolled if diagnosis and treatment occurred < 3 years prior to randomization).
3. Anticipation of need for a major surgical procedure or radiation therapy (RT) during the study.
4. Treatment with chemotherapy, radiotherapy, surgery, immunotherapy, biological therapy, or any other investigational anticancer agent within 4 weeks prior to start of study treatment.
5. History of cardiac disease:
   - Congestive heart failure defined as Class II to IV per New York Heart Association (NYHA) classification.
   - Active coronary artery disease (CAD).
   - Previously diagnosed bradycardia or other cardiac arrhythmia defined as Grade 2 or higher according to NCI CTCAE, version 4.0, or uncontrolled hypertension.
   - Myocardial infarction that occurred within 6 months prior to start of study treatment (myocardial infarction that occurred > 6 months before the start of study treatment is permitted).
6. Malabsorption syndrome, chronic diarrhea (lasting > 4 weeks), inflammatory bowel disease, or partial bowel obstruction.

Subject Eligibility Criteria: (continued)	7. Known metastatic brain or meningeal tumors, unless the subject is > 6 months from definitive therapy, has a negative imaging study within 4 weeks of first dose of study treatment, and is clinically stable (no concomitant therapy, including supportive therapy with steroids or anticonvulsant medications) with respect to the tumor at the time of first dose of study treatment. 8. Uncontrolled seizure disorder, spinal cord compression, or carcinomatous meningitis. 9. Pericardial or pleural effusion (eg, requiring drainage) or pericardial involvement with the tumor. Subjects with minimal pleural effusion may be eligible upon request by Investigator and approval by Sponsor. 10. Clinically significant active infection that requires antibiotic therapy. 11. Previous administration of ARQ 197 (or other known c-MET inhibitor). 12. Substance abuse or medical, psychological or social conditions that may, in the opinion of the Investigator, interfere with the subject's participation in the clinical trial or evaluation of the clinical trial results. 13. Any condition that is unstable or that could jeopardize the safety of the subject and the subject's protocol compliance, including known human immunodeficiency virus (HIV), hepatitis B virus (HBV) or hepatitis C virus (HCV) infection. 14. Inability to swallow oral medications. 15. Pregnant or nursing females.

Dosage Form, Dose and Route of Administration:	**Irinotecan and Cetuximab (Phase 1 and Phase 2):** A standard treatment schedule of irinotecan every 14 days in combination with cetuximab every 14 days will be used in this study. • Cycle 1 Day 1: Cetuximab 500 mg/m^2 IV infusion over 120 minutes, followed 60 minutes later with irinotecan IV infusion over 30 to 90 minutes at 180 mg/m^2. • All other treatment visits (starting with Cycle 1 Day 15): Cetuximab at 500 mg/m^2, IV infusion over 60 minutes followed by irinotecan IV infusion over 30 to 90 minutes at 180 mg/m^2. **ARQ 197:** ARQ 197 is supplied as a 120-mg capsule. **Phase 1**: ARQ 197 will be administered by mouth, with a meal, in escalating doses of 120 mg BID, 240 mg BID, and 360 mg BID to 3 separate cohorts of 3 or 6 subjects each. The recommended Phase 2 dose (RP2D) will be determined based on the observation of protocol-specified dose-limiting toxicities (DLT). If 0 of 3 initially treated subjects experience an ARQ 197-related DLT by day 29 of continuous twice-daily dosing, then dose escalation will occur. **Phase 2**: ARQ 197 will be administered at the RP2D determined in Phase 1. Matching placebo capsule will be administered orally BID to the control arm.
Study Endpoints:	**Phase 1**: The primary endpoint of this portion of the study is the determination of the RP2D, based on the assessment of DLTs. **Phase 2**: Primary Endpoint: • The primary end point is PFS.

Study Endpoints: (continued)	Secondary Endpoints: • The secondary end points are overall survival (OS) and objective response rate (ORR). Exploratory Endpoints: • Changes in EGFR mutations, BRAF mutations, EGFR FISH, c-MET FISH, IHC for total c-MET, and PTEN in tumors. • Changes in HGF, VEGF, soluble c-MET, and sVEGFR in plasma. • Additional biomarkers, as new data suggest. • Time-to-deterioration of HRQOL.
Statistical Analyses:	**Efficacy**: Comparisons of PFS between treatment groups will be made using the stratified log-rank test adjusting for the effects of the stratifications factors (ie, baseline ECOG performance status [0 versus 1] and best overall response to prior therapy [complete response (CR) and partial response (PR) and stable disease (SD) and progressive disease (PD)]) as well as using the Cox proportional hazards regression model. Point estimates and corresponding 95% confidence intervals (CIs) will be provided for median PFS and median OS by treatment group. Within the same Cox model, point estimates of hazard ratios and two-sided 95% CI will be obtained. In addition, Kaplan-Meier product limit estimates will be plotted for PFS and OS by treatment group. Estimates of the ORR and corresponding two-sided 95% CI will also be presented by treatment group. **Safety**: Adverse events (AEs) will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and summarized for the number and percentage of subjects reporting treatment-emergent AEs (TEAEs). AEs/toxicities reported by the subject or noted by the Investigator and laboratory test results (hematology and blood chemistry) will be graded according to the NCI CTCAE, Version 4.0, and will be listed and summarized.

Statistical Analyses: (continued)	**Biomarkers**: Descriptive statistics for biomarker values by scheduled measurement time as well as for change from baseline will be computed and provided, if appropriate.
	Pharmacokinetics: The plasma concentration–time profile of ARQ 197 in subjects will be analyzed using population pharmacokinetics. The results will be published in a separate pharmacokinetics report outside the clinical study report for this study.

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1 Cunningham D, Humblet Y, Siena S, Khayat D, Bleiberg H, Santoro A, et al. Cetuximab monotherapy and cetuximab plus irinotecan in irinotecan-refractory. metastatic colorectal cancer. N Engl J Med. 2004 Jul 22;351(4):337-45.