REPORT SYNOPSIS

Name of Sponsor/Company: ArQule, Inc.	Individual Study Table Referring to Part of the Dossier Volume: Page:	*(For National Authority Use Only)*
Name of Test Product: ARQ 197		
Name of Active Ingredient: (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		

Title of Study:	A Randomized Phase 2 Study of Erlotinib plus ARQ 197 versus Erlotinib plus Placebo in Previously Treated Subjects with Locally Advanced or Metastatic Non-Small Cell Lung Cancer (ARQ 197-209)
Phase of Development:	2
Study Period:	First subject first visit date: 20 Oct 2008 Last subject last visit date: 19 May 2011
Investigator(s):	The principal investigator for this study was Lecia V. Sequist, MD, at the Massachusetts General Hospital, Boston, MA. The details of all investigators who participated in this study are provided in Appendix 16.1.4.
Study Centers:	Study ARQ 197-209 was conducted at a total of 33 study centers with 16 centers in the US, 6 centers in Germany, 5 centers in Poland, 4 centers in Russia, and 1 center each in the Ukraine and Latvia. Study centers in the United States (US) were: Akerley (126), Badarinath (130), Camacho (107), Fidler (108), Gabrail (124), Gerber (116), Ghraowi (100),Goldman (002), Henderson (101), Kruger (128), Kennedy and Mena (115), Samaha (114), Senzer (102), and Sequist (105, 132, 133); in Russia: Byakhov (209), Orlov (203), Severtsev (211), and Moiseyenko (219); in the Ukraine: Shparyk (308);in Poland: Koralewski (417), Ramlau (418), Sawrycki (413), Serwatowski (420), and Szczesna (419); in Germany: Brugger (506), Eschbach (510), Manegold (511), Reck (507), Sebastian (508), and von Pawel (509); and in Latvia: Ratiani (601).
Publications (references):	Schiller J H, Akerley WL, Brugger W, Ferrari D, Garmey EG, Gerber DE, et al. Results from ARQ 197-209: ARQ 197 A Global Randomized Placebo-Controlled Phase 2 Clinical Trial Comparing Erlotinib Plus ARQ 197 to Erlotinib Plus Placebo in Previously Treated EGFR Inhibitor Naïve Patients with Locally Advanced or Metastatic Non-Small Cell Lung Cancer. ASCO; 2010; Chicago, IL, June 2010; Sequist LV, von Pawel J, Garmey EG, Akerley WL, Brugger W, Ferrari D, et al. Randomized Phase 2 Study of Erlotinib Plus ARQ 197 Versus Erlotinib Plus Placebo, in Previously Treated Non-small Cell Lung Cancer ESMO, Milan, Italy, October 2010; Sequist LV, von Pawel J, Garmey EG, Akerley WL, Brugger W, Ferrari D, et al. Randomized Phase II Study of Erlotinib Plus Tivantinib Versus Erlotinib Plus Placebo in Previously Treated Non-Small-Cell Lung Cancer. J Clin Oncol. 2011 Aug 20;29(24):3307-15.

Name of Sponsor/Company: ArQule, Inc.	Individual Study Table Referring to Part of the Dossier Volume: Page:	*(For National Authority Use Only)*
Name of Test Product: ARQ 197		
Name of Active Ingredient: (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		

Primary Study Objectives/Hypothesis:	The primary objective was to evaluate progression-free survival (PFS) among all eligible subjects (Intent-to-Treat [ITT] Population) treated with erlotinib plus ARQ 197 (EA or ARQ 197 combination arm) compared to erlotinib plus placebo (EP or placebo combination arm).
Secondary Study Objectives:	The secondary objectives were as follows: • To evaluate PFS among subsets of eligible subjects treated with the ARQ 197 combination arm compared to subjects treated with the placebo combination arm including: all evaluable subjects; subjects with non-mutant V-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog (KRAS) and Epidermal Growth Factor Receptor (EGFR)-associated tumors (EGFR exon 19 deletion or exon 21 L858R mutation or EGFR fluorescent in-situ hybridization [FISH]-positive); subjects with EGFR-associated tumors only; subjects with non-mutant KRAS only; and subjects with mesenchymal-epithelial transition factor (MET) over-expressing tumors only (Aperio digital scanning immunohistochemistry [IHC] score > 50) (ie, MET-positive tumors only). • To evaluate overall survival among all eligible subjects (ITT Population) and subsets of eligible subjects treated with the ARQ 197 combination arm compared to subjects treated with the placebo combination arm including: all evaluable subjects; subjects with non-mutant KRAS and EGFR-associated tumors; subjects with EGFR-associated tumors only; subjects with non-mutant KRAS only; and subjects with MET-positive tumors only. • To determine the objective response rate (ORR) among all eligible subjects (ITT Population) and subsets of eligible subjects treated with the ARQ 197 combination arm compared to subjects treated with the placebo combination arm including: all evaluable subjects; subjects with non-mutant KRAS and EGFR-associated tumors; subjects with EGFR-associated tumors only; subjects with non-mutant KRAS only; and subjects with MET-positive tumors only. • To determine the ORR among eligible subjects (ITT Population) treated with the double-blind placebo combination arm following the event of progression on-study and subsequent unblinded crossover to receive OL ARQ 197 combination arm treatment. • To further characterize the safety of ARQ 197 in combination with erlotinib in non-small cell lung cancer (NSCLC) subjects.
Exploratory Study Objectives	There were no exploratory objectives named in the protocol or the Statistical Analysis Plan (SAP); however the SAP Version 2.0, dated 22 Mar 2010 did refer to exploratory efficacy variables.

Name of Sponsor/Company: ArQule, Inc.	Individual Study Table Referring to Part of the Dossier Volume: Page:	*(For National Authority Use Only)*
Name of Test Product: ARQ 197		
Name of Active Ingredient: (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 Design/Methodology

This was a global, multicenter, randomized, placebo-controlled, double-blind, Phase 2 study designed to compare the efficacy and safety of treatment with erlotinib 150 mg once daily (QD) plus ARQ 197 360 mg twice daily (BID) (ARQ 197 combination arm) versus treatment with erlotinib QD plus placebo BID (placebo combination arm) in NSCLC subjects previously treated with a chemotherapy regimen (other than erlotinib or other EGFR inhibitors). The planned number of subjects was 154 (77 subjects per arm) at up to 50 study sites.

Pre-study Period (up to 7 days)

Following the informed consent process and prior to the start of any study required procedures, the Investigator or associate established the availability of appropriate pathology specimens. Potentially eligible subjects entered a pre-study period (up to 7 days) when they underwent screening procedures.

Double-blind Treatment Period (28-day cycles)

Eligible subjects were randomly assigned to receive double-blind treatment consisting of 4-week (28-day) cycles of treatment with either the ARQ 197 or the placebo combination arm. Treatment continued until progression of disease, unacceptable toxicity, or another discontinuation criterion was met.

OL Crossover Treatment Period (28-day cycle)

Following confirmed progression of disease, all eligible subjects were unblinded. Those subjects who were randomly assigned to receive the double-blind placebo combination arm directly entered the crossover period and received OL ARQ 197 combination arm treatment, which continued until progression of disease, unacceptable toxicity, or another discontinuation criterion was met.

Addendum for ARQ 197-299 Extension Study

After evaluation of all primary and secondary endpoints outlined in the protocol and SAP, the following subjects could migrate from the present study (ARQ 197-209) to an extension protocol (ARQ 197-299):

- ARQ 197 combination arm subjects who were stable per Response Evaluation Criteria in Solid Tumors (RECIST Version 1.0) criteria or were receiving clinical benefit (as determined by the Investigator and Medical Monitor)
- Placebo combination arm subjects who were stable per RECIST criteria and were from sites who had ARQ 197 combination arm subjects who met the above criteria

Prior to Institutional Review Boards/ Independent Ethics Committees approval of the extension protocol, ARQ 197 combination arm subjects remained blinded on the current study until RECIST progression per CT or MRI evaluation using

Name of Sponsor/Company: ArQule, Inc.	Individual Study Table Referring to Part of the Dossier Volume: Page:	*(For National Authority Use Only)*
Name of Test Product: ARQ 197		
Name of Active Ingredient: (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 Design/Methodology (continued)	RECIST criteria Version 1.0 or until the ARQ 197-299 extension was approved and informed consent obtained. **End-of-Treatment Visit (±7 days), Safety Follow-up Visit (30 days), and Survival Follow-ups Visits (±14 days)** All subjects had an End-of-Treatment Visit (±7 days), a Safety Follow-up Visit 30 days after their last dose of assigned treatment, and after discontinuation of treatment, Survival Follow-ups every 3 months (±14 days) until a date of death was obtained. During the study, data on tumor measurement and survival status were collected for the evaluation of PFS, overall survival, and ORR. To characterize the safety profile of ARQ 197 in combination with erlotinib, subjects were monitored throughout the study for adverse events (AEs), and for changes in laboratory values, vital signs, electrocardiograms (ECGs), and physical examination findings.
Duration of Treatment for Individual Subject:	The treatment for an individual subject continued until progression of disease, unacceptable toxicity, or another discontinuation criterion was met. All subjects were unblinded at the time of confirmed radiographic progression. Following progression and prior to unblinding, eligible subjects randomly assigned to the double-blind placebo combination arm were offered the opportunity to receive treatment with OL EA and were followed for ORR following progression.
Number of Subjects:	Planned: 154 subjects (77 subjects per arm) Screened: 173 subjects Enrolled/Randomized: 167 (84/83) subjects Completed/Discontinued: 148 (74/74) subjects as of 20 Aug 2010 Ongoing at Time of Analysis: 19 subjects.
Diagnosis and Main Criteria for Study Entry	This study enrolled adult subjects with histologically or cytologically confirmed inoperable locally advanced or metastatic (Stage IIIB/IV) NSCLC who had received at least 1 prior chemotherapy regimen (which did not include erlotinib or other EGFR-inhibiting agents); had measurable disease (as defined by RECIST Version 1.0); had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1; adequate bone marrow, liver, and renal functions; and confirmed availability of archival pathology samples (10 unstained paraffin-embedded slides) or tissue block suitable for subsequent analysis of KRAS, EGFR, and MET. Subjects were required to meet all eligibility criteria to be enrolled.

Name of Sponsor/Company: ArQule, Inc.	Individual Study Table Referring to Part of the Dossier Volume: Page:	*(For National Authority Use Only)*
Name of Test Product: ARQ 197		
Name of Active Ingredient: (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		

Investigational Product and Comparator Information:	**ARQ 197** Dose: 360 mg BID for a total daily dose of 720 mg Dosage Form: white opaque capsule Route of Administration: oral (PO), 1 hour before or 2 hours after meals Lot Number for 60 mg capsules: 8D044-P1, 8F074-P1, 8K121-P1, and 8K122-P1. Packaging Information: packaged as ARQ 197 or Placebo 60 mg capsules in 90-count bottles. Both placebo and ARQ 197 were identical in appearance. **Matching Placebo for ARQ 197** Dose: 0 mg BID for a total daily dose of 0 mg Dosage Form: white opaque capsule Route of Administration: PO, 1 hour before or 2 hours after meals Lot Number for 0 mg capsules: 8D043-P1 and 8F075-P1 Packaging Information: packaged as ARQ 197 or Placebo 60 mg capsules in 90-count bottles. Both placebo and ARQ 197 were identical in appearance. **Erlotinib** Dose: 150 mg QD for a total daily dose of 150 mg Dosage Form: nearly white film-coated tablet (European Union [EU]: biconvex; US: convex) Route of Administration: PO, at least 1 hour before or 2 hours after food Lot Number for 150 mg tablets: P426201/WK60596.003, 8686801-44491A0, B2000, B2030B01, B2033B01, B2034B01, B2036B01, B2037B01, and B1034 Lot Number for 100 mg tablets: P426101/WK60596.005, 6552501-4401B0, B2001, and B1009. Packaging Information for EU supply: packaged in cartons containing 3x10 tablets in foil blisters for a total of count of 30 tablets per carton. Packaging Information for US supply: packaged in 30-count bottles.

Criteria for Evaluation:

Efficacy:

The primary efficacy variable was PFS.

Secondary variables included overall survival time, ORR, the number and percentage of subjects in each RECIST response category, and ORR for crossover subjects.

Prognostic Variables: evaluation of pathology specimens.

Pharmacodynamics/Pharmacokinetics: Not done

Safety: AEs, laboratory tests, vital signs, ECOG performance status, physical examination, ECG results, and concomitant medications and procedures.

Name of Sponsor/Company: ArQule, Inc.	Individual Study Table Referring to Part of the Dossier Volume: Page:	*(For National Authority Use Only)*
Name of Test Product: ARQ 197		
Name of Active Ingredient: (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		

Statistical Methods

Analysis of Efficacy:

The primary efficacy variable was PFS in the ITT Population after the goal of 120 events was reached. After 120 PFS events were reached, data for all subjects were to be unblinded and an analysis of PFS performed. All analyses for PFS ultimately contained 122 PFS events (generated 23 Mar 2010 based on 10 Feb 2010 data cut-off). The PFS analysis was conducted on the complete clinical study data set, but no p-values were determined; no overall survival analyses were performed at the time of PFS analysis. Final overall survival and safety analyses were planned to be performed at the end of the study after all subjects had a minimum survival follow-up time of at least 8 months from the time of enrollment. Additional efficacy analyses were conducted on 129 PFS events (generated on 27 Sep 2010 based on 07 May 2010 data cut-off).

All efficacy analyses were performed in both the ITT and Evaluable Population, with ITT as the primary population for PFS. The PFS curve was estimated using the Kaplan-Meier (product-limit) method and presented graphically for each treatment group. Median PFS time was calculated based on Kaplan-Meier estimates and the 95% confidence interval (CI) for the median PFS was calculated using the method provided by Brookmeyer and Crowley (1982) for each treatment group. The unadjusted log-rank test was performed to compare the treatment groups. The Cox proportional hazards model was used to estimate the hazard ratio and the 95% CI. The model included treatment as the only factor with no other adjustment.

Overall survival was analyzed similarly to the PFS. Six-month and 1-year overall survival rates were estimated based on the Kaplan-Meier estimate. The 95% CIs for the survival rates were estimated based on the asymptotic normality approach. Both PFS and overall survival were also analyzed using the proportional hazards model. The model included the treatment group and prognostic and biomarker variables as factors. Overall survival was analyzed similarly to the PFS. Six-month and 1-year overall survival rates were estimated based on the Kaplan-Meier estimate. The 95% CIs for the survival rates were estimated based on the asymptotic normality approach. Both PFS and overall survival were also analyzed using the proportional hazards model. The model included the treatment group and prognostic and biomarker variables as factors. The ORR and the corresponding 95% CIs were calculated. The number and percentage of subjects for each RECIST (Version 1.0) category were analyzed similarly to the ORR. A logistic regression analysis was performed for the ORR. The model included the treatment group and the prognostic and biomarker variables as factors.

Analysis of Safety:

Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 11.1 and summarized by the number and percentage of subjects reporting AEs.

Adverse events/toxicities reported by the subject or noted by the Investigator and laboratory test results were graded according to the National Cancer Institute (NCI) Common Terminology Criteria for AEs (CTCAE), Version 3.0 and were listed and summarized.

Name of Sponsor/Company: ArQule, Inc.	Individual Study Table Referring to Part of the Dossier Volume: Page:	*(For National Authority Use Only)*
Name of Test Product: ARQ 197		
Name of Active Ingredient: (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		

Summary:

Efficacy Results

A total of 167 subjects in the ITT Population, 139 subjects in the Evaluable Population, and 35 subjects in the Crossover Population were included in the assessment and analysis of efficacy variables.

Median PFS in the ITT Population was 113 days in the double-blind ARQ 197 combination arm compared with 68 days in the double-blind placebo combination arm. This difference between the treatment groups was not statistically significant (hazard ratio=0.81; log rank test p=0.2422). Similar results were seen within the Evaluable Population (113 days for subjects in the ARQ 197 combination arm compared to 105 days for subjects in the placebo combination arm [hazard ratio=0.82; p=0.3021]). All analyses for PFS were based on a database snapshot at the time of 122 PFS events (generated 23 Mar 2010 and based on 10 Feb 2010 data).

When adjusting for key prognostic factors, PFS analysis for the ITT Population using the Cox regression model results in a hazard ratio for the ARQ 197 combination arm subjects versus the placebo combination arm subjects of 0.68 (95% CI: 0.47, 0.98; p=0.0384). The model included the treatment group and the following prognostic and biomarker variables as factors: time from diagnosis, prior chemotherapy regimens, smoking, age, sex, histology, ECOG performance status at baseline, brain/other central nervous system metastases at baseline, MET gene copy number, EGFR mutation status, and KRAS mutation status. Analyses were based on a database snapshot at the time of 122 PFS events (generated 23 Mar 2010 and based on 10 Feb 2010 data).

A comparison between the ARQ 197 combination arm and the placebo combination arm in subpopulations of subjects with a non-squamous cell histology tumor (ITT Population) showed a PFS hazard ratio of 0.71 (95% CI: 0.46, 1.10; p=0.1210). Median PFS was 132 days in ARQ 197 combination arm subjects and 68 days in placebo combination arm subjects. Analyses were based on a database snapshot at the time of 122 PFS events (generated 23 Mar 2010 and based on 10 Feb 2010 data).

Median overall survival in the ITT Population was 256 days in the double blind ARQ 197 combination arm compared to 206 days in the double blind placebo combination arm. The hazard ratio was 0.87 (Cox-regression model p=0.4710). Similar results were seen within the Evaluable Population, with a median survival of 302 days in the ARQ 197 combination arm compared to 265 days in the placebo combination arm (hazard ratio: 0.83; p=0.4161).

Compared to placebo combination therapy, ARQ 197 combination therapy showed a PFS hazard ratio of 0.38 (95% CI: 0.14, 0.99; p=0.0403) and an overall survival hazard ratio of 0.34 (95% CI: 0.13, 0.88; p=0.0205) in subjects in the ITT Population with the tumor subtypes of MET FISH positive and EGFR wild-type.

Name of Sponsor/Company: ArQule, Inc.	Individual Study Table Referring to Part of the Dossier Volume: Page:	*(For National Authority Use Only)*
Name of Test Product: ARQ 197		
Name of Active Ingredient: (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		

Summary (continued):

Safety Results

Of the 167 subjects in the Safety Population, 84 subjects received treatment with the ARQ 197 combination arm and 83 subjects received treatment with the placebo combination arm.

During the double-blind period, within the ITT Population, subjects in the ARQ 197 combination arm received treatment for up to 447 days (14.7 months) and subjects in the placebo combination arm received treatment for up to 484 days (15.9 months). Subjects in the Crossover Population received treatment with erlotinib up to 233 days and with ARQ 197 up to 234 days (7.7 months, each treatment).

Treatment-emergent AEs (TEAEs) were reported in 165 subjects (98.8%) in the Safety Population overall; the 5 most frequently reported TEAEs for all subjects were rash (59.3%), diarrhea (50.9%), fatigue (35.3%), anorexia (31.1%), and nausea (26.9%). The rate of subjects reporting at least 1 TEAE was the same between the ARQ 197 combination arm (98.8%) and the placebo combination arm (98.8%).

Treatment-emergent AEs of CTCAE Grade 3 or higher severity were reported in 107 subjects (64.1%) in the Safety Population overall; the most common severe TEAEs were dyspnea (10.2%), rash (8.4%), disease progression (7.8%), diarrhea (7.2%), anemia (6.6%), fatigue (5.4%), and pulmonary embolism (5.4%). The rate of TEAEs of CTCAE Grade 3 or higher severity was similar between the ARQ 197 combination (63.1%) and the placebo combination (65.1%) arms.

AEs considered by the Investigator to be at least possibly related to study treatment were reported in 94 subjects (56.3%) in the Safety Population overall; the most common treatment related AEs were diarrhea (28.7%), rash (28.1%), fatigue (13.2%), anorexia (12.0%), nausea (10.8%), and vomiting (9.0%). The rate of AEs possibly related to study treatment was similar between the ARQ 197 (56.0%) and placebo (56.6%) combination arms.

Hematologic TEAEs (ie, neutropenia, anemia) were of particular interest as known effects of ARQ 197; 14.3% of subjects in the ARQ 197 combination arm developed anemia compared with 13.3% of subjects in the placebo combination arm; 6.0% of subjects in the ARQ 197 combination arm developed neutropenia compared with 3.6% of subjects in the placebo combination arm. Neither of these differences was statistically significant, and these percentages are similar to those observed with ARQ 197 monotherapy.

TEAEs with an outcome of death were reported in 38 subjects (22.8%) in the Safety Population overall. The rate of subjects who experienced TEAEs with an outcome of death was slightly lower in the ARQ 197 combination arm (17 subjects, 20.2%) when compared with the placebo combination arm (21 subjects, 25.3%).

Serious TEAEs were reported in 74 subjects (44.3%) in the Safety Population overall. The most common SAE in this population was disease progression (7.8%). The most notable difference in SAEs between treatment groups was the SAEs of dyspnea (2.4% in the ARQ 197 combination arm

Name of Sponsor/Company: ArQule, Inc.	Individual Study Table Referring to Part of the Dossier Volume: Page:	*(For National Authority Use Only)*
Name of Test Product: ARQ 197		
Name of Active Ingredient: (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		

Summary (continued):

Safety Results (continued)

versus 8.4% in the double blind placebo combination arm) and pulmonary embolism (2.4% for the ARQ 197 combination arm versus 7.2% in the double blind placebo combination arm). Serious TEAEs considered by the Investigator at least possibly related to study treatment were reported for 18 subjects overall (10.8%).

In the Safety Population overall, 35 subjects (18 subjects in the ARQ 197 combination arm, 17 subjects in the placebo combination arm) were discontinued from treatment due to TEAEs. The most common TEAE leading to treatment discontinuation was diarrhea (3.0%). Treatment emergent AEs that led to discontinuation in more than 1 subject in either treatment group were vomiting, nausea, dyspnea, disease progression, and anemia. The rate of discontinuations due to a serious TEAE was similar between the ARQ 197 combination arm (21.4%) and placebo combination arm (20.5%) treatment groups.

For mean change from baseline in hematologic laboratory values, no clinically meaningful between-treatment-group differences were observed. Individual clinically significant results included:

7 ARQ 197 combination arm subjects who experienced clinically significant decreases in red blood cell (RBC) analytes and 7 ARQ 197 combination arm subjects who experienced decreases in neutrophils, platelets, or leukocytes or related TEAEs. Most of these decreases in hematologic values were considered related to study drug and most were resolved by the time of study discontinuation.

For mean change from baseline in non-hematologic laboratory values, no clinically meaningful between-treatment-group differences were observed with the exception of an increased mean change from baseline in liver function values in the placebo combination arm. Clinically significant non-hematologic laboratory values reported in the ARQ 197 combination arm were rare and most were resolved by the time of study discontinuation. No clinically significant values were reported for coagulation parameters. Other isolated instances of clinically significant laboratory abnormalities were expected in this high risk population.

Bradycardia occurred infrequently and was reported as a TEAE in 4 subjects in the ARQ 197 combination arm (Subjects 116-0010, 203-0148, 128-0153, and 114-0173). One of these events was considered serious (Subject 116-0010) and possibly related to ARQ 197 treatment and not related to erlotinib treatment; therapy was temporarily interrupted and resolution of the event was within a day. Subject 116-0010 entered the study with clinically significant sinus bradycardia. Other isolated instances of clinically significant ECG abnormalities, such as tachycardia and atrial fibrillation, were infrequent and similarly distributed across the treatment arms.

ARQ 197 treatment in combination with erlotinib appears to be well tolerated. The occurrence of TEAEs in the 2 treatment groups was similar and appears consistent with the monotherapy safety profiles of ARQ 197 and erlotinib. The incidences of severe TEAEs, serious adverse events (SAEs), and deaths were comparable between the 2 treatment groups.

<table>
<tr><td>Name of Sponsor/Company:
ArQule, Inc.</td><td rowspan="3">Individual Study Table Referring to Part of the Dossier
Volume:
Page:</td><td rowspan="3">(For National Authority Use Only)</td></tr>
<tr><td>Name of Test Product:
ARQ 197</td></tr>
<tr><td>Name of Active Ingredient:
(3R,4R)-3-(5,6-Dihydro-4H-pyrrolo[3,2,1-ij]quinolin-1-yl)-4-(1H-indol-3-yl)pyrrolidine-2,5-dione</td></tr>
<tr><td colspan="3">Conclusions:

No statistically significant difference was demonstrated for the ARQ 197 combination arm when compared to the placebo combination arm in median PFS (hazard ratio=0.81; p=0.2422) or in median overall survival (hazard ratio=0.87; p=0.4710).
Median PFS in the ITT Population was 113 days in the double blind ARQ 197 combination arm, compared with 68 days in the double blind placebo combination arm. The difference between the treatment groups for the ITT Population was not statistically significant (log rank test p=0.2422). The hazard ratio was 0.81 (95% CI: 0.57; 1.15). Similar results were seen within the Evaluable Population.
When adjusting for key prognostic factors, PFS analysis for the ITT Population was statistically significant using the Cox regression model and resulted in a hazard ratio of 0.68 for the ARQ 197 combination arm subjects versus the placebo combination arm subjects (95% CI: 0.47, 0.98; p=0.0384). The model included the treatment group and the following prognostic and biomarker variables as factors: time from diagnosis, prior chemotherapy regimens, smoking, age, sex, histology, ECOG performance status at baseline, brain/other central nervous system metastases at baseline, MET gene copy number, EGFR mutation status, and KRAS mutation status.
Overall, the ARQ 197 combination treatment revealed a trend in improving PFS and OS. The trend of improvement was stronger in certain subgroups: non-squamous cell sub-group and KRAS mutant subgroup. The trends in these subgroups merit further investigation.
ARQ 197 combination treatment was well tolerated.</td></tr>
<tr><td colspan="2">Date of the Report:</td><td>31 Oct 2012</td></tr>
</table>