ArQule Announces Publication of Preclinical Data for ARQ 531, a Reversible Inhibitor of Both Wild Type and Mutant BTK

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Data Support ARQ 531 as a Potential First- and Best-In-Class Reversible BTK Inhibitor, with the Potential to Address Emerging Resistance to Irreversible BTK Inhibitors

BURLINGTON, Mass.--(BUSINESS WIRE)--Aug. 13, 2018-- ArQule, Inc. (Nasdaq:ARQL), today announced the publication of preclinical study data for ARQ 531, the Company's rationally-designed, reversible inhibitor of both wild type and C481S-mutant Bruton's tyrosine kinase (BTK). The studies, published in *Cancer Discovery*, were conducted in collaboration with researchers at The Ohio State University. Data from these studies demonstrated efficacy in *in vitro* and *in vivo* hematologic malignancy models that recapitulate the most common mechanisms of resistance to irreversible BTK inhibitors, including ibrutinib.

Highlights from the manuscript (link here) include:

Differentiated Crystal Structure and Biochemical Profile

- The crystal structure of ARQ 531 bound to BTK elucidates the mechanism of BTK inhibition that is not dependent on the specific amino acid residue at position 481 (eg. C or S)
- Recombinant BTK biochemical assays of ARQ 531 and ibrutinib show similar inhibition for wild type BTK, however ibrutinib has dramatically lower inhibition, binding affinity and residence time for mutant BTK

"Relapsed and refractory patients that develop resistance to ibrutinib have poor outcomes and limited treatment options," said Brian Schwartz, M.D., Chief Medical Officer and Head of R&D at ArQule. "ARQ 531 was rationally-designed and selected to address this unmet need by inhibiting both wild type and mutant BTK. The published crystal structure and biochemistry clearly demonstrate the mechanism by which ARQ 531 maintains binding and inhibition of mutant BTK in conditions where ibrutinib cannot."

Established Activity in Multiple Cellular and Murine Models of Hematological Malignancies

- Exhibited dose dependent toxicity in human primary CLL cells (mutant and wild type)
- Inhibited CLL cell migration *in vitro*
- Established superiority to ibrutinib in an engraftment murine model of CLL
- Showed activity against other B-cell signaling pathways
- Demonstrated efficacy in a murine model of Richter's transformation

John Byrd, M.D., the Warren Brown Chair of Leukemia Research at The Ohio State University stated, "The inhibition profile of ARQ 531 may confer distinct advantages over ibrutinib, potentially expanding the patient population beyond those with a C481S mutation who may benefit from treatment. Targeting multiple kinases in the B cell activation pathway may provide more durable responses to treatment while also delaying the emergence of treatment resistance. Jennifer Woyach, M.D., Associate Professor of Medicine at The Ohio State University, added, "I am particularly encouraged by the CLL mouse model data which established the superior efficacy of ARQ 531 compared to ibrutinib and the efficacy of ARQ 531 in the model of Richter's transformation as this is an extremely aggressive disease with very few treatment options."

About ArQule

ArQule is a biopharmaceutical company engaged in the research and development of targeted therapeutics to treat cancers and rare diseases. ArQule's mission is to discover, develop and commercialize novel small molecule drugs in areas of high unmet need that will dramatically extend and improve the lives of our patients. Our clinical-stage pipeline consists of five drug candidates, all of which are in targeted, biomarker-defined patient populations, making ArQule a leader among companies our size in precision medicine. ArQule's pipeline includes: ARQ 531, an orally bioavailable, potent and reversible inhibitor of both wild type and C481S-mutant BTK, in Phase 1 for patients with B-cell malignancies refractory to other therapeutic options; Miransertib (ARQ 092), a selective inhibitor of the AKT serine/threonine kinase, in a phase 1/2 company-sponsored study for Overgrowth Diseases, in a Phase 1 study for ultra-rare Proteus syndrome conducted by the National Institutes of Health (NIH), and in Phase 1b in combination with the hormonal therapy, anastrozole, in patients with advanced endometrial cancer; ARQ 751, a next generation AKT inhibitor, in Phase 1 for patients with AKT1 and PI3K mutations; Derazantinib, a multi-kinase inhibitor designed to preferentially inhibit the fibroblast growth factor receptor (FGFR) family, in a registrational trial for iCCA; and ARQ 761, a β-lapachone analog being evaluated as a promoter of NQO1-mediated programmed cancer cell necrosis, in Phase 1/2 in multiple oncology indications in partnership with the University of Texas Southwestern Medical Center. ArQule's current discovery efforts are focused on the identification and development of novel kinase inhibitors, leveraging the Company's proprietary library of compounds.

About BTK and ARQ 531

Bruton's tyrosine kinase, BTK, is a therapeutic target that has been clinically proven to inhibit B-cell receptor signaling in blood cancers. ARQ 531 is an orally bioavailable, potent and reversible BTK inhibitor. Biochemical and cellular studies have shown that ARQ 531 inhibits both the wild type and

C481S-mutant forms of BTK. The C481S mutation is a known resistance mechanism for first generation irreversible BTK inhibitors. In preclinical studies, ARQ 531 has demonstrated good oral bioavailability as well as favorable pharmacokinetic, pharmacodynamic and metabolic properties.

Forward Looking Statements

This press release contains forward-looking statements regarding preclinical experiments and with ARQ 531. These statements are based on the Company's current beliefs and expectations and are subject to risks and uncertainties that could cause actual results to differ materially. Positive information about pre-clinical results does not ensure that clinical trials will be successful. For example, ARQ 531 may not demonstrate promising therapeutic effect in man; in addition, it may not exhibit an adequate safety profile in planned or later stage or larger scale clinical trials as a result of known or as yet unanticipated side effects. The results achieved in later stage trials may not be sufficient to meet applicable regulatory standards or to justify further development. Problems or delays may arise during clinical trials or in the course of developing, testing or manufacturing ARQ 531 that could lead the Company to discontinue development. Even if later stage clinical trials are successful, unexpected concerns may arise from subsequent analysis of data or from additional data. Obstacles may arise or issues may be identified in connection with review of clinical data with regulatory authorities. Regulatory authorities may disagree with the Company's view of the data or require additional data or information or additional studies. In addition, we and are collaborators are utilizing diagnostic tests to identify patients in the Phase 1 trial with the BTK C481S mutation and expect to utilize diagnostic tests in other clinical trials with ARQ 531. We or our collaborators may need to develop and register these or other diagnostic tests as companion diagnostics with the FDA.We or our collaborators may encounter difficulties in developing and obtaining regulatory approval for companion diagnostics, including issues relating to access to certain technologies, selectivity/specificity, analytical validation, reproducibility, or clinical validation. Any delay or failure by our collaborators or us to develop or obtain regulatory approval of companion diagnostics could delay or prevent approval of our product candidates. Drug development involves a high degree of risk. Only a small number of research and development programs result in the commercialization of a product. For more detailed information on the risks and uncertainties associated with the Company's drug development and other activities, see the Company's periodic reports filed with the Securities and Exchange Commission. The Company does not undertake any obligation to publicly update any forward-looking statements.

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