ARQ 531, a Novel and Reversible Inhibitor of Bruton’s Tyrosine Kinase, Displays Favorable Oral Bioavailability and Exposure in Patients with B-cell Malignancies

Terence Hall, Yi Yu, Sudharshan Eathiraj, Deborah Stephens, Jennifer Woyach, Ian Flynn, Ronald E. Savage, and Brian Schwartz

ArQule, Inc., Burlington, MA; Huntsman Cancer Institute, Salt Lake City, Utah; Ohio State University, Columbus, OH; Sarah Cannon Research Institute, Nashville, TN

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Background
 Bruton’s tyrosine kinase (BTK) is a key regulator of the B-cell receptor (BCR) signaling, the majority of which are dependent on BCR BTK. BTK signaling is specifically activated and contributes to pathogenesis of B-cell tumors and lymphomas. Despite impressive clinical activity, BTK inhibitors are not currently approved for the treatment of B-cell malignancies due to their ability to induce resistance mechanisms. Resistance to BTK inhibition is caused by secondary resistance mechanisms that contribute to the resistance mechanism, including BTK’s autophosphorylation at Ser2036/2037, which is prominent during continuous BTK inhibition.

ARQ 531, a potential reversible inhibitor of BTK and BTK-C4815 mutant

Inclusion/Exclusion Criteria
Key Inclusion Criteria
- Patients aged ≥12 years
- Relapsed or refractory CLL/SLL, WM, B-cell NHL who have received at least two lines of prior therapy
- Prior therapy must include a BTK inhibitor in diseases for which approved
- Adequate hematologic and non-hematologic performance status (ECOG ≤ 1, Karnofsky ≥70)
- Adequate organ function
- A washout period of at least 5 times the half-life after the last dose of any
- Male or female
- ≤1.5 × upper limit of normal (ULN) for ALT and AST
- ≤3 × ULN for bilirubin
- ≤3 × ULN for total protein
- ≤3 × ULN for creatinine

Key Exclusion Criteria
- Pregnant or lactating women
- Active infection
- Severe allergic/immunologic response to ARQ 531
- Any other condition that makes the patient inappropriate for study participation

Methods
ARQ 531 is a novel, reversible, ATP-binding site inhibitor of BTK. The study was designed as a Phase I trial with dose-escalation (3+3 design) and continual cohorts design. All patients received oral ARQ 531 once daily for 28 days as a treatment cycle.

In vitro experiments
- ARQ 531 displays dose-dependent inhibition of pBTK in normal PBMCs, with an IC50 value of 110 μM for CYP3A4/5 suggesting a high selectivity for BTK. The plasma half-life in monkeys ranged from 1 to 30 mg/kg. The plasma half-life in monkeys ranged from 11.5 to 22.7 hours.

In vivo experiments
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RESULTS

ARQ 531 Potently Inhibits pBTK in Normal Human PBMCs

Mean suppression of pharmacodynamic marker pBTK achieved of 145 nM

ARQ 531 Displays Dose-Dependent Increase in Plasma Following Single Oral Doses to Male Monkeys

Mean plasma exposure (Cmax, AUClast) in Cohort 1 patients were 1.53 nM.

CONCLUSIONS
- ARQ 531 potently inhibits BTK phosphorylation in human PBMCs with an in vitro IC50 of 1.53 nM.
- Pharmacokinetic studies in monkeys showed that increases in ARQ 531 plasma exposures were close to dose proportional as the dose was increased from 1 to 30 mg/kg. The plasma half-life in monkeys ranged from 11.5 to 22.7 hours.
- ARQ 531 is not metabolized by any of the major drug metabolizing CYP450 enzymes and has a %RSD of 110 μM for CYP3A4/5 suggesting a low potential for drug drug interactions when combined with other cancer therapeutics metabolized by CYP3A4/5.
- At the initial (lowest) dose of 5 mg of ARQ 531, a mean Cmax has been achieved of 145 nm.
- Preliminary evidence of target inhibition seen at low dose levels.
- Dose escalation continues in patients with relapsed/refractory B-cell malignancy.

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