A Phase 1 Dose Escalation Study of ARQ 531 in Selected Patients with Relapsed or Refractory Hematologic Malignancies

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BACKGROUND

Preclinical studies demonstrated that ARQ 531 targets ibrutinib resistant BTK inhibitors, cases of primary resistance and secondary resistance have emerged with poor outcomes and limited treatment options.

• The majority of CLL patients who become resistant to irreversible BTK inhibitors such as ibrutinib develop the BTK-C481S mutation (Woyach et al)
• ARQ 531 is a orally bioavailable, potent and reversible inhibitor of both wild type and C481S mutant BTK. It has demonstrated superior to ibrutinib in B-cell lines, and targets BTK resistant CLL and CLL-B cell line models (Eathiraj et al, and Flinn, et al)
• ARQ 531 is under investigation as a monotherapy in this Phase 1 dose escalation study to evaluate safety, pharmacology and anti-cancer activity in patients with relapsed or refractory B-cell malignancies, including but not limited to patients with BTK-resistant ibrutinib C481S mutations.

STUDY DESIGN

Ongoing Phase I, open-label, single arm, multicenter, 3 + 3 dose-escalation study of ARQ 531 in patients with selected hematologic malignancies (NCT03162536).

Patient Eligibility

• Safety/efficacy
• Recommended Phase 2 dose and dosing schedule
• Pharmacokinetic and Pharmacodynamic profile
• Preliminary evidence of anti-cancer activity

Key Eligibility Criteria

• Must be 18 years of age, ECOG PS 0-2
• Relapsed or refractory CLLS, MCL, or cell lines that have received at least 2 prior lines of prior therapy.
• Patients who have prior exposure to an approved BTK inhibitor are eligible if they have received a prior treatment with a BTK inhibitor that was not ibrutinib, such as om替patin, idelalisib, or bevazaplatin for anti-CD20 chimeric cell therapy.
• For MCL, prior therapies included anthracyclines and rituximab.
• For patients with low grade lymphoma must be progressing and require treatment
• Disease status requirements
• For CLL patients, symptomatic disease that mandates treatment
• For MCL patients, measurable disease by imaging criteria
• For ALL patients, minimal disease of 2.5 times the upper limit of normal
• Good organ function
• No prior anti-cancer treatment within 5 weeks of dosing, 4 weeks for low dose
• Nutritional status is a crucial for tumor suppression
• No concurrent serious or uncontrolled co-morbid conditions

METHODS

All dose and disease response assessments

• Tumor response by RECIST v1.1 (CIC v 4.0)
• Tumor response was evaluated during screening, every 4 cycles for the first 3 cycles, and at every cycle following.

Patient accrual

• For all patient populations: Recruitment for initial treatment escalation was based on the following guidelines:
• For ALL patients: Consideration for additional cycles/staging, and immune response assessment of Hodgkin’s and non-Hodgkin’s lymphoma: The Lugano Classification
• For CLL patients: Consideration for additional cycles/staging, and immune response assessment of Hodgkin’s and non-Hodgkin’s lymphoma: The Lugano Classification

All responses were evaluated by the principal investigator or designated responsible investigator.

PK/Pharmacokinetics

• PK samples were collected on day 1 and day 2 of Cycle 1 at day 1 (pre-dose and at 2, 4, 6, 8, and 12 hours post dose), and at 3, 6, 9, and 12 hours post dose in Cohort 2 patients, and at 3, 6, and 12 hours for Cohorts 3-6 patients. PK samples were evaluated using validated CLC/CLC methodology.

ANOVA

• Whole blood samples were collected at pre dose and at the post dose on Cycle 1 Day 1 (Cycle 2, 3, 4, 6, and 8) and post dose on Cycle 1 Day 2 (Cycle 3, 4, 6, and 8) for Cohorts 1 to 6 (N=20). All samples were evaluated using validated CLC/CLC methodology

RESULTS

Patient Enrollment Status

• 20 patients have been enrolled and treated in cycles at 3 study sites, 16 patients are still enrolled

• Cohort 7 (15 mg QD) is open for enrollment with 3 additional patients enrolled and continuing on study. The data from these 3 patients are not included in this presentation

• Dose escalation is ongoing in Cohort 6 (Cohort 5) may be continued in incremental steps up to 33 mg.

Mean Plasma Concentration-Time Profiles of ARQ 531 for Cohorts 1 through 6

Target Engagement and ARQ 531 PK/PD Correlations

• Mean plasma C3L levels in the pre dose and post dose time period reduction between Cycle 1 and 2 were 67 and 50 mg/L, respectively. Overall, ARQ 531 treatment led 30% reduction in C3L irrespective of poor response (C 1 to 3 30 mg).

• ARQ 531 suppressed C3L levels in CLL patients harboring the BTK-C481S mutation.

Suppression of C3L, Plasma Biomarker of BCR Pathway Activation

• Mean plasma C3L levels in the pre-dose and post-dose time period reduction between Cycle 1 and 2 were 67 and 50 mg/L, respectively. Overall, ARQ 531 treatment led to greater reduction in C3L irrespective of poor response (C 1 to 3 30 mg).

• ARQ 531 suppressed C3L levels in CLL patients harboring the BTK-C481S mutation.

CONCLUSIONS

• ARQ 531 was well-tolerated at doses levels of 5 to 45 mg QD, supporting continued dose escalation

• Increases in plasma exposure (AUC, Cmax) are close to dose proportional and the Cmax at Cycle 1, Day 6 ranged from 18 to 38 hours and currently supports a QD dosing regimen

• ARQ 531 demonstrated target engagement with profound pBTK reduction in cohorts 4 to 6 (C0, 30 and 45 mg QD). Importantly, C3L levels were reduced in patients harboring either wild-type or C481S mutations

• Anti-tumor activity was observed in heavily pretreated CLL patients with BTK-C481S mutations with increasing tumor suppression seen at higher dose levels

• Anti-tumor activity was observed in one of three patients with follicular lymphoma

REFERENCES

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