A Phase 1 Dose Escalation Study of ARQ 531 in Patients With Relapsed or Refractory B-cell Lymphoid Malignancies

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BACKGROUND

The BTK Inhibitor ARQ 531 Targeted Bruton’s-Tyrosine Kinase (BTK) and other Bruton’s Tyrosine Kinase (BTK) in B-cell malignancies. The majority of patients who progressed or received BTK inhibitor therapy, such as Bruton, became resistant to treatment due to BTK-C481S mutation (42%)

ARQ 531 is a selective, potent and irreversible Bruton’s Tyrosine Kinase BTK inhibitor which demonstrated efficacy in R/R B-cell malignancies, including refractory CLL, Richter’s transformation, and other B-cell malignancies (Stein et al. et al.)

ARQ 531 was orally administered in an open-label, phase 1 dose-escalation study to evaluate safety, pharmacology and anti-cancer activity in patients with relapsed or refractory B-cell malignancies, including non-Hodgkin’s lymphoma and other B-cell malignancies (Stein et al. et al.)

STUDY DESIGN

Eligibility

• Patients with relapsed and refractory B-cell malignancies

Methods

• Safety and tolerability
• Pharmacokinetic profile
• Preliminary evidence of performance profile

Key Eligibility Criteria

• history of ≤ 1 prior systemic therapy
• current hematologic malignancy that is progressive or refractory to available therapy
• measurable disease ≥ 1 cm
• No prior allogeneic bone marrow transplant
• Low grade lymphoma must be progressing and require treatment
• For Bruton’s Tyrosin kinase patients, measurable disease by imaging
• For ARQ 531, patients must have a history of normal cardiac function
• For Bruton’s Tyrosin kinase patients, a history of cancer is allowed if the patient was treated and in remission for ≥ 5 years
• No prior placement bone marrow transplant
• ARQ 531 has been given to normal

All and Disease Response Assessments

• Pts. enrolled at ≥ 45 mg QD (n=3)

PK Analysis

• Plasma PK samples were collected on Day 1 and Day 22 of Cycle 1 at predose and 0.5, 1, 2, 4, 8, 24, 48 h post-dose

PhD Assessment

• Whole blood was collected on each cycle day and stored at −80°C until analyzed using multiplex Cytokine Panel.

PATIENT ENROLLMENT STATUS

• As of May 10, 2019, 36 patients have been treated in 7 cycles of 2 cycles, 1 cycles

• Patients are continuing or study safety data from 7 (mg) cohort are available in this paper

• Four patients were dosed at 65 mg QD; one patient was dosed at 45 mg QD

RESULTS

ARQ 531 Demonstrates Robust Clinical Responses in Patients with CLL (BTK-C481S), Richter’s Transformation (RT) and Follicular Lymphoma (FL)

Best Response in Patients Who Received ≥45 mg QD as Starting Dose or Dose Increase

Cohort 7 (65 mg QD) PRs in 4 of 6 Evaluable CLL (BTK C481S) Patients

Response in Patient 34 (Richter’s Transformation)

CT Scan images of lymph nodes before and after 2 months of therapy with ARQ 531

ARQ 531 Suppressed CELLS Levels in CLL (BTK-C481S) Patients

ARQ 531-induced lymphopenia observed in 3/3 patients treated at 65 mg QD

CONCLUSIONS

ARQ 531 is well-tolerated at 65 mg QD and has a manageable safety profile in multiple B-cell malignancies

PK data show that cohorts receiving ≥45 mg QD of ARQ 531 exhibited steady-state mean Cmax of above 1 µM. The plasma half-life ranges from 20-30 hours and is associated with complete BTK inhibition and CELS suppression

Robust anti-tumor activity observed in heavily pretreated R/R CLL patients harboring BTK-C481S mutation with an ORR of 46% (4/9 responses in evaluable patients) achieved in 65 mg Cohort

A partial response was observed in the first patient with Richter’s transformation, as supported by pre-clinical studies, suggesting that ARQ 531’s distinct MDA is intended to target this highly aggressive medical need

Further clinical development of ARQ 531 in lymphoid resistant B/R CLL, Richter’s transformation and other B-cell malignancies is currently ongoing

REFERENCES

1. Stein et al. (2007) Reduced Bruton’s Tyrosine Kinase Inhibitor to its Essential Kinase Kinase 2 (BTK) mimic: A potent and selective Bruton’s Tyrosine Kinase (BTK) inhibitor.
2. Raff et al. (2007) Bruton’s Tyrosine Kinase (BTK) inhibitors: Bruton’s Tyrosine Kinase and Other Targets.

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