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

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BACKGROUND

Non-Hodgkin’s lymphoma (NHL) is a heterogeneous group of malignancies characterized by diverse clonal expansions of B or T lymphocytes. Patients with NHL typically have chemotherapy regimens as first-line treatment which are often followed by second-line treatments and are often refractory to chemotherapy. Patients with NHL that develop resistance to these anti-cancer regimens often have limited therapeutic options.

ARQ 531 is a potent and selective small molecule inhibitor of Bruton’s tyrosine kinase (BTK) with preclinical activity in NHL tumor models. BTK is a key upstream kinase in BCR pathway and has demonstrated potential utility in NHL and B-cell malignancies.

METHODS

ARQ 531 was dosed daily at escalating levels in Part B of a 3+3 study design with starting dose level of 5 mg QD in Cohort 1. Cohorts 2 through 4 were derived from a factorially designed study with 3 dose levels and 3 dose levels for Cohort 5. Treatment was dose escalated up to 15 mg QD. Hematologic malignancies included patients with follicular lymphoma (FL), diffuse large B-cell lymphoma (DLBCL), mantle cell lymphoma (MCL), and small lymphocytic lymphoma (SLL).

RESULTS

ARQ 531 was well-tolerated at dose levels 5, 10, and 15 mg QD supporting continued dose escalation. ARQ 531-related grade 1 and grade 2 AEs were reported in 4 of 11 (36.4%) patients. None of the drug-related AEs identified thus far were observed in more than one patient. The half-life of ARQ 531 ranged from 22 to 72 hours suggesting the potential for sustained target inhibition and supporting a QD dosing regimen. Preliminary PK shows increases in exposure are close to dose proportional.

CONCLUSIONS

ARQ 531 is a potent and selective small molecule inhibitor of BTK with preclinical activity in NHL tumor models. Patients with NHL that develop resistance to these anti-cancer regimens often have limited therapeutic options. ARQ 531 is well-tolerated at dose levels 5, 10, and 15 mg QD supporting continued dose escalation. ARQ 531-related grade 1 and grade 2 AEs were reported in 4 of 11 (36.4%) patients. None of the drug-related AEs identified thus far were observed in more than one patient. The half-life of ARQ 531 ranged from 22 to 72 hours suggesting the potential for sustained target inhibition and supporting a QD dosing regimen. Preliminary PK shows increases in exposure are close to dose proportional.

Preliminary signs of anti-tumor activity was observed. Dose escalation is ongoing.