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

Abstract # LB-018
AACR Annual Meeting
April 14-18, 2018, Chicago, IL

Terence Hall[1], Yi Yu[1], Sudharshan Eathiraj[1], Deborah Stephens[2], Jennifer Woyach[3], Ian Flynn[4], Ronald E. Savage[1], and Brian Schwartz[1]
[1]ArQule, Inc., Burlington, MA; [2]Huntsman Cancer Institute, Salt Lake City, Utah; [3]Ohio State University, Columbus, OH; [4]Sarah Cannon Research Institute, Nashville, TN

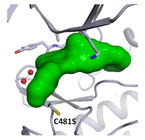
BACKGROUND

Bruton's tyrosine kinase (BTK) is a key regulator of the B-cell receptor (BCR) signaling, the majority of B-cell malignancies are dependent on BCR function. BCR signaling pathway is specifically activated and contributes to pathogenesis of B-cell leukemia and lymphomas. Despite impressive clinical activity of BTK inhibitors in multiple B-cell malignancies, cases of primary and secondary resistance have emerged. BTK-C481S mutation is a predominant resistance mechanism with ibrutinib, there are other mutations and resistance mechanisms that contribute to the secondary resistance mechanisms, including Richter's transformation of CLL.

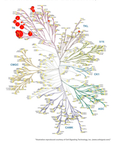
ARQ 531, a potent reversible inhibitor of BTK and BTK-C481S mutant

Distinct kinase selectivity profile with potent anti-tumor activity in CLL and DLBCL tumor models

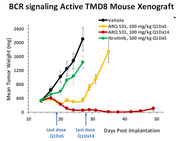
Non-covalent Reversible Inhibitor



Distinct Kinase Selectivity



Anti-tumor Activity in Constitutive BCR signaling Active TMD8 Mouse Xenograft



STUDY DESIGN

- Ongoing Phase 1, open-label, single arm, multicenter, dose-escalation study of ARQ 531 in subjects with select hematologic malignancies (NCT03162536).
- The dose escalation period of the study follows the 3 + 3 dose escalation design and is open to subjects with B-cell NHL, SLL/CLL, and WM.
- The treatment doses of the first and second cohorts will be 5 mg qd and 10 mg qd, respectively. After that, the dose will be increased by ≤ 50% of the previous cohort until a dose limiting toxicity (DLT) occurs.
- After a DLT is observed in at least 1 subject out of 3, the cohort will be expanded to 6 subjects. If no more DLTs are observed and after agreement between the Investigators and Medical Monitor, the dose escalation will follow the modified Fibonacci schema (increases by ≤ 33% at each step). In addition, if a median ARQ 531 C_{max} exposure of 548 ng/mL (~1 µM) or $AUC_{0\text{-}24}$ of 8980 ng*h/mL is reached, the dose escalation will follow the modified Fibonacci schema. A treatment cycle is defined as 28 days of continuous dosing with ARQ 531.

Dose Escalation Schema

3+3 Study Design
Relapsed / refractory hematologic malignancies

CLL
MCL
WM
DLBCL
B-cell Lymphoma

- Cohort 7: 65 mg daily (n = 3*)
- Cohort 6: 45 mg daily (n = 3*)
- Cohort 5: 30 mg daily (n = 3*)
- Cohort 4: 20 mg daily (n = 3*)
- Cohort 3: 15 mg daily (n = 3*)
- Cohort 2: 10 mg daily (n = 3*)
- Cohort 1: 5 mg daily (n = 3*)

[a]If a DLT occurs in 1 of 3 treated subjects in a cohort, an additional 3 subjects will be treated

METHODS

Inclusion/Exclusion Criteria

Key Inclusion Criteria

- 18 years of age and older.
- Relapsed or refractory CLL/SLL, WM, B-cell NHL who have received at least 2 prior lines of systemic therapy.
- Prior therapy must include a BTK inhibitor in diseases for which approved therapy includes a BTK inhibitor (i.e., CLL/SLL, WM, and mantle cell lymphoma). Subjects with DLBCL must have failed, refused, or be ineligible for autologous stem cell transplant. Subjects with low grade lymphoma must be progressing and requiring treatment.
- Disease status requirement:
- For CLL subjects, symptomatic disease that mandates treatment.
- For B-cell NHL subjects, measurable disease by imaging scan.
- For WM, serum immunoglobulin M (IgM) with a minimum IgM level of ≥ 2 times the upper limit of normal (ULN).
- Eastern Cooperative Oncology Group (ECOG) performance status of ≤ 2.

Key Exclusion Criteria

- Had immunotherapy, radiotherapy, radioimmunotherapy, biological therapy, chemotherapy, or treatment with an investigational product within 4 weeks prior to treatment initiation (or oral therapy within 1 week prior to treatment initiation).
- Subjects who were intolerant to a BTK inhibitor
- Subjects currently being treated with the following drugs:
  - CYP 2C9 substrates with a narrow therapeutic index (such as warfarin, phenytoin)
  - CYP 2C8 substrates with a narrow therapeutic index (such as paclitaxel)
  - CYP 2C19 substrates with a narrow therapeutic index (such as S-mephenytoin)
  - CYP 2D6 substrates with a narrow therapeutic index (such as thioridazine, pimozide)
- P-gp substrates with a narrow therapeutic index (such as digoxin)
- A washout period of at least 5 times the half-life after the last dose of any of the above treatments is required for a subject to be eligible for study enrollment.

Experimental Methods

Assessment of pBTK(Y223) in human PBMC
Normal human PBMCs were treated with various concentrations of ARQ 531 for 2 hours. Western blot analysis was performed to assess pBTK(Y223) and total BTK. Images were captured using FUJI LAS3000 and the intensity of corresponding bands was determined by densitometry analysis Multi Gauge V3.1 software. The ratio of pBTK/BTK was determined and sample untreated was designated as 100%. IC_{50} was determined by Graphpad Prism software.

Monkey PK Analysis
Monkey plasma PK samples were collected at approximately 0.25, 0.5, 1, 2, 4, 8, 12, 24, 36, 48, and 72 hours postdose and stored at -70˚C until analyzed using validated LC/MS/MS methodology. PK parameters were determined using Phoenix 64/WinNonlin 7.0 software.

Human PK Analysis
Subject plasma PK samples were collected on Day 1 and Day 22 of Cycle 1 at predose, and 1, 2, 4, 6, 8, 10, and 24 hours postdose and stored at -70˚C until analyzed using validated LC/MS/MS methodology. PK parameters were determined using Phoenix 64/WinNonlin 7.0 software.

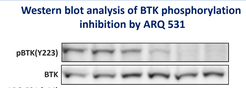
In Vitro CYP450 Metabolism
CYP reaction phenotyping was performed using human recombinant CYP enzymes (hrCYPs) by an *in vitro* intrinsic clearance approach. ARQ 531 at a single concentration (1.0 µM) was incubated with an individual hrCYP (20 pmol CYP/mL) or insect control (negative control without expression of CYP enzymes, 0.1 mg protein/mL) in phosphate buffer (100 mM, pH 7.4) containing $MgCl_2$ (5 mM) and NADPH (1 mM). The reaction was initiated by the addition of NADPH, followed by incubation at 37ºC. Aliquots of the incubation solutions were sampled at 0, 5, 10, 30, and 60 minutes. All samples were assayed by LC-MS/MS.

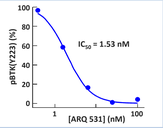
PD Assessment
Serial PD analysis of pBTK (Y223) and total BTK ratio in whole blood lysates of patients treated with ARQ 531 was measured using MesoScale Discovery (MSD) immuno assay technology.

RESULTS

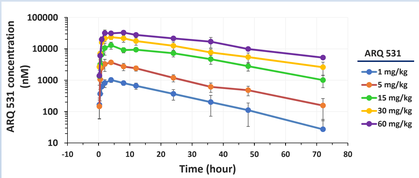
ARQ 531 Potently Inhibits pBTK in Normal Human PBMCs

Western blot analysis of BTK phosphorylation inhibition by ARQ 531



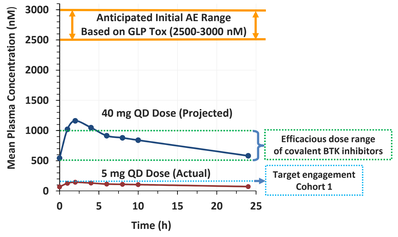


ARQ 531 Displays Dose-Dependent Increase in Plasma Following Single Oral Doses to Male Monkeys



Dose Level (mg/kg)		C_{max} (nM)	T_{max} (hr)	$AUC_{0\text{-}t}$ (nM·hr)	$t_{1/2}$ (hr)
1	Mean	1,040	3.67	22,600	11.5
	SD	192	0.8	6620	2.1
5	Mean	3840	3.33	80,500	17.3
	SD	700	1.03	17,700	6.59
15	Mean	13,100	3.67	379,000	16
	SD	3,430	0.816	62,100	1.65
30	Mean	23,900	5.33	718,000	22.7
	SD	3760	2.07	179000	5.49
60	Mean	34,500	4.67	848,000	20.7
	SD	5,790	2.73	362,000	4.27

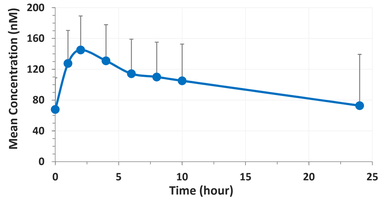
Actual and Estimated Human Exposures Based on Preclinical Data



ARQ 531 is not Metabolized by any of the Major Human Drug Metabolizing CYP450 Enzymes

CYP	% Remaining of ARQ 531				
	0 min	5 min	10 min	30 min	60 min
CYP1A2	100	104	106	109	86
CYP2C8	100	107	107	110	101
CYP2C9	100	106	100	109	94
CYP2C19	100	101	107	111	95
CYP2D6	100	105	104	106	106
CYP3A4	100	104	93	88	86
Negative control	100	111	112	115	100

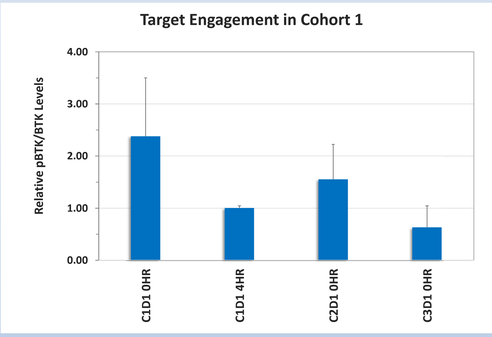
Pharmacokinetic Profile of ARQ 531 on Cycle 1 Day22 in Cohort 1 Patients Treated with 5 mg Dose



Pharmacokinetic Parameters of ARQ 531 in Cohort 1

Dose	Treatment Visit		T_{max} (h)	C_{max} (nM)	AUC_{last} (h*nM)	$t_{1/2}$ (h)
5 mg QD	Cycle 1 Day 22	Mean (n=3)	2	145	2009	27.1
		SD	0	44	1312	16.1
		%RSD	0	30	65	59.5

Mean Suppression of Pharmacodynamic Marker pBTK in Cohort 1 (n=3) Treated with 5 mg QD of ARQ 531



CONCLUSIONS

- **ARQ 531 potently inhibits BTK phosphorylation in human PBMCs with an *in vitro* IC_{50} 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 K_I value 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 C_{max} 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**