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 Targets Ibrutinib-Resistant CLL and other B-cell Malignancies

- Despite major therapeutic advances in B-cell malignancies, cases of primary and secondary resistance have emerged with poor outcomes and limited treatment options
- The majority of CLL patients who progress on covalent BTK inhibitor therapy, such as ibrutinib, become resistant to treatment due to BTK-C481S mutation (Woyach *et al.*)
- ARQ 531 is an orally bioavailable, potent and reversible dual inhibitor of both wild type and C481S-mutant BTK. It has demonstrated superiority over ibrutinib in CLL and DLBCL mouse models and targets ibrutinib-resistant CLL, Richter's transformation, and other B-cell malignancies (Reiff *et al.* and Eathiraj *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 ibrutinib resistant BTK-C481S mutations

STUDY DESIGN

Ongoing phase 1, open-label, single arm, multicenter, 3 + 3 dose-escalation study of ARQ 531 in patients with selected hematologic malignancies (NCT03162536)

Primary Endpoints
- Safety and tolerability
- Recommended phase 2 dose and dosing schedule

Secondary Endpoints
- Pharmacokinetic and pharmacodynamic profile
- Preliminary evidence of anti-tumor activity

Key Eligibility Criteria	▶ M/F ≥ 18 years of age; ECOG PS ≤ 2 ▶ Relapsed or refractory CLL/SLL, WM, B-cell NHL who have received at least 2 prior lines of systemic therapies ▶ Prior therapy for CLL/SLL, WM and mantle cell lymphoma patients must include an approved BTK inhibitor. Patients with DLBCL must have failed, refused, or be ineligible for autologous stem cell transplant. Patients with low grade lymphoma must be progressing and require treatment ▶ Disease status requirements: ▪ For CLL patients, symptomatic disease that mandates treatment ▪ For B-cell NHL patients, measurable disease by imaging scan ▪ For WM patients, minimum IgM level of ≥ 2 times upper limit of normal ▶ Good organ function ▶ No prior oral anti-cancer treatment within 1 week of dosing; 4 weeks for all others ▶ No prior allogeneic bone marrow transplant ▶ No concurrent serious co-morbidities that could limit patients' full participation and compliance
AE and Disease Response Assessments	▶ TEAEs assessed per CTCAE v. 4.03 ▶ Disease responses were evaluated during screening, every 3 cycles for the first 12 cycles, and at every 6 cycles thereafter. Best response will be determined based on the following guidelines: ▪ For B-cell NHL patients: Recommendations for initial evaluation, staging, and response assessment of Hodgkin's and non-Hodgkin's lymphoma: The Lugano Classification (2014) ▪ For WM patients: Guidelines on the diagnosis and management of Waldenström macroglobulinemia (2014) ▪ For CLL patients: Guidelines for the diagnosis and treatment of chronic lymphocytic leukemia: a report from the International Workshop on Chronic Lymphocytic Leukemia updating the National Cancer Institute–Working Group 1996 guidelines (2008)
PK Analysis	Plasma PK samples were collected on Day 1 and Day 22 of Cycle 1 at pre-dose, and 1, 2, 4, 6, 8, 10, and 24 hours post-dose and stored at -80˚C until analyzed using validated LC/MS/MS methodology
PD Assessment	Whole blood samples were collected at pre-dose and 4-hour post-dose on Cycle 1 Day 1. Samples were lysed in the presence or absence of protein phosphatase/protease inhibitors and were frozen at -80 deg C. The pBTK (Y223) and total BTK levels in patient's whole blood lysates samples were analyzed by electrochemiluminescence sandwich ELISA assay using Meso Scale Discovery (MSD) immunoassay technology. CCL3 levels in plasma samples were determined using an ELISA assay

PATIENT ENROLLMENT STATUS

- As of May 10, 2019, 34 patients have been treated in 8 cohorts at 3 study sites, 16 patients are continuing on study (only safety data from 75 mg cohort are included in this poster)
- Five patients were dose escalated to 65 mg QD; one patient was dose escalated to 45 mg QD

Treatment Cohorts

Dose escalation ↑
- Cohort 8: 75 mg QD (n=4)
- Cohort 7: 65 mg QD (n=10)
- Cohort 6: 45 mg QD (n=3)
- Cohort 5: 30 mg QD (n=3)
- Cohort 4: 20 mg QD (n=3)
- Cohort 3: 15 mg QD (n=4)
- Cohort 2: 10 mg QD (n=4)
- Cohort 1: 5 mg QD (n=3)

Patients Currently on Study Starting or Escalated Doses

- 3 patients on 75 mg QD (1 DLBCL, 1 CLL, 1 Richter's)
- 11 patients on 65 mg QD (10 CLL BTK-C481S, 1 Richter's)
- 2 patients on 45 mg QD (1 FL, 1 CLL BTK-C481S)

Intra-patient dose escalation is allowed if the higher dose is well tolerated and safe

RESULTS

Patient Demographics

	Cohorts 1 to 8 (N = 34)
Median age (Range)	65 (47-82) years
Gender, N (%)	
Male	30 (88%)
Female	4 (12%)
Race, N (%)	
Caucasian	32 (94%)
Black or African American	2 (6%)
Tumor type, N (%)	
CLL/SLL	24 (71%)
B-cell NHL	10 (29%)
Follicular	4 (12%)
Mantle Cell	1 (3%)
Diffuse Large B Cell	2 (6%)
Richter's	2 (6%)
Missing	1 (3%)
Baseline ECOG PS, N (%)	
0	12 (35%)
1	21 (62%)
2	1 (3%)
Known BTK-C481S mutation status in CLL patients, N (%)	21 (88%)
Median number (range) of prior systemic therapy	4 (1-12)
Chemotherapy	32(95%)
Targeted and immunotherapy	
Anti-CD20/19 antibody	32(95%)
BTK inhibitor (all CLL patients)	25(78%)
PI3K inhibitor	9(28%)
BCL2 antagonist	7(22%)
Lenalidomide	7(22%)
CDK inhibitor	6(19%)
CC-122	5(16%)

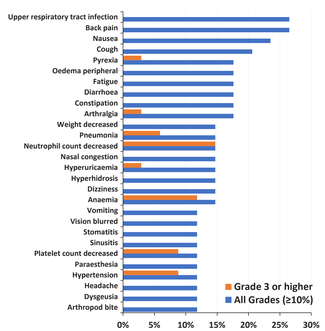
* BTK-C481S status of 3 CLL patients is unknown
Preliminary unmonitored data as of 10 May 2019

Treatment-emergent Adverse Events

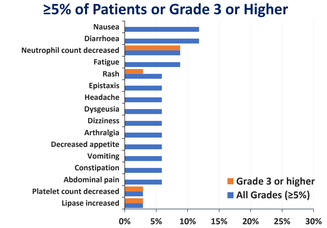
Summary of TEAEs	All Subjects (N=34) n (%)
Any TEAEs	31 (91.2)
Severe (Grade 3 or Higher) TEAEs	19 (55.9)
Serious TEAEs	10 (29.4)
Drug-Related TEAEs	18 (52.9)
Drug-Related Serious TEAEs	1 (2.9)
Drug-Related Severe (Grade 3 or Higher) TEAEs	5 (14.7)
TEAEs Leading to Treatment Discontinuation	6 (17.6)
TEAEs Leading to Study Discontinuation	5 (14.7)
TEAEs Classified as DLTs	1* (2.9)

* A drug-related DLT occurred in one CLL subject at 65 mg QD, grade 3 rash generalized (from head to toe). The AE of grade 3 rash occurred on study Day 10 and was assessed as SUSAR. After temporary on hold, re-challenged on study Day 22 at 45 mg QD, the rash recurred and the subject discontinued study treatment on the same day.

TEAEs in ≥10% of Patients



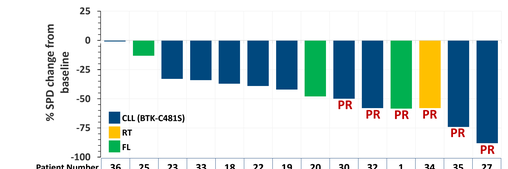
ARQ 531-Related TEAEs in ≥5% of Patients or Grade 3 or Higher



Preliminary unmonitored data as of 10 May 2019

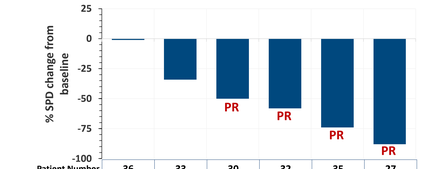
ARQ 531 Demonstrates Robust Clinical Responses in Patients with CLL (BTK-C481S), Richter's Transformation (RT) and Follicular Lymphoma (FL)

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



Patient Number	36	25	23	33	18	22	19	20	30	32	1	34	35	27
Starting Dose (mg QD)	65	65	45	65	30	45	30	45	65	65	5	65	65	65
Prior Lines of Therapy	4	3	12	3	9	9	6	2	8	4	3	4	2	3

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



Patient Number	36	33	30	32	35	27
Starting Dose (mg QD)	65	65	65	65	65	65
Prior Lines of Therapy	4	3	8	4	2	3

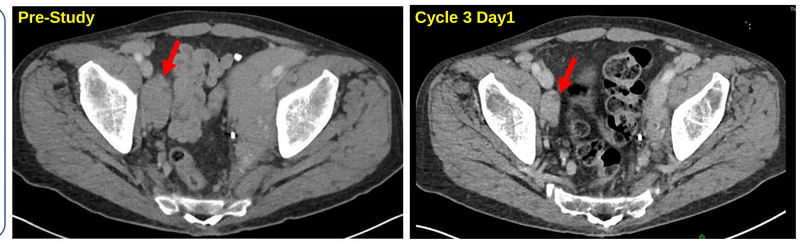
Preliminary unmonitored data as of 10 May 2019

Response in Patient 34 (Richter's Transformation)

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

Patient 34 had CLL and was treated with 4 prior lines of therapy, including ibrutinib and R-CHOP, but relapsed due to Richter's transformation.

The patient initiated ARQ 531 therapy at 65 mg QD and achieved a PR after 2 months with 58% tumor reduction, and continues on treatment.



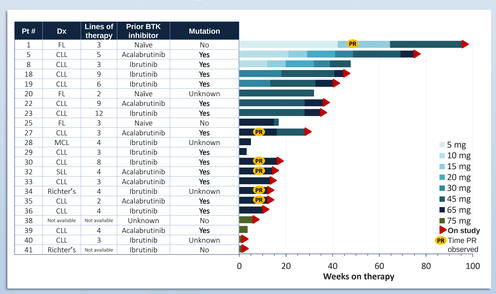
Response by Treatment Cohort

Treatment Cohort	Responses
45 mg QD	
(Starting or dose escalated) • 8 Pts treated • 2 Pts discontinued, 6 Pts continuing • 1 Pt continuing at 45 mg • 5 Pts dose escalated to 65 mg	1 Partial response • FL 5 Stable disease • 4 CLL (BTK-C481S) • 1 FL 2 Progressive disease • 2 CLL (BTK-C481S)
65 mg QD	
(Starting dose) • 10 Pts treated • 3 Pts discontinued • 7 Pts continuing treatment • 8 Pts evaluable for response ➢ 6 CLL (BTK-C481S) ➢ 1 Richter's transformation ➢ 1 FL	5 Partial responses • 4 CLL (BTK-C481S) • 1 RT 3 Stable disease • 2 CLL (BTK-C481S) • 1 FL

Preliminary unmonitored data as of 10 May 2019

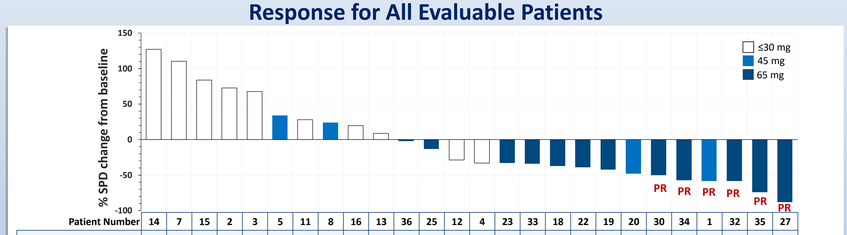
Time on Treatment: Patients Dosed at ≥45 mg QD (Starting or Escalated Doses)

Pt #	Dx	Lines of therapy	Prior BTK inhibitor	Mutation
1	FL	3	Naïve	No
5	CLL	5	Acalabrutinib	Yes
8	CLL	3	Ibrutinib	Yes
18	CLL	9	Ibrutinib	Yes
19	CLL	6	Ibrutinib	Yes
20	FL	2	Naïve	Unknown
22	CLL	9	Acalabrutinib	Yes
23	CLL	12	Ibrutinib	Yes
25	FL	3	Naïve	No
27	CLL	3	Acalabrutinib	Yes
28	MCL	4	Ibrutinib	Unknown
29	CLL	3	Ibrutinib	Yes
30	CLL	8	Ibrutinib	Yes
32	SLL	4	Acalabrutinib	Yes
33	CLL	3	Acalabrutinib	Yes
34	Richter's	4	Ibrutinib	Unknown
35	CLL	2	Acalabrutinib	Yes
36	CLL	4	Ibrutinib	Yes
38	Not available	Not available	Unknown	No
39	CLL	4	Acalabrutinib	Yes
40	CLL	3	Ibrutinib	Unknown
41	Richter's	Not available	Ibrutinib	No



Preliminary unmonitored data as of 10 May 2019

Response for All Evaluable Patients



Patient Number	14	7	15	2	3	5	11	8	16	13	36	25	12	4	23	33	18	22	19	20	30	34	1	32	35	27
Starting Dose (mg QD)	20	10	20	5	5	10	15	10	30	20	65	65	15	10	45	65	30	45	30	45	65	65	5	65	65	65
Prior Lines of Therapy	3	4	2	6	6	5	8	3	5	8	4	3	5	3	12	3	9	9	6	2	8	4	3	4	2	3

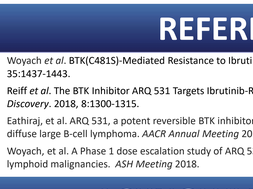
Preliminary unmonitored data as of 10 May 2019

ARQ 531 PK Profile and Dose-Dependent Target Engagement in Patients

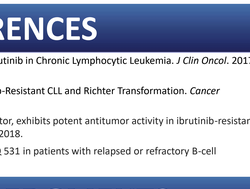
ARQ 531 Preliminary Mean PK Parameters (Cohort 7)

Patients (N)	Dose (mg QD)	C1D1 C_{max} (nM)	C1D1 $AUC_{0\text{-}24h}$ (h*nM)	C1D1 Half-life (h)	C1D22 C_{max} (nM)	C1D22 $AUC_{0\text{-}24h}$ (h*nM)	C1D22 Half-life (h)
8	65	1342	17686	23	2631	44770	30

Steady-state Concentrations of ARQ 531 Was Reached >1 µM at 65 mg QD



pBTK Inhibition vs C_{max} of ARQ 531 by Cohort



ARQ 531 Suppressed CCL3 Levels in CLL (BTK-C481S) Patients

ARQ 531-Induced Lymphocytosis Resolved During Treatment Course

Mean values from Cohort 65 mg (Pts 27, 30, 32, 33, 34 and 36)

Preliminary unmonitored data as of 10 May 2019

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 C_{min} of above 1 µM. The plasma half-life ranges from 20-30 hours and is associated with complete pBTK inhibition and CCL3 suppression
- Robust anti-tumor activity observed in heavily pretreated R/R CLL patients harboring BTK-C481S mutation with an ORR of 66% (4/6 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 MOA is amenable to target this highly unmet medical need
- Further clinical development of ARQ 531 in ibrutinib resistant R/R CLL, Richter's transformation and other B-cell malignancies is currently ongoing

REFERENCES

- Woyach *et al*. BTK(C481S)-Mediated Resistance to Ibrutinib in Chronic Lymphocytic Leukemia. *J Clin Oncol*. 2017, 35:1437-1443.
- Reiff *et al*. The BTK Inhibitor ARQ 531 Targets Ibrutinib-Resistant CLL and Richter Transformation. *Cancer Discovery*. 2018, 8:1300-1315.
- Eathiraj, et al. ARQ 531, a potent reversible BTK inhibitor, exhibits potent antitumor activity in ibrutinib-resistant diffuse large B-cell lymphoma. *AACR Annual Meeting* 2018.
- Woyach, et al. A Phase 1 dose escalation study of ARQ 531 in patients with relapsed or refractory B-cell lymphoid malignancies. *ASH Meeting* 2018.

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