The BTK Inhibitor ARQ 531 Targets Ibrutinib-Resistant CLL and Richter Transformation. Cancer Discov. 2018 Oct;8(10):1300-1315

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

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BACKGROUND

- Despite impressive clinical response of ibrutinib 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 become resistant to irreversible BTK inhibitors such as ibrutinib develop the BTK-C481S mutation (Woyach *et al.*,)
- ARQ 531 is an orally bioavailable, potent and reversible 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 and Richter's transformation (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 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 the upper limit of normal (ULN)
- 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

METHODS

AE and disease response assessments
- TEAEs / related AE 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
  - For WM patients: Guidelines on the diagnosis and management of Waldenström macroglobulinemia
  - 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

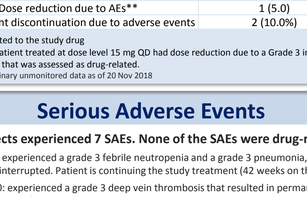
PK Analysis
- Plasma PK samples were collected on Day 1 and Day 22 of Cycle 1 at pre-dose, and 1, 2, 4, 6, 8, 10, and 24 hours post-dose and stored at -80˚C until analyzed using validated LC/MS/MS methodology

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

RESULTS

Patient Enrollment Status

- 20 patients have been enrolled and treated in 6 cohorts at 3 study sites, 8 patients are continuing on study
- Cohort 7 (65 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 and, absent DLTs, may be continued in successive increments of up to 33.3%



Patient Demographics

	Cohorts 1 to 6 (N=20)
Median age (Range)	66.5 (53-83) years
Gender, N (%)	
Male	18 (90%)
Female	2 (10%)
Race, N (%)	
Caucasian	19 (95%)
Black or African American	1 (5%)
Tumor type, N (%)	
CLL	15 (75%)
FL	3 (15%)
DLBCL	2 (10%)
ECOG PS, N (%)	
0	8 (40%)
1	11 (55%)
2	1 (5%)
Known BTK-C481S mutation status in CLL patients (15*), N (%)	12 (80%)
Median number (range) of prior systemic therapy	5.5 (1-12)
Chemotherapy	18 (90%)
Targeted and immunotherapy	
Anti-CD20 antibody	18 (90%)
BTK inhibitor (all CLL patients)	15 (75%)
BCL2 antagonist	7 (35%)
PI3K inhibitor	6 (30%)
Lenalidomide	4 (20%)
CC-122	4 (20%)
CDK inhibitor	4 (20%)

* BTK-C481S status of 3 CLL patients is unknown

Preliminary unmonitored data as of 20 Nov 2018

Summary of DLTs, SAEs and AEs

Events	Cohorts 1 to 6 (N=20)
Dose-limiting toxicities	0
Any Serious adverse events*	4 (20.0%)
Any adverse events	20 (100.0%)
≥ Grade 3 adverse events	11 (55.0%)
ARQ 531-related adverse events	10 (50.0%)
Treatment interruption and/or dose reduction	4 (20.0)
• Dose reduction due to AEs**	1 (5.0)
Treatment discontinuation due to adverse events	2 (10.0%)

*Not related to the study drug
** One patient treated at dose level 15 mg QD had dose reduction due to a Grade 3 increased lipase that was assessed as drug-related.
Preliminary unmonitored data as of 20 Nov 2018

Serious Adverse Events

4 subjects experienced 7 SAEs. None of the SAEs were drug-related
- Pt 8: experienced a grade 3 febrile neutropenia and a grade 3 pneumonia, treatment was interrupted. Patient is continuing the study treatment (42 weeks on therapy)
- Pt 10: experienced a grade 3 deep vein thrombosis that resulted in permanent treatment discontinuation
- Pt 11: experienced a grade 3 hyperkalemia that resulted in permanent treatment discontinuation. In addition, the patient experienced a grade 3 lung infection
- Pt 18: experienced two events of grade 3 cellulitis, treatment was interrupted. Patient is continuing the study treatment (21 weeks on therapy)

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Treatment Emergent Adverse Events

Preferred Term	All (N=20)		ARQ 531-Related (N=20)	
	All Grade N (%)	Grade 3-4 N (%)	All Grade N (%)	Grade 3-4 N (%)
Upper respiratory tract infection	6 (30.0)	0	0	0
Nausea	6 (30.0)	0	3 (15.0)	0
Weight decreased	4 (20.0)	0	0	0
Back pain	4 (20.0)	0	0	0
Dizziness	4 (20.0)	0	2 (10.0)	0
Cough	4 (20.0)	0	0	0
Constipation	3 (15.0)	0	1 (5.0)	0
Diarrhea	3 (15.0)	0	2 (10.0)	0
Vomiting	3 (15.0)	0	2 (10.0)	0
Fatigue	3 (15.0)	0	1 (5.0)	0
Edema peripheral	3 (15.0)			
Pyrexia	3 (15.0)	0	0	0
Fall	3 (15.0)	0	0	0
Neutrophil count decreased	3 (15.0)	3 (15.0)	2 (10.0)	2 (10.0)
Platelet count decreased	3 (15.0)	2 (10.0)	1 (5.0)	1 (5.0)
Weight increased	3 (15.0)	0	0	0
Anemia	2 (10.0)	1 (5.0)	0	0
Ear pain	2 (10.0)	0	0	0
Febrile neutropenia	2 (10.0)	2 (10.0)	0	0
Vision blurred	2 (10.0)	0	0	0
Hyperhidrosis	2 (10.0)	0	0	0
Pneumonia	2 (10.0)	0	0	0
Hyperuricemia	2 (10.0)	0	0	0
Arthralgia	2 (10.0)	0	1 (5.0)	0
Headache	2 (10.0)	0	2 (10.0)	0
Nasal congestion	2 (10.0)	0	0	0
Lipase increased	1 (5.0)	1 (5.0)	1 (5.0)	1 (5.0)

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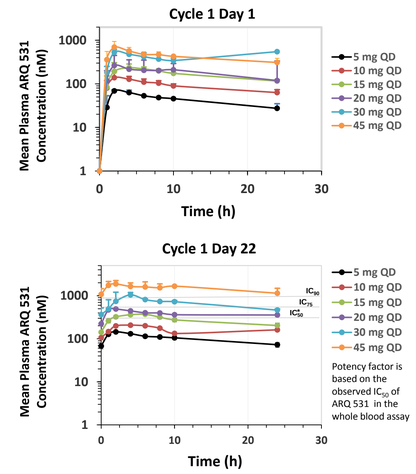
Mean Plasma Concentration-Time Profiles of ARQ 531 for Cohorts 1 through 6



ARQ 531 Preliminary Mean PK Parameters Cohorts 1 through 6

Patients (N)	Dose mg QD	Cycle 1 Day 1			Cycle 1 Day 22		
		C_{max} (nM)	AUC_{0-24h} (h*nM)	Half-life (h)	C_{max} nM	AUC_{0-24h} h*nM	Half-life (h)
3	5	69	1024	27	145	2009	27
4	10	152	2162	23	229	3817	22
4	15	251	3874	21	398	6726	25
3	20	301	4162	20	528	9177	18
3	30	530	5966	12	911	14699	23
3	45	695	9988	29	1874	33940	38

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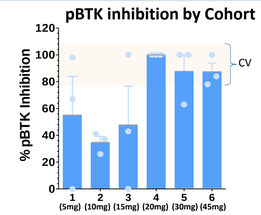
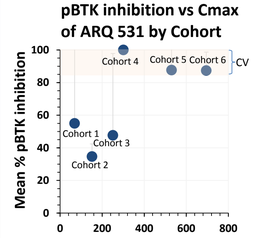
Target Engagement and ARQ 531 PK/PD Correlations





- Low dose range cohorts (1 to 3) showed an average 50% inhibition; profound pBTK reductions were achieved at ≥ 20 mg dose levels
- However, one patient in the first cohort (5mg) achieved complete pBTK reduction, was later dose escalated and achieved a confirmed partial response

CV: Variability of pBTK/BTK ratio determination in the validated whole blood assay was ~±15%

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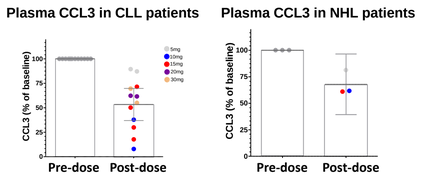
Suppression of CCL3, Plasma Biomarker of BCR Pathway Activation

- Mean plasma CCL3 levels in the pre-dose and post-dose (maximum reduction between Cycle 1 and 2) were 97 and 59 pg/mL, respectively. Overall, ARQ 531 treatment led to 39% reduction in CCL3 level, irrespective of starting dose (5 to 30 mg)
- ARQ 531 suppressed CCL3 levels in CLL patients harboring the BTK-C481S mutation



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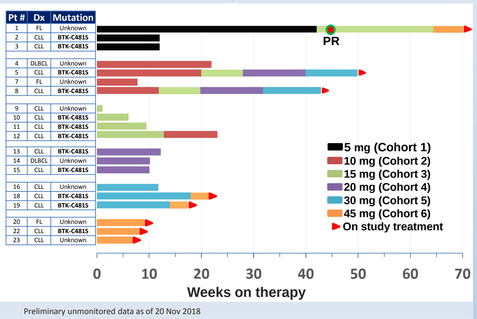
Treatment Cohort, Dose and Duration



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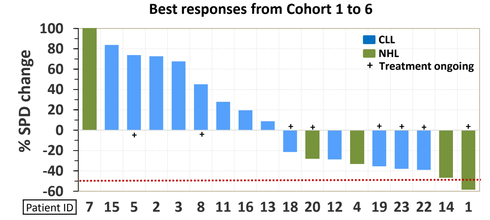
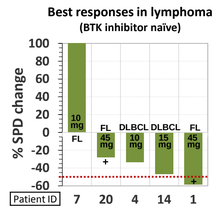
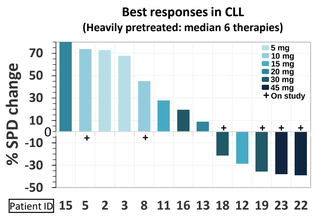
ARQ 531 Demonstrates Preliminary Anti-tumor Activity in Multiple B-cell Malignancies







- Among 5 NHL patients, one PR and 3 SDs with significant tumor reductions were observed
  - One patient with follicular lymphoma refractory to R-CHOP and SYK/JAK inhibitor treatment achieved a partial response and is continuing the study treatment after 16 months
- Among 15 CLL patients, 8 patients harboring BTK-C481S mutation had stable diseases including 5 patients with tumor reductions >20%

Preliminary unmonitored data as of 20 Nov 2018

CONCLUSIONS

- **ARQ 531 was well-tolerated at dose levels of 5 to 45 mg QD, supporting continued dose escalation**
- **Increases in plasma exposure (C_{max}, AUC) are close to dose proportional and the half-life at Cycle 1, Day 22 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 (20, 30 and 45 mg QD). Importantly, CCL3 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**
- **A durable partial response was observed in one of three patients with follicular lymphoma**

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.

ACKNOWLEDGMENTS

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