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

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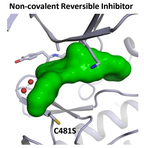
BACKGROUND

Bruton's tyrosine kinase (BTK) is a key regulator of the B cell receptor (BCR) signaling pathway that contributes to survival, proliferation and trafficking of malignant B cells. Despite impressive clinical response of ibrutinib in B-cell malignancies, cases of primary and secondary resistance have emerged with poor outcomes and no established treatment options. The underlying drug resistance mechanisms are complex and diverse, in ~80% of relapsing CLL patients development of resistance is associated with BTK-C481S mutation as well as PLCγ mutations. ARQ 531 is a reversible ATP competitive inhibitor of BTK and does not require C481 residue for binding. With its distinct kinase selectivity profile, ARQ 531 targets multiple oncogenic signals of BCR signaling pathway and has demonstrated potent inhibitory activity in CLL and DLBCL mouse models.

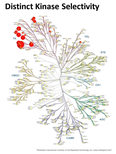
ARQ 531, a potent reversible inhibitor of BTK and BTK-C481S mutant

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

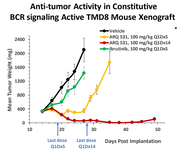
Non-covalent Reversible Inhibitor



Distinct Kinase Selectivity



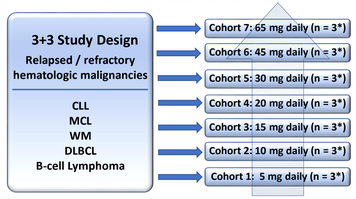
Anti-tumor Activity in Constitutive BCR signaling Active TMD8 Mouse Xenograft



STUDY DESIGN & METHODS

- Ongoing Phase 1, open-label, single arm, multicenter, dose-escalation study of ARQ 531 in subjects with selected hematologic malignancies (NCT03162536).

Dose Escalation Schema



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

Key Inclusion Criteria

- 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.

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).
- Intolerant to a BTK inhibitor
- CYP 2C9, 2C8, 2C19, 2D6 substrates and P-gp substrates with a narrow therapeutic index (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.)

PK Analysis

Subject 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

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. CCL3 levels in plasma samples were determined using an ELISA assay.

RESULTS

Patient Demographics

	N=11
Median age (Range)	68 (58-79) years
Gender, N (%)	
Male	11 (100%)
Female	0 (0%)
Race, N (%)	
White	11 (100%)
Tumor type, N (%)	
CLL	8 (73%)
DLBCL	1 (9%)
FL	2 (18%)
ECOG, N (%)	
0	6 (55%)
1	5 (45%)
Median number (range) of prior systemic therapy	5 (1-9)
Chemotherapy	10 (91%)
Targeted and immuno therapy	
Anti-CD20 antibody	11 (100%)
BTK inhibitor	8 (73%)
PI3K inhibitor	4 (36%)
BCL2 antagonist	2 (18%)
Anti-CD19 antibody	1 (9%)
Known BTK-C481S mutation status in CLL patients, N (%)	7 (87%)

* Date cut-off date: 8 Apr 2018, preliminary unmonitored data.

Dose-Limiting Toxicities (DLTs) and Severe/Serious Adverse Events (AEs)

- No DLTs observed
- No ARQ 531-related ≥ Grade 3 AEs observed
- No ARQ 531-related serious AEs observed
- MTD/RP2D was not reached

MTD: maximum tolerated dose; RP2D: recommended phase 2 dose

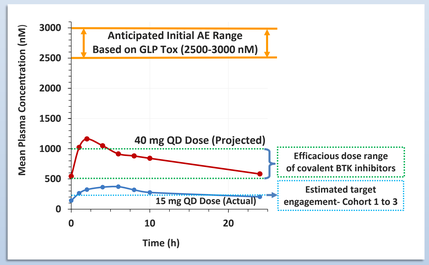
* Date cut-off date: 8 Apr 2018, preliminary unmonitored data.

ARQ 531-Related Adverse Events

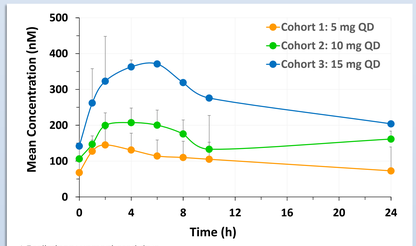
Preferred Term	All Grade N (%)	≥ Grade 3 N (%)
Patient with at least one ARQ 531-related TEAE	4 (36.4%)	0
Diarrhea	1 (9.1)	0
Nausea	1 (9.1)	0
Vomiting	1 (9.1)	0
Fatigue	1 (9.1)	0
Pneumonia	1 (9.1)	0
Hypernatremia	1 (9.1)	0
Arthralgia	1 (9.1)	0
Groin pain	1 (9.1)	0
Dizziness	1 (9.1)	0
Headache	1 (9.1)	0

* Date cut-off date: 8 Apr 2018, preliminary unmonitored data.

Actual and Estimated Human Exposures Based on Preclinical Data



Mean Plasma Concentration-Time Profiles (Cycle 1, Day22) of ARQ 531 for Cohorts 1 through 3



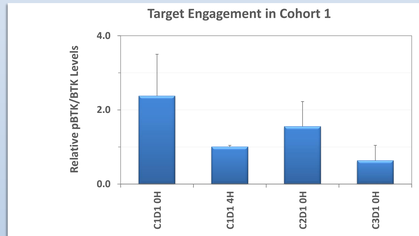
* Preliminary unmonitored data.

ARQ 531 (Cycle 1, Day 22) Pharmacokinetic Parameters (Cohorts 1 through 3)

Dose		T_{max} (h)	C_{max} (nM)	AUC_{last} (h*nM)	$t_{1/2}$ (h)
5 mg QD	Mean (n=3)	2	145	2009	27.1
	SD	0	44	1312	16.1
	%CV	0	30	65	59.5
10 mg QD	Mean (n=4)	10	229	3817	22.4
	SD	10	29	917	6.2
	%CV	105	13	24	28
15 mg QD	Mean (n=3)	4	398	6726	25.2
	SD	2	55	122	-
	%CV	50	14	2	-

* Preliminary unmonitored data.

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

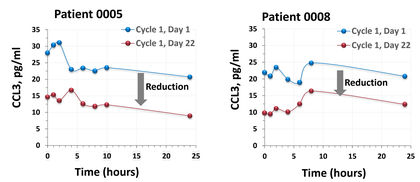


* Preliminary unmonitored data.

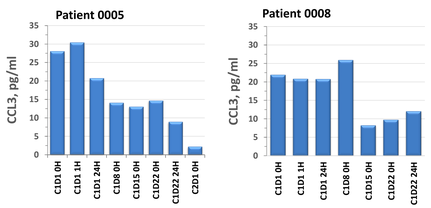
CCL3, Plasma Biomarker of BCR Pathway Activation is Suppressed in CLL Patients with BTK-C481S Mutation

Reduction in CCL3 Levels in Cohort 2 (10 mg) Patient Plasma Samples

Time Profile of CCL3 levels on Cycle 1, Day 1 and Day 22



CCL3 levels on Different Treatment Days



Reduction in CCL3 Level in Cohort 1 (5 mg) patients was not observed

* Preliminary unmonitored data.

Treatment Cohort, Dose and Duration

Cohort	Dose Level	Number of Patients	Median Time on Treatment*	Number of Patients Continuing Treatment	Reasons off Study
1	5 mg QD	3	12 weeks (range 1 to 46 weeks)	1	Clinical PD (n=2)
2	10 mg QD	4		2	Clinical PD (n=1) Radiographic PD (n=1)
3	15 mg QD	4		1	Clinical PD (n=1) Physician's decision (n=1) Data not available (n=1)

Data cut-off: 30 May 2018, preliminary unmonitored data.

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

- **Patient 020-0001**, a 58 years old white male with grade III follicular lymphoma, who has received 3 prior anti-cancer systemic regimen (R-CHOP, PI3K Delta inhibitor, and Syk / JAK inhibitor), received ARQ 531 at 5 mg QD. Tumor Responses showed a maximum reduction of 35% and treatment is ongoing.
- **Patient 122-0004,** a 69 years old white male with grade III DLBCL, who has received 1 prior anti-cancer therapy of rituximab received ARQ 531 at 10 mg QD. The tumor was reduced by 33%, ARQ 531 was discontinued after 20 weeks on study treatment due to clinical progression.
- **Patient 056-0012,** a 69 years old white male with CLL/SLL with BTK C481S mutation, who has received 5 prior systemic regimens (chemotherapy, dinaciclib, ibrutinib, venetoclax and CC-122 + obinutuzumab) received ARQ 531 at 15 mg QD and showed 29% tumor reduction after 8 weeks and he is continuing study treatment.

Data cut-off: 30 May 2018, preliminary unmonitored data.

CONCLUSIONS

- **ARQ 531 was well-tolerated at dose levels of 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 27 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**