ARQ 531 – Next Generation BTK-Inhibitor

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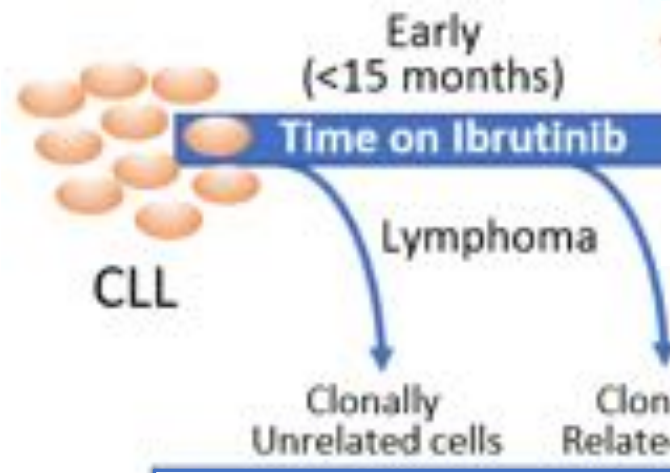
Disclosures of Deborah Stephens

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Acerta	x						
Arqule	x						
Gilead	x						
Verastem	x						

ARQ 531 Overview

- Rationale for development
- Mechanism of action
- Pre-clinical Studies
- Phase 1 Clinical Trial
- Future Development Plans

Clinical Concern: Ibrutinib-Resistant CLL



Richter's transformation
Median overall survival = 3.9m
Ibrutinib tx must be modified

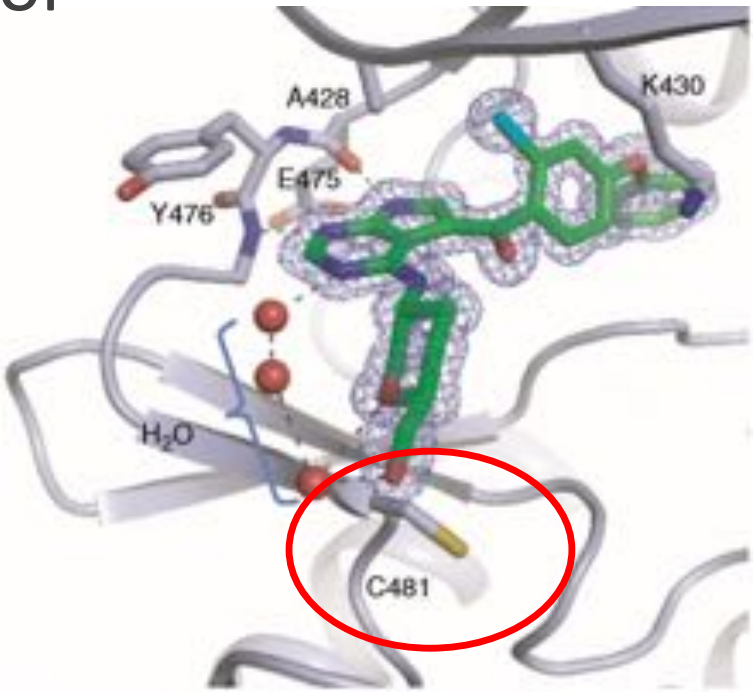
Woyach *et al.*, JCO 2017 Ahn *et al.*, Blood 2017

Clinical Need:
Agents that are effective against **ibrutinib-resistant CLL**

BTK is excellent target for CLL:
Develop BTK-inhibitor with an alternate binding site

ARQ 531: Mechanism of Action

- Non-covalent, reversible BTK-inhibitor
  - No interaction with C481
- Potent BTK-inhibitor
  - IC_{50} WT BTK = 0.85 nM
  - IC_{50} C481S BTK = 0.39 nM

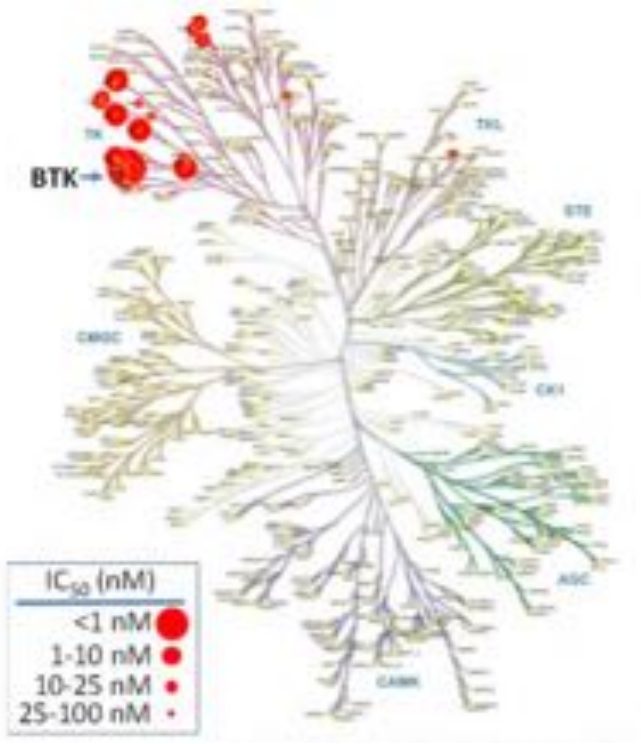


Structure from Reiff, Cancer Discovery 2018

ARQ 531: Mechanism of Action

- Selective BTK-inhibitor

Kinase	Kinase Inhibition Average IC_{50} (nM)	
	ARQ 531	Ibrutinib
BTK	0.85	1.5
TEC	5.8	10
ITK	>10,000	4.9
EGFR	290	5.3



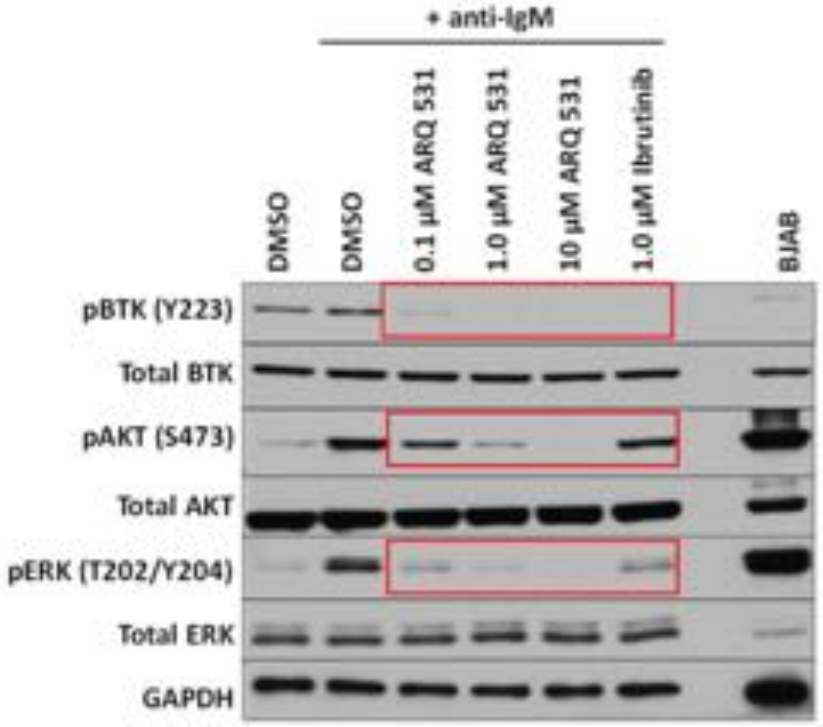
Structure from Reiff, Cancer Discovery 2018

Comparison of Mechanism with Ibrutinib

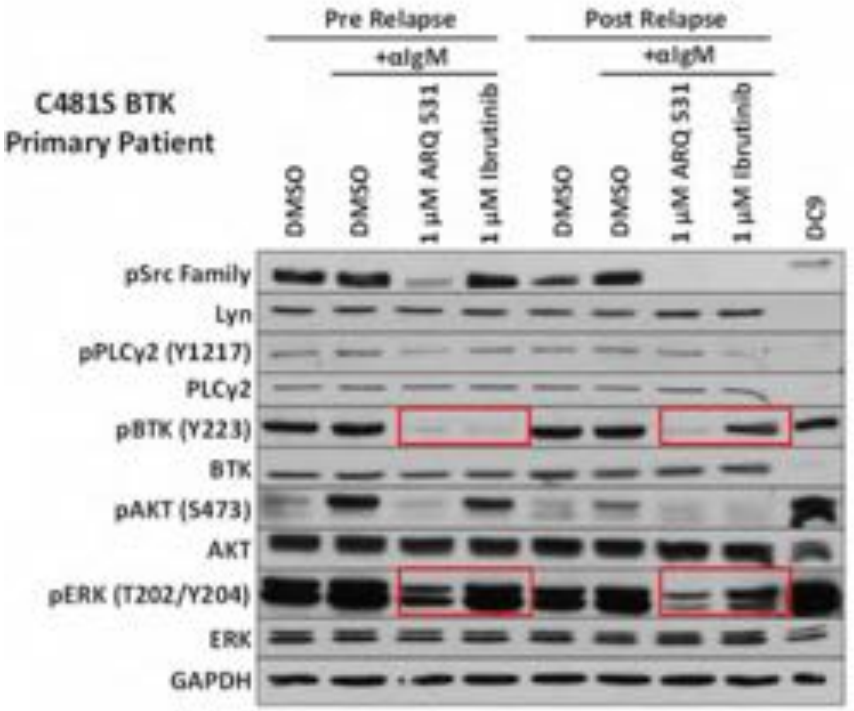
Feature	Ibrutinib	ARQ 531
Target	BTK	BTK
Type of Bond	Irreversible, Covalent	Reversible, Non-covalent
Requires C481 residue for binding	Yes	No
Blockade of autoactivation sites on BTK	Y223	Y223 and Y551
Drug interactions	Major Substrate of CYP3A4	Does not induce CYP1A2, CYP2B6, CYP3A4 Does not inhibit CYP3A4 CYP2C8 (inhibitor)
Half Life (steady state)	4-6 h	18-37.9 h (22 days)

Preclinical Data: Cells

Potent suppression of downstream BCR signaling pathways in patient derived primary CLL cells

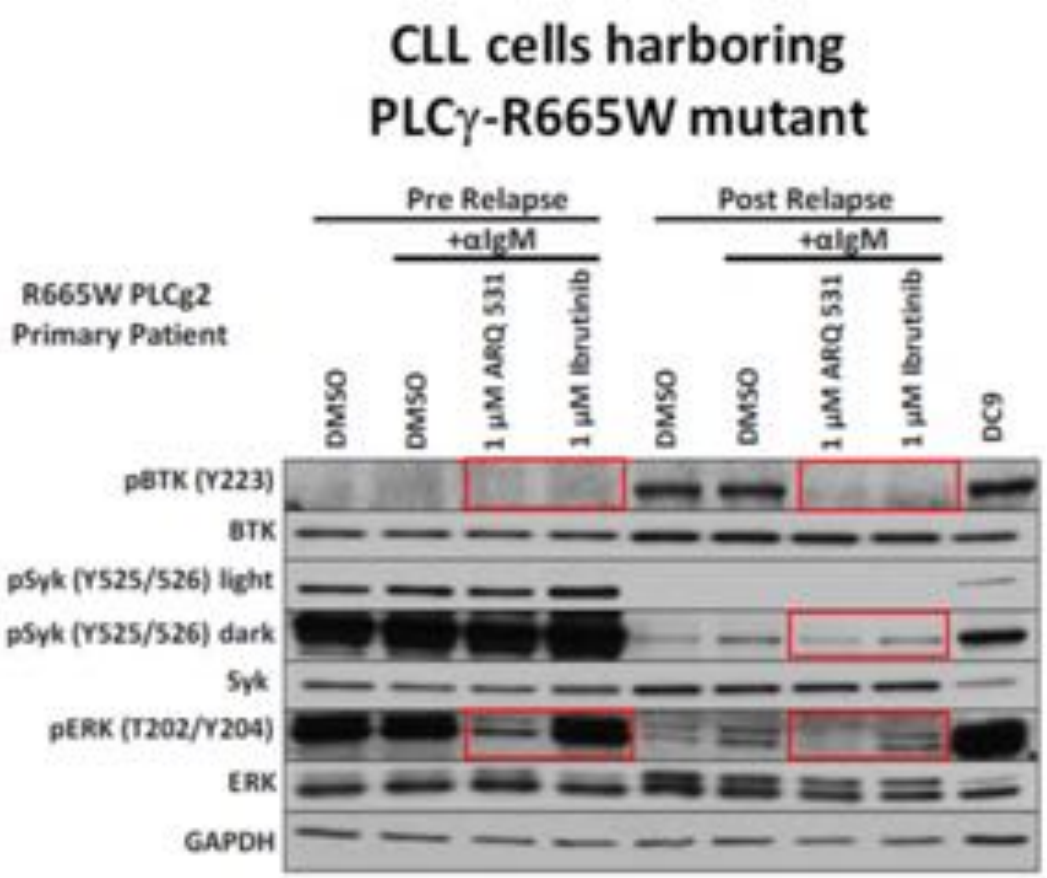


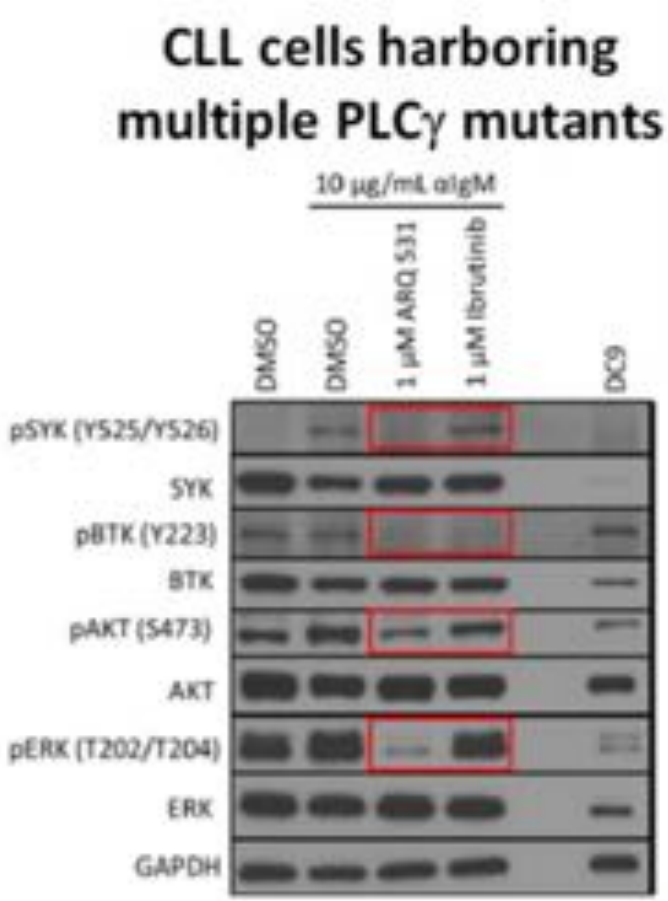
Inhibition of BTK-C481S mediated downstream kinase signaling in Ibrutinib resistant CLL cells



Reiff, Cancer Discovery 2018

Preclinical Data: Cells

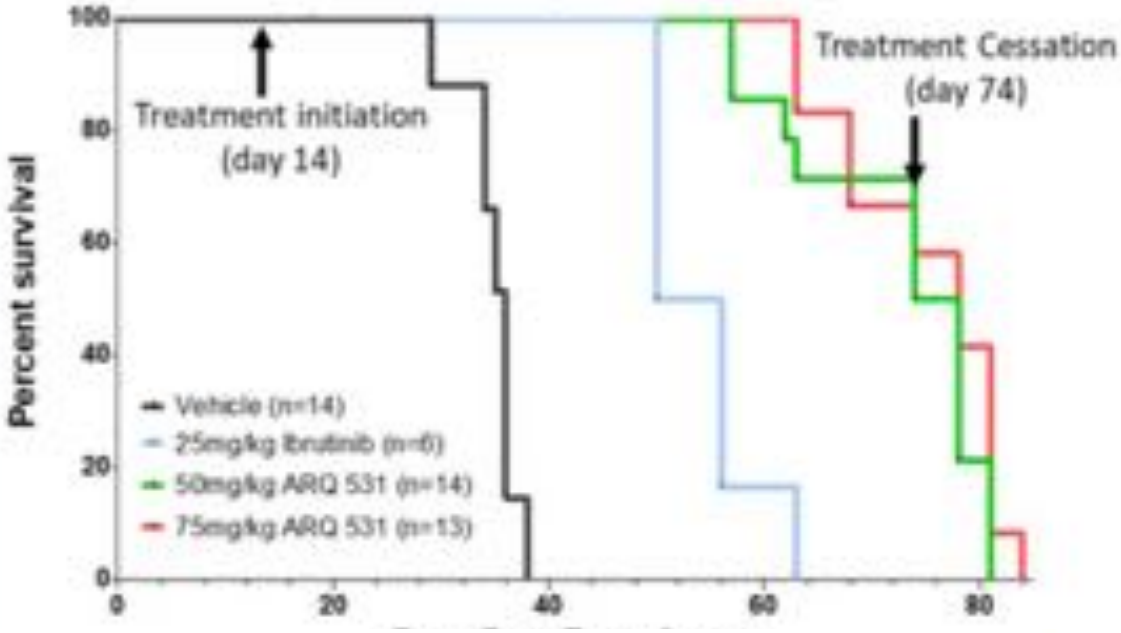




Reiff, Cancer Discovery 2018

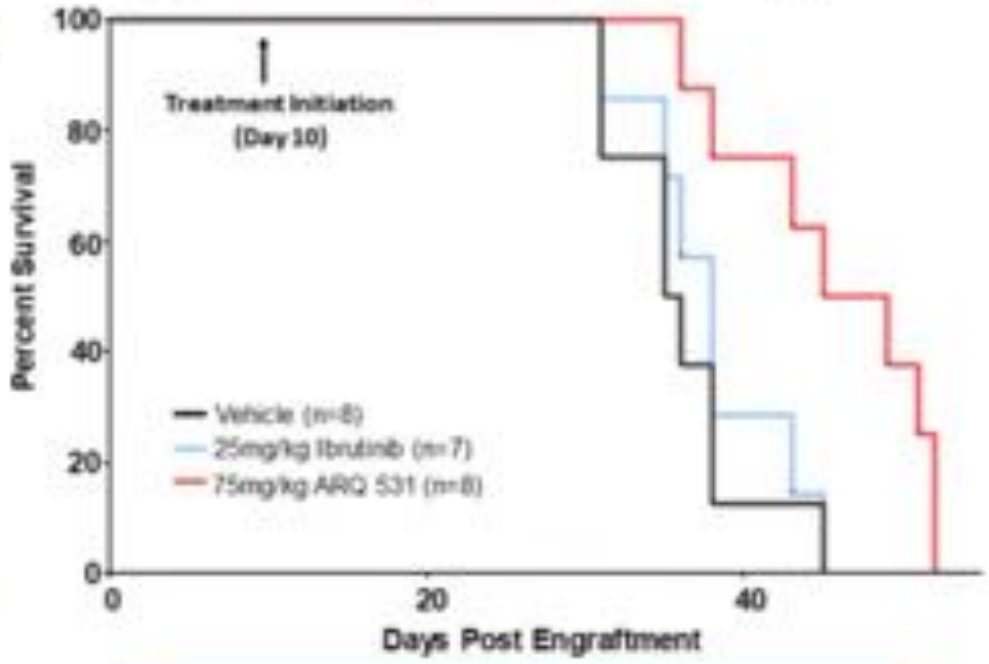
Spontaneous CLL-like leukemia

ARQ 531 improves survival of C57BL/6 mice engrafted with Eμ-TCL1 leukocytes



Disease phenotype of Richter's transformation

ARQ 531 improves survival of C57BL/6 mice engrafted with Eμ-MYC/TCL1 leukocytes



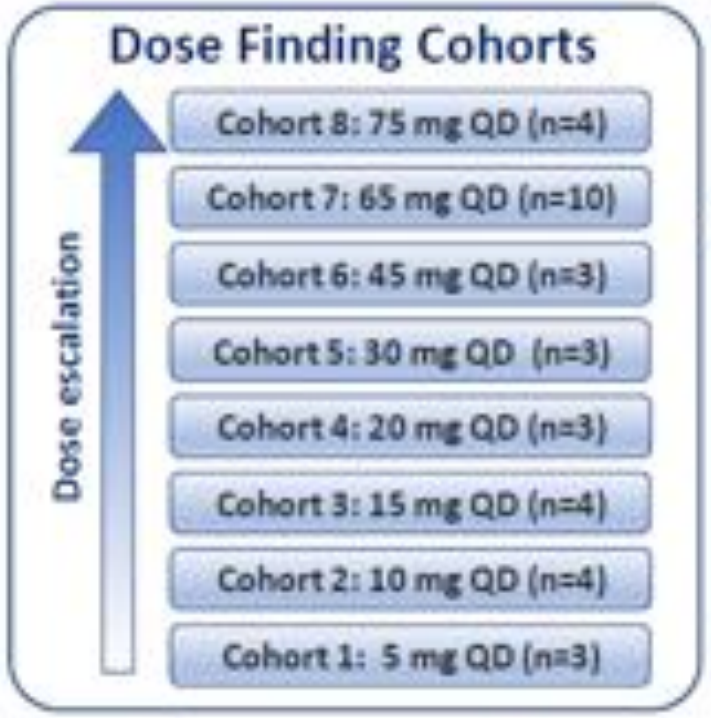
Reiff, Cancer Discovery 2018

Phase I Clinical Trial: CLL/NHL/WM

- Primary Objectives:
  - Safety and tolerability of single agent ARQ 531
  - Determine recommended phase 2 dose (RP2D) and schedule
- Secondary Objectives
  - Assess PK profile and PD activity
  - Obtain preliminary evidence of efficacy

- Eligible patients:
  - CLL/SLL
  - B-cell Non-Hodgkin lymphoma
  - Waldenstrom's macroglobulinemia
  - Relapsed/refractory to 2+ prior regimens

Phase I Clinical Trial: Schema



ClinicalTrials.gov Identifier: NCT03162536

Phase I: Baseline Characteristics

Demographic	N = 40
Median age (range)	65.5 (47-82)
Tumor Type	
CLL/SLL	26 (65%)
Richter's Transformation	6 (15%)
Follicular Lymphoma	4 (10%)
Diffuse Large B-cell Lymphoma	3 (7.5%)
Mantle Cell Lymphoma	1 (2.5%)
Median prior therapies (range)	4 (1-12)
> 4 prior therapies	23 (58%)
Known C481S BTK mutation	22 (85%)*
Prior BTK inhibitor	32 (80%)
Prior BCL2 inhibitor	10 (25%)

*BTK mut status is unknown in 4 CLL patients

Phase I: Toxicity

- Recommended Phase 2 Dose (RP2D)
  - 65mg daily dose: 1 patient with grade 3 rash
  - Expanded to 10 patients with no other dose limiting toxicity
  - 75mg daily dose (n=4):
    - All patients experienced grade 2 AEs that led to dose reduction (n=3) or discontinuation (n=1)
  - **RP2D = 65mg daily**

Phase I: Toxicity

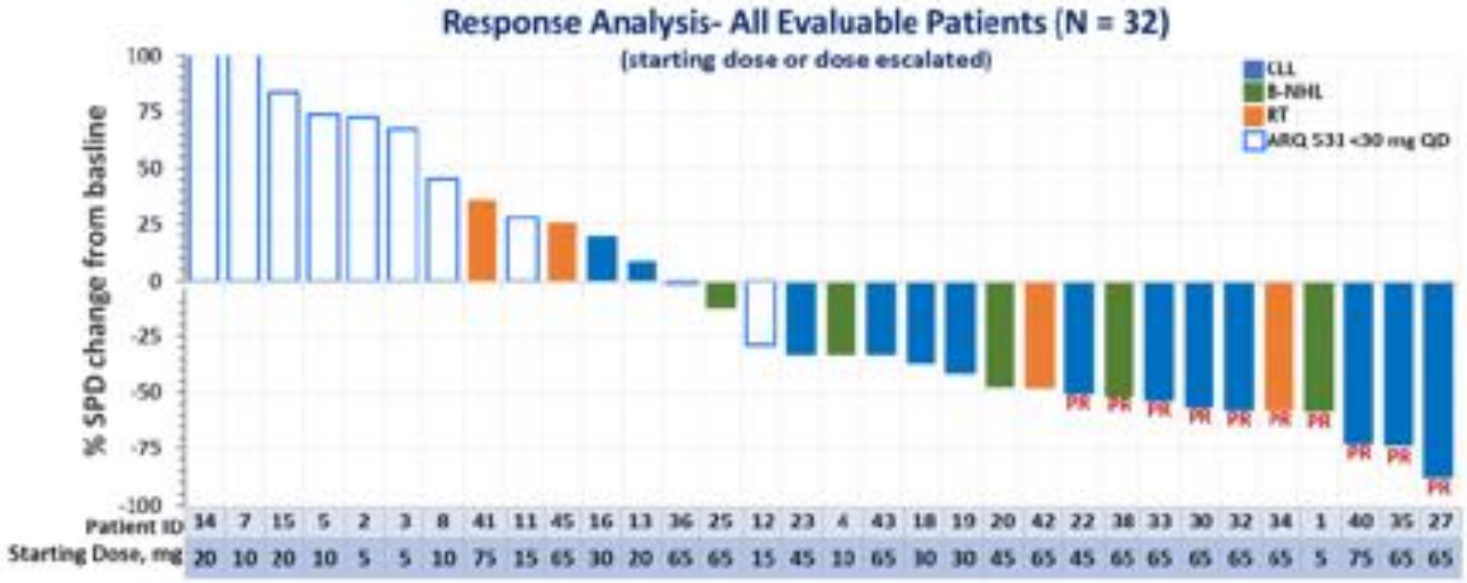
Most Common Drug-related AEs in ≥2 Patients	
Event	**N (%)**
Nausea	4 (10)
Diarrhea	4 (10)
Fatigue	3 (7.5)
↓ Neutrophils	3 (7.5)
Dysgeusia	3 (7.5)
Rash	3 (7.5)

Most Common Grade 3 Drug-related AEs	
Event	**N (%)**
↓ Neutrophils	3 (7.5)
↓ Platelets	1 (2.5)
Rash	1 (2.5)
Cellulitis	1 (2.5)
↑ Lipase	1 (2.5)

Notable AEs (not assigned as drug-related)	
Event	**N (%)**
Arthralgia	4 (10)
Epistaxis	2 (5)
Atrial Fibrillation	0

Phase I: Response

- ORR = 31% (10/32)
- ORR ≥65mg = 73% (8/11)



Response by Initial Dosing Cohort (Evaluable Population)

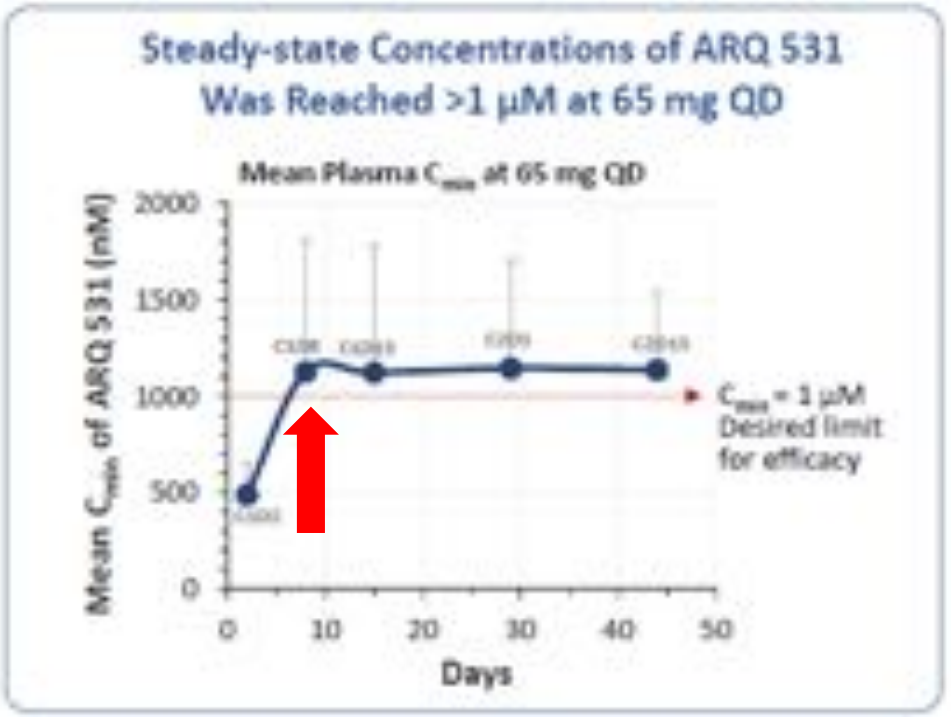
Response type	5 mg (N=3)	10 mg (N=4)	15 mg (N=1)	20 mg (N=3)	30 mg (N=3)	45 mg (N=3)	65 mg (N=8)	75 mg (N=3)	Expansion 65 mg (N=3)	Total (N=33)
Partial Response (PR), n	1	0	0	0	0	1	6	2	0	10
Stable Disease (Nonresponsive), n	0	1	2	1	3	2	2	1	3	15
Progressive Disease (PD), n	2	3	1	2	0	0	0	0	1	9
Objective Response Rate (ORR: CR+PR), n	1	0	0	0	0	1	6	2	0	10

Preliminary unmonitored data as of July 15, 2019

- RT patients 2 of 4 had reduction in LAD

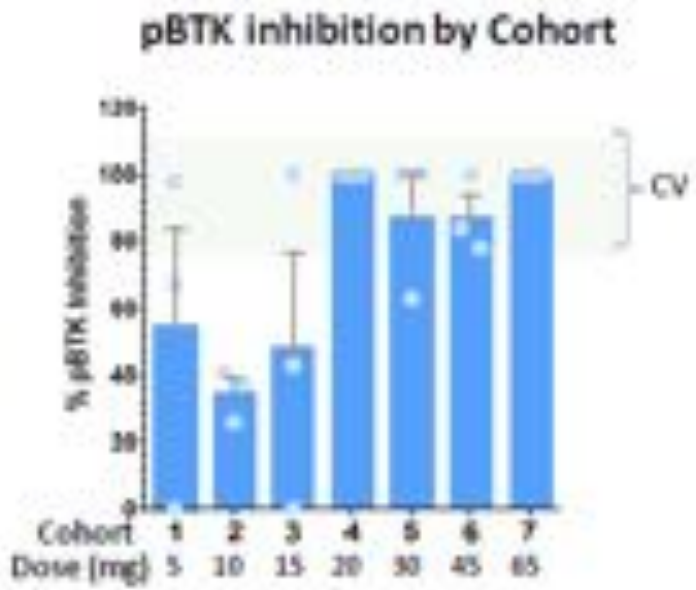
Phase I: PK Data

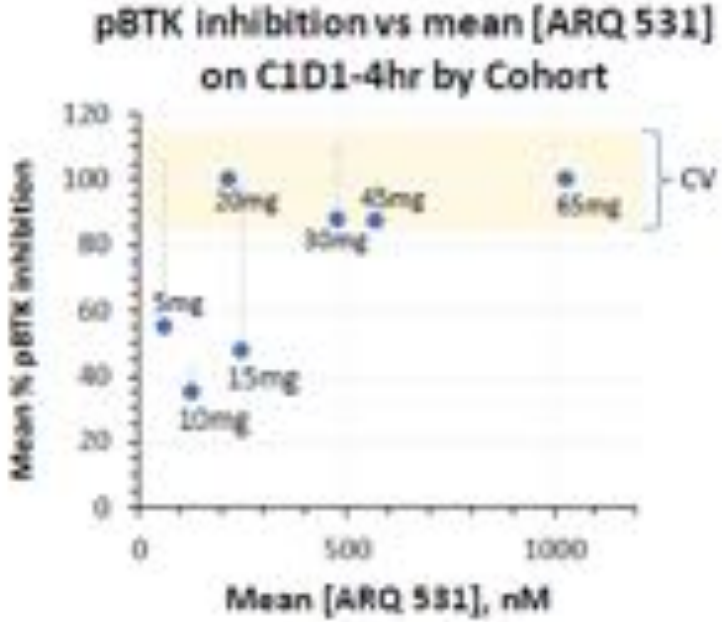
PK Property	ARQ 531	Ibrutinib
Dose	65mg QD	420 mg QD
C_{max} (nM)	3268	272
$AUC_{0\text{-}24hr}$ (h*nM)	55210	1960
C_{max}/AUC ratio	0.059	0.139
Half-life (h)	30	4-6



Phase I: PD Data

- pBTK/BTK ratios measured whole blood samples on C1D1 (4h post-dose)
- Full pBTK inhibition above 20mg dose
- Long $t_{1/2}$ at steady state suggests sustained pBTK inhibition over 24 hr.

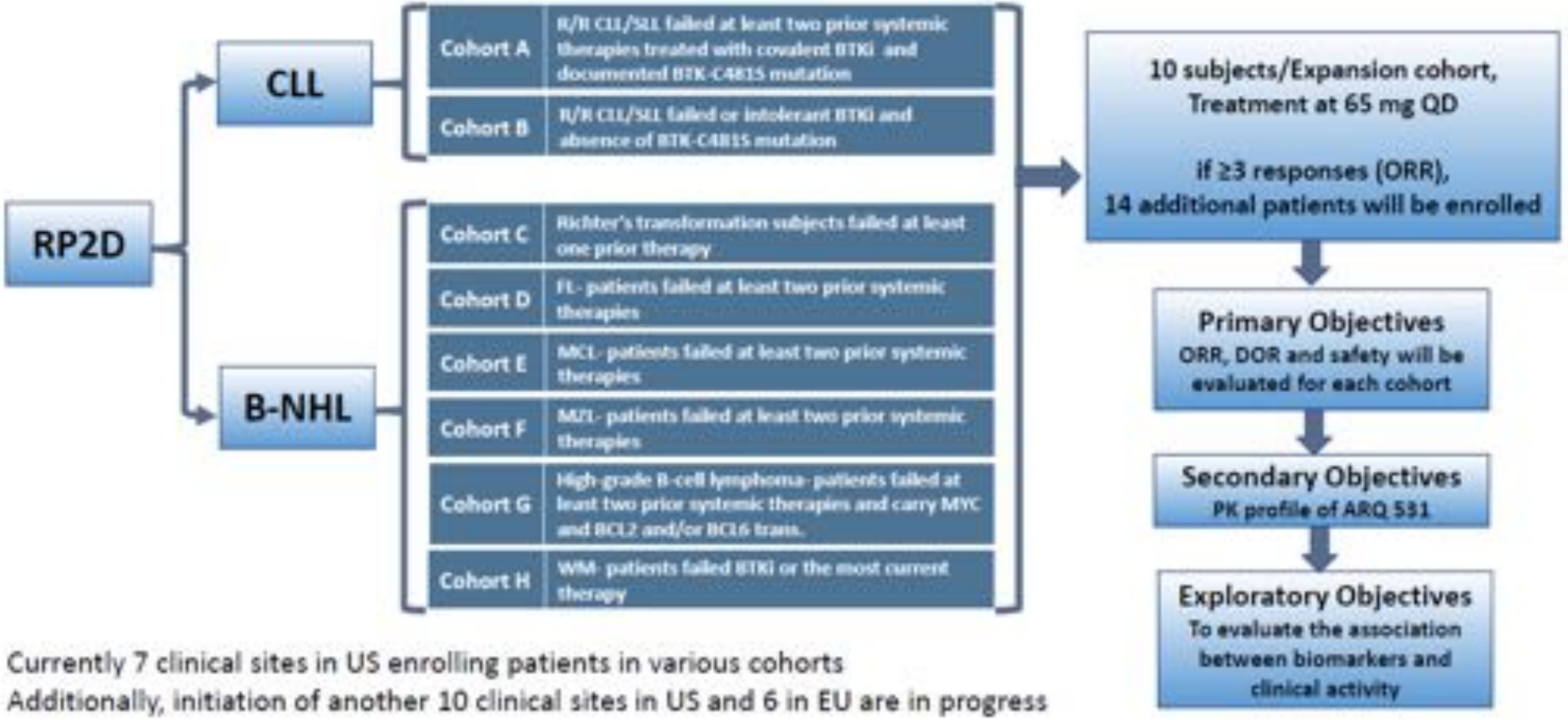




Phase I: Summary

- Recommended Phase 2 Dose = 65mg daily
- ARQ 531 is tolerable (monitor for rash, fatigue, cytopenias)
- Early evidence of efficacy was noted especially in patients with:
  - Ibrutinib-refractory CLL
  - Heavily-pretreated CLL
  - Richter's transformation
- Next Steps: Phase 2 study is ongoing

Phase 2 Study



Currently 7 clinical sites in US enrolling patients in various cohorts
Additionally, initiation of another 10 clinical sites in US and 6 in EU are in progress

Future Development Plans

- Potential combination with
  - Venetoclax
  - Anti-CD20 antibodies
  - PI3K-inhibitors
  - FCR or RCHOP
  - Ibrutinib
  - Lenalidomide
  - PD1-inhibitors
  - CART
- Planned Future Studies:
  - Phase II: CLL R/R C481S mutated
  - Phase I: Combination of ARQ 531 plus venetoclax or obinutuzumab
  - Phase III: CLL R/R BTK C481S mutated: FDA discussions underway

Summary

- ARQ 531 is a potent non-covalent reversible inhibitor of BTK
- ARQ 531's inhibition of BTK is not dependent on binding to the C481 moiety of BTK
- ARQ 531 has shown early evidence of clinical efficacy in
  - Ibrutinib-refractory CLL
  - Heavily-pretreated CLL
  - Richter's transformation
- Phase 2 study of ARQ 531 as a single agent are ongoing
- Phase 1 combination studies and phase 3 confirmatory studies are under development

Thank You

Mentors:

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- John Philips, Utah
- Sonali Smith, U Chicago
- Jonathan Friedberg, Rochester

Huntsman Lymphoma Team:

- Colleagues, APCs
- Pharmacy, Nursing, Research Team

Patients and Families:

- Without you, research is not possible