Update on non-Marketing Approved Non-Covalent BTKi in Chronic Lymphocytic Leukemia (CLL)

John C. Byrd, MD

The Gordon and Helen Hughes Taylor Professor and Chair

Department of Internal Medicine

The University of Cincinnati

Disclosure Information

Financial Conflict due to Company Ownership or Patents
Vincerx Pharmaceuticals, Inc
Eilean Therapeutics, Inc
Patents with OSU related to DHODH
Kurome

Other Industry Involvement (no self financial conflict).
Kartos Pharmaecuticals (advisory board)
Newave Pharmaceuticals (research support for clinical trials)
Orange Grove Bio (research support for clinical trials)
Neurix (research support for clinical trials)
Syndax (research support for clinical trials)

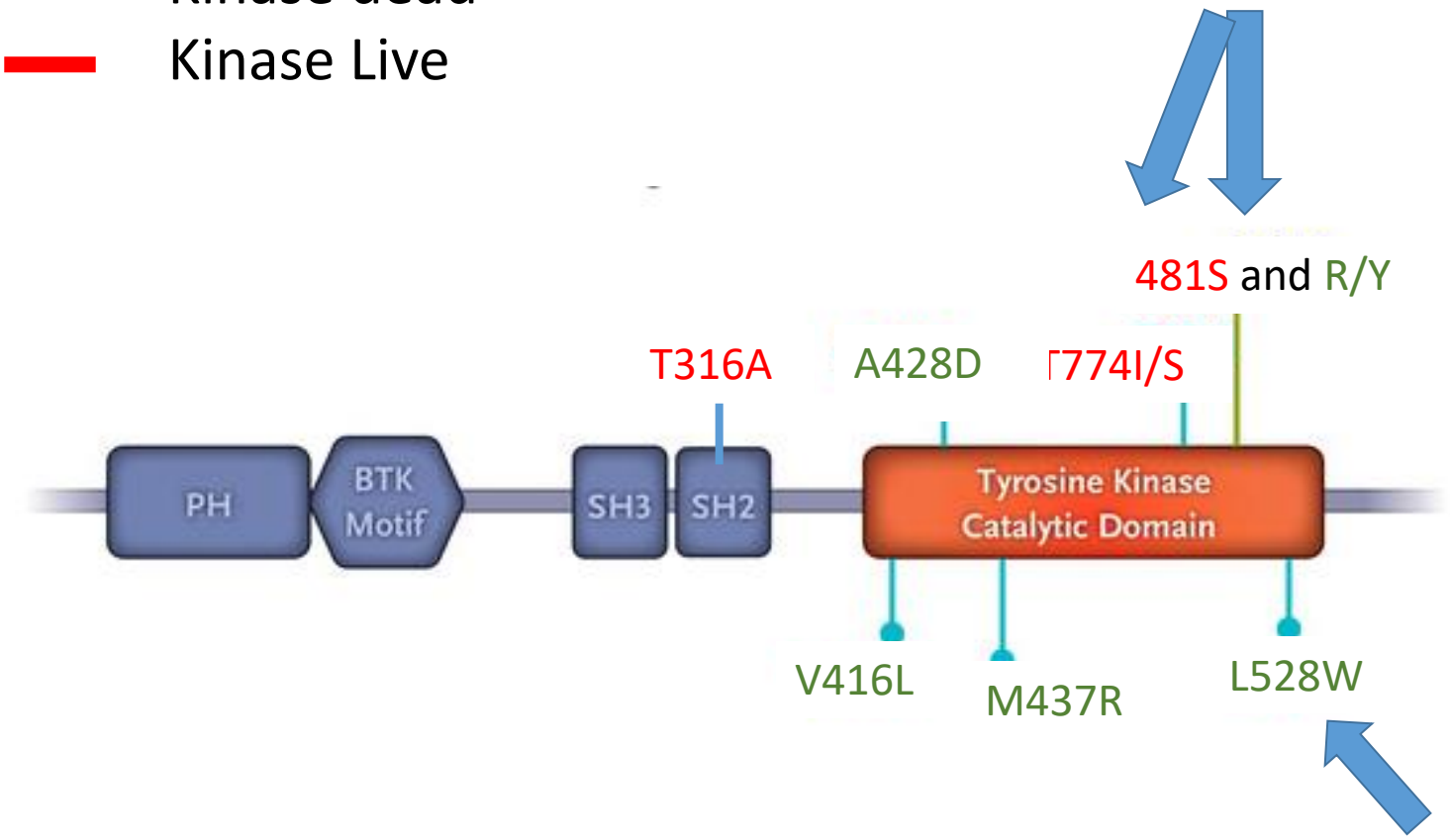
Why do we need a non-Covalent BTK inhibitor in CLL?

- Common mechanism of resistance to covalent BTK inhibitors include C481S which makes acalabrutinib inactive and ibrutinib a weak non-covalent inhibitor
- Non-covalent inhibitors targeting BTK kinase domain with long half life (continuous BTK coverage) still target C481S mutations
- Rationale comes forward to target ATP binding pocket with long-acting non-covalent BTKi brings forth Pirtobrutinib (approved) and Nemtabrutinib (ARQ531)

Kinase dead

Kinase Live

Ibrutinib,Acalabrutinib and Zanubrutinib



Non-Covalent Inhibitors: everywhere but C481S

Zanubrutinab

Ideal Properties for a non-Covalent BTK Inhibitors

- Highly selective for BTK (many non-specific BTK inhibitors)
- ADME properties that minimize interactions with other medications (CLL pts are older)
- Long plasma half life (to continuously cover target with once or twice daily dosing)
- Good oral absorption not influenced by food or gastric pH
- Active against T474I gatekeeper mutation

Fenebrutinib (GDC-0853)

- Pre-clinical activity in both de novo and also C481S mutant CLL as measured by BCR signaling inhibition, CXCL12 migration, CpG stimulated proliferation, and stromal protection
  - Only off target (100 fold difference FGF and BMX) with good ADME and pharmacology properties

  Reiff S et al: *Blood* 132: 1039–1049, 2018
- First in man phase 1 study in CLL/NHL performed showed biologic and clinical activity in CLL (PR or > in 8 of 24) including those with C481S mutations with favorable safety profile
  - Phase 1 study stopped prematurely before DLT determined due to commercial reasons; pursued broadly in autoimmune diseases

  Byrd JC et al: *OncoTarget* 9:13023-13035*, 2018*

ARQ-531 (Nemtebrutinib)

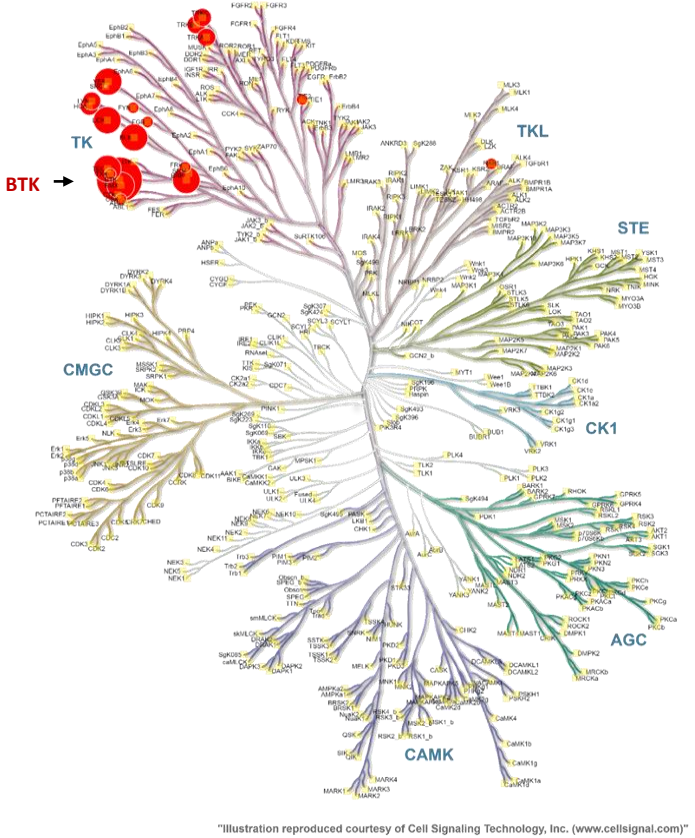
- Screened from a large chemical library of Arqule for enhanced activity against BTK C481S mutant
- Pre-clinical activity in both de novo and also C481S mutant CLL as measured by BCR signaling inhibition, CXCL12 migration, CpG stimulated proliferation, and stromal protection
- Enhanced apoptosis as compared to both ibrutinib and acalabrutinib
- Enhanced in vivo activity in TCL1 transgenic mouse model of CLL as compared to ibrutinib

Reiff S, et al. Cancer Discovery 8:1300-1315, 2018

Nemtabrutinib Is a Nonselective, Reversible BTK Inhibitor

Kinase	Biochemical Inhibition IC_{50} (nM)
BRK	2.5
LCK*	3.9
YES*	4.2
BMX**	5.2
TEC**	5.8
BLK*	9.7
TrkB***	12
TrkA***	13
HCK*	18
LYNa*	19
TrkC***	19
FGR*	26
Tie2	29
FYN*	32
RAF1	35
TXK**	36
CSK	45
FRK*	48
MEK1	599
ITK	>10,000

* Src family kinases
** TEK family kinases
*** Trk family kinases



"Illustration reproduced courtesy of Cell Signaling Technology, Inc. (www.cellsignal.com)"

IC_{50} (nM)
<1 nM
1-10 nM
10-25 nM
25-100 nM

Nemtabrutinib Phase 1 Study

- Multicenter, single arm, dose escalation trial using 3 + 3 design examining 8 distinct doses (5, 10, 15, 20, 30, 45, 65 and 75 mg)
- Eligibility for trial included
  - → CLL, SLL, or B-cell NHL
  - → Relapsed disease with at least 2 prior therapies with no therapy options
  - → Eastern Cooperative Oncology Group performance status of 2 or less
  - → Absolute neutrophil count ≥ 1,000/μL, hemoglobin ≥ 8 mg/dL, and platelets ≥ 50,000/μL (≥25,000 for those with documented marrow involvement)
  - → Creatinine clearance was required to be ≥ 60 mL/min.
  - → Total bilirubin was required to be ≤ 1.5 times upper limit of normal
  - → ALT/AST were required to be ≤ 2.5 times upper limit of normal.
  - → Patients with prior allogeneic stem cell transplant, active CNS disease, and intercurrent disease that limited toxicity assessment were all excluded
- Intra-patient dose escalation allowed after a level cleared safety evaluation to assure patient equipoise

Nemtabrutinib Doses and DLT Definition

Dose Escalation occurred with following cohorts

5 mg QD
10 mg QD
15 mg QD
20 mg QD
30 mg QD
45 mg QD
65 mg QD
75 mg QD

DLT was defined by occurrence of

1. NCI CTCAE grade 5 treatment emergent adverse event (TEAE)
2. Any NCI CTCAE grade 3 non-hematologic TEAE except alopecia, nausea, vomiting, diarrhea, and transient grade 3 laboratory anomalies that recover within 1 week without intervention
3. Any NCI CTCAE 3. Grade 3 hematologic TEAE that do not recover to grade 1 or baseline within 7 days with the exception of grade 3 lymphocytosis
4. NCI CTCAE grade 4 non-hematologic or hematologic TEAE
5. Any other toxicity that represents a clinically significant hazard to the patient per investigator discretion.

Nemtabrutinib Patient Characteristics

Characteristic, n (%)	CLL/SLL (n=29)	NHL (n=17)	WM (n=1)	All Pts (n=47)
Median age (range), years	65 (48-86)	68 (47-82)	71	65 (47-86)
Male	23 (79.3)	16 (94.1)	1 (100.0)	40 (85.1)
ECOG performance status				
0-1	28 (97)	15 (88.2)	0	43 (91)
2	1 (3)	2 (11.8)	1 (100)	4 (9)
Median prior Rx (range)	9 (2-18)	6 (2-12)	13 (13)	8 (2-18)
Prior Therapies				
Acalabrutinib	10 (34.5)	1 (5.9)	0	11 (23.4)
Ibrutinib	21 (72.4)	9 (52.9)	1 (100)	29 (61.7)
Venetoclax	7 (24.1)	4 (23.5)	0	11 (23.4)
Chemoimmunotherapy[a]	9 (31.0)	12 (70)	0	21 (45)
IGHV Unmutated	21 (72.4)	-	-	21 (44.7)
Del(17p)	7 (24.1)	-	-	7 (14.9)
TP53 mutation	11 (37.9)	-	-	11 (23.4)
BTK mutation	24 (82.8)	5 (29.4)	-	29 (61.7)

Nemtabrutinib Study History

- Patients were escalated to 75 mg without occurrence of a DLT.
- At 75 mg dosing, four patients had significant recurrent rash, taste disturbance, swallowing discomfort, and other toxicity that limited investigator enthusiasm to raise the dose
- The 65 mg daily was chosen as the recommended phase 2 dose (RP2D). Followed by expansion into this cohort
- Pharmacology was linear through all dose levels with . Geometric mean C_{max} ranged from 145 to 2593 nM and Css at 65 mg exceeding 1 uM

Nemtabrutinib[13] Adverse Events

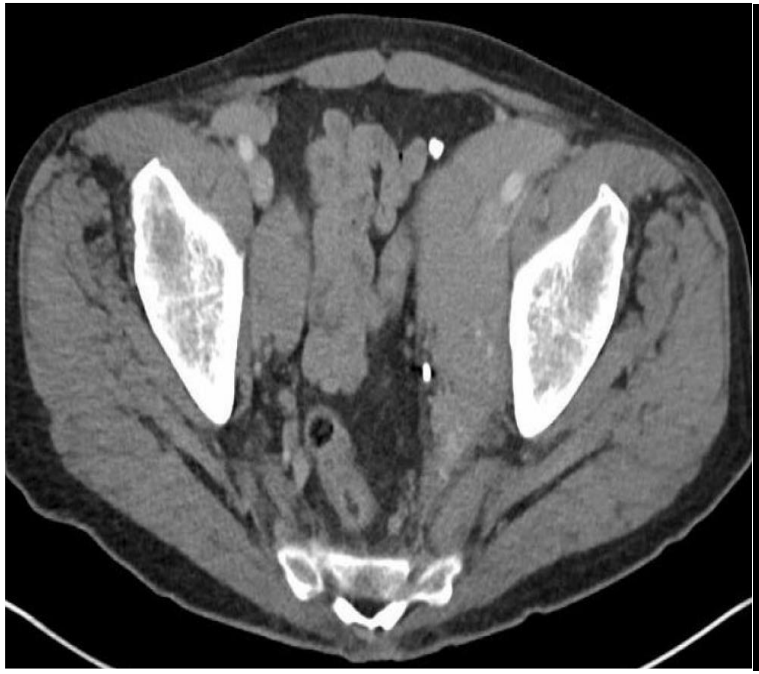
Adverse Event, n (%)	Grade 1-2 N (%)	Grade 3 N (%)	Grade 4 N (%)	Grade 5 N (%)	Total N = 47
All TEAEs	9 (19)	25 (53)	10 (21)	3 (6)	47 (100)
Hematologic					
Anemia	1 (2)	5 (11)	0	0	6 (13)
Neutropenia	1 (2)	6 (13)	5 (11)	0	12 (26)
Thrombocytopenia	1 (2)	2 (4)	4 (9)	0	7 (15)
Febrile neutropenia	0	6 (13)	1 (2)	0	7 (15)
Non-Hematologic (20% or greater)					
Arthralgia	14 (30)	1 (2)	0	0	15 (32)
Back pain	13 (27)	3 (6)	0	0	16 (34)
Constipation	15 (32)	1 (2)	0	0	16 (34)
Cough	17 (36)	0	0	0	17 (36)
Diarrhea	13 (27	0	0	0	13 (27)
Dizziness	12 (26)	0	0	0	12 (26)
Dyspnea	10 (22)	1 (2)	0	1 (2)	12 (26)
Fall	11 (23)	0	0	0	11 (23)
Fatigue	15 (32)	1 (2)	0	0	16 (34)
Headache	14 (30)	0	0	0	13 (30)
Hypertension	8 (17)	7 (14)	0	0	15 (32)
Nasal congestion	10 (21)	0	0	0	10 (21)
Nausea	15 (32)	0	0	0	15 (32)
Peripheral edema	16 (34)	0	0	0	16 (34)
Rash	13 (28)	2 (4)	0	0	9 (32)
Upper respiratory infection	12 (26)	0	0	0	12 (26)
Vomiting	10 (21)	0	0	0	10 (21)
Weight increase	10 (21)	0	0	0	10 (21)
Paraesthesia	10 (21)	0	0	0	10 (21)

Nemtabrutinib Efficacy

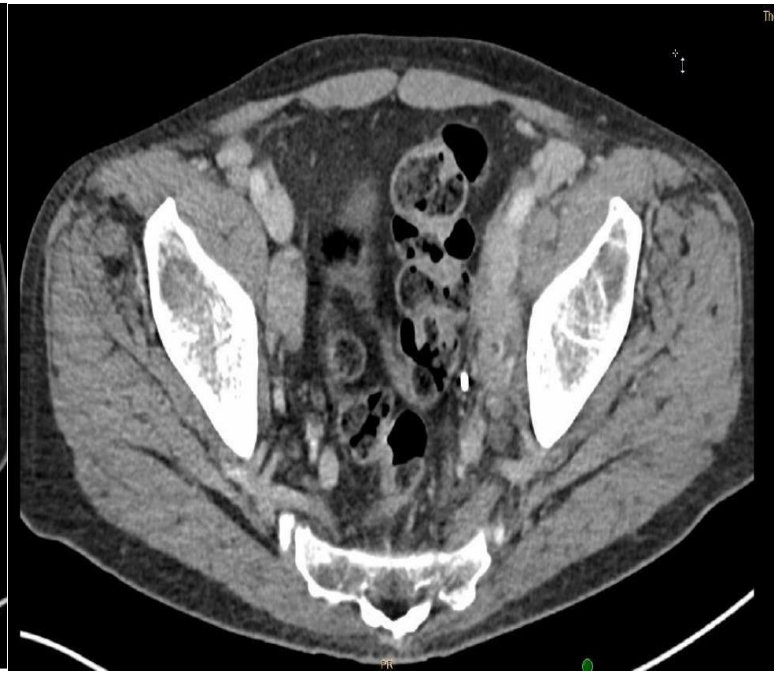
- Chronic lymphocytic leukemia
  - → 8 of 29 ((28%) responded with 6 PR, 1 PR-L and 1 CR
  - → 6 of 8 treated at 65 mg or higher responded
  - → Median PFS 16.7 months for all and NR for those at 65 mg dose
- Non-Hodgkin's Lymphoma
  - → 5 of 18 (28%) responded, all PRs
  - → Histology of response included Richter's transformation (3 of 6 responding), DLBCL and follicular NHL
- Median time to first response was 1.9 months
- Median time to best response was 4.6 months

Richter's Transformation (3/6 respond)

Pre Therapy (Richter's)



Cycle 3 of Nemtabrutinib



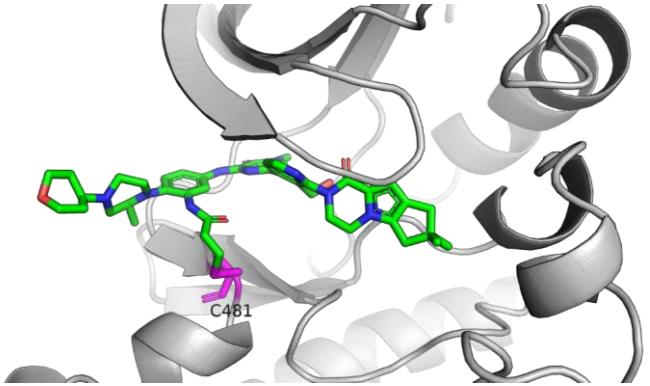
Nemtabrutinib after Merck Acquisition

- Review of pharmacology and pharmacodynamic modeling led team to believe further dose-escalation could occur and phase 1 was re-initiated
- After additional study, it was determined that the 65 mg dose was the recommended phase 2 dose
- Subsequent Phase 3 studies have initiated
  - BELLWAVE-008 Nemtabrutinib versus FCR or BR in previously untreated CLL without TP53 mut/del
  - ELLWAVE-010 Nemtabrutinib + Rituximab versus Venetoclax + Rituximab in previously treated CLL
  - BELLWAVE-011: Nemtabrutinib verus Acalabrutinib or Ibrutinib in previously untreated CLL

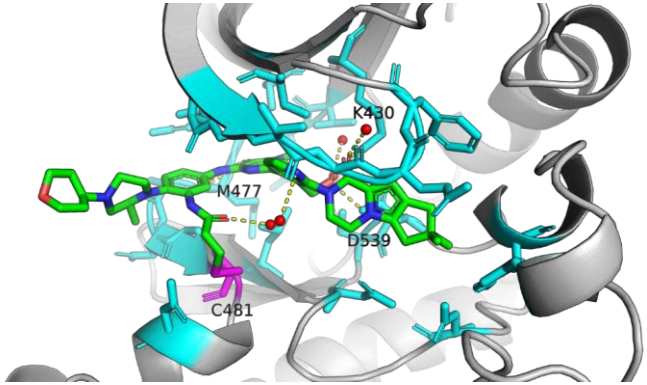
LP-168: A Dual Covalent and non-Covalent BTKi

- LP-168 has 700-fold selectivity toward BTK vs only other target TEC
- LP-168 inhibits WT BTK (IC_{50}= 0.11 nM) and C481S BTK (IC_{50}=1.0 nM).
- LP-168 inhibited BCR signaling in CLL cells, migration capacity towards CXCL12 and CXCL14, and diminished production of CCL3 and CCL4.
- LP-168 demonstrated cytotoxicity toward wild type, C481S, and T474I mutant TMD8 cells
- LP-168 has superior pre-clinical activity to ibrutinib in both the Eμ-TCL1 and Eμ-MTCP1 model of CLL

Covalent Binding



Non-Covalent Interactions



Gordon B and Woyach J, ASH 2028

First in Man Study of LP-168

- Phase 1, 4 center (OSU, UC, Duke and U Utah) dose escalation study
- 3+3 design with optional expansion at each dose level
- Eligible patients: B-cell NHL and CLL with two prior therapies
  - CrCl ≥ 60 mL/min
  - AST/ALT ≤ 1.5 x ULN, Bili ≤ 1.5 x ULN
  - Platelets ≥ 20,000
  - Washout 2 days from prior BCR inhibiting agents

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Dose Level	Dose per Day
100 mg	daily
150 mg	daily
200 mg	daily
150 mg	twice daily
300 mg	daily

Patient Demographics

- Median age 70 (range 41-85) with 92% being male
- ECOG performance status 0-1 in 98%
- Median prior therapies: 3 (range 1-8); 92% BTKi, 42% BLC2
- 37 CLL, 4 MCL, 2 MZ, and 2 WM
- Of 37 CLL patients, genomic features include
  - IGHV un-mutated 27 pts
  - 17p deletion, TP53 mutation, or both in 20 pts
  - 11q deletion in 16 pts
  - Complex karyotype 11 pts
- Of 37 patients, resistance mutations included
  - BTK C481S 21
  - BTK C481F/Y/R 6
  - BTK gatekeeper 9
  - BTK WT 11
  - PLCG2 5
- c

Woyach J et aL ASH 2023

Treatment Emergent Adverse Events with Incidence ≥ 20%

Toxicity	Any Grade n (%)	Grade ≥ 3 n (%)
Diarrhea	19 (42.2)	1 (2.2)
Fatigue	16 (35.6)	1 (2.2)
Arthralgia	15 (33.3)	1 (2.2)
Constipation	14 (31.1)	1 (2.2)
Headache	14 (31.1)	0
Cough	12 (26.7)	0
Dizziness	11 (24.4)	0
Nausea	11 (24.4)	0
Nasal congestion	10 (22.2)	0
Contusion	9 (20.0)	0
Vomiting	9 (20.0)	0

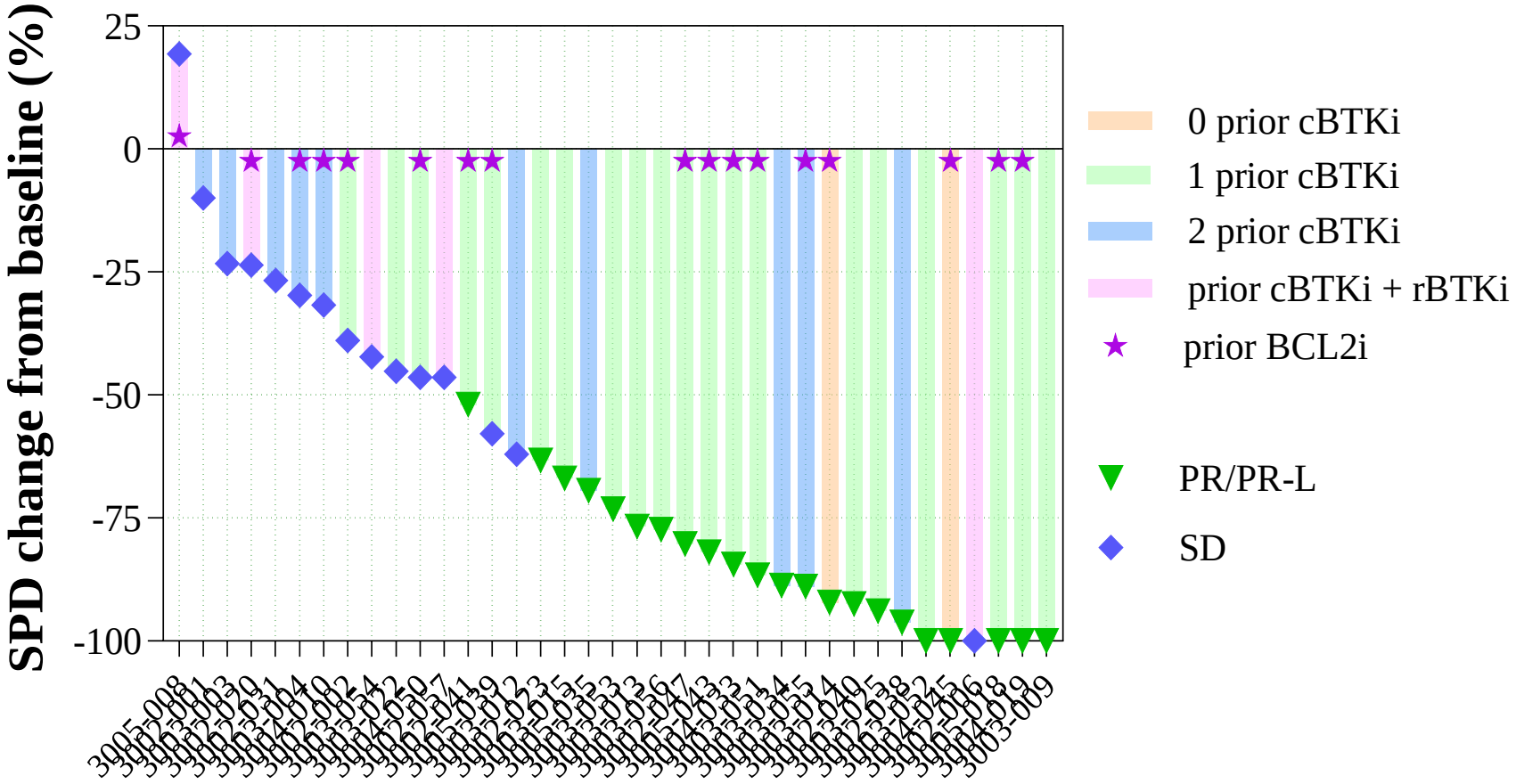
Adverse Events of Special Interest (TEAE)

Toxicity	Any Grade n (%)	Grade ≥ 3 n (%)
Atrial fibrillation	0	0
Bleeding*	9 (20.0)	0
Bruising	13 (28.9)	0
Hemorrhage**	7 (15.6)	1 (2.2)
Hypertension	5 (11.1)	1 (2.2)
Infections	28 (62.2)	7 (15.6)
Neutropenia	7 (15.6)	6 (13.3)

No dose limiting toxicities were identified

3 patients discontinued therapy due to toxicity:

Efficacy by Best Response (CLL/SLL Cohort)



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Response: CLL/SLL Cohort at Original Dose

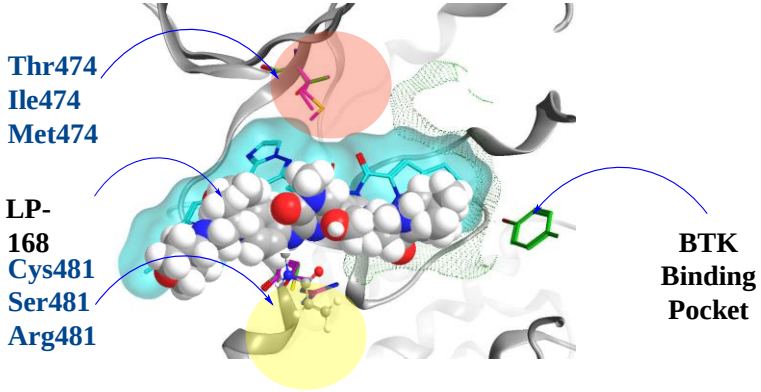
Best Overall Response	100 mg	150 mg QD	200 mg QD	150 mg BID	300 mg QD
N	13	5	4	8	7
ORR n(%)	4 (30.8%)	1 (20%)	3 (75%)	6 (75%)	5 (71.4%)
CR n(%)	0	0	0	0	0
PR or PR-L n(%)	4 (30.8%)	1 (20%)	3 (75%)	6 (75%)	5 (71.4%)
SD n(%)	9 (68.2%)	4 (80%)	1 (25%)	2 (25%)	2 (28.6%)
PD n(%)	0	0	0	0	0
Duration of Treatment, median (range), cycles	24.9 (3.0-27.9)	19.9 (7.0-21.7)	15.4 (12.6-18.4)	11.0 (4.0-15.0)	8.0 (4.9-12.5)

Response Rate in Select Patient Subsets (≥200mg QD)

Best Overall Response	All Patients	Only 1 Prior BTKi	BTKi + BCL2i	TP53 Alteration
N	19	11	8	10
ORR n(%)	14 (73.7%)	9 (81.8%)	6 (75.0%)	7 (70.0%)
CR n(%)	0	0	0	0
PR or PR-L n(%)	14 (73.7%)	9 (81.8%)	6 (75.0%)	7 (70.0%)
SD n(%)	5 (26.3%)	2 (18.2%)	2 (25.0%)	3 (30.0%)
PD n(%)	0	0	0	0

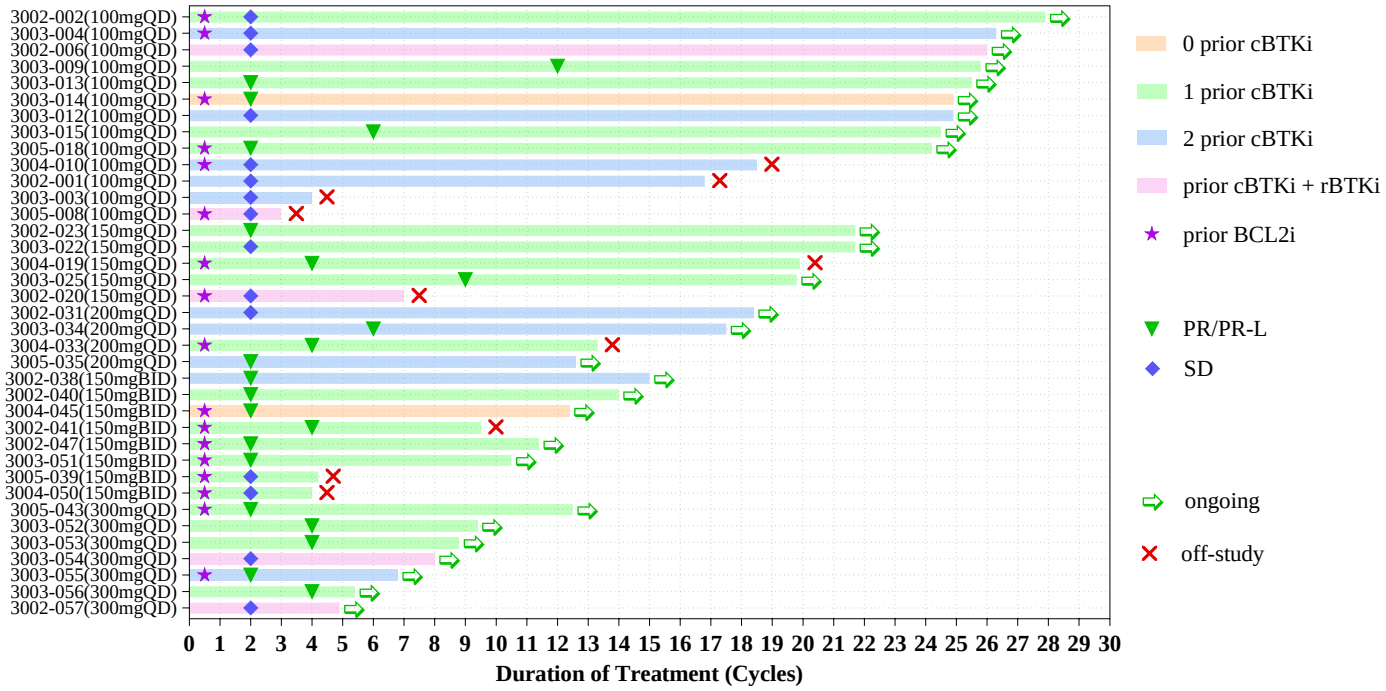
Efficacy in Patients with T474 Mutations

BTK T474 mutation (at least 200 mg/day)	
N	7
ORR n(%)	5 (71.4%)
CR n(%)	0
PR or PR-L n(%)	5 (71.4%)
SD n(%)	2 (28.6%)
PD n(%)	0



Gatekeeper Mutation	Other Genomic Abnormalities
T474I (12.7%)	BTK C481S(26.2%) , XPO1; del(17p), del(11q), del(13q)
T474I (18.4%)	BTK C481Y(24.6%) , XPO1, SF3BI; del(17p), del(11q), del(13q)
T474I (11.4%)	BTK C481S (3.1%) , NOTCH1, BCOR, FUBP1, DNMT3A; del(13q)
T474F (29%)	BTK C481S (73.9%), TP53, SF3B1, BRAF; del(17p), del(11q)
T474I (4.4%)	BTK C481S(0.7%), A428D(33.5%); del(17p), del(13q)
T474I (89%)	BTK C481S(7.8%),C481R(0.8%),C481V(30.8%); del(11q), del(13q)
T474I (44.2%)	NOTCH1, SF3B1 mutations; del(13q), 8q+
T474F (3.2%)	TP53, XPO1, SF3B1, PTPN11; del(17p)

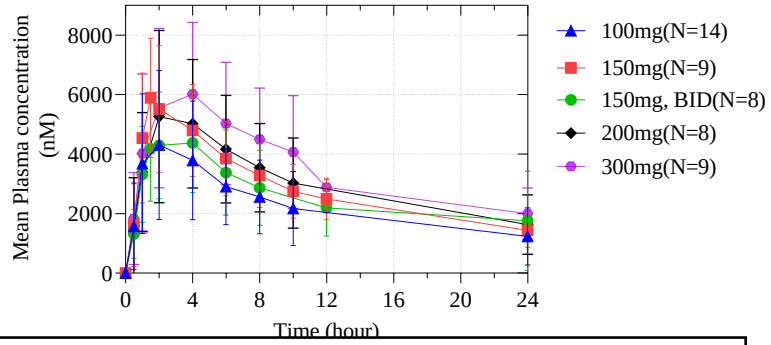
Duration of Therapy (CLL/SLL Cohort)



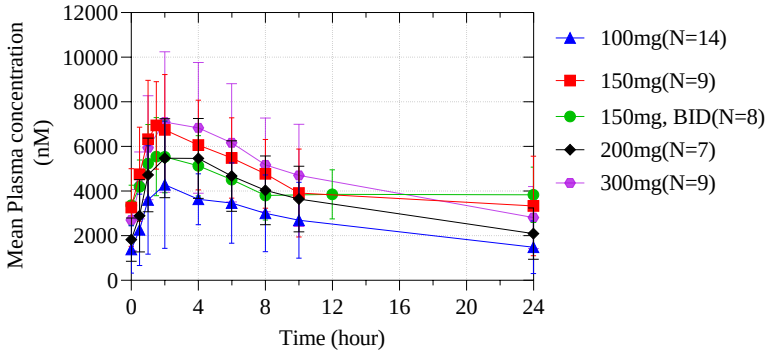
Median duration of treatment 14 cycles (range 3.0-27.9 cycles) as of 11/14/2023

Pharmacokinetics of LP-168

LP-168 PK C1D1-C1D2



LP-168 PK C1D8-C1D9



C1D1 – C1D2 PK

Dose (mg)	N	$AUC_{0\text{-}12h}$ (h*nM)	AUC_{inf} (h*nM)	C_{max} (nM)	T_{max} (h)	$T_{½}$ (h)
100mg	14	34,935.2±17,378.9	82,603.6±60,072.1	4,441.0±2,450.2	2 (2, 4)	14.2±4.0
150mg	9	44,496.1±13,587.5	96,181.7±35,879.2	5,762.4±2,200.5	2 (1.5, 2)	13.4±2.4
150mg, BID	8	38,154.3±14,102.0	69,070.8±27,098.6	4,737.8±1,641.6	2 (1.5, 4)	9.6±1.8
200mg	8	45,441.9±19,271.3	109,963.5±61,117.3	5,658.6±2,575.1	3 (2, 4)	14.8±4.0
300mg	9	54,823.0±19,785.1	130,775.2±52,991.2	6,396.5±2,556.3	2 (2, 4)	14.4±3.4

Conclusions and Future Directions for LP-168

- LP168 demonstrates safety and significant early efficacy in this phase 1 trial
- Efficacy and PK support a dose of 200 mg or 300 mg daily as RP2D
- Activity in patients with gatekeeper mutations and other high-risk features is encouraging
- Expansion of current clinical studies and combinations with other therapeutics relevant to CLL should be pursued

Future Directions with 3rd and 4th Generation BTKi

- Given different patterns of resistance, it will be important to define resistance patterns to avoid confounding response to full covalent inhibitors
- Given broad inhibitory mechanism of Nemtabrutinib, resistance patterns may be different from more selective agents
- Trials in earlier therapy that focus on combinations with these agents warranted
  - Obinutuzumab
  - Bi-specific CD20 antibodies
  - BLC2 inhibitors
  - MALT1 inhibitors