So after 3 phase trials favoring ibrutinib, does CIT any role?

THE UNIVERSITY OF TEXAS
MD ANDERSON
CANCER CENTER

Ibrutinib, Fludarabine, Cyclophosphamide, and Obinutuzumab (iFCG) for Firstline Treatment of Patients with CLL with Mutated *IGHV* and without *TP53* Aberrations

Nitin Jain, Philip Thompson, Jan Burger, Alessandra Ferrajoli, Gautam Borthakur, Prithviraj Bose, Zeev Estrov, Tapan Kadia, Koichi Takahashi, Naveen Garg, Xuemei Wang, Rashmi Kanagal-Shamanna, Keyur Patel, Wanda Lopez, Ana Ayala, William Plunkett, Varsha Gandhi, Hagop Kantarjian, Susan O'Brien, Michael Keating, William Wierda

Department of Leukemia, MDACC

ASH 2018, Abstract 185

Firstline Ibr+FC+Obi (iFCG) in Patients with *IGHV* Mutations and Without *TP53* Mutations

Key eligibility criteria

- Previously untreated CLL meeting iwCLL criteria for treatment
- Age ≥ 18 years, ECOG 0-2
- IGHV mutated and NO del (17p)/*TP53* mutation

iFCG 3 courses[a]

- Ibr 420 mg/d PO continuous
- G 100 mg c1 d1, 900 mg c1 d2, 1000 mg c1 d8 & 15; 1000 mg c2-3 d1
- Flu 25 mg/m^2 and Cyclo 250 mg/m^2 on c1 d2, 3, & 4; c2-3 d1, 2, & 3

Ibr for 9 courses (all patients) +
G for 3 courses (if CR/CRi with BM U-MRD4)
or
G for 9 courses (if PR and/or BM MRD^{pos})

→ After 12 courses
BM U-MRD4 → stop Ibr
BM MRD+ → Ibr

Primary endpoint: CR/CRi with U-MRD in BM after 3 courses iFCG

Response assessments (2008 iwCLL) using PB, BM and CT q3mo during first year; BM MRD (10^{-4}) by flow q3mo during first year

After Ibr discontinuation at 1 year, serial MRD assessed in blood q6mo

[a]Required antiviral prophylaxis (acyclovir/valacyclovir), optional PJP prophylaxis; G-CSF optional early in trial and required later.

Jain et al. ASH 2018. Abstract 185. https://clinicaltrials.gov/ct2/show/NCT02629809.

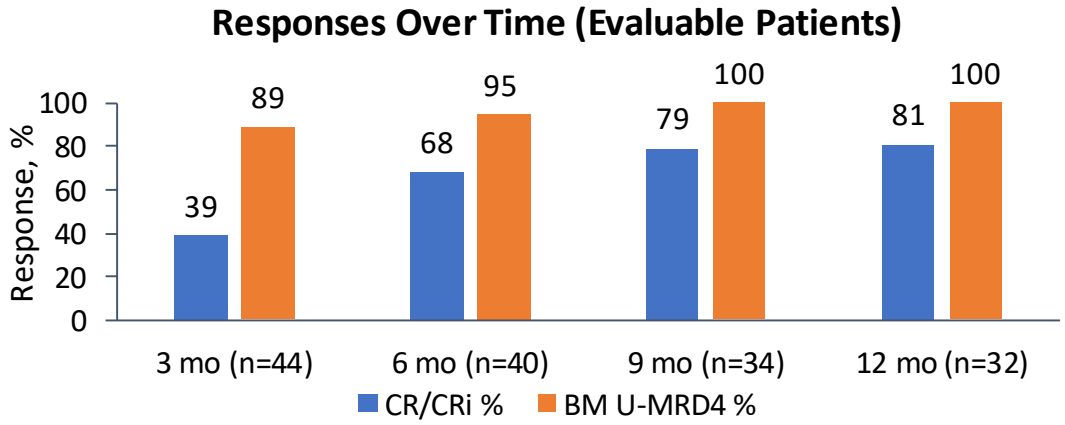
- 44/45 completed 3 cycles iFCG
- Patient characteristics: median age 60 y, 49% Rai III/IV, and 69% del(13q)

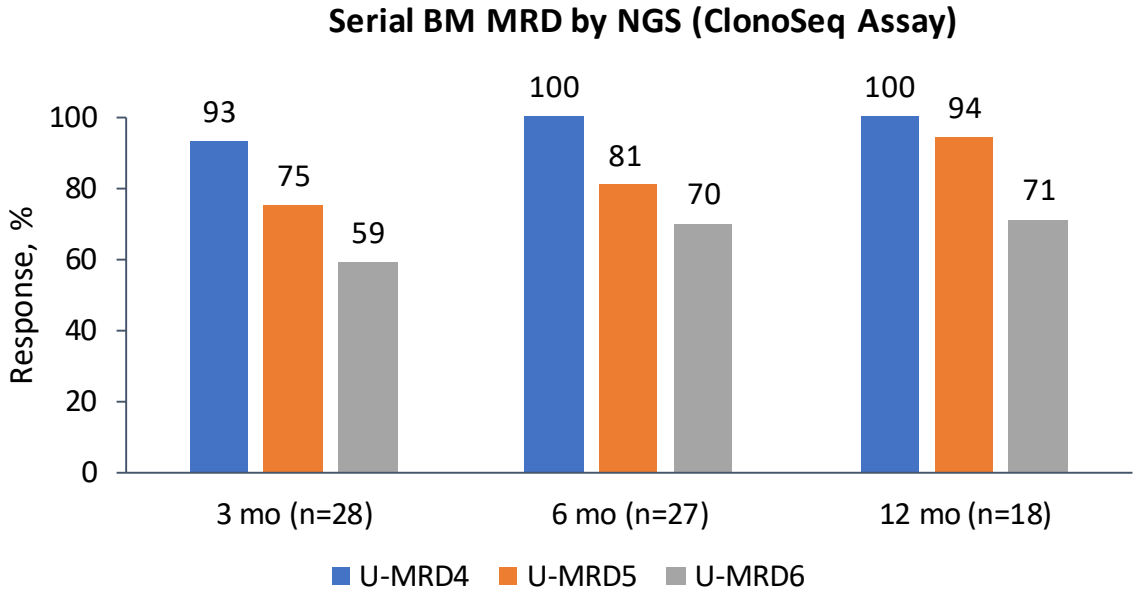
Adverse Events, %	iFCG (N=45)
Grade 3/4 neutropenia	
Cycles 1-3	53
After prophylactic G-CSF during cycles 1-3	33
Cycles 4-12	27
Grade 3/4 thrombocytopenia	
Cycles 1-3	38
Cycles 4-12	5
Grade 3/4 infections[a]	27
Neutropenic fever	
Prior to G-CSF use	14
After prophylactic G-CSF	0
Infusion-related reactions	
All grade	42
Grade 3/4	4
Grade 3/4 transaminitis	13
All grade atrial fibrillation	11

[a]Of the 5 cases with neutropenic fever, 4 were culture negative, and one was PJP PNA; 2 each of pneumonia and (not neutropenic) and cellulitis and 1 each of pulmonary MAC infection, acute cholecystitis, and colitis were reported. No cases of invasive fungal infection.

Firstline Ibr+FC+Obi (iFCG) in Patients with *IGHV* Mutations and Without *TP53* Mutations

Outcomes (Evaluable)	iFCG (n = 44)	
Median follow-up, mo (range)	22.3 (3.5-32.1)	
After 3 cycles iFCG, n/N (%)	**Response**	**BM U-MRD4**
ORR	44 (100)	39/44 (89)
CR/CRi	17 (39)	17/17 (100)
PR	27 (61)	22/27 (81)
Median PFS and OS	Not reached	





[a]For MRD6 sensitivity (cycle 3, n=22; cycle 6, n=23; cycle 12, n=14)

- 32 patients reached 1 year follow-up
  - All 32 had BM U-MRD4 (26 CR/CRi, 6 PR) and discontinued Ibr
  - Median follow-up after stopping Ibr: 13.6 mo (range, 1.4-20.7)
  - No patient had MRD or clinical relapse

Summary

- **iFCG achieves high rate of BM U-MRD4 in previously untreated patients with CLL with *IGHV* mutation**
- **No patient has progressed and all patients who have stopped Ibr maintain MRD negativity**

Jain et al. ASH 2018. Abstract 185.

What is the future of front line therapy after ibrutinib?

THE UNIVERSITY OF TEXAS
MD ANDERSON
CANCER CENTER

Combined Ibrutinib and Venetoclax in Patients with Treatment-Naïve High-Risk Chronic Lymphocytic Leukemia (CLL)

Nitin Jain, Michael Keating, Philip Thompson, Alessandra Ferrajoli, Jan Burger, Gautam Borthakur, Koichi Takahashi, Zeev Estrov, Nathan Fowler, Tapan Kadia, Marina Konopleva, Yesid Alvarado, Musa Yilmaz, Courtney DiNardo, Prithviraj Bose, Maro Ohanian, Naveen Pemmaraju, Elias Jabbour, Koji Sasaki, Rashmi Kanagal-Shamanna, Keyur Patel, Jeffrey Jorgensen, Naveen Garg, Xuemei Wang, Katrina Sondermann, Nichole Cruz, Chongjuan Wei, Ana Ayala, William Plunkett, Hagop Kantarjian, Varsha Gandhi, William Wierda

Phase 2 Firstline Ibrutinib and Venetoclax in High-Risk CLL

Key eligibility criteria

- Treatment-naïve CLL meeting 2008 iwCLL criteria
- ≥ 1 high-risk feature: del(17p), mutated TP53, del(11q), *IGHV* unmutated, and/or age ≥ 65 y

Part 1
Ibr 420 mg/d for 3 cycles (continued c4-27) +
Cycle 4-27 added Ven weekly ramp-up to 400 mg/d

Combo administered for 24 cycles

Patients with BM U-MRD4 (10^{-4}) at 24 cycles of combined therapy stop Ibr

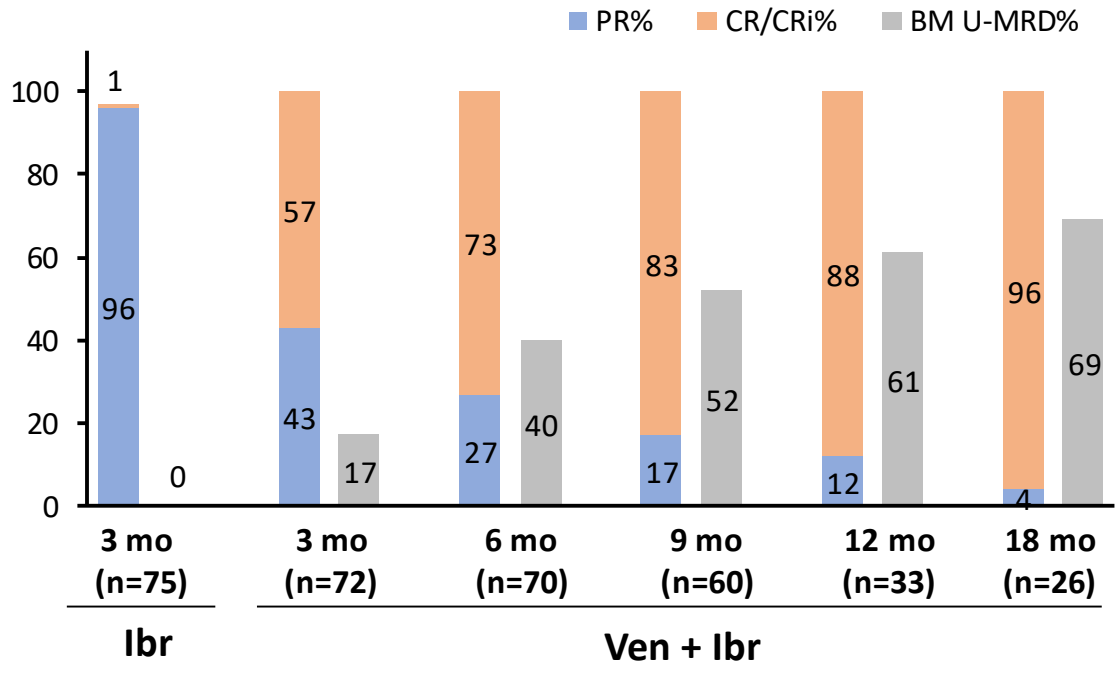
Patients with MRD-positive CLL continued Ibr

Response assessed PB, BM and CT (2008 iwCLL) after cycle 3 of Ibr, and q6mo during year 2 of Ibr + Ven

Primary endpoint: CR/CRi

Jain et al. ASH 2018. Abstract 186.
https://clinicaltrials.gov/ct2/show/NCT02756897.

- 92% of patients had *IGHV* unmutated, TP53, or del(11q)
- n=75 initiated Ven; median follow-up was 14.8 mo (range, 5.6-27.5)



- 76% of patients ≥65 y (n=17) achieved UMRD4 at 12 mo of Ibr+Ven
- U-MRD4 responses were seen across subgroups, including *IGHV* unmutated, del(17p), and *TP53*, *NOTCH1*, and *SF3B1* mutations

Phase 2 Firstline Ibrutinib and Venetoclax in High-Risk CLL

Progression

- No patient had CLL progression
- 1 high-risk CLL (unmutated *IGHV*, *NOTCH1* mutation) patient developed Richter transformation

Discontinuations and dosing

- 11 (14%) patients have discontinued treatment: 5 during ibr mono and 6 during IV combo
- Ibr and Ven dose reductions: 44% and 24%
- 6 pts stopped Ibr due to AEs and continued Ven alone

TLS

- 80% high risk and 48% of medium risk patients had down-grading of TLS risk category
- 3 patients had lab TLS (no clinical TLS)

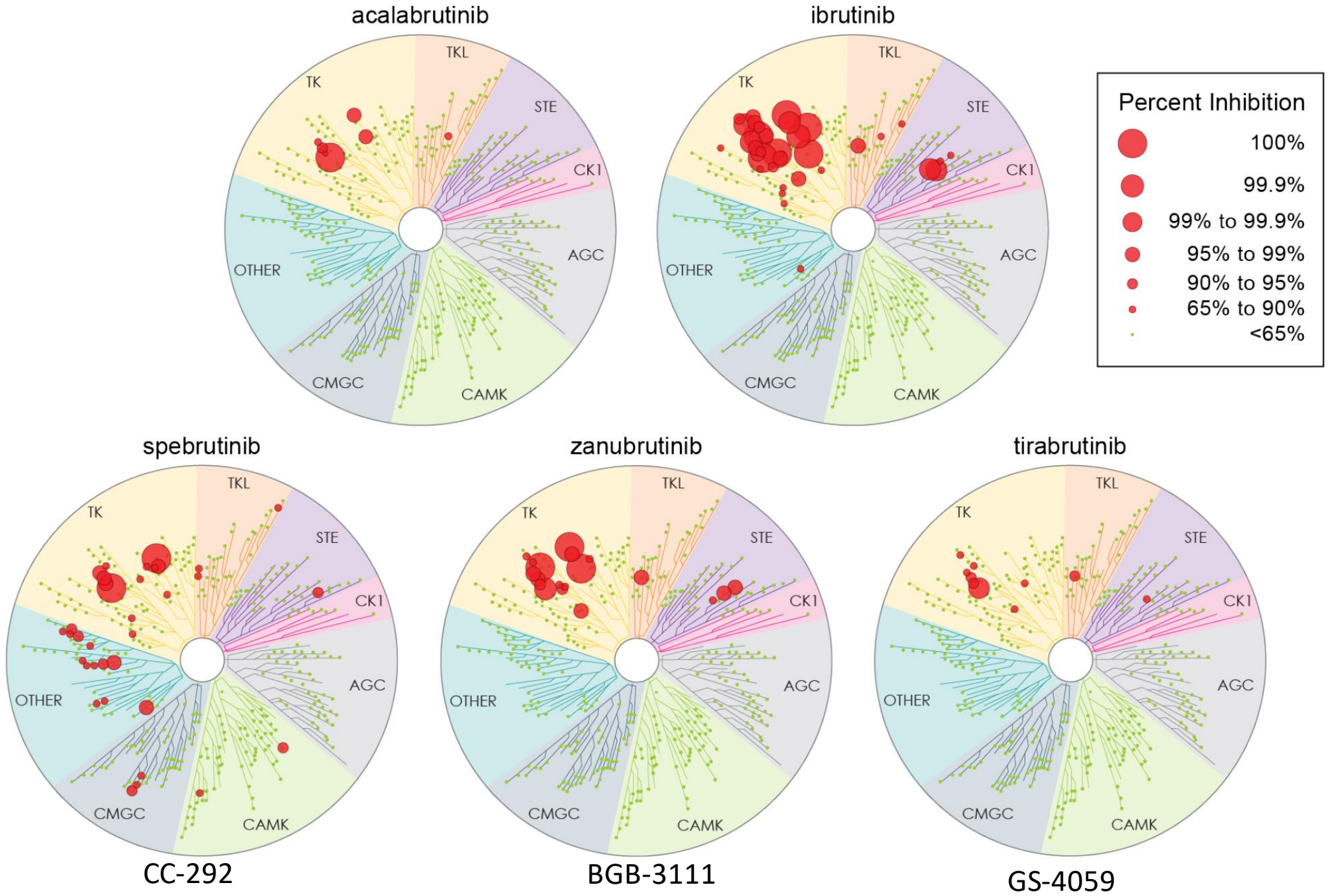
Safety

- Most common nonhematologic AEs were easy bruising (60%), arthralgia (48%), and diarrhea (41%)
- Grade 3/4 neutropenia 48%; (5% neutropenic fever)
- Any grade atrial fibrillation/flutter in 15% (10% grade ≥3)
- Grade ≥3 infections in 18%

Summary

- **Ibr + Ven is a safe and effective chemotherapy-free oral regimen for patients with high-risk TN CLL**
- **Responses improved with ongoing therapy and were observed in older patients and across high-risk subgroups**

Jain et al. ASH 2018. Abstract 186.



CC-292

BGB-3111

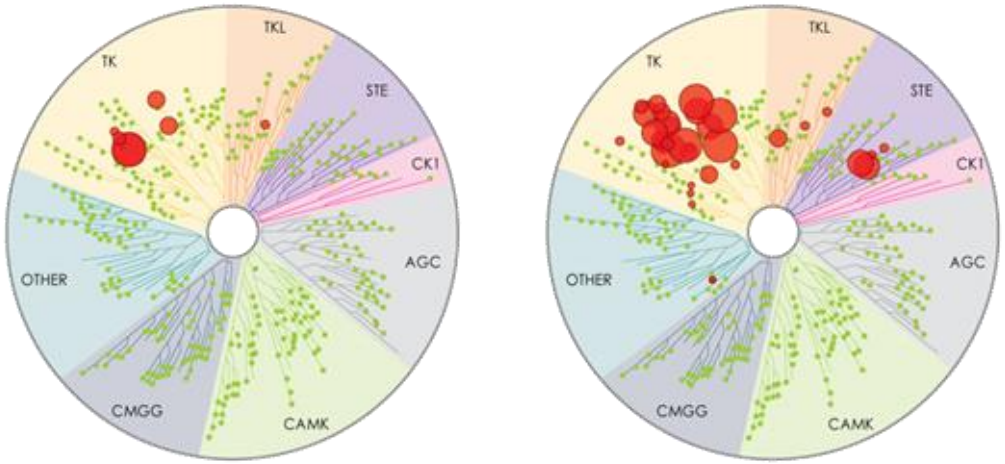
GS-4059

Acalabrutinib

- Highly-selective, potent kinase inhibitor
- Designed to minimize off-target activity with minimal effects on TEC, EGFR, or ITK signaling

Kinase selectivity profiling at 1 μM

Acalabrutinib **Ibrutinib**



The size of the red circle is proportional to the degree of inhibition.

Kinase Inhibition IC_{50} (nM)		
Kinase	**Acalabrutinib**	**Ibrutinib**
BTK	5.1	1.5
TEC	126	10
BMX	46	0.8
TXK	368	2.0
ERBB2	~1000	6.4
EGFR	>1000	5.3
ITK	>1000	4.9
JAK3	>1000	32
BLK	>1000	0.1

Phase 1/2 Study of Acalabrutinib in TN CLL (ACE-CL-001)

TN CLL/SLL with ECOG 0-2
Acalabrutinib 100 mg BID (n=62) or 200 mg QD (n=37)[a]

Primary endpoints: Safety
Secondary endpoints: ORR by investigator (2008 iwCLL with modification for lymphocytosis), DOR, PFS
Exploratory endpoints: TTR (PR/CR), EFS, BTK occupancy, changed in T/NK/monocyte cell counts

Patient Characteristics, n (%)	All Patients (N = 99)
Median age, y (range)	64 (33-85)
Bulky lymph nodes (≥ 5 cm)	46 (46)
Rai stage III/IV	47 (47)
Genomic status	
IGHV unmutated	57/92 (62)
Complex karyotype	12/60 (20)
TP53 or *NOTCH1* mutation	10/66 (15)
del(17p)	9/91 (10)

[a]Patients started on 200 mg QD and then switched to 100 mg BID.
Byrd et al. ASH 2018 Abstract 692.

- At a median of 42 mo, 89% patients remain on study treatment
- 5% discontinued due to AEs

Efficacy, n (%)[a]	All Patients (N = 99)
ORR	96 (97)
CR	5 (5)
PR	91 (92)
ORR in each high-risk subgroup, %	100
Median TTR, mo (range)	3.7 (2-22)
Median time to CR, mo (range)	28
36-mo DOR, % (95% CI)	98 (90-99)
36-mo PFS, % (95% CI)	97 (91-99)

- Median PFS was not reached
- BTK occupancy was 97%-99% throughout BID dosing at steady state
- No clinically meaningful changes in T-cell counts

Phase 1/2 Study of Acalabrutinib in TN CLL (ACE-CL-001)

Most Common AEs in Year 1, n (%)	Any Grade
Diarrhea	33%
Headache	44%
Upper respiratory tract infection	20%
Contusion	23%
Arthralgia	22%
Petechiae	16%
Ecchymosis	16%
Hypertension	12%

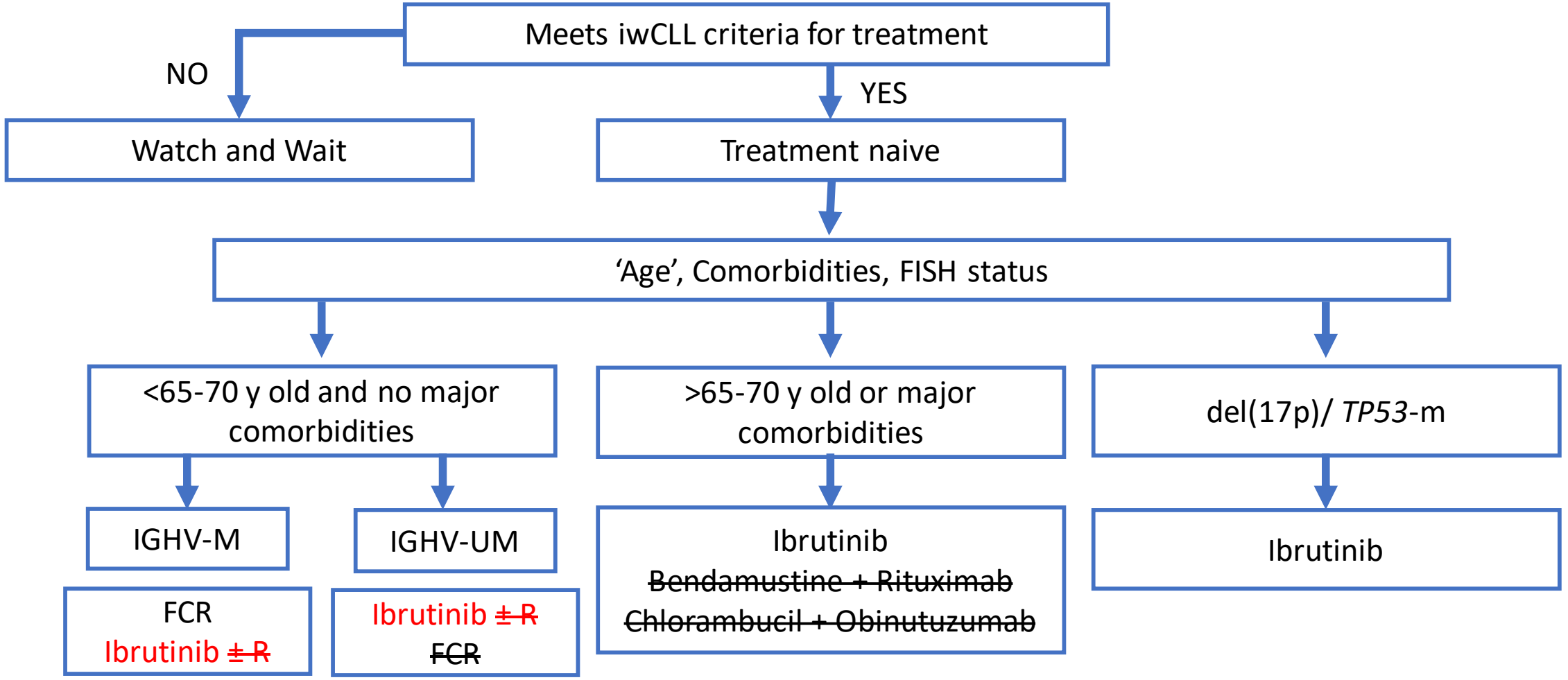
- Atrial fibrillation: 6% all grades, 2% Gr 3+
- Most common bleeding events (64% overall); none leading to discontinuation
  - Contusion (39%)
  - Petechiae (18%)
  - Ecchymosis (16%)
- 35% SAEs mainly due to infection (n=9)and sinusitis (n=2)
- AEs leading to discontinuation: 3 SPM, 1 gr 4 sepsis, 1 gr 3 UTI
- 1 gr 5 multiorgan failure in setting of pneumonia (unrelated)

Summary

- **Acalabrutinib monotherapy produced high response rates and an acceptable safety profile in patients with TN CLL**

Data cut-off: Septebmer 4, 2018. Byrd et al. ASH 2018 Abstract 692.

CLL Front Line Treatment Algorithm post ASH 2018



Treatment for Relapsed/Refractory CLL

MURANO: Feasibility of Time-Limited VenR in R/R CLL

- Median treatment exposure: 24.4 mo VR vs 5.5 mo BR

PFS (median follow-up of 36.0 mo)

- VR (n=194) was superior to BR (n=195)
  - Median PFS: NR with VR vs 17.0 mo with BR HR=0.16 (95% CI, 0.12-0.23)
  - 3-y PFS: 71% VenR vs 15% BR
  - PFS benefit consistent across subgroups

OS

- VR superior to BR (HR=0.5; 95% CI, 0.30-0.85)
- 3-y OS: 88% with VR vs 80% with BR

- 130/194 (67%) VenR patients completed 2 y of treatment without PD

Grade 3/4 AEs (≥5% in any arm), n (%)[a]	VenR (n = 194)	BR (n=188)
Neutropenia[b]	114 (59)	75 (40)
Anemia[b]	21 (11)	26 (14)
Thrombocytopenia	11 (6)	19 (10)
Febrile Neutropenia	7 (4)	18 (10)
Pneumonia	10 (5)	15 (8)
Infusion-related reaction	4 (2)	10 (5)

[a]AE reporting period longer with VenR vs BR.
[b]Neutropenia and anemia were higher in VenR combo period than Ven monotherapy period.

- 33% of patients did not complete 2 yrs VR regimen
- 21% due to reasons other than PD/death

Seymour et al. ASH 2018. Abstract 184.
https://clinicaltrials.gov/ct2/show/NCT02005471.

MURANO: Feasibility of Time-Limited VenR in R/R CLL

- PFS in first 12 mo after Ven completion
  - 6-mo PFS: 92% (95% CI, 87%-97%)
  - 12-mo PFS: 87% (95% CI, 81%-94%)
- Significant predictors of PD : MRD status, *TP53* and/or del(17p)

MRD Status Off-Therapy (median f/u 9.9 mo)	PD-free	PD
uMRD ($<10^{-4}$; n=83)	98%	2%
Low MRD+ (10^{-4} - $<10^{-2}$; n=23)	87%	13%
High MRD+ ($\geq 10^{-2}$; n=14)	21%	79%
Missing (n=10)	100%	0

Predictors of PD at EOT, n/N (%)		No PD	PD	*P* Value
PB MRD at EOT	uMRD	81/83 (98)	2/83 (2)	**< 0.0001**
	Low-MRD+	20/23 (87)	3/23 (13)	
	High-MRD+	3/14 (21)	11 /14 (79)	
del(17)p	Yes	22/28 (79)	6/28 (21)	0.09
	No	82/90 (91)	8/90 (9)	
TP53 mutation	Present	19/26 (73)	7/26 (27)	**0.02**
	Absent	94/103 (91)	9/103 (9)	
TP53 mut. and/or del(17p)	Neither present	73/78 (94)	5/78 (6)	**0.01**
	At least 1 present	33/43 (77)	10/43 (23)	
del(11)q	Yes	31/32 (97)	1/32 (3)	0.25
	No	51/58 (88)	7/58 (12)	
IGHV mut. status	Present	36/38 (95)	2/38 (5)	0.14
	Absent	71/84 (85)	13/84 (15)	
No. prior therapies	1	69/78 (88)	9/78 (12)	0.79
	≥2	45/52 (87)	7/52 (13)	
Bulky disease	<5 cm	58/67 (87)	9/67 (13)	1.0
	≥5 cm	46/53 (87)	7/53 (13)	
Nodal status at EOCT	<1.5 cm	59/64 (92)	5/64 (8)	0.08
	≥1.5-<2 cm	21/23 (91)	2/23 (9)	
	≥2 cm	30/39 (77)	9/39 (23)	

Summary

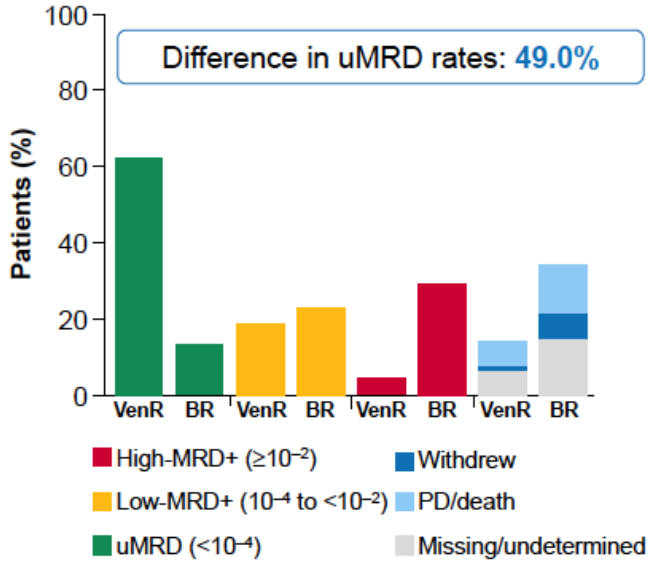
- **At median 3-y follow-up, VenR shows clinically meaningful benefit for PFS and OS over BR and with no new safety signals**
- **High rate of uMRD and MRD status with VenR were strong predictors of durable PFS following drug cessation**
- **Low rate of progression and safety profile following completion of Ven treatment supports the feasibility of VenR**

Seymour et al. ASH 2018. Abstract 184.

MURANO: VenR vs BR in R/R CLL MRD and Long-Term Outcomes

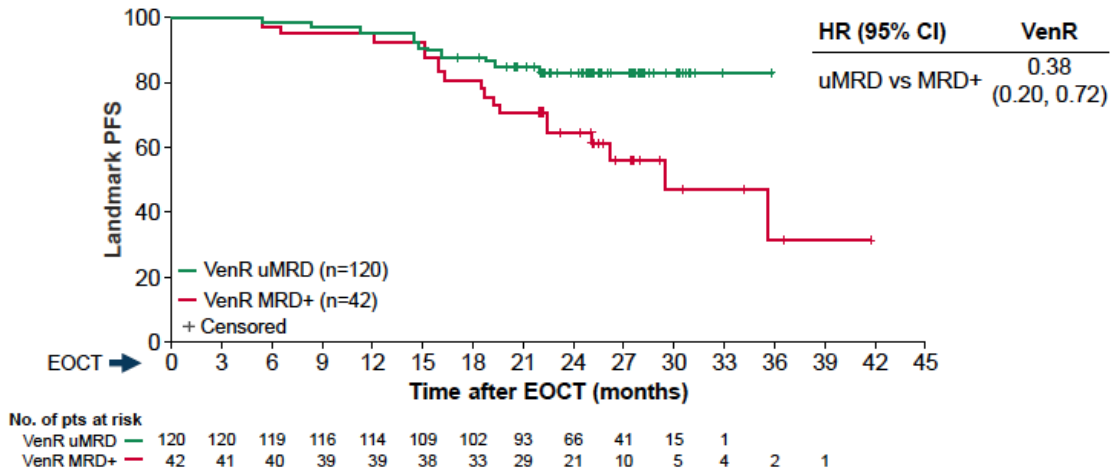
- Long-term analysis of MRD and PFS following completion of therapy by all patients
- PB MRD by ASO-PCR and/or flow at c4d1, EOCT; mo 9, every 3 mo for 3 y, then every 6 mo
- Categories:
  - uMRD ($<10^{-4}$)
  - Low MRD+ (10^{-4} – $< 10^{-2}$)
  - High MRD+ ($\geq 10^{-2}$)

PB uMRD rates were higher with VenR than BR at EOCT



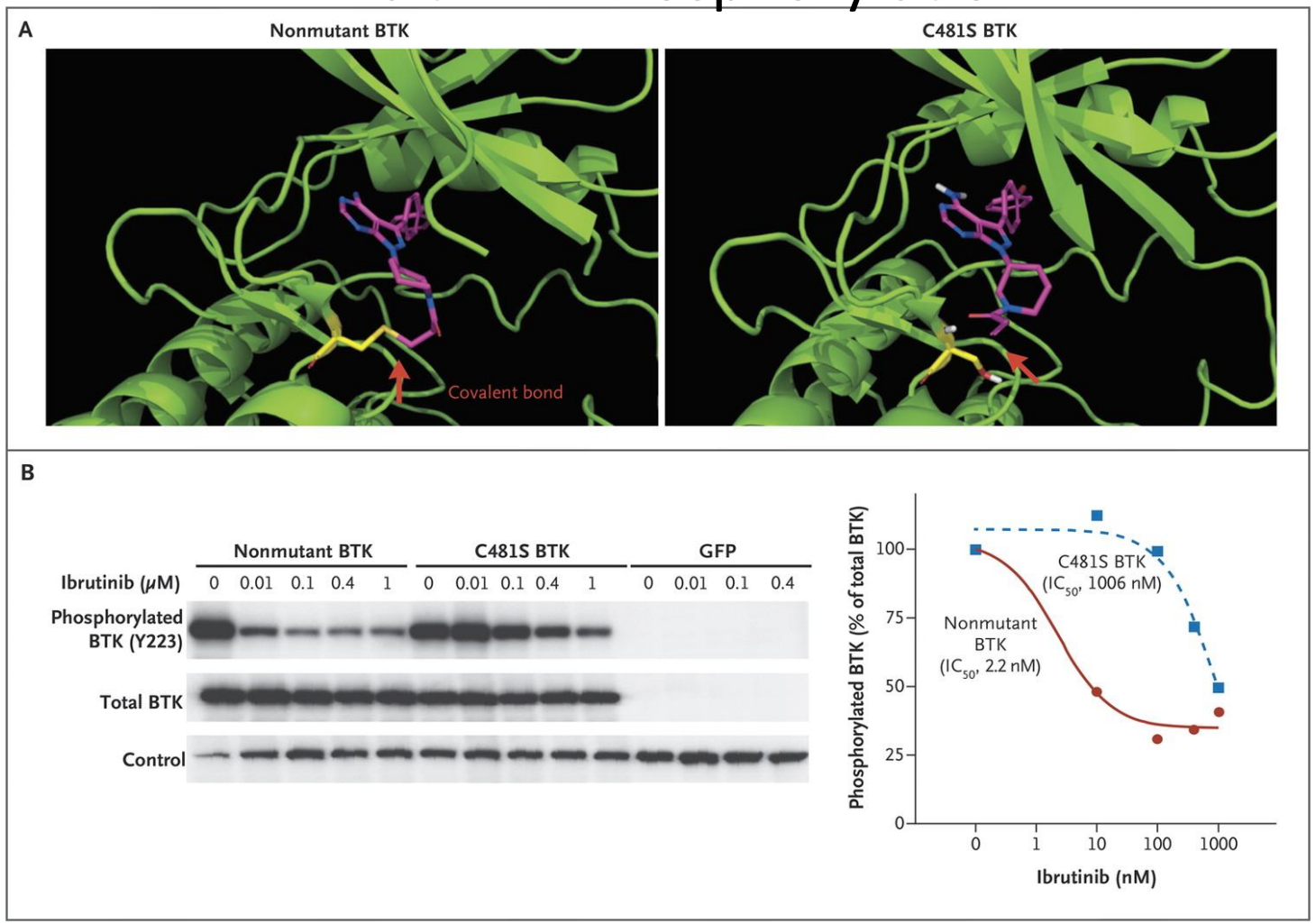
- Median 36.0 mo of follow-up
- uMRD rates at EOCT (mo 9) and mo 24 in high risk:
  - del(17p) and/or *TP53:* 56.9% (n=72) and 51.2% (n=43)
  - Unmutated *IGVH:* 61% (n=123) and 66.7% (n=84)

uMRD status at EOCT was highly predictive of prolonged PFS



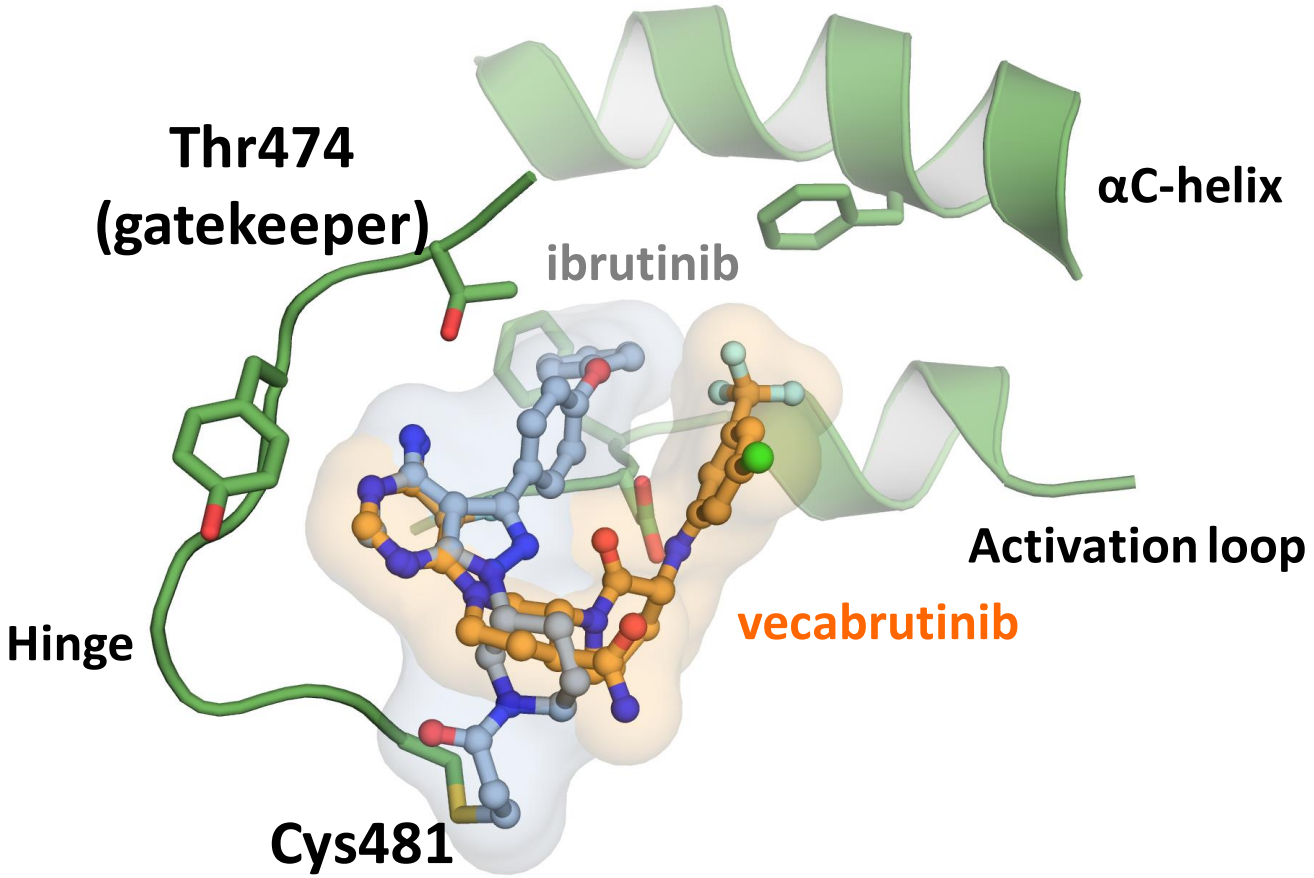
Kater et al. ASH 2018 Abstract 695.

Effect of C481S Mutation of Bruton's Tyrosine Kinase (BTK) on Ibrutinib Binding and the Ability of Ibrutinib to Inhibit BTK Phosphorylation.



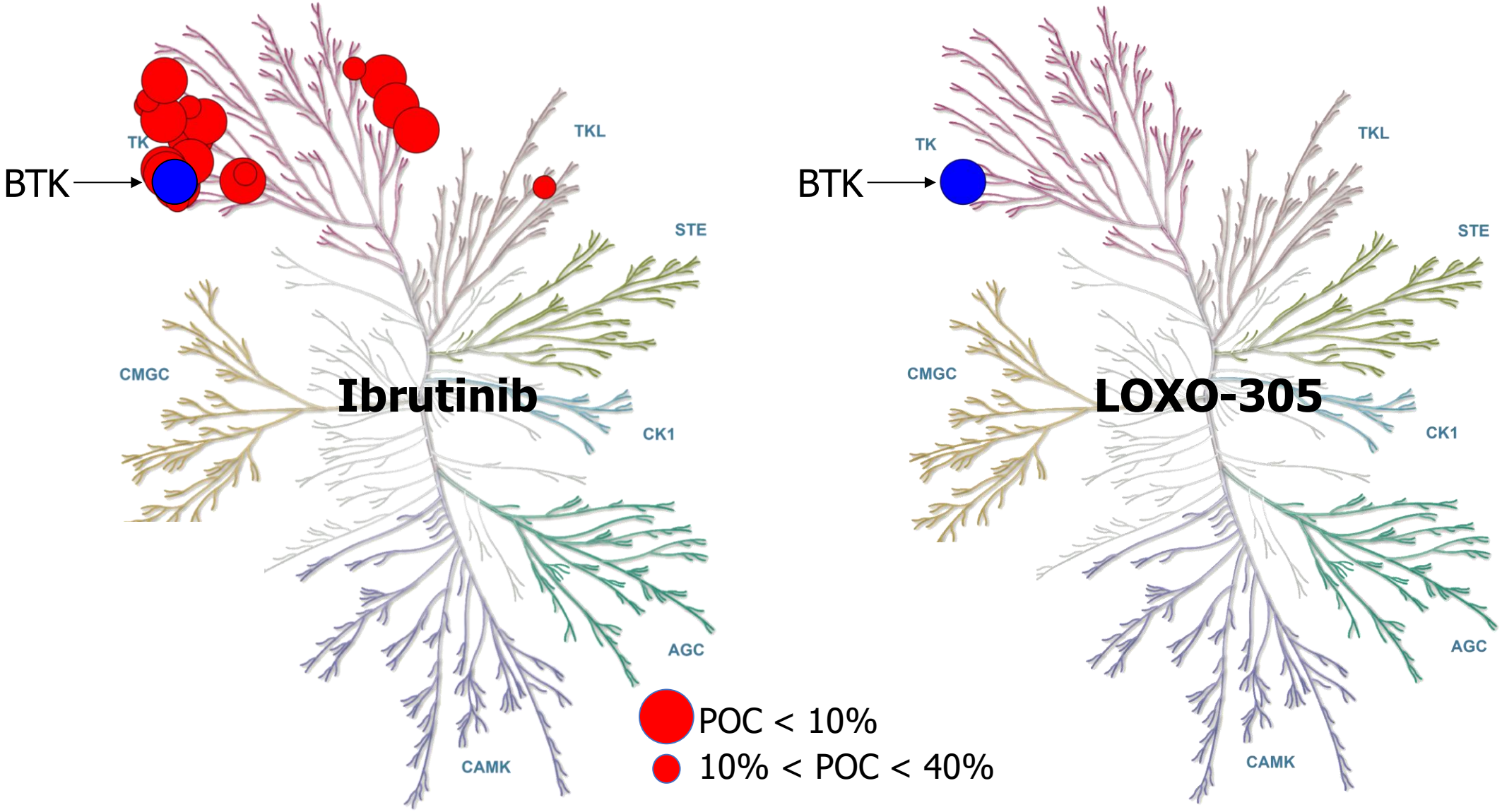
Furman RR et al. N Engl J Med 2014;370:2352-2354.

Vecabrutinib



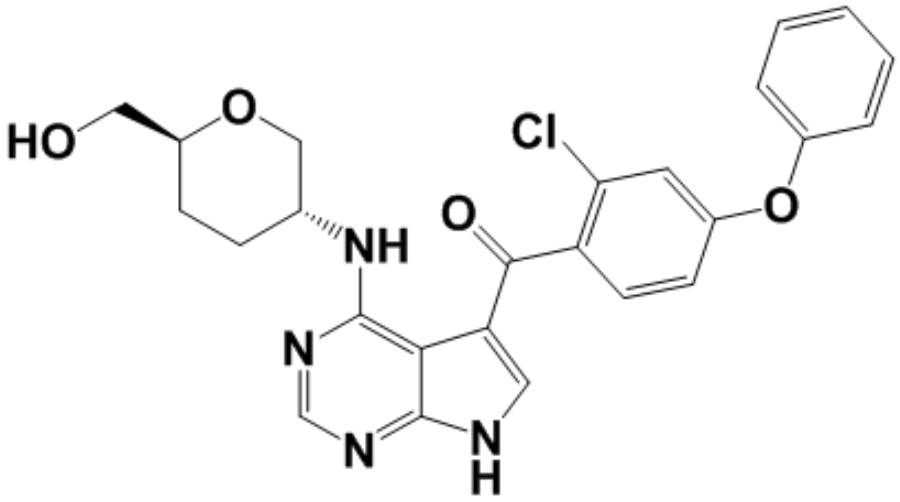
- Vecabrutinib interacts with a distinct set of residues in the αC-helix

LOXO-305

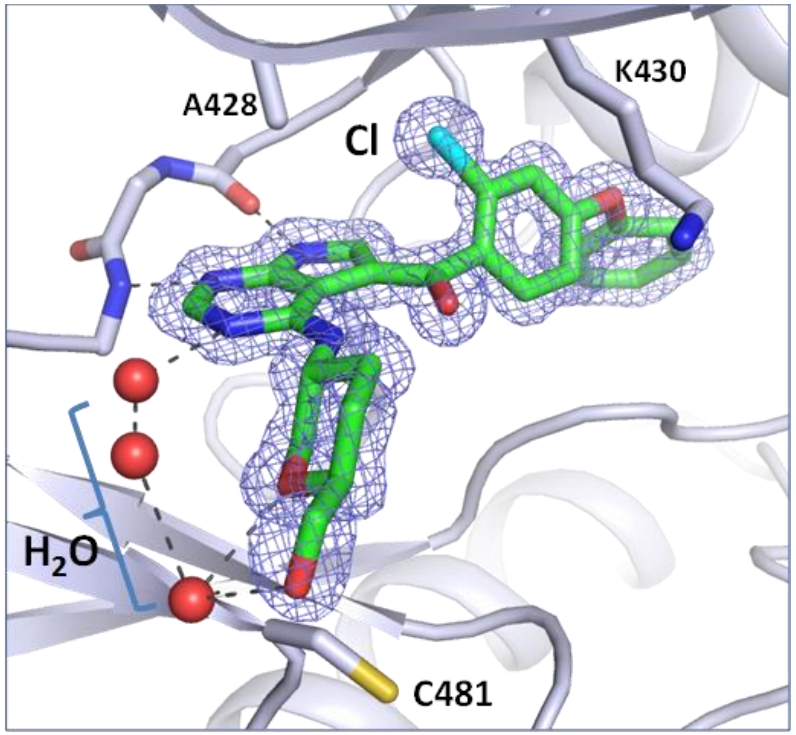


Each agent tested at 100 nM, n=369 kinases, kinases with % control < 40 shown

ARQ 531



ARQ 531



- Reversible inhibition of BTK
- Occupies the ATP binding pocket – non C481
- Orally bioavailable

Reiff et al, Cancer Discovery, in press

Conclusions

- Ibrutinib has show superior PFS vs chemoimmunotherapy in 3 phase III trials and has become an excellent front line therapy.
- Anti-CD20 does not seem to add benefit to ibrutinib in front line therapy.
- IgHV mutational status is a valid marker for therapy stratification in all patients but younger ones with IgHV mutated may still benefit from FCR and FCR combinations.
- Venetoclax +CD20MoAb is becoming a great alternative for 2nd line.
- New combinations (I+V and O+V=CLL14) will soon allow time limited therapy in front line settings.

Thank you

javier.pinilla@moffitt.org