What is New In CLL?

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2022: Relevant questions

- Is treatment for asymptomatic early CLL indicated?
  - High risk patients?
- Does chemotherapy have a role in CLL in 2022?
- Time limited versus indefinite treatment
- Which BTKi
- MRD yes or no?
- Beyond BTKi and BCL2 (”double-refractory”)

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Cell Based Prognostic Factors

- CLL FISH defects [1]
  - 17p13 deletion (TP53)
  - 11q23 deletion (ATM)
  - Trisomy 12
  - Normal
  - 13q14 deletions (miR-15/16)

Hierarchy

Bad

Good

- Immunoglobulin Heavy Chain Variable Region (*IGHV*)
  - ≤ 2 % mutation= non mutated
    - *Worse time to therapy and duration of response to therapy*
- CD38 status (≥ 30%=bad)
- ZAP-70 status (≥ 20%=bad)

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IWCLL-NCI: Indications to Initiate Treatment for CLL

- Constitutional symptoms referable to CLL
- Progressive marrow failure (cytopenias)
- Autoimmune anemia ± thrombocytopenia poorly responsive to steroids or other
- Massive (>6 cm) or progressive splenomegaly
- Massive (>10 cm) or progressive lymphadenopathy
- Progressive lymphocytosis, >50% increase over 2 months or lymphocyte doubling time <6 months
- **No early treatment, even for high-risk patients**

iwCLL-NCI = International Workshop on CLL-National Cancer Institute.
Hallek et al, Blood 2016.

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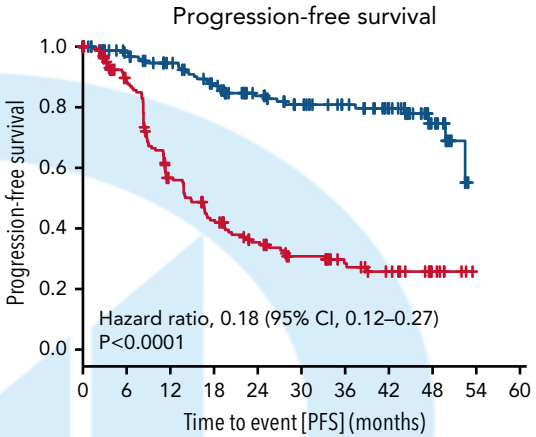
CLL12: Ibrutinib vs Placebo for Asymptomatic CLL pts with high risk features (17pDel, unmutated IGVH)

Risk assessment	
del(17p)	IGHV
del(11q)	ECOG PS
Thymidine kinase	Sex
β2 microglobulin	Age

Increased risk of progression



No OS benefit
Watch and Wait remains SOC

Langerbeins et Al. Blood 2022

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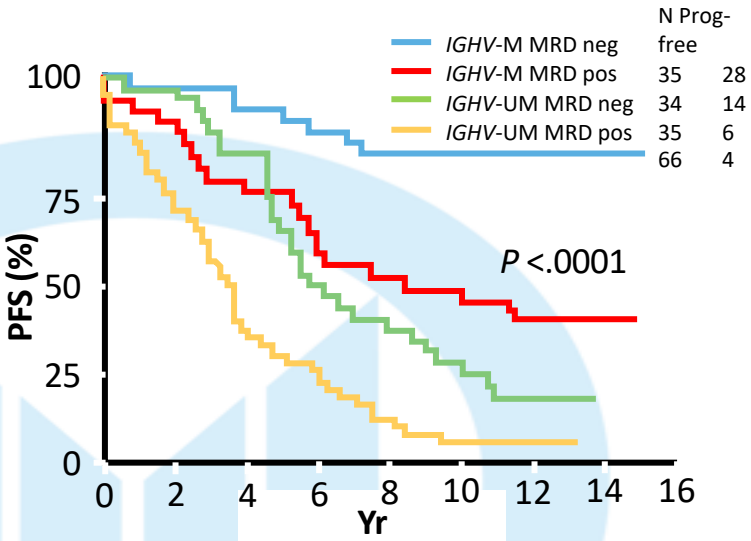
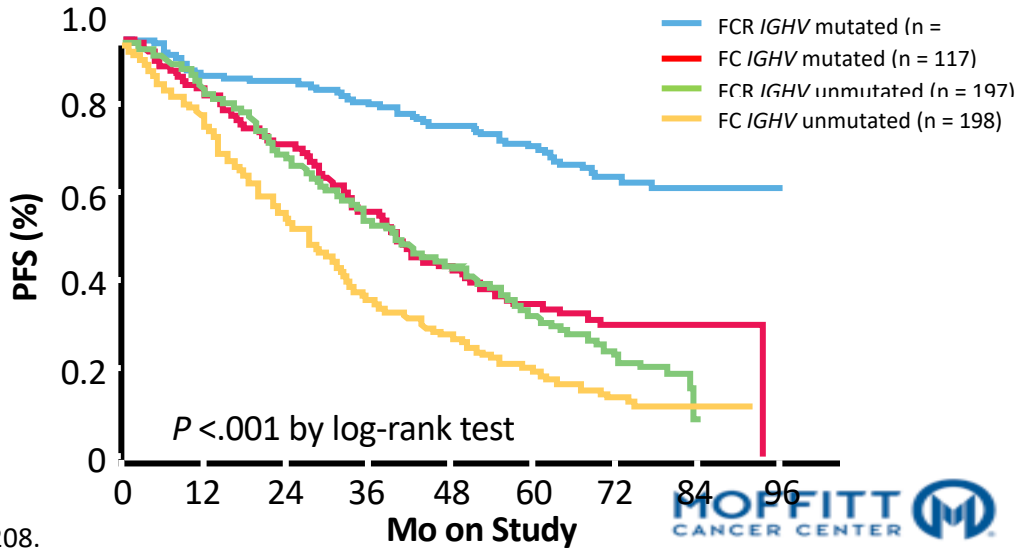
Is it the end of chemoimmunotherapy (CIT) in CLL?

- **Essentially yes**
- Some may still treat young patients (≤65 yr of age) with FCR if they have *IGHV* mutated CLL and no high-risk genomic abnormalities (logistics, cost, access)





Thompson. Blood. 2016;127:303. Fischer. Blood. 2016;127:208.

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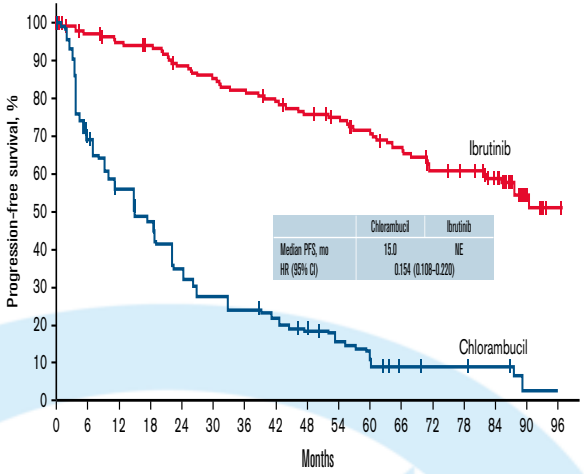
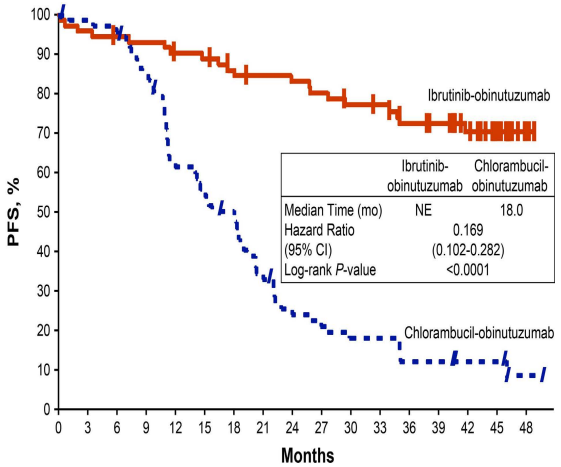
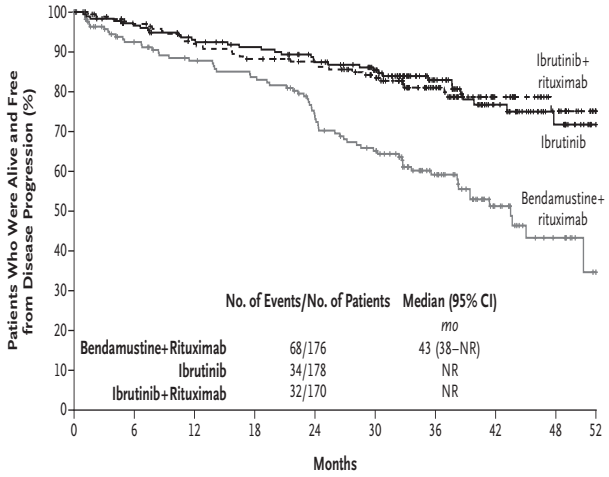
BTKi improves PFS over over CIT in CLL elderly patients or w/ coexistent comorbidities



RESONATE-2
Ibrutinib vs Chlorambucil
8-y follow up



ILLUMINATE
Ibrutinib +O vs Chlorambucil + O
4-y follow up



ALLIANCE
Ibrutinib + R vs Ibrutinib vs BR

Barr at Al, Blood Advances 2022, Moreno et Al. Haematologica 2022, Woyach et al, NEJM 2018

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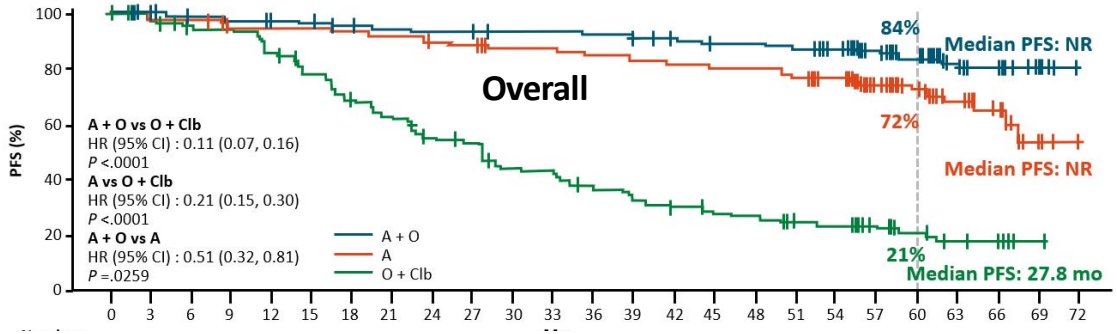
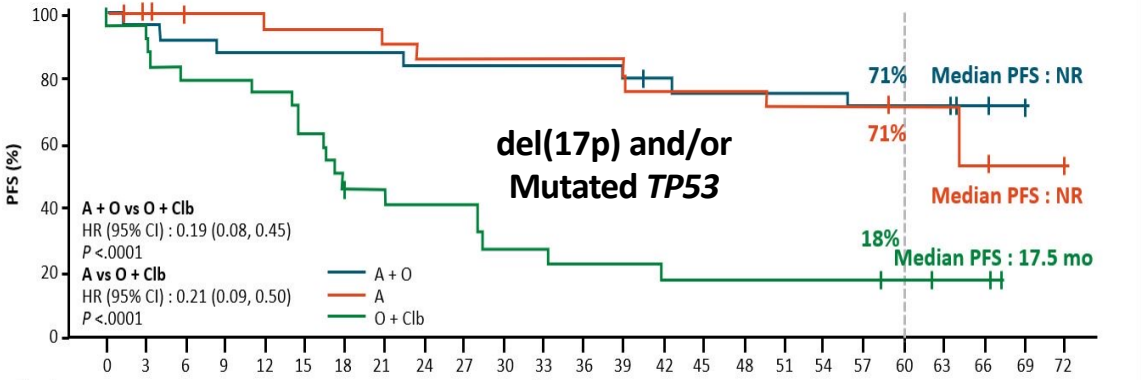
ELEVATE-TN 5-Yr PFS Update: A ± O vs O + Chlorambucil in Treatment-Naive CLL

Patients with untreated CLL aged ≥65 or 18-64 yr with comorbidities (N = 535)

- **Acalabrutinib + Obinutuzumab** (n = 179)
- **Acalabrutinib** (n = 179)
- **Obinutuzumab + Chlorambucil** (n = 177)





Primary endpoint:

IRC-assessed PFS for **A + O** vs **O + Clb**; after interim analysis, PFS assessed by investigator

Sharman. Leukemia. 2022;36:1171. Sharman. ASCO 2022. Abstr 7539.

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Consistent benefit of BTKi over CIT in TP53 mutation patients

Study	Population	Design	Pts with 17p/TP53 (n)	Total (n = 274)
ALLIANCE	Fit, older, del 17p allowed	Ph 3: BR vs I vs IR	51	Median not reached for I or IR vs 7 mo BR
iLLUMINATE	Unfit (CIRS>6, CrCl<70, or TP53mut/del	Ph3: O-Ibr vs O-Clb	29	Median PFS: Ibr-O: NR O-Clb: 11.3 mo
ELEVATE-TN	Unfit (CIRS>6, CrCl< 70)	Ph3: O-Clb vs Acala vs Acala-O	61	24 months PFS Acala-O: 95% O-Clb: 19%

Woyach et Al. NEJM 2018, Moreno el al, Lancet Oncol 2019, Sharman et al. Lancet 2020.

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Time Limited vs Indefinite Therapy

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GLOW: Fixed-Duration Ibrutinib + Venetoclax vs Chlorambucil + Obinutuzumab in Frontline CLL

- International, open-label, randomized phase III trial

Stratified by IGHV status, del(11q) presence

Patients with previously untreated CLL; aged ≥65 yr or <65 yr with CIRS >6 or CrCl <70 mL/min; **no del(17p) or known *TP53* mutation**; ECOG PS 0-2
(N = 211)

→ **Ibrutinib** 420 mg PO QD x 3 cycles followed by **Ibrutinib** + **Venetoclax*** 12 cycles
(n = 106)

→ **Chlorambucil** 0.5 mg/kg on Days 1, 15 x 6 cycles + **Obinutuzumab** 1000 mg on Days 1-2, 8, 15 of cycle 1 and Day 1 of cycles 2-6
(n = 105)

→ *If IRC-confirmed PD and active disease requiring tx, eligible for subsequent single-agent ibrutinib*

*Ramp-up from 20 to 400 mg over 5 wk starting in cycle 4.

- **Primary endpoint:** PFS per IRC
  - 71 PFS events to detect effect size with HR of 0.5 (80% power, 2-sided α = 0.05)
- **Key secondary endpoints:** uMRD in BM, CR rate per IRC, ORR per IRC, OS, safety

Kater et al . EHA 2021.

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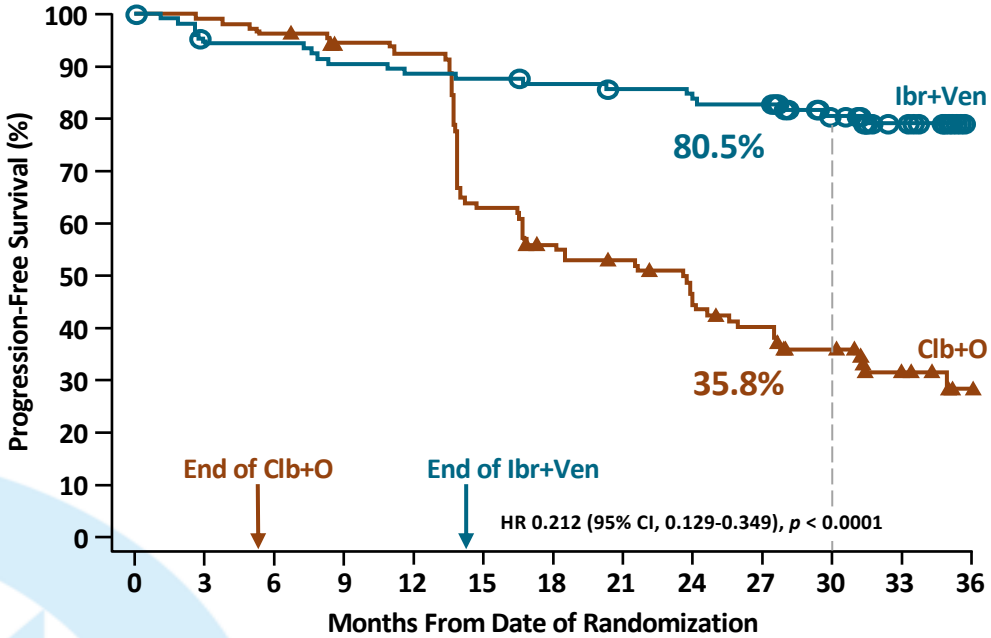
GLOW: 34m follow up Progression Free Survival



Patients at risk

Ibr+Ven	106	98	98	94	92	91	89	87	86	84	71	42	1
Clb+O	105	104	101	96	94	64	55	51	43	37	30	13	3

Overall survival HR 0.76 (95% CI, 0.35-1.64), with 11 deaths for Ibr+Ven vs 16 for Clb+O

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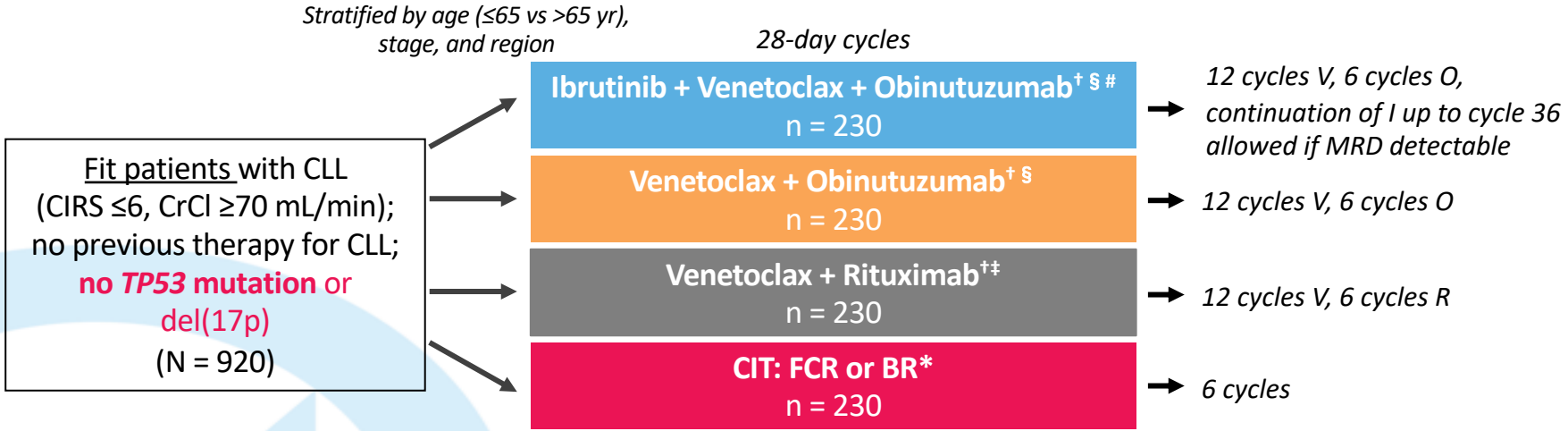
Munir, ASH 2021.

GAIA/CLL13: Time-Limited First-line Venetoclax + Anti-CD20 Ab ± Ibrutinib for CLL

- Multicenter, randomized, open-label phase III study



- **Primary endpoints**: MRD negativity (<1 CLL cell per 10,000 leukocytes analyzed [0.01%]) for venetoclax + obinutuzumab vs CIT; PFS for I + V + obinutuzumab vs CIT

*≤65 yr, FCR; >65 yr: BR. †V standard ramp up 20-400 mg, then 400 mg/day, cycles 3-12. ‡Rituximab 375/500 mg/m^2 day 1, cycles 1-6.
§ Obinutuzumab 1000 mg Day 1, 8, 15 of cycle 1, then Day 1 of cycles 2-6. #I 420 mg/day from Day 1, cycle 1.

Eichhorst. EHA 2022. Abstr LB2365. NCT02950051.

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GAIA/CLL13: Baseline Characteristics- Well balanced

Parameter	Total	CIT	V + R	V + O	I + V + O
Patients (ITT), n	926	229 (FCR: 150; BR: 79)	237	229	231
Median age, yr (range)	61 (27-84)	61 (29-84) (FCR: 55; BR: 71)	62 (27-84)	62 (31-83)	60 (30-84)
Median CIRS score (range)	2 (0-7)	2 (0-6)	2 (0-7)	2 (0-6)	2 (0-7)
IGHV mutation status, n (%)*					
▪ Mutated	380 (41.0)	95 (41.5)	95 (40.1)	89 (39.0)	101 (43.7)
▪ Unmutated	518 (56.0)	131 (57.2)	134 (56.5)	130 (57.0)	123 (53.2)
▪ Not evaluable	27 (2.9)	3 (1.3)	8 (3.4)	9 (3.9)	7 (3.0)

*1 missing sample in the V + O arm.

Eichhorst. EHA 2022. Abstr LB2365.

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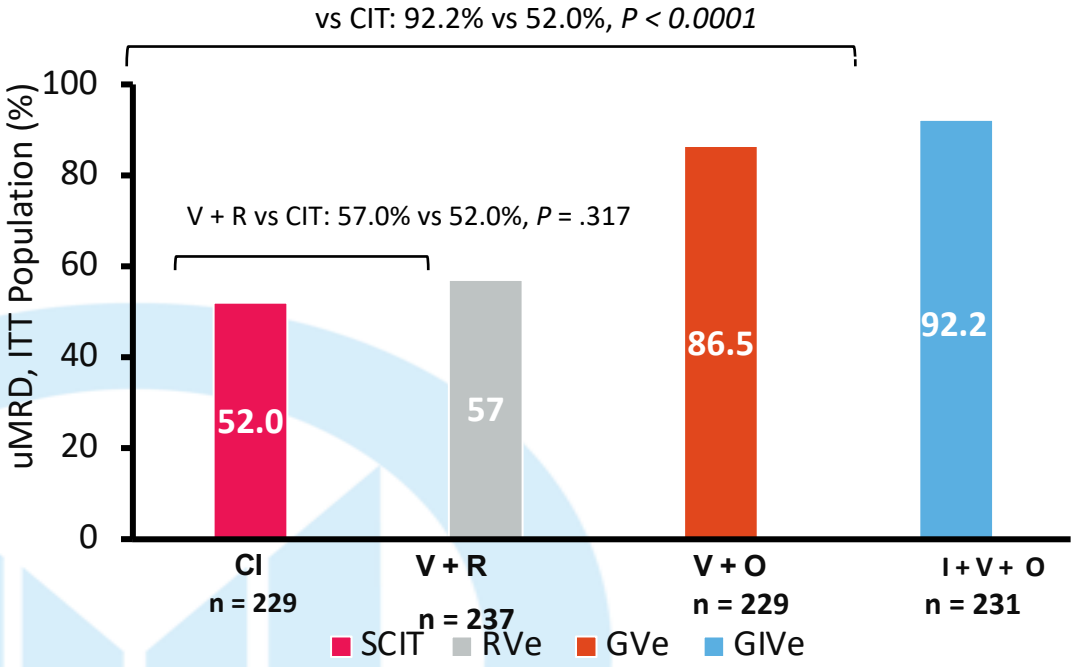
GAIA/CLL13: uMRD in PB at 15 Mo



Regimen	uMRD, % (97.5% CI)
I + V + O	92.2 (87.3-95.7)
V + O	86.5 (80.6-91.1)
V + R	57.0 (49.5-64.2)
CIT	52.0 (44.4-59.5)

Eichhorst. ASH 2021. Abstr 71. Eichhorst. EHA 2022. Abstr LB2365

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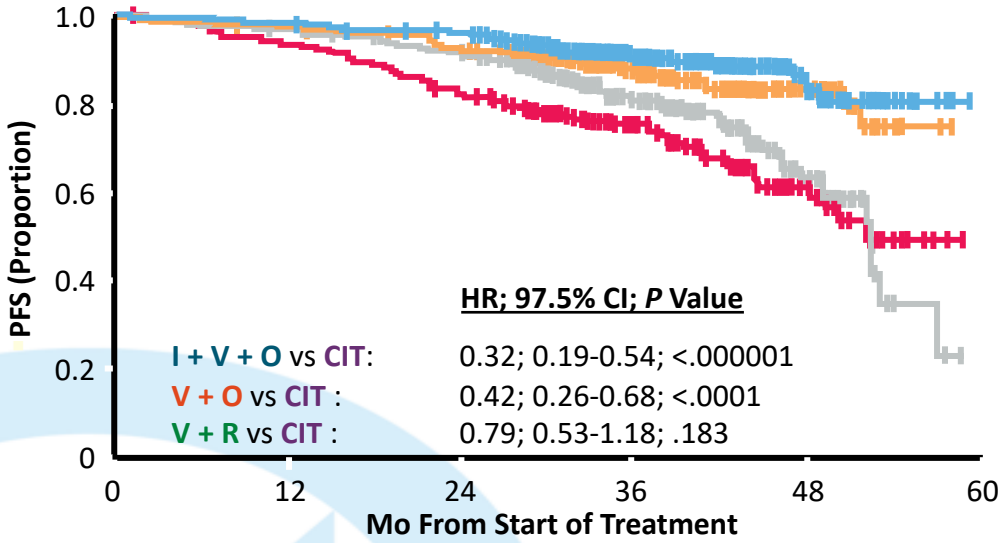
GAIA/CLL13: PFS at 3 Yr



CIT	229	197	172	98	28
V + R	237	226	212	119	32
V + O	229	221	208	125	42
I + V + O	231	227	217	132	44

Regimen	Median PFS, Mo	3-Yr PFS, %
I + V + O	NR	90.5
V + O	NR	87.7
V + R	52.3	80.8
CIT	52.0	75.5

- Median follow-up: 38.8 mo (range: 0-59.2)

Eichhorst. EHA 2022. Abstr LB2365.

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BTKi or BCL2 inhibitor?

BTK inhibitor

- Easy to administer
- Indefinite treatment
- Cardiac risks: Afib, HTN
- Bleeding risk
- More effective in 17pDel or TP53 mutations?

BCL2 inhibitor

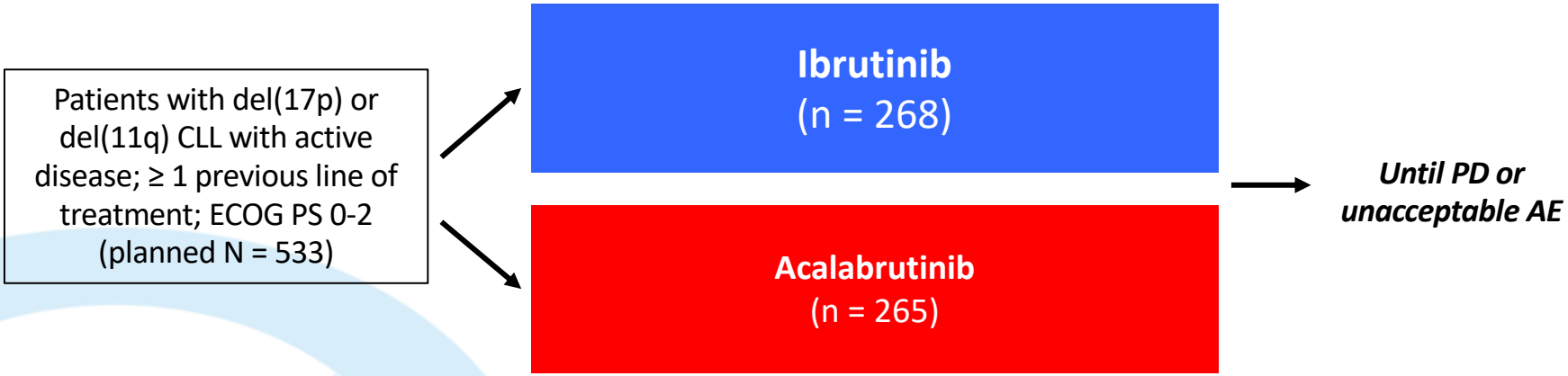
- Logistics: IV administration of antiCD20 and ramp up
- Concerns of TLS
- Limited duration treatment
- Better for low risk but high risk?

BTKi head to head comparisons

- ELEVATE RR
- ALPINE

ELEVATE-RR: Ibrutinib vs Acalabrutinib in Patients With High-Risk Relapsed/Refractory CLL

Final analysis of randomized, multicenter, open-label, noninferiority phase III trial



Primary endpoint: PFS

Secondary endpoints: OS; incidence of treatment-emergent AEs, atrial fibrillation; Richter's transformation; grade ≥3 infections

FPI October 2015 – LPI November 2017 (25 mo)

Final analysis: 279 IRC PFS events, data cutoff 9/2020

Byrd. ASCO 2021. Abstr 7500.

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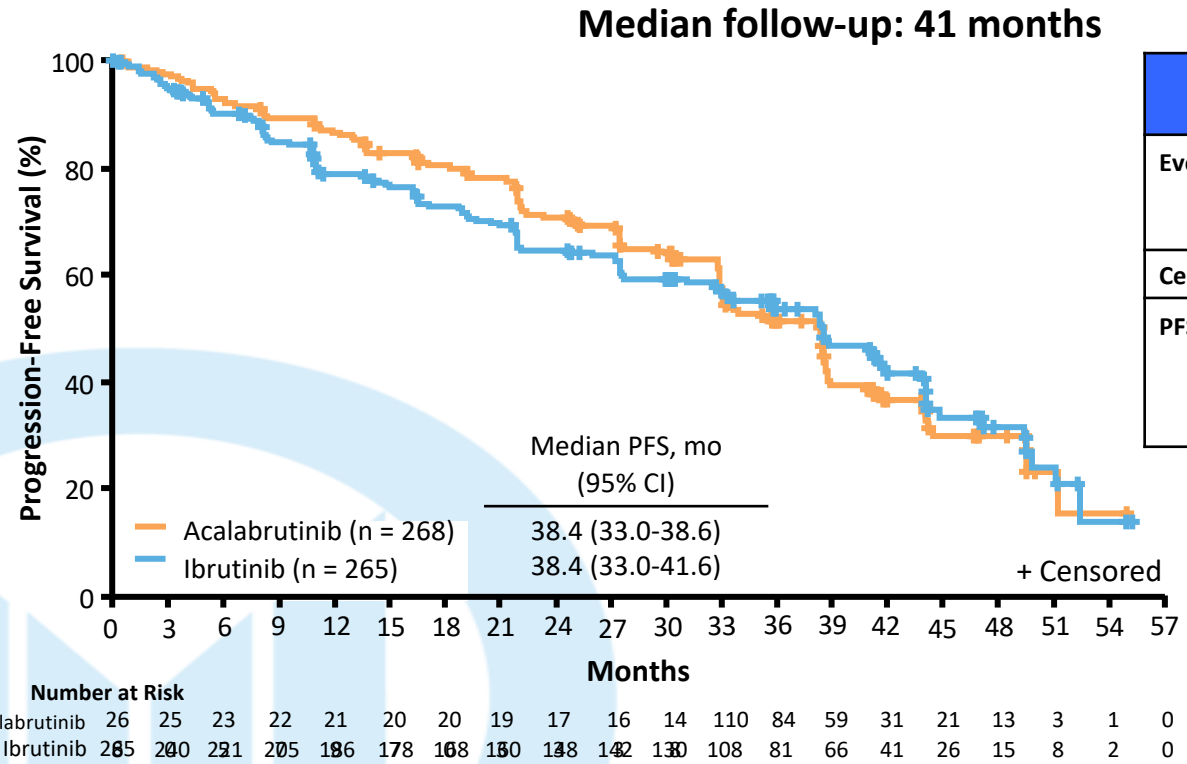
ELEVATE-RR: Noninferiority Met on IRC-Assessed PFS



	Acalabrutinib (n = 268)	Ibrutinib (n = 265)
Events, n (%)	143 (53.4)	136 (51.3)
Death	22 (8.2)	28 (10.6)
PD	121 (45.1)	108 (40.8)
Censored, n (%)	125 (46.6)	129 (48.7)
PFS (95% CI), %		
12 months	86.7 (81.8-90.3)	78.8 (73.1-83.4)
24 months	70.9 (64.8-76.1)	64.5 (58.1-70.2)
36 months	51.4 (44.7-57.8)	53.8 (47.0-60.1)

Noninferiority achieved if upper bound of the 95% CI of HR is less than the prespecified NI margin of 1.429

Byrd. ASCO 2021. Abstr 7500.

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ELEVATE-RR: AEs of clinical interest

AE, n (%)	Acalabrutinib (n = 266)		Ibrutinib (n = 263)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Cardiac events ▪ Atrial fibrillation/flutter ▪ Ventricular arrhythmias	64 (24.1) **25 (9.4)** 0	23 (8.6) 13 (4.9) 0	79 (30.0) **42 (16.0)** 3 (1.1)	25 (9.5) 10 (3.8) 1 (0.4)
Bleeding events ▪ Major bleeding events	**101 (38.0)** 12 (4.5)	10 (3.8) 10 (3.8)	**135 (51.3)** 14 (5.3)	12 (4.6) 12 (4.6)
Hypertension	**25 (9.4)**	11 (4.1)	**61 (23.2)**	24 (9.1)
Infections	208 (78.2)	82 (30.8)	214 (81.4)	79 (30.0)
ILD/pneumonitis	7 (2.6)	1 (0.4)	17 (6.5)	2 (0.8)
SPMs, excluding NMSC	24 (9.0)	16 (6.0)	20 (7.6)	14 (5.3)

Byrd. ASCO 2021.

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ALPINE: Ibrutinib vs Zanubrutinib in Patients With Relapsed/Refractory CLL

- Ongoing randomized, multicenter phase III trial

- Primary endpoint: ORR
- Secondary endpoints: PFS, DoR, OS; safety, patient-assessed QoL

Hillmen et al. EHA 2021.

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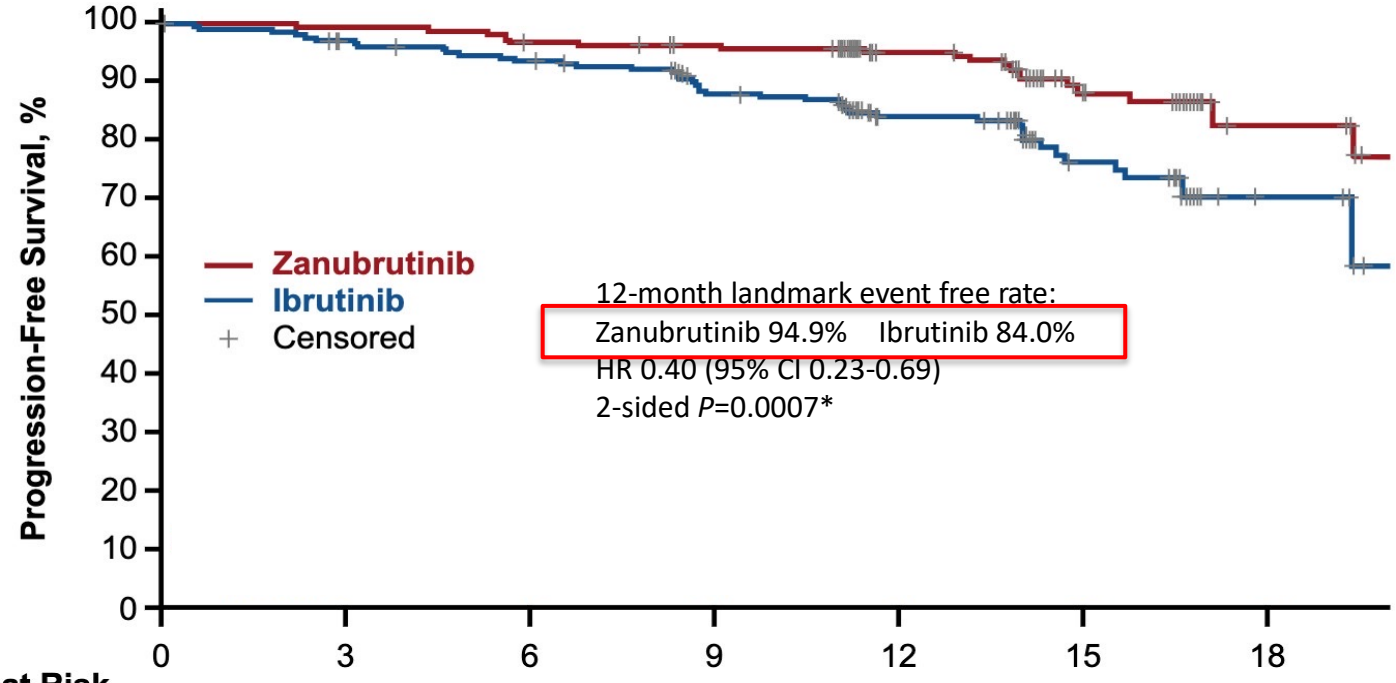
ALPINE: ORR by Investigator Assessment

	Zanubrutinib (n=207), n (%)	Ibrutinib (n=208), n (%)
Primary endpoint:	162 (**78.3**) 95% CI: 72.0, 83.7	130 (**62.5**) 95% CI: 55.5, 69.1
ORR (PR+CR)	Superiority 2-sided *P*=0.0006 compa	red with pre-specified alpha of 0.0099
CR/CRi	4 (1.9)	3 (1.4)
nPR	1 (0.5)	0
PR	157 (75.8)	127 (61.1)
ORR (PR-L+PR+CR)	*183 (88.4)*	*169 (81.3)*
PR-L	21 (10.1)	39 (18.8)
SD	17 (8.2)	28 (13.5)
PD	1 (0.5)	2 (1.0)
Discontinued or new therapy prior to 1st assessment	6 (2.9)	9 (4.3)
	del(17p) (n=24), n (%)	**del(17p) (n=26), n (%)**
ORR (PR+CR)	20 (83.3)	14 (53.8)

CR, complete response; CRi, complete response with incomplete bone marrow recovery; D/C, discontinuation; DOR, duration of response; NE, not evaluable;

Hillmen et al. EHA 2021.

ALPINE: PFS by Investigator Assessment



Hillmen et al. EHA 2021.

Safety Summary

Safety Analysis Population	Zanubrutinib (n=204) n (%)	Ibrutinib (n=207) n (%)
Any AE	195 (95.6)	205 (99.0)
Any grade ≥3 AE	114 (55.9)	106 (51.2)
Serious AEs	56 (27.5)	67 (32.4)
Fatal AEs	8 (3.9)	12 (5.8)
AEs leading to dose reduction	23 (11.3)	25 (12.1)
AEs leading to dose interruption	81 (39.7)	84 (40.6)
AEs leading to treatment discontinuation	16 (7.8)	27 (13.0)

Hillmen et al. EHA 2021.

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Additional AEs of Special Interest

Safety Analysis Population	Zanubrutinib (n=204), n (%)		Ibrutinib (n=207), n (%)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Cardiac disorders[a]	28 (13.7)	5 (2.5)	52 (25.1)	14 (6.8)
Atrial fibrillation and flutter (key 2º endpoint)	**5 (2.5)**	**2 (1.0)**	**21 (10.1)**	**4 (1.9)**
Hemorrhage Major hemorrhage[b]	73 (35.8) 6 (2.9)	6 (2.9) 6 (2.9)	75 (36.2) 8 (3.9)	6 (2.9) 6 (2.9)
Hypertension	34 (16.7)	22 (10.8)	34 (16.4)	22 (10.6)
Infections	122 (59.8)	26 (12.7)	131 (63.3)	37 (17.9)
Neutropenia[c]	58 (28.4)	38 (18.6)	45 (21.7)	31 (15.0)
Thrombocytopenia[c]	19 (9.3)	7 (3.4)	26 (12.6)	7 (3.4)
Secondary primary malignancies Skin cancers	17 (8.3) 7 (3.4)	10 (4.9) 3 (1.5)	13 (6.3) 10 (4.8)	4 (1.9) 2 (1.0)

Hillmen et al. EHA 2021.

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Ibrutinib or second generation BTKi?

Ibrutinib

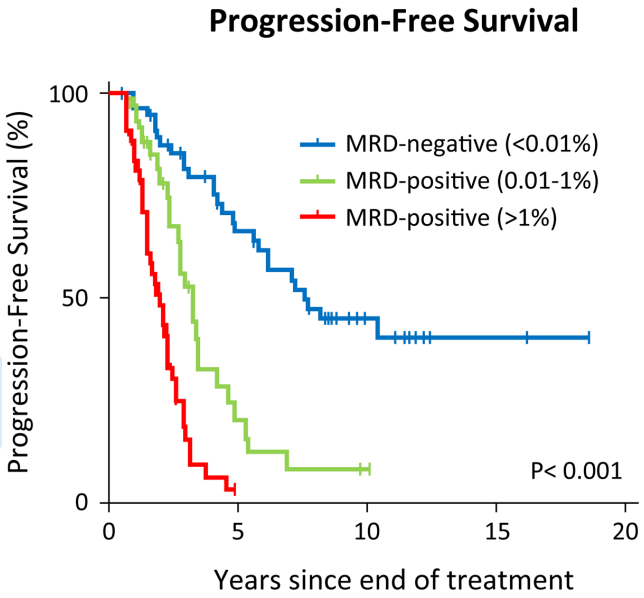
- Long term efficacy (> 8 years)
- Compliance (once a day versus BID)
- Familiarity
- Drug interactions

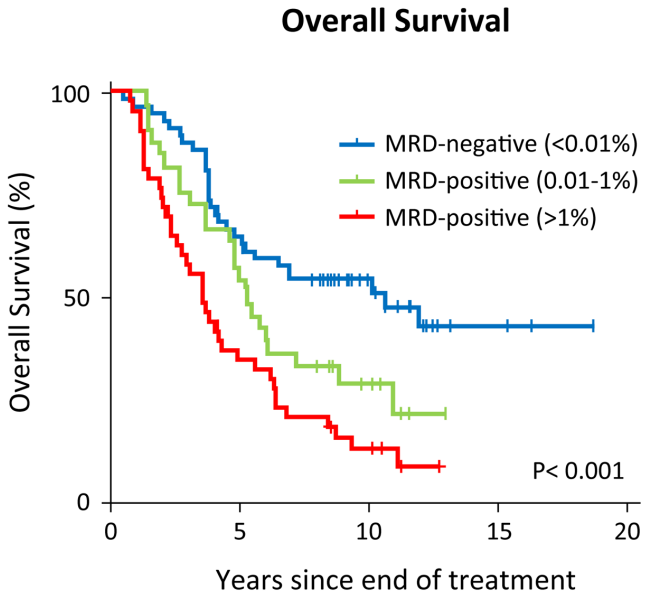
2nd generation BTKi

- Less follow up time
- Better toxicity profile (less Afib, HTN, bleeding and discontinuations)
- Drug interactions (acalabrutinib with PPIs- novel formulation available)

MRD or not MRD?

MRD predicts outcomes in CLL





MRD assessed at the end of treatment is an independent predictor if PFS and OS in CLL

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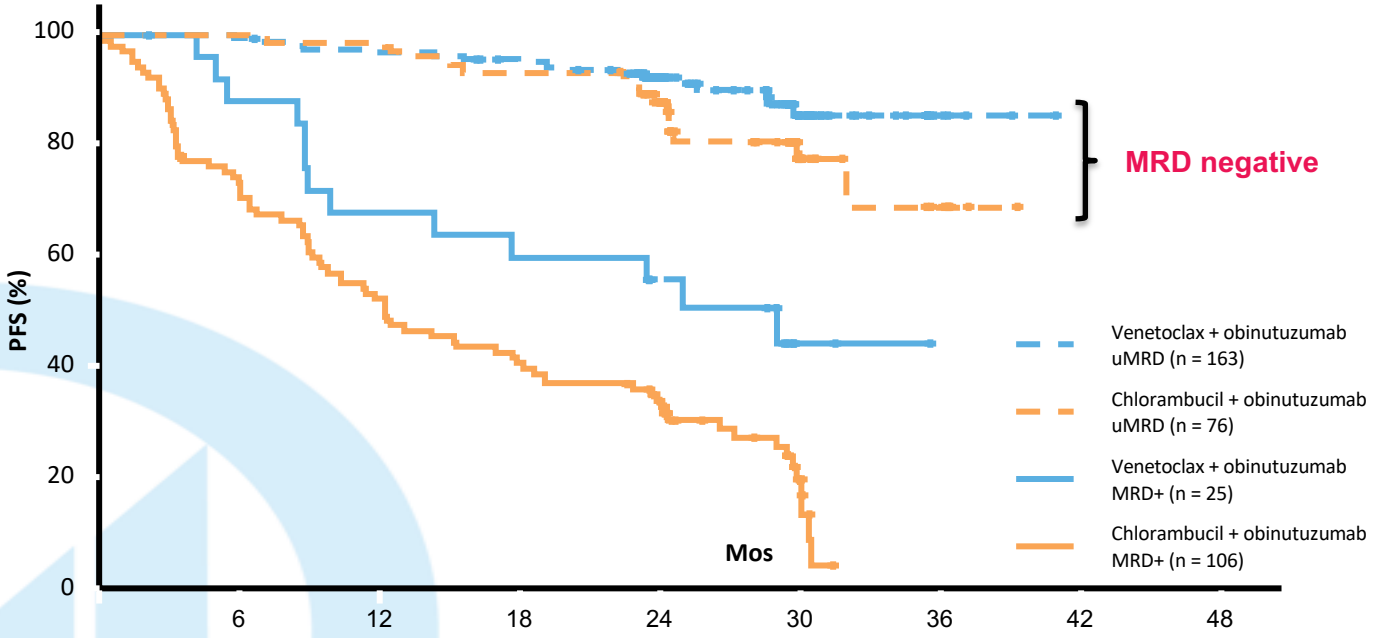
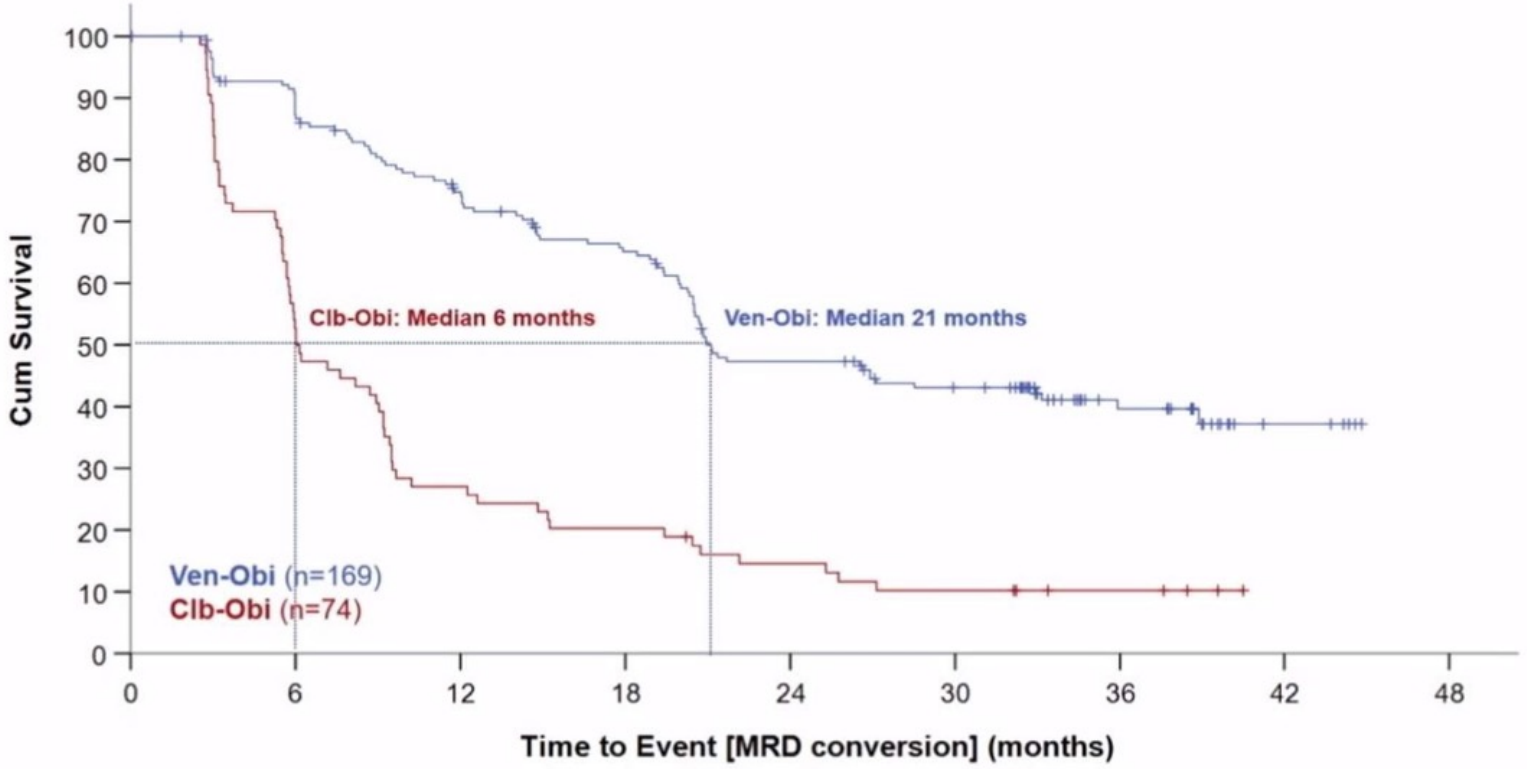
Kwok et al. *Blood* 2018.

CLL14: Landmark PFS by MRD Status at End of Therapy



Fischer et al. ASH 2019. Abstract 36.

CLL14: Time to MRD Conversion (from > 10^{-4} by NGS at EoT)



Al-Sawaf O et al. EHA 2021 abstract S146.

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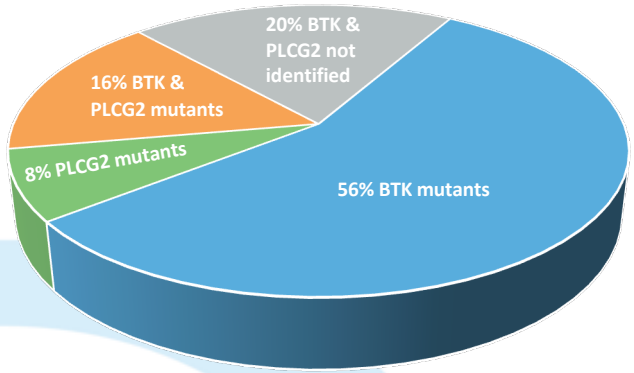
MRD conclusions

- MRD is prognostic of PFS and OS in CLL
- No standard treatment strategy based on MRD yet (trials are ongoing)
- Technology: flow cytometry? NGS?
- Cost
- Patient education

Beyond BCL2 and BTKi (double refractory)

Pirtobrutinib (LOXO-305): Selective Noncovalent BTK Inhibitor

Acquired Resistance to Ibrutinib in Patients With Progressive CLL[1]



- *BTK* C481 mutations are principal reason for progressive CLL after treatment with covalent BTK inhibitors[2]
- *BTK* C481 mutations impair target inhibition by covalent BTK inhibitors[2]

- BRUIN[3]: Phase I/II study of pirtobrutinib in patients with CLL/SLL or B-cell NHL

Outcome	All CLL/SLL Patients (n = 139)
ORR, % (95% CI)	63 (55-71)
Best response, n (%)	
▪ CR	0
▪ PR	69 (50)
▪ PR-L	19 (14)
▪ SD	45 (32)

AE, n (%)	Any Grade* (All Patients, n = 323)
Fatigue	65 (20)
Diarrhea	55 (17)
Contusion	42 (13)
Bruising	53 (16)
Rash	35 (11)

1. Lampson. Expert Rev Hematol. 2018;11:185. 2. Mato. Lancet. 2021;397:892.
3. Mato. ASH 2020. Abstr 542.

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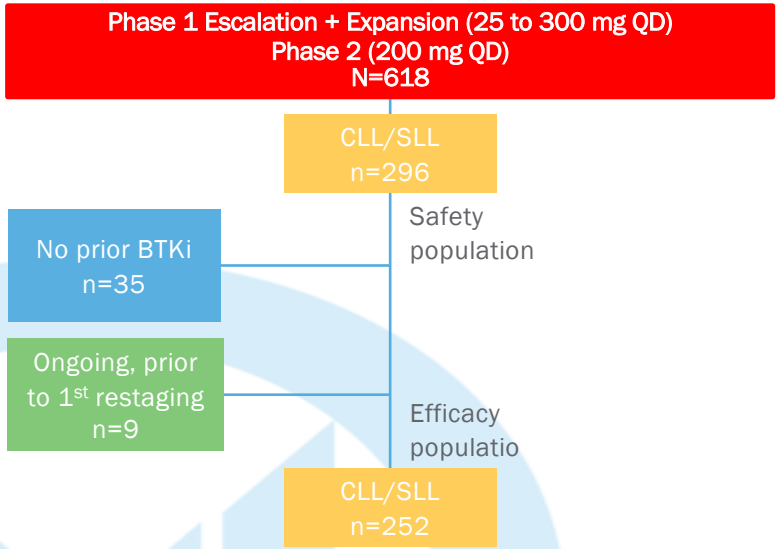
Updated Results From the BRUIN Phase 1/2 Trial of Pirtobrutinib in Patients With R/R CLL/SLL: Study Design and Patients

Key Eligibility Criteria

- R/R CLL/SLL or other B-cell NHL requiring treatment
- ECOG PS ≤2



Primary endpoint: MTD/RP2D identification
Secondary endpoints: ORR, DOR, PFS, pharmacokinetics, safety

BTKi-Pretreated Patient Characteristics		(N=261)
Median age (range), years		69 (36-88)
ECOG PS, n (%)	0	138 (53)
	1	104 (40)
	2	19 (7)
Median prior systemic therapies, n (range)		3 (1-11)
Mutation status, n (%)	BTK C481-mutant	89 (43)
	BTK C481-WT	118 (57)
	PLCG2-mutant	33 (16)
Prior therapies, n (%)	**BTKi**	**261 (100)**
	Anti-CD20 mAb	230 (88)
	Chemotherapy	207 (79)
	BCL2i	**108 (41)**
	PI3Ki	51 (20)
High-risk molecular features, n (%)	del(17p)	51 (28)
	TP53 mutation	64 (37)
	TP53 & del(17p)	38 (27)
	Unmutated *IGHV*	168 (84)
	del(11q)	45 (25)

- 196/261 (75%) discontinued prior BTKi use due to PD and 65/261 (25%) discontinued due to toxicity

Data cutoff date: 16 July 2021.
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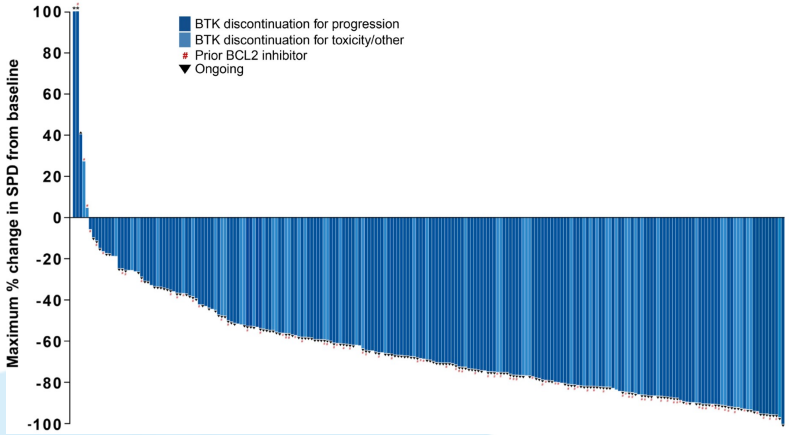
Updated Results From the BRUIN Phase 1/2 Trial of Pirtobrutinib in Patients With R/R CLL/SLL: Efficacy

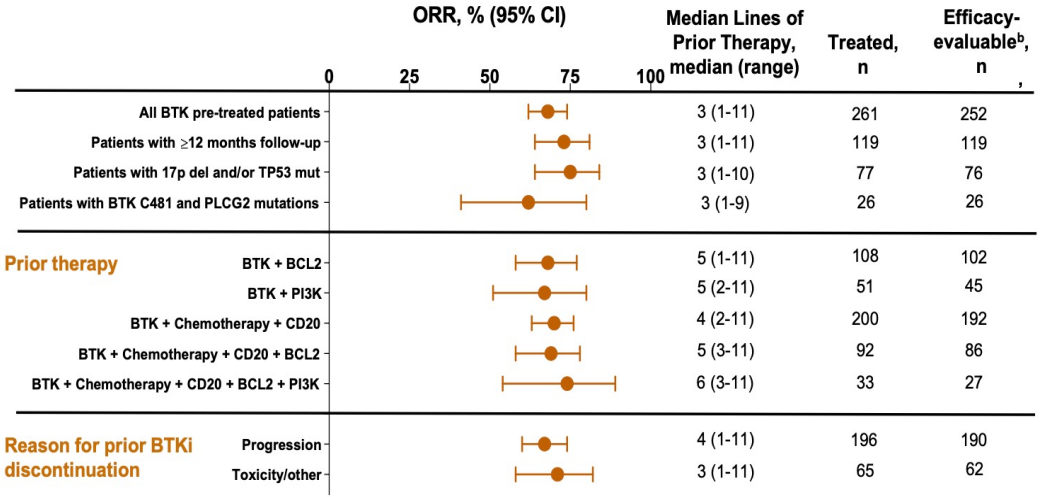
Efficacy in BTKi-Pretreated CLL/SLL



Efficacy Evaluable BTK Pre-Treated CLL/SLL Patients (n=252)		
Overall response rate[a], % (95% CI)		68 (63-74)
Best response, n (%)	CR	2 (1)
	PR	137 (54)
	PR-L	32 (13)
	SD	62 (25)

[a]ORR includes patients with a best response of CR, PR, and PR-L.

Efficacy Regardless of Other Prior Therapy



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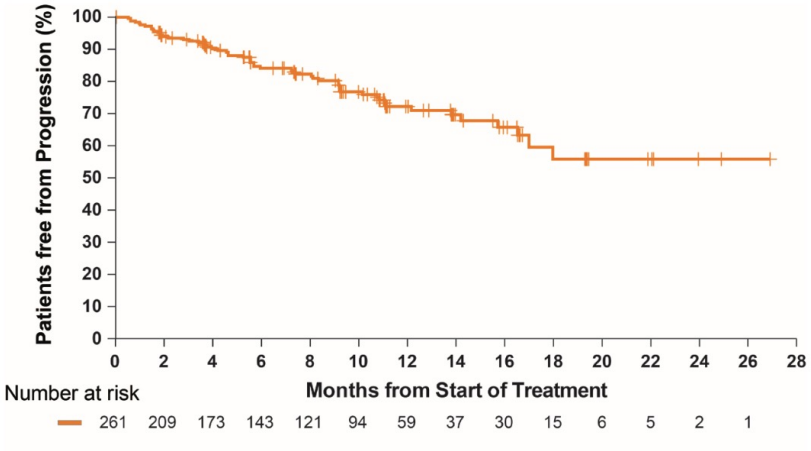
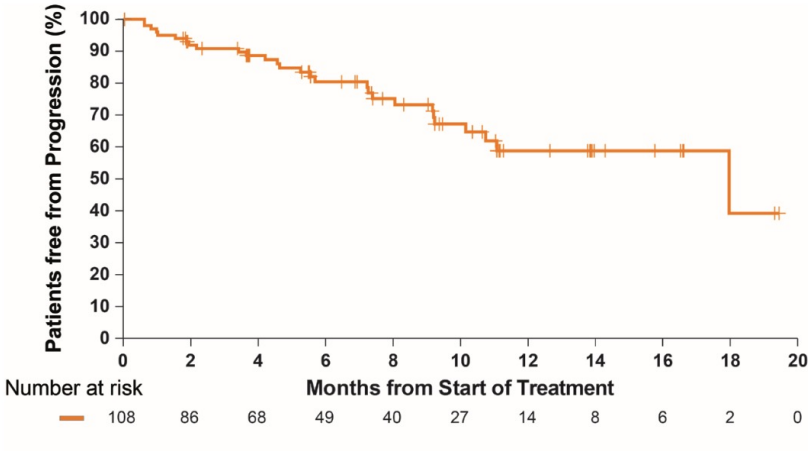
Updated Results From the BRUIN Phase 1/2 Trial of Pirtobrutinib in Patients With R/R CLL/SLL: PFS

PFS in at Least BTKi Pretreated Patients, Median Prior LOT = 3



Median PFS: Not Estimable (95% CI: 17.0 months – Not Estimable)

PFS in at Least BTKi and BCL2i Pretreated Patients, Median Prior LOT = 5



Median PFS: 18 months (95% CI: 10.7 months – Not Estimable)

- 74% (194/261) of BTKi-pretreated patients remain on pirtobrutinib
- Median follow-up: 9.4 months (0.3-27.4) for all BTKi-pretreated patients
- BTK C481 mutation status was not predictive of pirtobrutinib benefit

Data cutoff date: 16 July 2021.
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Updated Results From the BRUIN Phase 1/2 Trial of Pirtobrutinib in Patients With R/R CLL/SLL: Safety and Summary

AEs at All Doses and Patients (N=618), %		TEAEs in ≥15% of patients				Treatment-Related AEs	
		Any Grade	Grade 1	Grade 2	Grade 3	Any Grade	Grade 3/4
Fatigue		23	13	8	1	9	1
Diarrhea		19	15	4	<1	8	<1
Neutropenia		18	1	2	8	10	8
Contusion		17	15	2	-	12	-
AEs of special interest	Bruising	22	20	2	-	15	-
	Rash	11	9	2	<1	5	<1
	Arthralgia	11	8	3	<1	3	-
	Hemorrhage	8	5	2	1[a]	2	<1
	Hypertension	7	1	4	2	2	<1
	AFib/Flutter	2[b]	-	1	<1	<1	-

Takeaways

- Pirtobrutinib demonstrated efficacy in patients previously treated with BTKi
- Efficacy was independent of BTK C481 mutation status, reason for prior BTKi discontinuation, or other prior therapies
- Favorable safety and tolerability was observed

Data cutoff date: 16 July 2021. [a] Represents 6 events (all grade 3), including 2 cases of post-operative bleeding, 1 case each of GI hemorrhage in the setting of sepsis, NSAID use, chronic PUD, and one case of subarachnoid hemorrhage in setting of traumatic bike accident. [b] Of 10 total afib/aflutter TEAEs, 3 occurred in patients with a prior medical history of afib, 2 in patients presenting with concurrent systemic infection, and 2 in patients with both.

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