CHRONIC LYMPHOCYTIC LEUKEMIA

Salvage therapy

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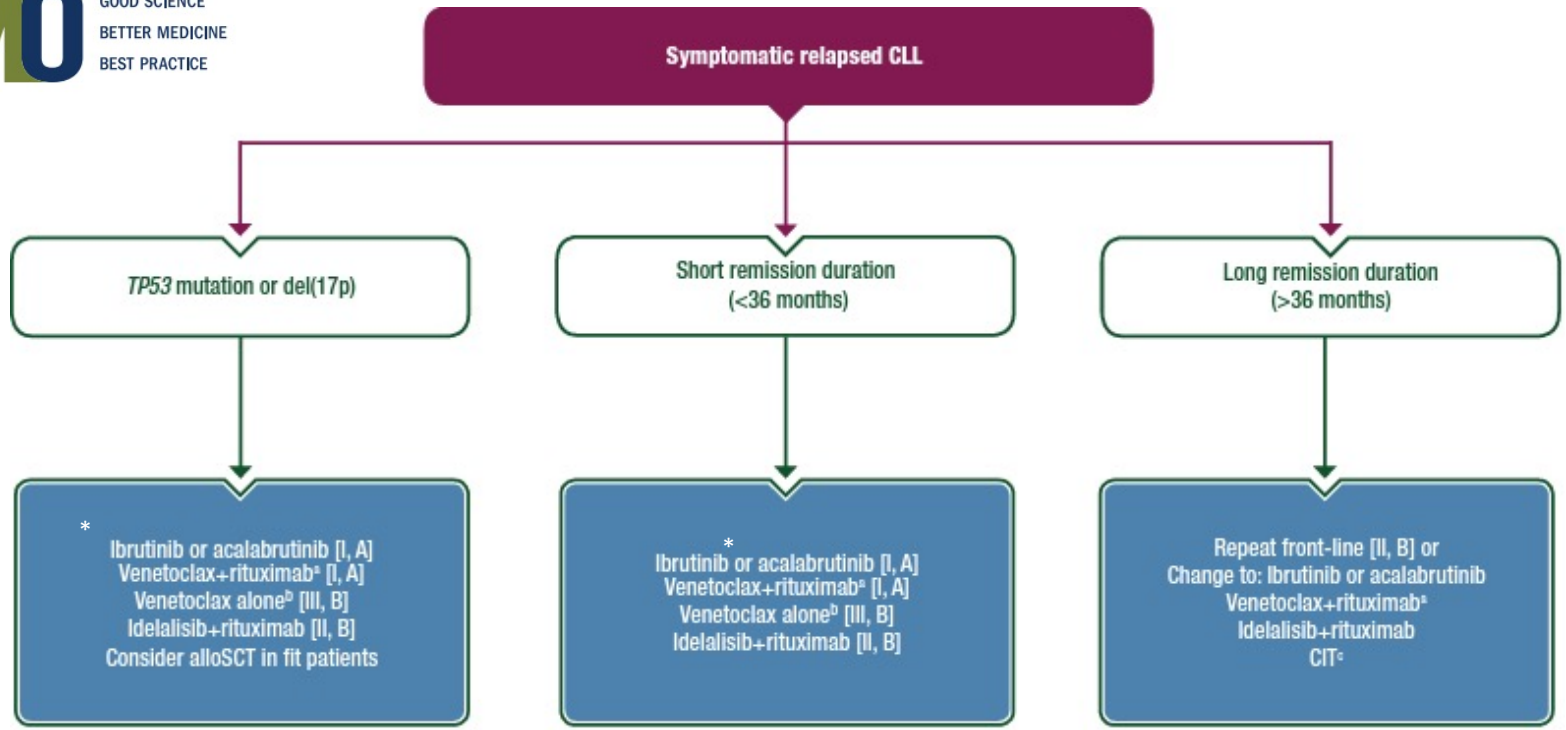
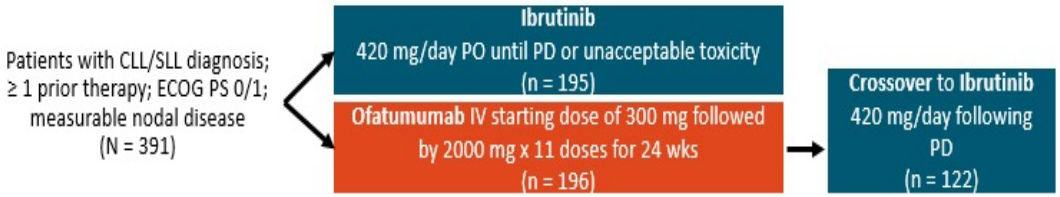
	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Janssen					x	x	
AstraZeneca					x	x	
Abbvie	x				x	x	
Beigene						x	
Takeda	x				x	x	

2021 GUIDELINES: R/R PATIENTS WITH CLL

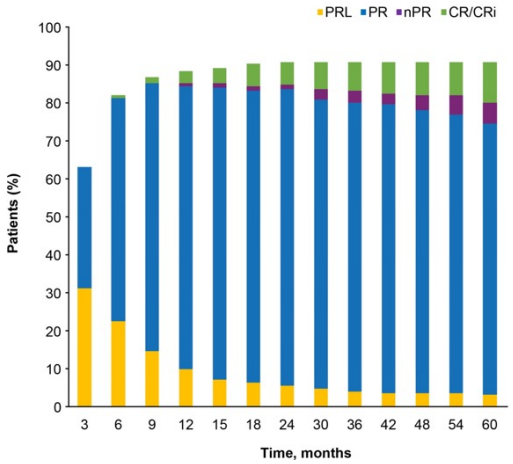
ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE



Ibrutinib in R/R patients with CLL: the Resonate trial

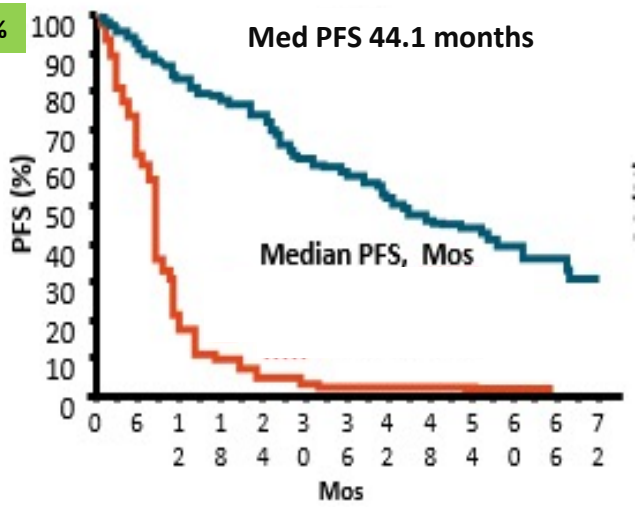


Cumulative best response over time

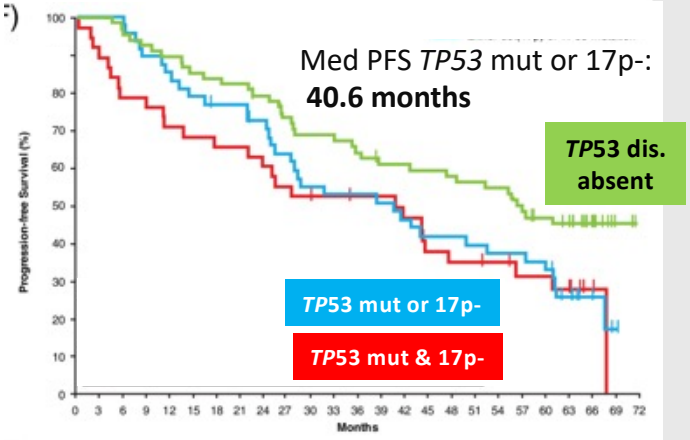


PFS

CR= 10.8%

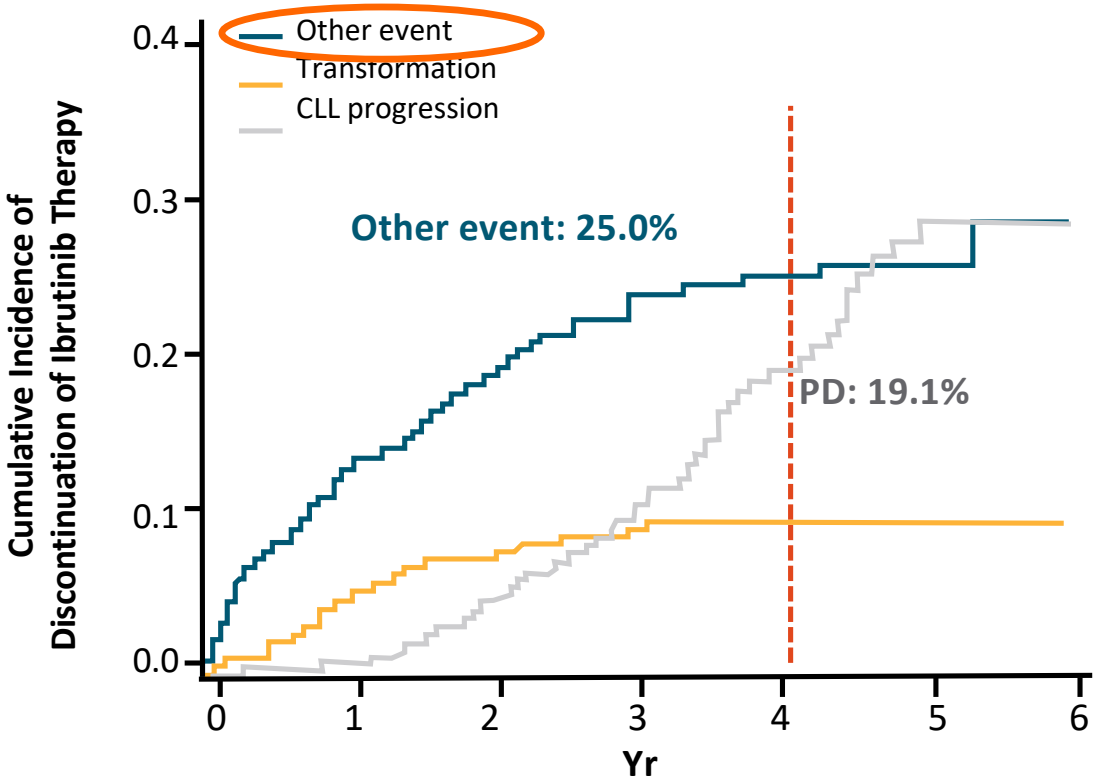


PFS by *TP53* disruption



Munir et al. Am J Hematol. 2019

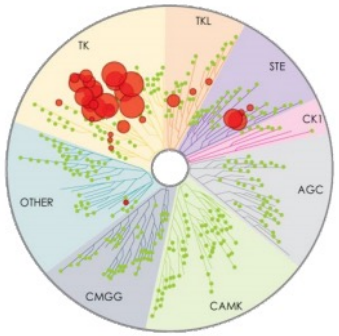
Ibrutinib Discontinuation Across 4 Clinical Trials



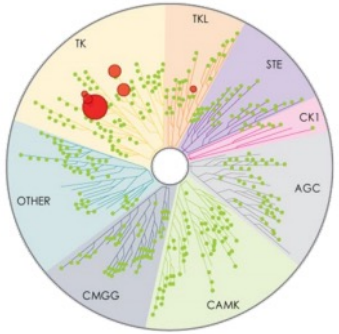
Woyach. JCO. 2017;35:1437. 2. Lampson. Expert Rev Hematol. 2018;11:185. 3. Mato. ASH 2019. Abstr 501. 4. Burger. Leukemia. 2020;34:787.

Second generation BTK inhibitors

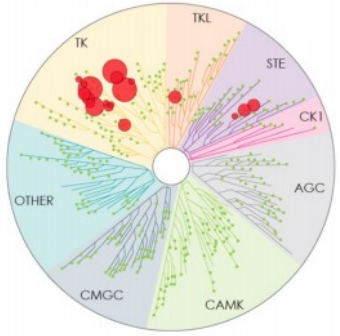
Ibrutinib



Acalabrutinib



Zanubrutinib



IC_{50}/EC_{50} (nM)

Kinase	Ibrutinib	Acalabrutinib	Zanubrutinib
BTK	1.5	5.1	0.5
TEC	10	126	44
ITK	4.9	> 1000	50
BMX	0.8	46	1.4
EGFR	5.3	> 1000	21
ERBB4	3.4	16	6.9
JAK3	32	> 1000	1377
BLK	0.1	> 1000	2.5

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

Adults with previously treated CLL requiring therapy (iwCLL 2008 criteria)

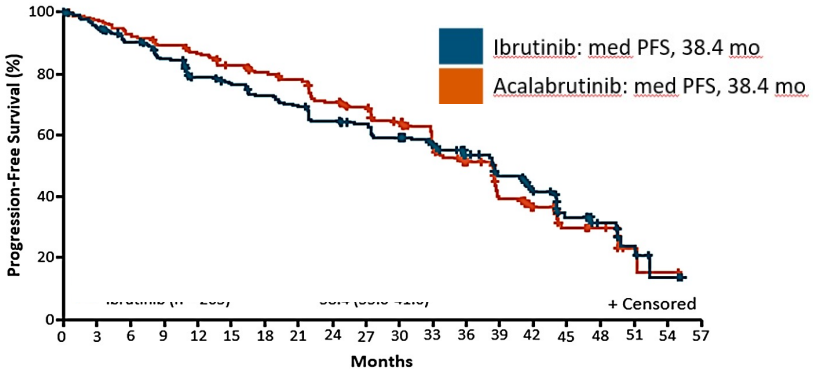
Presence of del(17p) or del(11q)
ECOG PS ≤ 2

→ **Ibrutinib** (n = 268)

→ **Acalabrutinib** (n = 265)

→ *Until PD or unacceptable AE*

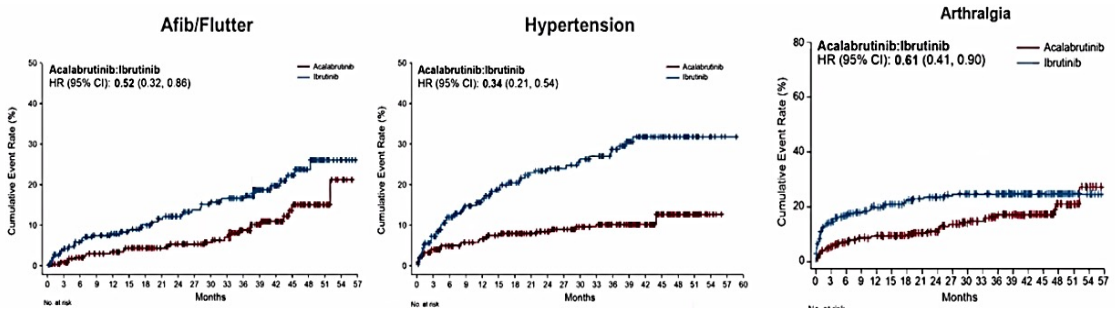
PFS



AEs of special interest

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

Median follow-up: 41 months



Byrd et al., JCO 2021; Seymour. ASH 2021. Abstr 3721.

ALPINE TRIAL: Ibrutinib vs Zanubrutinib in Patients With R/R CLL

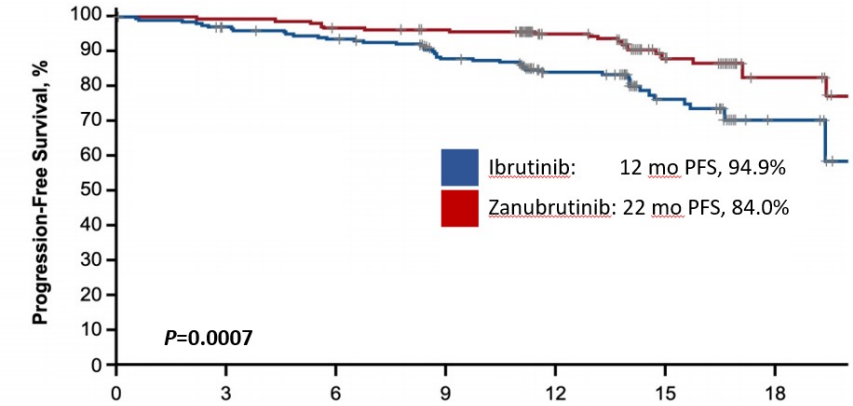
Ongoing randomized, multicenter phase III trial

Patients with CLL requiring treatment
R/R to ≥ 1 previous treatment
ECOG PS 0-2
Adequate organ function
No clinically significant cardiac disease
(planned N = 400)

Ibrutinib 420 mg PO QD

Zanubrutinib 160 mg PO BID

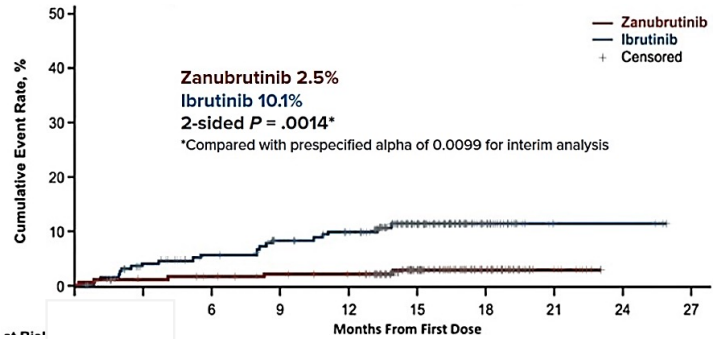
Until PD or unacceptable AE



Response

	Zanubrutinib (n=207), n (%)	Ibrutinib (n=208), n (%)
Primary endpoint: ORR (PR+CR)	162 (**78.3**)	130 (**62.5**)
	95% CI: 72.0, 83.7	95% CI: 55.5, 69.1
	Superiority 2-sided *P*=0.0006 compared with pre-specified alpha of 0.0099	

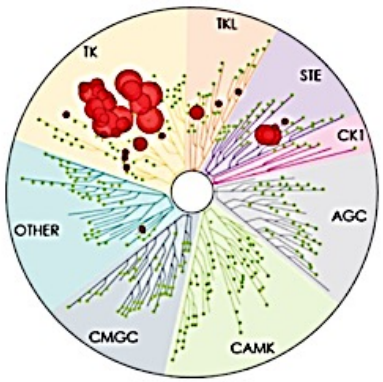
Safety Analysis Population	Zanubrutinib (n=204), n (%)		Ibrutinib (n=207), n (%)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Cardiac disorders[a]	28 (13.7)	5 (2.5)	52 (25.1)	14 (6.8)
Atrial fibrillation and flutter (key 2º endpoint)	**5 (2.5)**	**2 (1.0)**	**21 (10.1)**	**4 (1.9)**
Hemorrhage	73 (35.8)	6 (2.9)	75 (36.2)	6 (2.9)
Major hemorrhage[b]	6 (2.9)	6 (2.9)	8 (3.9)	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	17 (8.3)	10 (4.9)	13 (6.3)	4 (1.9)
Skin cancers	7 (3.4)	3 (1.5)	10 (4.8)	2 (1.0)



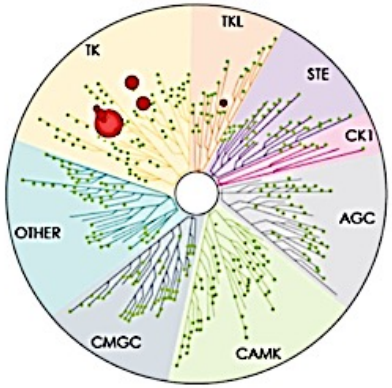
Hillmen et al. EHA 2021

Covalent Irreversible

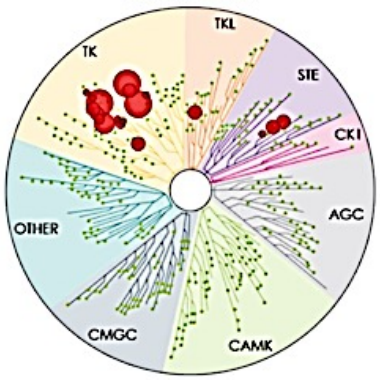
ibrutinib



acalabrutinib

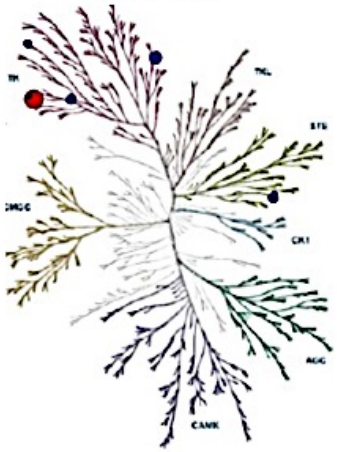


zanubrutinib



Non-Covalent Reversible

LOXO-305



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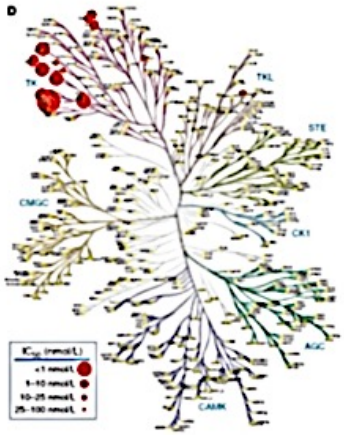
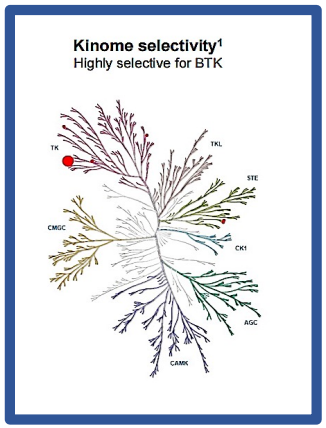
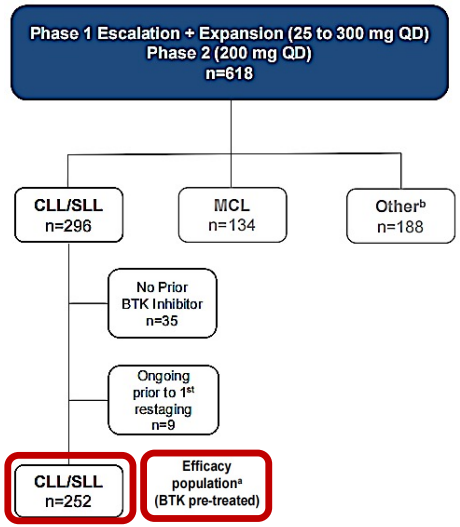


Reversible BTK inhibitors designed to overcome resistance mutations in patients who progress while on BTK inhibitors

Pirtobrutinib in R/R CLL/SLL: Results From The Phase 1/2 BRUIN Study





Characteristics	N = 261
Median age, years (range)	69 (36-88)
Female, n (%)	84 (32)
Male, n (%)	177 (68)
ECOG PS[a], n (%)	
0	138 (53)
1	104 (40)
2	19 (7)
Median number of prior lines of systemic therapy (range)	3 (1-11)
Prior therapy, n (%)	
BTK inhibitor	261 (100)
Anti-CD20 antibody	230 (88)
Chemotherapy	207 (79)
BCL2 inhibitor	108 (41)
PI3K inhibitor	51 (20)
CAR-T	15 (6)
Stem cell transplant	6 (2)
Allogeneic stem cell transplant	5 (2)
Autologous stem cell transplant	1 (<1)
Reason discontinued prior BTKi, n (%)	
Progressive disease	196 (75)
Toxicity/Other	65 (25)

Baseline Molecular Characteristics[a]	
Mutation status, n (%)	
BTK C481-mutant	89 (43)
BTK C481-wildtype	118 (57)
PLCG2-mutant	33 (16)
High Risk Molecular Features, n (%)	
17p deletion	51 (28)
TP53 mutation	64 (37)
17p deletion or TP53 mutation	77 (36)
Both 17p deletion and TP53 mutation	38 (27)
IGHV unmutated	168 (84)
11q deletion	45 (25)

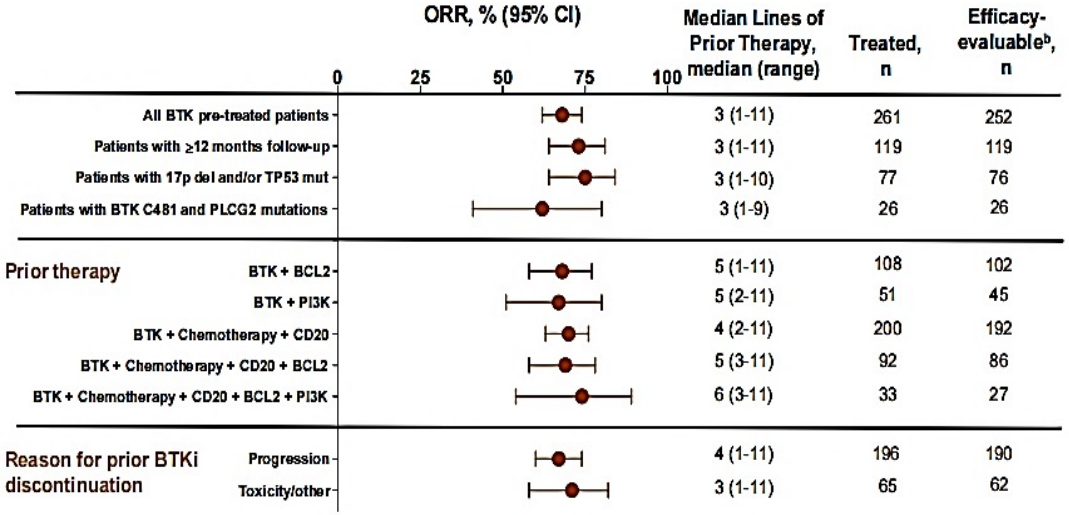
- Nanomolar potency against WT & C481-mutant BTK in cell and enzyme assays[2]
- >300-fold selectivity for BTK vs 370 other kinases[2]
- Due to reversible binding mode, BTK inhibition not impacted by intrinsic rate of BTK turnover[2]
- Favorable pharmacologic properties allow sustained BTK inhibition throughout dosing interval[2]

Mato et al. 2021 ASH. Abstract #391

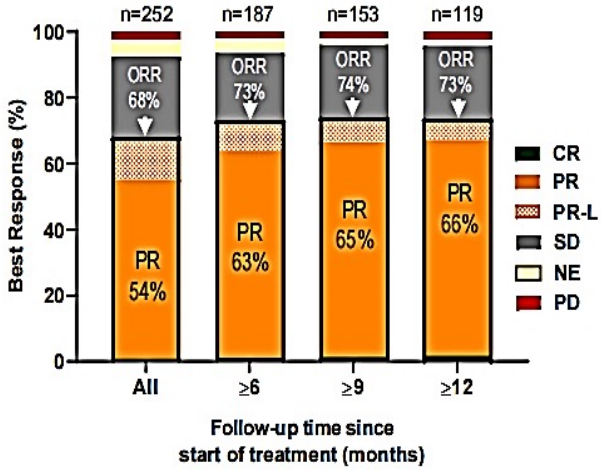
Pirtobrutinib in R/R CLL/SLL: Results From The Phase 1/2 BRUIN Study

Efficacy evaluable BTK pre-treated CLL/SLL Patients[a]	n = 252
Overall Response Rate, % (95% CI)[b]	68 (62 – 74)
Best response	
CR, n (%)	2 (1)
PR, n (%)	137 (54)
PR-L, n (%)	32 (13)
SD, n (%)	62 (25)

Pirtobrutinib Efficacy Regardless of Other Prior Therapy[a]



Overall Response Rate Over Time[c]

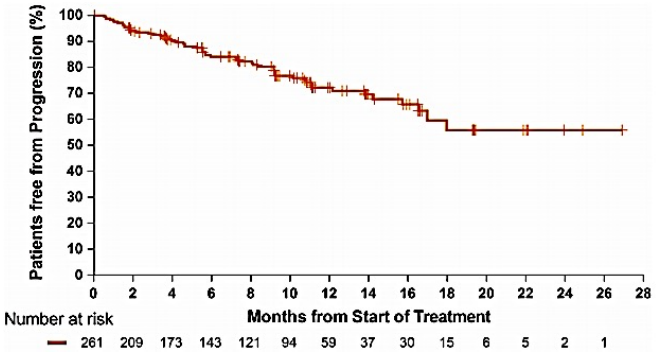


Mato et al. 2021 ASH. Abstract #391

Pirtobrutinib, in R/R CLL/SLL: Results From The Phase 1/2 BRUIN Study

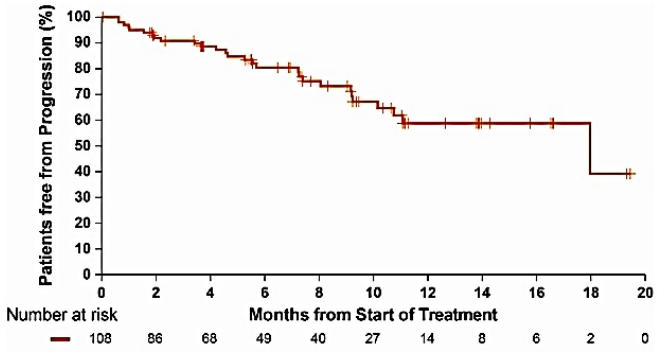
PFS in at least BTK pre-treated patients
Median prior lines = 3

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

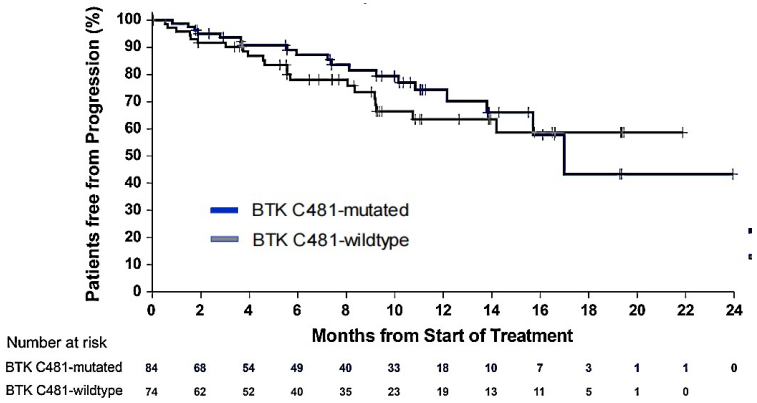


PFS in at least BTK and BCL2 pre-treated patients
Median prior lines = 5

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



Progression-free survival by BTK C481 mutation status[a] in CLL/SLL patients with progression on a prior BTK inhibitor

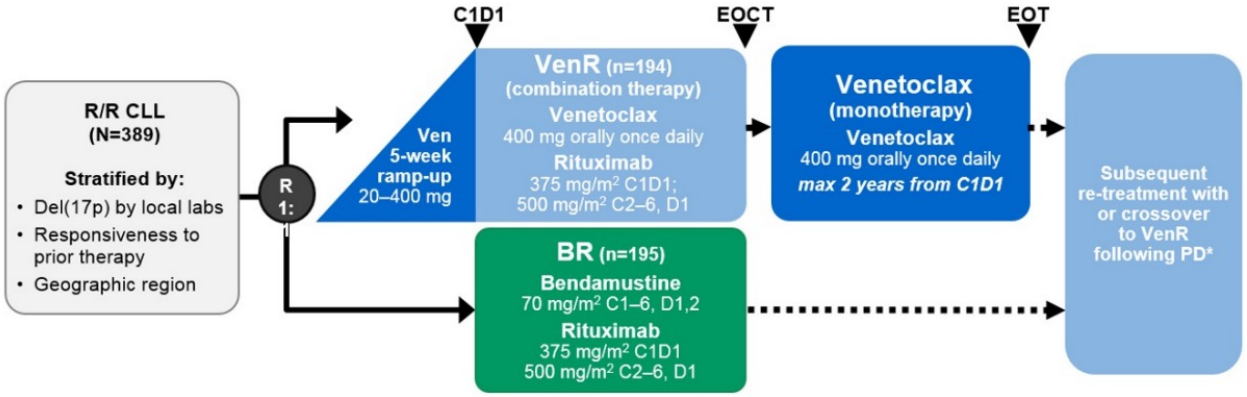


74% of BTK pre-treated patients remain on pirtobrutinib

Median follow-up of 9.4 months

Mato et al. 2021 ASH. Abstr. #391

MURANO TRIAL: VR vs. BR in R/R patients with CLL



Primary Endpoint:
- **INV-assessed PFS**

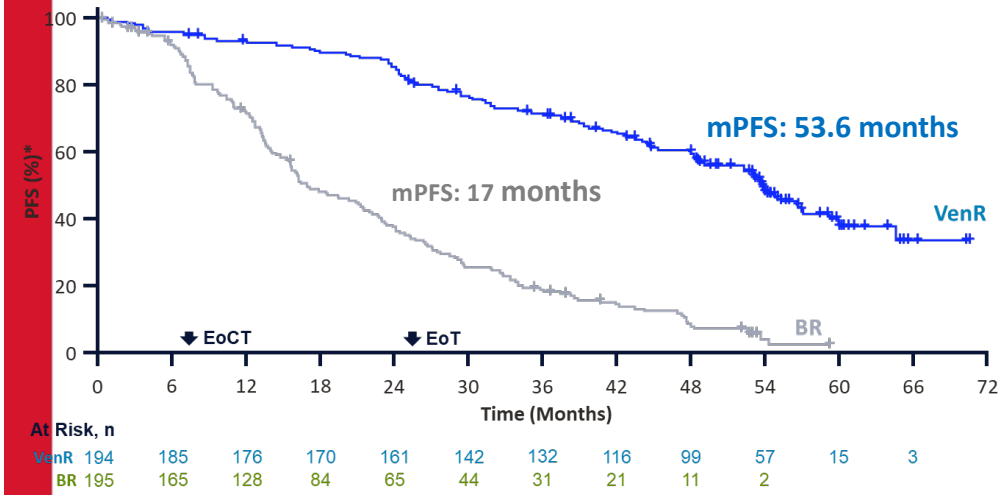
Key Secondary Endpoints:
- IRC-assessed PFS
- PFS in patients with del(17p)
- ORR (CR, CRi, nPR, PR) at EoCT
- OS, rates of MRD clearance, DoR, EFS, TTNT

Key Inclusion Criteria
- 1–3 lines of prior therapy, including ≥1 chemotherapy-containing regimen
- Prior bendamustine only if DoR was ≥2 years (i.e. not refractory or resistant to prior BR)
- ECOG PS ≤1

Kater AP, *et al. J Clin Oncol* 2020

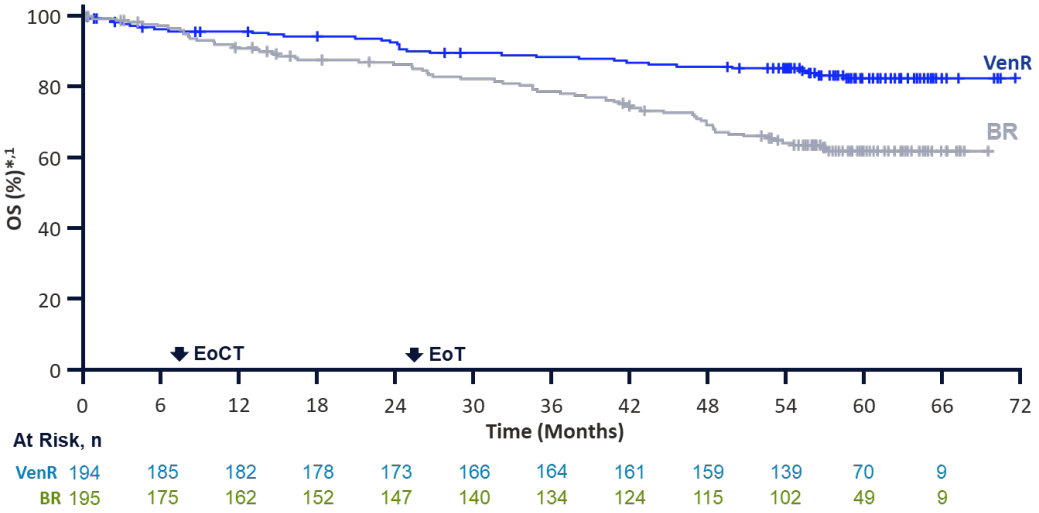
MURANO- 59 months follow-up: PFS and OS

PFS (final analysis)



	VenR (n=194)	BR (n=195)
Median PFS, months (95% CI)	53.6 (48.4–57.0)	17.0 (15.5–21.7)
HR (95% CI), p-value	0.19 (0.15–0.26) stratified p<0.0001†	

OS (final analysis)

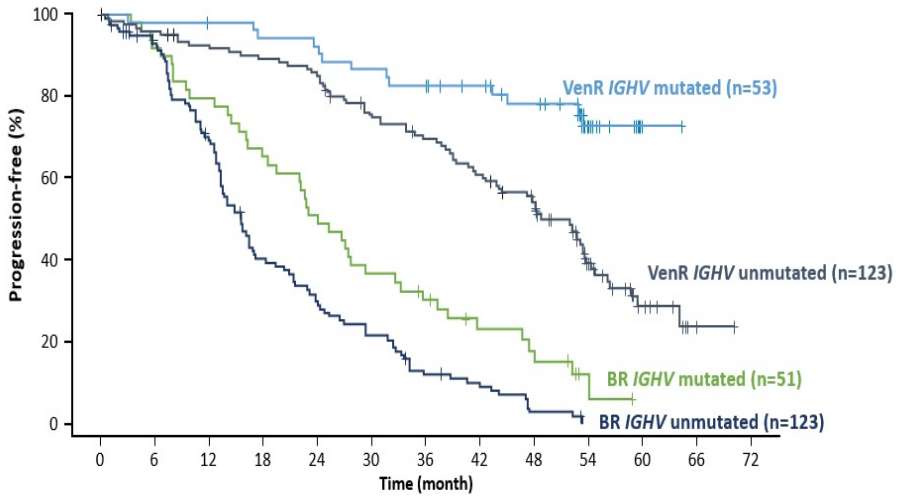


	VenR (n=194)	BR (n=195)
Median OS,[1] months	NE	NE
HR (95% CI),[1] stratified p-value	0.40 (0.26–0.62) p<0.0001†	

Kater *et al.* ASH 2020

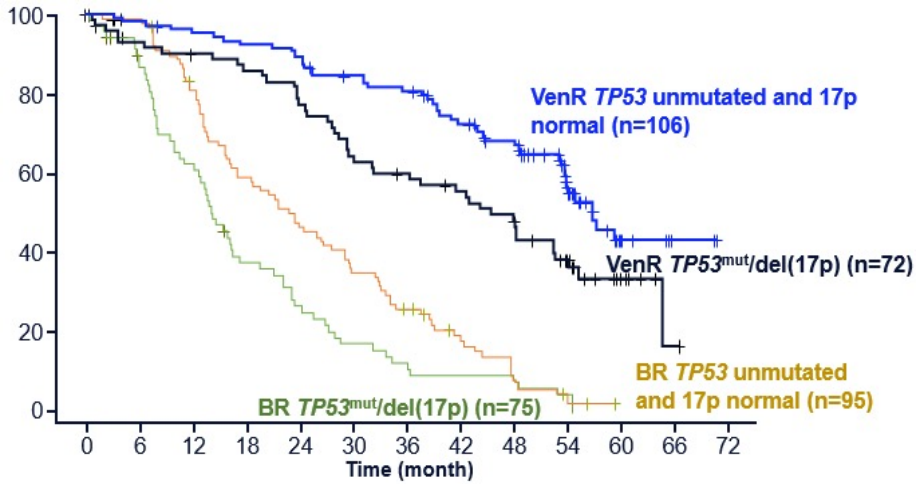
MURANO TRIAL: IMPACT OF IGHV MUTATIONAL STATUS AND *TP53* DISRUPTION ON PFS

PFS by IGHV mutational status



Median PFS, months	VenR	BR	HR (95% CI)
Unmutated *IGHV*	52.2	15.7	0.19 (0.13–0.26)
Mutated *IGHV*	NE	24.2	0.14 (0.07–0.26)

PFS by *TP53* mutation and/or del(17p) status (FISH)

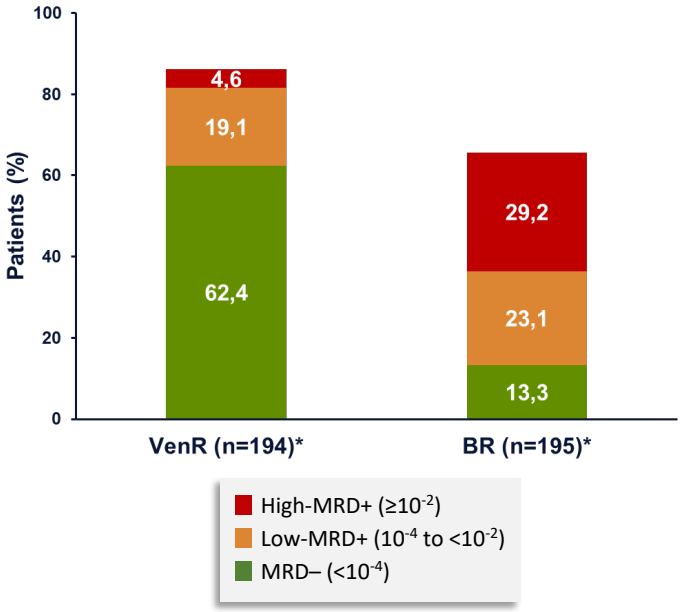


Median PFS, months	VenR	BR	HR (95% CI)
No *TP53*^{mut} or del(17p)	56.6	22.9	0.18 (0.12–0.26)
TP53^{mut} and/or del(17p)	45.3	14.2	0.26 (0.17–0.38)

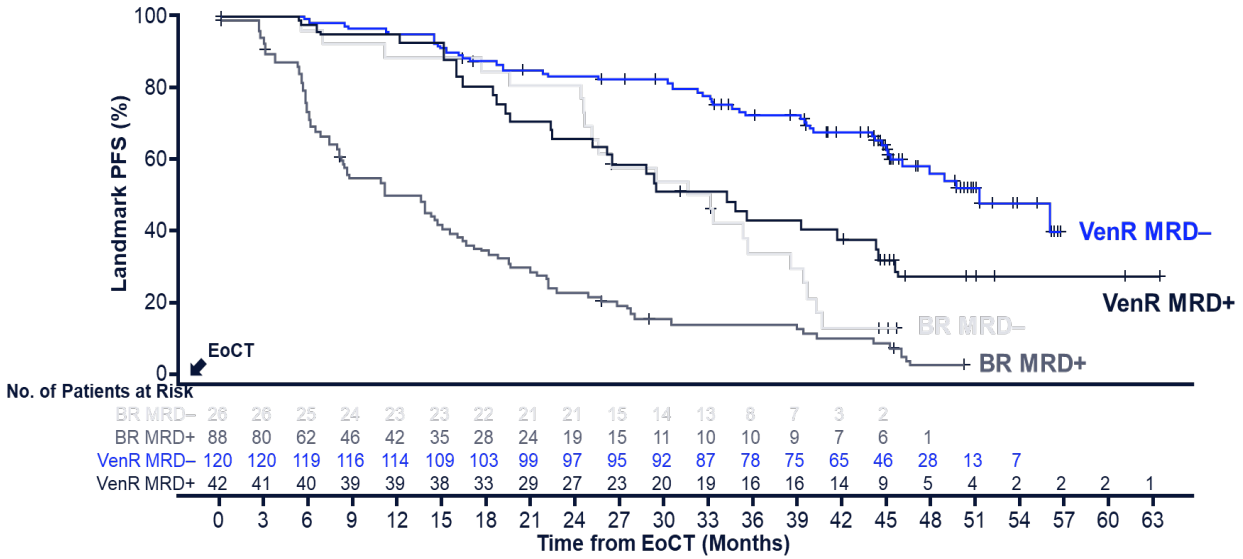
Harrup RA, *et al.* ASH 2020;

MURANO: 59 months follow-up: MRD and PFS by MRD

MRD Status at EoCT



Landmark PFS Analyses Based on PB MRD Status at EoCT in Patients Completing 2 Years of VenR

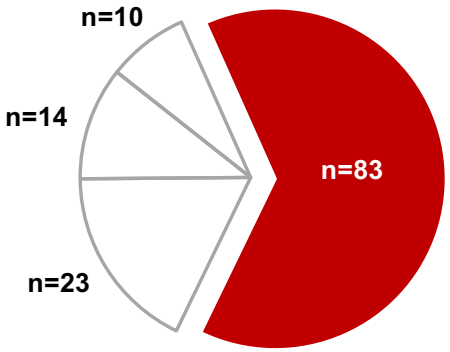


Patients in the VenR arm with uMRD at EOT::
61.3% PFS rate at 36 months post-EOT.

Kater AP, *et al. J Clin Oncol* 2019; **37:**269–277.

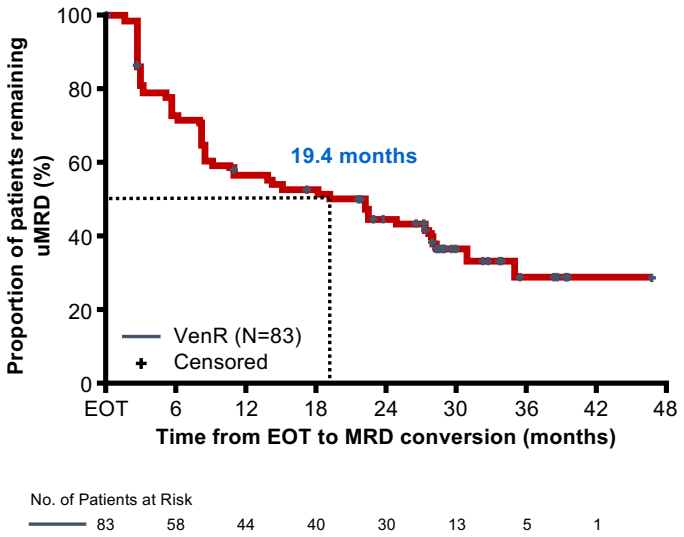
MURANO: DELAY BETWEEN MRD CONVERSION AND CLINICAL PD

MRD status at EOT (N=130)



Time from EOT to MRD Conversion

Median 19.4 months
(95% CI 8.7; 28.3)

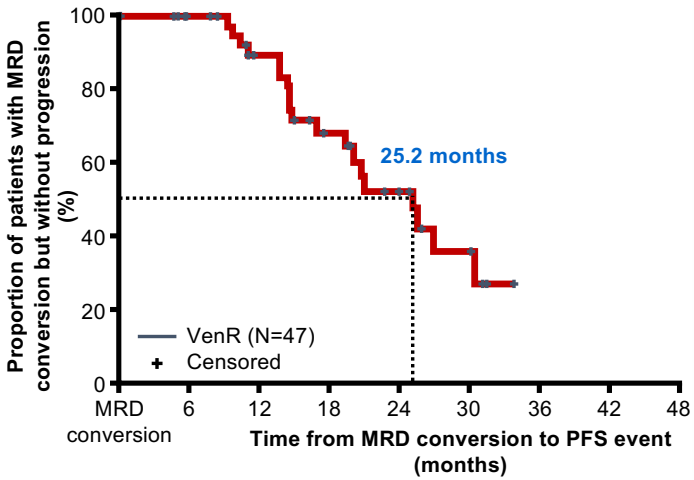


No. of Patients at Risk

VenR (N=83)	83	58	44	40	30	13	5	1

Time from MRD conversion to PD*

Median 25.2 months
(95% CI 19.4; 30.4)



No. of Patients at Risk

VenR (N=47)	47	40	30	19	11	6

N=130; uMRD <1 CLL cell/10,000 leukocytes
*Investigator-assessed PD according to International Workshop on Chronic Lymphocytic Leukemia (iwCLL) criteria

Kater AP, et al. ASH 2020

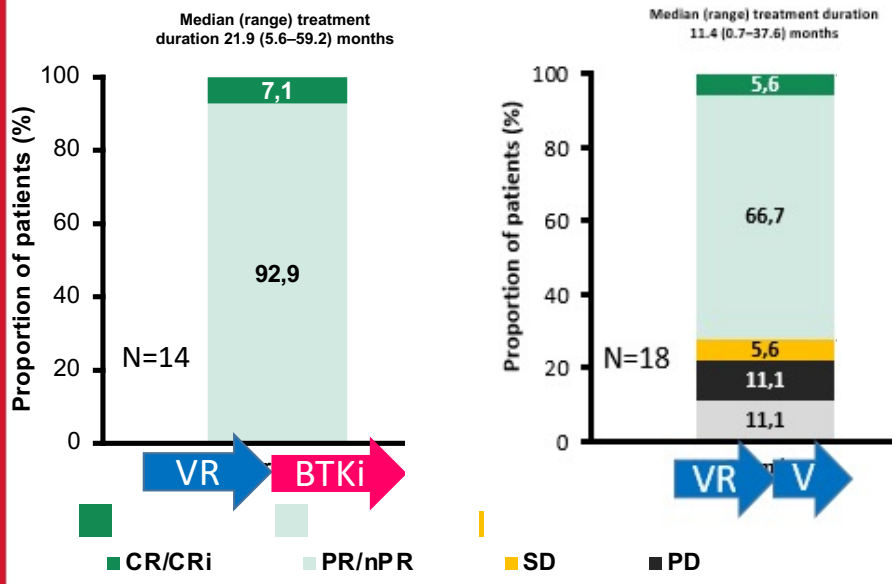
Subsequent Targeted Therapies, in R/R CLL Previously Treated With Venetoclax

Murano trial: prior treatment VenR

Subsequent therapy (ITT):
BTKi-based
(patients BTK naïve)
Best ORR
100%

Subsequent therapy (ITT):
venetoclax

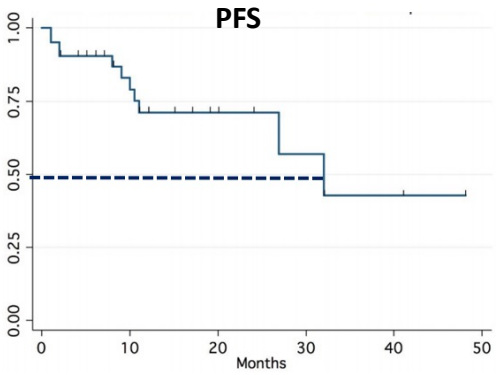
Best ORR
72.2%



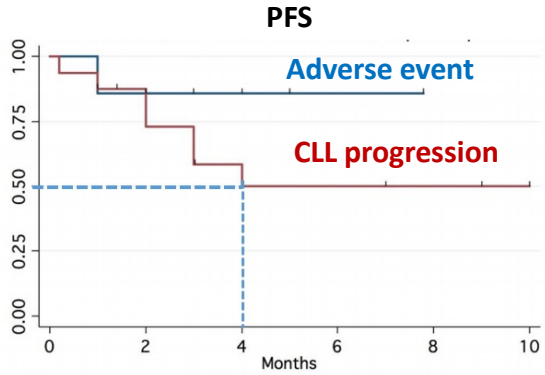
Harrup et al., ASH 2020

Multicentre study (326 patients): prior treatment Ven±R

BTKi naïve patients



BTKi exposed patients



Mato et al. Clin Cancer Res 2020

Grazie!

Novità dal Meeting della Società Americana di Ematologia

Genova, 17-18-19 febbraio 2022

TRANSCEND CLL 004: liso-cel CAR T-cell therapy (Lisocabtagene Maraleucel) for patients with R/R CLL/SLL

Monotherapy Cohort

Patients with R/R CLL/SLL; either standard-risk (≥3 prior tx failed) or high-risk disease (≥2 prior tx failed); ineligible for BTKi or prior BTKi failure; ECOG PS 0/1

Age, 63 yrs
High Risk features, 83%,
Median prior Tx, 4
Prior ibrutinib, 100%
Prior venetoclax, 65%
Prior IBR-Ven, 65%

Lymphodepletion*

Fludarabine 30 mg/m^2 +
Cytarabine 300 mg/m^2 x 3 days

→

Dose Escalation

Phase I Monotherapy
Liso-cel DL1 or DL2†
(n = 23)

→

Dose Expansion (mTPI-2 Design)
28-Day DLT Period

Phase II Monotherapy
Liso-cel DL2†

Liso-cel successfully manufactured for 23/24 patients (96%)

100 x 10^6 CAR+T cells selected as the recommended dose

Combination Cohort

Patients with R/R CLL/SLL; either progressing on ibrutinib at enrollment with high-risk features and did not attain CR on ibrutinib for ≥6 mo, *BTK* or *PLCγ2* mutations, or prior ibrutinib without contraindications to reinitiating ibrutinib

Age, 60 yrs
High Risk features, 95%,
Median prior Tx, 4
Prior ibrutinib, 100%
Prior venetoclax,53%

Fludarabine 30 mg/m^2 +
Cytarabine 300 mg/m^2 x 3 days

→

Phase I Combination
Liso-cel DL1 or DL2† +
Ibrutinib 420 mg
(n = 19)

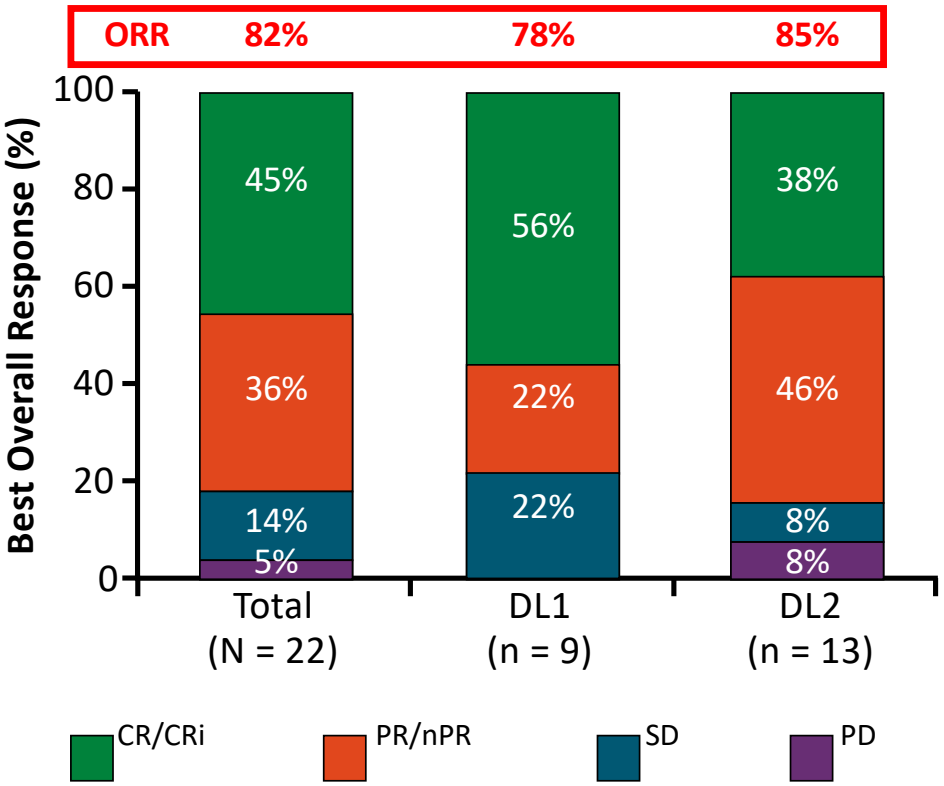
→

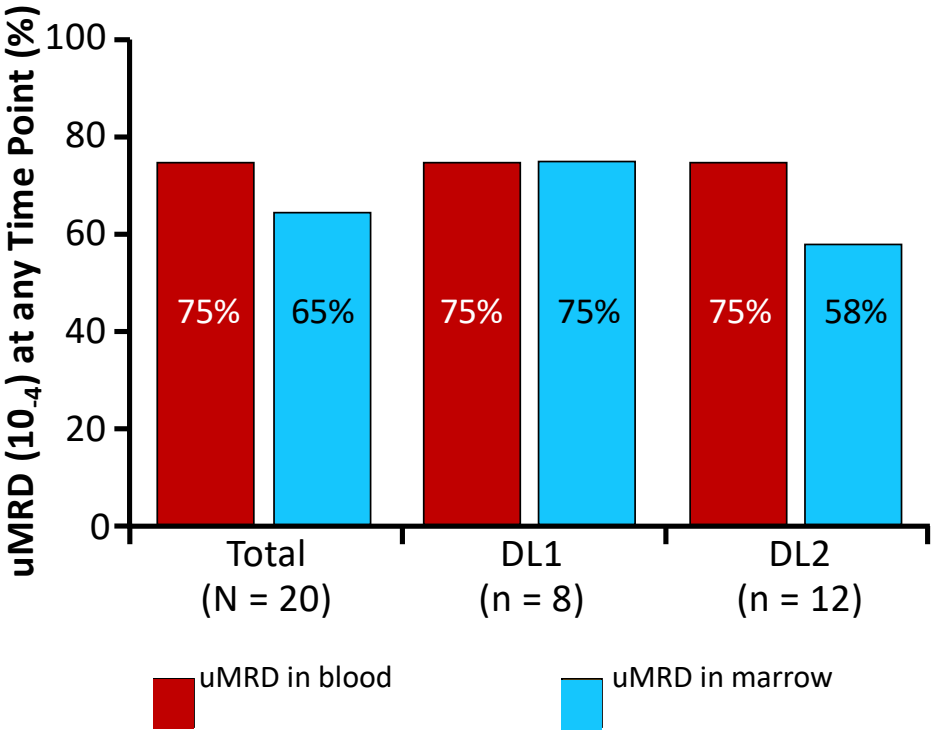
Phase I Combination
Liso-cel DL2† +
Ibrutinib 420 mg

*Leukapheresis at enrollment; bridging therapy permitted during liso-cel manufacturing; measurable disease reconfirmed before lymphodepletion. †DL1: 50 x 10^6 CAR+ T-cells. DL2: 100 x 10^6 CAR+ T-cells.

Siddiqi et al, Blood 2022

TRANSCEND CLL 004 Monotherapy: Efficacy



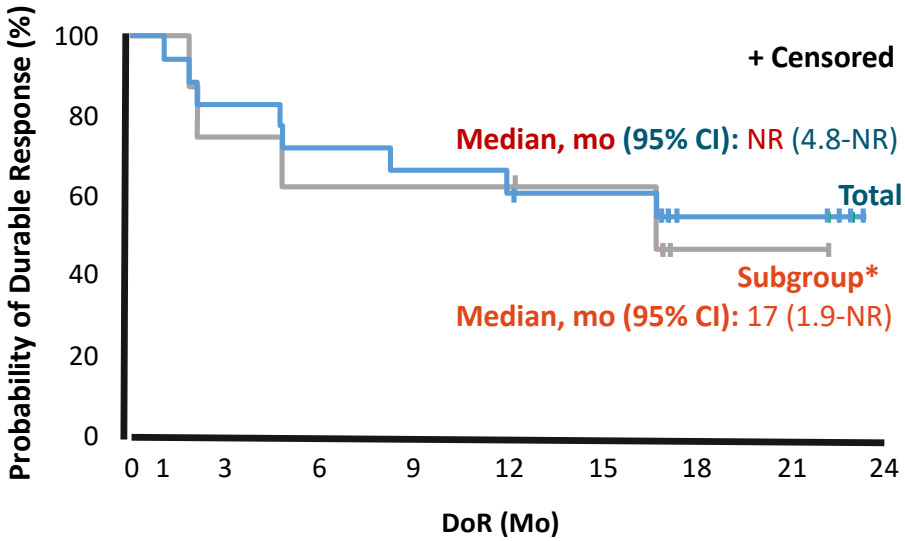


68% of patients achieved a response by day 30 and 6 (27%) experienced deepening of responses over time

Siddiqi et al, Blood 2022

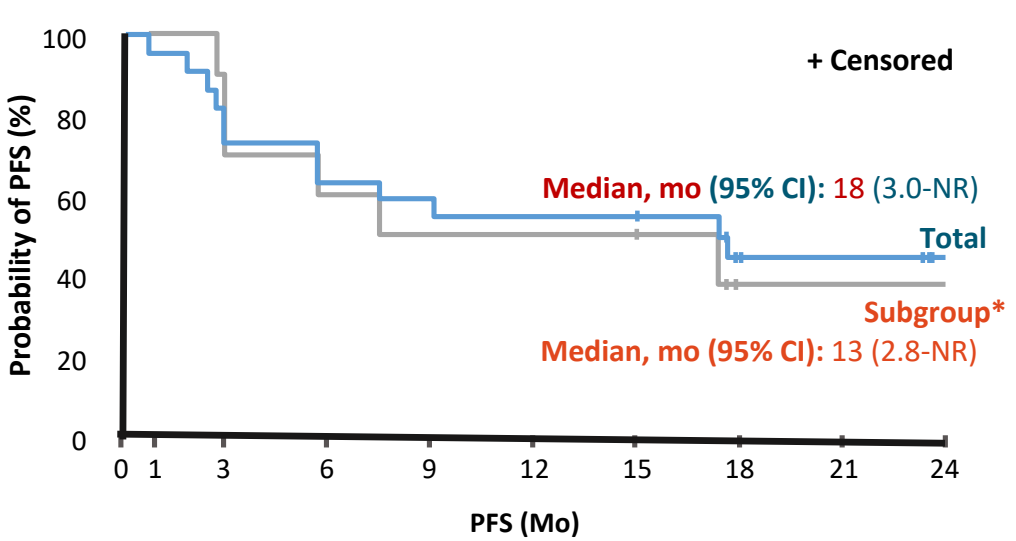
TRANSCEND CLL 004 Monotherapy: DoR and PFS After Median Follow-up of 24 Mo

Duration of Response



Total	18	18	15	13	12	11	10	6	6	0
Subgroup*	8	8	6	5	5	5	4	1	1	0

Progression-Free Survival



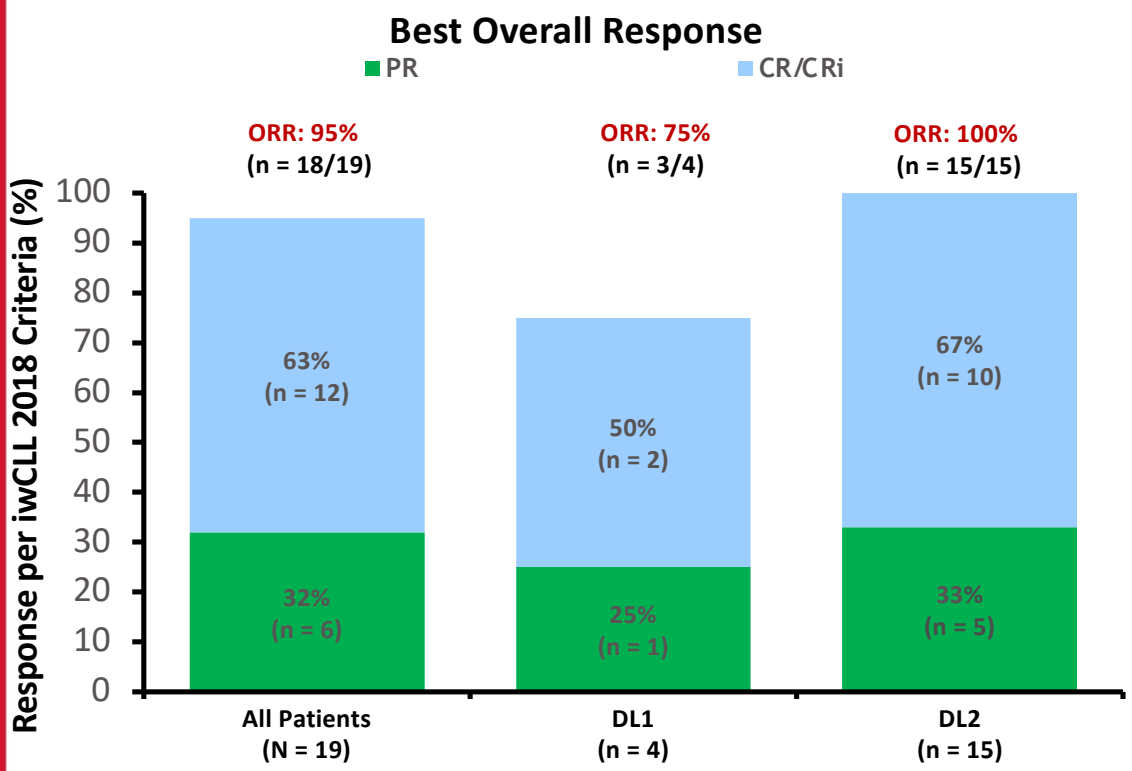
	22	21	18	14	13	12	12	8	6	4
Subgroup*	10	10	9	6	5	5	5	2	1	1

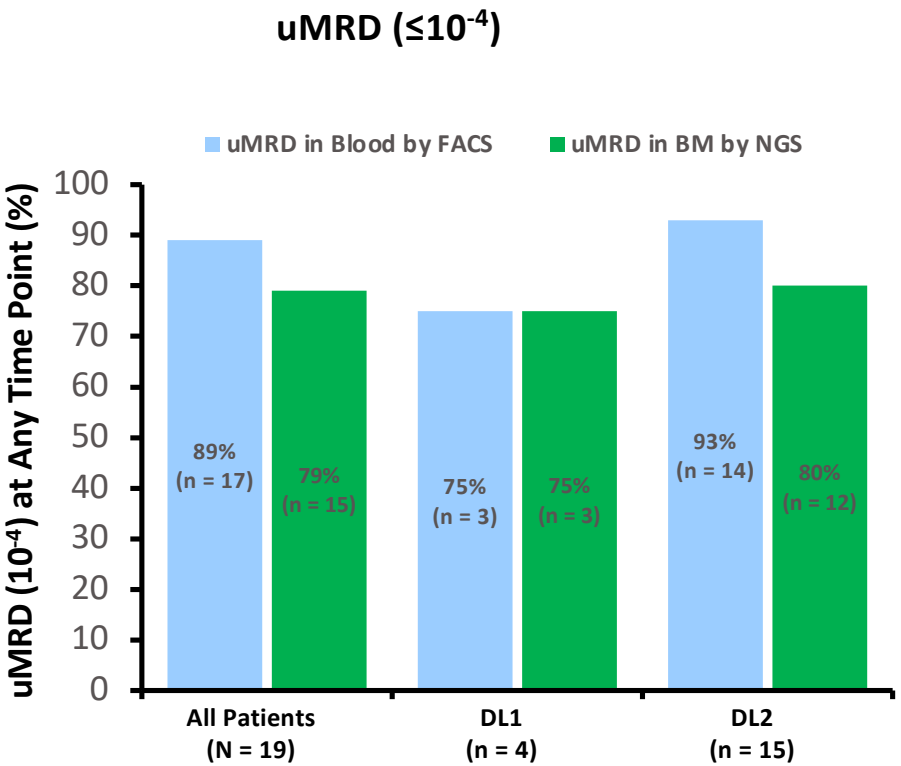
*Defined as those with progressive disease on BTKi and who failed venetoclax due to PD, intolerance, or failure to response after ≥3 mo.

Five of 22 patients (23%) progressed with RT.

Siddiqi et al, Blood 2022

TRANSCEND CLL 004 Combination: Efficacy With Ibrutinib + Liso-cel





- No PD observed during first mo after liso-cel
- All ORs were achieved by Day 30 postinfusion

- 1 patient (DL1) experienced SD for 6 mo and later progressed

Wierda. ASH 2020