Impatto clinico terapeutico: LLC

Paolo Ghia

BOLOGNA

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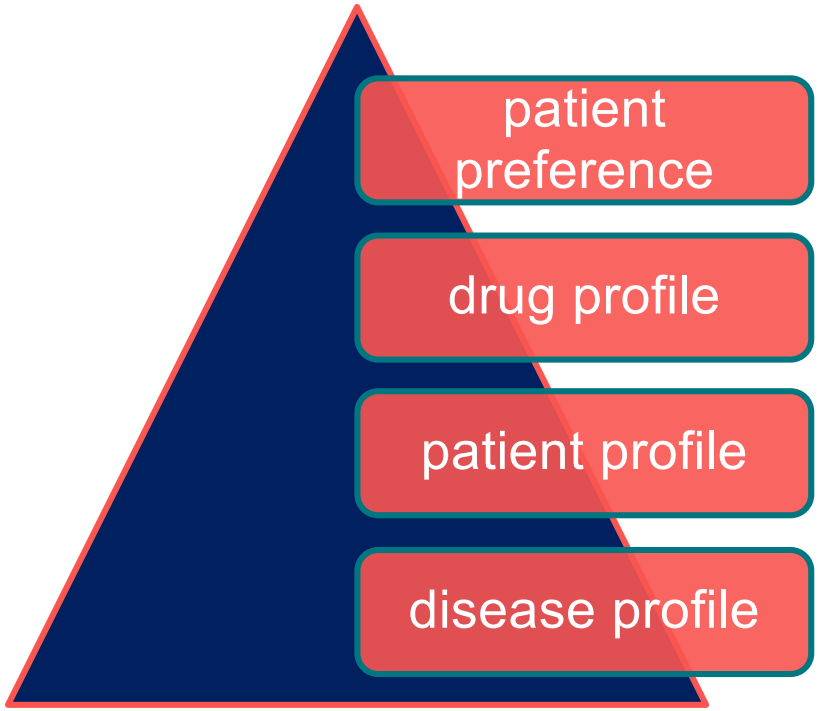
Starhotels Excelsior

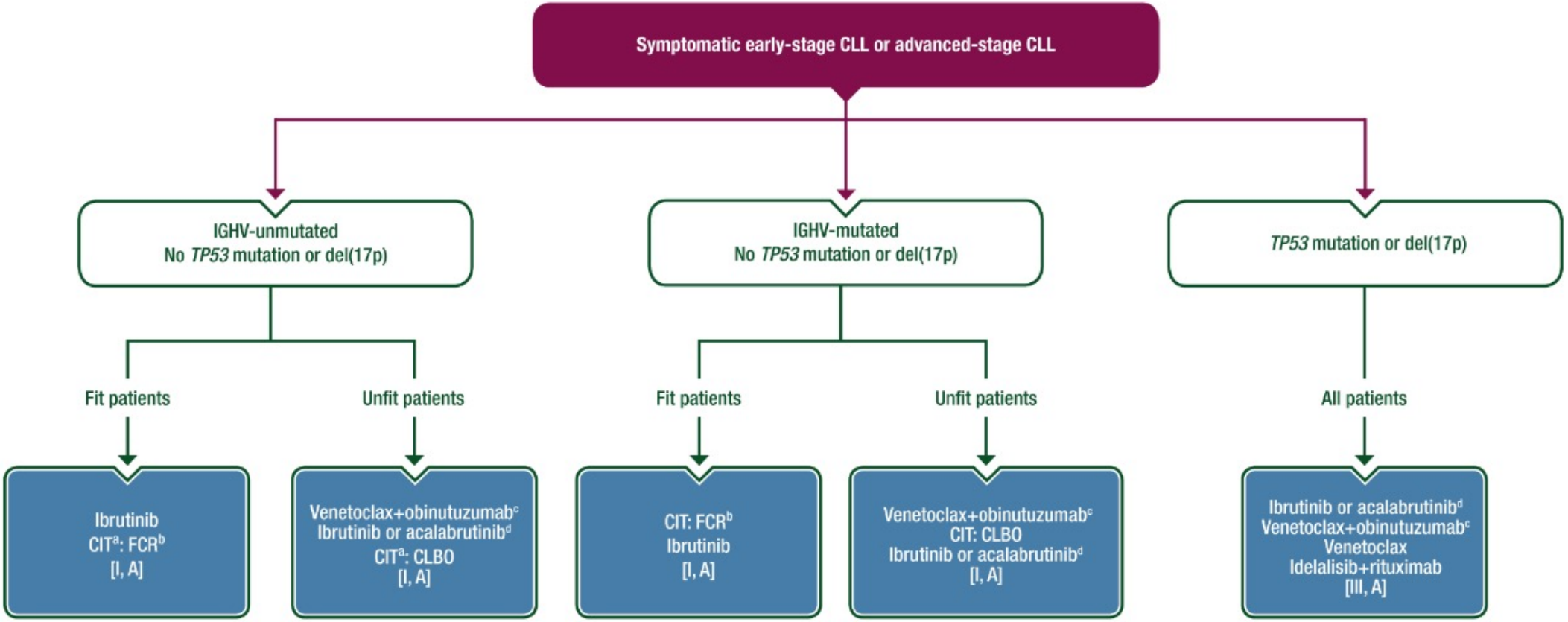
Disclosures of PAOLO GHIA

Company name	Research support	Employee	Consultant	Stockholder	Speakers fees	Advisory board	Other
AstraZeneca	x		x		x	x	
AbbVie	x		x		x	x	
ArQule/MSD			x			x	
BeiGene			x		x	x	
CelGene/Juno/BMS			x			x	
Janssen	x		x		x	x	
Lilly/Loxo			x		x	x	
Sanofi			x			x	
Roche			x			x	

Personalized management in CLL



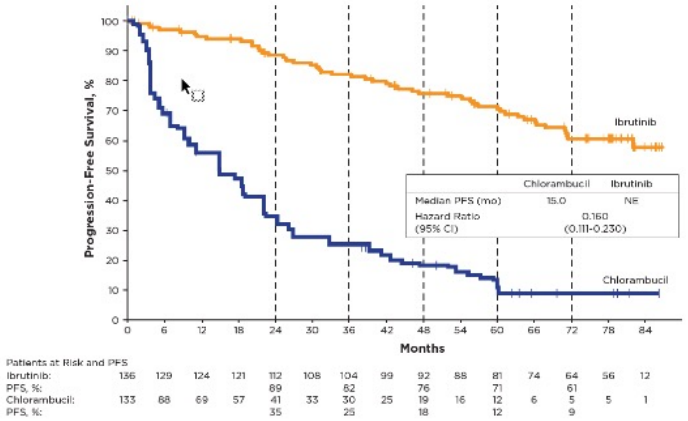
ESMO Clinical Practice: frontline therapy



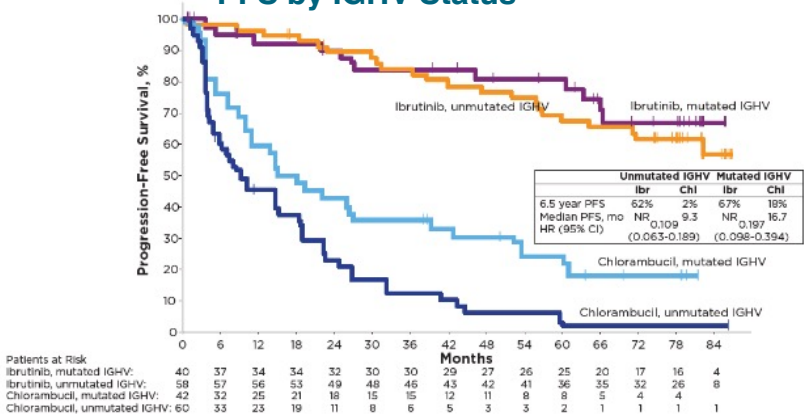
Eichhorst et al., Ann Oncol. 2021 Jan;32(1):23-33

Ph3 RESONATE-2 with up to 7 years of follow-up: 1L ibrutinib

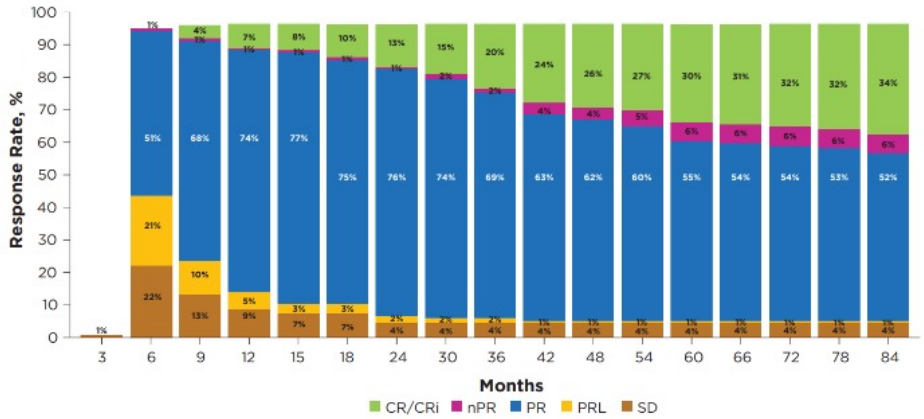
PFS: Ibrutinib vs chlorambucil



PFS by IGHV Status



Response increase over time: CR/CRi 34%



- **Longest follow-up of any Ph3 1L studies of targeted agents**
- **61% of patients are alive and progression-free at 6.5 years. 6.5-year OS: 78%.**
- Ibr benefit similar in pts with mIGHV and uIGHV, and response including CR/CRi continued to deepen over time.
- **Only 16 (12%) pts progressed while receiving ibr.**
- Close to 50% of pts remain on therapy; dose adjustments effectively managed most AEs

Median Follow-up: 74.9 months

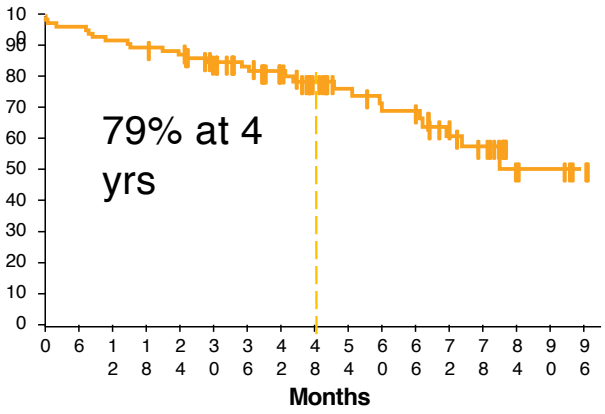
Ghia et al., EHA 2021; EP636 (poster presentation)

Efficacy of First-Line Ibrutinib for CLL With *TP53* Aberrations

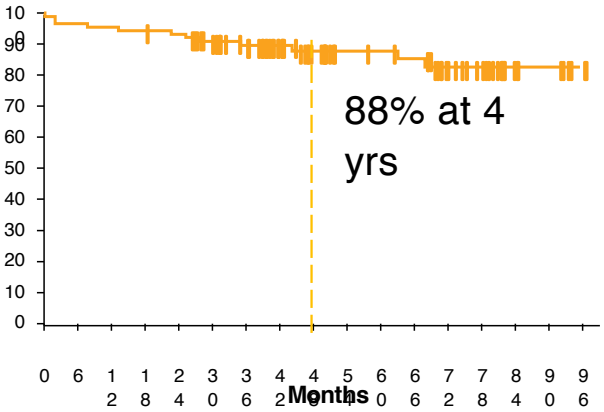
Pooled analysis: 4-year follow-up

	PCYC-1122e (NIH study)	RESONATE-2	iLLUMINATE	ECOG1912
N	34	11	18	26
Regimen	Ibr	Ibr	Ibr + Obinu	Ibr + Ritux
Patients	del(17p)/ *TP53*mut	*TP53*mut	del(17p)/ *TP53*mut	*TP53*mut

Progression-free Survival

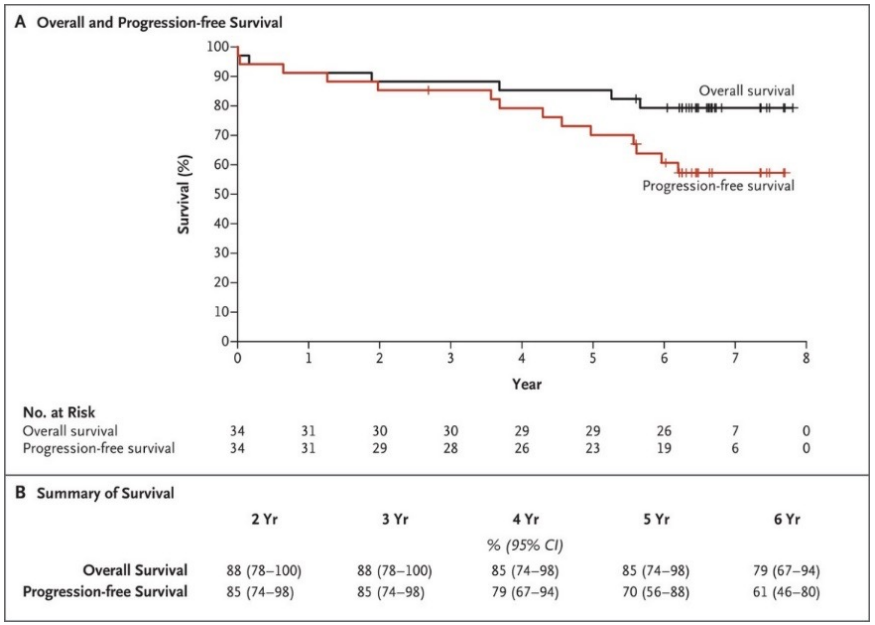


Overall Survival



Allan J, et al., Presented at ASH 2020. #2219

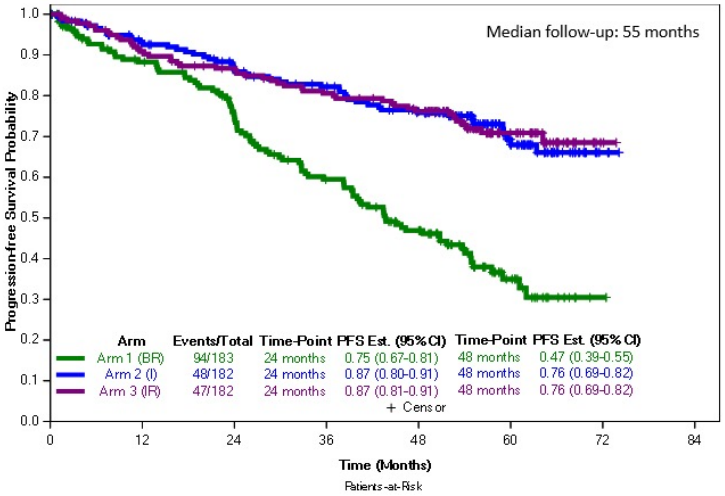
Phase 2 NIH study



IE Ahn et al. N Engl J Med 2020;383:498-500

Alliance A041202 : ibrutinib-based regimens vs bendamustine+R

PFS



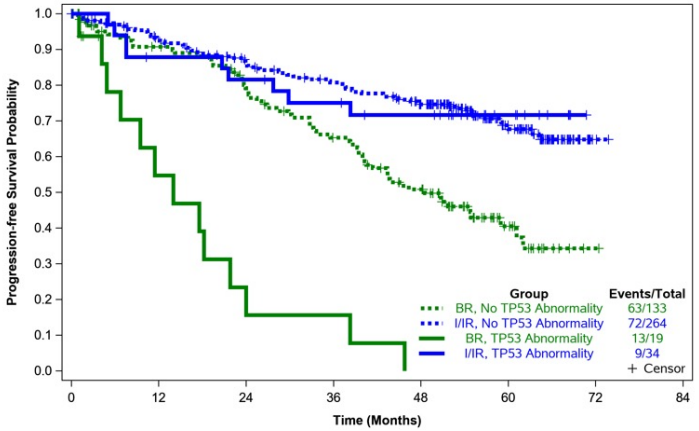
Pairwise Comparisons

I vs BR:
Hazard Ratio 0.36
95% CI: 0.26-0.52
P <0.0001

IR vs BR:
Hazard Ratio 0.36
95% CI: 0.25-0.51
P <0.0001

IR vs I:
Hazard Ratio 0.99
95% CI: 0.66-1.48
P = 0.96

PFS: *TP53* abnormalities



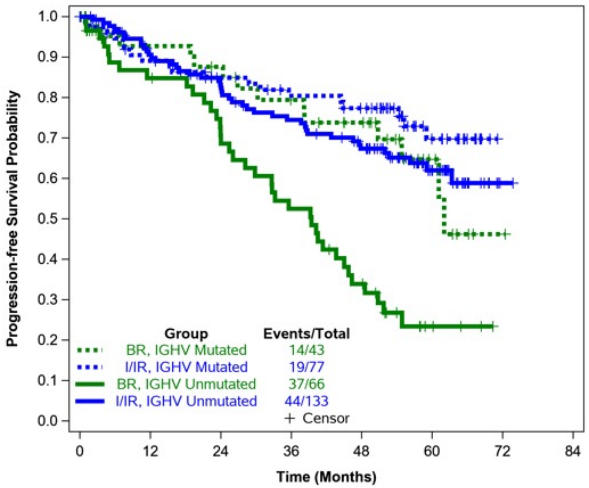
Treatment Effect I/IR vs BR

No *TP53* Abn
Hazard Ratio 0.39
95% CI: 0.27-0.55

TP53 Abn
Hazard Ratio 0.07
95% CI: 0.03-0.18

Interaction P = 0.0006

PFS: IGHV status

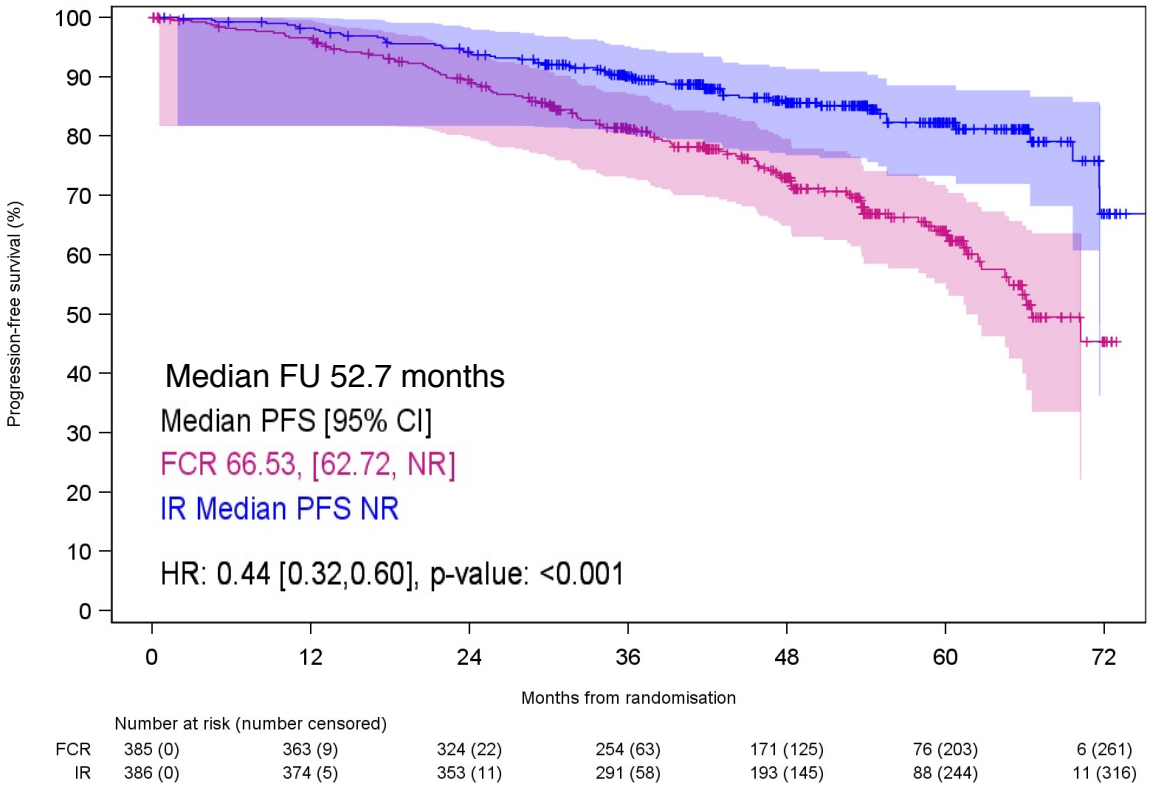


Third planned interim analysis of Arms 2 and 3 vs Arm 1; second planned interim analysis of Arm 3 vs Arm 2
Median follow-up = 55 months

Woyach et al., ASH 2021; abstract 639

NCRI FLAIR Trial: Ibrutinib + R vs FCR

Primary endpoint: PFS



IWCLL Response 3-months post-treatment with FCR/R

	FCR (n=385)	IR (n=386)
CR	233 (60.5%)	81 (21.0%)
PR	106 (27.6%)	271 (70.2%)
SD/PD/NR	46 (11.9%)	34 (8.8%)

Proportion of participants with MRD negativity* in the bone marrow at 3-months post-treatment with FCR/R

	FCR (n=385)	IR (n=386)
MRD Negative	213 (55.3%)	15 (3.9%)
MRD Positive	140 (36.4%)	357 (92.5%)
N/A	32 (8.3%)	14 (3.6%)

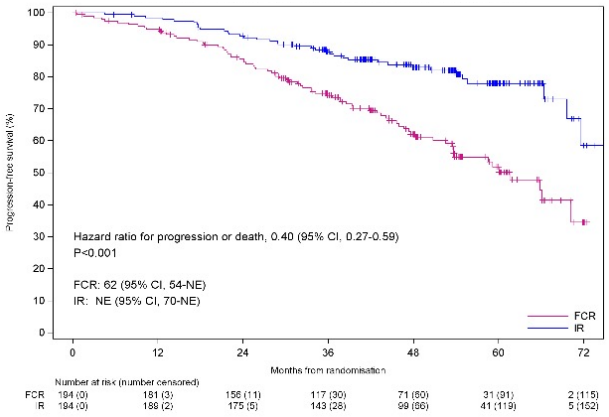
***, MRD flow cytometry <1 CLL cell/10,000 (IWCLL criteria)**

A greater percentage of participants in the FCR arm became MRD negative in the bone marrow 3-months post-treatment compared to the IR arm (55.3% vs 3.9%)

Hillmen et al., ASH 2021; abstract 642

NCRI FLAIR Trial: Ibrutinib + R vs FCR

IGHV unmutated excl. Subset 2 CLL (n=388)



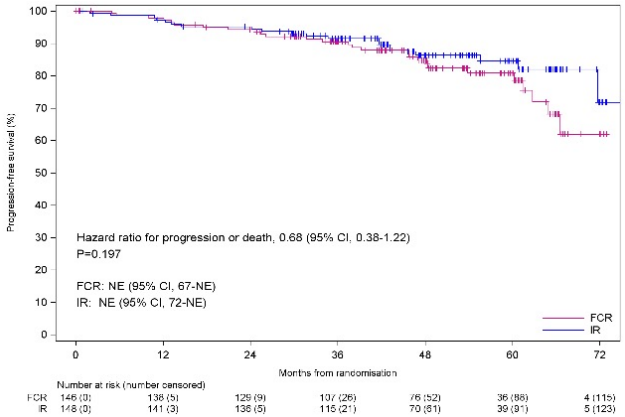
PFS by IGHV mutation status

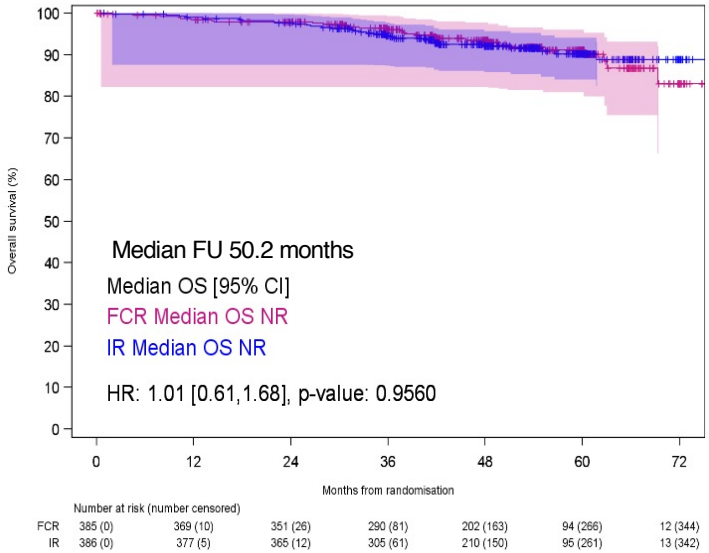
Stereotype Subset 2: n=46 (FCR 20; IR 26) →
HR for PD or death 0.32 (95% CI, 0.06-1.76), p=0.191

Deaths in FCR arm were predominantly secondary haematological malignancies, Richter's transformation and infections.

Deaths in IR arm were predominantly CV-related and non-haematological malignancies.

IGHV mutated CLL excl. Subset 2 (n=294)





Cause of death * *, Deaths at any time in FU	FCR (n=29)	IR (n=30)
CLL	4	3
Non-haematological malignancy	4	7
AML/MDS	3	0
ALL	1	0
Richters transformation	3	1
Infections (non-COVID)	6	4
COVID-19	3	3
Haemorrhage	1	2
Cardiac	2	9
Other	2	1

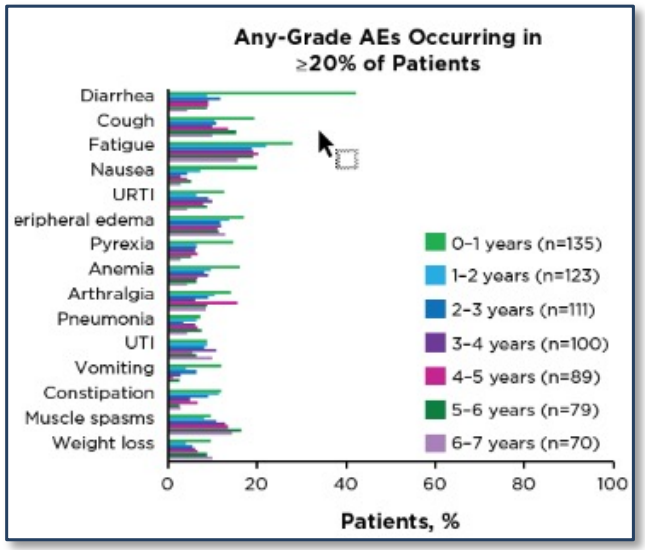
Treatment after progression

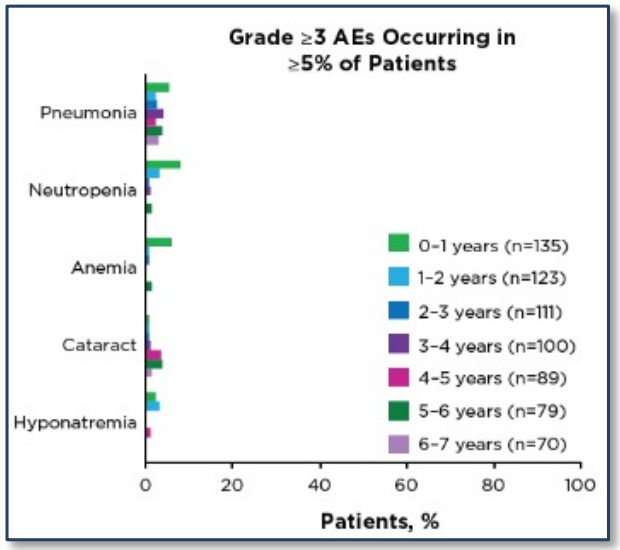
	FCR (n=56)	IR (n=19)
Therapy for Richter's transformation or Hodgkin's		
CHOP-R (5) or ABVD (1)	4	2
Therapy for relapsed CLL		
BTKi	38	0
Idelalisib + R	1	1
Venetoclax + R	8	5
CIT (FCR/BR/ChIR)	4	10
Rituximab	1	1
Targeted therapy for CLL	47/52 (90%)	6/17 (35%)

Hillmen et al., ASH 2021; abstract 642

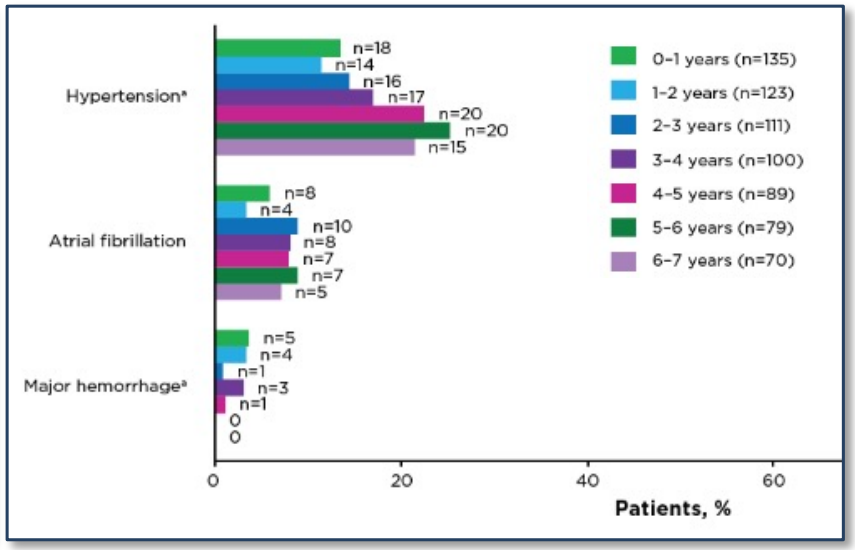
RESONATE-2: AEs with Up to 7 Years of Follow-up

Prevalence of most frequent AEs over time in ibrutinib-treated patients





AEs of clinical interest over time in patients treated with ibrutinib



- 66/79 patients (84%) had an AE that had a complete resolution following a dose hold of at least 7 days
- 31 patients (23%) experienced AEs leading to dose reductions.
  - AEs occurring in >1 patient were thrombocytopenia (n=3), and anemia, arthralgia, diarrhea, fatigue, and palpitations (n=2, each).
- At current follow-up (up to 7 years), 31 patients (23%) experienced AEs as the primary cause of ibrutinib discontinuation.
  - AEs occurring in >1 patient were atrial fibrillation (n=5), pneumonia (n=3), and palpitations (n=2).

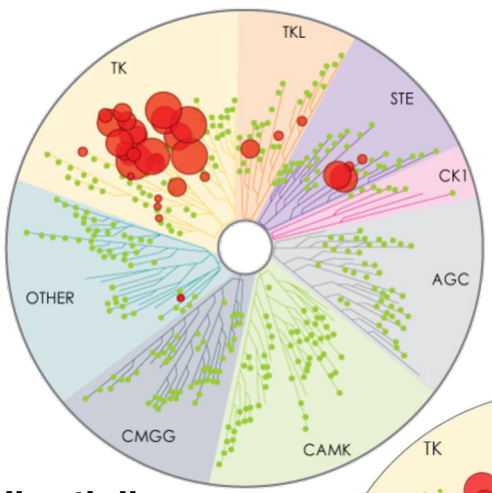
Ghia et al., EHA 2021; EP636 (poster presentation)

Kinase Selectivity of BTK Inhibitors

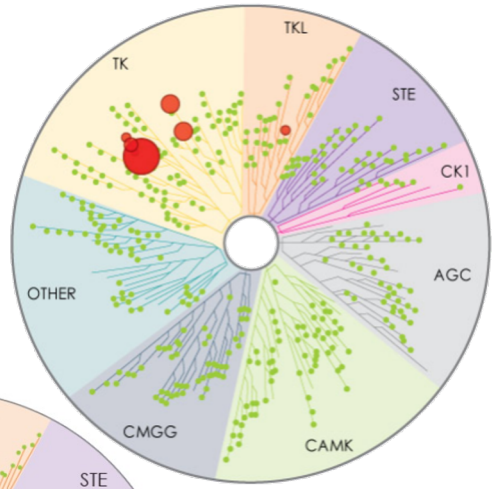
Kinase	Ibrutinib	Acalabrutinib	Zanubrutinib
	IC_{50}/EC_{50} (nM)		
BTK	1.5	5.1	0.5
TEC	10	126	44
ITK	4.9	>1000	50
BMX	0.8	46	1.4
EGFR	5.3	>1000	21
ERBB4	3.4	16	6.9
JAK3	32	>1000	1377
BLK	0.1	>1000	2.5

Kinase Selectivity Profiling at 1 μmol/L (in vitro)

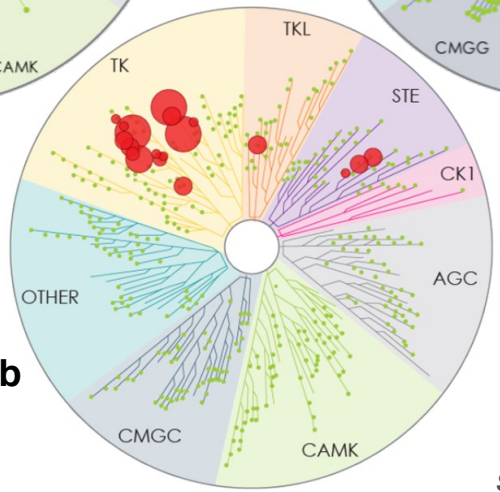
Larger red circles represent stronger inhibition



Ibrutinib



Acalabrutinib



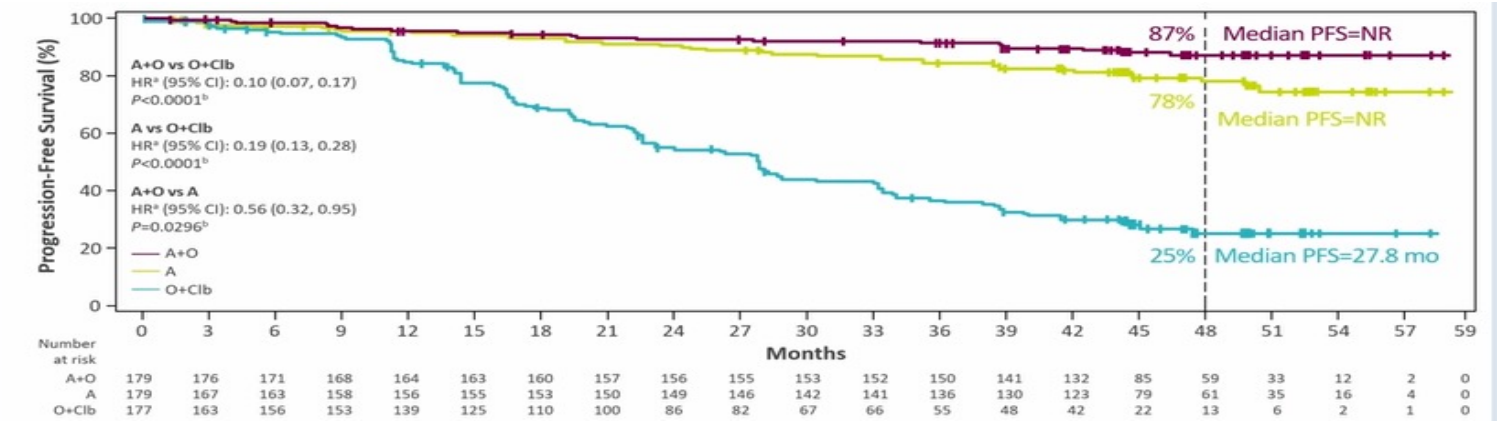
Zanubrutinib

Sharman et al., EHA 2021; S148 (oral presentation)

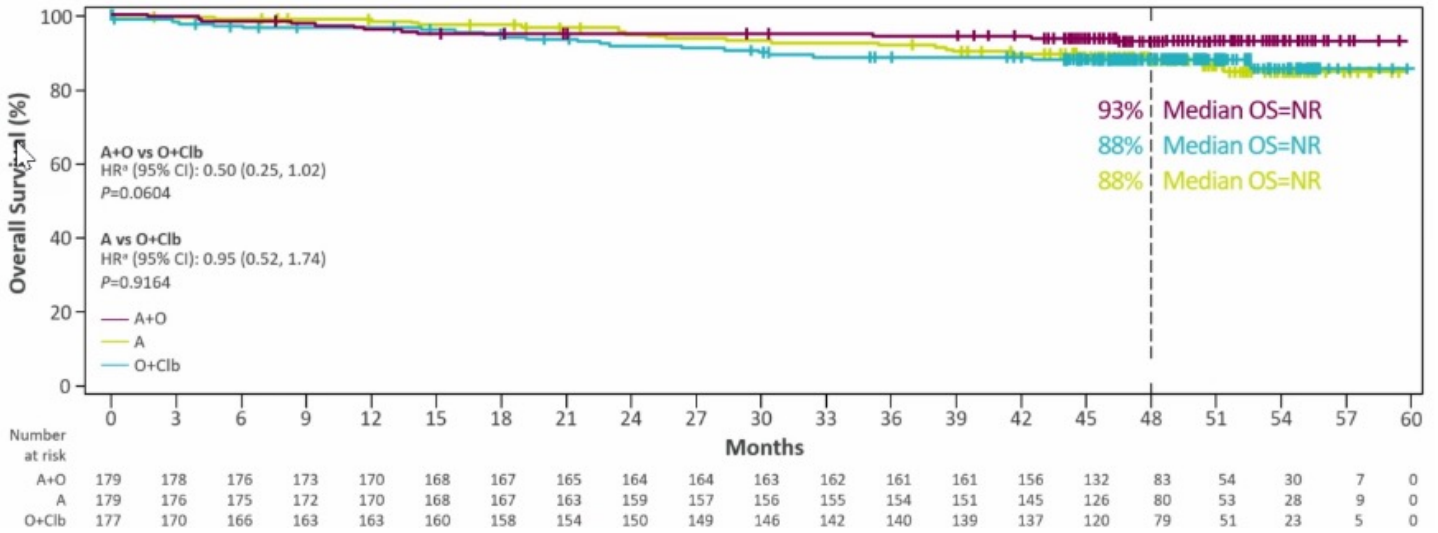
Slide credit: clinicaloptions.com

Phase 3 ELEVATE TN Study: acalabrutinib ± obinutuzumab

Investigator assessed PFS

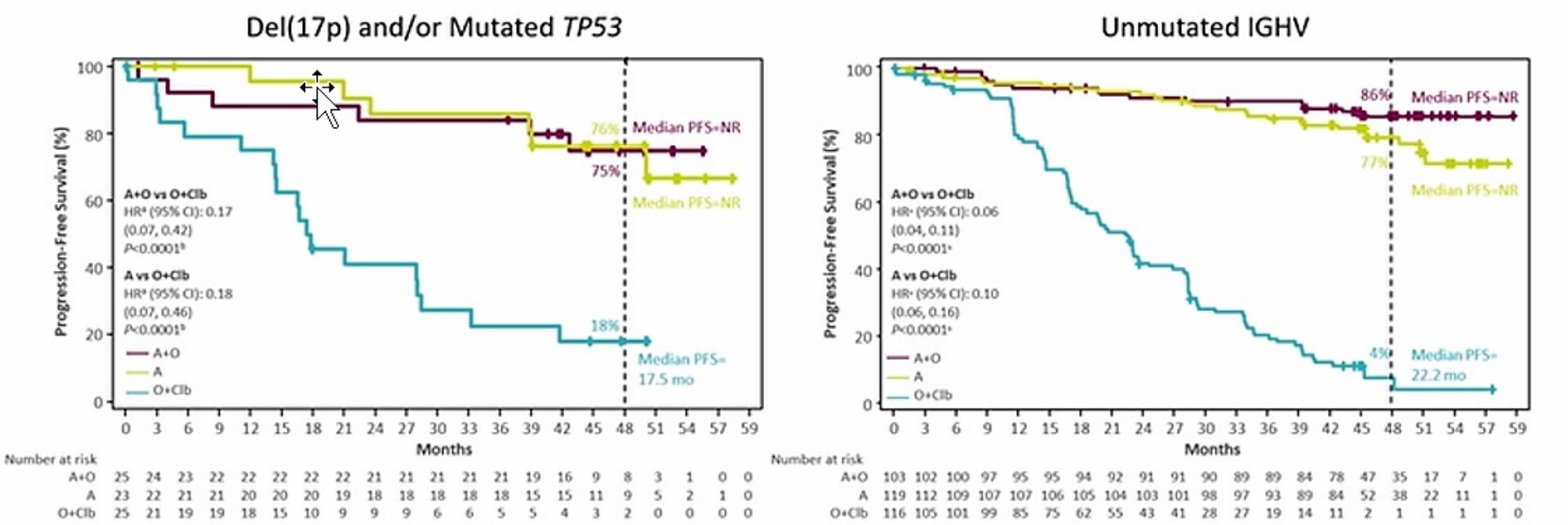


Overall Survival



Sharman et al., EHA 2021; S148 (oral presentation)

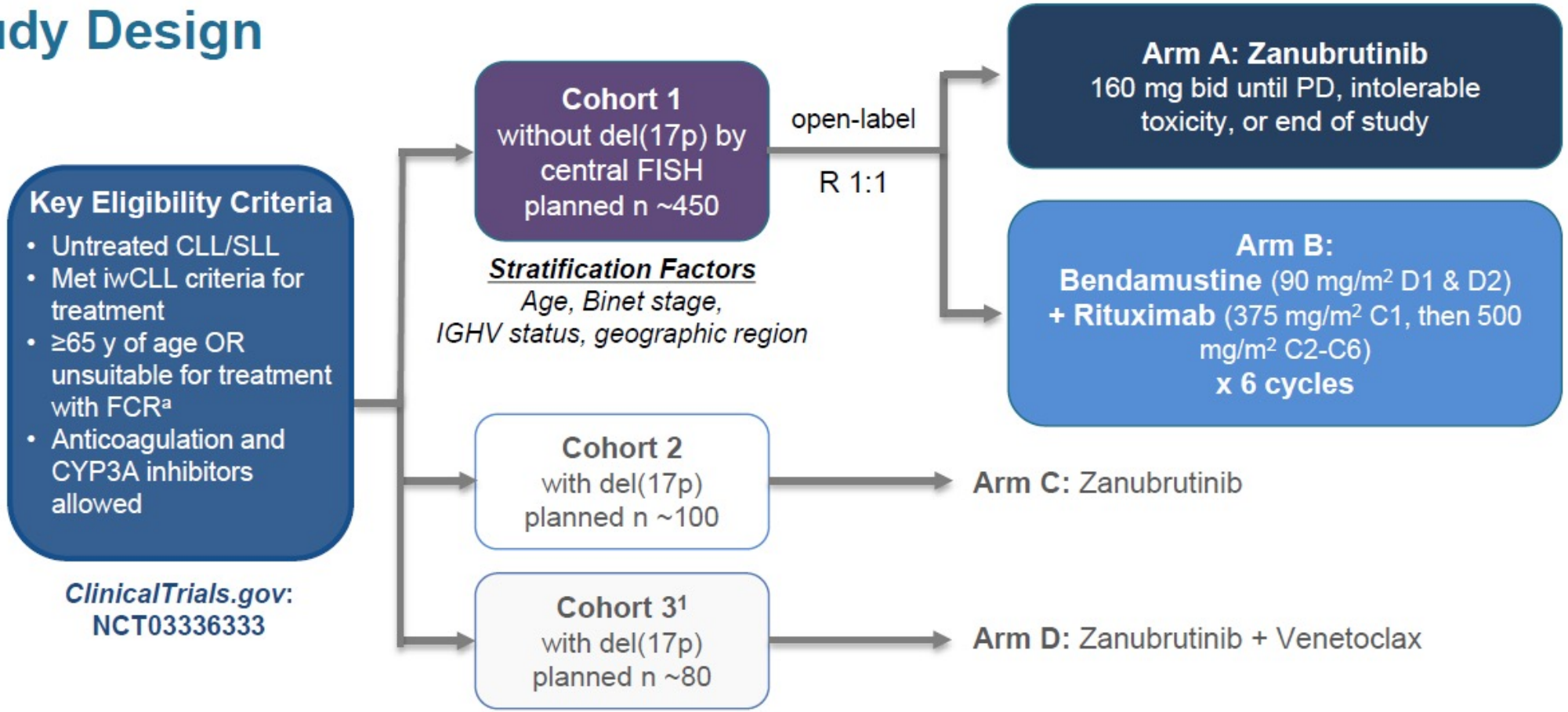
ELEVATE TN: PFS according to *TP53* and IGHV status



Sharman et al., EHA 2021; S148 (oral presentation)

SEQUOIA (BGB-3111-304): Zanubrutinib vs BR in TN CLL

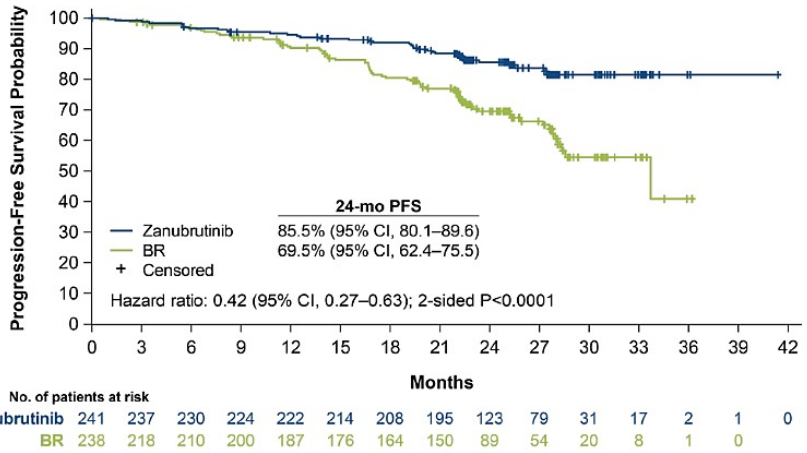
Study Design



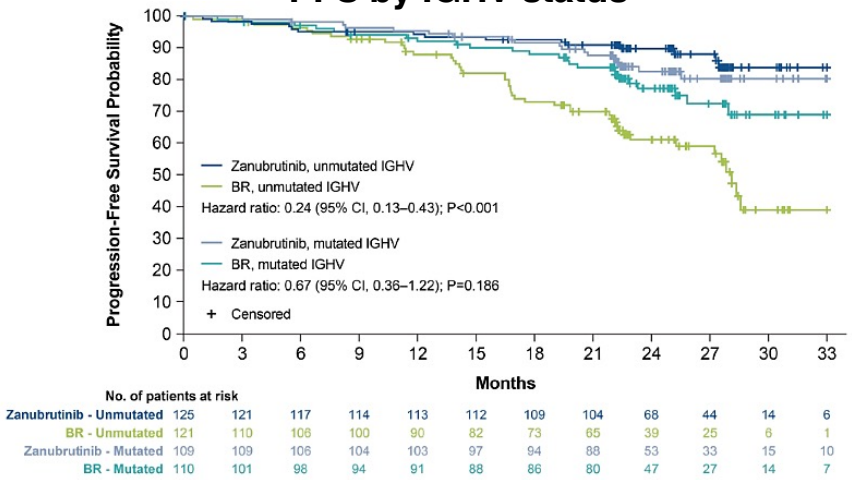
Tam et al., ASH 2021; abstract 396

SEQUOIA (BGB-3111-304)

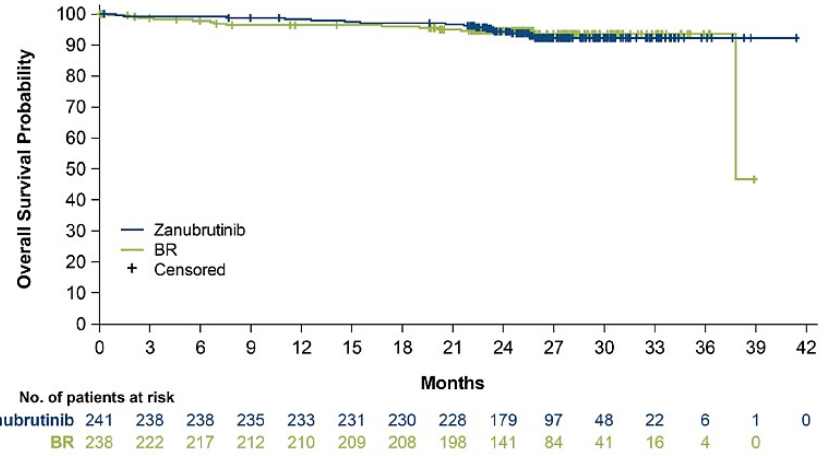
PFS



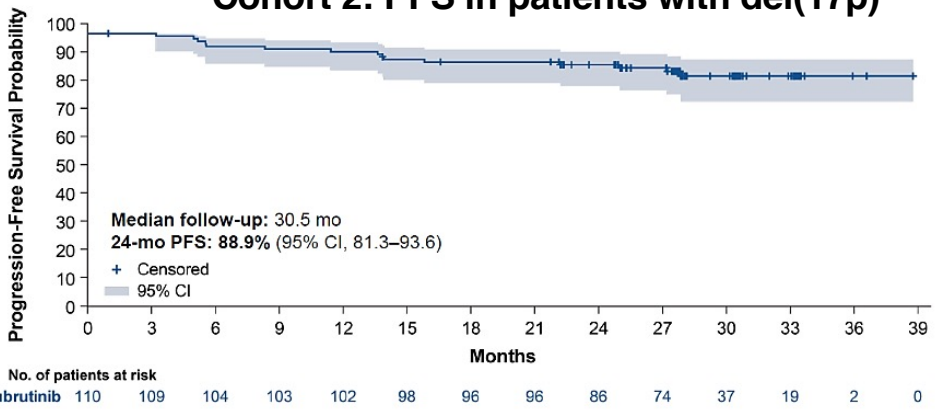
PFS by IGHV status



OS



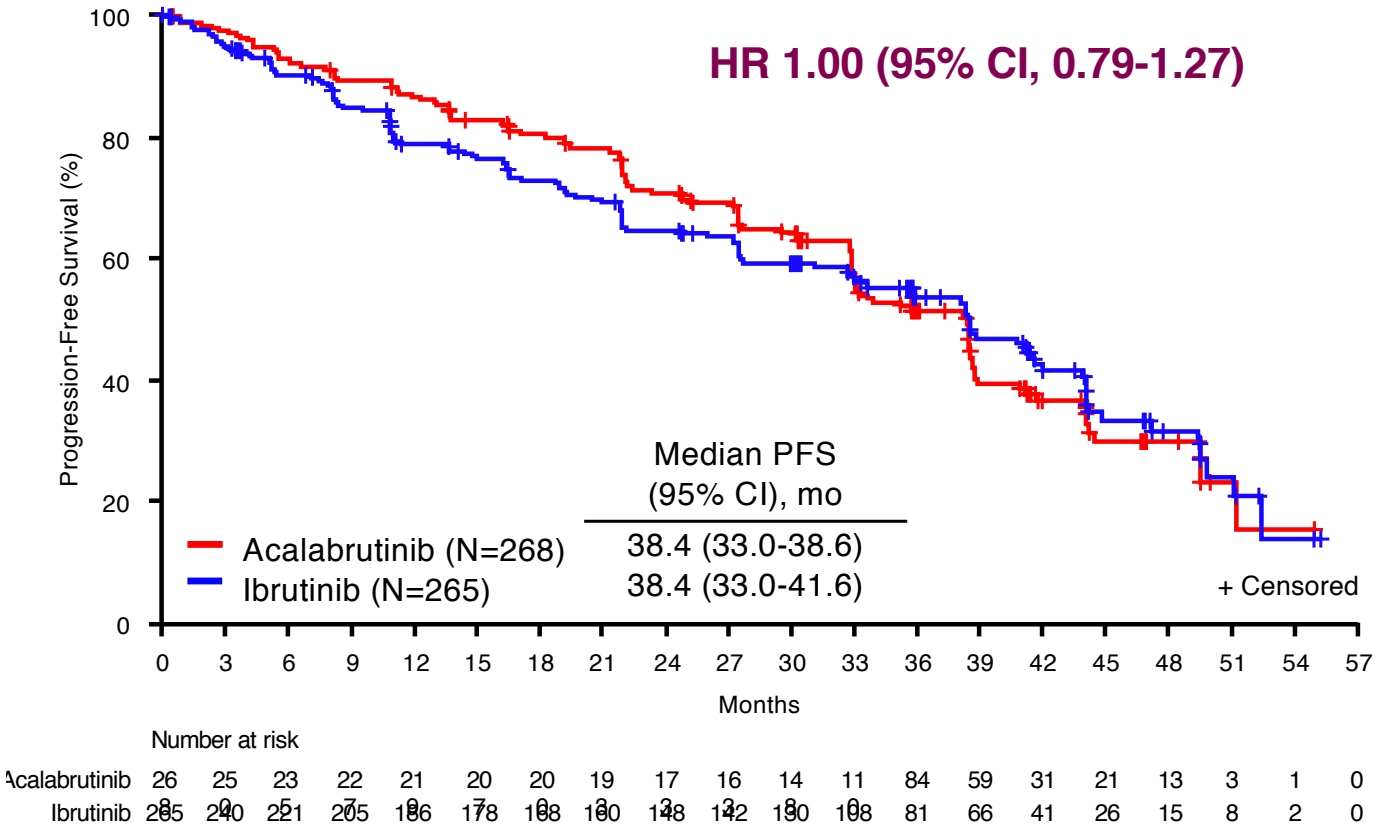
Cohort 2: PFS in patients with del(17p)



Tam et al., ASH 2021; abstract 396

Phase 3 ELEVATE RR study: Ibrutinib vs acalabrutinib

IRC-Assessed PFS



HR, hazard ratio; IRC, independent review committee; PFS, progression-free survival.

Median follow-up 41 months

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

Byrd J et al, Oral presentation ASCO 2021

Phase 3 ELEVATE RR study: Ibrutinib vs acalabrutinib

Events, n (%)	Any grade		Grade ≥3	
	Acalabrutinib (n=266)	Ibrutinib (n=263)	Acalabrutinib (n=266)	Ibrutinib (n=263)
Diarrhea[a,b]	92 (34.6)	**121 (46.0)**	3 (1.1)	**13 (4.9)**
Headache[a,b]	**92 (34.6)**	53 (20.2)	**4 (1.5)**	0
Cough[a]	**77 (28.9)**	56 (21.3)	2 (0.8)	1 (0.4)
URTI	71 (26.7)	65 (24.7)	5 (1.9)	1 (0.4)
Neutropenia	56 (21.1)	65 (24.7)	52 (19.5)	60 (22.8)
Pyrexia	62 (23.3)	50 (19.0)	8 (3.0)	2 (0.8)
Arthralgia[a]	42 (15.8)	**60 (22.8)**	0	2 (0.8)
Hypertension[a,b]	23 (8.6)	**60 (22.8)**	11 (4.1)	**23 (8.7)**
Anemia	58 (21.8)	49 (18.6)	31 (11.7)	34 (12.9)
Fatigue[b]	54 (20.3)	44 (16.7)	**9 (3.4)**	0
Nausea	47 (17.7)	49 (18.6)	0	1 (0.4)
Contusion[a]	31 (11.7)	**48 (18.3)**	0	1 (0.4)
Pneumonia	47 (17.7)	43 (16.3)	28 (10.5)	23 (8.7)
Atrial fibrillation[a]	24 (9.0)	**41 (15.6)**	12 (4.5)	9 (3.4)
Thrombocytopenia	40 (15.0)	35 (13.3)	26 (9.8)	18 (6.8)

Secondary endpoint

Higher incidence in **bold red** for terms with statistical differences.
Among most common AEs above, grade 5 were reported in 5 (1.9%) acalabrutinib patients (pyrexia, n=1; pneumonia, n=4) and 4 (1.5%) ibrutinib patients (URTI, n=1; pneumonia, n=3).
[a]Based on Barnard's exact test, two-sided P-value <0.05 without multiplicity adjustment for any grade events.
[b]Based on Barnard's exact test, two-sided P-value <0.05 without multiplicity adjustment for grade ≥3 events.
Includes AEs reported at ≥15% incidence (any grade) in either arm.
AE, adverse event; URTI, upper respiratory tract infection.

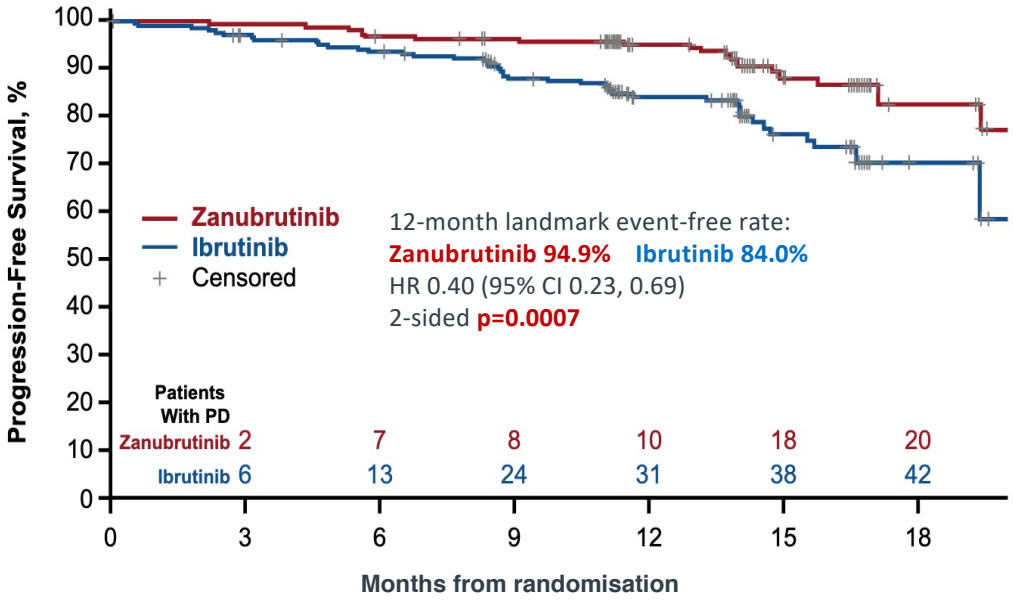
Byrd J et al, Oral presentation ASCO 2021

Phase 3 ALPINE study: Ibrutinib vs zanubrutinib in RR CLL

ORR by investigator assessment

	Zanubrutinib (n=207), n (%)	Ibrutinib (n=208), n (%)
Primary endpoint: ORR (PR+CR)	162 (78.3) 95% CI: 72.0, 83.7	130 (62.5) 95% CI: 55.5, 69.1
	Superiority 2-sided *P*=0.0006 compared with pre-specified alpha of 0.0099	
CR/CRi	4 (1.9)	3 (1.4)
nPR	1 (0.5)	0
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)

PFS by investigator assessment



CR, complete response; CRi, CR with incomplete bone marrow recovery; nPR, nodular partial response; ORR, overall response rate; PD, progressive disease; PFS, progression-free survival; PR, partial response; PR-L, partial response with lymphocytosis; SD, stable disease

Hillmen P, et al. Oral presentation at EHA 2021 (Abstract LB1900)

Phase 3 ALPINE study: 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 2° 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)

AE, adverse events. All events are of any grade unless otherwise specified.
[a] Cardiac disorders leading to treatment discontinuation: zanubrutinib 0 patients and ibrutinib 7 (3.4%) patients.
[b] Includes hemorrhages that were serious or grade ≥3 or CNS hemorrhages of all grades.
[c] Pooled terms including neutropenia, neutrophil count decreased, and febrile neutropenia; thrombocytopenia and platelet count decreased.

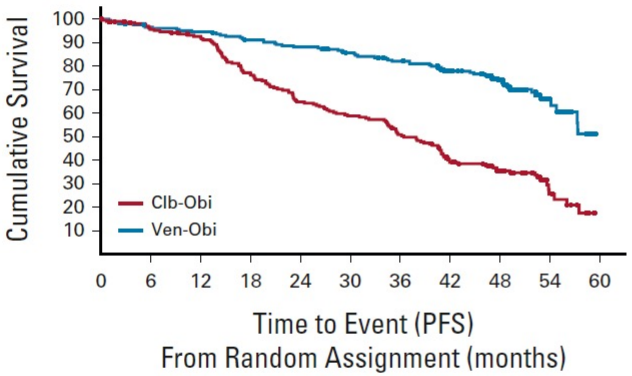
ALPINE study. Hillmen et al. LB1900 EHA 2021

Fixed duration: present and future

CLL14 Phase 3 trial: venetoclax + obinutuzumab[1,2]

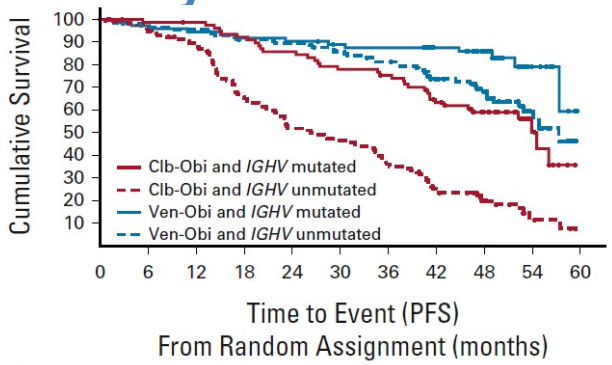
Median observation time = 52.4 months

Overall PFS



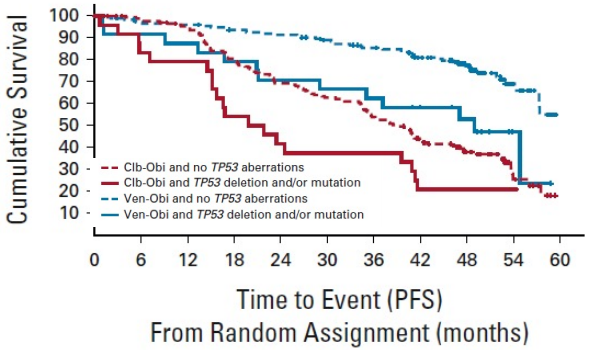
	Median PFS	4-year PFS rate
Ven-Obi	NR	74.0%
Clb-Obi	36.4 months	35.4%
	HR 0.33, 95% CI 0.25, 0.45 p<0.0001	

PFS by IGHV status



	Median PFS
Ven-Obi & IGHV mutated	NR
Ven-Obi & IGHV unmutated	57.3 months
Clb-Obi & IGHV mutated	54.5 months
Clb-Obi & IGHV unmutated	26.9 months

PFS by *TP53* status



	Median PFS
Ven-Obi & no *TP53* del/mutated	NR
Ven-Obi & *TP53* del/mutated	49.0 months
Clb-Obi & no *TP53* del/mutated	38.9 months
Clb-Obi & *TP53* del/mutated	20.8 months

CI, confidence interval; del, deletion; HR, hazard ratio; IGHV, immunoglobulin heavy chain; m, months; NR, not reached; Obi, obinutuzumab; PFS, progression-free survival; *TP53*, tumour protein p53; Ven, venetoclax

1. Al-Sawaf O, et al. J Clin Oncol 2021;39:4049–4060; 2. Al-Sawaf O, et al. Oral presentation at EHA 2021 (Abstract S146)

CLL14 Phase 3 trial: venetoclax + obinutuzumab

Most frequent grade ≥3 AEs

	Venetoclax-obinutuzumab (N=212)		Chlorambucil-obinutuzumab (N=214)	
	During treatment	After treatment	During treatment	After treatment
Neutropenia	51.9%	4.0%	47.2%	1.9%
Thrombocytopenia	13.7%	0.5%	15.0%	0.0%
Anaemia	7.5%	1.5%	6.1%	0.5%
Febrile neutropenia	4.2%	1.0%	3.3%	0.5%
Leukopenia	2.4%	0.0%	4.7%	0.0%
Pneunomia	3.3%	3.0%	2.8%	1.4%
Infusion-related reaction	9.0%	0.0%	9.8%	0.5%
Tumour lysis syndrome	1.4%	0.0%	3.3%	0.0%

AML, acute myeloid leukaemia; MDS, myelodysplastic syndromes; SPM, second primary cancers; T-NHL, T-cell non-Hodgkin lymphoma

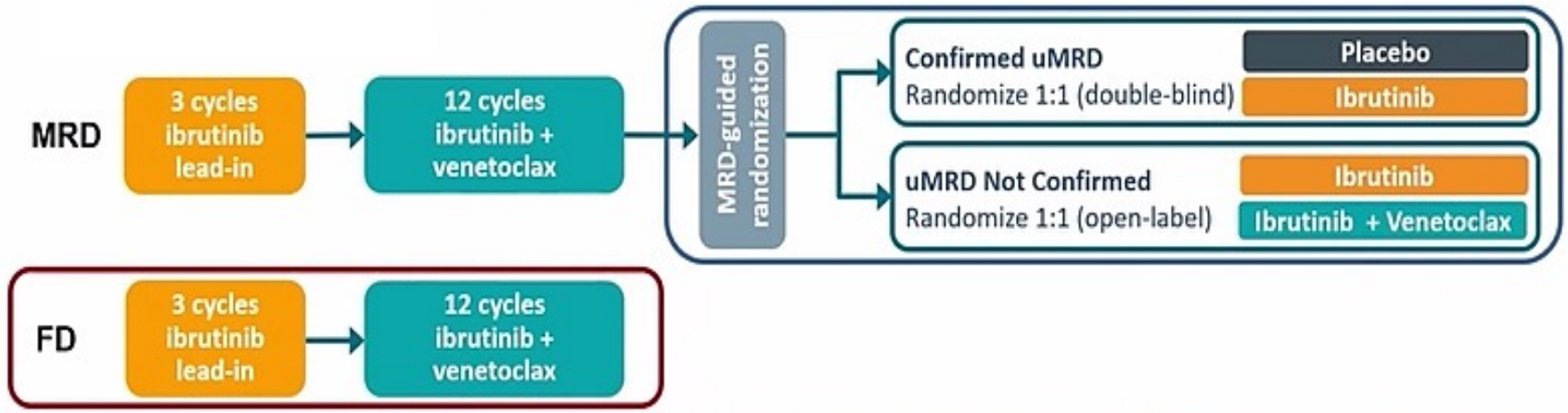
Al-Sawaf O, et al. Oral presentation at EHA 2021 (Abstract S146)

Second primary malignancies

	Venetoclax-obinutuzumab (N=212)	Chlorambucil-obinutuzumab (N=214)
Overall total number of events	**47**	**42**
Number of patients with at least one SPM	40 (18.9%)	30 (14.0%)
Non-melanoma skin cancer	19 (8.9%)	18 (8.4%)
Melanoma	8 (3.7%)	3 (1.4%)
Prostate cancer	4 (1.8%)	3 (1.4%)
Colon cancer	2 (0.9%)	2 (0.9%)
Lung cancer	2 (0.9%)	2 (0.9%)
Bladder cancer	2 (0.9%)	0
Breast cancer	2 (0.9%)	0
Hepatocellular carcinoma	0	1 (0.5%)
Pancreatic cancer	0	1 (0.5%)
Haematological cancer (MDS, AML, T-NHL)	3 (1.4%)	1
Other	2 (0.5%)	3 (1.4%)

CAPTIVATE Phase 2 trial: 1L ibrutinib + venetoclax

CAPTIVATE is an international, multicentre Phase 2 study evaluating 3 cycles of ibrutinib followed by 12 cycles of combined ibrutinib + venetoclax that comprises two cohorts: MRD and FD[1,2]



uMRD rates with 12 cycles of combined ibrutinib + venetoclax[3]

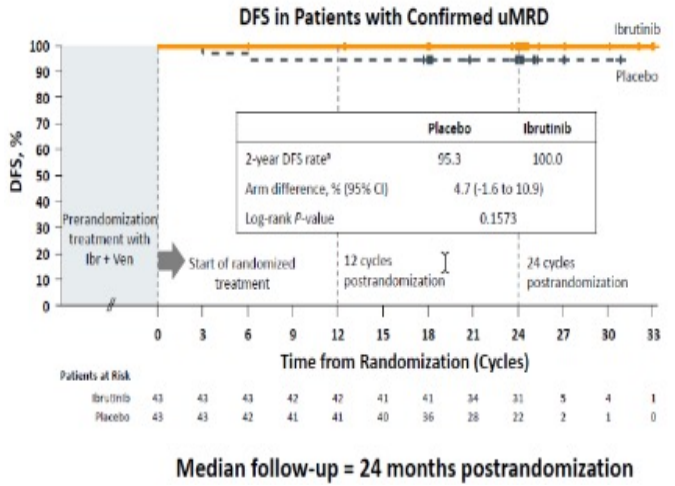
	Peripheral blood (n=163)	Bone marrow (n=155)
Best response of uMRD in evaluable patients (95% CI)	**75%** (69, 82)	**72%** (65, 79)

1L, first-line; CI, confidence interval; FD, fixed duration; MRD, minimal residual disease; uMRD, undetectable MRD

1. Ghia P, et al. Oral presentation at ASCO 2021 (Abstract 7501); 2. Allan JN, et al. Oral presentation at EHA 2021 (Abstract S147); 3. Wierda WG, et al. Oral presentation at iwCLL 2021 (Abstract 1084132)

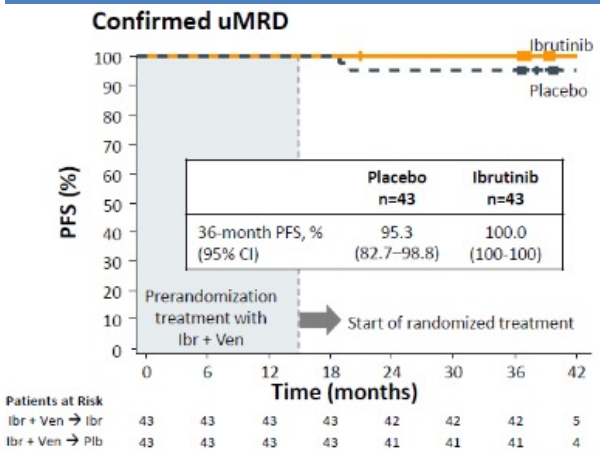
CAPTIVATE Phase 2 trial: DFS from the MRD cohort

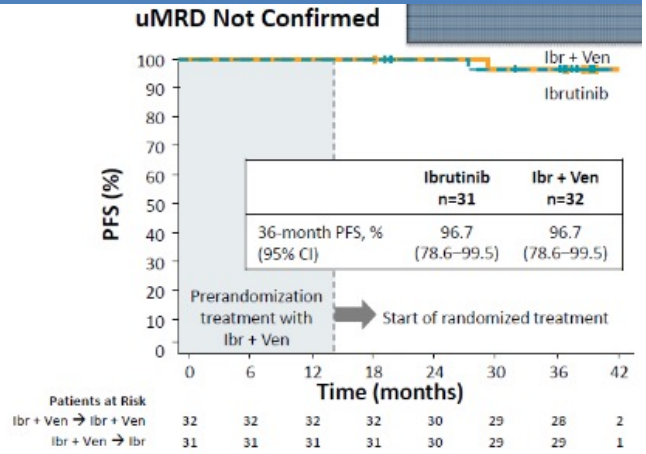
No new DFS events occurred since primary



Median follow-up = 24 months postrandomization

3-year PFS rates were ≥95% across all randomised arms





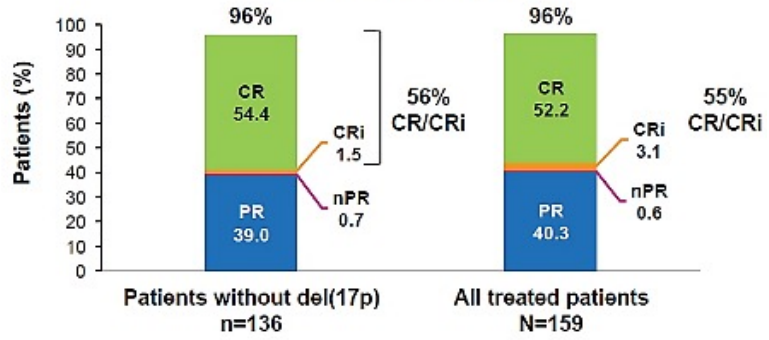
Median follow-up = 38 months

CI, confidence interval; DFS, disease-free survival; Ibr, ibrutinib; MRD, minimal residual disease; Plb, placebo; uMRD, undetectable MRD; Ven, venetoclax

Ghia P, et al. Oral presentation at ASH 2021 (Abstract 68)

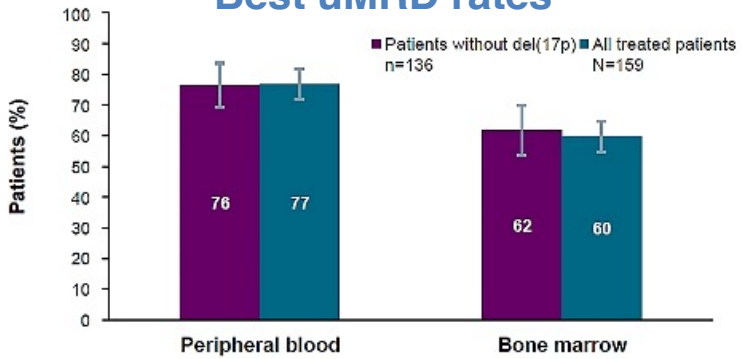
CAPTIVATE Phase 2 trial: primary analysis of the FD cohort

Best overall response

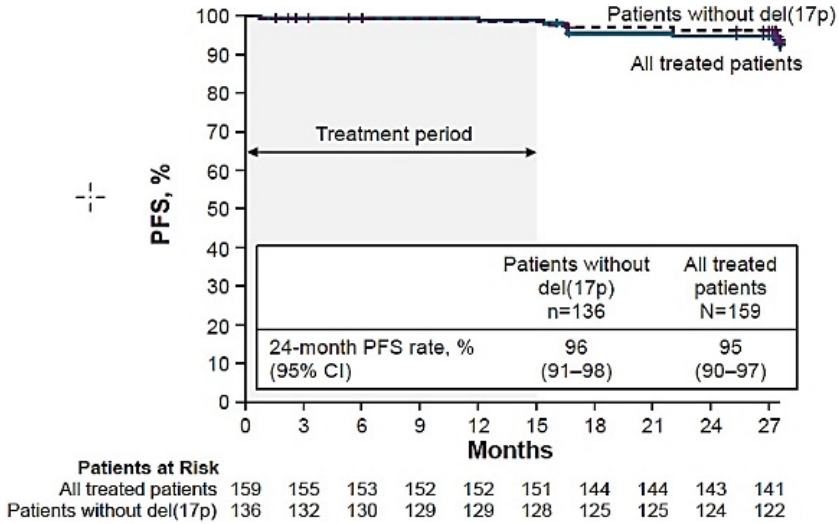


DOCR ≥12 cycles n/N (%)	66/76 (87)	78/88 (89)*

Best uMRD rates



PFS



Patients at Risk										
All treated patients	159	155	153	152	152	151	144	144	143	141
Patients without del(17p)	136	132	130	129	129	128	125	125	124	122

Estimated 24-month PFS rates

- Unmutated IGHV: 93% (95% CI 85, 97)
- Mutated IGHV: 97% (95% CI 88, 99)

CI, confidence interval; CR, complete response; CRi, CR with incomplete bone marrow recovery; DOCR, duration of CR; FD, fixed duration; IGHV, immunoglobulin heavy chain; MRD, minimal residual disease; uMRD, undetectable MRD; PFS, progression-free survival; PR, partial response

Ghia P, et al. Oral presentation at ASCO 2021 (Abstract 7501)

A glimpse into the future

Third generation of BTK-inhibitors

-

Relapsed/Refractory CLL

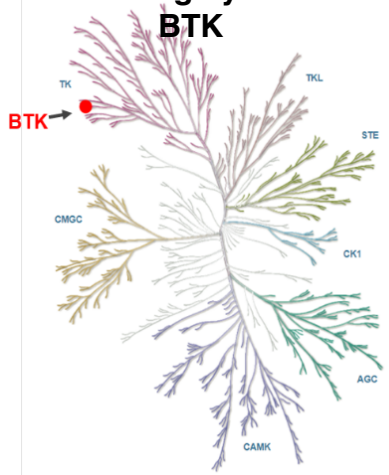
Third generation BTK inhibitors

LOXO-305
Pirtobrutinib

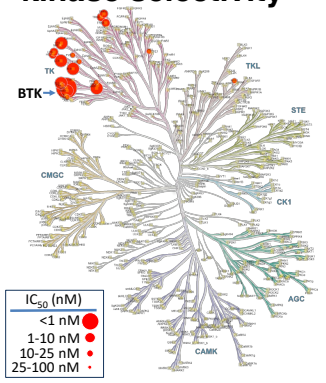
MK-1026 (ARQ531)
Nemtabrutinib

- They bind **REVERSIBLY** to BTK
- They are **DUAL INHIBITORS** of both wild type and C481S mutated BTK

LOXO-305 is highly selective for BTK

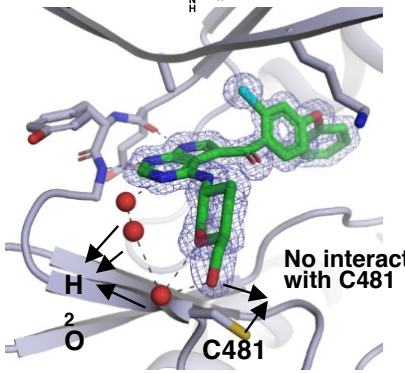


ARQ 531 exhibits distinct kinase selectivity



In addition to BTK, ARQ 531 inhibits TEC, TRK and SRC family kinases

ARQ 531 is a non-covalent reversible inhibitor of BTK



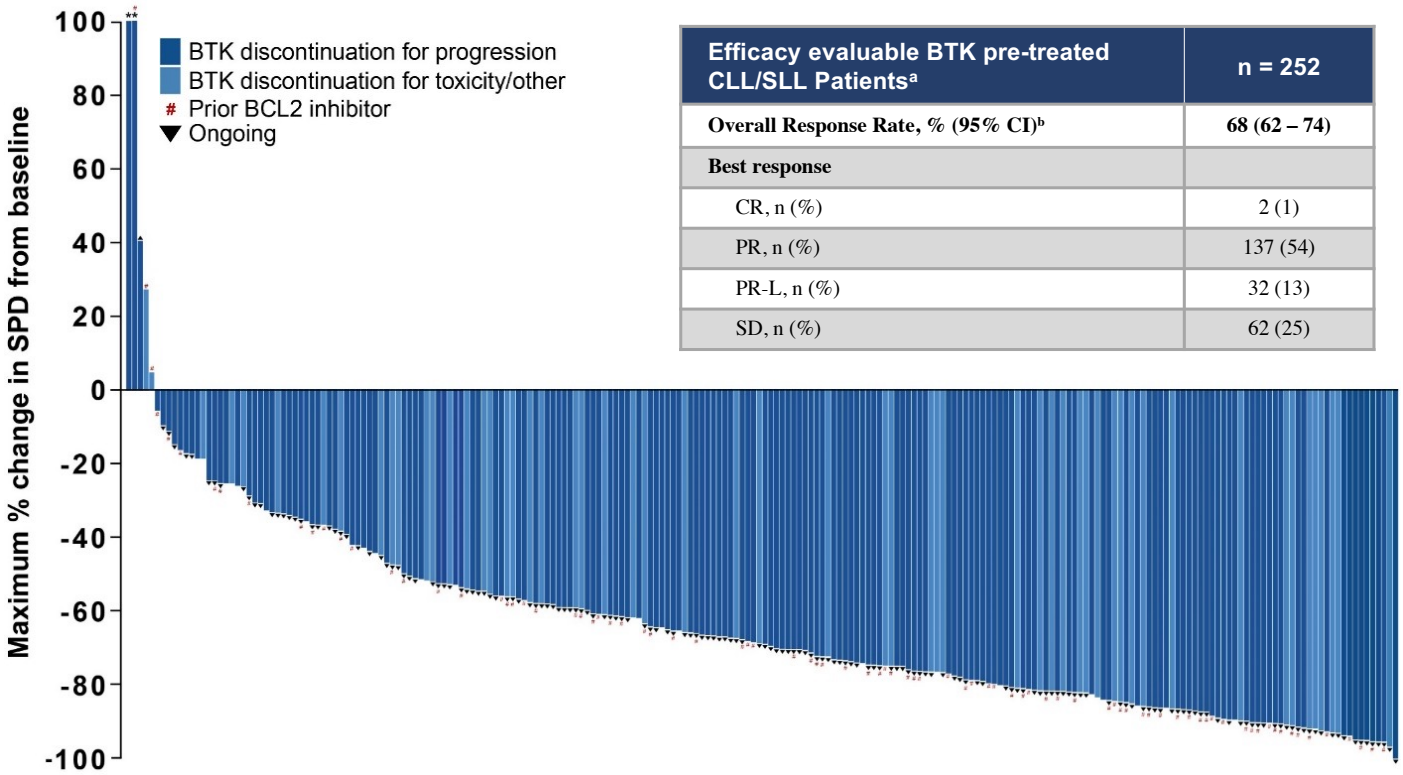
Crystal structure of BTK/ARQ 531 complex at 1.1 Å resolution

Bond DA & Woyach JA. Curr Hematol Malig Rep. 2019

Reiff et al., Cancer Discovery 2018

Phase 1/2 BRUIN study: Pirtobrutinib in RR CLL

Baseline Molecular Characteristics	
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)
Reason discontinued prior BTKi, n (%)	
Progressive disease	196 (75)
Toxicity/Other	65 (25)



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)

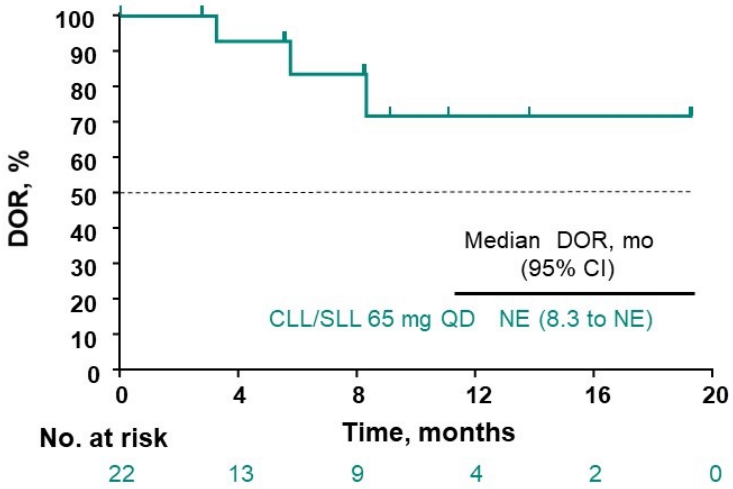
Efficacy was independent of BTK C481 mutation status, the reason for prior BTK discontinuation or other classes of prior therapy received

Mato et al., ASH 2021; abstract 391

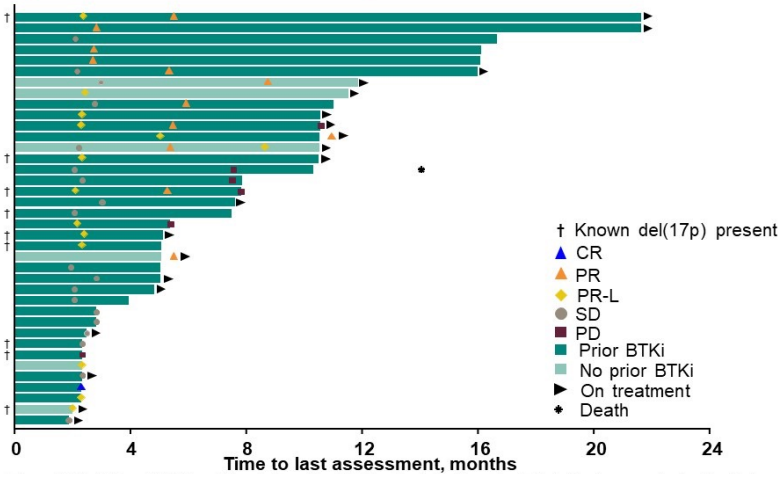
MK-1026 (ARQ531)

Characteristic, n (%)	CLL/SLL 65 mg QD N = 51
Prior lines, median (range)	4 (1-18)
Prior BTK inhibitor therapy	43 (84.3)
ECOG PS 0	14 (27.5)
1	32 (62.7)
2	5 (9.8)
IGHV Unmutated	30 (58.8)
Mutated	2 (3.9)
Unknown	19 (37.3)
Del (17p) Present	12 (23.5)
Absent	33 (64.7)
Missing	6 (11.8)
BTK C481S Present	32 (62.7)
Absent	12 (23.5)
Unknown/Missing	7 (13.7)

n (%) [95% CI]	CLL/SLL 65 mg QD N = 38[a]
ORR	**22 (57.9%)**
	[40.8-73.6]
CR	1 (2.6%) [0.0-13.8]
PR	12 (31.6%) [17.5-48.6]
PR-L	9 (23.7%) [11.4-40.2]
SD	15 (39.5%) [24.0-5.6]

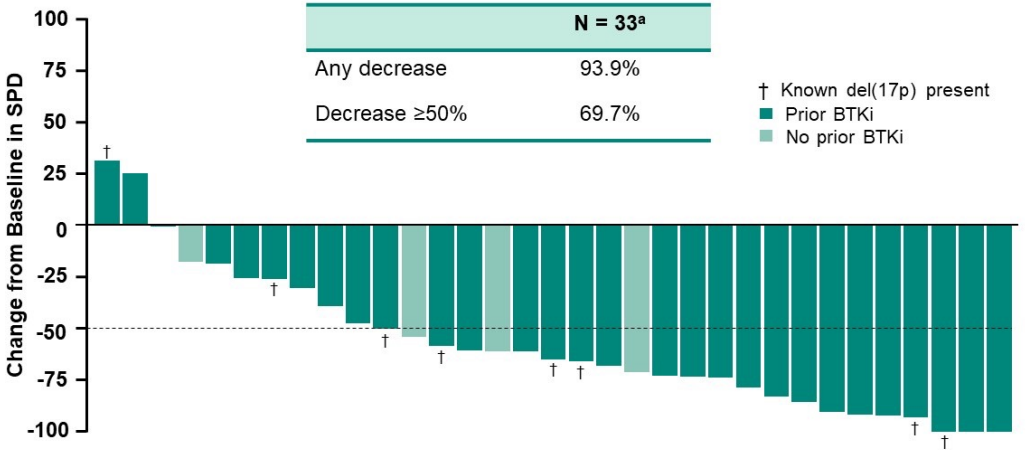


Treatment duration response



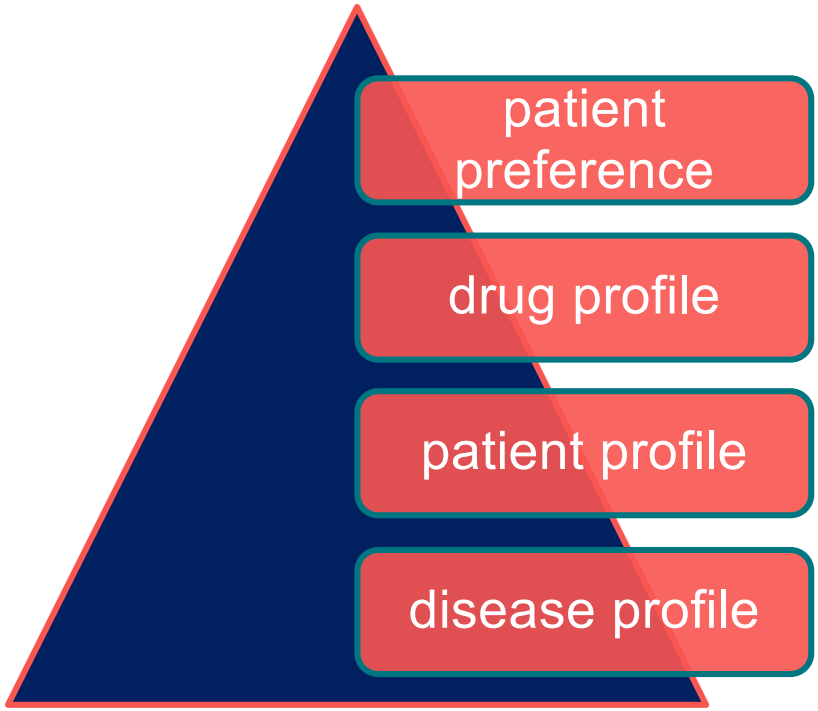
Percent change from baseline

	N = 33[a]
Any decrease	93.9%
Decrease ≥50%	69.7%



Woyach et al., ASH 2021; abstract 392

Personalized management in CLL



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