



**HOT
NEWS**

IN HEMATOLOGY

Sindromi
linfoproliferative
ed oltre...

Impatto clinico terapeutico: LLC

Paolo Ghia - Milano

PADOVA

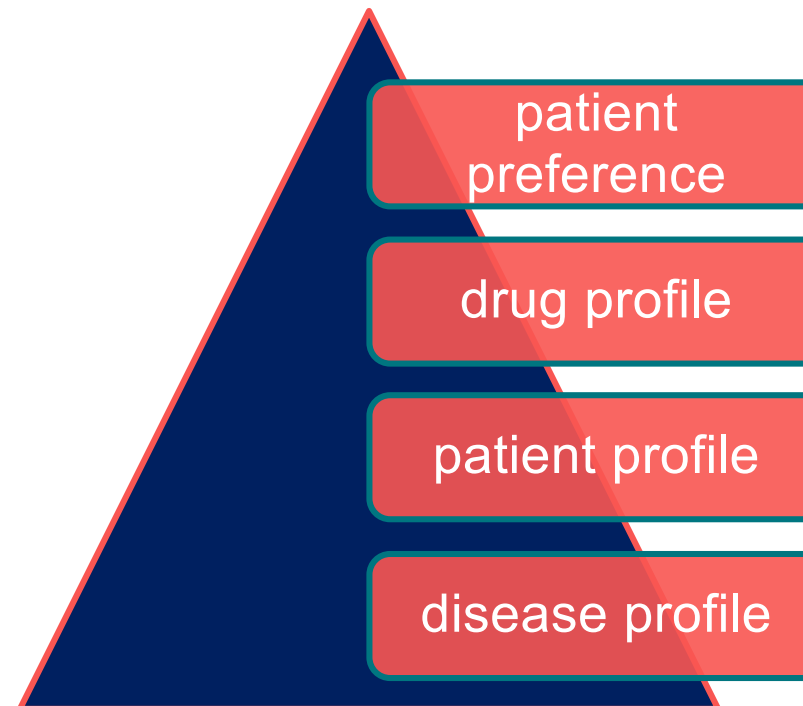
21 Marzo 2022

Hotel NH Mantegna

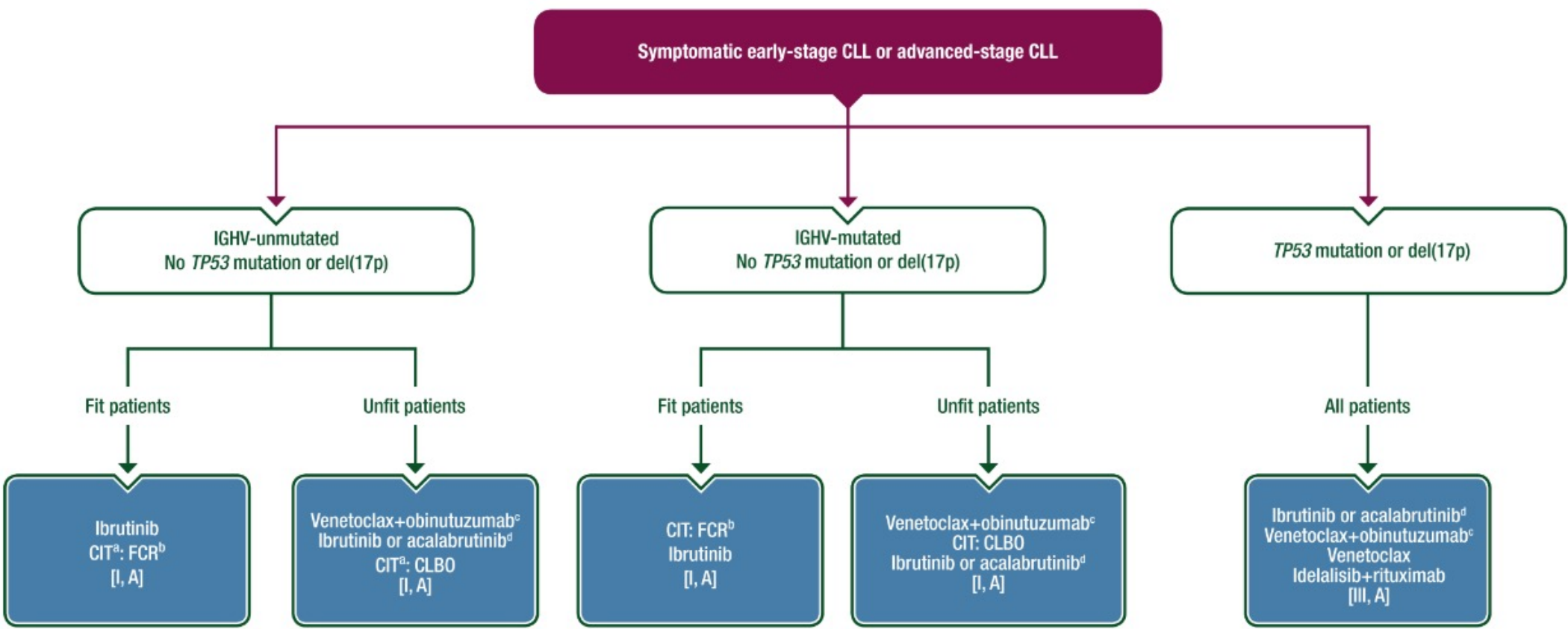
Disclosures of PAOLO GHIA

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

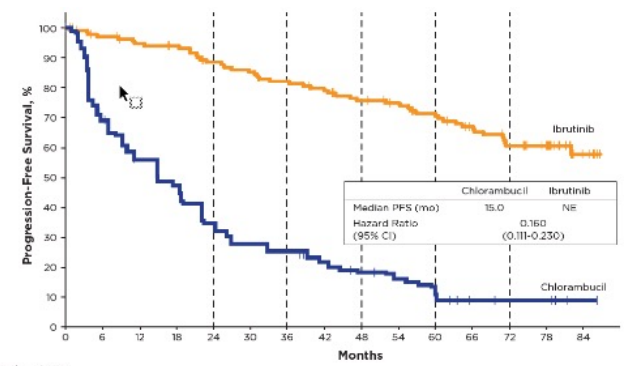


ESMO Clinical Practice: frontline therapy



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

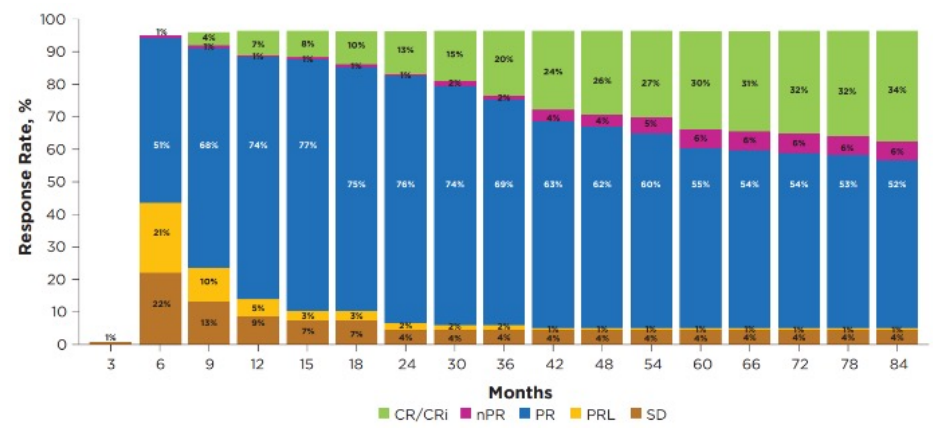
PFS: Ibrutinib vs chlorambucil



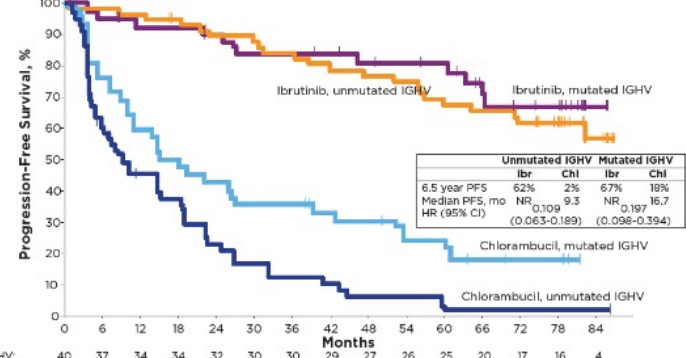
Patients at Risk and PFS

Months	0	6	12	18	24	30	36	42	48	54	60	66	72	78	84
Ibrutinib: PFS, %:	136	129	124	121	112	108	104	99	92	88	81	74	64	56	12
Chlorambucil: PFS, %:	133	68	69	57	41	33	30	25	19	16	12	6	5	5	1

Response increase over time: CR/CRi 34%



PFS by IGHV Status



Patients at Risk

Months	0	6	12	18	24	30	36	42	48	54	60	66	72	78	84
Ibrutinib, mutated IGHV:	40	37	34	34	32	30	30	29	27	26	25	20	17	16	4
Ibrutinib, unmutated IGHV:	58	57	56	53	49	48	46	43	42	41	36	35	32	26	8
Chlorambucil, mutated IGHV:	42	32	25	21	18	15	15	12	11	8	8	5	4	4	
Chlorambucil, unmutated IGHV:	60	33	23	19	11	8	6	5	3	3	2	1	1	1	

- 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

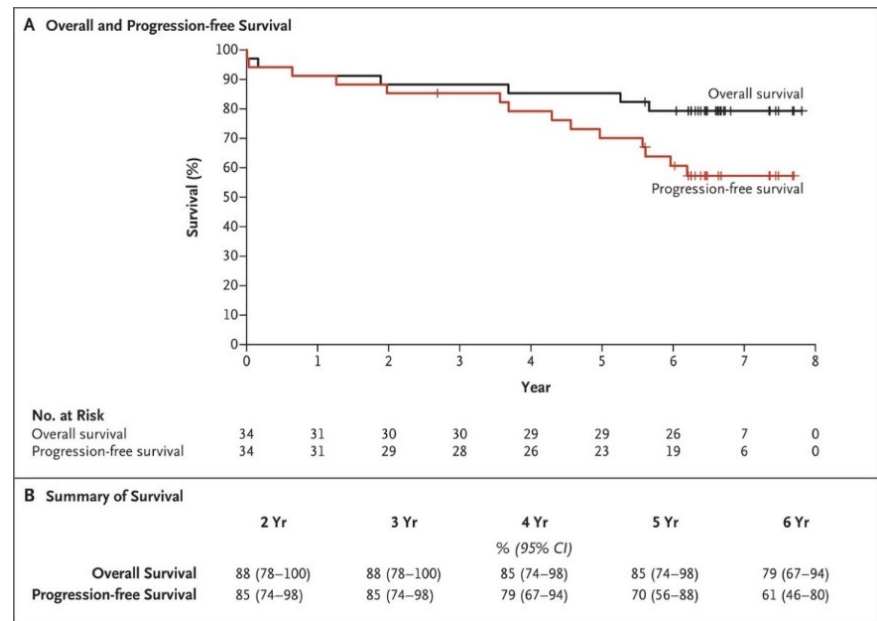
Ghia et al., EHA 2021; EP636 (poster presentation)

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

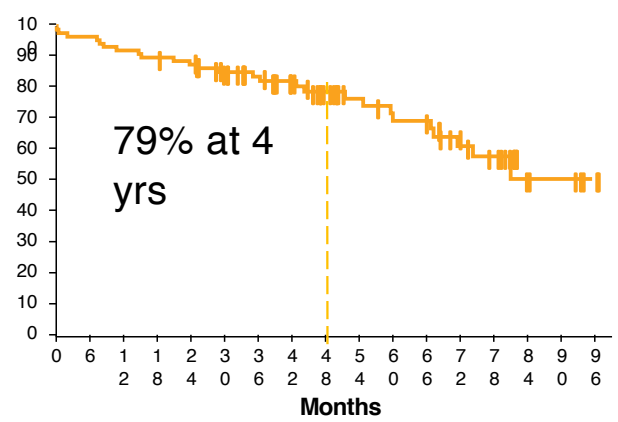
Pooled analysis: 4-year follow-up

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

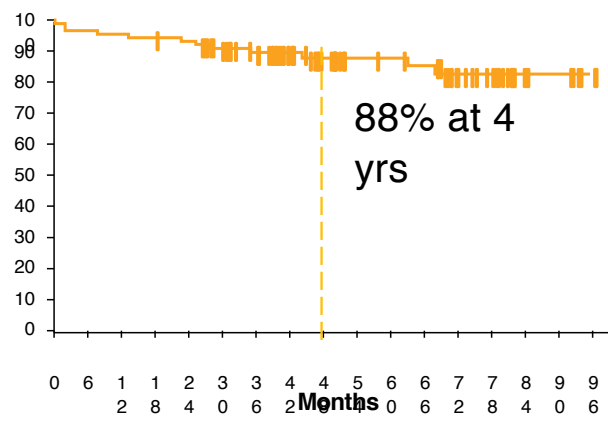
Phase 2 NIH study



Progression-free Survival



Overall Survival

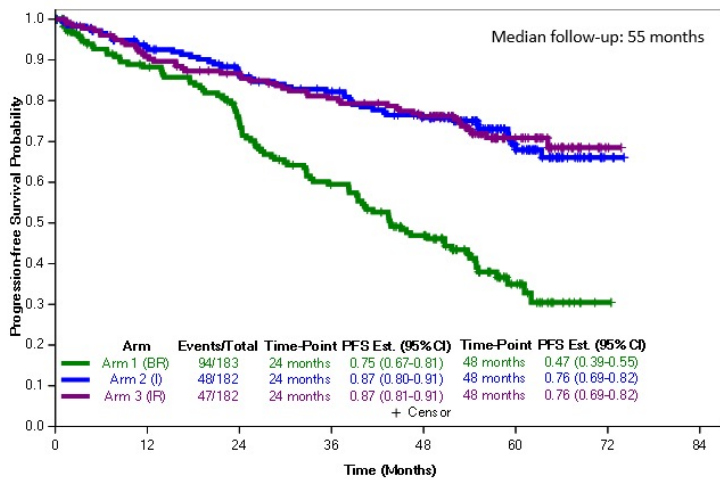


Allan J, et al., Presented at ASH 2020. #2219

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

Alliance A041202 : long term results* show continued advantage of ibrutinib-based regimens vs bendamustine + rituximab

PFS



Pairwise Comparisons

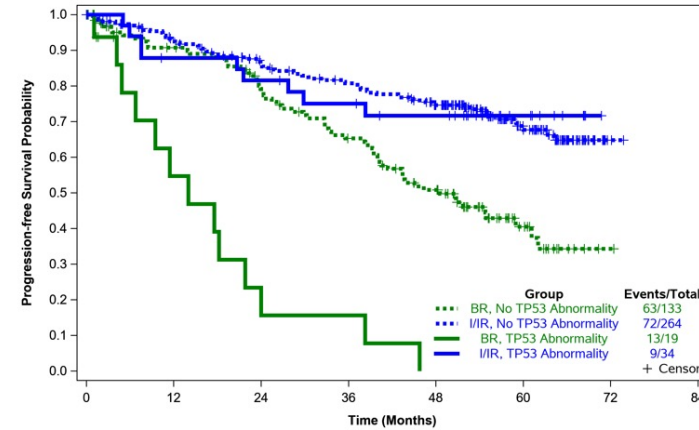
I vs BR:
 Hazard Ratio 0.36
 95% CI: 0.26-0.52
 P < 0.0001

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

Arm	183	139	114	87	63	20	1	0
Arm 1 (BR)	183	139	114	87	63	20	1	0
Arm 2 (I)	182	158	142	131	114	52	4	0
Arm 3 (IR)	182	156	142	130	117	44	2	0

PFS: TP53 abnormalities

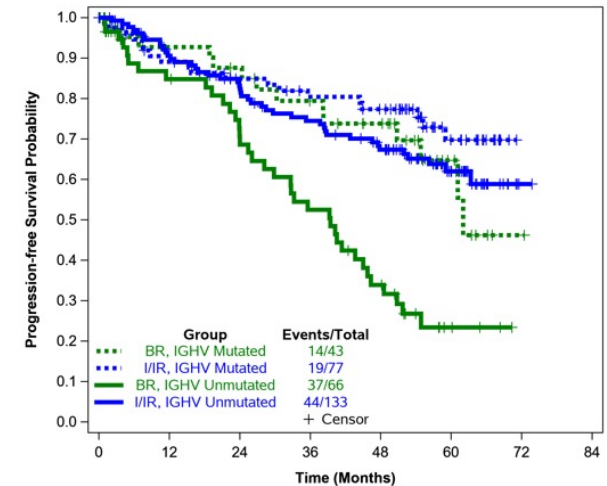


Treatment Effect
I/IR vs BR

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

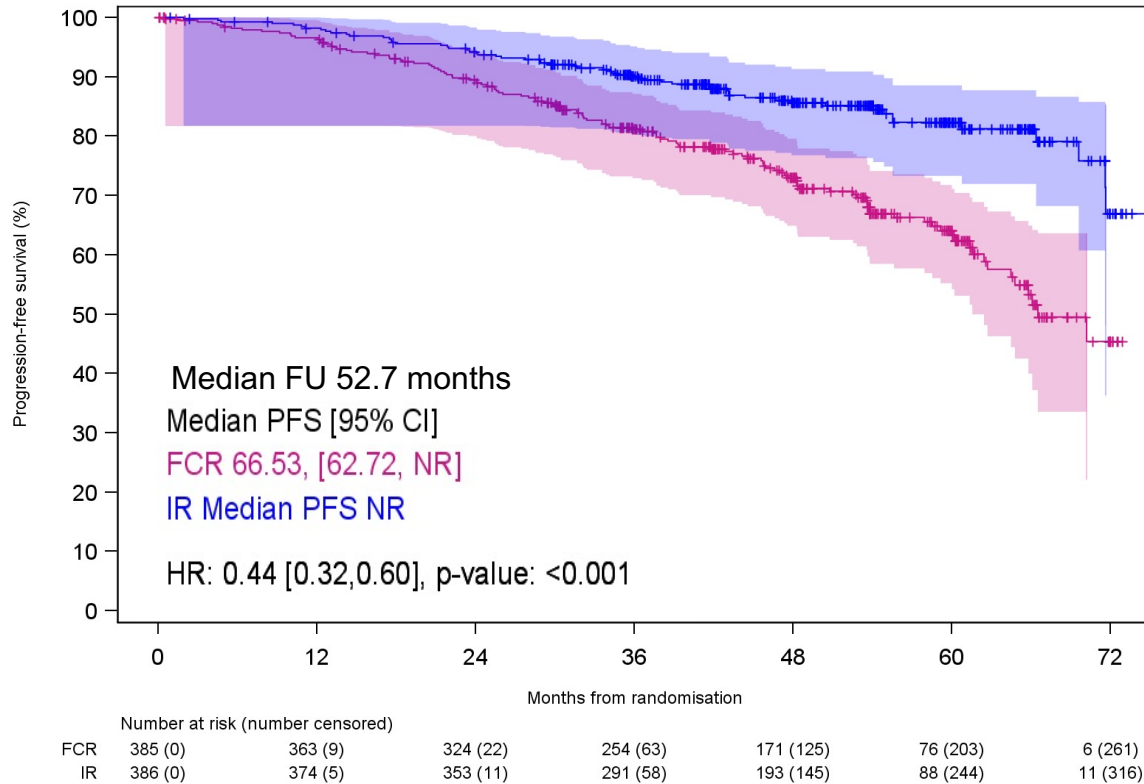
PFS: IGHV status



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

Phase III NCRI FLAIR Trial: Ibrutinib plus rituximab 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%)

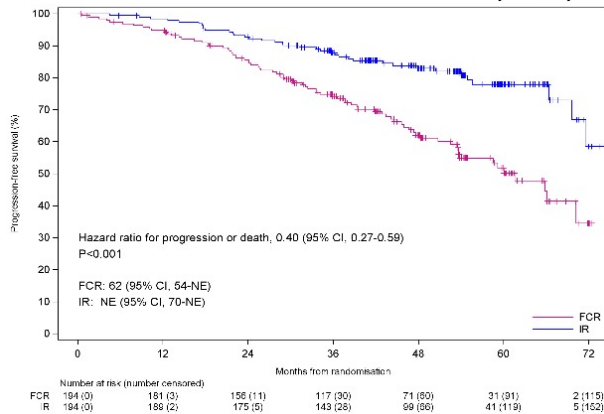
*; MRD flow cytometry <1 CLL cell/10,000 (IWCLL criteria)

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%)

Phase III NCRI FLAIR Trial: Ibrutinib plus rituximab vs FCR

PFS by IGHV mutation status

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

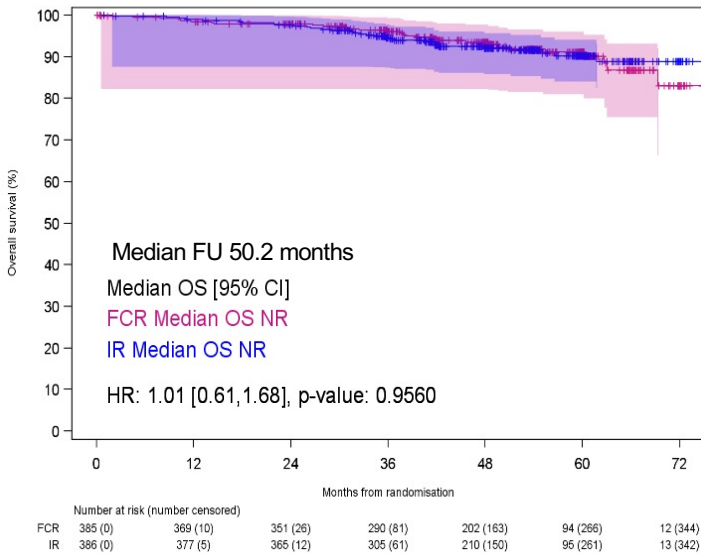
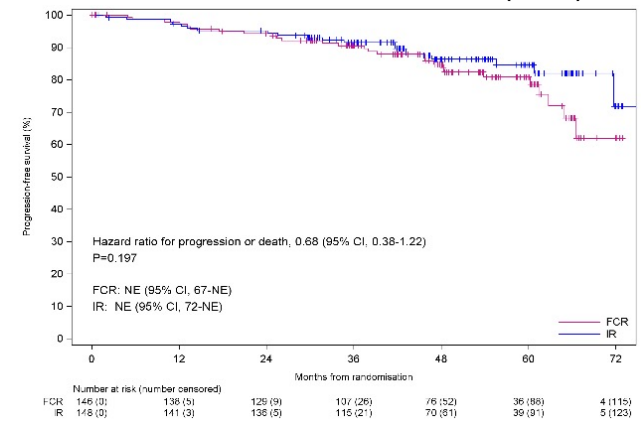


Stereotype Subset 2: n=46 (FCR 20; IR 26) →
HR for PD or death 0.32 (95% CI, 0.06-1.76), p=0.191

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)



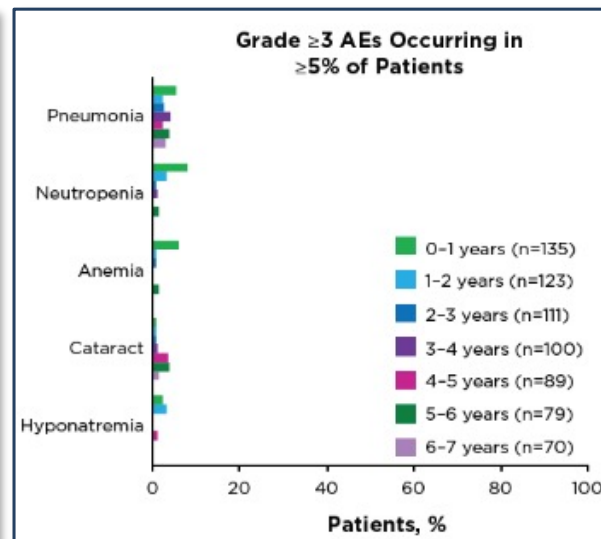
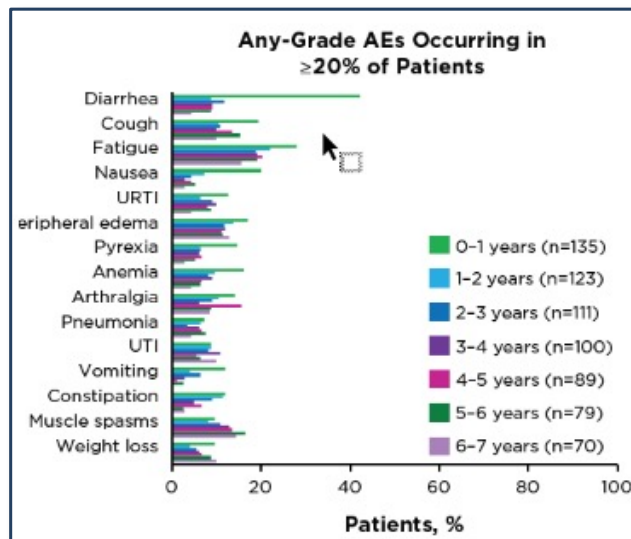
Cause of death *	FCR (n=29)	IR (n=30)
*, Deaths at any time in FU		
CLL	4	3
Non-haematological malignancy	4	7
AML/MDS	3	0
ALL	1	0
Richters transformation	3	1
Infections (non-COVID)	6	4
COVID-19	3	3
Haemorrhage	1	2
Cardiac	2	9
Other	2	1

Treatment after progression

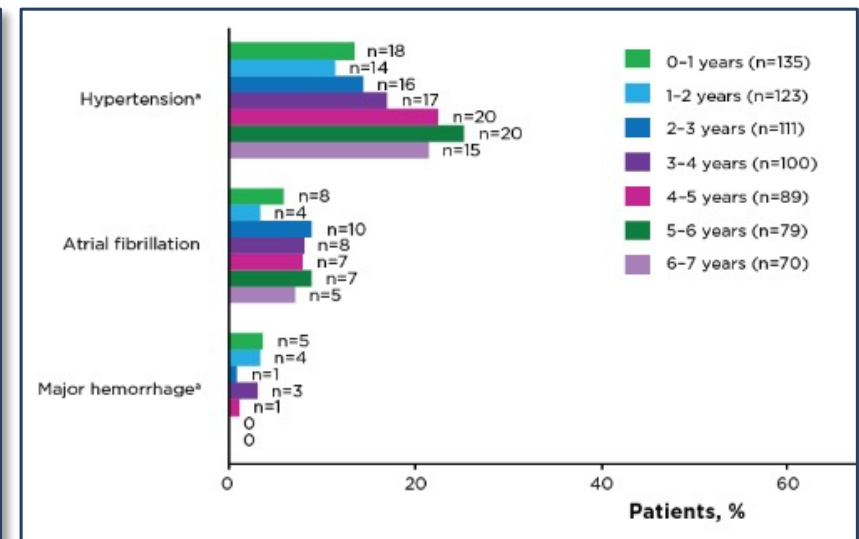
	FCR (n=56)	IR (n=19)
Therapy for Richter's transformation or Hodgkin's		
CHOP-R (5) or ABVD (1)	4	2
Therapy for relapsed CLL		
BTKi	38	0
Idelalisib + R	1	1
Venetoclax + R	8	5
CIT (FCR/BR/ChIR)	4	10
Rituximab	1	1
Targeted therapy for CLL	47/52 (90%)	6/17 (35%)

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).

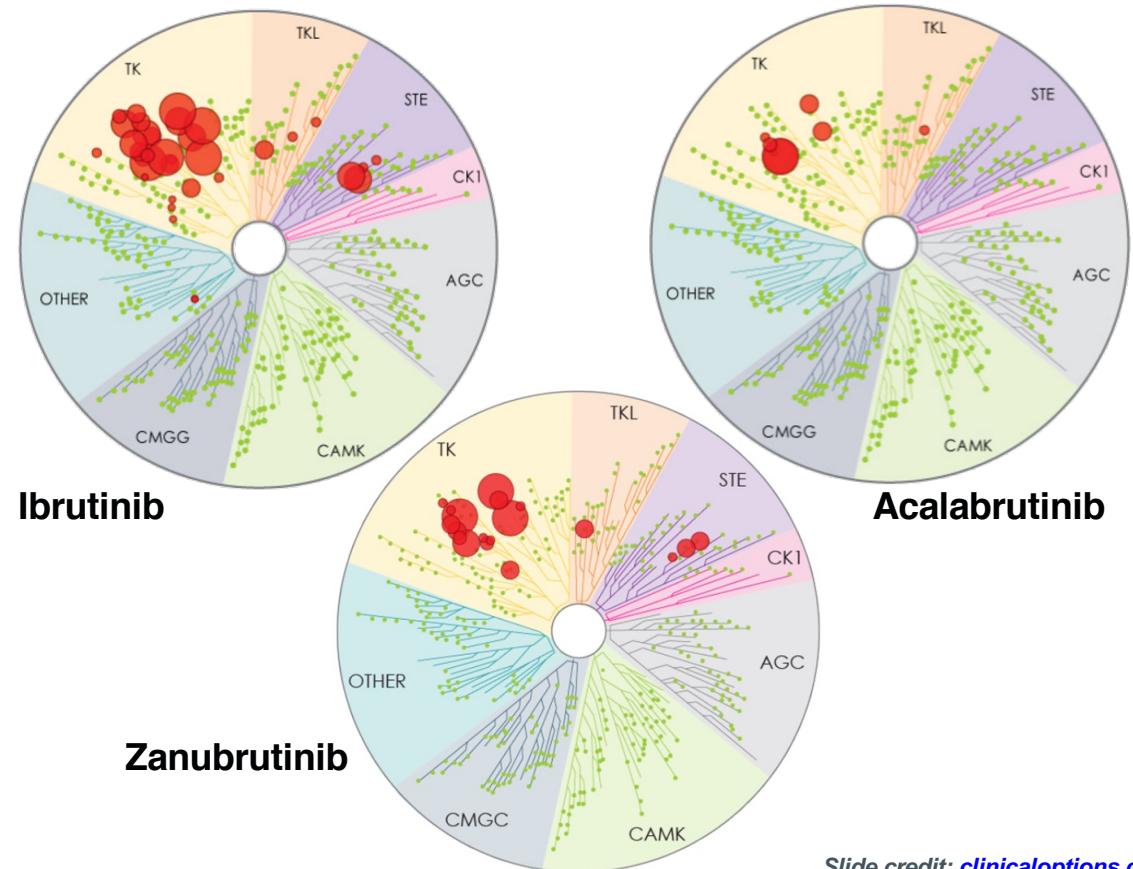
Kinase Selectivity of BTK Inhibitors

Kinase Selectivity Profiling at 1 $\mu\text{mol/L}$ (in vitro)

Larger red circles represent stronger inhibition

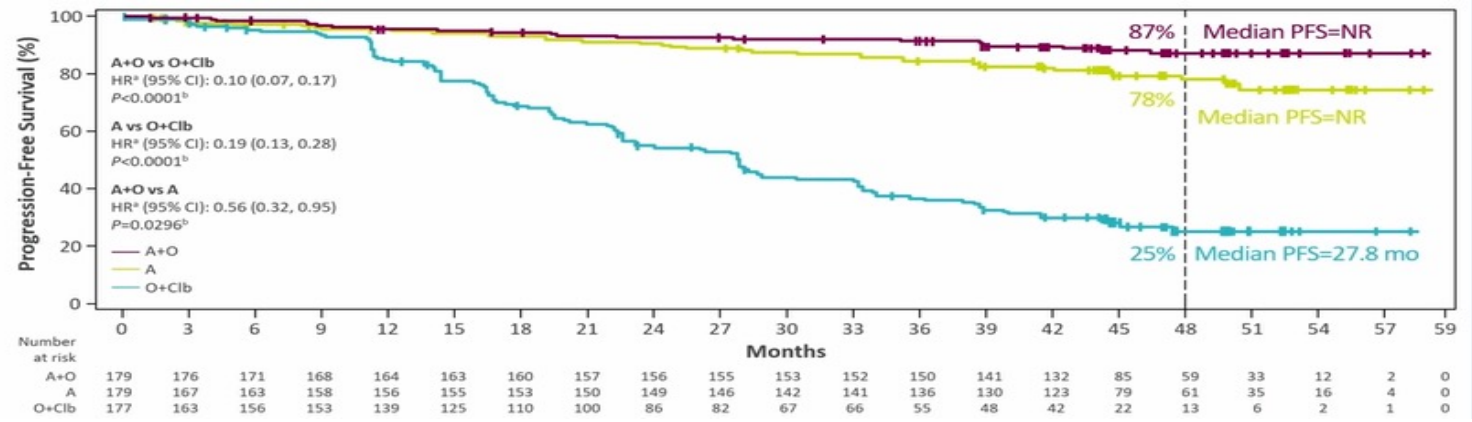
$\text{IC}_{50}/\text{EC}_{50}$ (nM)

Kinase	$\text{IC}_{50}/\text{EC}_{50}$ (nM)		
	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

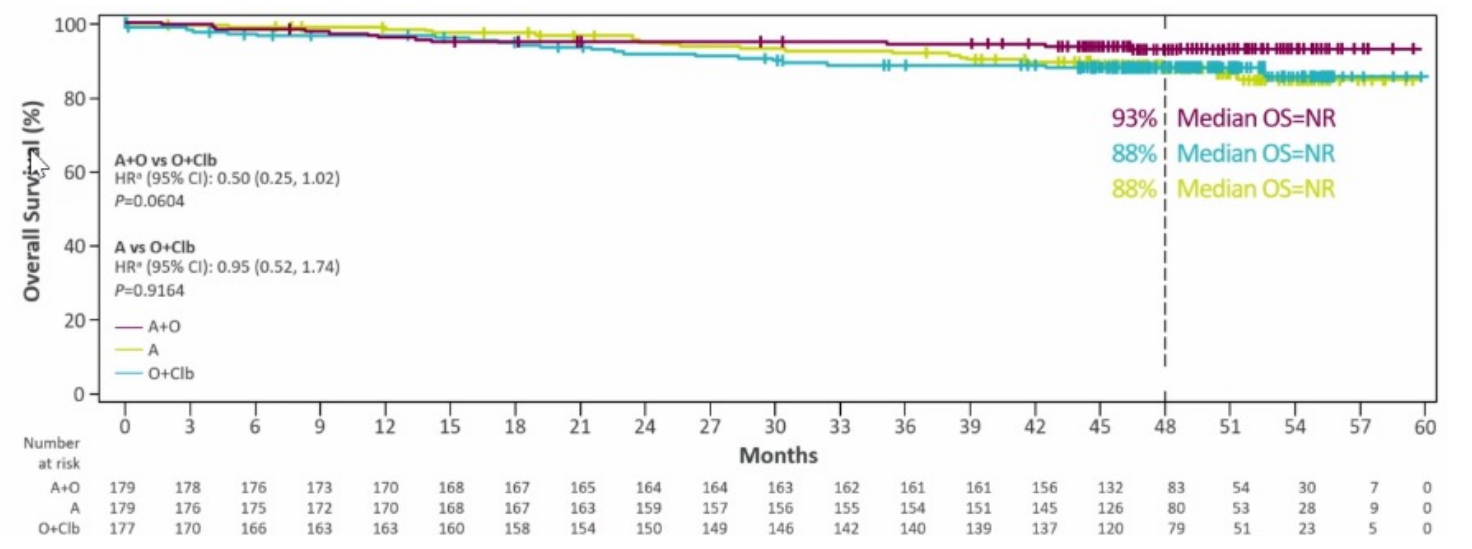


Phase 3 ELEVATE TN Study: acalabrutinib ± obinutuzumab

Investigator assessed PFS



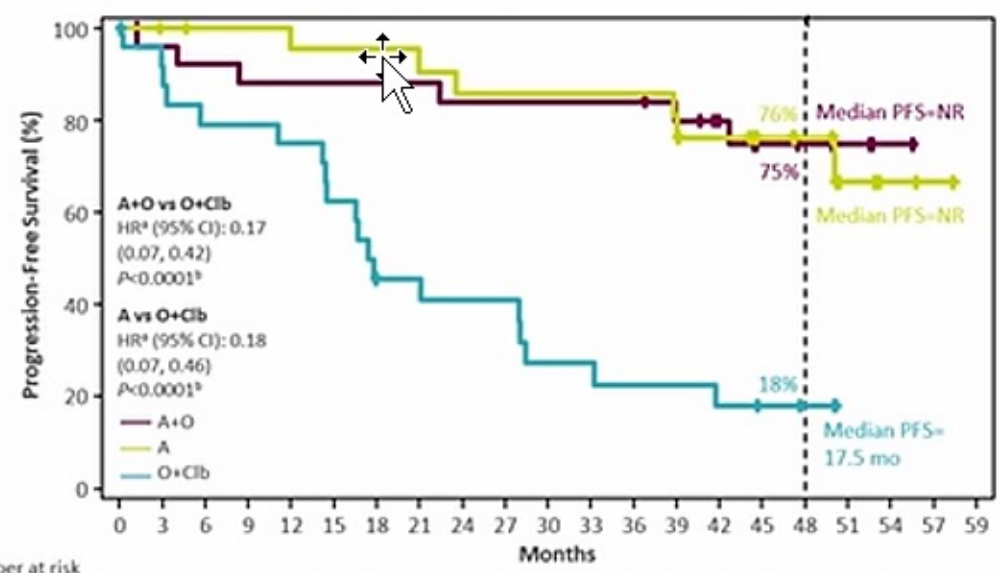
Overall Survival



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

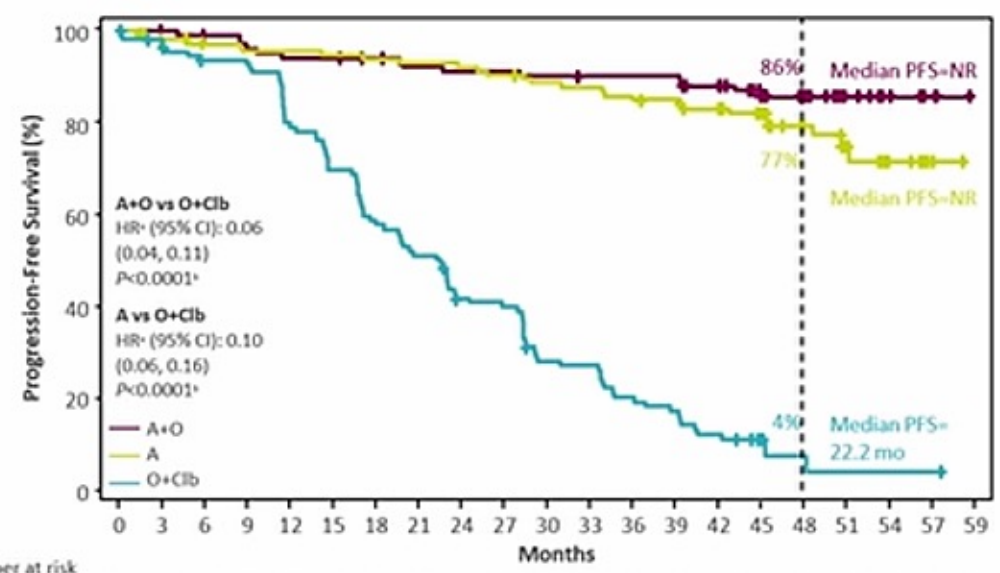
ELEVATE TN: PFS according to TP53 and IGHV status

Del(17p) and/or Mutated TP53



Number at risk	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48	51	54	57	59
A+O	25	24	23	22	22	22	22	22	21	21	21	21	21	19	16	9	8	3	1	0	0
A	23	22	21	21	20	20	20	19	18	18	18	18	18	15	15	11	9	5	2	1	0
O+Clb	25	21	19	19	18	15	10	9	9	9	6	6	5	5	4	3	2	0	0	0	0

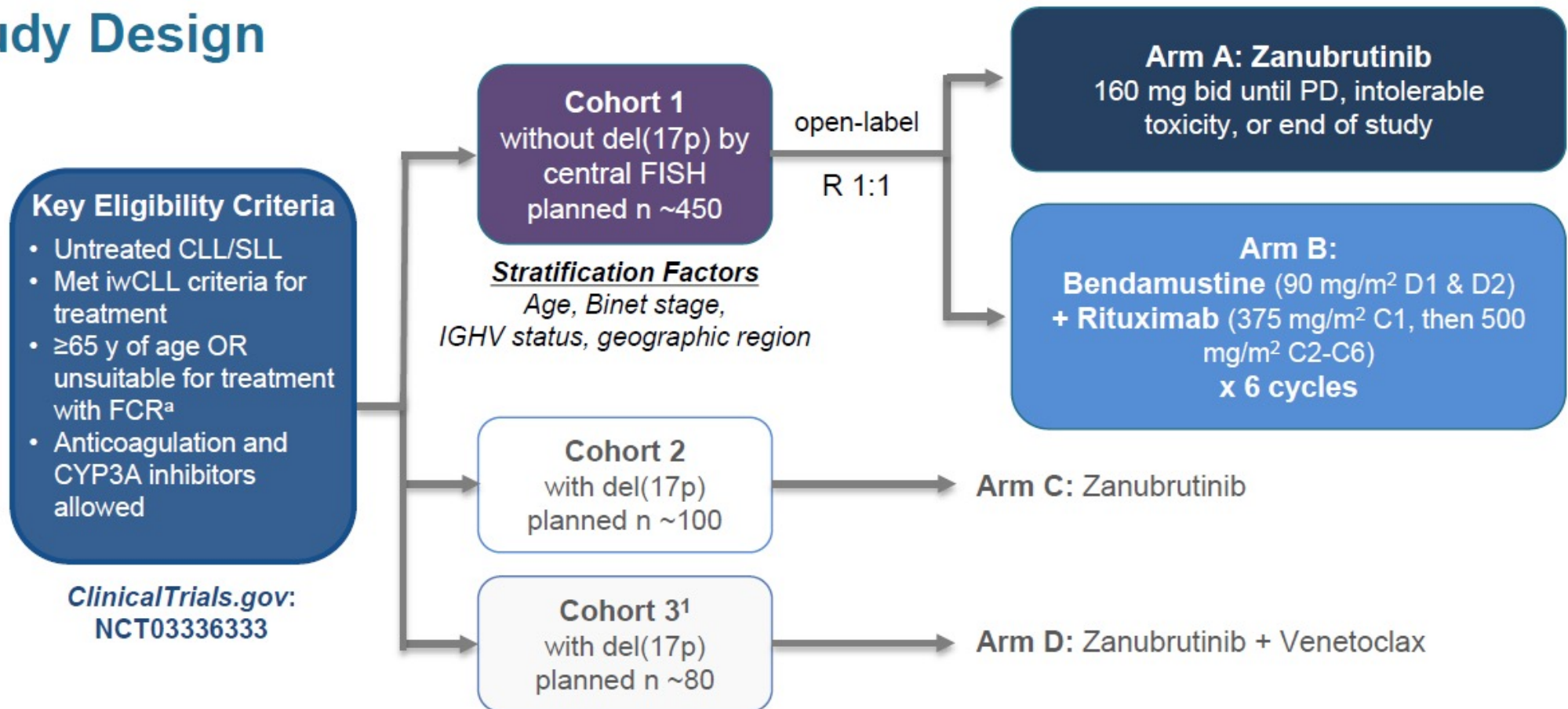
Unmutated IGHV



Number at risk	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48	51	54	57	59
A+O	103	102	100	97	95	95	94	92	91	91	90	89	89	84	78	47	35	17	7	1	0
A	119	112	109	107	107	106	105	104	103	101	98	97	93	89	84	52	38	22	11	1	0
O+Clb	116	105	101	99	85	75	62	55	43	41	28	27	19	14	11	2	1	1	1	1	0

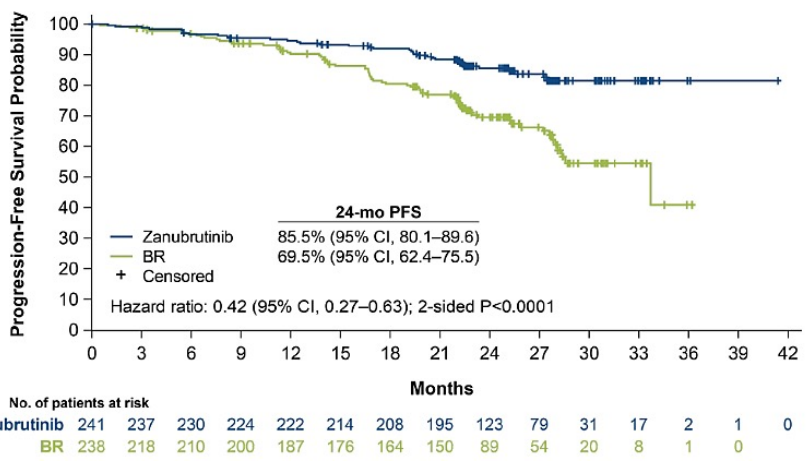
SEQUOIA (BGB-3111-304): Zanubrutinib vs BR in TN CLL

Study Design

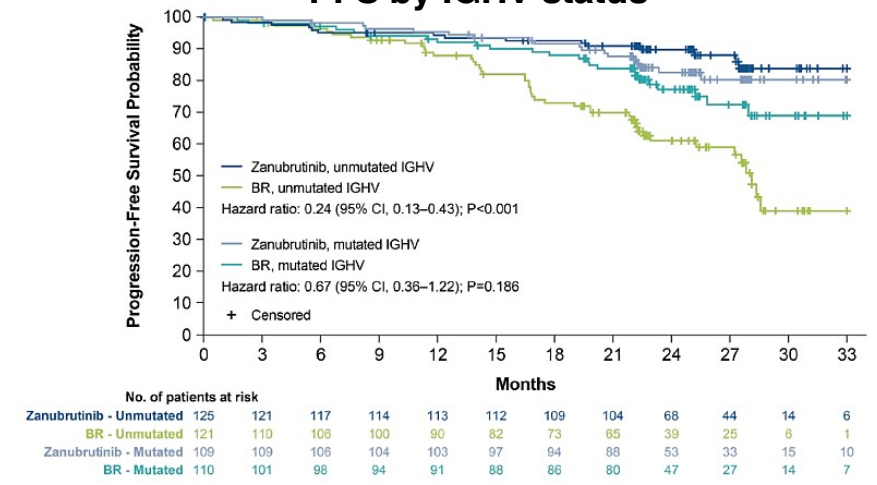


SEQUOIA (BGB-3111-304)

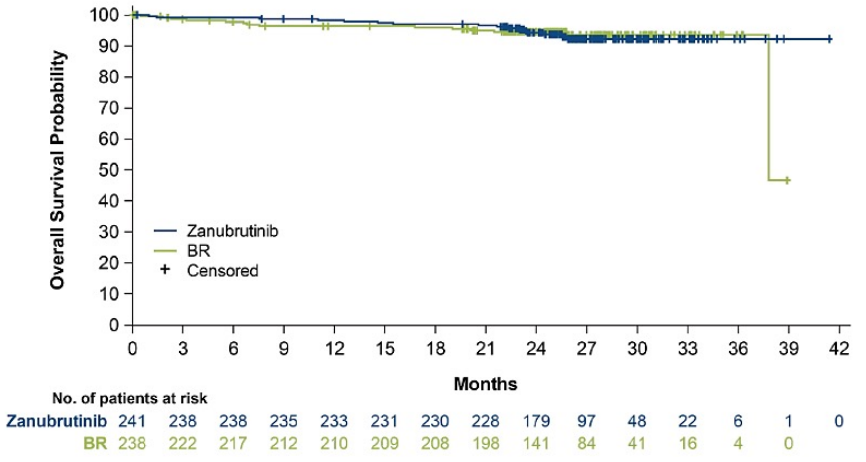
PFS



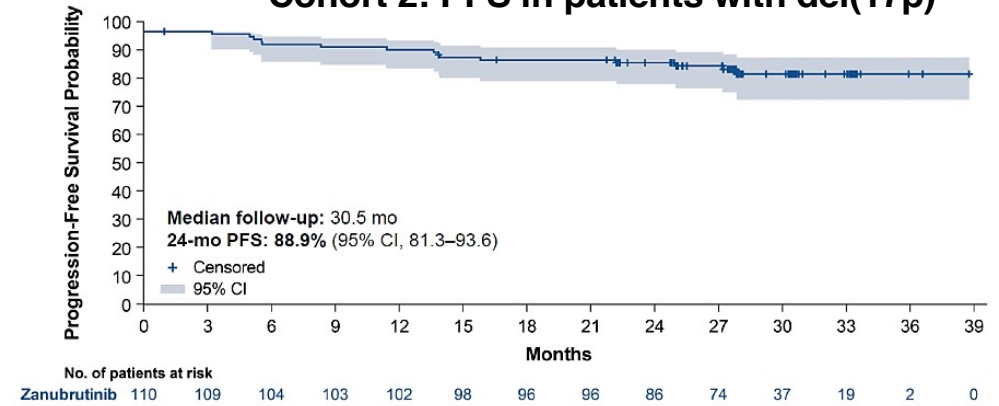
PFS by IGHV status



OS



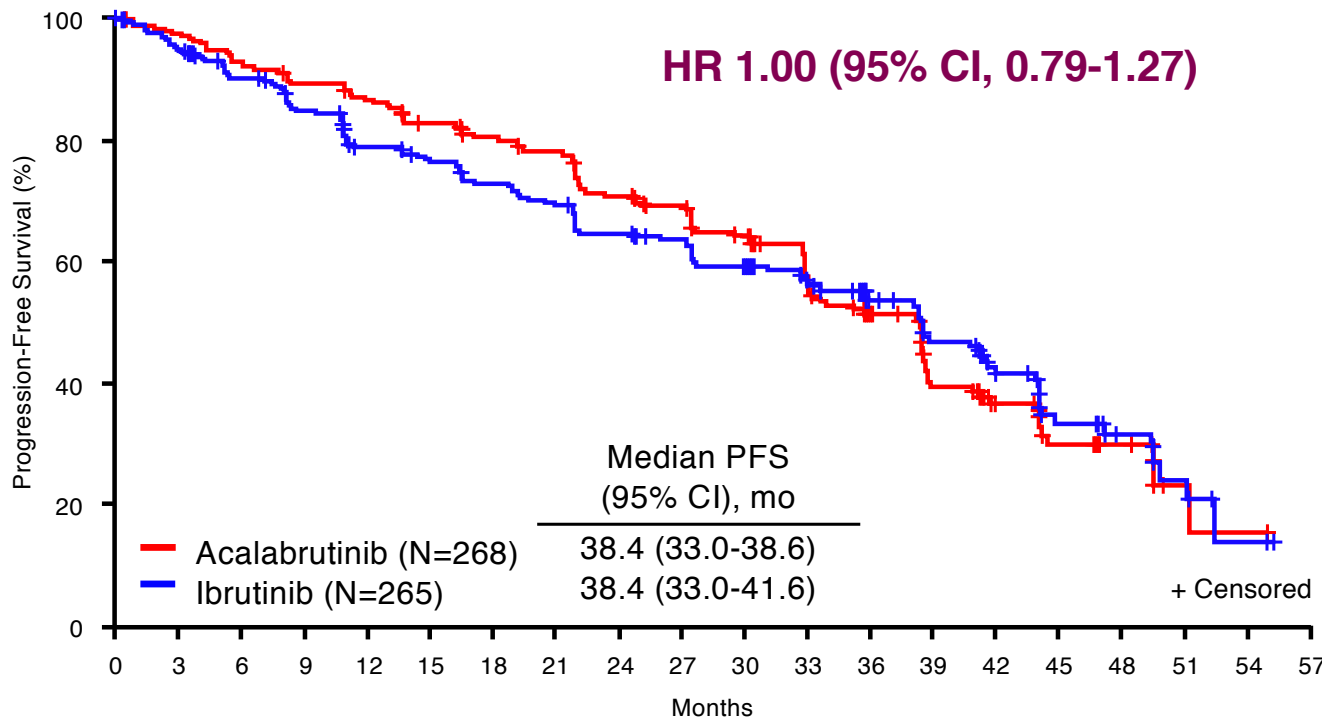
Cohort 2: PFS in patients with del(17p)



Phase 3 ELEVATE RR study: Ibrutinib vs acalabrutinib

IRC-Assessed PFS

HR 1.00 (95% CI, 0.79-1.27)



	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48	51	54	57
Acalabrutinib	26	25	23	22	21	20	20	19	17	16	14	11	8	5	3	2	1	1	1	0
Ibrutinib	265	240	221	205	186	178	168	160	148	142	130	108	81	66	41	26	15	8	2	0

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

Median follow-up 41 months

	Acalabrutinib (N=268)	Ibrutinib (N=265)
Events, n (%)		
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

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)

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).

^aBased on Barnard's exact test, two-sided P-value <0.05 without multiplicity adjustment for any grade events.

^bBased on Barnard's exact test, two-sided P-value <0.05 without multiplicity adjustment for grade ≥ 3 events.

Includes AEs reported at $\geq 15\%$ incidence (any grade) in either arm.

AE, adverse event; URTI, upper respiratory tract infection.

Secondary
endpoint

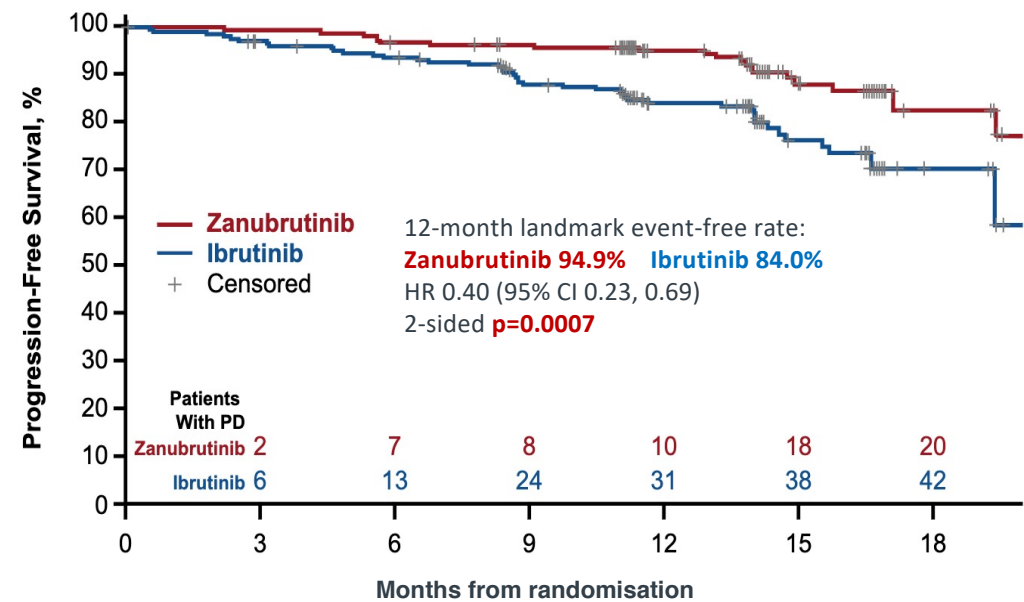


Phase 3 ALPINE study: Ibrutinib vs zanubrutinib in RR CLL

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 1 st 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

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	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)

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.

A glimpse into the future

Third generation of BTK-inhibitors

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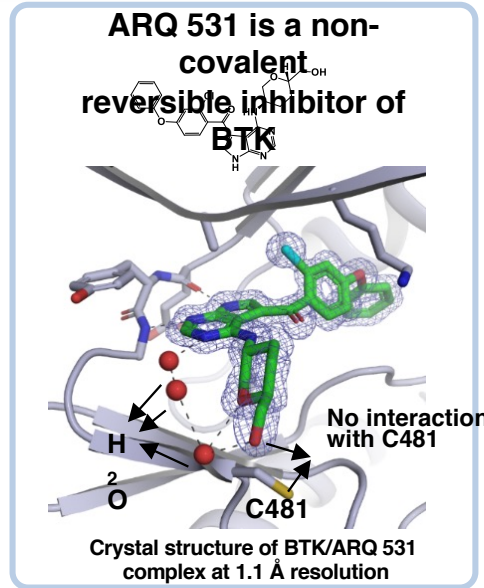
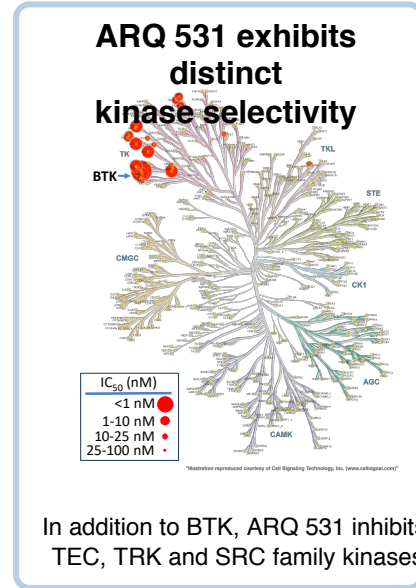
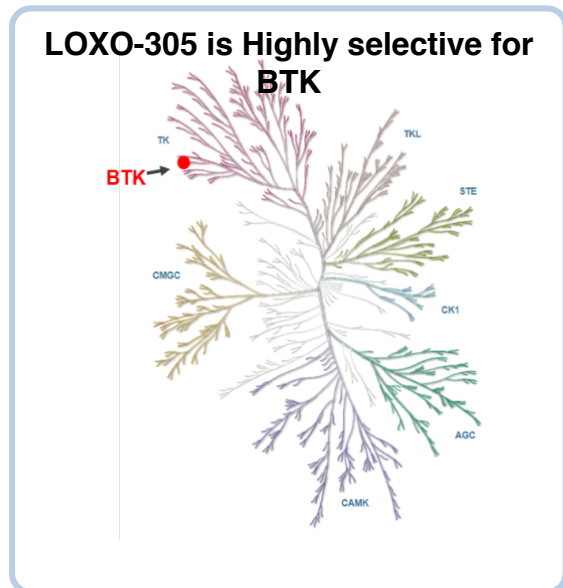
Relapsed/Refractory CLL

Third generation BTK inhibitors

LOXO-305
Pirtobrutinib

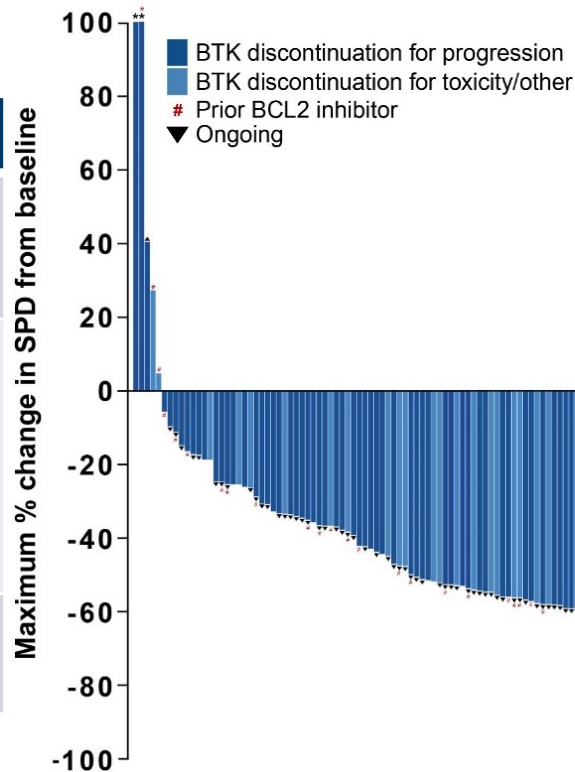
MK-1026 (ARQ531)
Nemtabrutinib

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



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)
<i>TP53</i> mutation	64 (37)
17p deletion or <i>TP53</i> mutation	77 (36)
Both 17p deletion and <i>TP53</i> mutation	38 (27)
IGHV unmutated	168 (84)
11q deletion	45 (25)
Reason discontinued prior BTKi, n (%)	
Progressive disease	196 (75)
Toxicity/Other	65 (25)

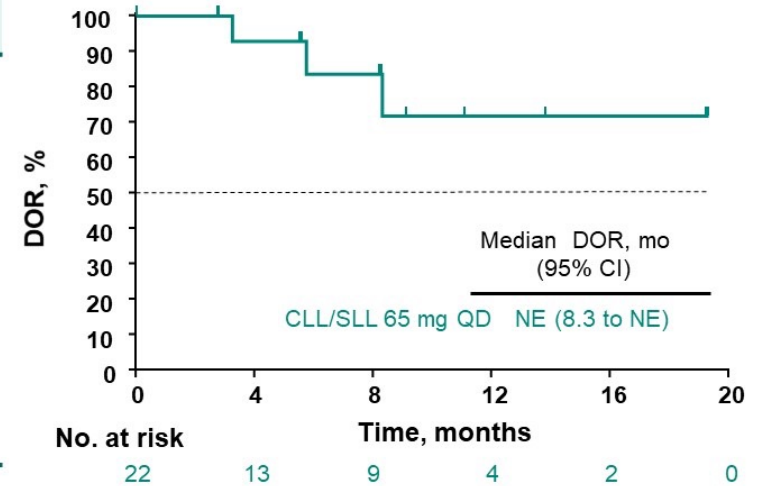


Efficacy evaluable BTK pre-treated CLL/SLL Patients ^a	n = 252
Overall Response Rate, % (95% CI)^b	68 (62 – 74)
Best response	
CR, n (%)	2 (1)
PR, n (%)	137 (54)
PR-L, n (%)	32 (13)
SD, n (%)	62 (25)

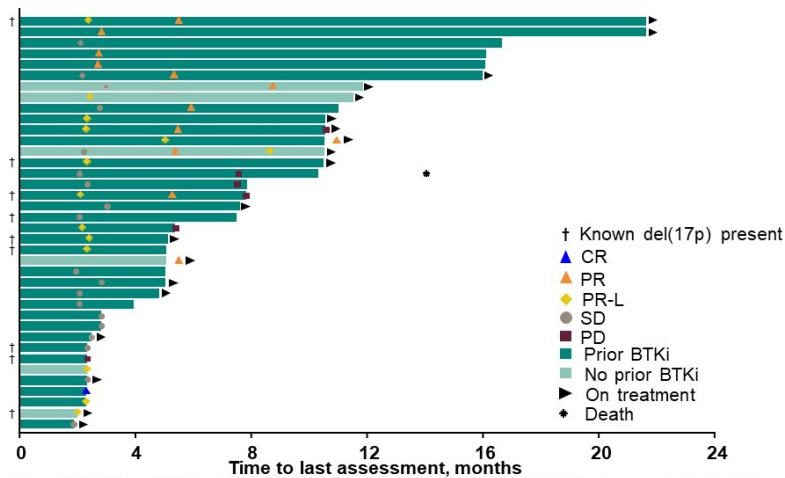
Efficacy was independent of BTK C481 mutation status, the reason for prior BTK discontinuation or other classes of prior therapy received

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)

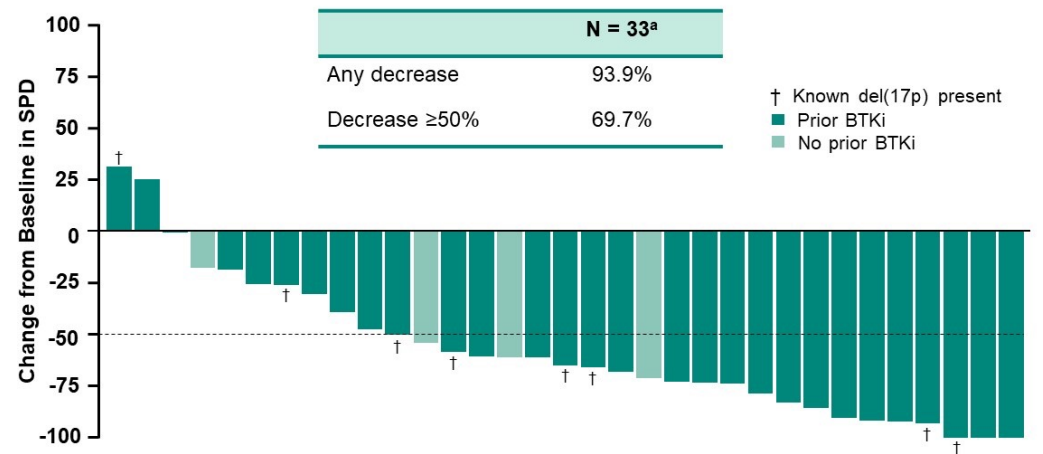
n (%) [95% CI]	CLL/SLL 65 mg QD N = 38 ^a
ORR	22 (57.9%) [40.8-73.6]
CR	1 (2.6%) [0.0-13.8]
PR	12 (31.6%) [17.5-48.6]
PR-L	9 (23.7%) [11.4-40.2]
SD	15 (39.5%) [24.0-55.6]



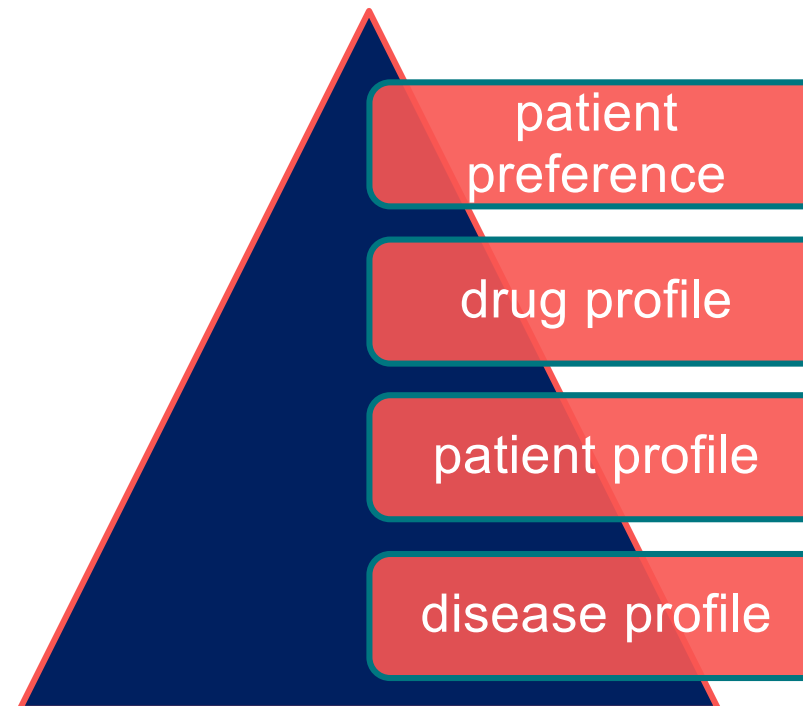
Treatment duration response



Percent change from baseline



Personalized management in CLL





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Division of Experimental Oncology

Padova, 21 Marzo 2022
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B Cell Neoplasia Unit

Alessandro Campanella, Daniela Belloni, Silvia Bonfiglio, Jessica Bordini, Michela Frenquelli, Francesca Gandini, Silvia Heltai, Chiara Lenzi, Eleonora Perotta, Athanasios Pseftogkas, Pamela Ranghetti, Lydia Scarfò

Strategic Research Program on CLL

Elisa Albi, Antonella Capasso, Maria Colia, Eloise Scarano, Lydia Scarfò, Luana Schiattone, Virginia Sgarlato

CERTH, Thessaloniki

Anna Vardi, Thomas Chatzikonstantinou, Stavroula Ntoufa, Aliko Xochelli, Anastasia Hadzidimitriou, Andreas Agathangelidis, Katerina Gemenetzi, Christina Karamanidou, Maria Gounari, Kostas Stamatopoulos

Karolinska Institut, Stockholm

Lesley Ann Sutton, Panayotis Baliakas, Viktor Ljungstrom, Richard Rosenquist

