New developments in CLL post ASH 20203

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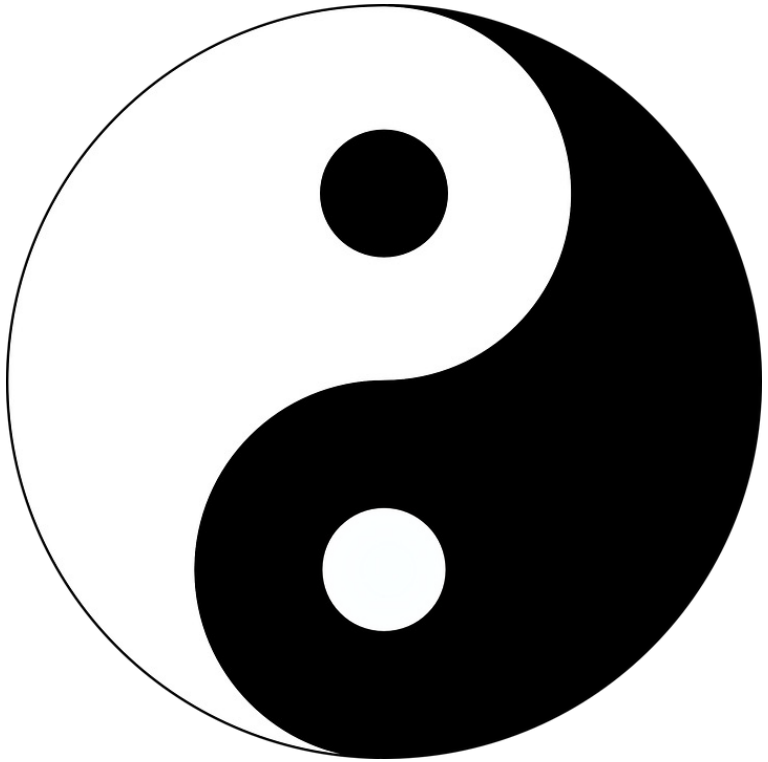
The dilemma continue between long term therapy vs fixed duration

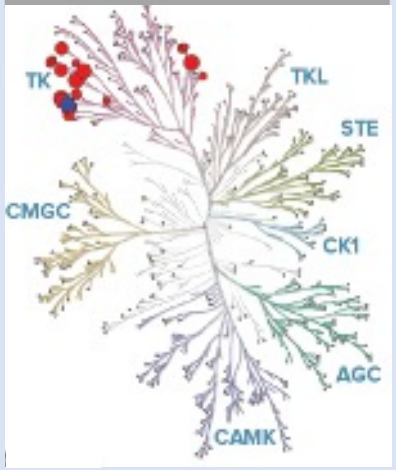


Author’slide

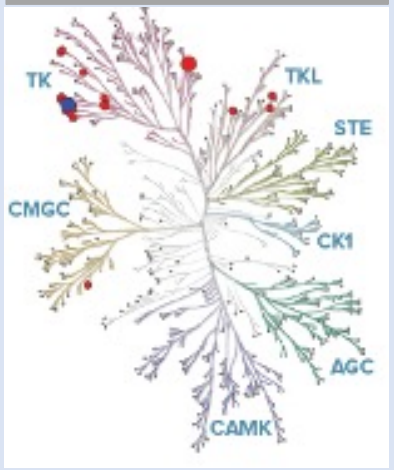
Several Covalent BTKi to Consider With Differences in BTKi Specificity, MOA, and Potential for Off-Target Effects

Covalent

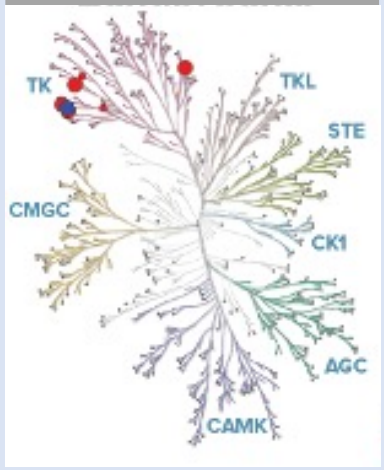
Ibrutinib[1]

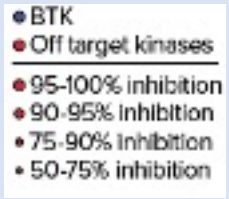


Acalabrutinib[1]



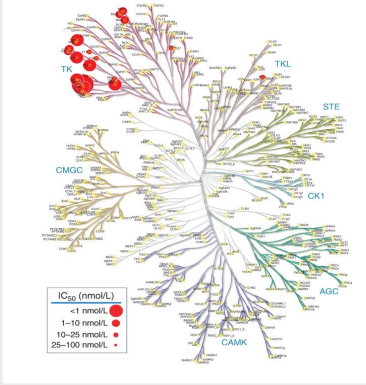
Zanubrutinib[1]



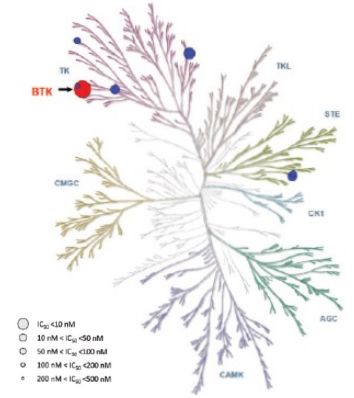


Noncovalent

Nemtabrutinib[2]



Pirtobrutinib[3]



1. Shadman M, et al. *Lancet Haematol*. 2023;10(1):e35-e45. 2. Reiff SD, et al. *Cancer Discov*. 2018;8(10):1300-1315.
3. Brandhuber B, et al. SOHO 2018. Abstract CLL-200.

ASH 2023 updates on trials

Front line BTKi

Ibrutinib NIH 10y

ELEVATE TN 6y

Captivate 5y

Glow 5y

GAIA 4y

Ibrutinib for CLL with TP53 alterations or for patients ≥ 65, 10 years

Study design

Single center, phase 2, investigator-initiated study
Registered NCT01500733

Enrolled 84 patients January '12 to January '14

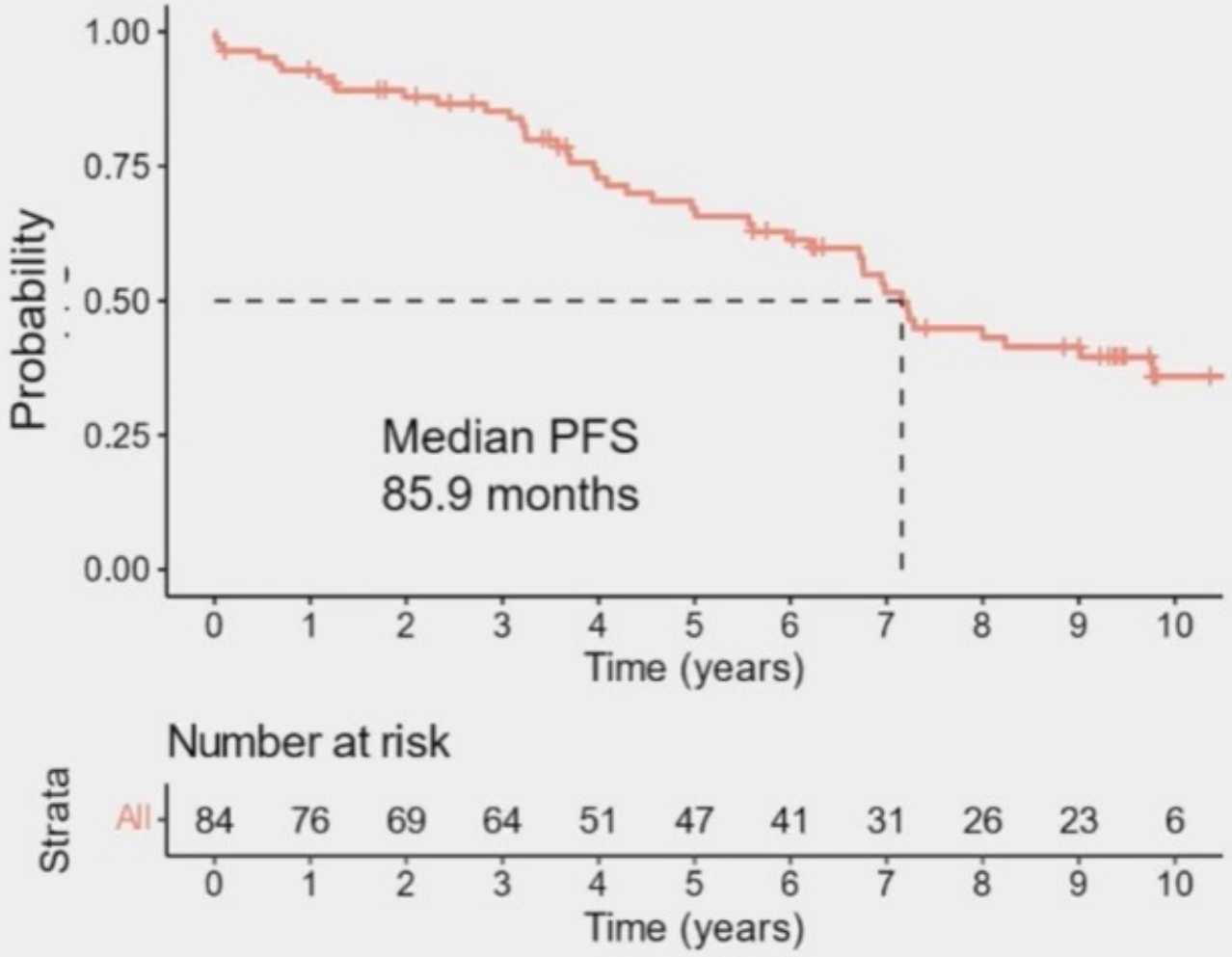
Patient characteristics

	TP53 cohort (n=50)	≥ 65 years (n=34)
Treatment status		
Tx-naïve	34 (68%)	18 (53%)
Relapsed/refractory	16 (32%)	16 (47%)
Median age (years)	62	69
Female	20 (40%)	16 (47%)
Male	30 (60%)	18 (53%)
Rai stage III/IV	32 (64%)	26 (76%)
IGHV, unmutated	34 (68%)	23 (68%)
TP53 alteration		
Del17p (>10% nuclei)	46 (92%)	0
TP53 mutation	4 (8%)	0

Itsara A, et al. ASH 2023. Abstract 201.

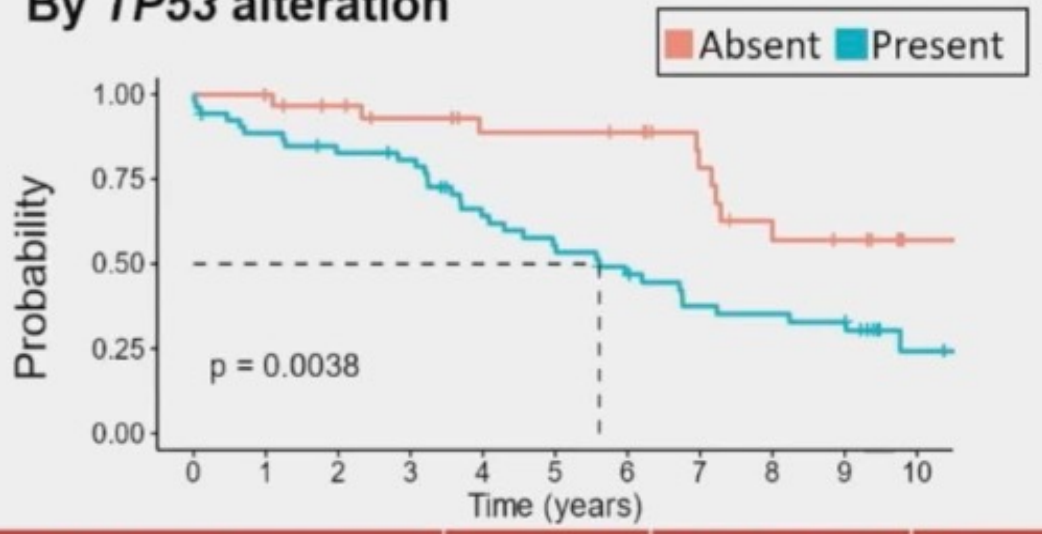
Progression-free survival (median follow-up 113 months)

All patients



Data cut 12-31-2022

By *TP53* alteration

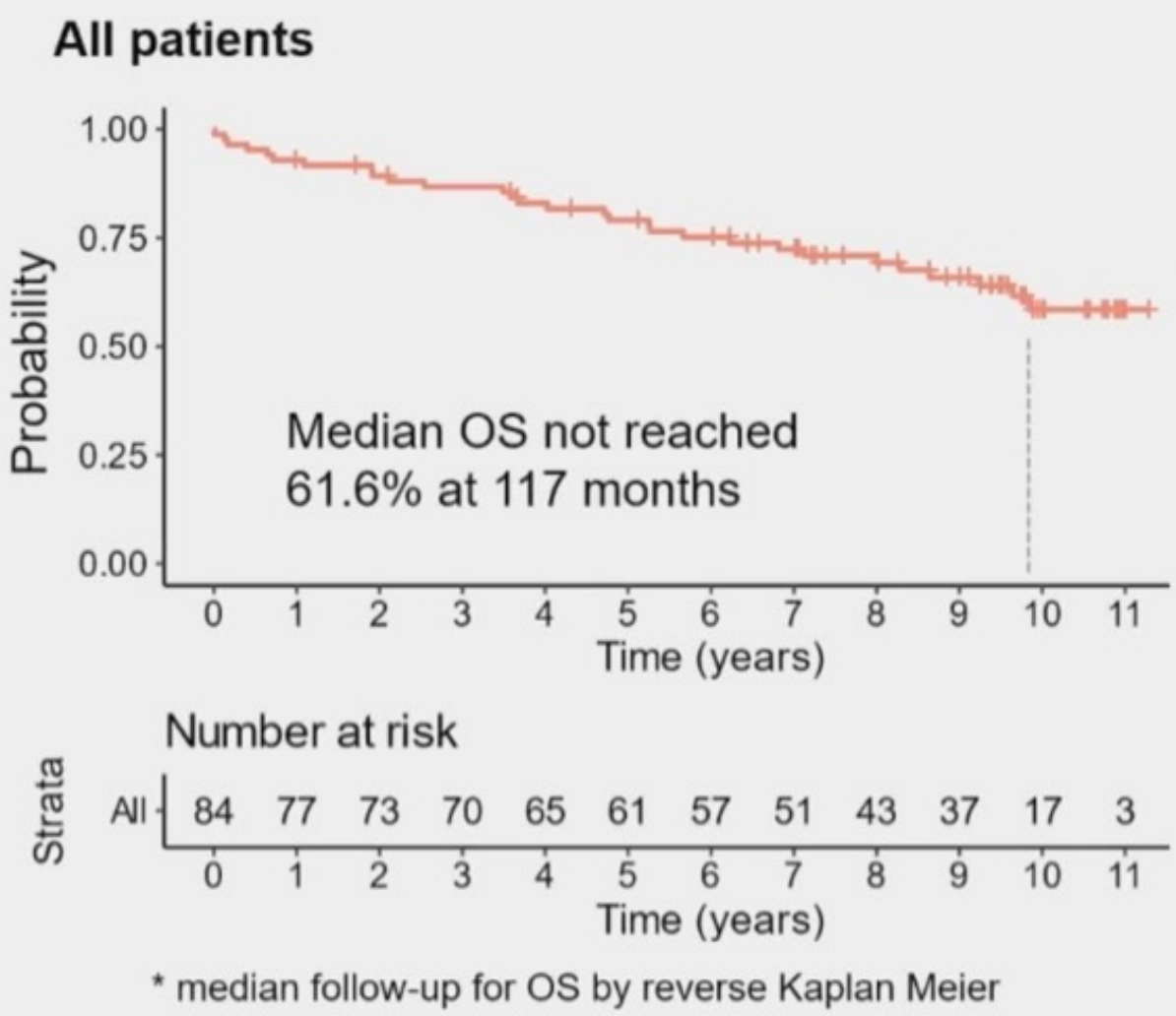


Risk category		mPFS (mo)	% PFS at mFU*	*P* =
TP53 alteration	Absent Present	NR 67.3	56.9% 30.3%	.004
Therapy status	TN Rel/ref	108 49	48.7% 22.4%	.016
IGHV	M U	117.2 80.6	57.1% 29.7%	.057

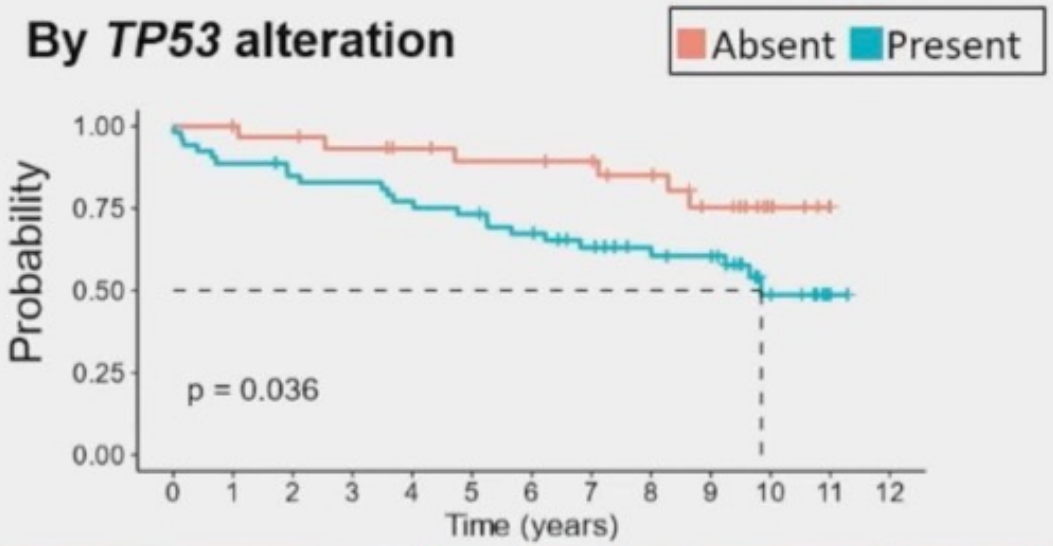
TN; treatment-naïve; rel/ref – relapsed/refractory;
IGHV, M, mutated; U, unmutated

Itsara A, et al. ASH 2023. Abstract 201.

Overall survival (median follow-up 117 months)*



* median follow-up for OS by reverse Kaplan Meier



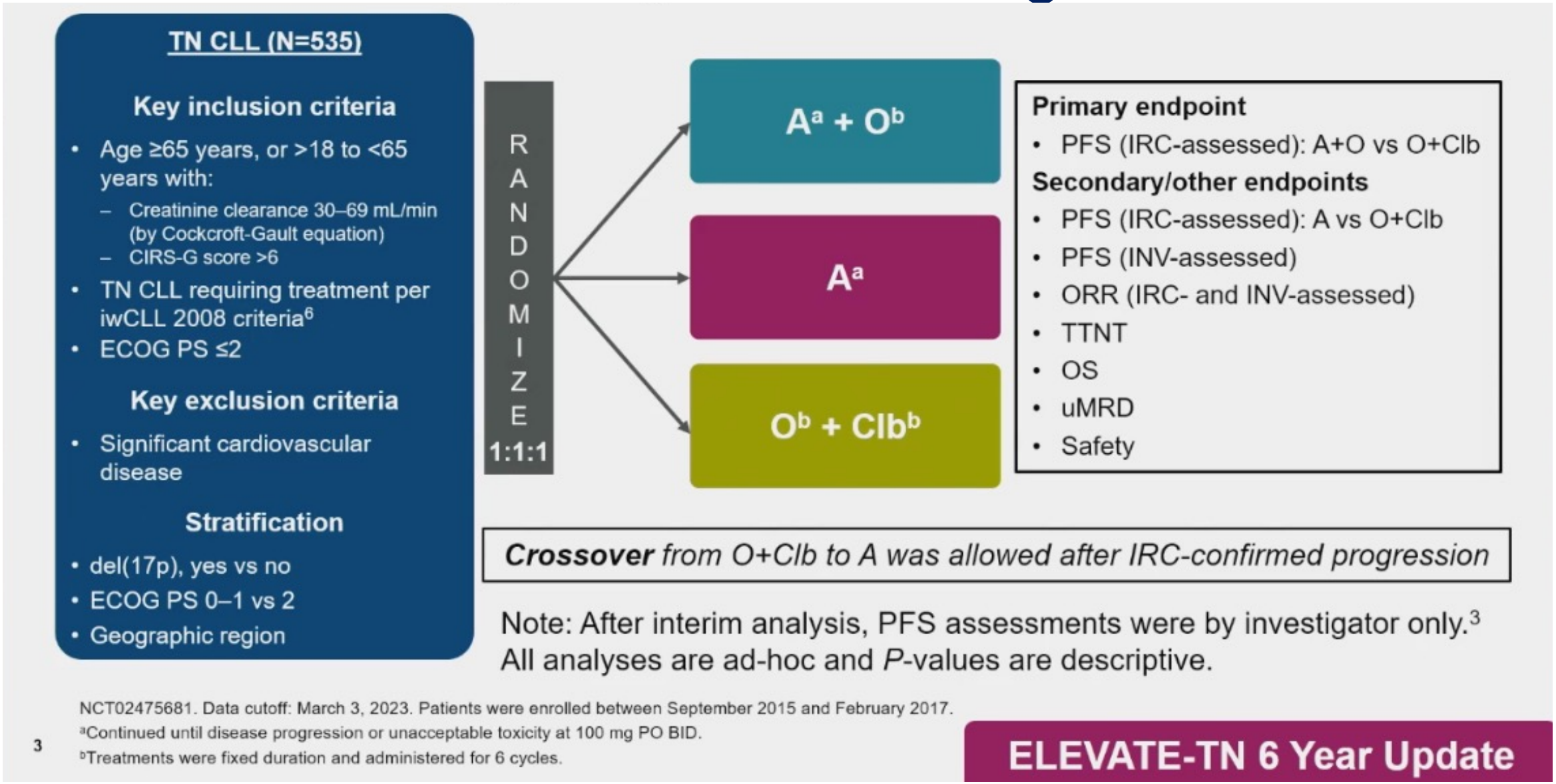
Risk category		mOS (m0)	% OS at mFU*	*P* =
TP53 alteration	Absent Present	NR 118	75.3 54.1	.036
Therapy status	TN Rel/ref	NR 104	73.8 41.6	.004
IGHV	M U	NR 118	77 52.7	.036

TN; treatment-naïve; rel/ref – relapsed/refractory;
IGHV, M, mutated; U, unmutated

Data cut 12-31-2022

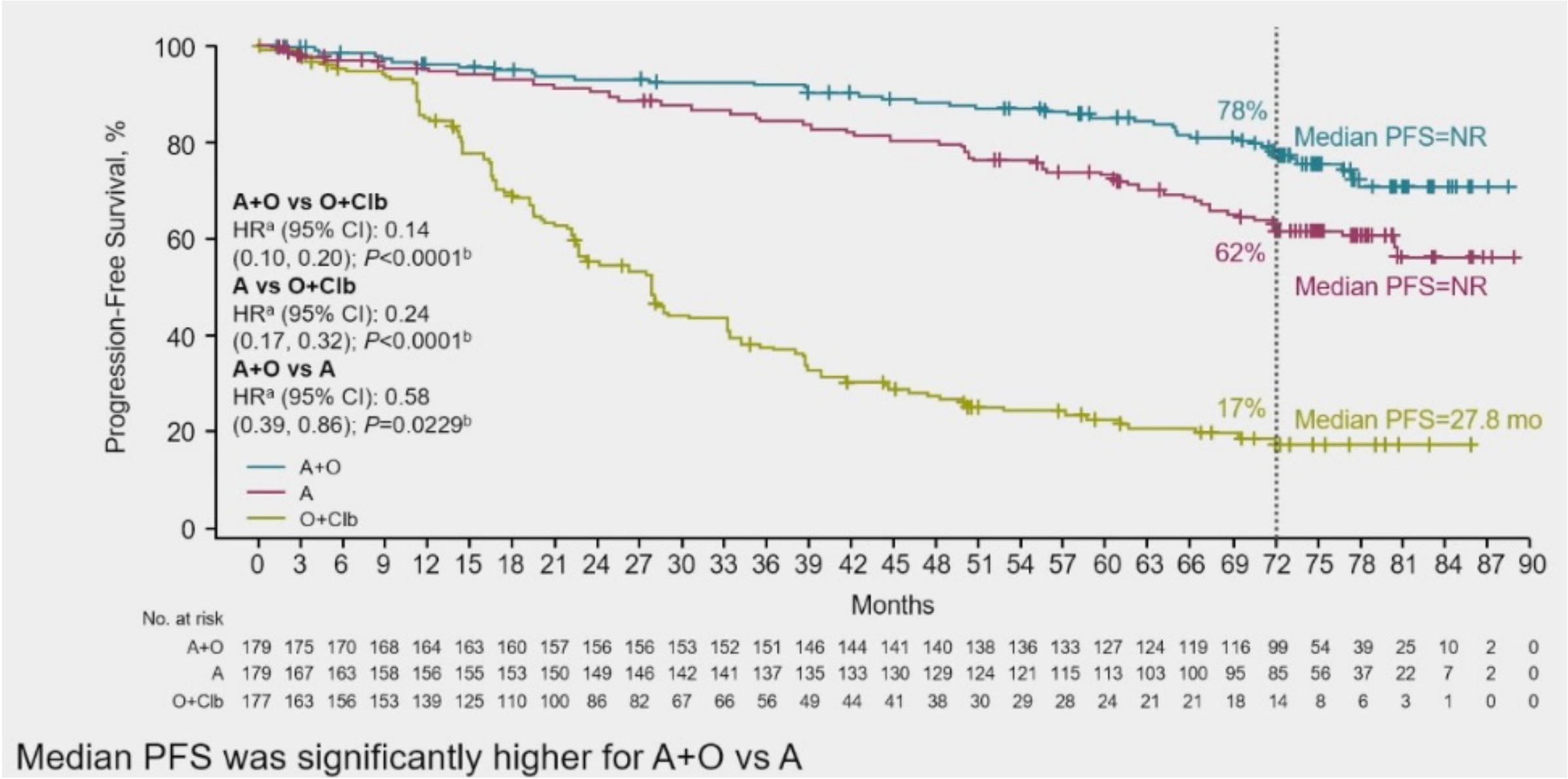
Itsara A, et al. ASH 2023. Abstract 201.

ELEVATE-TN Trial Design



Sharman J, et al. ASH 2023. Abstract 636.

PFS Update in ELEVATE-TN



Median PFS was significantly higher for A+O vs A

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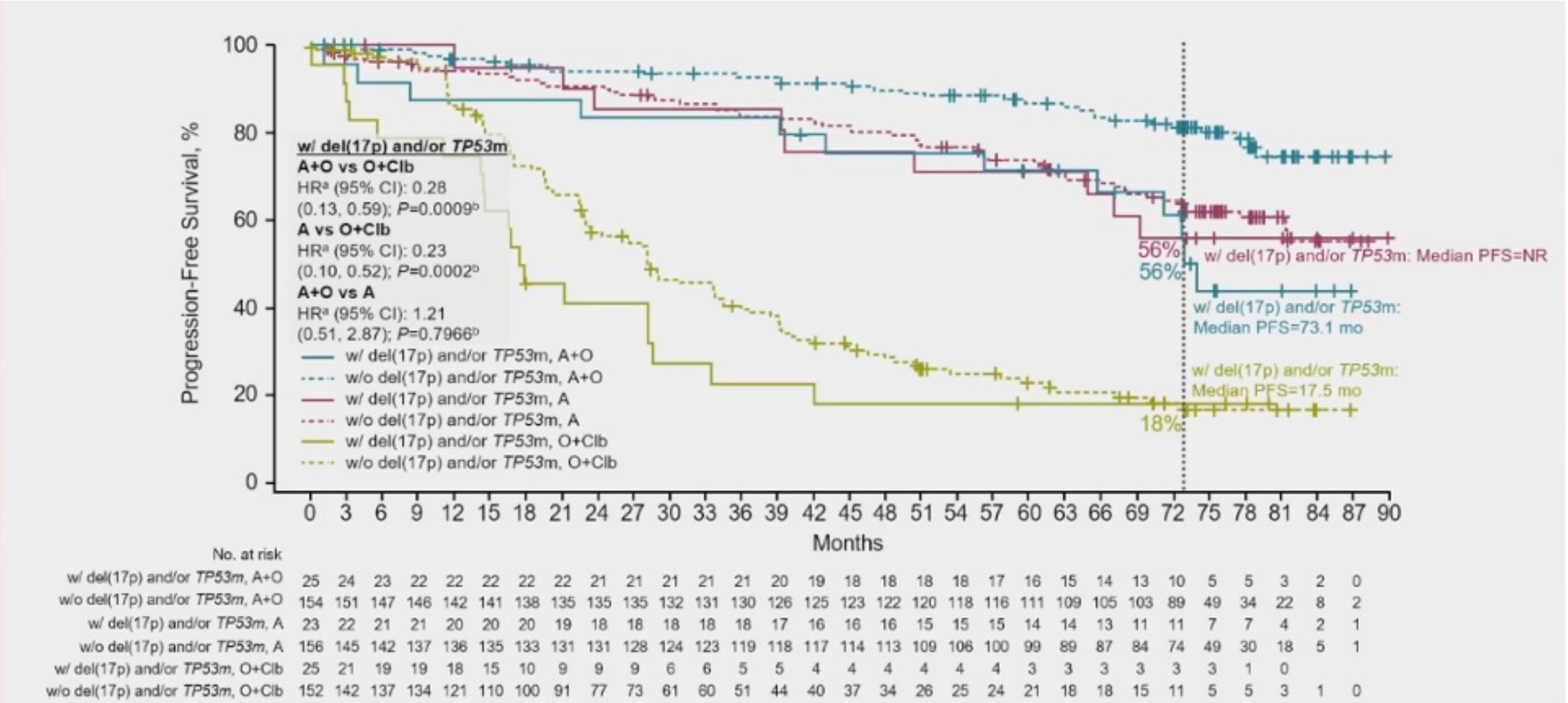
Impact of del(17p) and/or TP53m by Treatment Arm



No. at risk																														
w/ del(17p) and/or *TP53m*, A+O	25	24	23	22	22	22	22	22	21	21	21	21	21	20	19	18	18	18	18	17	16	15	14	13	10	5	5	3	2	0
w/o del(17p) and/or *TP53m*, A+O	154	151	147	146	142	141	138	135	135	135	132	131	130	126	125	123	122	120	118	116	111	109	105	103	89	49	34	22	8	2
w/ del(17p) and/or *TP53m*, A	23	22	21	21	20	20	20	19	18	18	18	18	18	17	16	16	16	15	15	15	14	14	13	11	11	7	7	4	2	1
w/o del(17p) and/or *TP53m*, A	156	145	142	137	136	135	133	131	131	128	124	123	119	118	117	114	113	109	106	100	99	89	87	84	74	49	30	18	5	1
w/ del(17p) and/or *TP53m*, O+Clb	25	21	19	19	18	15	10	9	9	9	6	6	5	5	4	4	4	4	4	4	3	3	3	3	3	3	1	0		
w/o del(17p) and/or *TP53m*, O+Clb	152	142	137	134	121	110	100	91	77	73	61	60	51	44	40	37	34	26	25	24	21	18	18	15	11	5	5	3	1	0

Sharman J, et al. ASH 2023. Abstract 636.

ASH 2023 updates and new trials

Front line fixed duration

Captivate 5y

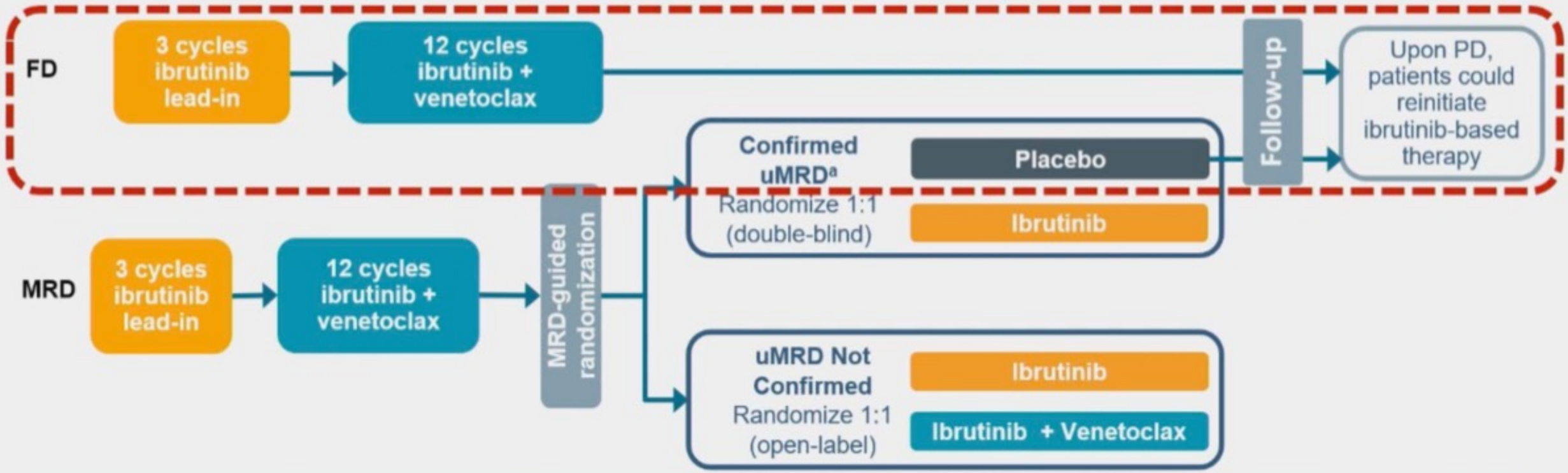
Glow 5y

GAIA 4y

FLAIR

CAPTIVATE Study Design

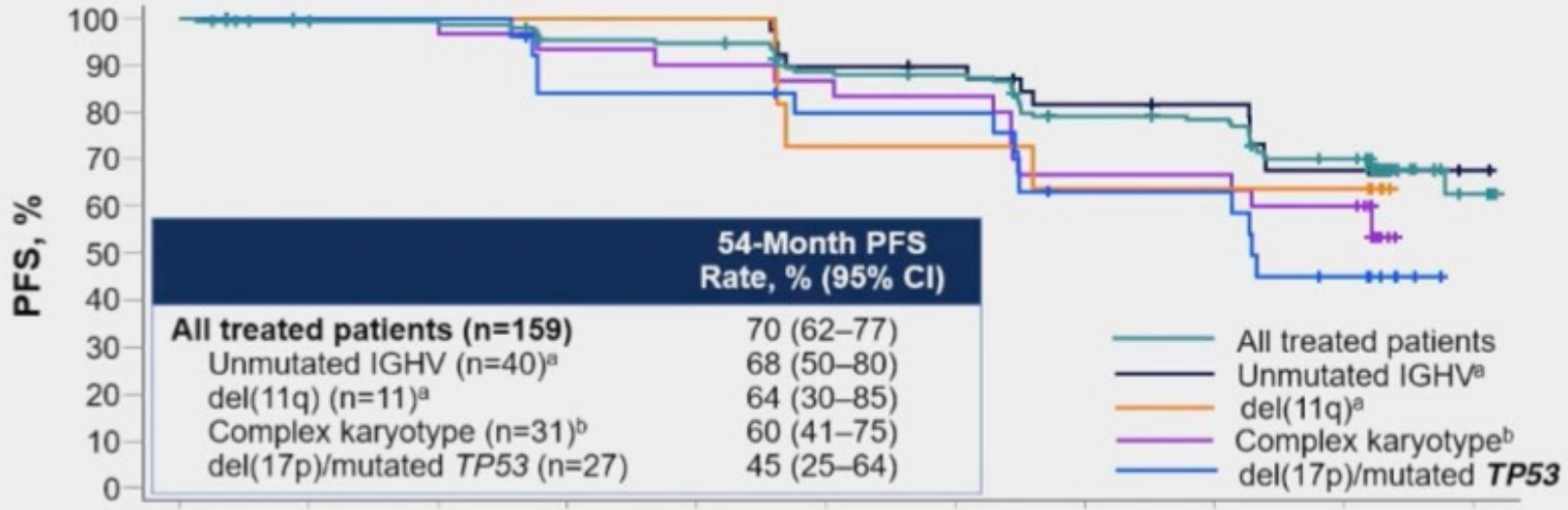
- CAPTIVATE (PCYC-1142; NCT02910583) is an international, multicenter phase 2 study evaluating first-line treatment with ibrutinib + venetoclax that comprises 2 cohorts: MRD[1] and FD[2]
  - Per protocol, patients with PD after completion of fixed-duration ibrutinib + venetoclax in the FD cohort or MRD cohort placebo arm could reinitiate treatment with single-agent ibrutinib
  - Patients with PD >2 years after treatment completion in the FD cohort could be retreated with the fixed-duration regimen (3 cycles of ibrutinib then 12 cycles of ibrutinib + venetoclax)



Ghia et al ASH 2023

FD Cohort: Overall Median PFS Was Not Reached With Up To 5 Years Of Follow-Up

- With median time on study of 56 months (range, 1–61), 54-month PFS and OS rates were 70% (95% CI, 62–77) and 97% (95% CI, 93–99), respectively
  - PFS promising across most high-risk features; numerically lower in those with del(17p)/mutated *TP53*



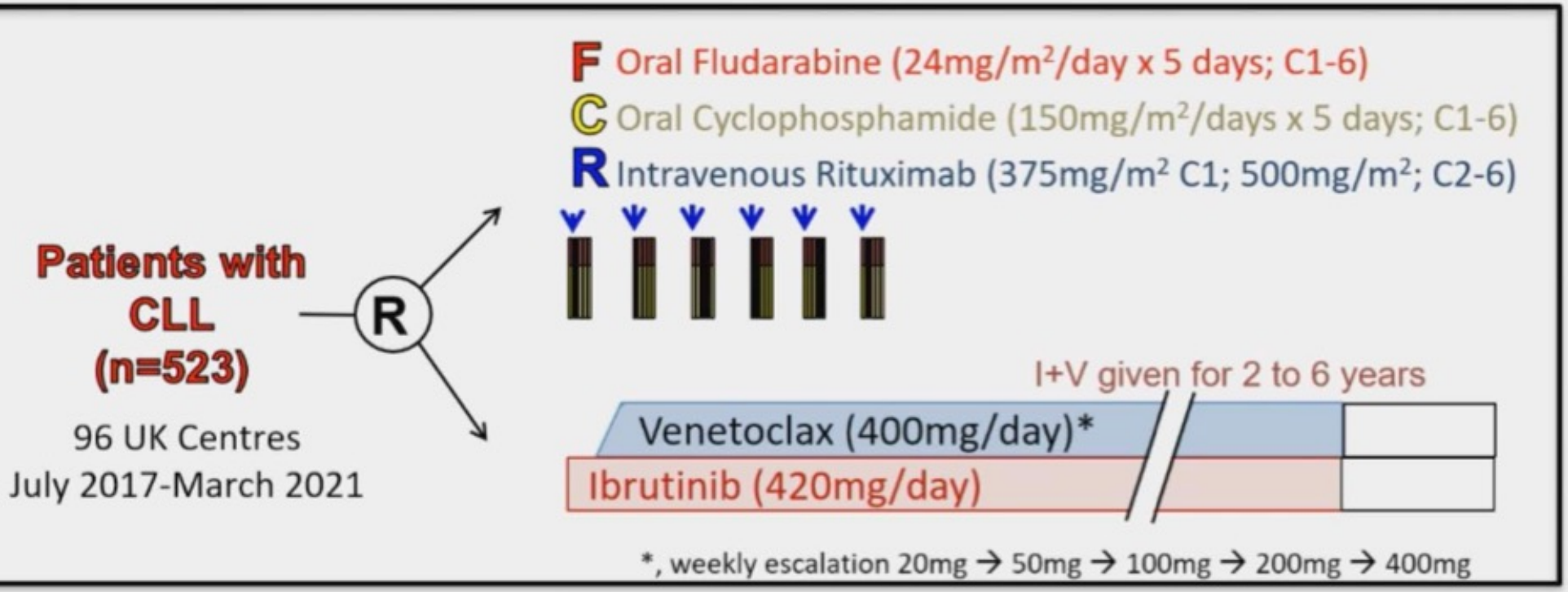
Patients at risk

All treated patients	159	153	152	144	143	132	130	115	113	99	11
Unmutated IGHV[a]	40	39	39	39	39	35	34	30	29	24	1
del(11q)[a]	11	11	11	11	11	8	8	7	7	7	0
Complex karyotype[b]	31	31	31	28	27	26	25	20	20	18	0
del(17p)/mutated ***TP53***	27	26	26	21	21	19	19	14	14	9	0

- Best response rates remain: CR/CRi, 58%; ORR, 96%[1]
  - In patients who achieved CR/CRi (n=92), median duration of CR/CRi was not reached

Ghia et al ASH 2023

Flair FCR vs I+V: Trial design



Primary end-point:
To assess whether I+V is superior to FCR in terms of PFS

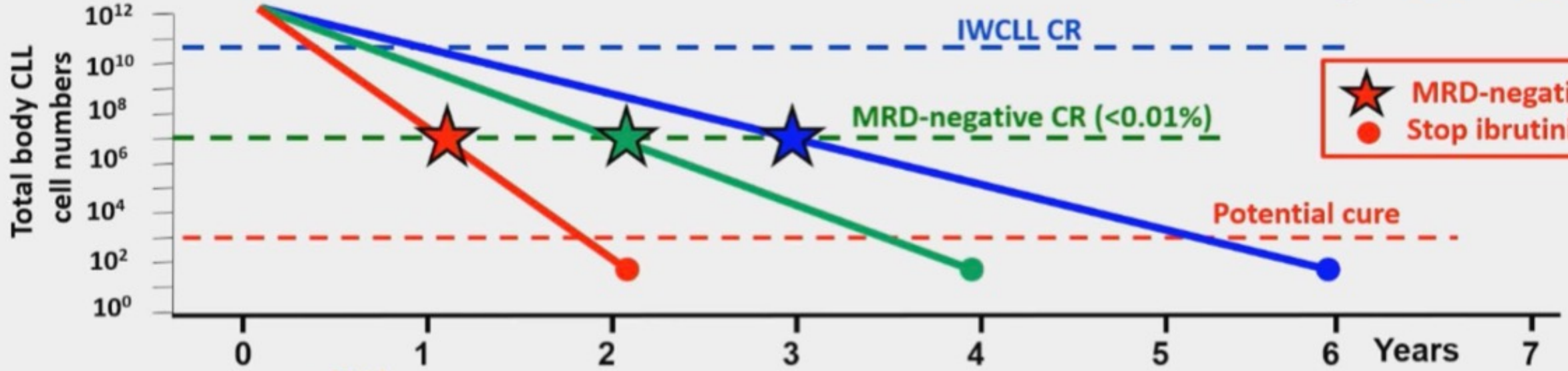
Key secondary end-points:
Overall survival
Response incl. MRD
Safety and toxicity

Key Inclusion Criteria:

- Previously untreated CLL requiring therapy by IWCLL criteria
- Considered fit for FCR
- ≤75 years old

Key Exclusion Criteria:
Prior therapy for CLL; History of Richter's transformation; >20% TP53 deletion by FISH; Concomitant warfarin (or equivalent) Symptomatic cardiac failure or angina

Stopping rules for ibrutinib + venetoclax in Flair



Testing schedule
(Central lab, MRD flow, MRD negative <1 CLL cell in 10^4)

If PB MRD negative repeat after 3 months and then PB and BM at 6 months – if all MRD negative then first PB MRD negative result is time to MRD negativity

Defining treatment duration
2 to 6 years Ibrutinib or both ibr+venetoclax
Double time after MRD negative

Restart ibrutinib + venetoclax if becomes MRD positive prior to Year 6

Hillmen *et al.*, Abstract 631, ASH 2023

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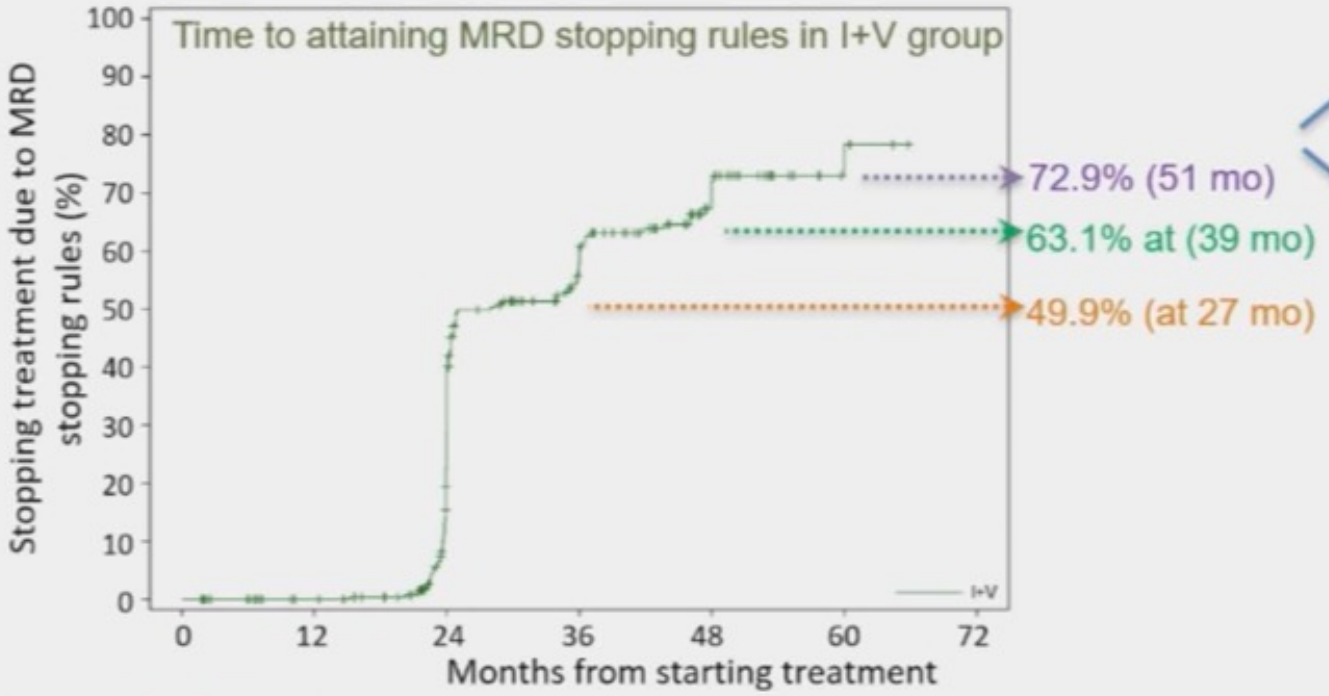
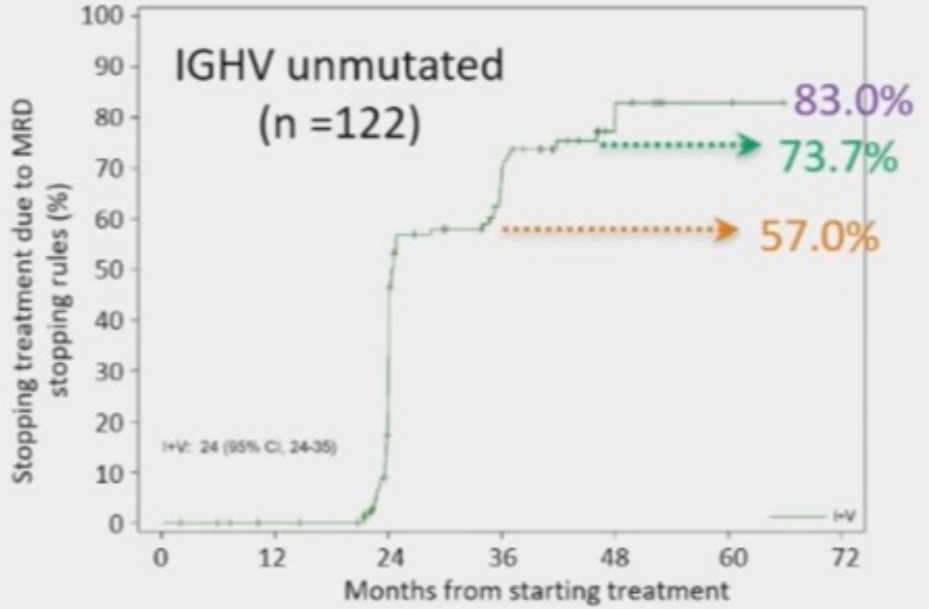
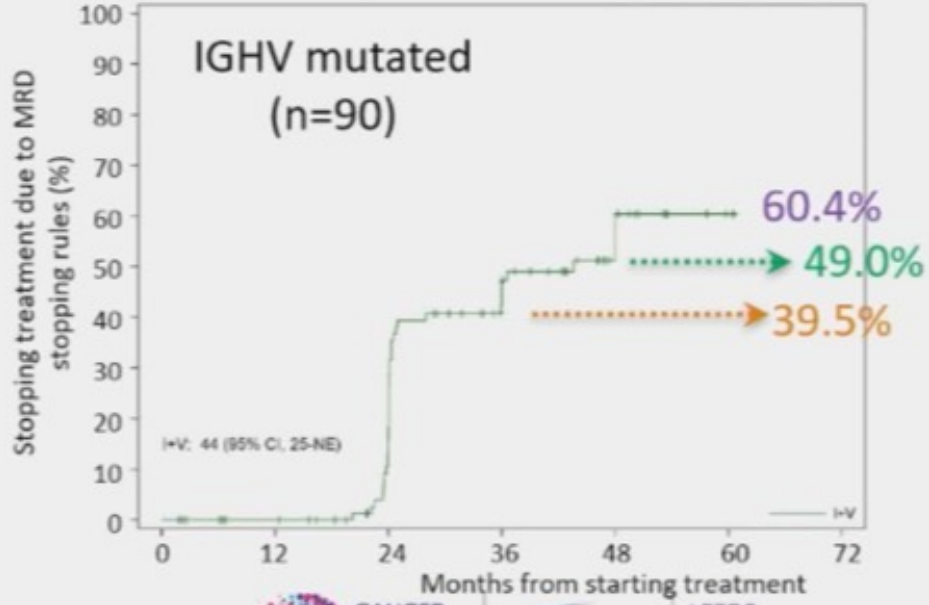
Flair iwCLL response and MRD stopping rules

iwCLL Responses

	Complete Response/CRi		Overall Response		BM uMRD
	9 months	Anytime	9 months	Anytime	Anytime
FCR	49%	71.5%	76.4%	83.7%	40.3%
I+V	59.2%	92.3%	86.5%	95.4%	61.9%
	Odds ratio: 1.51 P<0.05		Odds ratio: 2.0 P<0.005		







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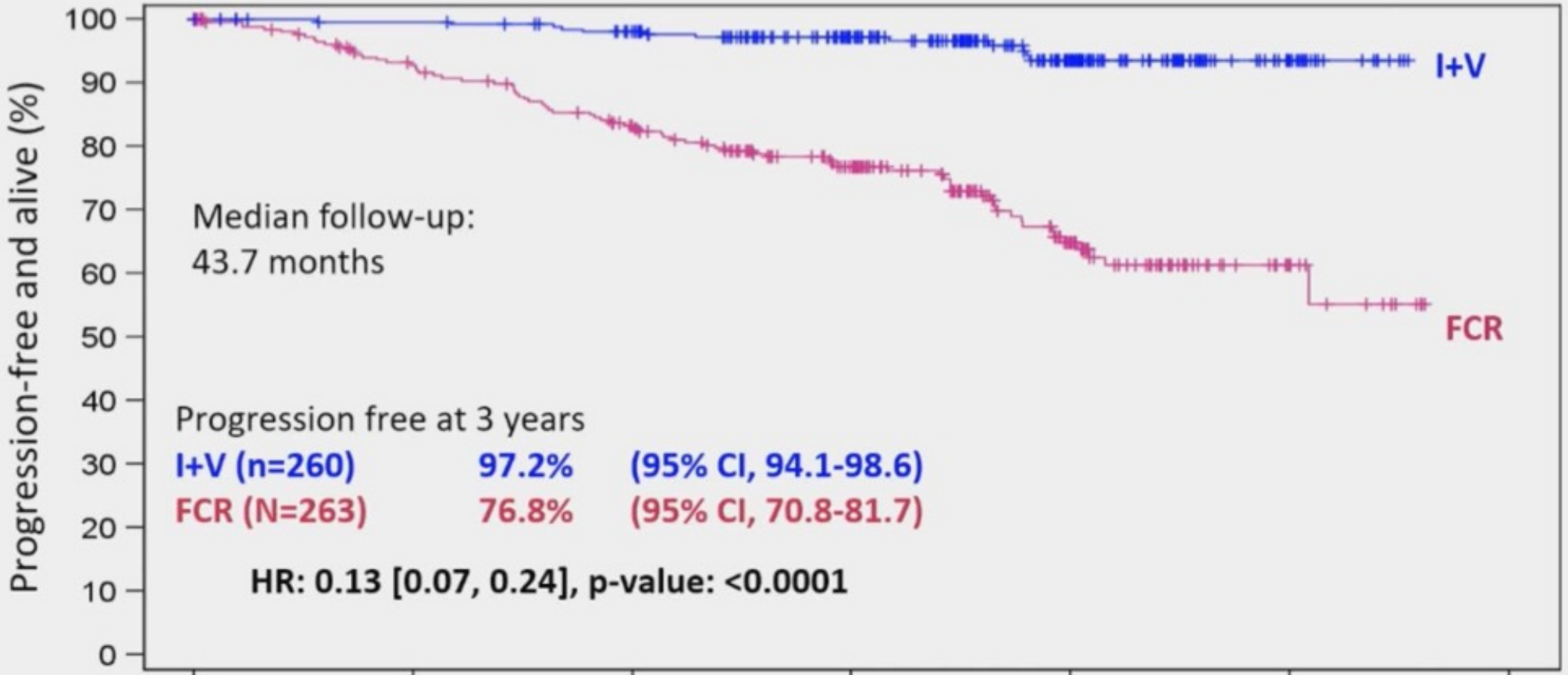
Flair Primary end-point: PFS for FCR versus I+V



No. at risk						
I+V	260	253	239	183	99	21	0
FCR	263	227	194	145	68	12	0

National Cancer Research Institute

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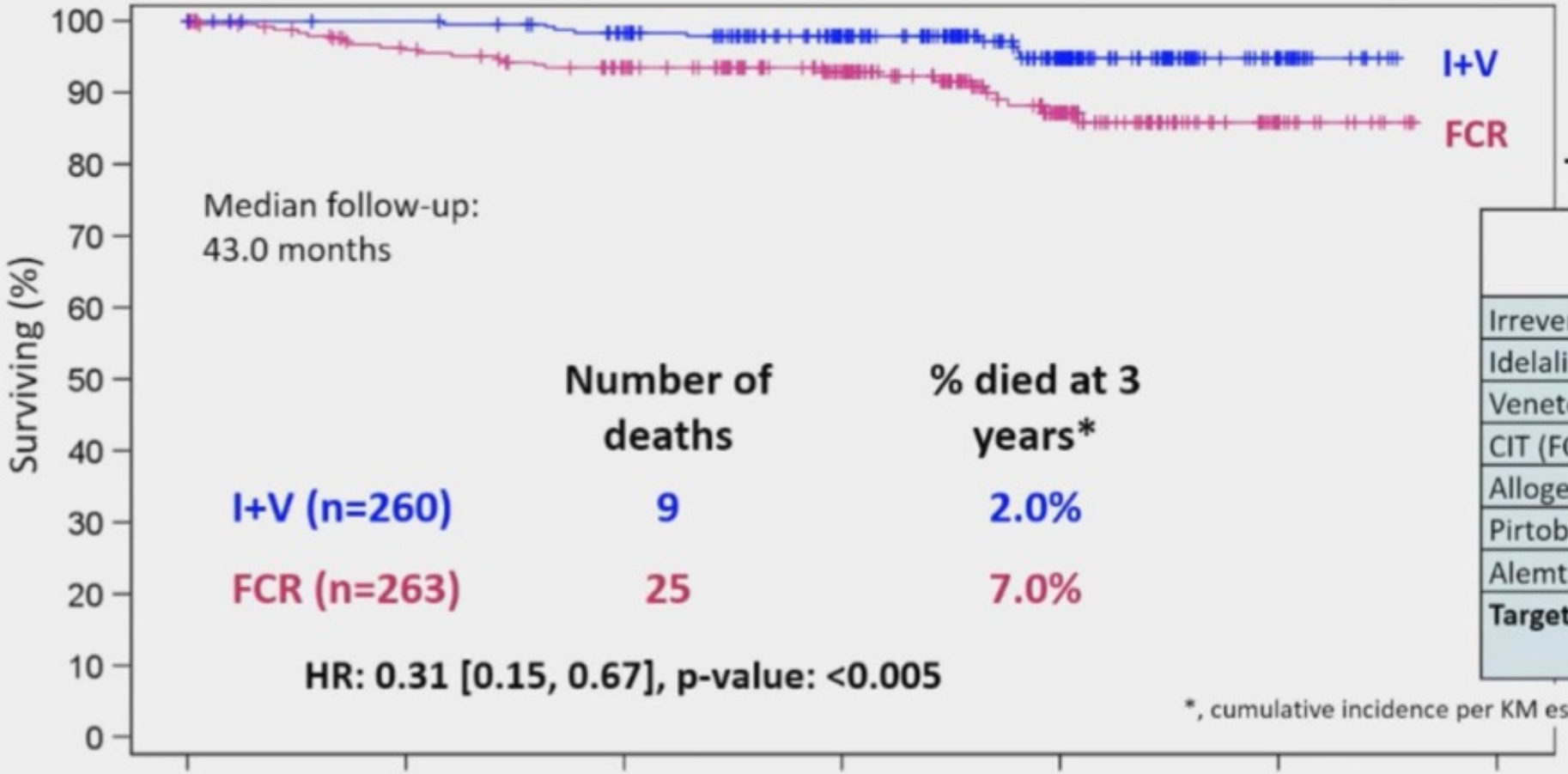
Flair Overall Survival in FCR versus I+V



Treatment after progression

	FCR (n=42)	I+V (n=5)
Irreversible BTKi	23	2
Idelalisib + R	1	0
Venetoclax + R	11	0
CIT (FCR/BR/ChlR)	6	1
Allogeneic SCT	1	0
Pirtobrutinib	0	1
Alemtuzumab	0	1
Targeted therapy for CLL	**35/42 (83%)**	**3/5 (60%)**

ASH 2023 updates on trials

Relapsed/Refractory

Alpine 40m

Bruin 30m

ALPINE Study Design

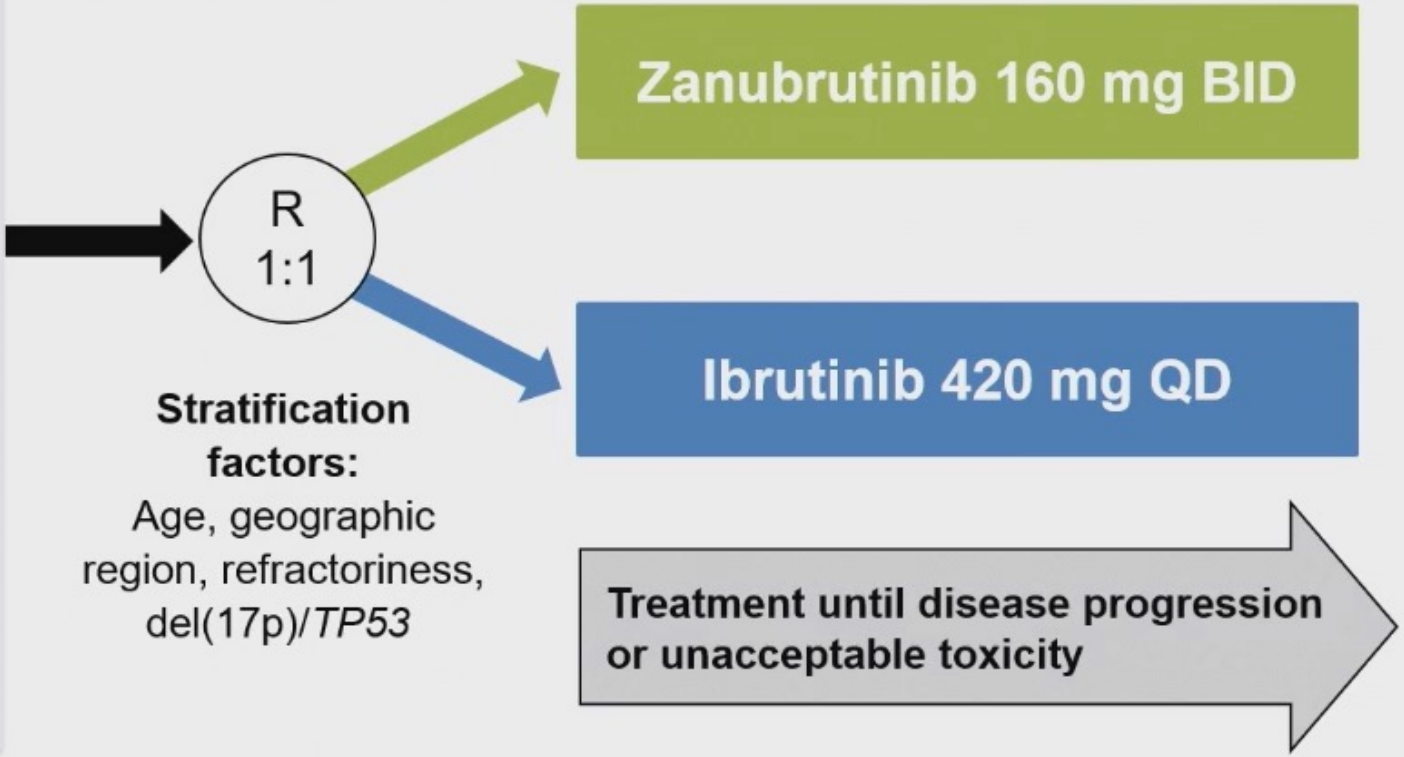
R/R CLL/SLL with ≥1 prior treatment
(N=652)

Key Inclusion Criteria

- R/R to ≥1 prior systemic therapy for CLL/SLL
- Measurable lymphadenopathy by CT or MRI
- Requires treatment per iwCLL

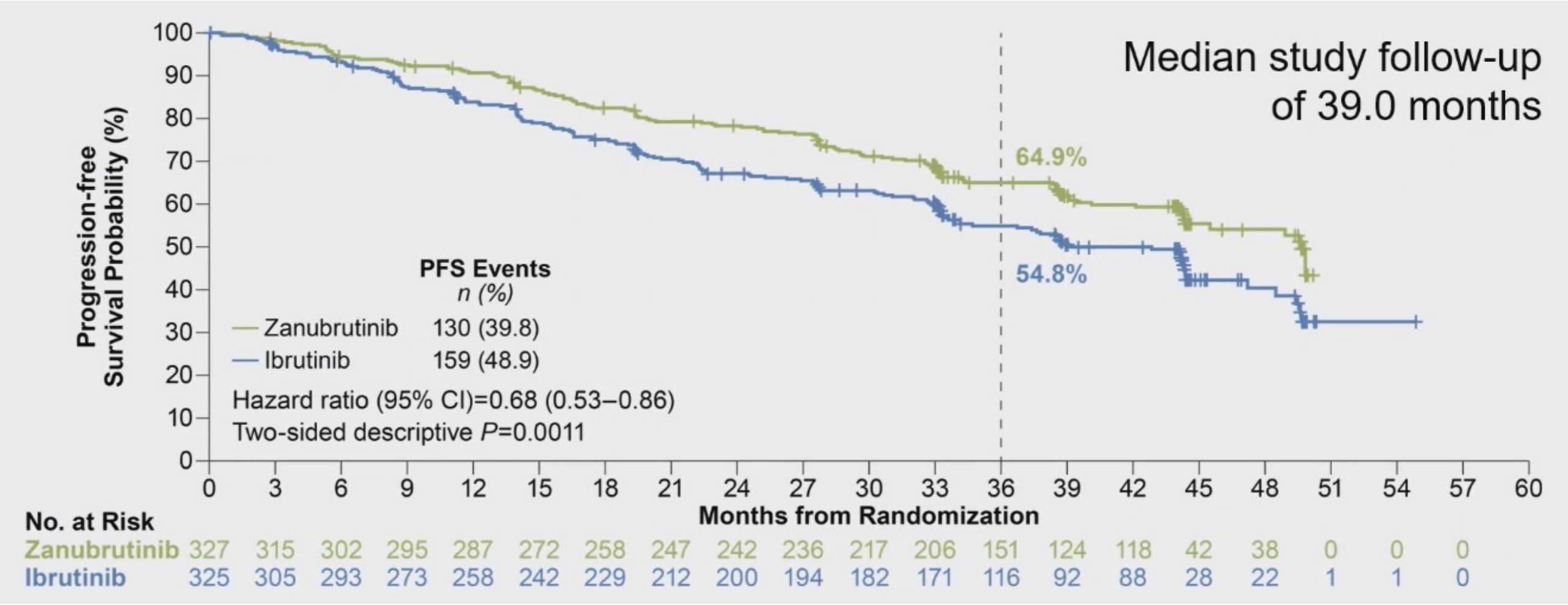
Key Exclusion Criteria

- Prior BTK inhibitor therapy
- Treatment with warfarin or other vitamin K antagonists



Brown J, et al. ASH 2023. Abstract 202.

Zanubrutinib: PFS Benefit at 39 Months



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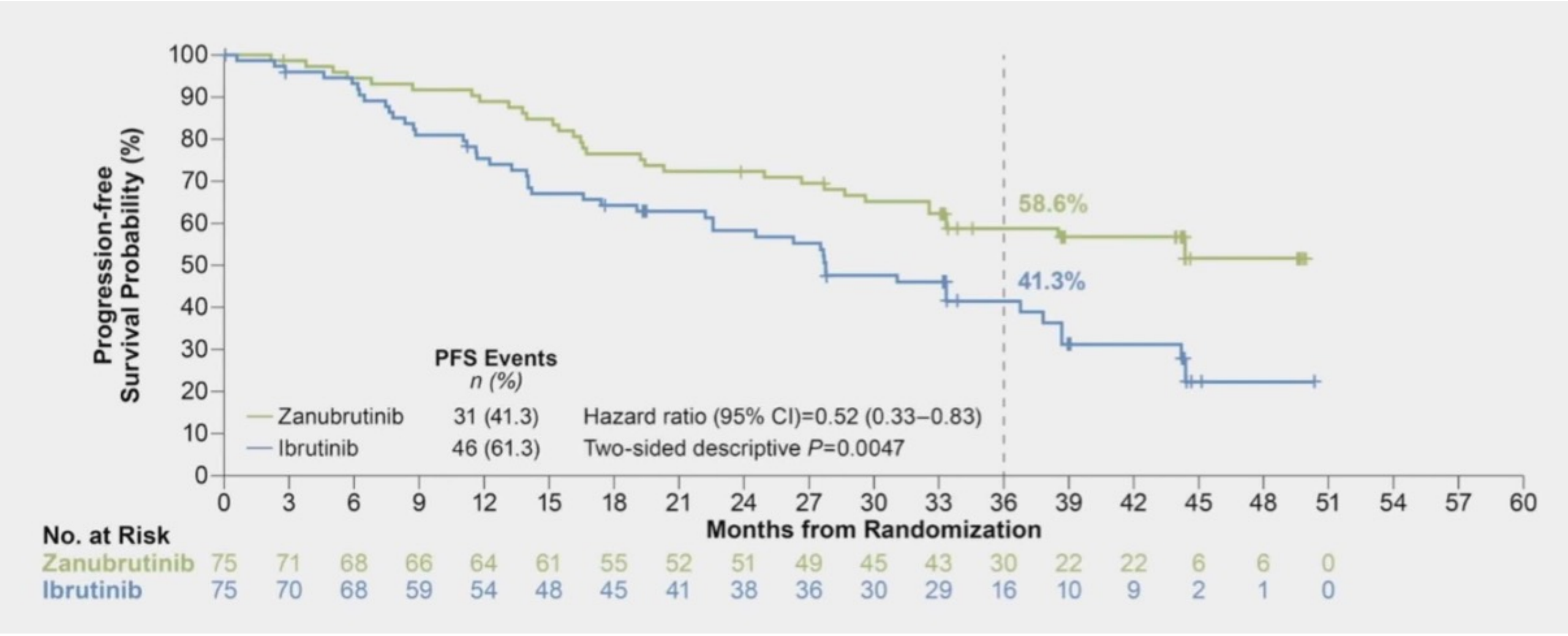
Zanubrutinib: PFS Benefit at 39 Months in del17p/TP53



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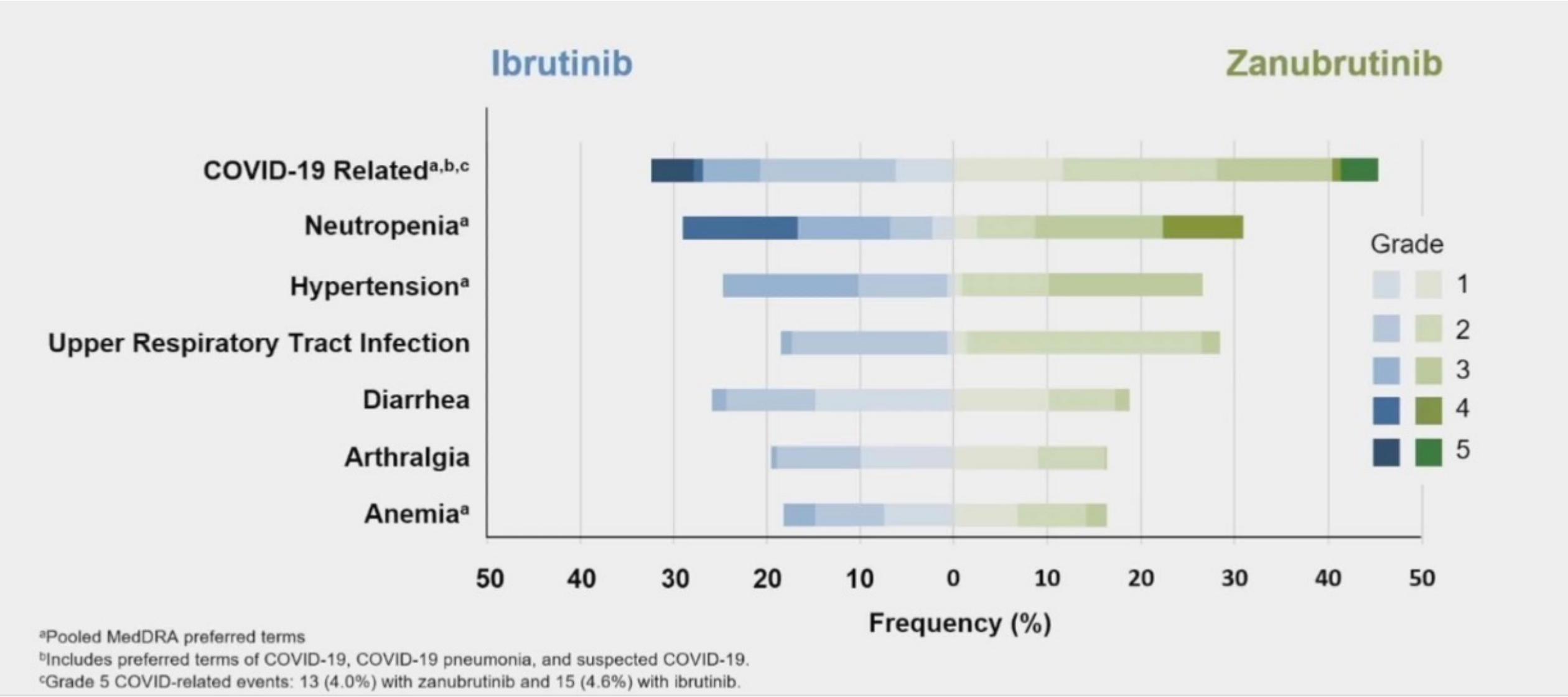
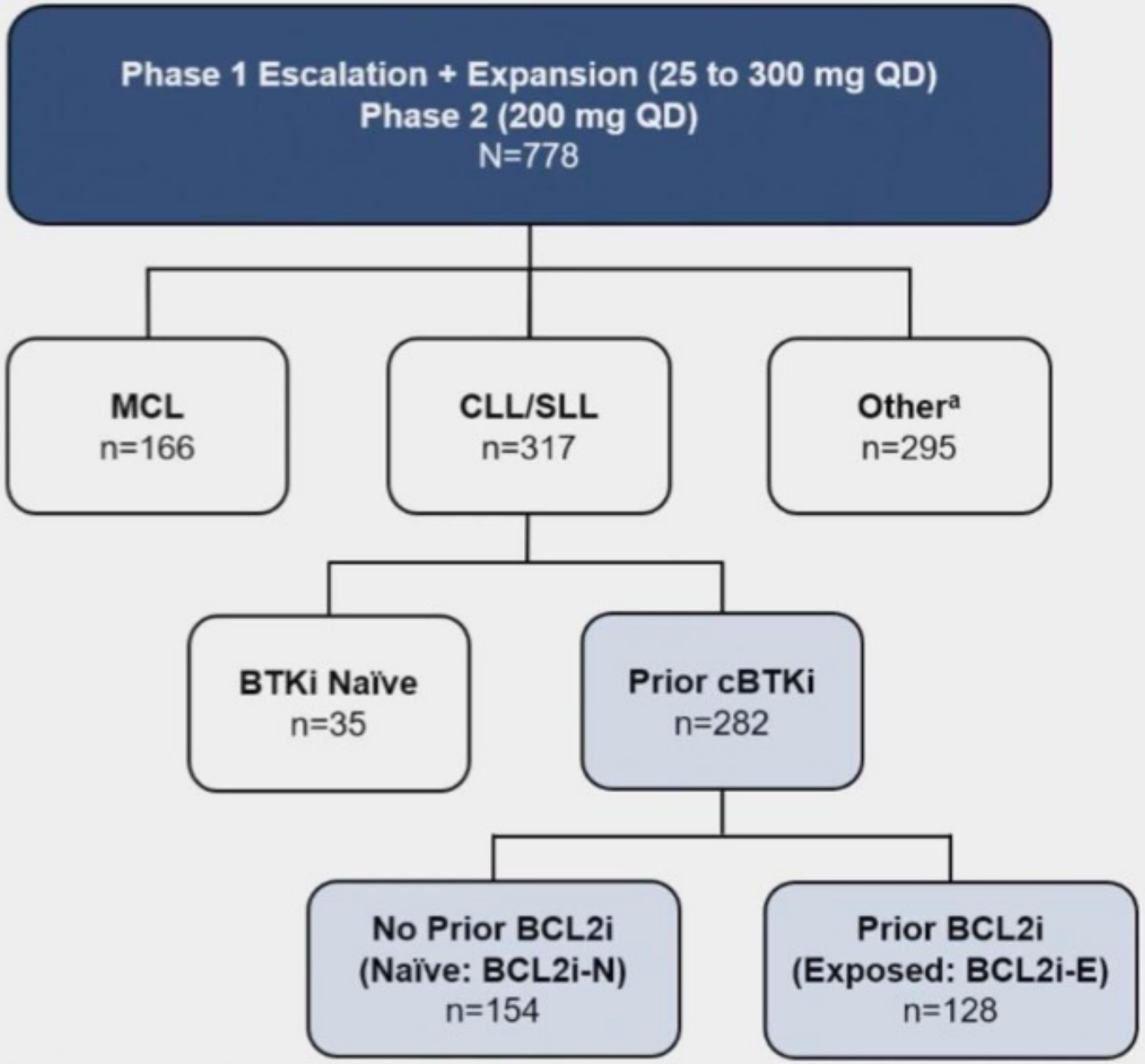
Alpine: most common Adverse effects by grade



[a]Pooled MedDRA preferred terms
[b]Includes preferred terms of COVID-19, COVID-19 pneumonia, and suspected COVID-19.
[c]Grade 5 COVID-related events: 13 (4.0%) with zanubrutinib and 15 (4.6%) with ibrutinib.

Brown J, et al. ASH 2023. Abstract 202.

Phase 1/2 BRUIN Study: Design, Eligibility and Enrollment



Phase 1 3+3 design

- 28-day cycles
- Intra-patient dose escalation allowed
- Cohort expansion permitted at doses deemed safe

Eligibility

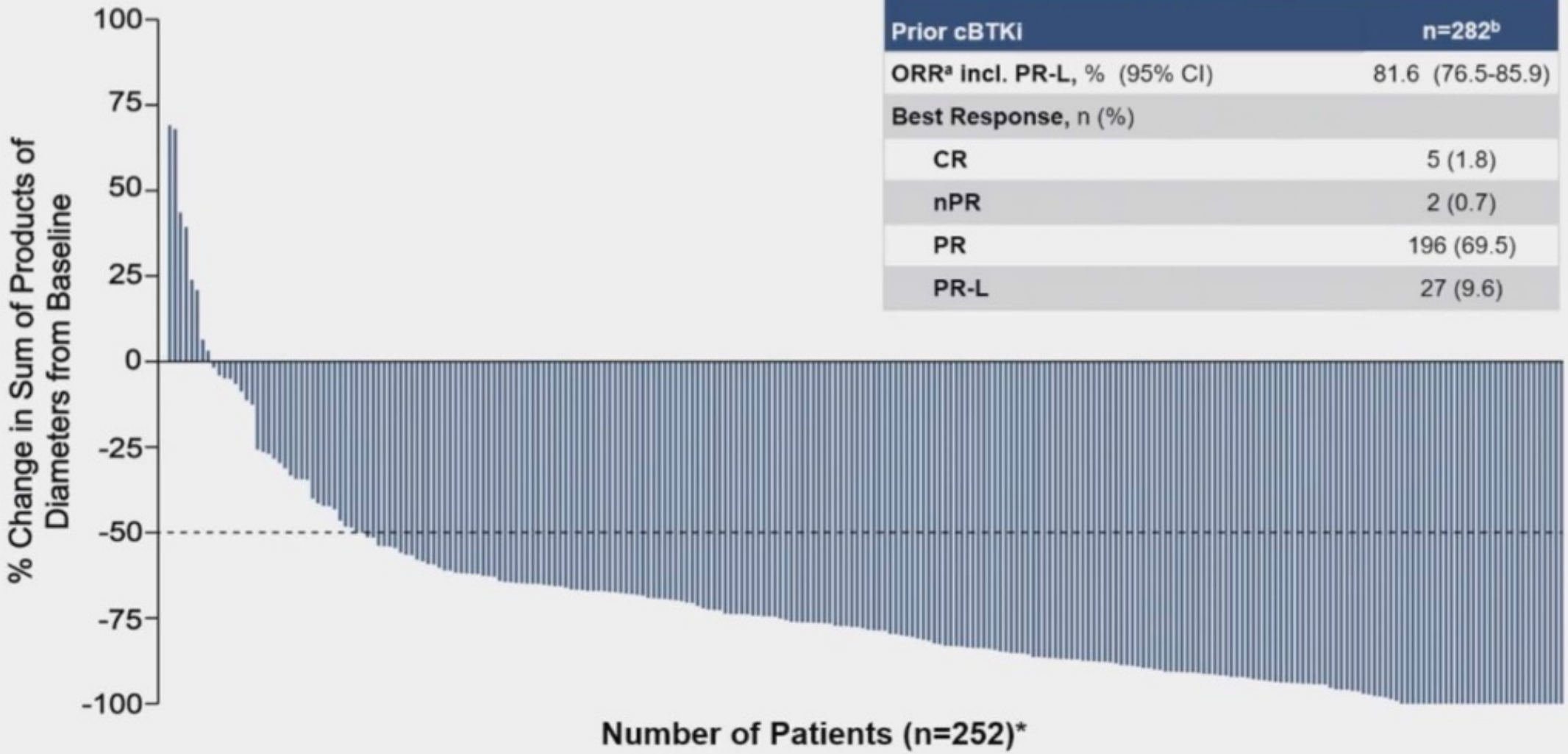
- Age ≥18
- ECOG PS 0-2
- Active disease and in need of treatment
- Previously treated

Key endpoints

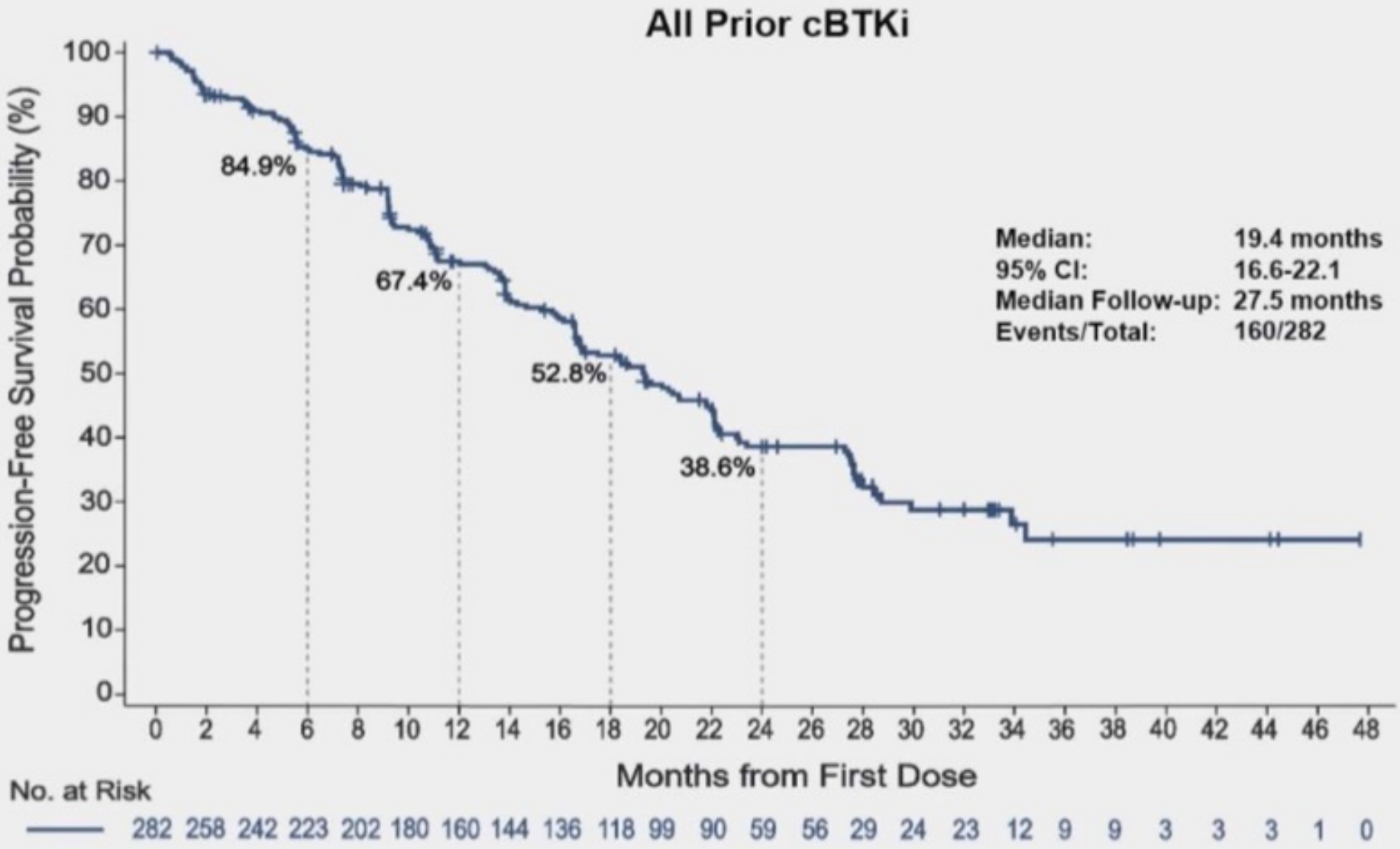
- Safety/tolerability
- Determine MTD and RP2D
- Pharmacokinetics
- Efficacy (ORR according to iwCLL 2018 criteria, DoR, PFS, and OS)

Pirtobrutinib Efficacy in All Patients with CLL/SLL who Received Prior cBTKi

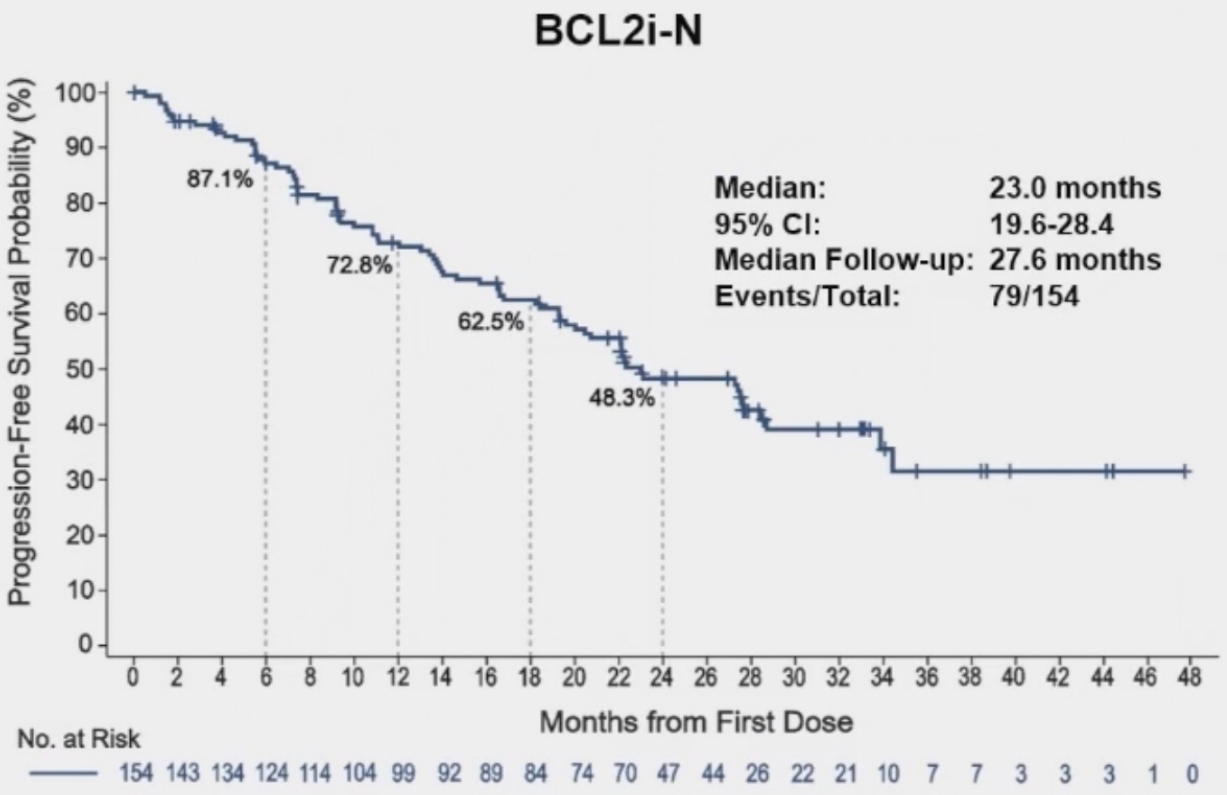
Prior cBTKi	n=282[b]
ORR[a] incl. PR-L, % (95% CI)	81.6 (76.5-85.9)
Best Response, n (%)	
CR	5 (1.8)
nPR	2 (0.7)
PR	196 (69.5)
PR-L	27 (9.6)

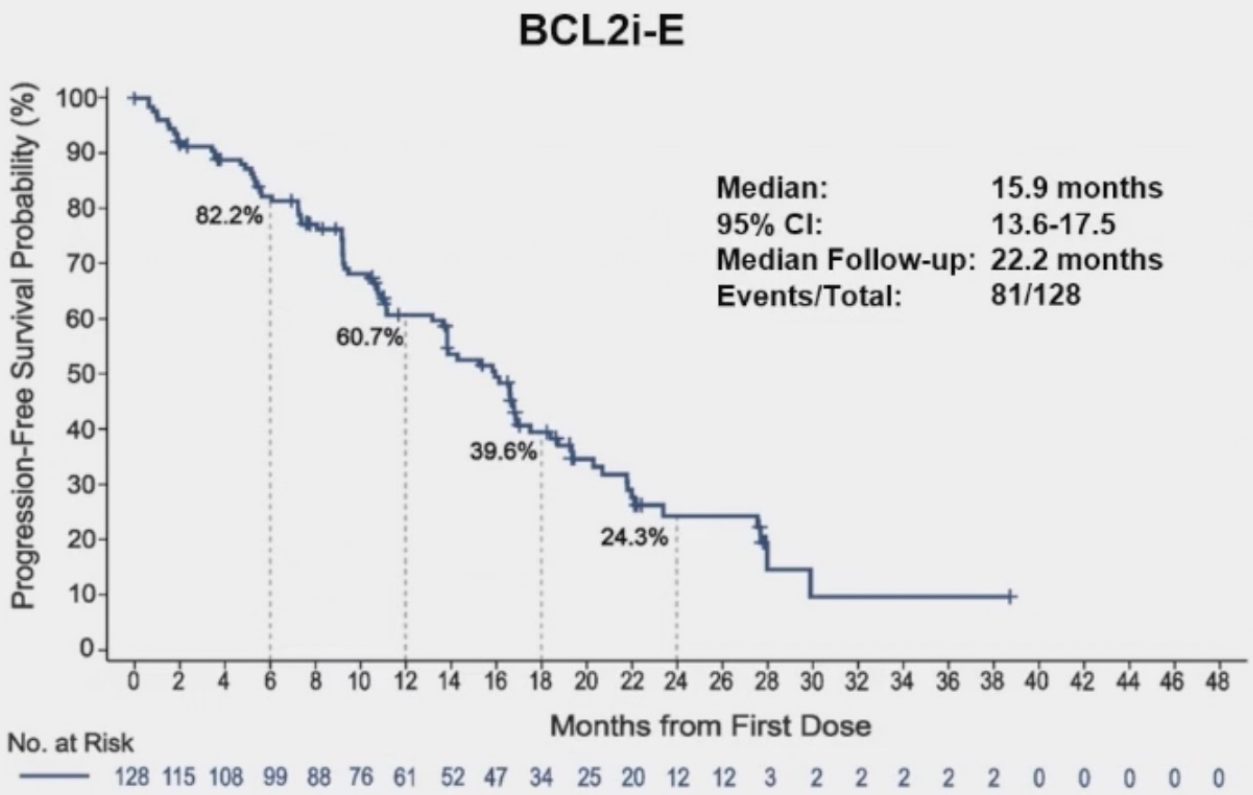


Pirtobrutinib Progression-Free Survival in Patients with Prior cBTKi



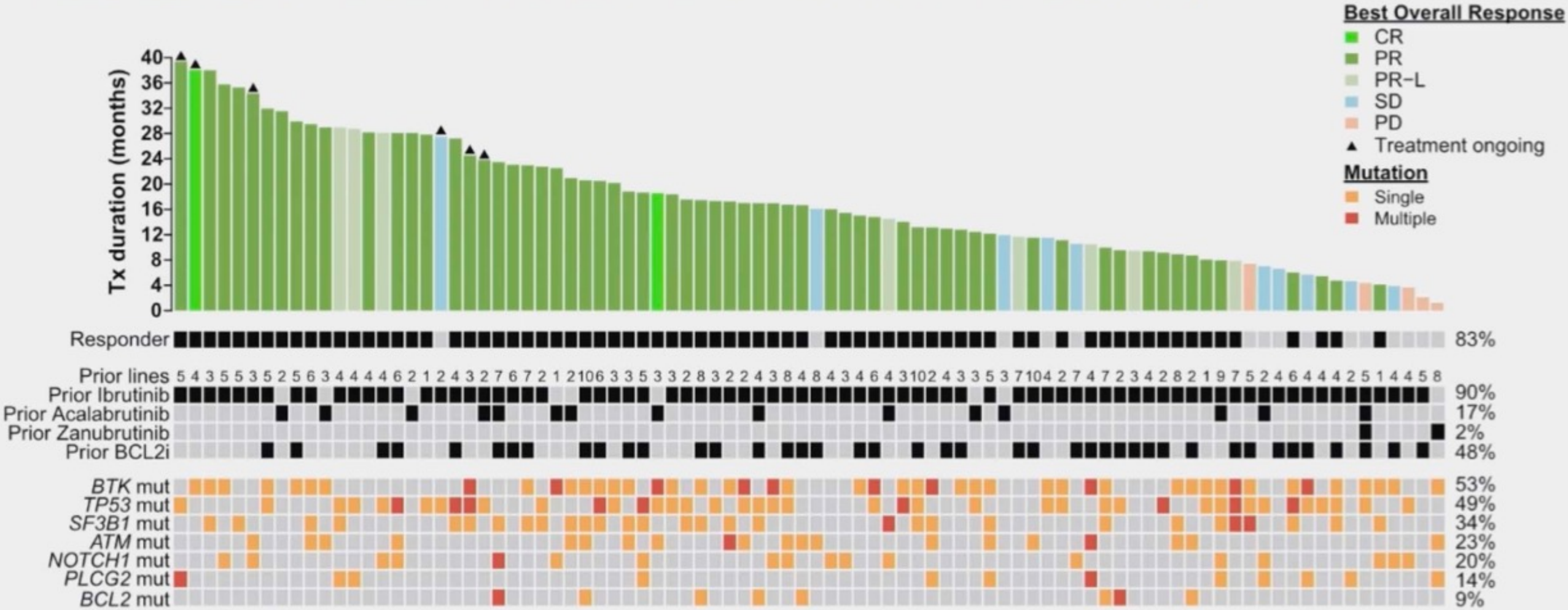
Pirtobrutinib Progression-Free Survival with Prior cBTKi, with or without Prior BCL2i





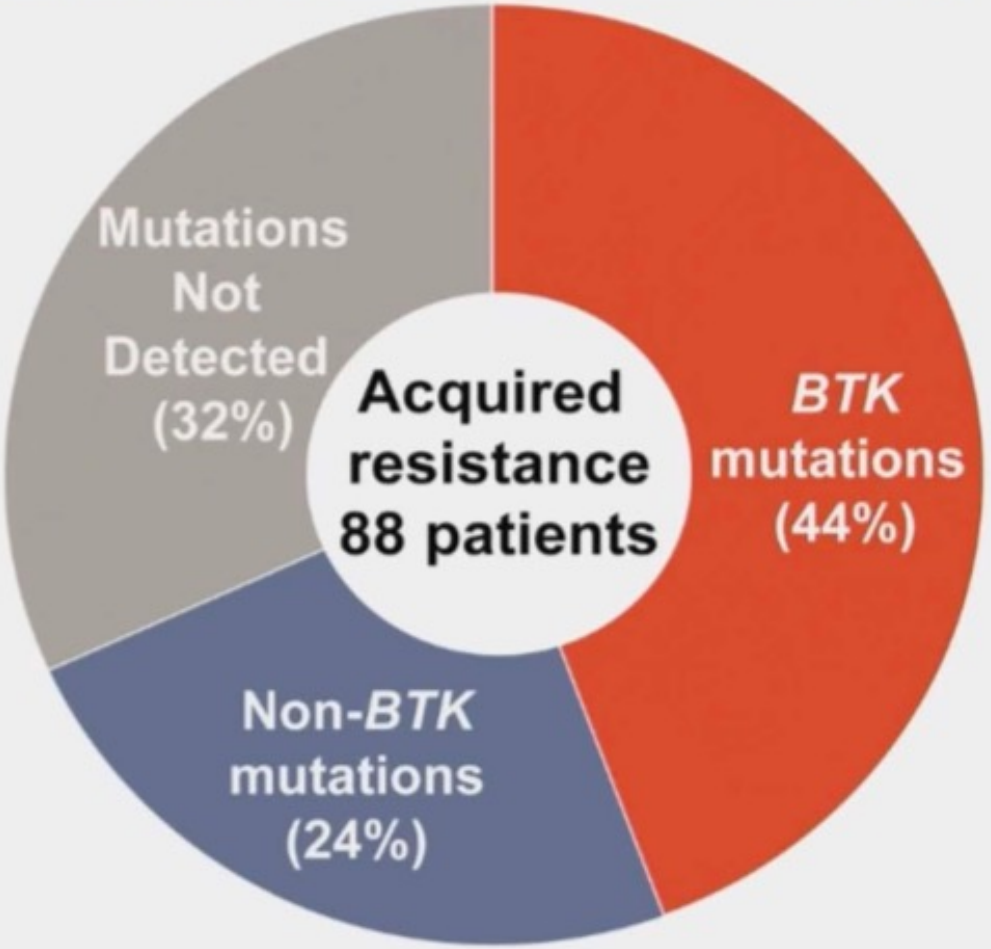
ASH 2023 BTKi mutations data

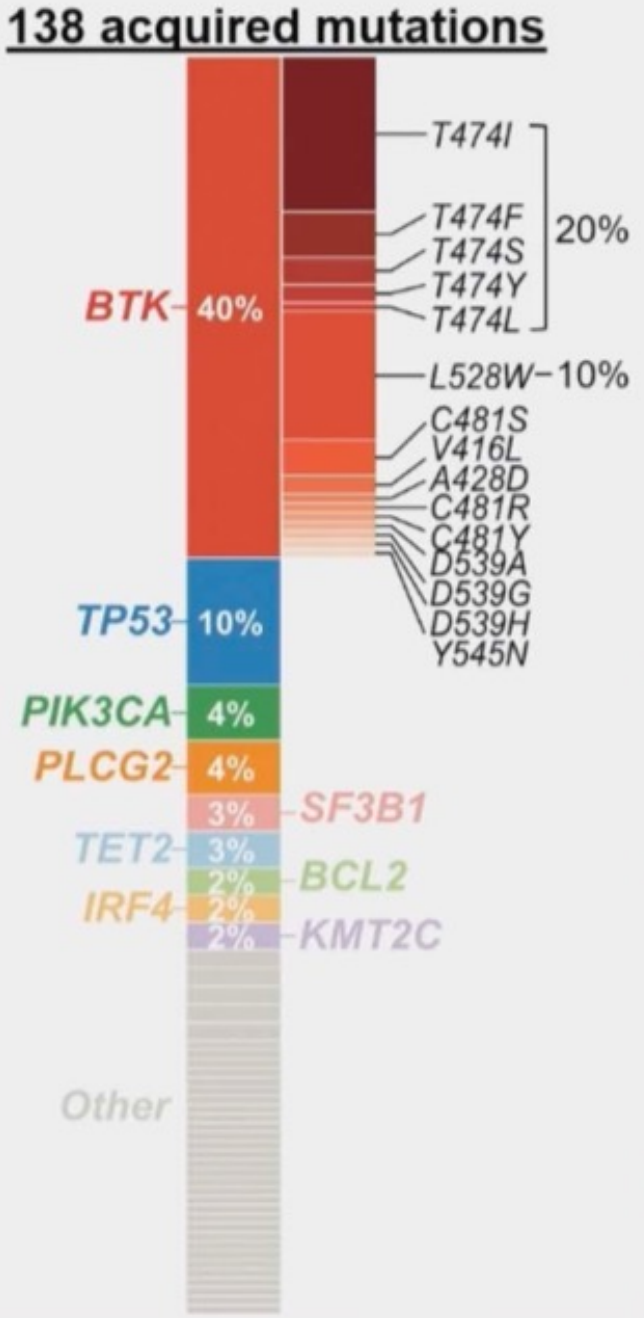
Baseline Genomics in Patients with PD on Pirtobrutinib (n=88)



- The most common mutations detected at baseline were *BTK* (53%), *TP53* (49%), *SF3B1* (34%), *ATM* (23%), *NOTCH1* (20%), *PLCG2* (14%), *BCL2* (9%)
- Pirtobrutinib demonstrated efficacy, with an ORR of 83% (73/88)
  - Baseline genomic features did not predict response to pirtobrutinib treatment

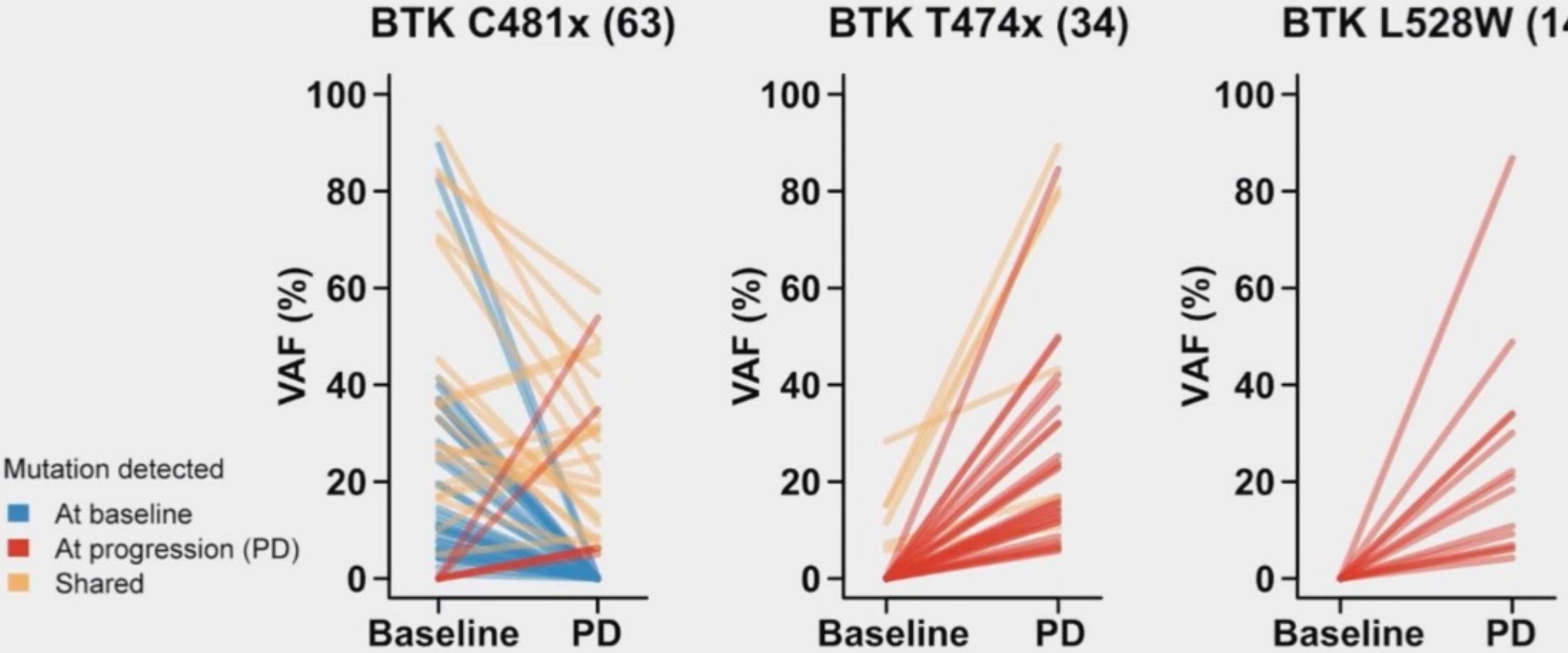
Acquired Mutations were Detected at PD in 68% of Patients





- 68% (60/88) acquired mutations at PD
  - 44% (39/88) had at least one acquired *BTK* mutation at PD
    - 64% (25/39) who acquired a *BTK* mutation had a *BTK* mutation at baseline
- 56% (49/88) did not acquire a *BTK* mutation
  - The most frequently acquired non-*BTK* mutation was *TP53*
- 32% (28/88) had no acquired mutations detected at PD

The Majority of *BTK* Acquired Mutations were T474x and L528W



- Decrease/clearance of C481x[a] clones observed at progression in 84% (36/43) patients (clearance = 23/43, 53%)
- *BTK* C481S/Y/R, T474x[a], L528W, other kinase mutations arose at/near progression (55 mutations in 39 patients, VAF range 3-86%)
- ORR was similar across groups regardless of the acquired *BTK* mutation (T474x, 22/23, 96%; L528W; 11/14, 79%)

Conclusions

- Patient preferences and Individualized therapy should be taken into consideration to choose between fixed duration or tx until progression.
- Great options for front line CLL: **Long term therapy**
  - First generation **ibrutinib** show great long term efficacy supported by multiple Phase III trials as well data for del17p/TP53 more discontinuation for AEs and CVs toxicity.
  - Second gen BTKi, **acalabrutinib** also showing excellent data with better tolerability.
  - **Zanubrutinib** now approved with great data in front line and good tolerability.
- Great options for front line CLL: **Fixed duration**
  - **Obinutuzumab+venetoclax**: great efficacy with deep MRD responses.
  - **Ibrutinib+venetoclax**: approved in EU, new FLAIR data against FCR.
  - Triple therapies trials ongoing but unclear benefits but GAIA showing better PFS in uIgHV for triple
- **Relapsed/Refractory CLL**
  - **Zanubrutinib** continue to show superiority to ibrutinib in Alpine
  - **BTK mutational profile will be** an important tool to define BTKi sequencing
  - **Pirtobrutinib** now approved after BTK and bcl2 exposure
  - Others non covalent inhibitors on their way.
  - Protein degraders entering Phase I/II
  - CART pending possible approval and evaluation in a Phase III