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Advances in Chronic Lymphocytic Leukemia

ASH 2023 Abstract Review

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Disclosures

- **Consulting**
  - **Abbvie, Adaptive Biotech, ADC Therapeutics, AstraZeneca, BeiGene, Genentech, Janssen, Lilly, NeoGenomics, Pharmacyclics**
- **Honoraria**
  - **Abbvie, Adaptive Biotech, AstraZenenca, BeiGene, Janssen, Pharmacyclics**
- **Research Funding**
  - **BeiGene, Genentech, Janssen,**
- **DMSB**
  - **MERCK**

CLL ASH Updates Overview

- CLL at ASH in Review
- Frontline Studies
  - ELEVATE-TN
  - UK FLAIR
  - CLL13
  - GLOW/CAPTIVATE
- Relapsed Studies
  - ALPINE Update
  - BRUIN updates
  - Focus on BTK Degraders

CLL Impact at ASH 2023

- **4 Oral Sessions**
  - **3 Saturday**
    - **17 Abstracts**
  - **1 Sunday**
    - **6 Abstracts**
- **Poster Sessions**
  - **203 Posters Focused on CLL**

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ELEVATE-TN

ELEVATE-TN study design

Sharman et al ASH 2023

TN CLL (N=535)

Key inclusion criteria

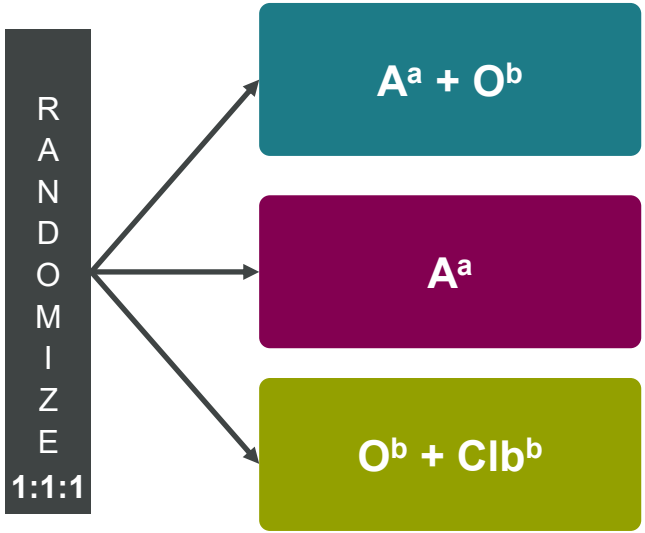
- Age ≥65 years, or >18 to <65 years with:
  - Creatinine clearance 30–69 mL/min (by Cockcroft-Gault equation)
  - CIRS-G score >6
- TN CLL requiring treatment per iwCLL 2008 criteria[6]
- ECOG PS ≤2

Key exclusion criteria

- Significant cardiovascular disease

Stratification

- del(17p), yes vs no
- ECOG PS 0–1 vs 2
- Geographic region



Primary endpoint

- PFS (IRC-assessed): A+O vs O+Clb

Secondary/other endpoints

- PFS (IRC-assessed): A vs O+Clb
- PFS (INV-assessed)
- ORR (IRC- and INV-assessed)
- TTNT
- OS
- uMRD
- Safety

***Crossover** from O+Clb to A was allowed after IRC-confirmed progression*

Note: After interim analysis, PFS assessments were by investigator only.[3] All analyses are ad-hoc and *P*-values are descriptive.

NCT02475681. Data cutoff: March 3, 2023. Patients were enrolled between September 2015 and February 2017.

[a]Continued until disease progression or unacceptable toxicity at 100 mg PO BID.

[b]Treatments were fixed duration and administered for 6 cycles.

Patient disposition

Sharman et al ASH 2023

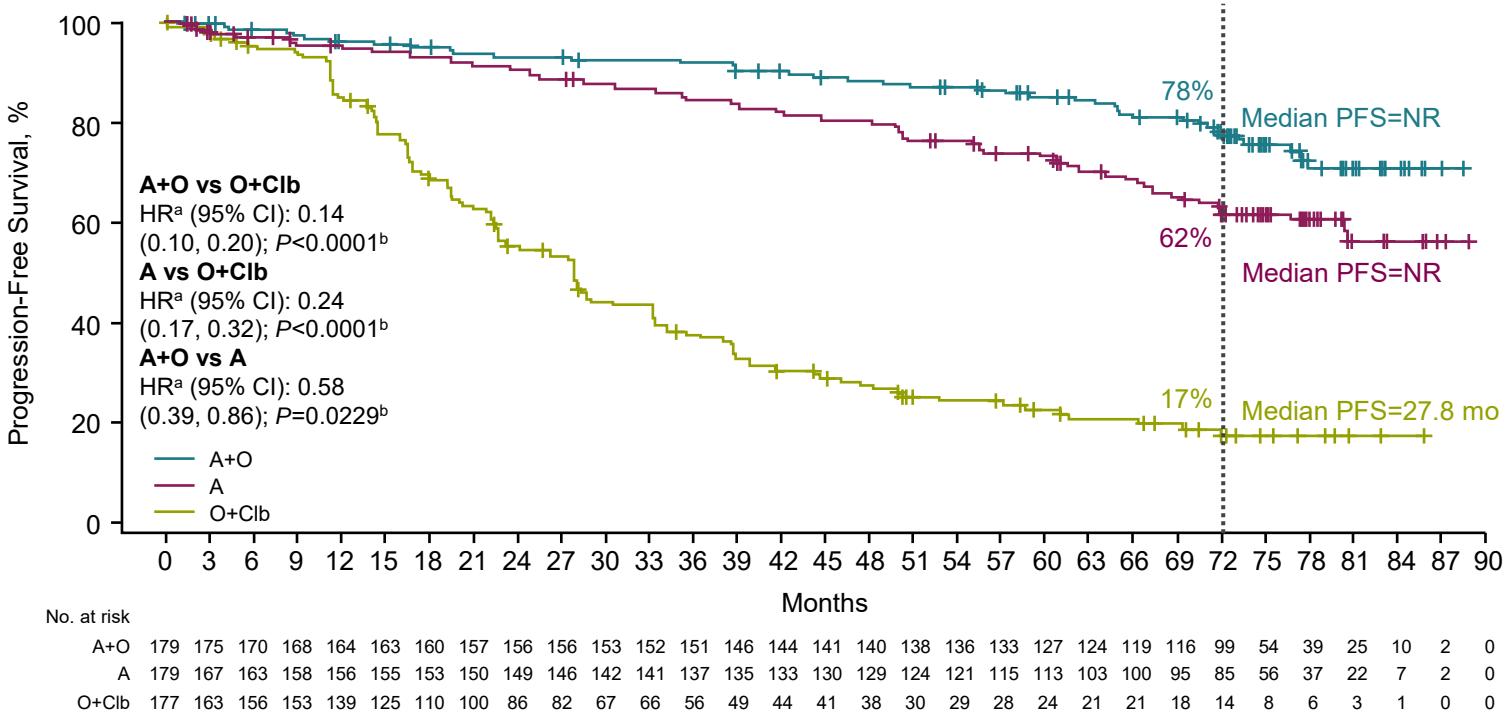
Characteristic	A+O (n=179)	A (n=179)	O+Clb (n=177)
Median study follow-up, mo (range)	74.6 (1.7, 89.0)	74.5 (0.1, 88.8)	73.3 (0.0, 88.8)
Treated with ≥1 dose of study drug	179 (100.0)	178 (99.4)	169 (95.5)
Randomized but not treated	0	1 (0.6)	8 (4.5)
Treatment status[a]			
Ongoing	96 (53.6)	84 (46.9)	0
Completed regimen	–	–	136 (76.8)
Discontinued regimen	83 (46.4)	95 (53.1)	41 (23.2)
Death	5 (2.8)	16 (8.9)	3 (1.7)
AE	38 (21.2)	32 (17.9)	25 (14.1)
Acalabrutinib-related AE	9 (5.0)	13 (7.3)	–
Lost to follow-up	2 (1.1)	1 (0.6)	1 (0.6)
CLL progressive disease	10 (5.6)	25 (14.0)	4 (2.3)
Withdrawal of consent	5 (2.8)	3 (1.7)	6 (3.4)
Investigator's discretion	13 (7.3)	13 (7.3)	0
Other	10 (5.6)	5 (2.8)	2 (1.1)

Crossover to A monotherapy	O+Clb (n=177)
Crossed over	79 (44.6)
Discontinued A monotherapy	32 (40.5)
AE	10 (12.7)
CLL progressive disease	13 (16.5)
Death	3 (3.8)
Withdrawal of consent	1 (1.3)
Investigator's discretion	1 (1.3)
Other	4 (5.1)

Data are n (%) unless otherwise specified.

[a]Treatment status refers to the period on treatment. For A-containing arms, patients are treated to progression or unacceptable toxicity; treatment period is 6 months fixed duration for O+Clb.

Median PFS was significantly higher for A-containing arms vs O+Clb

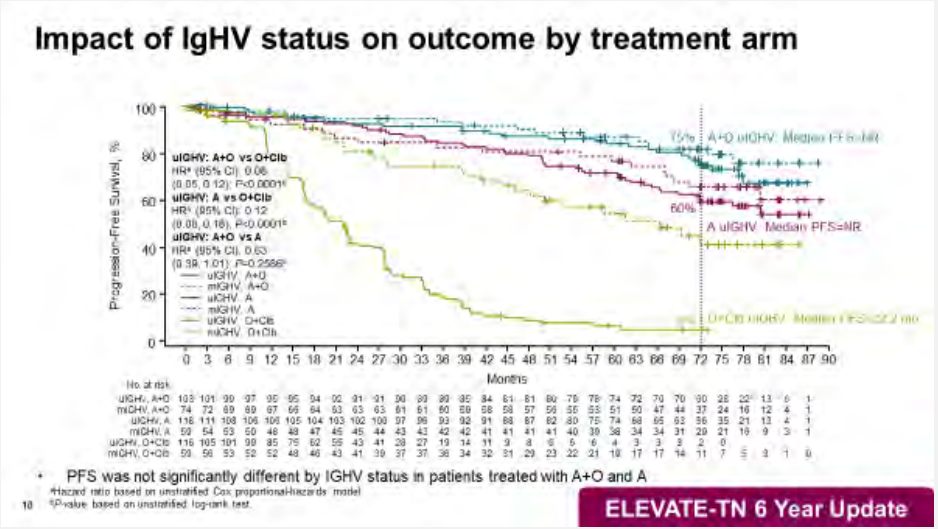


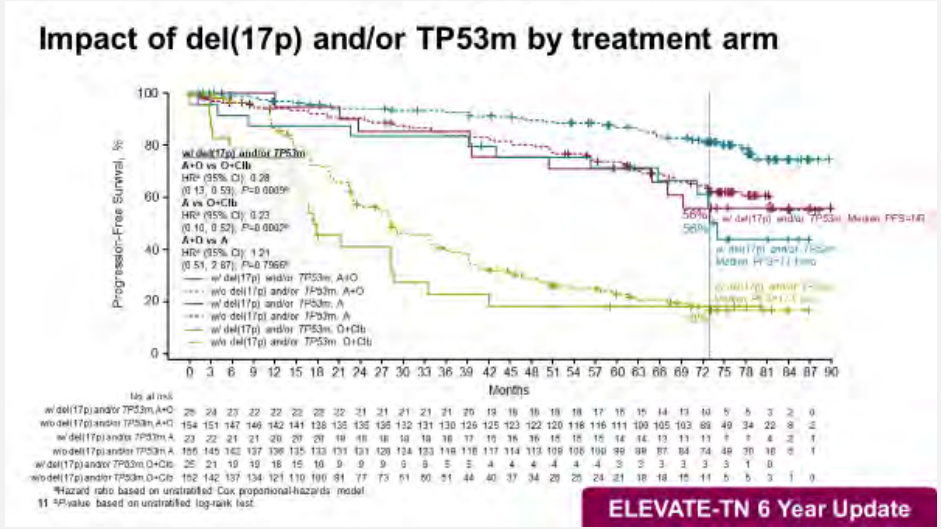
- Median PFS was significantly higher for A+O vs A

Sharman et al ASH 2023

[a]Hazard ratio based on stratified Cox proportional-hazards model.
[b]*P*-value based on stratified log-rank test.

PFS and IGHV and TP53 Mutational Status





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Sharman et al ASH 2023

Events of clinical interest were similar in both A-containing arms and consistent with previous results[3-5]

Sharman et al ASH 2023

ECI Category ECI Subcategory	A+O (n=178)		A (n=179)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Cardiac events	49 (27.5)	22 (12.4)	42 (23.5)	21 (11.7)
Atrial fibrillation	13 (7.3)	3 (1.7)	16 (8.9)	3 (1.7)
Bleeding	95 (53.4)	12 (6.7)	81 (45.3)	8 (4.5)
Major bleeding	16 (9.0)	12 (6.7)	10 (5.6)	8 (4.5)
Hypertension[a]	20 (11.2)	8 (4.5)	20 (11.2)	9 (5.0)
Infections	147 (82.6)	63 (35.4)	144 (80.4)	50 (27.9)
SPMs	36 (20.2)	18 (10.1)	35 (19.6)	9 (5.0)
SPMs excluding non-melanoma skin	24 (13.5)	13 (7.3)	22 (12.3)	7 (3.9)

Data are n (%).

[a]Hypertension events were based on Standardized MedDRA query (SMQ) Hypertension (narrow).

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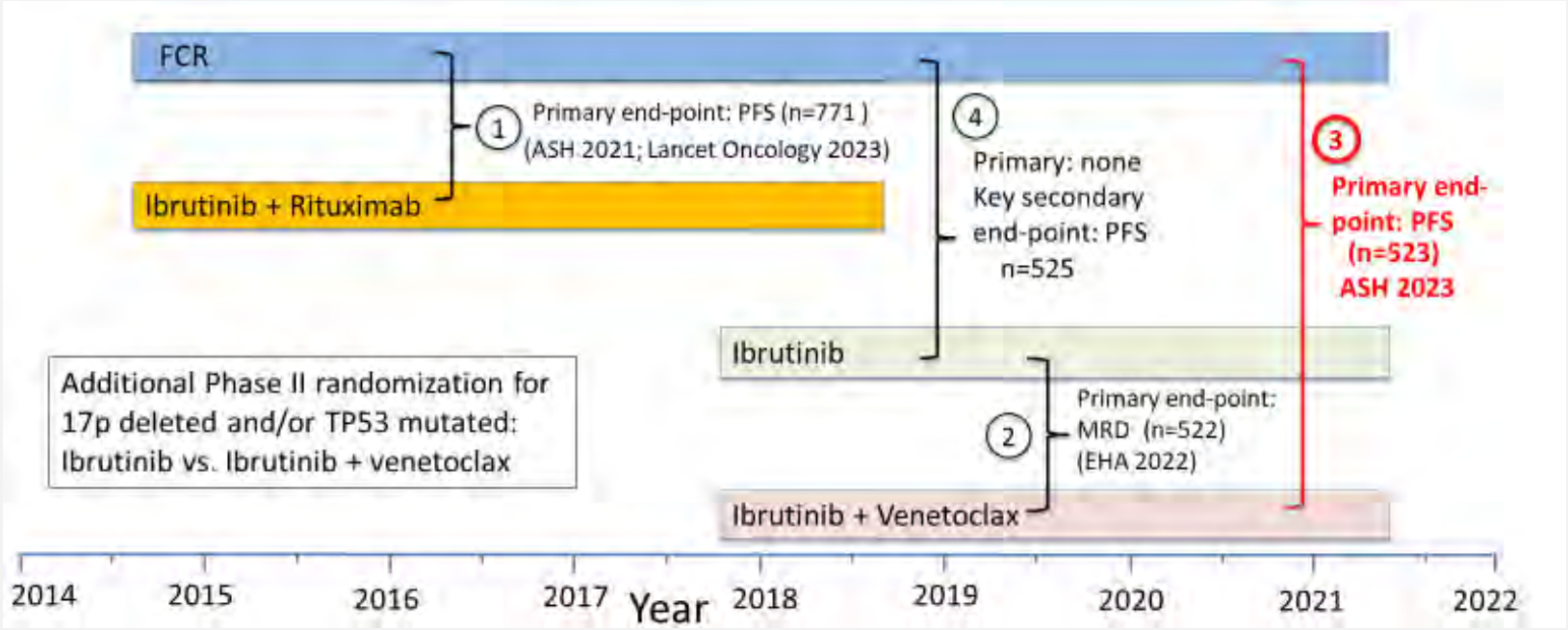
UK FLAIR

UK Flair Study Design



Hillmen et al ASH 2023,
Hillmen et al NEJM 2023

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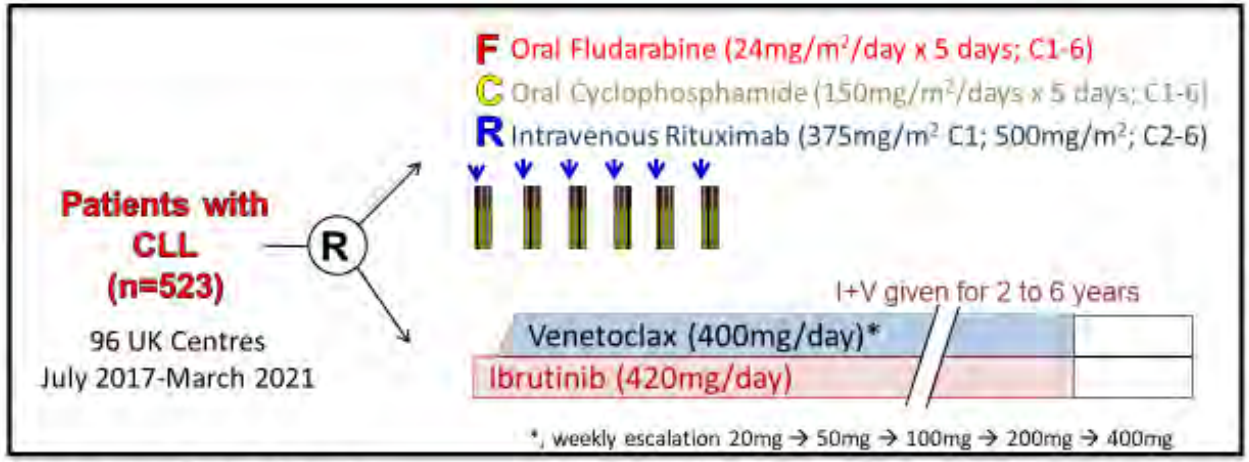
UK FLAIR: FCR vs IV Endpoints



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

Hillmen et al ASH 2023,
Hillmen et al NEJM 2023

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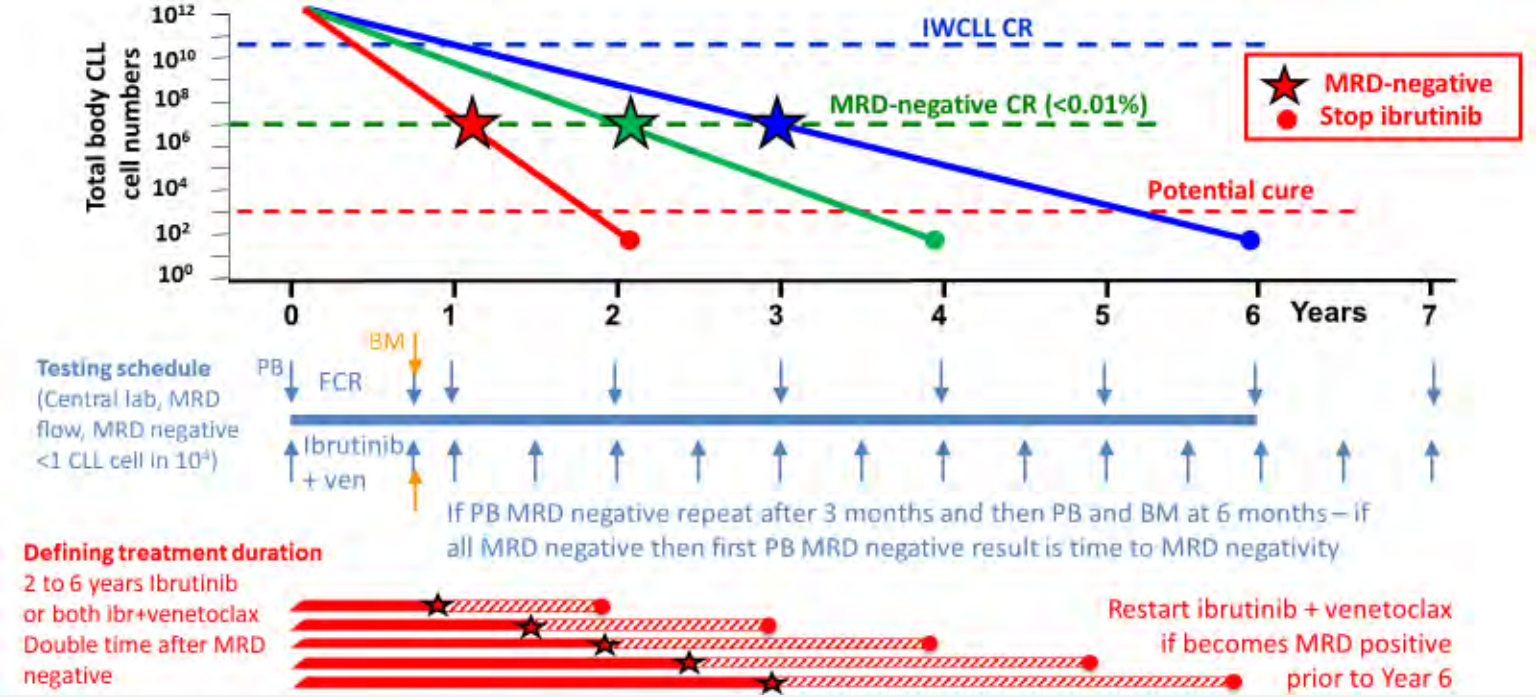
UK FLAIR Stopping Rules



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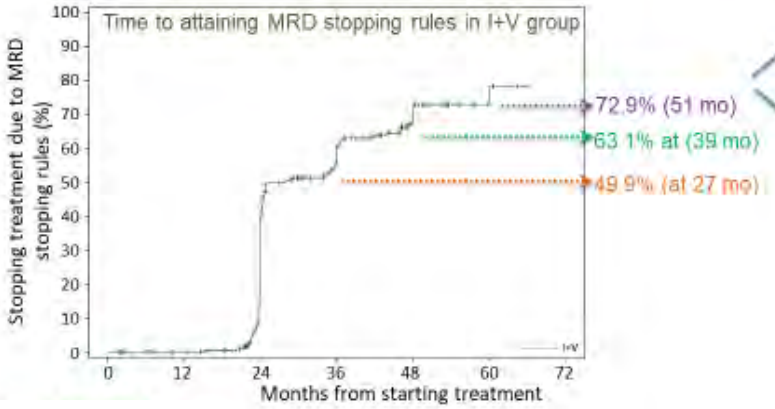
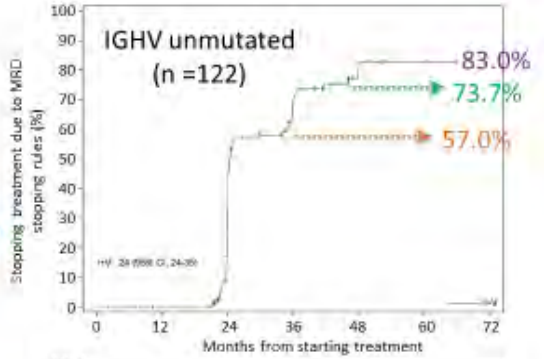
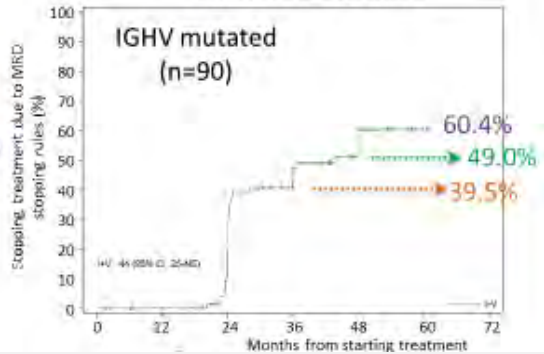
UK FLAIR: Response Adapted Therapy Increases MRD Negativity Over Time

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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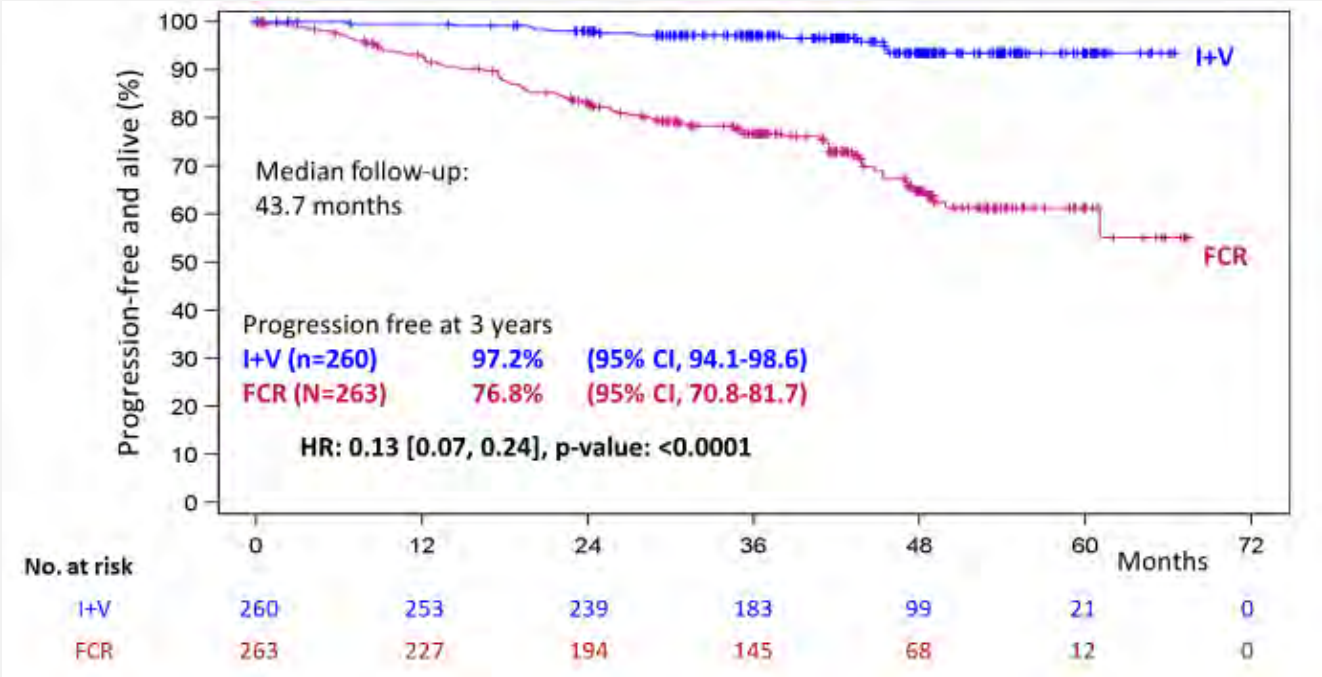
UK FLAIR: Primary Endpoint PFS



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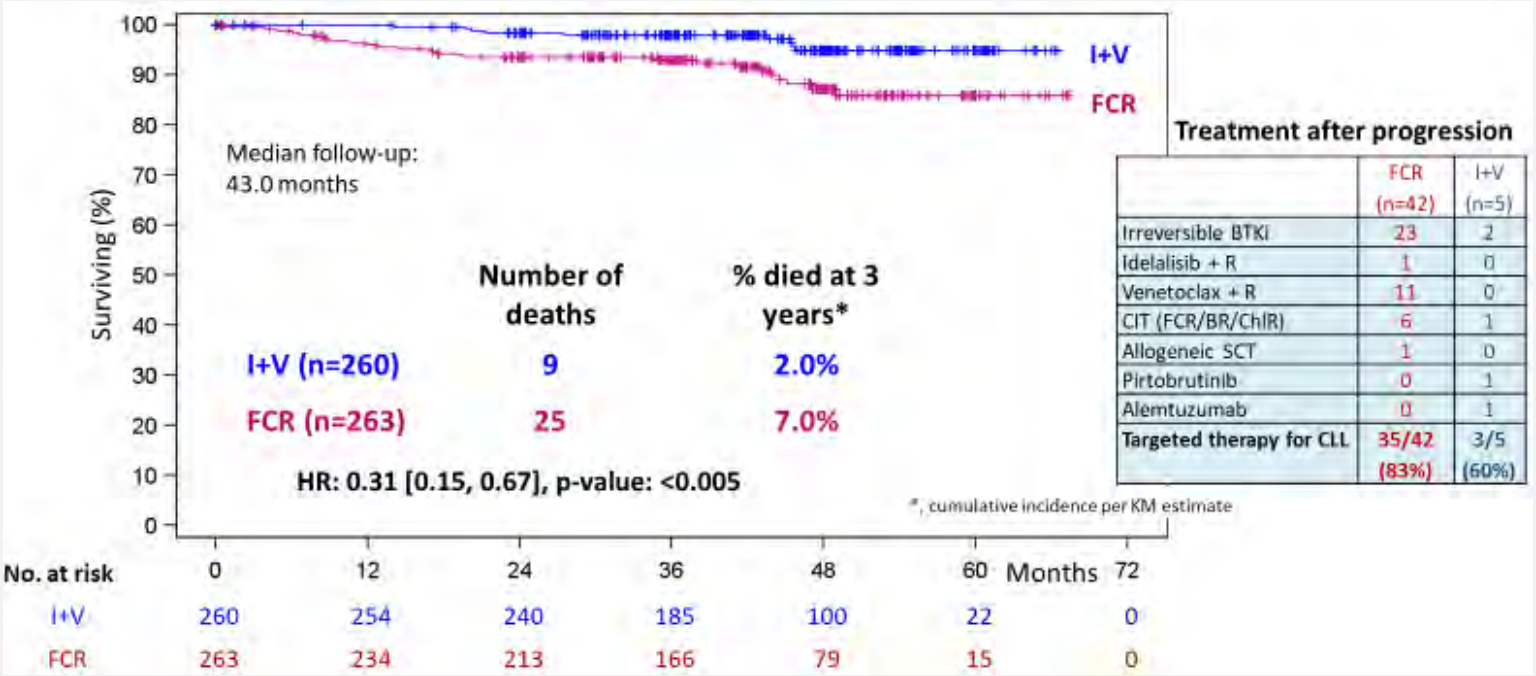
UK FLAIR: Overall Survival



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%)**

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UK FLAIR: Cause of Death and SPM

- 31 deaths have occurred in the safety population. 23 from FCR participants and 8 from I+V.
- 7 deaths have been assessed as related to treatment (6 FCR; 1 I+V)
- 13 deaths were related to SAEs or SUSARs (8 FCR; 5 I+V)
- 2 of the 3 cardiac deaths in the I+V arm occurred after treatment was completed (35 days and 411 days later)

	FCR	I+V
Infection	7	1
Sudden/Cardiac	2	3
COVID-19	2	2
Richter's transformation	2	1
Non-haem malignancy	2	1
Allogeneic SCT – infection	1	0
Allogeneic SCT – GvHD	1	0
Disease progression	1	0
Hemorrhage	1	0
Lymphoma	1	0
Treatment related MDS/BMF	3	0
Total:	**23**	**8**

Secondary malignancies (SM)

	FCR	I+V
Incidence rate of cancers per 100 person-years	**5.4**	**2.6**
(95% CIs)	(5.11, 5.68)	(2.40, 2.79)

	FCR	I+V
BCC/SCC	16	13
MDS/AML	8	1
Lymphoma	5	3
Prostate/urological	5	1
Lung	3	0
GI	3	1
Breast	1	1
Melanoma	1	1
Myeloma	1	0
Endocrine	0	1
Other	5	2
Total patients*	**39**	**17**

*, some patients had more than one SM

Hillmen et al ASH 2023,
Hillmen et al NEJM 2023

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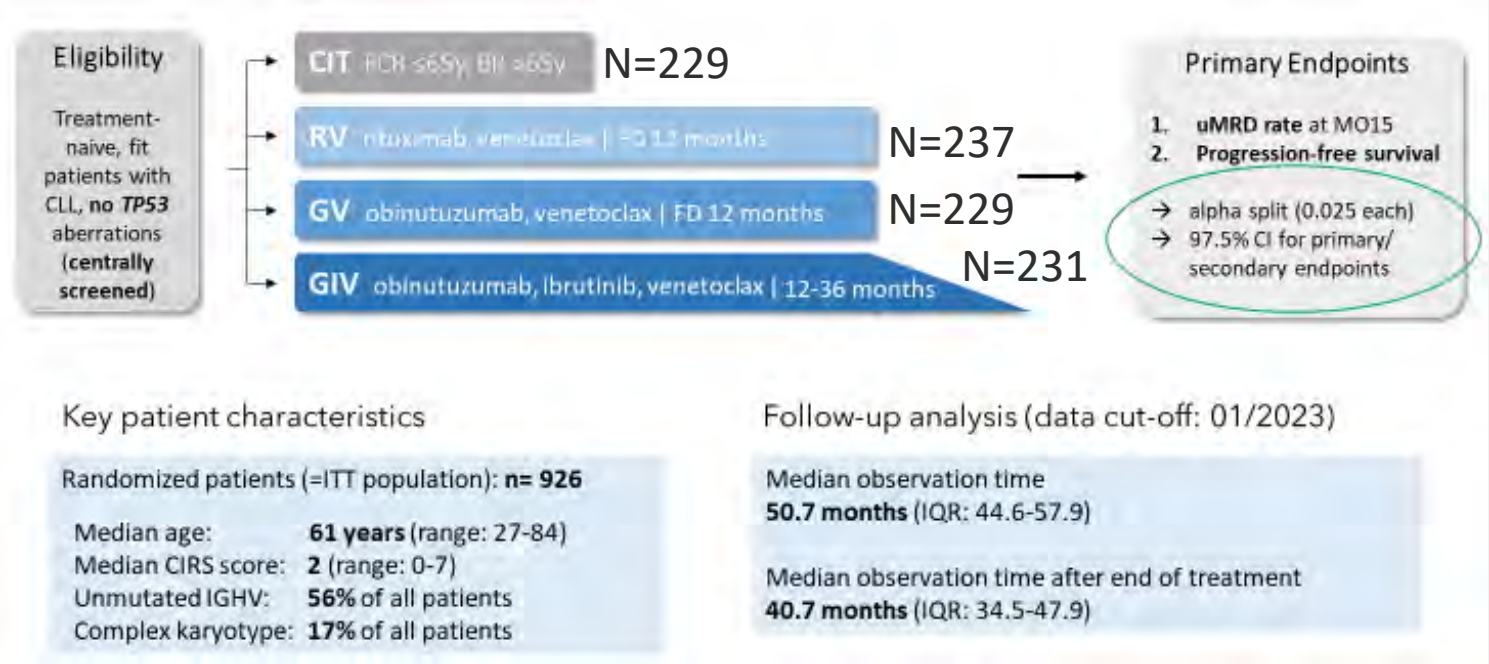
GAIA/CLL13

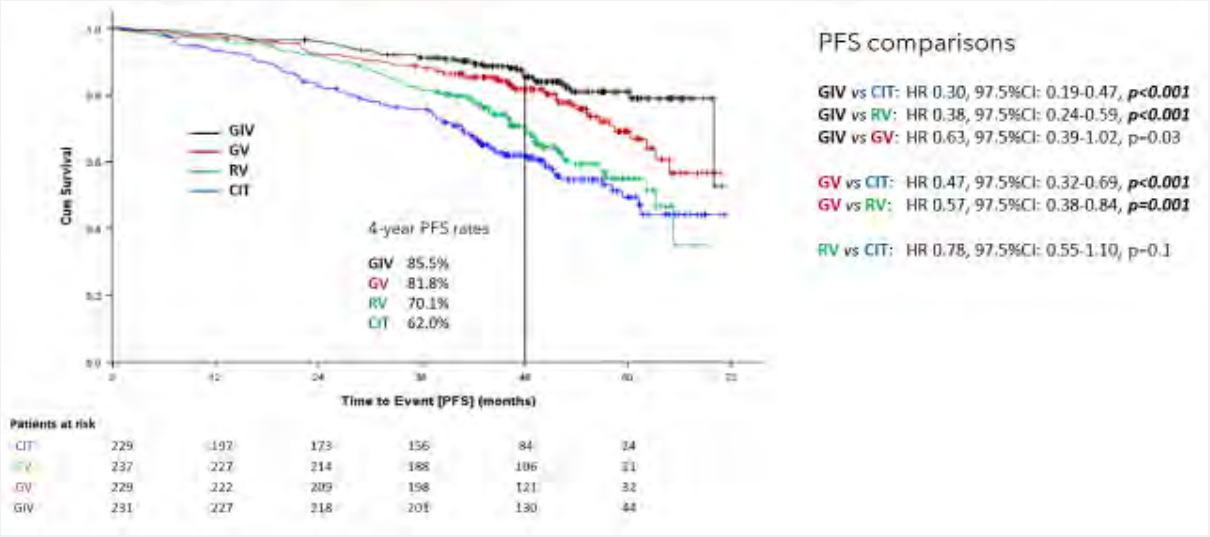
GAIA/CLL13: Study Design Schema



Furstenau et al ASH 2023

CLL13: Improved PFS with Obinutuzumab based regimens

mFU: 50.7m



PFS comparisons

GIV *vs* CIT: HR 0.30, 97.5%CI: 0.19-0.47, ***p<0.001***
GIV *vs* RV: HR 0.38, 97.5%CI: 0.24-0.59, ***p<0.001***
GIV *vs* GV: HR 0.63, 97.5%CI: 0.39-1.02, p=0.03

GV *vs* CIT: HR 0.47, 97.5%CI: 0.32-0.69, ***p<0.001***
GV *vs* RV: HR 0.57, 97.5%CI: 0.38-0.84, ***p=0.001***

RV *vs* CIT: HR 0.78, 97.5%CI: 0.55-1.10, p=0.1

CIT	RV	GV	GIV
Early treatment discontinuation (patients, %)			
40 (18.5)	18 (7.6)	14 (6.1)	31 (13.4)
- of these, due to AE (patients, %)			
32 (14.8)	11 (4.6)	9 (3.9)	27 (11.7)

4-year OS rates

GIV	95.0%
GV	95.1%
RV	96.2%
CIT	93.5%

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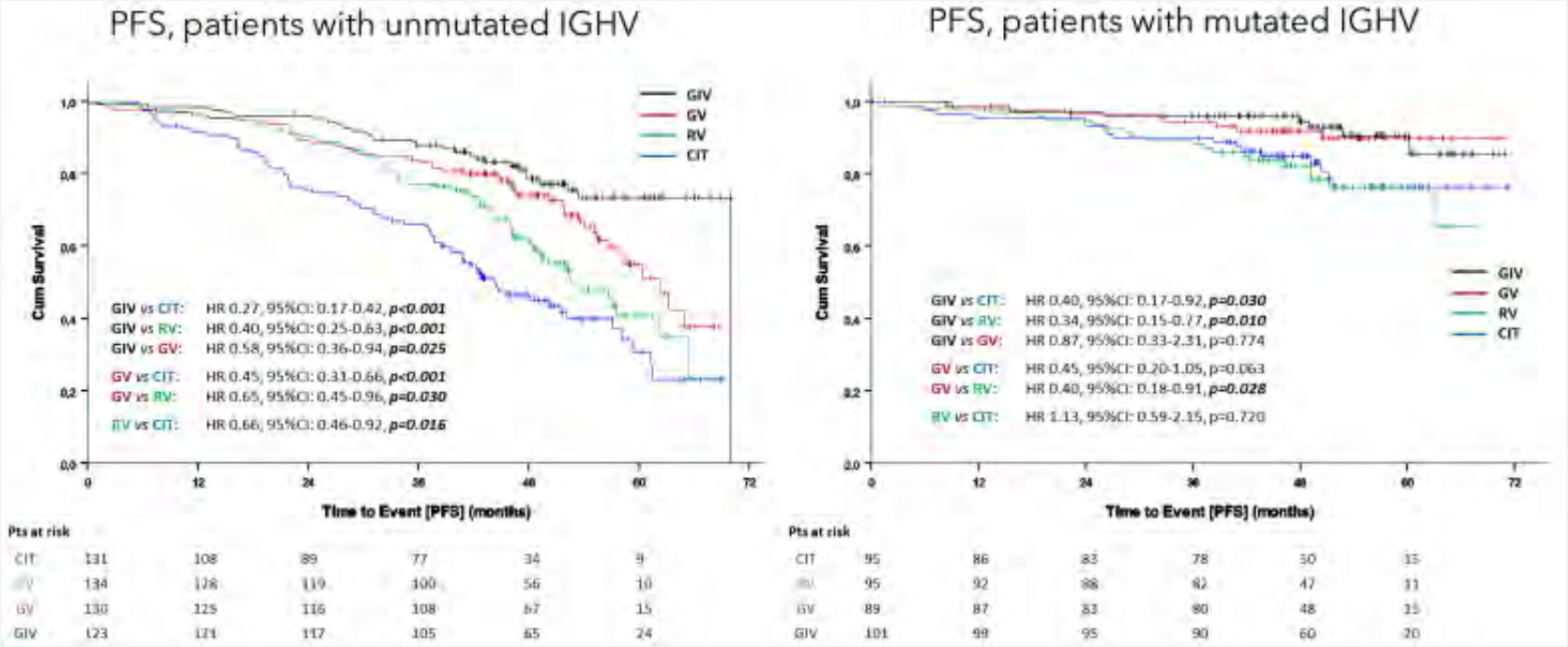
CLL13: PFS and IGHV Mutational Status



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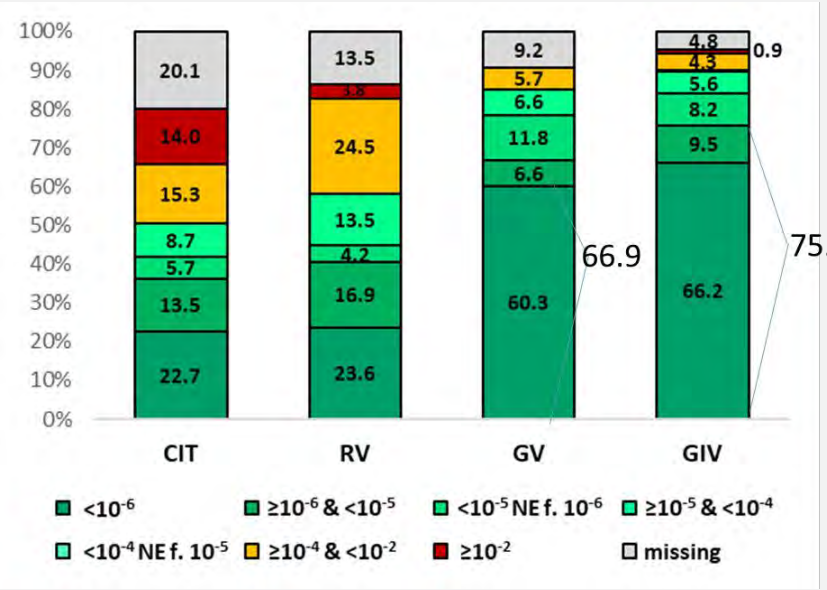
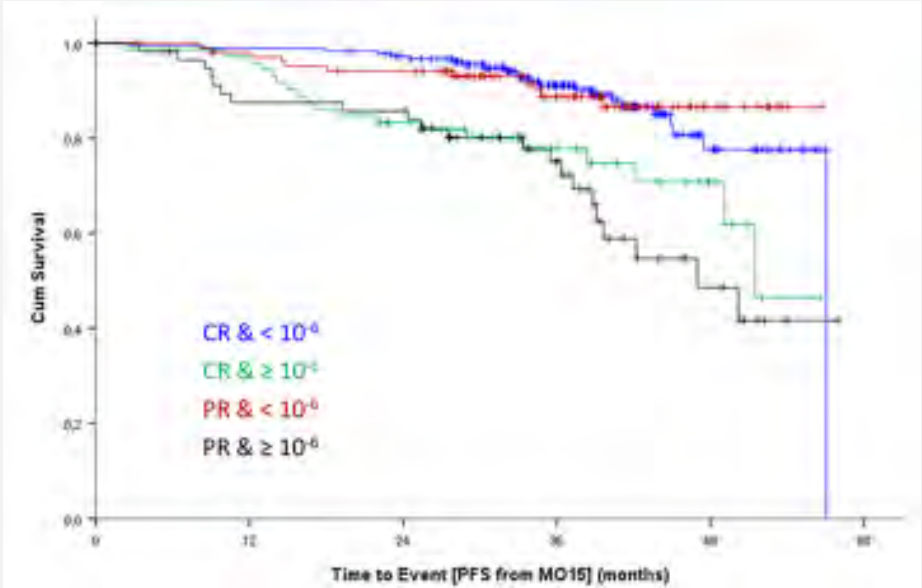
CLL13: PB MRD Rates and PFS Depending on MRD and Response





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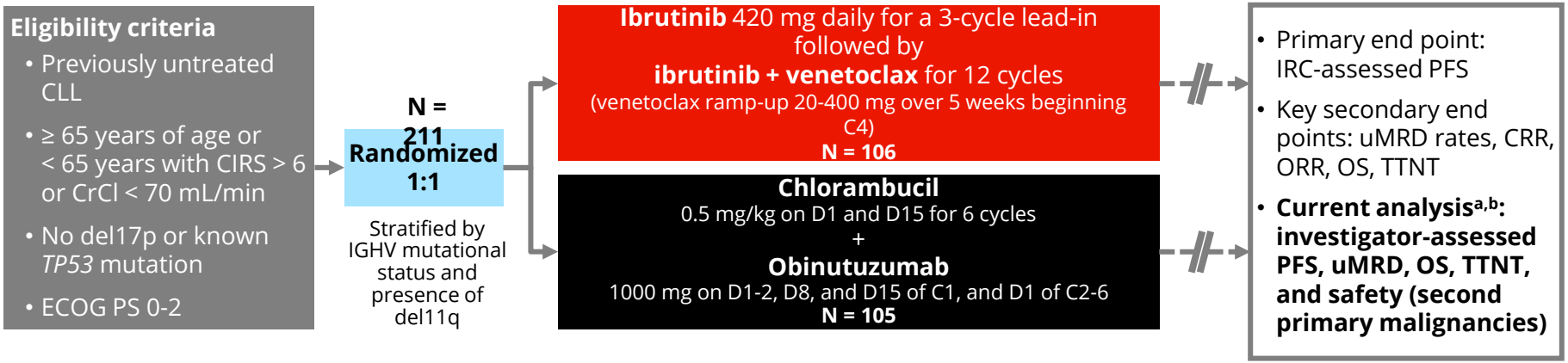
GLOW/CAPTIVATE

GLOW: Phase 3 GLOW Study (NCT03462719)



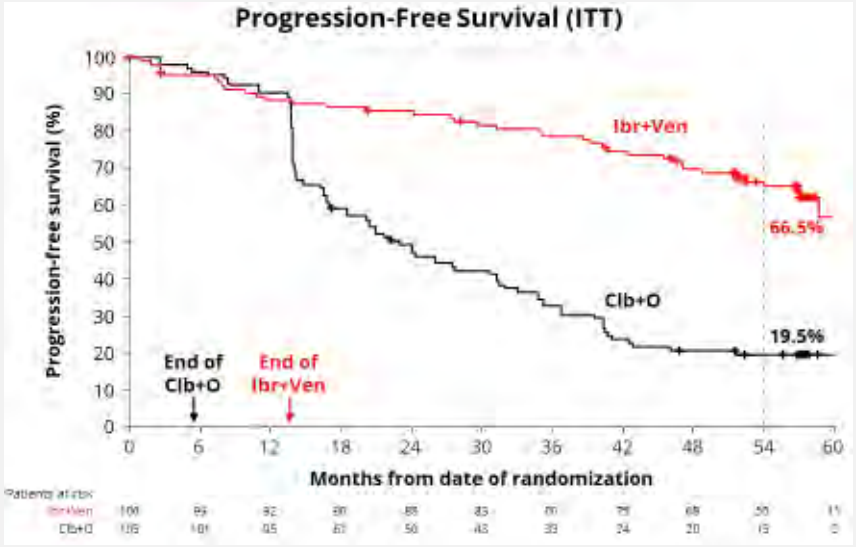
- Baseline characteristics (presented previously) were generally balanced between arms and reflective of an elderly and/or comorbid population[1]
- IGHV status at baseline:
  - Ibr+Ven arm: mIGHV 30.2%, uIGHV 63.2%
  - Clb+O arm: mIGHV 33.3%, uIGHV 54.3%

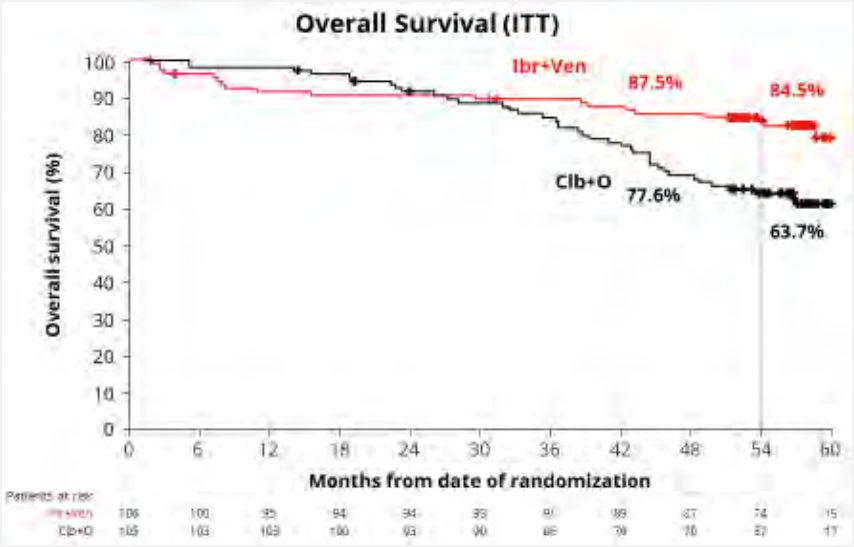
[a]All *p* values are nominal. [b]uMRD in PB by NGS via Clonoseq assay.
C, cycle (28 days); CIRS, Cumulative Illness Rating Scale score; CrCl, creatinine clearance; CRR, complete response rate; D, day; ECOG PS, Eastern Cooperative Oncology Group performance status; IRC, independent review committee; mIGHV, mutated IGHV; NGS, next-generation sequencing; ORR, overall response rate; PB, peripheral blood; uIGHV, unmutated IGHV.

1. Niemann CU, et al. *Lancet Oncol*. 2023;24:1423-1433.

Presented by George Follows at the 65th ASH Annual Meeting and Exposition; December 9-12, 2023; San Diego, CA, USA

GLOW: PFS and OS





- **Ibr+Ven reduced the risk of progression or death by 74%** versus Clb+O
  - HR 0.256 (95% CI, 0.172-0.382); $p < 0.0001$
- Estimated 54-month PFS rates at 57 months of follow-up:
  - **66.5%** for Ibr+Ven
  - **19.5%** for Clb+O

- **Ibr+Ven reduced the risk of death by 55%** versus Clb+O
  - HR 0.453 (95% CI, 0.261-0.785); $p = 0.0038$
- Estimated 54-month OS rates:
  - **84.5%** for patients treated with Ibr+Ven
  - **63.7%** for patients treated with Clb+O

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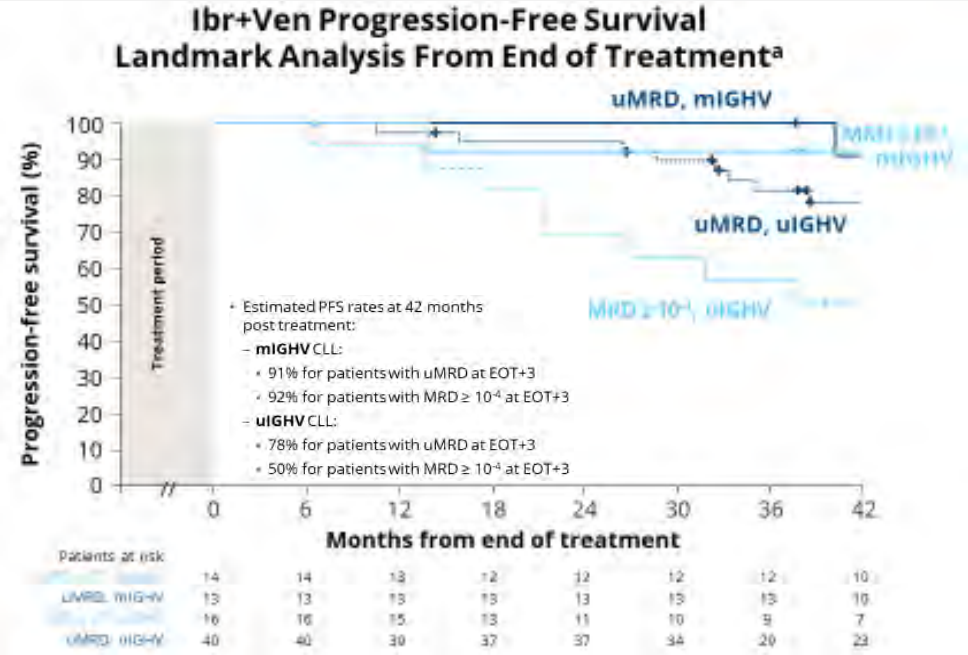
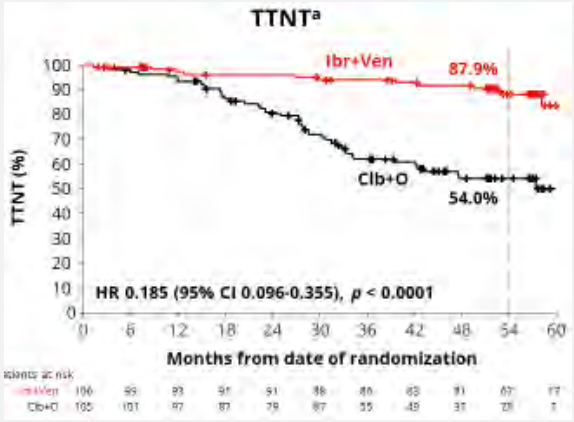
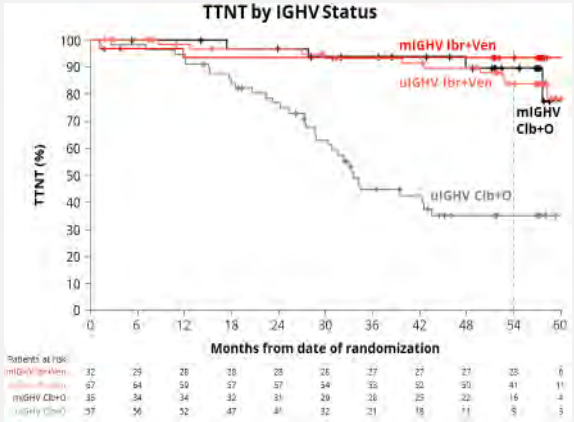
GLOW: PFS (IGHV and MRD) & TTNT (IGHV)







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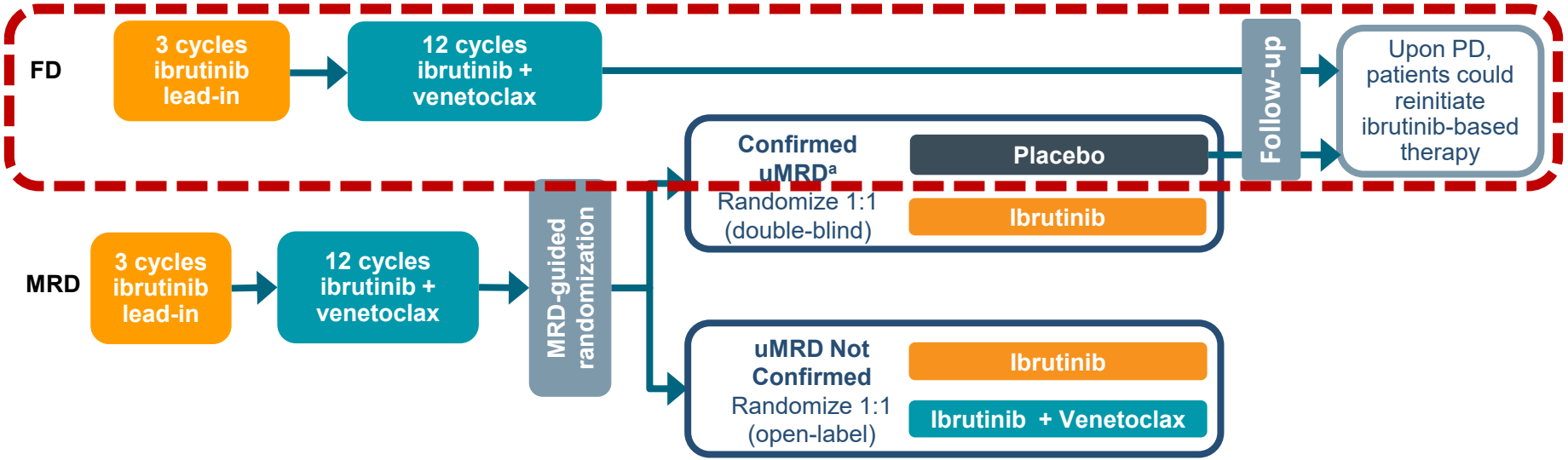
CAPTIVATE Study Design

- 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)



FD, fixed duration; MRD, minimal residual disease; PD, progressive disease.
[a]Confirmed uMRD was defined as uMRD ($<10^{-4}$ by 8-color flow cytometry) serially over at least 3 cycles in both peripheral blood and bone marrow.
[1]Wierda, WG. *J Clin Oncol.* 2021;39:3853-3865. [2]Tam CS et al. *Blood.* 2022;139:3278-3289.

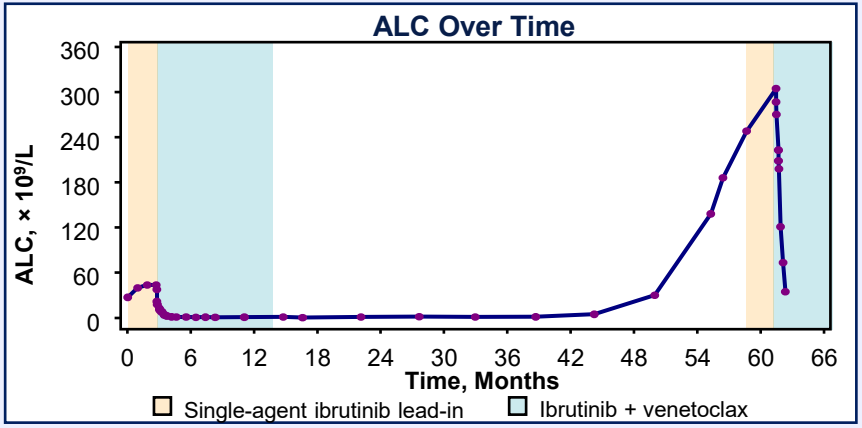
Ghia et al ASH 2023

Evaluation of *BTK*, *PLCG2*, and *BCL-2* Mutations in Patients with PD

- Samples collected at PD after fixed-duration treatment from 40 patients were evaluated for mutations in *BTK/PLCG2* or *BCL-2* associated with resistance to ibrutinib or venetoclax[a]
  - Median time from start of treatment to PD for these patients was 3.2 years (range, 1.4–4.2)
- No *BTK* or *PLCG2* mutations were identified in the 40 patients evaluated
- In 1 of 40 patients, an acquired subclonal mutation in *BCL-2* (A113G, VAF 8.3%) was identified
  - *BCL-2* A113G identified previously in patients with PD on venetoclax, usually in combination with *BCL-2* G101V (66-100% of cases), the most common venetoclax resistance mutation[1-3]
  - Emergence of subclonal *BCL-2* A113G in the absence of co-occurring *BCL-2* mutations has unclear clinical significance

Patient With *BCL-2* (A113G) at PD

- With initial fixed-duration ibrutinib + venetoclax:
  - uMRD (<0.01%) achieved in both PB and BM by C13 and maintained in PB until C31
  - CR achieved at C10 and maintained through C49
- PD occurred 3 years after EOT
- After PD, reinitiated fixed-duration ibrutinib + venetoclax
  - To date, the patient has PR-L after 4 months of retreatment (3 months of ibrutinib and 1 month of ibrutinib + venetoclax)



BM, bone marrow; C, cycle; PB, peripheral blood; PLCG2, phospholipase C gamma 2; PR-L, partial response with lymphocytosis; VAF, variant allele frequency.

[a]Resistance-associated variants in *BTK*, *PLCG2*, or *BCL-2* were assessed by next-generation sequencing using a custom panel with a limit of detection of 1% VAF.

[1]Popovic R et al, *Am J Hematol.* 2022;97(2):e47-e51. [2]Kotmayer L et al, *Int J Mol Sci.* 2023;24:5802. [3]Lucas F et al, *Blood.* 2020;135:2192-2195.

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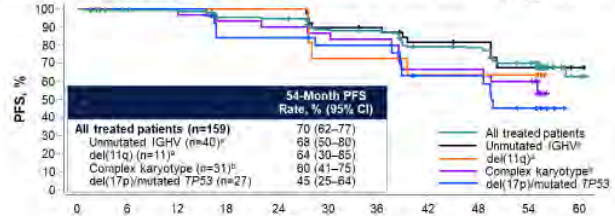
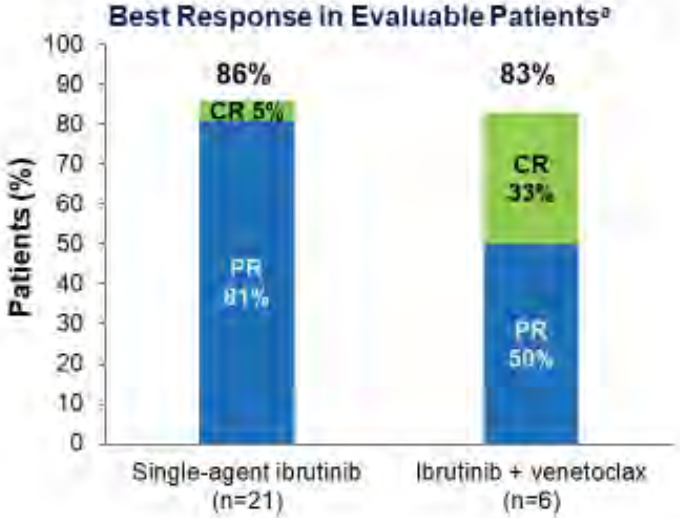
CAPTIVATE: FD/Placebo PFS and Retreatment Responses

- 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*



- 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

- Median time on retreatment:
  - 17 months (range, 0–45) for single-agent ibrutinib (n=22)
  - 14 months (range, 5–15) for ibrutinib + venetoclax (n=6)



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Relapsed CLL

ALPINE

ALPINE Study Design

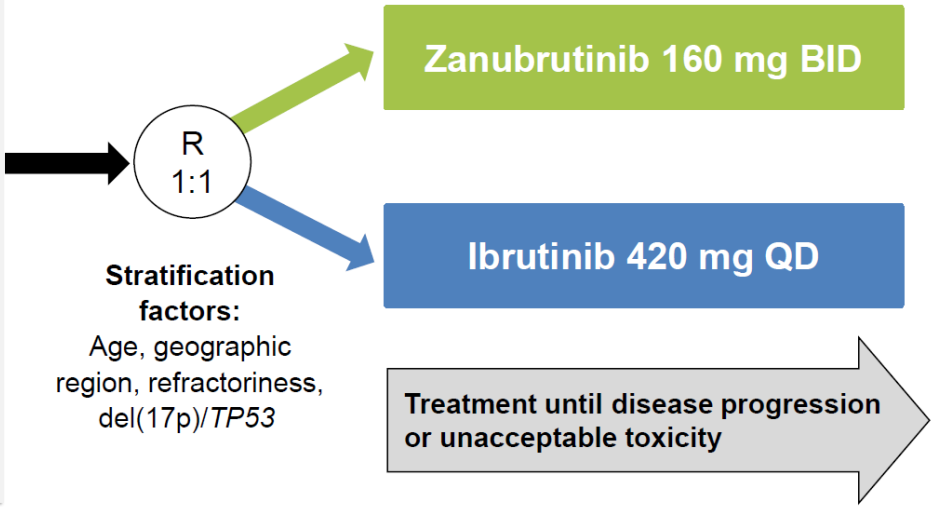
R/R CLL/SLL with ≥1 prior treatment
(N=652)

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 JR, Eichhorst B, Hillmen P, et al. *N Engl J Med*. 2023;388:319-332.

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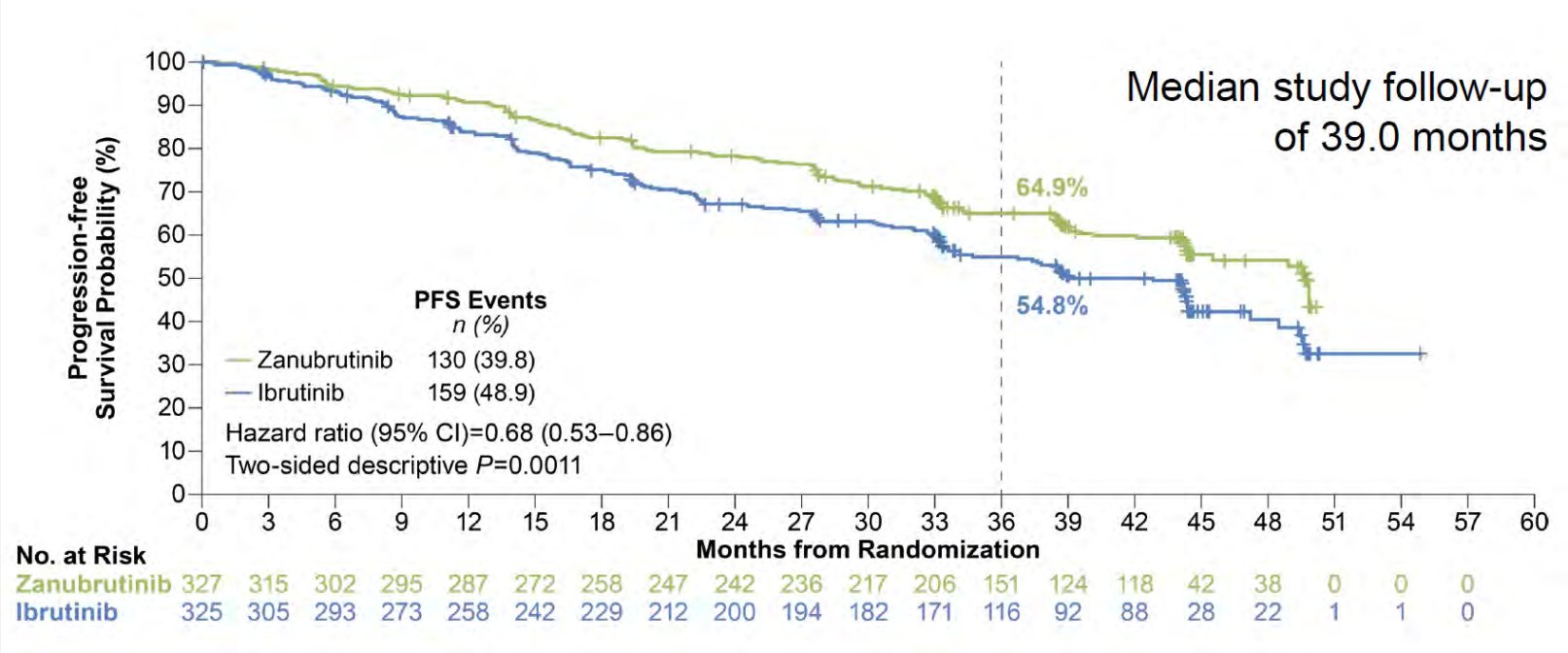
ALPINE: PFS 39months



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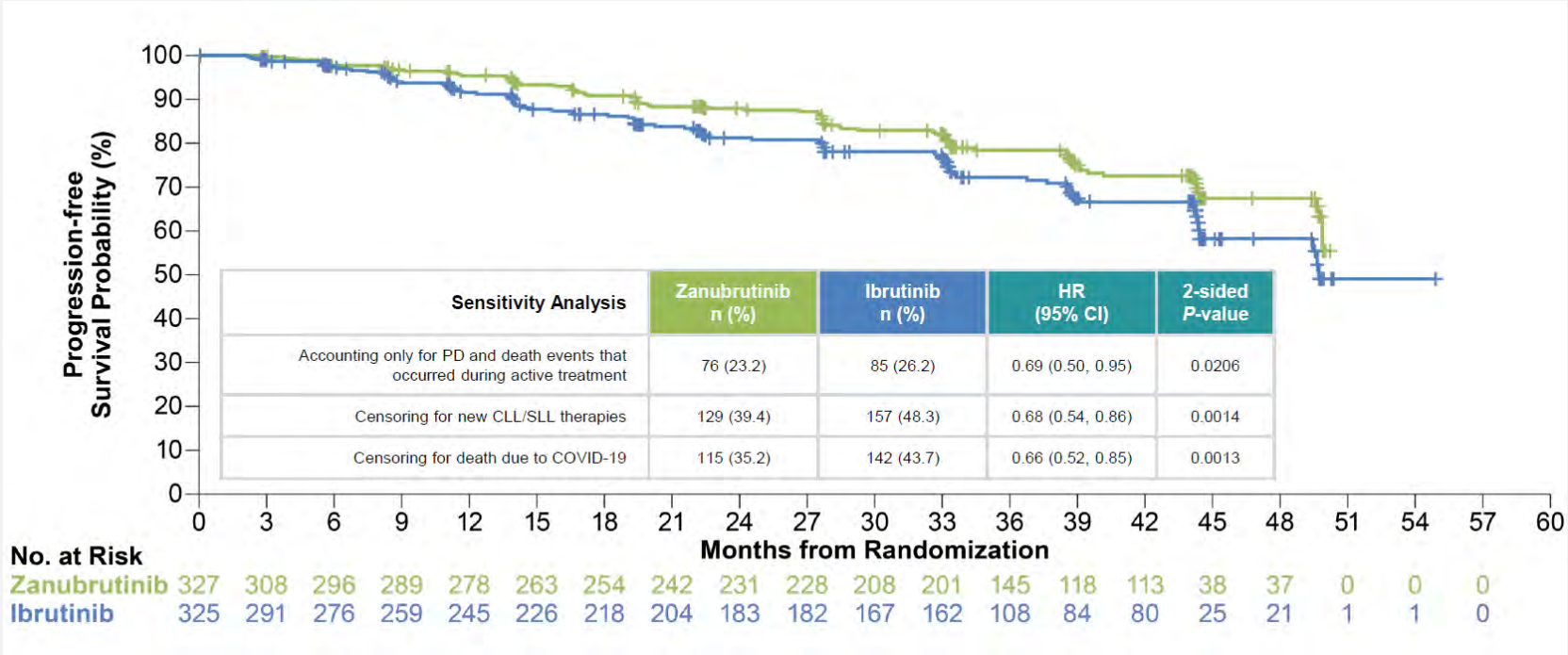
ALPINE: Sensitivity Analysis



Sensitivity Analysis	Zanubrutinib n (%)	Ibrutinib n (%)	HR (95% CI)	2-sided *P*-value
Accounting only for PD and death events that occurred during active treatment	76 (23.2)	85 (26.2)	0.69 (0.50, 0.95)	0.0206
Censoring for new CLL/SLL therapies	129 (39.4)	157 (48.3)	0.68 (0.54, 0.86)	0.0014
Censoring for death due to COVID-19	115 (35.2)	142 (43.7)	0.66 (0.52, 0.85)	0.0013

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ALPINE: AESI

	Zanubrutinib (n=324)		Ibrutinib (n=324)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Infection	264 (81.5)	115 (35.5)	260 (80.2)	111 (34.3)
Opportunistic Infections	8 (2.5)	6 (1.9)	13 (4.0)	5 (1.5)
COVID-19 Related[b]	**145 (44.8)**	**56 (17.3)**	**105 (32.4)**	**38 (11.7)**
Bleeding	142 (43.8)	12 (3.7)	144 (44.4)	13 (4.0)
Major Hemorrhage	13 (4.0)	12 (3.7)	16 (4.9)	13 (4.0)
Hypertension	**86 (26.5)**	**53 (16.4)**	**80 (24.7)**	**47 (14.5)**
Atrial fibrillation/flutter	**22 (6.8)**	**10 (3.1)**	**53 (16.4)**	**16 (4.9)**
Anemia	53 (16.4)	7 (2.2)	59 (18.2)	11 (3.4)
Neutropenia	**100 (30.9)**	**72 (22.2)**	**94 (29.0)**	**72 (22.2)**
Thrombocytopenia	43 (13.3)	12 (3.7)	53 (16.4)	19 (5.9)
Second primary malignancies	46 (14.2)	26 (8.0)	52 (16.0)	19 (5.9)

	Zanubrutinib (n=324)	Ibrutinib (n=324)
Cardiac adverse events	**80 (24.7)**	**112 (34.6)**
Serious cardiac adverse events	**11 (3.4)**	**31 (9.6)**
Cardiac adverse events leading to treatment discontinuation	**3 (0.9)**	**15 (4.6)**
Ventricular extrasystoles	1 (0.3)	0
Atrial fibrillation/flutter	1 (0.3)	6 (1.9)
Cardiac failure	1 (0.3)	2 (0.6)
Cardiac arrest	0	2 (0.6)[b]
Cardiac failure acute	0	1 (0.3)[b]
Congestive cardiomyopathy	0	1 (0.3)[b]
Myocardial infarction	0	1 (0.3)[b]
Palpitations	0	1 (0.3)
Ventricular fibrillation	0	1 (0.3)

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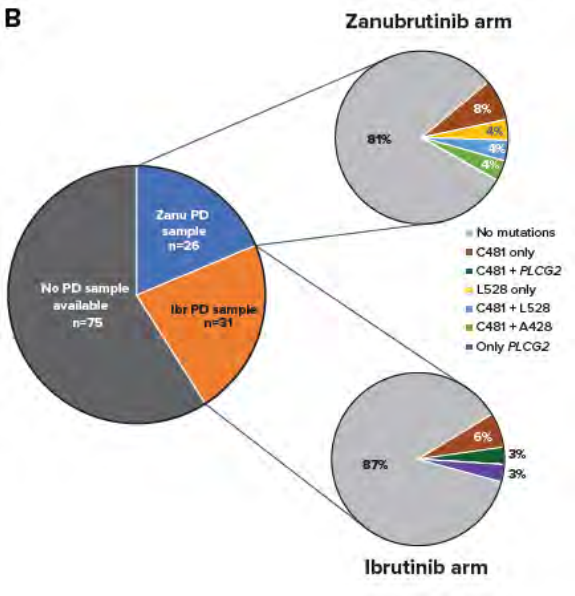
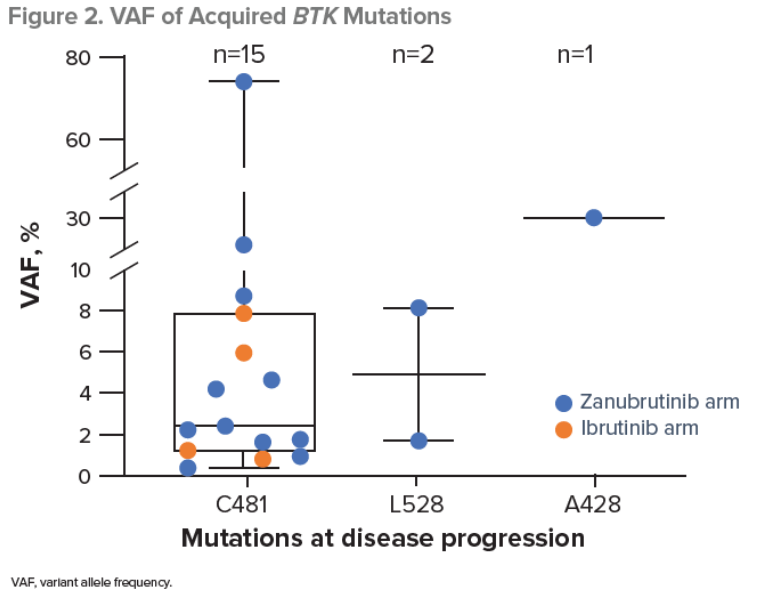
ALPINE: Mutational Resistance Profiles Suggest Few Develop Kinase Dead Mutations

57 Pt PD
on Drug
7 had BTK
mutations
5 Zanu
3 Ibr





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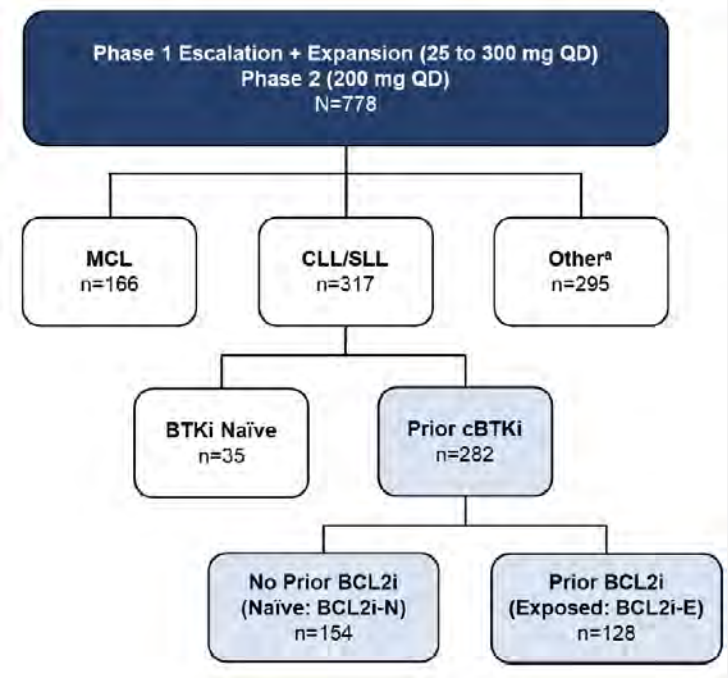
BRUIN

Pirtobrutinib

BRUIN: Subject Grouping and Risk Features



Characteristics	Prior cBTKi (n=282)	BCL2i-N (n=154)	BCL2i-E (n=128)
Median time from diagnosis to first dose, years (IQR)	11 (8-15)	11 (7-15)	12 (8-15)
Reason for any prior BTKi discontinuation[a], n (%)			
Progressive disease	217 (77)	110 (71)	107 (84)
Toxicity/Other	64 (23)	43 (28)	21 (16)

Baseline Molecular Characteristics[b]	Prior cBTKi (n=282)	BCL2i-N (n=154)	BCL2i-E (n=128)
Mutation status, n/n available (%)			
BCL2 mutated	19/246 (8)	0/133 (0)	19/113 (17)
BTK C481-mutant	96/245 (39)	57/138 (41)	39/107 (36)
PLCG2-mutant	18/245 (7)	10/138 (7)	8/107 (8)
High Risk Molecular Features, n/n available (%)			
17p deletion and/or TP53 mutation	104/217 (48)	57/123 (46)	47/94 (50)
IGHV unmutated	193/225 (86)	100/125 (80)	93/100 (93)
Complex Karyotype	33/73 (45)	17/41 (42)	16/32 (50)
11q deletion	47/202 (23)	28/115 (24)	19/87 (22)

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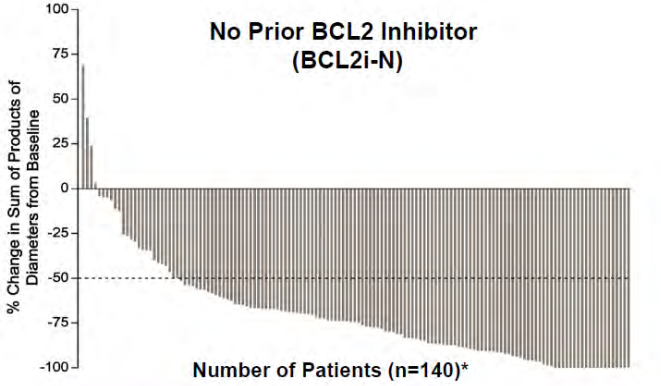
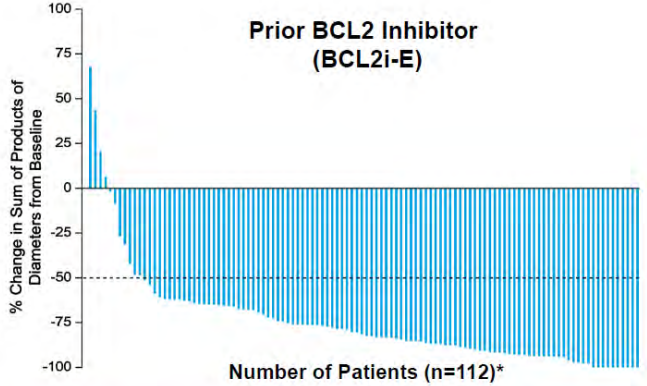
BRUIN: Response and Drug Class Exposure





BCL2i-N	(n=154)[b]
ORR[a] incl. PR-L, % (95% CI)	83.1 (76.2-88.7)
Best Response, n (%)	
CR	5 (3.2)
nPR	2 (1.3)
PR	108 (70.1)
PR-L	13 (8.4)

BCL2i-E	(n=128)[c]
ORR[a] incl. PR-L, % (95% CI)	79.7 (71.7-86.3)
Best Response, n (%)	
CR	0 (0)
nPR	0 (0)
PR	88 (68.8)
PR-L	14 (10.9)

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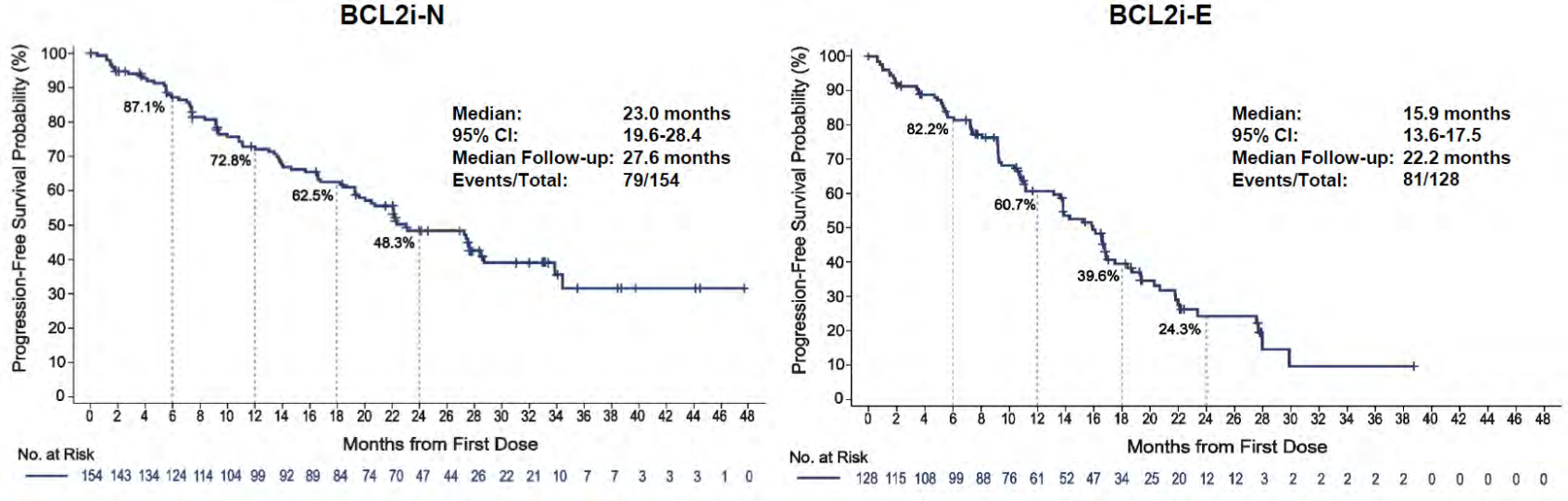
BRUIN: PFS and Drug Class Exposure



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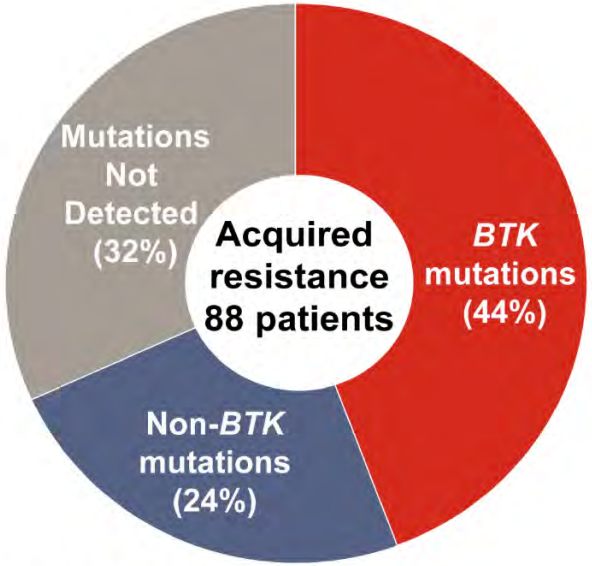
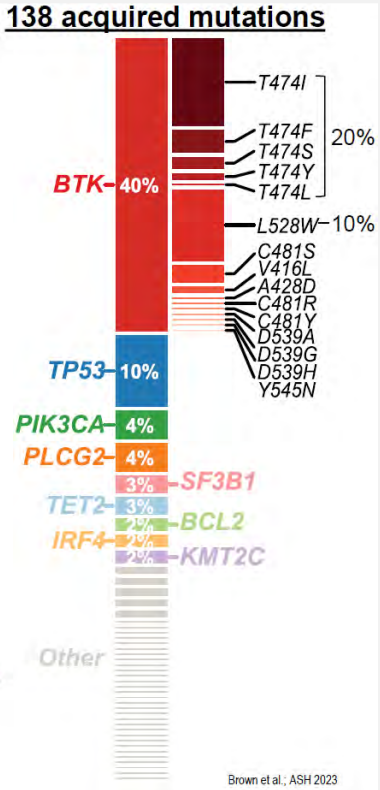
BRUIN: Acquired Mutational Status on Pirtobrutinib





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

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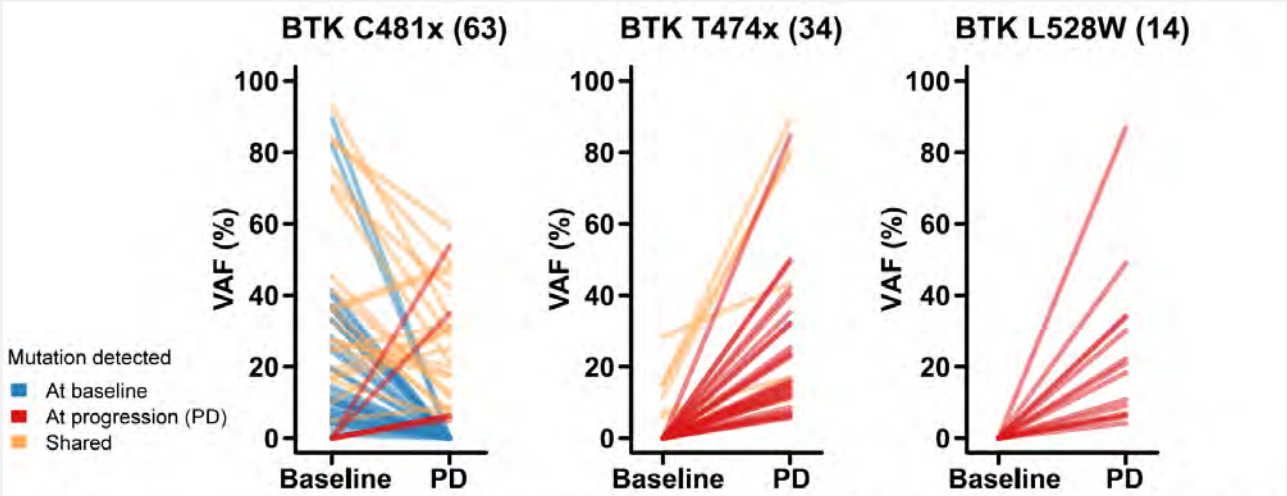
BRUIN: BTK Clearance/Acquisition Rates



- 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%)

26% of Patients Acquired T474x
16% of Patients Acquired L528W
37% were present at baseline

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Conclusions From ASH 2023

- **Better Understanding Regarding Potential Role of Finite Over Fixed Duration**
  - **Relevance/Applicability???**
- **New Expectations for TTNT after Doublet FD combinations**
- **Evidence of Response and Lack of Acquired Resistance Mutations After FD Combination Approaches in Frontline Settings with Oral Combinations**
- **Longer Follow-up Demonstrates Ongoing Activity of Zanu over Ibr with Low Numbers of Kinase Dead Mutations as Mechanism of Resistance**
- **Pirtobrutinib Data Shed light on Potential Sequencing cBTKi->ncBTKi**
- **Clear evidence for non C481S mutations as MoR for Pirto,**
  - **Cycling cBTKi vs Potential role of Degrader in Kinase Dead???**


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