LEUCEMIA LINFATICA CRONICA, OGGI... ED OLTRE

BTKi di prima e seconda generazione: qual è la “griglia di partenza”?

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

ROADMAP

- To identify the key clinical challenges of BTKi molecules in CLL
- To define a possible «starting grid» for BTKi in 1L and R/R CLL patients
- To define the potential advantages of prioritizing the use of one molecule over another, taking into account the impact of CLL biological characteristics, mechanisms of resistance to cBTKi, and AEs (i.e.: off-target)
- To give the floor to my colleague, to discuss the topic of safety

REAL-WORLD EVALUATION OF TREATMENT DISCONTINUATION AND HEALTHCARE RESOURCE UTILIZATION IN PATIENTS WITH CHRONIC LYMPHOCYTIC LEUKEMIA OR SMALL LYMPHOCYTIC LYMPHOMA

DATA SOURCE:

- ***Symphony Integrated Dataverse*** (open-claims database, integrated with electronic medical record data)
- Study period: from January 1, 2013, to March 31, 2023,
- Patients included : with index date (date of treatment initiation) between January 1, 2020, and December 31, 2022 (index period)

OBJECTIVES

- **to examine real-world outcomes among patients with CLL/SLL**

INCLUSION CRITERIA

- Age ≥18 years with ≥1 diagnosis of CLL or SLL
- Initiated a **1L or 2L treatment during the index period**
- Continuous enrollment in the database for 365 days prior to or 90 days after the index date

COHORTS

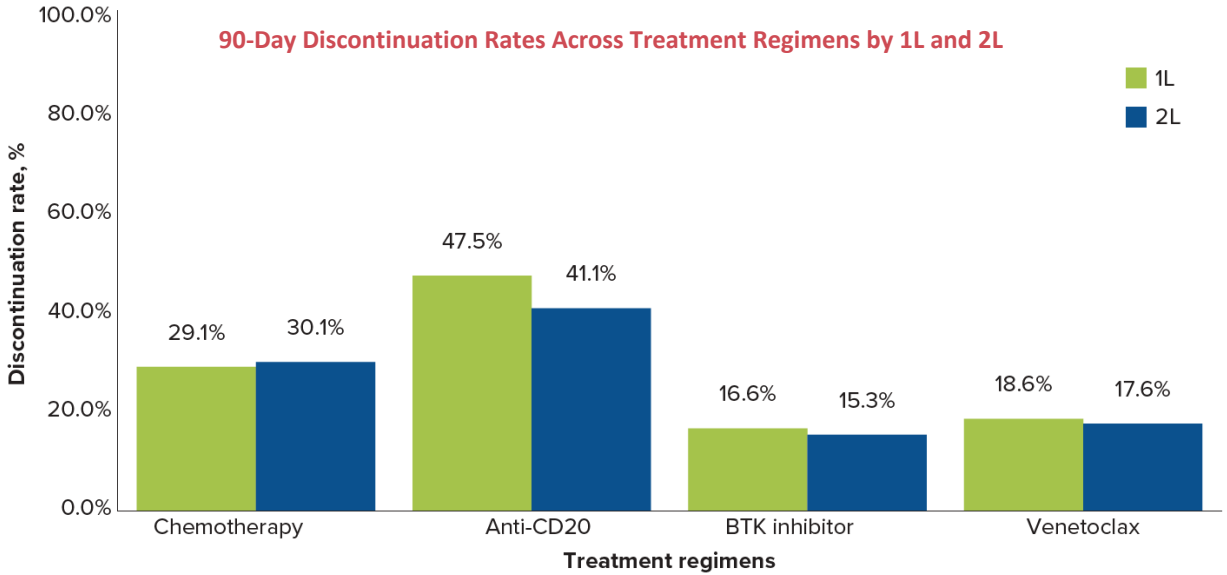
Cohorts were developed based on treatment regimens and stratified by line of therapy (1L and 2L)

- **Chemotherapy** (including bendamustine-based)
- **Anti-CD20–based**
- **BTK inhibitor** (ibrutinib- and acalabrutinib-based; zanubrutinib use was not captured)
- Venetoclax-based

Chanan-Khan AA et al. ASH 2023, abstr #5144.

RWE AND DISCONTINUATION RATES ACROSS 1L AND 2L

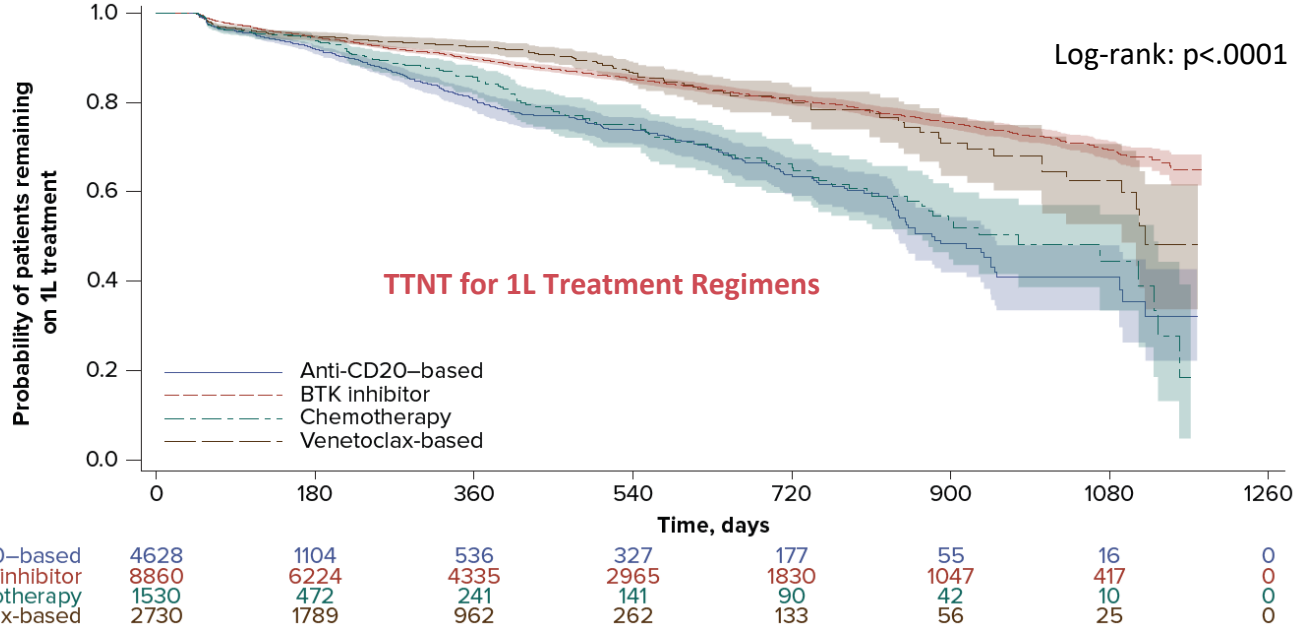
- ✓ Across 1L and 2L, **90-day discontinuation rates were lowest for BTK inhibitor-based regimens** (16.6% and 15.3%), followed by venetoclax-based regimens (18.6% and 17.6%), chemotherapy-based regimens (29.1% and 30.1%), and anti-CD20–based regimens (47.5% and 41.1%)
- ✓ Discontinuation rates reported in 1L and 2L treatments were statistically significant (p<.0001)



Chanan-Khan AA et al. ASH 2023, abstr #5144.

RWE: REGRESSION OF TREATMENT REGIMEN AND TTNT FOR 1L TREATMENT

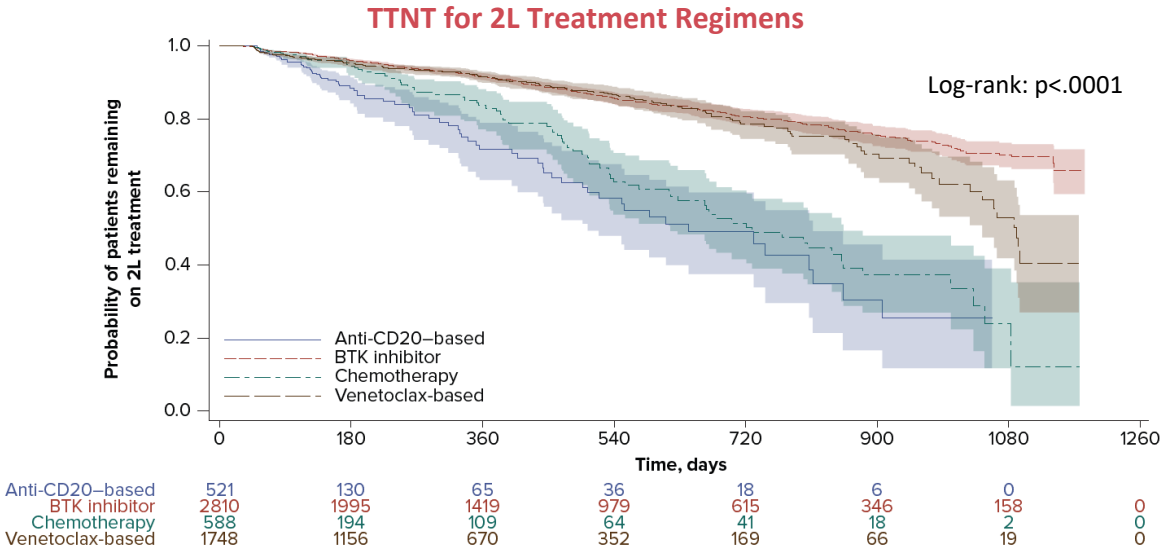
Within 1L, anti-CD20–based and chemo-based regimens had significantly (p<.0001) shorter TTNT compared with BTKi-based regimens, in both the univariate and multivariate models, suggesting patients on anti-CD20 and chemotherapy-based regimens moved onto subsequent treatment sooner.



Chanan-Khan AA et al. ASH 2023, abstr #5144.

RWE: REGRESSION OF TREATMENT REGIMEN AND TTNT FOR 2L TREATMENT

Similar results were found in 2L, but significantly longer TTNT was also identified with venetoclax-based regimens



Regression of Treatment Regimen and Discontinuation:

In both 1L and 2L settings and across both univariate and multivariate models, the risk of discontinuation was significantly higher for anti-CD20–based, chemotherapy-based, and venetoclax-based regimens compared with BTK inhibitor-based regimens

Chanan-Khan AA et al. ASH 2023, abstr #5144.

RWE AND EMERGING CONCLUSIONS

- **BTKi therapy emerges as the leading treatment strategy for both initial and subsequent lines of therapy**
- BTKi therapy, the primary treatment regimen across first-line and second-line therapies, has significantly **lower discontinuation rates and healthcare resource utilization, and longer TTNT, compared with other treatment regimens**
- The majority of patients in the study had CLL; those patients with SLL had poorer outcomes
- Findings from this study may not be generalizable to other populations or settings outside of this specific data source
- Further studies are needed to evaluate real-world clinical outcomes of CLL/SLL regimens to support evidence-based treatment decisions

Chanan-Khan AA et al. ASH 2023, abstr #5144.

BTKi REGULATORY STATUS IN CLL/SLL

	In the US	In the EU
Covalent		
Ibrutinib[1,2]	Approved	Approved **(including in combination with venetoclax)**
Acalabrutinib[3,4]	Approved; FD combinations being assessed (AMPLIFY; MAJIC)	Approved (in combination with CD20)
Zanubrutinib[5,6]	Approved; FD combinations being assessed (SEQUOIA; NCT05168930)	Approved
Non-covalent		
Pirtobrutinib[7]	Approved (RR CLL)	Phase 3
Nemtabrutinib[8]	Phase 3 (NCT04728893)	

NEXT STEP:
fixed-duration BTKi-venetoclax combinations

1. Imbruvica® (ibrutinib) FDA prescribing information.
2. Imbruvica® (ibrutinib) EMA prescribing information.
3. Calquence® (acalabrutinib) FDA prescribing information.
4. Calquence® (acalabrutinib) EMA prescribing information.
5. Brukinsa®(zanubrutinib) FDA prescribing information.
6. Brukinsa®(zanubrutinib) EMA prescribing information.
7. Japirca® (pirtobrutinib) FDA prescribing information.
8. www.clinicaltrials.gov

BOX PLOT FOR PLANNING THERAPEUTIC OPTIONS IN CLL

STEP 1: Select best front-line CT-free approach

OBSERVATIONS:

No prospective comparative data
for BTKi vs Ven

CLL17 will be the most informative study to answer this question (1st line…)

STEP 2:

1.Frontline BTK-exposed

2.Frontline Ven-exposed

Upon relapse or progression, 3 major considerations in selecting next therapy

STEP 3: CONSIDERATIONS FOR STEP 1 & 2:

Consideration 1: Levels of evidence

Prospective data/interventional study (randomized data, single arm)
Prospective registry data
Retrospective "real-world" data

Consideration 2: Available options

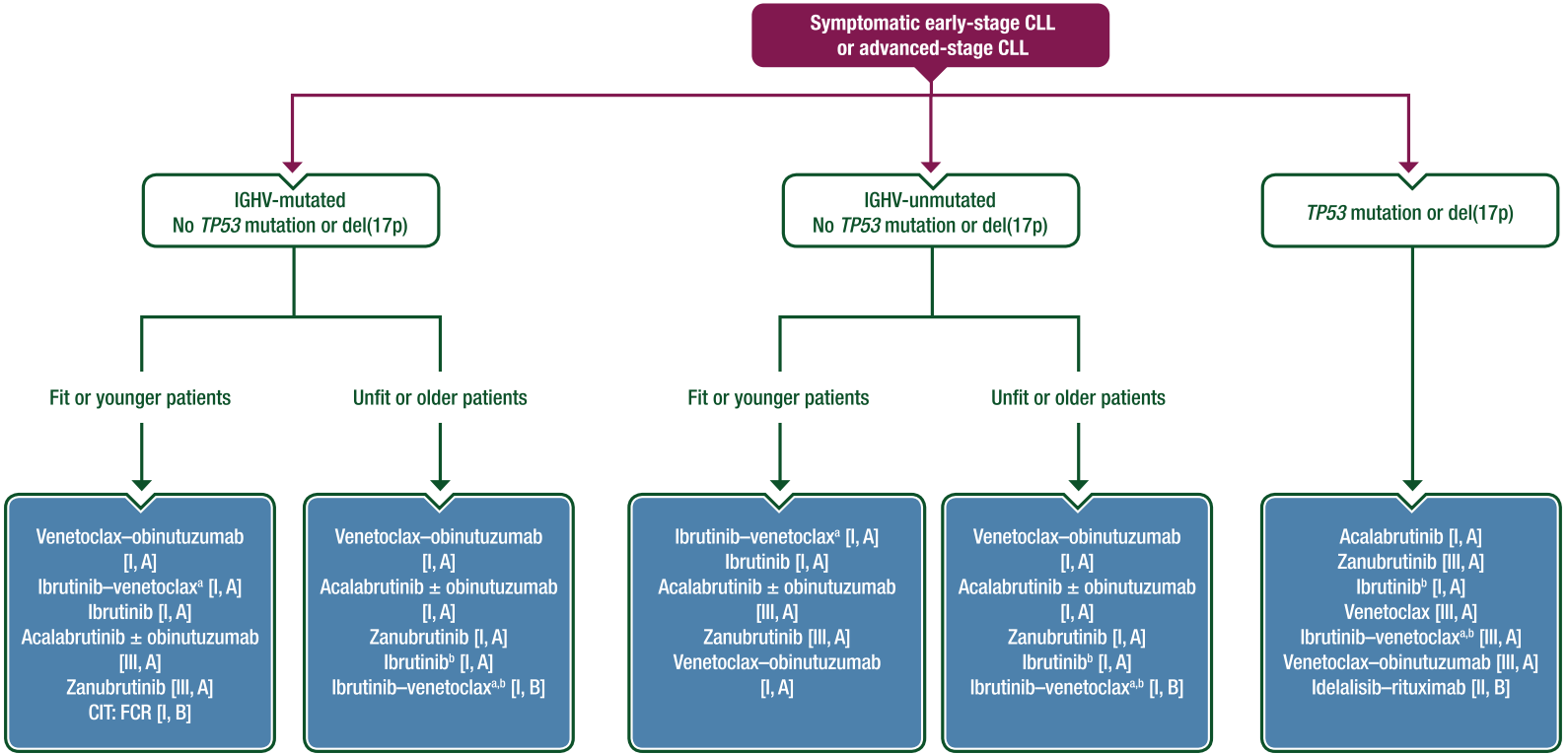
What frontline therapy
Consequence of the order of approval rather than tumor biology

Consideration 3: Reasons for discontinuation

Completion of planned therapy with subsequent PD
Intolerance/AEs
PD (known or unknown resistance mechanisms)

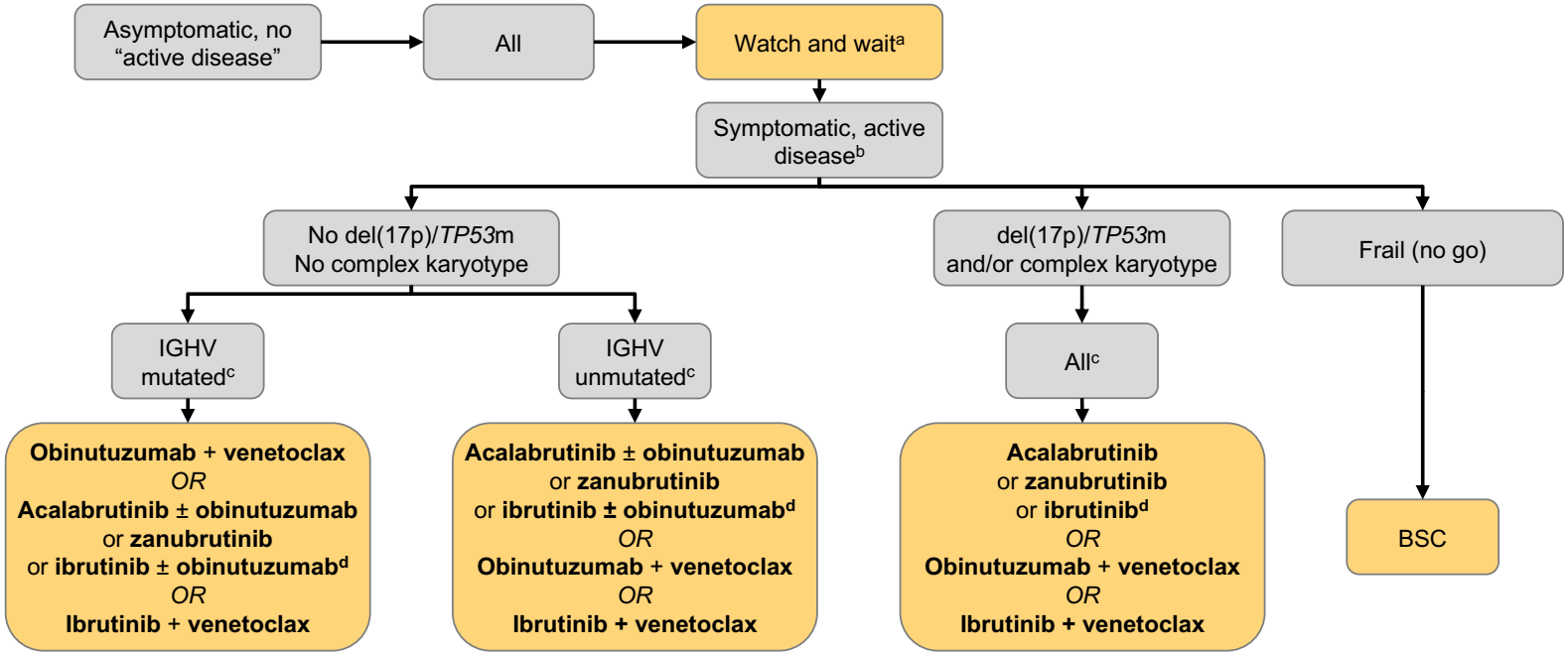
HOW TO BEST ORGANIZE CLL THERAPY?

ESMO 1L GUIDELINES, 2024



Eichhorst B et al. ESMO Clinical Practice Guideline interim update on new targeted therapies in the first line and at relapse of chronic lymphocytic leukaemia. Ann Oncol 2024; 35(9): 762-768.

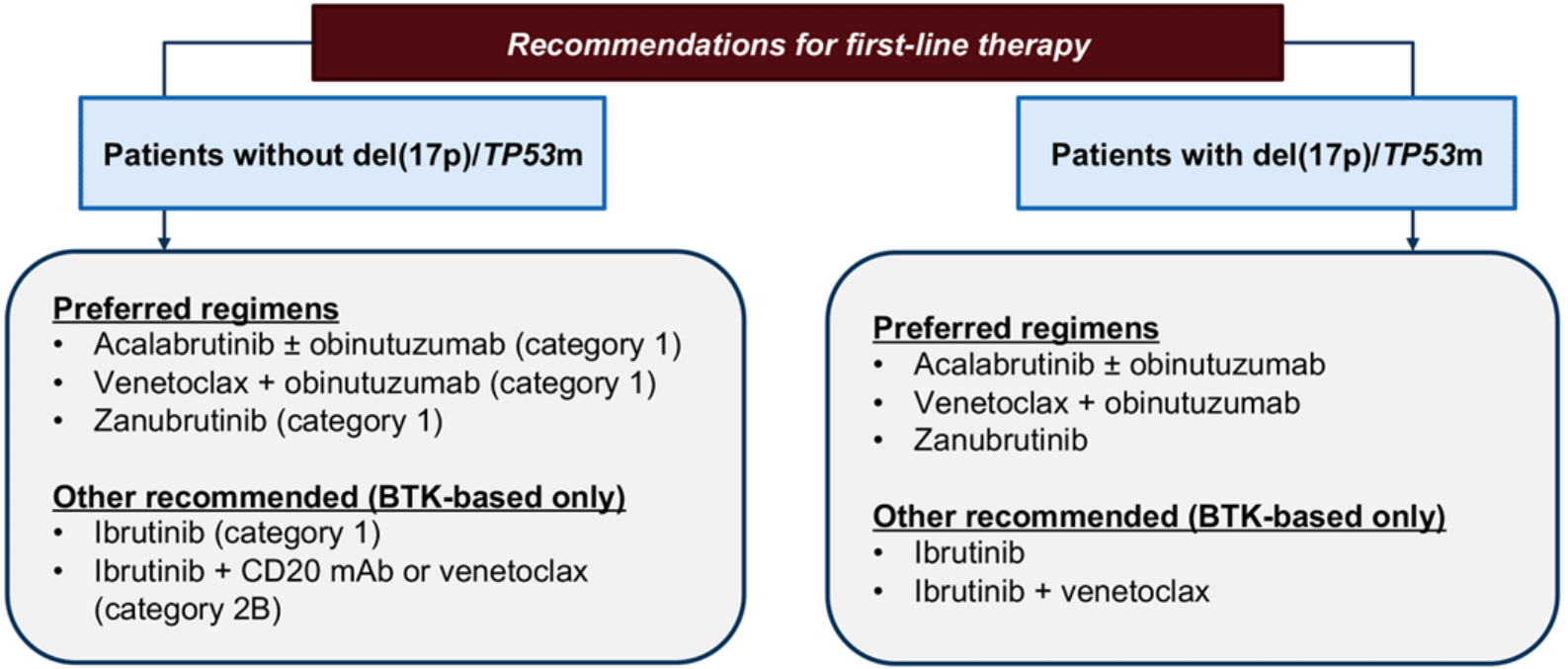
OTHER EU GUIDELINES: ONKOPEDIA 1L, 2023



[a] Waiting behavior. [b] Active disease according to iwCLL 2018 criteria. [c] The ranking of the following therapies presents one possibility. Due to the current data situation, it is not binding. The individual comorbidity profile, aspects of adherence, application effort/logistics of the therapeutic intervention, and patient preference for the final therapy determination should be taken into account. [d] If A or Z is contraindicated or not available, I (± G) remains a therapy option, taking into account increased cardiac adverse events. A and Z were not systematically evaluated in younger/fit patients in first-line therapy.

https://www.onkopedia.com/de/onkopedia/guidelines

NCCN 1L GUIDELINES, 2024



NCCN Clinical Practice Guidelines in Oncology.
Chronic Lymphocytic leukemia/Small Lymphocytic Lymphoma. Version 3.2024.

IN THE EVERYDAY CLINICAL SETTING...

FIRST LINE

- **IBRUTINIB**
  - ACALABRUTINIB
  - ZANUBRUTINIB
  - VENETOCLAX
- **ACALABRUTINIB**
  - IBRUTINIB
  - ZANUBRUTINIB
  - VENETOCLAX
- **ZANUBRUTINIB**
  - IBRUTINIB
  - ACALABRUTINIB
  - VENETOCLAX

IN THE EVERYDAY CLINICAL SETTING...

FIRST LINE

- **VEN-OBI**
  - IBRUTINIB
  - ACALABRUTINIB
  - ZANUBRUTINIB
  - VENETOCLAX

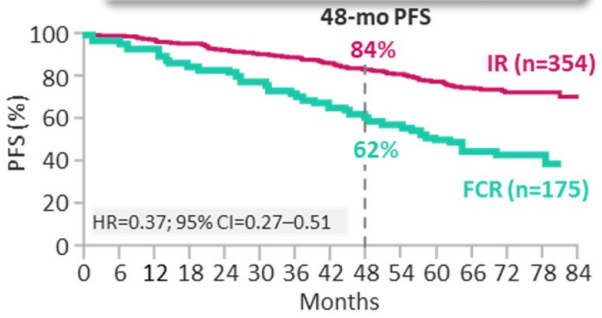
?

- **I + V**
  - IBRUTINIB
  - ACALABRUTINIB
  - ZANUBRUTINIB
  - VENETOCLAX

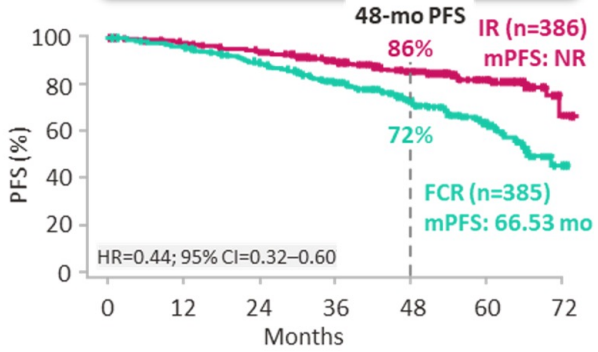
?

IBRUTINIB IN TN CLL PATIENTS: FROM YOUNG FIT TO ELDERLY UNFIT

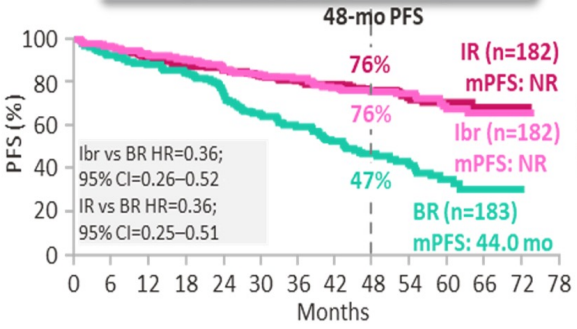
ECOG-1912: INV-assessed[1] PFS
(median follow-up: 70 months)[2]



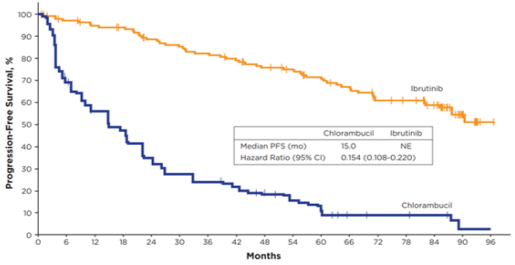
FLAIR: INV-assessed PFS
(median follow-up: 52.7 months)[5]



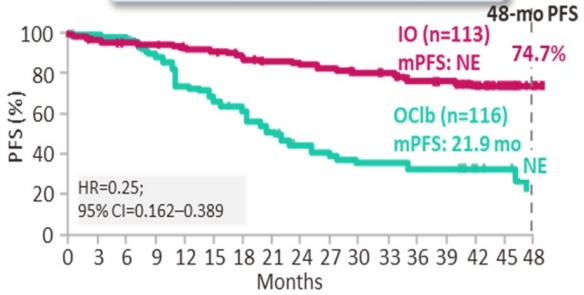
Alliance A041202: INV-assessed PFS
(median follow-up: 55 months)[3]



RESONATE-2[6]
8-year follow-up

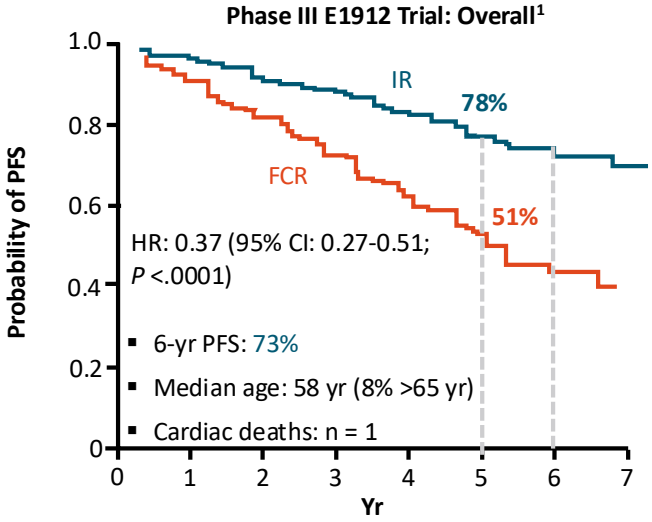


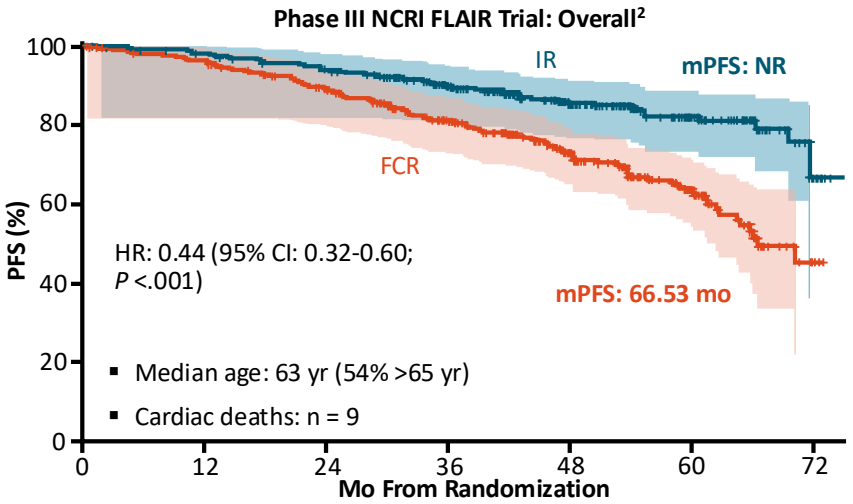
iLLUMINATE: INV-assessed PFS
(median follow-up: 45 months)[4]



1. Shanafelt TD *et al. N Engl J Med* 2019; 381 (5): 432–443. 2. Shanafelt TD *et al. Blood* 2022; 140 (2): 112–120. 3. Woyach J *et al. Blood* 2021; 138 (Suppl_1): 639. 4. Moreno C *et al. Haematologica* 2022; 107 (9): 2108–2120. 5. Hillmen P *et al.* Oral presentation at ASH 2021; Georgia, USA, December 11–14, 2021 (Session 642). 6 Barr PM *et al. Blood Adv* 2022; 6 (11): 3440–3450.

FIRST-GENERATION COVALENT BTKi: EARLIER ROLE AS 1L THERAPY FOR CLL





Outcomes with ibrutinib in combination with rituximab in CLL:

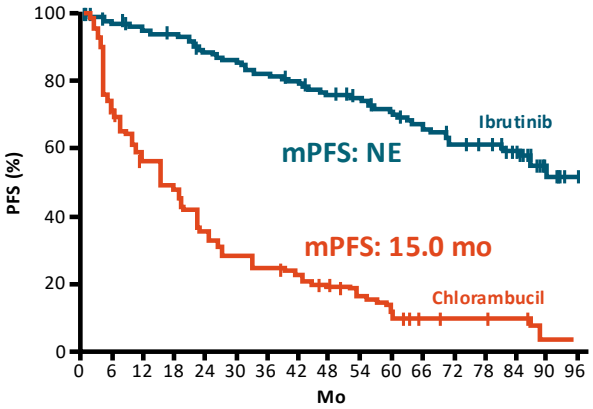
✓ Superior to CIT in younger and older patients

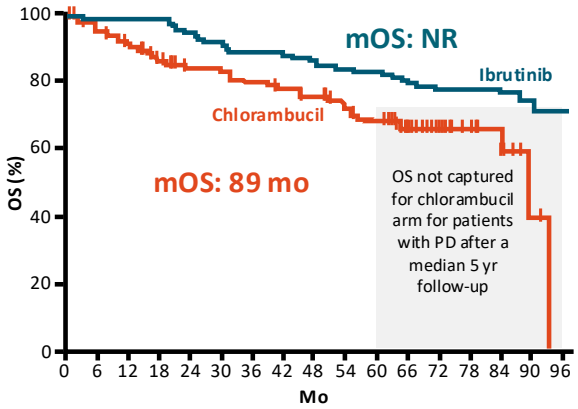
✓ Superior to FCR in patients ≤ 65 yrs in PFS and OS

1. Shanafelt T et al. Blood 2022; 140: 112.
2. Hillmen P et al. Blood 2021: 138: 642.

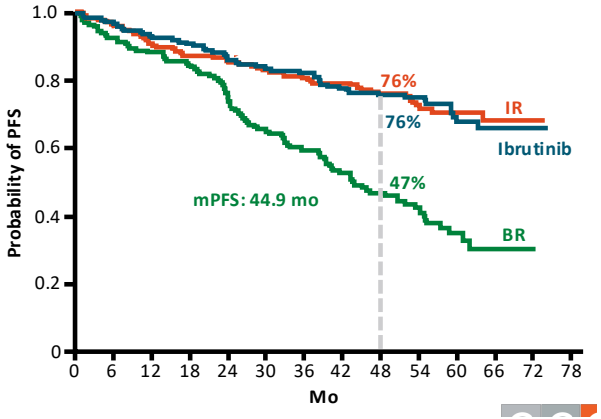
FIRST-GENERATION COVALENT BTKi: EARLIER ROLE AS 1L THERAPY FOR CLL

RESONATE-2 Trial: Overall[1,2]
(Patients aged ≥65 yr with untreated CLL)





A041202 Trial: Overall[3]
(Patients aged ≥65 yr with untreated CLL)



Outcomes with ibrutinib alone or in combination with rituximab in CLL:

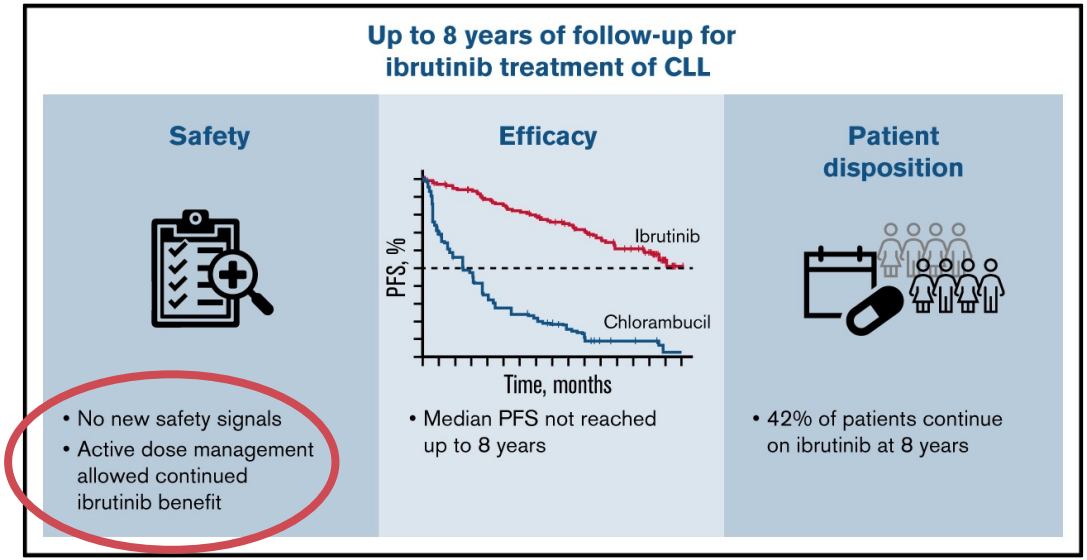
✓ Superior to chlorambucil in patients ≥ 65 yrs in PFS and OS (RESONATE-2)

✓ Superior to BR in patients ≥ 65 yrs in PFS

✓ Associated with AF, bleeding, bruising, hypertension, myalgias, arthralgias, and diarrhea (treatment was discontinued in 41% of patients in the RESONATE-2 trial, mostly due to AEs)

1. Barr PM et al. Blood Adv 2022; 6: 3440. 2. Burger JA et al. Leukemia 2020; 34: 787.
3. Woyach J et al. Blood 2024; 143: 1616.

RESONATE-2: UP TO 8 yr OF FOLLOW-UP



FINAL ANALYSIS OF THE RESONATE-2 STUDY: UP TO 10 YEARS OF FOLLOW-UP OF FIRST-LINE IBRUTINIB TREATMENT IN PATIENTS WITH CHRONIC LYMPHOCYTIC LEUKEMIA/SMALL LYMPHOCYTIC LYMPHOMA

….Final analysis, representing up to 10 years of follow-up (median 9.6 years for the Ibr arm and 5.6 years for the Clb arm).

Patients treated with Ibr demonstrated a significant and sustained PFS benefit versus patient treated with Clb.

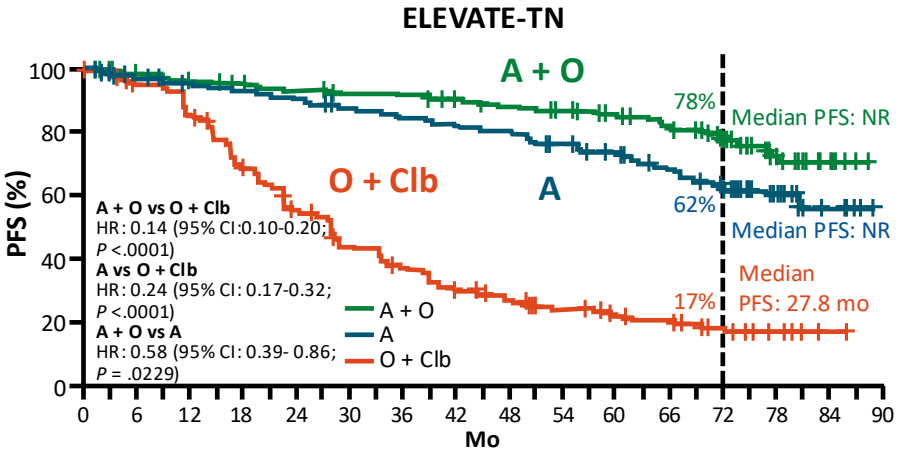
Median PFS:
Ibr arm: 8.9 years
Clb arm: 1.3 years

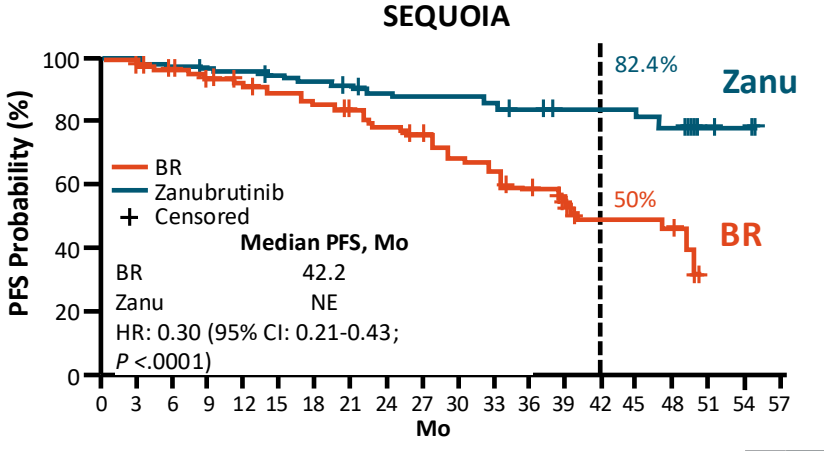
PFS rate at 9 years of FU:
Ibr arm: 49.7%
Clb arm 4.4%

Barr PM et al. Up to 8-year follow-up from RESONATE-2: first-line ibrutinib treatment for patients with chronic lymphocytic leukemia. Blood Advances 2022; 6 (11): 3440-3450.

Burger J et al. Final analysis of the RESONATE-2 study: up to 10 years of follow-up of first-line ibrutinib treatment in patients with chronic lymphocytic leukemia/small lymphocytic lymphoma. EHA 2024, abstr #670.

NEXT-GENERATION COVALENT BTKi: FEWER AEs AND SUPERIOR TO CIT



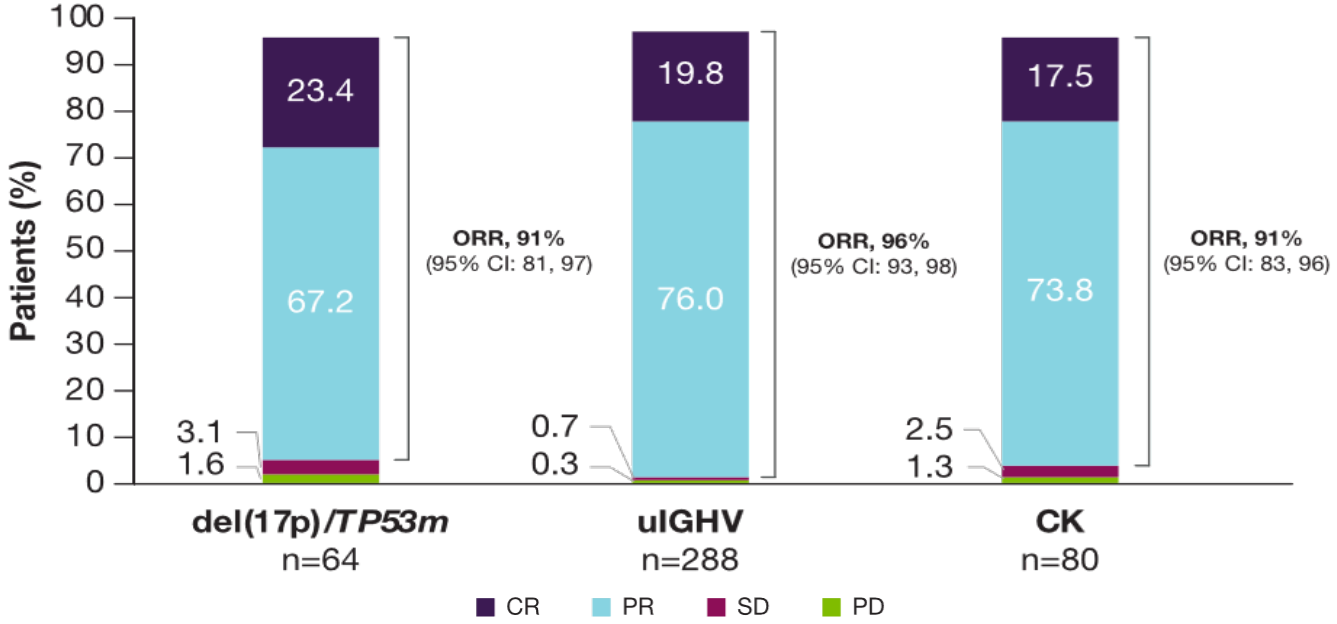


- ✓ Acalabrutinib +/- obinutuzumab is superior to CIT in PFS
- ✓ Zanubrutinib is superior to CIT in PFS
- ✓ Lower rates of AF, hypertension, serious bleeding
- ✓ Discontinuation due to AEs was approximately 10%

1. Sharman JP et al. ASH 2023, abstr #636.
2. Ramakrishnan V et al. ASH 2023, abstr# 1902.

WHAT HAPPENS WITH SECOND GENERATION COVALENT BTKi? ACALABRUTINIB

3 clinical studies in TN CLL: CL-001 (TN cohort), CL-003 (TN cohort) and ELEVATE-TN (n=321)

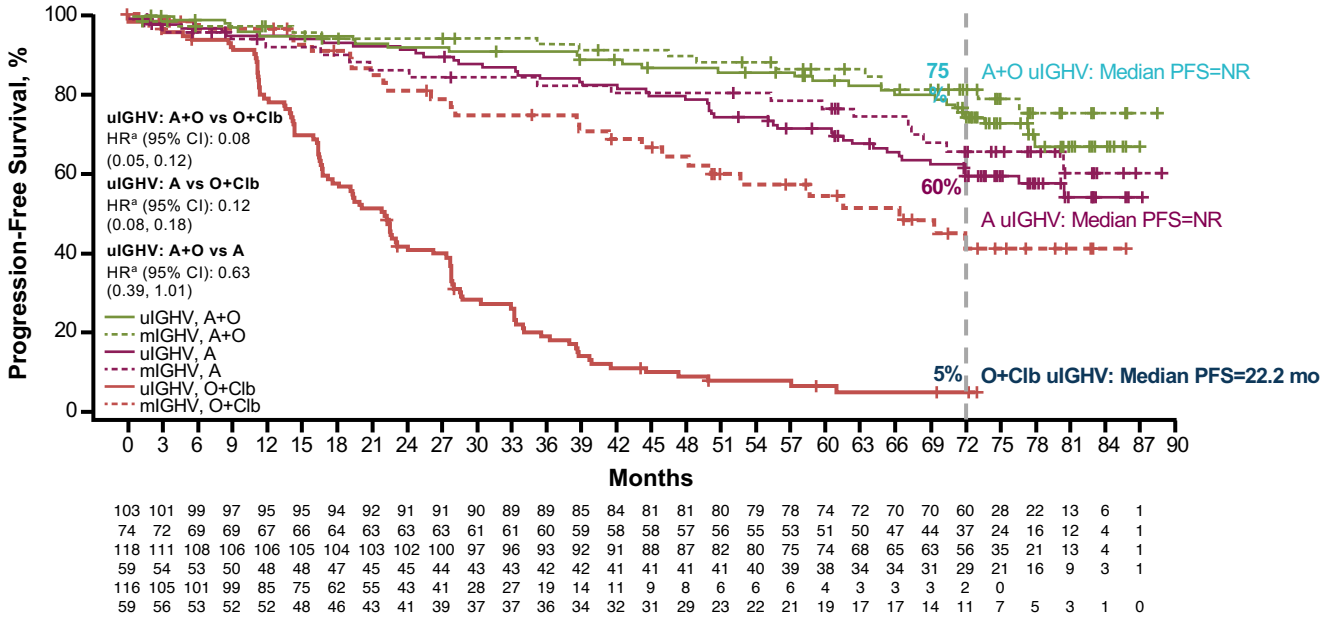


Davids MS et al. Long-term efficacy of Acalabrutinib-based regimens in patients with chronic lymphocytic leukemia and higher-risk genomic features: pooled analysis of clinical trial data. EHA 2022, abstr #667.

ELEVATE TN: INVESTIGATOR-ASSESSED PFS IN PATIENTS WITH uIGHV

PFS result in A-treated patients with uIGHV was consistent with overall result

Median PFS was NR in patients with uIGHV treated with A+O and A vs. 22.2 months in O+Clb arm

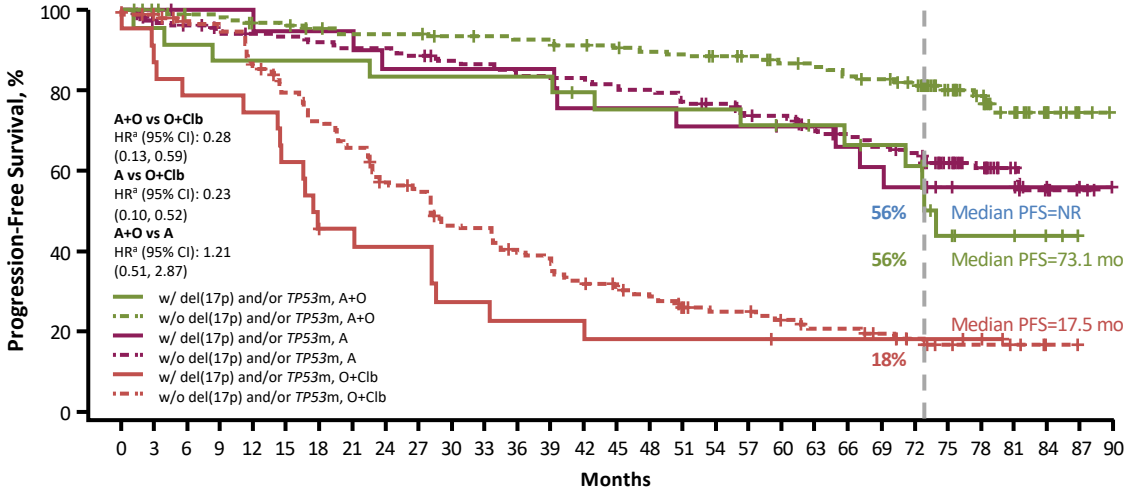


[a]Hazard ratio was based on unstratified Cox-Proportional-Hazards model.

A = acalabrutinib; CI = confidence interval; Clb = chlorambucil; HR = hazard ratio; IGHV = immunoglobulin heavy chain variable; mIGHV = mutated IGHV; NR = not reached; O = Obinutuzumab; PFS = progression free survival; uIGHV = unmutated IGHV; vs = versus.

Sharman JP et al. ASH 2023, abstr #636.

ELEVATE TN: INVESTIGATOR-ASSESSED PFS IN PATIENTS WITH *del17p* AND/OR *TP53*^{MUT}



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

[a]Hazard ratio based on unstratified Cox proportional-hazards model.
A = acalabrutinib; CI = confidence interval; Clb = chlorambucil; HR = hazard ratio; NR = not reached; O = Obinutuzumab; PFS = progression free survival; *TP53* = tumour protein p53; vs = versus.

Sharman JP et al. ASH 2023, abstr #636.

ZANUBRUTINIB IN TN CLL: SEQUOIA STUDY

Cohort 1

- Untreated CLL/SLL
- ≥ 65 y of age OR unsuitable for treatment with FCR^
- Without *del(17p)* by central FISH

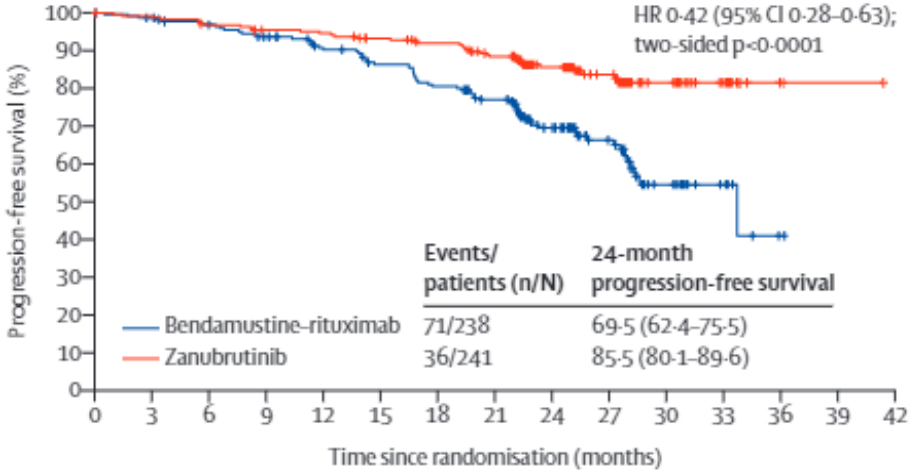
randomize

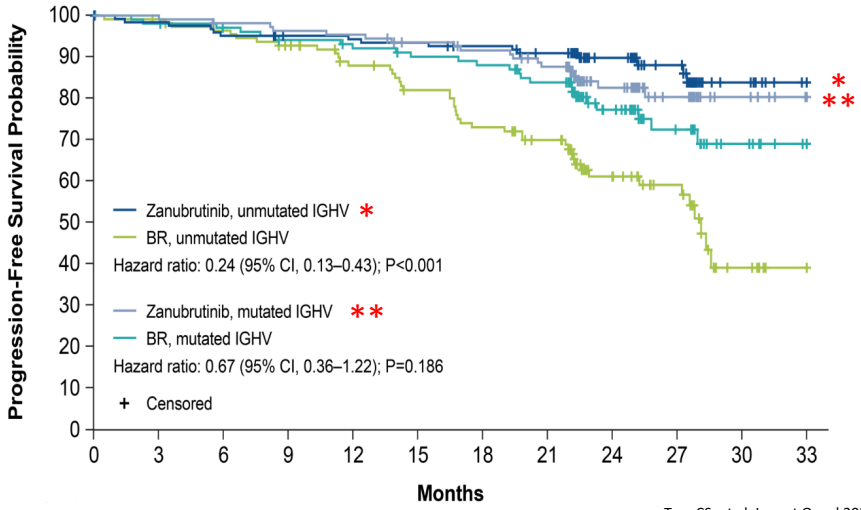
- Zanubrutinib
- Bendamustine* + rituximab*

* 6 cycles

^Defined as Cumulative illness rating score> 6, CrCl < 70 mL/min, or a history of previous severe infection or multiple infections within the last 2 years; †6 cycles. FISH, fluorescence in situ hybridization.

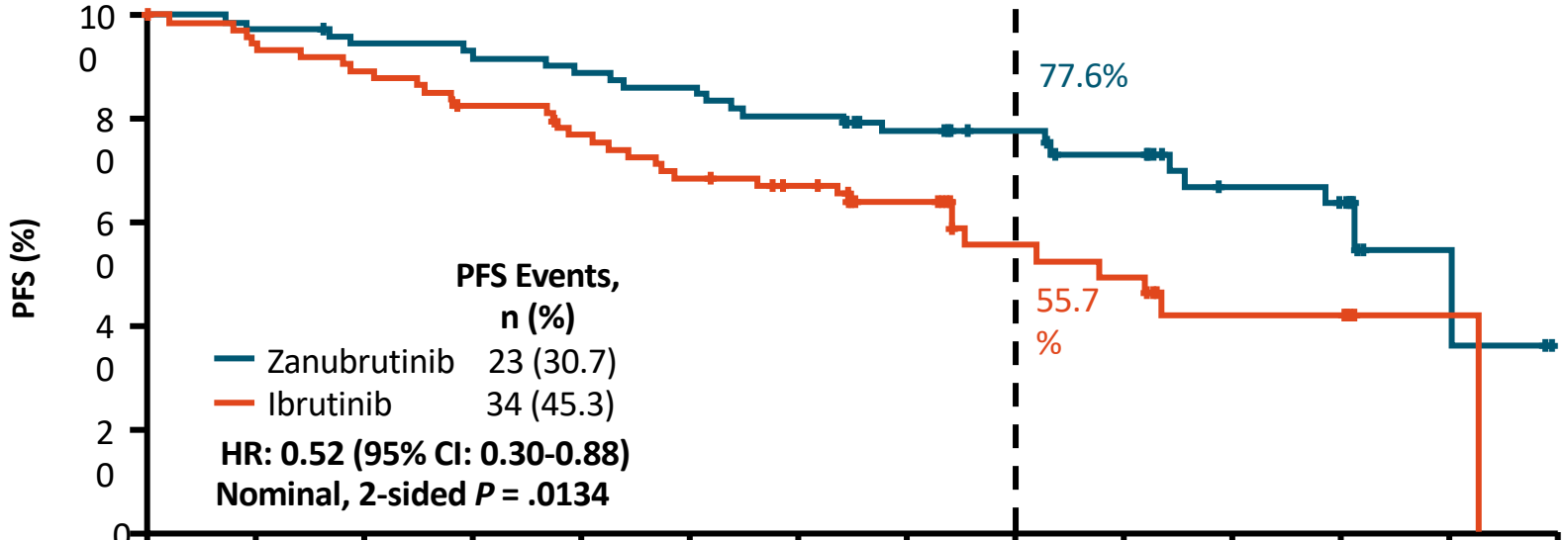
Median Follow-up 26.2 m





Tam CS, et al. Lancet Oncol 2022.

ALPINE: IRC-ASSESSED PFS IN PATIENTS WITH del(17p) AND/OR *TP53*^{MUT}

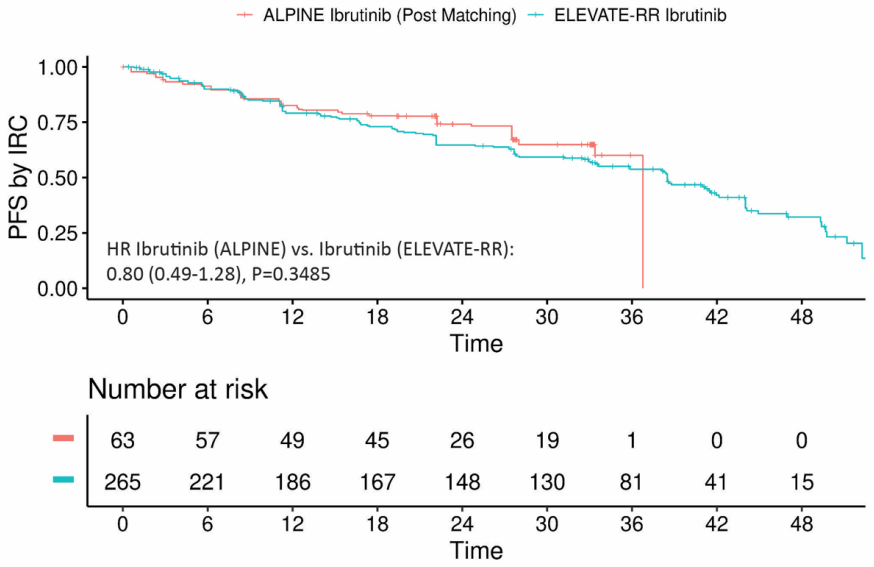


Patients at Risk, n

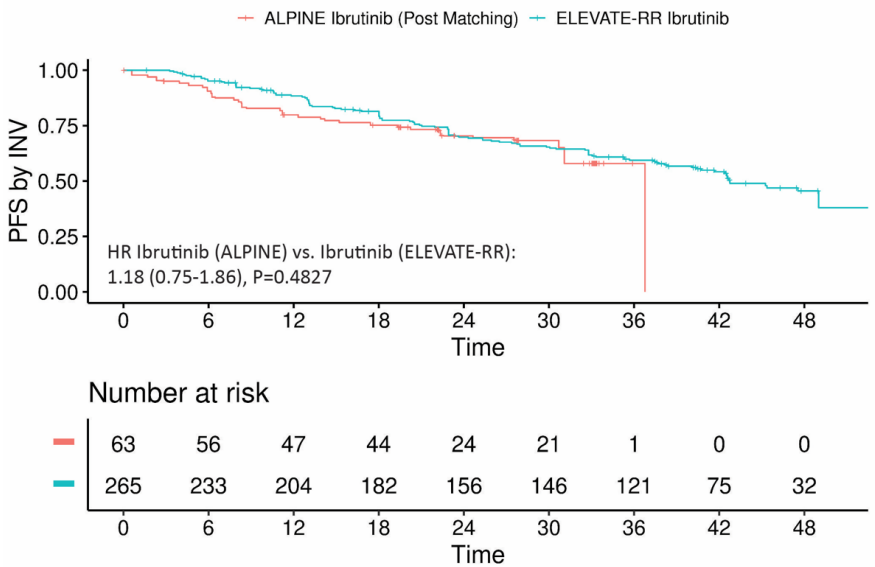
Zanubrutinib	75	71	68	67	64	62	58	49	35	30	21	19	3	0
Ibrutinib	75	70	66	60	44	49	45	34	18	16	10	10	2	0

Brown J et al. NEJM 2023; 26;388(4): 319-332.

Comparing PFS-IRC of ibrutinib arms across Alpine and Elevate-RR



Comparing PFS-INV of ibrutinib arms across Alpine and Elevate-RR

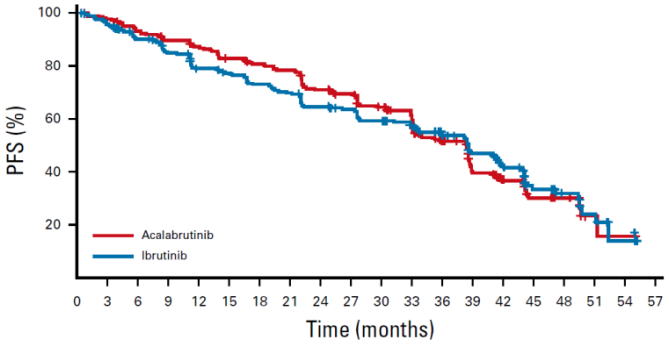


Shadman M et al. Similar efficacy of Ibrutinib arms across ALPINE and ELEVATE-RR trials in Relapsed/Refractory Chronic Lymphocytic Leukemia: A Matching-Adjusted Indirect Comparison. ASH 2023, abstr #4655.

EFFICACY COMPARISON IN PREVIOUSLY TREATED PATIENTS: FIRST AND SECOND GENERATION BTKi

Ibrutinib vs Acalabrutinib (ELEVATE-RR)

PFS: HR 1.00, Median follow up: 40.9 months



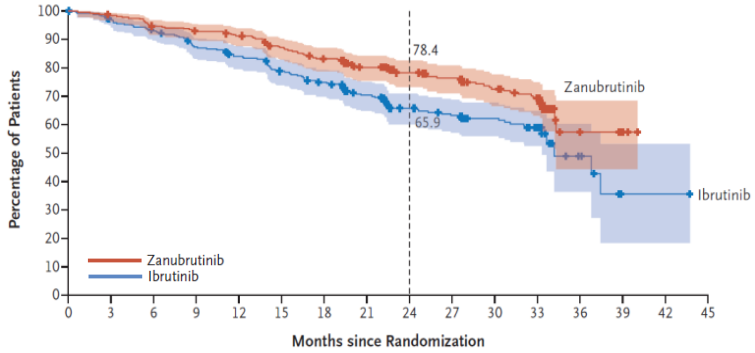
No. at risk:

Acalabrutinib	268	250	235	227	219	207	200	193	173	163	148	110	84	59	31	21	13	3	1	0
Ibrutinib	265	240	221	205	186	178	168	160	148	142	130	108	81	66	41	26	15	8	2	0

	ORR	On Treatment	Deaths
Acalabrutinib	81.0%	46.3%	23.5%
Ibrutinib	77.0%	41.1%	27.5%

Ibrutinib vs Zanubrutinib (ALPINE)

PFS: HR 0.65, Median follow up: 29.6 months



No. at Risk

Zanubrutinib	327	316	303	297	290	274	260	221	165	158	122	111	12	2	0
Ibrutinib	325	306	293	273	259	241	227	186	128	121	97	87	9	1	1	0

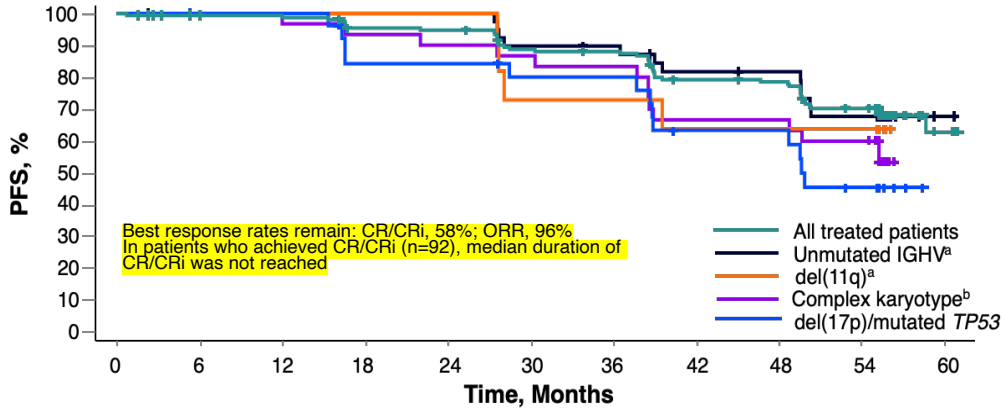
	ORR	On Treatment	Deaths
Zanubrutinib	86.2%	72.8%	14.8%
Ibrutinib	74.2%	58.5%	18.3%

Byrd JC et al. Acalabrutinib versus Ibrutinib in previously treated chronic lymphocytic leukemia: results of the first randomized phase III trial. J Clin Oncol 2021; 39(31): 3441-3452.

Brown JR et al. Zanubrutinib or Ibrutinib in Relapsed or Refractory Chronic Lymphocytic Leukemia. N Engl J Med 2023; 388: 319-332.

CAPTIVATE: 4-yr FU ANALYSIS FROM FD COHORT – IGHV, CK, *del11q*, *del17p/TP53*^{MUT}

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



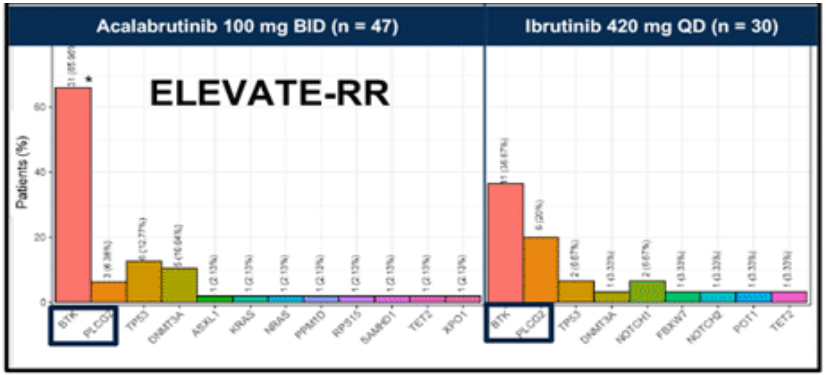
	54-Month PFS Rate, % (95% CI)
All treated patients (n=159)	70 (62–77)
Unmutated IGHV (n=40)[a]	68 (50–80)
del(11q) (n=11)[a]	64 (30–85)
Complex karyotype (n=31)[b]	60 (41–75)
del(17p)/mutated *TP53* (n=27)	45 (25–64)

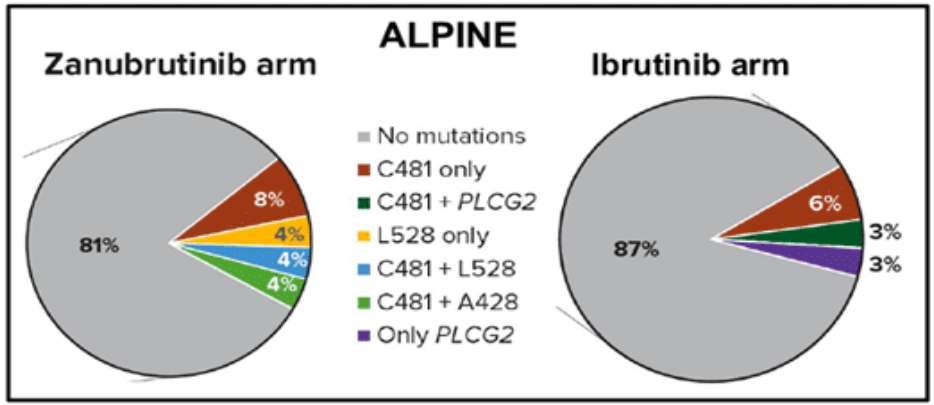
	With Feature		Without Feature	
High-Risk Feature	**n**	**5-y PFS, % (95% CI)**	**n**	**5-y PFS, % (95% CI)**
Del(17)p/*TP53*m	27	41 (21-59)	129	73 (64-80)
CK[a]	31	57 (37-72)	102	72 (61-80)
Del(11q)[b]	11	41 (30-85)	74	79 (67-87)

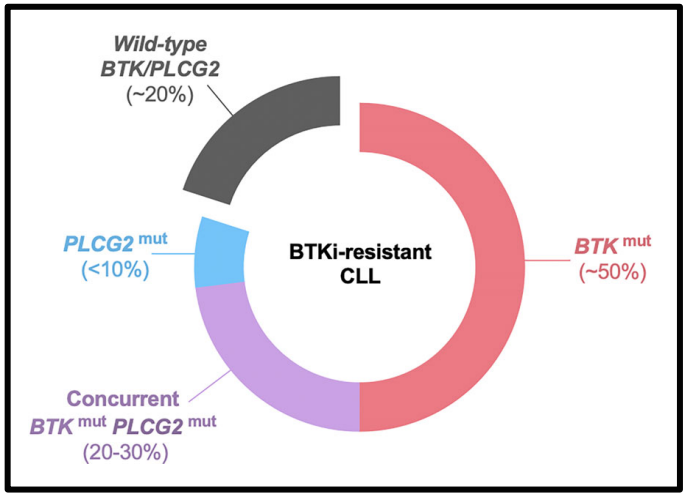
[a]Excluding patients with del(17p)/mutated *TP53* or complex karyotype. [b]Defined as ≥3 abnormalities by conventional CpG-stimulated cytogenetics.

Barr PM et al. J Clin Oncol 2023;41(suppl 16). Abstr #7535.
Ghia P et al. ASH 2023, abstr #633. ICML 2023, abstr #155.
Wierda W et al. ASCO 2024, abstr #7009.

LEARNING ABOUT RESISTANCE FROM THE MONOTHERAPY EXPERIENCE WITH BTKi







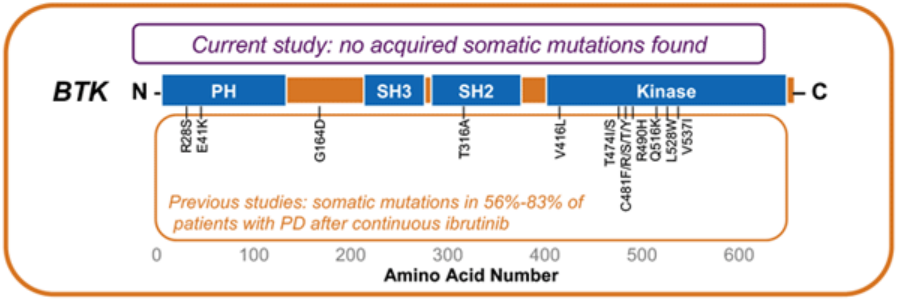
Woyach C et al. ICML 2023, abstr #163.
Brown JR et al. ASH 2023, abstr #1890.

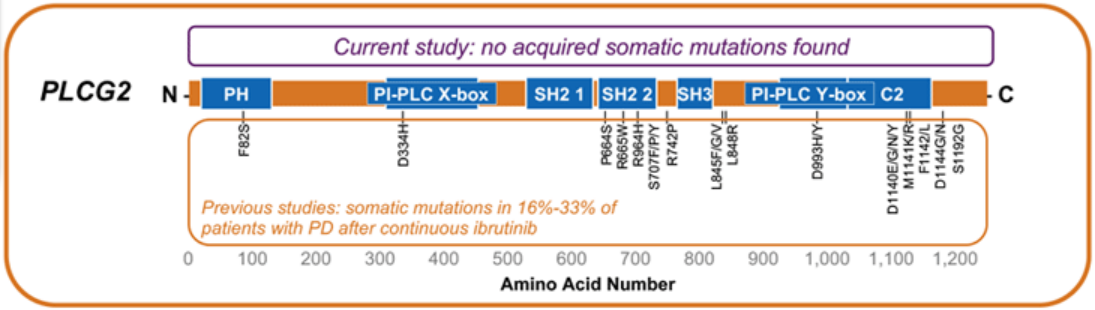
Adapted from: Ahn I, Brown JR. Targeting Bruton's Tyrosine Kinase in CLL. Front Immunol 2021; 12: 687458.

WILL FIXED DURATION BTKi/BCL-2i MITIGATE DOWNSTREAM RESISTANCE?

CAPTIVATE: after first-line treatment with FD ibrutinib + venetoclax, no BTK, BCL2, and PLCG2 mutations detected

Assessment in 25 of 29 patients with progressive disease





Jain N et al. Clin Cancer Res 2024; 30: 498-505.

TO CONCLUDE…

CHOICE OF BTKi & STARTING GRID:
- ✓ Efficacy
- ✓ Sequencing
- ✓ Resistance (covalent BTKi *vs* non covalent BTKi)
- ✓ Toxicity

SWITCH BTKi FOR INTOLERANCE: POSSIBLE

SECOND GENERATION BTKi HAVE FEWER CV AEs
- ✓ Lower rates of AF compared to ibrutinib for both
- ✓ Acalabrutinib likely has less hypertension

NOT ALL AEs ARE LESS FREQUENT WITH NEWER AGENTS
- ✓ Bleeding event reduction is unclear
- ✓ Headache more frequent with acalabrutinib
- ✓ Neutropenia more frequent with zanubrutinib

ROADMAP

- To identify the key clinical challenges of BTKi molecules in CLL
- To define a possible «starting grid» for BTKi in 1L and R/R CLL patients
- To define the potential advantages of prioritizing the use of one molecule over another, taking into account the impact of CLL biological characteristics, mechanisms of resistance to cBTKi, and AEs (i.e.: off-target)
- To give the floor to my colleague, to discuss the topic of safety

THANKS FOR YOUR ATTENTION