FRENCH INNOVATIVE
LEUKEMIA ORGANIZATION

Treating relapsed/refractory CLL

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Disclosures

- AbbVie, AstraZeneca, BeiGene, Janssen, Gilead

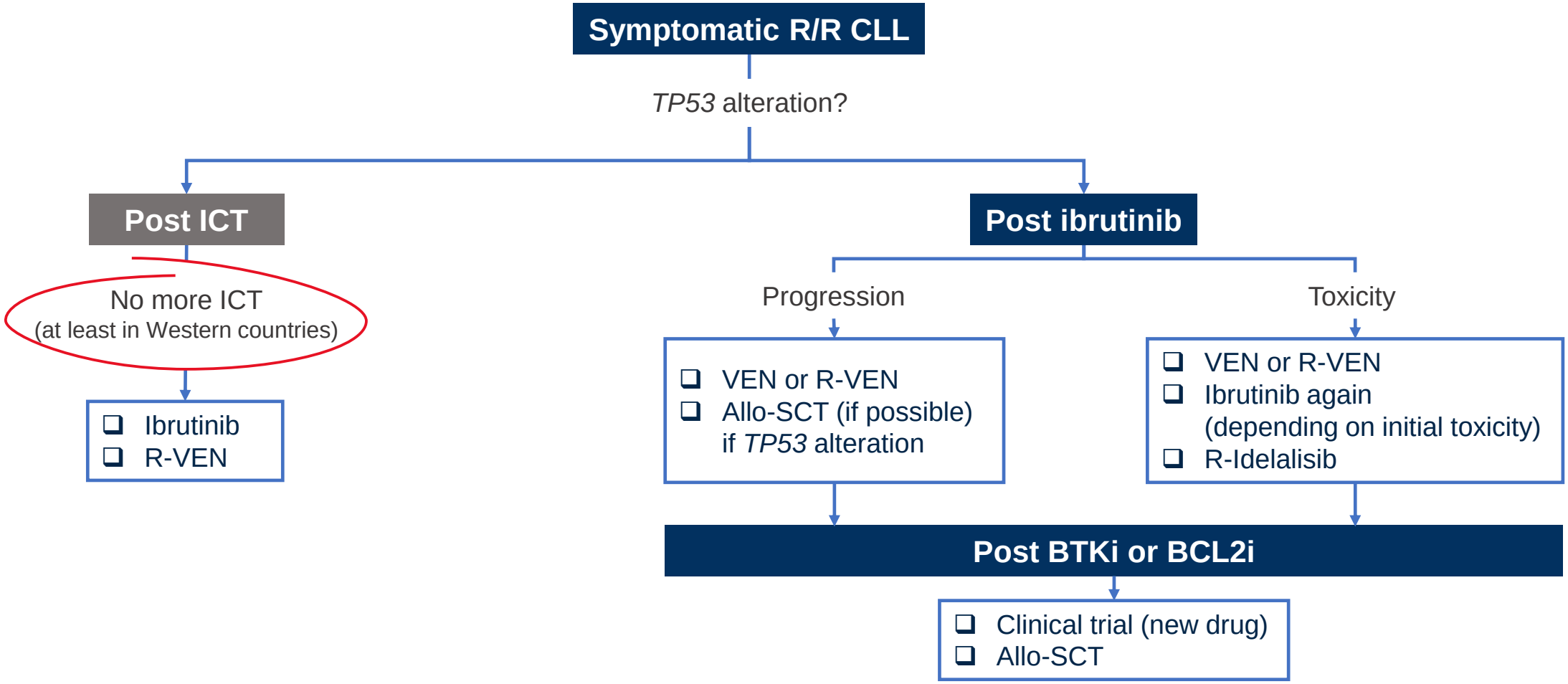
Questions to be asked

- Are there any indications of transformation to Richter’s syndrome?
- Symptomatic CLL relapse? (if not, watch and wait)
- What was the previous treatment?
  - Chemoimmunotherapy (FCR, BR, O+chlorambucil)
  - BTKi
  - BCL2i
  - Doublet (a few cases in 2023)
- Any toxicities from the previous treatment?
- Ongoing treatment? Refractory CLL
  - If not: Time since previous treatment?
- Are there any relevant comorbidities?

This slide reflects the speaker’s opinion.
BCL2i, B-cell lymphoma 2 inhibitor; BR, bendamustine-rituximab; FCR, fludarabine, cyclophosphamide and rituximab; O, obinutuzumab.

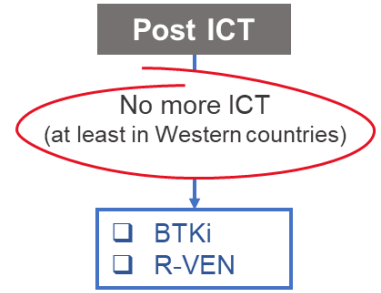
FILO-CLL guidelines

Algorithm for treatment of relapsed CLL in 2021

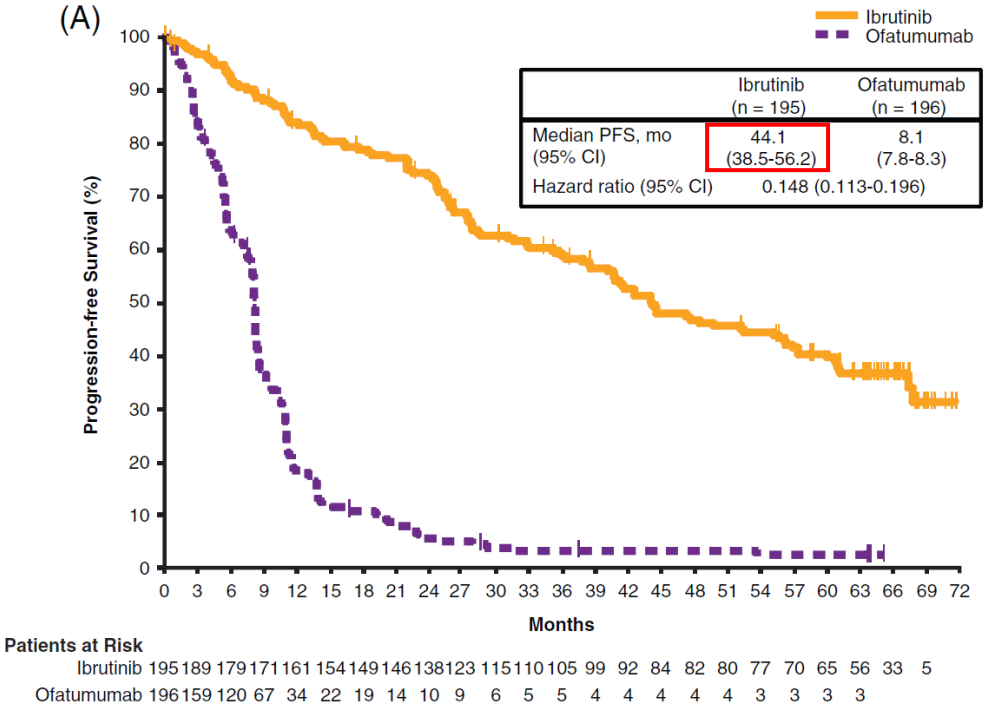


Allo-SCT, allogeneic stem cell transplant; BCL2i, B-cell lymphoma 2 inhibitor; ICT, immunochemotherapy; R, rituximab; R/R, relapsed/refractory; VEN, venetoclax.
Adapted by speaker from Quinquenel A *et al. HemaSphere* 2020; 4 (5): e473.

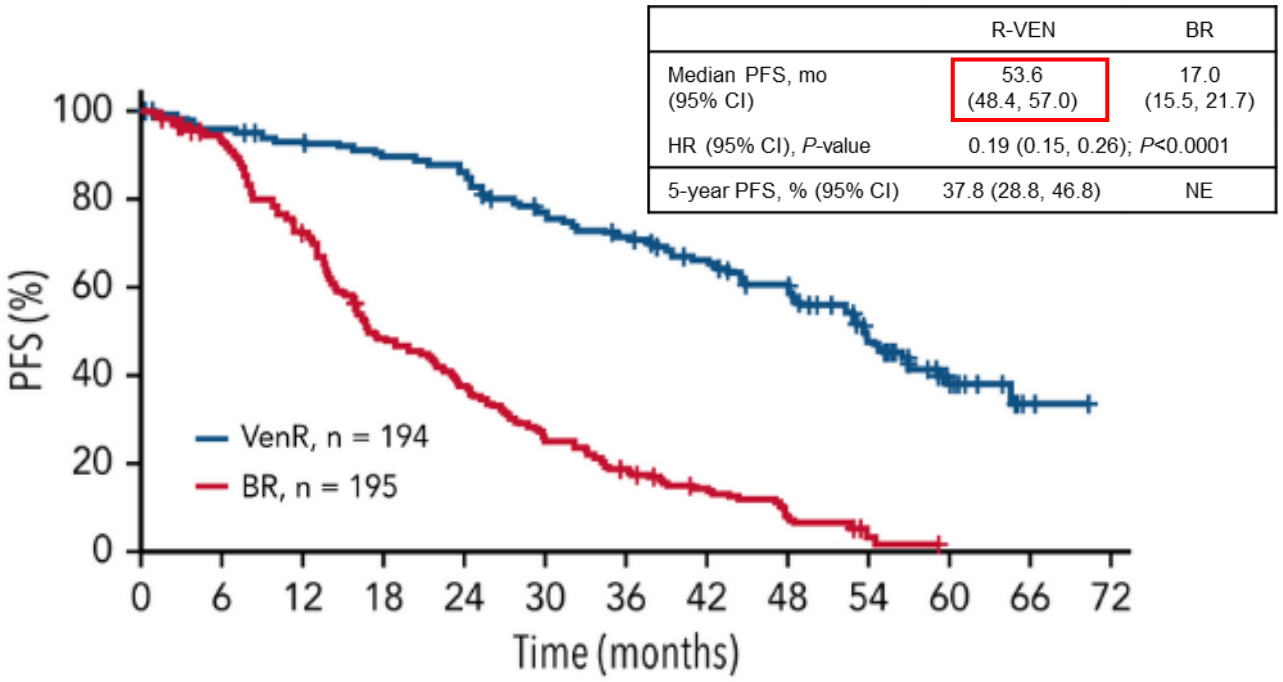
First relapse post ICT
A choice of two targeted therapies?



BTKi (ibrutinib): RESONATE trial[1]



BCL2i (venetoclax+R): MURANO trial[2]



This slide includes data from different clinical trials. These data are meant for demonstration purposes only and are not meant for cross-trial comparison purposes.

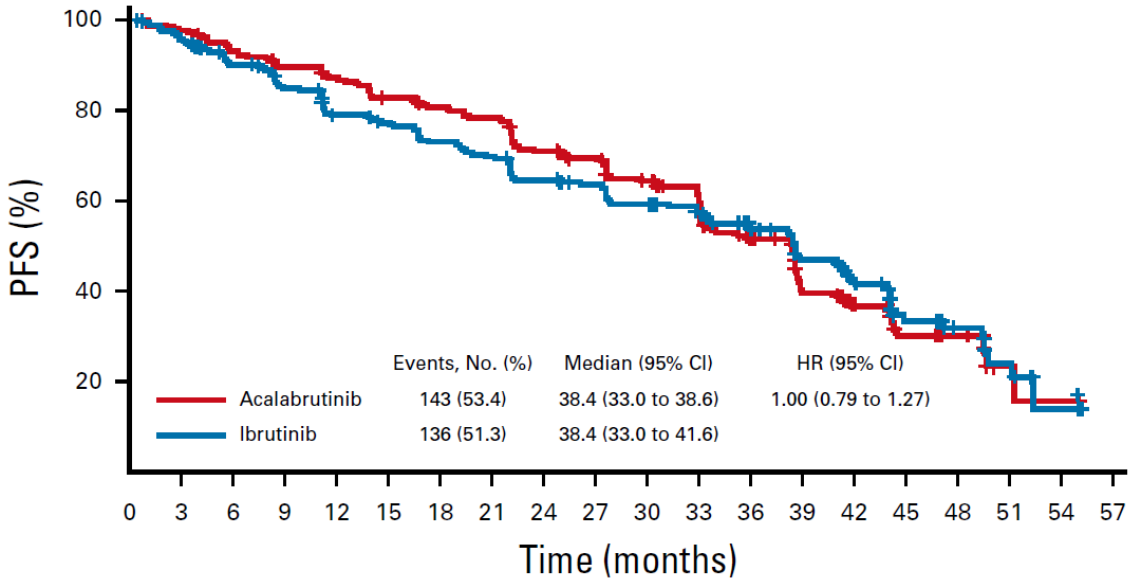
BR, bendamustine-rituximab; BCL2i, B-cell lymphoma 2 inhibitor; CI, confidence interval; HR, hazard ratio; ICT, immunochemotherapy; NE, not estimable; PFS, progression-free survival; R, rituximab; VEN, venetoclax.

1. Munir T *et al. Am J Hematol*.2019;94:1353–1363. 2. Seymour JF, *et al. Blood*. 2022; 140 (8): 839–850.

BTKi: Head-to-head comparison

Acalabrutinib vs ibrutinib: ELEVATE R/R

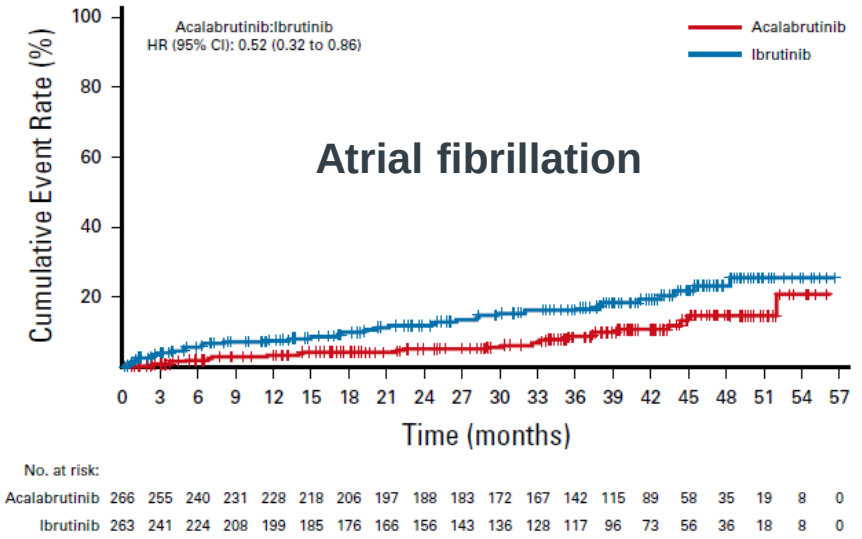
PFS (median follow up: 40.9 months)



No. at risk:

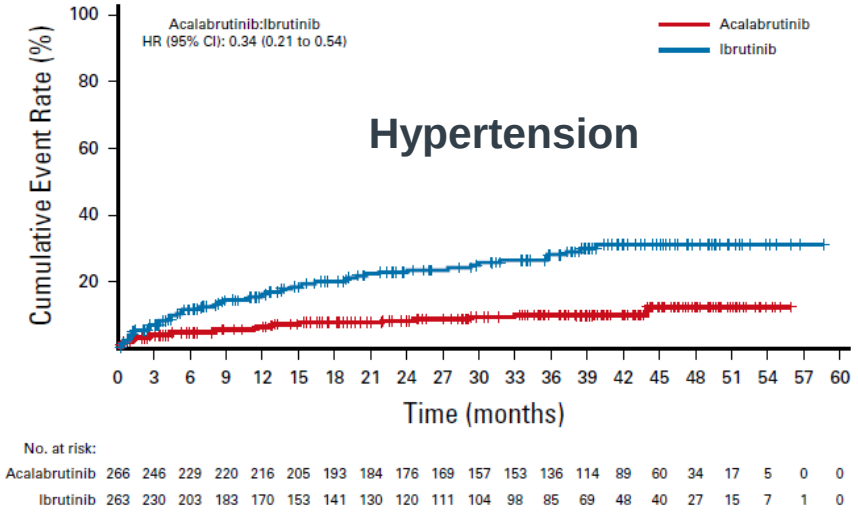
Acalabrutinib	268	250	235	227	219	207	200	193	173	163	148	110	84	59	31	21	13	3	1	0
Ibrutinib	265	240	221	205	186	178	168	160	148	142	130	108	81	66	41	26	15	8	2	0

- Similar PFS, less toxicity (cardiac)



No. at risk:

Acalabrutinib	266	255	240	231	228	218	206	197	188	183	172	167	142	115	89	58	35	19	8	0
Ibrutinib	263	241	224	208	199	185	176	166	156	143	136	128	117	96	73	56	36	18	8	0



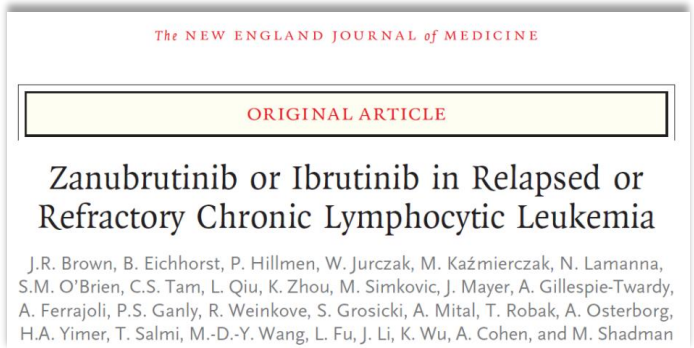
No. at risk:

Acalabrutinib	266	246	229	220	216	205	193	184	176	169	157	153	136	114	89	60	34	17	5	0	0
Ibrutinib	263	230	203	183	170	153	141	130	120	111	104	98	85	69	48	40	27	15	7	1	0

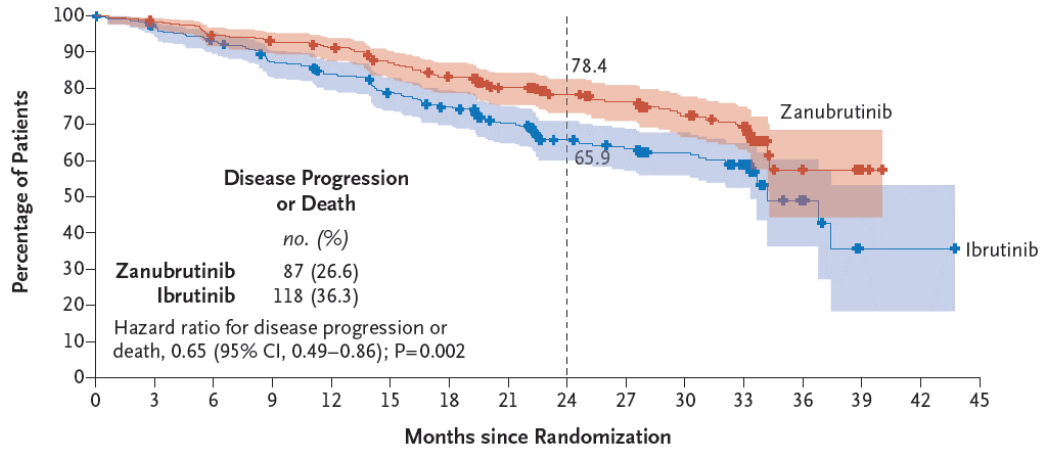
CI, confidence interval; HR, hazard ratio; PFS, progression-free survival; R/R, relapsed/refractory.
Byrd JC *et al. J Clin Oncol* 2021; 39 (31): 3441–3452.

BTKi: Head-to-head comparison
Zanubrutinib vs ibrutinib: ALPINE

- Phase 3 multinational study in R/R CLL (N=652)
- Primary endpoint: Overall response (INV; non inferiority)
- Secondary endpoints (hierarchical): PFS (INV), incidence of AF or flutter
- PFS significantly superior with zanubrutinib vs ibrutinib

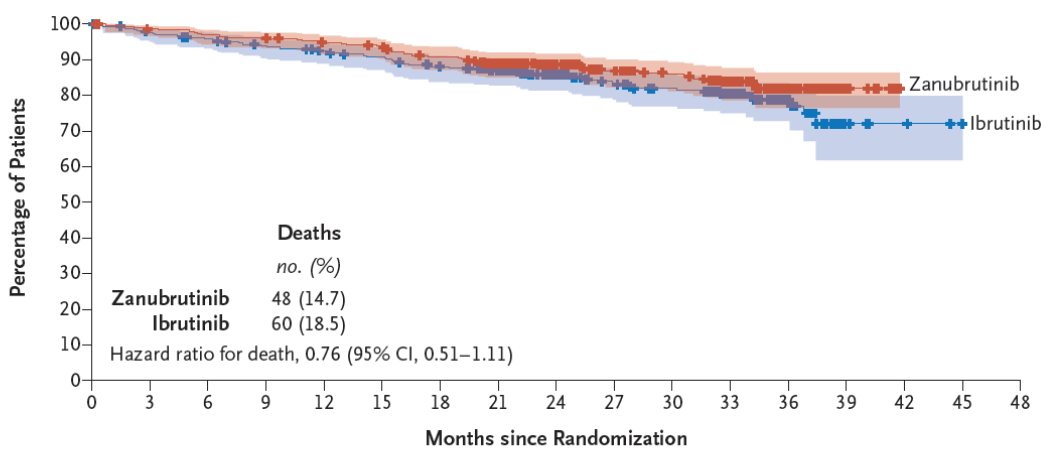


PFS



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

OS



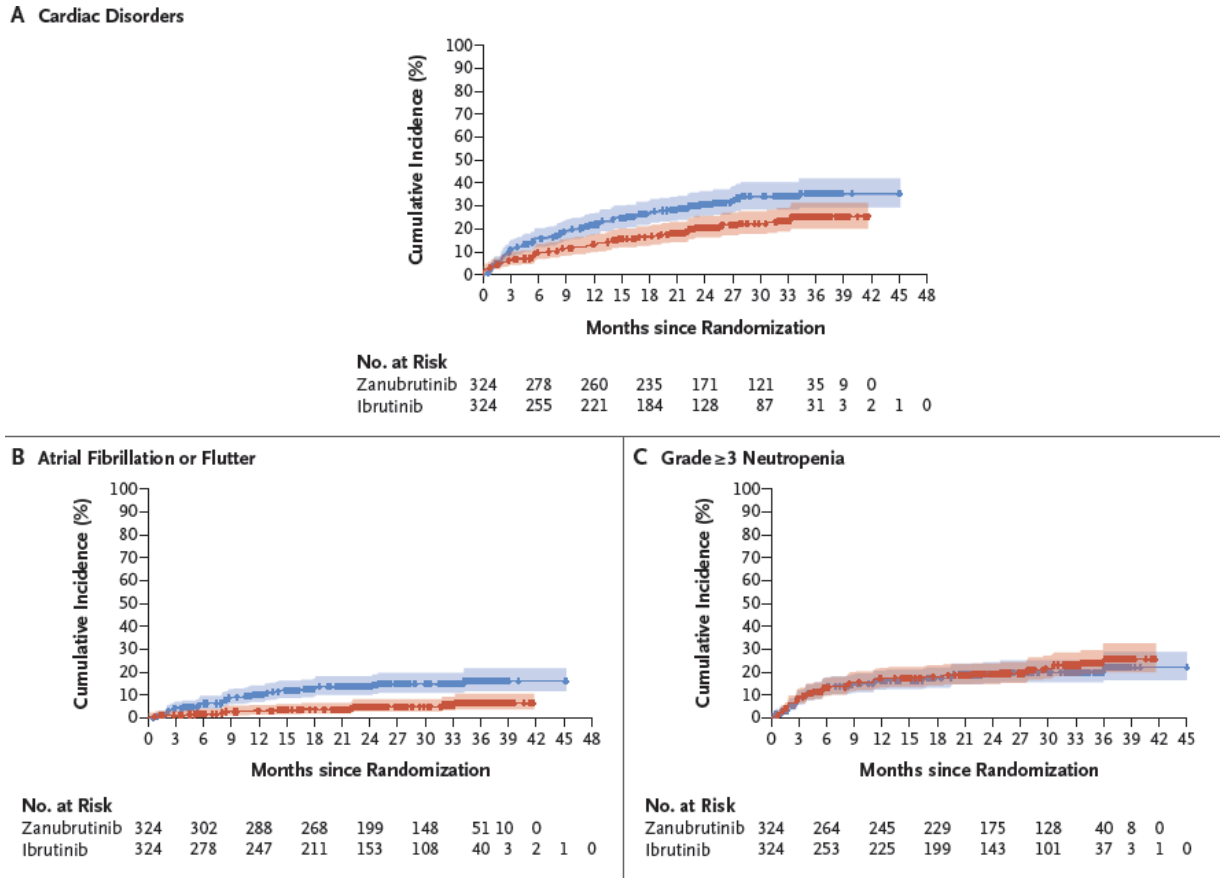
No. at Risk																
Zanubrutinib	327	319	313	310	303	298	287	268	224	185	169	134	56	8	0	
Ibrutinib	325	314	307	297	290	283	271	255	200	171	156	124	50	7	3	1	0

Median follow up: 29.6 months

AF, atrial fibrillation; CI, confidence interval; INV, investigator-assessed; PFS, progression-free survival; OS, overall survival; R/R, relapsed/refractory.

Brown JR *et al. N Engl J Med* 2023; 388 (4): 319–332.

BTKi: Head-to-head comparison
Zanubrutinib vs ibrutinib: ALPINE



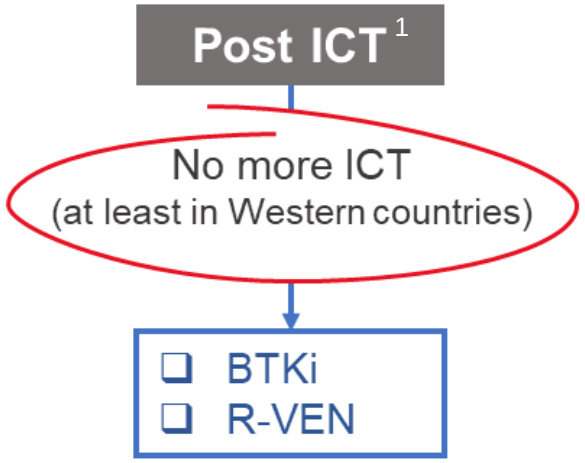
- Fewer cardiac adverse events

AEs on treatment*	Zanubrutinib (n=324)	Ibrutinib (n=324)
≥1 adverse event, n (%)	318 (98.1)	321 (99.1)
Grade ≥3 adverse events, n (%)	218 (67.3)	228 (70.4)
Grade ≥3 adverse events reported in >2% of the patients in either trial group, n (%)		
Neutropenia	52 (16.0)	45 (13.9)
Hypertension	48 (14.8)	36 (11.1)
Covid-19–related pneumonia	23 (7.1)	13 (4.0)
Covid-19	22 (6.8)	16 (4.9)
Pneumonia	19 (5.9)	26 (8.0)
Decreased neutrophil count	17 (5.2)	14 (4.3)
Syncope	9 (2.8)	4 (1.2)
Thrombocytopenia	9 (2.8)	12 (3.7)
Anemia	7 (2.2)	8 (2.5)
Atrial fibrillation	6 (1.9)	12 (3.7)
Increased blood pressure	4 (1.2)	10 (3.1)
Serious adverse events, n (%)		
All serious adverse events	136 (42.0)	162 (50.0)
Events leading to dose reduction	40 (12.3)	55 (17.0)
Events leading to dose interruption	162 (50.0)	184 (56.8)
Events leading to treatment discontinuation	50 (15.4)	72 (22.2)
Events leading to death	33 (10.2)	36 (11.1)

*Safety population. AE, adverse event.

Brown JR *et al. N Engl J Med.* 2023; 388 (4): 319–332.

First relapse post ICT: BTKi or BCL2i?



Co-morbidities?

Oral vs IV+oral?

Fixed duration or not?

Biological characteristics? (*TP53* alteration)

Doublets in the future?

On-going trials in the R/R setting:

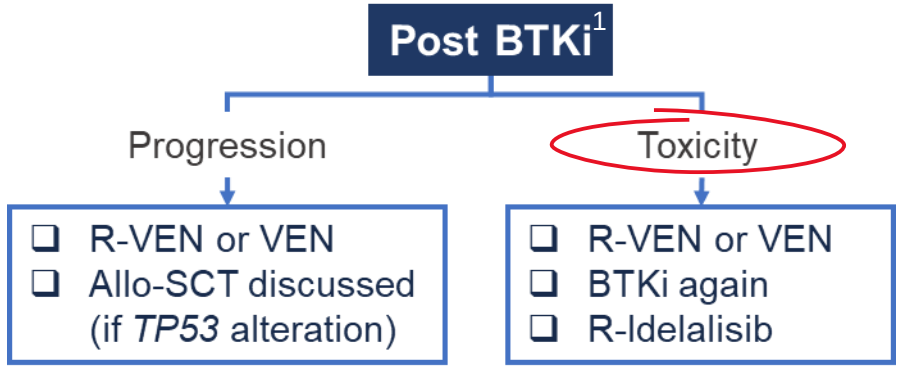
- CLARITY[2]
- VISION/HOVON141[3]

This slide reflects the speaker's opinion.

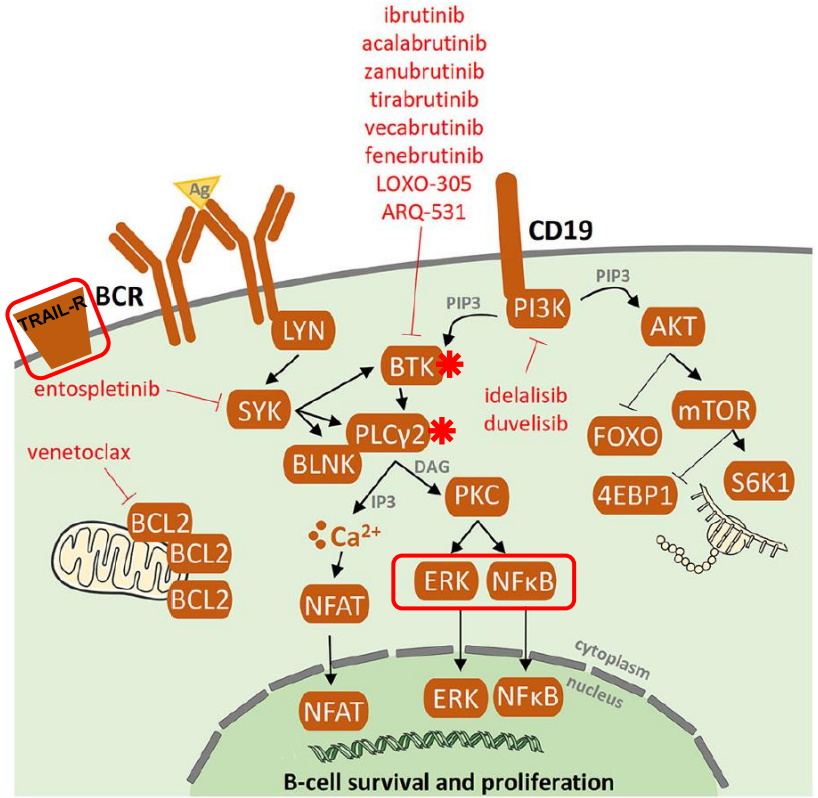
BCL2i, B-cell lymphoma 2 inhibitor; ICT, immunochemotherapy; IV, intravenous; R/R, relapsed/refractory; R, rituximab; TP53, tumor protein 53; VEN, venetoclax.

1. Adapted by speaker from Quinquenel A *et al. HemaSphere* 2020; 4 (5): e473. 2. Hillmen P *et al. J Clin Oncol* 2019; 17 (30): 2722–2729. 3. Kater AP *et al*. *Lancet Oncol* 2022; 23 (6): 818–828.

Relapse post BTKi treatment



What about BTKi resistance? Mutations?



BTK and PLCG2[4]

RESONATE-2 study of first-line ibrutinib in CLL

- In the ibrutinib arm at up to 8 years follow up:[2]
  - 42% continued with ibrutinib[2,3]
  - 22% discontinued due to PD or death[3]
  - 24% discontinued due to toxicity[3]

Allo-SCT, allogeneic stem cell transplant; BCL2i, B-cell lymphoma 2 inhibitor; ICT, immunochemotherapy; PD, progressive disease; R/R, relapsed/refractory; R, rituximab; VEN, venetoclax

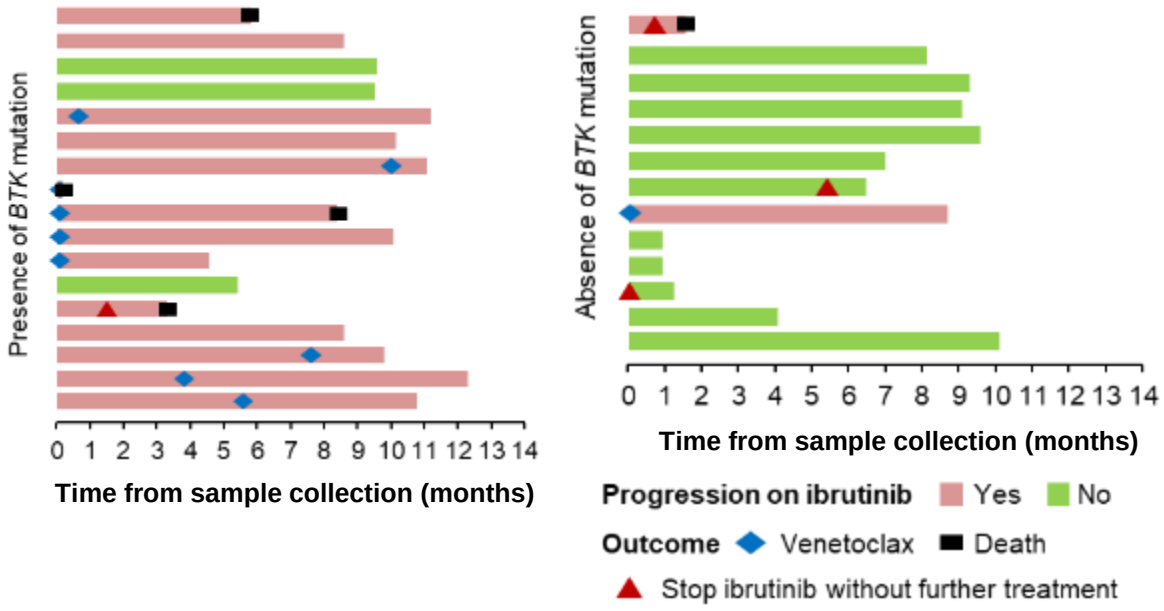
1. Adapted by speaker from Quinquenel A *et al. HemaSphere* 2020; 4 (5): e473. 2. Barr PM *et al. Blood Adv*. 2022; 6 (11): 3440–3450. 3. Barr PM *et al. Blood Adv*. 2022; 6 (11): 3440–3450 – supplementary appendix.
4. Sedlarikova L *et al. Front Oncol* 2020; 10: 894.

Prevalence of BTK mutations?

Real-life CLL cohort still on ibrutinib after at least 3 years of treatment

- 204 patients (French early-access program)
- 63 (31%) were still on ibrutinib after 3 years
- 30 patients had a CLL clone: NGS
- BTK and PLCG2 mutations in 57% and 13%, respectively
  - mFU of 8.5 months from sample collection
  - Presence of a BTK mutation was significantly associated with subsequent CLL progression

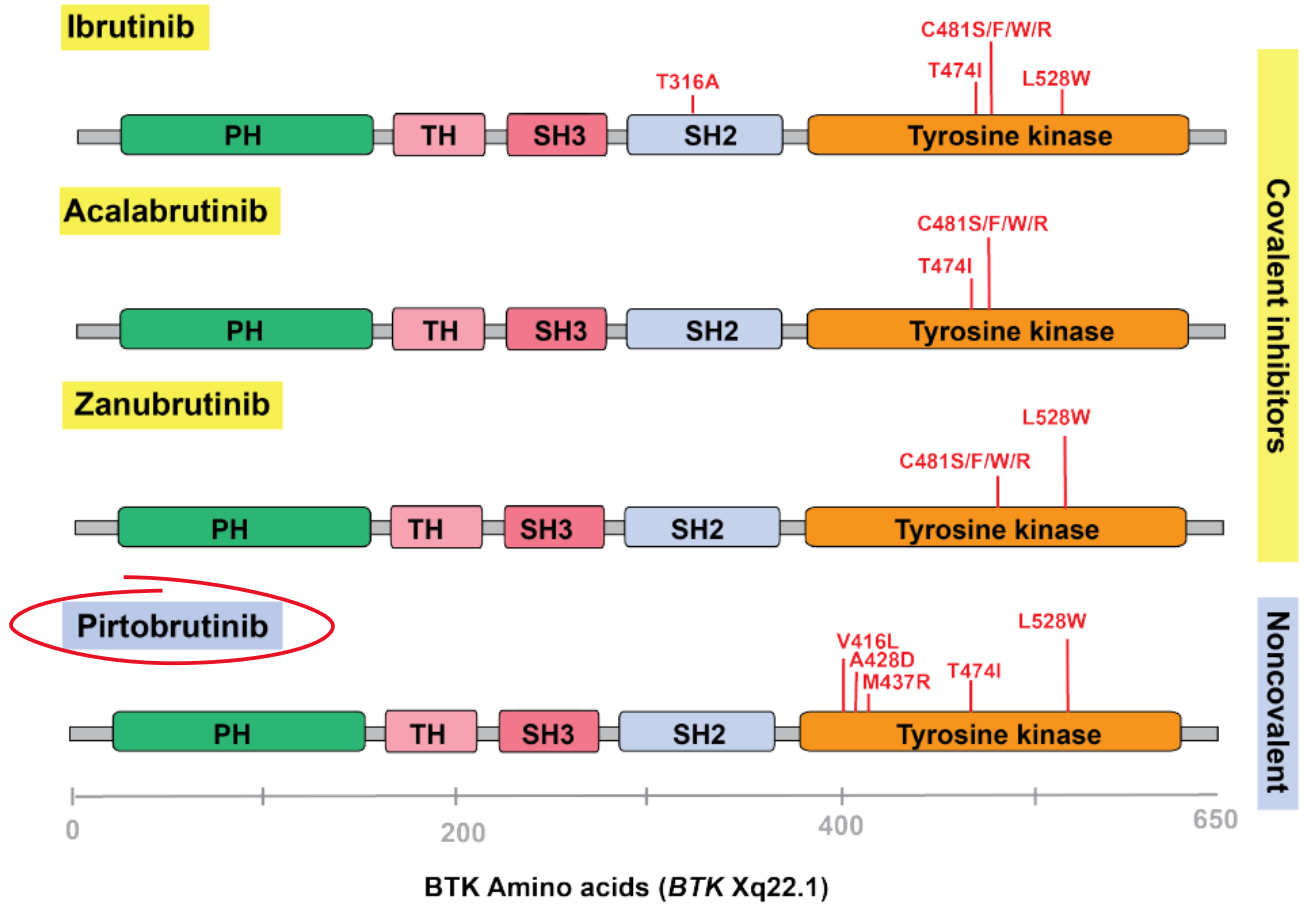
57% of patients had BTK mutations after 3 years of ibrutinib treatment (R/R patients)



mFU, median follow up; NGS, next generation sequencing; R/R, relapsed/refractory.
Quinquenel A *et al. Blood* 2019; 134 (7): 641–644.

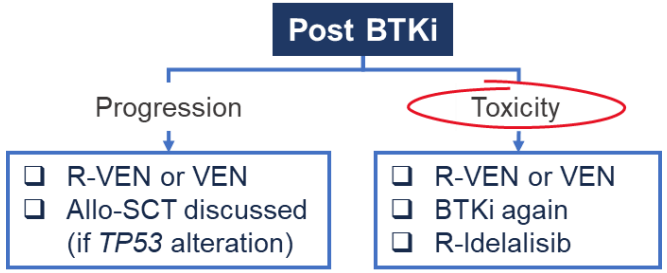
BTK mutations can occur with covalent and non-covalent BTKis

A new option, but resistance mutations already observed



PH, pleckstrin homology domain; TH, Tec homology domain; SH, Src homology domain.
Montoya S *et al*. Oral presentation at ASH 2022; New Orleans, LA, USA, December 10–13, 2022 (Abstract 750).

Next-generation BTKis may provide benefit in patients intolerant to ibrutinib



Study ACE-CL-208

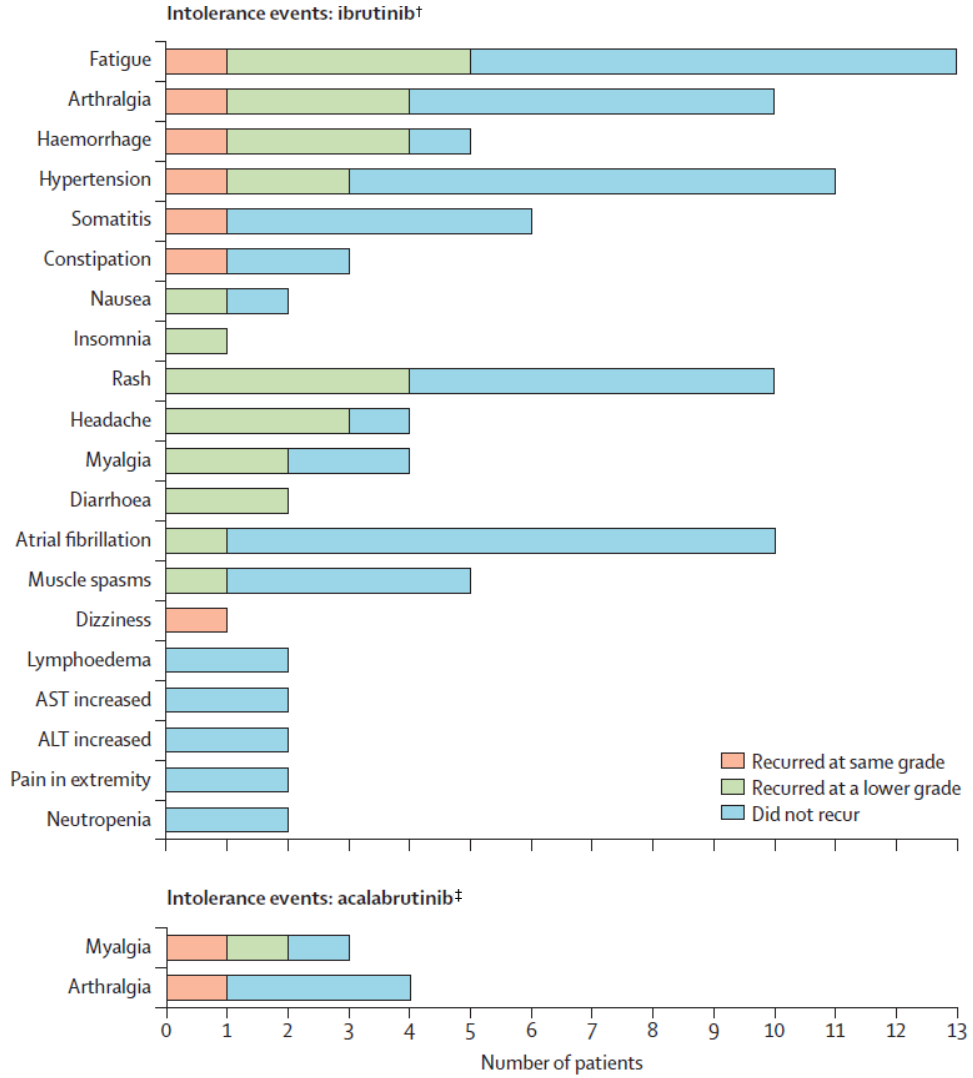
- 60 patients with CLL treated with acalabrutinib following ibrutinib intolerance
- With mFU of 34.6 months, 17% of patients had discontinued acalabrutinib
- ORR: 73%
- mPFS: not reached
- PFS at 3 years: 58%

Adverse event, n	Prior ibrutinib intolerance AEs*	Acalabrutinib experience from same patients			
		Total	Lower grade	Same grade	Higher grade
Atrial fibrillation	16†	2	2	0	0
Diarrhea	7	5	3	2	0
Rash	7	3	3	0	0
Bleeding‡	6	5	3	2	0
Arthralgia	7§	2	1	1	0
Total	41	24	18	6	1

*Among 60 patients meeting the study enrollment criteria, 41 patients had a medical history of one or more (43 events in total) of the following categories of ibrutinib-intolerance events: atrial fibrillation, diarrhea, rash, bleeding, or arthralgia. † Includes patients with atrial flutter (n=2). ‡ Events categorized as bleeding included ecchymosis, hemorrhage, epistaxis, contusion, hematuria, and subdural hematoma. All but one patient experienced a different type of bleeding event with acalabrutinib compared with ibrutinib treatment. § Includes one patient with arthritis.
Allo SCT, allogeneic stem cell transplant; mFU: median follow up; mPFS, median progression-free survival; ORR, overall response rate; R, rituximab; TP53, tumor protein 53; VEN, venetoclax.
Rogers KA *et al*. *Haematologica* 2021; 106 (9): 2364–2373.

Zanubrutinib for patients intolerant to ibrutinib and/or acalabrutinib

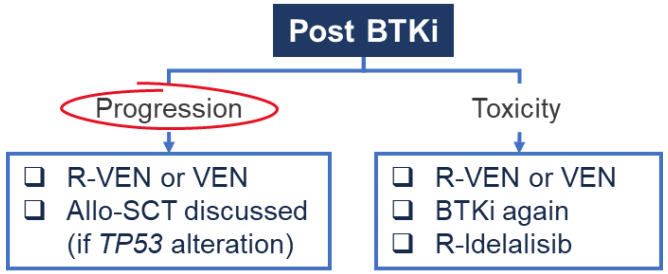
- 67 patients with B-cell malignancies* treated with zanubrutinib following:
  - Intolerance to ibrutinib (n=57; cohort 1)
  - Intolerance to acalabrutinib or acalabrutinib and ibrutinib (n=10; cohort 2)
- Cohort 1 after mFU of 12.0 months
  - 16% of patients (n=9) had discontinued zanubrutinib
  - ORR: 63%
- Cohort 2 after mFU of 10.4 months
  - 20% of patients (n=2) had discontinued zanubrutinib
  - ORR: 71%
- Overall mPFS not reached; 18-month PFS: 83.8%

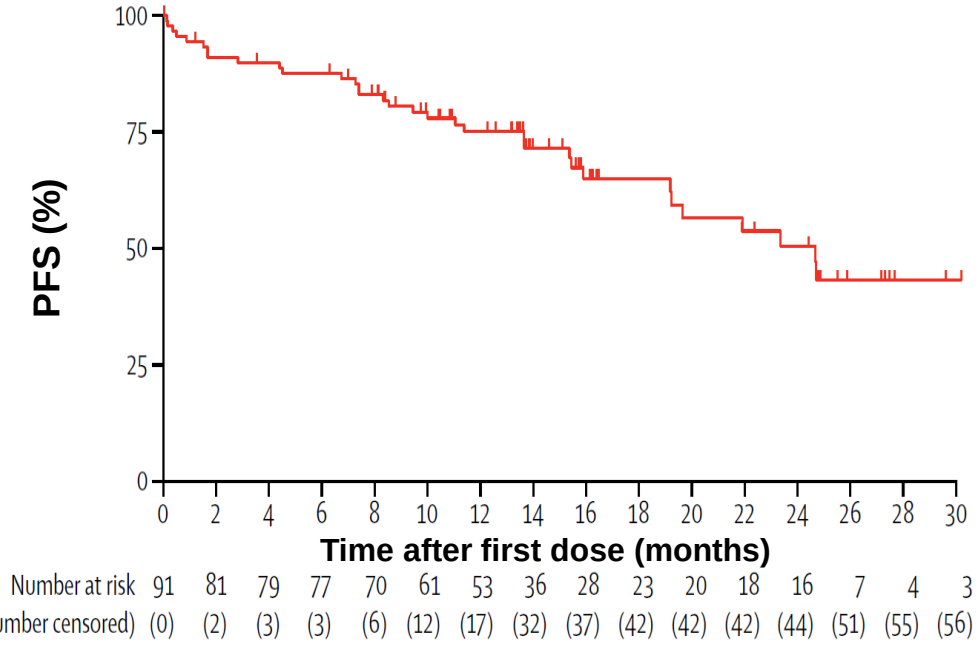


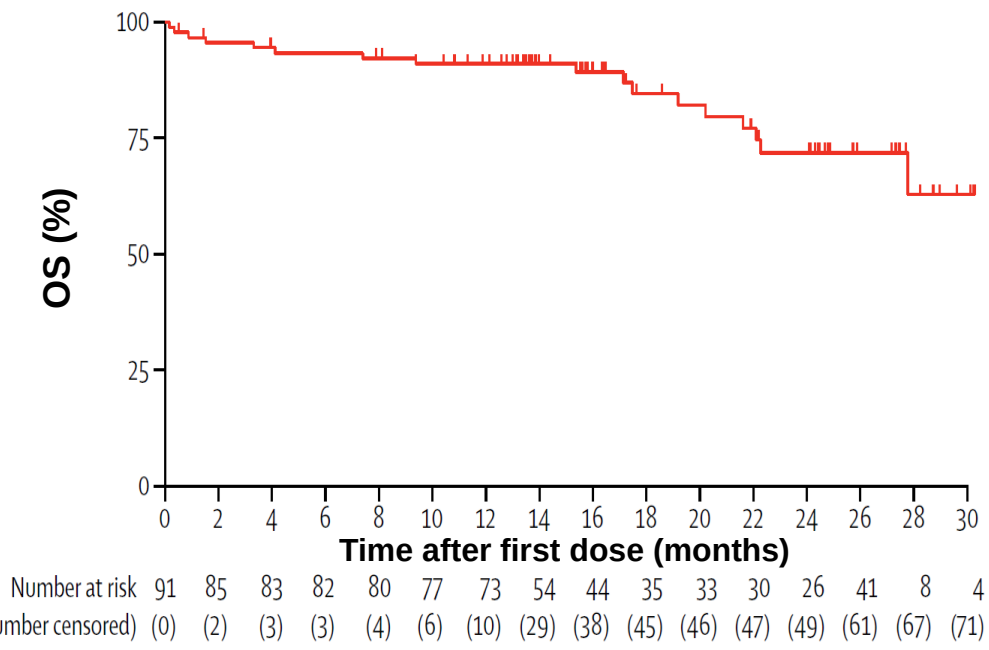
*Chronic lymphocytic leukemia (n=43), mantle cell lymphoma (n=3), marginal zone lymphoma (n=3), small lymphocytic lymphoma (n=7), Waldenström's macroglobulinemia (n=11). †18 additional ibrutinib-related intolerance events (arthritis, bone pain, bronchitis, embolism, irregular heart rate, malaise, pericardial effusion, pleural effusion, pneumonia, psoriasis, pyrexia, sinusitis, subcutaneous abscess, supraventricular tachycardia, aminotransferases increased, ventricular extrasystoles, vertigo, and vomiting) occurred in one patient and did not recur on zanubrutinib (data not shown). ‡11 additional acalabrutinib-related intolerance events (abdominal pain, asthenia, atrial fibrillation, dyspepsia, fatigue, groin pain, headache, insomnia, malaise, pain in extremity, and rash) occurred in one patient and did not recur on zanubrutinib (data not shown).
mFU, median follow up; mPFS, median progression-free survival; ORR, overall response rate.
Shadman M *et al*. *Lancet Oncol* 2023; 10 (1): e35–e45.

Venetoclax for relapse post BTKi treatment

- 91 R/R CLL patients post ibrutinib
- ORR 65%, MRD-blood 42%, mPFS 25 months



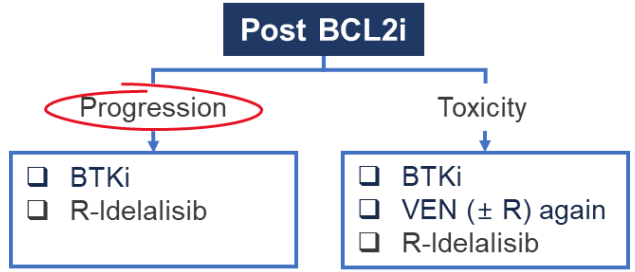




Allo SCT, allogeneic stem cell transplant; mPFS, median progression-free survival; MRD, minimal residual disease; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; R, rituximab; R/R, relapsed/refractory; TP53, tumor protein 53; VEN, venetoclax.

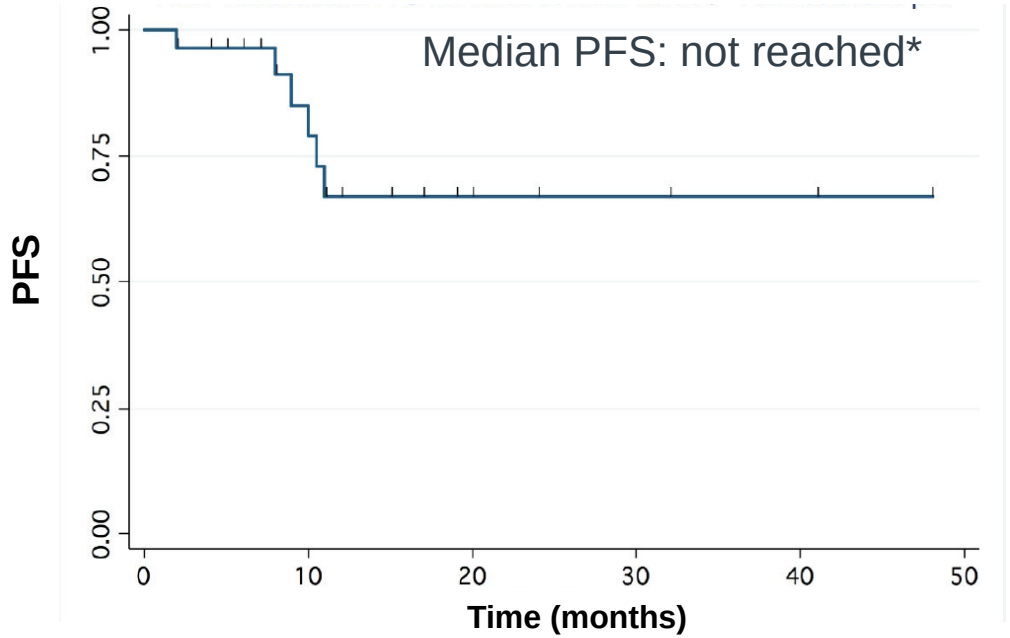
Jones JA *et al. Lancet Oncol* 2018; 19 (1): 65–75.

Treatment post BCL2i relapse?

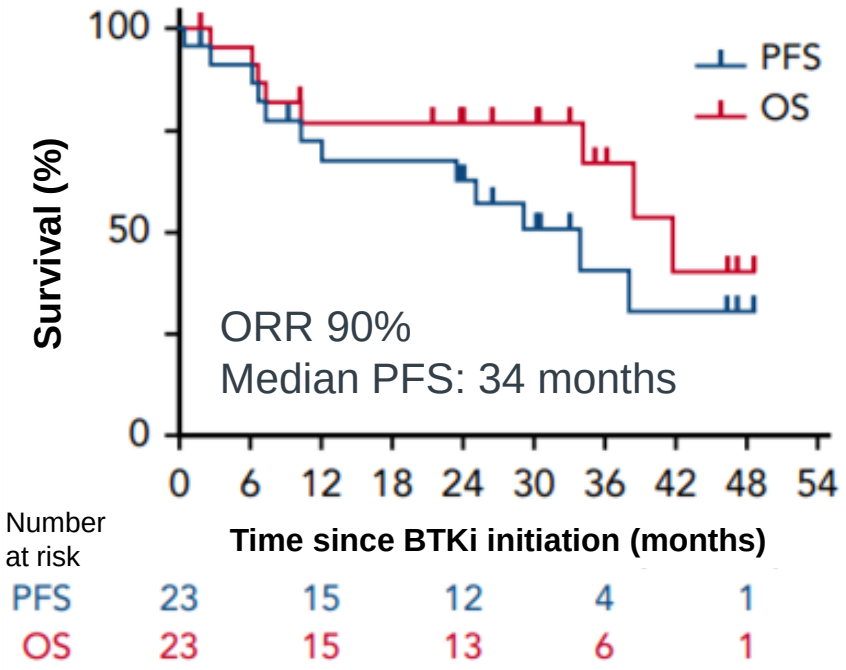


- Less frequent occurrence; no prospective trials
- Retrospective studies of BTKis in patients who progressed on venetoclax[1,2]

PFS on BTKi in BTKi-naïve patients (n=29)[1,3]



PFS/OS on BTKi after PD on venetoclax[2]

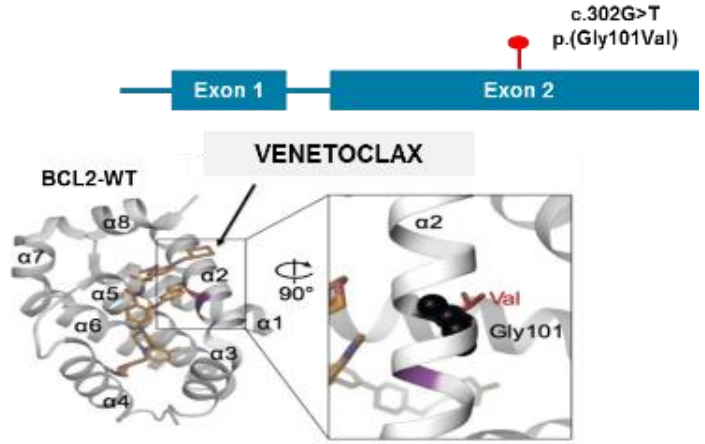


*Median follow up 7.7 months (range 1–48 months)

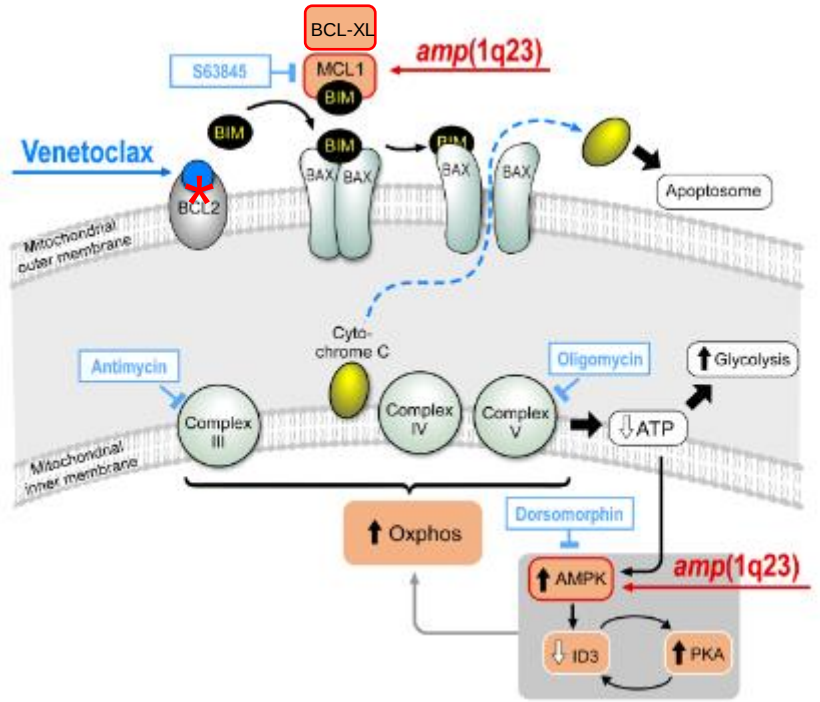
BCL2, B-cell lymphoma 2; mPFS, median progression-free survival; ORR, overall response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; R, rituximab; VEN, venetoclax.

1. Mato AR *et al. Clin Cancer Res* 2020; 26 (14): 3589–3596. 2. Lin VS *et al. Blood 2020*; 135 (25): 2266–2270. 3. Mato AR *et al. Clin Cancer Res* 2020; 26 (14): 3589–3596 – Supplemental figure 2.

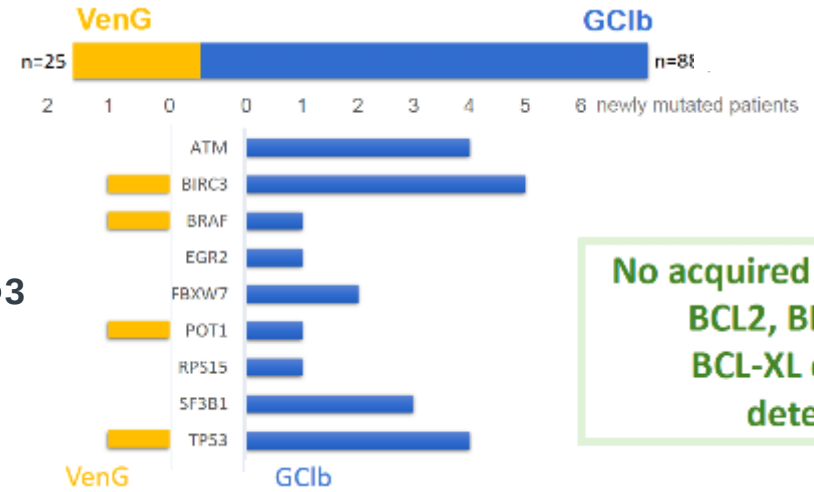
Resistance to BCL2 inhibitors



BCL2 and amp(1q)[1,2]



What about fixed duration of treatment?[3]



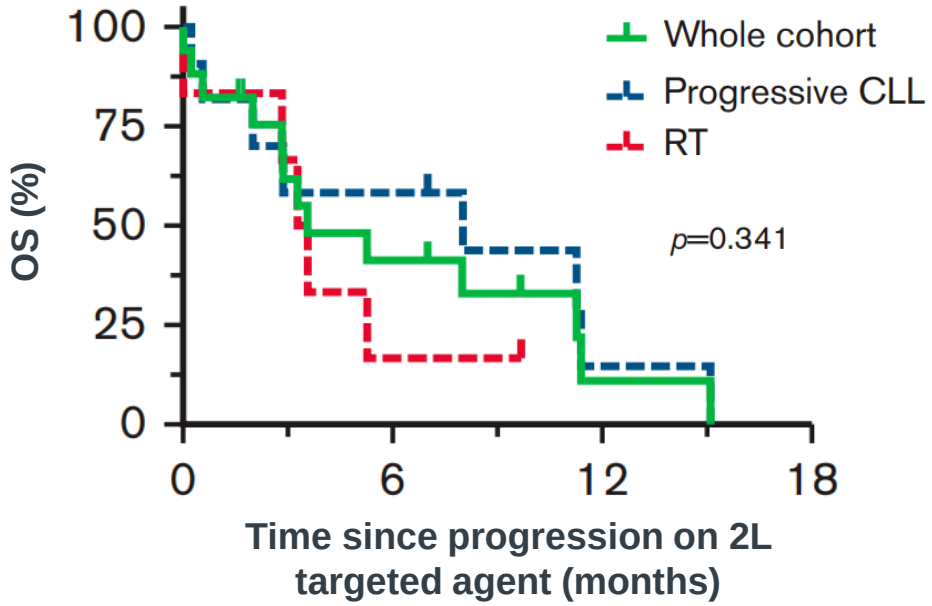
No acquired mutations in BCL2, BIM, BAX, BCL-XL or MCL1 detected

AMPK, AMP-activated protein kinase; BAX, BCL2-associated X; BCL2, B-cell lymphoma 2; BCL-XL, B-cell lymphoma-extra large; BIM, BVL2-like protein 11; GClb, obinutuzumab plus chlorambucil; ID3, inhibitor of DNA binding 3; MCL1, myeloid cell leukemia sequence 1; PKA, protein kinase A; VenG, obinutuzumab plus venetoclax.

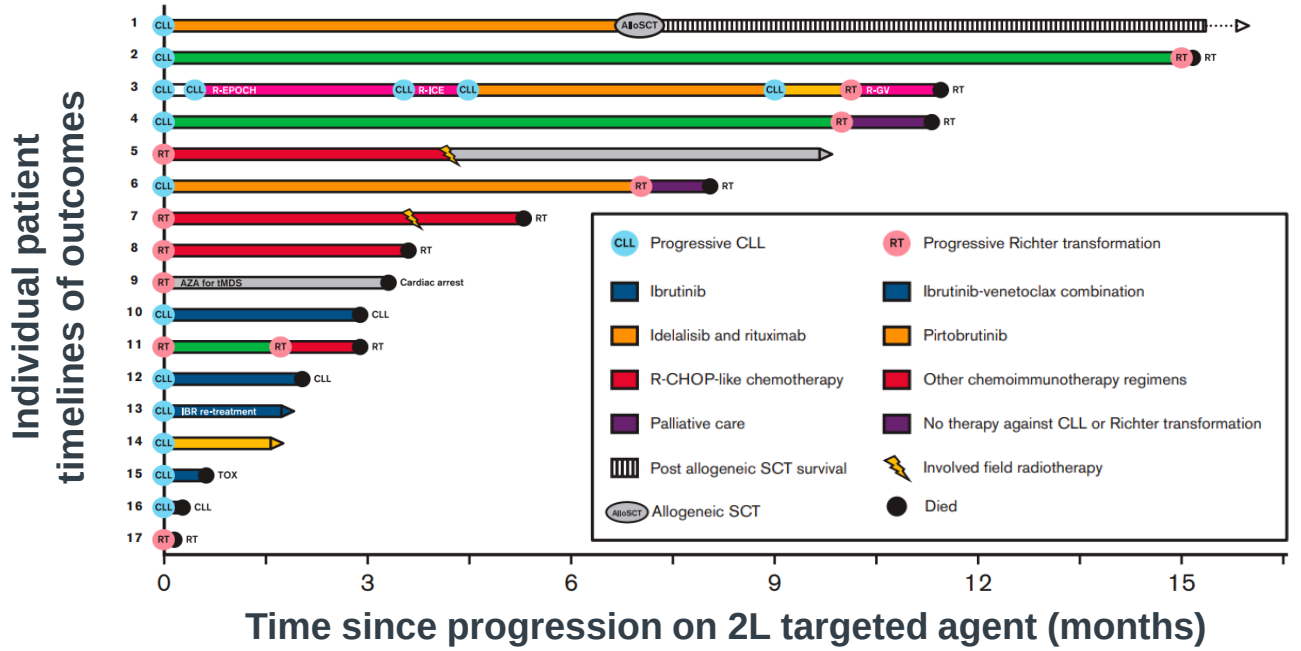
1. Blomberry P *et al. Cancer Discov* 2019; 9 (3): 342–353. 2. Guièze R *et al*. *Cancer Cell* 2019; 36 (4): 369–384.e13. 3. Tausch E Oral presentation at European Hematology Association 2021 Virtual, June 9–17, 2021.

Double-refractory (BTKi/BCL2i) patients

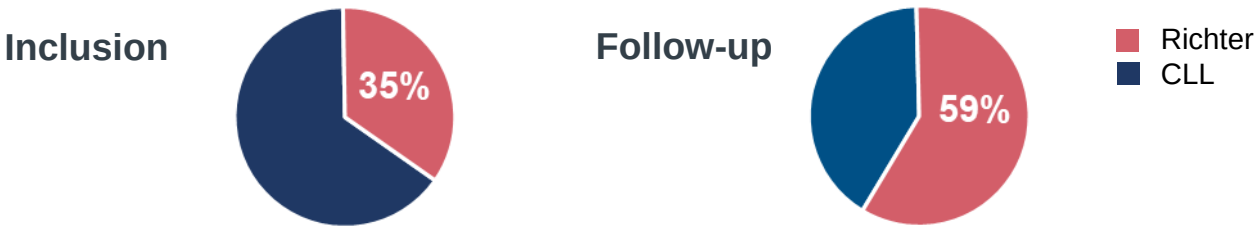
Median OS: 3.6 months



No. at risk					
Whole	17	9	6	4	1
CLL	11	5	5	3	1
RT	6	4	1	1	



Death due to progression in 76% of patients (RT n=8, CLL n=3)



2L, second-line; BCL2i, B-cell lymphoma 2 inhibitor; OS, overall survival; R-CHOP, rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone; RT, Richter transformation; SCT, stem cell transplant.
Lew TE *et al. Blood Adv* 2021; 5 (20): 4054–4058.

How to manage BTKi resistance?
Future options

Does not induce resistance?

- Fixed duration of treatment (MRD guidelines?)
  - One treatment?
  - Doublet? Triplet?

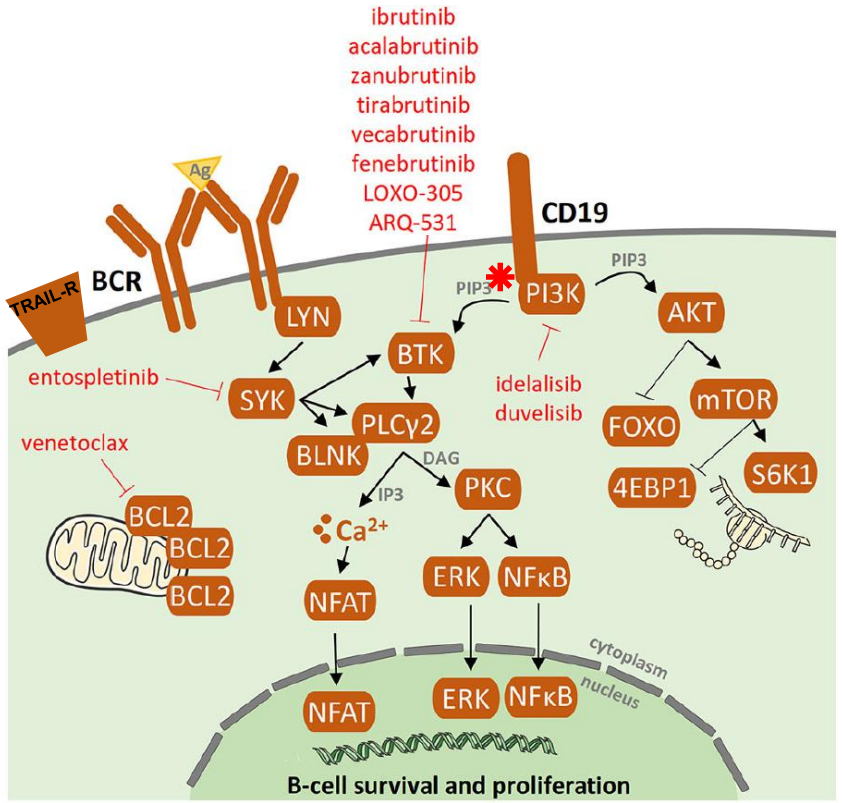
New mechanisms of BTK inhibition?

- Non-covalent BTK inhibitors
  - Pirtobrutinib
  - MK1026
- BTK degrader?
  - NRX-0492
  - BGB-16673

Other targets? Post BTK: BTK/PLCG2?

- PKCß inhibitors?

BCR signaling pathway and BCR inhibitors[1]



Acting on another BCR pathway?

- PI3K inhibitors

Choose according to the type of mechanism/mutation?

This slide reflects the speaker's opinion. BCR, B cell receptor; MRD, minimal residual disease; PI3K, phosphoinositide 3-kinase; PKCß, protein kinase C beta; PLCG2, phospholipase C gamma 2.

1. Sedlarikova L *et al. Front Oncol* 2020; 10: 894.

Fixed-duration BTKi regimen?
STAIR trial

Does not induce resistance?

- Fixed-duration of treatment (MRD guidelines?)
  - One treatment?
  - Doublet? Triplet?

Fixed duration of BTKi (and retreatment if needed): STAIR trial

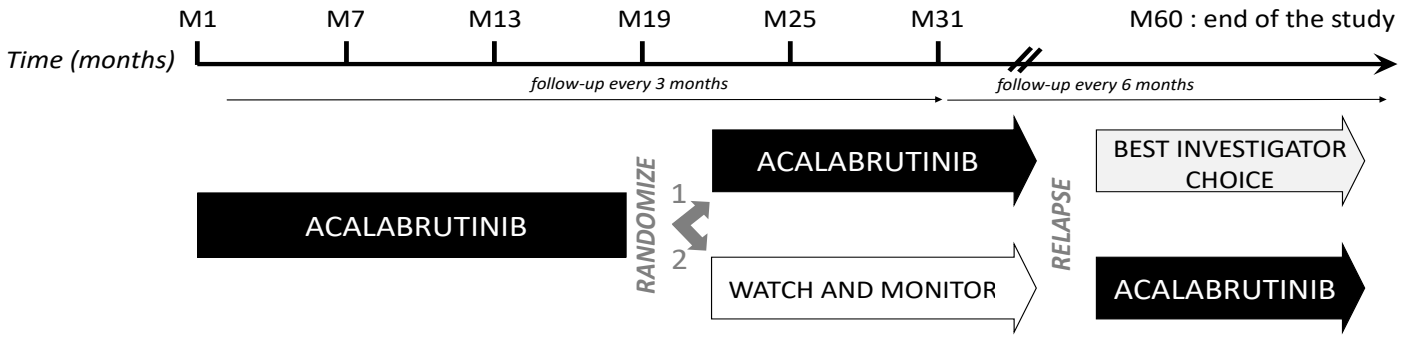
Inclusion criteria[1]

- CLL first-line
- >70 years of age
- CIRS >6 or 30 < CrCl < 69 mL/min
- Any *IGHV* or *TP53* status

STAIR

STop and restart **A**calabrutinib **I**n f**R**ail patients with previously untreated CLL[1]

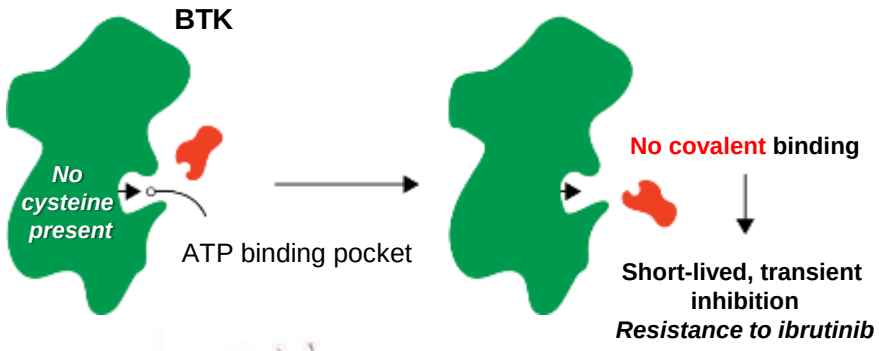
FRENCH INNOVATIVE LEUKEMIA ORGANIZATION

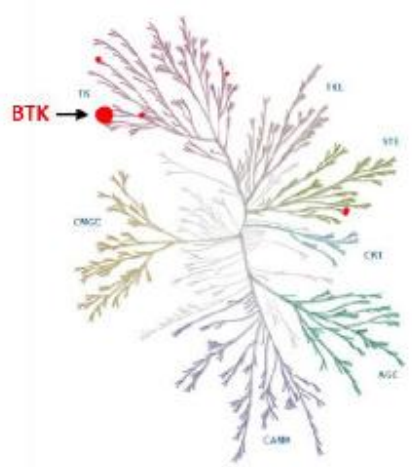


This slide reflects the speaker's opinion.
CIRS, Cumulative Illness Rating Scale; CrCl, creatinine clearance; IGHV, immunoglobulin heavy chain variable region; MRD, minimal residual disease.
1. Clinicaltrials.gov STAIR. Available at: https://clinicaltrials.gov/ct2/show/NCT04963946. Accessed March 2023.

Non-covalent BTK inhibitors

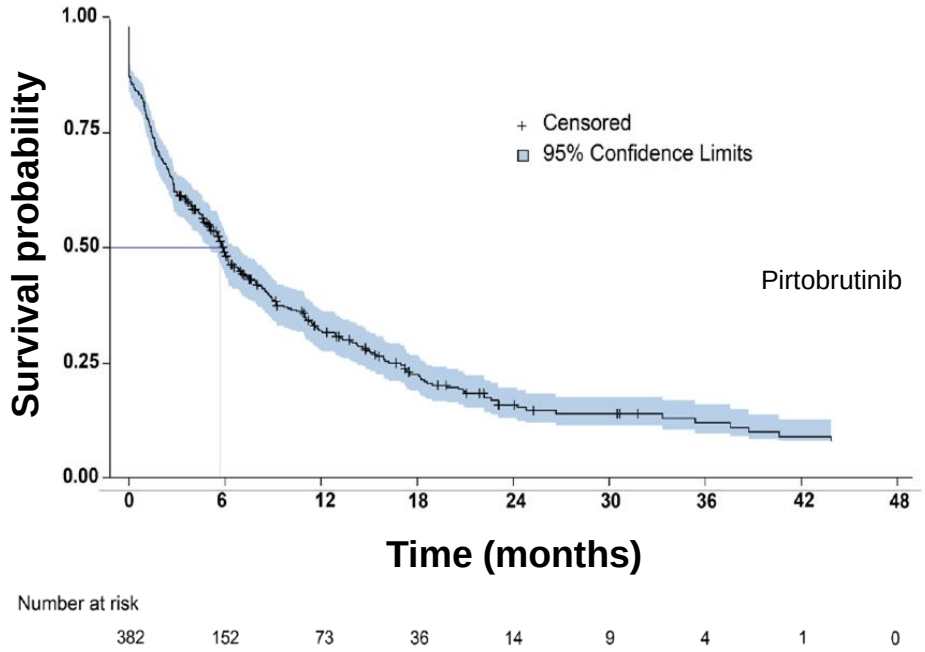
- **Pirtobrutinib[1]**
- MK1026





Time from cBTKi/BCL2i discontinuation to subsequent treatment failure or death[2]

Median OS: 5.5 months (95% CI: 4.3–6.0)

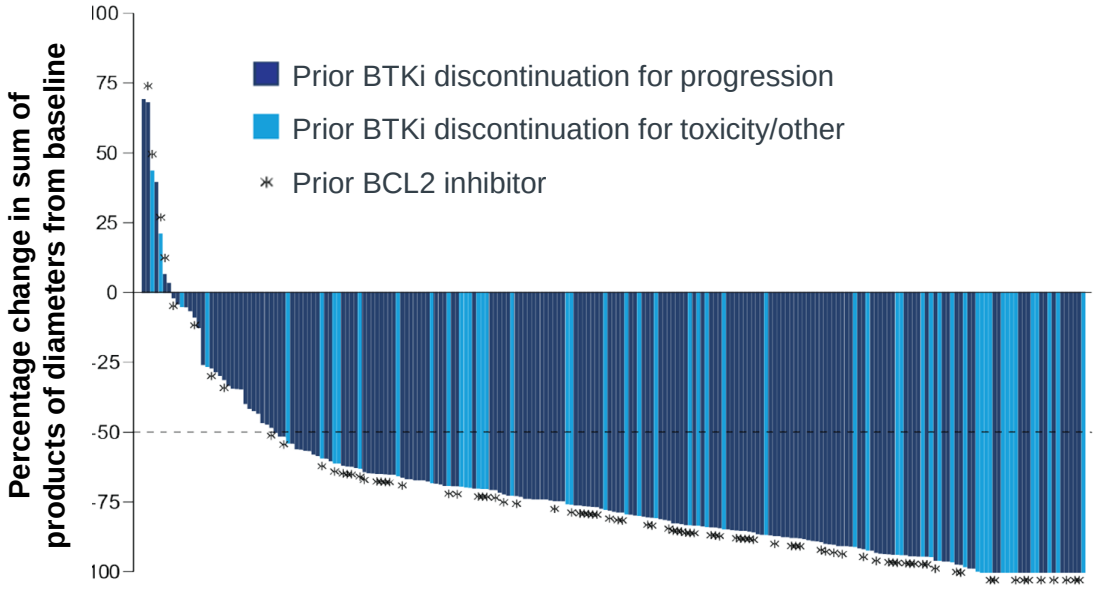


ATP, adenosine triphosphate; BCL2i, B-cell lymphoma 2 inhibitor; cBTKi , covalent BTKi; CI, confidence interval; OS, overall survival.

1. Wiester A *Haematologica* 2015; 100 (12): 1495–1507. 2. Mato AR *et al.* Oral presentation at the 64th American Society of Hematology Annual Meeting; New Orleans, LA, USA, December 10–13 2022 (Abstract 961).

Non-covalent BTK inhibitor
Pirtobrutinib

- Phase I/II study[1]
  - 276 R/R CLL patients
- Inclusion criteria[2]
  - >18 years of age
  - ECOG PS: 0–2
- Prior treatment[1]
  - cBTKi: 100%
  - BCL2i: 44%
  - Progressed on cBTKi: 75%



		BTKi pre-treated CLL/SLL, n	Response Evaluable Cohort, n	ORR, % (95% CI)	Median PFS, months (95% CI)	Estimated 12-month PFS rate, % (95% CI)	Estimated 18-month PFS rate, % (95% CI)
Overall		276	273	74 (68-79)	19.4 (16.6-22.3)	68 (62-74)	54 (46-61)
Age	≥75	57	56	71 (58-83)	20.1 (15.7- NE)	78 (63-87)	62 (44-75)
	<75	219	217	74 (68-80)	18.7 (16.6- NE)	66 (58-73)	52 (43-60)
At least prior BTKi and BCL2i	Yes	122	119	73 (64-81)	14.1 (11.1-18.7)	58 (47-68)	42 (29-55)
	No	154	154	74 (66-81)	22.1 (18.4-NE)	75 (67-82)	62 (52-70)
Del(17p) and/or *TP53* mutation	Yes	99	98	80 (70-87)	16.6 (13.8-22.1)	69 (58-78)	47 (33-59)
	No	107	107	67 (58-76)	19.4 (14.1-NE)	66 (55-75)	58 (46-68)
BTK C481 status*	Mutated	85	85	81 (71-89)	17.0 (13.8-20.3)	69 (57-79)	49 (35-61)
	Unmutated	91	91	65 (54-75)	20.3 (13.8-NE)	63 (52-73)	54 (40-65)
Reason for Prior BTKi discontinuation	Disease progression	206	205	73 (66-79)	18.6 (13.9-20.3)	66 (58-73)	50 (41-59)
	Intolerance & Other	68	66	76 (64-85)	NE (18.4-NE)	77 (64-86)	67 (51-79)

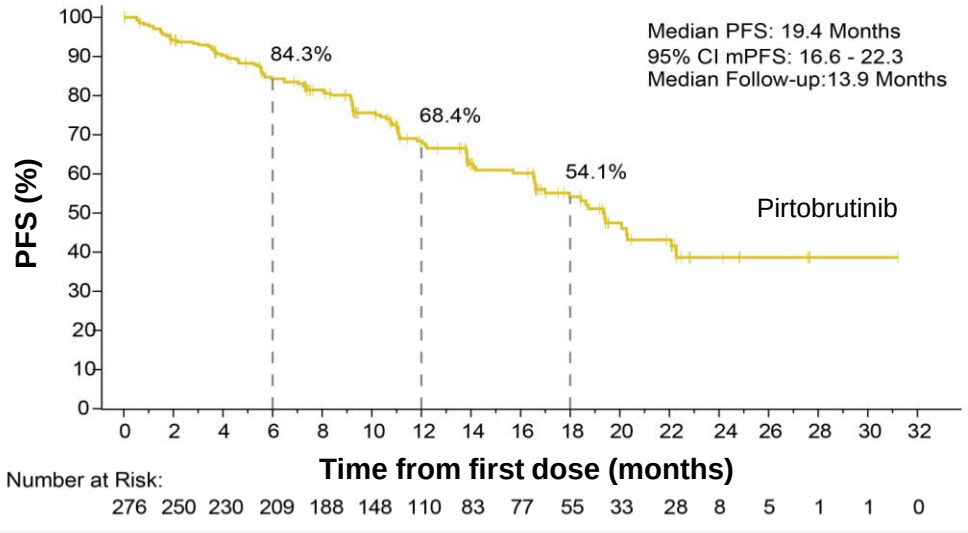
	Prior BTKi n=247	Prior BTKi+BCL2i n=100
ORR, % (95% CI)	**82.2 (76.8–86.7)**	**79.0 (69.7–86.5)**
Best response		
CR, n (%)	4 (1.6)	0 (0.0)
PR, n (%)	177 (71.7)	70 (70.0)
PR-L, n (%)	22 (8.9)	9 (9.0)
SD, n (%)	26 (10.5)	11 (11.0)

BCL2i, B-cell lymphoma 2 inhibitor; cBTKi , covalent BTKi; CI, confidence interval; CR, complete response; ORR, overall response rate; PFS, progression-free survival; PR, partial response; PR-L, partial response with rebound lymphocytes; R/R, relapsed/refractory; SD, stable disease; SLL, small lymphocytic lymphoma.

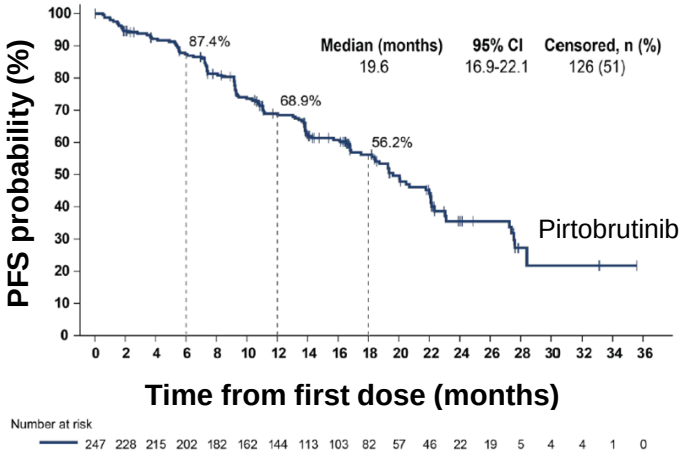
1. Mato AR *et al.* Abstract 961 presented at the 64th American Society of Hematology (ASH) Annual Meeting; New Orleans, LA, USA, December 10–13 2022. 2. Mato AR *et al.* Oral presentation at the 64th American Society of Hematology (ASH) Annual Meeting; New Orleans, LA, USA, December 10–13 2022 (Abstract 961).

Non-covalent BTK inhibitor
Pirtobrutinib

PFS in cBTKi pre-treated CLL/SLL

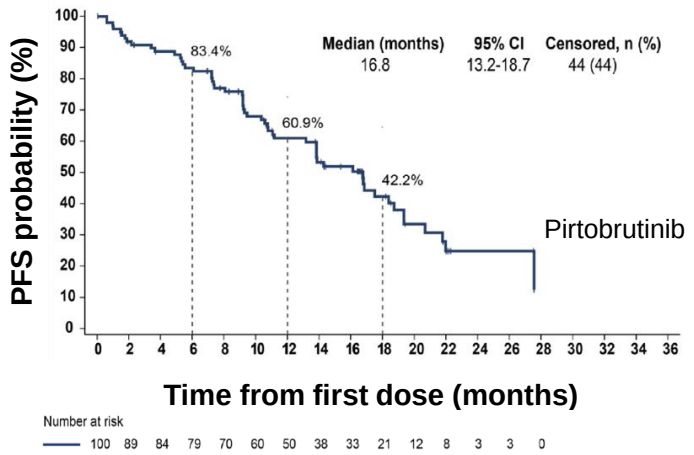


All prior BTKi patients, median prior lines = 3



mFU 19.4 months for patients who received prior BTKi

Prior BTKi and BCL2i patients, median prior lines = 5



mFU 18.2 months for patients who received prior BTKi and BCL2i

BCL2i, B-cell lymphoma 2 inhibitor; cBTKi , covalent BTKi; CI, confidence interval; mFU, median follow-up; PFS, progression-free survival.

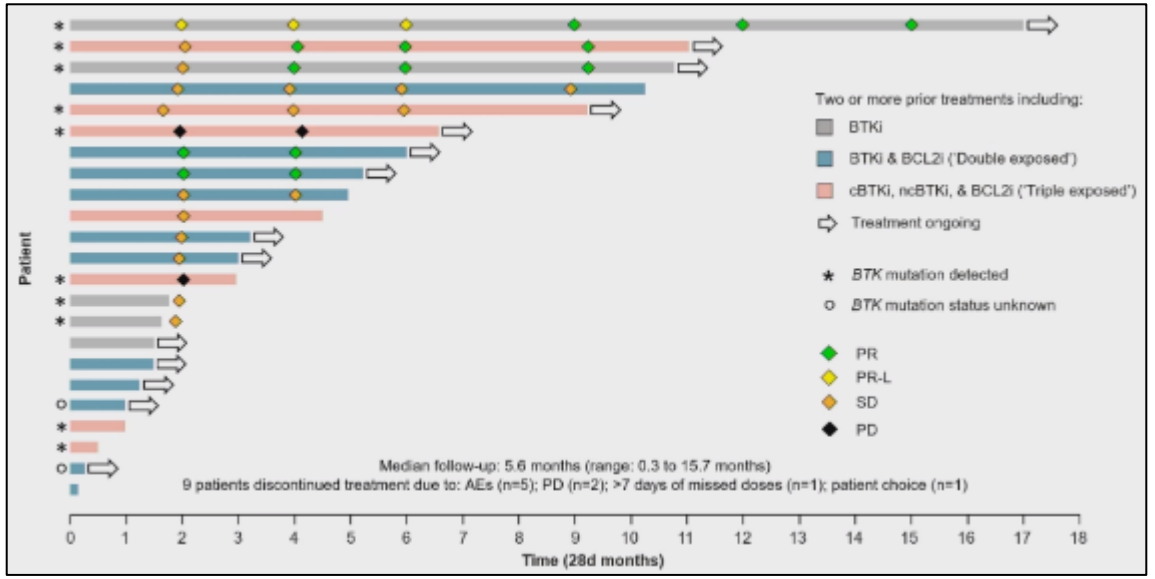
1. Mato AR et al. Abstract 961 presented at the 64th American Society of Hematology (ASH) Annual Meeting; New Orleans, LA, USA, December 10–13 2022. 2. Mato AR *et al.* Oral presentation at the 64th American Society of Hematology (ASH) Annual Meeting; New Orleans, LA, USA, December 10–13 2022 (Abstract 961).

BTK degraders

- NX-2127: CLL Phase 1b expansion cohort at 100 mg dose
  - MTD not established
  - 100 mg chosen as expansion dose based on PD, efficacy, and safety profile

Characteristics	CLL (n=23)
Median age, years (range)	75 (61–90)
Female, n (%) **Male**, n (%)	9 (39.1) 14 (60.9)
Lines of prior therapy, median (range) BTKi, n (%) Pirtobrutinib, n (%) BTKi and BCL2i, n (%) cBTKi, ncBTKi, and BCL2i, n (%)	5 (2–11) 23 (100) 8 (34.8) 18 (78.3) 7 (30.4)
BTK* mutation present, n (%) C481 L528W T474 V416L	10 (48) 5 (24) 4 (19) 3 (14) 1 (5)
BCL2* mutation present, n (%)	4 (19)
PLCG2* mutation present, n (%)	0 (0)

Disease-evaluable patients	n=15
Objective response rate,† % (95% CI)	33 (12–62)
Best response, n (%)	
CR	0 (0)
PR	5 (33.3)
SD	5 (33.3)
PD	2 (13.3)
NE[b]	3 (20)



*Specific mutations are not additive as some patients have multiple BTK mutations †ORR includes CR, CRi, nPR, PR-L, and PR.
BCL2i, B-cell lymphoma 2 inhibitor; BTK, Bruton tyrosine kinase; cBTKi, covalent BTKi; CLL, chronic lymphocytic leukemia; CR, complete remission; MTD, maximal tolerated dose; ncBTKi, non-covalent BTKi; PD, progressive disease; PLCG2, phospholipase C gamma 2; PR, partial response; PR-L, partial response with lymphocytosis; SD, stable disease. Mato AR *et al.* Oral presentation at the 64th American Society of Hematology (ASH) Annual Meeting; New Orleans, LA, USA, December 10–13 2022 (Abstract 965).

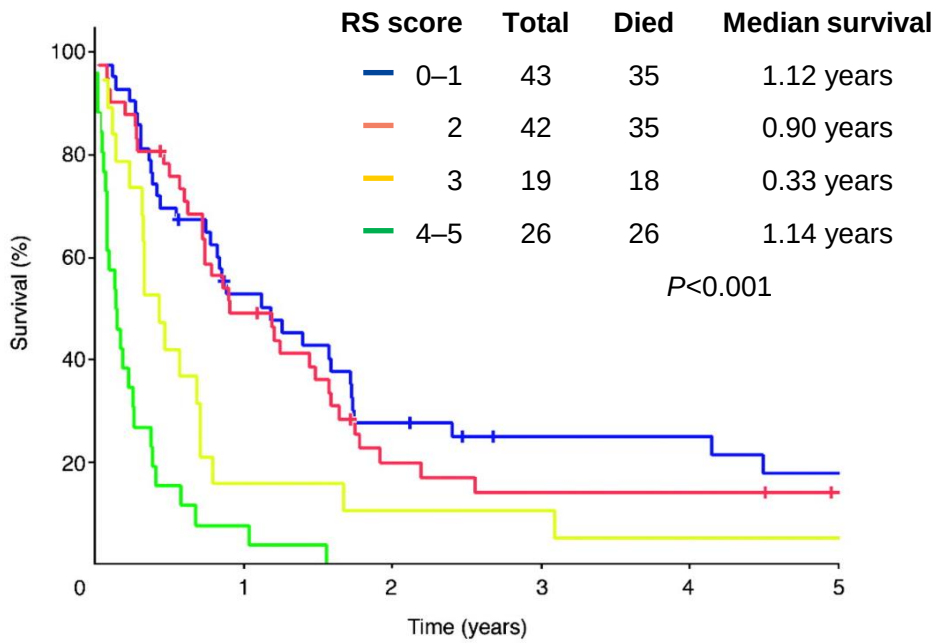
Richter's syndrome

- Aggressive lymphoma (DLBCL ~90%, HD ~10%)[1]
  - Described in 1928 by Maurice Richter[2]
- Prognosis
  - RS score[3]
  - 2011 case series[4]
    - ECOG-PS
    - Response to RS induction treatment
    - *TP53* disruption
  - Clonally unrelated RS associated with longer survival than clonally related disease[4]
    - Median PFS of 62.5 vs 14.2 months

RS score: factors independently prognostic of OS[3]

Risk Factors	RR	*P*
Performance status (0 or 1 *v* 2-4)	2.02	.006
Lactate dehydrogenase (< 1.5× normal *v* > 1.5× normal)	1.82	.003
Platelet count (> 100 × 10^9/L *v* < 100 × 10^9/L)	1.69	.012
Tumor size (< 5 cm *v* > 5 cm)	1.61	.022
Prior therapies (0-1 *v* > 1)	1.62	.024

Survival by RS score risk group (N=130)[3]

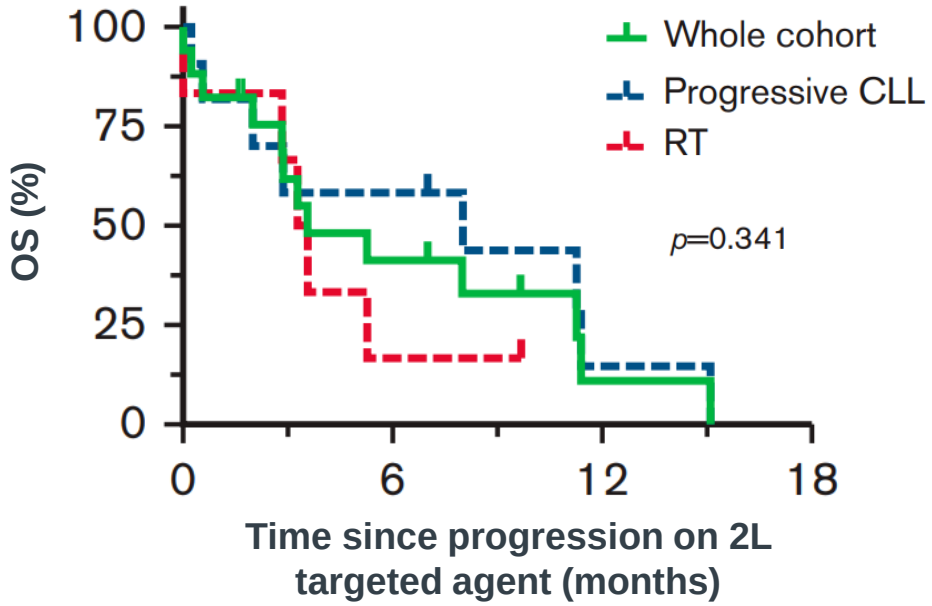


DLBCL, diffuse large B cell lymphoma; ECOG-PS, Eastern Cooperative Oncology Group performance status; HD, Hodgkin's disease; OS, overall survival; PFS, progression-free survival; RR, relative risk; RS, Richter's syndrome; TP53, tumor protein 53.

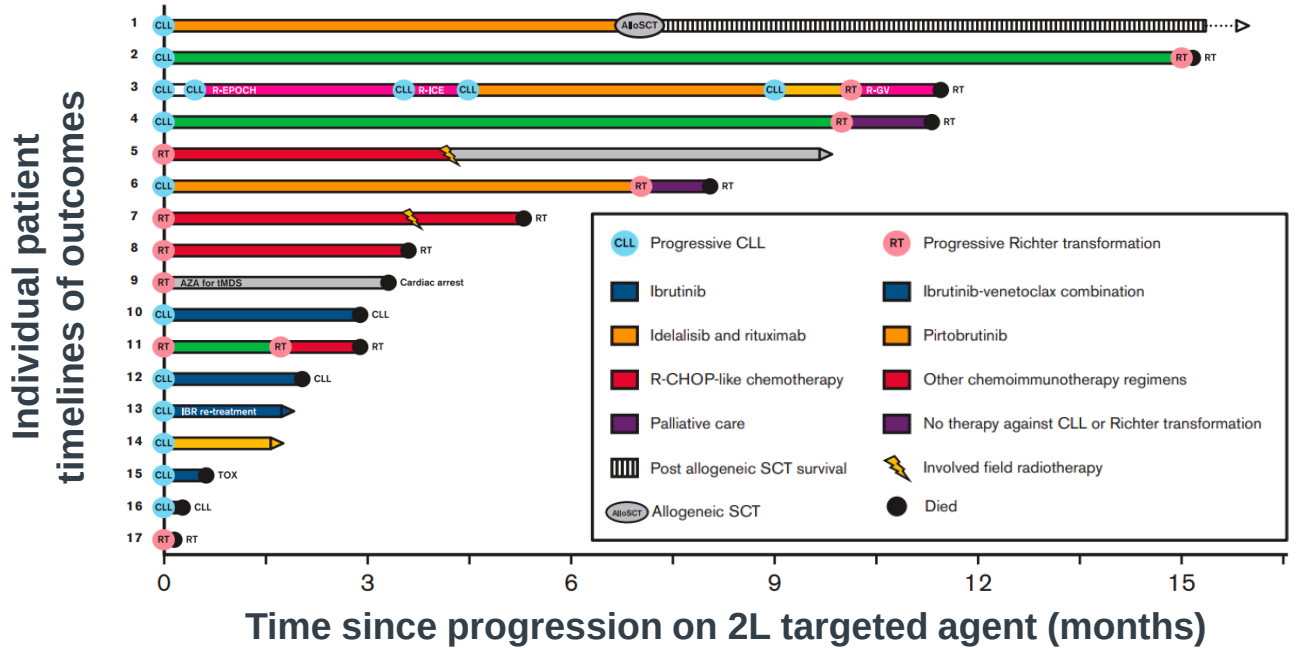
1. Thompson PA *et al*. *Hematology Am Soc Hematol Educ Program*. 2022; 2022 (1): 329–336. 2. Richter MN. *Am J Pathol* 1928; 4 (4): 285–292. 3.Tsimberidou AM *et al. J Clin Oncol* 2006; 24 (15): 2343–2351.
4. Rossi D *et al. Blood* 2011; 117 (12): 3391–3401.

RS in double-refractory patients

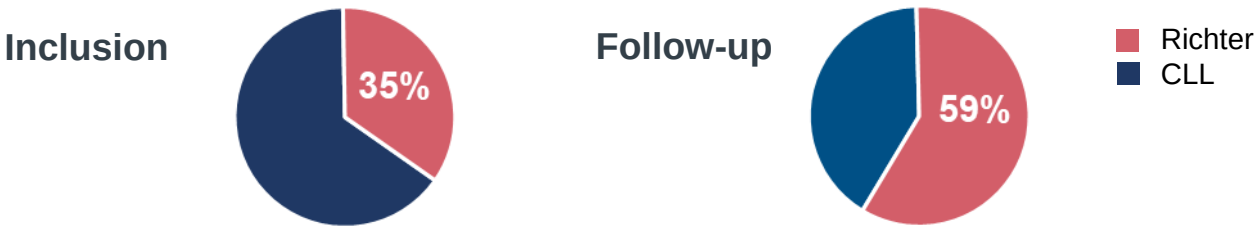
Median OS: 3.6 months



No. at risk					
Whole	17	9	6	4	1
CLL	11	5	5	3	1
RT	6	4	1	1	

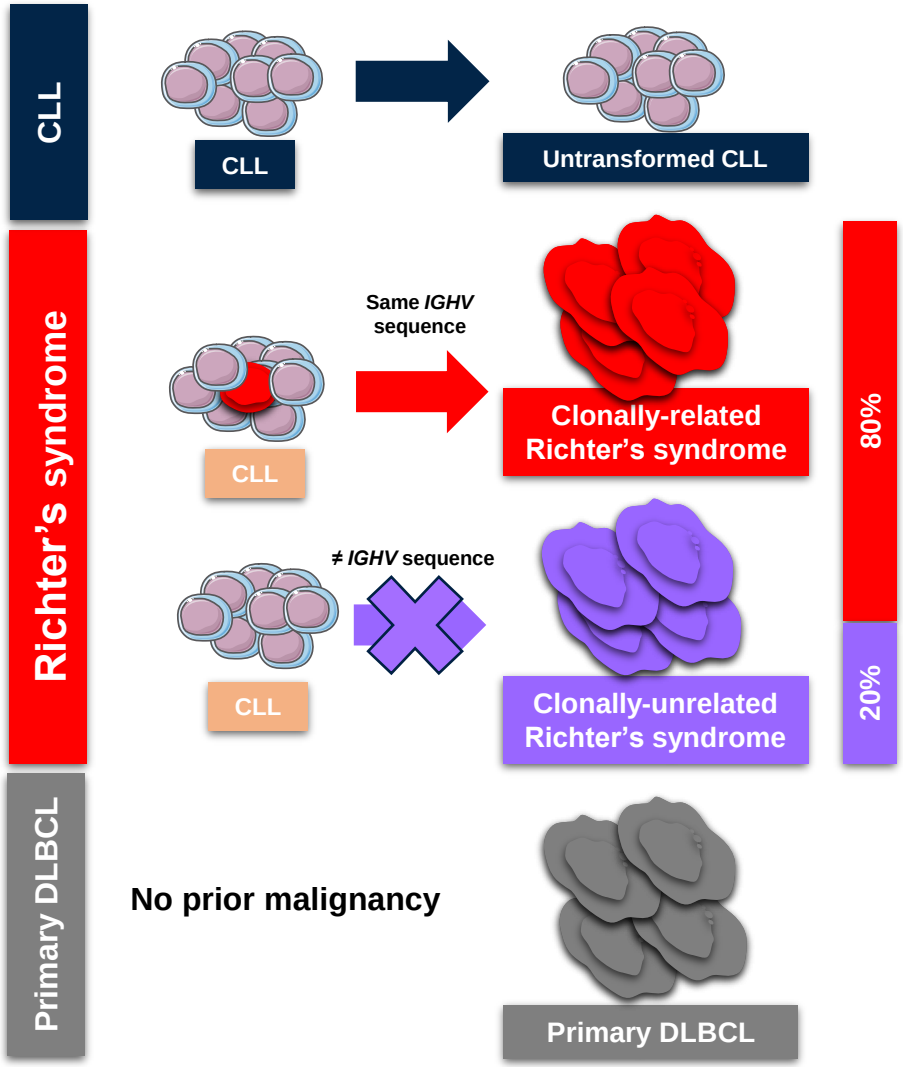


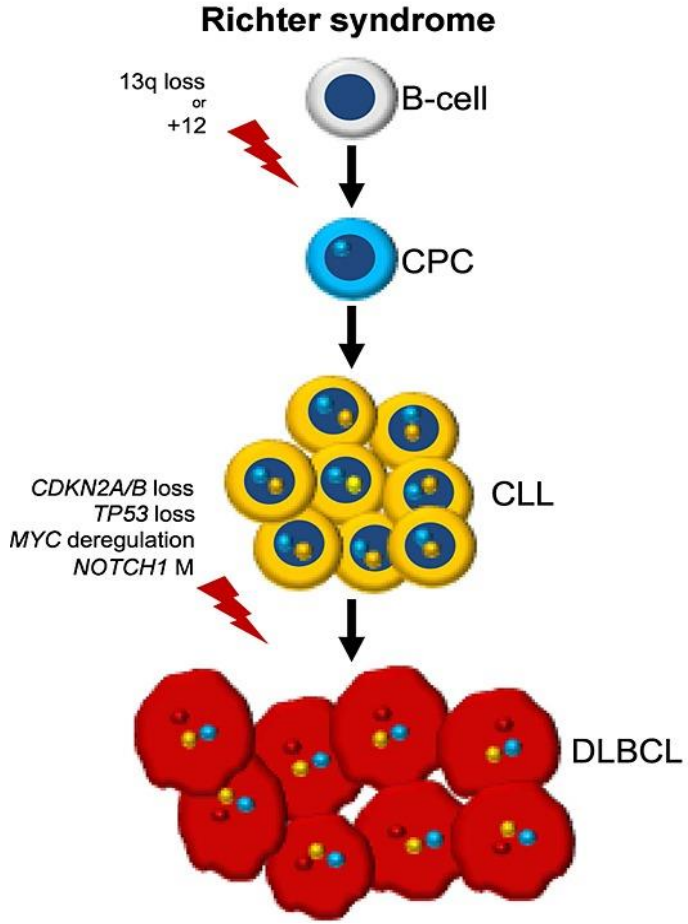
Death due to progression in 76% of patients (RT n=8, CLL n=3)



2L, second-line; BCL2i, B-cell lymphoma 2 inhibitor; OS, overall survival; R-CHOP, rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone; RT, Richter transformation; SCT, stem cell transplant.
Lew TE *et al. Blood Adv* 2021; 5 (20): 4054–4058.

RS genomic profile is different to *de novo* DLBCL





CLL, chronic lymphocytic leukemia; CPC, common progenitor cell; DLBCL, diffuse large B-cell lymphoma; IGHV, immunoglobulin heavy chain variable.

Fabbri G *et al*. *J Exp Med* 2013; 210 (11): 2273–2288; Chigrinova E *et al*. *Blood* 2013; 122 (15): 2673–2682; Rossi D. *Hematol Oncol* 2015; 33 Suppl 1: 70–74.

Immunochemotherapy in RS

Anti-CD20-based regimens

Reference	Treatment	n	CR (%)	ORR (%)	Overall survival (median or %)
Clinical trials					
Eyre *Br J Haematol* 2016[1]	O-CHOP	37	27	46	11 months
Langerbeins *Am J Hematol* 2014[2]	R-CHOP	15	7	67	21 months
Tsimberidou *Clin Lymphoma Myeloma Leuk* 2013[2]	OFAR	35	8.6	42.9	7 months
Tsimberidou *J Clin Oncol* 2008[2]	OFAR	20	10	50	8 months
Tsimberidou *Cancer* 2003[2]	R-hyper-CVXD-R-MA	30	18	43	8.5 months
Tsimberidou *Leuk Lymph* 2002[2]	FACPGM	15	5	5	2.2 months
Dabaja *Leuk Lymph* 2001[2]	Hyper-CVXD	29	38	41	10 months
Giles *Blood* 1996[2]	PFA/CFA	12	18	45	17 months
Retrospective studies					
Rogers *Br J Haematol* 2018[2]	R-EPOCH	46	n/a	37	6 months
Durot *Eur J Haematol* 2015[3]	DHAP/ESHAP	28	25	43	8 months
Tsimberidou *J Clin Oncol* 2006[4]	Chemotherapy	79	n/a	34	8 months
	Chemoimmunotherapy	47	n/a	47	

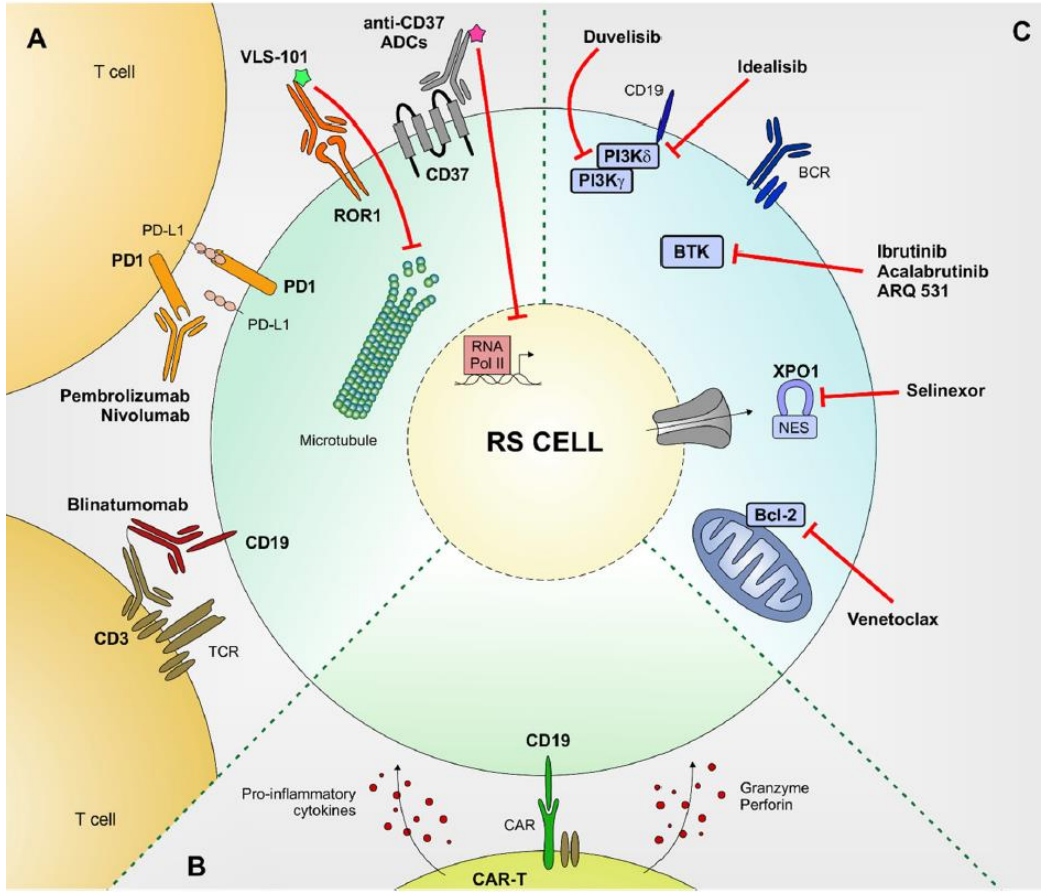
This slide includes data from different clinical trials. These data are meant for demonstration purposes only and are not meant for cross-trial comparison purposes.

CFA, cyclophosphamide, fludarabine and arabinosyl cytosine; CR, complete response; DHAP, dexamethasone, cytarabine, cisplatin; ESHAP, etoposide, methylprednisolone, cytarabine, cisplatin; FACPGM, fludarabine, cytarabine, cyclophosphamide, cisplatin and GM-CSF; GM-CSF, granulocyte-macrophage colony-stimulating factor; Hyper-CVXD, cyclophosphamide, vincristine, liposomal daunorubicin, and dexamethasone; ICT, immunochemotherapy; O-CHOP, obinutuzumab, cyclophosphamide, doxorubicin, prednisolone and vincristine; OFAR, oxaliplatin, fludarabine, cytarabine and rituximab; ORR, overall response rate; PFA, cis-platinum, fludarabine, and arabinosyl cytosine; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; R-EPOCH, rituximab, etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin; R-hyper-CVXD-R-MA, hyper-CVXD plus rituximab and GM-CSF alternating with methotrexate and cytarabine plus rituximab and GM-CSF.

1. Eyre TA *et al*. *Br J Haematol* 2016; 175 (1): 43–54.
2. Thompson PA *et al*. *Hematology Am Soc Hematol Educ Program* 2022 (1): 329–336. 3. Durot E *et al*. *Eur J Haematol* 2015; 95 (2): 160–167. 4. Tsimberidou AM *et al*. *J Clin Oncol* 2006; 24 (15): 2343–2351.

Dose-adjusted R-EPOCH + venetoclax in RS

- Phase 2 study: venetoclax + DA-R-EPOCH
- 26 patients:
  - 50% CR
  - 11/13 undetectable MRD BM (CLL)
  - 3 PR
- mPFS: 10.1 months
- mOS: 19.6 months
- Acceptable hematological toxicity
- No TLS



BM, bone marrow; CLL, chronic lymphocytic leukemia; CR, complete remission; DA, dose-adjusted; DA-R-EPOCH, etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin; mPFS, median progression-free survival; mOS, median overall survival; MRD, minimum residual disease; PR, partial remission; R-EPOCH, rituximab, etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin; RS, Richter's syndrome; TLS, tumor lysis syndrome.

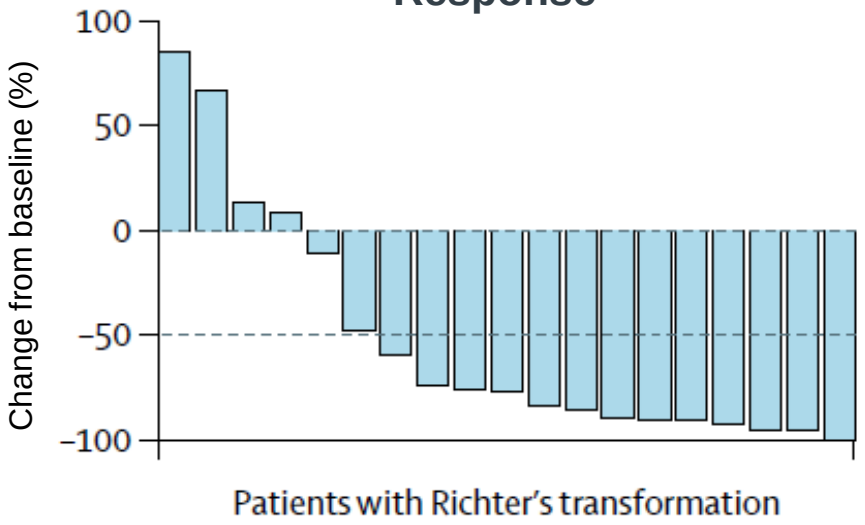
1. Davids MS *et al*. *Blood* 2022; 139 (5): 686–689. 2. Ianello A, *et al. Curr Treat Options Oncol*. 2022; 23 (4): 526–542.

Checkpoint inhibitors in RS
Nivolumab (anti-PD-1) + ibrutinib

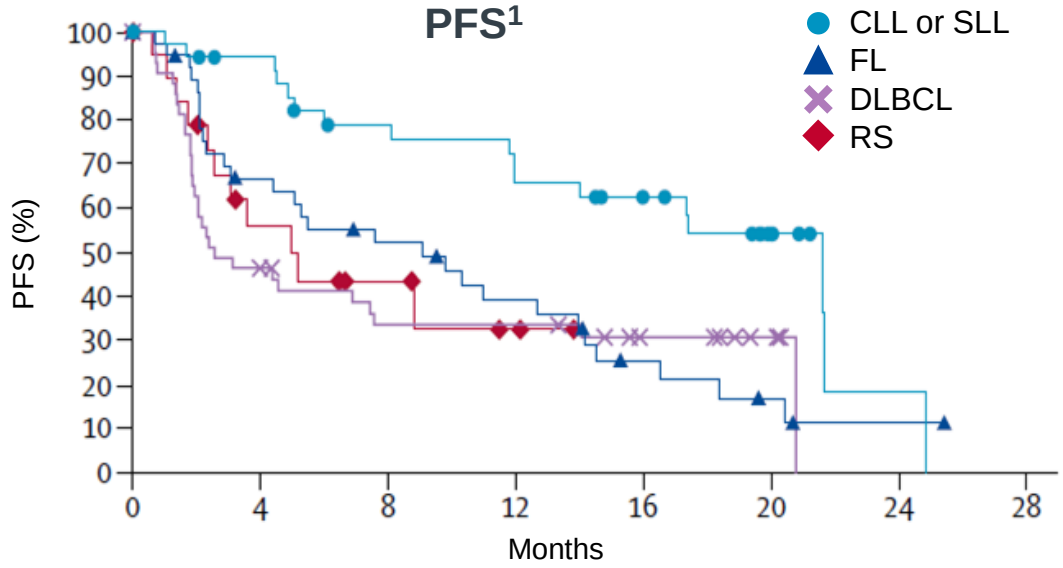
- Phase 1/2a study (dose escalation, efficacy)[1]
- Response
  - 13 (**65%**) of 20 patients with RS
  - Median duration of response: 13 months
- Neutropenia grade >2: 28%
  - No febrile neutropenia in the RS group

- Phase 2 study (RS, N=23)[2]
- Response
  - 10 (**43%**) patients (CMR, n=8)
  - Median duration of response: 9.3 months
- Median overall survival: 13.8 months

Response[1]



PFS[1]



CLL, chronic lymphocytic leukemia; CMR, complete metabolic response; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; PFS, progression-free survival; RS, Richter's syndrome; SLL, small lymphocytic lymphoma. 1. Younes A *et al. Lancet Haematol* 2019; 6 (2): e67–e78. 2. Jain N *et al. Blood* 2018; 132 (supplement 1): 296.

Other trials in RS: Phase 2 studies

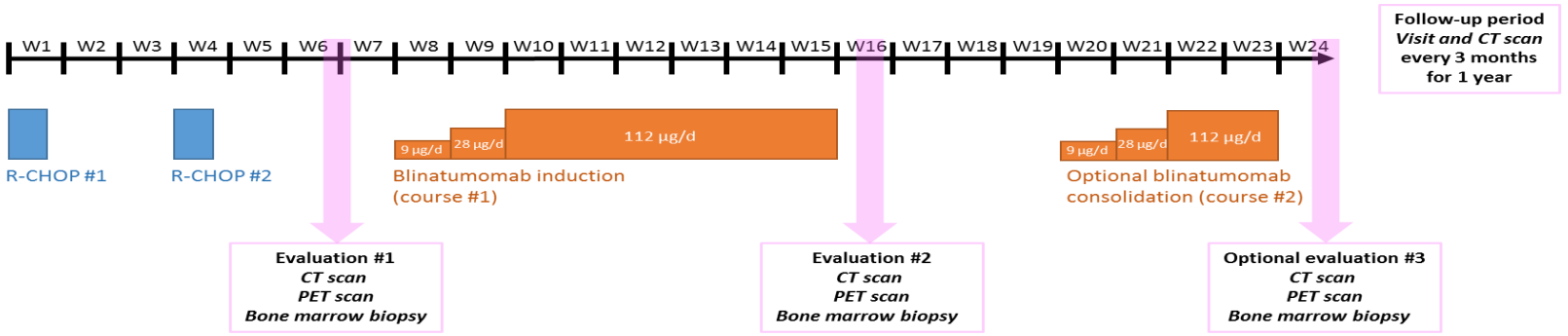
Reference	Treatment
NCT02362035	acalabrutinib + pembrolizumab
NCT03899337	acalabrutinib + R-CHOP
NCT03054896	R-EPOCH/R-CHOP + venetoclax
NCT04271956	zanubrutinib + tislelizumab
NCT03892044	duvelisib + nivolumab
NCT03884998	copanlisib + nivolumab
NCT02846623	atezolizumab + obinutuzumab + venetoclax
NCT04082897	atezolizumab + obinutuzumab + venetoclax
NCT03534323	duvelisib + venetoclax
NCT03145480	ibrutinib + obinutuzumab + CHOP
NCT04939363	obinutuzumab + ibrutinib + venetoclax
NCT03113695	obinutuzumab, HDMP, lenalidomide
NCT04679012	polatuzumab vedotin with chemotherapy

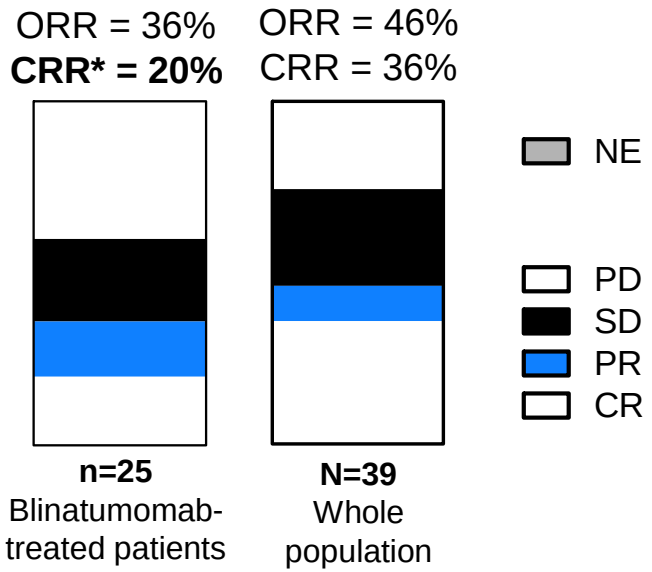
CHOP, cyclophosphamide, doxorubicin, vincristine and prednisone; HDMP, high dose methylprednisolone; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; R-EPOCH, rituximab, etoposide phosphate, prednisone, vincristine sulfate, cyclophosphamide and doxorubicin hydrochloride.

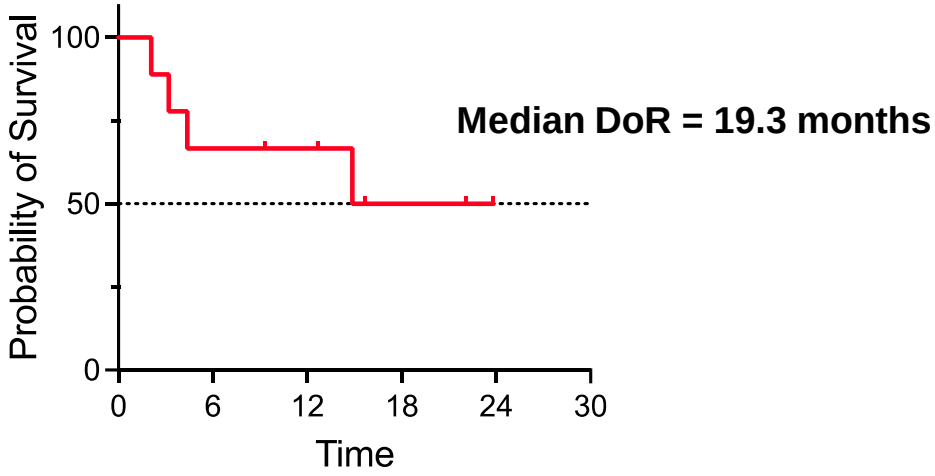
BLINART study

Blinatumomab after R-CHOP debulking for patients with RS

N = 41 RS (DLBCL)[1]







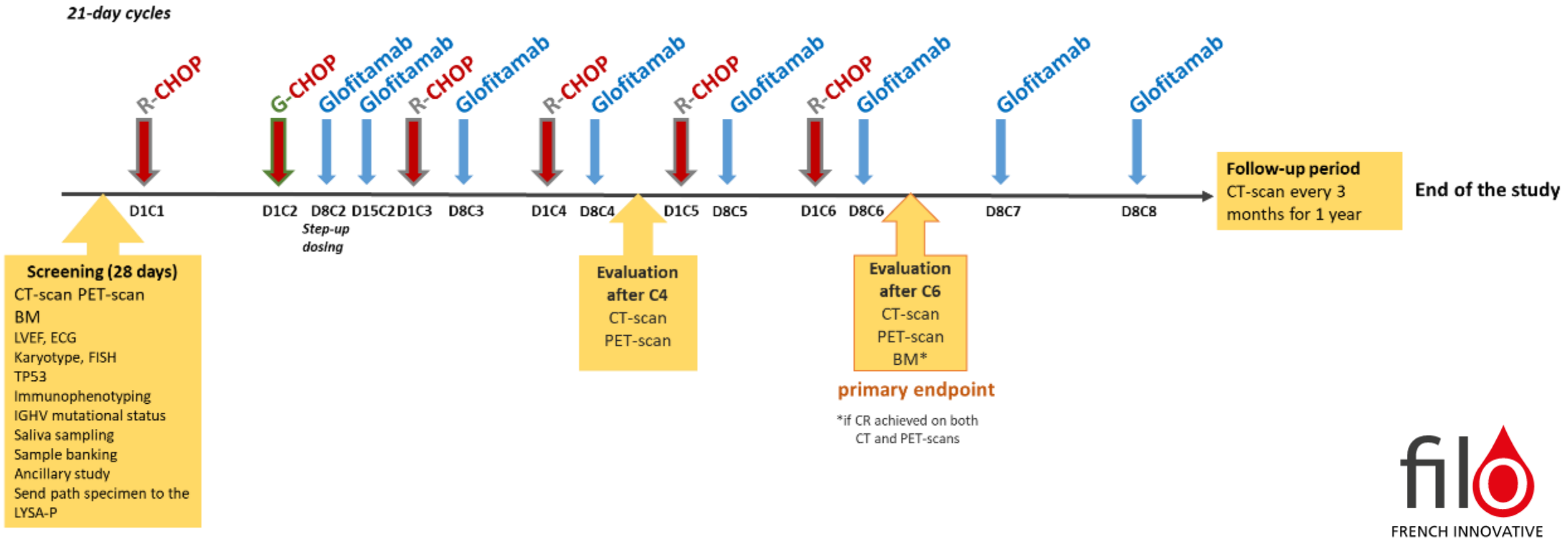
*Primary endpoint.

CR, complete remission; CRR, complete response rate; CT, computerized tomography; d, day; DLBCL, diffuse large B-cell lymphoma; DoR, duration of response; NE, not estimable; PD, progressive disease; PET, positron emission tomography; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; RS, Richter's syndrome; SD, stable disease.

1. Guièze R et al. Poster at the 64th American Society of Hematology (ASH) Annual Meeting; New Orleans, LA, USA, December 10–13 2022 (Abstract 2952).

Bispecifics: GLORIFY study

Glofitamab CD3xCD20 antibody plus R/G-CHOP as front-line therapy for RS

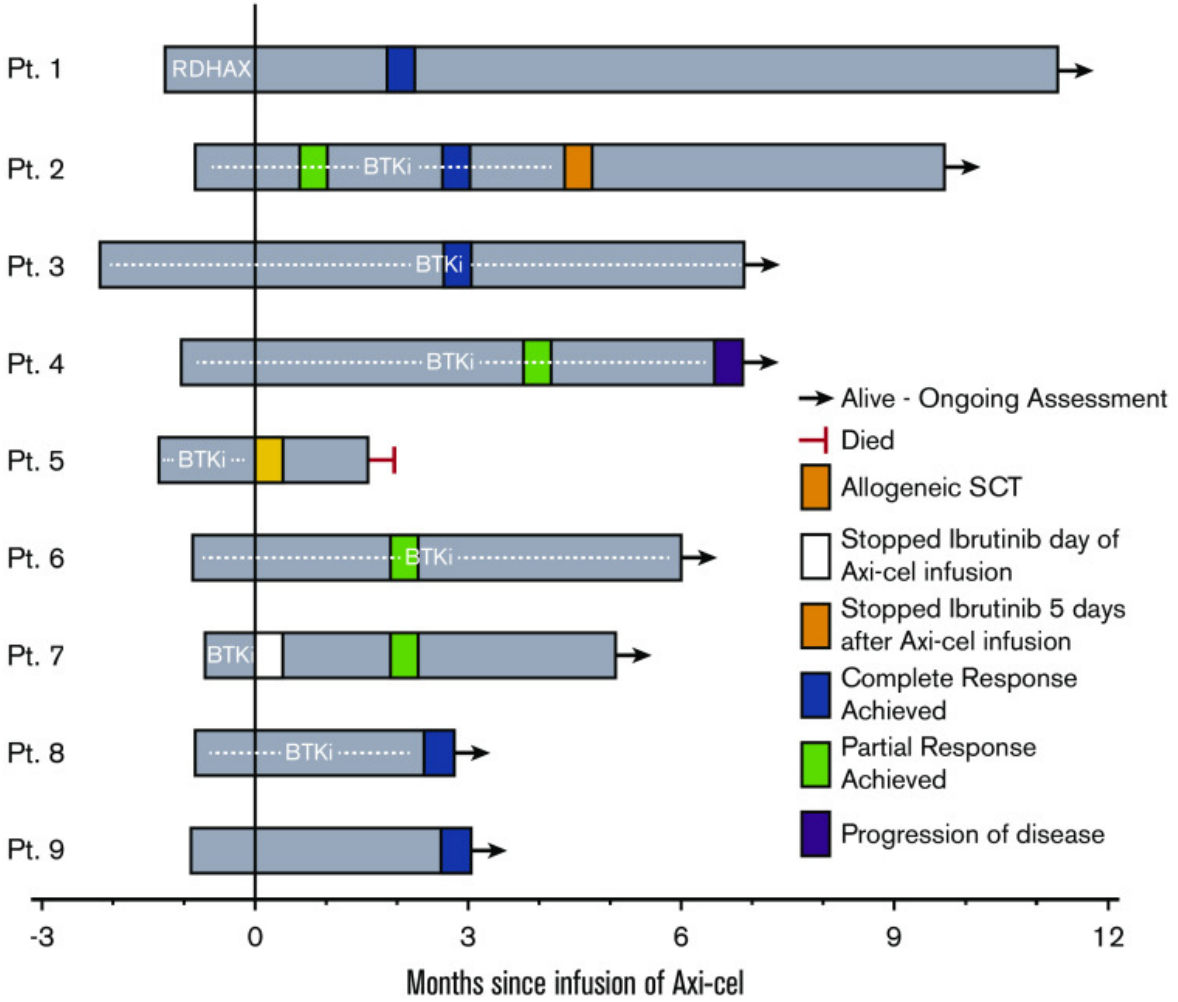


FRENCH INNOVATIVE LEUKEMIA ORGANIZATION

BM, bone marrow; C, cycle; CR, complete remission; CT, computerized tomography; D, day; ECG, electrocardiogram; FISH, fluorescence in situ hybridization; G-CHOP, obinutuzumab, cyclophosphamide, doxorubicin, vincristine, and prednisone; IGHV, immunoglobulin heavy chain variable; LVEF, left ventricular ejection fraction; LYSA-P, digital pathology platform; PET, positron emission tomography; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; RS, Richter's syndrome. Speaker personal communication.

CAR-T cell therapy in patients with RS

- DESCAR-T registry (Lysa)[1]
- 9 patients treated with axi-cel[2]
  - Median age of 64 years
  - 7 patients received BTKi as bridging therapy
- Toxicity[2]
  - CRS in all 9 patients (Grade >2 in 1 patient)
  - ICANS Grade ≥3 in 3 patients
- Efficacy[2]
  - 8 ORR (5 CR and 3 PR)
  - Median FU of 6 months
- Guieze R, *et al*. ASH 2022[1]



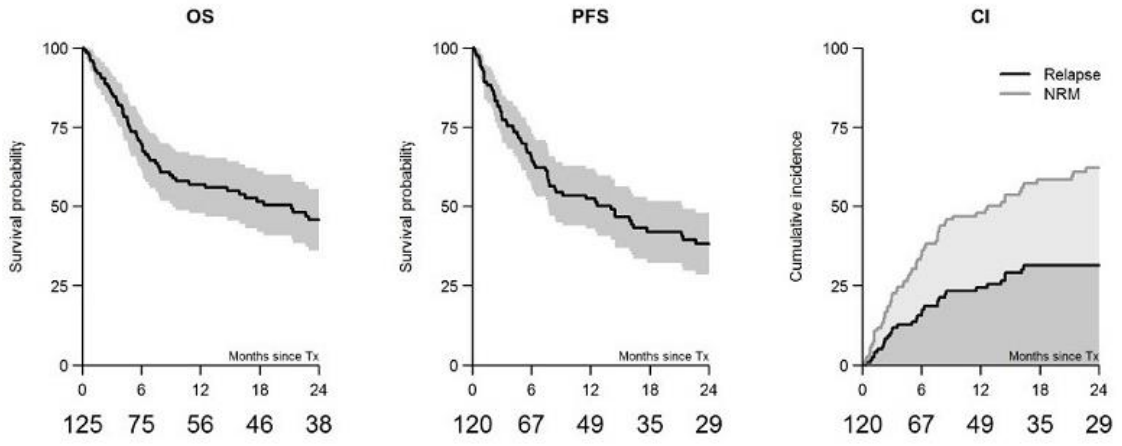
CAR-T, chimeric antigen receptor T-cell; CR, complete remission; CRS, cytokine release syndrome; FU, follow-up; ICANS, immune effector cell–associated neurotoxicity syndrome; ORR, overall response rate; PR, partial remission; Pt, patient; RDHAX; rituximab, dexamethasone, cytarabine, and oxaliplatin; RS, Richter's syndrome; SCT, stem cell transplantation.

1. Guièze R *et al*. Poster at the 64th American Society of Hematology (ASH) Annual Meeting; New Orleans, LA, USA, December 10–13 2022 (Abstract 1652). 2. Kittai SA *et al*. *Blood Adv* 2020; 4 (19): 4648–4652.

Stem cell transplant in patients with RS
EBMT-center cases (2008–2018)

Allogeneic SCT (n=125)

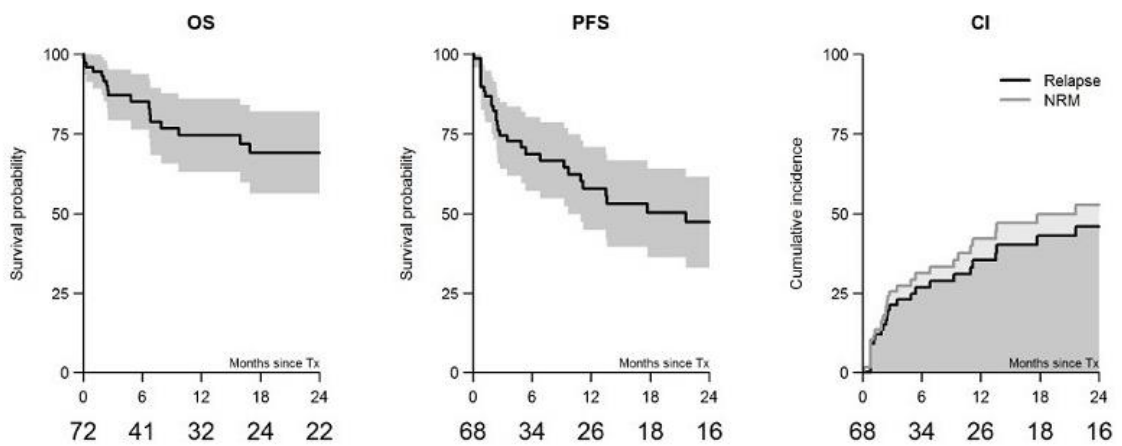
2-year OS: 46%



48-month follow-up

Autologous SCT (n=72)

2-year OS: 69%

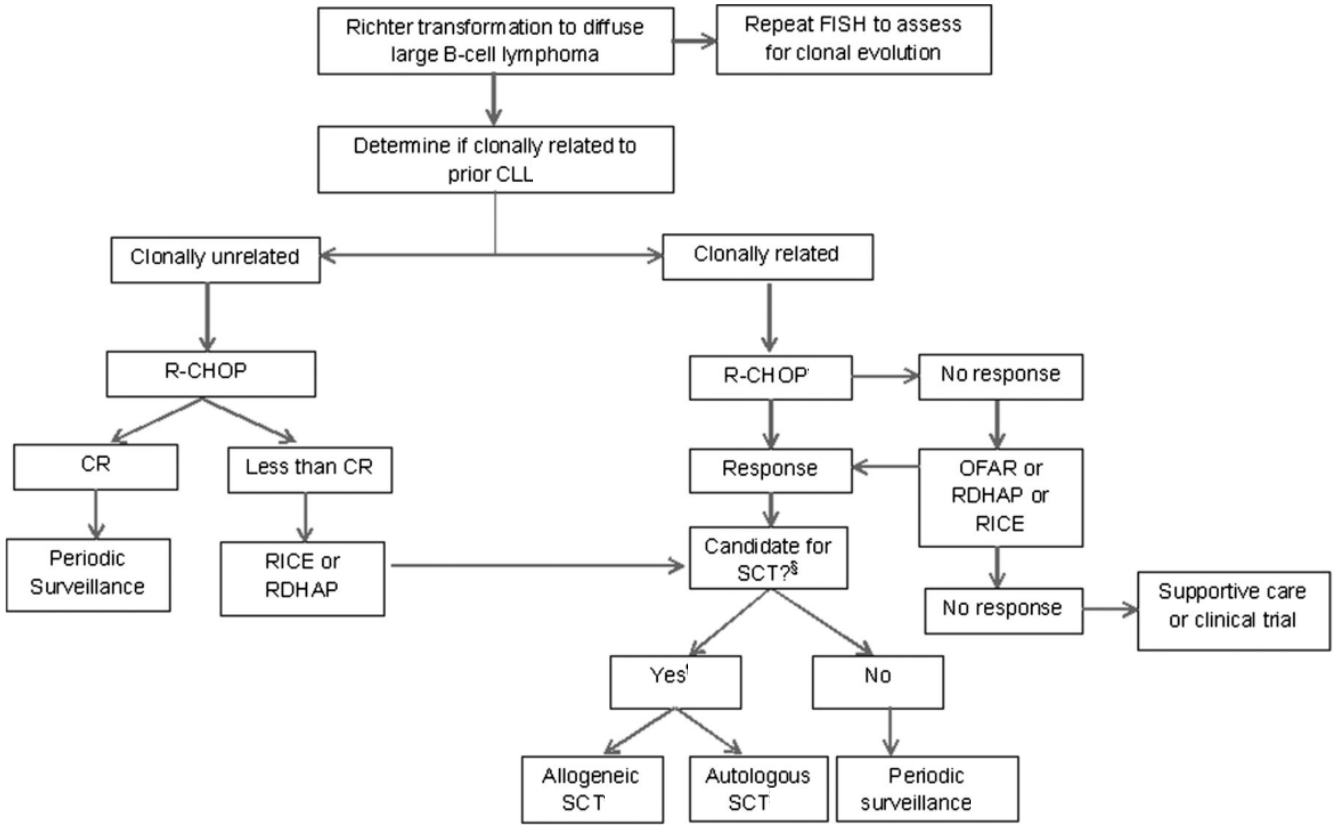


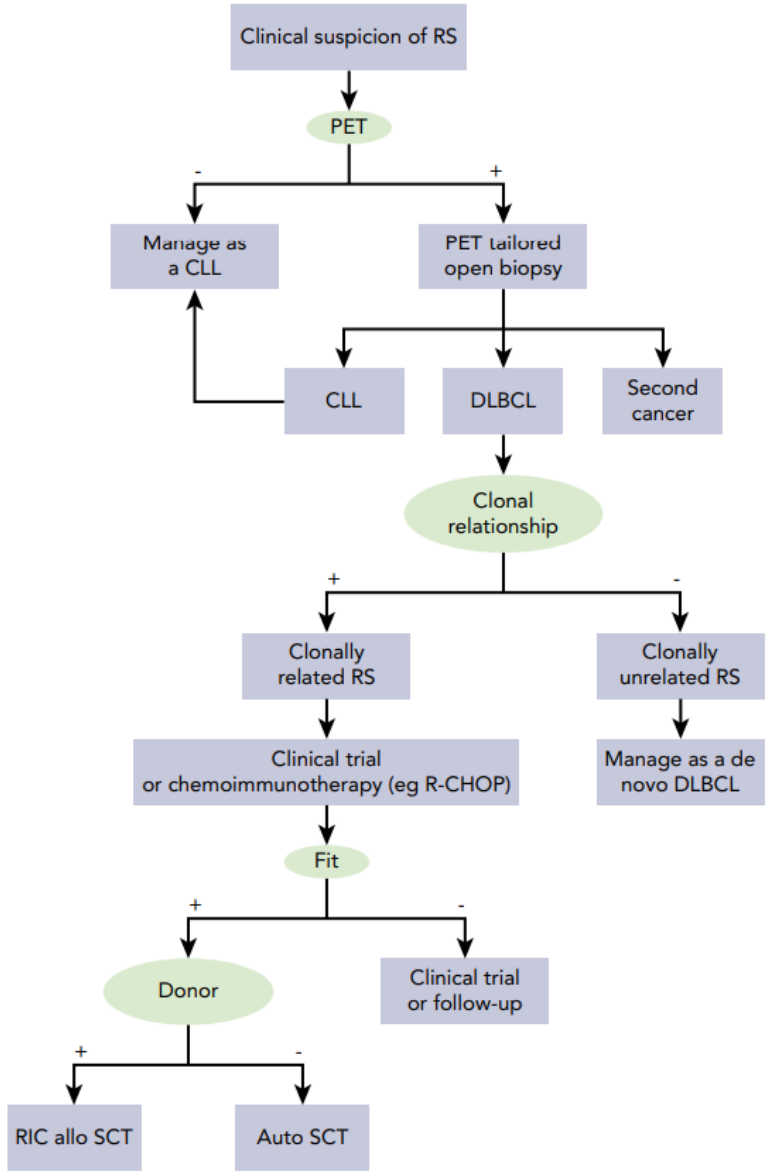
12-month follow-up

CI, cumulative incidence; EBMT, European Society for Blood and Marrow Transplantation; NRM, non-relapse mortality; OS, overall survival; PFS, progression-free survival; RS, Richter's syndrome; SCT, stem cell transplantation; Tx, treatment.

Tournilhac O *et al. Blood* 2019; 134 (Suppl 1): 2053.

RS management algorithms





CLL, chronic lymphocytic leukemia; CR, complete response; DLBCL, diffuse large B-cell lymphoma; FISH, Fluorescence In Situ Hybridization; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; OFAR, oxaliplatin, fludarabine, cytarabine and rituximab; PET, positron emission tomography; RIC, reduced-intensity conditioning; RDHAP, rituximab, dexamethasone, cytarabine and cisplatin; RICE, rituximab, ifosfamide, and etoposide; RS, Richter syndrome; SCT, stem cell transplantation.

Parikh SA *et al*. *Blood* 2014; 123 (11): 1647–1657; Rossi J *et al*. *Blood* 2018; 131 (25): 2761–2772.

Summary

- Differentiate prior treatment failure due to toxicity versus refractory disease[1]
- Be sure there are no arguments for Richter Syndrome[1]
- Double refractory CLL and RS are two “medical needs” in CLL treatment in 2023[2]
- Analysis of BTK or BCL2 resistance (if possible) is necessary to adapt the next treatment[1,3]
- Choice of treatment depends on:[1,2]
  - Previous treatment
  - Genetic characteristics (*TP53* alteration? Complex karyotype?) to be assessed at each relapse
  - Treatment toxicities
  - Comorbidities
- No chemotherapy doesn’t mean no toxicity[2]

1. Quinquenel A *et al. HemaSphere* 2020; 4 (5): e473. 2. Speaker opinion. 3. Xu Y *et al. Exp Hematol Oncol* 2022; 11 (1): 31.