Richter Syndrome

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Richter Syndrome

- Aggressive histological transformation of CLL
  - DLBCL – 90%
  - Hodgkin Lymphoma – 10%
- Occurs in 2-10% CLL patients
- More common in men
- Poor Prognosis
  - CR rates with chemoimmunotherapy about 20%
  - <20% long term survival with CIT

Richter Syndrome

- High risk genomics of CLL increase risk for RS[1]
  - Unmutated *IGHV*
  - *IGHV* stereotyped subset number 8 (IGHV4-39-IGHJ5)
  - *NOTCH1* mutations
  - *TP53* mutation or deletion
  - Del11q
- RS clonally related (CR-DLBCL-RS) to a previous CLL diagnosis (80% of cases) have worst outcomes
  - Genomically distinct from non-clonally related
  - *TP53* mutation (60%-80%), *CDKN2A* deletion (30%), *MYC* overexpression (40%), and activating *NOTCH1* mutation (~30%)[2]
  - 50% of clonally related RS has stereotyped *IGHV* (usually *IGHV4-39/IGHD6-13/IGHJ5*)
  - Clonally unrelated RS: low rates of *TP53* mut (20%), and only rarely present stereotyped *IGHV*
- 80% of CR-DLBCL-RS have overexpression of PD-1[3]

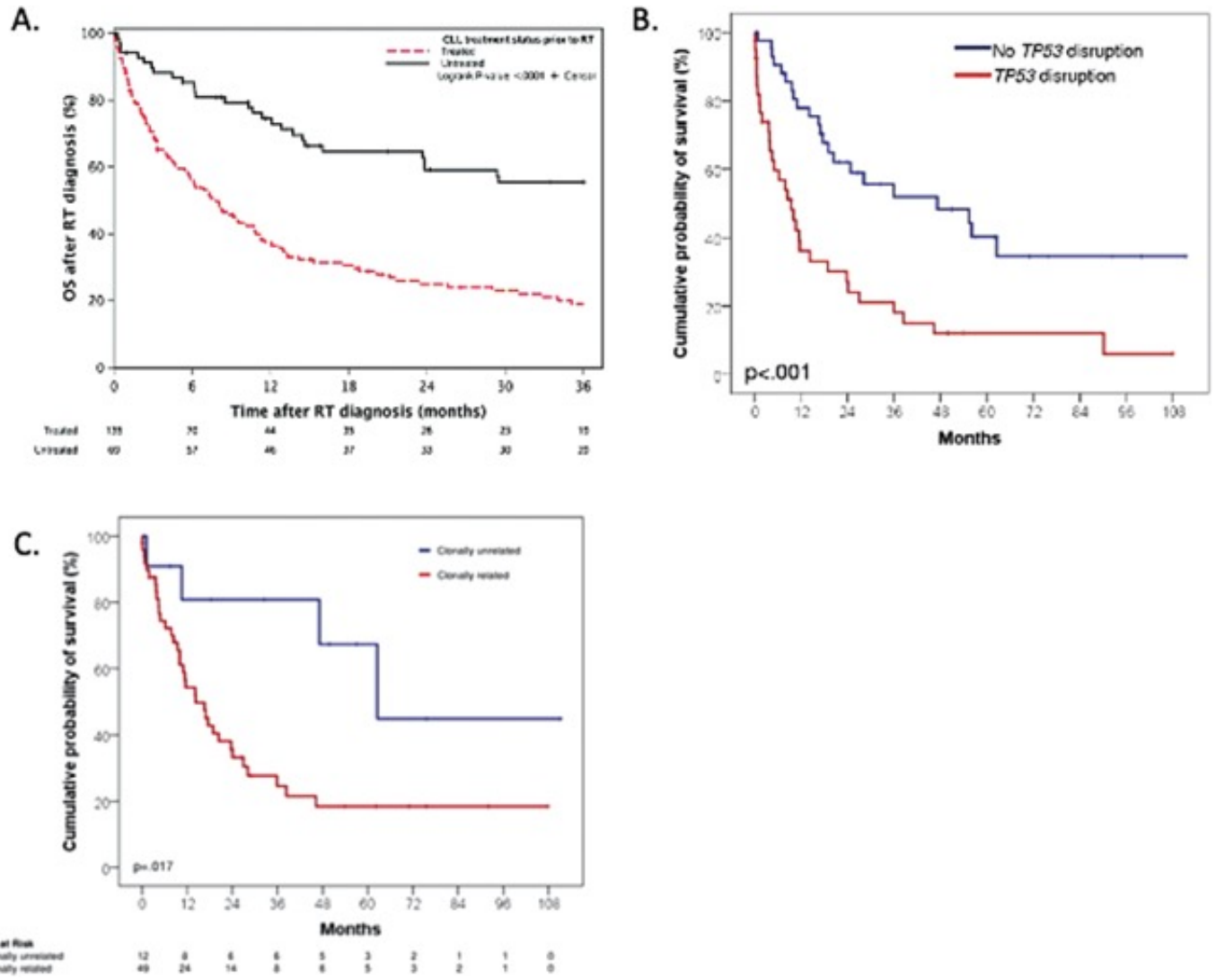
1- Rossi et al, Blood 2018; 2-Chigrinova et al, Blood 2013; He et al, J Am Surg Pathol 2017

Prognosis

A- Patients with DLBCL-RS without previous treatment for CLL vs treated patients - PFS; median 46.3 vs 7.8 months

B- *TP53* mutation vs wild-type median PFS of 9.4 months vs 47.1 months

C- Clonally unrelated vs related median PFS of 62.5 months vs 14.2 months



Thompson et al, ASH 2022

How to treat Richter Syndrome?

Try establishing clonal relation

- Best way: sequence *IGHV* from initial CLL and DLBCL for matching
- Light chain restriction is not adequate to establish clonal relationship
- If *IGHV* sequencing not possible, may check NGS panel for typical mutations: if *TP53* mut, *NOTCH1* mut or *CDKN2A/B del* more likely to be clonally related
- Check PD-1 expression by IHC – may be good surrogate marker for clonal relatedness
- If <u>not</u> clonally related – treat as *de novo* DLBCL

Chemoimmunotherapy

- Low CR rates
- Median OS 6-21 months

Study and years of patient recruitment	Regimen	n	Median age (years)	Results		
				ORR	CRR	Median OS
Anthracycline-containing regimens						
Langerbeins et al[16] (2003–2008)	R-CHOP	15	69 (N/A)	67%	7%	21 months
Dabaja et al[17] (published 2000)	HyperCVXD	29	61 (36–75)	41%	38%	10 months
Tsimberidou et al[18] (1999–2001)	Rituximab and GM-CSF with alternating hyperCVAD and MTX/cytarabine	30	59 (27–79)	43%	18%	8.5 months
Rogers et al[19] (2006–2014)	R-EPOCH	46	67 (38–83)	39%	N/A	5.9 months
Platinum-containing regimens						
Tsimberidou et al[20] (2004–2006)	OFAR1	20	59 (34–77)	50%	20%	8 months
Tsimberidou et al[21] (2007–2010)	OFAR2	35	63 (40–81)	43%	8.6%	6.6 months
Fludarabine-containing regimens						
Giles et al[22] (1992-1996)	PFA or CFA	12	59 (49–74)	45%	N/A	17 months
Tsimberidou et al[23] (1997–2001)	FACPGM	15	62 (42–74)	5%	5%	2.2 months

Thompson and Siddiqi, ASH 2022

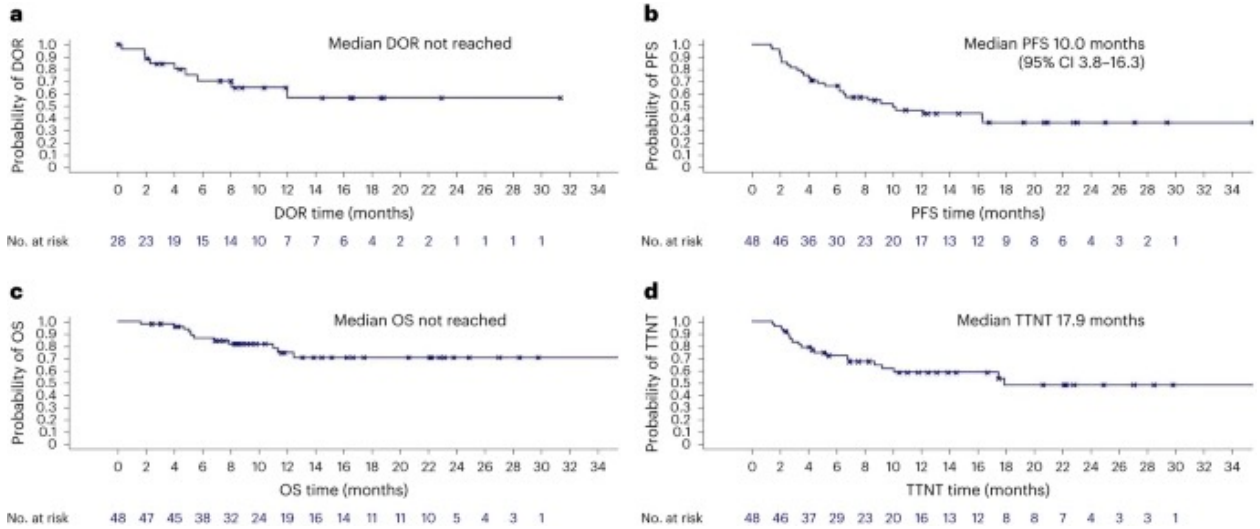
BTK inhibitors

- Acalabrutinib for RS (Eyre et al, Lancet Haematol 2021)
  - Acalabrutinib 200 mg twice daily for untreated DLBCL-RS
  - ORR 40%; CR 8%. Duration of Response 6.2 months, median PFS 3.2 months
- Pirtobrutinib (Wierda et al, ASH 2022, Lancet Haematol 2024)
  - 75 pts. ORR 50%, CR 13%; median PFS 3.7 months
- Zanubrutinib (Tam et al, Hemasphere 2023)
  - 13 patients. ORR 61.5%; CR 15.4%, mPFS:17.3 months

PD1/PDL1 inhibitors

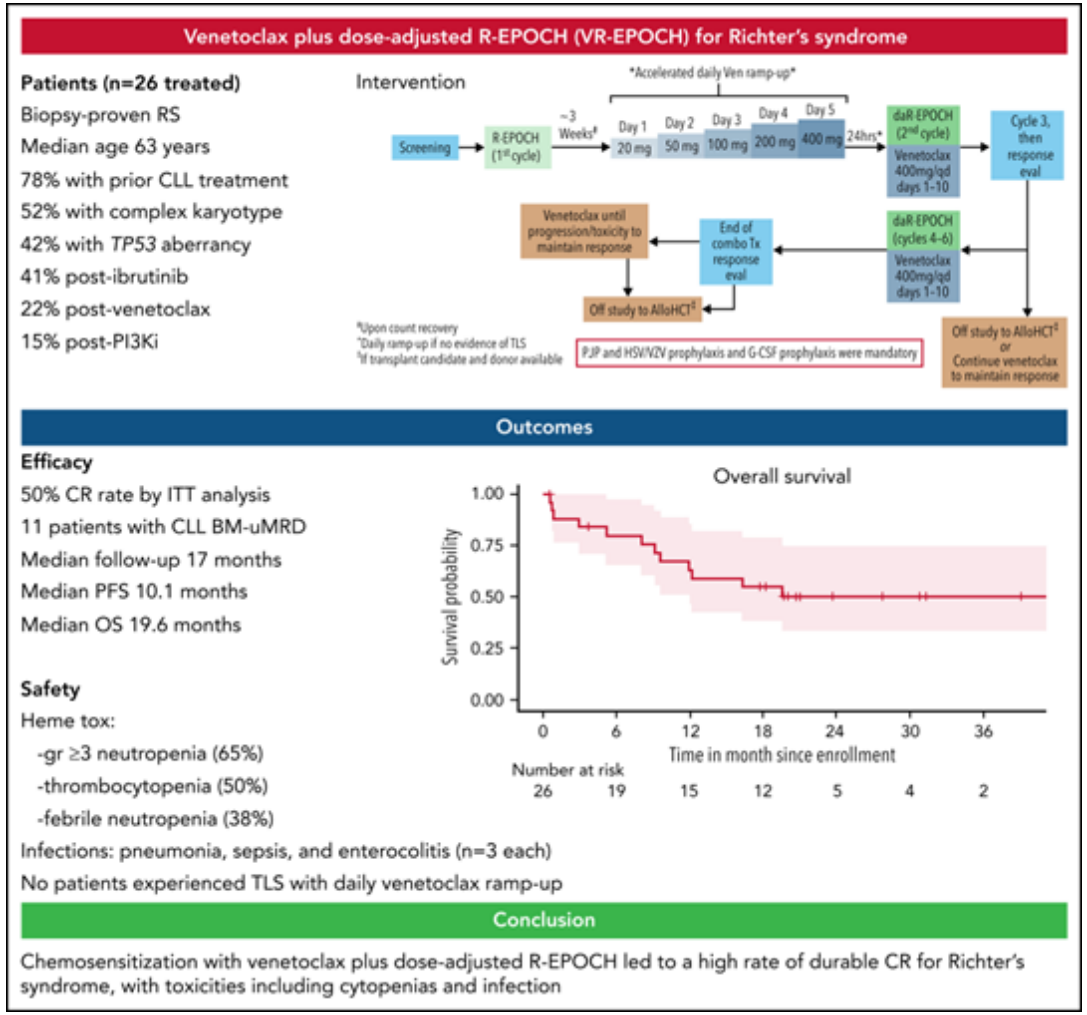
- Pembrolizumab (Ding et al, Blood 2017)
  - ORR 44%; CR 11%, mPFS 10.7 months
- Nivolumab + ibrutinib (Jain et al, Blood Advances 2023)
  - ORR 42%, CR 34%, median OS 13 months
- Tislelizumab + Zanubrutinib (Al-Sawaf et al, Nature Med 2023)

ORR 58.3%
CR 18.8%



Venetoclax

- Ven single agent (Davids et al, JCO 2017)
  - ORR 43%, no CR
- Venetoclax + DA-EPOCH-R
  - Davids et al, Blood 2022 →
- Ven + R-CHOP (Davids, ICML 2023)
  - ORR 68%, CR 48%
  - Median OS 19.5 mos
  - Gr3+ neutropenia (36%), anemia (32%), thrombocytopenia (40%), Febrile neutropenia (32%)



A multicenter study of venetoclax-based treatment for patients with Richter transformation of chronic lymphocytic leukemia

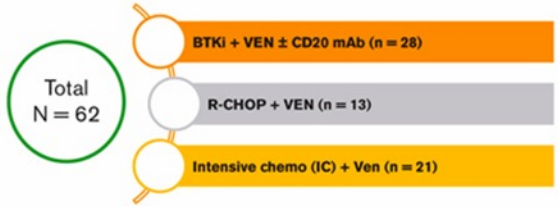
Introduction

- Patients with RT, developed from CLL, have poor prognosis with chemoimmunotherapy (CIT) regimens used for DLBCL.
- Venetoclax has single-agent activity in RT and potential synergy with CIT.

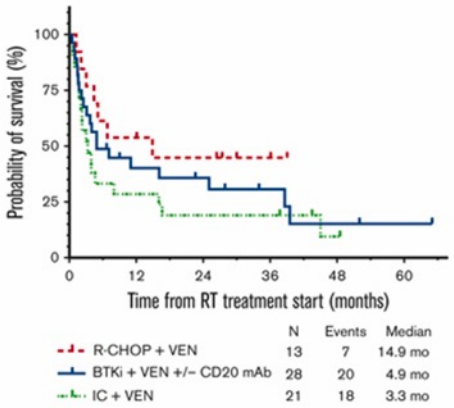
Aim

- To evaluate the outcomes of patients with RT treated with venetoclax-based treatment, outside clinical trials, including novel-novel combinations and CIT combinations.

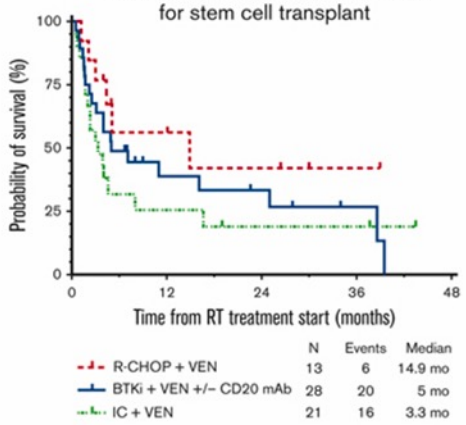
Results



Progression-free survival



Progression-free survival censored for stem cell transplant



Complete Response and Progression-Free Survival Stratified by Baseline Characteristics

Variable	CR N (%)	OR [95% CI], *P* value	Median PFS Months [range]	HR [95% CI], *P* value
Previously received VEN for CLL				
Yes, n = 15	2 (13)	0.40 [0.10-1.63], .33	3.3 [2.8-3.7]	1.19 [0.6-2.36], .61
No, n = 47	19 (40)		6.8 [0-15.5]	
Previously received BTKi for CLL				
No, n = 7	2 (29)	0.49 [0.16-1.48-], .33	11 [0-22.2]	0.99 [0.52-1.88], .98
Yes, n = 21	5 (24)		4.6 [3.6-5.7]	
Del(17p) in CLL (n = 59)				
Yes, n = 23	3 (13)	0.15 [0.04-0.6], .01	4.4 [2.2-6.6]	1.75 [0.95-3.22], .07
No, n = 36	18 (50)		11 [0-23.7]	
TP53 mutation in CLL (n = 41)				
Yes, n = 20	6 (30)	0.39 [0.11-1.41], .26	2.3 [0-7.1]	0.56 [0.27-1.19], .13
No, n = 21	11 (52)		16.6 [0-44]	
Complex karyotype in CLL (n = 54)				
Yes, n = 25	7 (28)	0.55 [0.18-1.73], .46	8 [0-23.5]	0.93 [0.49-1.76], .82
No, n = 29	12 (41)		4.4 [2.5-6.3]	
LDH >ULN (n = 58)				
Yes, n = 44	14 (32)	0.47 [0.14-1.59], .37	4.6 [0.82-8.5]	1.12 [0.55-2.30], .75
No, n = 14	7 (50)		6.8 [0-20.3]	
LDH >2×ULN				
Yes, n = 23	7 (30)	0.66 [0.22-2], .65	4 [3.2-4.8]	1.33 [0.71-2.47], .37
No, n = 35	14 (40)		7.1 [0-21.5]	
Adenopathy ≥5cm (n = 55)				
Yes, n = 25	7 (28)	0.58 [0.19-1.82], .52	4 [2.8-5.2]	1.45 [0.77-2.74], .25
No, n = 30	12 (40)		8 [0-20.5]	
Adenopathy ≥10cm				
Yes, n = 8	1 (13)	0.23 [0.03-2.03], .31	2.3 [0-4.9]	1.77 [0.73-4.3], .20
No, n = 47	18 (38)		8 [0-18.6]	
Highest SUV >10 (n = 49)				
Yes, n = 33	12 (36)	0.74 [0.22-2.48], .86	4 [3-6]	1.19 [0.58-2.44], .64
No, n = 16	7 (44)		8 [0-32.9]	

Abbreviations: CR, complete response; OR, Odds ratio; PFS, progression-free survival; VEN, venetoclax: BTKi, Bruton tyrosine kinase inhibitors; CLL, chronic lymphocytic leukemia; LDH, lactate dehydrogenase; ULN, upper limit of normal; SUV, standardized uptake values.

Information not available in all patients

Conclusion

- In difficult-to-treat RT patient population, venetoclax-based combination regimens achieve high response rates, particularly with the use of R-CHOP + venetoclax.
- Survival outcomes remained poor overall.
- Durable PFS and OS was observed in a small subset of patients irrespective of alloHSCT.
- Prospective clinical trials evaluating venetoclax or novel combinations are ongoing.

blood advances Visual Abstract

Hampel et al, Blood Advances 2024

Phase II Obinutuzumab + Ibrutinib + Venetoclax for RS – GIVeRS regimen
Tadmor et al, ASH 2024

- 12 cycles (Obin for 6 cycles)
- 12 patients
- 67% treatment naïve
- High 3 month metabolic response (40% CR) but short duration
  - mPFS 4.4 months
  - mOS 7.8 months

CAR-T Cell Therapy

- Retrospective analysis – Kittai et al, J Clin Oncol 2024
  - 69 patients
  - Median 4 prior lines of therapy for CLL and/or RS
  - ORR 63%, CR 46%
  - Median PFS 4.7 months
  - Median OS 8.5 months
  - For patients in CR, median duration of response was 27.6 months
- European/Israel analysis – Beyar-Katz et al, ASH 2024
  - 54 patients
  - ORR 65%, CR 50%
  - Median OS 14.4 months
  - For pts with CR/PR, median PFS was 24.6 months

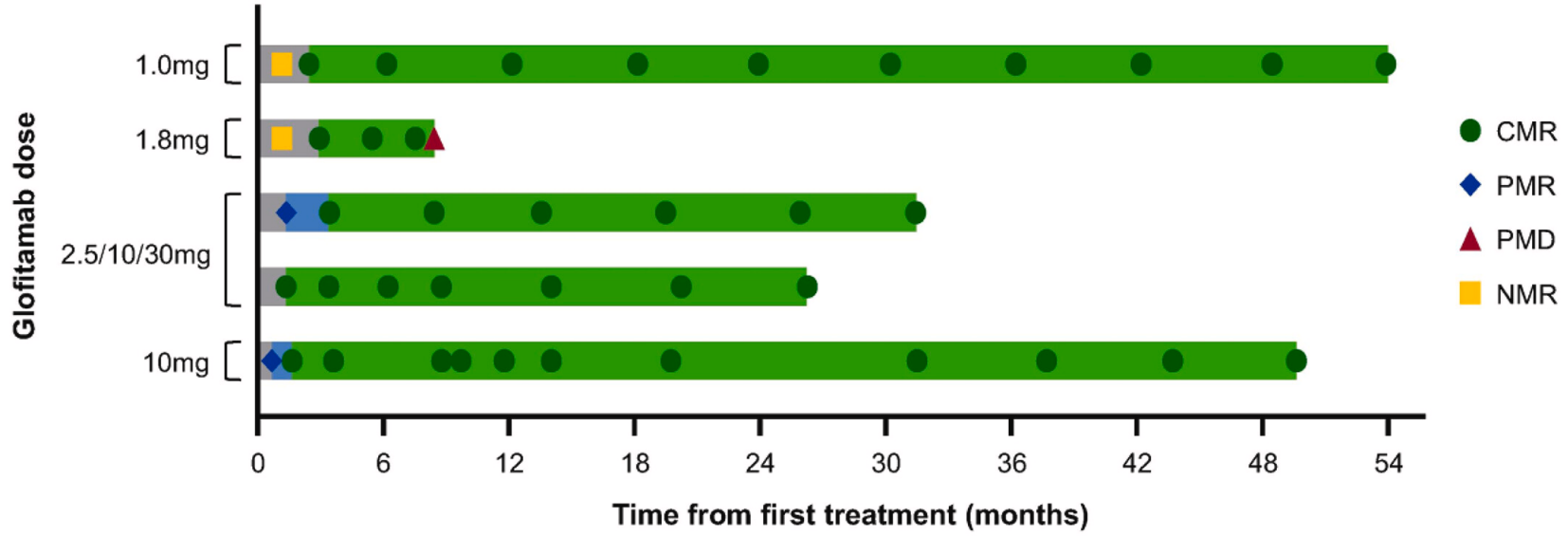
CAR-T cell Therapy

- Real world experience Liso-cel for Richter (Winter et al, ASCO 24)
  - 30 patients
  - ORR 76%
  - CR 66%
  - Median DOR not reached. 12-month DOR 77%
  - 12 months PFS 54%
  - 12 months OS 67%

Bispecific antibodies

- Glofitamab – Carlo-Stella et al, ICML 2023
  - 12 cycles with Obinutuzumab pre-treatment in cycle 1
  - ORR 63.3%; CR 45.5%
  - 80% of CRs were ongoing at 2 years data cut

Figure: Durability of complete response in patients with Richter's transformation who received glofitamab monotherapy.



CMR, complete metabolic response; NMR, no metabolic response; PMD, progressive metabolic disease; PMR, partial metabolic response.

Bispecific antibodies

- Epcoritamab – RS cohort of EPCORE-CLL-1 (Kater et al, SOHO 2024, EHA 2024)
  - 2 or less prior lines of therapy for RS
  - SQ epcoritamab until progression

Baseline Characteristics

Characteristic	Total N=42
Median age, y (range)	69 (50–80)
Male, n (%)	32 (76)
Ann Arbor stage, n (%)[a]	
I	2 (5)
II	1 (2)
III	**15 (36)**
IV	**23 (55)**
TP53 aberration	
Yes[b]	**19 (45)**
No[c]	13 (31)
Missing	10 (24)
Median time from initial CLL/SLL diagnosis to disease transformation, y (range)	8 (0–23.9)
Median time from disease transformation to first dose, mo (range)	2 (0.4–86.5)

Characteristic	Total N=42
Prior CLL/SLL or RT therapy, n (%)[d]	**40 (95)**
Median number of prior lines of CLL/SLL therapy (range)[e]	**2 (1–7)**
Prior CLL/SLL therapy, n (%)	**31 (74)**
Chemoimmunotherapy, n/n (%)	23/31 (74)
Targeted agents, n/n (%)	23/31 (74)
BCL-2 inhibitor, n/n (%)	17/31 (55)
BTK inhibitor, n/n (%)	21/31 (68)
CAR T-cell therapy, n/n (%)	1/31 (3)
Prior RT therapy, n (%)	**20 (48)**
Chemoimmunotherapy, n/n (%)[f]	20/20 (100)
R-CHOP, n/n (%)	15/20 (75)
Targeted agents, n/n (%)	8/20 (40)
BCL-2 inhibitor, n/n (%)	4/20 (20)
BTK inhibitor, n/n (%)	6/20 (30)

CAR, chimeric antigen receptor; CVAD, cyclophosphamide, vincristine, doxorubicin, and dexamethasone. [a]Ann Arbor stage was missing for 1 patient. [b]*TP53* mutated or del17p positive. [c]Both *TP53* unmutated and del17p negative. [d]Two patients had neither prior CLL/SLL therapy nor prior RT therapy. [e]Among 31 patients who received prior CLL/SLL therapy. [f]Two patients received R-EPOCH and 1 patient received hyper-CVAD.

Best Overall Response and by Line of Therapy

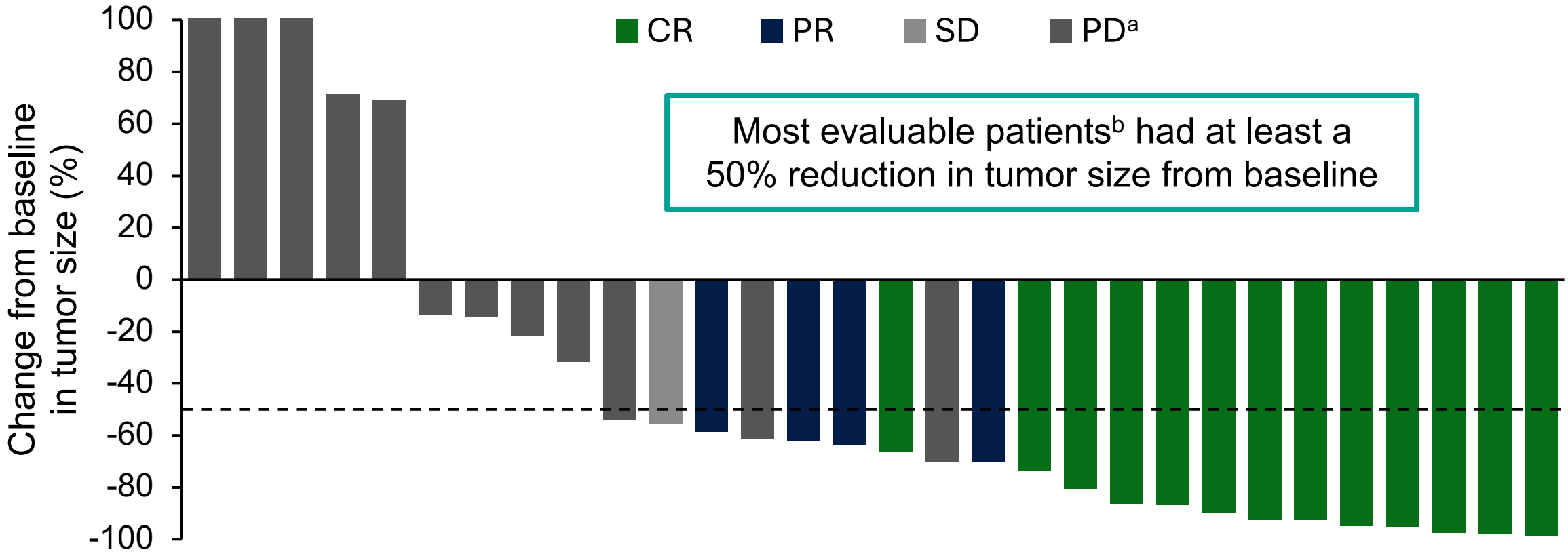
Response, n (%)[a]	Total Efficacy Evaluable n=38[b]	1L RT n=20	2L+ RT n=18
Overall response	**20 (53)**	**12 (60)**	**8 (44)**
Complete response	16 (42)	10 (50)	6 (33)
Partial response	4 (11)	2 (10)	2 (11)
Stable disease	1 (3)	0	1 (6)
Progressive disease	14 (37)	6 (30)	8 (44)

Median follow-up: 12.9 mo (range, 0.5+ to 28.6). [a]Based on modified response-evaluable population, defined as patients with ≥1 target lesion at baseline and ≥1 postbaseline response evaluation and/or patients who died within 60 d of first dose. Response assessment according to Lugano 2014 criteria. [b]Three patients died without postbaseline assessment (2 in the 1L RT population and 1 in the 2L+ RT population).

High response rates observed, particularly in 1L RT patients

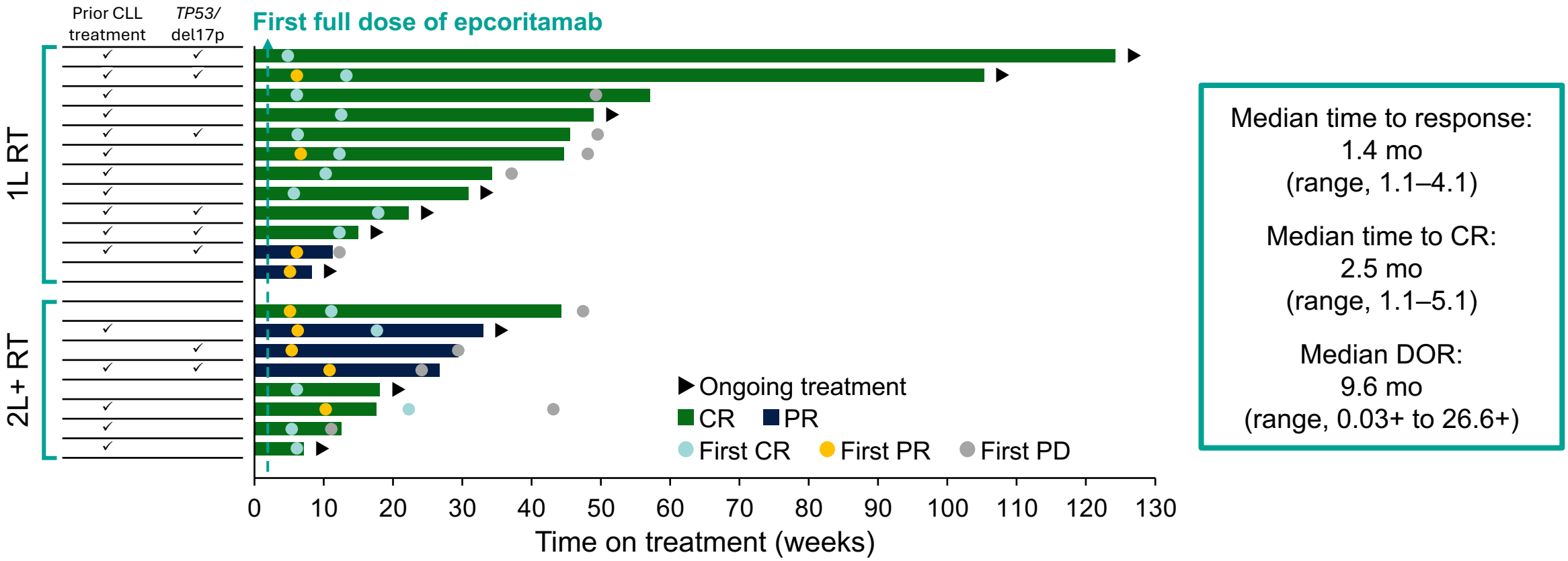
1L, previously untreated; 2L+, second line or later.

Best Tumor Reduction From Baseline



Response assessed using PET-CT per Lugano criteria.[1] CR was complete metabolic response. PD, progressive disease; PR, partial response; SD, stable disease. [a]Patients with a reduction in tumor size may have had new lesions per PET-CT. [b]Includes patients evaluable for postbaseline sum of perpendicular diameters. **1.** Cheson BD, et al. *J Clin Oncol.* 2014;32:3059-68.

Responses Occurred Early and Are Ongoing in Most 1L RT Patients



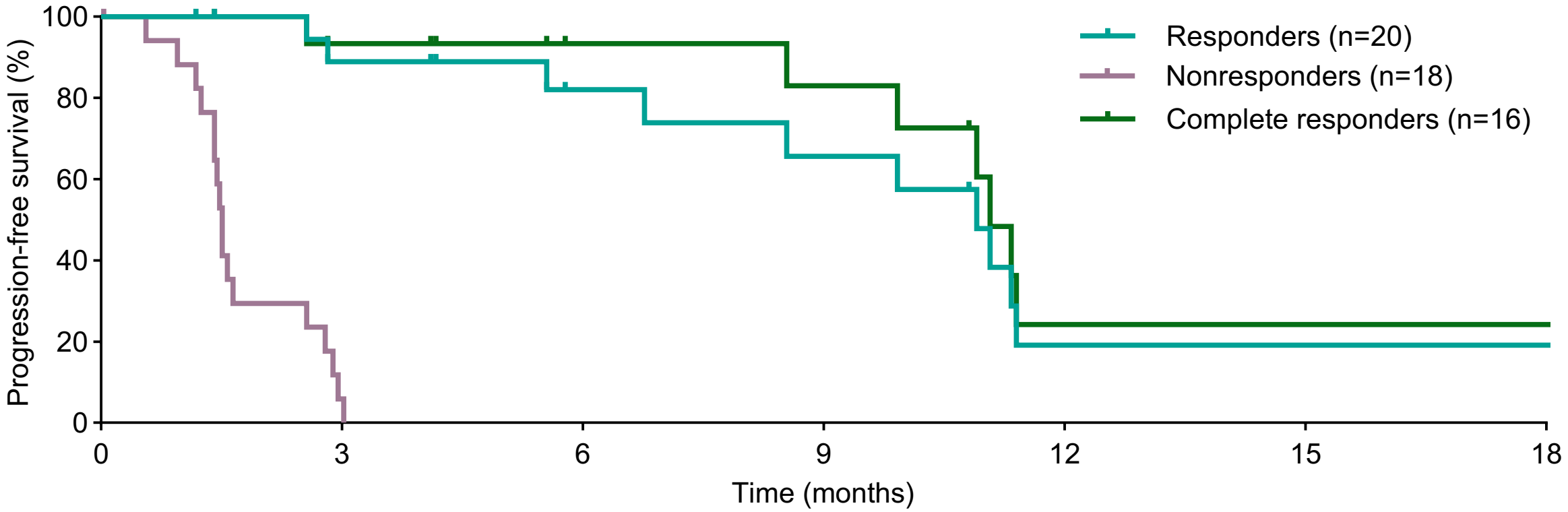
Median time to response:
1.4 mo
(range, 1.1–4.1)

Median time to CR:
2.5 mo
(range, 1.1–5.1)

Median DOR:
9.6 mo
(range, 0.03+ to 26.6+)

Median follow-up: 12.9 mo (range, 0.5+ to 28.6). Median number of treatment cycles initiated (range): 3 (1–32). Median duration of treatment (range): 2.7 mo (0.3–28.6). Tumor response was evaluated by PET-CT obtained Q6W until week 24, and then Q24W until disease progression. Per protocol, patients continued to receive scans if they discontinued treatment for reasons other than PD. Patient characteristics are shown at left. DOR, duration of response.

Progression-Free Survival

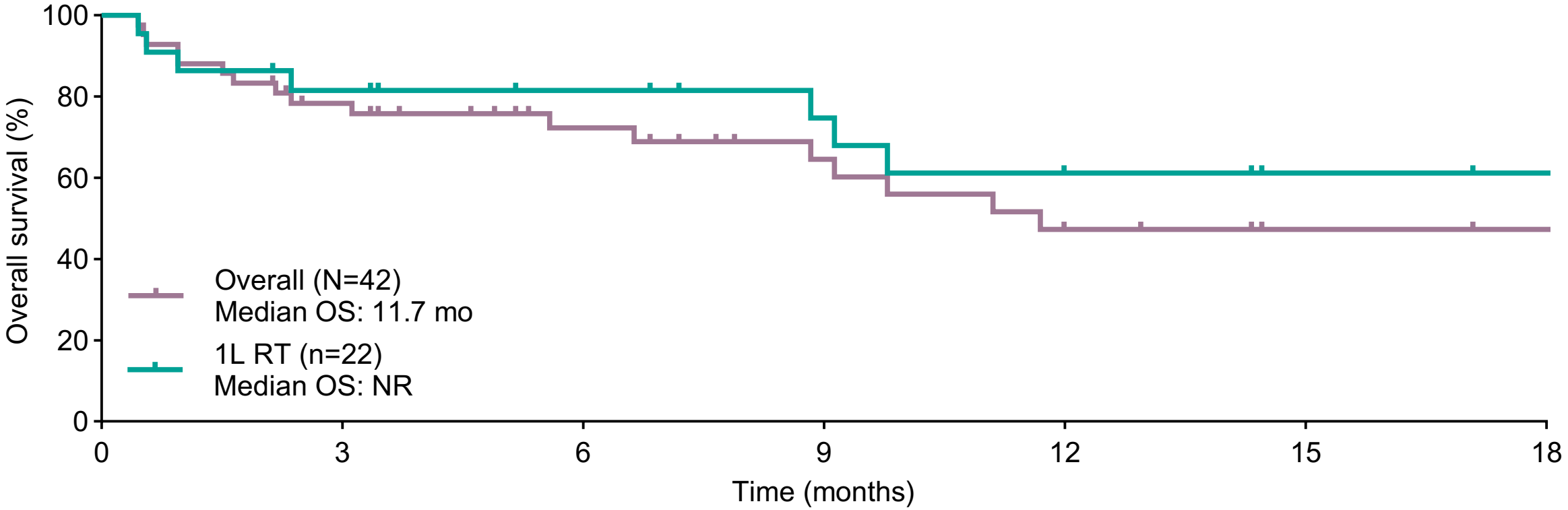


Number at risk

20	15	10	8	2	2	2
18	1	0				
16	13	9	8	2	2	2

Median follow-up: 12.9 mo (range, 0.5+ to 28.6). Median progression-free survival for the overall population was 2.9 months.

Overall Survival



Number at risk

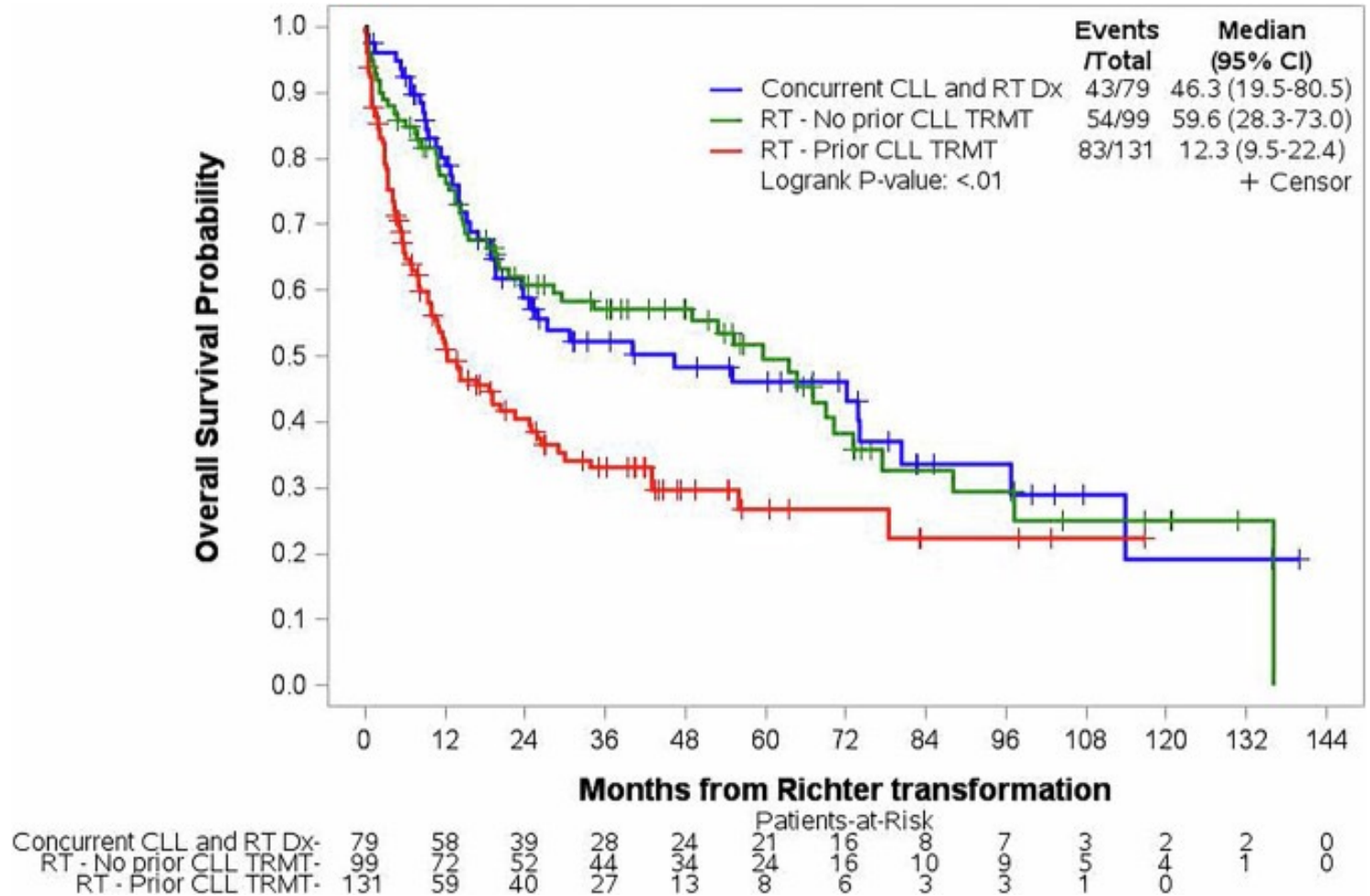
42	30	21	15	10	7	6
22	17	14	11	8	6	5

Median follow-up: 12.9 mo (range, 0.5+ to 28.6). Eighteen patients had subsequent therapy; of these, 4 patients had allogeneic stem cell transplant and 2 patients received CAR T. NR, not reached; OS, overall survival.

Outcomes of patients with Richter transformation who received no prior chemoimmunotherapy for their CLL
Kittai et al, Blood Cancer J 2025

- No study has focused on RT that has developed without prior CIT
- Important to evaluate RS that develops in patients who have only received targeted therapies
- Retrospective, 309 patients included in 3 categories:
  - Concurrent CLL and RT diagnosis (both diagnosed within 3 months) -25%
  - RT-No prior CLL treatment (CLL and RT diagnosed more than 3 months apart, but no CLL therapy) – 32%
  - RT-Prior CLL treatment (prior CLL therapy with targeted agents only)-42%

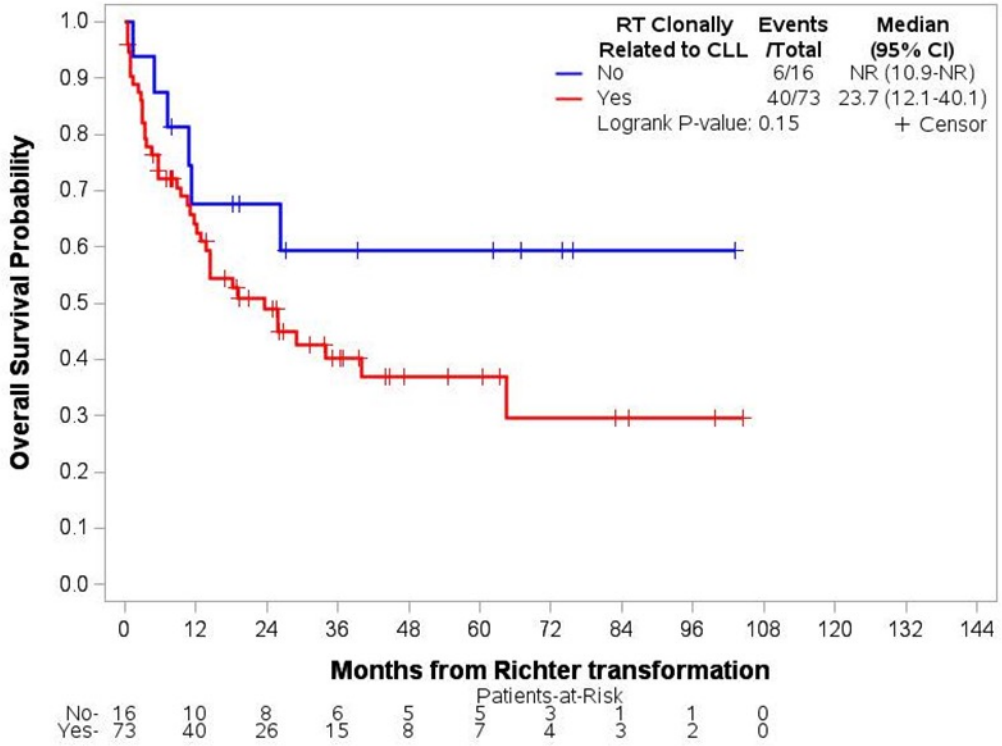
- Median time to RT diagnosis
  - 50.4 months for RT-no prior CLL treatment
  - 54.4 months for RT-prior CLL treatment
- 29% had clonal relationship tested, with 82% had clonally related disease
  - Median OS for patients with clonally-unrelated RT was not reached
  - Median OS for clonally related RT was 23.7 months


Overall Survival Probability
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
Events /Total
Median (95% CI)
Concurrent CLL and RT Dx 43/79 46.3 (19.5-80.5)
RT - No prior CLL TRMT 54/99 59.6 (28.3-73.0)
RT - Prior CLL TRMT 83/131 12.3 (9.5-22.4)
Logrank P-value: <.01
+ Censor
0 12 24 36 48 60 72 84 96 108 120 132 144
Months from Richter transformation
Patients-at-Risk
Concurrent CLL and RT Dx- 79 58 39 28 24 21 16 8 7 3 2 2 0
RT - No prior CLL TRMT- 99 72 52 44 34 24 16 10 9 5 4 1 0
RT - Prior CLL TRMT- 131 59 40 27 13 8 6 3 3 1 0

- 74.5% of patients received CIT as treatment
- 13.9% received CIT + targeted therapy
- 6.8% received targeted therapy without CIT
- Patients in the RT-prior CLL treatment group had lower ORR (57.8%) to treatment than the other groups (ORR 84%)

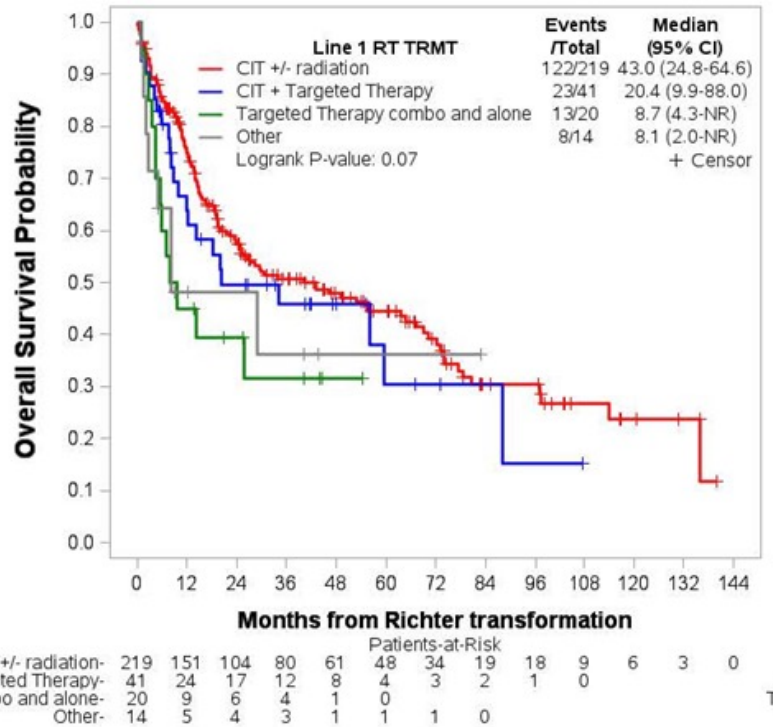
Overall Cohort (n=294)[1]					
	CIT +/- radiation (n=219)	CIT + Targeted Therapy (n=41)	Targeted Therapy combo and alone (n=20)	Other[3] (n=14)	p-valu
Response, N (%)					
CR	115 (55.0%)	21 (51.2%)	2 (11.1%)	4 (33.3%)	
PR	38 (18.2%)	8 (19.5%)	3 (16.7%)	2 (16.7%)	
SD	6 (2.9%)	0 (0.0%)	5 (27.8%)	0 (0.0%)	0.000
PD	42 (20.1%)	10 (24.4%)	6 (33.3%)	3 (25.0%)	
Early Death[2]	8 (3.8%)	2 (4.9%)	2 (11.1%)	3 (25.0%)	
Unknown	10	0	2	2	
PFS					
Number of Events	128	24	14	8	
Median PFS in months	30.6	19.2	6.0	7.5	0.05
(95% CI)	(20.7-54.8)	(6.9-59.2)	(1.5-25.1)	(0.8-NR)	
Median Follow-up in months (range)	40.5 (0.9-139.7)	40.2 (4.1-106.9)	33.7 (13.3-53.8)	25.0 (4.7-82.3)	
OS					
Number of Events	122	23	13	8	
Median OS in months	43.0	20.4	8.7	8.1	0.07
(95% CI)	(24.8-64.6)	(9.9-88.0)	(4.3-NR)	(2.0-NR)	
Median Follow-up in months (range)	39.4 (1.1-139.9)	36.9 (5.3-107.6)	40.2 (13.7-54.4)	26.2 (5.0-83.0)	
RT – Prior CLL TRMT (n=122)[1]					
	CIT +/- radiation (n=74)	CIT + Targeted Therapy (n=20)	Targeted Therapy combo and alone (n=19)	Other[3] (n=9)	p-valu
Response, N (%)					
CR	33 (46.5%)	6 (30.0%)	2 (11.8%)	3 (37.5%)	
PR	14 (19.7%)	4 (20.0%)	3 (17.7%)	2 (25.0%)	
SD	2 (2.8%)	0 (0.0%)	5 (29.4%)	0 (0.0%)	0.04
PD	18 (25.4%)	8 (40.0%)	5 (29.4%)	2 (25.0%)	
Early Death[2]	4 (5.6%)	2 (10.0%)	2 (11.8%)	1 (12.5%)	
Unknown	3	0	2	1	
PFS					
Number of Events	48	14	13	5	
Median PFS in months	13.9	4.9	6.8	28.7	0.50
(95% CI)	(9.7-24.6)	(1.0-NR)	(2.2-NR)	(0.0-NR)	
OS					
Number of Events	45	13	12	5	
Median OS in months	19.2	9.9	9.5	29.1	0.71
(95% CI)	(11.7-29.9)	(2.9-NR)	(4.3-NR)	(1.4-NR)	

OS based on clonal relationship

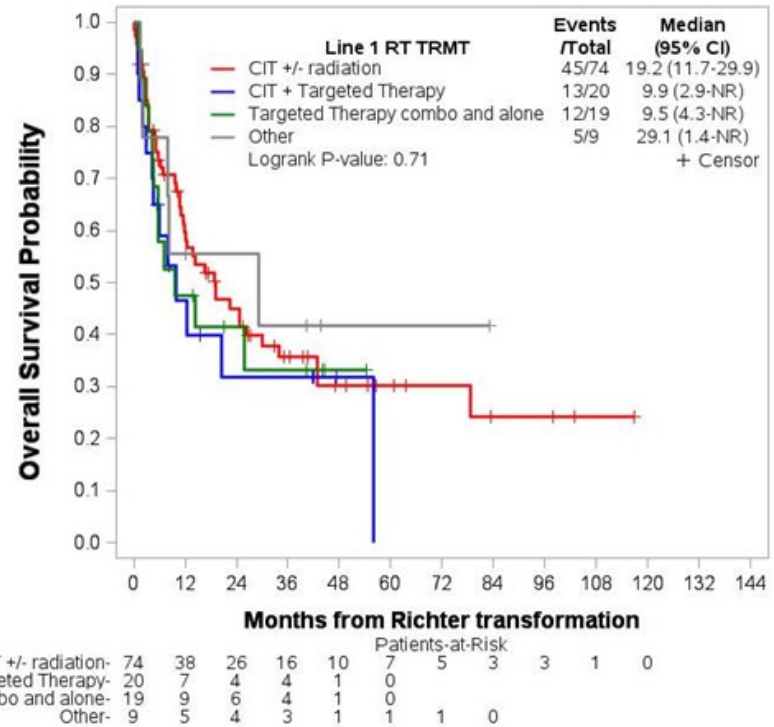


Overall Survival by first line of therapy. A) Entire Cohort. B) RT-Prior CLL treatment group.

A



B



- 46 patients received an allogeneic stem cell transplantation
  - median OS was 54.5 months from transplant
- 55 patients had CAR-T
  - ORR 62.7%
  - Median OS 9 months from CAR-T
- Median OS for entire cohort was 25.8 months
  - For patient who had received prior non-CIT treatment for CLL, median OS was 12.3 months

Allogeneic stem cell transplantation

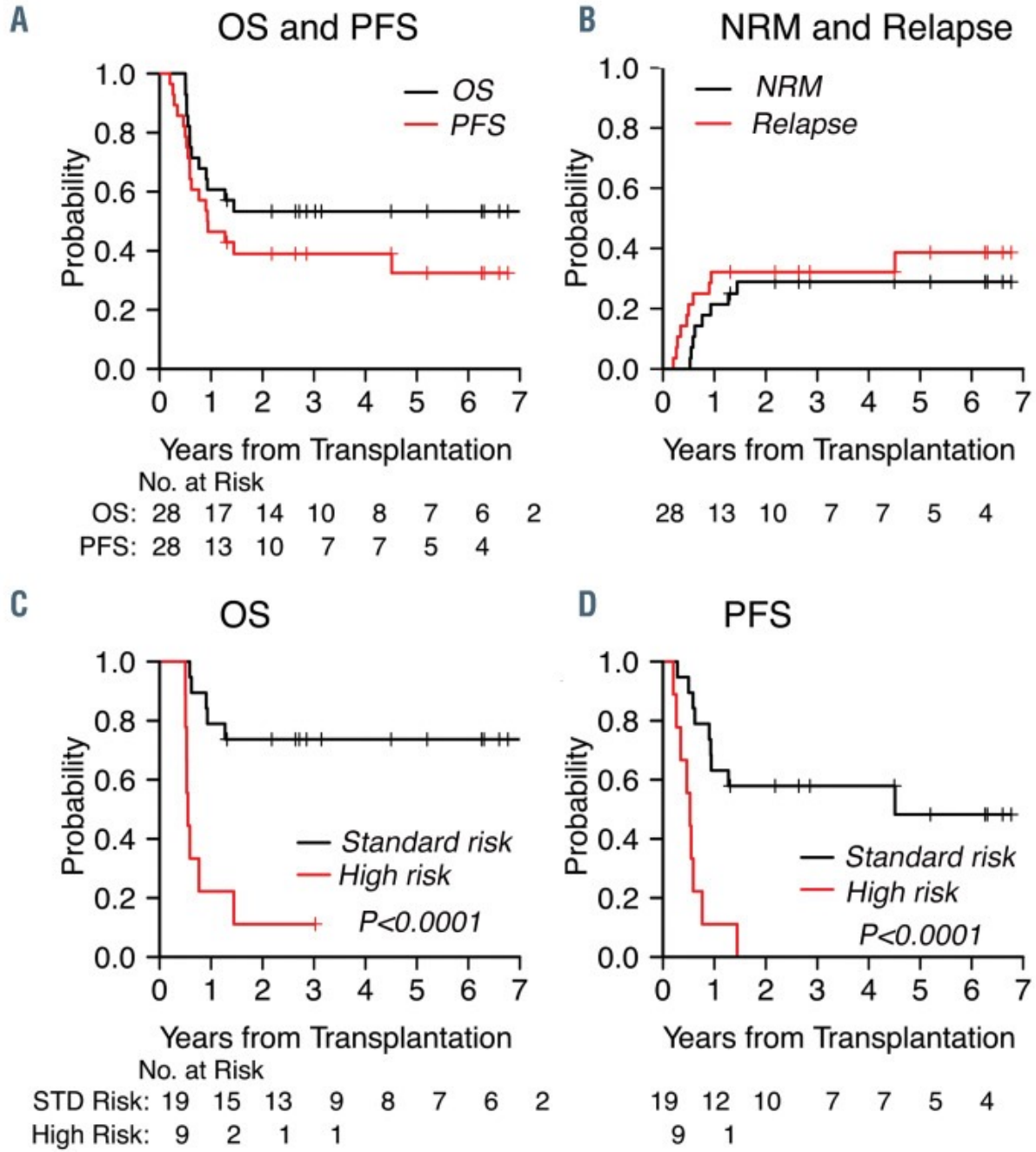
- Dana Farber experience (Kim et al, Haematologica 2021)

	All (N=28) (95% CI)	High Risk (N=9) (95% CI)	Standard Risk (N=19) (95% CI)	P	Age ≥65 (N=10) (95% CI)	Age<65 (N=18) (95% CI)	P
4-yr OS	53% (33-70)	11%* (0.6-39)	74% (48-88)	<0.0001	40% (12-67)	61% (35-79)	0.16
4-yr PFS	39% (21-56)	0%	58% (33-76)	<0.0001	10% (0.6-36)	55% (30-74)	0.006
4-yr NRM	29% (13-47)	33%* (5-67)	21% (6-42)	0.21	20% (2-50)	34% (13-56)	0.58
4-yr Relapse	32% (16-50)	56% (16-83)	21% (6-42)	0.054	70% (25-91)	11% (2-30)	0.007
6 mo. Grade 2-4 aGvHD	36% (19-54)	56% (17-82)	21% (6-42)	0.013			
6 mo. Grade 2-4 aGvHD	18% (6-34)	37% (6-71)	11% (1.7-29)	0.12			
2 yr cGvHD	52% (30-70)	25% (2.5-60)	61% (33-80)	0.43			

	OS HR (95% CI)	PFS HR (95% CI)	NRM sHR (95% CI)	Relapse sHR (95% CI)
Grade II-IV aGvHD	3.94 (1.36-12.4)	2.05(0.8-5.09)	7.36 (1.59-34)	0.53 (0.1-2.81)
P	0.016	0.13	0.01	0.45

Log-rank was used for comparisons of overall survival (OS) and progression-free survival (PFS). Gray test was used for comparisons of non-relapse mortality (NRM), relapse and graft-*versus*-host disease (GvHD). The table presents results of univariable analysis for the effect of grade 2-4 acute GvHD (aGvHD) on outcomes. Cox model was used for OS and PFS and cause-specific Cox model was used for NRM and relapse. Occurrence of grade 2-4 aGvHD was treated as a time dependent variable. HR: hazard ratio; CI: confidence interval; mo: months; yr: years; cGvHD: chronic GvHD. *8-year estimate as the last patient in this cohort was censored at 96.3 months.

High-risk defined as High LDH + Thrombocytopenia

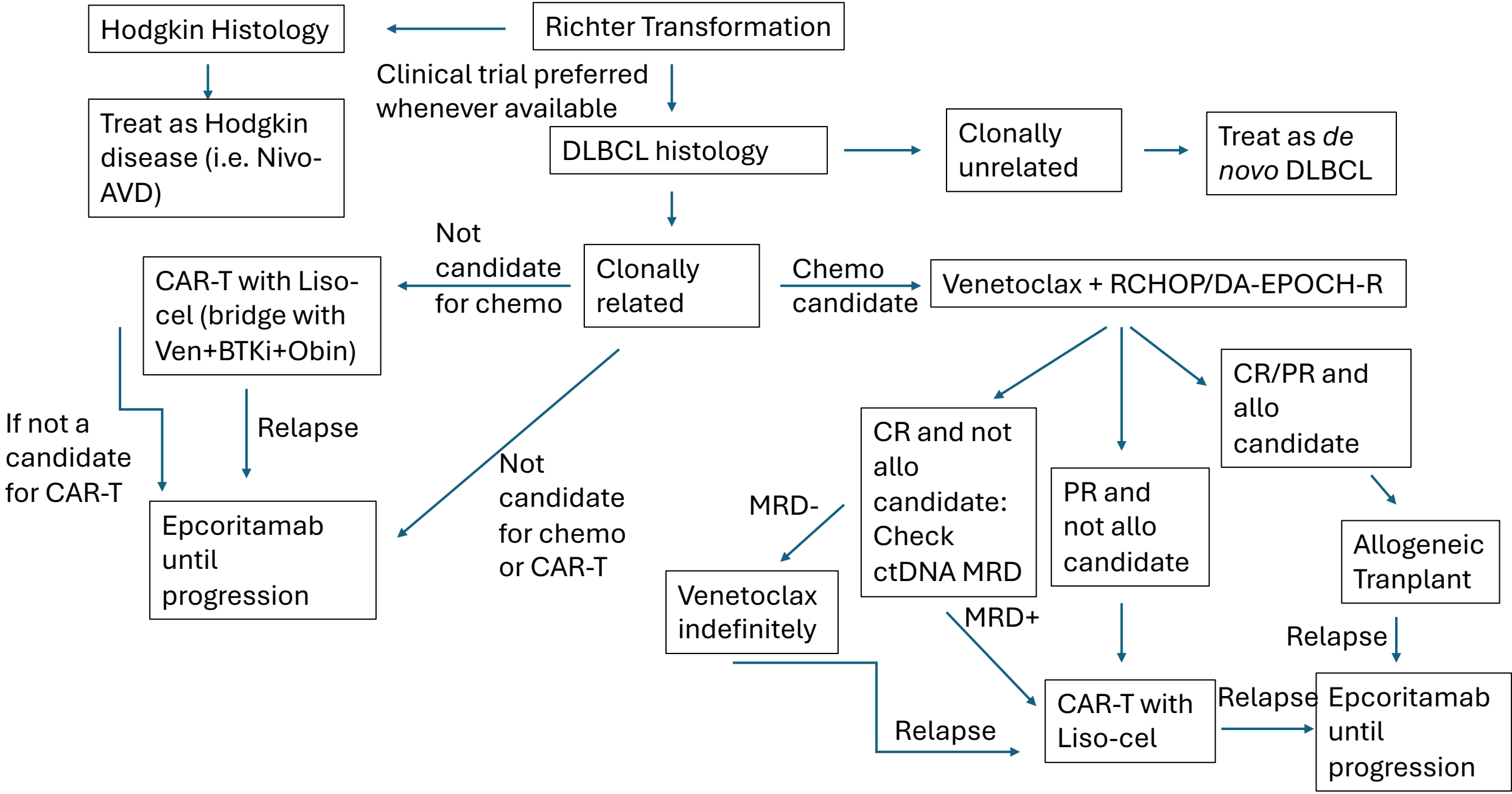


Kim et al, Haematologica 2021

Allogeneic Stem Cell Transplantation

- EBMT experience (Guieze et al, Bone Marrow Transpl 2024)
- 66 patients undergoing allo between 2008-2018
- 42% in CR at time of transplant
- 3 year PFS and OS: 29% and 39%
- Patients in CR at transplant had better PFS (39% vs. 21%, $p = 0.032$)
- 38% NRM at 3 years

How I treat Richter Syndrome


Hodgkin Histology
Richter Transformation
Clinical trial preferred whenever available
Treat as Hodgkin disease (i.e. Nivo-AVD)
DLBCL histology
Clonally unrelated
Treat as *de novo* DLBCL
Not candidate for chemo
Clonally related
Chemo candidate
Venetoclax + RCHOP/DA-EPOCH-R
CAR-T with Liso-cel (bridge with Ven+BTKi+Obin)
If not a candidate for CAR-T
Relapse
Not candidate for chemo or CAR-T
Epcoritamab until progression
CR and not allo candidate: Check ctDNA MRD
PR and not allo candidate
CR/PR and allo candidate
MRD-
Venetoclax indefinitely
MRD+
Allogeneic Tranplant
Relapse
Relapse
CAR-T with Liso-cel
Relapse
Epcoritamab until progression