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# Richter's Transformation: the most important advances

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# Disclosures

AstraZeneca – Research funding, advisory board participation, speaking engagements

Abbvie – Advisory board participation

BeiGene – Research funding

BMS – Consulting

Eli Lilly – Advisory board participation, speaking engagements

Janssen – Speaking engagements

Galapagos – Advisory board participation

# Agenda

Is the incidence of RT really decreasing?

Have we made improvements in the survival of RT since the development of targeted agents?

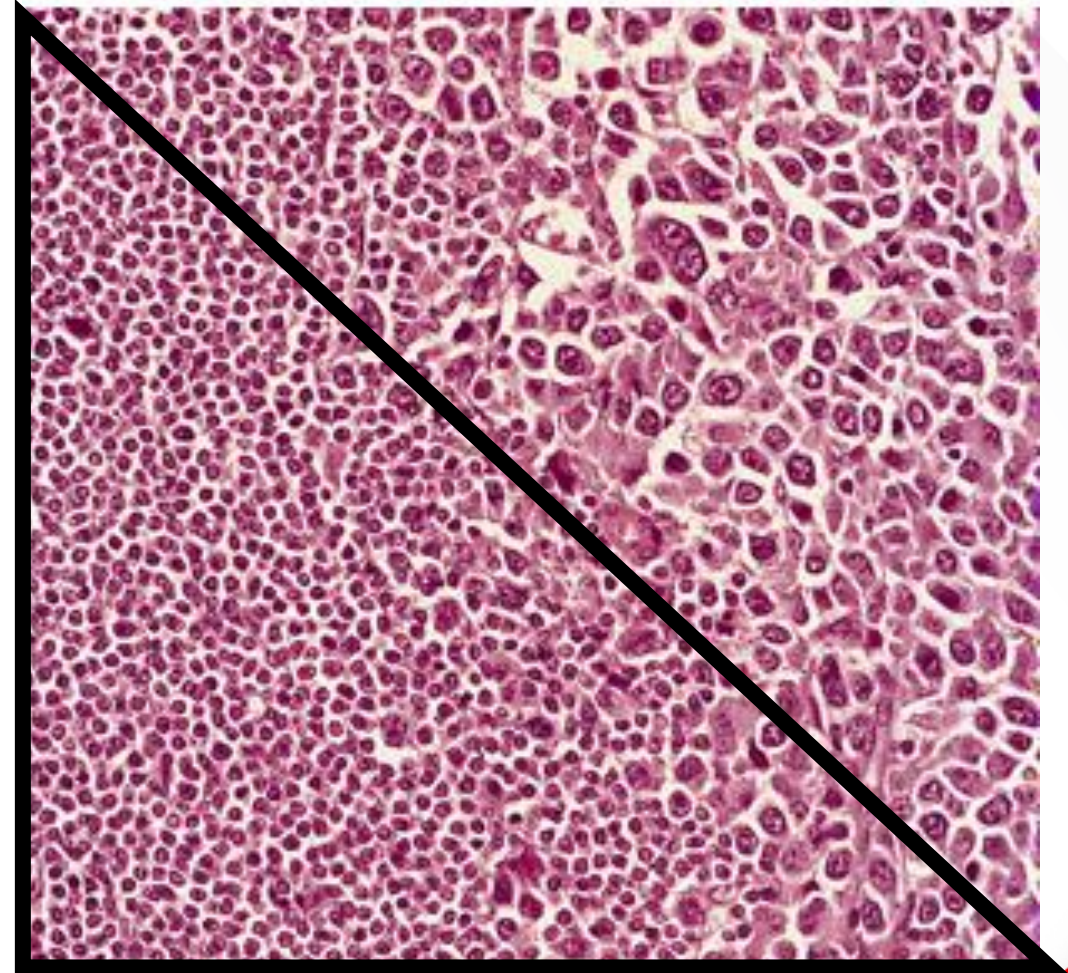
My TN approach

CART for RT

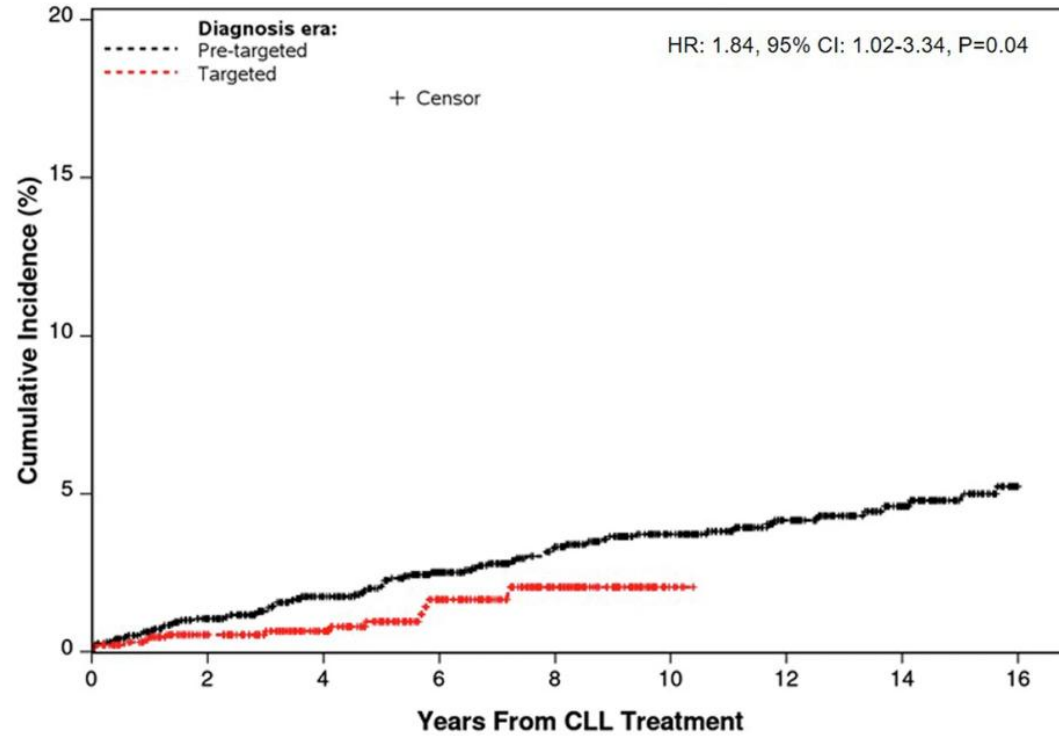
Can we get on the same page on the study of RT?

# What is Richter Transformation (RT)?

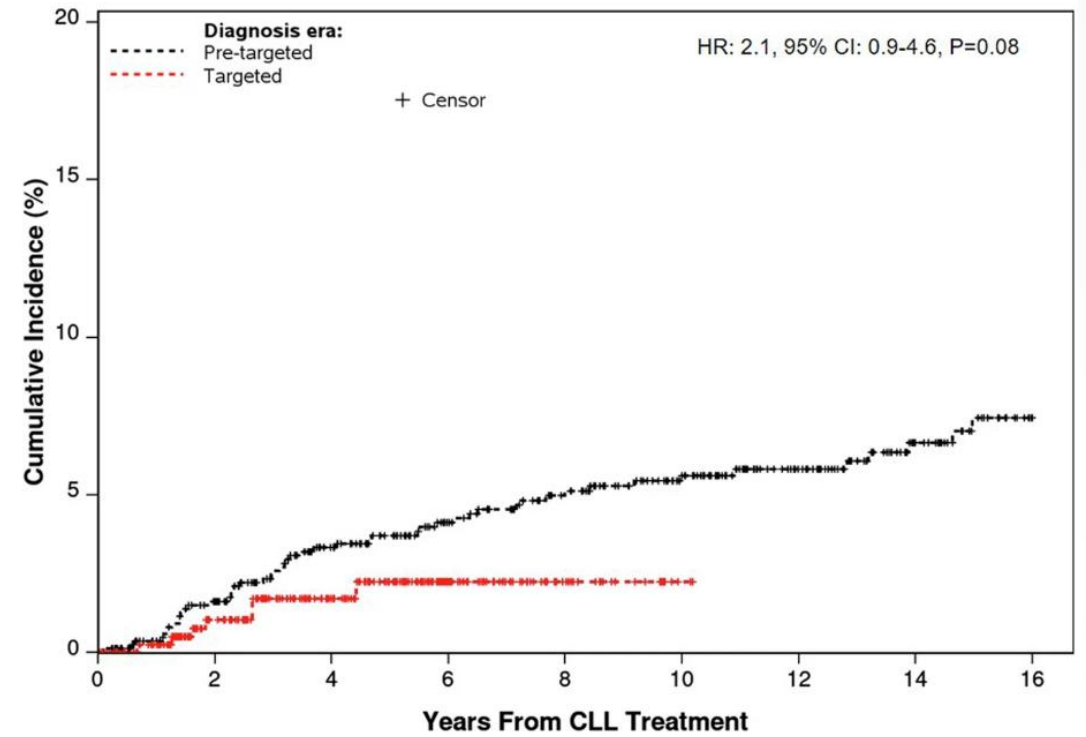
- RT: Diffuse Large B-Cell lymphoma occurring in the setting of CLL
- It can either be:
  - Clonally related – CLL turns into DLBCL
  - Clonally unrelated – DLBCL in a patients with CLL



# Incidence of RT appears to be declining



Pre-targeted	1975	1710	1518	1325	1162	962	705	473	308
Targeted	1362	1059	661	360	150	15	0		



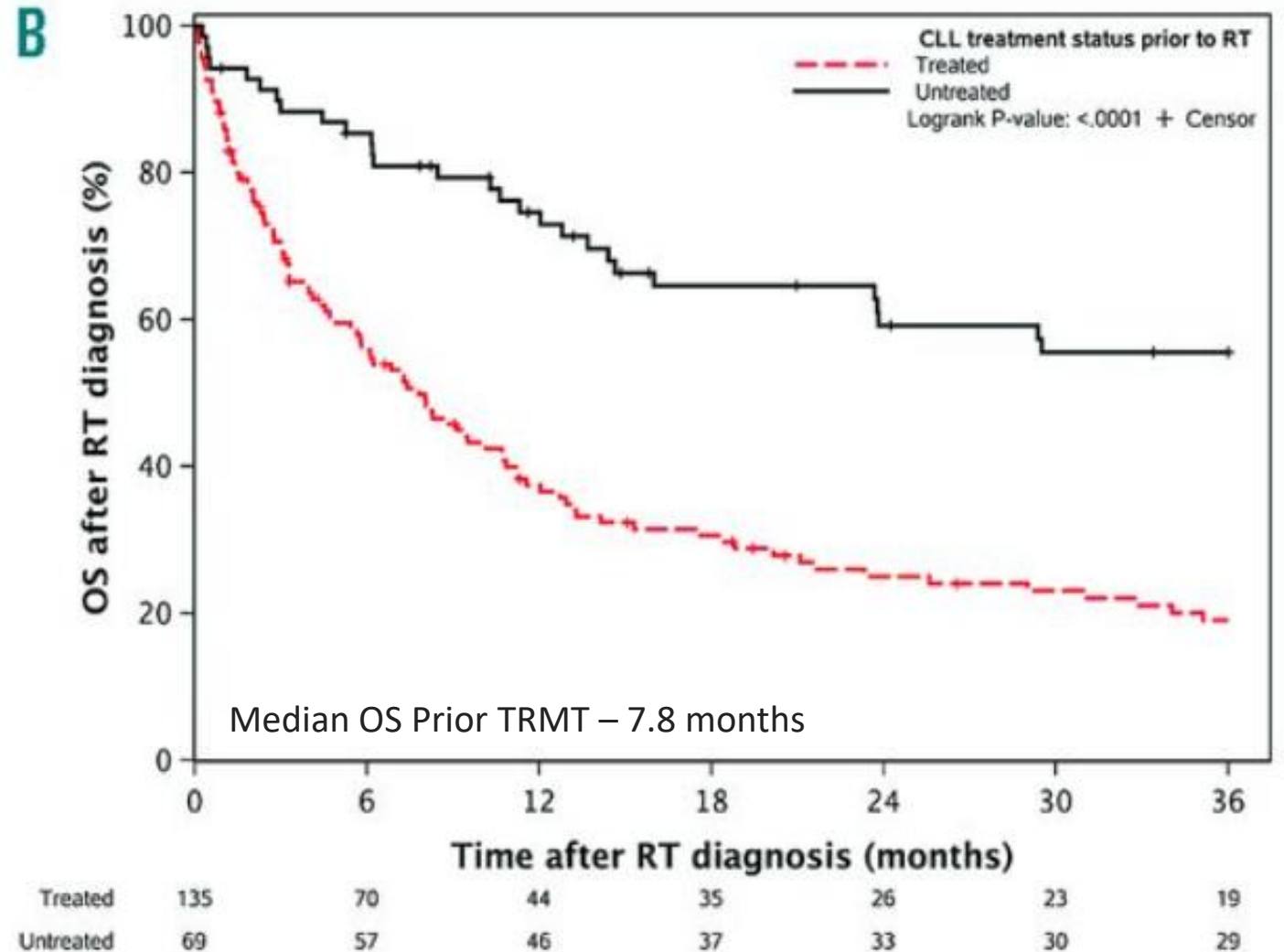
Pre-targeted	893	731	589	475	387	282	189	109	50
Targeted	475	314	176	78	26	2	0		

# Outcomes of RT before modern era

N=204

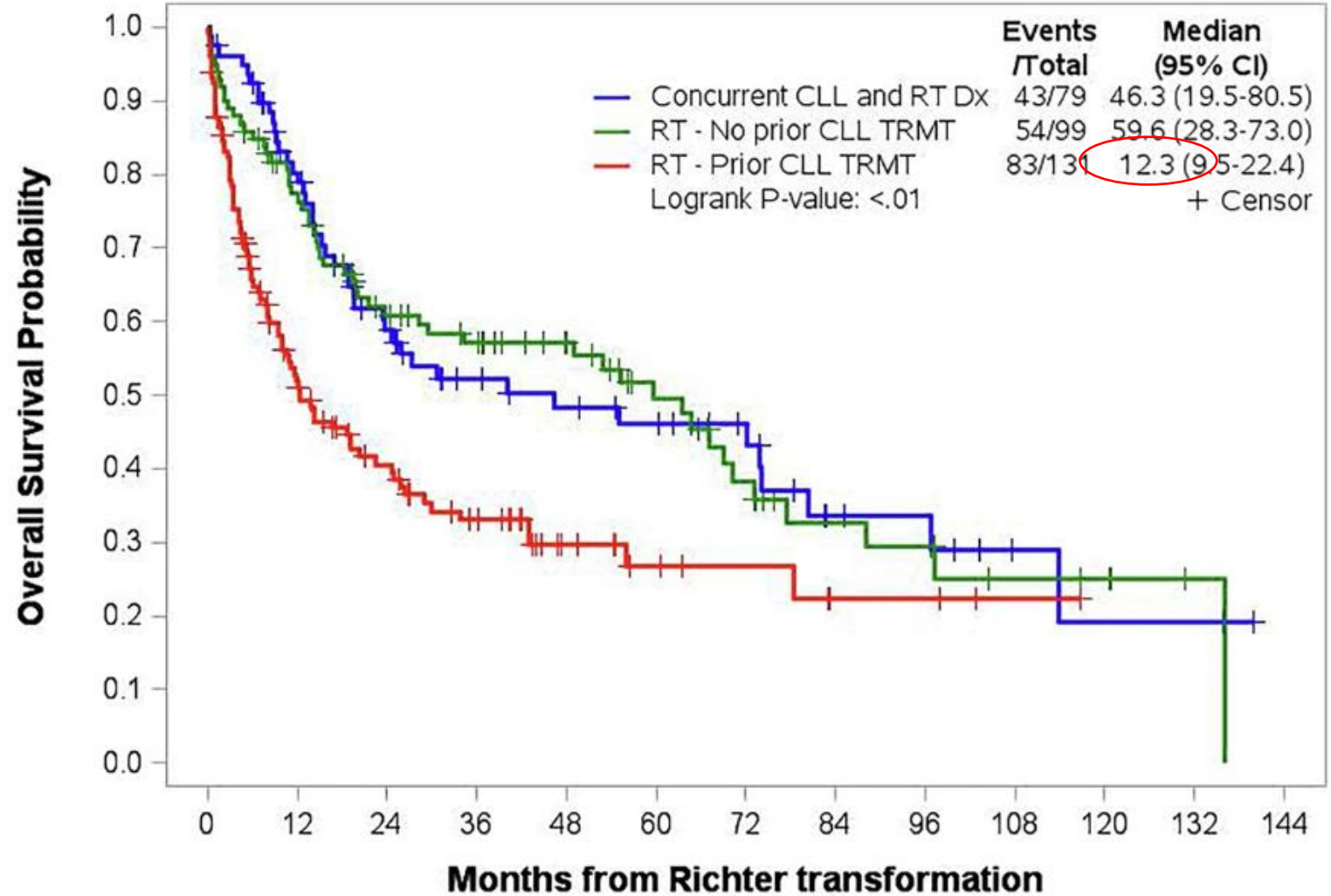
Median follow-up time - 67 months  
-mOS – 12 months

27 patients received prior novel agent



# Outcomes of RT in the modern era of therapy

N=409  
 Median follow-up time - 39.4  
 -mPFS - 25.1 months  
 -mOS – 25.8 months

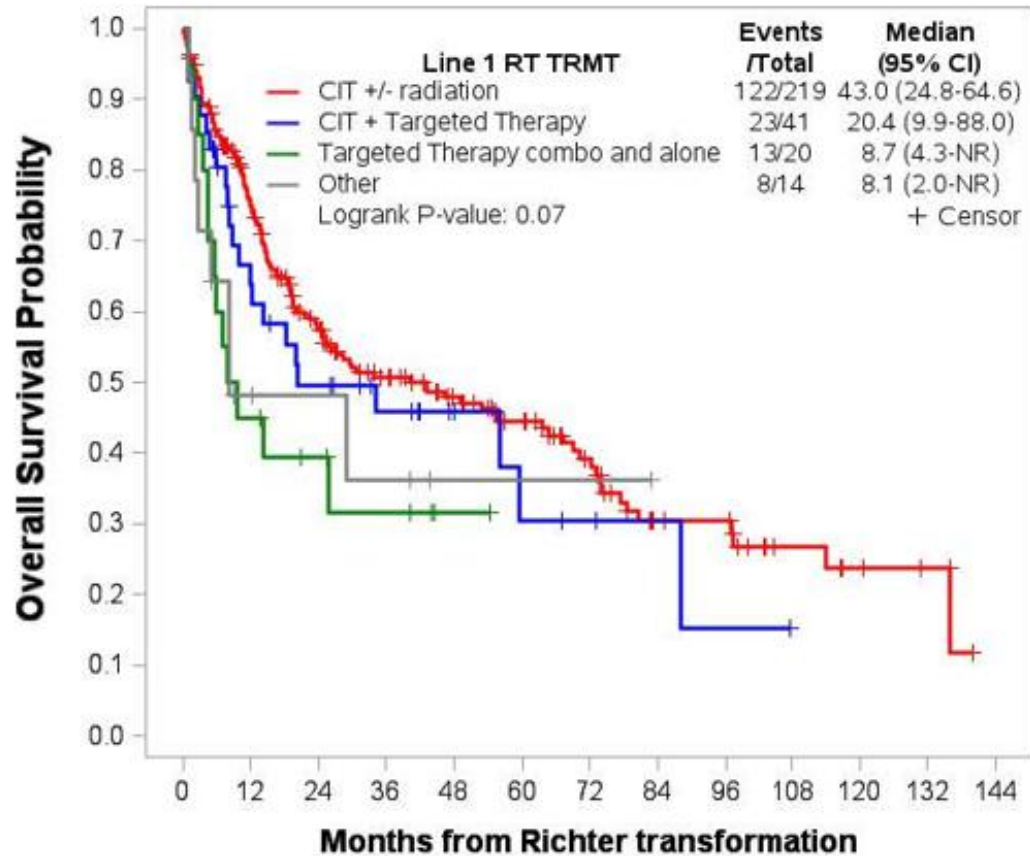


	0	12	24	36	48	60	72	84	96	108	120	132	144
Concurrent CLL and RT Dx-	79	58	39	28	24	21	16	8	7	3	2	2	0
RT - No prior CLL TRMT-	99	72	52	44	34	24	16	10	9	5	4	1	0
RT - Prior CLL TRMT-	131	59	40	27	13	8	6	3	3	1	0		

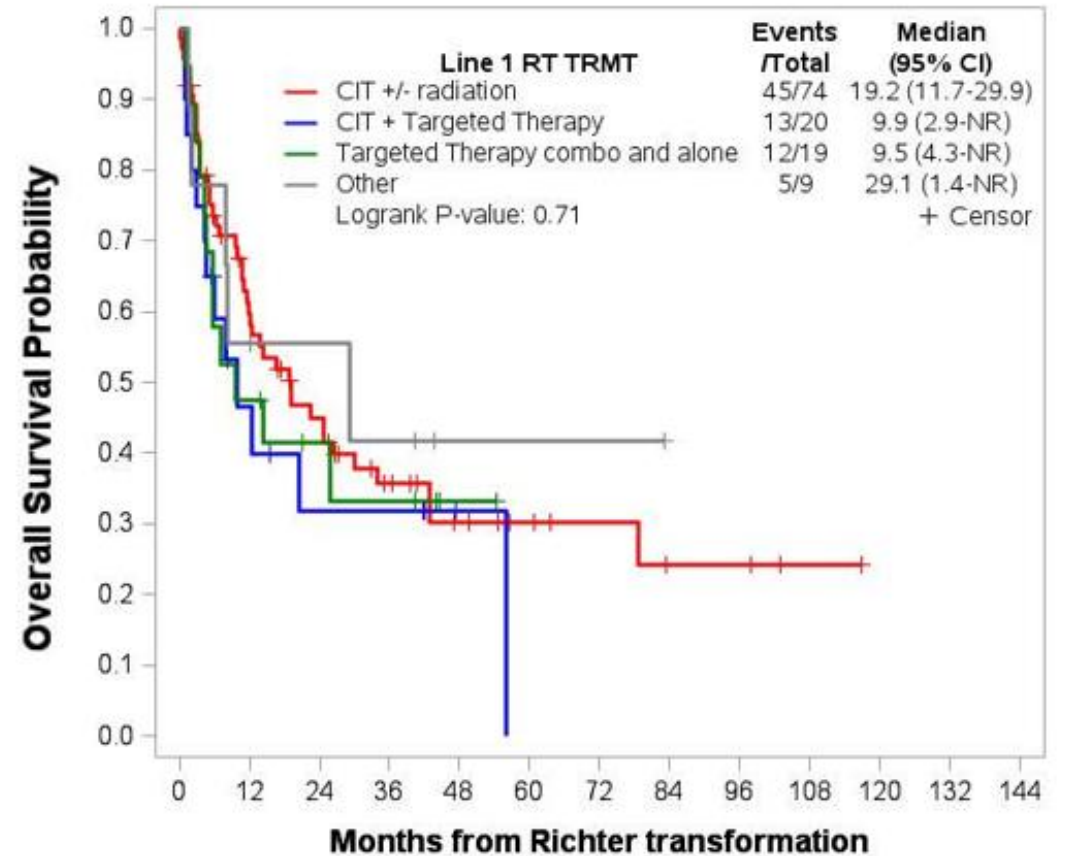
Patients-at-Risk

# Any treatments particularly well in this cohort?

### Entire Cohort



### CLL Treated Cohort



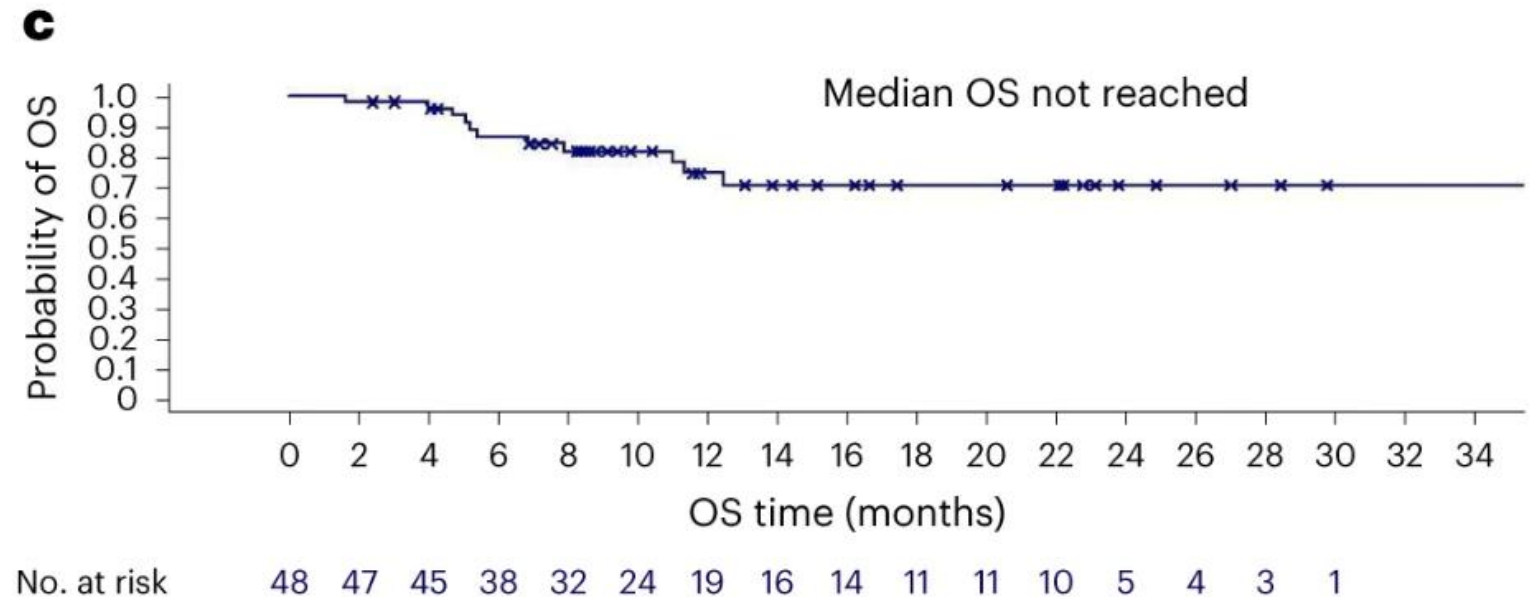
## My treatment approach

### Clinical trial #1

Pick something other than just RCHOP if you can.

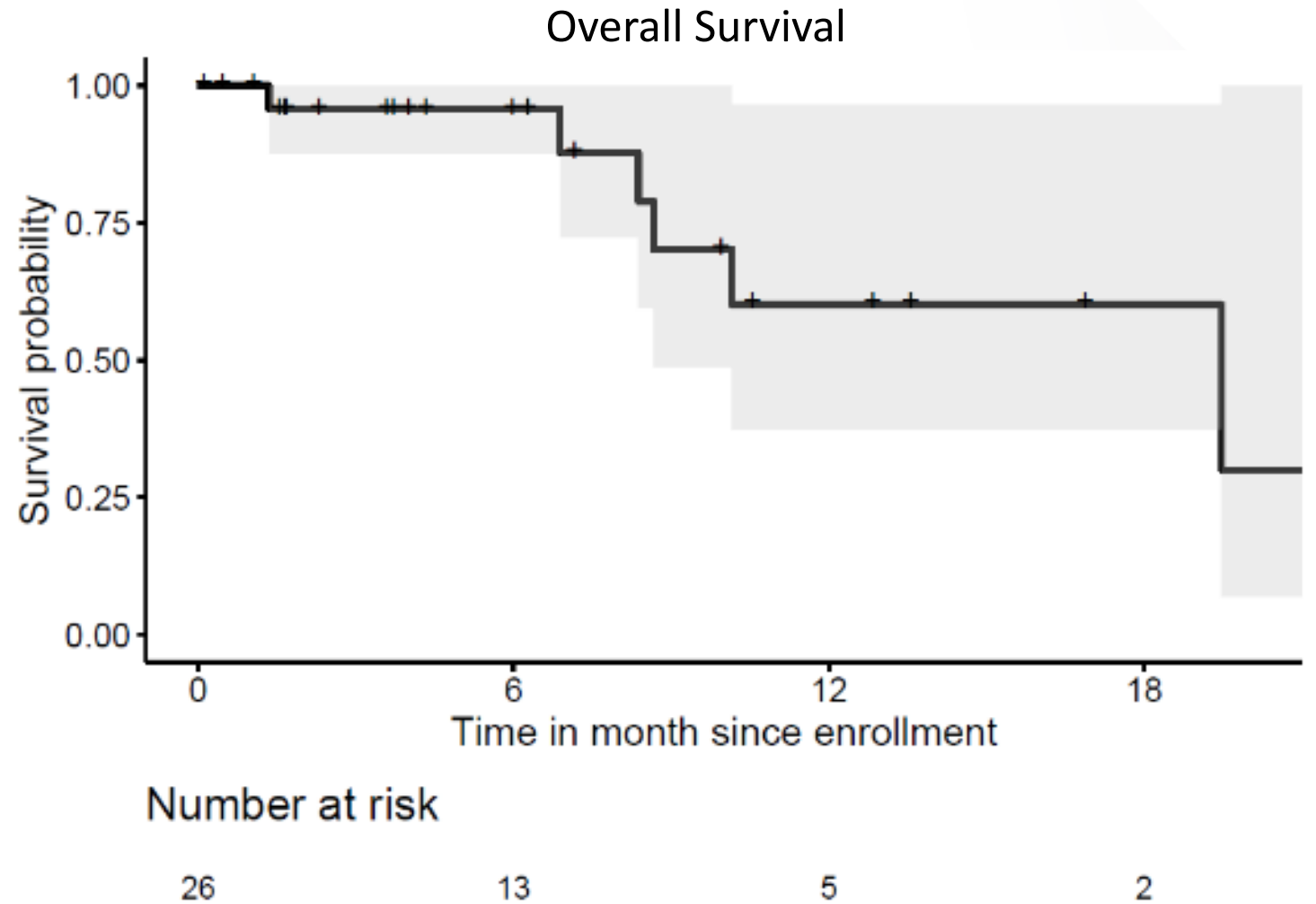
# Zanubrutinib + Tislelizumab

- N = 59 Patients
- Untreated CLL – 25%
- Untreated RT – 20.8%
  
- ORR - 58.3%
  - 18.8% CR
- Median follow up 13.9 months
  - Median OS NR



# Venetoclax + RCHOP

- N=26
- ≥Gr 3 heme toxicity:
  - neutropenia (36%)
  - anemia (32%)
  - thrombocytopenia (40%)
  - febrile neutropenia (32%)
- 3 pts have died due to infection



# Pirtobrutinib

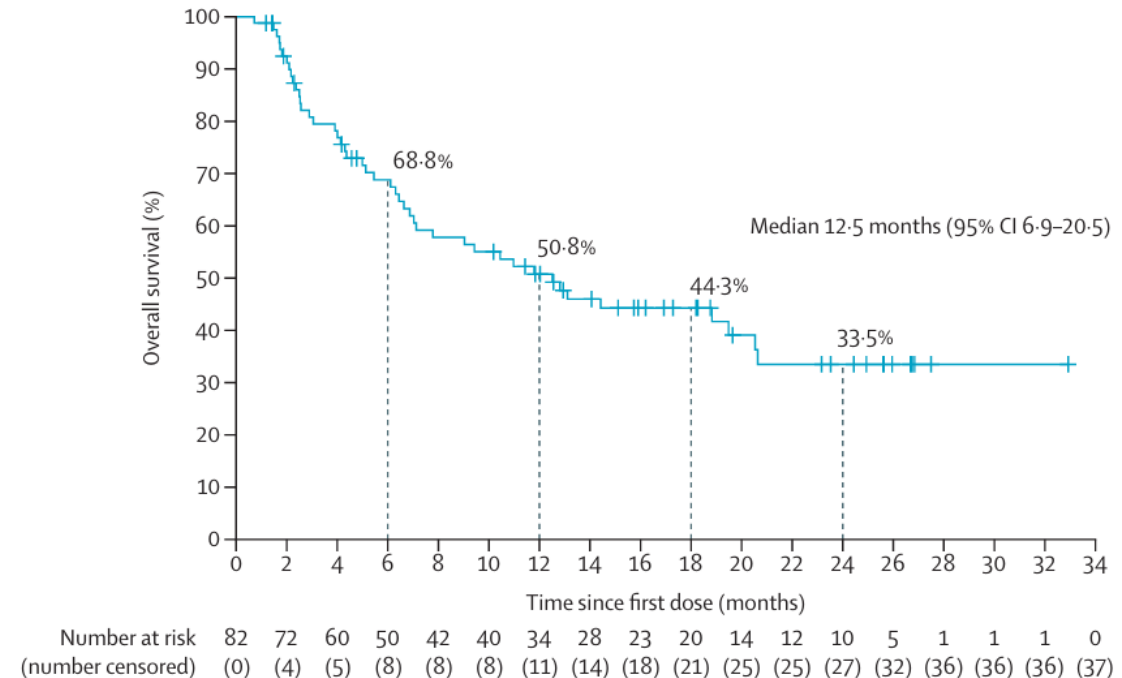
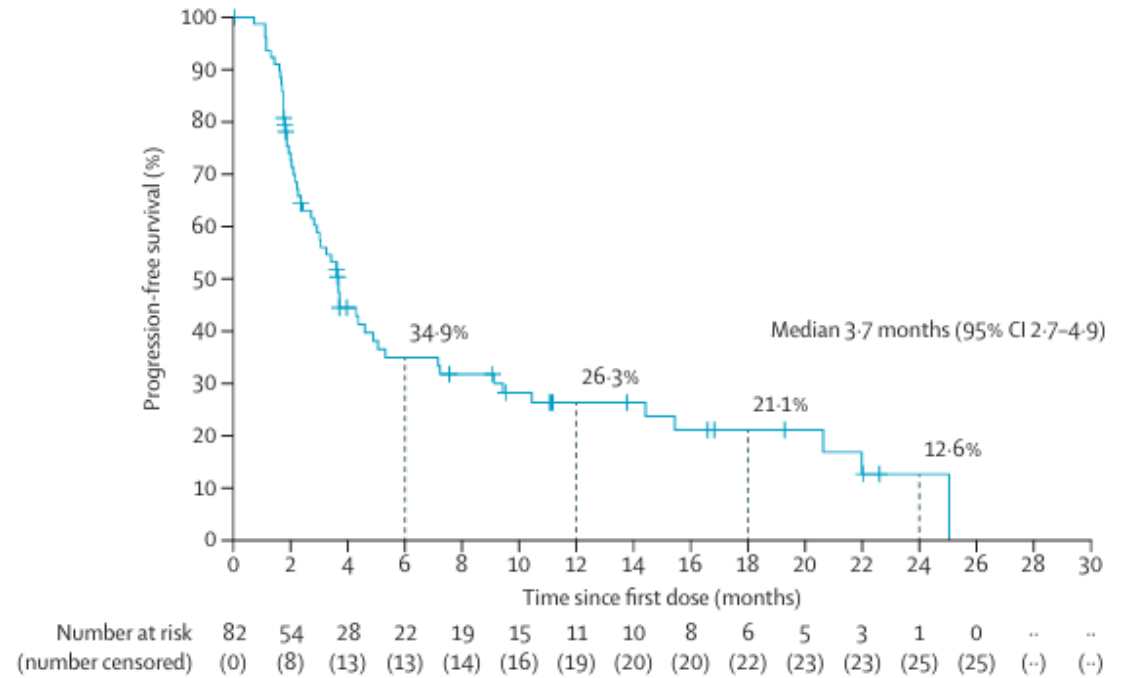
Median (range) of previous lines of CLL therapy	2 (0-13)
Median (range) of previous lines of RT therapy	2 (0-8)
Median (range) of previous lines of CLL and RT therapy	4 (0-13)

## Previous CLL therapy

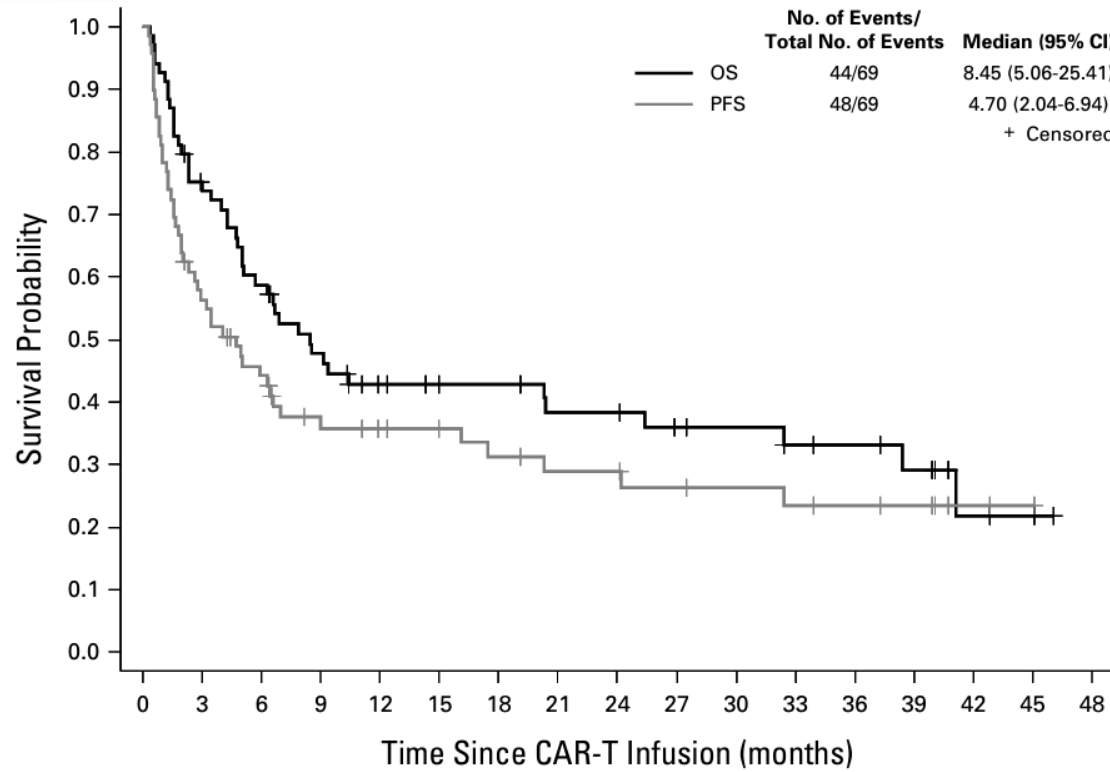
Yes	65 (79%)
No	17 (21%)
Anti-CD20 antibody	54 (66%)
Covalent BTK inhibitors	51 (62%)
Chemoimmunotherapy	43 (52%)
BCL-2 inhibitors	40 (49%)

## Previous RT therapy

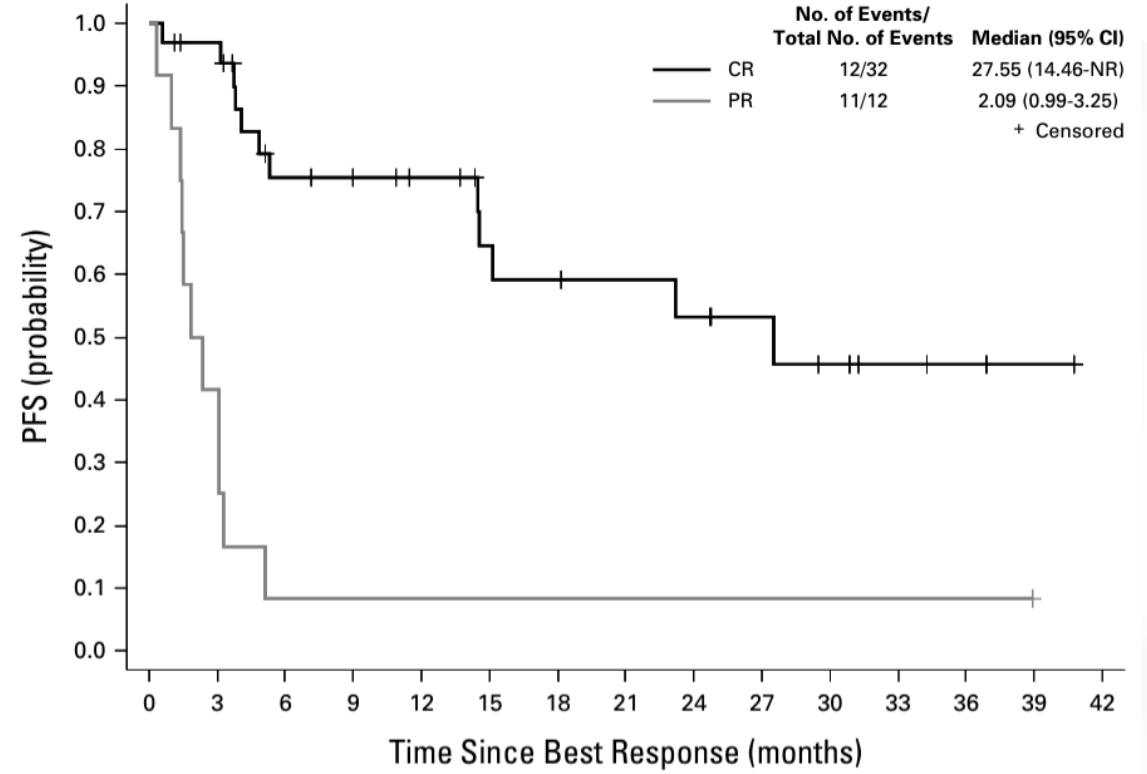
Yes	74 (90%)
No	8 (10%)
Anti-CD20 antibody	64 (78%)
Chemoimmunotherapy	62 (76%)
BCL-2 inhibitors	31 (38%)
Covalent BTK inhibitors	28 (34%)



# CART for RT



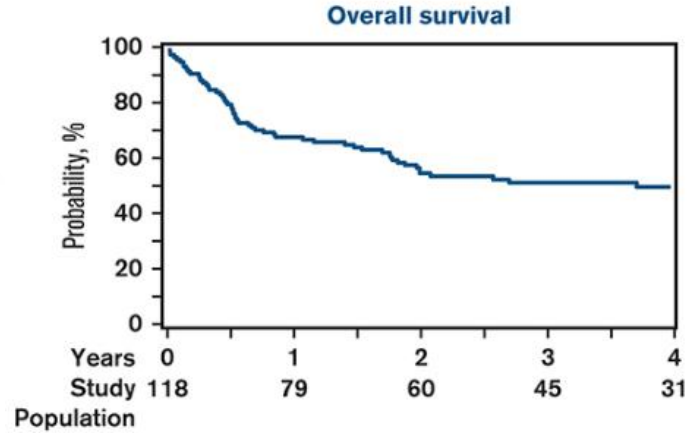
Number at risk:	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48
OS	69	39	23	20	17	13	10	3	0								
PFS	69	28	18	14	12	9	7	2	0								



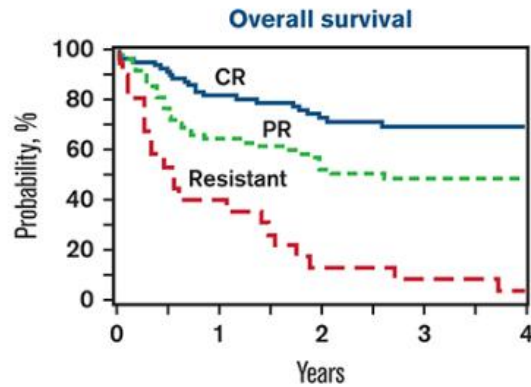
Number at risk:	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42
CR	32	20	16	11	9	5	2	0							
PR	12	1	1	1	1	1	1	1	0						

# Transplant for RT

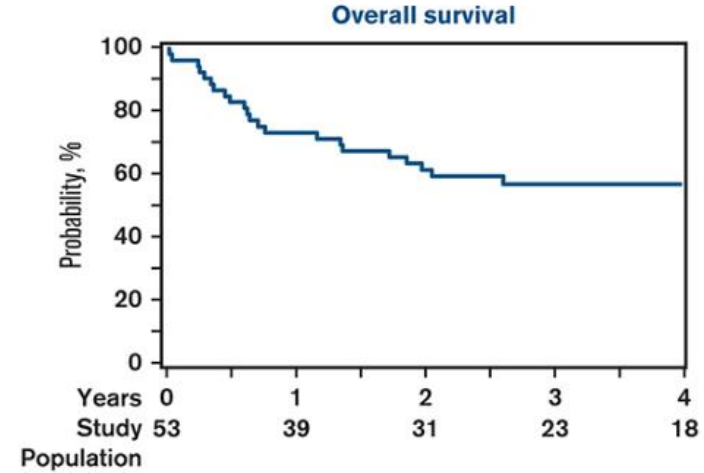
**N = 118 DLBCL-RS who underwent allogeneic HCT**  
**3 yr OS = 52%**



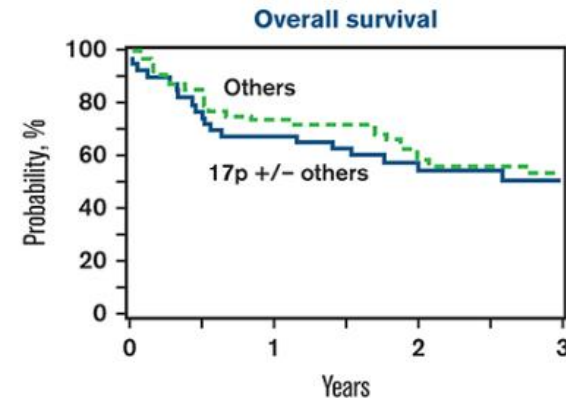
**3 yr OS after allogeneic HCT by disease status at HCT**  
**3 yr OS: CR 77%, PR 57%, Resistant 15%**



**N = 53 DLBCL-RS who underwent autologous HCT**  
**3 yr OS = 57%**



**3 yr OS after allogeneic HCT in 17pdel vs others**  
**3 yr OS: 17pdel 50%, Others 54%**



# AlloSCT vs CART in the Modern Era

Total N = 309

46 got allo-HSCT

ORR was 78.6% (31 CR, 2 PR, 9 PD)

Median OS was 54.5 months

55 got CAR-T

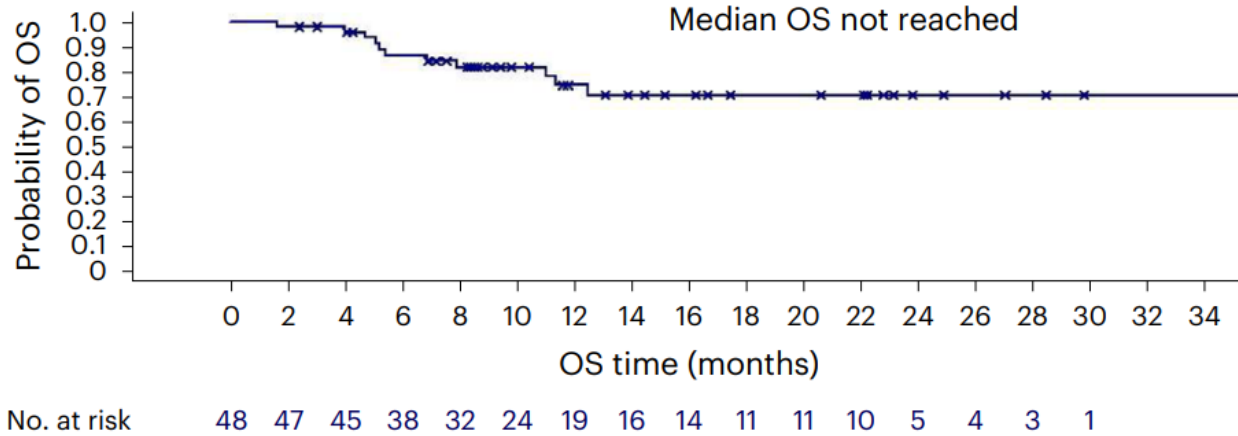
ORR was 62.7% (23 CR, 9 PR, PD 19)

Median OS was 9.0 months

Create RT consensus statements that will define the prognosis, of RT, recommendations, or guidelines streamline the workup of RT, establish currently existed for Richter baseline standards for clinical trial transformation, and discuss future goals.

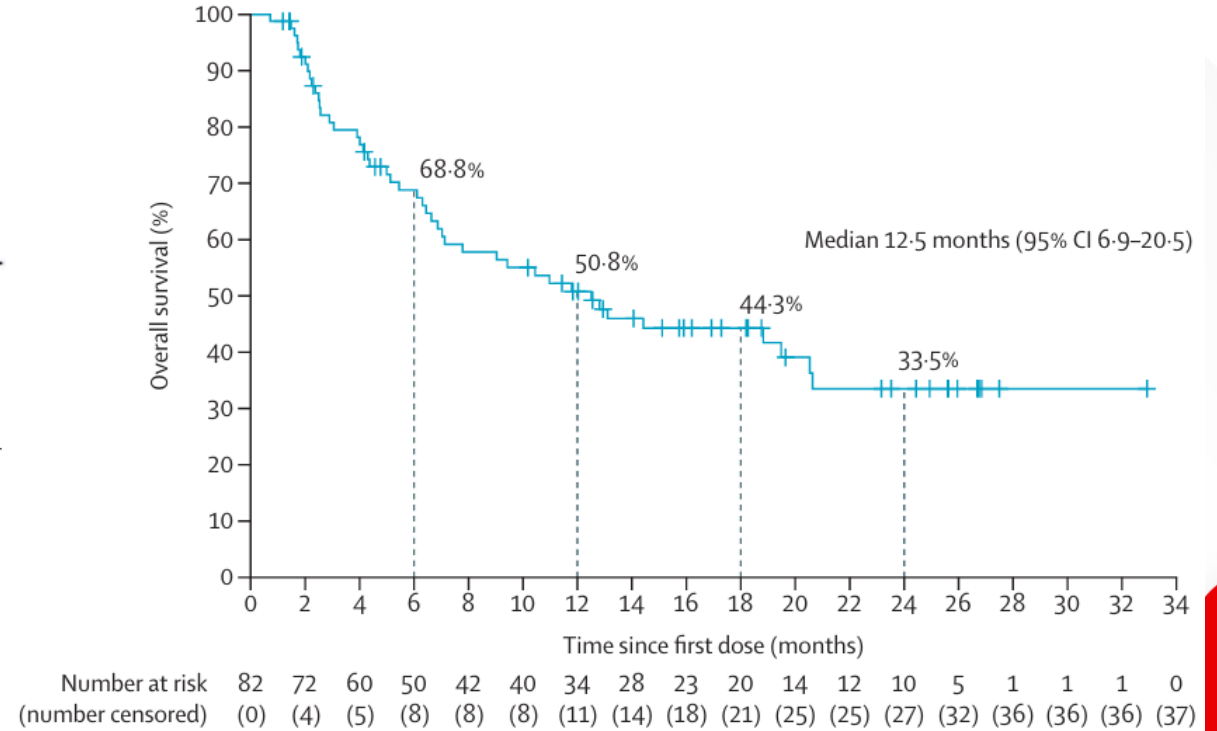
# Evaluation of clinical trials

Tislelizumab + Zanubrutinib for RT



- Used the refined Lugano criteria for immunotherapy
- Stated that their responses matched iwCLL criteria for response

Pirtobrutinib for RT



- Used standard Lugano criteria
- Does not state that iwCLL was used to compare response

## ERIC Recommendations

- 5 Lead Authors
- 24 International Experts in RT
  - 10 Countries, 3 Continents
- Delphi Method
- 5 Meetings over the course of a year

**40 Consensus Statements**

# Most impactful statements

## Diagnosis/ Prognosis



- We strongly recommend attaining an excisional biopsy on the most metabolically active, accessible lymph node for diagnosis.
- Current standard of care treatment with RCHOP-like regimens has poor efficacy.

Epidemiology and prevalence		
1.1.1	B	RT occurs in 2 to 10% of patients with CLL.
1.1.2	B	RT can occur in patients who have not received any treatment or who have received only targeted therapies for their CLL.
1.1.3	R	More data are required to determine if risk of RT changes with exposure to different treatment types.
1.1.4	G	There are no therapeutic strategies proven to reduce the risk of RT in CLL.
Diagnosis		
1.2.1	G	RT should be suspected in patients with clinical decline, B-symptoms, elevated LDH, rapidly enlarging lymphadenopathy, and/or discordant response to CLL treatment.
	rk	There should be strong consideration for RT in patients with discordant enlarging lymphadenopathy (e.g. one nodal group growing rapidly compared to others).
1.2.2	B	In patients with a clinical suspicion of RT, a PET-CT should be attained.
1.2.3	G	The most accessible lesion with the highest avidity should be targeted for biopsy.
	rk	SUV avidity of <5 suggests a low likelihood of RT.
	rk	In cases where the most accessible lesion has avidity that is much lower than a less accessible lesion (e.g. an axillary node with an SUV of 6 versus a retroperitoneal node with an SUV of 22) we recommend attempting to biopsy the lesion with higher avidity.
1.2.4	B	Biopsy of the affected tissue for histology assessment is needed to diagnose RT.
1.2.5	G	We strongly recommend attaining an excisional biopsy for diagnosis.
	rk	Given the complexity in diagnosing RT from CLL, an excisional biopsy is recommended. However, we recognize there are clinical scenarios where an excisional biopsy is not possible. If an excisional biopsy is unable to be performed, we recommend multiple core biopsies. Fine needle aspirate is insufficient and cannot be used in the diagnosis of RT.
1.2.6	G	All efforts should be made to have pathology reviewed by an expert hemopathologist.
1.2.7	B	Clonal relationship of the RT tissue and antecedent CLL cells should be tested, as it is one of the strongest prognostic factors for RT survival: patients with clonally unrelated RT have a markedly better prognosis.
Prognosis		
1.3.1	B	The prognosis of RT is poor.
1.3.2	B	Current standard of care treatment with RCHOP-like regimens has poor efficacy.
	rk	In clinical practice, RCHOP followed by consolidative allogeneic stem cell transplantation in eligible patients is the most commonly applied regimen.

Prognostication		
2.1.1	B	TP53 aberrations in either CLL or RT tissue are associated with shortened OS.
2.1.2	B	Therapy for CLL prior to the development of RT is associated with poorer RT outcomes.
	rk	Insufficient data exists to determine if the type of CLL therapy (chemoimmunotherapy versus targeted therapeutics) influences prognosis of RT.
		Laboratory testing
2.2.1	G	Clonality should be determined by comparing IG gene rearrangement from the RT tissue to the IG gene rearrangement in the CLL cells.
	rk	We understand that this means of testing for clonality is not universal. However, we believe this to be the gold standard. If tissue specimen attained does not allow for this analysis, appropriate analysis per tissue attained should be performed. An additional biopsy should not be performed if alternative testing is possible with the tissue available.
2.2.2	R	At present, NGS of the RT tissue offers limited clinical value in determining prognosis.
2.2.3	G	No direct evidence supports testing of molecular resistance to BTK or BCL2 inhibitors in patients with RT.
	rk	It is unclear if “resistance mutations” confer resistance to BTK or BCL2 inhibitors in RT. However, clinical rationale based on evidence in CLL suggests that RT harboring these mutations may not be amenable to treatment with these agents.
2.2.4	R	If available, all attempts should be made to biobank RT samples for future characterization.
	rk	Paired germline tissue should be stored along with malignant tissue for use in future genetic sequencing.
		Staging/Pre-Treatment Assessment
2.3.1	G	We recommend using a pre-treatment PET-CT to establish the extent of the disease.
2.3.2	G	Unlike standard DLBCL, we recommend bone marrow biopsy at time of treatment to determine presence of bone marrow disease, and to assess status of CLL.

Eligibility criteria for clinical trials		
3.1.1	R	If at all possible, patients with RT should be treated on clinical trials.
	rk	We recognize that enrollment to clinical trials can be difficult given rapid disease progression, concurrent CLL, and comorbidities of patient population.
3.1.2	R	Due to rapid disease progression attributed to RT, disease stabilization with one cycle of protocol specific debulking treatment should not be considered an absolute exclusion criterion from clinical trials evaluating treatment-naïve regimens.
	rk	Clinical trials should be designed to facilitate rapid initiation of therapy. However, it is common for patients with RT to present with reduced performance status or organ dysfunction due to the disease and may require therapy for stabilization. Therefore, we believe that therapy meant to stabilize the disease should be allowable prior to clinical trial enrollment for treatment-naïve disease. "One cycle of debulking treatment" could include a course of steroids, but not immune or chemotherapy to minimize the risk of a biased efficacy or toxicity assessment of experimental treatments.
3.1.3	R	Allow for the minimal or no wash-out period possible when considering prior therapy.
3.1.4	R	New RT-directed clinical trials should ensure liberal inclusion and exclusion criteria.
	rk	Given the need for novel therapies for patients with RT we believe all patients should be treated on trial. Therefore, patients with co-morbid conditions that could tolerate the treatment entailed in the trial, should be allowed on trial. Specifically, we should not be excluding patients from trial if patients have cytopenia due to the underlying CLL or RT, or if the disease is responsible for poor performance status.
3.1.5	R	Active or symptomatic CLL should not be an exclusion to enroll on RT clinical trials.
Endpoints of clinical trials		
3.2.1	R	Given the short survival of patients with RT, we consider a survival endpoint (i.e. PFS, and OS) to be the primary endpoint of choice for RT phase 3 or randomized phase 2 clinical trials.
3.2.2	R	RT clinical trials should assess depth of response and correlate it with survival outcomes.
3.2.3	R	Samples should be collected prospectively on trials for exploratory analysis.
	rk	Plasma is typically a biologic sample feasible for prospective collection, however nodal tissue can be stocked during and after treatment. Sample collection is particularly worthwhile at time of progression.
Response assessments		
3.3.1	R	Given RT is associated with short survival, we recommend designing clinical trials that include an early response assessment, typically within 1-3 cycles of treatment.
3.3.2	R	We strongly recommend using the PET-CT-Based response per the Lugano criteria to assess response of patient with RT treated on clinical trials.
3.3.3	R	In clinical trials, we recommend PET-CT monitoring at regular intervals (e.g. 3-6 months), and a PET-CT if there is suspicion for progression.
3.3.4	R	A biopsy to distinguish residual CLL from refractory RT is recommended when the end of treatment PET-CT demonstrates persistent Deauville 4 or 5 lesions.
	rk	The biopsy should be of the highest SUV avid lesion, that is most amenable to biopsy. If it all possible, the biopsy should be an excisional biopsy. This biopsy can also be used to distinguish whether these lesions represent non-malignant changes versus residual/refractory disease.
3.3.5	R	As recommended for standard of care, in clinical trials, we recommend a pre-treatment bone marrow biopsy to determine the extent of CLL and RT in the bone marrow.
3.3.6	R	For patients with pre-treatment marrow disease, we recommend a bone marrow biopsy at restaging to determine the extent of CLL and RT disease status to confirm CR.
	rk	Patients with detectable CLL by peripheral blood flow cytometry at restaging do not need an additional bone marrow biopsy to assess CLL disease response.
3.3.7	R	Response of RT and CLL should be objectively assessed and reported based on both Lugano criteria as well as iwCLL guidelines.
Toxicity assessment		
3.4.1	R	We recommend using CTCAE criteria to assess non-hematologic toxicity grade.
3.4.2	R	We recommend using iwCLL criteria for assessing hematologic toxicity grade.
Other		
3.5.1	R	In clinical trials, we recommend determining clonality.
	rk	RT trials should not be limited to clonally related disease. We recommend pre-planned subgroup analysis of patients with clonally related versus unrelated disease. All efforts should be made to determine clonality in a timely fashion with the possibility in the future to stratify patients at enrolment based on the clonal relatedness. Central determination of clonal relationship should be considered; additionally results of clonal relationship are not needed to begin therapy on clinical trials.
3.5.2	R	If possible, on clinical trial central review of pathology by an expert hemopathologist should occur.^

## Interesting Trials in the pipeline that I am aware of:

- Glofitamab -> Glofi + Atezolizumab or Glofi + Polatuzumab
- Pirtobrutinib + RCHOP vs. RCHOP
- RT2 – Randomized Trial
- Liso-cel + Zanubrutinib
- Liso-cel + Ibrutinib + Nivolumab

## Conclusions

- Incidence is decreasing, and survival improving
- Designated RT trials are needed
- Groups needs to work together to streamline their approach and study of RT
- Collaborative studies are underway



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