

A wide-angle, high-angle aerial photograph of the Chicago skyline at night. The city is illuminated with warm yellow and orange lights, contrasting with the dark blue and black sky. The dense cluster of skyscrapers is visible, with the Willis Tower being a prominent feature in the center. The image has a slightly desaturated, artistic feel.

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Richter's Syndrome

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Disclosure Information

- I have the following relevant financial relationships to disclose:
 - Consulting: Janssen, Pharmacyclics, Beigene, Karyopharm, Innate
 - Research Funding: Arqule, JUNO, Acerta, MingSight, Verastem, Gilead, Karyopharm
- I will discuss the following off-label and or investigational use in my presentation:
 - No therapy is approved specifically for Richter's syndrome, therefore all therapy is off-label or investigational

Richter's Syndrome Overview

- Definition
- Risk Factors
- Biology: Clonal Relationship
- Treatment Options
 - Chemoimmunotherapy
 - Immunotherapy
 - Novel agents
- Summary

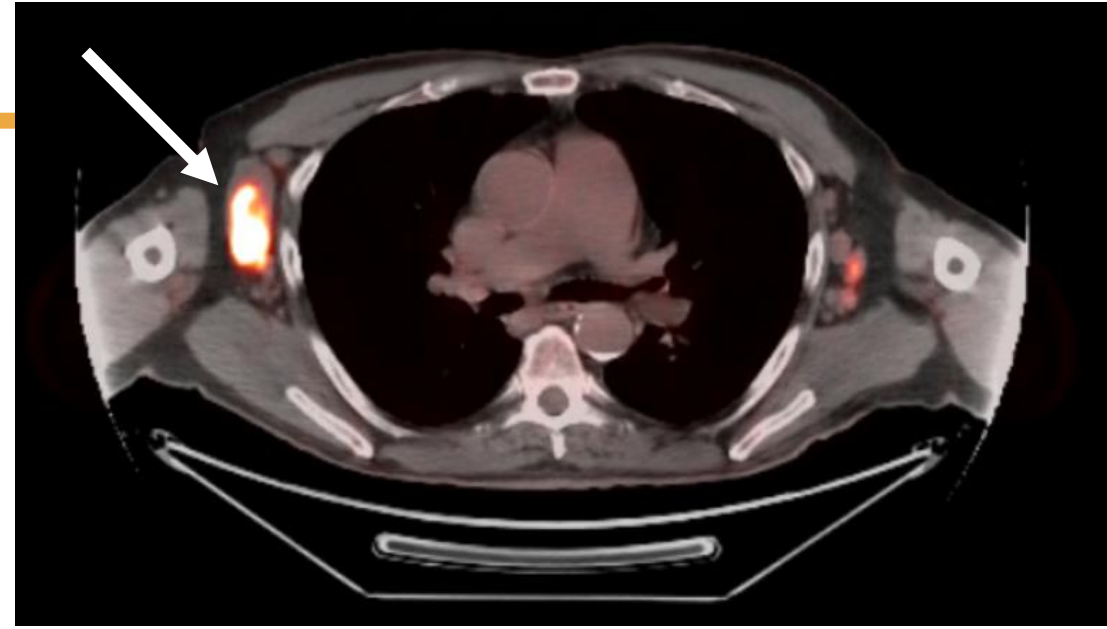
Definition

Richter's Syndrome

- Originally described in 1928 by Maurice Richter
- Transformation of CLL into a more aggressive lymphoma
- Occurs in up to 16% of CLL patients over lifetime
- 90% Diffuse large B-cell lymphoma
- ~5-9% Hodgkin lymphoma

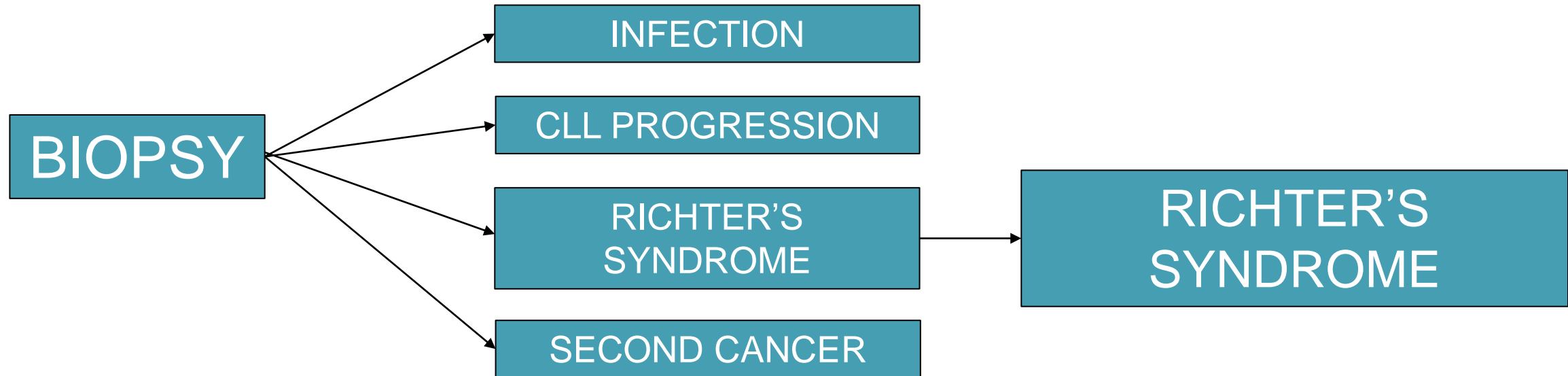
Case

- 65M diagnosed with CLL 8 years ago
- Unmutated IgVH
- FCR x 4 – 6 years ago: Remission
- Ibrutinib for the last 1.5 year
- Presents with ECOG PS 1
 - Progressive LAD
 - Drenching night sweats
- WBC 15, Hgb 10.7, Platelets 87, LDH 3 x ULN
- PET is shown: R axillary node (5.7 x 2.1 cm) SUV = 32



Diagnosis

- Only indication for PET in CLL patients
- Selection biopsy site with SUV ≥ 10
 - Sensitivity 91%
 - Specificity 95%



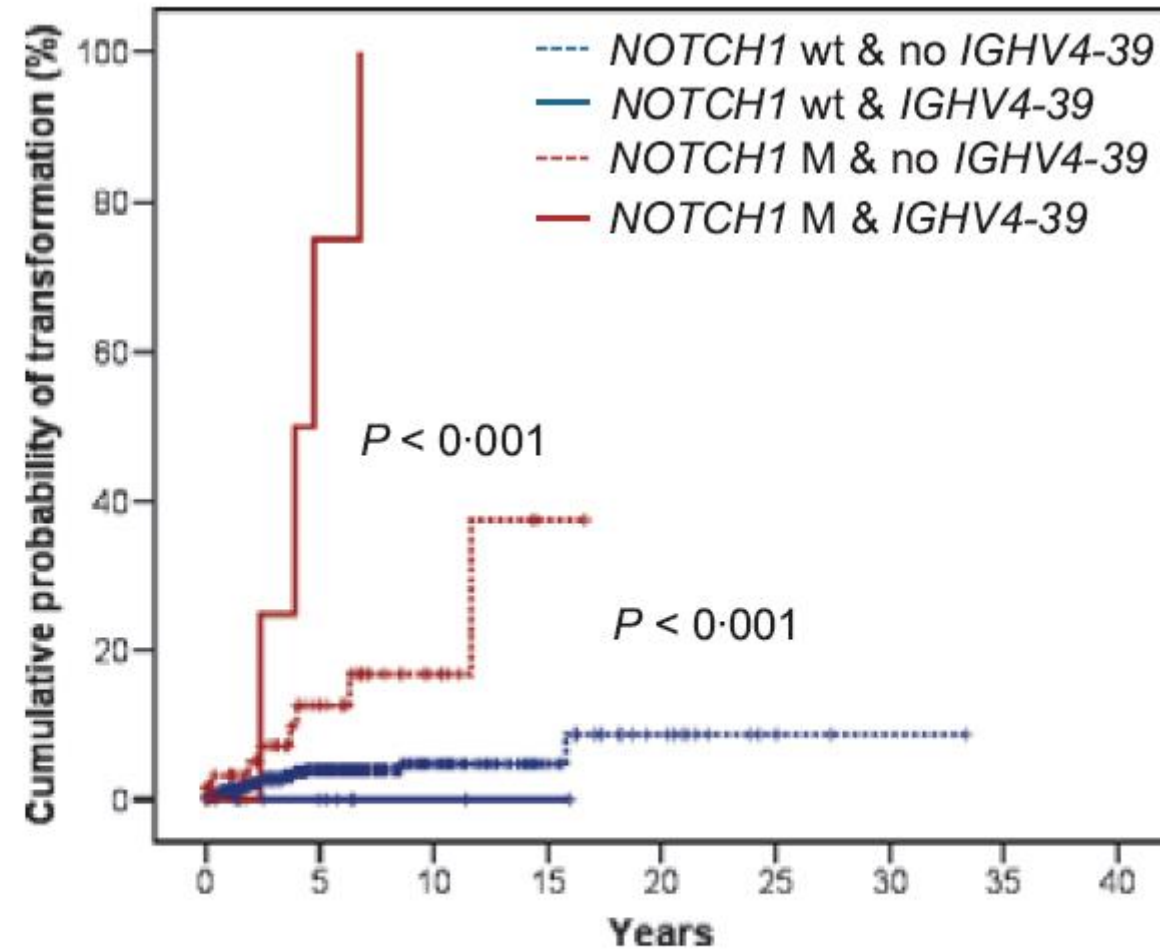
Risk Factors

Risk Factors: Clinical

- Many clinical and molecular risk factors identified:
 - At RS Diagnosis:
 - More lines of prior therapy at RS diagnosis
 - At CLL Diagnosis:
 - Younger age
 - Lymph nodes > 3 cm
 - Advanced Rai Stage
 - Elevated beta-2-microglobulin

Risk Factors: Molecular

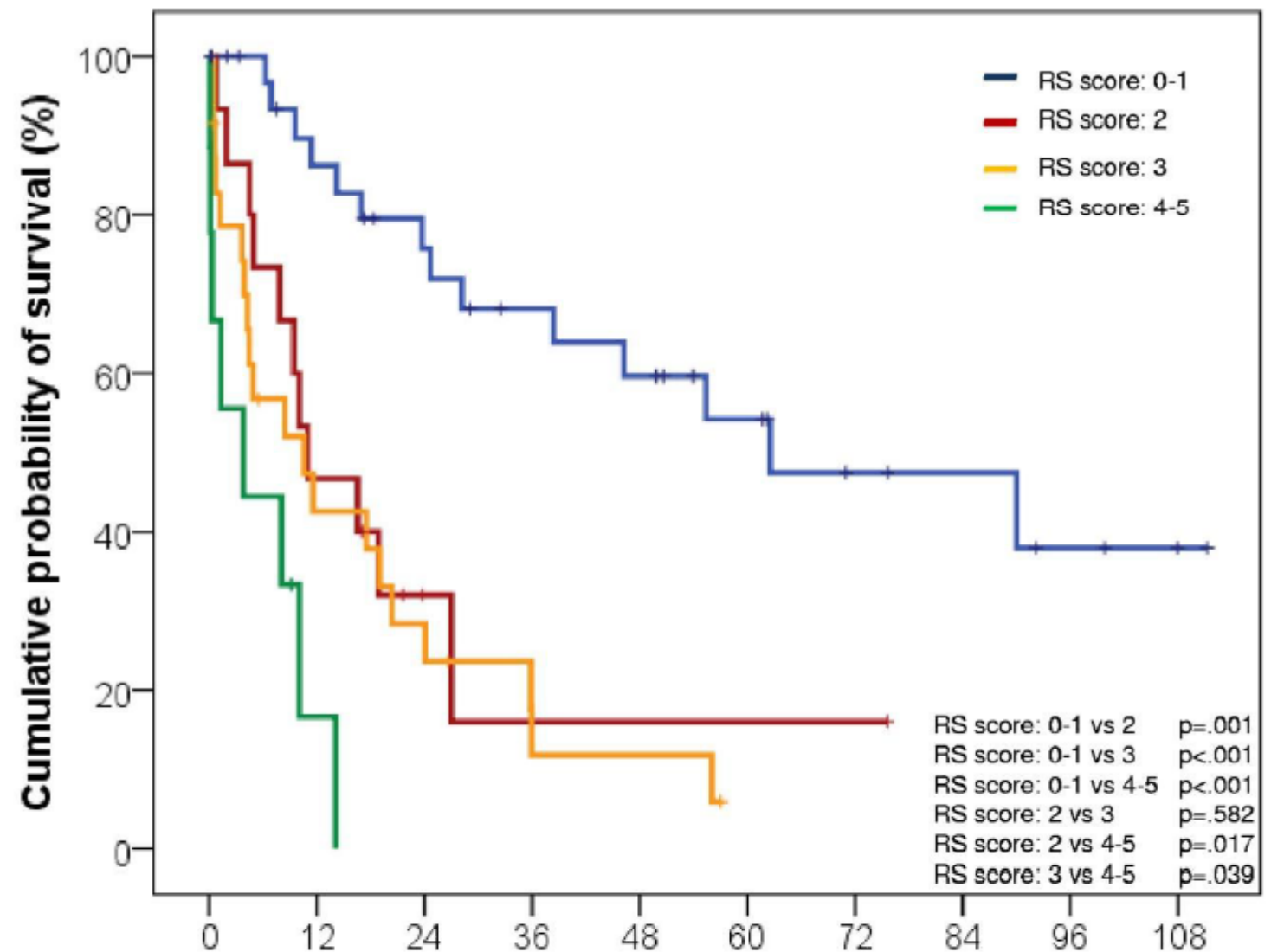
- Unmutated IgVH, del17p, del11q
- 40 Patients with RS
- *TP53* (60% of samples)
- *NOTCH1* (40% of samples)
- *NOTCH1* = 5 year risk 18.5%
- + IGHV4-39 = 5 year risk 70%!
- *SF3B1* = protective



No. at Risk									
<i>NOTCH1</i> wt & no <i>IGHV4-39</i>	519	273	90	30	11	3	1	0	0
<i>NOTCH1</i> wt & <i>IGHV4-39</i>	12	12	12	12	0	0	0	0	0
<i>NOTCH1</i> M & no <i>IGHV4-39</i>	67	27	8	1	0	0	0	0	0
<i>NOTCH1</i> M & <i>IGHV4-39</i>	7	1	0	0	0	0	0	0	0

Prognosis

- Richter's Score:
 - ECOG PS >1
 - LDH > 1.5 ULN
 - Plt <100
 - Tumor Size > 5 cm
 - # prior CLL Tx > 1
- Our patient: RScore of 4
 - Median OS = 3.8 months



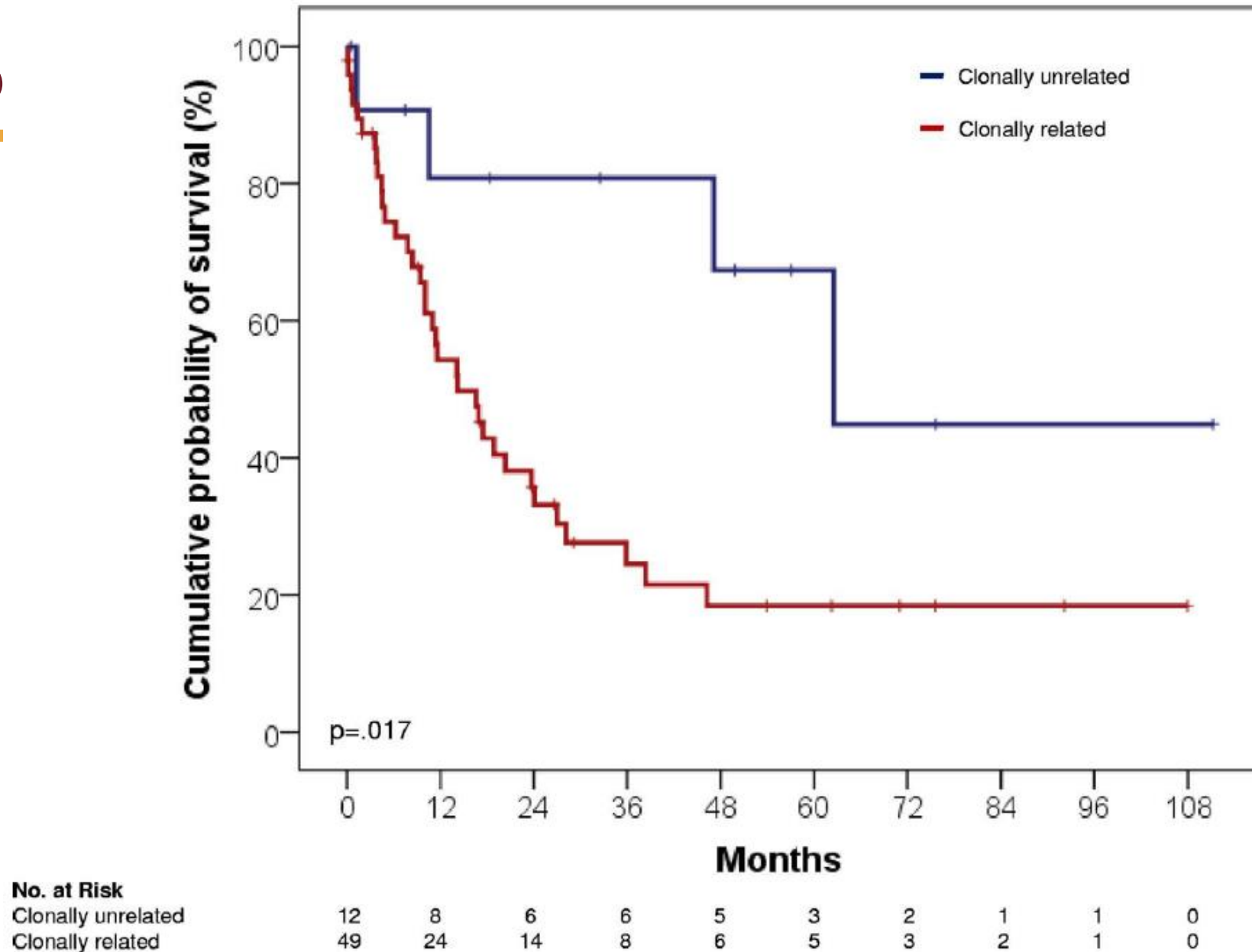
No. at risk

	0	12	24	36	48	60	72	84	96	108
RS score: 0-1	34	25	20	16	14	10	6	5	3	1
RS score: 2	15	7	2	1	1	1	1	0	0	0
RS score: 3	24	9	6	2	2	0	0	0	0	0
RS score: 4-5	9	1	0	0	0	0	0	0	0	0

Biology

Clonal Relationship

- 80% Clonally Related
- Median OS
 - Unrelated = 62.5 mos
 - Related = 14.2 mos
 - (P=0.017)
- Our patient = clonally related



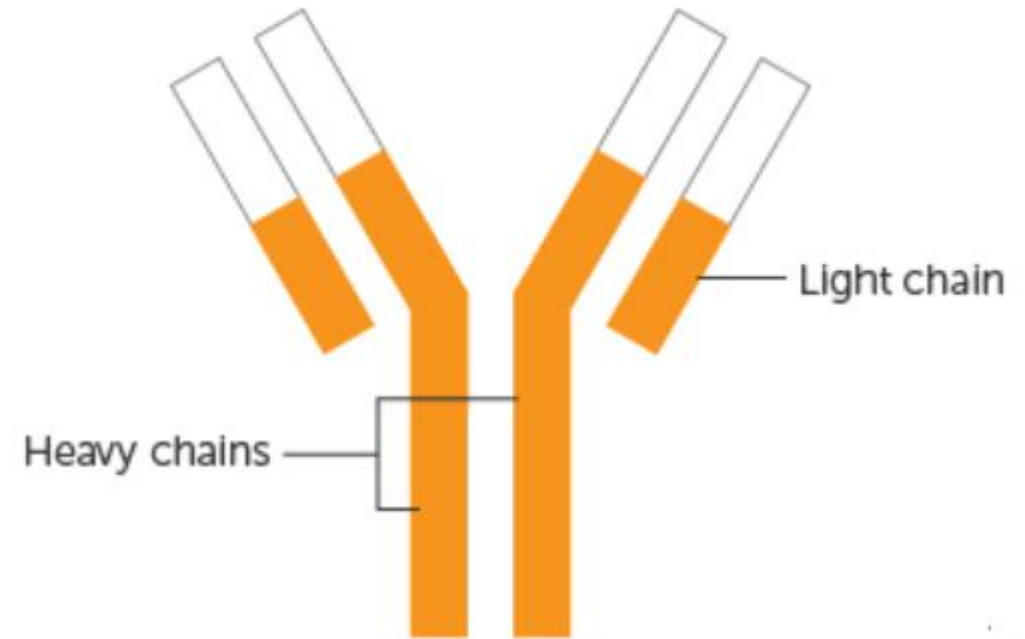
Determining Clonal Relationship

- Surrogate Markers:

	Unrelated	Related
BCL6 translocation	Possible	Rare
Overexpression of PD1	Rare	Likely

- Common Method to Evaluate:

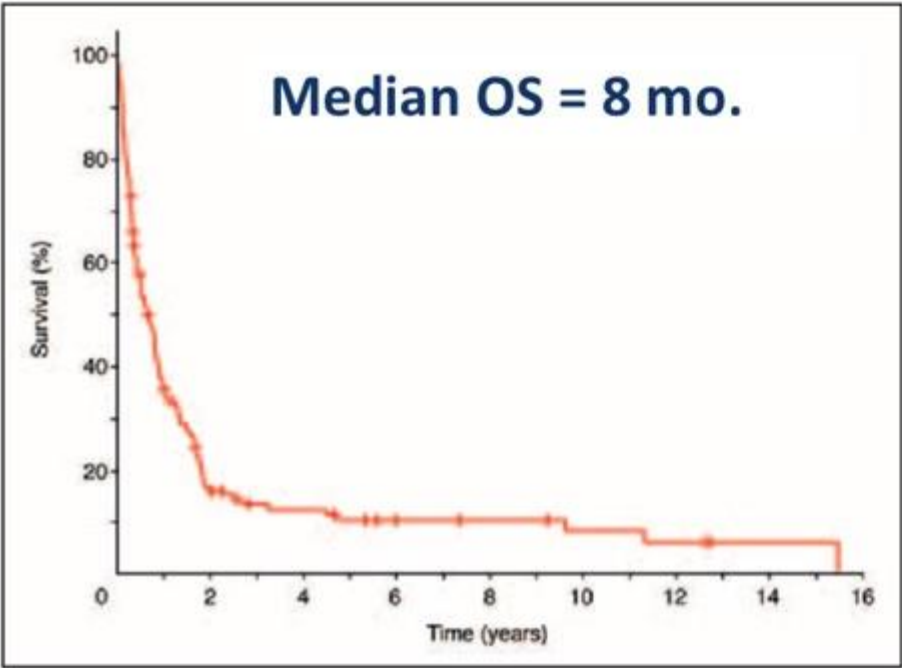
- PCR for immunoglobulin heavy and light chain clones
- Best if clonal population is >10% of the population identified
- Recommend testing blood for CLL clone and section of lymph node or bone marrow heavily involved with lymphoma
- Can be done on FFPE tissue



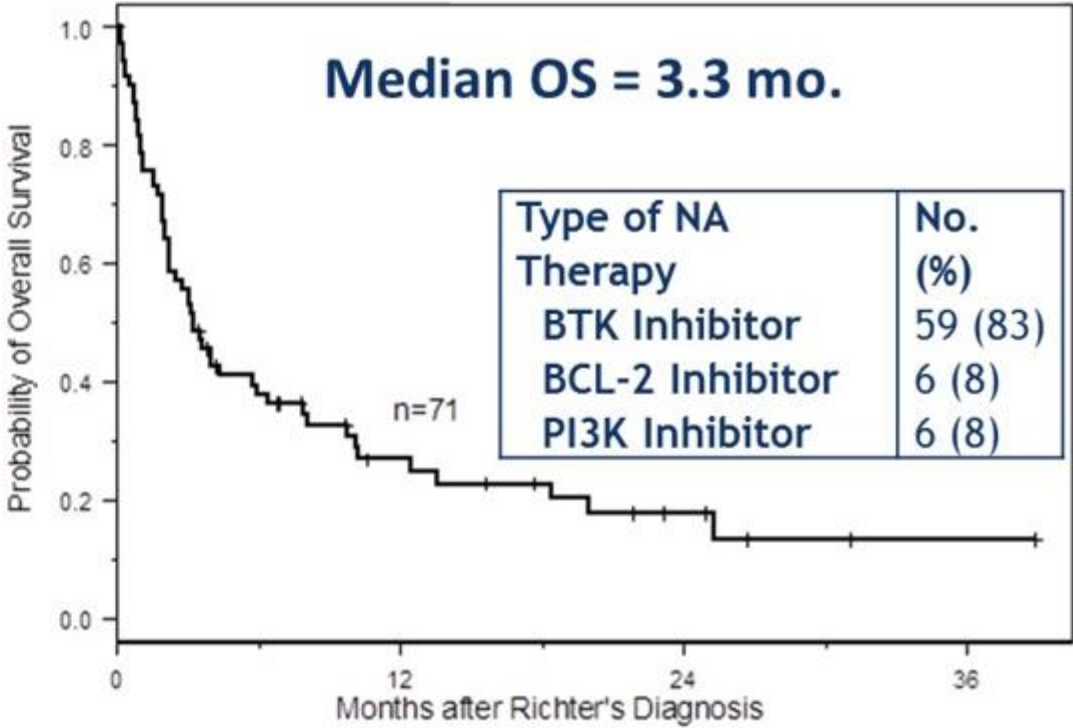
Treatment

Survival Over Time

RS after Chemoimmunotherapy



RS after Novel Kinase Inhibitors



Chemoimmunotherapy in RS

Select Chemoimmunotherapy Regimens in RS

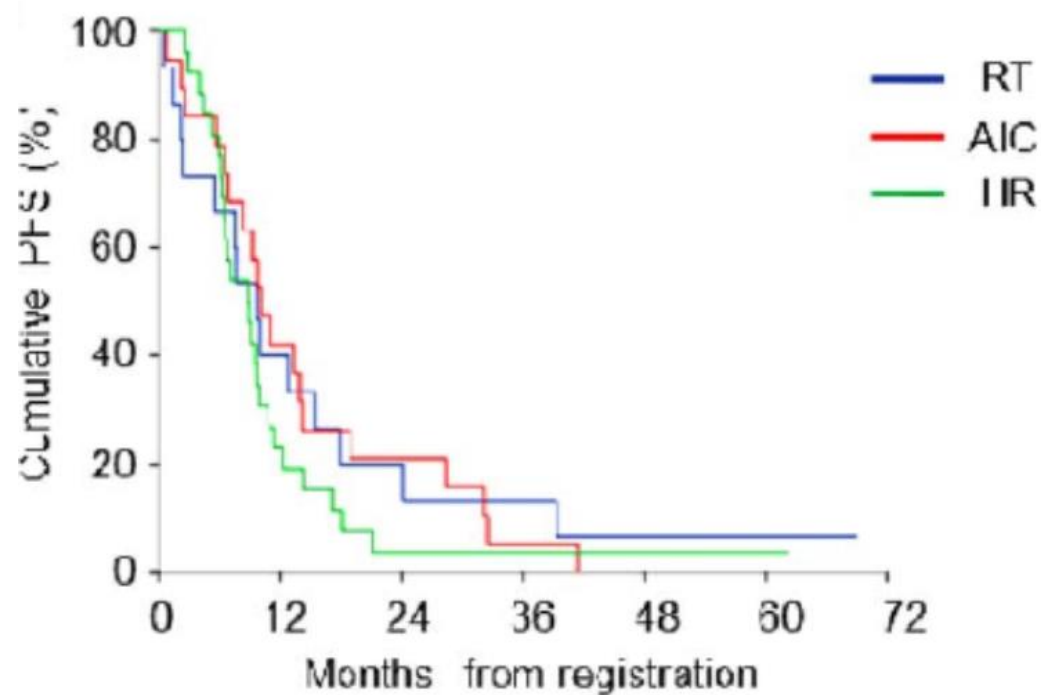
Regimen	N	ORR (%)	OS (mos)	Ref
RCHOP	15	67	21	Langerbeins (2014)
OCHOP+O	37	44	11	Eyre (2016)
hypCVAD	29	44	10	Dabaja (2001)
hypCVAD-R MA	30	41	10	Tsimberidou (2003)
OFAR1	20	50	8	Tsimberidou (2008)
OFAR2	35	39	6	Tsimberidou (2013)
REPOCH*	46	39	6	Rogers (2015)
*Retrospective				

RCHOP

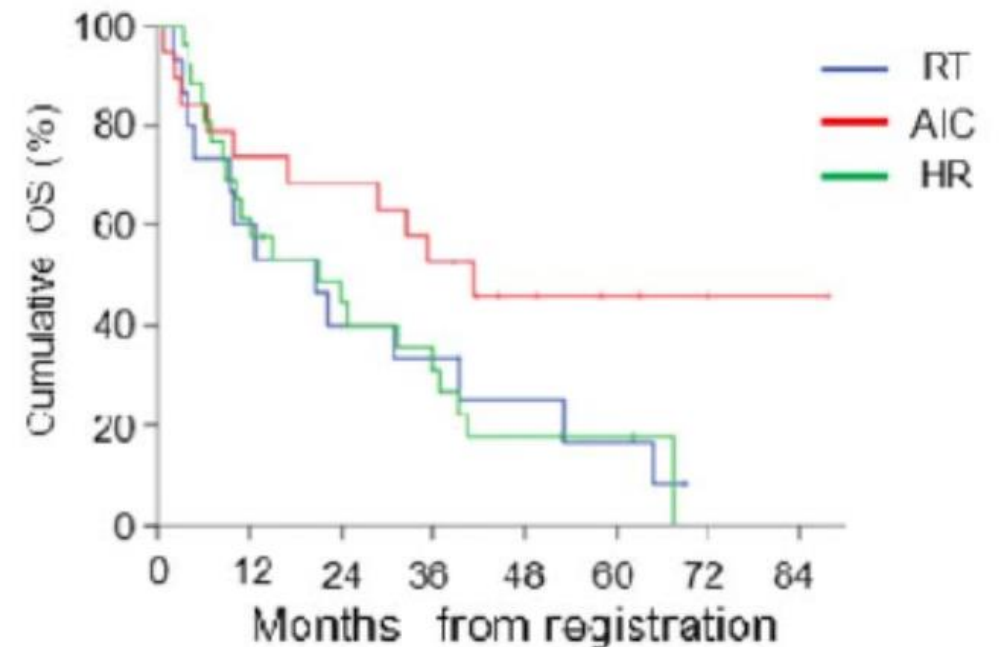
Median Follow-up 69 mos

- 15 RT patients
- ORR = 67% (CR 7%)

Median PFS = 10 mos

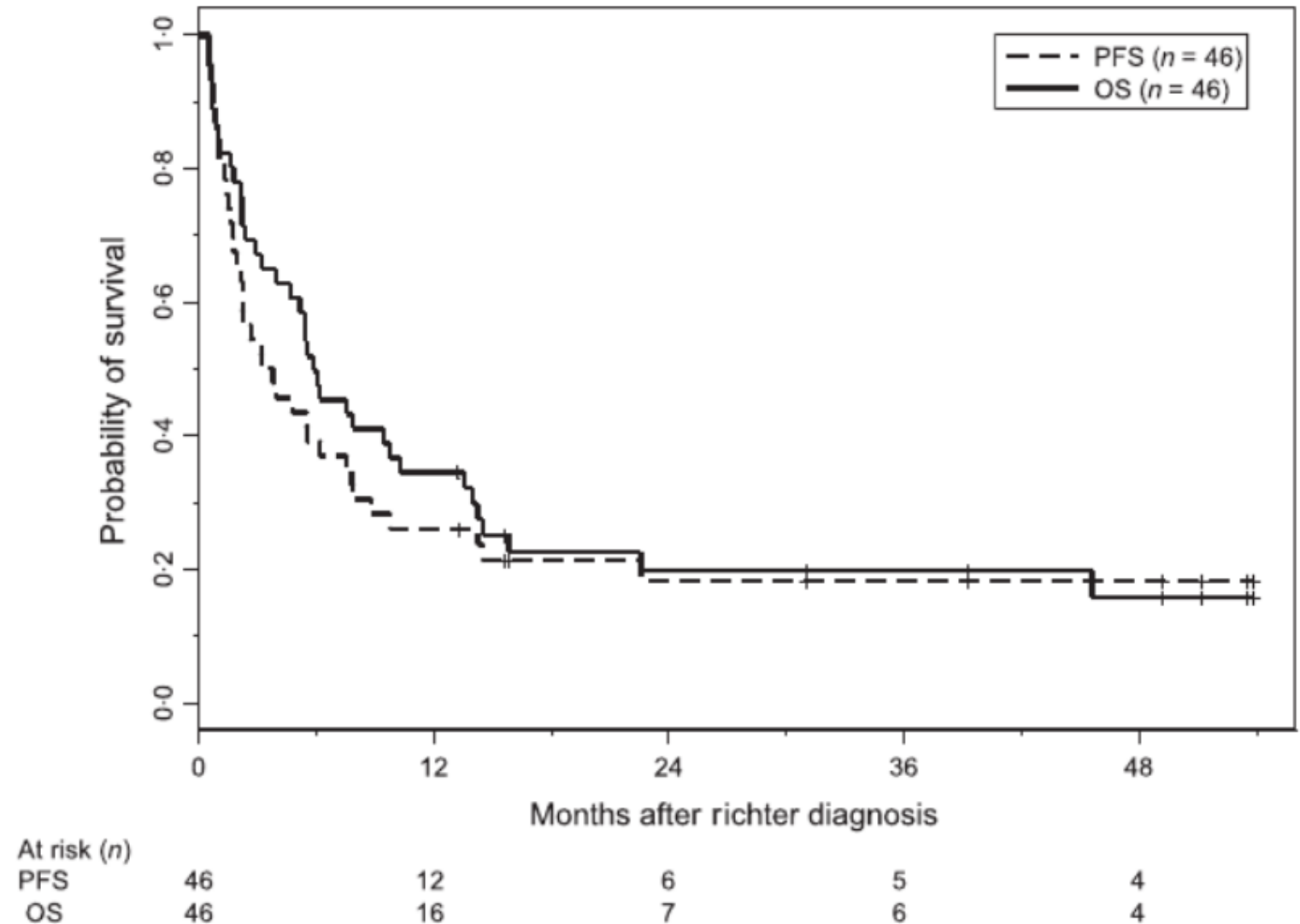


Median OS = 21 mos

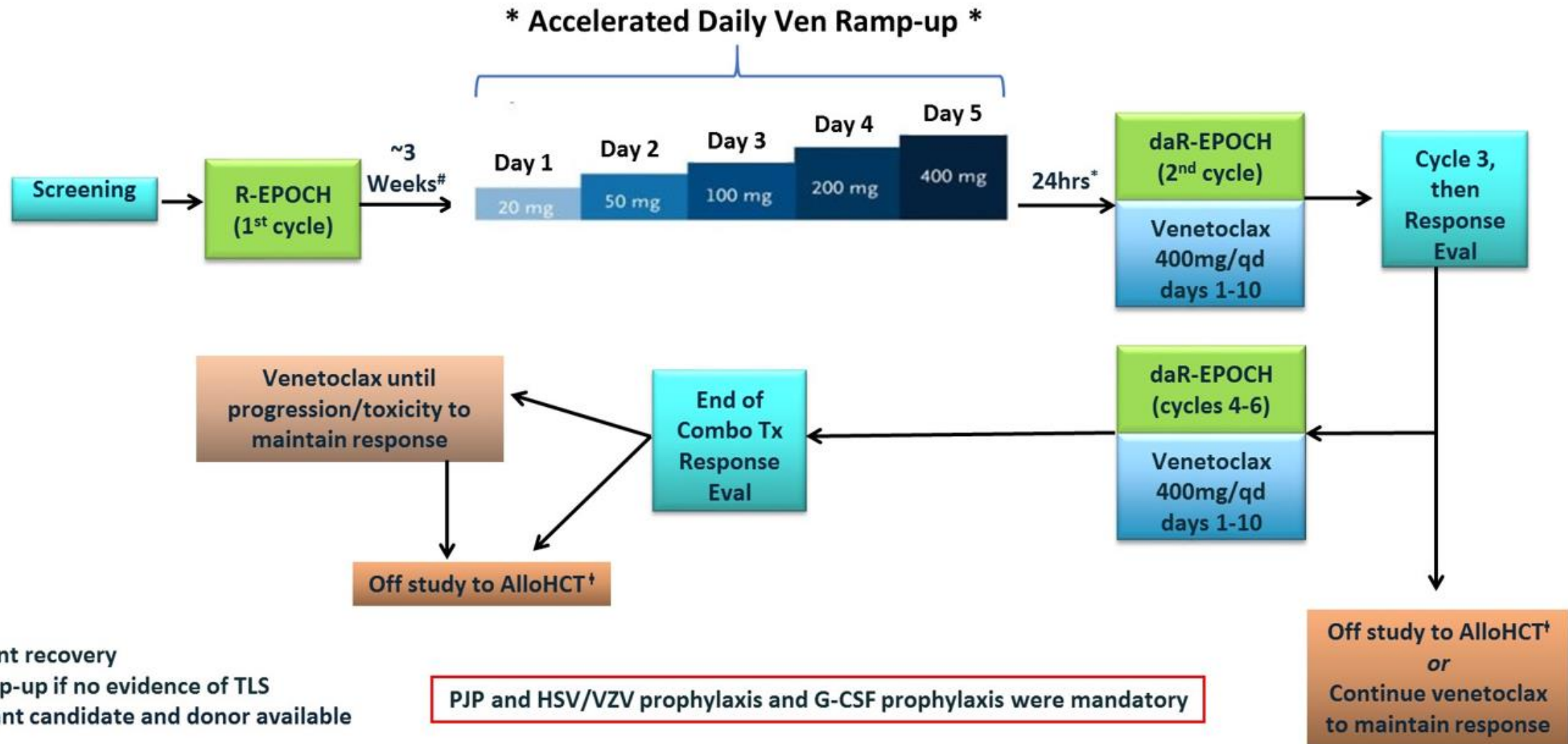


REPOCH

- Retrospective
- 46 RT patients
- Median PFS 3.5 mos
- Median OS 5.9 mos
- Toxic:
 - 30% died without progression or response



REPOCH + Venetoclax (BCL2 inhibitor)



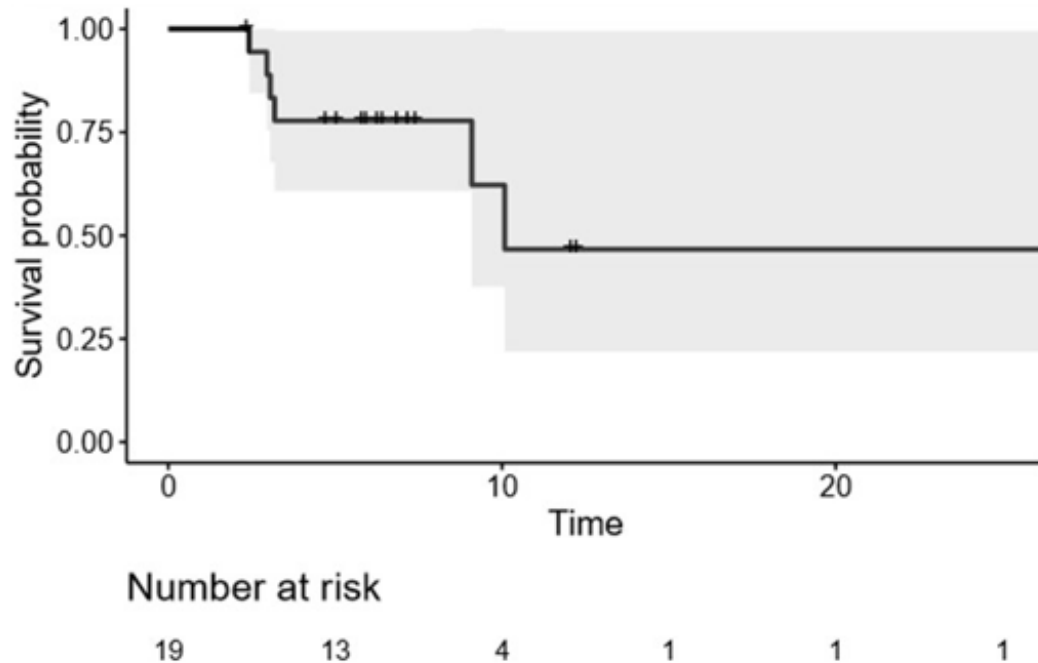
REPOCH + Venetoclax

- Phase 2 Study
- 3 Institutions
- 26 Patients Enrolled
 - Median Age = 63 (44-77)
 - Del(17p) = 26%
 - TP53 Mutation = 44%
 - Median Prior Therapies = 2 (0-5)
- ORR by ITT = 62%
- CR by ITT = 50%
- 8/17 (47%) patients initially deemed candidate for alloHCT proceeded to transplant

REPOCH + Venetoclax

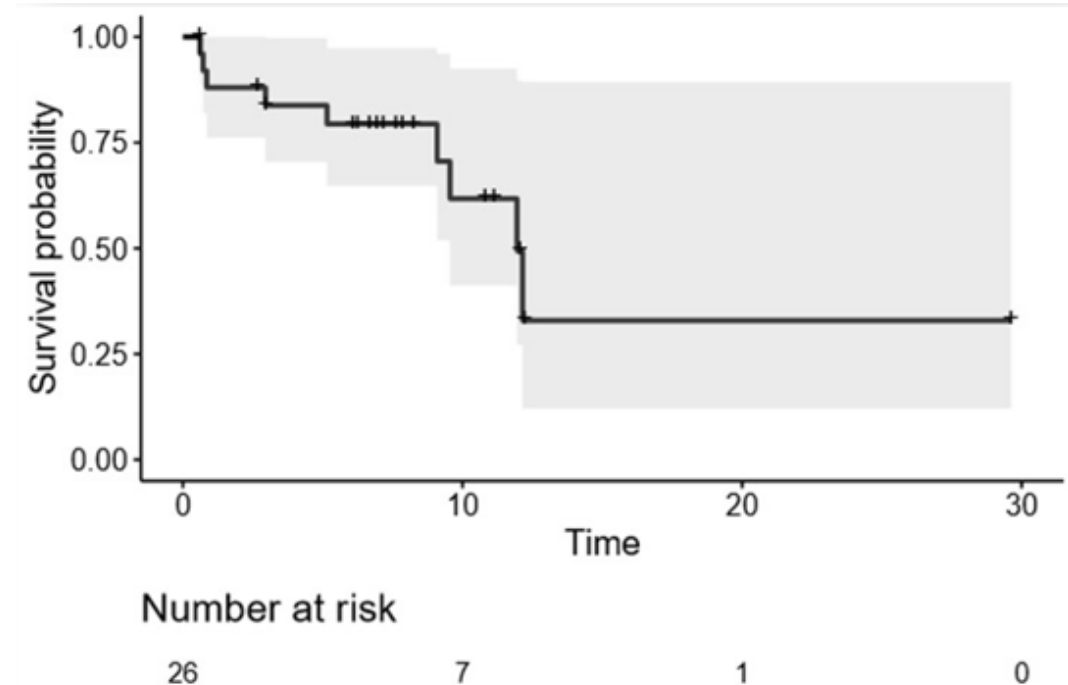
Median Follow-up 9.3 mos

PFS: Censored at alloHCT



Median PFS: 16.3 mos

OS: Censored at alloHCT

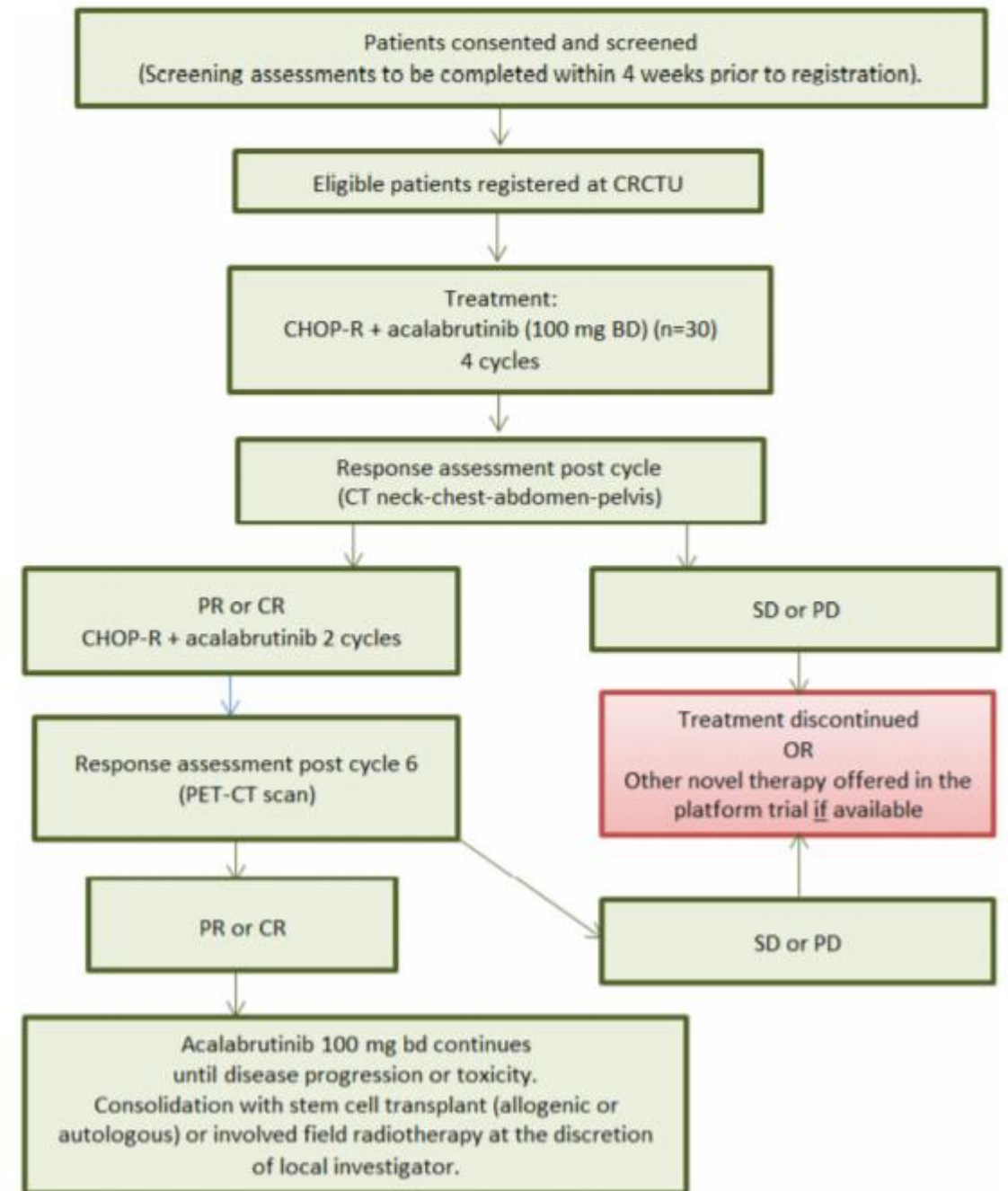


Median OS: 16.3 mos

Future Direction: Cohort with VRCHOP Therapy

STELLAR

- RCHOP vs RCHOP+ acalabrutinib
- Platform to test novel agents

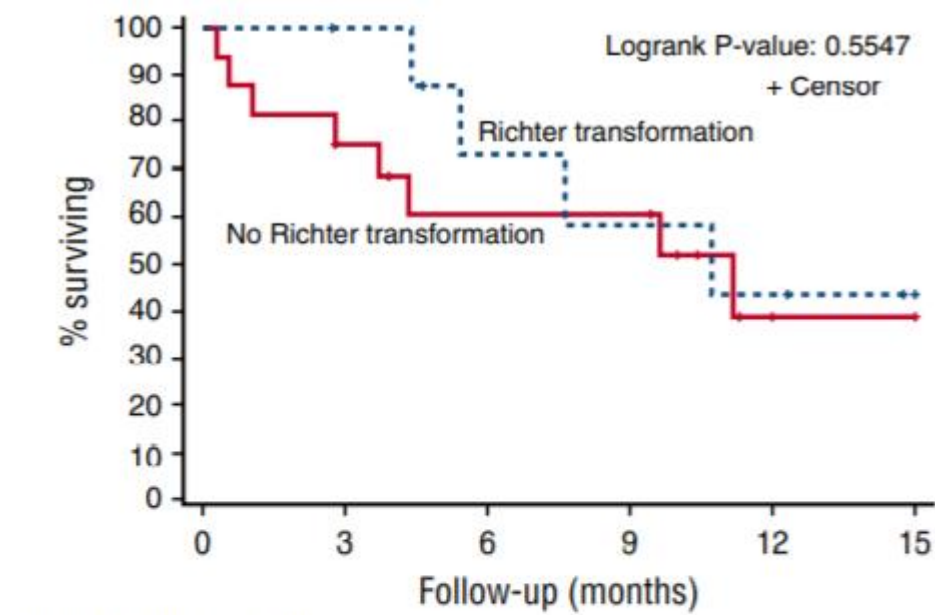
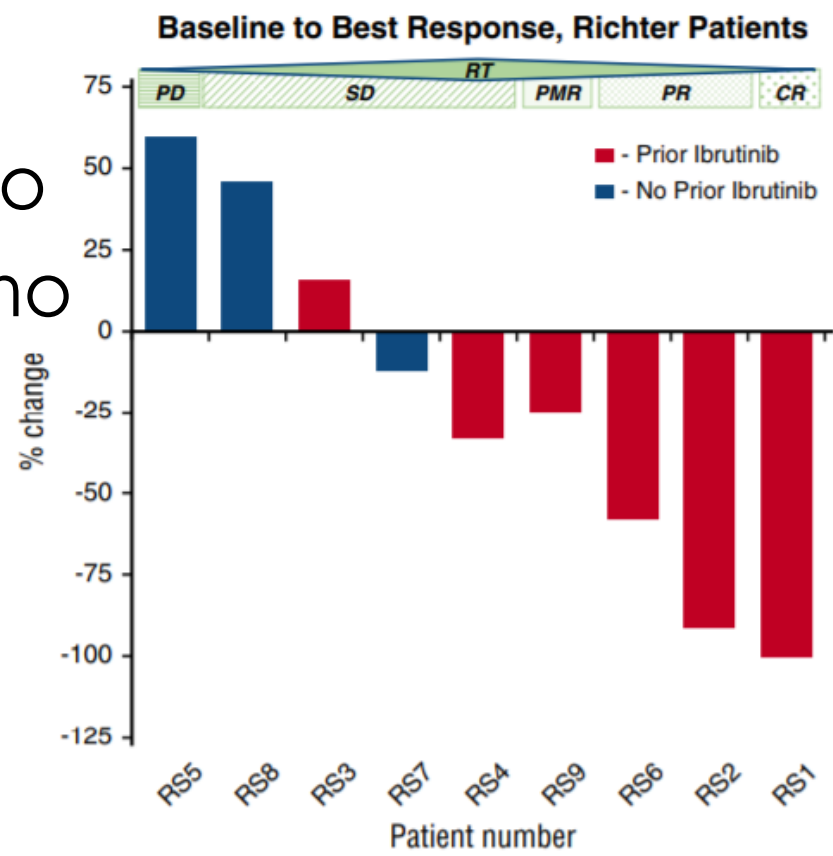


Immunotherapy in RS

Pembrolizumab

Median Follow-up 10.4 mos

- PD1 Inhibitor
- 200mg Q3 weeks
- 9 RS patients
- Median PFS 5.4 mo
- Median OS 10.7 mo

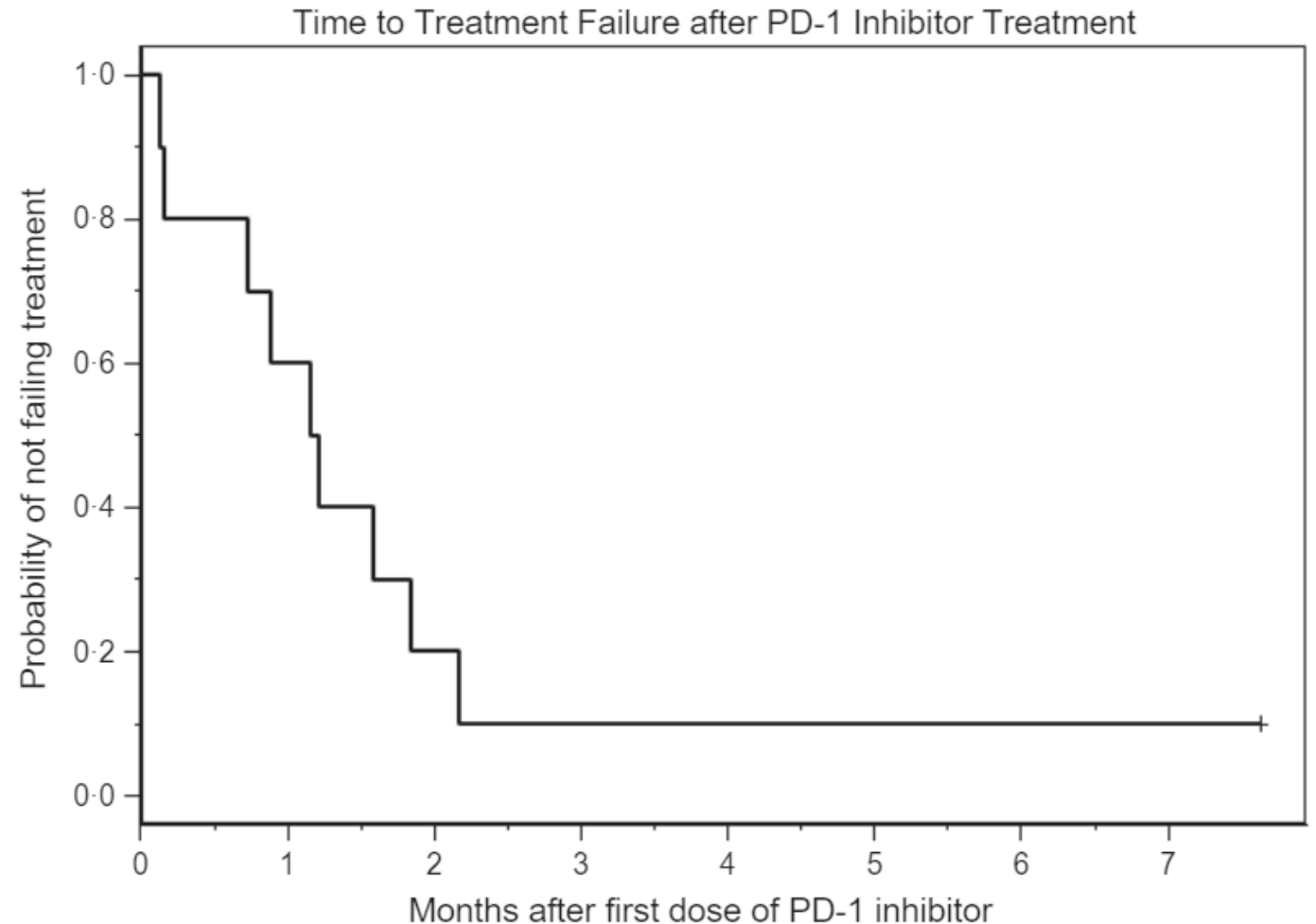


Richter transformation

Patients-at-Risk					
No- 16	11	8	8	1	1
Yes- 9	8	5	4	3	1
Number of Censored Patients					
No- 0	1	1	0	5	0
Yes- 0	1	1	0	0	2

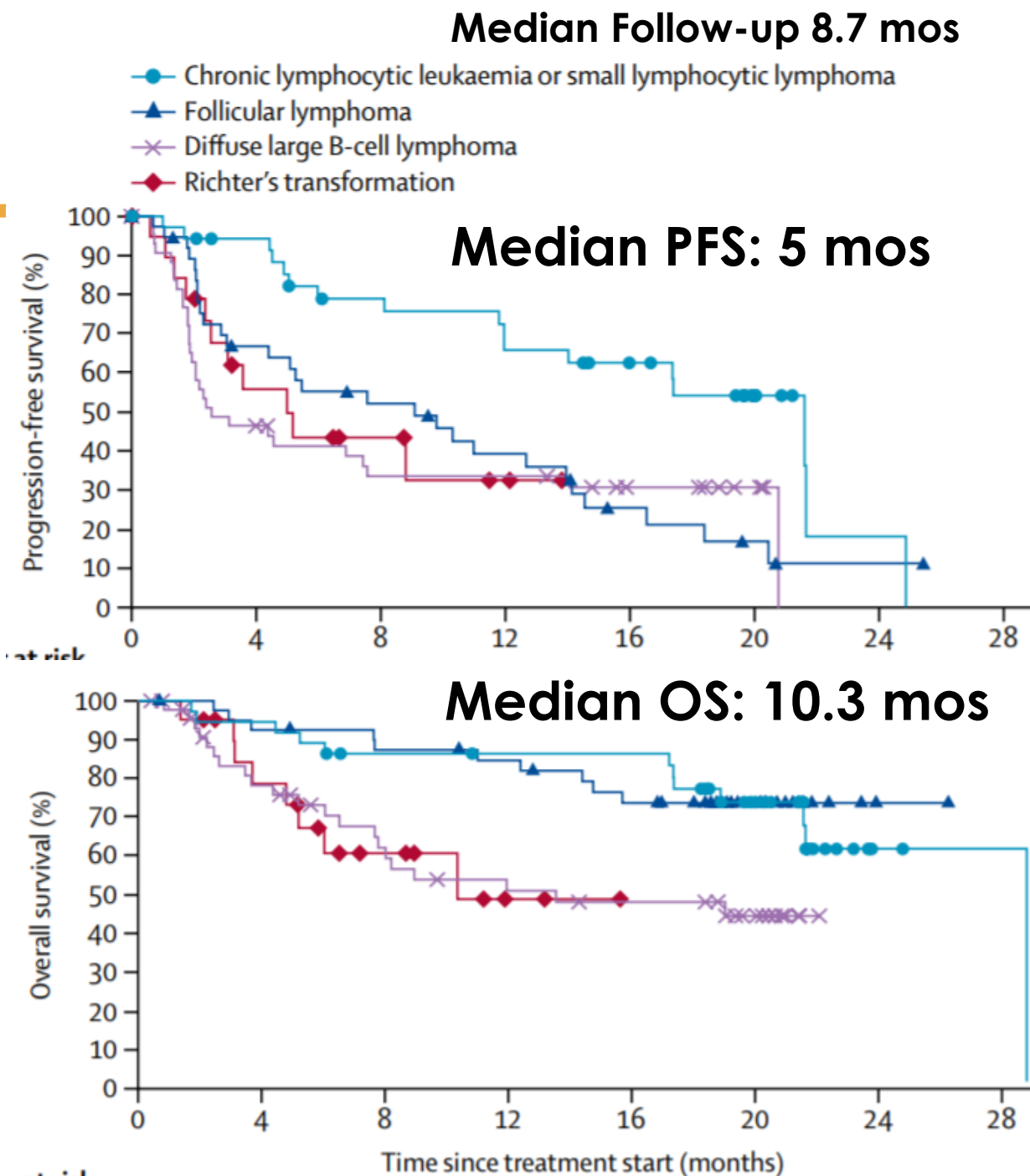
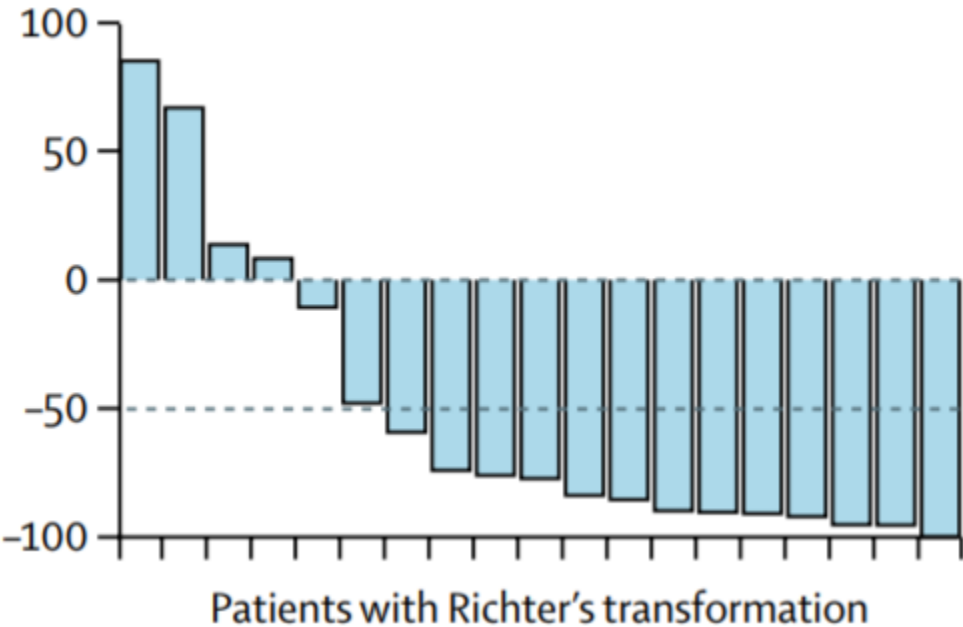
PD1 Retrospective

- 10 RS patients
- 7 = nivolumab
- 3 = pembrolizumab
- Median time to treatment failure 1.2 mo
- Median OS from time of PD1 = 2 mos
- Median OS from RT = 4.2 mos

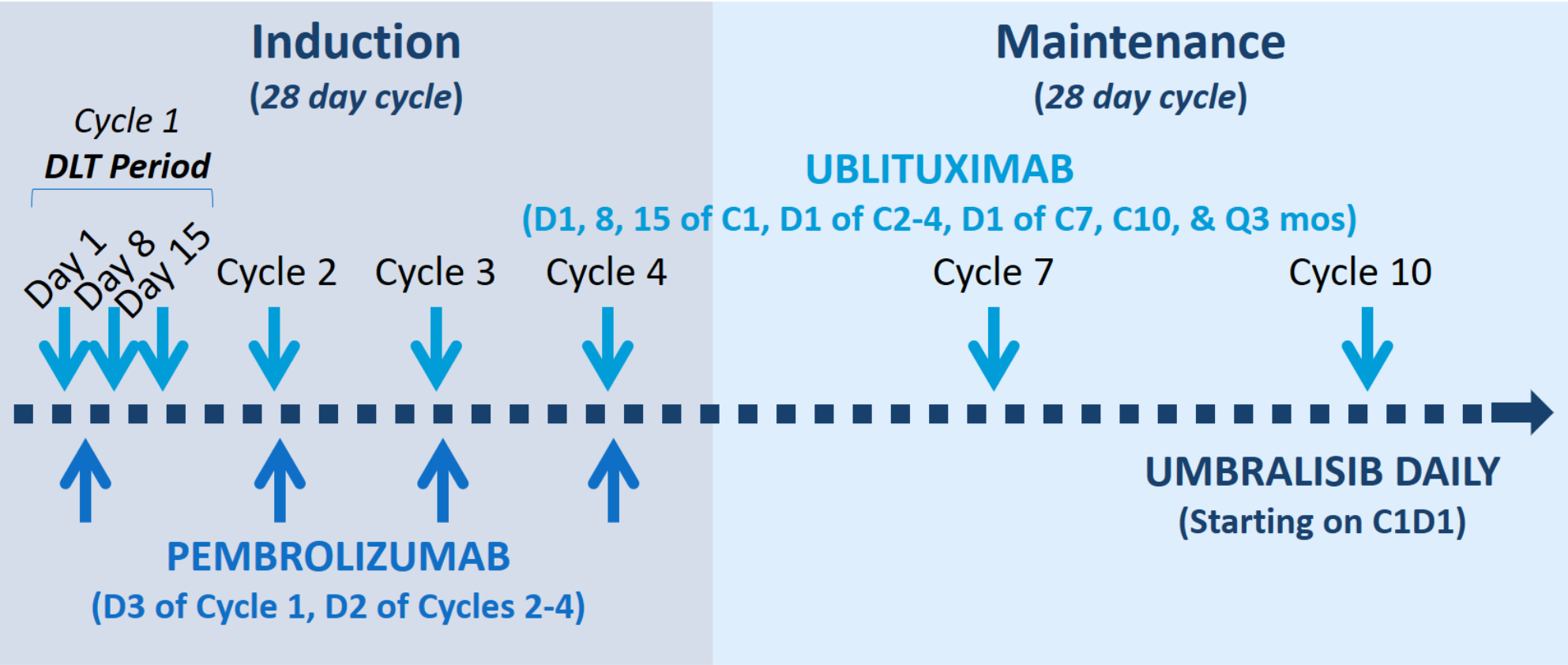


Nivolumab + Ibrutinib

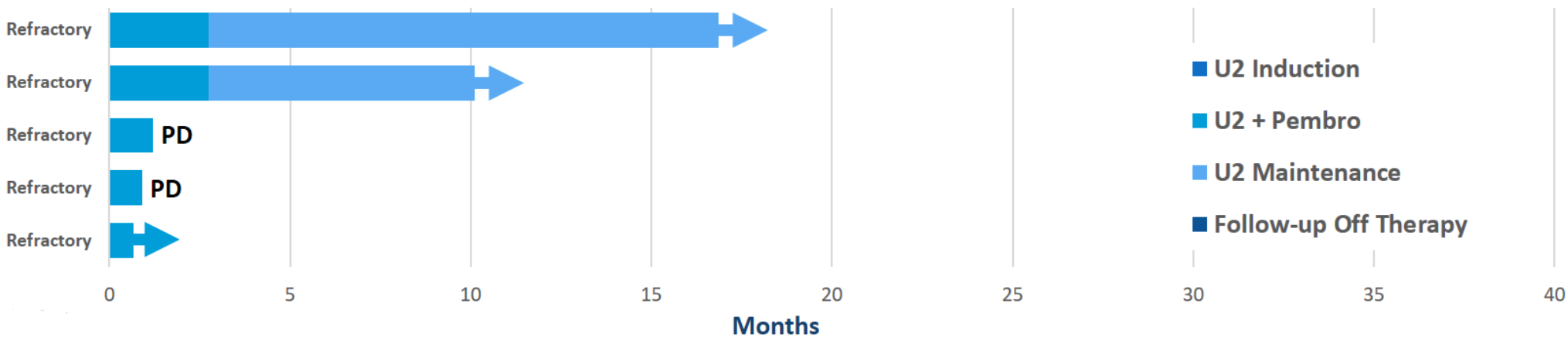
- 20 RS Patients
- 3mg/kg Q2 + 560mg ibrutinib
- ORR 65% (CR 10%)



U2-Pembro



Richter's

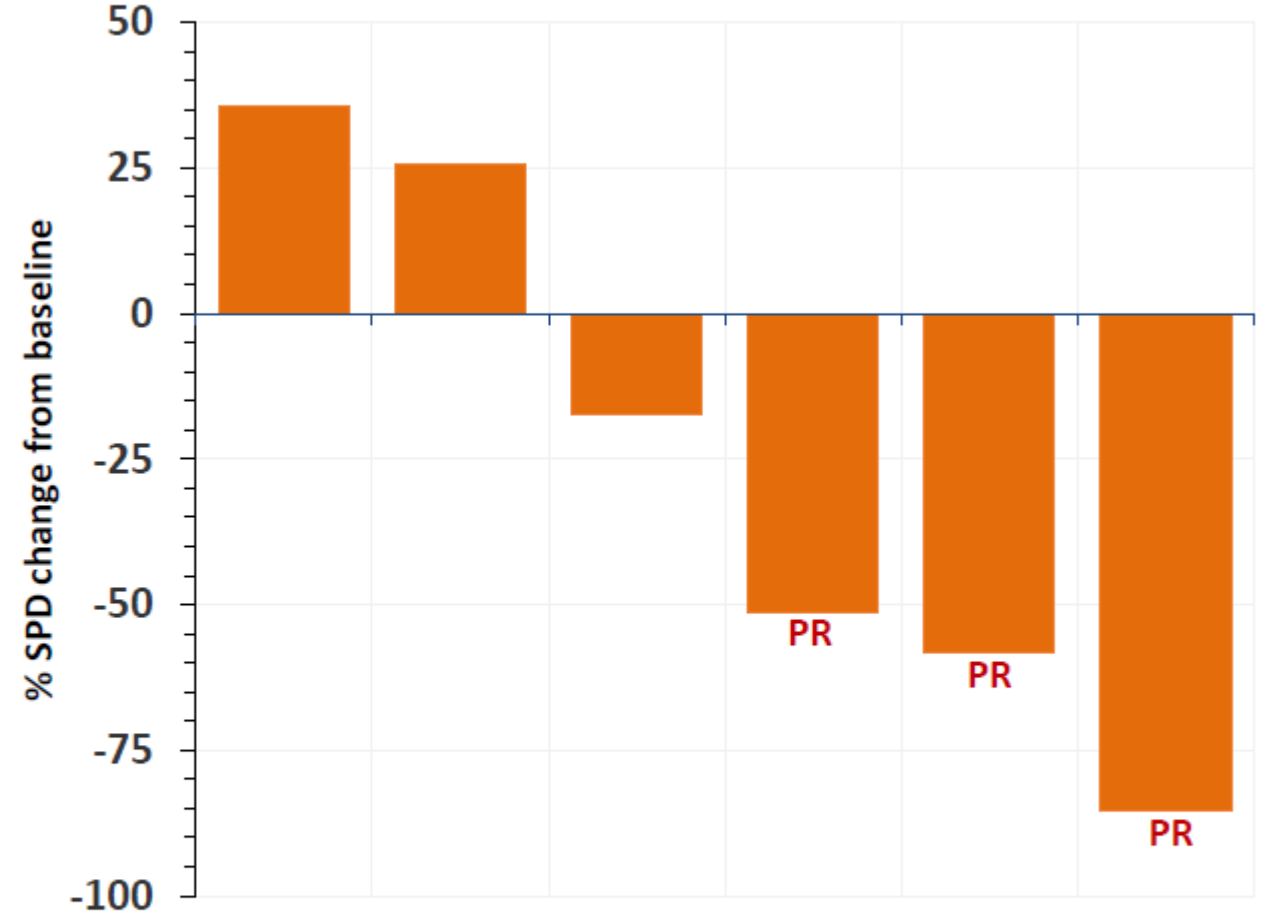


Select Other Novel Therapies in RS

ARQ531

- 3rd Generation Reversible BTK Inhibitor
- Phase 1 Study
- Recommended Dose = 65mg daily

Best Responses in Richter's Transformation Evaluable Patients Treated at 65 mg QD (N =6)



Pt #	41	45	122-36	42	34*	47
Weeks on therapy	10	13	12	19	26	12
IGHV unmutated	Yes	Yes	Yes	Yes	No	Yes
Del 17p/del 11q/ del 13q		Yes	Yes		Yes	Yes

* MYC(+)/BCL6(+) positive

Additional Therapies/Combinations of Interest

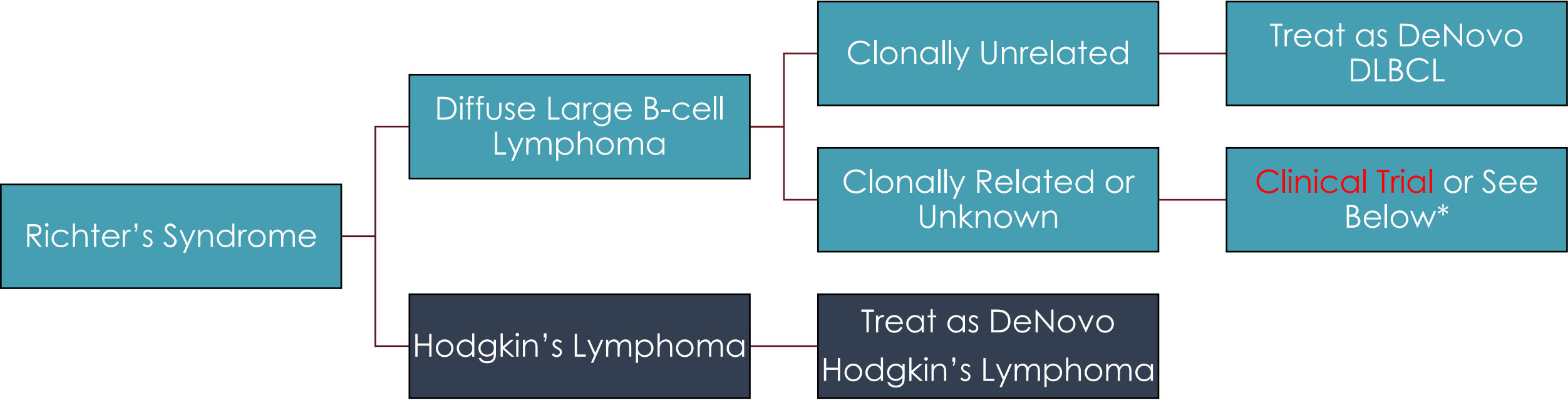
- CART (CD19-directed)
- Blinatumumab (CD3/CD19 bispecific antibody)
- Selinexor (selective inhibitor of nuclear export)
- G-CHOP + Ibrutinib
- Obinutuxumab + HDMP + Ibrutinib
- Etc...

Transplant?

EGBMT Group*	N	3yr OS (%)	NRM (%)
Autologous SCT	34	59	12
Allogeneic SCT	25	36	26
CR/PR at alloSCT	15	41	17
PD at alloSCT	9	17	44

*Retrospective

AutoSCT and AlloSCT are options in the setting of chemotherapy-sensitive RS



Suggested Regimens*

- RCHOP or REPOCH +/- venetoclax
- PD1 + BTKi
- Consider alloSCT if remission is achieved

Case

- No current clinical trial
- REPOCH x 3: Some response but < partial
- Added venetoclax D1-10 with cycle 4
- Clinically responding
- Will continue venetoclax maintenance as is not candidate for transplant d/t comorbidities

Summary

- Richter's syndrome is a rare and deadly complication of CLL
- Clinical and molecular risk factors can predict transformation and survival
- Clonally related RS is more common and shorter survival
- Many therapies have been tested, but significant improvements are still needed
- Consider enrollment of these patients on clinical trial

Advisory
Committee



Glenn



Phillips

Primary Mentors



Deininger



Byrd



Patients, Families,
Colleagues

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Key
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Boucher