Treatment Approach to Richter syndrome in the era of novel therapies

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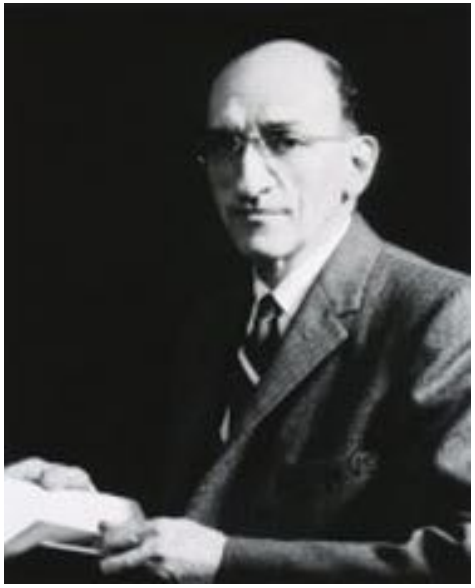
Overview

- Overall of clinical challenge
- Value of PET-CT
- Immunochemotherapy outcomes
- Novel therapies
- Novel therapy – chemotherapy combinations

Richter's Syndrome

- Aggressive, life-threatening syndrome after a 46 year old patient presented with rapidly fatal generalized lymphadenopathy and hepatosplenomegaly.
- Richter's syndrome (RS) was formally coined following 4 autopsies: ''reticular cell sarcoma'' arising in known B-CLL.
- Majority B-CLL transformations to ABC type DLBCL.
- Rare transformations to cHL, Burkitt lymphoma, LBL.



1928, Maurice Richter

M. N. Richter, 1928
P. Lortholary et al., 1964

Retrospective studies describing the cumulative incidence of RS in pts with CLL

Reference	Study period	Cohort restricted to newly diagnosed CLL patients	No. of CLL patients	No. of patients with biopsy-proven RS	Median follow up of CLL, years	Rate of RS (%)	Median time to development of RS, years (range)
Mauro et al, 1999	1984-1994	No	1011	18	NR	**1**	NR
Tsimberidou et al, 2006	1975-2005	No	3986	148	NR	**3.7**	NR
Rossi et al, 2008	1996-2006	No	185	17	4	**9.1**	1.9 (0-6.8)
Alipour et al, 2008	1969-2007	No	465	24	NR	**5**	5 (0.1-21)
Rossi et al, 2009	NR	No	783	69	3.5	**8.8**	1.9 (NR)
Fan et al, 2012	2004-2010	No	149	16	3.5	**10.7**	2.7 (0-6.5)
Parikh et al, 2013	2000-2011	Yes	1641	37	4	**2.1**	1.8 (0-11.7)

PET in RS in immunochemotherapy era

- 332 patients with biopsy + PET-CT
- 95 RS vs 117 aggressive CLL vs 120 indolent CLL.
- Median SUVmax: 17.6, 6.8, and 3.7

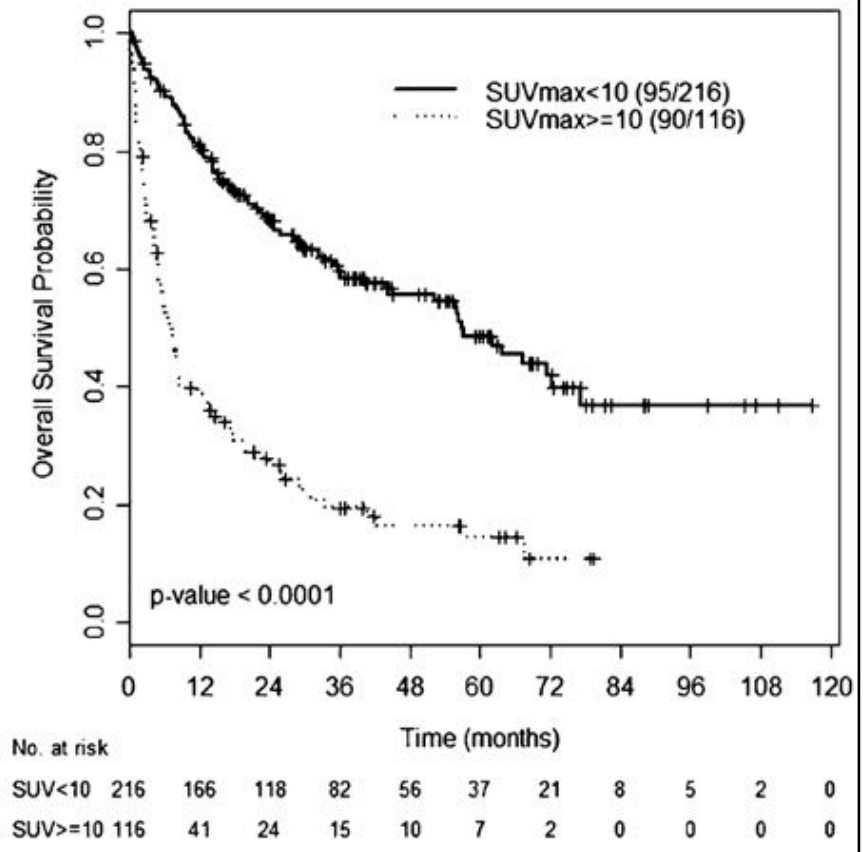
SUVmax ≥ 5

- sensitivity 88%, specificity 47%, PPV 38%, and NPV 92% for confirmed RS.

Table 3. Multivariable logistic regression model for OS

Variable	HR	95% CI	*P*
All patients (n = 332)			
SUV_{max} ≥10	2.3	1.59-3.32	<.0001
PS ≥2	2.3	1.56-3.38	<.0001
Bulky disease	1.7	1.24-2.34	.001
Age ≥65 y	1.45	1.08-1.95	.01
HAC + RS (n = 212)			
PS ≥2	1.96	1.34-2.88	.0006
SUV_{max} ≥10	1.92	1.32-2.78	.0006
Bulky disease	1.62	1.14-2.29	.007

CI, confidence interval; HR, hazard ratio.



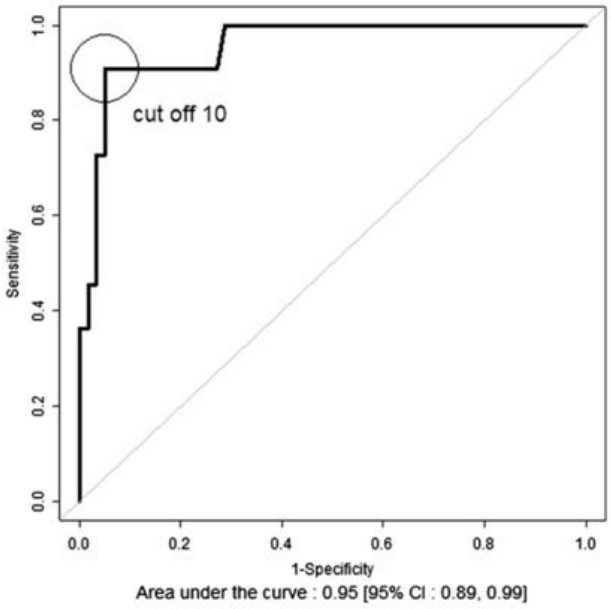
Falchi et al, Blood 2014

PET in RS in immunochemotherapy era

- 240 patients 18F-FDG-PET-CT.
- 10% RS (mSUVmax **>10**) vs 42% ‘aggressive’ CLL (mSUVmax **4.5**) vs 34% 'stable’ CLL (mSUVmax **2.2**) vs 14% other

SUVmax >10

- Sensitivity and specificity ID RS in 91% and 95%, respectively
- Assuming RS prevalence 2.2%, PPV and NPV using >10 threshold: 28.7% and 99.8%, respectively;
- Assuming RS prevalence 8% RS prevalence, PPV and NPV: 60.6% and 99.2%, respectively.



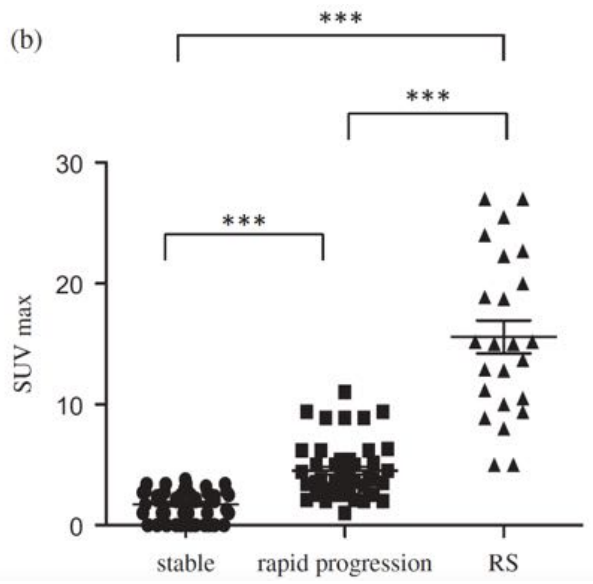


Figure 2. ROC analysis curve.

Michallet et al, Leukemia & Lymphoma 2016

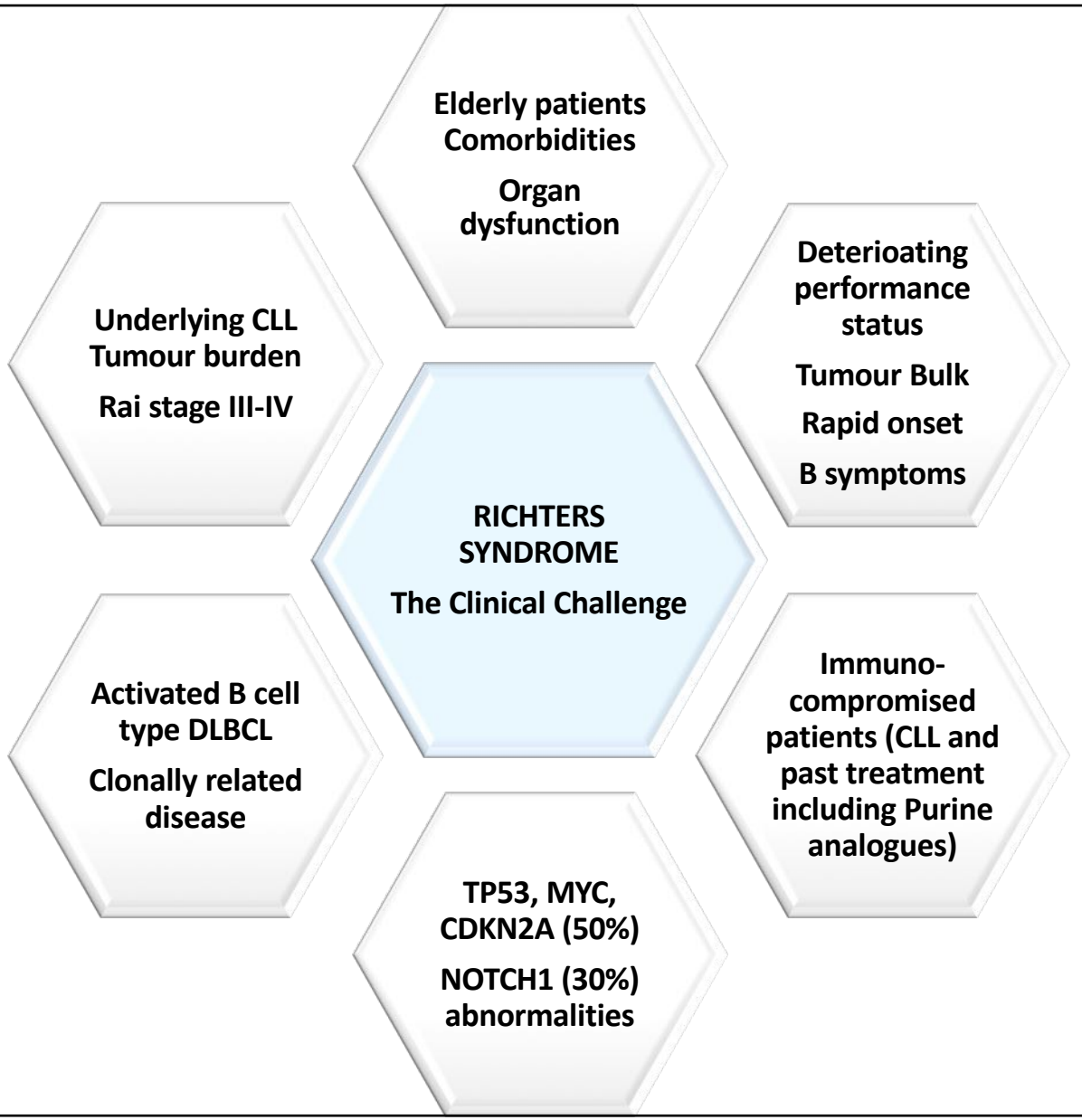
PET in RS in the post BCRi Era

- Screening PET-CT prior to venetoclax therapy phase II trial
- All with SUVmax ≥ 10 or high risk clinical features -> biopsy
- 167 patients screened
- 84 (50%) LN SUVmax ≥5
- 25 (15%) LN SUVmax ≥10
- 35 biopsied, 19 SUVmax ≥10; 16 SUVmax <10 + high risk features
- 8 RT (22%) (4.8% of 167 post BCRi)

SUVmax ≥10: sensitivity 71%, specificity 50%, PPV 26%, NPV of 88% for detection of biopsy-confirmed RT versus CLL PD post-BCRi (OR 2.5 [0.4–15], p=.318)

No difference in sensitivity with SUVmax ≥5 (71%)

Mato et al, Haematologica, 2019



Eyre & Schuh 2017

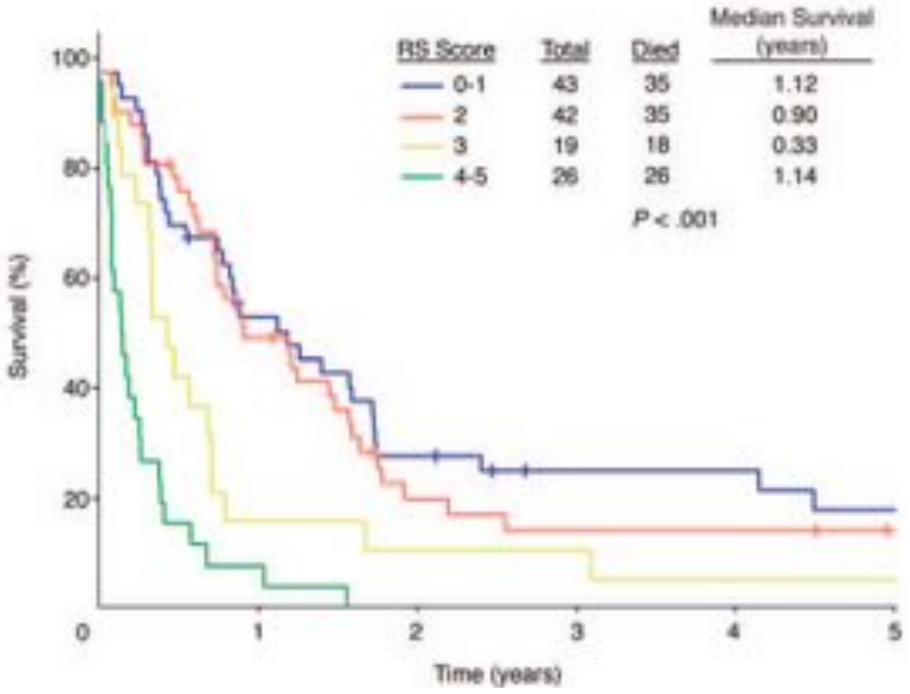
Historical (immuno)chemotherapy for patients with RS

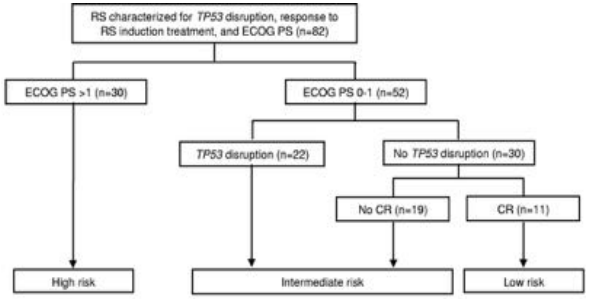
Reference	Treatment regimen	Accrual period	n	Median age, years (range)	Response rate (%)		Allogeneic SCT (%)	Grade 3/4 toxicity (%)			TRM (%)	Median survival
					CR	ORR		Neutropenia	Thrombopenia	Infection		
Anthracycline-containing regimens												
Langerbeins et al, 2014	R-CHOP	NR	**15**	69 (NR)	7	67	NR	55	65	28	3	**21 months**
Dabaja, 2001	HyperCVXD	NR	**29**	61 (36-75)	38	41	NR	100	79	39	14	**10 months**
Tsimberidou et al, 2003	Rituximab and GM-CSF with alternating hyperCVXD and MTX/cytarabine	1999-2001	**30**	59 (27-79)	27	43	NR	100	40	59	18	**8 months**
Platinum-containing regimens												
Tsimberidou et al, 2008	OFAR1	2004-2006	**20**	59 (34-77)	10	50	15	84	94	12	7	**8 months**
Tsimberidou et al, 2013	OFAR2	2007-2010	**35**	63 (40-81)	6	43	20	89	77	20	NR	**6.6 months**
Fludarabine-containing regimens												
Giles et al, 1996	PFA or CFA	1992-1996	**12**	59 (49-74)	18	45	NR	NR	NR	NR	NR	**17 months**
Tsimberidou et al, 2002	FACPGM	1997-2001	**15**	62 (42-74)	5	5	0	90	83	55	20	**2.2 months**
Radioimmunotherapy												
Tsimberidou et al, 2004	^{90}Y ibritumomab tiuxetan	2000-2002	**7**	56 (44-70)	0	0	0	29	71	13	NR	NR

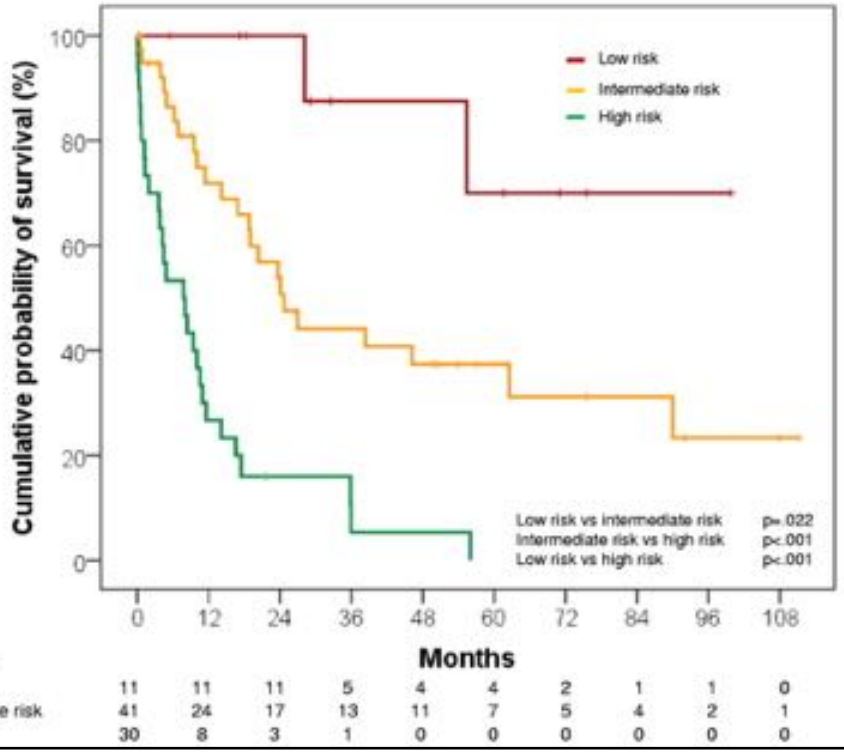
Classification RS into risk-of-death categories and survival

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

Abbreviation: RR, relative risk.



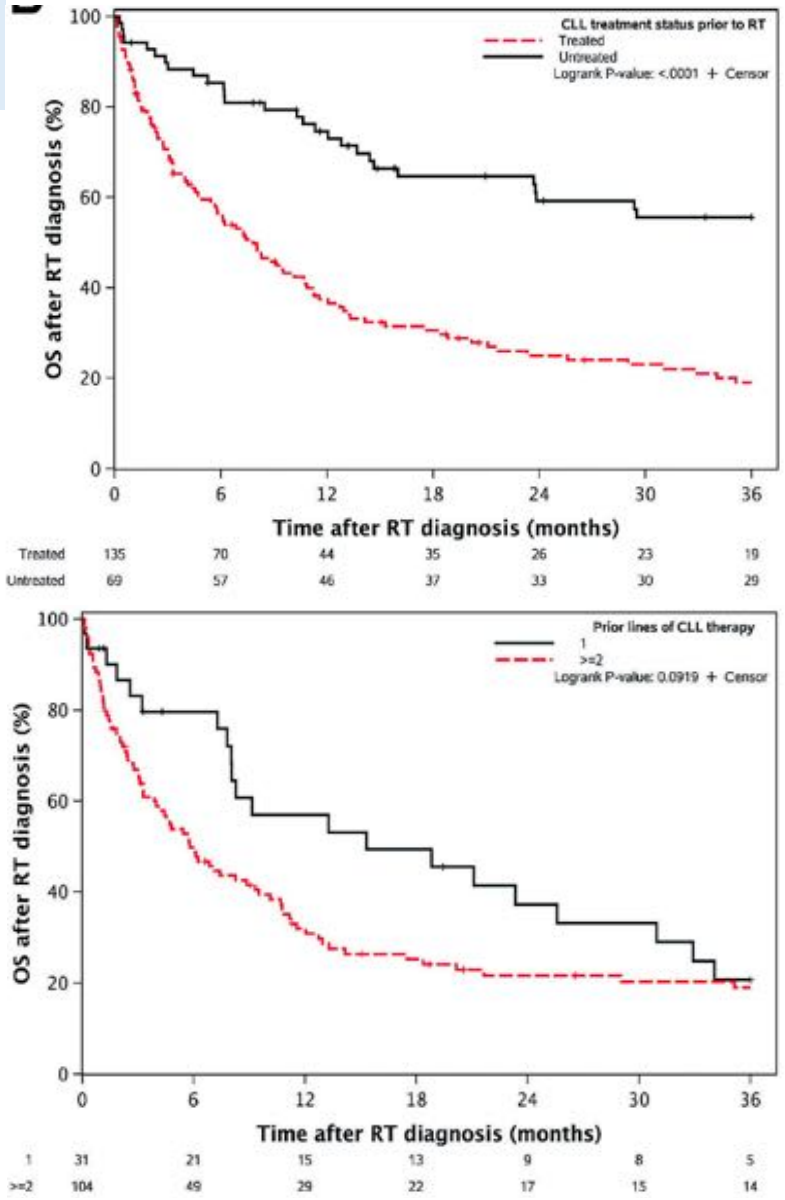




Tsimberidou AM, et al J Clin Oncol. 2006; Rossi et al. Blood 2011;117:3391-3401

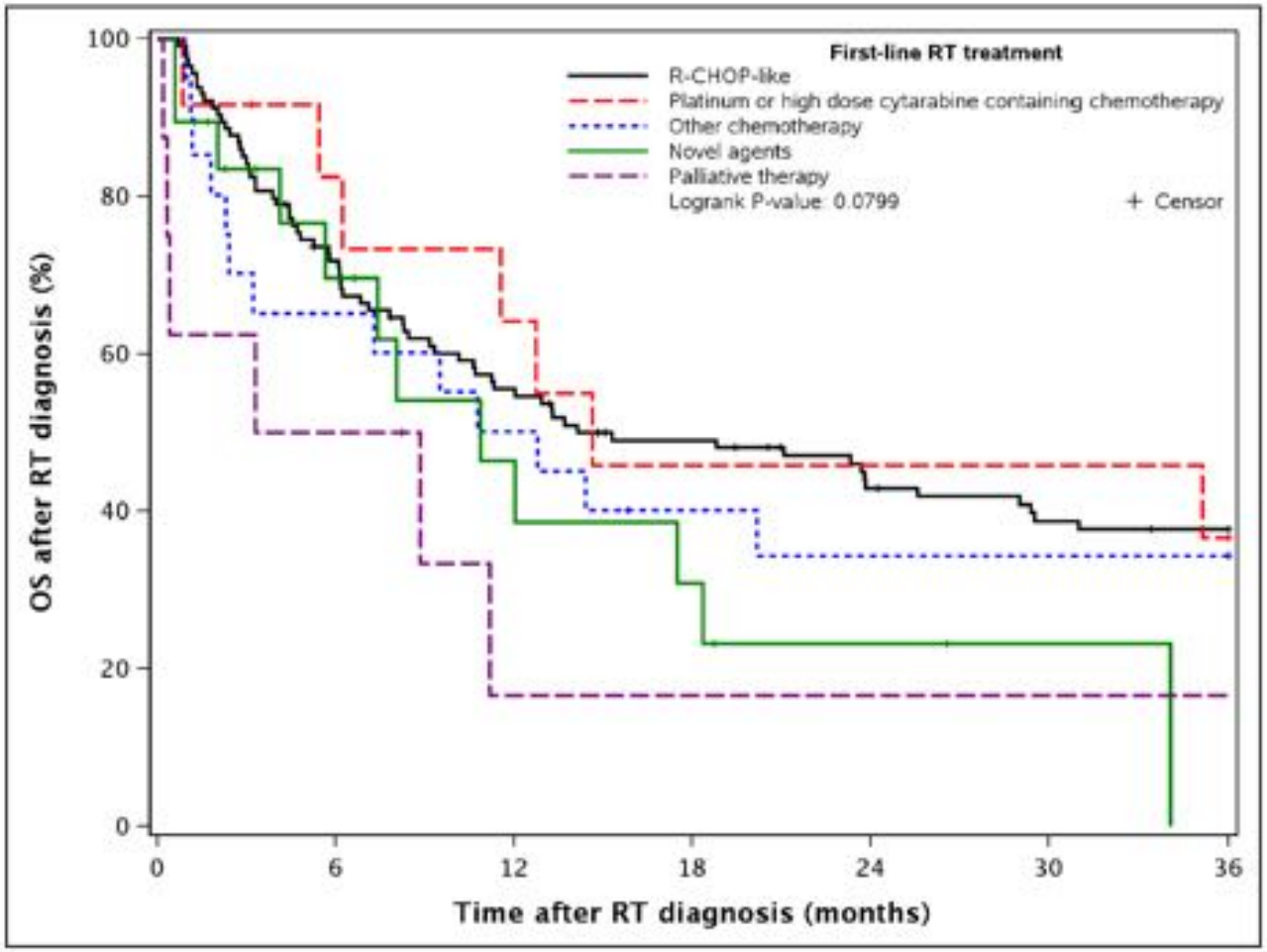
Outcome of treatment naïve patients

- 204 RS patients
- 1993-2018
- mOS 12.0 months.
- Rx naive: mOS: 46.3 vs 7.8m p<0.001.
- In MVA: raised LDH (HR 2.3, p=0.01), prior CLL Rx (HR 2.0, p=0.01), and age (HR 1.03, p=0.01) a/w worse OS.
- 12% SCT (20 autoSCT and 4 alloSCT), post-transplant mOS 55.4 months.



Wang et al, Haematologica, 2019

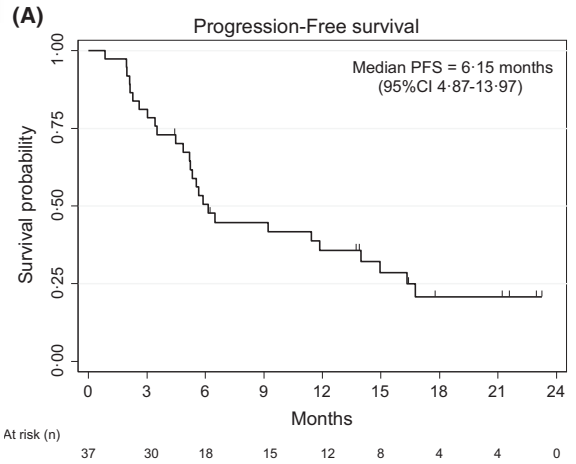
OS after RS by first line RT treatment

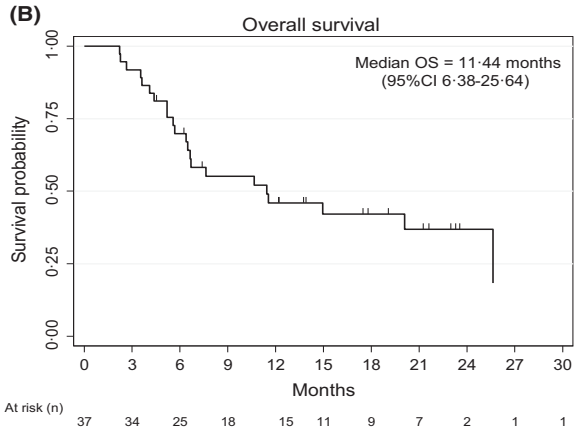


Wang et al, Haematologica, 2019

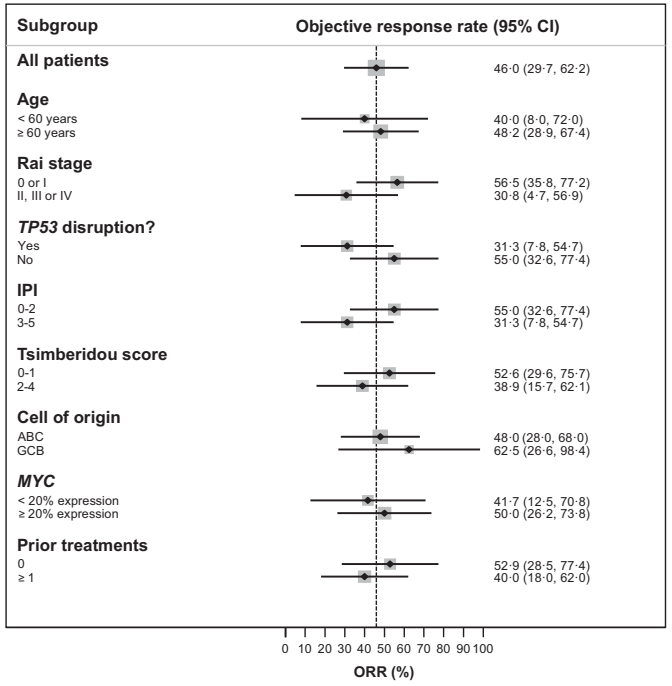
bjh research paper

NCRI phase II study of CHOP in combination with ofatumumab in induction and maintenance in newly diagnosed Richter syndrome



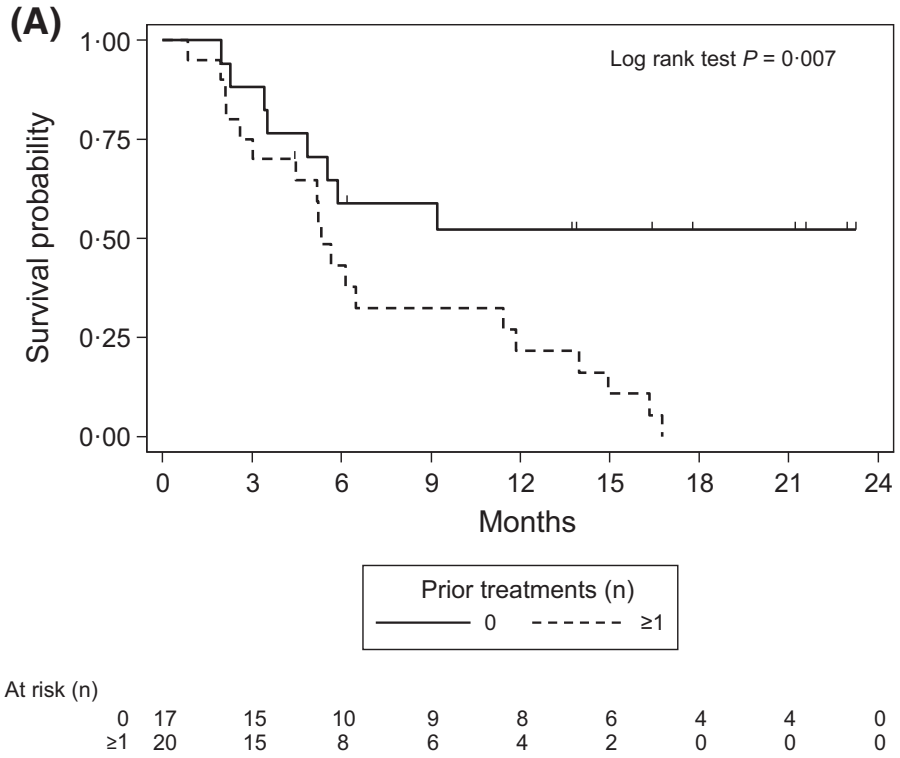


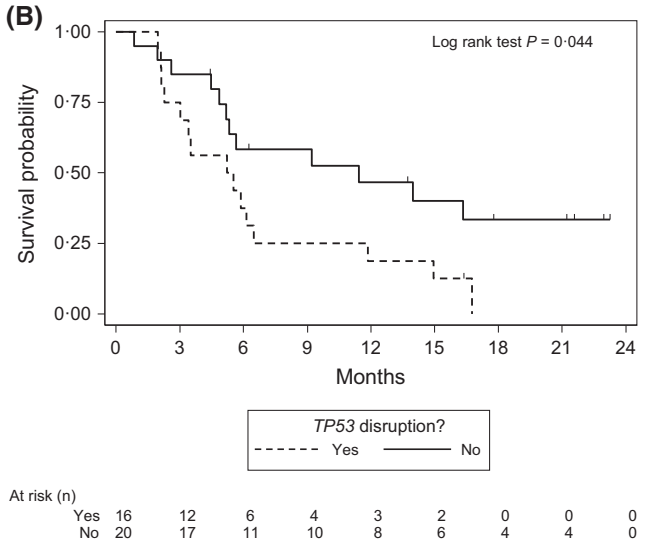
- 43 recruited; 37 evaluable
- 73% >60 years, 70% M
- >50% FC-based regimen as prior Rx for CLL
- ORR 65% after 4 cycles
- ORR 44% (CR 25%, PR 19%) at 6 cycles
- mPFS 6.1 m mOS 11.4m
- 7 platinum-salvage at PD: nil responders
- 1 salvaged with acalabrutinib -> alloSCT

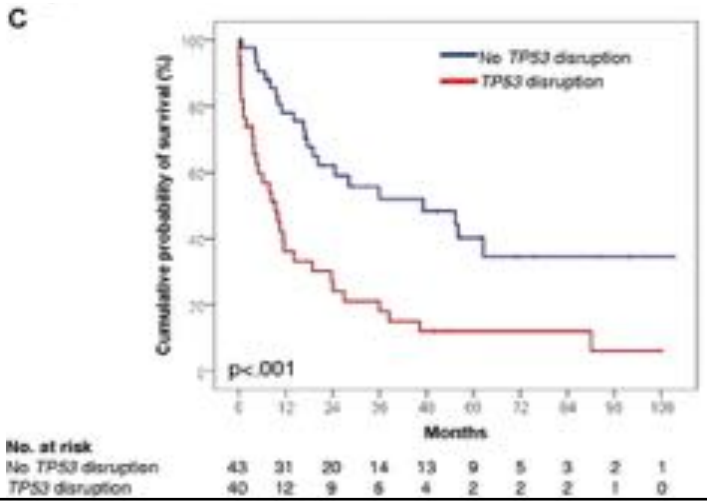


Eyre et al, BJH 2016

CHOP-Ofatumumab: Prior treatment lines / TP53 status



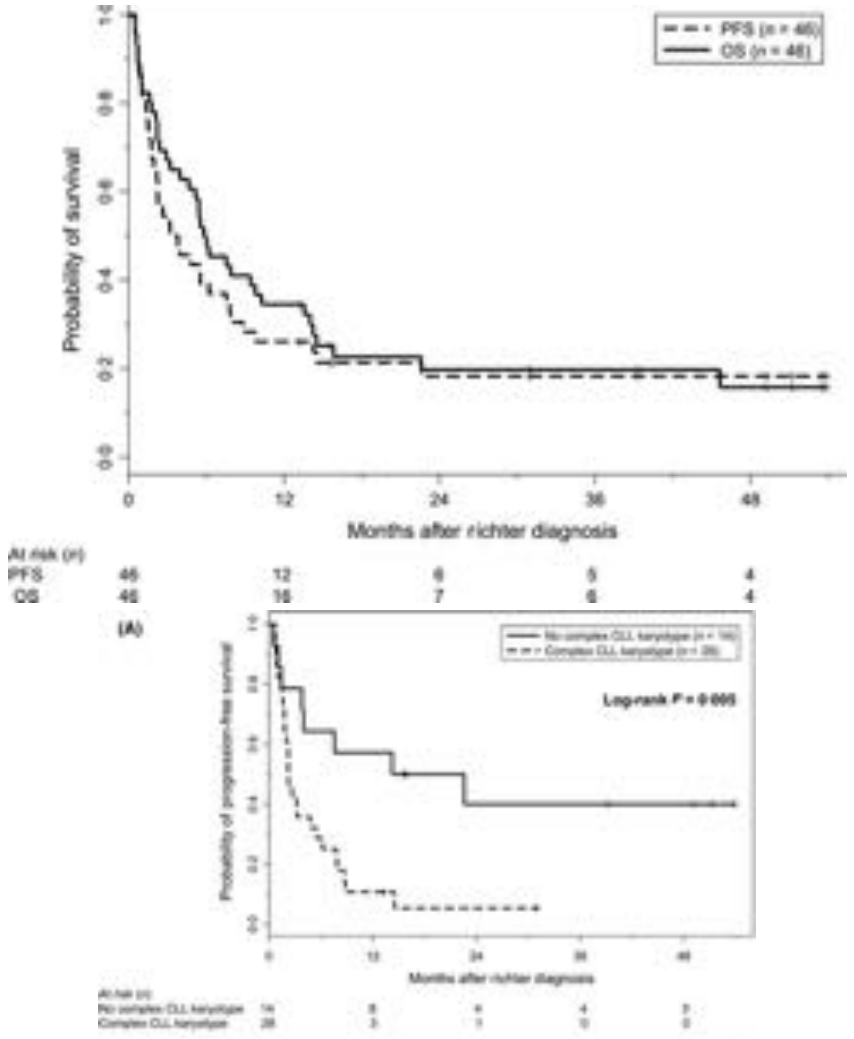




Eyre et al, BJH 2016, Rossi et al, Blood 2016

Value of intensification? First line R-EPOCH: single institution study

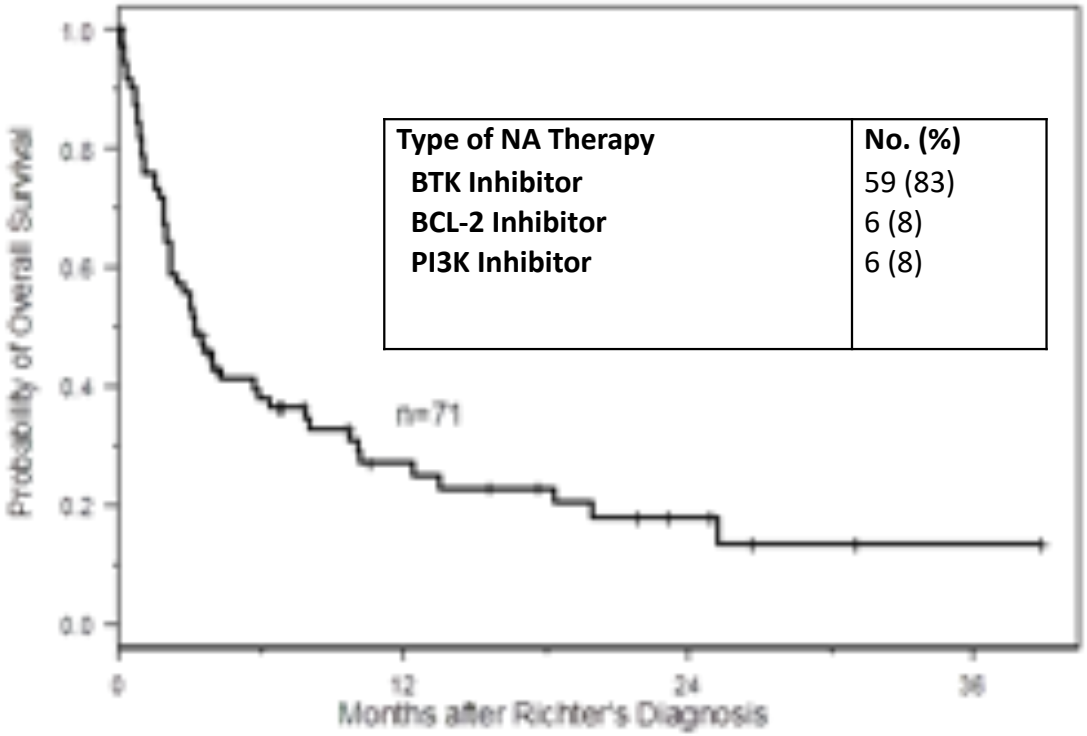
- N= 46
- mPFS 3·5m [95% CI 2·0–7·6]
- mOS 5·9m (95% CI 3·2–10·3)
- 30% died without PD or response.
- MVA: CK most significant predictor of decreased OS [HR 2·72, p=0·025], adjusting for no. of prior CLL Rx (p=0·036).



Rogers et al, BJH 2018

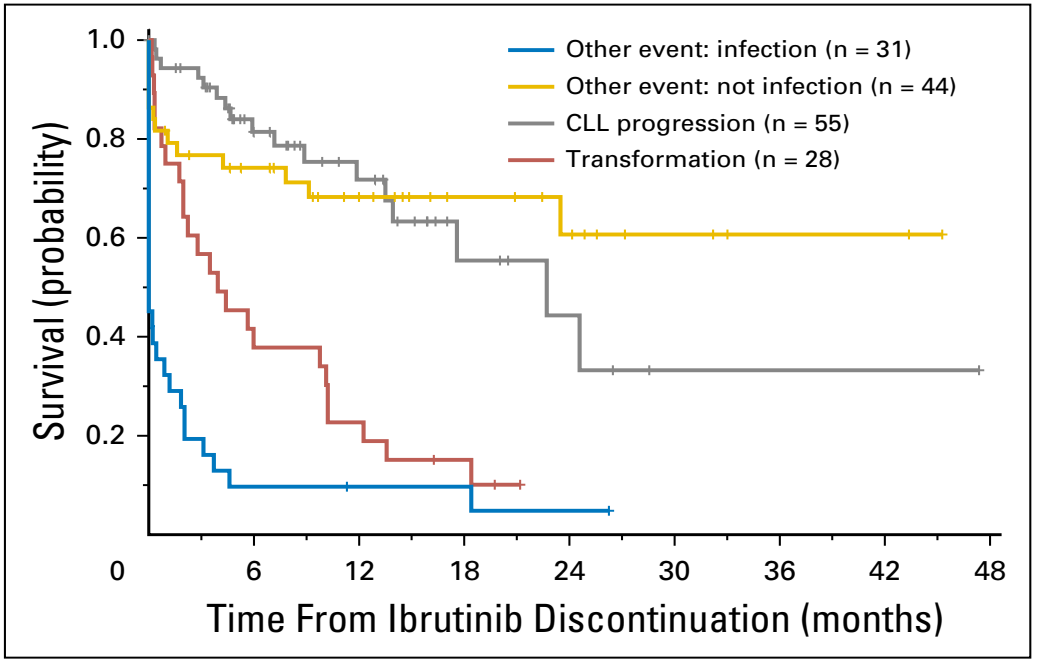
RS prognosis post Novel Agents

Median OS = 3.3 months



Type of NA Therapy	No. (%)
BTK Inhibitor	59 (83)
BCL-2 Inhibitor	6 (8)
PI3K Inhibitor	6 (8)

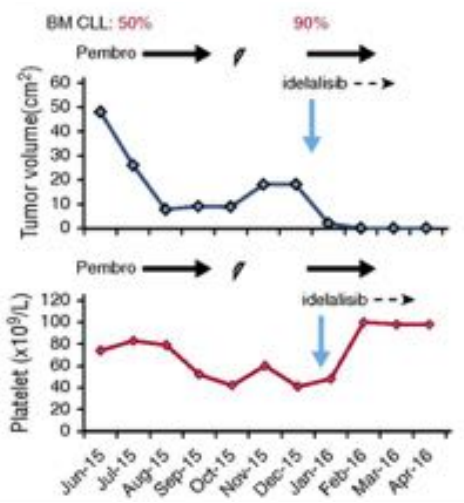
Median OS = 3.9 months

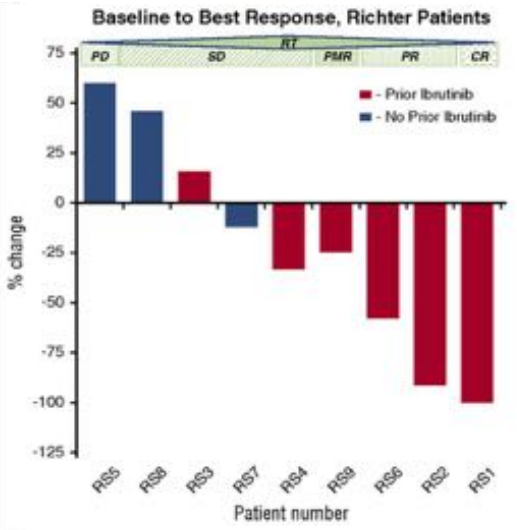


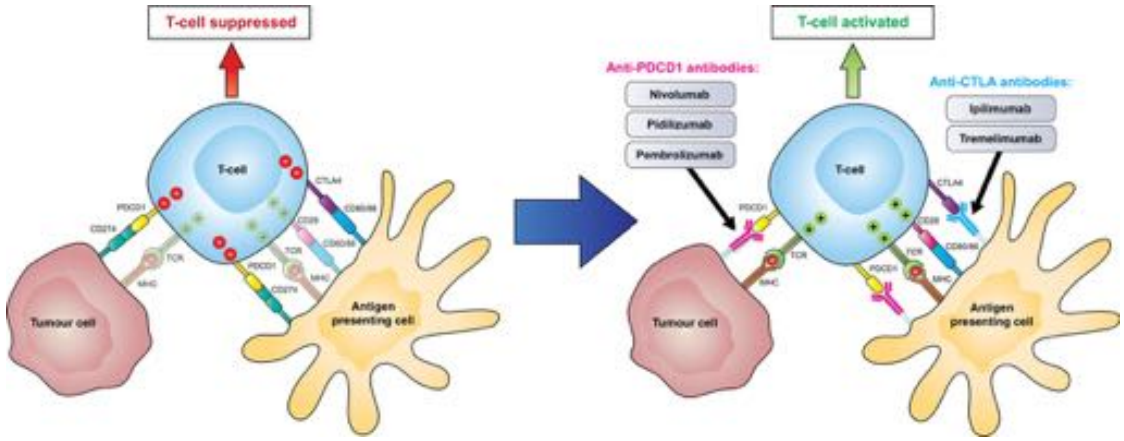
Davids et al., *J Clin Oncol* 35, no.15_suppl (May 2017) 7505; Woyach et al, JCO 2017

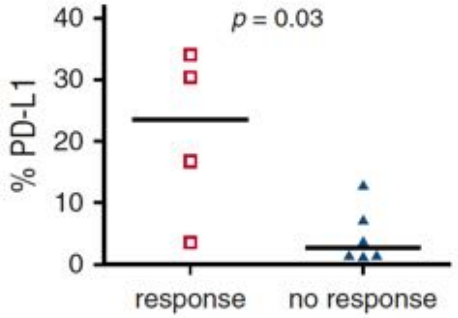
Pembrolizumab in Richter's transformation

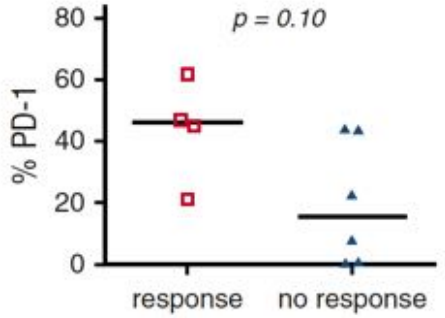
- 200 mg every 3 wks
- 16 relapsed CLL and 9 RT (all DLBCL)
- 60% prior ibrutinib.
- RT pts: median 5 (1-10) prior lines
- ORR 4/9 RT (44%); CLL 0%.
- All responses in RT prior ibrutinib.
- mPFS 5.4 months; mOS NR











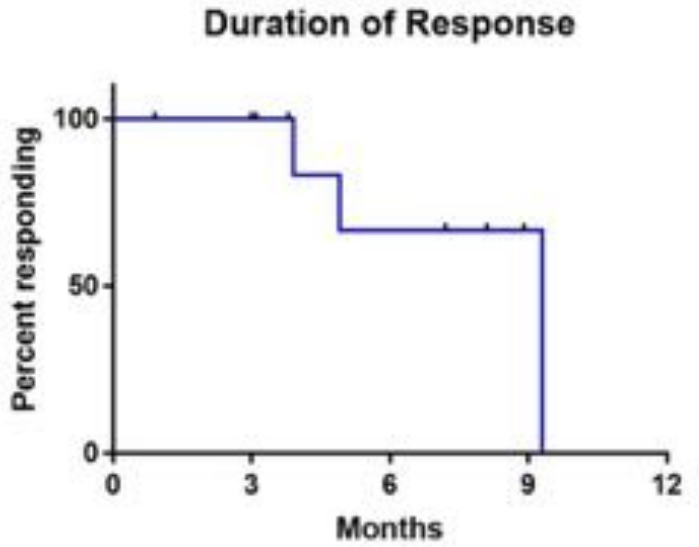
Ongoing international study of single agent pembrolizumab in CLL pts with RT (#NCT02576990).

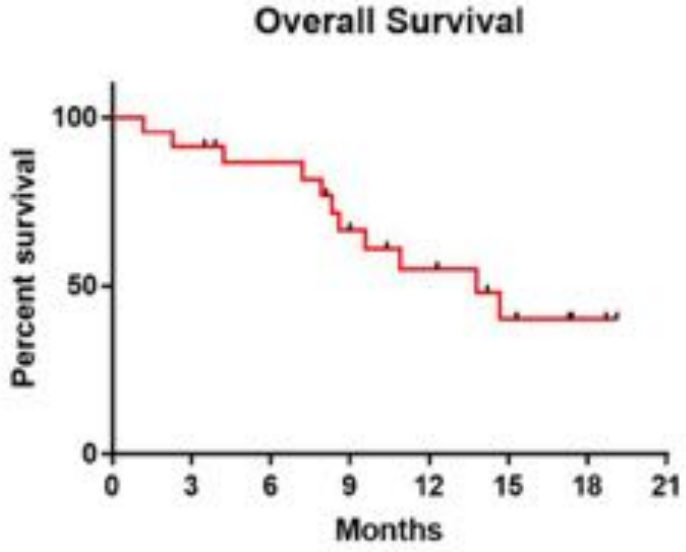
Ding W et al. Blood 2017

Nivolumab with ibrutinib in RT

- Nivolumab 3 mg/kg IV 2 weekly, up to 24 cycles.
  Ibrutinib 420 mg o.d. C2 D1 until PD/tox.

  N=23
  median 65 years (49-88).
  median prior Rx for CLL/RT 3 (0-10);
  ibrutinib (n=11), acalabrutinib (n=1), P13Ki (n=4), venetoclax (n=3), allo-SCT (n=2).
  ORR 43% (CMR, n=8; PMR, n=2).
  mDOR 9.3 months
  2 pts prior ibrutinib responded.
  4 underwent a subsequent allo-SCT after response.
  Median OS 13.8 months.
  1 pt G3 transaminitis; 1 G4 lipase/amylase elevation. 1 G2 pneumonitis, and 1 G2 uveitis.



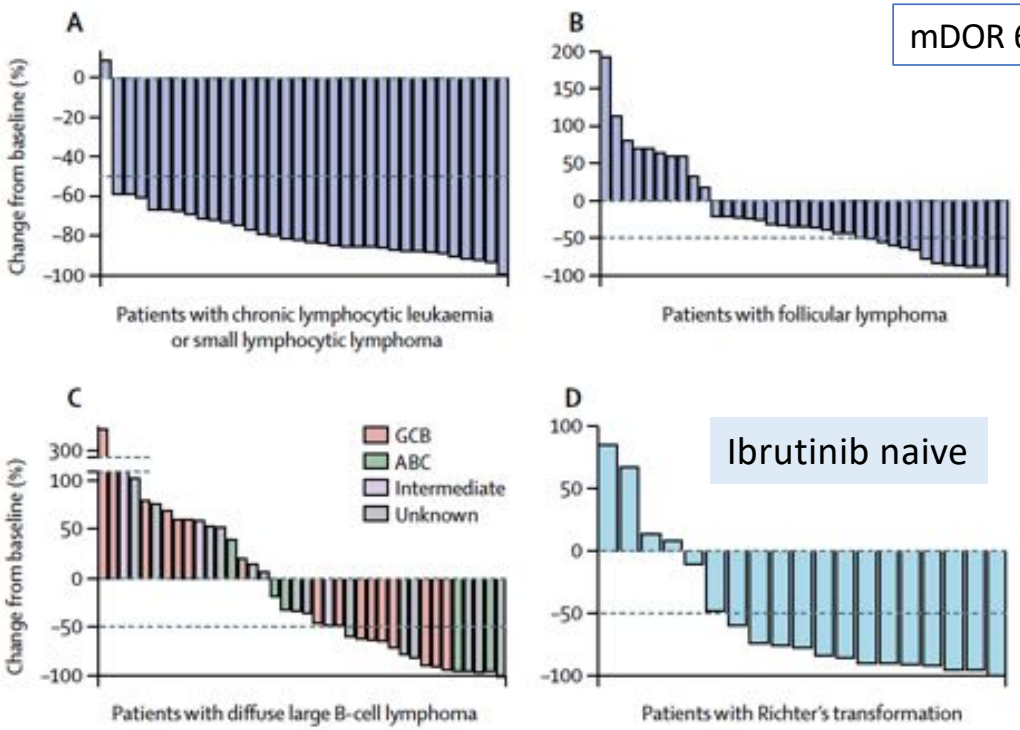


Jain et al, ASH 2018

Nivolumab with ibrutinib in RT

Response	CLL (n=36)	FL (n=40)	DLBCL (n=45)	RT (n=20)
ORR	75%	33%	36%	65%
CR	0%	10%	16%	10%
PR/PR-L	75%	23%	20%	55%

mDOR 6.9m



Ibrutinib naive

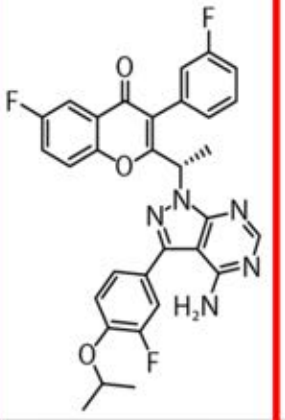
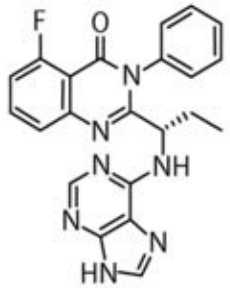
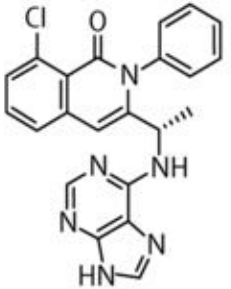
	Total (n=141)	Chronic lymphocytic leukaemia and small lymphocytic lymphoma (n=36)	Follicular lymphoma (n=40)	Diffuse large B-cell lymphoma (n=45)	Richter's transformation (n=20)
Age (years)	65·0 (54·0–71·0)	65·0 (57·0–71·0)	62·0 (52·5–70·0)	64·0 (46·0–74·0)	67·5 (56·0–70·5)
Sex					
Male	87 (62%)	27 (75%)	23 (58%)	29 (64%)	8 (40%)
Female	54 (38%)	9 (25%)	17 (43%)	16 (36%)	12 (60%)
Ethnic origin					
White	134 (95%)	36 (100%)	37 (93%)	41 (91%)	20 (100%)
Asian	5 (4%)	0	2 (5%)	3 (7%)	0
Other	1 (1%)	0	1 (3%)	0	0
Unknown or not reported	1 (1%)	0	0	1 (2%)	0
ECOG performance status					
0	70 (50%)	17 (47%)	30 (75%)	19 (42%)	4 (20%)
1	60 (43%)	18 (50%)	8 (20%)	21 (47%)	13 (65%)
2	11 (8%)	1 (3%)	2 (5%)	5 (11%)	3 (15%)
Previous lines of treatment	3·0 (2·0–3·0)	2·0 (1·0–2·5)	3·0 (2·5–4·0)	3·0 (2·0–3·0)	2·0 (1·0–3·0)
Previous alkylating agents	141 (100%)	36 (100%)	40 (100%)	45 (100%)	20 (100%)
Previous purine analogues	82 (58%)	28 (78%)	11 (28%)	32 (71%)	11 (55%)
Bulky disease (≥5 cm)	68 (48%)	26 (72%)	15 (38%)	17 (38%)	10 (50%)

Younes et al, Lancet Haematology 2018

U2 plus Pembrolizumab in Richter's transformation

Pi3Ki and PD1i: key interaction between Pi3K signalling and immune checkpoint surveillance: inhibition of Pi3K delta decreases PDL1 expression. Potential synergistic activity

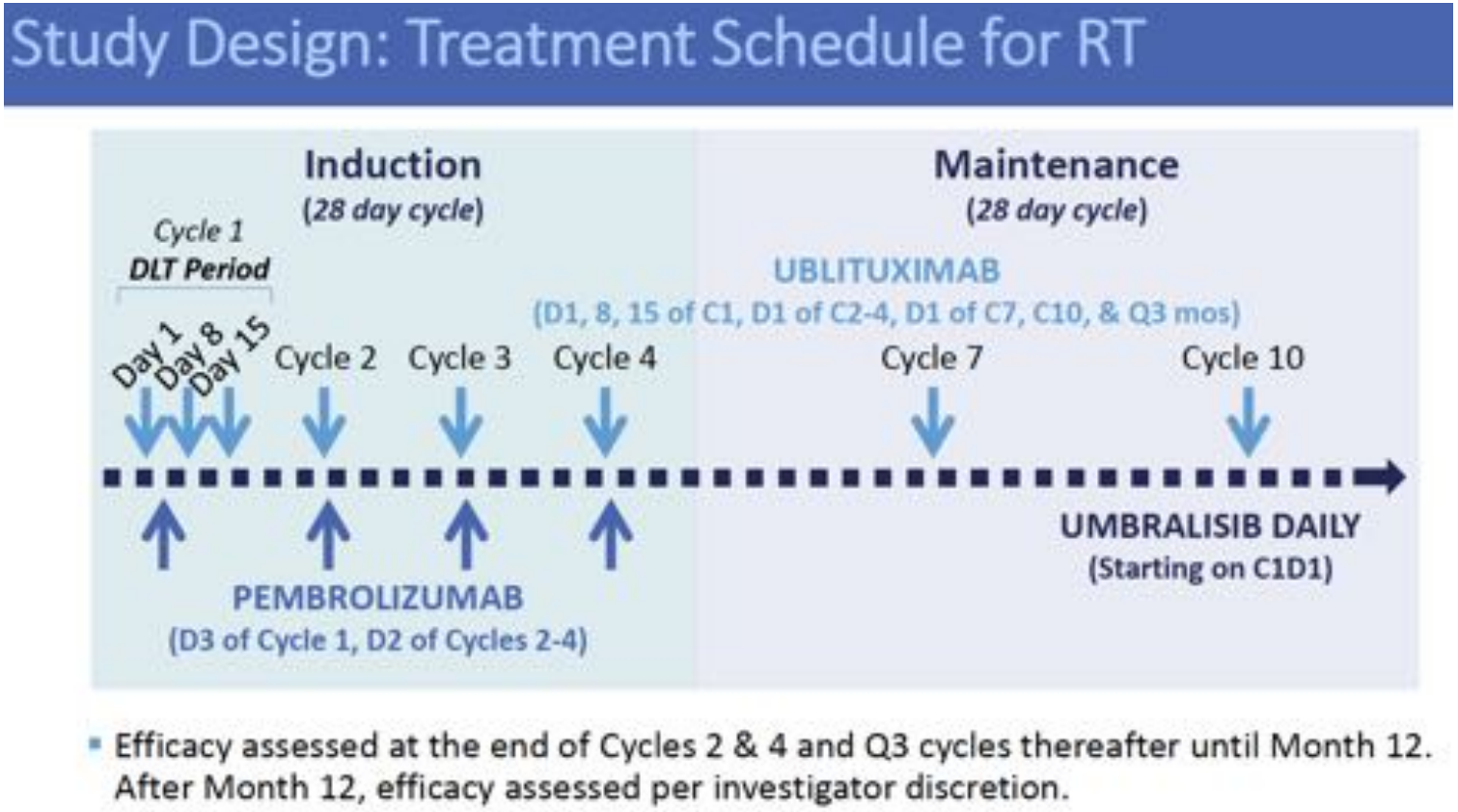
Umbralisib: next gen Pi3K delta inhibitor
-unique structure, improved tolerability / selectivity
-inhibition CK1ε**: potential regulator of T reg count and function. Less immune-related tox**

	Umbralisib	Idelalisib	Duvelisib
			
Isoform		K_d (nM)	
PI3Kα	>10 000	600	40
PI3Kβ	>10 000	19	0·89
PI3Kγ	1400	9·1	0·21
PI3Kδ	6·2	1·2	0·047
CK1ε	180	>30 000	>30 000

Mato et al, ASH 2018, ICML 2019

U2 plus Pembrolizumab in Richter's transformation

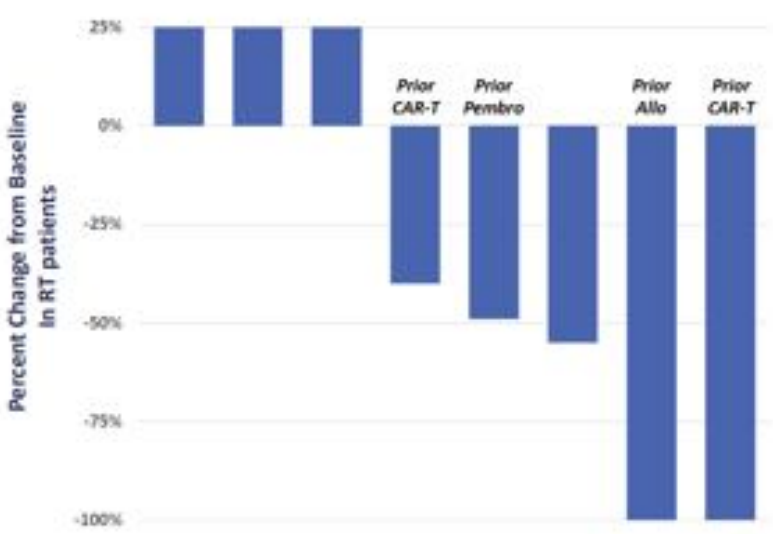
- **Phase I/II (3+3). U2+PEMBRO**
- RT pts: refractory or ineligible for immunochemotherapy
- Prior PD1 and PI3Ki not an exclusion



Mato et al, ASH 2018, ICML 2019

U2 plus Pembrolizumab in Richter's transformation

Richter's Transformation	
Evaluable for Safety, n	9
Evaluable for Efficacy[†], n	8
Median Age, years (range)	66 (53 - 73)
Male/Female	6 / 3
ECOG, 0/1/2	3 / 5 / 1
Prior Therapy Regimens, median (range)	5 (1 – 9)
Prior ibrutinib	8 (89%)
Refractory to prior ibrutinib	8/8 (100%)
Prior Chemo Regimen	9 (100%)
Prior idelalisib + rituximab	2 (22%)
Prior venetoclax	3 (33%)
Prior CAR-T / Allo Transplant	3 (33%)
Refractory to immediate prior therapy	8 (89%)
Bulky Disease, n (%)	8 (89%)



- Heavily refractory Richter's
  - 7/8 BTK Refractory
  - Durable responses observed

ORR N (%)	3 (38%)
CR N (%)	2 (25%)
PR N (%)	1 (12.5%)
SD N (%)	2 (25%)

Mato et al, ASH 2018, ICML 2019

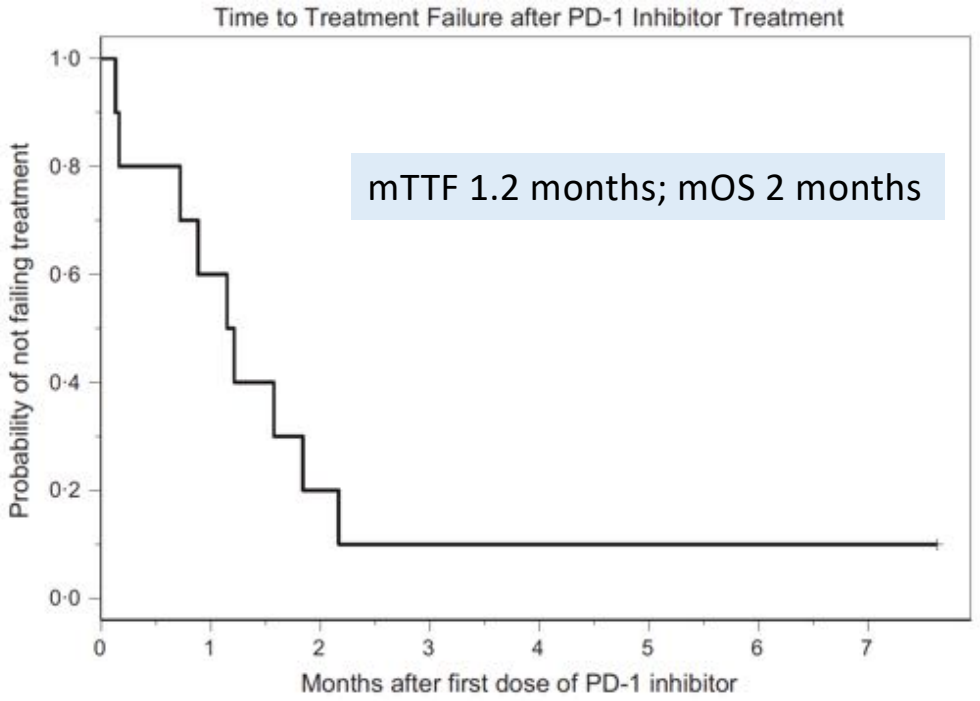
Checkpoint inhibition in RS outside of clinical trials

Patient and disease characteristics	*n* = 10
Age at RS diagnosis in years, median (range)	69 (52–79)
Men, *n* (%)	4 (40%)
Time from CLL diagnosis to RS in years, median (range)	8·1 (1·5–14)
Prior CLL treatments, median (range)	3·5 (1–11)
Prior BTK inhibitor exposure, *n* (%)	10 (100%)
Taking CLL treatment at time of RS diagnosis	8 (80%)
Ibrutinib	2
Acalabrutinib (clinical trial)	3
Venetoclax	1
Ibrutinib + venetoclax	2
High CLL risk features (any), *n* (%)†	10 (100%)
Complex CLL karyotype	6
Deletion 17p by FISH	7
IGHV unmutated*	8
RS histology DLBCL, *n* (%)	10 (100%)
EBER positive by IHC, *n* (%)	1 (11%)‡

nivolumab in 7/10 (70%)
pembrolizumab in 3/10 (30%).
3/10 added ibrutinib
1/10 added venetoclax

8/10 prior Novel targeted agent

1 responder; CNS disease (EBV+) -> bridged to alloSCT



mTTF 1.2 months; mOS 2 months

Rogers *et al*, 2016

Combination NA+ICT: Venetoclax plus R-DA-EPOCH

Phase II trial
Primary Endpoint: CR rate

Inclusion

RS, ECOG PS ≤ 2
ANC ≥ 1, plts ≥ 40 K/uL, Cr≤ 1.5 x ULN or CrCl ≥ 50 mL/min
Prior venetoclax eligible

Exclusion

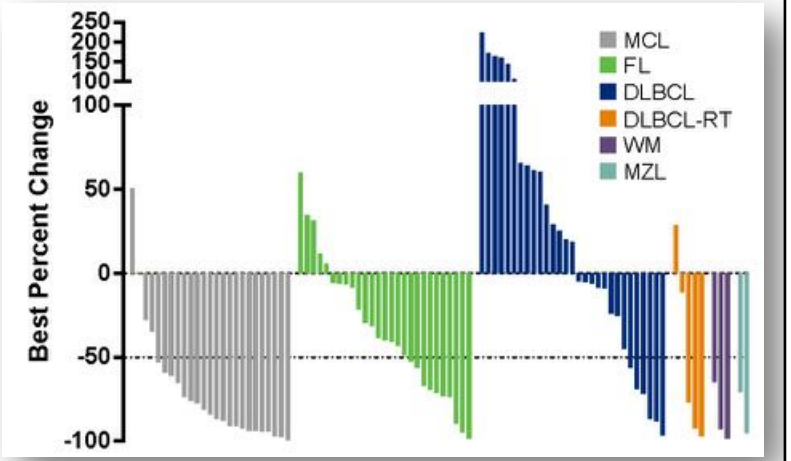
Hodgkin variant, Prior R-EPOCH, AlloSCT < 6m, CNS involvement

Secondary Endpoints:

- safety and toxicity
- ORR, CLL MRD, PFS, OS
- association of response with clonal-relatedness
- % alloSCT candidates who receive a SCT

Exploratory Endpoints:

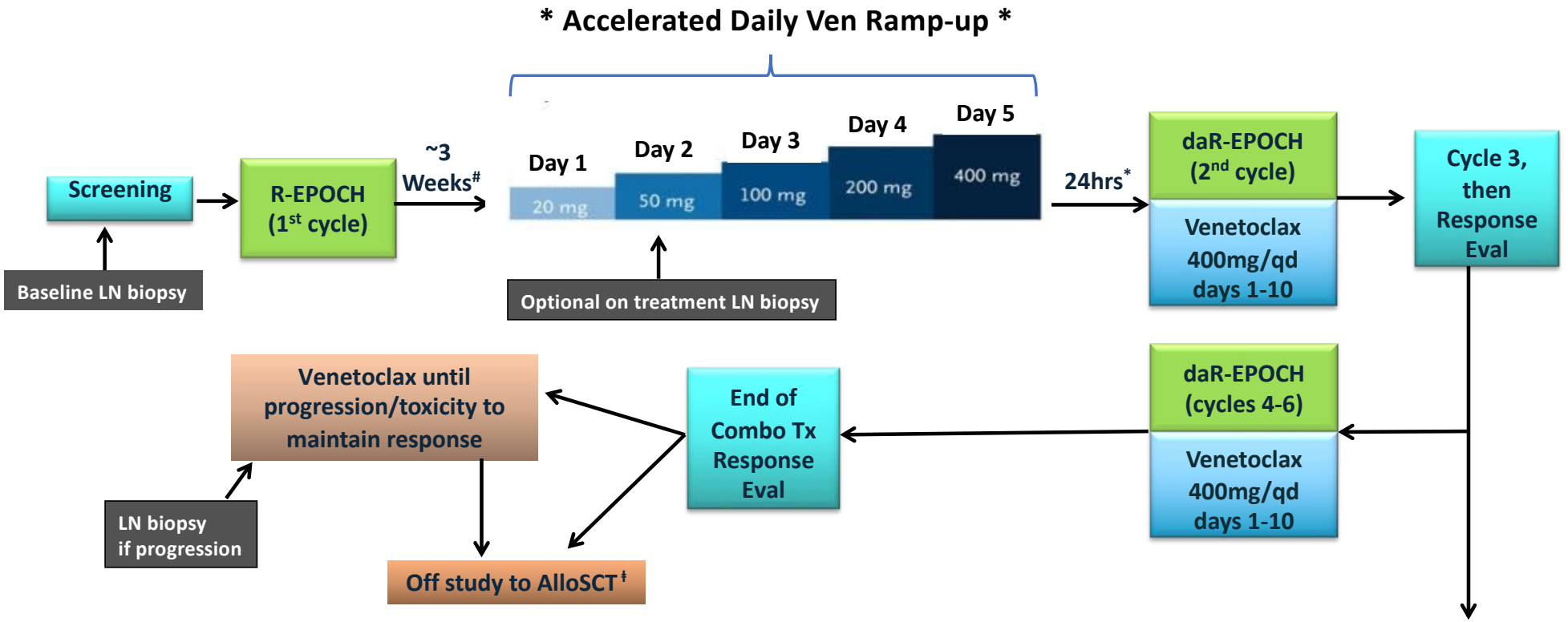
- Phenotypic (BH3 profiling) and genotypic (WES, single-cell RNASeq)



3/7 (43%) DLBCL-RT patients responded, all for > 1 year

Davids et al, ICML 2019

VR-EPOCH in Richter's Syndrome: Study Schema



Upon count recovery
* Pending TLS status
‡ If transplant candidate and donor available

Davids et al, ICML 2019

Venetoclax plus R-DA-EPOCH

- 26 patients received 1+ dose of treatment
- Median age: 63 years (49-77)
- Del(17p): 33%, TP53 mutation 29%, CK 43%
- Bulk >5 cm: 56%
- Median # prior CLL treatments: 2 (range 0-5)
- Prior CLL therapies:
  - CIT (n=17), ibrutinib (n=9), venetoclax (n=3), idelalisib (n=2), duvelisib (n=1)
  - 5 patients previously untreated

- CR 12/18 (67%)
- All CRs had uBM-MRD for CLL
- ORR 14/18 (78%)
- 5/9 (56%) pts eligible -> alloSCT
- 4/5 still in CR (4-20 months post-alloSCT)
- 7 died (4 PD including 2 during C1 before ven, and 1 each due to sepsis, sudden death, and GVHD post alloHCT)
- 1 patient withdrew consent during cycle 1

Davids et al, ICML 2019

VR-EPOCH in Richter's Syndrome: Adverse Events

≥Grade 3 Hematologic Toxicities

- Neutropenia: 45%
- Anemia: 35%
- Thrombocytopenia:25%

≥Grade 3 Non-hematologic Toxicities

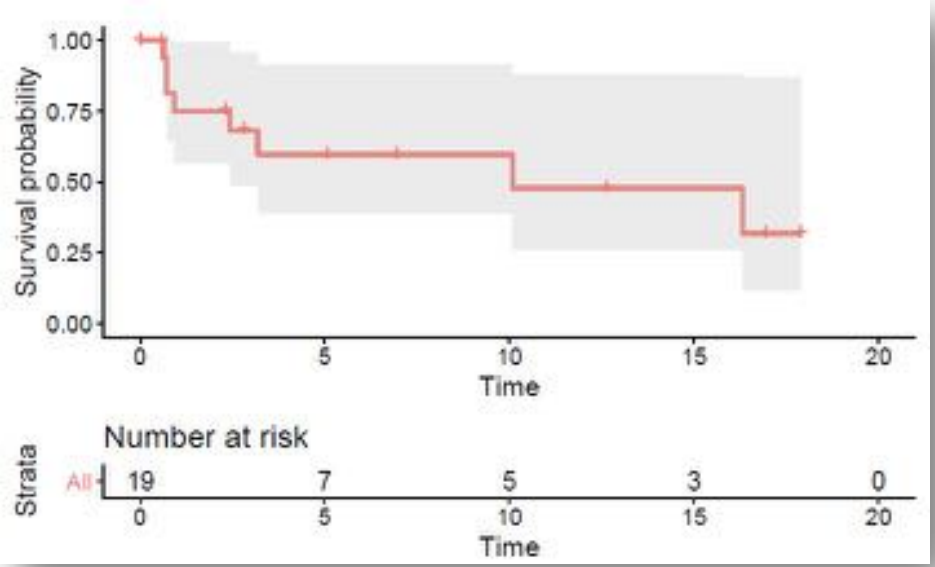
- NF 20%
- Hypocalcemia and hypophosphatemia: 15% each
- Infections: sepsis (n=3, 1 fatal) during C1 of R-EPOCH (despite GCSF, prior to starting ven)
- 1 pt each with influenza A, norovirus, G4 infectious enterocolitis on combination
- 1 sudden death in hospital during C1 prior to ven, presumed cardiopulmonary

No TLS occurred with daily ven ramp-up after 1 cycle of R-EPOCH (n=20)

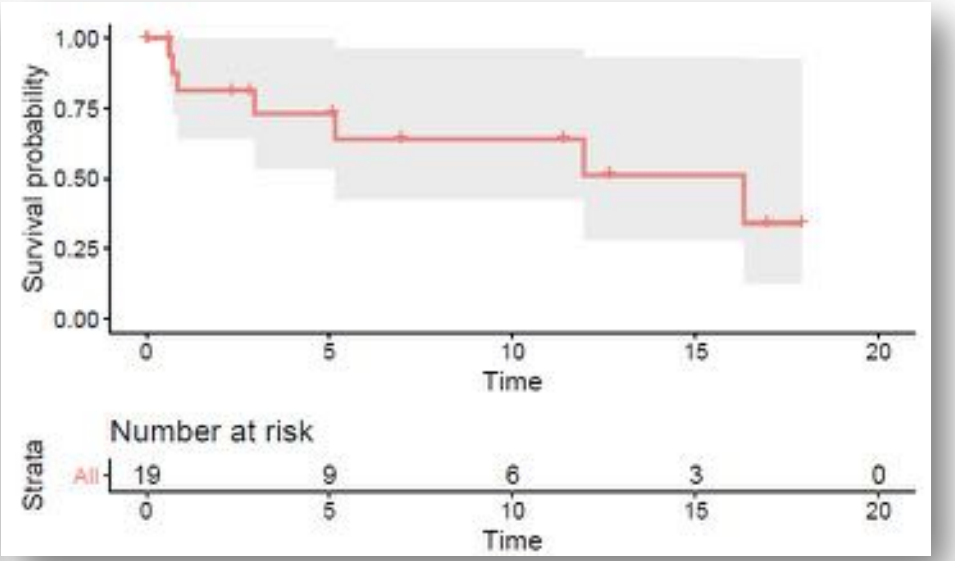
Davids et al, ICML 2019

Venetoclax plus R-DA-EPOCH

mPFS 10.1 months



mOS 16.3 months

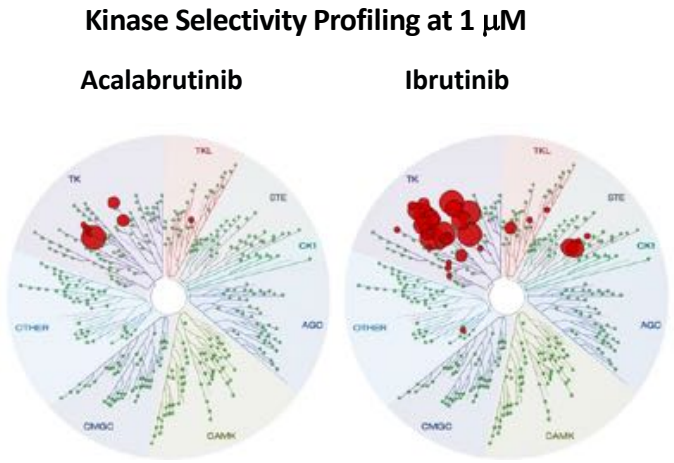


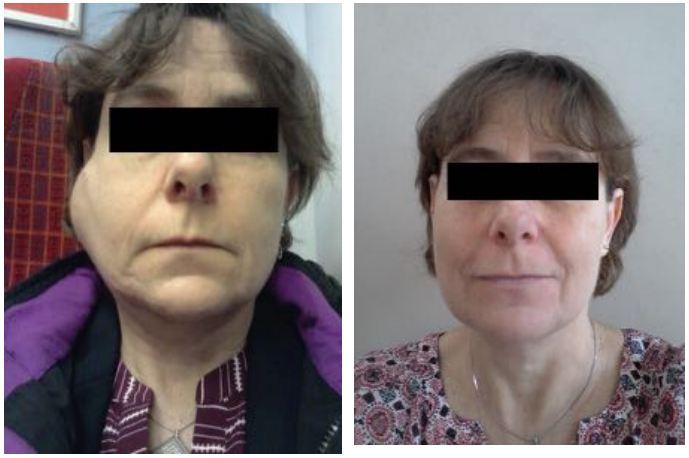
Davids et al, ICML 2019

Acalabrutinib in RS

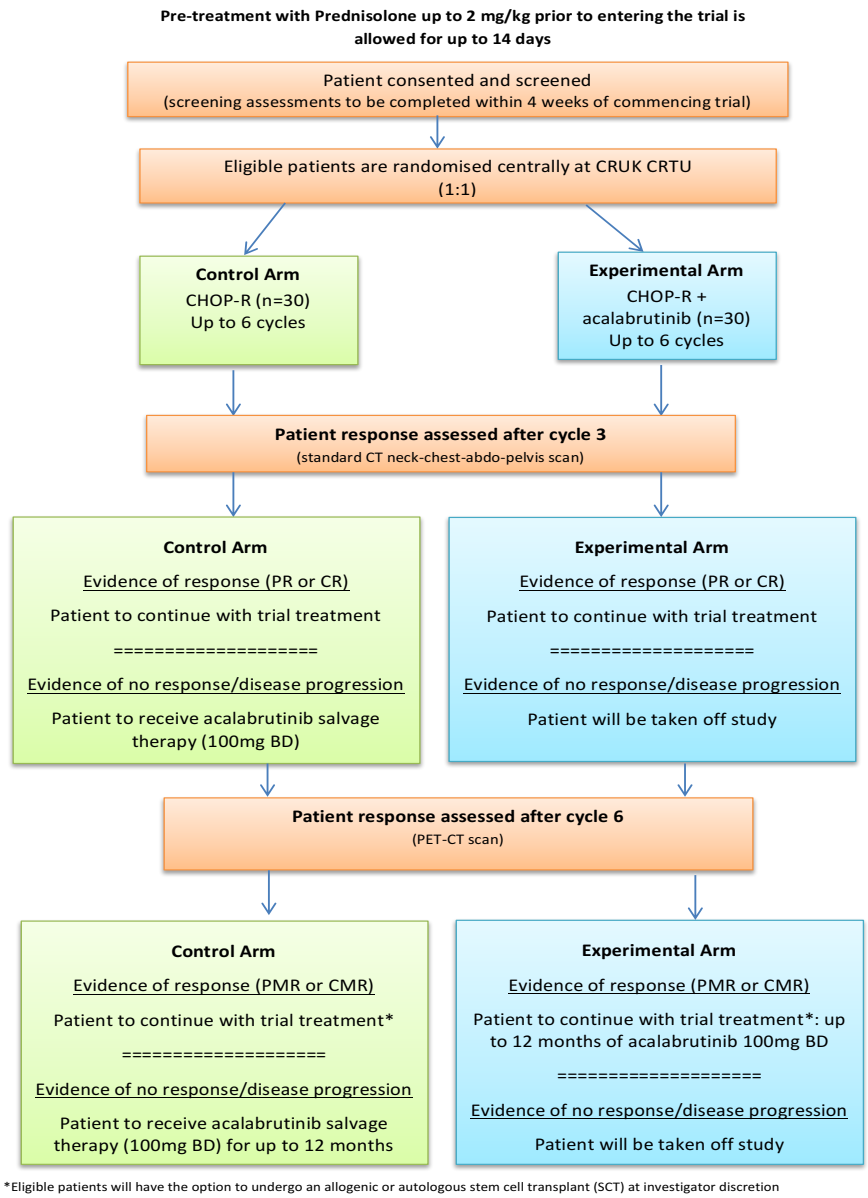
- N = 29, 200 mg b.d. until PD / toxicity
- Median 66y (43-82y). Median time: diagnosis 5y (1-21y)
- Median prior Rx (CLL or RS): 4 (0-13). 41% prior ibrutinib.
- 27% TP53 disrupted
- 81% (13/16) unmutated *IGVH*.
- Single TRAE G3 event (anaemia).
- Nil discontinued due to toxicity. Headache (G1-2 in 35%), diarrhoea (G1-2 in 21%), anaemia (G1-2 in 14%).
- In evaluable (n = 21), ORR 38%; CR 3 (14%), PR 5 (24%).
- Median DoR 5.7 months (95% CI 0.3-7.5)
- 2 pts in CR -> alloSCT.
- N = 6 previous ibrutinib, 3 responded to acalabrutinib.

Hillmen *et al*, 2016, ASH abstract





The STELLAR trial

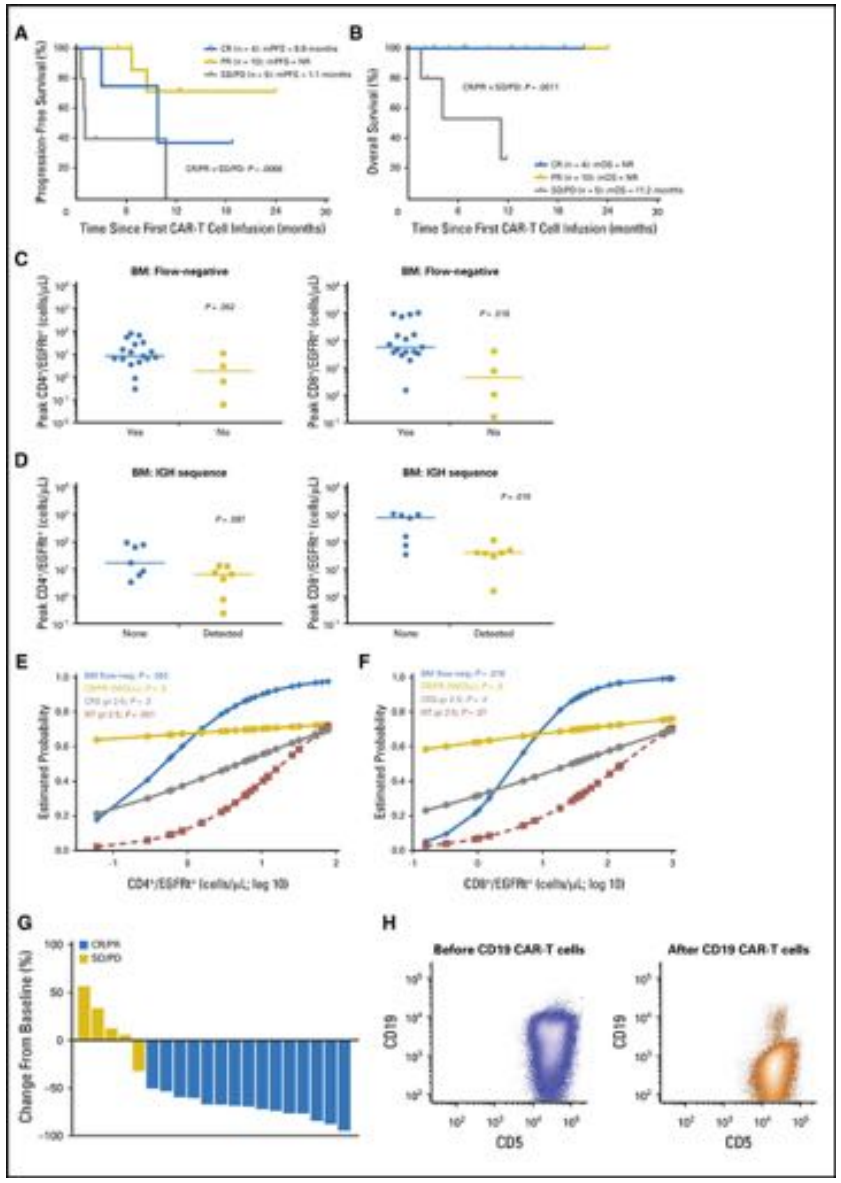


CAR-T in RS

Limited data available to date
<15 patients in literature

Turtle et al, JCO, 2017
Post ibrutinib failure
5 RT patients; data not reported separately.

Gauthier et al, ASH Abstract, 2018
CAR-T alone or combined with ibrutinib in R/R CLL and RT; 5 patients with RT; 'Partial responses' seen.



Turtle et al, JCO, 2017; Gauthier et al, ASH Abstract, 2018

Conclusions

- RT remains a clear clinical challenge and area of unmet need
- PET-CT value in excluding RT; less sensitive in NA era
- Standard immunochemotherapy often inadequate; equivalent ORR to *de novo* DLBCL in TP53 intact, Rx-naïve
- BCL2 in combination with chemotherapy promising
- PD1i with BCRi promising; small numbers and short follow up
- Acalabrutinib randomised phase II trial recruiting