Richter’s Syndrome

The Dark Side of Chronic Lymphocytic Leukemia

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Disclosures

- Support: Roche, Janssen, Takeda
- Advisory Board: Janssen
- Speaker Bureau: Janssen, Takeda
- Research: Janssen, Millenium, Bayer, Celtrion, Merck

Richter's Syndrome

- First described by Maurice Richter in 1928 as *generalized reticular cell sarcoma*
- By definition, the transformation of CLL into a more aggressive lymphoma, most commonly DLBCL
- 1-12% of patients with CLL, depending on diagnosis criteria
- Prognosis is usually poor, with survival ranges of 5-8 months

THE AMERICAN JOURNAL OF PATHOLOGY

VOLUME IV JULY, 1928 NUMBER 4

GENERALIZED RETICULAR CELL SARCOMA OF LYMPH NODES ASSOCIATED WITH LYMPHATIC LEUKEMIA*

MAURICE N. RICHTER, M.D.

(From the Department of Pathology, Columbia University, and the Pathological Laboratories, Bellevue Hospital, New York, N. Y.)

Richter M. Am J Pathol. 1928 Jul; 4(4): 285–292.7
WHO Classification of Tumours of Hematopoetic and Lymphoid Tissues

How common is RS?

Reference	Study design	Patients	RS	RS prevalence
Maddocks-Christianson, 2007	Retrospective	962	14	1%
Robak, 2004	Retrospective	1487	15	1%
Catovsky, 2007	**Clinical trial**	777	13	2%
Mauro, 1999	Retrospective	1011	22	2%
Parikh, 2012	Retropsective	1641	37	2%
Tsimberidou, 2006	Retrospective	3986	148	4%
Fisher, 2012	**Clinical trial**	817	33	4%
Alipour, 2008	Retrospective	465	24	5%
Tabuteau, 1999	Retrospective	620	37	6%
Keating, 1998	**Clinical trial**	174	13	7%
Solh, 2012	**Clinical trial**	521	34	7%
Rossi, 2009	Retrospective	783	69	9%
Rossi, 2008	Retrospective	185	17	9%
Thornton, 2005	Retrospective	101	12	12%

Richter’s Transformation is not a late event in CLL. It is, otherwise, a biological driven process.

Median time to RS: 1.8 – 5 years

Fan L et al, Leuk Lymphoma 2012
Rossi et al, Br J Hematol 2008
Rossi et al, Clin Can Res 2009

Risk Factors for Rs

- Genetic Polymorphisms
  - CD38, LRP4, *BCL*-2
- Clinical features
  - Advanced Rai Stage
  - Lymph nodes > 3cm
- Baseline Characteristics
  - IGVH-status
  - Absence of 13q
  - CD49d expression
  - ***NOTCH1* mutation**
  - ***TP53* disruptions**

Not performed outside trials

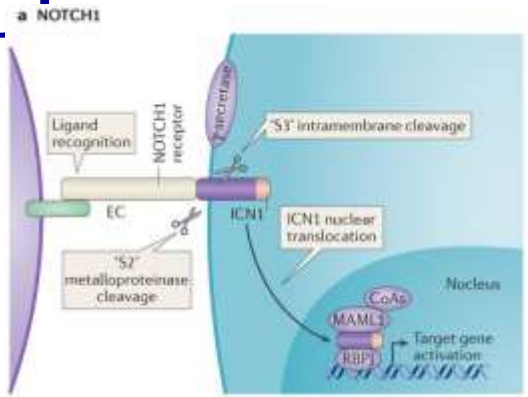
Inespecific

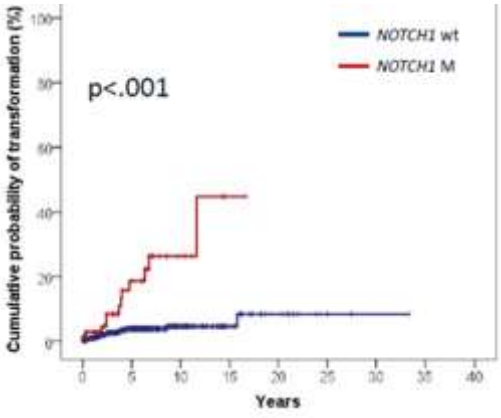
Clinical revelant

Parikh S et al, Blood 2014

NOTCH1 Mutations in CLL

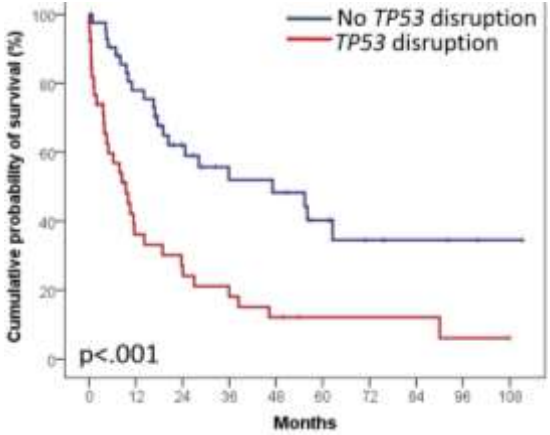
- *NOTCH1* mutations in ~10% of CLL patients
  - 3.77x risk of death and shorter overall survival
  - Impact similiar of *TP53* disruptions
- ~25% of patients with trisomy12
  - 20% of refractory patients
  - 31% of RS



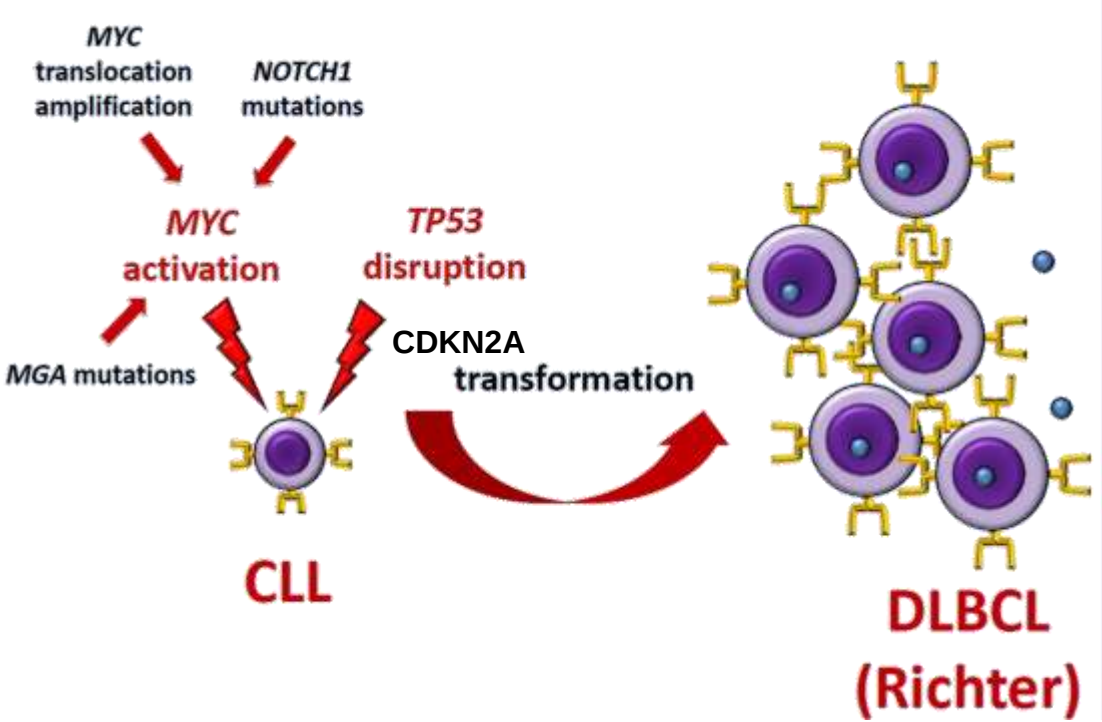


TP53 disruptions in RS

- *TP53* disruptions in up to 50% of RS
  - Usually occurs previous to RT
  - At transformation, 20% deletions of CDKN2A (9q21)
- TP53 disruptions holds prognostic value in RS
- *TP53* cases usually show higher Ki67, are ABC-subtype
  - Usually exclusive to *NOTCH1* mutations
  - Can occur with *MYC* mutations

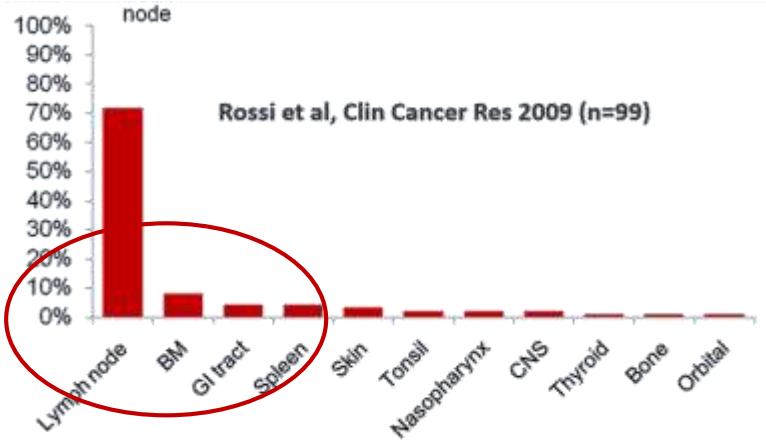


So what's going on on RT?



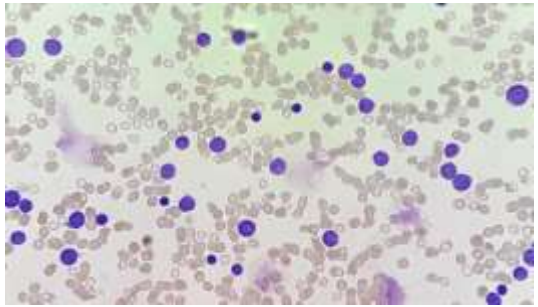
Clinical Suspicion of RS

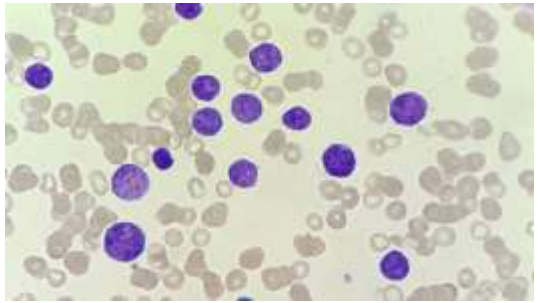
- Declining performance status
- B symptoms
- Bulky disease
- **Discordant growth of localized lymph nodes**
- **Unusual extranodal involvement**
- Sudden and excessive rise in levels of LDH

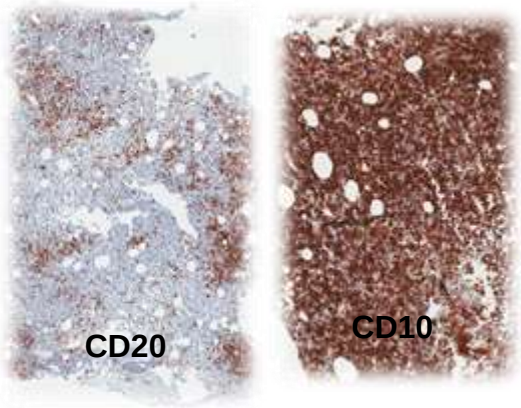


Clinical Suspicion of RS

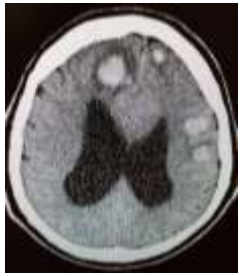
- Don’t forget to look at the PB slides!

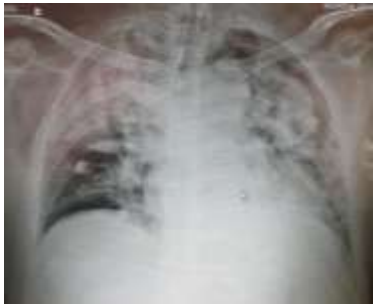






Bone Marrow:
Infiltration by DLBCL, GCB phenotype





PET-CT in RS

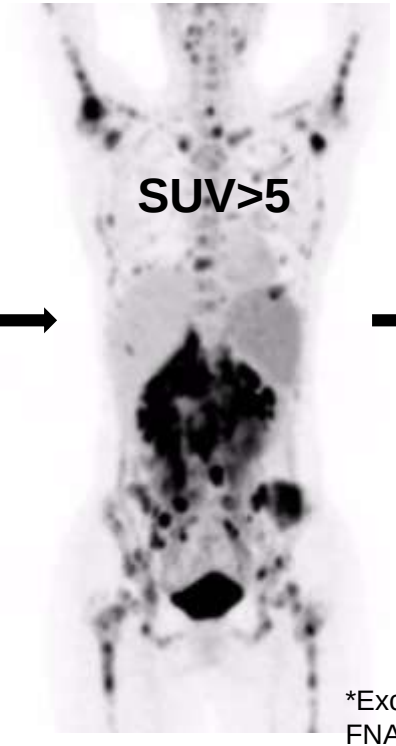
- Bruzzi et al, 2006:
  - Mean SUV CLL-U: 4.5 x 17.6 RS
  - Cutoff of 5: PPV of 53% and NPV of 97%

- Michallet et al, 2015:
  - SUV of 10 can discriminate RS x Accelerated CLL
  - Sensitivity 91%, Specificity 95%

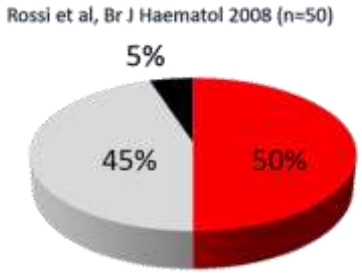
- Perini et al, not yet published:
  - n=104
  - Best cut-off for discriminating iNHL from aNHL was 6
    - Sensibility: 83%, Specificity 65%

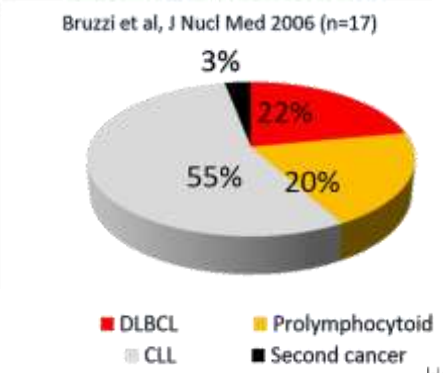
Bruzzi et al J Nucl Med 2006
Michallet et al, Blood 2014

Diagnostic Approach in RS

Clinical Suspicion → 

→ Biopsy* at high SUV site





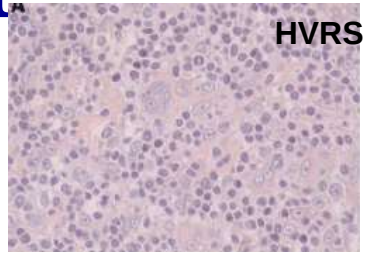
*Excisional prefered:
FNA insuficient 53% of patients (Falchi, Blood 2014)

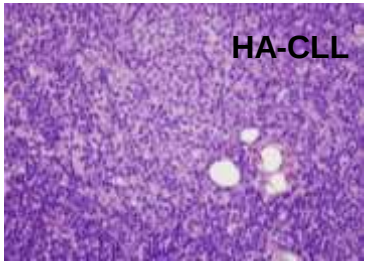
Hospital

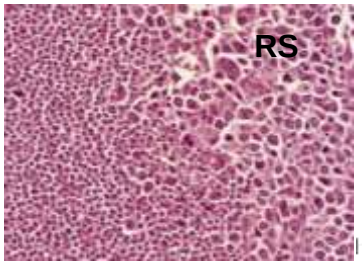
Biopsy is MANDATORY

- Biopsy-proven diagnosis is mandatory
  - Hodgkin's variant of RS (HvRS)
  - Accelerated or Histologic Aggressive CLL
    - Expanded proliferation centers, Ki67>40%
    - Prognosis inferior to CLL but superior to RS

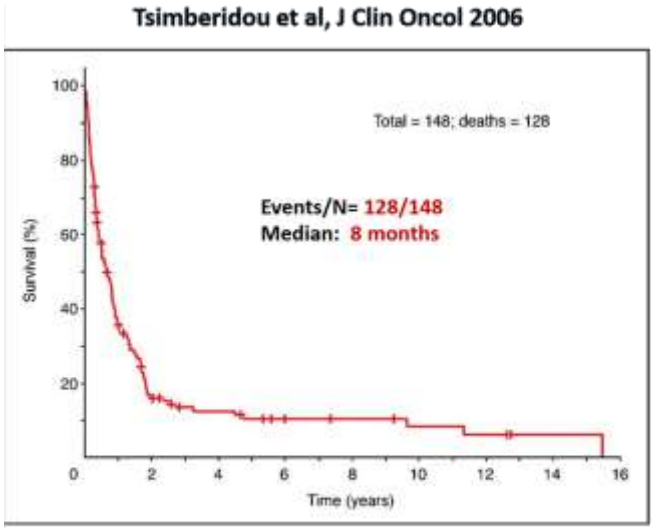
    (76 x 34 x 4.3, p<0.001)
    - In pts with SUVmax>10, HAC and RS have similar outcomes
- DLBCL: >90% ABC-phenotype by Hans' Algorithm
  - 82.5% concordance by central review
  - BCL-6 generally negative

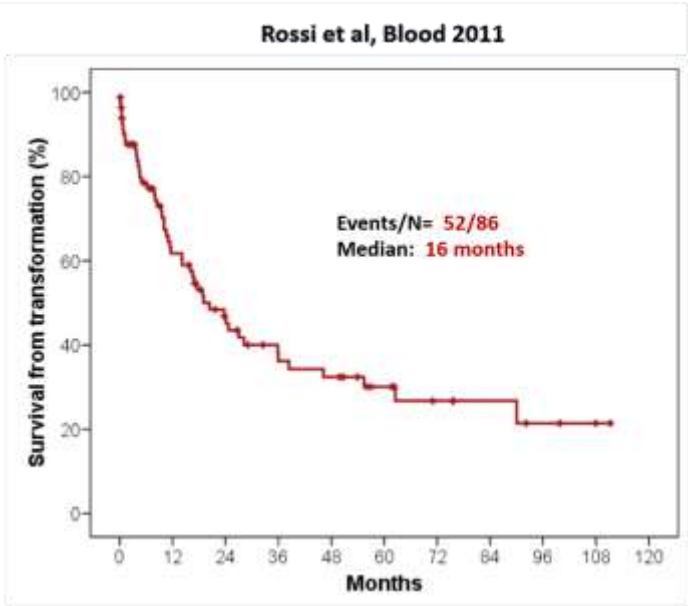






RS: What are we dealing with?



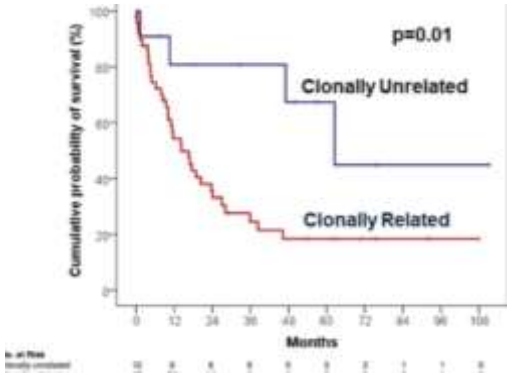


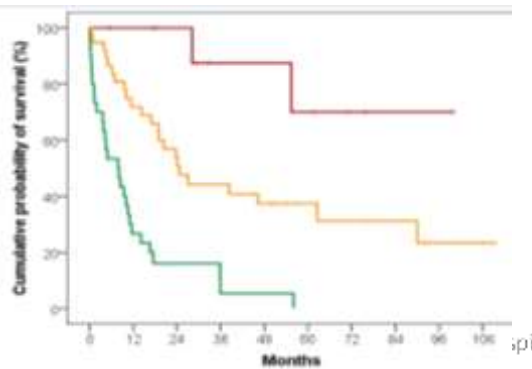
Hospital

Refining Prognosis

- Most importante prognostic factor is clonal relationship with underlying CLL
  - 80% are clonally related
  - Not usually perform
  - Light-chain restriction discordant = unrelated

- Multiple clinical scores. Easiest by Rossi et al:
  - PS>1
  - *TP53* disruptions
  - CR after treatment





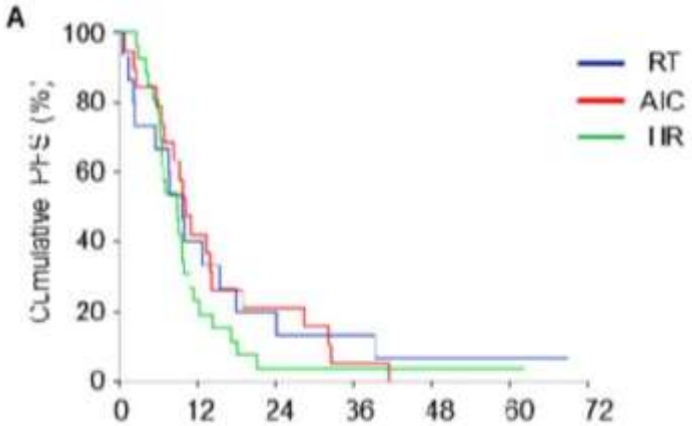
Treatment Basics

- Avoid delays in treatment
  - Rapid progressive disease
- Don’t wait for additional tests to search for a donor
  - Median time to progression about 6-8 months
- p53 mutations should be performed!
  - Clinical revelant

Which chemo to use?

R-CHOP in RS

- Phase II of R-CHOP in HR-CLL, RT and CLL-AIC
  - RT (n=15)
  - ORR: 67%, CR 7%
  - PFS: 10 months, OS: 21 months
  - Lower LDH, Higher Hb and longer period from CLL diagnosis to transformation



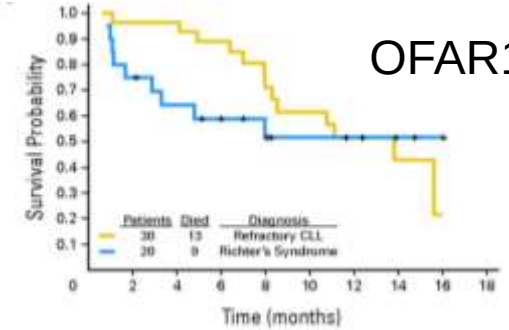
- High incidence of infectious complications
  - 28% severe infections

Langerbeins et al. AJH 2014

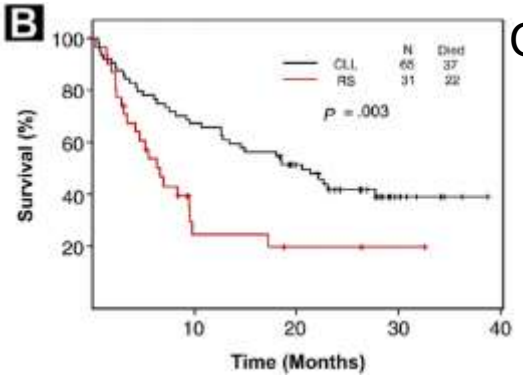
OFAR in RS

- Two studies: OFAR1 and OFAR2 (Oxa: 25/30x4 and AraC: 500mgx3/1gx2)
- OFAR1: Phase II
  - RT (n=20)
  - ORR: 50%, CR 20%
  - FFS- 6 months: 47%
  - 15 patients on allo: 70% alive
- Phase I-II of OFAR2 in Aggressive R/R and RT
  - RT (n=35)
  - ORR: 38%, CR 6,5%
  - Median Survival 6.6 months
  - 9 patients on allo: no deaths

OFAR1



OFAR2

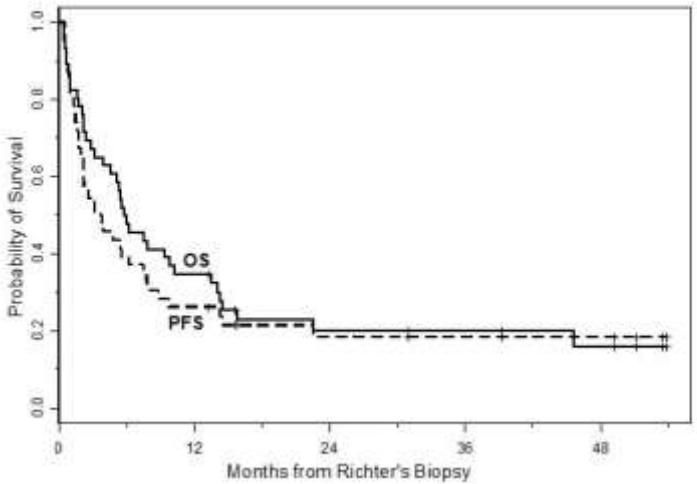


Tsimberidou et al. JCO 2008
Tsimberidou et al. CLM 2013

R-DA-EPOCH in RS

- Single Center (Ohio University) study of 46 patients
  - 56% Complex Karyotype
  - 49% del(17p)
  - Only 19% of patients completing 6 cycles
- ORR: 38% with 20% CR
  - Median PFS: 3.5 months
  - Median OS: 5.9 months
- Risk of death higher for complex karyotype (HR 4.38, p=0.0002), del(17)(p13.1) (HR 3.04, p=0.003), higher number of CLL treatments (HR 1.16, p=0.004)

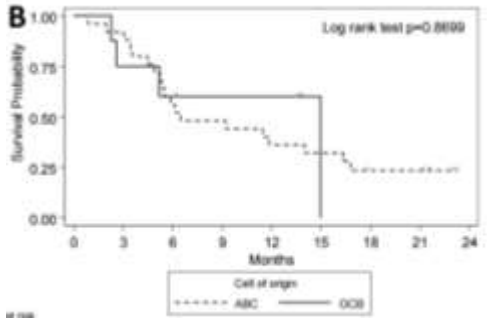
Figure 1. PFS and OS after RT diagnosis in patients treated with R-EPOCH

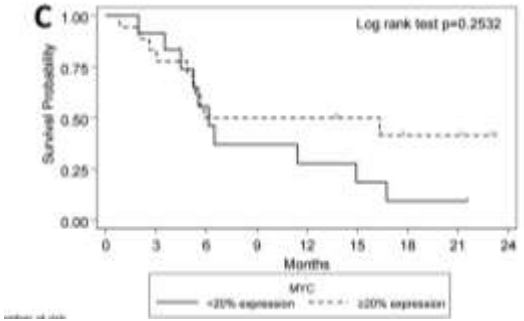


Rodgers et al, ASH 2015

O-CHOP: Phase 2 NCIR Trial

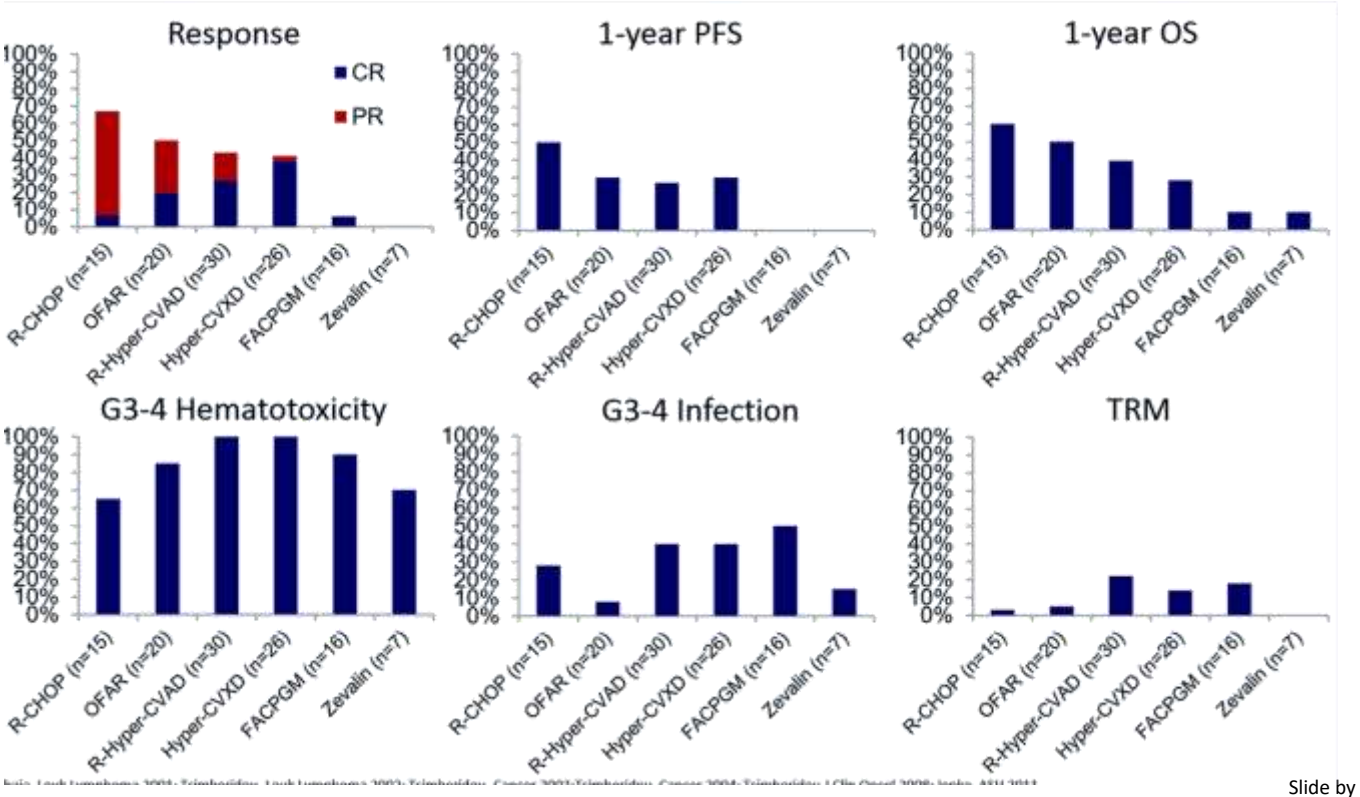
- CHOP + Ofatumumab
  - Cycle 1: 300 mg day 1, 1000 mg day 8, 1000 mg day 15; Cycles 2-6: 1000 mg day 1
  - 12 months ofatumumab maintenance (1000 mg given 8-weekly for up to six cycles)
- n=37
  - ORR: 46% CR: 27%
  - Median PFS: 6.2 months
  - Median OS: 11.4 months
- *TP53* intact and treatment naive patients with better outcomes





Eyre et al, BJH 2016

Chemotherapy in RS: Any clear winner?



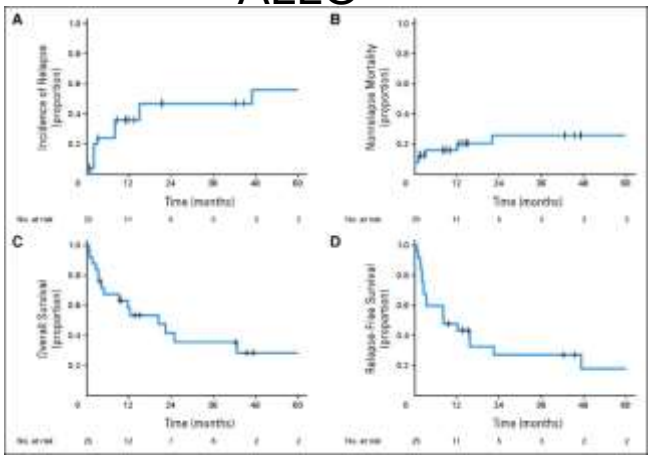
Slide by Davide Rossi

Transplant in RS

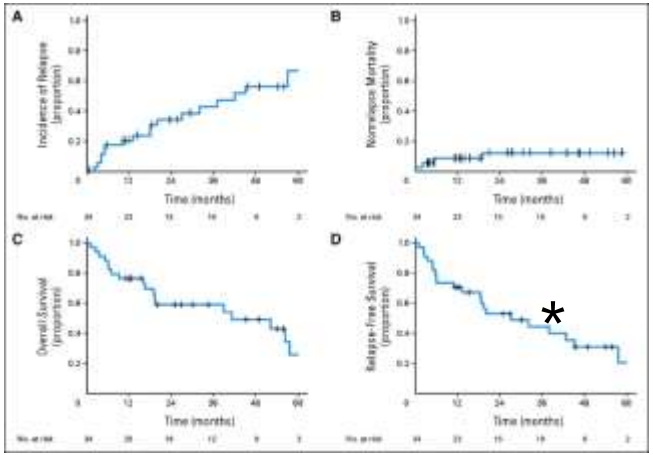
- EBMT retrospective study (n=59)
  - Auto (n=34) x Allo (n=25)
    - Clear selection bias (CR 32% x 4%; PD 9% x 32%)

*RS Specific RFS: 56%

ALLO



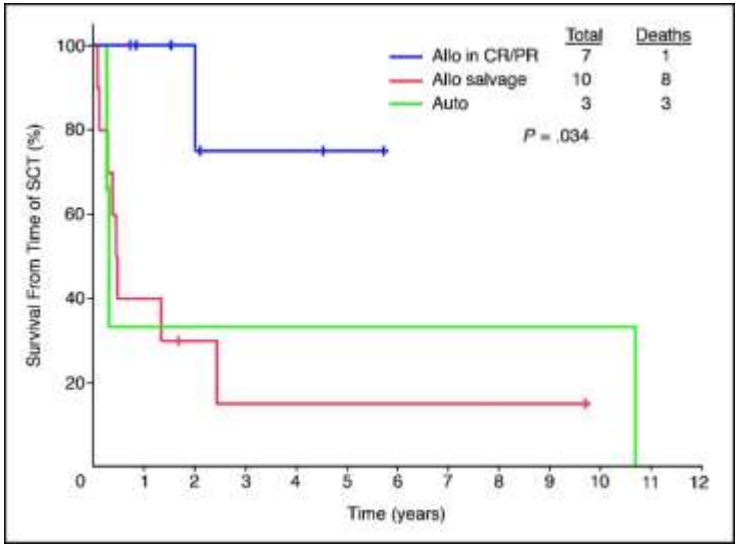
AUTO



Cwynarski et al, JCO 2012

Transplant in RS

- MD Anderson's Data:
  - Only ~10% of RS patients going to Transplant
  - n=20
  - OSS of 75% for allo in ≥PR, 27% for no SCT, and 21% for relapsed or refractory RS who underwent allogeneic or autologous SCT as salvage therapy (*P* = .019)



Tsimberidou et al, JCO 2012

New Agents in RT

- Ibrutinib:
  - Mayo Clinic: 4 patients >PR on Ibrutinib
  - Lamar et al: 1 patient R+Ib achieving a 3-month lasting CR
  - Giri et al: 2 patients responding to Ib

- ABT-199
  - Phase 1 Monotherapy in R/R DLBCL
  - RS n=7
  - PR: 3, SD: 2

Gerecitano et al, ASH 2015

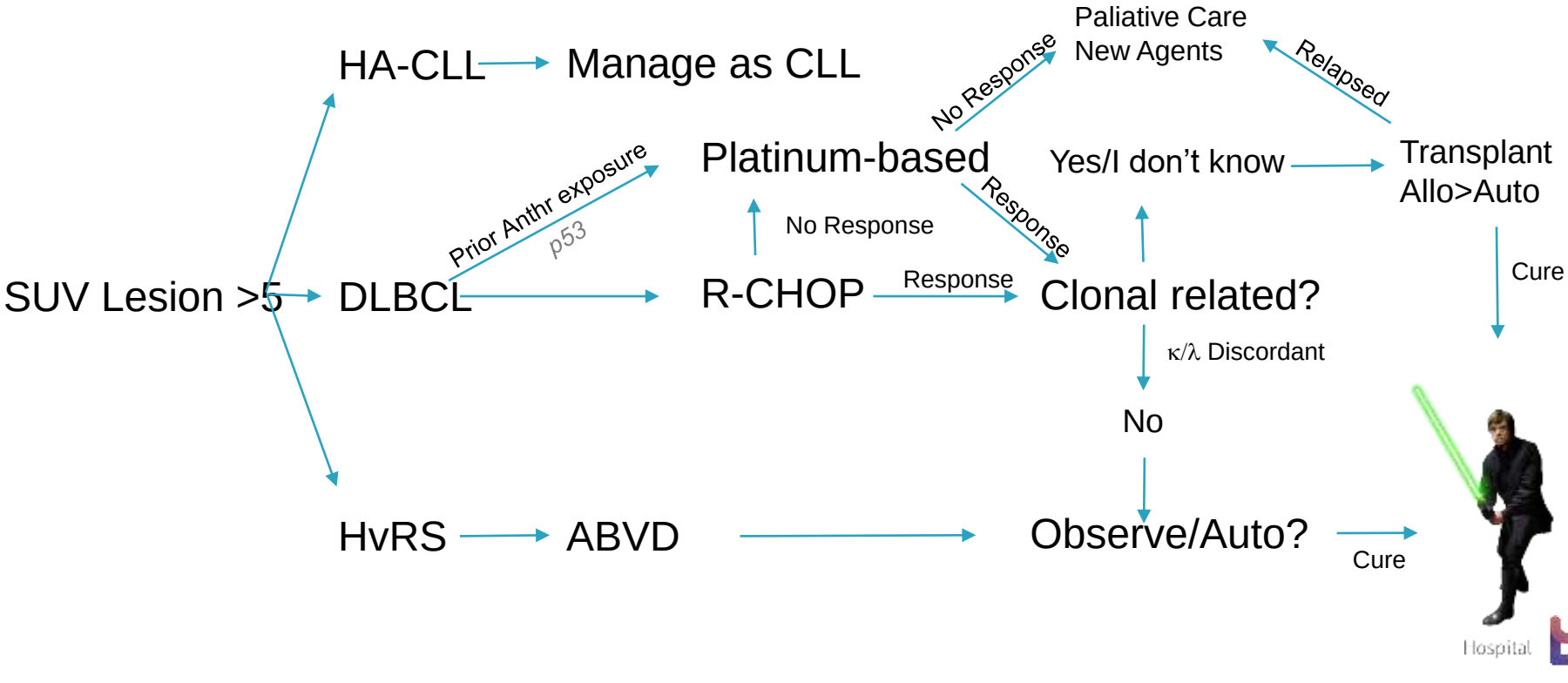
New Agents in RT

- Pembrolizumab:
  - 5 RS included in phase II trial
  - 4/5 patients treated with anthracycline-based regimens
  - 4/5 RS responded to Pembro, including 1 CR
  - Phase II trial of Pembro in R/R PMBL and RS open (guilherme.perini@einstein.br for details)

- Selinexor (Selective Inhibitor of XPO1):
  - 3 patients with RS, 1 CR, 2PR
  - Phase II open in 2014, but terminated

Ding et al, ASH 2015
Clinicaltrials.gov

In Conclusion:



- Thank You!