I "LINFOMI INDOLENTI"

Milano, Best Western Hotel Madison
26-27 gennaio 2026

La trasformazione istologica

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Disclosures of Chiara Rusconi

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Others
Celgene	X						
Takeda						X	X
Janssen						X	X
Roche							X
Abbvie							X
Gilead							X
Lilly						X	X

Histological trasformation (HT): definition

«purest and strictest definition»:

biopsy with the diagnosis of aggressive lymphoma in a patient with a previous histologically proven diagnosis of indolent non Hodgkin lymphoma

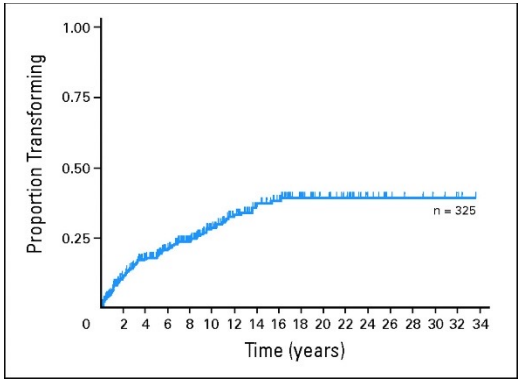
Montoto S, ASH 2015

- more frequent for FL than for other iNHL histotype
- most common aggressive histology: DLBCL

Agenda

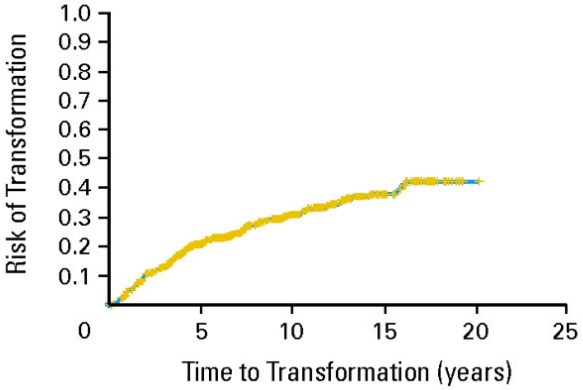
- Incidence and biology of HT
- Identification of FL patients at high risk for transformation
- Impact of first line FL therapy on HT
- Post HT treatment and outcome

Incidence of HT



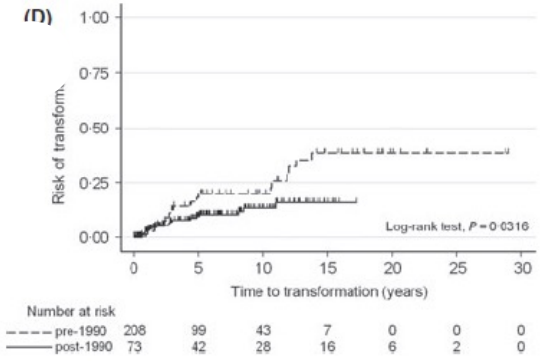
17% at 5 ys
28% at 10 ys

Montoto S et al, JCO 2007



30% at 10 ys

Al-Tourah AJ et al, JCO 2008

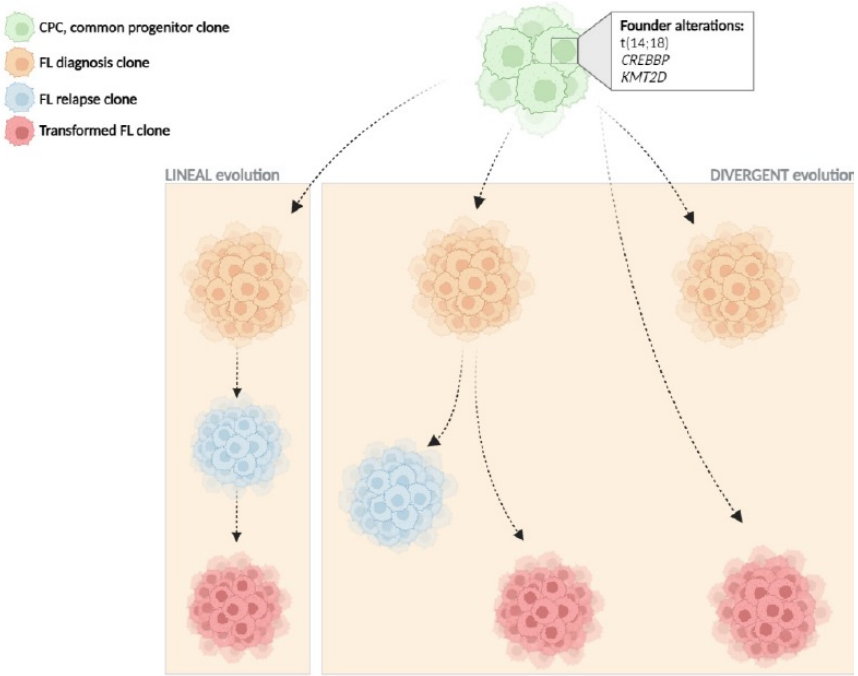


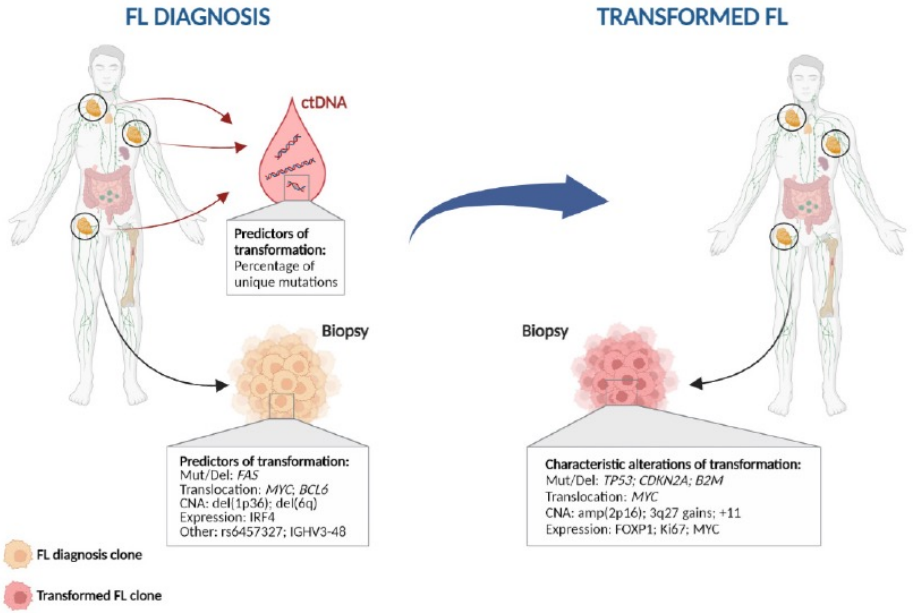
15% at 10 ys
26% at 14 ys

Conconi A et al, BJH 2012

HT of FL is reported to occur at a rate of 2% per year

Biological models for HT





Alcoceba M et al, Hemato 2022

Genetic risk for HT

Category	Variable	Biological Effect
IHQ and microenvironment	IRF4 expression	-
	MYC expression	-
	FOXP1 expression	-
Genomic variants	*TP53* mutation and deletion	Cell cycle
	B2microglobulin mutation and deletion	Immune surveillance
	FAS mutation and deletion	Apoptosis
	MYC mutation and translocation	Cell cycle
	CCND3 mutation	Cell cycle, JAK-STAT signalling
	EBF1 mutation	B-cell development
	GNA13 mutation	NF-kB/BCR signalling
	P2RY8 mutation	B-cell migration
	S1PR2 mutation	Proliferation
	CD58 mutation	Immune surveillance
	MYD88 mutation	NF-kB/BCR signalling
	CD79B mutation	NF-kB/BCR signalling
	BCL10 mutation	NF-kB/BCR signalling
	CDKN2A/B deletion	Cell cycle
	BCL6 translocation	B-cell differentiation
	2p16 (*REL*) amplification	NF-kB/BCR signalling
	3q27.3-q28 (*BCL6*) gains	B-cell differentiation
	Chromosomes 2, 5 and 11 gains	-
	Genomic complexity -copy-number changes-	-
	Genetic complexity -mutations-	-

Alcoceba M et al, Hemato 2022

Microenvironment and HT

Category	Variable
Clinical	High FLIPI (≥3)
IHQ and microenvironment	FL Grade 3A
	High IRF4 expression
	High levels of lymphoma-associated macrophages
	High density of CD21 Follicular dendritic cells
	High levels of CD4+, CD8+, CD57+, PD1+, and FOXP3+
	Follicular pattern of FOXP3+ T-cells
	Low tumour distance to blood vessels
Genomic variants	1p36, 6q deletions
	BCL6, *MYC* translocations
	16p CNN-LOH
	IGHV3-48 gene usage
	SNP rs6457327 (6p region)
	Circulating tumour DNA mutations

Alcoceba M et al, Hemato 2022

Clinical signs of possible HT

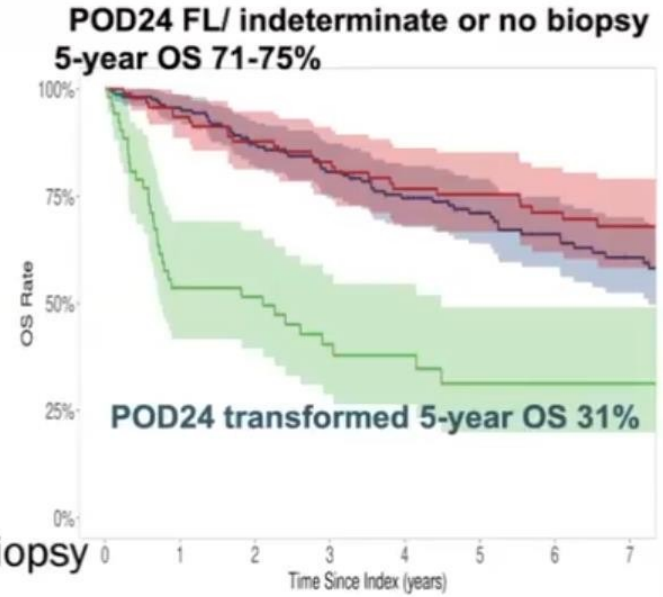
- Performance Status
- Anemia
- Hyper calcemia
- LDH>UNL
- Advanced stage disease
- Elevated FLIPI
- B symptoms
- Grade 3A (?)
- EN sites
- SUV max> 10
- N° of therapeutic lines pre HT

Wagner-Johnston ND et al, Blood 2015
Conconi A et al, BJH 2012
Montoto S et al, JCO 2007
Sarkozy C et al, JCO 2016

Outcomes of Early FL Relapse vs Early Transformation

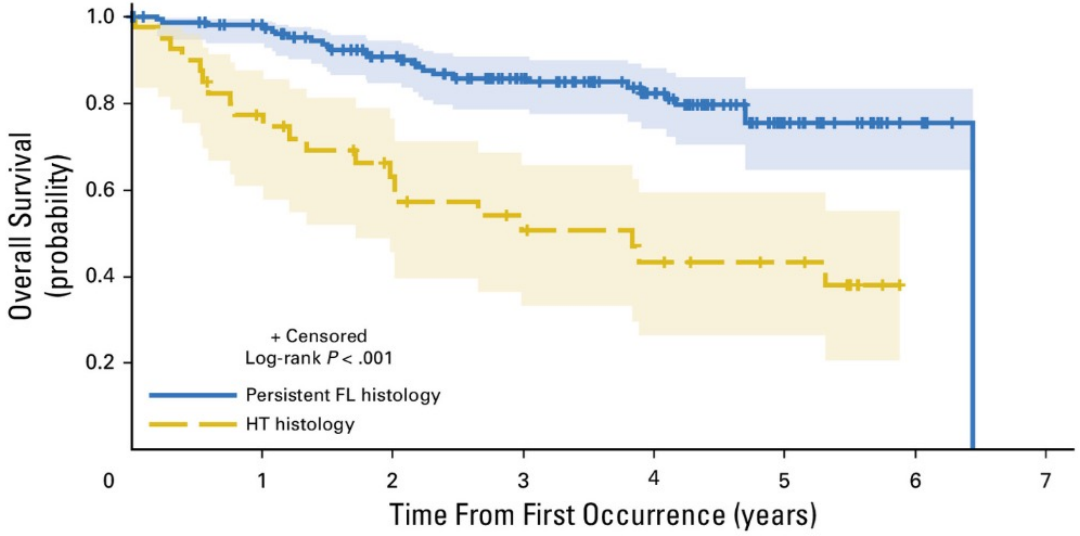
Lymphoma Epidemiology of Outcomes Consortium for Real World Evidence

- 1,122 patients with FL
- POD24 following 1st line treatment with BR, R-CHOP, or R-CVP (N=308)
- Biopsy at POD24:
  1. POD24 FL (52%)
  2. POD24 transformed (17%)
  3. POD24 indeterminate biopsy/no biopsy



Histologic transformation of FL is reported to occur at a rate of 2% per year

PRIMA Trial and HT

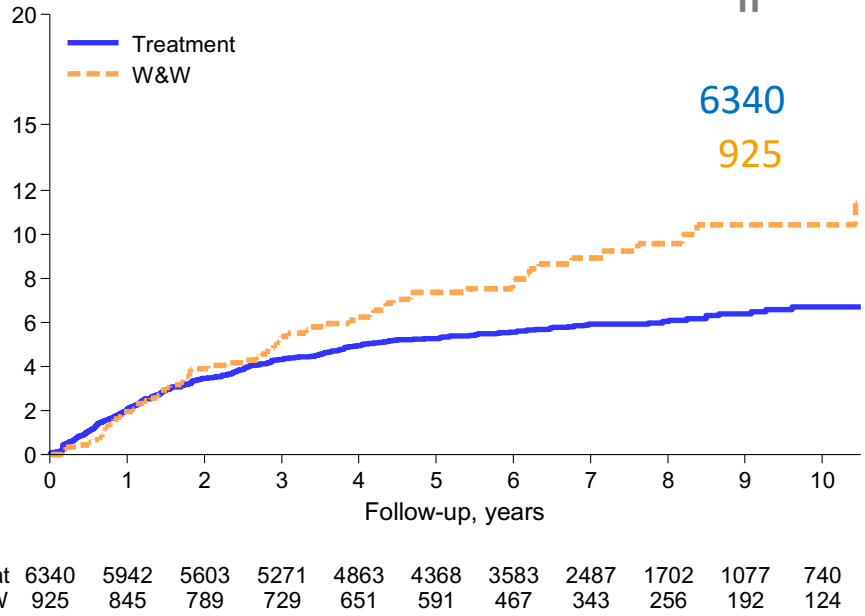


No. at risk								
Persistent FL histology	154	141	116	89	62	24	5	0
HT histology	40	29	21	15	12	9	0	

Altered performance status, anemia, high lactate dehydrogenase level, "B" symptoms, histologic grade 3a, and high Follicular Lymphoma International Prognostic Index scores at diagnosis were identified as HT risk factors

Sarkozy C et al, JCO 2016

FL first line therapy and HT

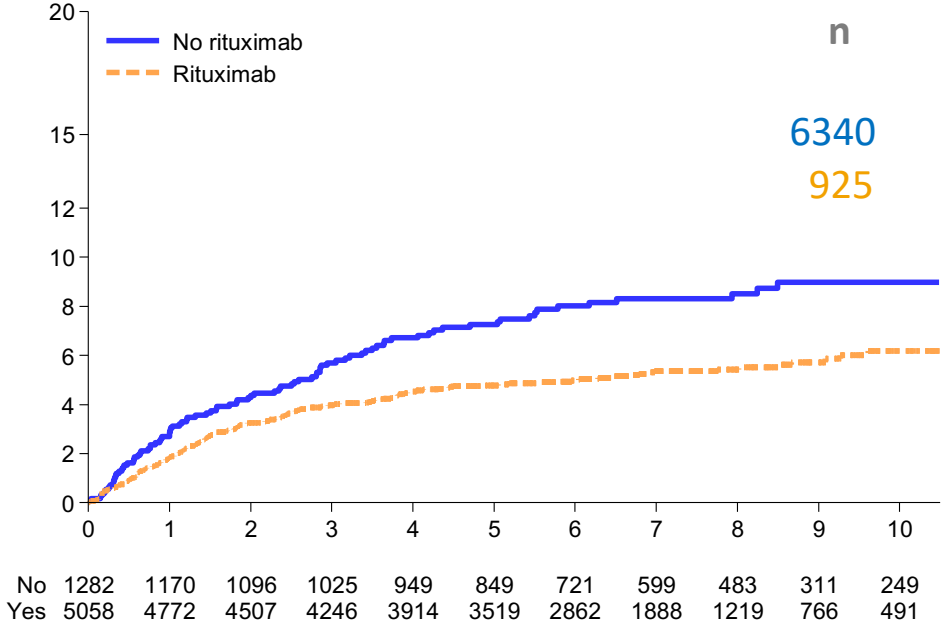


	n	tFL	CI% at 5-yr (95CI)	10-yr (95CI)
Treatment	6340	342	**5.3 (4.7-5.9)**	**6.7 (5.9-7.6)**
W&W	925	69	**7.4 (5.7-9.6)**	**10.4 (8.1-13.5)**

HR: 1.43 (95CI 1.10-1.85), p=0.007

Federico M et al, Lancet Haematol 2018

Rituximab exposure and HT



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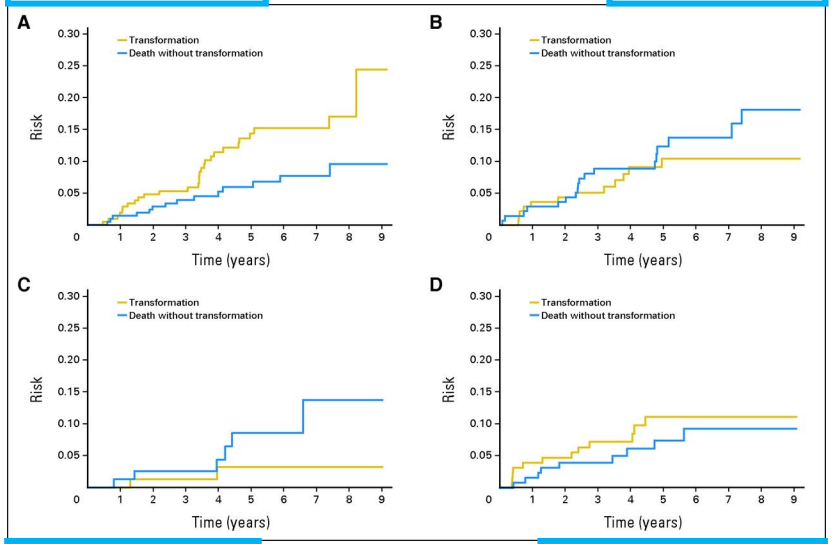
Federico M et al, Lancet Haematol 2018

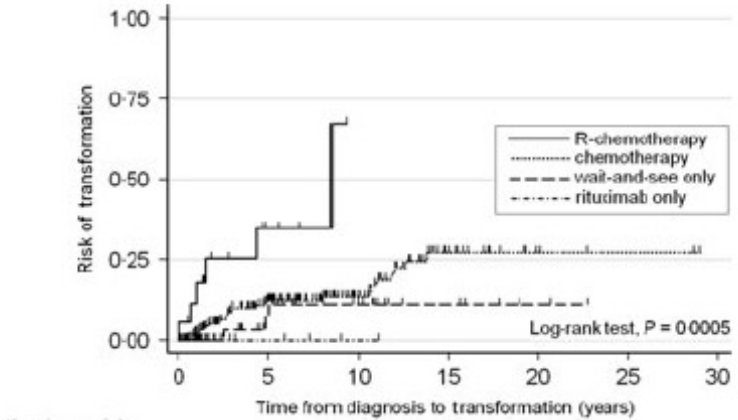
Observation

Alkylators



Rituximab √

Anthracycline



Number at risk

R-chemotherapy	18	4	0	0	0	0	0
chemotherapy	204	110	57	17	4	2	0
wait-and-see only	39	23	13	6	2	0	0
rituximab only	20	4	1	0	0	0	0

Link BK et al, JCO 2013

Conconi A et al, BJH 2012

Influence of initial therapeutic strategy on HT

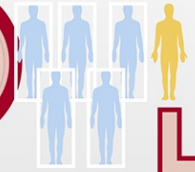
LymphoCare

	n	HR	P
observation vs initial therapy	481/2253	0.99 (0.64-1.54	0.98
Anthracycline vs no anthracycline in initial therapy	944/1309	0.73 (0.5-1.06	0.096
Rituximab vs non -rituximab regimen in initial therapy	1803/450	0.59 (0.39-0.90)	0.012

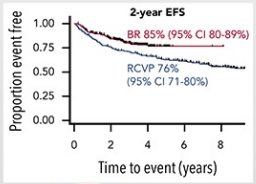
Wagner-Johnston ND et al, Blood 2015

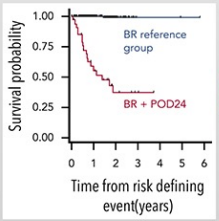
Early progression after BR is associated with high risk of transformation in advanced stage follicular lymphoma

296 BR treated FL pts

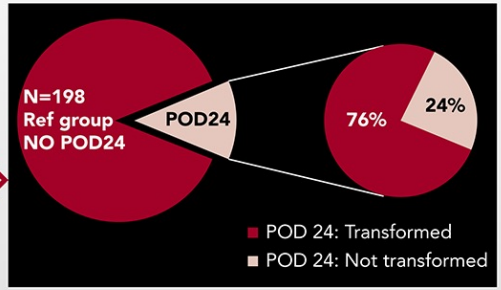


Good outcomes vs historical controls





Poor OS in POD24 subgroup

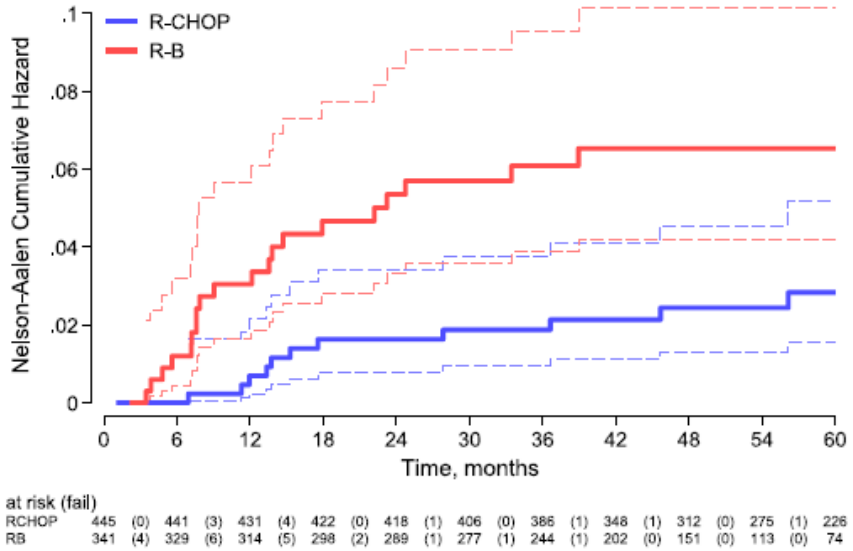


The occurrence of early progression (POD24) may be decreasing following the introduction of BR, but the majority of POD24 patients have transformed lymphoma.

BC CANCER
Provincial Health Services Authority

CL Freeman, R Kridel, AA Moccia, KJ Savage, D Villa, DW Scott, AS Gerrie, D Ferguson, F Cafferty, GW Slack, P Farinha, B Skinnider, JM Connors, LH Sehn

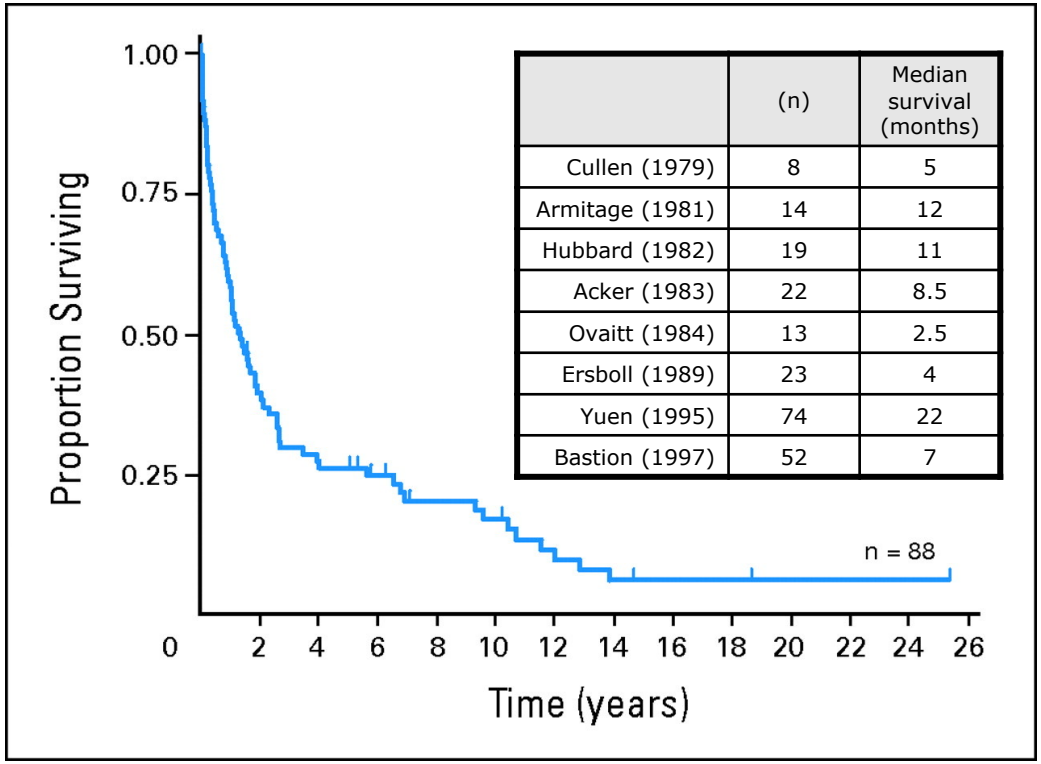
Impact of immunochemotherapy with R-bendamustine or R-CHOP for treatment naïve advanced-stage follicular lymphoma: A subset analysis of the FOLL12 trial by Fondazione Italiana Linfomi



The cumulative risk of tFL was very low for the whole study population, in line with recent observations,12,13 suggesting that the modern approach to FL staging, combined with the excellent disease control achieved by effective ICT, may have an important role in reducing the risk of tFL. Despite the context of a very low risk of tFL, we were still able to show **higher rates of tFL associated with RB than with R-CHOP**. This finding suggests a less protective role of RB for tFL

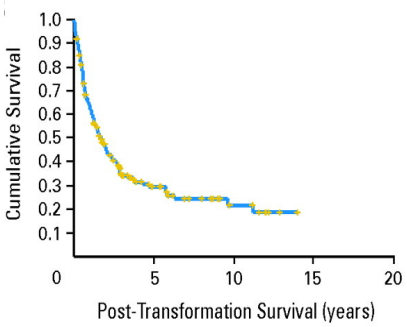
Nizzoli ME et al, Hematol Oncol 2023

Post HT prognosis (historical)

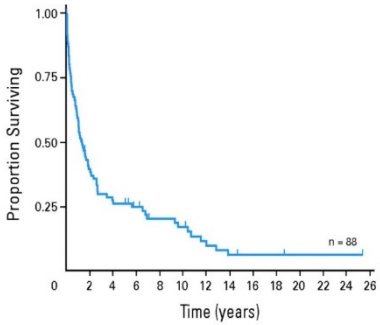


	(n)	Median survival (months)
Cullen (1979)	8	5
Armitage (1981)	14	12
Hubbard (1982)	19	11
Acker (1983)	22	8.5
Ovaitt (1984)	13	2.5
Ersboll (1989)	23	4
Yuen (1995)	74	22
Bastion (1997)	52	7

Montoto S et al, JCO 2007



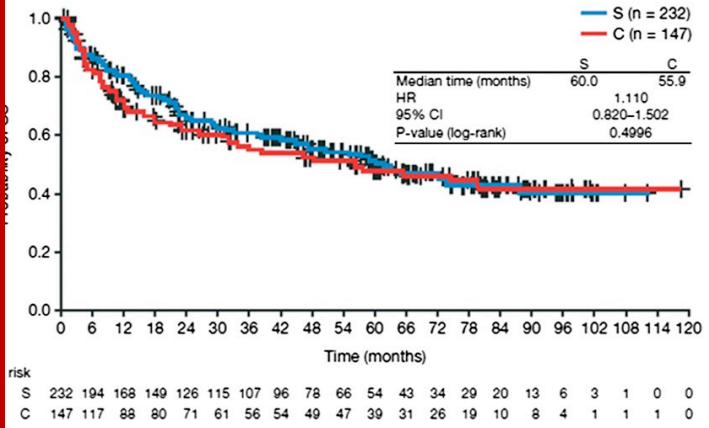
Al-Tourah AJ, JCO 2008



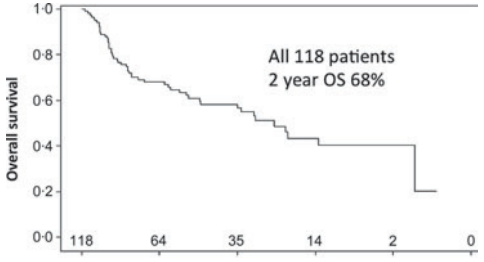
Montoto S, JCO 2007

Pre-Rituximab era

Rituximab era



Wagner-Johnston ND, Blood 2015

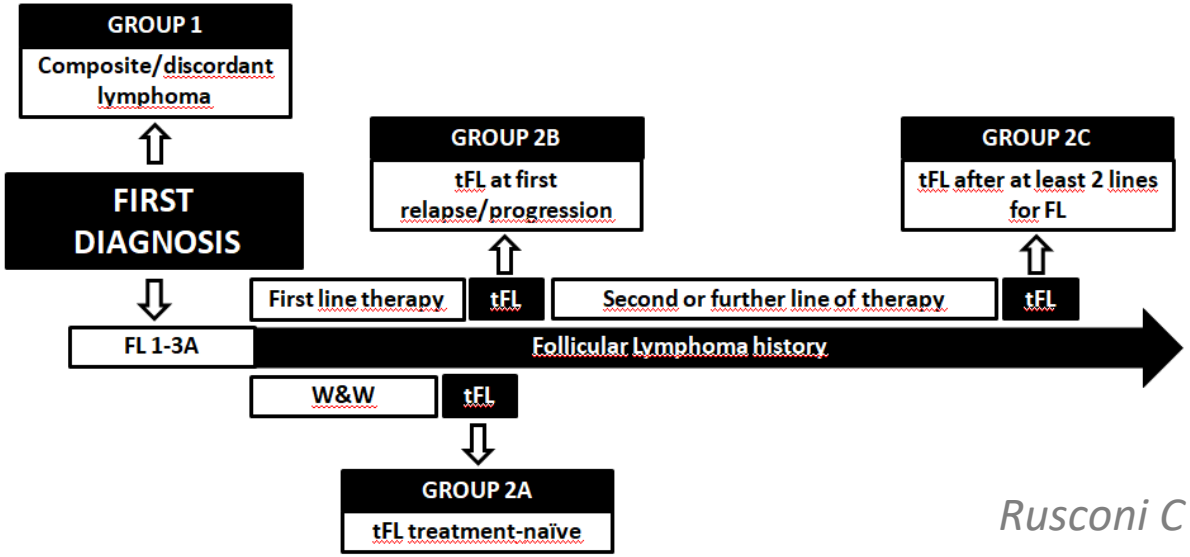


Ban-Hoefen M, BJH 2012

bjh short report

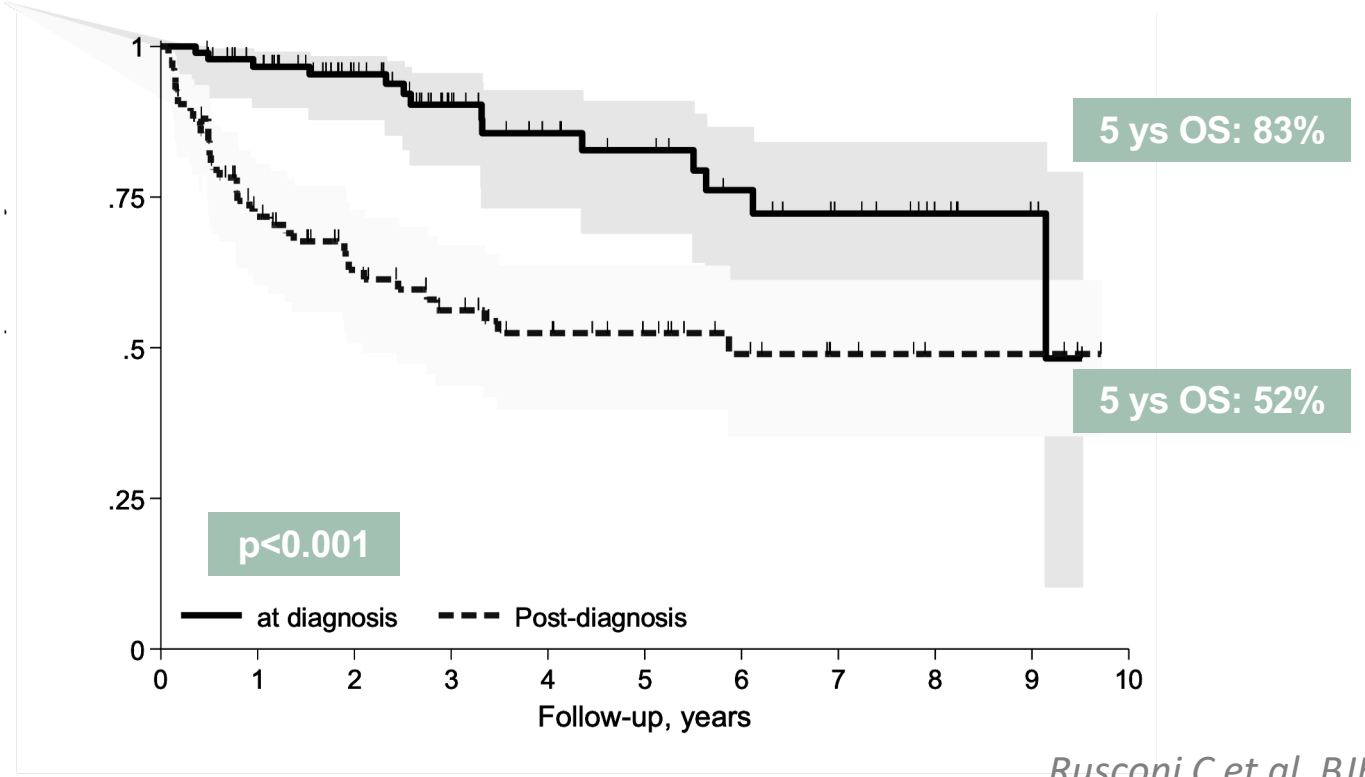
Outcome of transformed follicular lymphoma worsens according to the timing of transformation and to the number of previous therapies. A retrospective multicenter study on behalf of Fondazione Italiana Linfomi (FIL)

…heterogeneity of transformation!



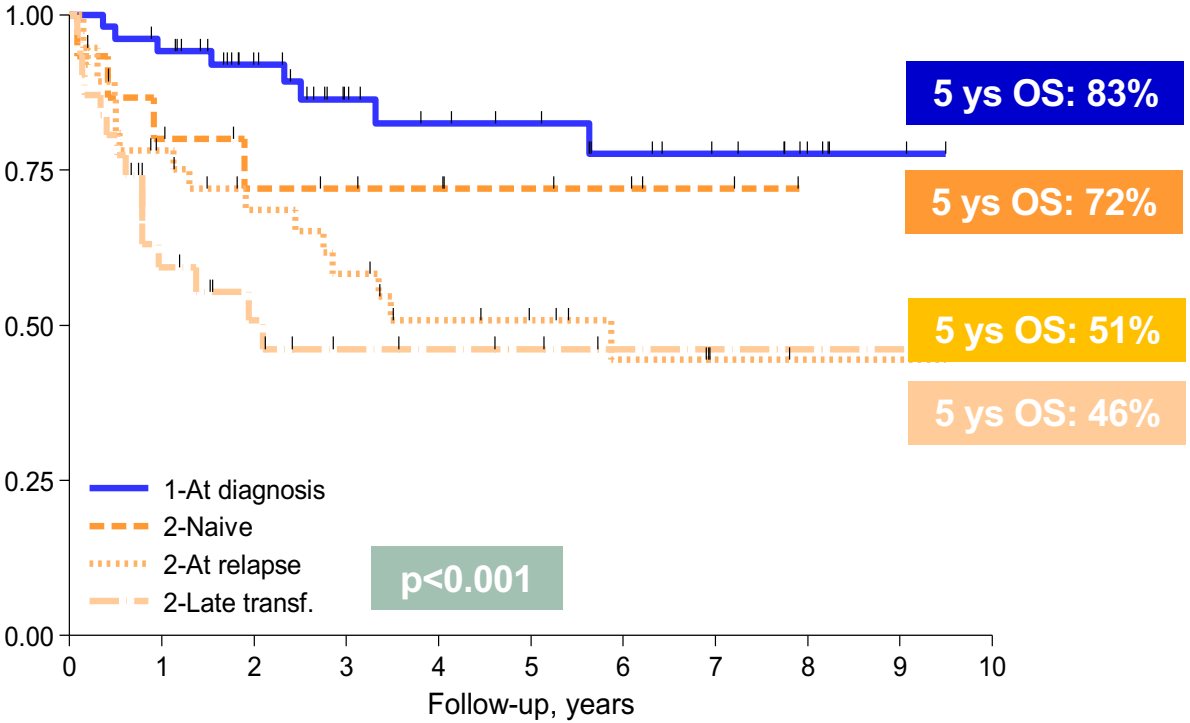
Rusconi C et al, BJH 2019

OS FOR GROUP 1 AND GROUP 2



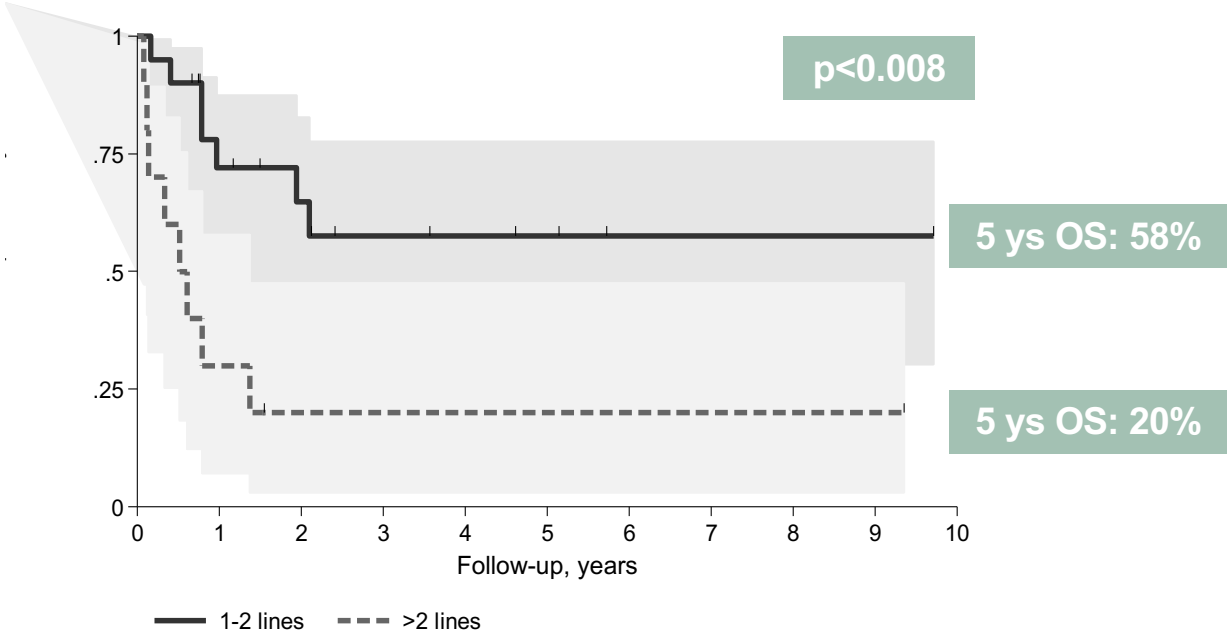
Rusconi C et al, BJH 2019

OS for Group 1 and Group 2A, 2B, 2C



Rusconi C et al, BJH 2019

LATE HT: OS ACCORDING TO NUMBER OF PREVIOUS THERAPY LINES



p<0.008

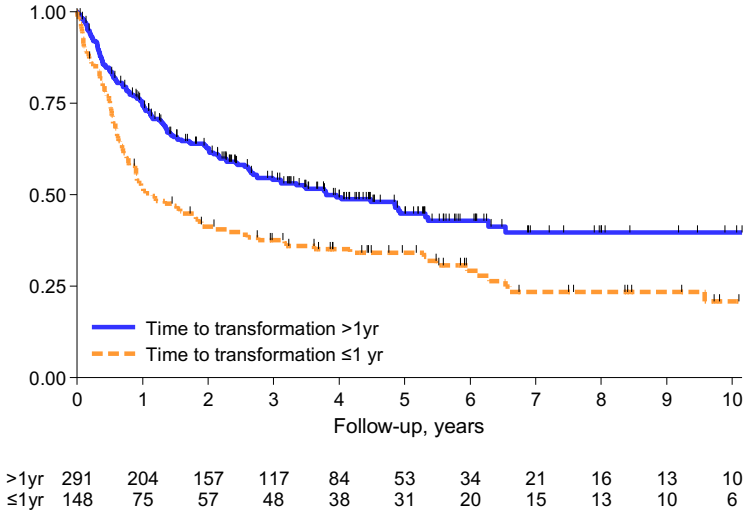
5 ys OS: 58%

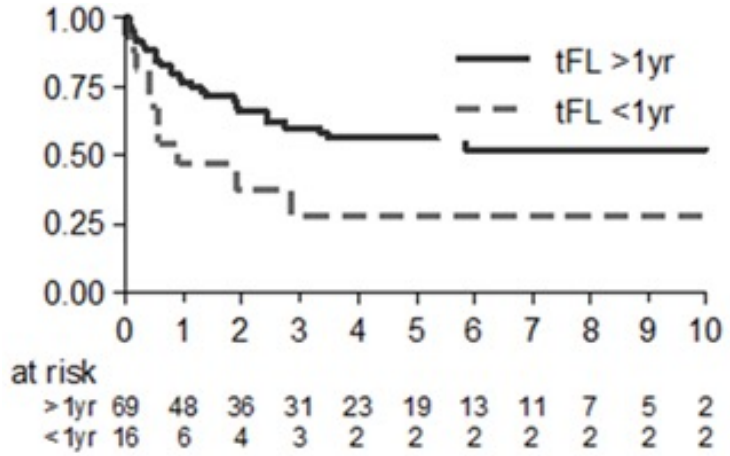
5 ys OS: 20%

≤2 lines: 20 pt; > 2 lines: 10 pts

Rusconi C et al, BJH 2019

Time to transformation and prognosis





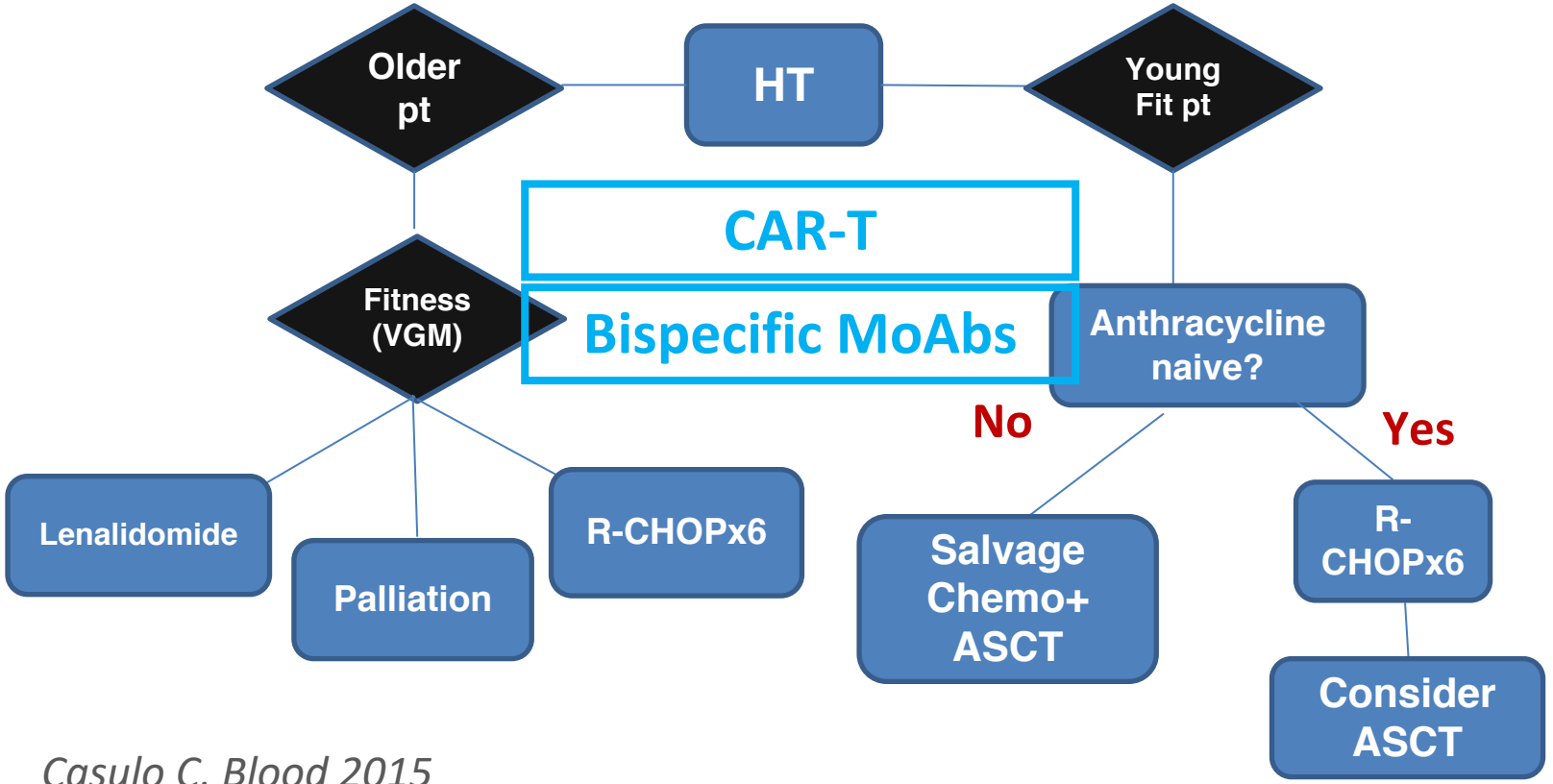
	SAT% at 5-yr (95CI)	HR (95CI)	p
>1yr	45 (38-81)	1.00	
≤ 1yr	34 (26-42)	1.64 (1.27-2.10)	<0.001

5 years OS: 56% vs 29%, p=0.023

Federico M et al, Lancet Haematol 2018

Rusconi C et al, BJH 2019

tFL treatment (historical?)



Casulo C, Blood 2015

FIL results on rituximab maintenance and ASCT consolidation for tFL

- **Group 1:**

  ASCT as first-line consolidation was not associated with a survival advantage

  Five-year PFS in Group 1 was 94% for patients receiving **RM** versus 53% for observation (p=0.024), with no difference in OS (p=0.130)

- **Group 2:**

  ASCT as consolidation strategy led to superior survival only in the subgroup of patients who did not receive anthracycline post-HT(5-year OS for ASCT vs no consolidation, 59% vs 29%, p=0.014)

  RM versus observation was not associated with any survival advantage

Rusconi C et al, BJH 2019

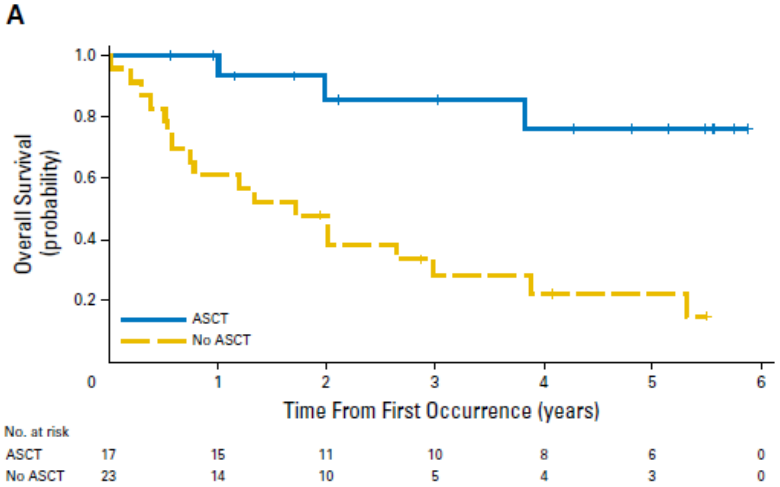
Post HT outcome: PRIMA Trial

1018 FL pts
6 ys f-up: 463 relapses, 194 histologically proven, 40 transformed

58% HT < 1 year
Response to first line ICHT and maintenance: no impact on risk of HT

After salvage therapy: 50% CR, 28% PD
Median OS: 3.8 ys

ASCT improved outcome of HT pts→ median OS for ASCT pts (17/40): not reached vs 1.7 y



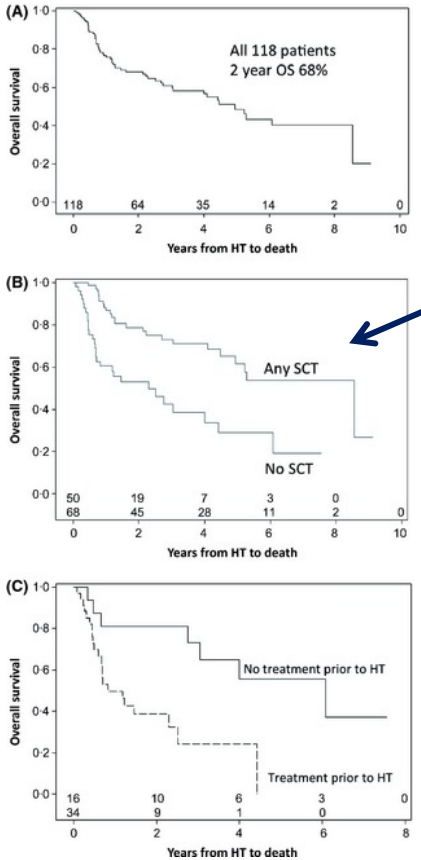
Sarkozy C et al, JCO 2016

Post HT outcome: NCCN Trial

OS all patients

Impact of stem cell transplant on OS

Impact of prior therapy



Younger, previous exposure to anthracycline, more chemo

Ban-Hoefen M, BJH 2012

American Journal of Hematology AJH

RESEARCH ARTICLE

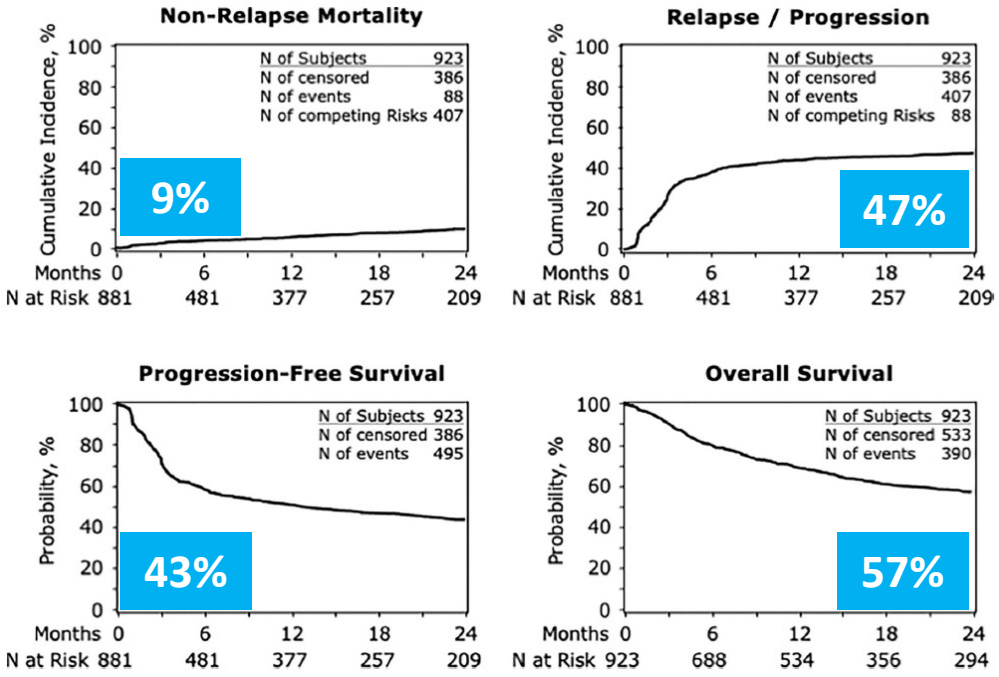
CD19 Directed CAR T Therapy for Transformed Follicular Lymphoma: A CIBMTR Analysis

- 923 adult patients with R/R tFL who received commercial CD19 CAR T therapy between 2017 and 2023
- Median age was 64 years (range: 30–86)
- Median prior lines of therapy was 4 (range: 1–18)
- Most patients (78%) received axicabtagene ciloleucel with 67% of patients having resistant disease at the time of CAR T infusion

Disease status prior to CAR T	
CR	38 (4.1)
PR	179 (19.4)
Resistant disease	617 (66.8)
Untreated	41 (4.4)
Unknown	48 (5.2)
Time from initial diagnosis to transformation, months- median (min-max)	24.6 (0.0–498.9)
Time from transformation to CAR T, months- median (min-max)	10.2 (1.2 – 258.0)
Bridging Therapy	
Yes	451 (48.9)
No	393 (42.6)
Not reported	79 (8.6)
Lymphodepletion regimen	
Bendamustine	64 (6.9)
Cyclophosphamide + Fludarabine	859 (93.1)
Type of CAR T Product	
Axi-cel	718 (77.8)
Tisa-cel	184 (19.9)
Liso-cel	21 (2.3)

Thiruvengadam SW et al, AJH 2025

- Median follow up: 25 months (range: 1–72) from CAR T infusion
- The overall response rate to CAR-T was 76% with a complete response rate of 63%
- Grade ≥ 3 CRS: 7.1%
- grade ≥ 3 ICANS: 21.6% pts
- Multivariable analysis suggested that resistant disease status at time of CAR T, use of bridging therapy, and high comorbidity index ≥3 were associated with inferior PFS and OS
- Older age ≥ 60 significantly increased risk of NRM

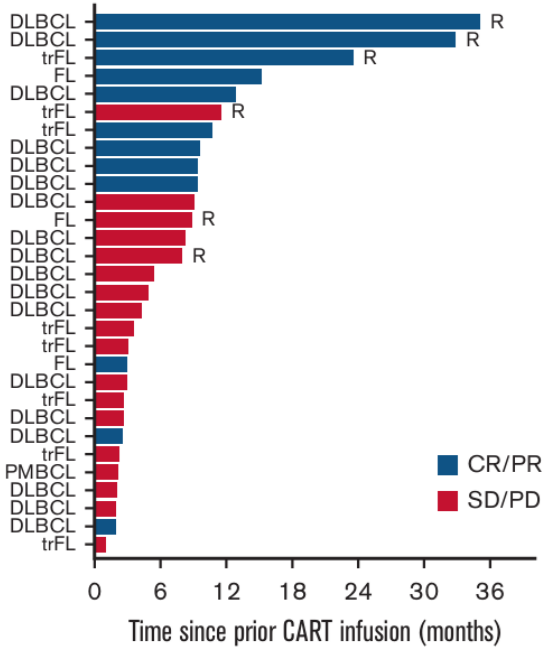


Thiruvengadam SW et al, AJH 2025

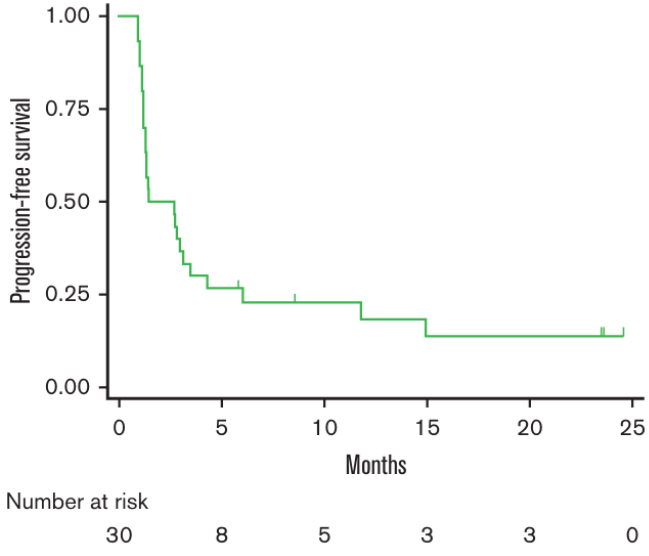
REGULAR ARTICLE

blood advances

Impact of prior CAR T-cell therapy on mosunetuzumab efficacy in patients with relapsed or refractory B-cell lymphomas



B-NHL subtype, n (%)	
DLBCL	19 (63)
trFL	7 (23)
PMBCL	1 (3)
FL	3 (10)
Cell of origin (DLBCL, trFL), n (%)	
GCB	14 (54)
Non-GCB	12 (46)
Unknown	1 (4)

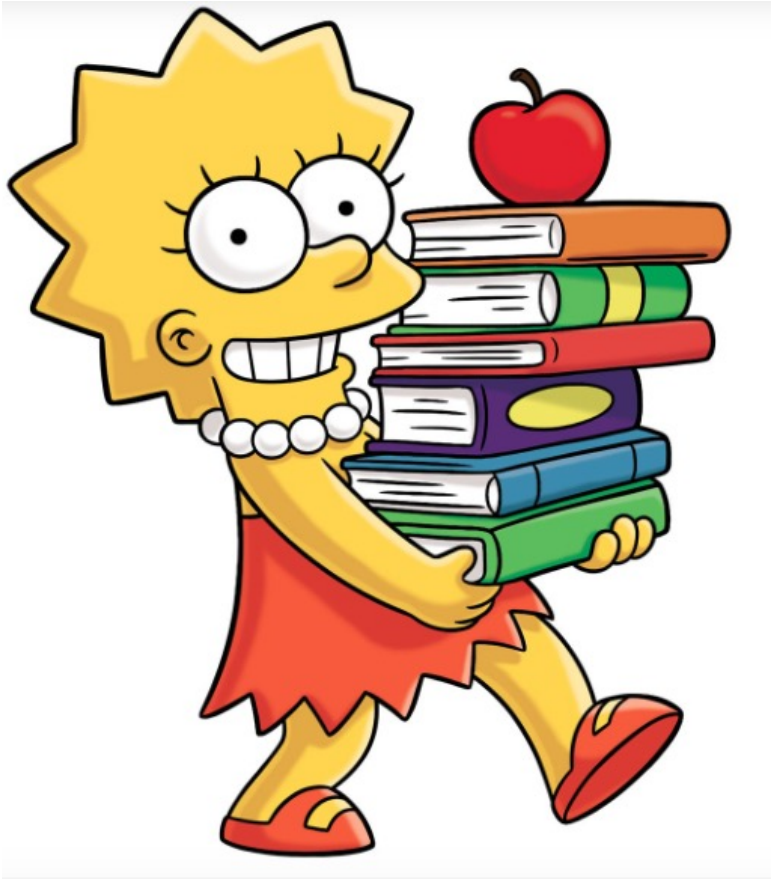


Chong EA et al, Blood Adv 2025

tFL: summary

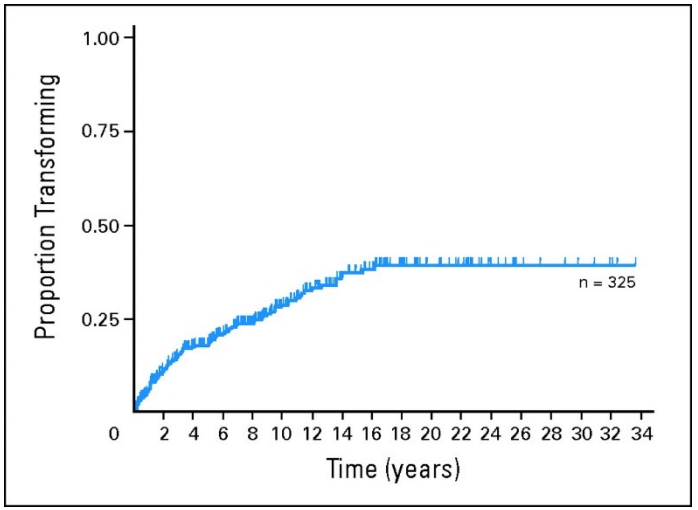
- Consider the hypotesis of HT at any FL relapse and/or in case of fast clinical deterioration and/or in pts whith early FL relapse (POD24)
- Rituximab (and anthracycline?) exposure protects FL pts form HT
- Better post HT outcome in the rituximab era
- ASCT should be consider as consolidation for younger pts, expecially if not treatment naïve at time of transformation
- CAR-T and bispecific antibodies will reshape soon treatment algorithm for transformed FL pts in the post rituximab era (see R/R DLBCL)

Grazie per l’attenzione



Bart's Series (Montoto et al. 2007)

- 325 patients with FL, median follow-up 15 years
- 70% of patients histology at each recurrence
- Biopsy proven transformation in 88 patients
- Median of 3 years form diagnosis
- Similar rate at each episode of recurrence

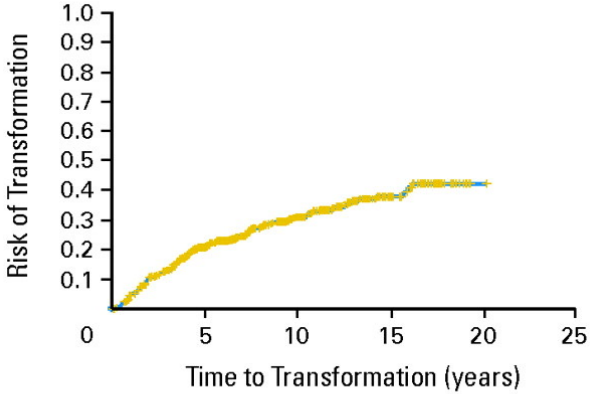


17% at 5 years
28% at 10yrs

Montoto, S. et al. J Clin Oncol; 25:2426-2433 2007

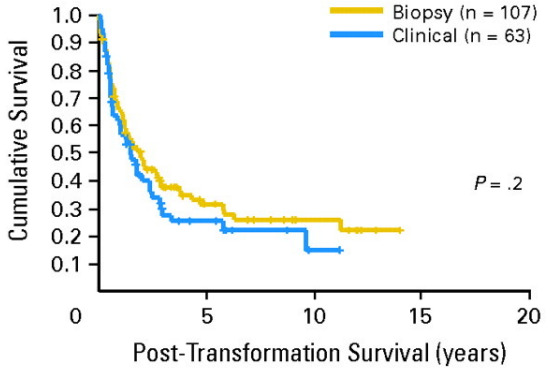
Annual risk of transformation = 3% per year

Risk of transformation



10 year risk 30%

Post transformation survival by method of diagnosis

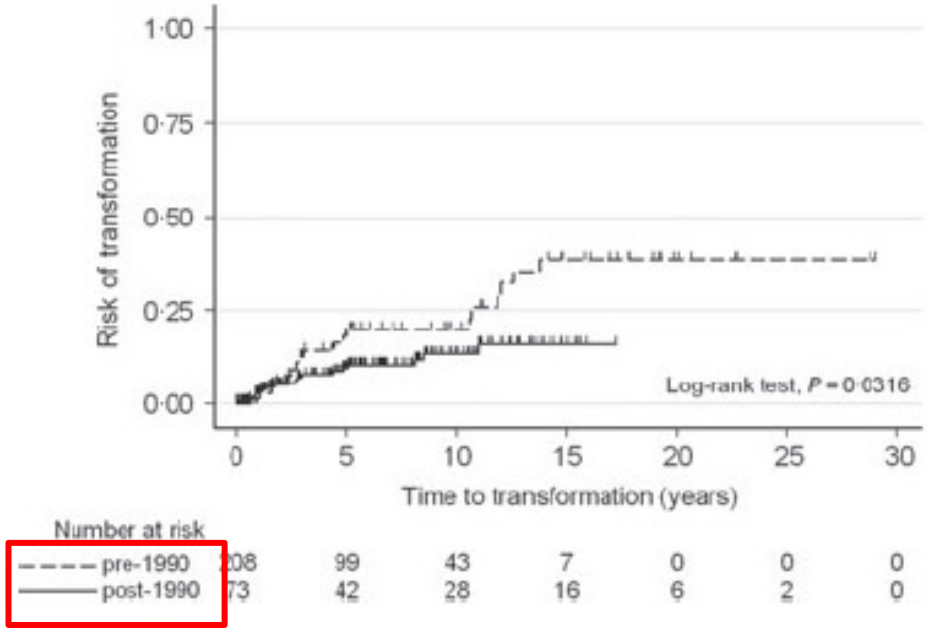


Al-Tourah A J et al. JCO 2008;26:5165-5169

Oncology Institute of Southern Switzerland

(Conconi et al 2012)

37 of 281 patients (histological) 1979-2007: 15% at 10yrs



Not significant in multivariate; but medial follow-up much shorter

Valutazione del rischio di trasformazione all'esordio di FL

Valutazione biologica:

- FOXP3+ T-cell
- TP53
- MDM2
- microenvironment
- NF-kB
- CDKN2A/B
- IRF4

Rossi D, Hematol Oncol 2015
Pasqualucci L, Cell Rep 2014
Blaker YN, BJH 2016

Valutazione clinica:

- Performance Status
- Anemia
- LDH>UNL
- Stadio avanzato
- Elevato FLIPI
- Sintomi B
- Grado 3A
- Sedi EN
- N linee terapeutiche pre tx

Wagner-Johnston ND, Blood 2015
Conconi A, BJH 2012

Terapia per FL:

- Dubbio ruolo protettivo delle antracicline
- Dubbio ruolo protettivo di W&W
- Dubbio ruolo protettivo di Rituximab monoterapia

Link BJ, JCO 2013
Ban-Hoefen M, BJH 2012
Al-Tourah AJ, JCO 2008

Diagnosi di trasformazione

Valutazione clinica:

- LDH>UNL
- Rapida crescita linfonodale
- Deterioramento PS
- Comparsa di sintomi B
- Ipercalcemia

Imaging:

- Elevato SUVmax (>10) alla trasformazione sospetto per trasformazione
- Biopsia PET-driven

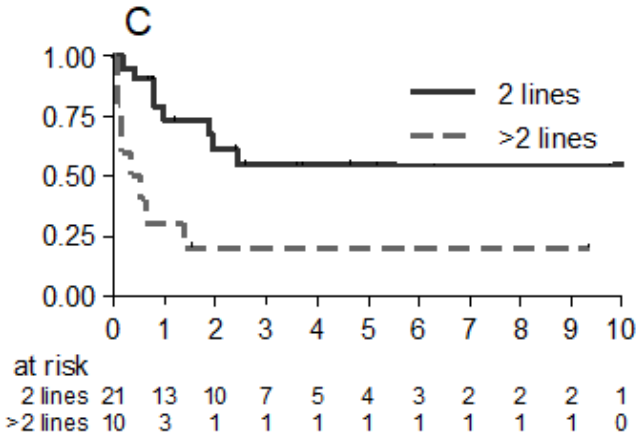
Paziente con caratteristiche suggestive di trasformazione alla I recidiva

Gold standard per la diagnosi di trasformazione: esame istologico

Al-Tourah AJ, JCO 2008
Wagner-Johnston ND, Blood 2015
Link BJ, JCO 2013

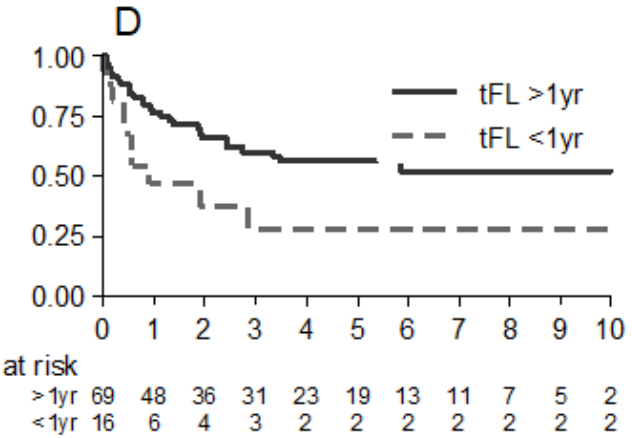
Noy A, Ann Oncol 2009
Smith SD, Blood 2015
Casulo C, Blood 2014

Post HT prognosis



** Only Group 2C*

5 years OS: 52% vs 20%, p=0.004



** Only Group 2*

5 years OS: 56% vs 29%, p=0.023

Rusconi C et al, BJH 2019