SINTOMA'25

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APOIO INSTITUCIONAL bp Educação e Pesquisa

O que me influencia na escolha da terapia em primeira linha no Linfoma Folicular?

Rafael Gaiolla

Professor de Hematologia

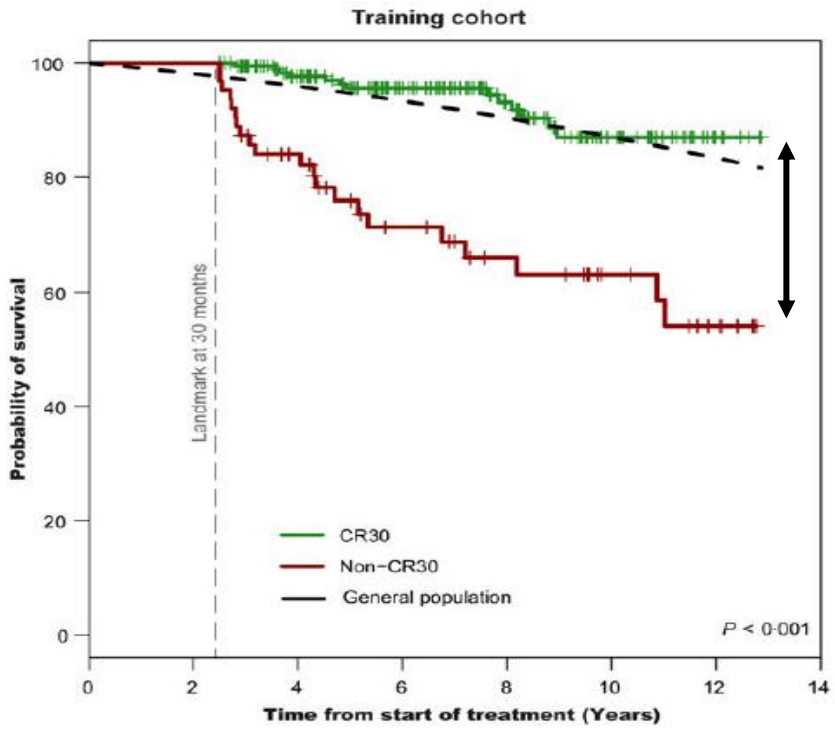
Faculdade de Medicina de Botucatu - UNESP

Declaração de Conflitos de Interesse

- Sem conflitos de interesse a declarar

Follicular Lymphoma - Overview

- Remarkable improvements in FL survival in the past decades (= addition of anti-CD20 antibody)
- Although FL is still considered incurable, most patients can reach a normal life expectancy
- In general:
  - ✓ Complete remission of nearly 70%
  - ✓ Median PFS of 6-7 years
  - ✓ Median survival 15-20 years



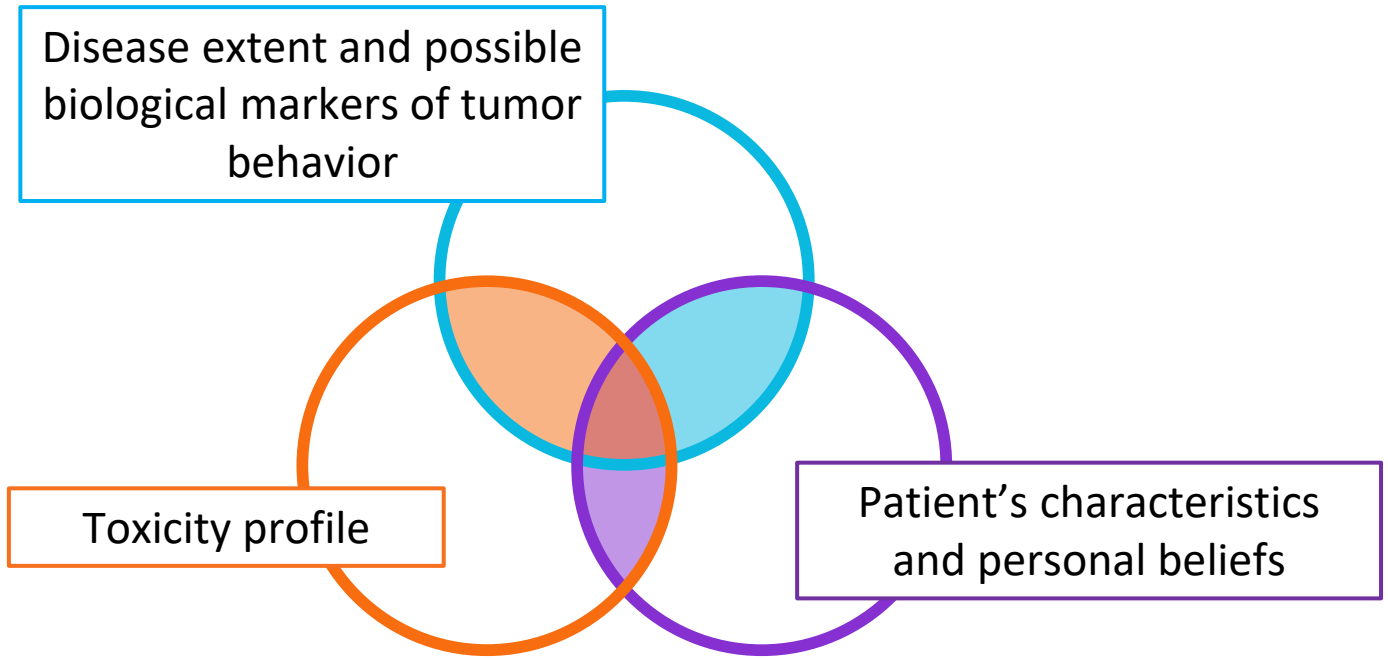
15-20% with a worse prognosis:

- Early progression
- No CMR after induction
- HT
- Aggressive disease

Maurer MJ et al. Am J Hematol 2016
Magnano L et al. Br J Haematol 2019
Tan D et al. Blood 2013
Bruna R et al. Haematologica 2019

What Are the Goals For FL Treatment?

- Although largely used, PFS is limited as a marker of **clinical benefit**
- The main goal in FL is to achieve and maintain a good quality of life
- The choice of treatment should be “personalized” and consider:



Maures MJ et al. Am J Hematol 2016 / Magnano L et al. Br J Haematol 2019 / Tan D et al. Blood 2013

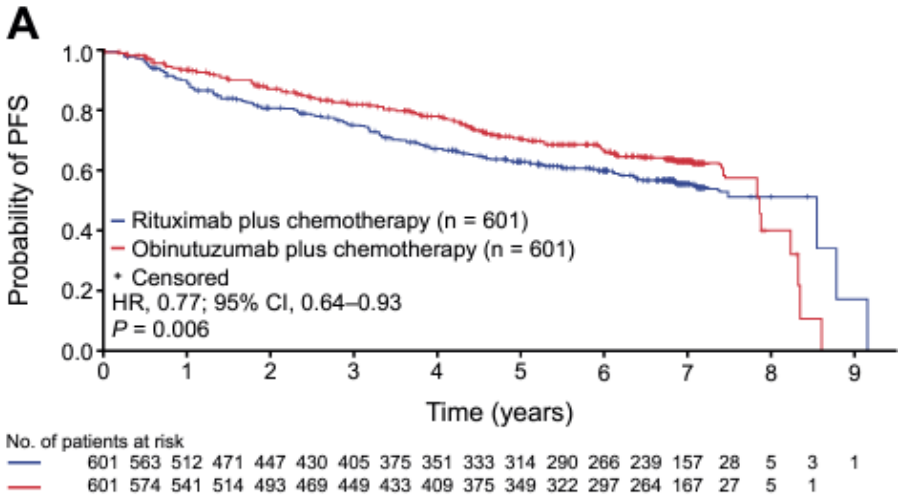
First-Line Treatment in FL (Symptomatic Disease)

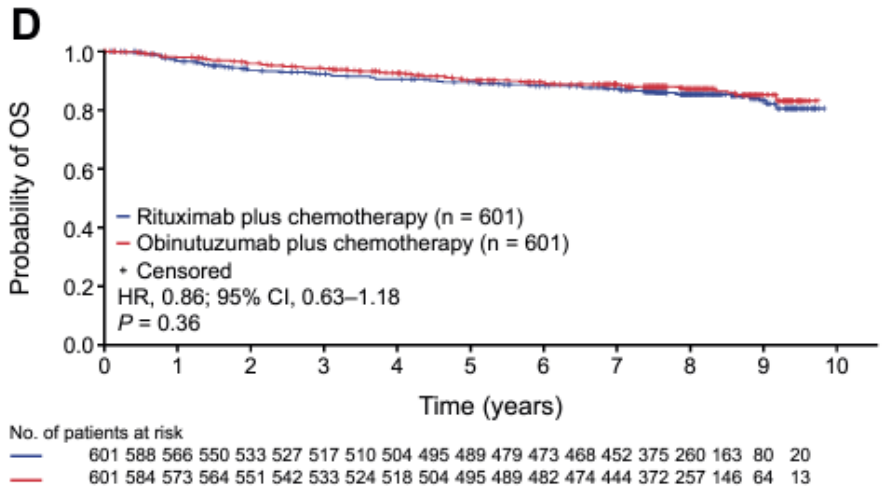
Study	Evaluated Regimens	Results	Observations
FOLL05 (N = 504) 	R-CHOP vs R-CVP vs R-FM	**PFS at 8 years** - R-CHOP ~ R-FM = 52% - R-CVP = 41% (p=0.003) **OS at 8 Years = 83%**	• R-FM more toxic, more secondary neoplasms • R-CVP less effective
STiL (N = 514) 	R-CHOP vs BR	- **BR improved mPFS: 69 x 31 mo** - BR >> TTNT **- OS at 10 Years = 93% vs 91%**	• **BR less toxic** • More skin reactions with BR • Included other lymphoma subtypes (MCL, MZL)
BRIGHT (N = 447) 	R-CHOP / R-CVP vs BR (non-inferiority for BR)	**PFS at 5 years** - R-CHOP/R-CVP = 55,8% - BR = 65,5% (p=0.025) - **OS at 5 Years = 81,7% e 85% (p=NS)**	• Comparable toxicity • Included other lymphoma subtypes (MCL, MZL)

Federico M et al. J Clin Oncol 2013 / Luminari S et al. J Clin Oncol 2018 / Rummel MJ et al. Lancet 2013 / Rummel MJ et al. J Clin Oncol 2019
Flinn IW et al. Blood 2014 / Flinn IW et al. J Clin Oncol 2019

Monoclonal Antibody Dilemma: R or G?

GALLIUM Study – Final Analysis with 8-year follow-up





	O-chemo (N=601)	R-chemo (N=601)	
7-year PFS	63,4%	55,7%	HR 0,77 (95%CI 0,64-0,93, p=0,006)
7-year OS	88,5%	87,2%	HR 0,86 (95%CI 0,63-1,18, p=0,36)

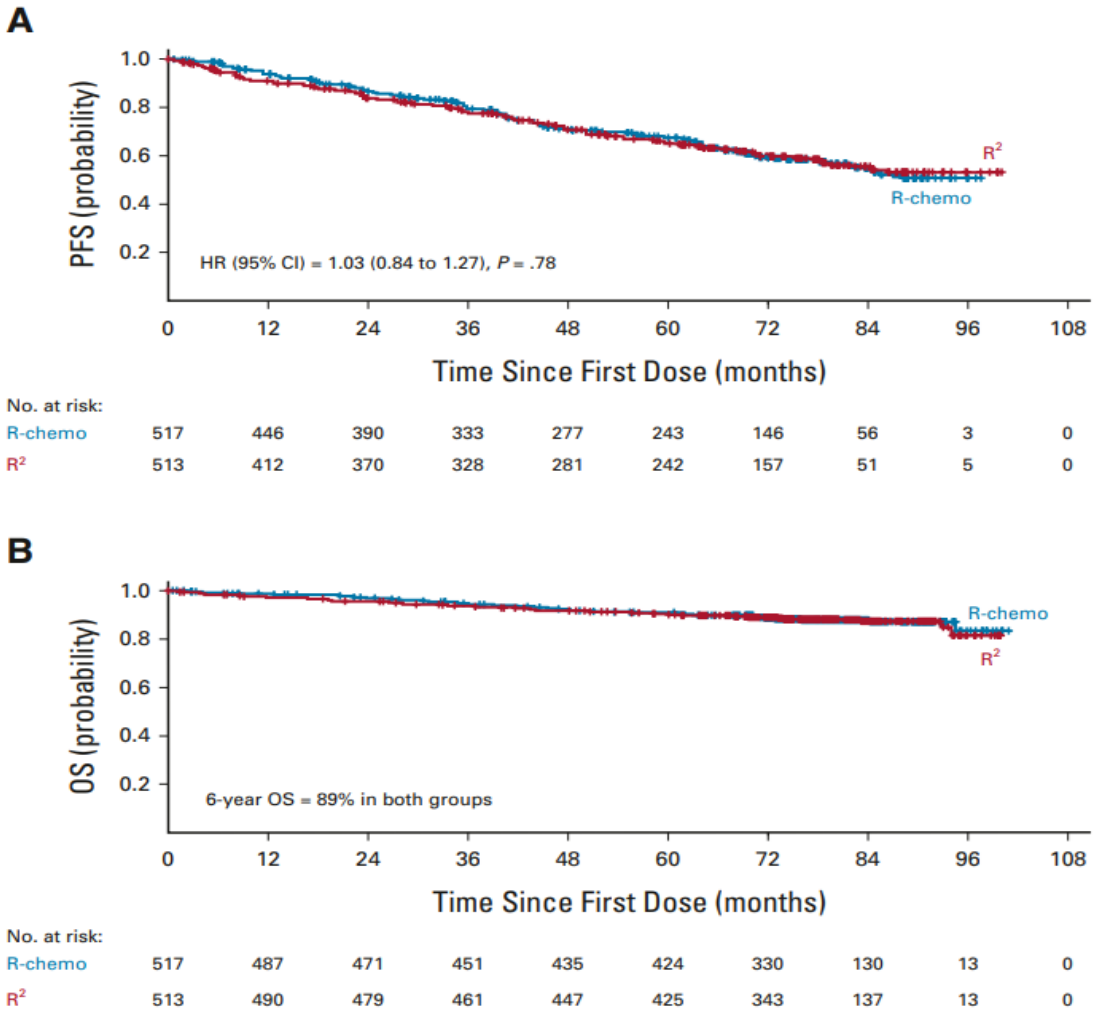
Obinutuzumab Arm:

- Higher incidence of neutropenia
- Higher incidence of Grade 3-5 febrile neutropenia
- Higher incidence of SAEs (48,9% x 43,4%)
- More deaths with Benda-Obinu

Marcus R et al. N Eng J Med 2017 / Townsend W et al. Hemasphere 2023

Chemo-Free Approach: the RELEVANCE Trial

R2 *versus* R-Chemo + R-maintenace (6-years follow-up)



N = 1030 patients, grades 1-3a FL

	R-chemo	R²	P
CR / CRu	53%	48%	0,1
PFS 5a	59%	60%	0,78
OS 5a	89%	89%	0,1

No diferences in histologic transformation or POD24

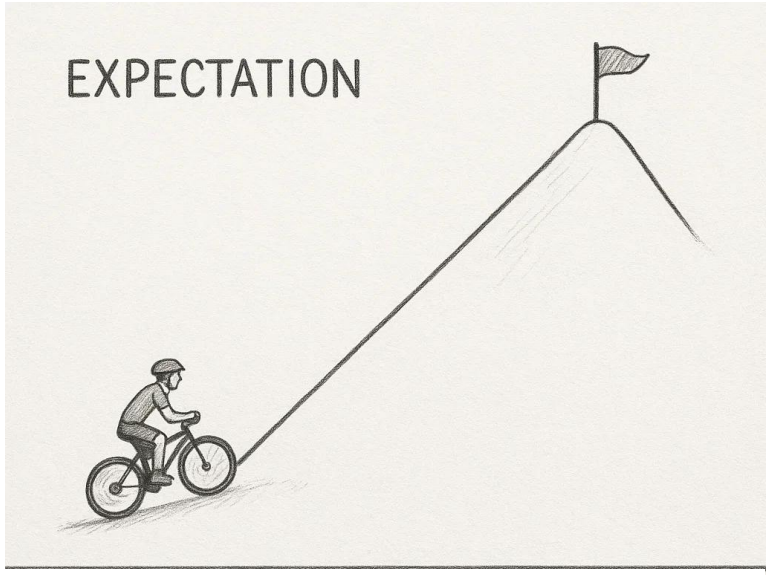
Morchhauser F et al. N Eng J Med 2018 / Morchhauser F et al. J Clin Oncol 2022

Treatment Options in FL – Pros and Cons

Drugs	Pros	Cons
CHOP	Excellent long-term disease control **High OS rates**	Hematological toxicity Anthracycline-related toxicity
CVP	Less toxic **High OS rates**	Inferior disease control Higher chances of a new treatment
Bendamustine	At least equal to CHOP for disease control Less hematological toxicity **High OS rates**	T-cell depletion Higher incidence of 2nd neoplasia? More infections (elderly)
Lenalidomide	Chemo-free approach Efficacy is comparable to CHOP	Specific AE (rash, fatigue, ↓neutro) Higher cost
Rituximab	Excellent long-term disease control, high OS rates Favourable toxicity profile	↑ infections when used as maintenance
Obinutuzumab	More "potent" than R (higher rates of DRM-) Increases PFS compared to R	More SAE (IRR, infections) Higher cost Modest PFS gain, no difference in OS

Hiddemann W et al. J Clin Oncol 2018 / Morchhauser F et al. N Eng J Med 2018 / Flinn IW et al. Blood 2014 / Rummel MJ et al. Lancet 2013 / Federico M et al. J Clin Oncol 2013 / Luminari S et al. J Clin Oncol 2018

What 1L Treatment Should I Choose?



Theory: “Consider your patient´s characteristics and treatment goals and pick the one you feel more comfortable with.”

Reality: “Well…lots of caveats to consider”

Important Questions for Daily Clinical Practice

- How far should I go in older/frail patients?
- How far should I go in young patients? Does more potency mean more efficacy?
- Should Grade 3A FL be managed differently?
- Does the FDG-uptake interfere with treatment choice?
- Can we predict POD24 or HT and modify the 1L treatment strategy?

How do these questions affect my treatment choice?

Treatment Toxicity in FL – Lessons Learned

Anthracyclin	Obinutuzumab	Bendamustine
• Higher rates of grade 3-4 AEs • Diven by ↑ hematological toxicity • 5-10% will develop clinical cardiopathy • 20-30% with subclinical alterations	• **More toxic than Rituximab (GALLIUM)** • Higher rates of SAE: 49% x 43% • Higher rates of grades 3-5 Aes: - neutropenia (47% x 40%) - febrile neutropenia (7.6% x 4.7%) • Higher rates of grade ≥ 3 infusion-related reactions (12% x 7%)	• **Higher rates of infections** • Higher cumulative incidence of bacterial, viral, fungal, and opportunistic infections • Higher incidence of serious infections • **More fatal events in patients ≥ 70 years during and after treatment (13% versus 2-4% with CHOP/CVP)** • **Delayed CD4 recovery (~2 y)**

Marcus R et al. N Eng J Med 2017 / Hiddemann W, et al. J Clin Oncol 2018 / Townsend W et al. Hemasphere 2023 / Fung M, et al. Clin Infect Dis 2018 / Martinez-Calle N, et al. Br J Haematol 2018 / Gaiolla R et al. Hematol Oncol 2021

Combining B plus G Potencially Increases the Risk of Infections

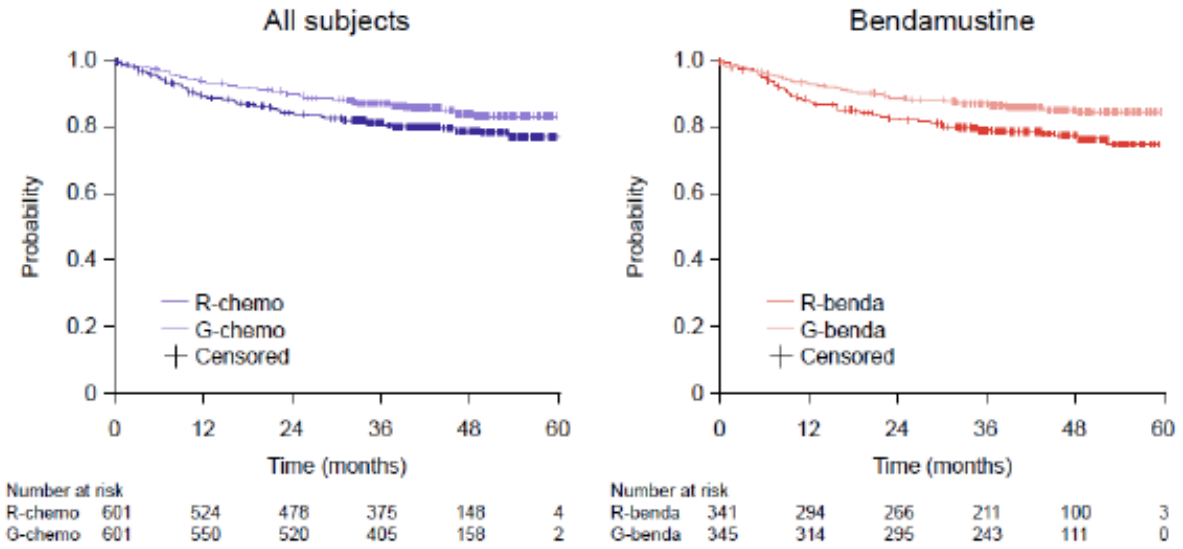
Grade 3–5 infections and grade 3 and 4 neutropenia adverse events by treatment arm and chemotherapy regimen in the follicular lymphoma safety population

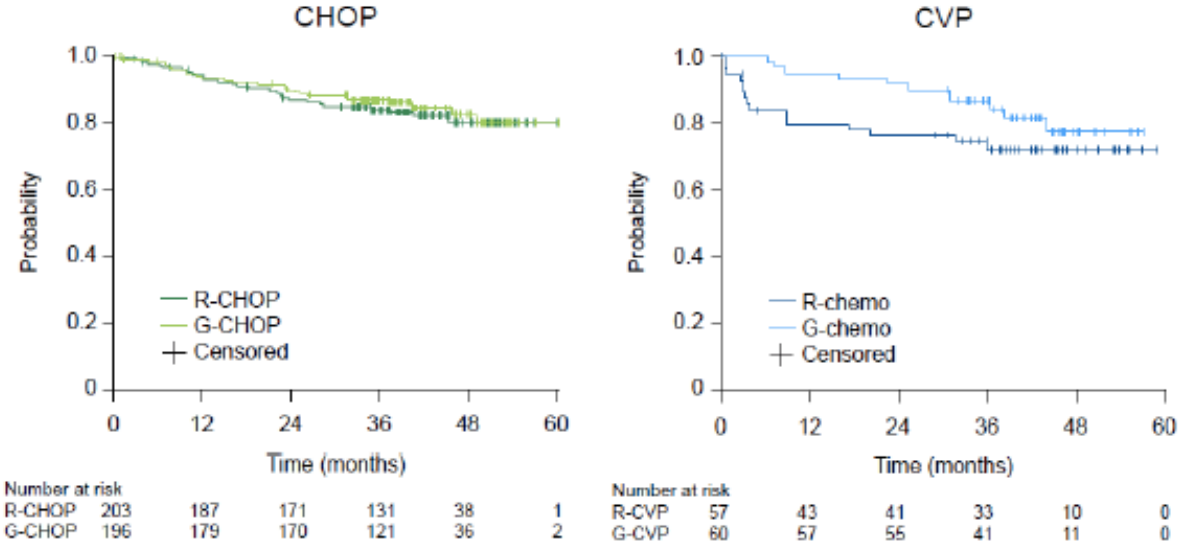
Number (%) of patients reporting ≥ 1 AE	Obinutuzumab + bendamustine	Rituximab + bendamustine	Obinutuzumab + CHOP	Rituximab + CHOP	Obinutuzumab + CVP	Rituximab + CVP
Grade 3–5 infections						
All study periods	89/338 (26)	66/338 (20)	23/193 (12)	25/203 (12)	8/61 (13)	7/56 (13)
Induction	27/338 (8)	26/338 (8)	14/193 (7)	13/203 (6)	3/61 (5)	4/56 (7)
Maintenance	51/305 (17)	39/300 (13)	7/178 (4)	11/186 (6)	5/57 (9)	1/40 (3)
Observation/follow-up	28/319 (9)	12/316 (4)	3/184 (2)	6/195 (3)	1/58 (2)	3/53 (6)
Grade 3 and 4 neutropenia						
All study periods	100/338 (30)	102/338 (30)	137/193 (71)	111/203 (55)	28/61 (46)	13/56 (23)
Induction	73/338 (22)	87/338 (26)	124/193 (64)	103/203 (51)	24/61 (39)	13/56 (23)
Maintenance	49/305 (16)	29/300 (10)	37/178 (21)	26/186 (14)	5/57 (9)	2/40 (5)
Observation/follow-up	6/319 (2)	1/316 (1)	4/184 (2)	1/195 (1)	1/58 (2)	0

Abbreviations: AE, adverse event; CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone; CVP, cyclophosphamide, vincristine, and prednisone.

Hiddemann W, et al. J Clin Oncol 2018

Younger patients: More potency, better results?





Time to a new anti-lymphoma treatment

- No differences for R-CHOP vs. O-CHOP
- O-Benda superior to R-Benda
- **Remember**: O-Benda more toxic, even for the youngers!

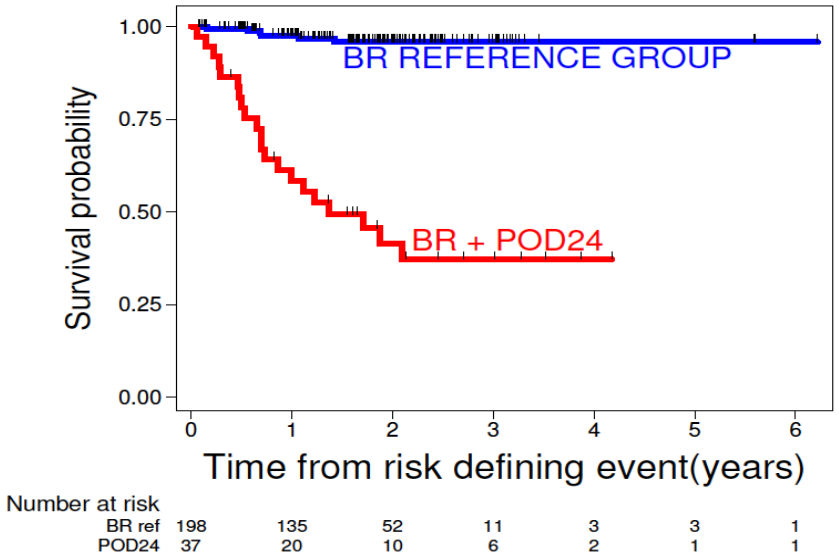
However…

- The study was not powered to assess differences in outcomes between the chemo groups
- Chemo groups were non-randomized

Hiddemann W et al. J Clin Oncol 2018

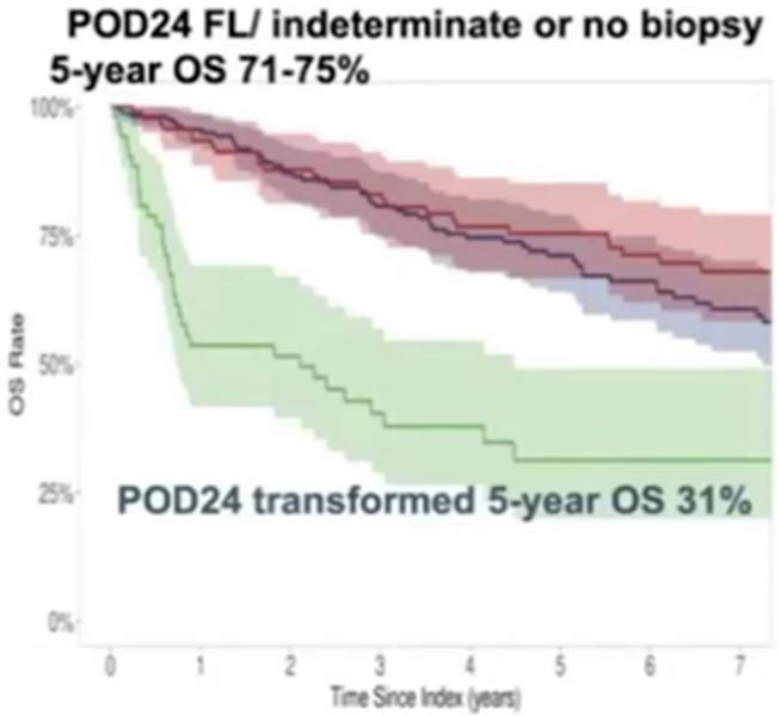
POD24 and Histological Transformation – Are They Related?

RWD from the British Columbia



- 13% of POD24
- 76% of POD24 with **confirmed** TH

The Lymphoma Epidemiology of Outcomes (LEO)



- N=1222 FL (308 early relapses)
- **17% with POD24 and HT**
- 52% with POD24 FL

Freeman CL et al. Blood 2019
Casulo C, et al. ASH 2024 abstract #1652

Known Risk Factors for Transformation

Risk Factors from multivariate analyses
FLIPI Score ≥ 3 • Age > 60 • Advanced stage • Hb <12g/dL • 4 nodal areas • Elevated LDH
Grade 3A FL
> 1 extranodal site
Age at diagnosis
Elevated LDH (baseline or anytime during treatment)
PET-CT SUV (controversial)

Sarkozy C, et al. J Clin Oncol 2016
Wagner-Johnston ND, et al. Blood 2015
Conconi A, et al. Br J Haemtol 2012
Ginne E, et al. Ann Oncol 2006
Link B, et al. J Clin Oncol 2013
Noy A, et al. Ann Oncol 2009
Li Z-W, et al. Cancer 2024

Risk Assessment Tools are Limited to Predict POD24

	Components	Risk groups	Survival	POD24
FLIPI	Age; stage; Hb; LDH; nodal sites	Low: 0–1 Intermediate: 2–3 High: 4–5	Low: 92% Intermediate: 90% High: 67%	Low/Intermediate: 4%-6% High: 7%-14%
FLIPI2	B2M; diameter lymph node; BMI; age	Low: 0 Intermediate: 1–2 High: 3–5	Low: 91% Intermediate: 69% High: 51%	
PRIMA-PI	B2M; BMI	Low: B2M ≤ 3, no BMI Intermediate: B2M ≤ 3 with BMI High: B2M > 3	Low: 69% Intermediate: 55% High: 37%	Low: 5% Intermediate: 7% High: 12%
FLEX	Male sex; sum of lesion dimension; grade 3A; extranodal sites; ECOG; Hb; B2M; NK cell count; LDH	Low: 0–2 High: 3–9	Low: 86% High: 68%	Low: 5% High: 8%
m7-FLIPI	FLIPI; ECOG; mutation status of 7 genes (*ARID1A*, *CARD11*, *CREBBP*, *EP300*, *EZH2*, *FOXO1*, *MEF2B*)	Low: <0.8 High: >0.8	Low: 77% High: 38%	Low: 7% High: 17%
POD24-PI	High-risk FLIPI; mutation status of 3 genes (*EP300*, *EZH2*, *FOXO1*)	Low: <0.71 High: >0.71	Low: 77% High: 50%	Low: 4% High: 14%

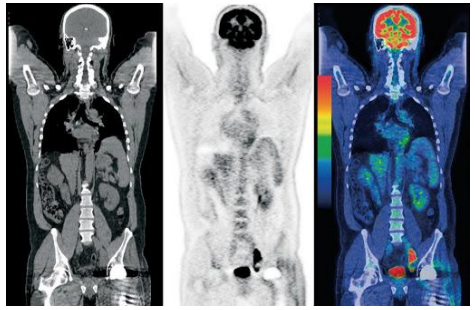
BMI, body mass index; Hb, hemoglobin.

*__FLIPI24__: age, hemoglobin, white blood cell count, LDH, and B2M

- Identified poor outcomes among patients with a high/very high-risk score
- Median EFS 1.8 years (95% CI, 1.3-3.28)
- 5-year OS of 65% (95% CI, 55.9-75.8)

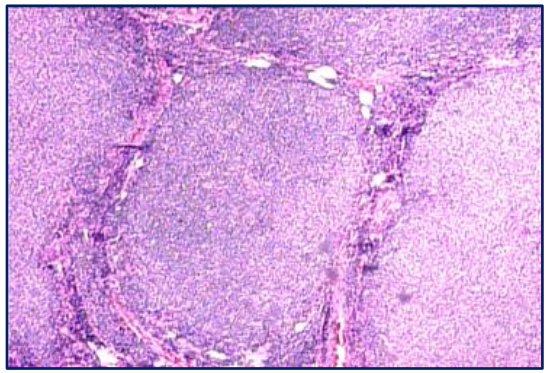
Mondello & Casulo. Hematology 2024
Maurer MJ, et al. Blood 2022

Driving Decisions in Clinical Practice



Biomarkers

- ctDNA – not yet available for routine use
- TMTV / SUVmax – potential role, but controversial results

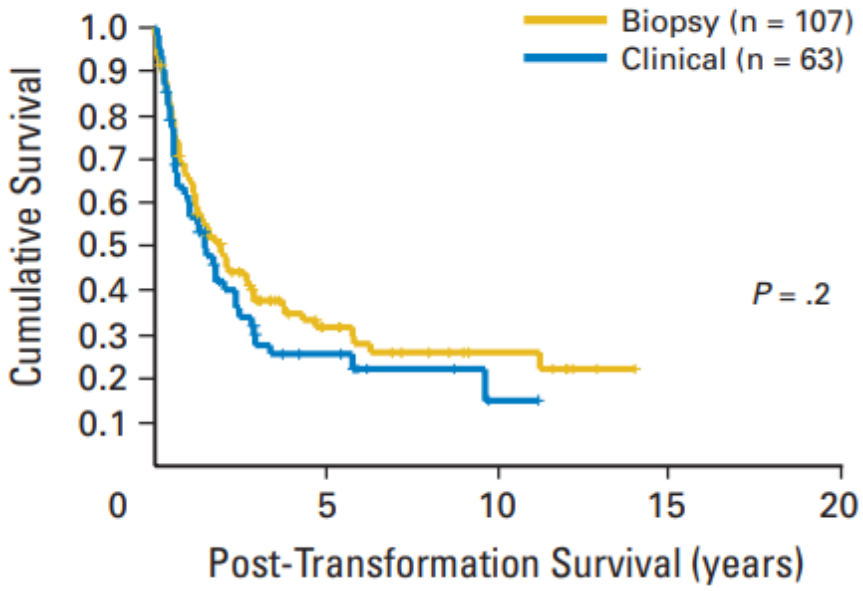


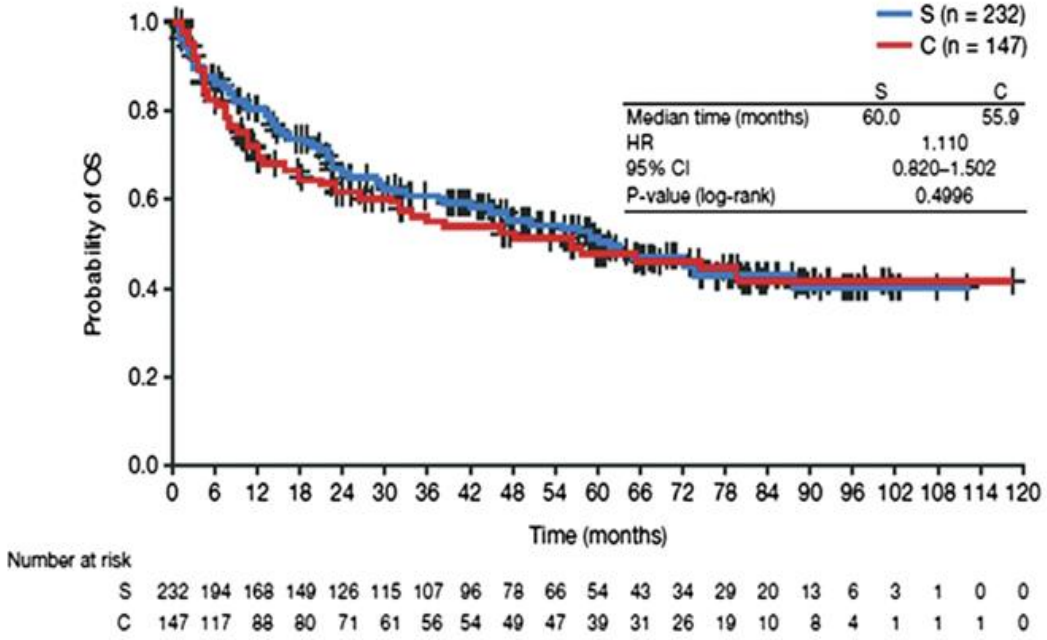
1. **Good-quality diagnostic biopsy**
   - Preferably driven by PET findings
   - > 1 site of biopsy if needed
   - Experienced hematopathologist

2. **Clinical and lab findings**
   - FL behavior = “kinetics”
   - B-symptoms
   - Altered Labs (**especially LDH**)

Mir F, et al. Blood 2020
Strati P, et al. Haematologica 2020
Mondello & Casulo. Hematology 2024

Can We Rely on Clinical Criteria for HT Suspicion?





Criteria for Diagnosis of Transformation	Clinical (n = 63) No.	Clinical (n = 63) %	Histologic (n = 107) No.	Histologic (n = 107) %
Elevated LDH	34	54	53	49
Rapid nodal growth	62	98	98	91
Extranodal, excluding BM	46	73	42	39
New B symptoms	17	27	32	30
New hypercalcemia	4	6	1	0.9

Abdulwahab J et al. J Clin Oncol 2008
Wagner-Johnston ND, et al. Blood 2019

Guiding 1L Treatment Choice in FL (*High Tumor Burden*)

FL scenario	Treatment Choice	Comments
<70 Years "usual" clinical presentation	**R-Benda** **R-CHOP**	If Benda is the choice: - PJP and zoster profilaxis - Monitor CD4 every 3 months until ≥ 200
≥70 Years	**R-CVP** R-mini-CHOP	- R-mini-CHOP if aggressive presentation - Avoid Benda or consider dose reduction (70mg/m^2) - Consider R-mono if frail
<70 Years Aggressive behavior	**R-CHOP**	- Consider R-mini-CHOP according to PS
When do I choose Obi?	- **Rarely...** - Can be considered in younger patients, when a PFS gain is the main goal - Be careful if combined with Benda (**use only in young and fit patients**)	
When do I choose R^2	- **Never...** - Not approved in Brazil as 1L - Higher cost - Could be considered if the patient is not suitable for chemo	

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Obrigado!

rafael.gaiolla@unesp.br

FACULDADE DE MEDICINA FMB 1963 BOTUCATU

unesp
UNIVERSIDADE ESTADUAL PAULISTA
"JÚLIO DE MESQUITA FILHO"