

Linfoma Folicular em 1ª Linha

Imunoquimioterapia, Abordagens Livres de Quimioterapia e
Estratégia Terapêutica

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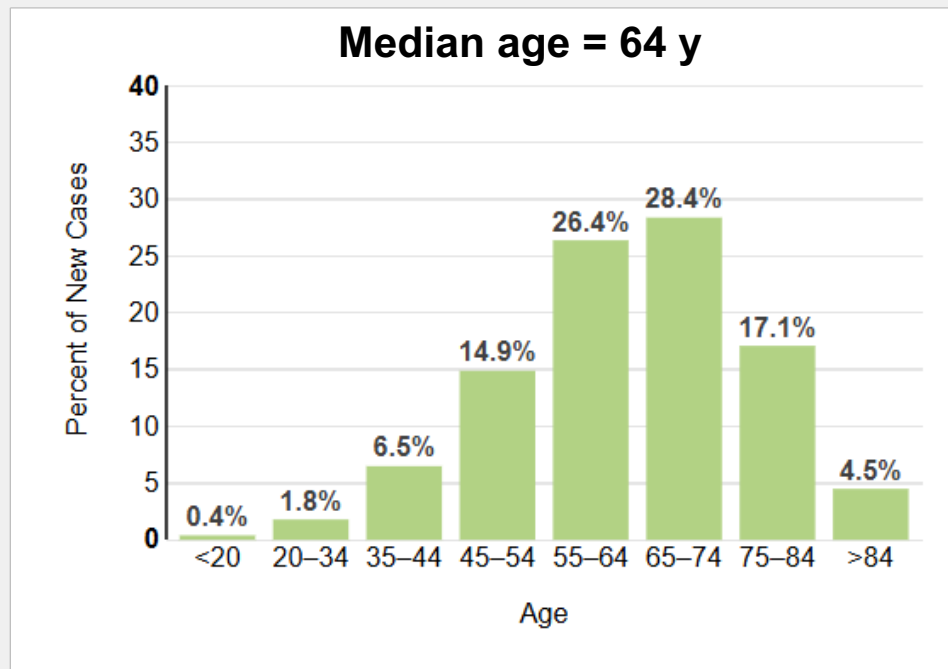
Faculdade de Medicina de Botucatu - UNESP



- Consultoria: Janssen, AbbVie, BeOne
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- Patentes e Royalties: NA
- Drogas Off-Label: NA

Follicular Lymphoma Overview

- The most frequent indolent lymphoma
- Although still considered incurable, most patients can reach a normal life expectancy
- In general:
 - ✓ Median PFS of 6-7 years
 - ✓ Median survival 15-20 years
- 15-20% will have a worse prognosis



What about FL in Brazil?

- Scarce epidemiological data
- Private *versus* Public – access issues
- Sicker patients with high-risk features are not uncommon



Considerations in FL Treatment

Disease-related

Disease extent and possible biological markers of tumor behavior

Risk of POD24, transformation, or early death

Therapy-related

Toxicity profile
Available drugs

Patient-related

Patient's characteristics and personal beliefs

- Achieve and maintain a good quality of life
- What to do if the patient relapses?

Important Questions for Daily Clinical Practice

- Low tumor burden follicular lymphoma – Active monitoring or rituximab?
- How do I decide to start a treatment – adhere strictly to GELF Criteria? Consider other high-risk features?
- Can we predict POD24 or HT and modify the 1L treatment strategy?
- How do I choose the 1L treatment: CHOP x Benda x Lenalidomide-based?
- How do I choose the Mab: Rituxi or Obinu?
- Is maintenance treatment necessary?



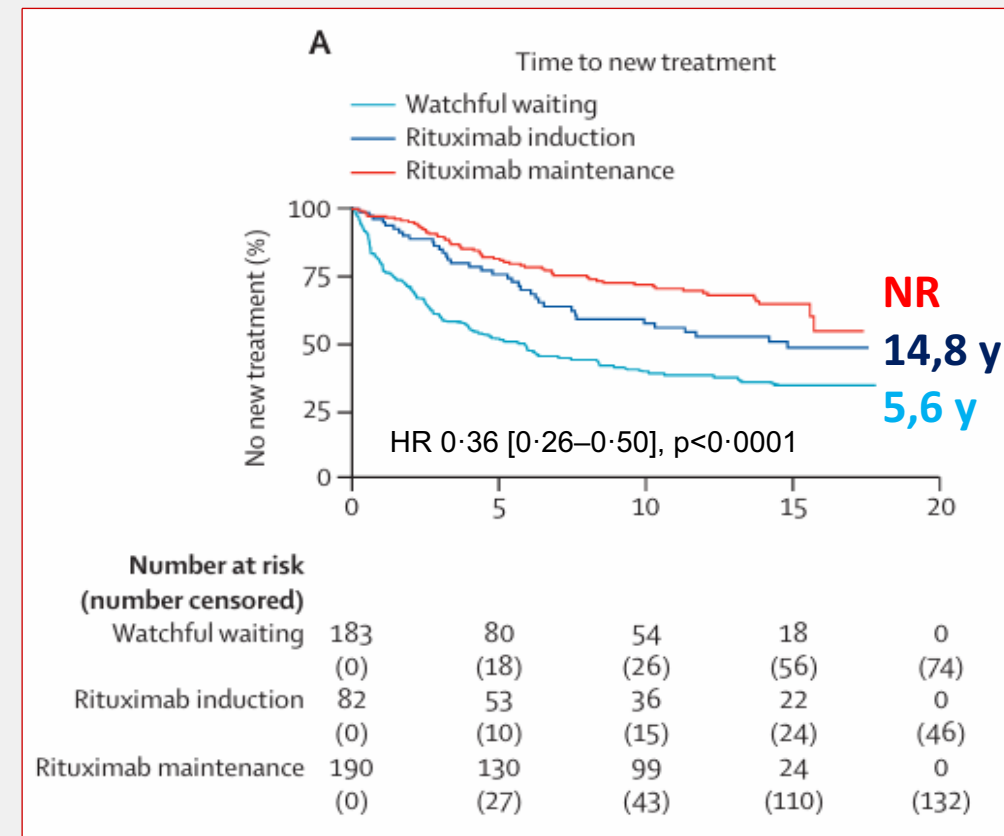
Low Tumor Burden FL Watch or Treat?

**Median FUP
15 years**

Early rituximab monotherapy versus watchful waiting for advanced stage, asymptomatic, low tumour burden follicular lymphoma: long-term results of a randomised, phase 3 trial

Michael Northend, William Wilson, Kushani Ediriwickrema, Laura Clifton-Hadley, Wendi Qian, Zaynab Rana, Tanya-Louise Martin, William Townsend, Moya Young, Fiona Miall, David Cunningham, Jan Walewski, Burhan Ferhanoglu, Kim Linton, Amanda Johnston, John F Seymour, David C Linch, Kirit M Ardesbna

- **% of treatment-free patients at 15 years:**
 - ✓ R-Maintenance: 65% (95% CI 56–72)
 - ✓ R-induction: 48% (36–60)
 - ✓ WW: 34% (27–42)
- No differences in OS: 68-73%
- No differences in time to second new treatment
- No differences in the risk of high-grade transformation
- Low toxicity



High Tumor Burden Criteria in FL

N = 2.222

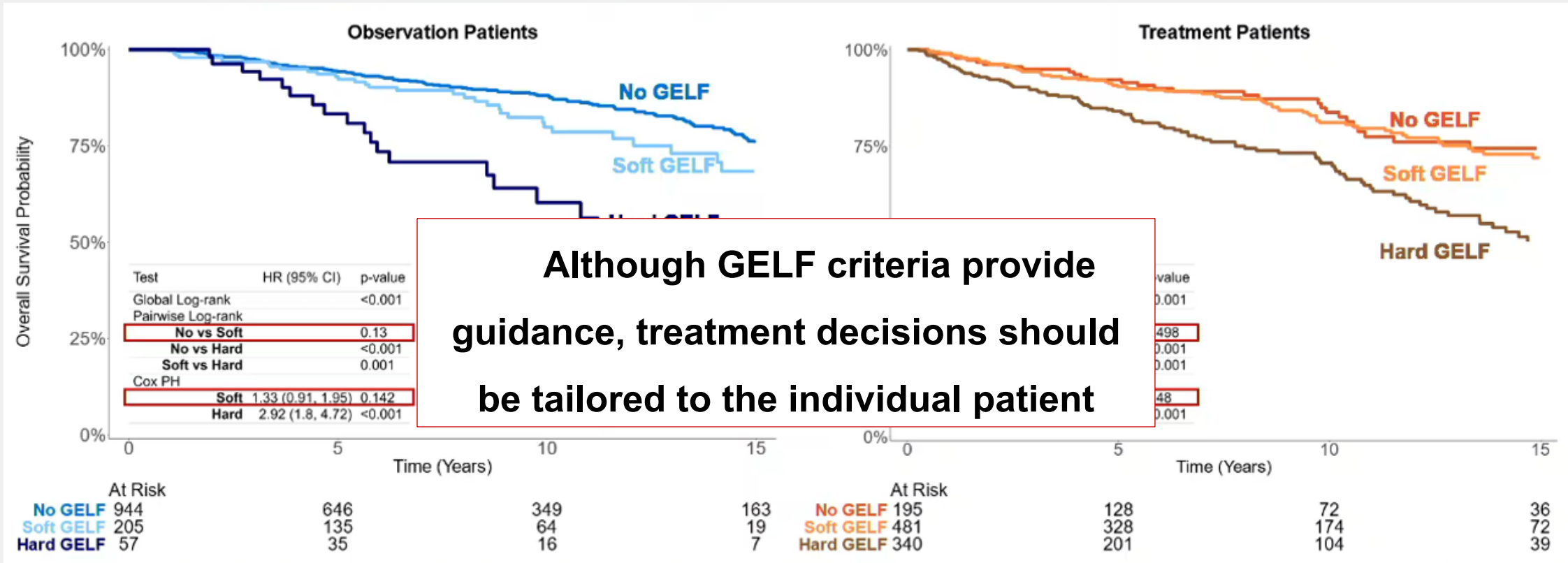
GELF Criteria

- Presence of B-symptoms
- 3 or more nodal áreas, each >3cm
- Largest lymph node or extranodal lesion ≥ 7cm
- Symptomatic splenomegaly
- Compression syndrome
- Serous effusion (pleural/peritoneal/pericardial)
- Lymphocytosis ≥ 5.000/mm³
- Cytopenias (platelets <100.000/mm³, neutrophils <1.000/mm³)

Characteristic	HR	95% CI	p-value	q-value ¹
B symptoms	1.45	1.02, 2.07	0.046	0.12
>3x3 nodes	0.94	0.68, 1.30	0.70	0.75
>7cm mass	1.08	0.81, 1.44	0.60	0.75
Splenomegaly	0.94	0.72, 1.24	0.67	0.75
Lymphocytosis	0.90	0.46, 1.76	0.75	0.75
Cytopenia	2.16	1.45, 3.24	<0.001	0.002
Serous Effusion	2.06	1.49, 2.83	<0.001	<0.001
Study Group			0.51	0.75
Observation	—	—		
Treatment	1.10	0.83, 1.45		

- 3 GELF criteria were associated with a significantly increased hazard of death
- They were defined as “HARD” GELF
- The remaining = “SOFT” GELF

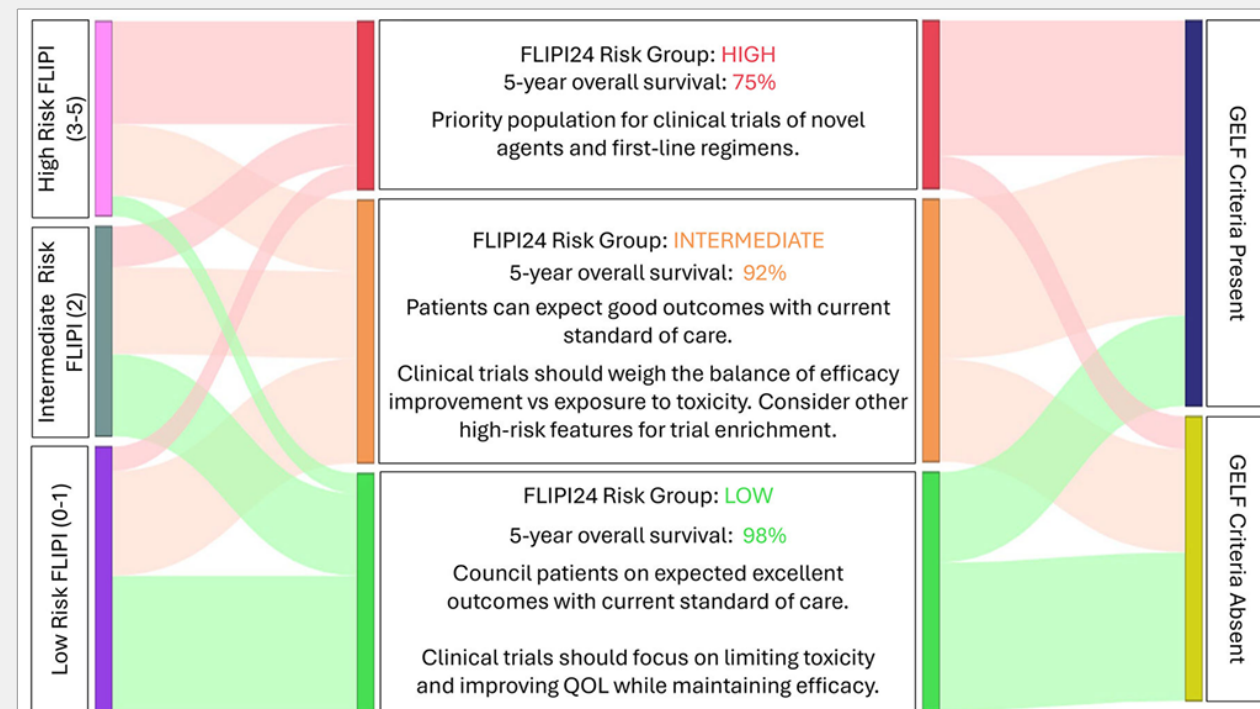
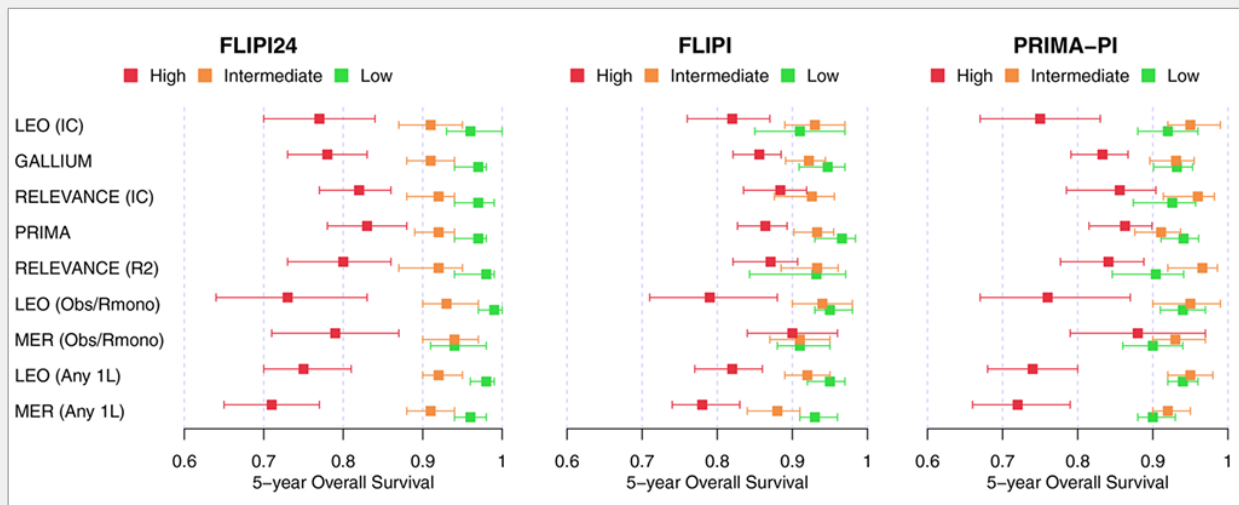
Impact of GELF Criteria on Survival



- Patients with “soft” GELF criteria had similar survival outcomes to those with no GELF at baseline in both groups
- Patients with “hard” GELF criteria at baseline had significantly shorter overall survival

FLIPI24 – A New Prognostic Model for Newly Diagnosed FL

- N = 3.577 from observational cohorts: 3 RCT + LEO and MER cohort for external validation
- Primary endpoint = EFS24 / Co-primary endpoint = OS

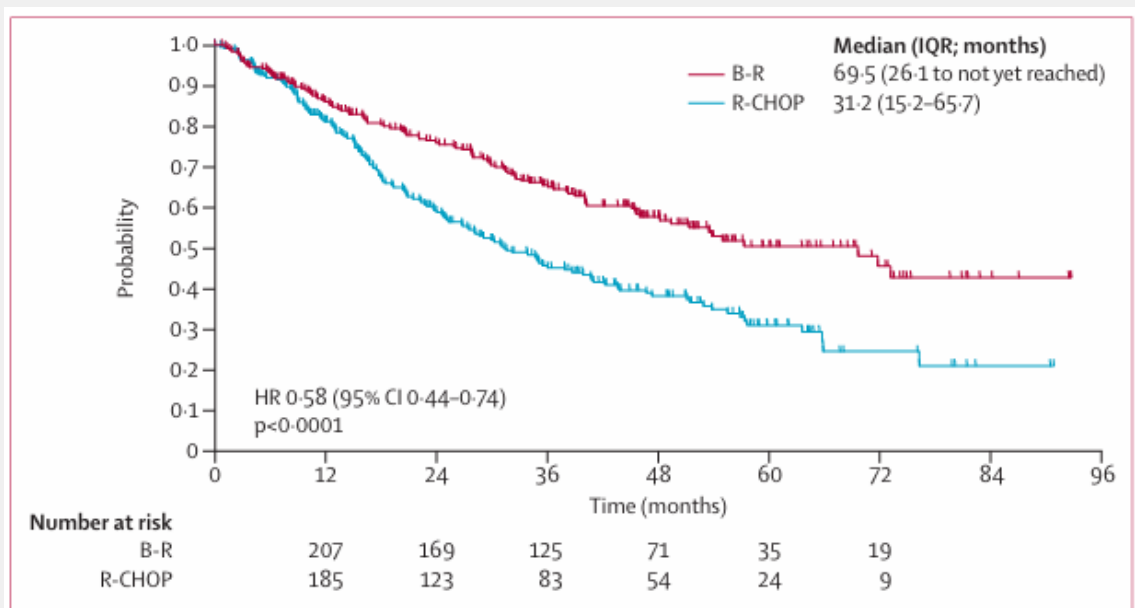


- Age, LDH, B2M, Hb and WBC
- A numerical output is the probability of an event in the first 24 months

Imuno-Chemotherapy in 1L FL

StiL Study

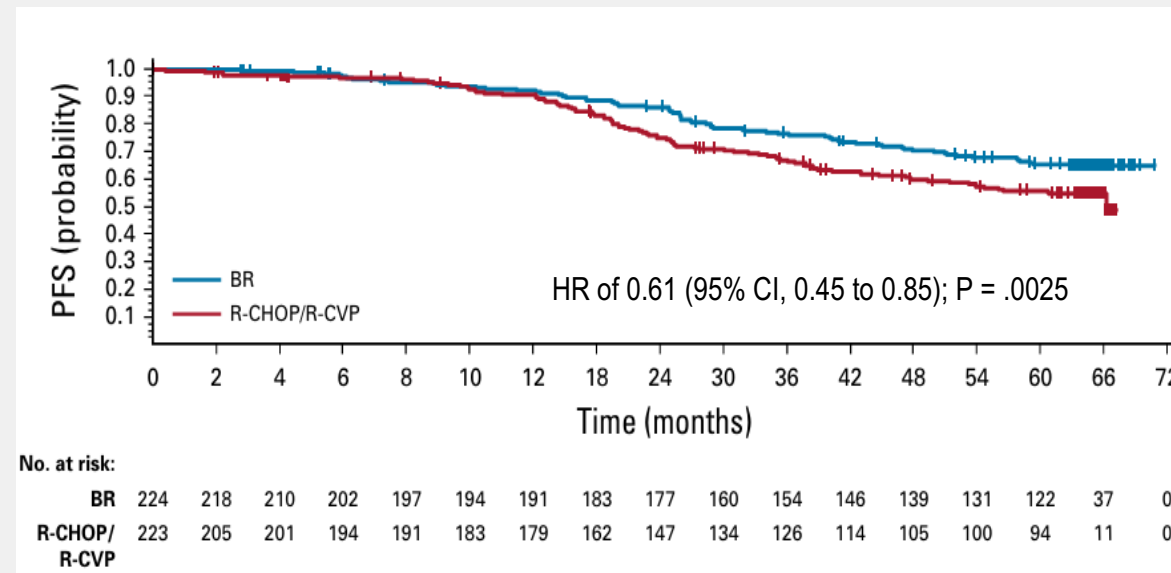
Non-inferiority trial of R-Benda *versus* R-CHOP



- No differences in OS (at 10y = 93% vs 91%)
- BR less toxic than R-CHOP (Heme-tox, alopecia, infections)

BRIGHT Study

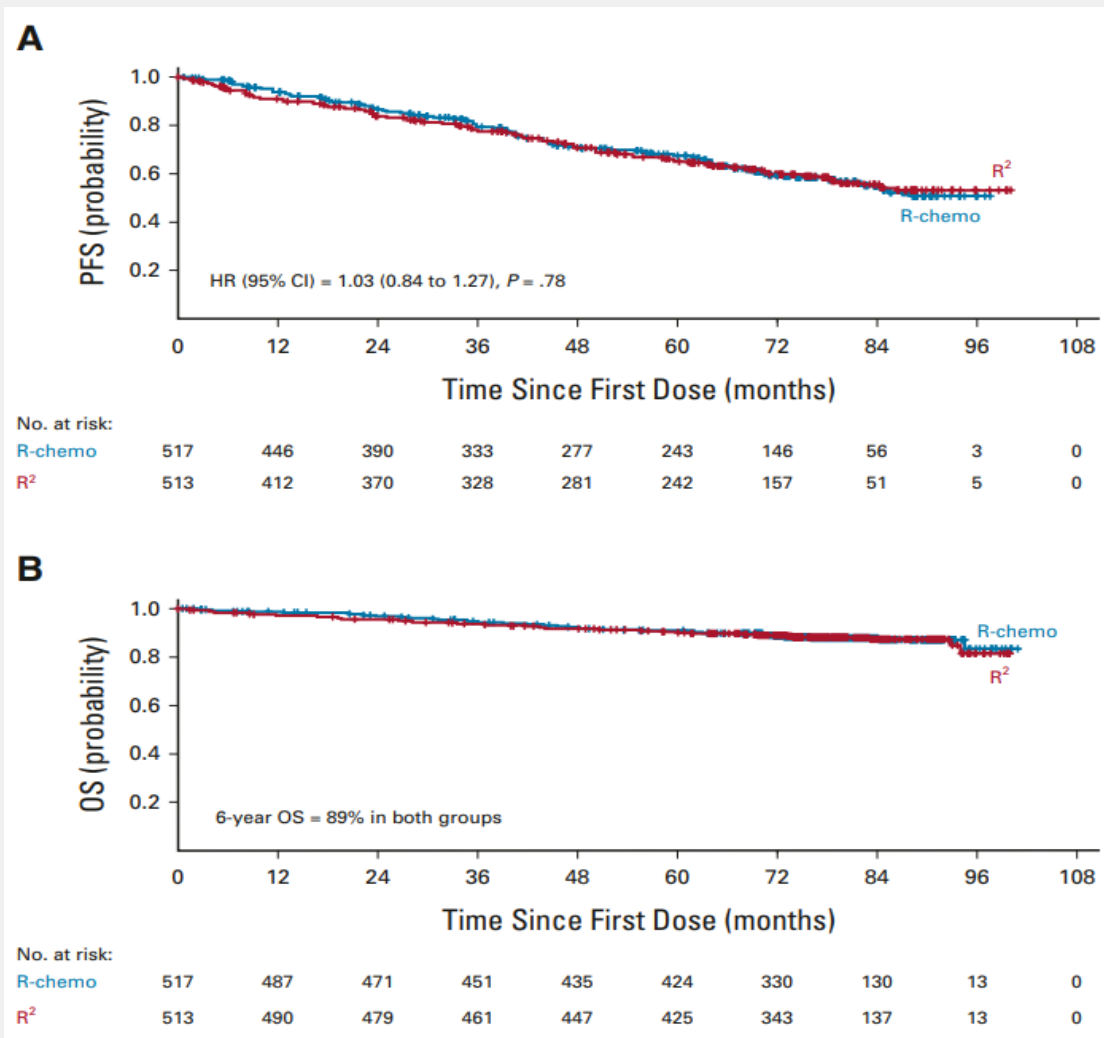
R-CHOP/R-CVP *versus* R-Benda



- No differences in OS (at 5y = 82% vs 85%)
- Slightly increased rates of 2nd malignancies with BR
- Higher rates of serious infections with BR

Chemo-free: RELEVANCE Trial

R2 versus R-Chemo + R-maintenance (10-year follow-up)



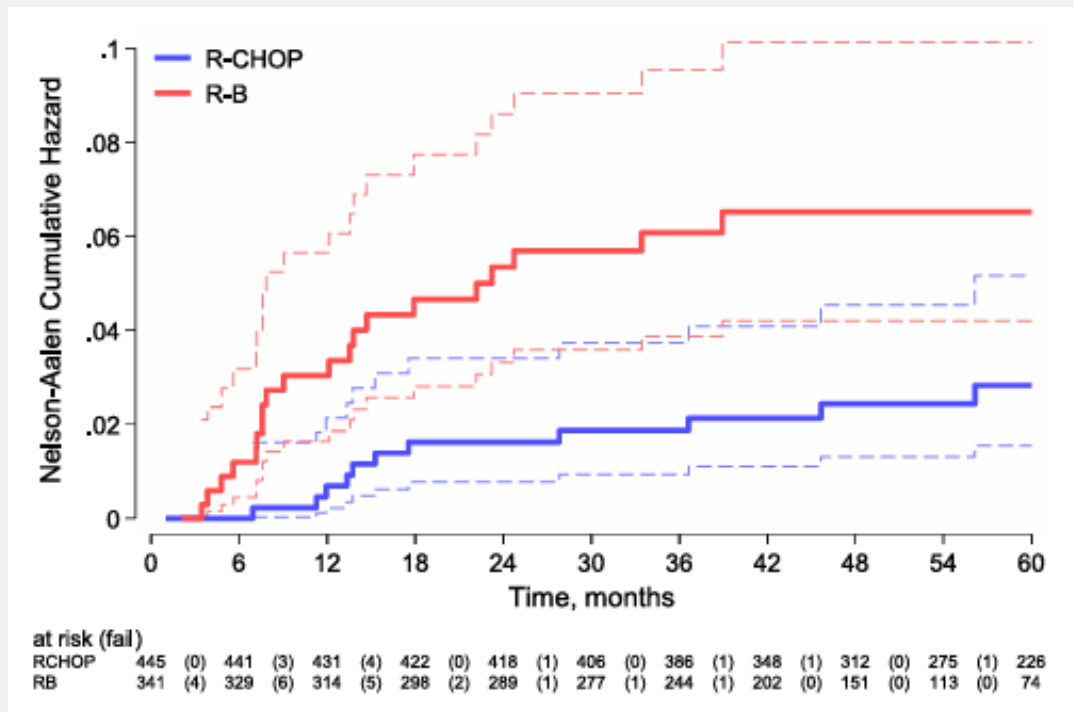
N = 1030 patients

	R-chemo	R ²
CR / CRu	53%	48%
10y-TTNLT	62.2%	66.3%
10y-OS	81.1%	82.4%

No differences in POD24
Only 9 HT

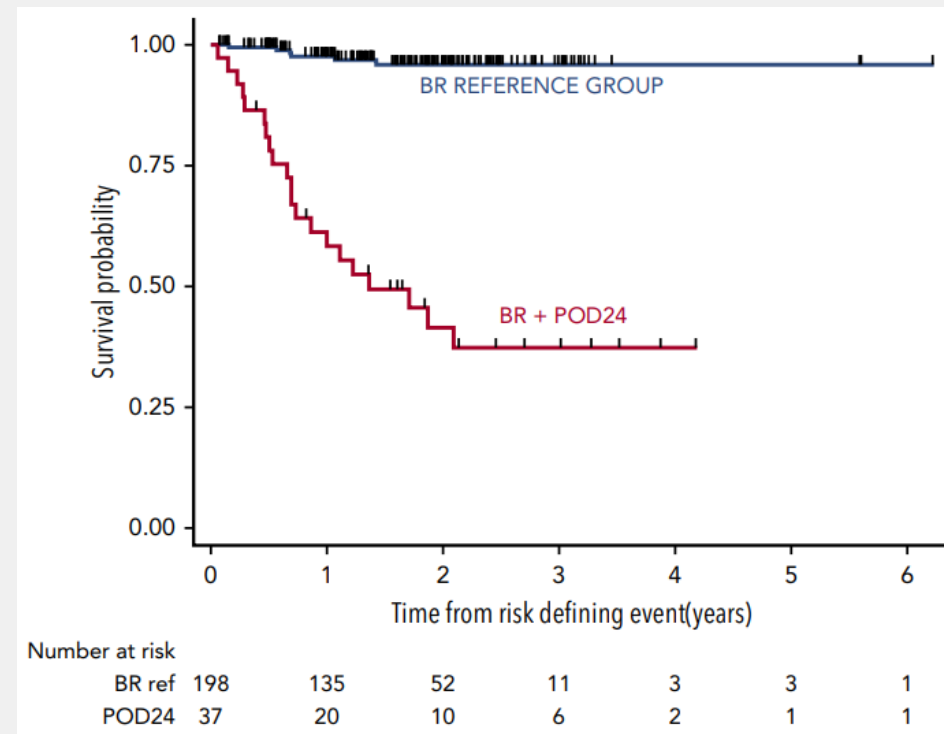
R-Benda May Not Be Enough to Mitigate the Risk of tFL

Post hoc analysis of the FOLL12 trial



Higher risk of tFL with R-Benda compared with R-CHOP
(non-randomized comparison)

Retrospective data from British Columbia

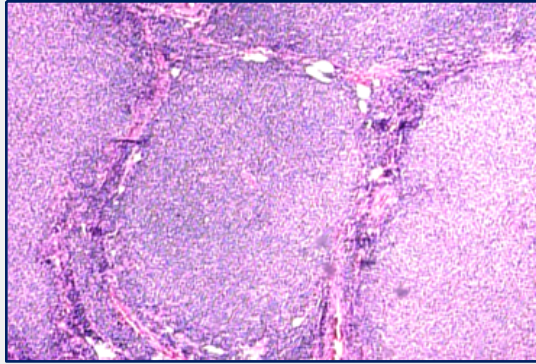


37% of BR-treated patients with POD24

76% had transformed disease

Elevated LDH at diagnosis was the only identifiable factor

Driving Decisions for 1L Choice in “Agressive” FL



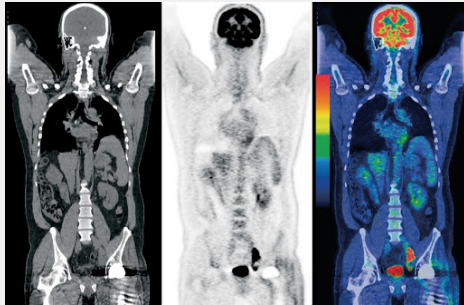
Good-quality diagnostic biopsy

- Preferably driven by PET findings
- > 1 site of biopsy if needed
- Experienced hematopathologist



Clinical and lab findings

- FL behavior = “kinetics”
- B-symptoms
- **Elevated LDH**
- Extranodal disease
- FLIPI ≥ 3



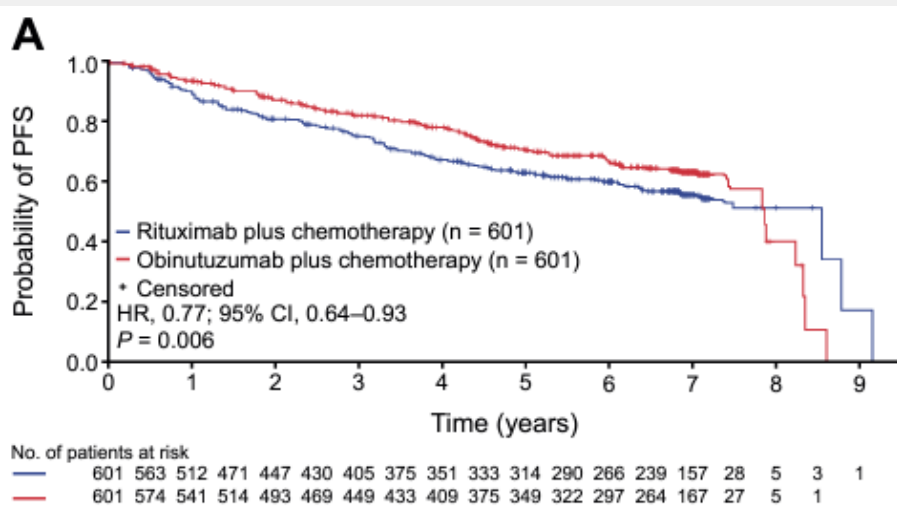
Potential biomarkers

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

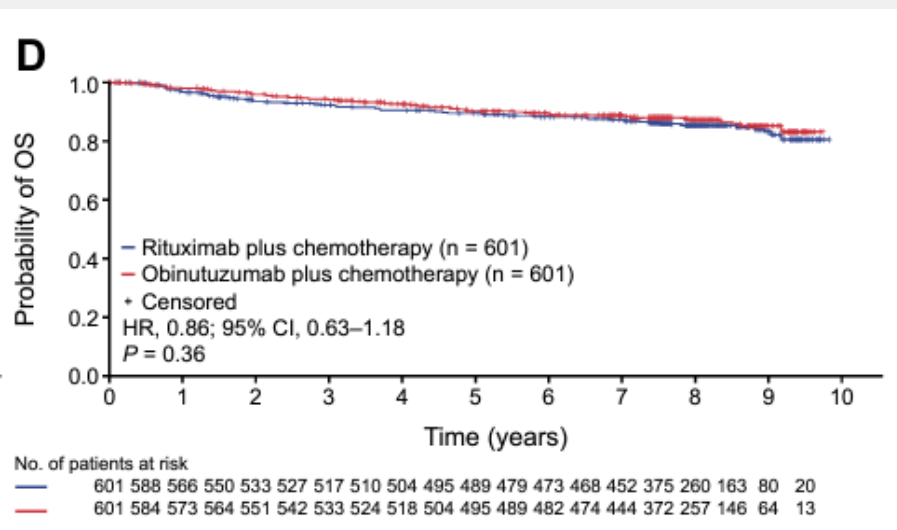
Prefer anthracycline-based treatment in patients perceived to have an increased risk of occult transformation

The Monoclonal Antibody Dilemma: Rituximab or Obinutuzumab?

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)

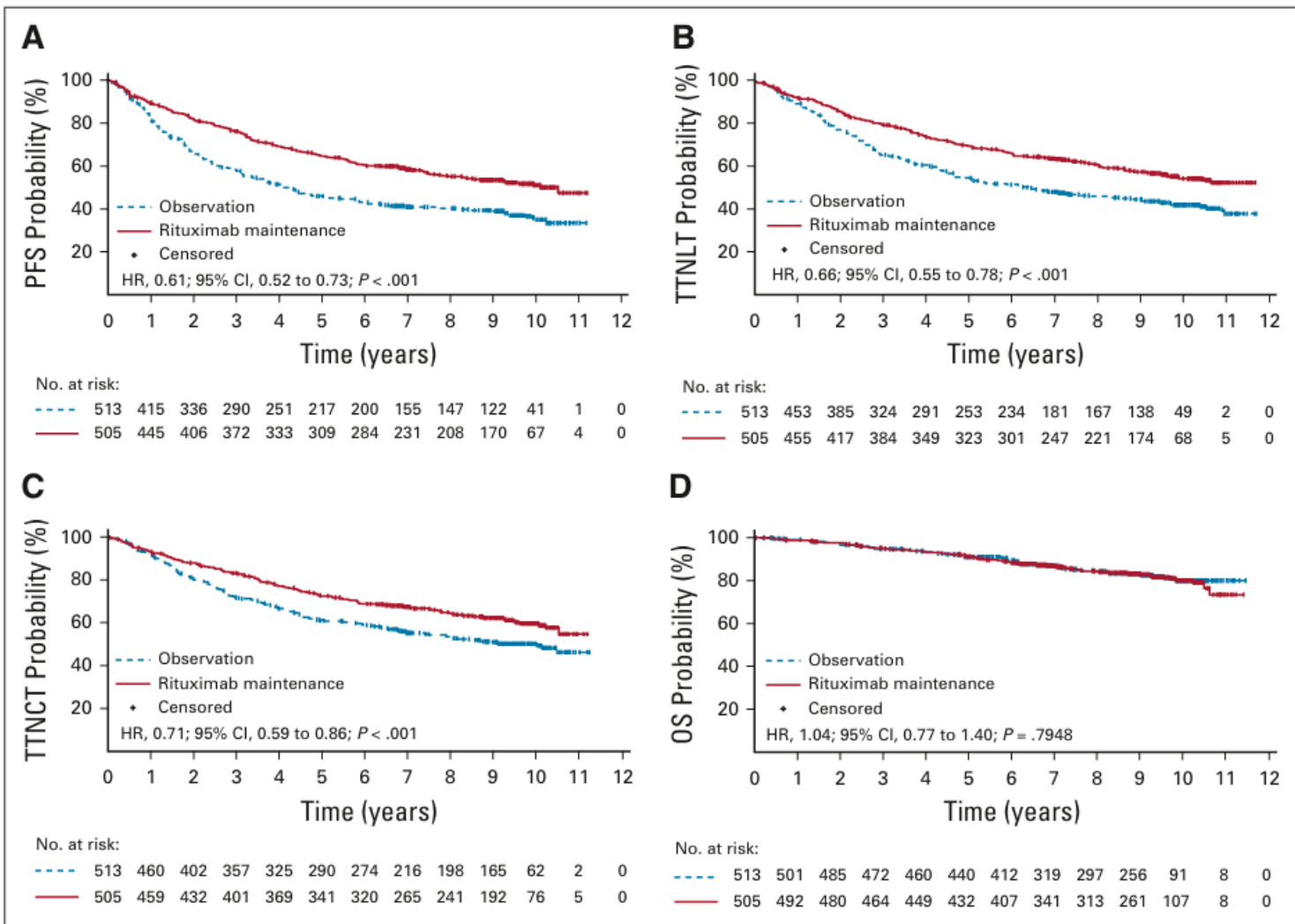


Obinutuzumab Arm:

- 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

Maintenance Treatment The PRIMA Trial

Final Analysis with 9-year follow-up



- Rituximab 375mg/m² every 8 weeks for 2y
- mPFS: 10.5 years vs. 4.1 years; $p < 0.0001$
- **No OS improvement**
- Higher rates of infections and G3/4 AE
- Controversial after BR induction, with a higher risk of infections
- PRIMA results should be interpreted according to each country's reality/system

Consider when:

- Longer time of disease control is important
- Limited access to further lines of therapy
- *** But carefully weigh the risk of infection**

The Brazilian Dual Scenario



NO (or LIMITED) access:

- Bendamustine (off-label for FL)
- Lenalidomide in 1L



Full access:

- Rituximab (1L and beyond)
- **Obinutuzumab**
- CHOP
- CVP
- **Maintenance therapy**



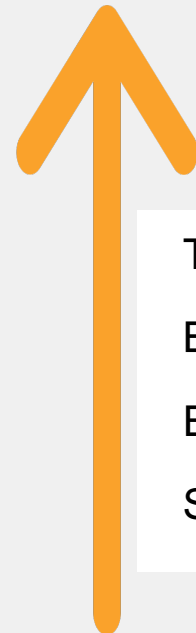
NO access:

- Bendamustine
- Lenalidomide
- Obinutuzumab
- Maintenance therapy

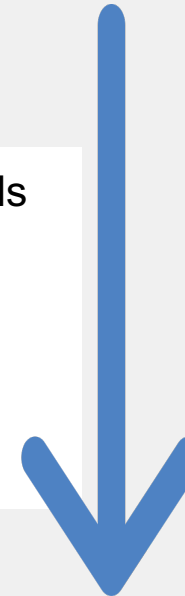


Full access:

- Rituximab (1L and beyond)
- CHOP
- CVP

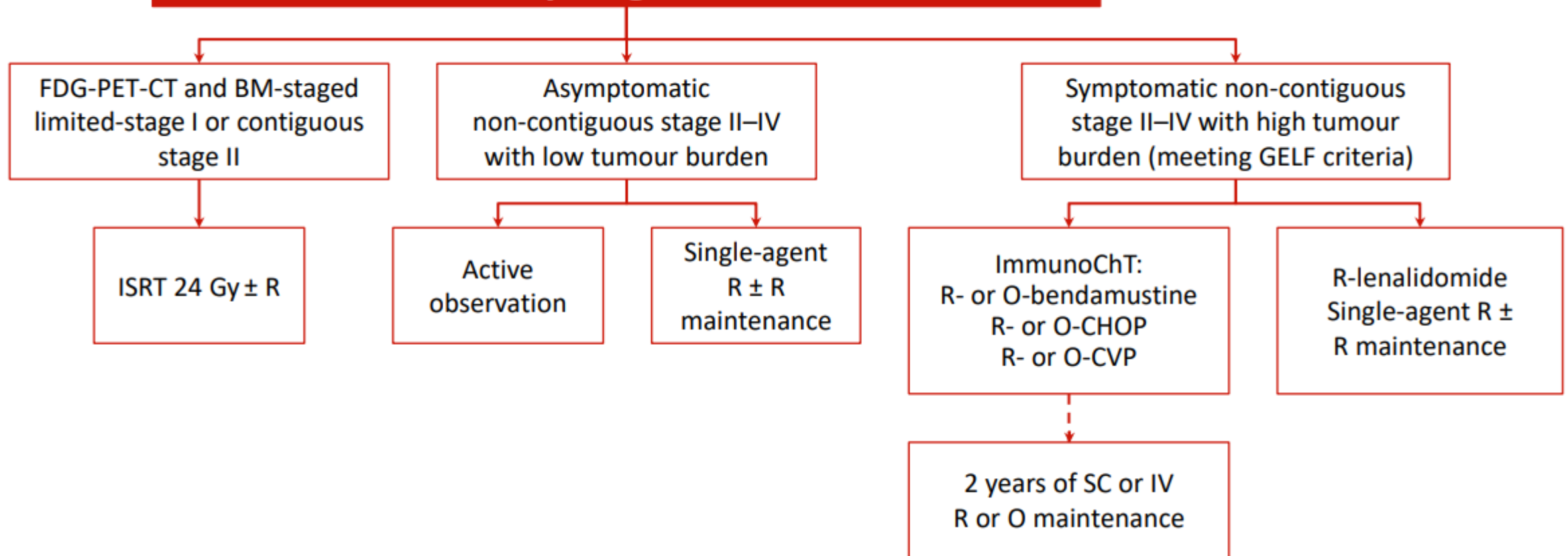


Timely access to diagnostic tools
Broad PET-CT availability
Educational level
Social / Economic status



ESMO 2025 Guidelines for Newly Diagnosed FL

Newly diagnosed FL



Guiding 1L Treatment Choice in FL

FL scenario	Treatment Choice	Comments
<70 Years “usual” clinical presentation	R-CHOP R-Benda	If Benda is the choice: - PJP and herpes 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
<75 Years Aggressive behavior	R-CHOP	- Consider R-mini-CHOP according to PS
Monoclonal antibody R or O?	- Preferably rituximab	- Obinu 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)
R ² in first line	- Rarely indicated	- Not approved in Brazil as 1L - Higher cost, similar efficacy to R-chemo - Could be considered if the patient is not suitable for chemo

Obrigado!

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