Indolent Lymphoma
*Workshop*

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# FOLLICULAR LYMPHOMA: US vs. Europe: different approach on first relapse setting?

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# European perspective in FL

There is not a common view on how to treat FL

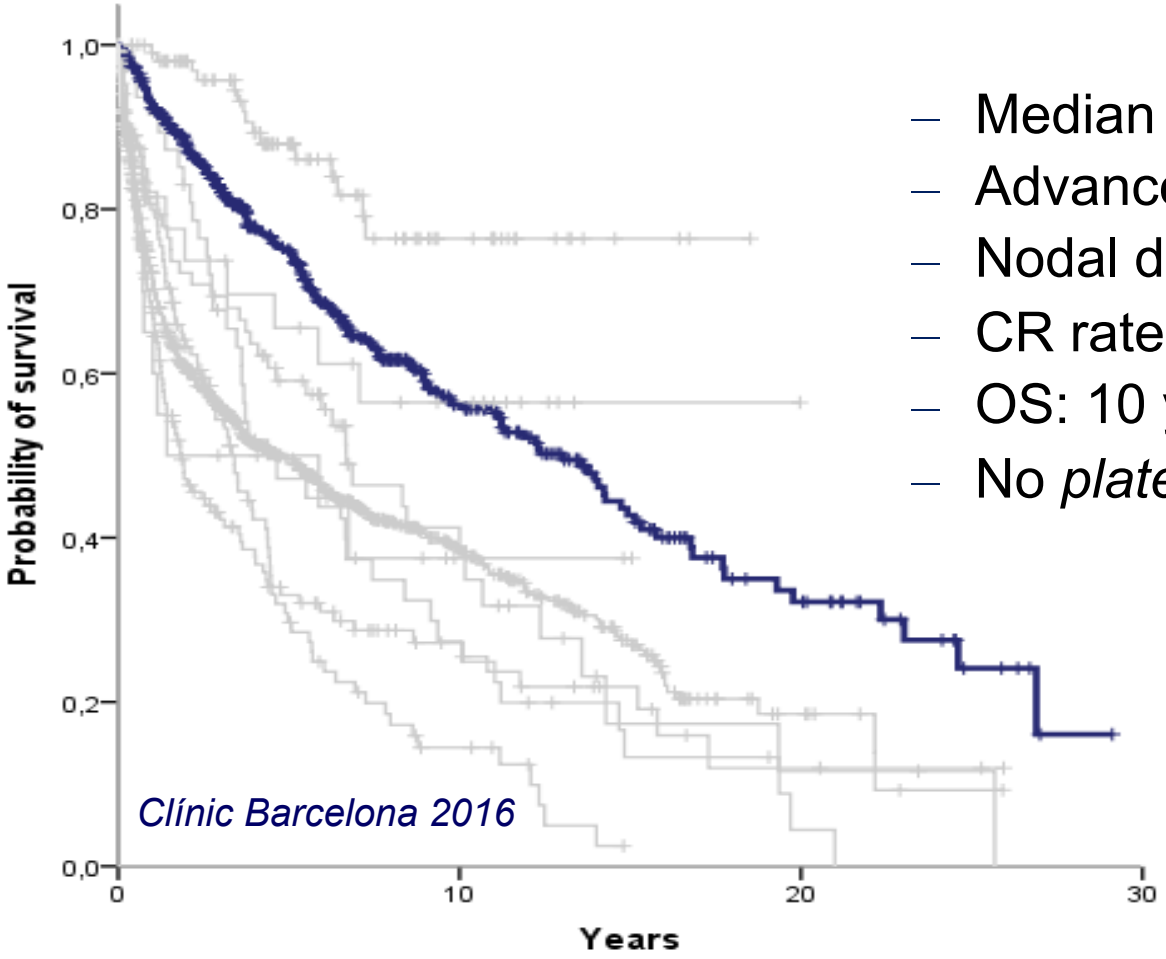
- Initial treatment
  - WW policy vs. R
  - R monotherapy vs. R-chemo
  - FL3a
  - Use of adriamycin
  - Maintenance
- At first relapse/progression

# Data on the therapeutic approach in European countries to 1st relapse in FL

- ESMO guidelines[1]
- Some national guidelines[2-6]
- Some real world data[7]

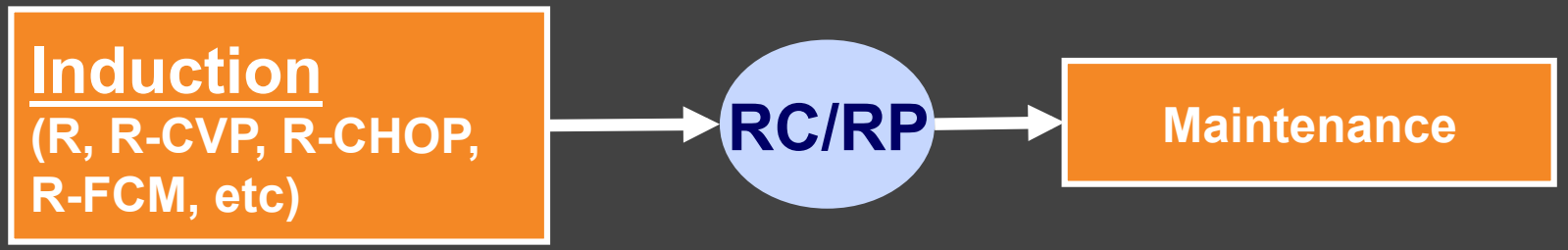

1. Dreyling M, Ann Oncol 2016 (suppl 5):v83-90
2. Debussche S, Belg J Hematol 2012;3:41-50
3. Zinzani PL, Am J Hematol 2013;88:185-92
4. López-Guillermo A, Leuk Lymph 2013;****
5. Provencio Pulla M, Clin Transl Oncol 2015;17:1014-9
6. McNamara C, Br J Haematol 2012;156:446-67
7. Alonso S, Br J Haematol 2017 (in press)

# Follicular lymphoma



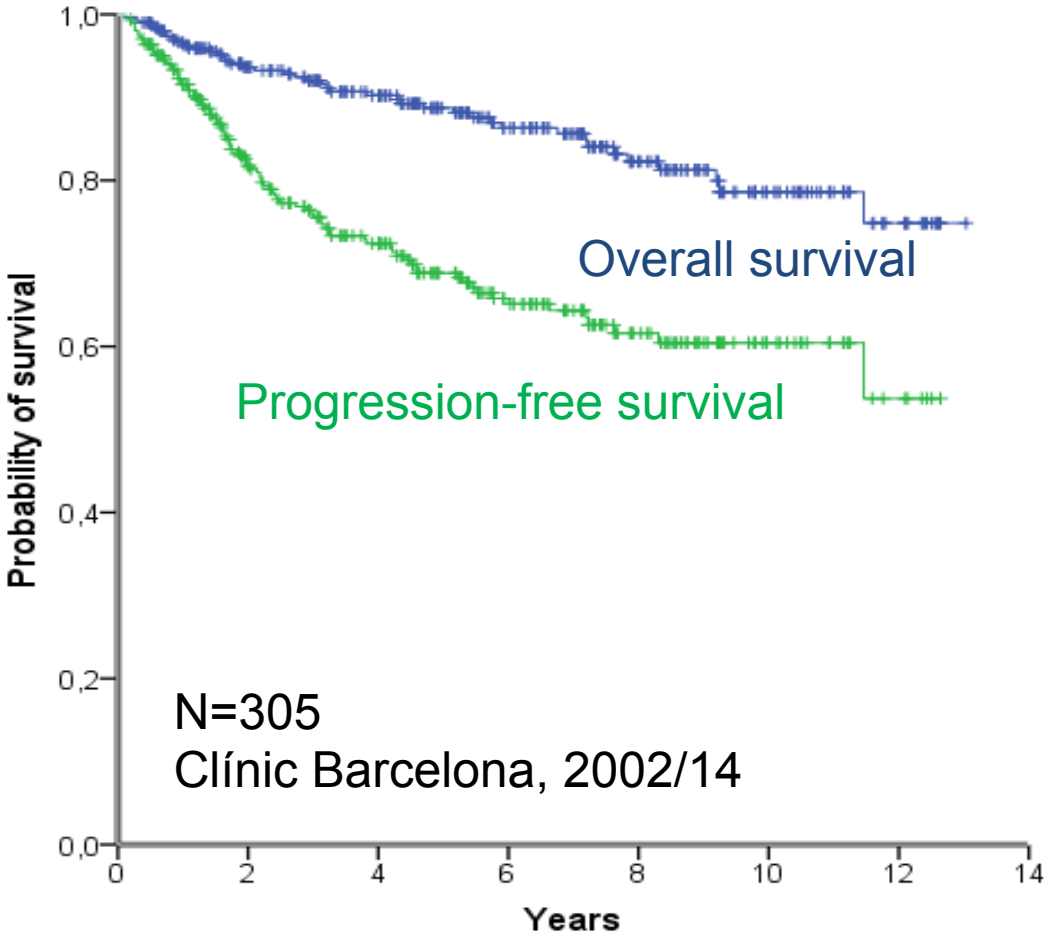

- Median age: 60 years
- Advanced stage: 80%
- Nodal disease; BM+
- CR rate: 10-80%
- OS: 10 years (↑)
- No *plateau* in PFS or OS curves

# Treatment of follicular lymphoma




In absence of treatment criteria: observation (WW policy)

# Follicular lymphoma treated with immunochemotherapy



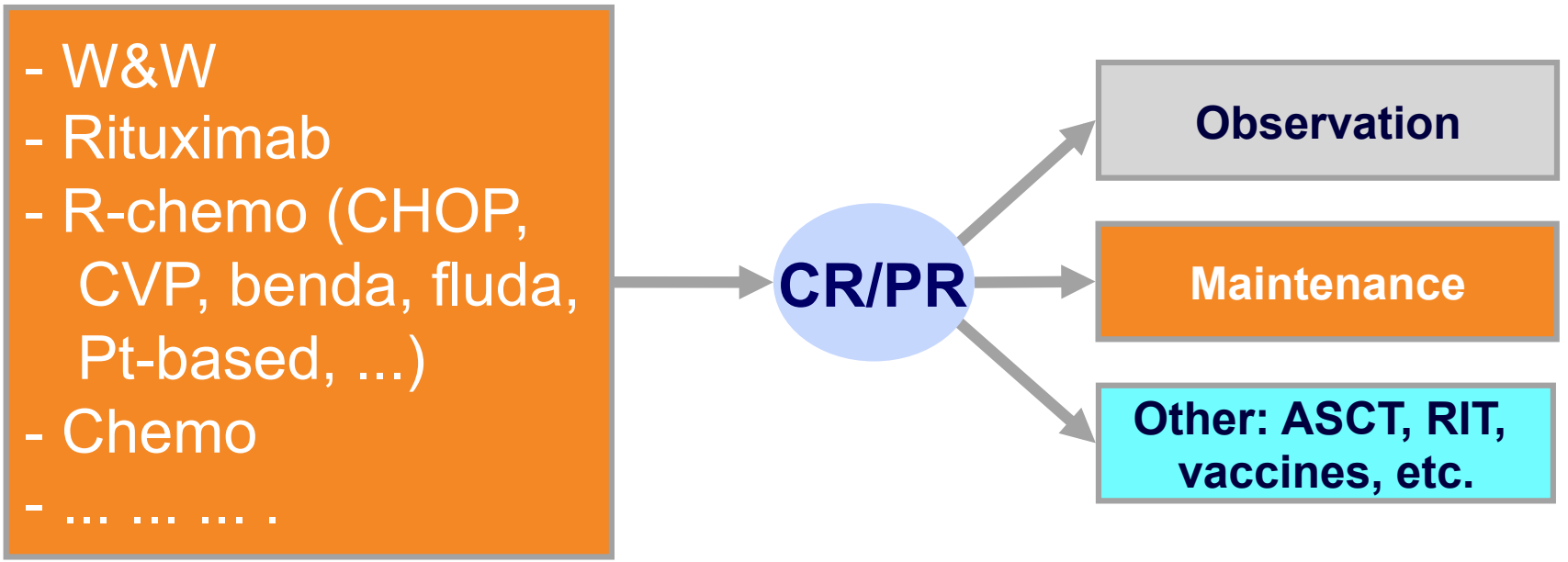

- Very long survival (median: 15-¿20? years)
- But, high risk of relapse (often one or more relapses during the follow-up)
- Still poor risk:
  - Early relapses
  - Histologic transformation

# 1st step: diagnosis
# Is mandatory a new biopsy?

- YES – everybody agrees on that[1]
  - "It is strongly recommended to obtain a new biopsy in order to exclude transformation"
  - "It may be useful to target the biopsy based on PET"
- However in real life:
  - In the GELTAMO series[2] (1734 patients consecutively diagnosed with FL (grades 1, 2 or 3a) in 18 Spanish centers between 2002 and 2012) a new biopsy was performed in only 41% of the cases showing lymphoma progression


1. Dreyling M, Ann Oncol 2016 (suppl 5):v83-90
2. Alonso S, Br J Haematol 2017 (in press)

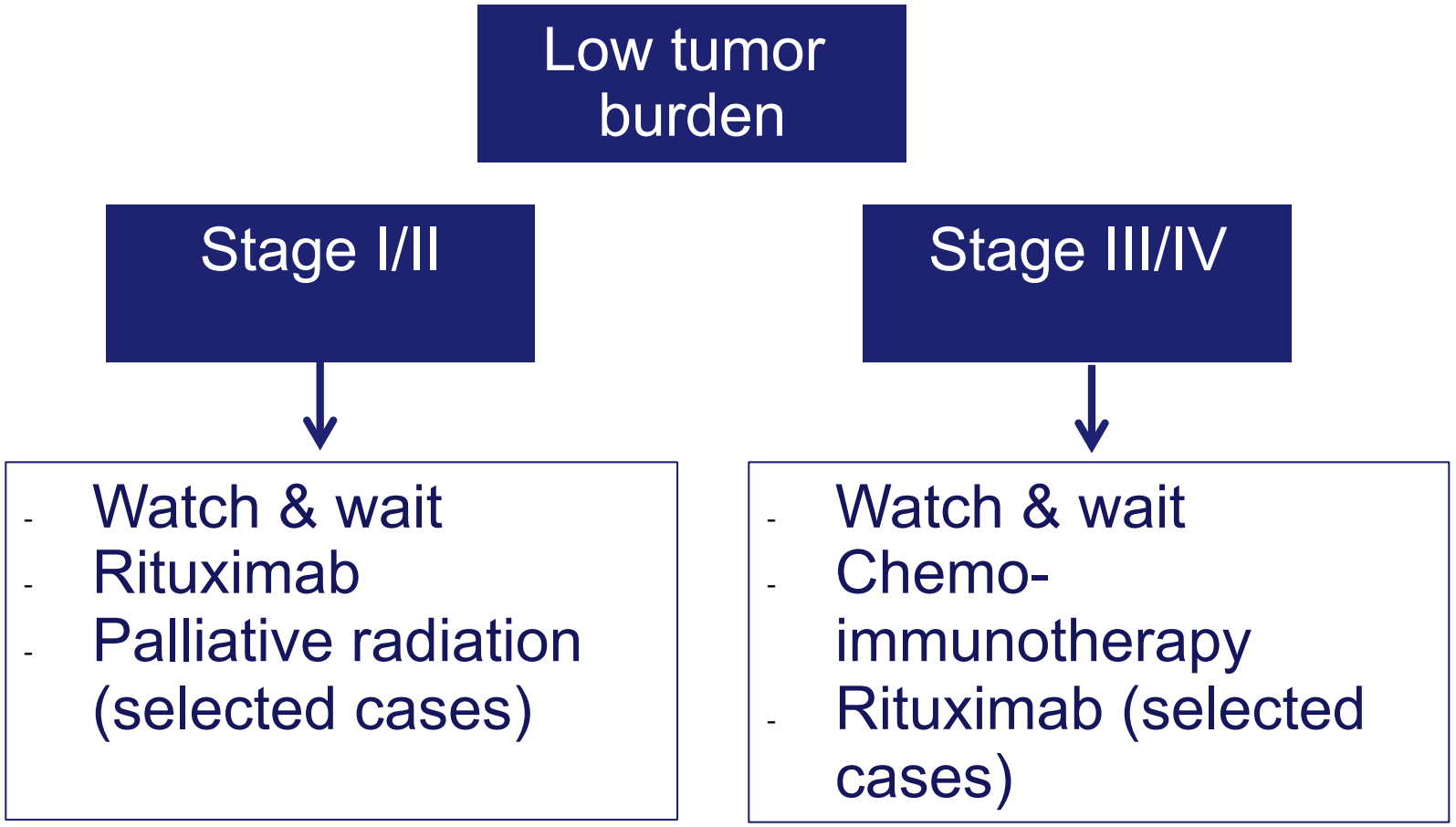
# Follicular lymphoma: treatment at relapse



# Relevant factors to decide treatment at 1st relapse/progression

- Prior (front line) treatment
- Duration of response
- Symptomatic or asymptomatic
- Risk factors at relapse (age, PS, stage, FLIPI, biology?…)
- Histologic transformation

# Follicular lymphoma Recommendations at first relapse




1. Dreyling M, Ann Oncol 2016 (suppl 5):v83-90

# Follicular lymphoma Recommendations at first relapse

**High tumor burden**

**Stage III/IV <65 years[a]**

Dependent on first-line regimen and remission duration

- Chemoimmunotherapy + rituximab maintenance
- Alternatively, radioimmunotherapy
- In early relapses, discuss high-dose consolidation with ASCT

**Stage III/IV >65 years[a]**

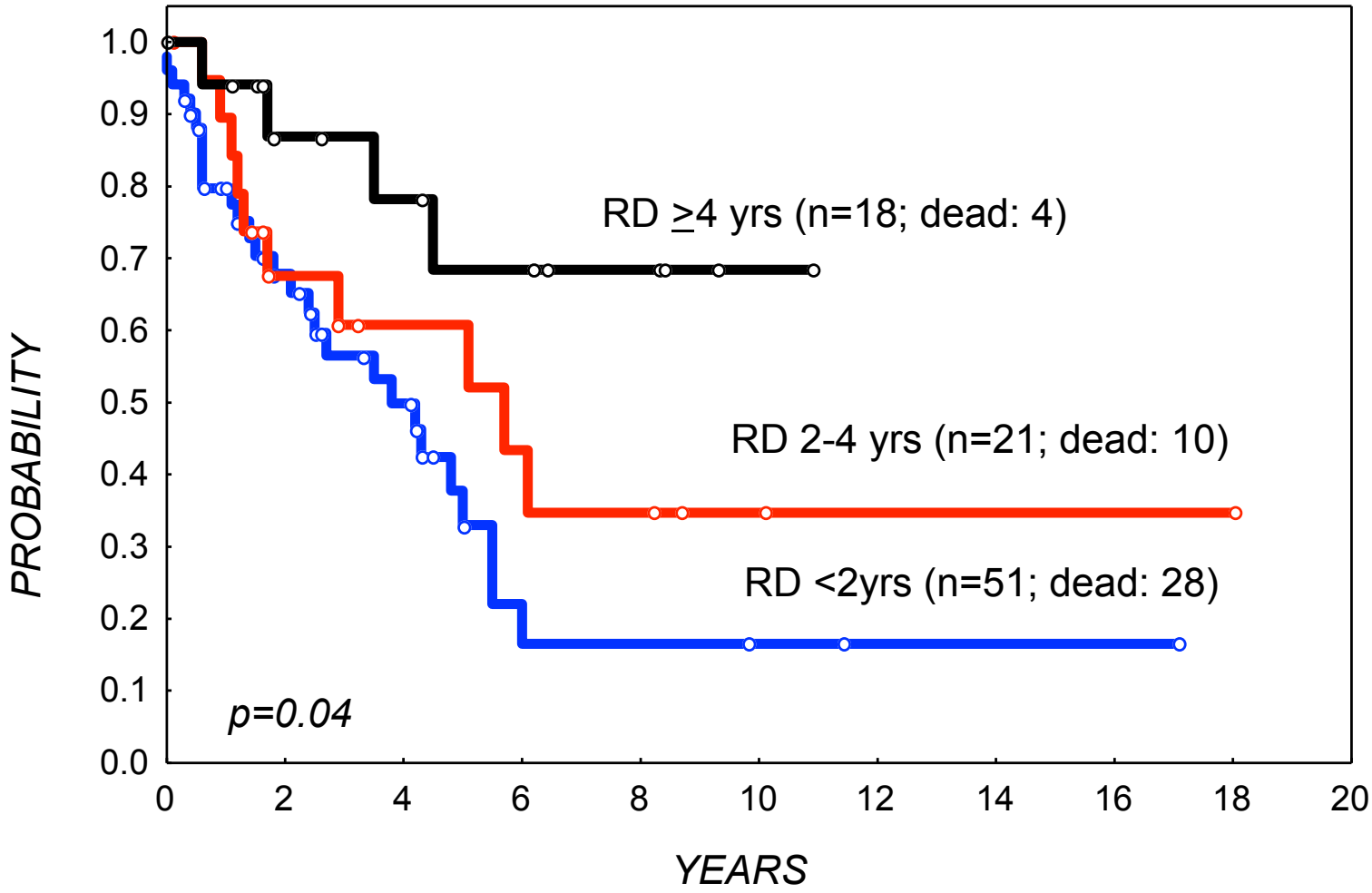
Dependent on first-line regimen and remission duration

- Chemoimmunotherapy + rituximab maintenance
- Alternatively, radioimmunotherapy

a: according to biological age

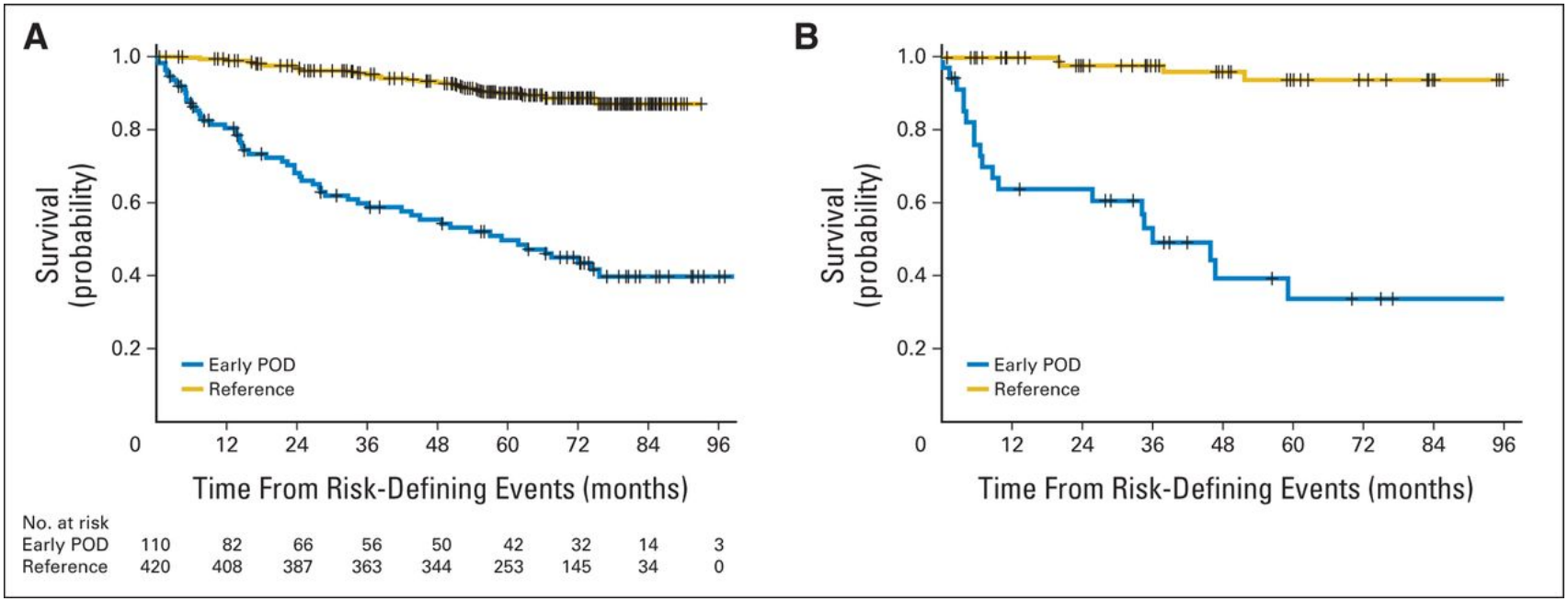
1. Dreyling M, Ann Oncol 2016 (suppl 5):v83-90

# FL: Survival from progression according to response duration (RD)



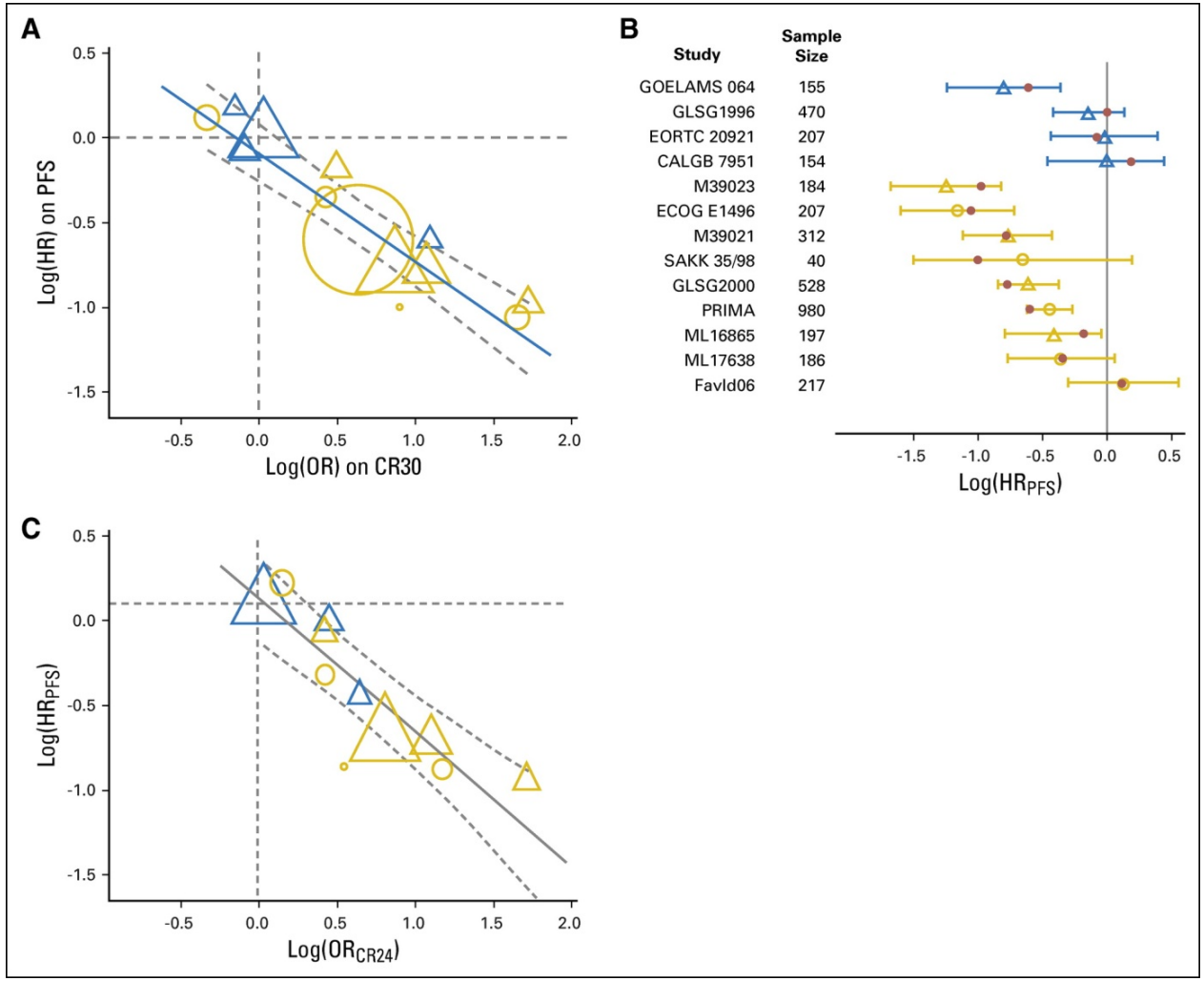

Montoto et al. Ann Oncol 2004;15:1484-9

**(A) Overall survival (OS) from a risk-defining event after diagnosis in patients who received rituximab with cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) chemotherapy in the National LymphoCare Study group.**



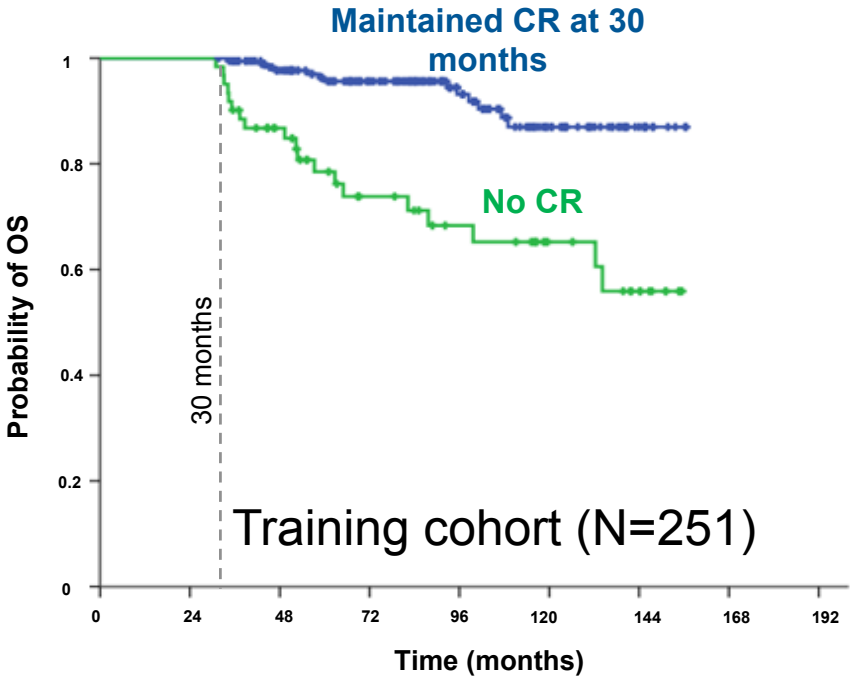

**Carla Casulo et al. JCO 2015;33:2516-2522**

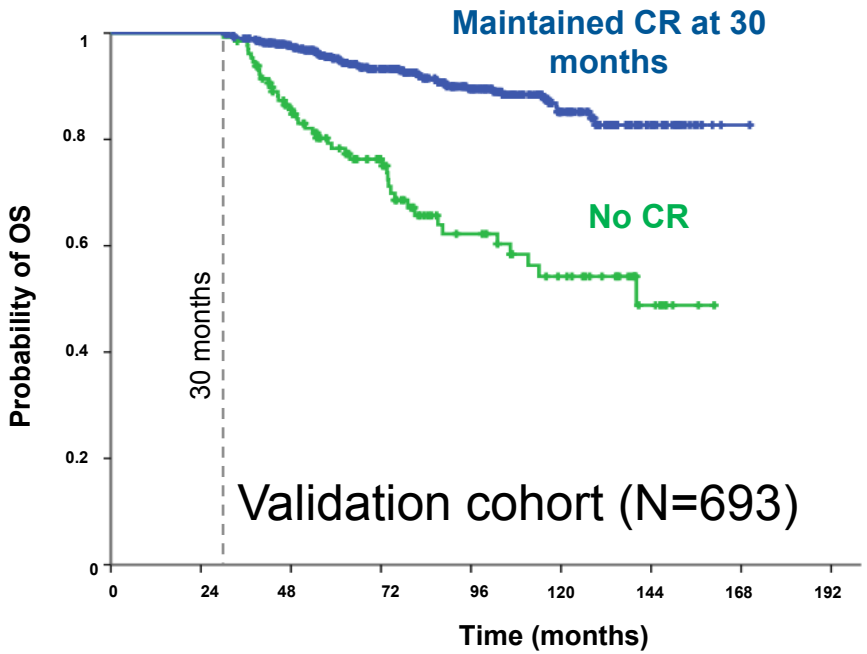
# Trial-level association between treatment effects on CR30 and PFS




Shi Q, J Clin Oncol 2016;35:552-60

# Patients with FL in maintained CR at 30 months show a survival similar to a sex- and age-matched Spanish general population




| Patients in maintained CR at 30 months | | |
|---|---|---|
| | Training (N=188) | Validation (N=499) |
| 10-yr OS (%) | 87 | 85 |
| 10-yr relative survival (%) | 100 | 100 |
| 10-yr decrease in life expectancy (%) | 0 | 0 |

Magnano L, et al, SEHH (#CO-013)

# Follicular lymphoma Recommendations at first relapse

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**Stage III/IV >65 years[a]**

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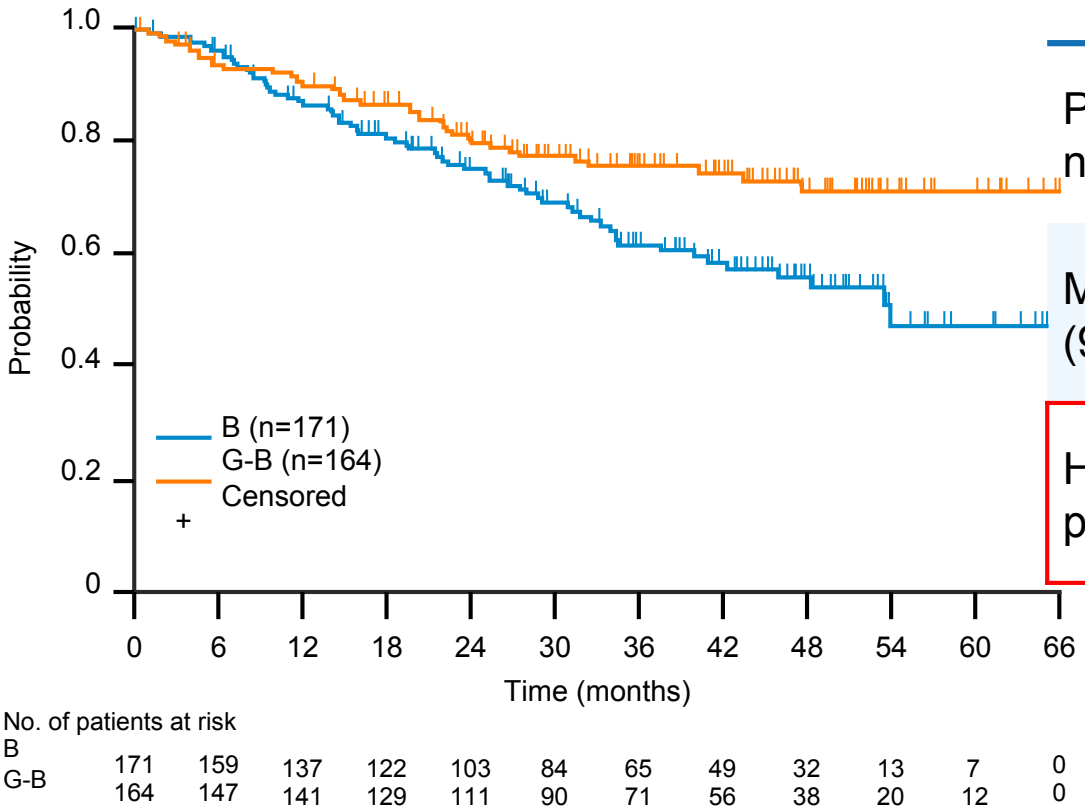
# FL at 1st relapse/progression

- Which chemotherapy?
  - In early relapses (<12-24 mo.) a non-cross-resistant regimen (benda after CHOP or vice versa)
  - Other options
    - Fluda combinations
    - Platinum-based regimens
    - Alkylating combinations
- Rituximab (R)?
  - Yes, if duration of previous response to R-containing regimen was >6-12 mo.
  - For R-refractory patients, obinutuzumab?
  - R monotherapy? “In symptomatic cases with low tumor burden”
- Radioimmunotherapy (elderly patients with comorbidities)

Dreyling M, Ann Oncol 2016 (suppl 5):v83-90

# OS in the FL population

*Kaplan-Meier plot of OS by treatment arm (FL)*




| | G-B, n=164 | B, n=171 |
|---|---|---|
| Pts with event, n (%) | 39 (23.8) | 64 (37.4) |
| Median OS (95% CI), mo | NR (NR, NR) | 53.9 (40.9, NR) |
| HR (95% CI), p-value* | 0.58 (0.39, 0.86), p=0.0061 | |

*Median follow-up (FL): 31.2 months*
*(vs 21.1 months in primary analysis)*

NR, not reached

*Stratified analysis; stratification factors: prior therapies, refractory type, geographical region

Cheson BD, ASH 2016

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# FL at 1st relapse/progression

Something else after induction?

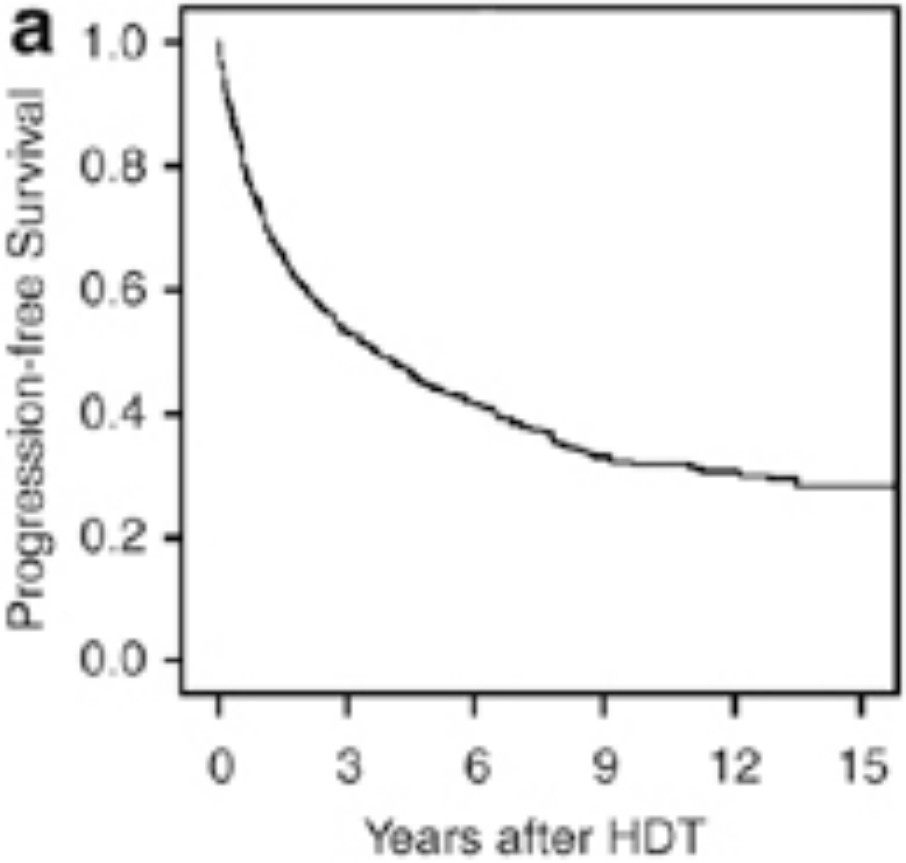
- Maintenance with Rituximab?
  - Yes, if not received R in 1st line (I, A)
  - After maintenance in 1st line? Probably not if relapsed during maintenance (IV, D)
- ASCT?
  - "Should be considered in patients who experience short-lived first remissions (<2-3 years) after rituximab-containing regimens" (I, B)
  - However, the general role of ASCT has to be re-defined in the rituximab era
  - Rituximab maintenance after ASCT may achieve some improvement in PFS (II, B)

Dreyling M, Ann Oncol 2016 (suppl 5):v83-90

# FL at 1st relapse/progression

Role for ASCT

- Rituximab mig … of ASCT in the treatmer…
- In the rituxima… …ted by at least two trials…
- Data in USA a… …of ASCT in FL is decreasi…
- Still it may hav… …ort previous respc…
- Rituximab doe… …f ASCT[6]
- A plateau in the PFS curve?[7]
- R Maintenance after ASCT[8]




1) Sebban, JCO 2008;26:3614; 2) Le Gouill, Haematologica 2011;96:1128; 3) Link Clin Oncol 2011;29(#8049); 4) van Oers, JCO 2010;28:2853; 5) Montoto, Haematologica 2013;98:1014; 6) El Najar ASH 2011(#502); 7) Montoto, Leukemia 2007;21:2324; 8) Pettengell, JCO 2013;31:1624

*EBMT Lymphoma Working Party*

# Consensus project on hemopoietic transplant in FL

- HDT-ASCR is not an appropriate treatment option to consolidate first remission in patients with FL responding to immunochemotherapy, outside the setting of clinical trials
- In patients in first relapse with chemo-sensitive disease HDT-ASCR is an appropriate treatment option to consolidate remission
- Allogeneic transplantation should be considered in patients with relapse after HDT-ASCR
- Reduced-intensity/ non-myeloablative conditioning regimens are generally more appropriate in patients receiving an allogeneic transplant.

*Montoto S, Haematologica 2013;98:1014-21*

# FL at 1st relapse/progression

**What about all the new drugs (mAb, small molecules, targeted therapy…)?**

- No new drug has been registered for 1st relapsed FL at the EMA
- Idelalisib accepted for 3rd line of later
- All the others are investigational
- Early relapsed patients (<2 years?) are very good candidate for clinical trials

# Conclusions

- Previous therapy and response duration are key factors to decide the treatment at 1st relapse
- Immuno-CT is the standard in most cases; rituximab maintenance and ASCT should be discussed individually
- Early relapsers (<2yrs?), who have a dismal prognosis, are the best candidates for clinical trials
- This situation might change in the next future with the new therapeutic armamentarium, including immunotherapy and small molecules with target effect