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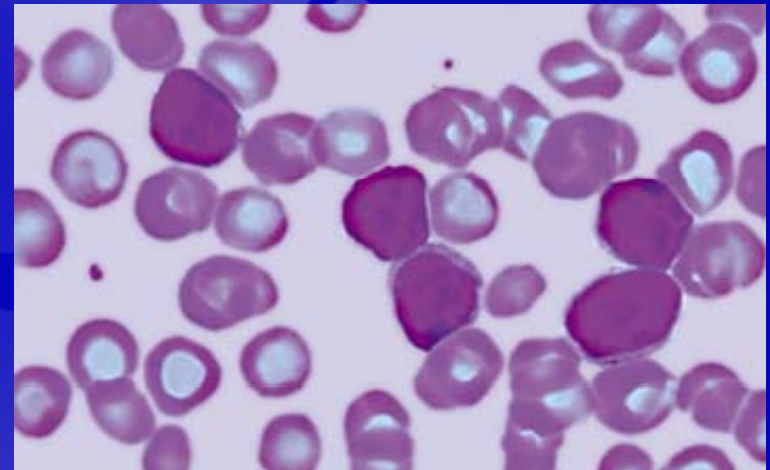
# **Update on Management of Chronic Lymphocytic Leukemia**

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# Confirming CLL

- **Confirmation by:**<sup>1</sup>
  - Blood count and smear
  - Immunophenotyping and flow cytometry
- **Typical phenotype:**
  - CD5+
  - CD19+
  - CD23+
- **Minimum needed to confirm diagnosis is**  
 $\geq 5 \times 10^9/l$  B lymphocytes in peripheral blood for  
 $\geq 3$  months<sup>1</sup>

Histopathology of CLL with typical lymphocytosis



# CLL: Incidence and Survival

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- **Most common leukemia in the United States**
  - 4500 estimated deaths annually <sup>1</sup>
- **Incidence is familial and age related**
  - Median age at diagnosis: 72 years
- **Overall 5-year survival for newly diagnosed disease (stage dependent): 60%<sup>[2]</sup>**
  - Lower survival in patients with aggressive CLL (< 2-3 years)<sup>[3]</sup>

1. Ries LAG, et al. *SEER Cancer Statistics Review, 1975-2004*, National Cancer Institute. Bethesda, MD, [http://seer.cancer.gov/csr/1975\\_2004/](http://seer.cancer.gov/csr/1975_2004/), based on November 2006 SEER data submission, posted to the SEER web site 2007.

2. Jemal A, et al. *CA Cancer J Clin.* 2005;55:10-30.

3. Binet JL, et al. *Cancer.* 1981;48:198-206.

## CLL: Disease Characteristics

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- **Clonal expansion of mature B lymphocytes that coexpress CD5 and CD19, CD20, or CD23**
- **Indolent**
  - Low tumor burden, normal marrow function
- **Progressive**
  - High tumor burden, impaired marrow function
- **Genetic losses on chromosomes 6, 11, 13, 17; gain of chromosome 12**
- **Significant immune deficiency**

# Prognostic Factors in CLL

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- Rai (United States) and Binet (Europe) staging systems
- Serology:  $\beta$ 2-microglobulin, thymidine kinase
- Immunoglobulin G heavy chain variable sequence mutation
- ZAP-70
- FISH cytogenetics: 17p-, 11q-, +12, 13q-
- CD38 on CLL cells

# CLL can significantly reduce lifespan

- Symptomatic patients who require treatment can have dramatically reduced life expectancy
- Treatment should aim for the longest time in remission and preservation of lifespan

General population <sup>1</sup>		CLL patients <sup>2-4</sup>	
Age (yrs)	Life expectancy (yrs)	Disease stage	Life expectancy (yrs)
60	21-24	Rai 0; Binet A	14-17
70	13-16	Rai I or II; Binet B	5-7
80	8-9	Rai III; Binet C	3

1. Office for National Statistics. Interim Life Tables, UK. 2008.

2. Montserrat E. *Hematology Am Soc Hematol Educ Program* 2006; 279-284.

3. Binet JL, et al. *Cancer* 1981; 48:198-206.

4. Rai KR, et al. *Blood* 1975; 46:219-234.

# CLL stage predicts survival and informs treatment decisions

Low risk  
Intermediate  
High risk

Rai staging	Binet staging	Survival (yrs)
0: Bone marrow and blood lymphocytosis only	A: Fewer than three enlarged nodes/nodal groups, Hb > 10 g/dl; platelets > 100 x 10 <sup>9</sup> l	14–17
1: Lymphocytosis with enlarged nodes	B: Three or more enlarged nodes/nodal groups Hb > 10 g/dl; platelets > 100 x 10 <sup>9</sup> l	
2: Lymphocytosis with enlarged spleen and/or liver		5–7
3: Lymphocytosis with anaemia		3
4: Lymphocytosis with thrombocytopenia	C: Hb < 10 g/dl; platelets < 100 x 10 <sup>9</sup> l regardless of number of lymphoid areas involved	

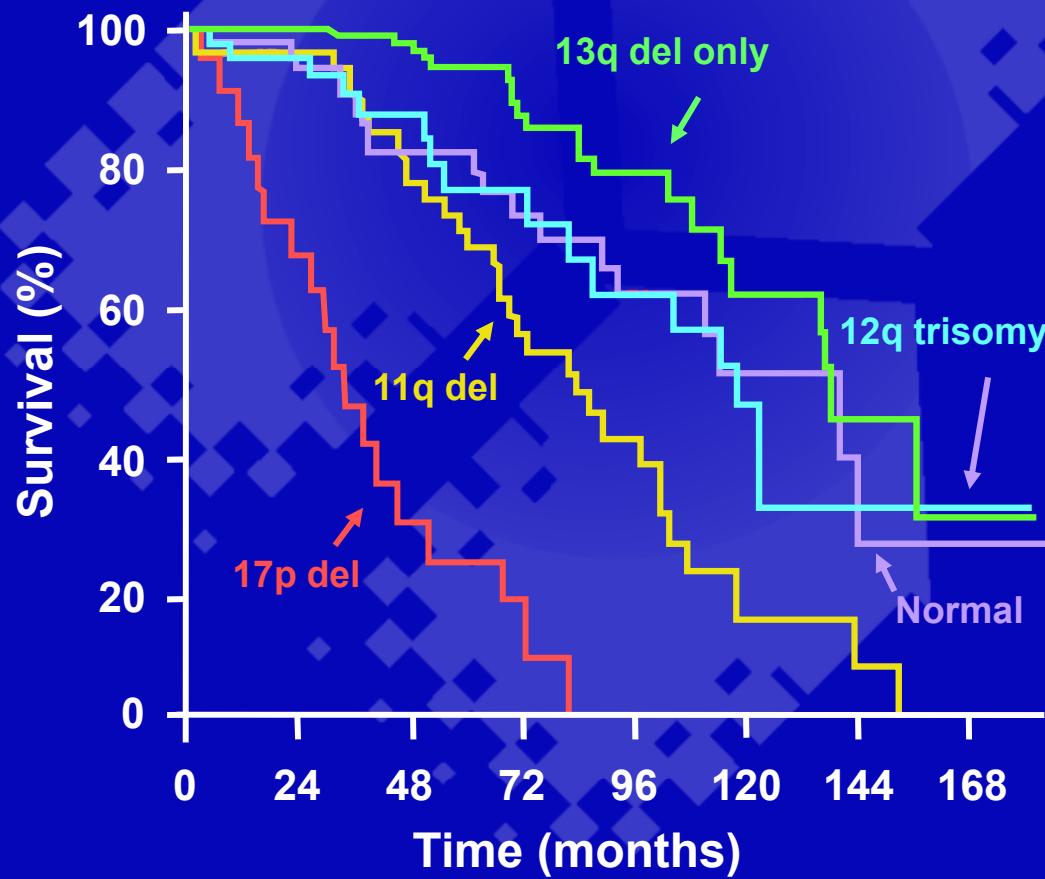
Watch and wait

Begin treatment

1. Rai KR, et al. *Blood* 1975; 46:219-234.  
2. Binet JL, et al. *Cancer* 1981; 48:198-206.

# Prognostic factors in CLL: Predicting survival

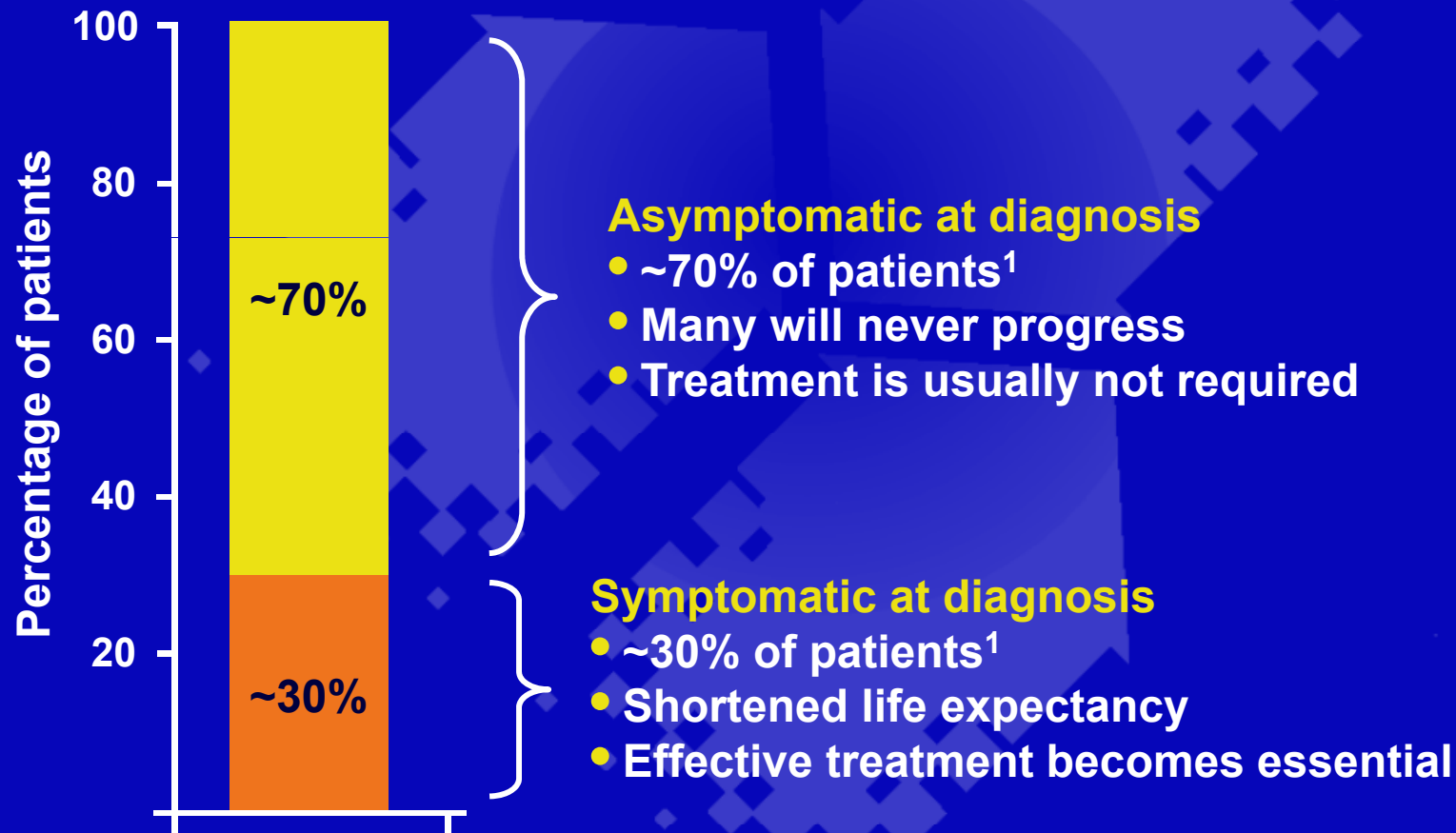
## Genomic aberrations (N = 325)



Dohner H, et al. *N Engl J Med* 2000; 343:1910–1916.

# Treatment is not necessary for most patients

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1. Hamblin TJ, et al. *Br J Haematol* 1987; 66:21–26.

# Which patients are eligible for the watch-and-wait approach?

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- Most CLL patients do not require treatment

## European Society for Medical Oncology (ESMO)<sup>1</sup>

- Binet stage A and B disease without symptoms, or
- Rai stage 0, I and II without symptoms
- The exception is patients with rapid disease progression, i.e. those with a lymphocyte doubling time < 6 months, who should be treated as patients with advanced CLL

## International Workshop on CLL<sup>2</sup>

- Asymptomatic Binet stage A and some stage B patients, or
- Asymptomatic Rai stage 0 and some stage I–II patients

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1. Eichhorst B, *et al. Ann Oncol* 2008; 19:ii60-ii62.  
2. Hallek M, *et al. Blood* 2008; ePub ahead of print.

# Which patients are eligible for treatment?

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- Patients with intermediate, high-risk, or active disease have significantly reduced life expectancy and require effective treatment
- Active disease defined as any of the following:
  - Progressive **marrow failure**
  - Massive/progressive/symptomatic **splenomegaly**
  - Massive nodes or progressive/symptomatic **lymphadenopathy**
  - Progressive **lymphocytosis**
  - Refractory autoimmune **anaemia** and/or **thrombocytopenia**
  - **Weight loss**, significant **fatigue**, **fever**, **night sweats**

# Transforming the way we approach CLL therapy

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- **Traditional treatment goal: control of symptoms**
  - Age is a factor
  - Treat to relieve symptoms
  - Continuous/intermittent treatment
  - No survival advantage for any tested treatment to date
- **New advances may allow treatment for remission and survival**
  - Treat to complete remission (CR)
  - Eliminate minimal residual disease (MRD)
  - Response predicts for survival: more CRs

# Extended survival is the ultimate goal of therapy

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Short-term  
measures



Overall response rate

Long-term  
outcomes



Response duration

PFS

OS

MRD



MRD predicts  
for survival<sup>1,2</sup>

1. Tam CS, et al. *Blood* 2008; 112:975-980.

2. Bosch F, et al. *Clin Cancer Res* 2008; 14:155-161.

## MRD predicts survival

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*“Future clinical trials that aim toward achieving long-lasting complete remissions should assess **minimal residual disease**, because the lack of leukemia persistence using these sensitive tests seems to have a strong, positive prognostic impact”*

International Workshop  
on CLL

# Complete Remission According to NCI-WG Response Criteria for CLL

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Symptomatology	None
Lymphocytes	$\leq 4000/\mu\text{L}$
Lymph nodes (liver/spleen)	No palpable disease
Neutrophils	$\geq 1500/\mu\text{L}$
Platelets	$> 100,000/\mu\text{L}$
Hemoglobin	$> 11.0 \text{ g/dL}$
<b>Bone marrow</b>	<b><math>&lt; 30\%</math> lymph; no nodules</b>
<b>CT Scanning</b>	
<b>Cytogenetics?</b>	

# Changes in CLL Therapy Since 2000

- **Fludarabine alone superior to chlorambucil**
  - Fludarabine-based regimens ± rituximab active in CLL
- **Role for alemtuzumab, nonablative transplantation**

CLL Treatment	Description	Response	Reference
FC	Superior to fludarabine alone as initial therapy	ORR: 94% CR: 24%	Eichhorst BF, et al. Blood. 2006;107:885-891.
FR	Superior to fludarabine alone	ORR: 90%	Byrd JC, et al. Blood. 2003;101:6-14
FCR	Highly active frontline regimen	ORR: 95% CR: 70%	Keating MJ, et al. J Clin Oncol. 2005;23:4079-4088.
Alemtuzumab	Active in frontline setting Superior to chlorambucil Useful in MRD	ORR: 83% CR: 24%	Hillmen P, et al. J Clin Oncol. 2007;25:5616-5623.

# FCR and FR in CLL

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- **Study of FCR in 224 CLL patients<sup>[1]</sup>**
  - CR: 70%
  - 69% of patients failure free at 4 years
  - Grade 3/4 fever, chills, and hypotension with rituximab in 6%
- **Phase II study of concurrent and sequential FR (N = 104)<sup>[2]</sup>**
  - Sequential FR vs concurrent FR, ORR: 77% vs 90%
  - Median response duration, survival not reached in either group at 23 months of follow-up
  - Both regimens generally tolerable
  - More grade 3/4 hematologic toxicity in concurrent regimen

1. Keating MJ, et al. J Clin Oncol. 2005;23:4079-4088.

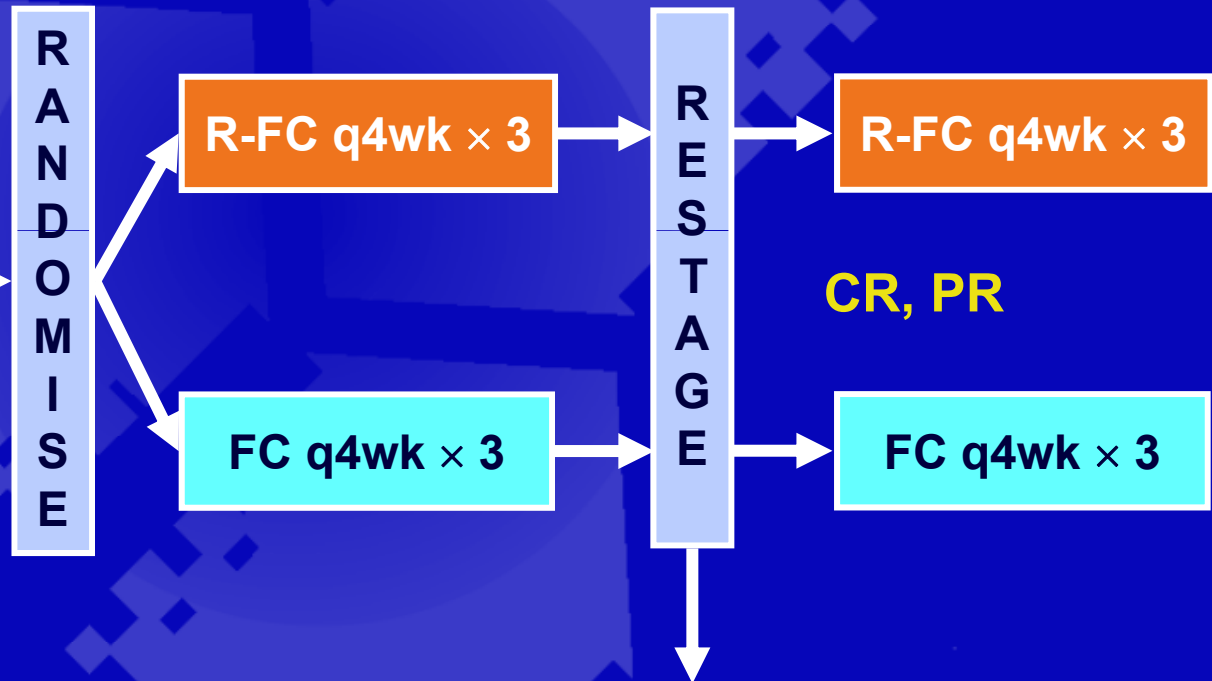
2. Byrd JC, et al. Blood. 2003;101:6-14.



**WHAT DOSE FOR RITUXIMAB IN FCR?**

# The REACH trial: R-FC vs FC in relapsed CLL

- CLL
- Binet A, B or C
- Relapsed disease, excl. fludarabine refractory
- ECOG PS 0–1
- N = 552



## Rituximab

Cycle 1: 375 mg/m<sup>2</sup>

Cycles 2–6: 500 mg/m<sup>2</sup>

## Fludarabine

25 mg/m<sup>2</sup> iv, day 1–3

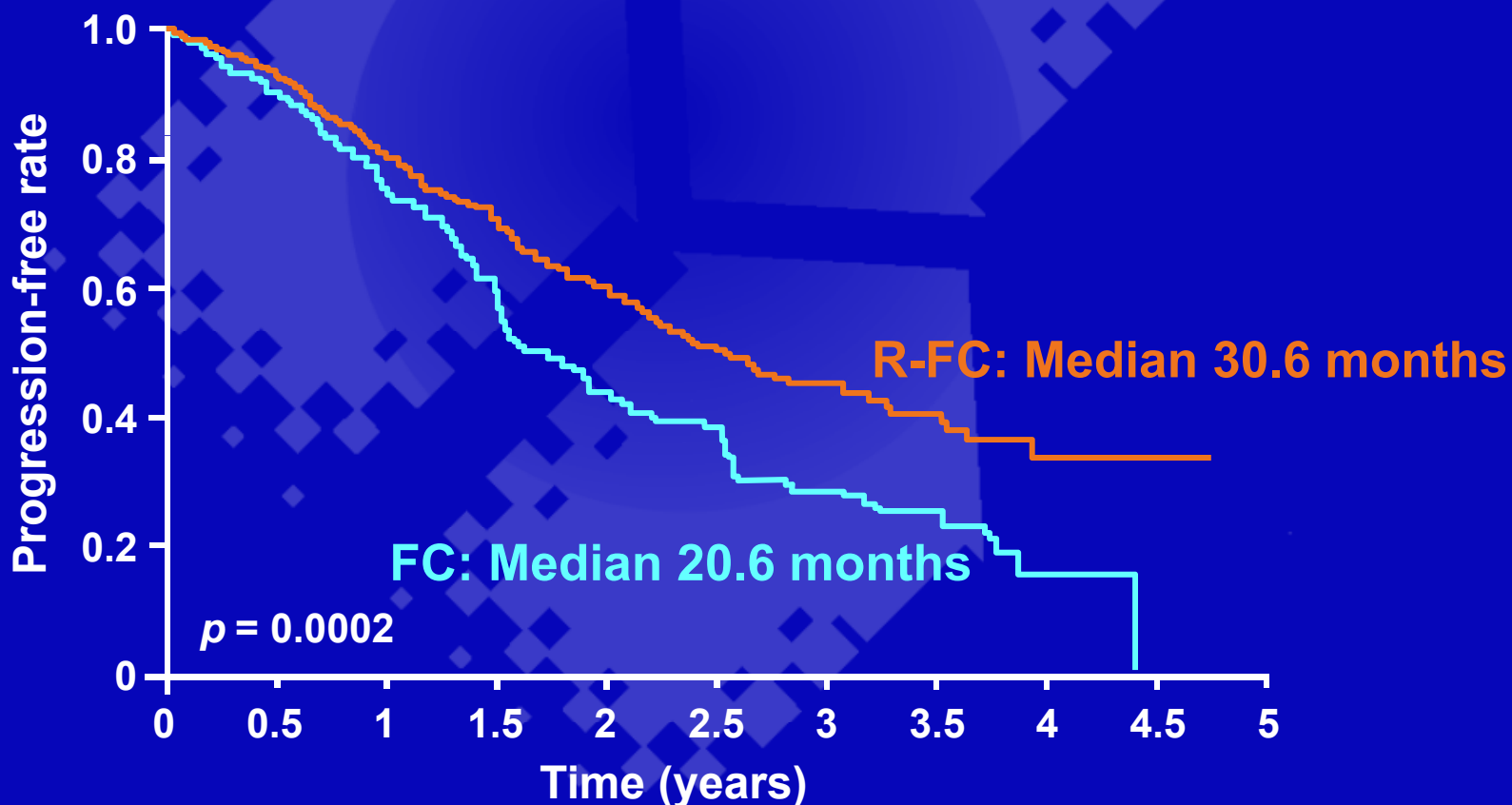
## Cyclophosphamide

250 mg/m<sup>2</sup> iv, day 1–3

**SD may continue treatment**  
**PD off study**

# Rituximab 500 mg/m<sup>2</sup> plus chemo significantly improves PFS vs chemo alone in relapsed CLL

- R-FC reduces the risk of progression, relapse or death by 35% compared with FC alone ( $p = 0.0002$ )

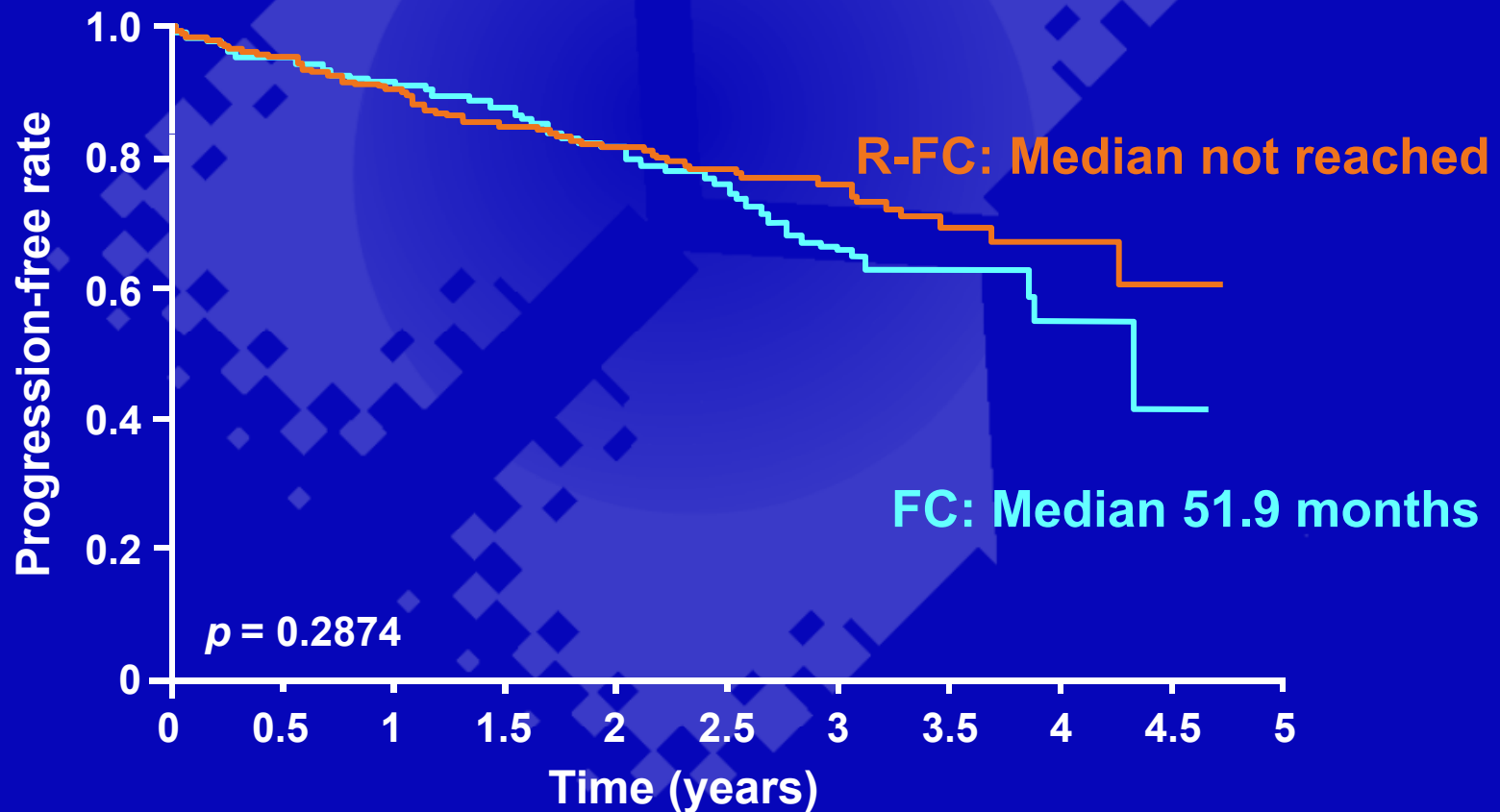


Median follow-up 25.3 months

Robak T, et al. *Blood* 2008;Abstract 15742.

# REACH: Overall survival

- R-FC reduces the risk of death by 17% compared with FC alone ( $p = 0.2874$ )



Median follow-up 25.3 months

Robak T, et al. *Blood* 2008;Abstract 15742.

# REACH: Summary

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- Rituximab plus FC is significantly superior to FC alone in relapsed/refractory CLL patients
- Results were robust and consistent in subgroups, including adverse prognostic groups
  - Binet C
  - 11q–
  - unmutated IgVH, ZAP-70 positive
- R-FC showed no new or unexpected safety findings

**Rituximab 500 mg/m<sup>2</sup> plus  
chemotherapy provides the longest  
remission for CLL patients**

**Relapsed disease: REACH**

# **New Approaches in Patients With CLL**

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- **Dose intensification of standard chemotherapy**
- **High-dose chemotherapy**
- **Allogeneic transplant**
- **Gene therapy**
- **New drugs**
- **Monoclonal antibodies (MoAbs)**
- **Combined chemoimmunotherapy**

# CLL Abstracts at ASH 2009

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1. CLL8 study – Hallek *et al*
2. MabThera-bendamustine – Fischer *et al*
3. MabThera-chlorambucil first line – Hillmen *et al*
4. MabThera monotherapy in refractory/poor-prognosis patients – Adiga and Wiernik
5. MabThera plus lenalidomide in relapsed CLL – Ferrajoli *et al*

# CLL8: MabThera-FC vs FC

## Phase III study in first-line CLL

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- **Randomised, Phase III study:**
  - **N = 817**
  - **Randomly assigned 6 cycles of MabThera-FC or FC only every 28 days:**
    - **MabThera-FC = 375 mg/m<sup>2</sup> for first cycle and 500 mg/m<sup>2</sup> for subsequent cycles**
    - **F = 25 mg/m<sup>2</sup> days 1–3 and C = 250 mg/m<sup>2</sup> days 1–3**
- **Patients in both treatment groups balanced in terms of disease stage, genomics, and general health**
- **Follow-up period 37.7 months**

# CLL8: Best response to treatment

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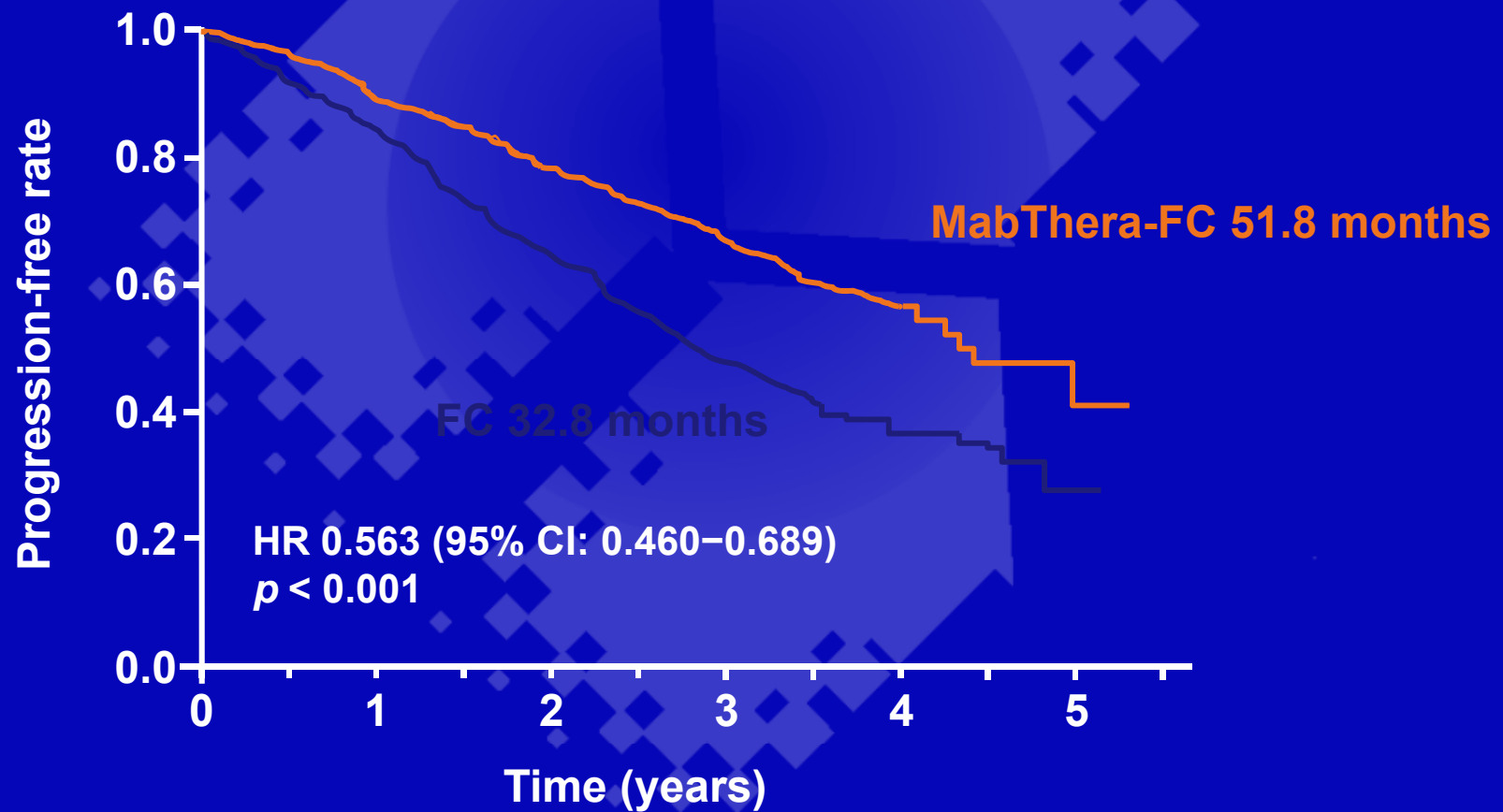
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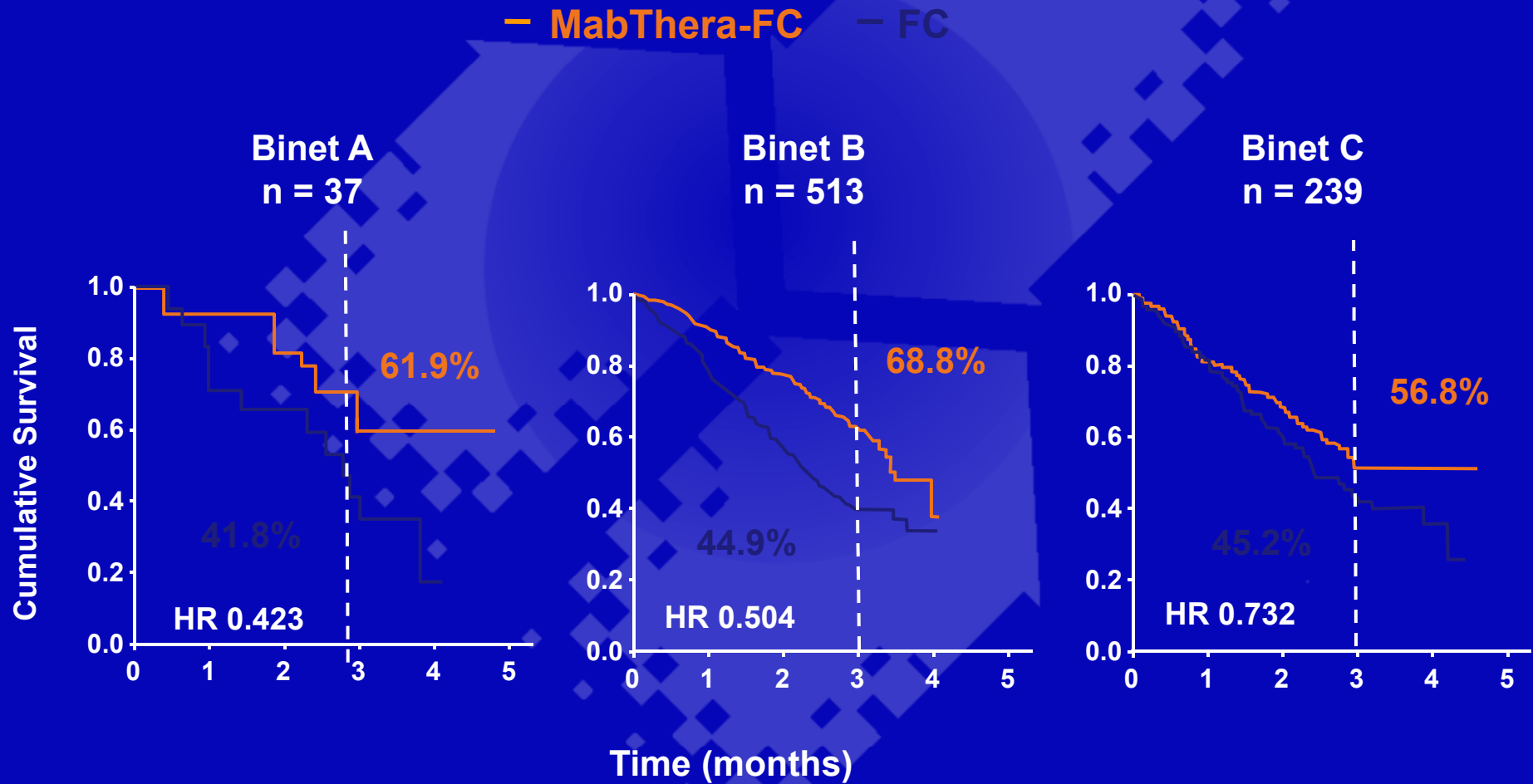
\*According NCI WG-Criteria; confirmatory BM assessment performed up to 6 months after final restaging

\*\*p < 0.01

# CLL8: PFS

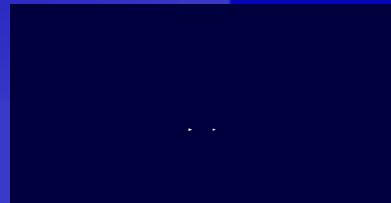


# CLL8: 3 yrs PFS according to stage

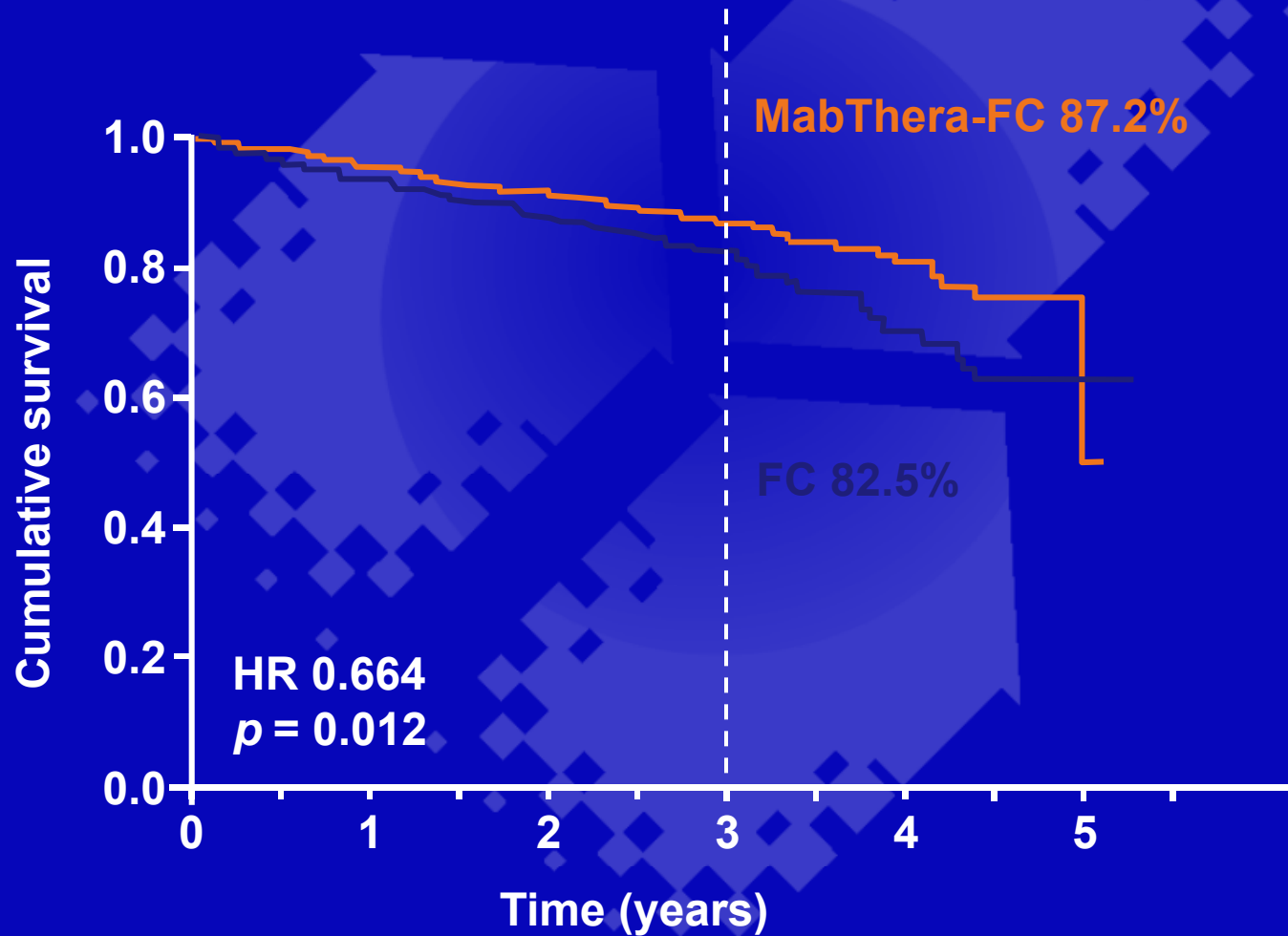


# Treatment efficacy in Binet stage C patients

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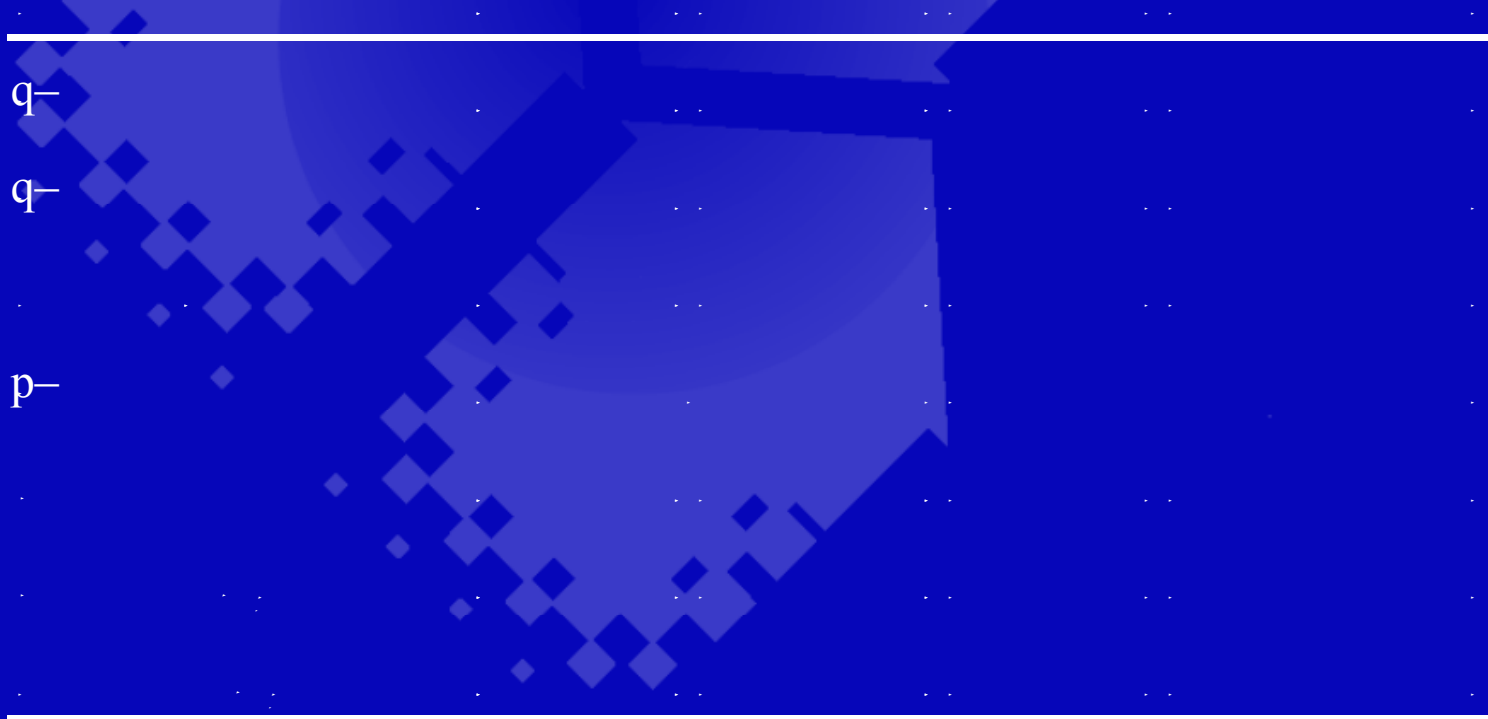


# CLL8: Overall survival



# CLL8: CR in different genetic subgroups

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## CLL8: Conclusions

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- **MabThera-FC significantly improves both PFS and OS compared with FC alone in first-line treatment of CLL**
- **At 37.7 months follow up the PFS benefit is significant in Binet stage A and B patients with a strong trend in stage C patients**
- **This is the first randomised trial to demonstrate that the choice of first line therapy improves the natural course of CLL**

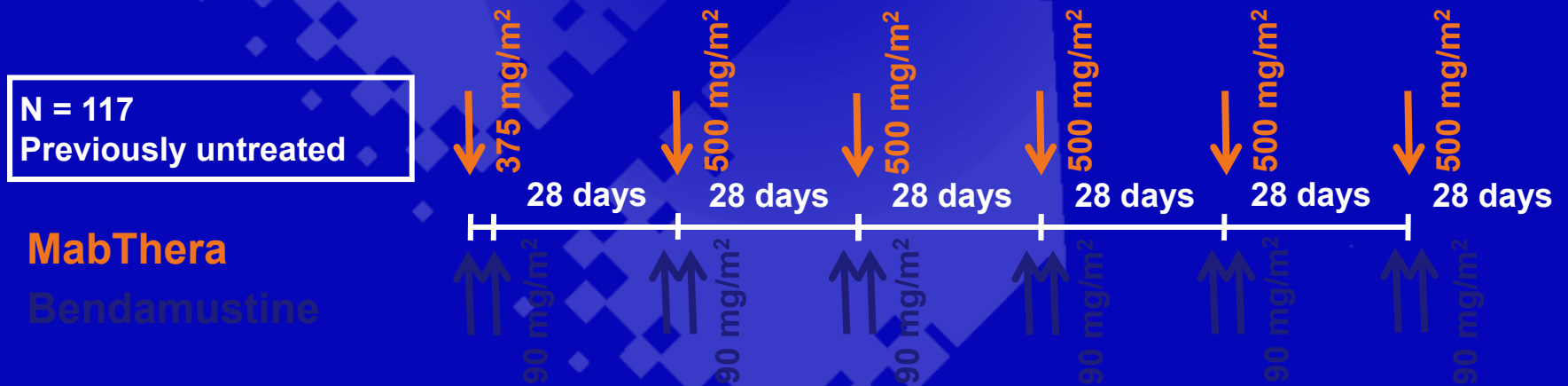
# MabThera + bendamustine in first-line CLL: Overview

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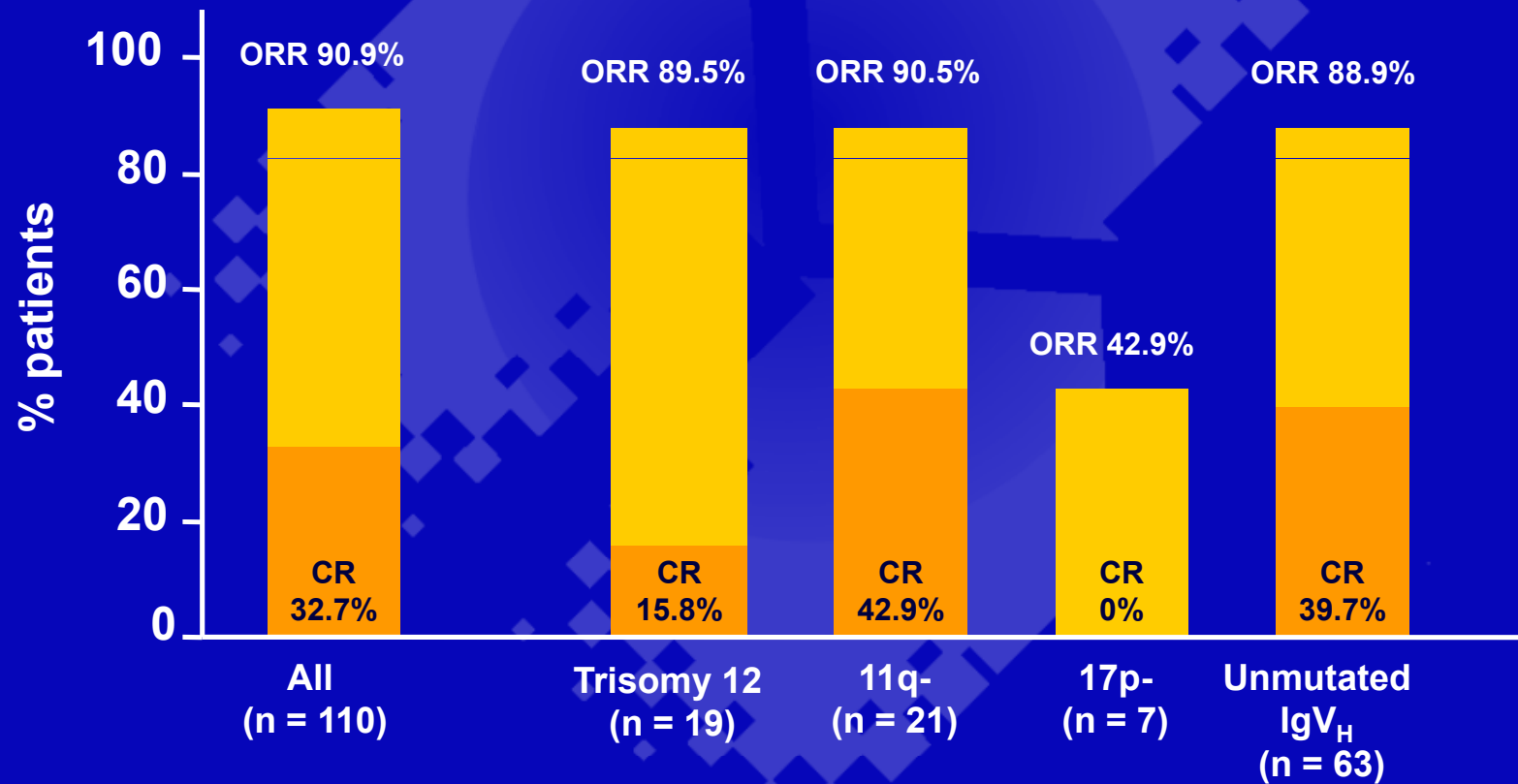
- **Indication: Previously untreated CLL**
- **Study: Single-arm phase II study (6 x MabThera-bendamustine)**
- **Primary objective: Overall response rate**

# MabThera + bendamustine in first-line CLL: Design

- Bendamustine has previously shown considerable efficacy and an excellent safety profile
- This makes bendamustine a good combination with MabThera in fludarabine-ineligible CLL patients



# MabThera + bendamustine in first-line CLL: Response rates



# MabThera + bendamustine in first-line CLL: Conclusions

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- MabThera-bendamustine is effective in first-line treatment of CLL with significant myelosuppression and infections but tolerable adverse events
- MabThera-bendamustine vs MabThera-FC is under evaluation in a phase III randomised trial (CLL10)

# RELAPSED / FLUDARABINE REFRACTORY CLL: OPTIONS

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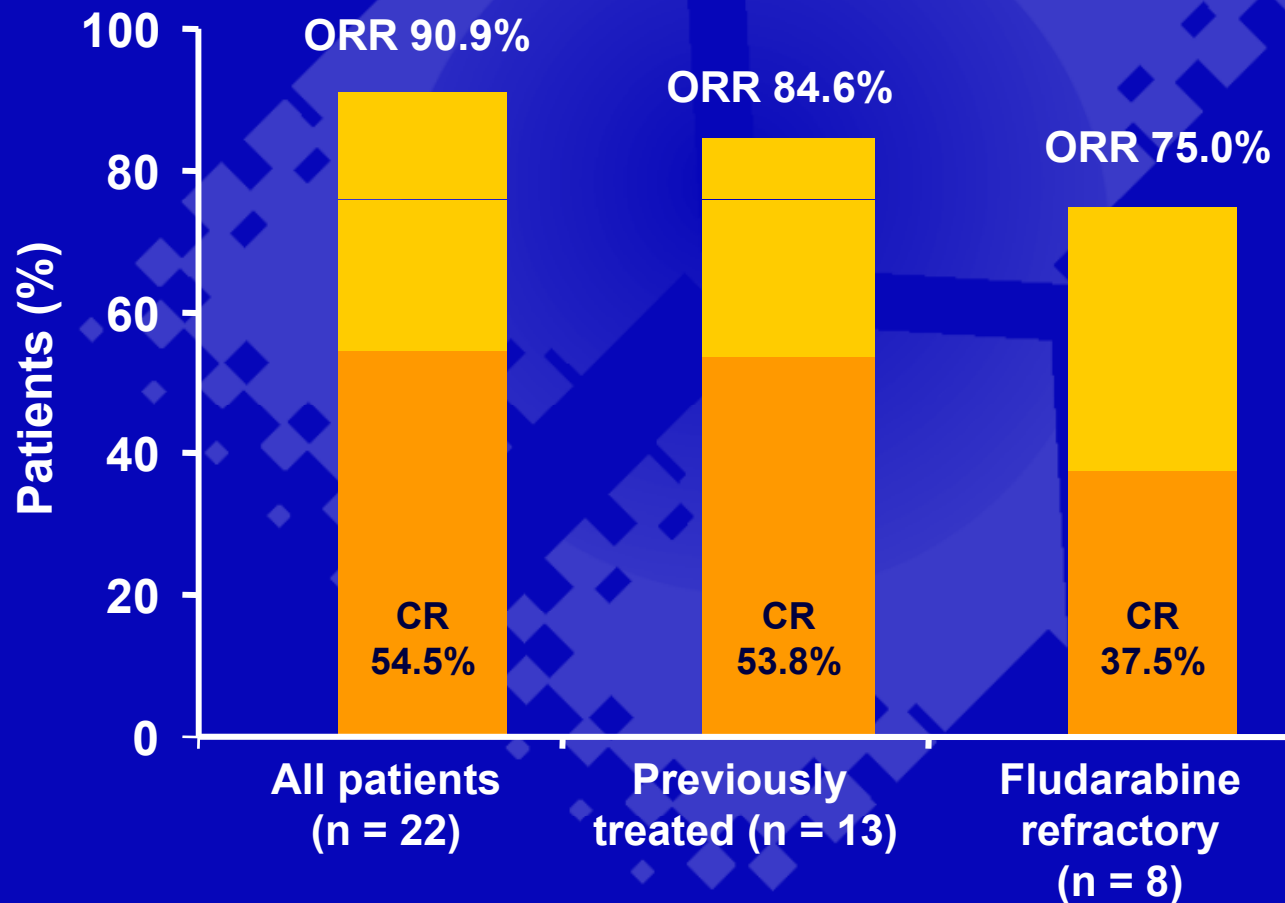
- **ALEMTUZUMAB: Anti CD 52 Antibodies**
- **BENDAMUSTINE: Mustine compound**
- **LENALIDOMIDE: Immunomodulatory Agent**
- **OFATUMUMAB: Complete humanised anti CD 20 Abs**
- **OXALIPLATINUM: Chemotherapy (OFAR)**
- **OBLIMERSON: Antisense(BCL2) antibodies**

# MabThera monotherapy in relapsed CLL: Overview

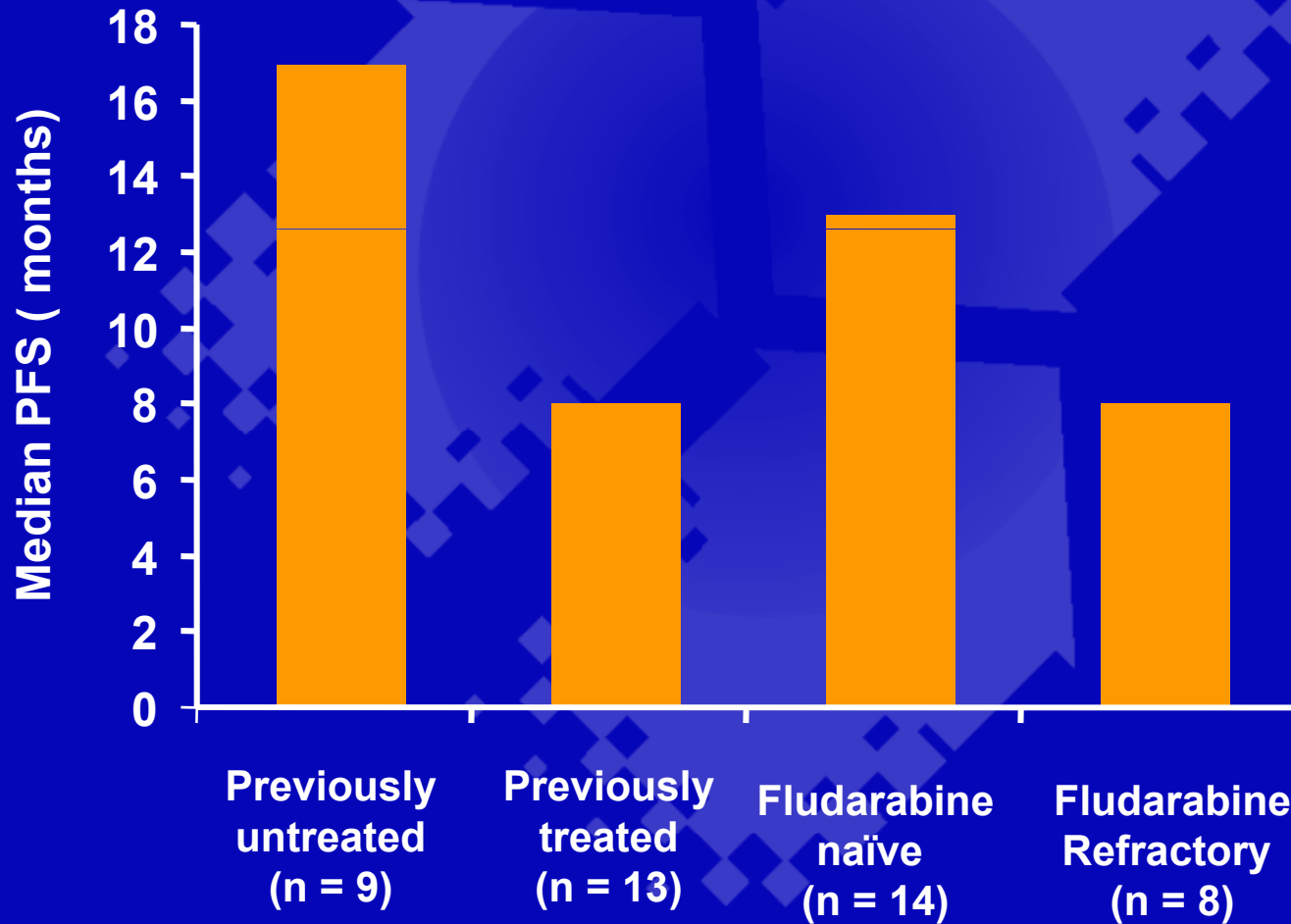
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- **Indication:** Untreated or relapsed/refractory CLL
- **Study:** Retrospective case series of patients treated with MabThera monotherapy
- **Endpoints:** Efficacy and safety endpoints were recorded and analysed

# MabThera monotherapy in relapsed CLL: Response rates



# MabThera monotherapy in relapsed CLL: PFS



# MabThera monotherapy in relapsed CLL: Conclusions

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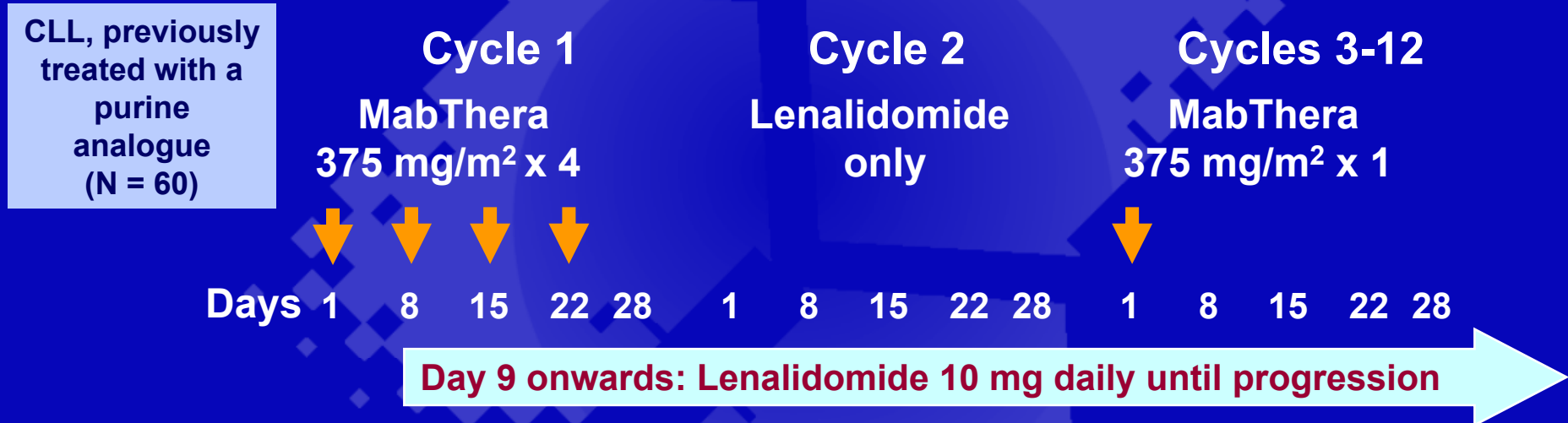
- High-dose single-agent MabThera was an effective treatment for treatment-refractory or poor-prognosis CLL, and was well tolerated
- High ORR and CR rates were seen even in patients who were fludarabine refractory
- Single-agent MabThera is at least as effective as other regimens available for fludarabine-refractory patients

# MabThera plus lenalidomide in relapsed CLL: Overview

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- **Indication:** Relapsed/refractory CLL, previously treated with a purine analogue
- **Study:** Single-arm phase II study (MabThera-lenalidomide)
- **Endpoints:**
  - Response rate
  - Safety
  - T-cell number and function

# MabThera plus lenalidomide in relapsed CLL: Study Design



- Total 14 doses of MabThera
- Allopurinol 300 mg Days 1–14 of cycle 1
- No antibiotic or antiviral prophylaxis
- No DVT prophylaxis

# MabThera plus lenalidomide in relapsed CLL: Conclusions

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- The combination of MabThera and lenalidomide is active in relapsed CLL
  - OR of 64% after 12 cycles
- Higher response rate and faster responses than with lenalidomide monotherapy
- Myelosuppression was the most frequent toxicity

# Conclusions

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- **Recent data reinforces the strong position of MabThera efficacy in first line and relapsed CLL providing patients years of life free from relapse and chemotherapy**
- **FCR continuing to be the most efficacious first line regimen**
- **Positive data for MabThera alone or in combination with Bendamustine or lenalidomide provide a different option for CLL patients**

## Initiatives in CLL Since 2000

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- Chemoimmunotherapy with FR and FCR
  - New standard of care
- Early initiation of therapy/prognostification
- Potential for cure  $\pm$  allogeneic transplantation
- Use of vaccines, gene therapy
- New agents active in CLL
  - Lenalidomide, flavopiridol, oblimersen (BCL2 antisense), ofatumumab

## CLL: Areas of Continuing Study

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- **The optimal role for alemtuzumab**
  - Frontline, consolidation
  - Combined with standard chemoimmunotherapy
- **The role of novel therapies in relapsed/refractory CLL**
  - Lenalidomide
  - Lumiliximab, ofatumumab

# Remaining Questions

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- **Post-remission maintenance/consolidation with rituximab/alemtuzumab**
- **NST while in remission**
- **Observation**



**Thank You**