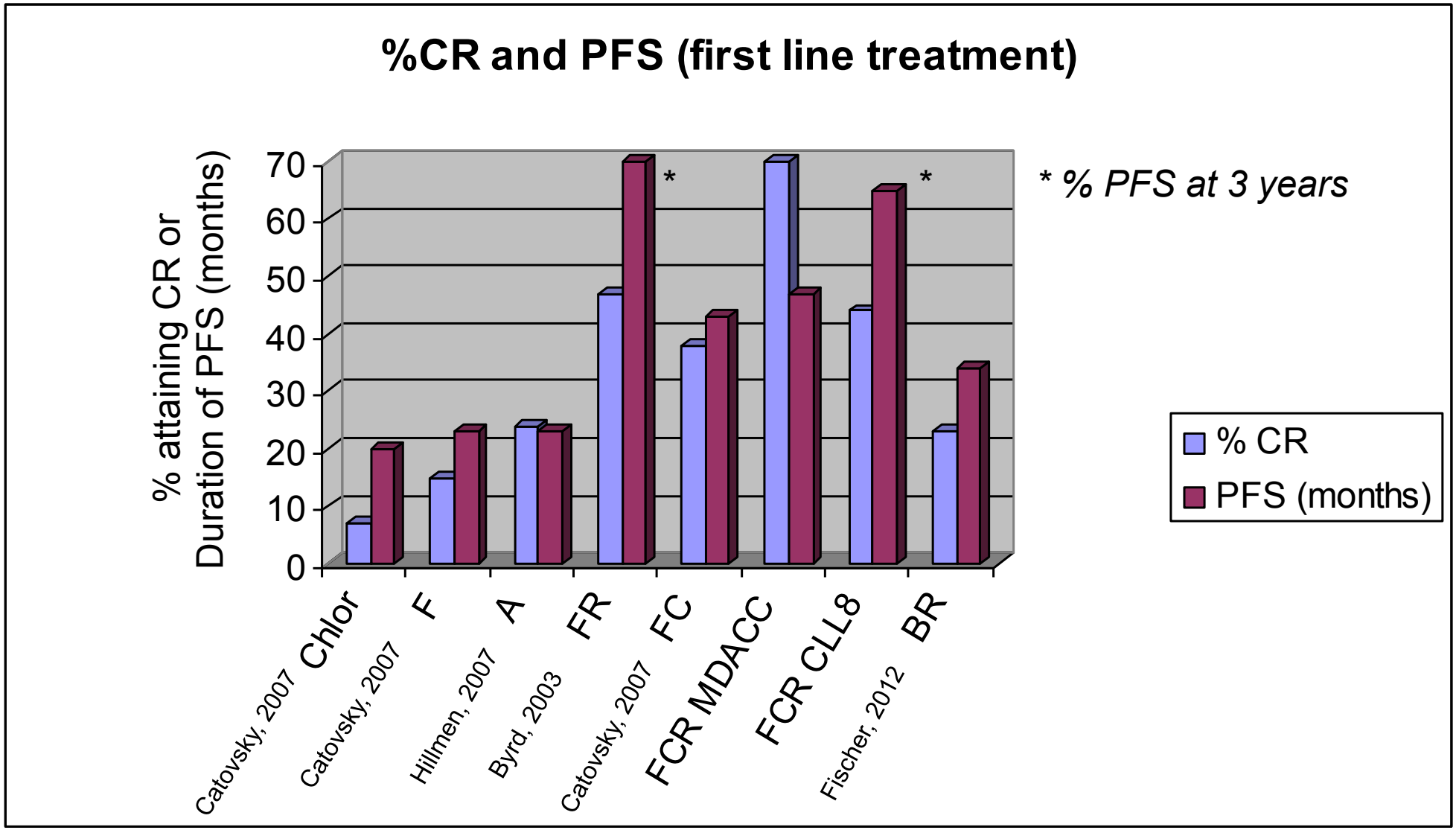
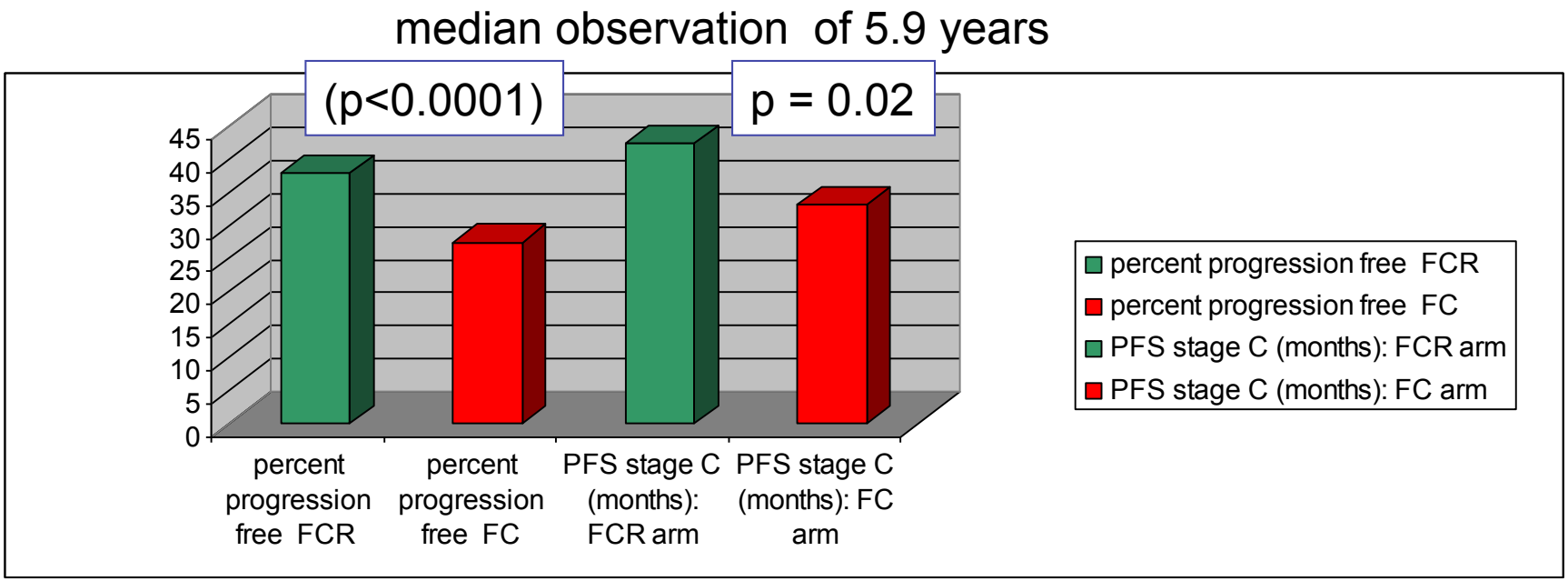
# Algoritmo terapeutico nella leucemia linfatica cronica


Antonio Cuneo
12 ottobre 2016 9.00 – 9.30

# Increasing efficacy of chemo/immunotherapy in first line (fit patients)



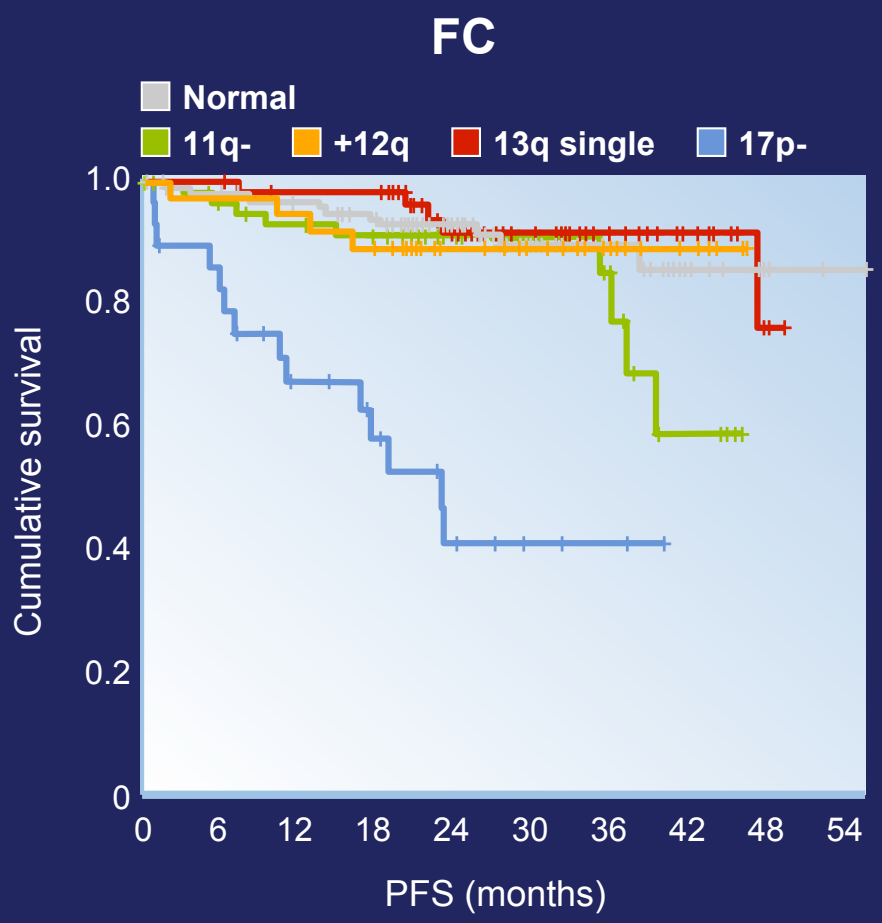
# FCR is the standard treatment in young and fit CLL

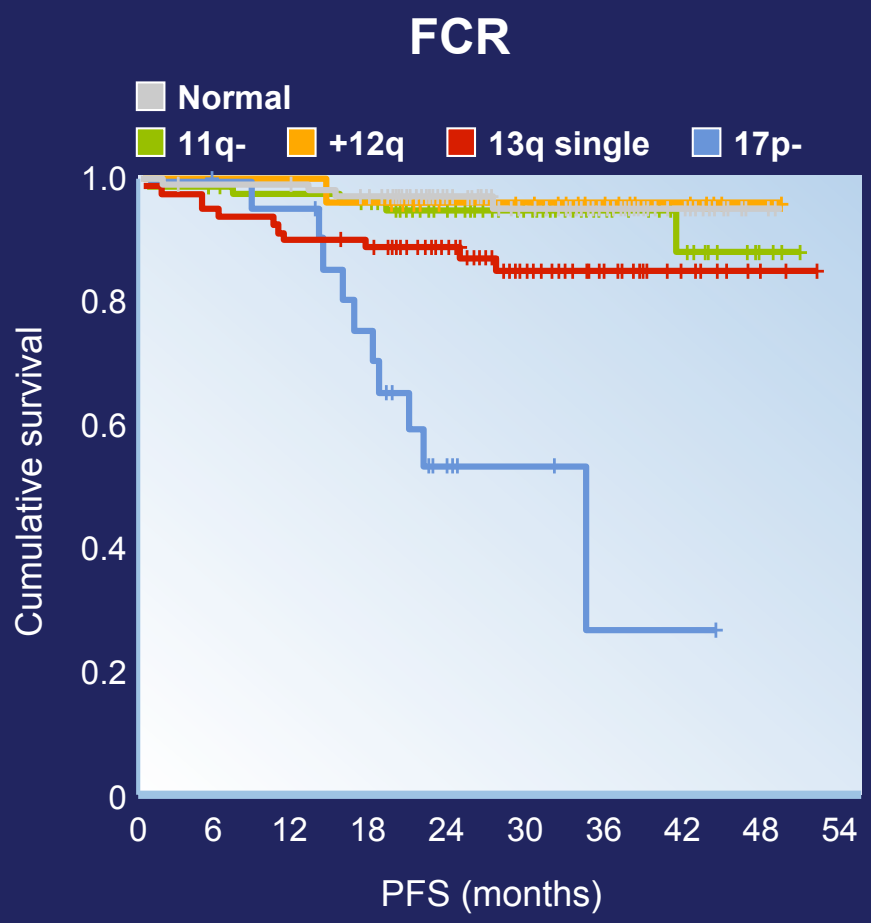



Fischer K et al.
Chemoimmunotherapy Based Treatment for CLL: Extended Follow up of the CLL8 Protocol
(ASH Annual Meeting Abstracts) 2012 120: Abstract 435

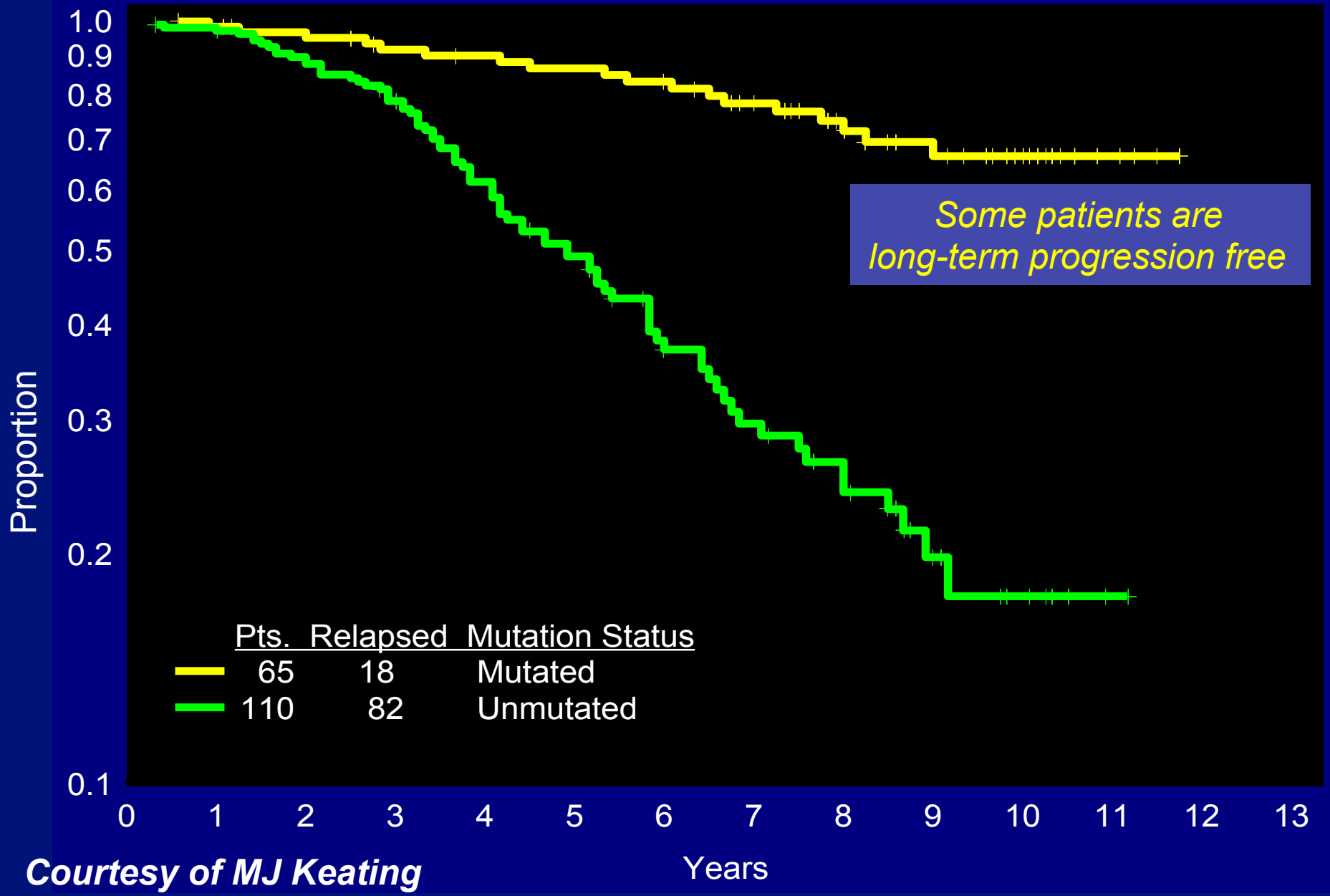
**Addition of rituximab to fluda and CTX in CLL: a randomised, open-label, phase 3 trial**
**M Hallek et al Lancet 2010; 376: 1164–74**

# Poor outcome for 17p- patients



# FCR Time to Progression by Mutation Status
## FCR300 (logarithmic scale)



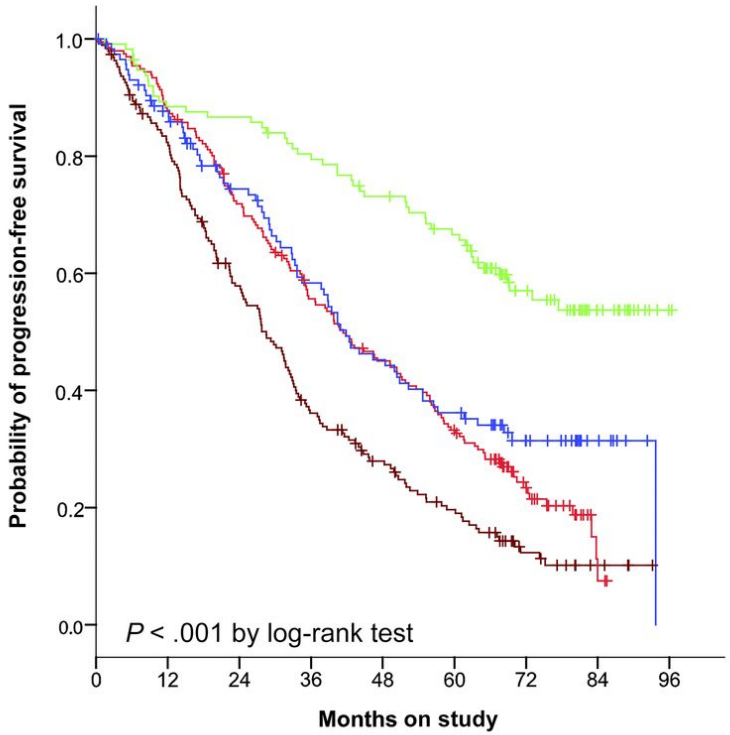

***Courtesy of MJ Keating***

# Are Ig-mutated CLL patients being cured by FCR?

- High proportion of **Ig-mutated** patients free of clinical relapse at 11 years
- By late 2013 **70 Ig-mutated** patients available to study residual disease status at 11 yrs still have no molecular evidence of disease

***Courtesy of MJ Keating***

# Long term PFS with FCR (GCLLSG – CLL8)




66% progression free
at 5r yrs with plateau?

FCR *IGHV* MUT patients (N=113)

FC *IGHV* MUT patients (N=117)

FCR *IGHV* UNM patients (N=197)

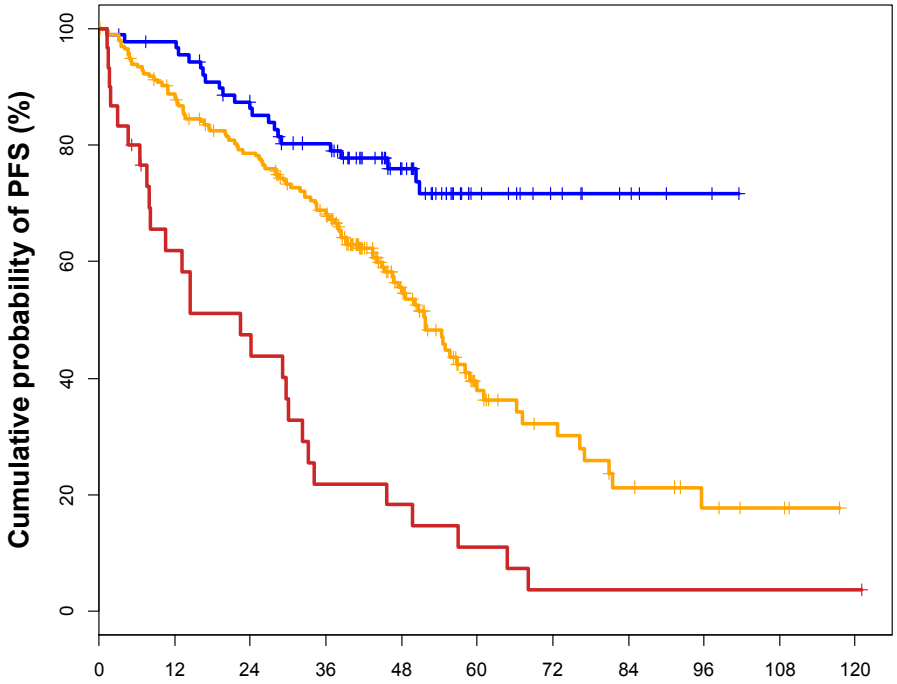
FC *IGHV* UNM patients (N=195)

| Number at risk | 0 | 12 | 24 | 36 | 48 | 60 | 72 | 84 | 96 |
|---|---|---|---|---|---|---|---|---|---|
| FCR *IGHV* MUT | 113 | 99 | 97 | 89 | 80 | 71 | 37 | 15 | 1 |
| FC *IGHV* MUT | 117 | 96 | 75 | 58 | 45 | 36 | 21 | 7 | 0 |
| FCR *IGHV* UNM | 197 | 173 | 140 | 106 | 85 | 61 | 25 | 2 | 0 |
| FC *IGHV* UNM | 195 | 153 | 105 | 65 | 45 | 30 | 12 | 4 | 0 |

Fischer K et al. Blood. 2016; 127:208-215

# PFS and OS after FCR: role of *IGHV* mutatonal status, 11q- and 17p- as prognostic factors

*IGVH* mutated
*IGVH* unmutated and/or 11q deletion
17p deletion



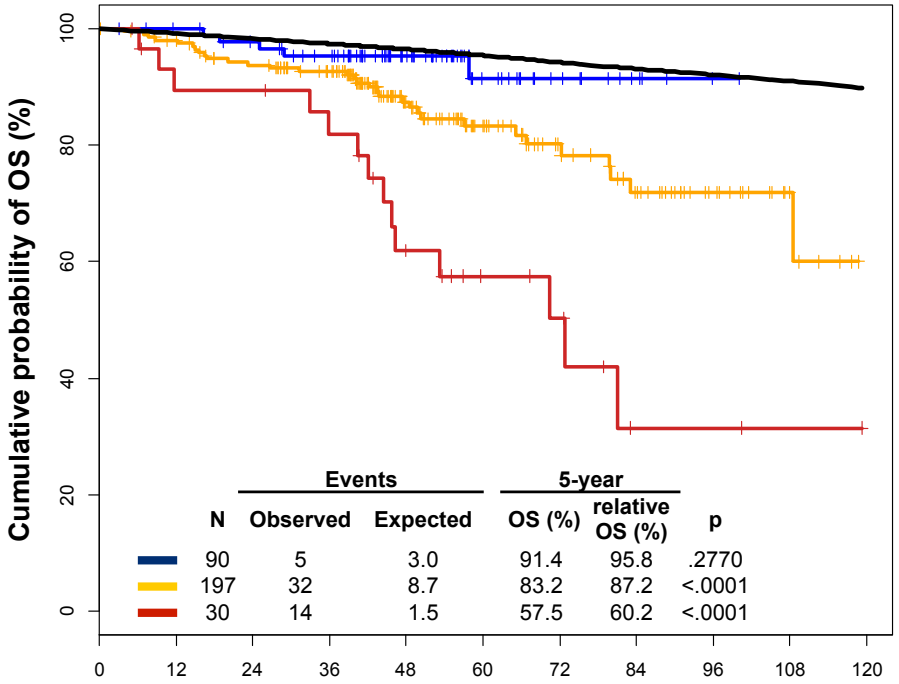

| No. at risk | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | 90 | 86 | 73 | 63 | 40 | 15 | 9 | 5 | 2 | 0 | 0 |
| | 197 | 170 | 147 | 122 | 59 | 23 | 15 | 9 | 5 | 3 | 0 |
| | 30 | 17 | 13 | 6 | 5 | 3 | 1 | 1 | 1 | 1 | 1 |

| | Events | Total | Median PFS | 95% CI |
|---|---|---|---|---|
| | 22 | 90 | nr | na |
| | 102 | 197 | 51.7 | 46.1-57.2 |
| | 27 | 30 | 22.5 | 8.5-36.4 |

Pairwise comparisons

| p | | | |
|---|---|---|---|
| | - | 0.0001 | <0.0001 |
| | 0.0001 | - | <0.0001 |
| | <0.0001 | <0.0001 | - |

*IGVH* mutated
*IGVH* unmutated and/or 11q deletion
17p deletion




| No. at risk | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | 90 | 87 | 82 | 74 | 50 | 22 | 12 | 6 | 2 | 0 | 0 |
| | 197 | 189 | 175 | 160 | 96 | 63 | 45 | 33 | 19 | 9 | 1 |
| | 30 | 25 | 25 | 23 | 15 | 10 | 7 | 3 | 2 | 1 | 1 |

| | Events | Total | 5-years OS | 95% CI |
|---|---|---|---|---|
| | 5 | 90 | 91.4 | 87.1-95.7 |
| | 32 | 197 | 83.2 | 80,0-86.4 |
| | 14 | 30 | 57.5 | 47.6-67.4 |

Pairwise comparisons

| p | | | |
|---|---|---|---|
| | - | 0.0341 | <0.0001 |
| | 0.0341 | - | 0.0004 |
| | <0.0001 | 0.0004 | - |

Rossi et al, Blood 2015

# *Age and outcome in CLL8*

PFS and OS at 3 years after randomisation in prognostic subgroups

| | | | FC | FCR | Hazard rate (95% CI) | p value |
|---|---|---|---|---|---|---|
| Age | <65 years (n=572) | PFS | 46% | 64% | 0·57 (0·45–0·73) | <0·0001 |
| | | OS | 85% | 87% | 0·68 (0·46–1·02) | 0·059 |
| | ≥65 years (n=245) | PFS | 43% | 68% | 0·55 (0·38–0·79) | 0·001 |
| | | OS | 77% | 88% | 0·63 (0·37–1·10) | 0·103 |

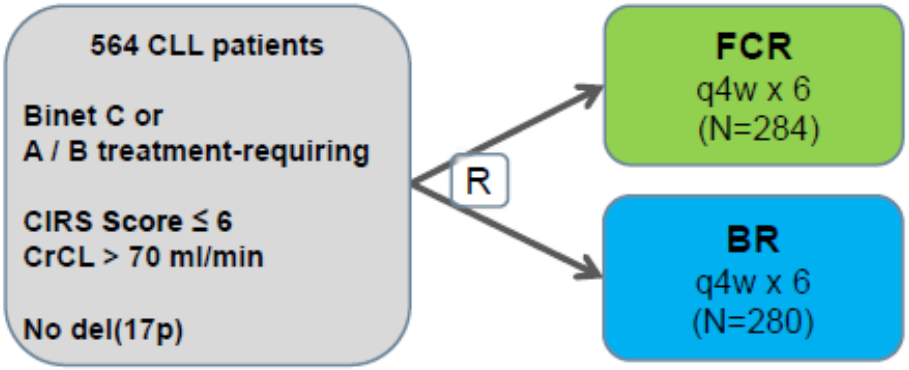
| | **<65 years (n=560)** | **≥65 years (n=240)** | **p** |
|---|---|---|---|
| Total number of patients with at least one grade 3 or 4 event | 375 (67%) | 183 (76%) | 0·009 |
| Haematological toxicity | 254 (45%) | 128 (53%) | 0·04 |
| Bacterial infection | 6 (1%) | 10 (4%) | 0·004 |

Data from Hallek M et al Lancet 2010; 376: 1164–74

# FCR vs BR in Previously Untreated and Physically Fit Patients with CLL: Final Analysis of the GCLLSG- CLL10 Study (17p- excluded per protocol)

- Study hypotheses
  - 1. BR non-inferior to FCR in terms of PFS
  - 2. BR potentially better tolerability compared to FCR
- Assumptions*:
- PFS @ 2 yearss
  - under FCR: 75%
  - under BR: > 67,5% for non-inferiority (7.5% difference or less)
  - → Complete 95% CI of the HR [λ BR/FCR] has to be < 1.388

## Study Design



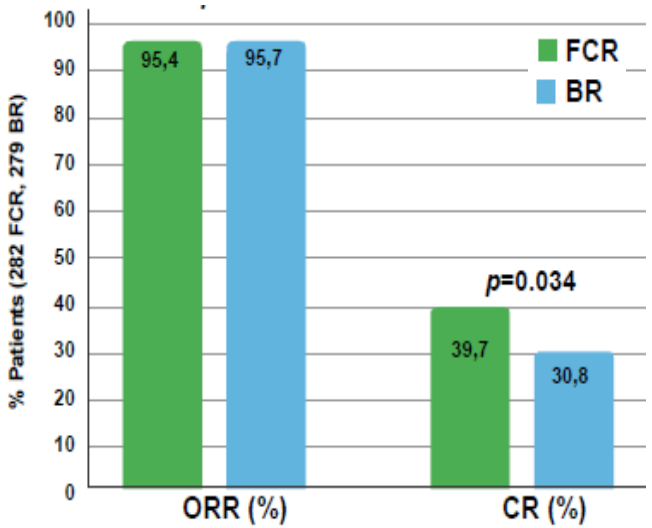

Median observation time for all patients: 37,1 (0-59,9) m

| Baseline patient characteristics | FCR n=284 | BR n=280 | p value |
|---|---|---|---|
| Med. age | 61 | 62,1 | 0,131 |
| Age > 65 | 30,5% | 38,7% | 0,042 |
| Age ≥ 70 | 14% | 22% | 0.020 |
| Male | 71,3% | 74,2% | 0,45 |
| Median time since diagnosis (m) | 21,6 | 24,6 | 0,846 |
| ECOG PS 0 | 64,1% | 64,1% | 0,194 |
| Med. CIRS | 2 | 2 | 0,489 |
| Binet A | 22,3% | 22,2% | 0,846 |
| Binet B | 37,3% | 38,4% | |
| Binet C | 40,4% | 39,4% | |
| IGHV unmutated | 55,3% | 67,8% | 0,003 |
| 11q deletion | 24,1% | 22,6% | 0,691 |
| Trisomy 12 | 12,4% | 12,2% | 1 |
| 13q deletion | 55% | 52,7% | 0,612 |
| s-TK (U/l) > 10.0 | 72,8% | 72,6% | 1 |
| s-β2m (mg/l) > 3.5 | 30,9% | 38,1% | 0,086 |

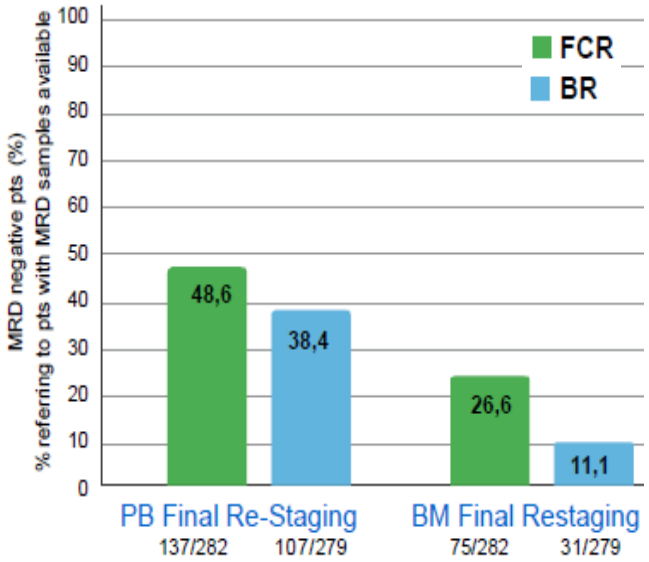
Eichhorst et al., ASH 2014, Abstract # 19

# FCR vs BR in Previously Untreated and Physically Fit Patients with CLL: Final Analysis of the GCLLSG- CLL10 Study

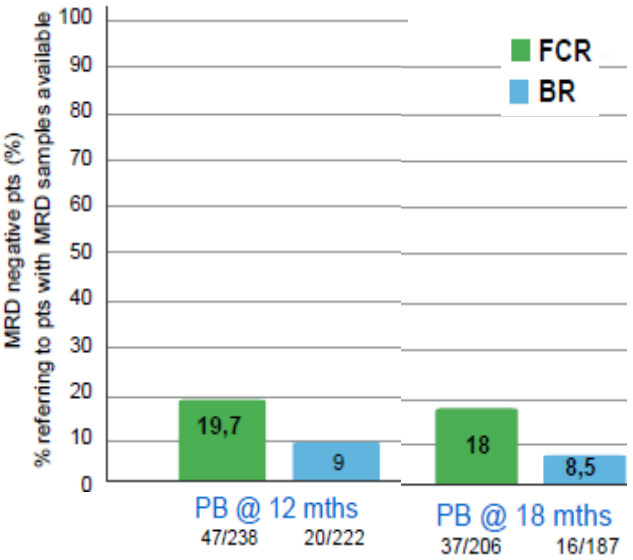
Best Response




MRD-negativity ($<10^{-4}$) in PB and BM at response

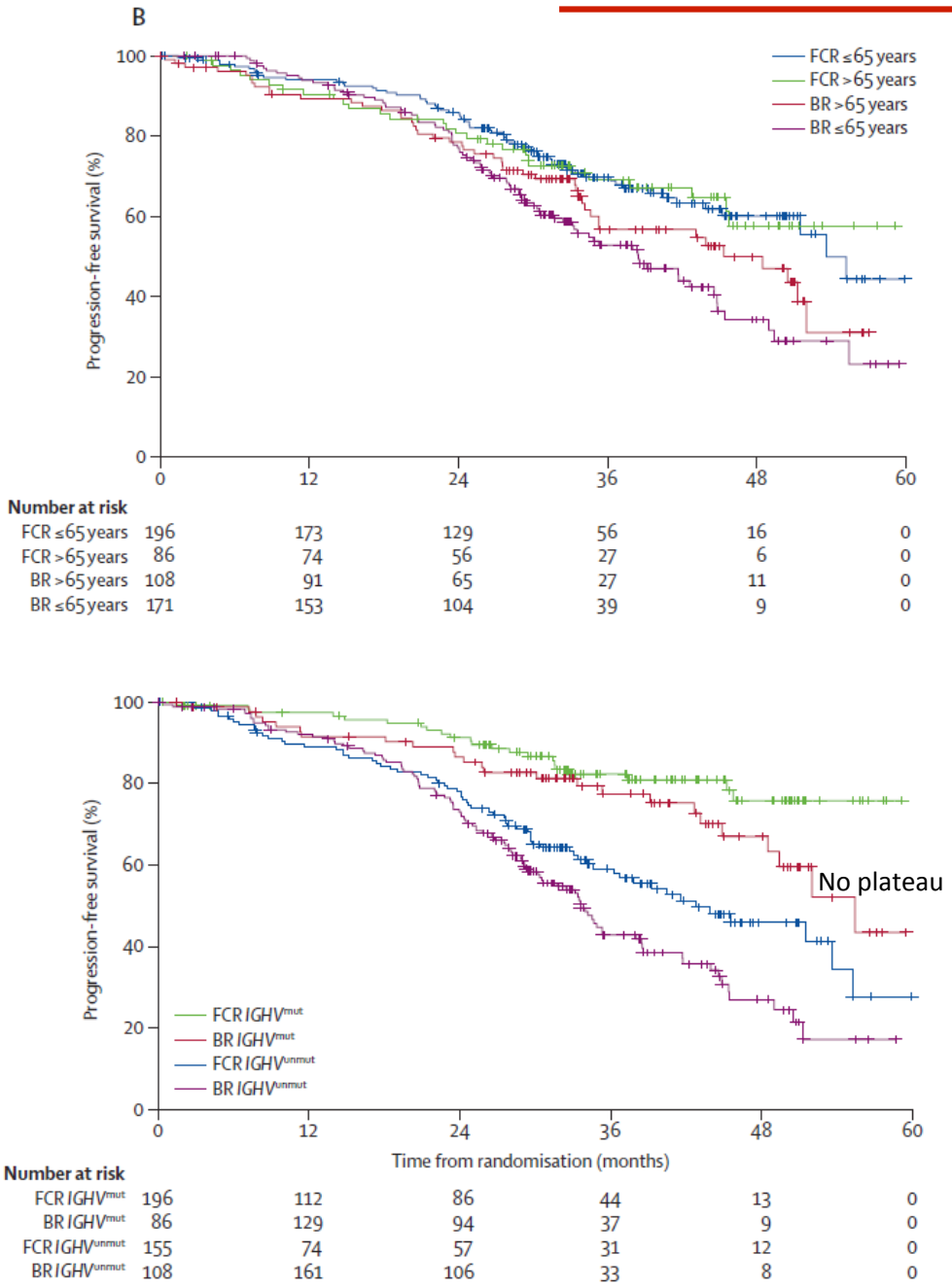


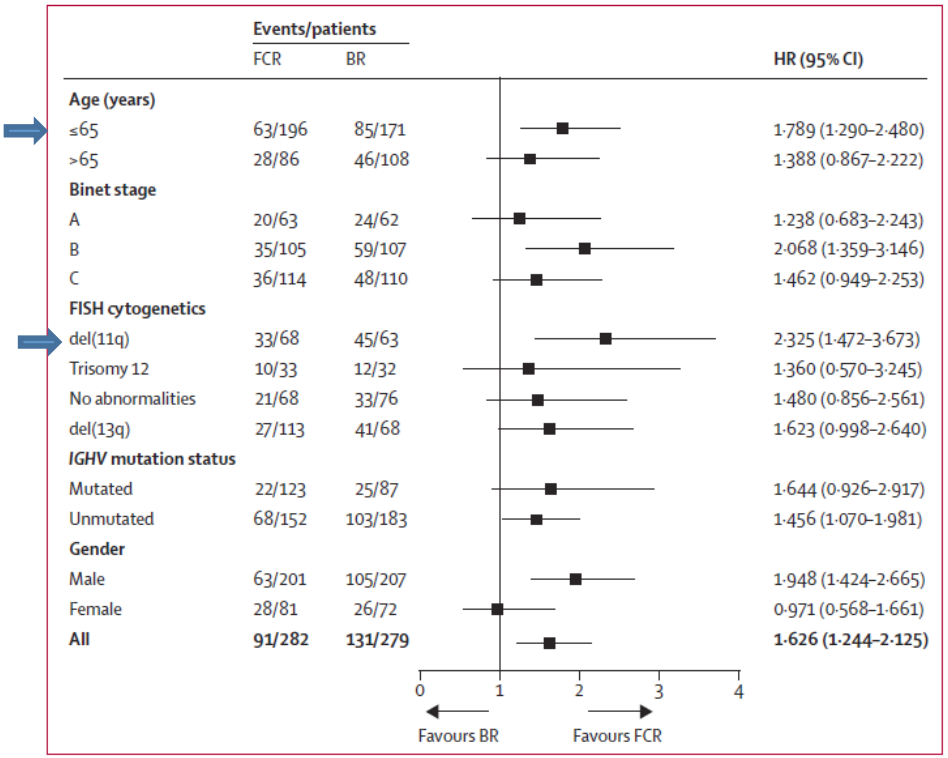

MRD-negativity ($<10^{-4}$) in PB at 12 and 18 months




Eichhorst et al., ASH 2014, Abstarct # 19

# CLL10: PFS according to risk groups




Eichhorst et al Lancet Oncol 2016;17:928-42

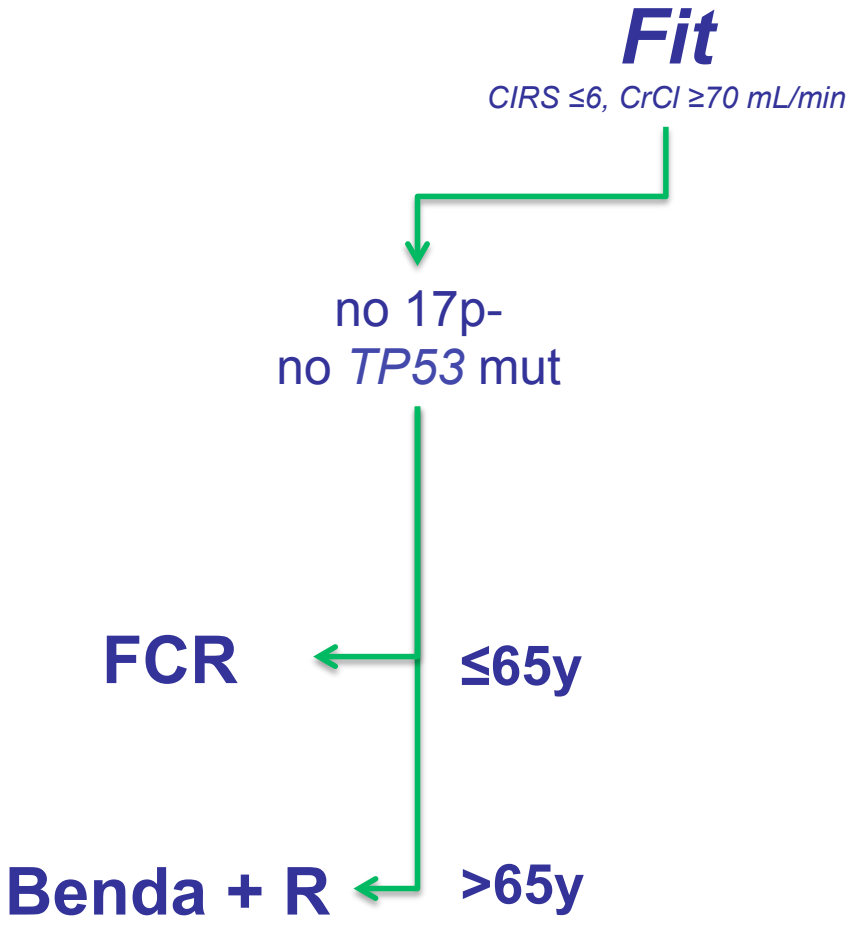
# CLL10 STUDY: FCR vs BR IN FRONT LINE

TOXICITY

| CTC Grade 3-5 AEs | | | |
|---|---|---|---|
| | **FCR (n=282)** | **BR (n=279)** | **p value** |
| All AEs | 90.8% | 78.5% | <0.001 |
| Hematotoxicity | 90.0% | 66.9% | <0.001 |
| Severe Neutropenia | 81.7% | 56.8% | <0.001 |
| Severe Infections | 39.0% | 25.4% | 0.001 |
| ≥ 65 yrs | 47.4% | 26.5% | 0.002 |
| Treatment Related Mortality | 3.9% | 2.1% | |

Eichhorst et al., ASH 2013

# Options for first line treatment in CLL




Cuneo A, personal view,
adapted from NCCN 2015; Hallek M. Am J Hematolol 2015; Stilgenbauer S Education book ASCO 2015

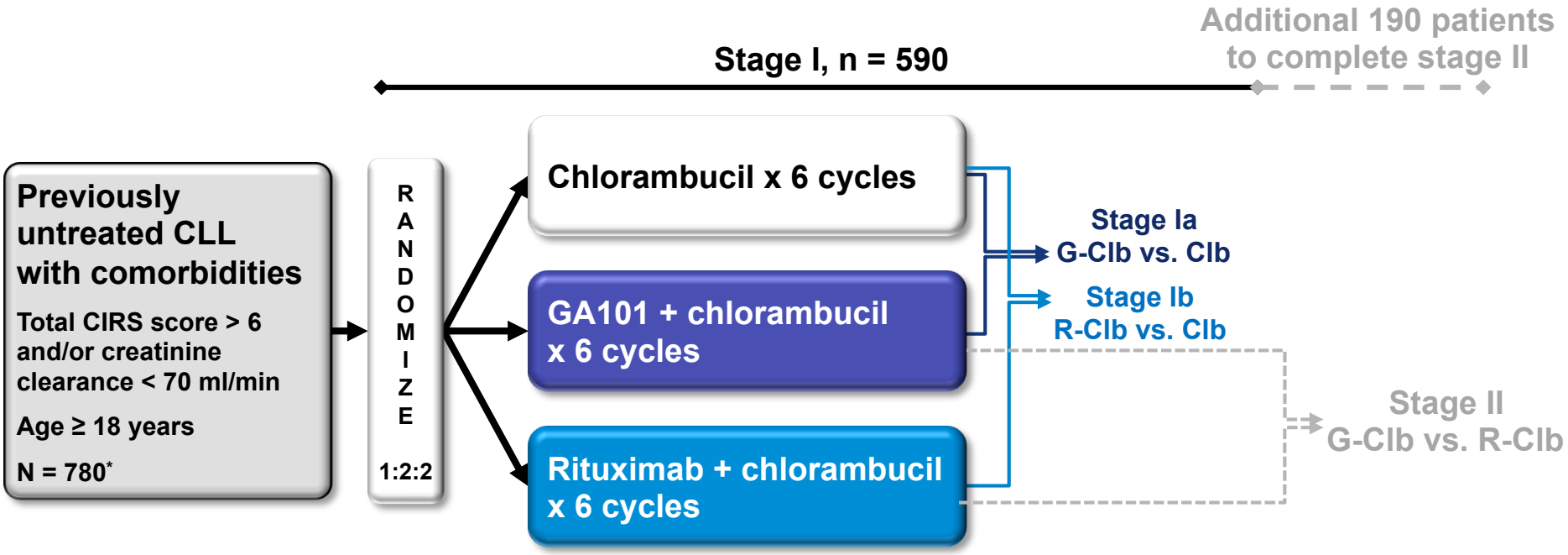
# Elderly CLL

## Efficacy of chlorambucil + Rituximab as first line treatment

| | No. of patients | Median age | Total dose of Chlor | %CR/CRi | Median PFS (months) |
|---|---|---|---|---|---|
|  | 100 | 70 | 420 mg/ sqm | 10 | 23,5 |
|  | 85 | 70 | 448 mg/ sqm | 19 | 34,7 |
|  | 233 | 73 | 6 mg / Kg | 8,3 | 15,7 |

UK: Hillmen P, JCO, Mar 17. [Epub ahead of print] 2014
Italy: Foà R on behalf of the GIMEMA group: Am J Hematol. 2014;89: 480-6
CLL11: Goede V, on behalf of CCLLSG: N Engl J Med. 2014;370:1101-10

# CLL11 Phase III: Study design



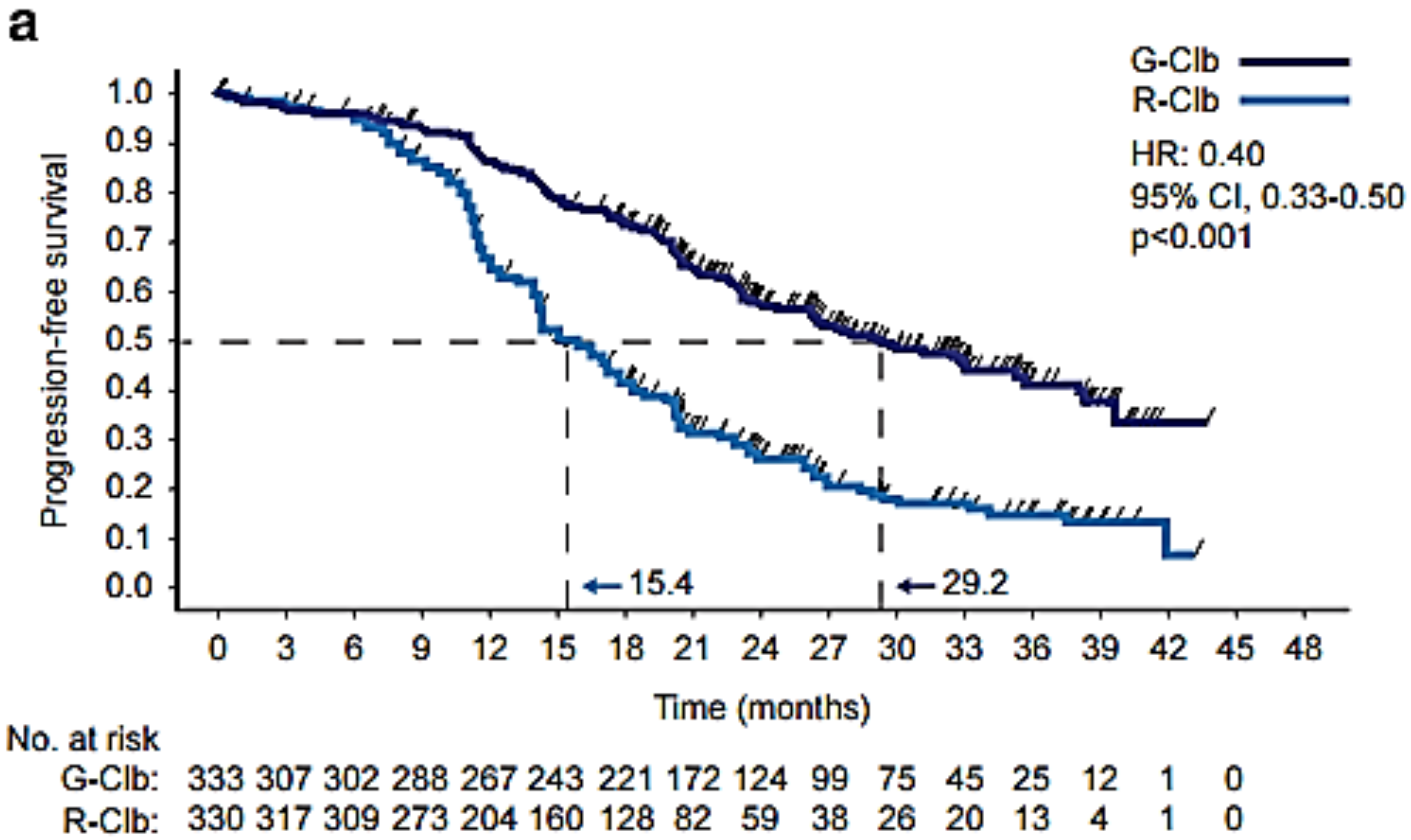

GA101: 1,000 mg Days 1, 8, and 15 Cycle 1; Day 1 Cycles 2–6, every 28 days

Rituximab: 375 mg/m$^2$ Day 1 Cycle 1, 500 mg/m$^2$ Day 1 Cycles 2–6, every 28 days

Clb: 0.5 mg/kg Day 1 and Day 15 Cycle 1–6, every 28 days

Goede V, *et al*. *J Clin Oncol* 2013: 31 suppl: Abstract 7004 (presentation update).
www.clinicaltrials.gov NCT01010061.

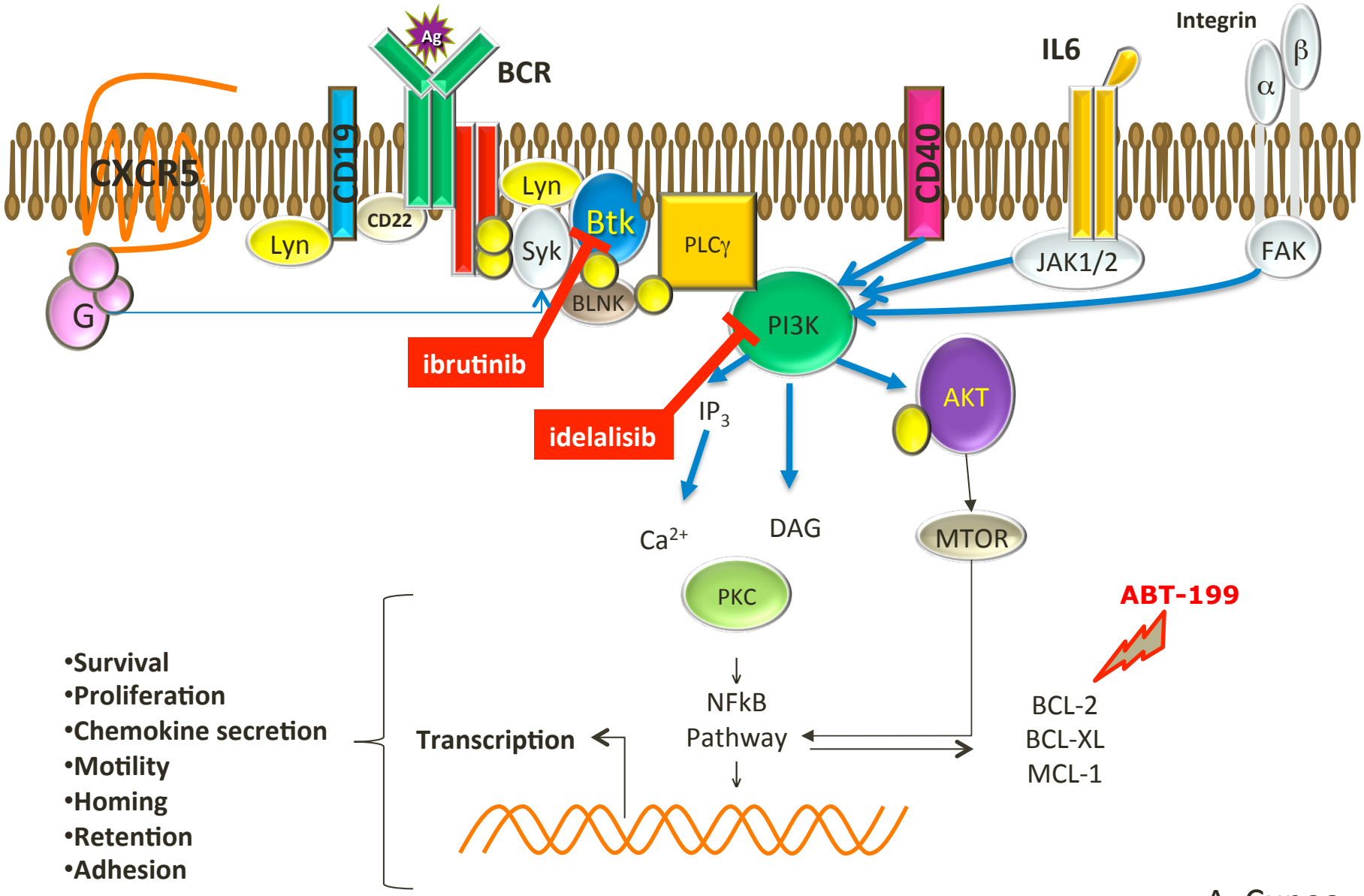
# Update results of CLL11




**Time to next antileukemic treatment was also longer with G-Clb than with R-Clb (42.7 versus 32.7 months, HR 0.54, 95% CI 0.40–0.72, Po0.001)**

Goede et al. Leukemia (2015) 29, 1602–1604; doi:10.1038/leu.2015.14; published online 17 February 2015

# IBRUTINIB and IDELALISIB + R are approved in Europe for first line treatment of CLL with 17p-/TP53 mutations




A. Cuneo

# La target therapy

First line

Relapsed/refractory CLL

Failure of a kinase targeted agent



# Ibrutinib for previously untreated and relapsed or refractory CLL with TP53 aberrations: a phase 2, single-arm trial.

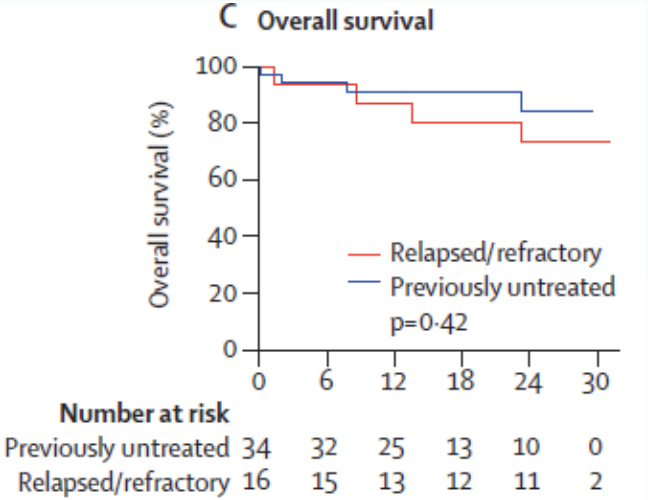
## Response to treatment

| | All evaluable patients (n=48) | Previously untreated patients (n=33) | Relapsed or refractory patients (n=15) |
|---|---|---|---|
| **Response at 24 weeks** | | | |
| Complete response | .. | .. | .. |
| Partial response | 24 (50%) | 18 (55%) | 6 (40%) |
| Partial response with lymphocytosis | 20 (42%) | 14 (42%) | 6 (40%) |
| Stable disease | 3 (6%) | .. | 3 (20%) |
| Progressive disease | 1 (2%) | 1 (3%) | .. |
| **Best response** | | | |
| Complete response | 5 (10%) | 4 (12%) | 1 (7%) |
| Partial response | 32 (67%) | 23 (70%) | 9 (60%) |
| Partial response with lymphocytosis | 8 (17%) | 5 (15%) | 3 (20%) |
| Stable disease | 2 (4%) | .. | 2 (13%) |
| Progressive disease | 1 (2%) | 1 (3%) | |

Farooqui MZ et al, Lancet Oncol. 2015 Feb;16(2):169-76

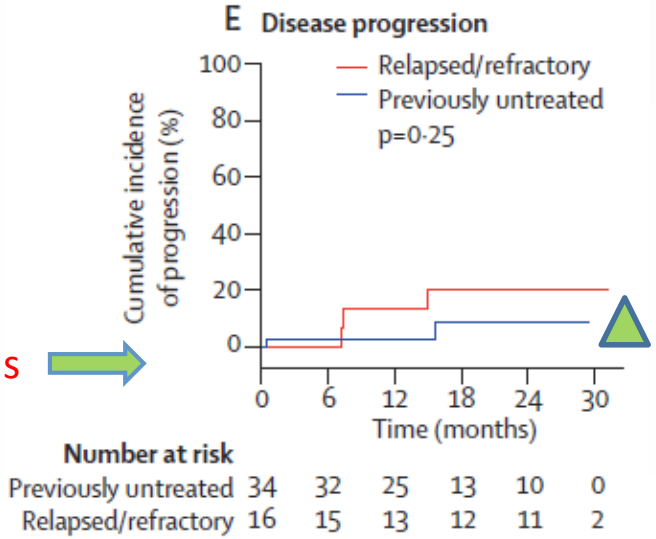
# Ibrutinib monotherapy in First-Line CLL: Impact of del(17p) on treatment response (Phase II)

Overall survival in subgroups by treatment history




Cumulative incidence of disease progression by treatment history

Median follow-up for the previously untreated cohort was 15 months

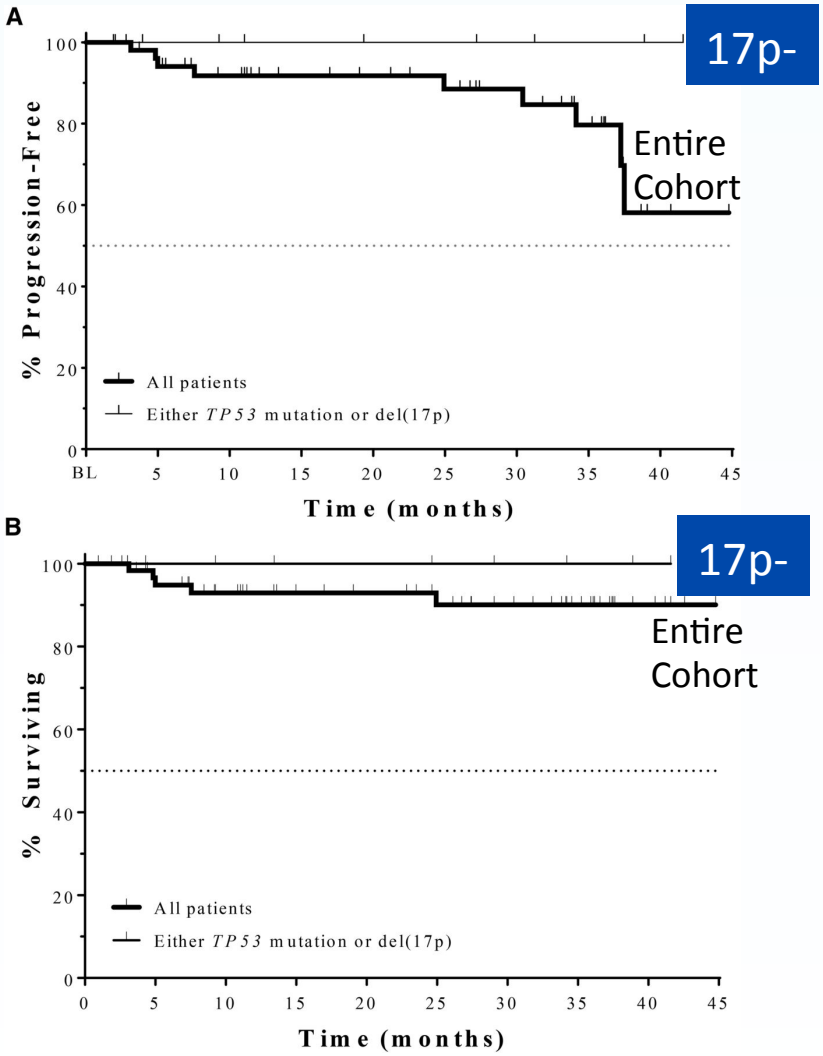



Farooqui M, *et al. Lancet Oncol* 2015;16:169–176.

# Idelalisib + Rituximab first-line therapy in the elderly

| Patients (%) | Idelalisib (n = 64)<br>with 17p-: 9 patients |
|---|---|
| **Treatment response[1]** | |
| ORR | 97* |
| CR | 19 |
| PR | 78 |
| **Safety[1]** | |
| Diarrhea/colitis (Grade 3) | 42 |
| Pneumonia (Grade 3) | 19 |
| AST/ALT (Grade 3) | 23 |

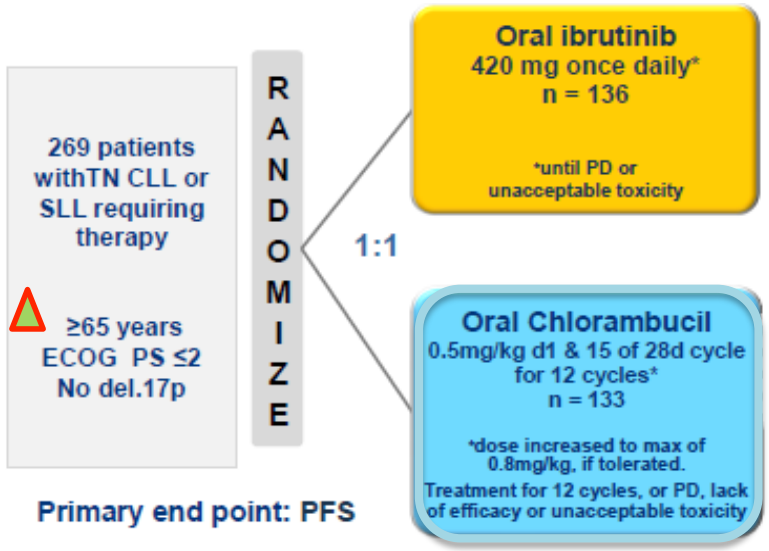
- Median age: **71 years** (65–90 years)[1]
- Median time to response: 1.9 months[1]
- Median time on idelalisib: **22.9 months**[1]
- Completed 48 weeks of therapy: 67%, most discontinuations due to AEs[1]



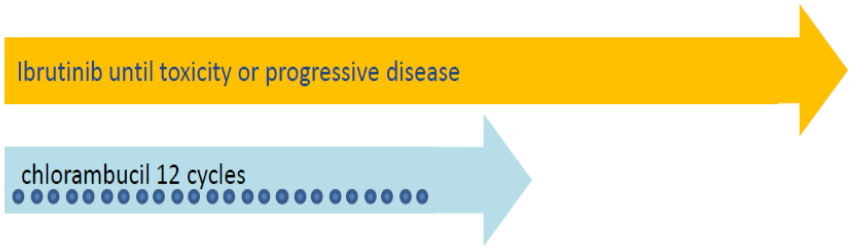

AE = adverse event; ALT = alanine transaminase; AST = aspartate transaminase.
* 3% of patients unevaluable.[1]

1. O'Brien S, *et al.* ASH 2014. Abstract 1994; 2. Lamanna N, *et al.* iwCLL 2013; 3. Zydelig SmPC, October 2014.

# Phase III RESONATE-2: Frontline Ibrutinib vs Chlorambucil in Elderly Patients With CLL




* ibrutinib for patients progressing on chlorambucil




**Baseline Characteristics**

| | Ibrutinib (N=136) | Chl (N=133) |
|---|---|---|
| Median age, years (range) | 73 (65-89) | 72 (65-90) |
| ≥70 years | 96 (71%) | 93 (70%) |
| ECOG PS 2 | 60 (44%) | 54 (41%) |
| CIRS >6 | 42 (31%) | 44 (33%) |
| CrCL <60ml/min | 60 (44%) | 67 (50%) |
| CLL | 123 (90%) | 126 (95%) |
| SLL | 13 (10%) | 7 (5%) |
| Rai stage III or IV | 60 (44%) | 62 (47%) |
| Bulky disease ≥5cm, | 54 (40%) | 40 (30%) |
| Del 11q22.3 | 29 (21%) | 25 (19%) |
| Unmutated IGHV | 58 (43%) | 60 (45%) |
| Baseline cytopenias, | 72 (53%) | 73 (55%) |

**Patient Disposition**

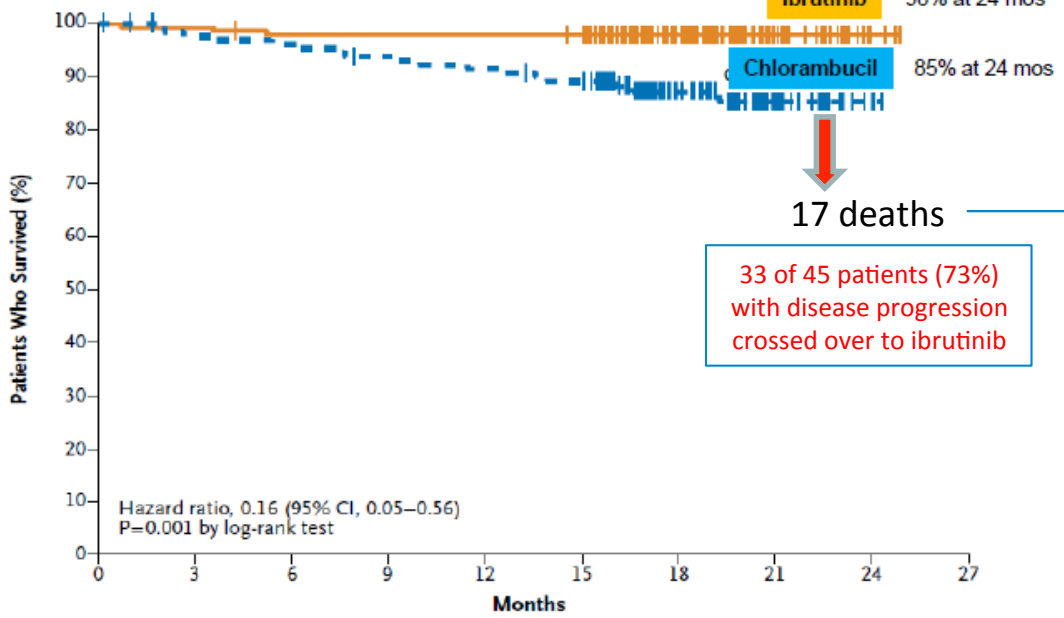
| | Ibrutinib (N=136)* | Chl (N=133)* |
|---|---|---|
| Medi.duration of follow-up, months | 18.4 | |
| Med.duration of treatment (range), months | 17.4 (0.7-24.7) | 7.1 (0.5-11.7) |
| Patients completing max.12 CHL cycles | - | 53 (40%) |
| Patients still on treatment at study closure | 118 | - |
| Patients on study follow up at study closure | 131 | 114 |
| Patients discontinued treatment | 17 | 79 |
| IRC confirmed disease progression | 2 | 6 |
| New anticancer therapy | 0 | 4 |
| Progressive disease | 0 | 11 |
| Lack of efficacy | 0 | 21 |
| Unacceptable toxicity/AE/death | 14 | 30 |
| Patient decision | 1 | 6 |
| Investigator decision | 0 | 37 |
| Other | 0 | 1 |

**1.5% vs 32%**

**10% vs 22,5%**

Burger et al. , NEJM 2015; Tedeschi et al., ASH 2015

# Phase III RESONATE-2: Frontline Ibrutinib vs Chlorambucil in Elderly Patients With CLL




3 deaths

- 2 unknown causes
  - 73 y.o. at home
  - 87 y.o. during sleep
- 1 klebsiella sepsis

17 deaths

33 of 45 patients (73%) with disease progression crossed over to ibrutinib

5 disease progressions, including 2 switched to ibrutinib

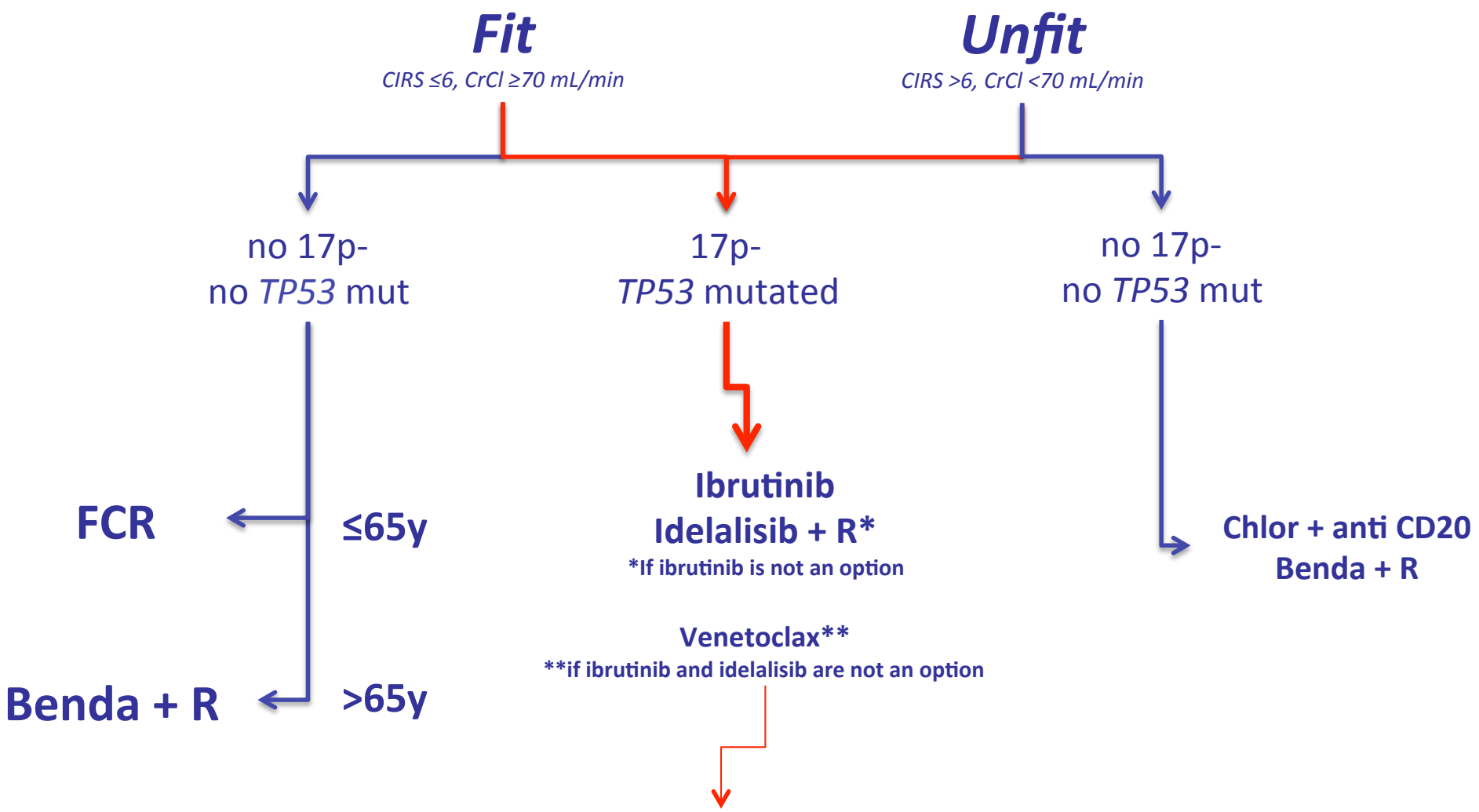
12 other causes, including 2 switched to ibrutinib

- 3 infections
- 2 strokes
- 2 secondary cancers
- 1 toxic hepatitis
- 1 PTE pulmonary
- 1 worsening of the general condition
- 2 unknown causes

- 84% reduction in the risk of death (HR 0.16; 95%CI, 0.05-0.56; P = 0.001)

Burger et al. , NEJM 2015; Tedeschi et al., ASH 2015

# Options for first line treatment in CLL




Cuneo A, personal view,
adapted from NCCN 2015; Hallek M. Am J Hematolol 2015; Stilgenbauer S Education book ASCO 2015

# La target therapy

First line

Relapsed/refractory CLL

Failure of a kinase targeted agent



# Poor outcome with conventional chemo/immunotherapy in fludarabine-refractory CLL and in patients with early relapse

| | Various regimens at MDACC in FA refractory and F refractory with bulky adenopathy | Ofatumumab in FA refractory and F refractory with bulky adenopathy | Various regimen in patients treated in GCLLSG protocols (***) |
|---|---|---|---|
| No. of patients | 99 | 138 | 305 |
| No. previous regimens (median) | NA | 4-5 | 1-2 (early relapse) |
| Percentage | | | |
| CR | 0 | 0-1 | NA |
| PR | 23 | 47-58 | NA |
| Months | | | |
| PFS | 2-3 | 5,7-5,9 | 11-18 |
| Survival | 9 | 13,7-15,4 | 30-61 |

Modified from: Cuneo A et al, Cancer Med, 2014

***Cramer P et al. Haematologica 2015 [Epub ahead of print]

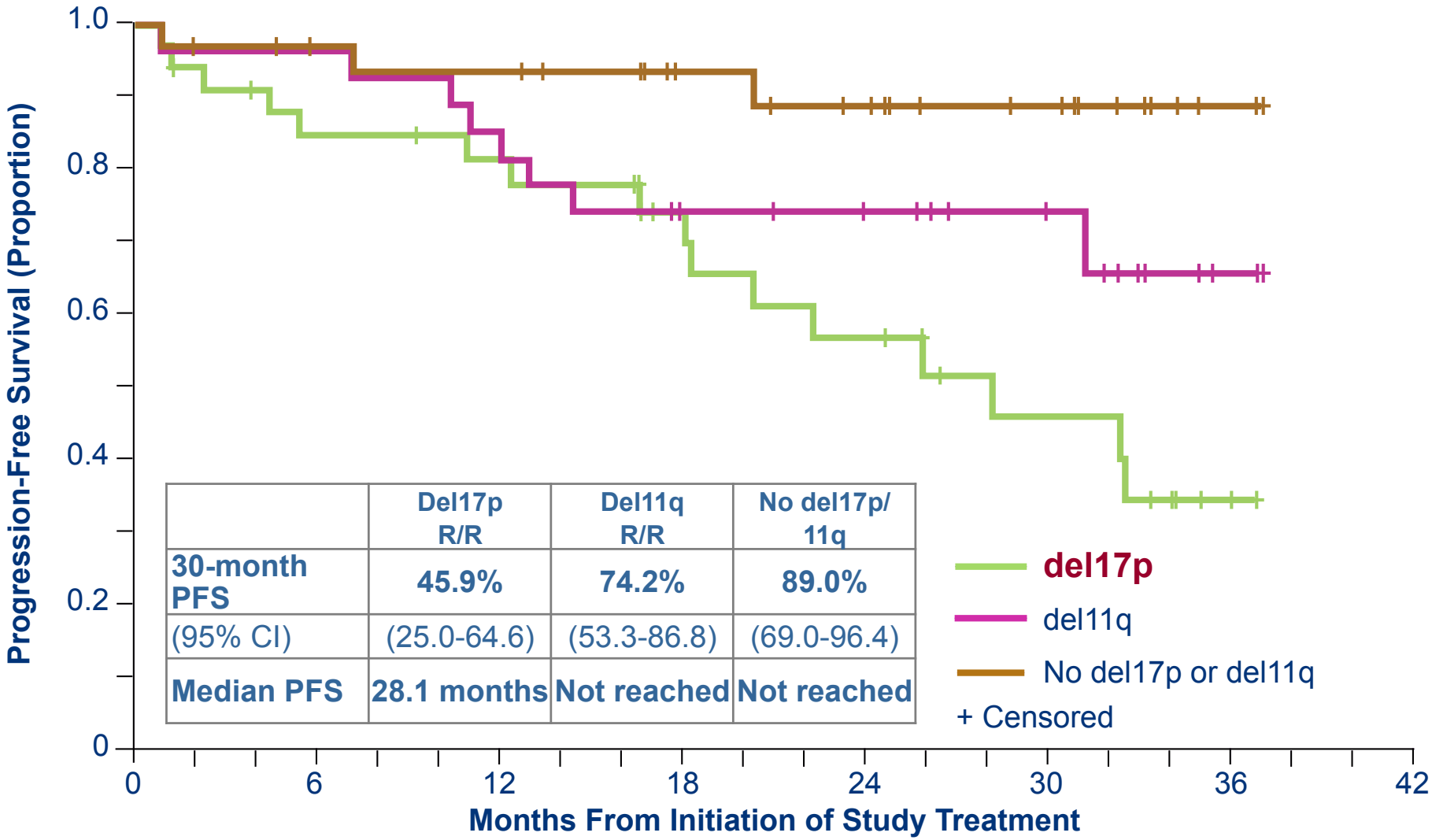
# ORR and PFS

## Ibrutinib (+/- R) in relapsed / refractory CLL

| Study | No. pts / median follow-up | % responding | PFS | % on treatment | % discontinued | | |
|---|---|---|---|---|---|---|---|
| | | | | | Disease Progression | Adverse Event | Other* |
| Byrd, NEJM 2013 | 85<br>21 months | 89%<br>71% NCI | 75% at 26 months | 64% | 13% | 8% | 16% |
| Byrd, NEJM 2014 | 195<br>9 months | 63%<br>43% NCI | 88% at 6 months | 86% | 5% | 4% | 5% |
| Burger, Lancet Oncol 2014 | 40<br>17 months | 95%<br>87% NCI | 78% at 18 months | 77% | 8% | 5% | 10% |
| Byrd JC Blood 2015 | 101<br>36 months | 90% | 69% at 30 months | 53% | 21% | 12% | 27% |

Byrd 2013: ibrutinib in rel/ref CLL
Byrd 2014: random ibrutinib vs ofatumumab in rel/ref CLL
Burger 2014: ibrutinib and rituximab in high risk CLL (4/40 pts were untreated and had 17p-rel)
O'Brien 2014: ASCO meeting 3 year post initiation of ibrutinib
* Stem cell transplant, Subject decision, investigator decision, 13% death

# PFS by Cytogenetics (FISH) in R/R Population




| | Del17p R/R | Del11q R/R | No del17p/ 11q |
|---|---|---|---|
| 30-month PFS | 45.9% | 74.2% | 89.0% |
| (95% CI) | (25.0-64.6) | (53.3-86.8) | (69.0-96.4) |
| Median PFS | 28.1 months | Not reached | Not reached |

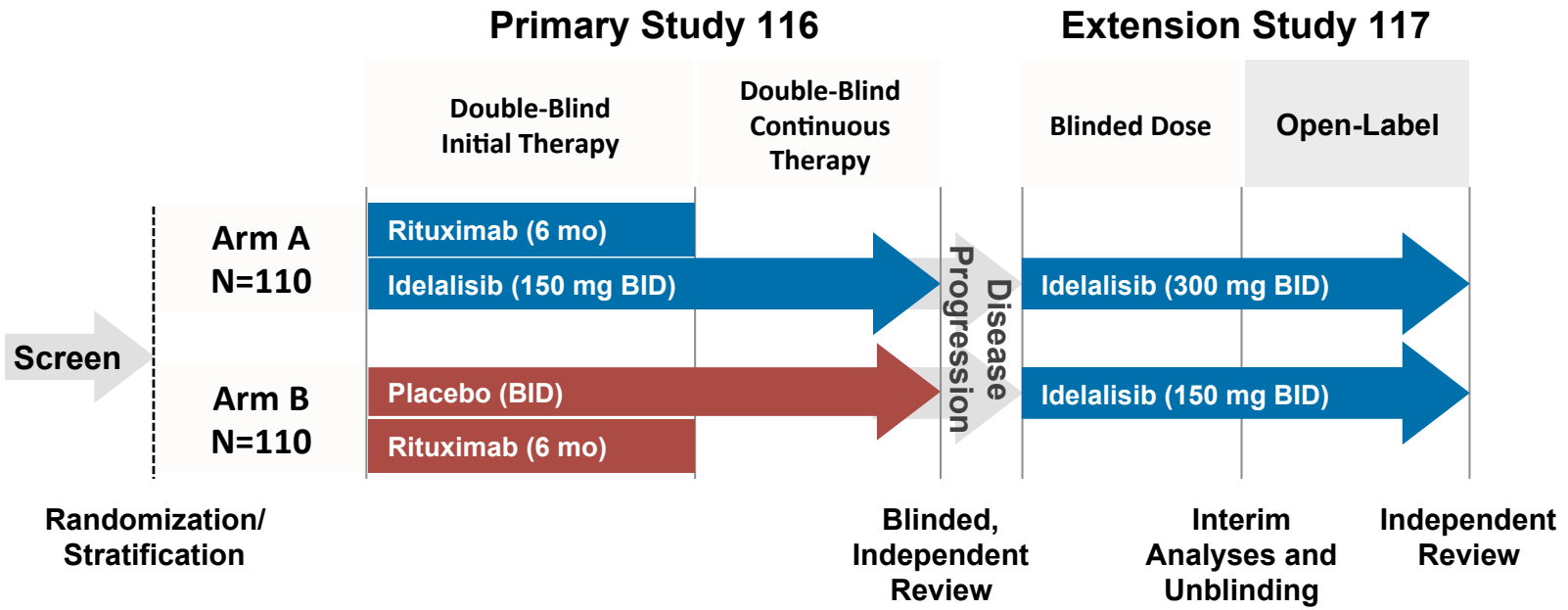
O'Brien S, et al. ASCO 2014; Oral/Abstract #7014.
Published by Byrd J et al. Blood 2015;125:2497-2506

Study GS-US-312-0116 (Phase 3)

# Idelalisib and Rituximab in rel/ref

**Population:**

Relapsed CLL warranting treatment (iwCLL); progression < 24 mo since last treatment




| | Median Follow-up, months | | |
|---|---|---|---|
| | IDELA + R | PBO + R | |
| 1st Interim Analysis | 4 | 4 | DMC halted trial (Furman NEJM 2014) 50% events |
| 2nd Interim Analysis | 6 | 5 | Blind ended (Coutre ASCO 2014) 63% events<br>• Arm A continues (amendment to be all 150mg)<br>• Arm B crosses over |
| Update | 13 | 11 | PFS, OS by subgroup analysis |

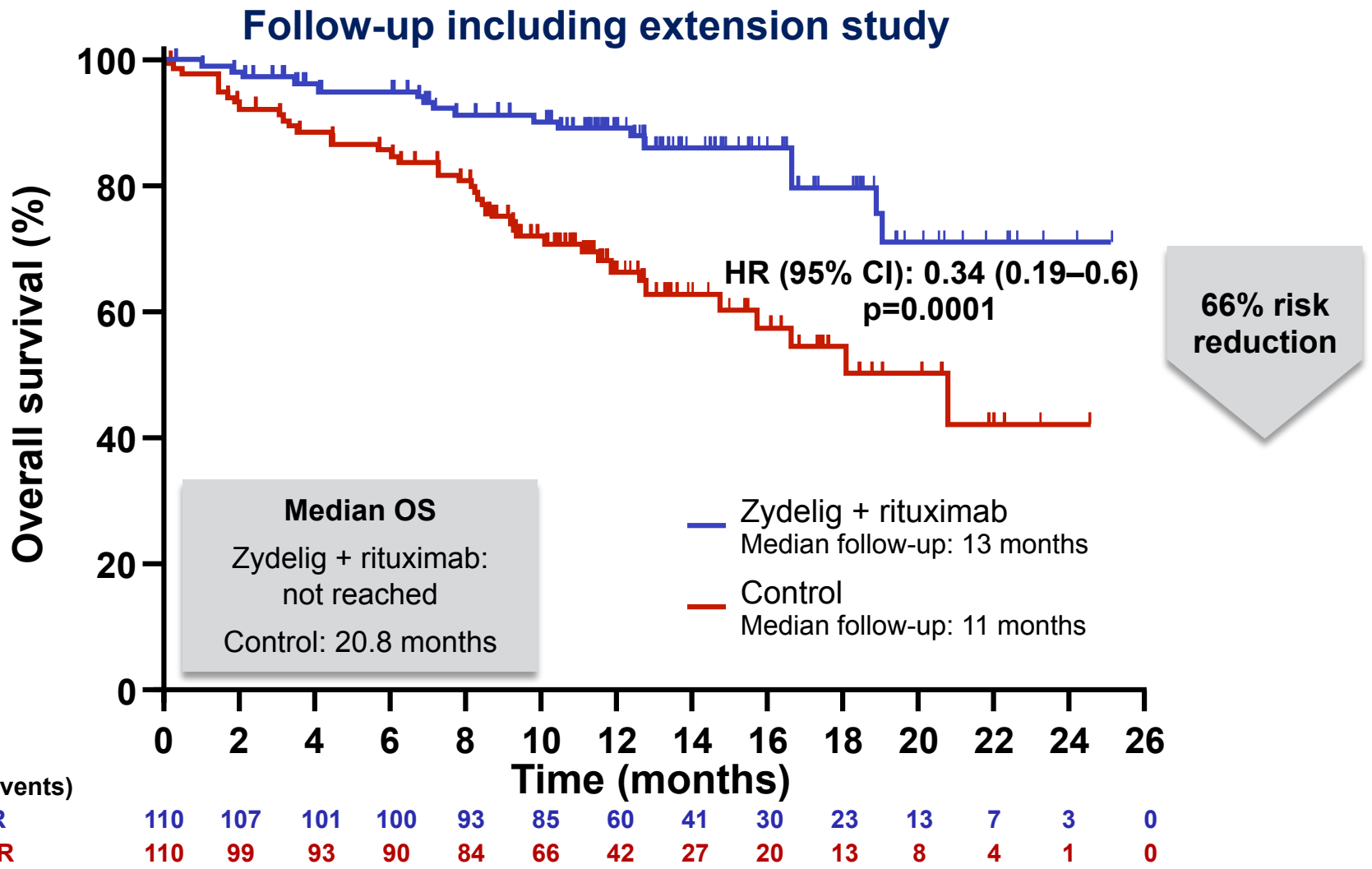
# Patients included in Study 116 were elderly, had a poor performance status and cytopenias

| | Typical relapsed CLL patient | Ibrutinib RESONATE population[3] | Zydelig + R Study 116 population[6] | Ofatumumab licensing study[4] (FA-ref/BF-ref) |
|---|---|---|---|---|
| Trial design | Registry | Open-label randomised | Double-blind placebo controlled | Non-randomised Phase II |
| Median age (years) | 72.5[1a] | 67 | 71 | 64/62 |
| ECOG PS, 1–3 (%) | N/A | 59 | 87 | 65 |
| ECOG PS, 2–3 (%) | 23.2[2b] | 0 | 28 | N/A |
| del(17p) and/or *TP53* mutation (%) | 42[5] | 33 | 43 | 29/18 |
| Blood count criteria | N/A | Platelets ≥30 x $10^9$/L<br>Neutrophils ≥0.75 x $10^9$/L | No restrictions<br>35% Grade 3 or 4 cytopenias | No blood counts or transfusion restrictions |

[a] German Tumour Registry Lymphatic Neoplasms (patients recruited between 2009 and 2013) at start of second-line therapy (n=186)
[b] Ipsos Healthcare Global Oncology Monitor real world evaluation of CLL patient from Germany, France, UK, Spain and Italy (n=5163)
[c] Equivalent to Karnofsky score 0–70
ECOG: Eastern Cooperative Oncology Group


1. Knauf W, *et al. Hematol Oncol* 2014 [published online ahead of print].
2. Ysebaert L, *et al.* EHA 2014 abstract P1275).
3. Byrd JC, *et al. N Engl J Med* 2014; 371–323 (incl online suppl).
4. Hx-CD20-406 Wierda WG, *et al. J Clin Oncol* 2010; 28:1749–1755.
5. Lozanski G, *et al. Blood* 2004; 103:3278–3281.
6. Furman RR, *et al. N Engl J Med* 2014; 370:997–1007.

# Difference in efficacy of Zydelig + rituximab maintained despite crossover in the extension study



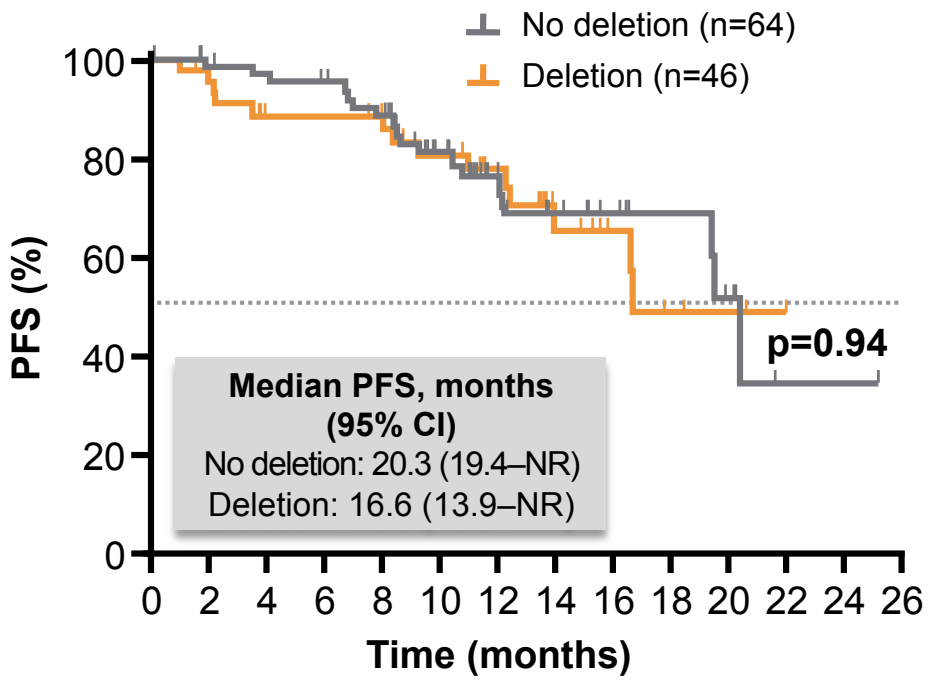

As randomised, including crossover study

Sharman JP, *et al*. ASH 2014 (Abstract 330; oral presentation).

# Del(17p) or *TP53* prognostic factors do not impact on the efficacy of Zydelig + R

## Second interim analysis: PFS

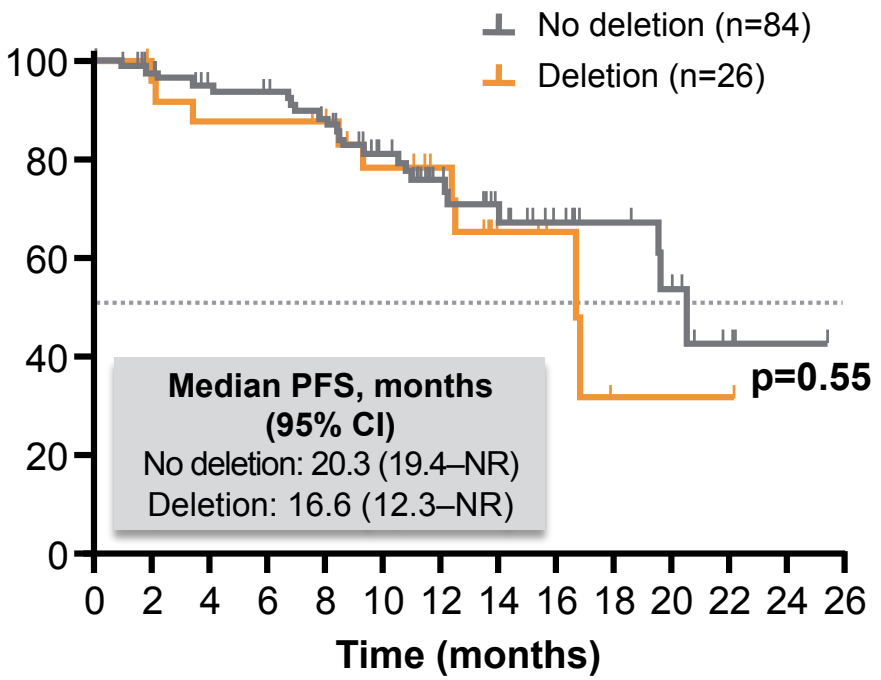
### Del(17p)/*TP53* mutation




**Number at risk**

| | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| No del | 64 | 61 | 59 | 59 | 52 | 37 | 21 | 14 | 11 | 8 | 4 | 1 | 1 | 1 |
| Del | 46 | 41 | 36 | 36 | 33 | 30 | 22 | 12 | 8 | 4 | 3 | 0 | 0 | 0 |

### Del(17p)




| | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| No del | 84 | 78 | 73 | 71 | 65 | 49 | 31 | 20 | 15 | 11 | 6 | 1 | 1 | 1 |
| Del | 26 | 23 | 22 | 22 | 20 | 17 | 12 | 6 | 4 | 1 | 1 | 0 | 0 | – |

Sharman JP, *et al.* ASH 2014 (Abstract 330; oral presentation).

# FDA approves Venetoclax on april 11th 2016 for patients with CLL and 17p- who have been treated with at least one prior therapy

## Baseline Characteristics

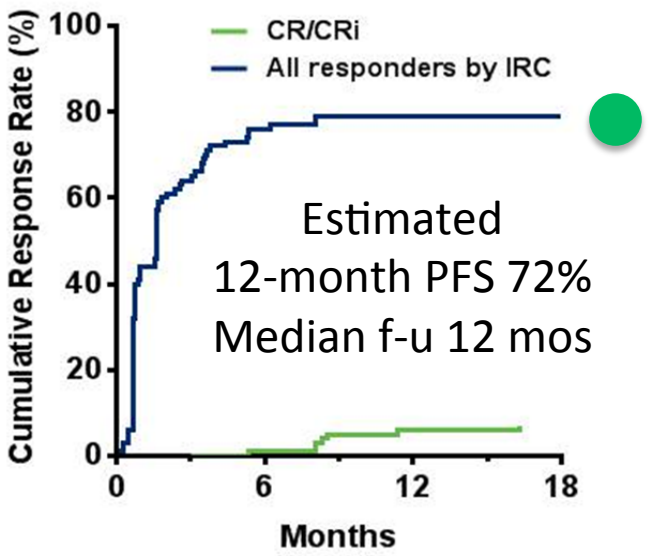
| N=107[a] | n (%) |
|---|---|
| Median age (years), range | 67, 37–85 |
| Male | 70 (65) |
| Prior therapies: median, range | 2, 1–10 |
| Prior bendamustine / refractory | 54 (50) / 38 (70) |
| Prior fludarabine / refractory | 78 (73) / 34 (44) |
| Prior CD20 mAb | 90 (84) |
| ECOG grade 1/2 | 56 (52) / 9 (8) |
| One or more nodes ≥ 5 cm | 57 (53) |
| ALC ≥25 x $10^9$/L | 54 (51) |
| TLS risk category | |
| Low | 19 (18) |
| Medium | 43 (40) |
| High | 45 (42) |
| Rai stage III or IV | 51(48) |
| *IGHV* unmutated | 30 (81) |

[a]Includes 1 patient without 17p–; [b]Low defined as ALC<25 and nodes <5cm, medium defined as ALC>20 OR nodes ≥5 and < 10cm), high defined as (ALC>25 nodes ≥5 and < 10cm OR nodes > 10cm

Adapted from Stilgenbauer et al. Oral Presentation at ASH 2015, Orlando, Florida. 6

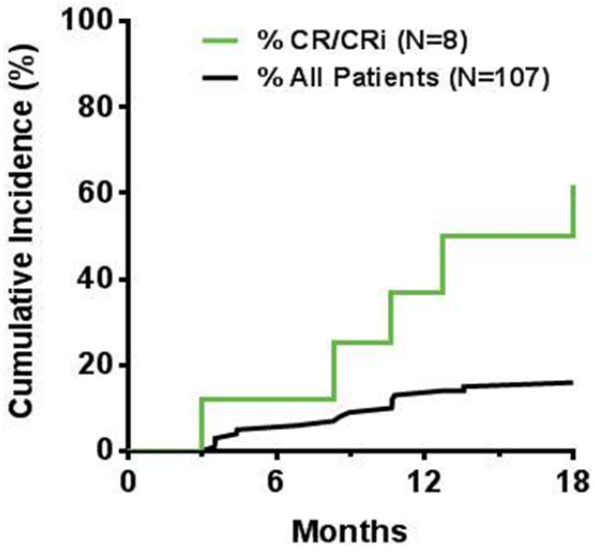
# Cumulative Incidence of Response

## iwCLL Response




- Median time-to-first response: 0.8 months (0.1–8.1)
- Median time to CR/CRi: 8.2 months (3.0–16.3)

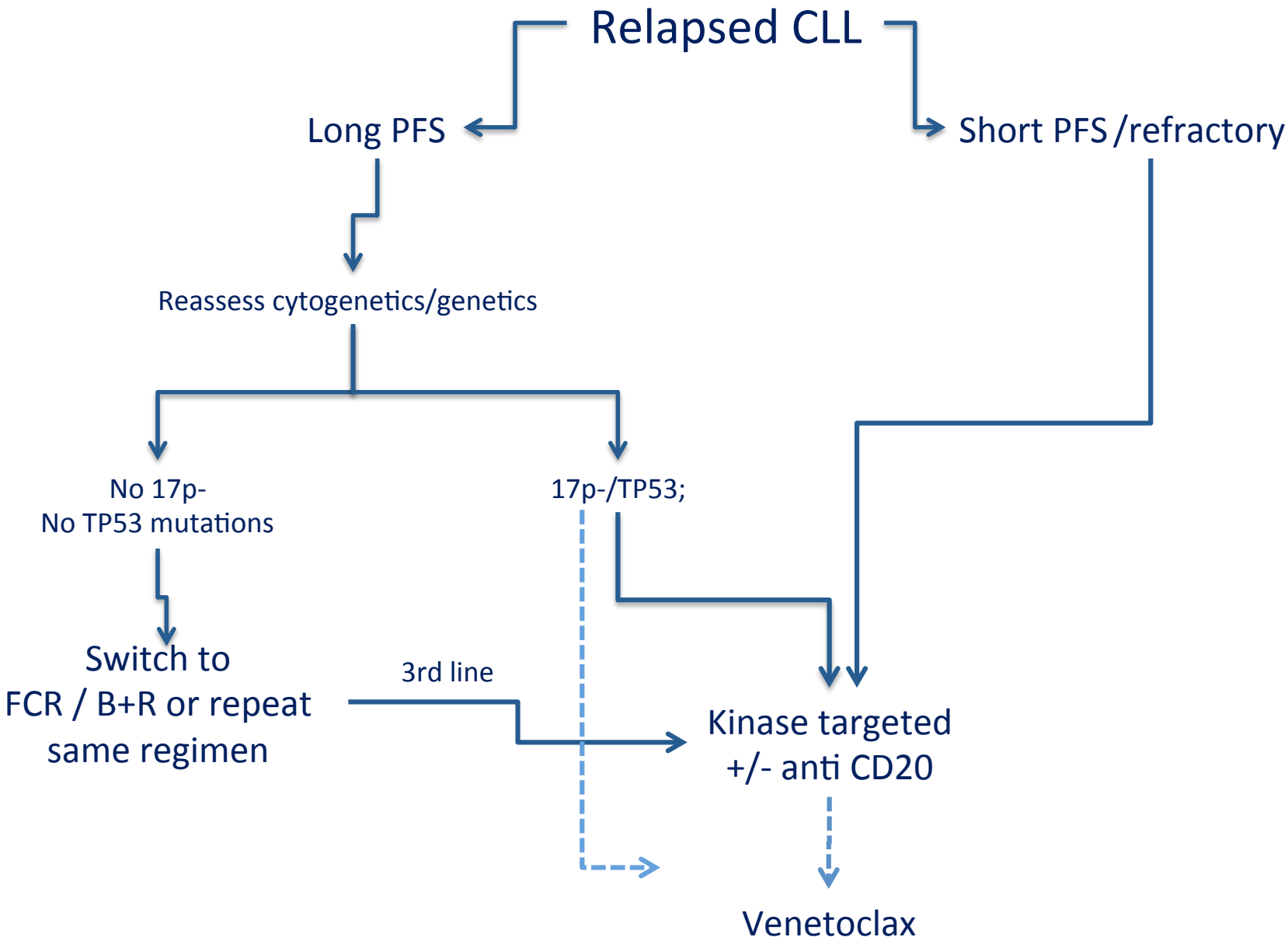
## MRD-Negativity




- Of 45 patients tested, 18 achieved MRD-negativity in peripheral blood

Adapted from Stilgenbauer et al. Oral Presentation at ASH 2015, Orlando, Florida. [11]

# Proposed treatment algorithm for relapsed/refractory CLL toady



# La target therapy

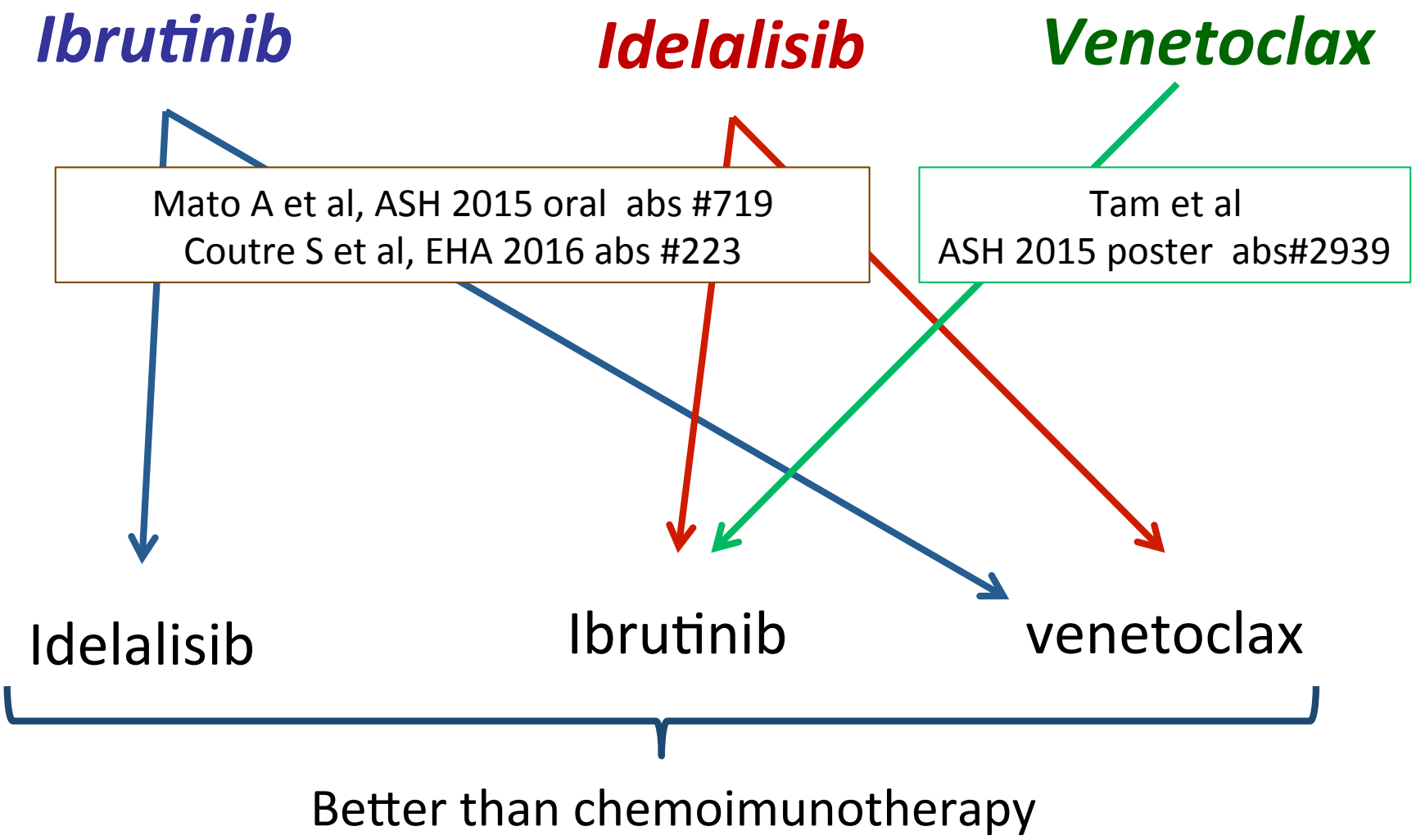
First line

Relapsed/refractory CLL

Failure of a kinase targeted agent



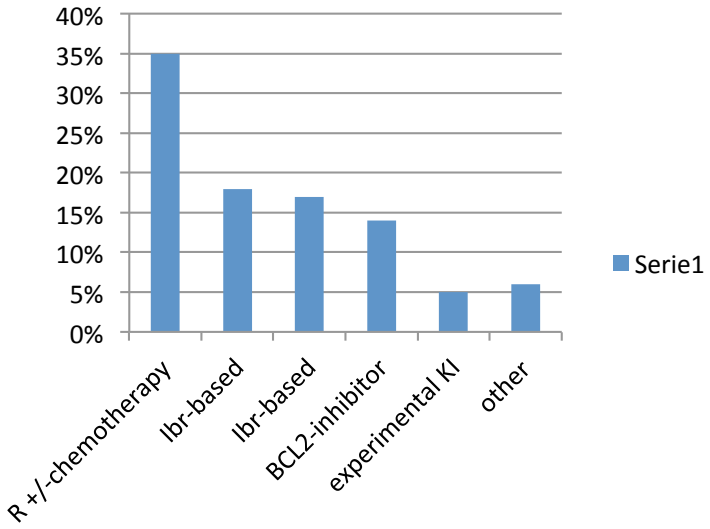
# Possibility to cross in case of discontinuation (toxicity or progression)

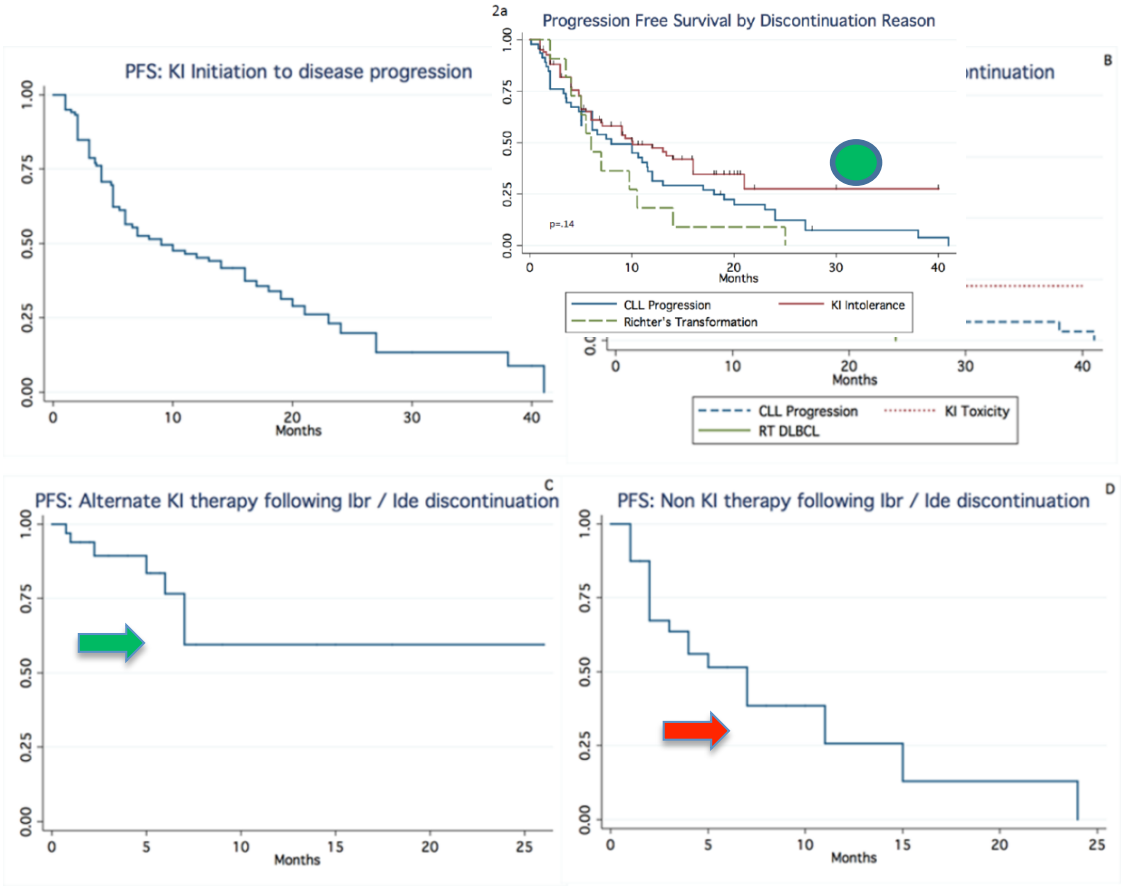


# Type of treatment and outcome after KI discontinuation

123 patients

Mato A et al, ASH abs #719; Blood 2016

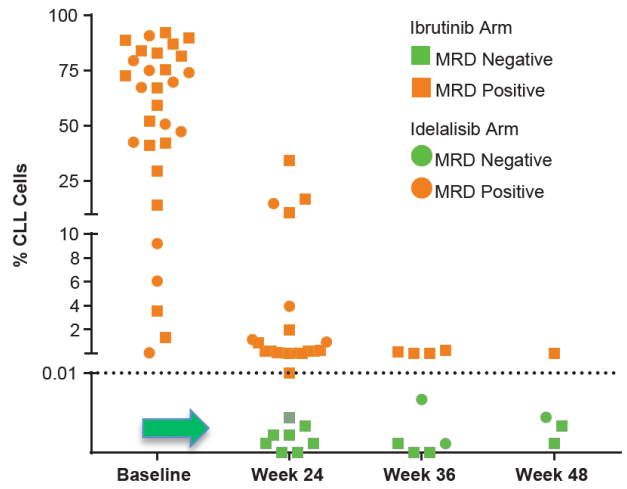


# Type of treatment and outcome after KI discontinuation

64 patients treated by venetoclax
Coutre et al., EHA 2016, #P559

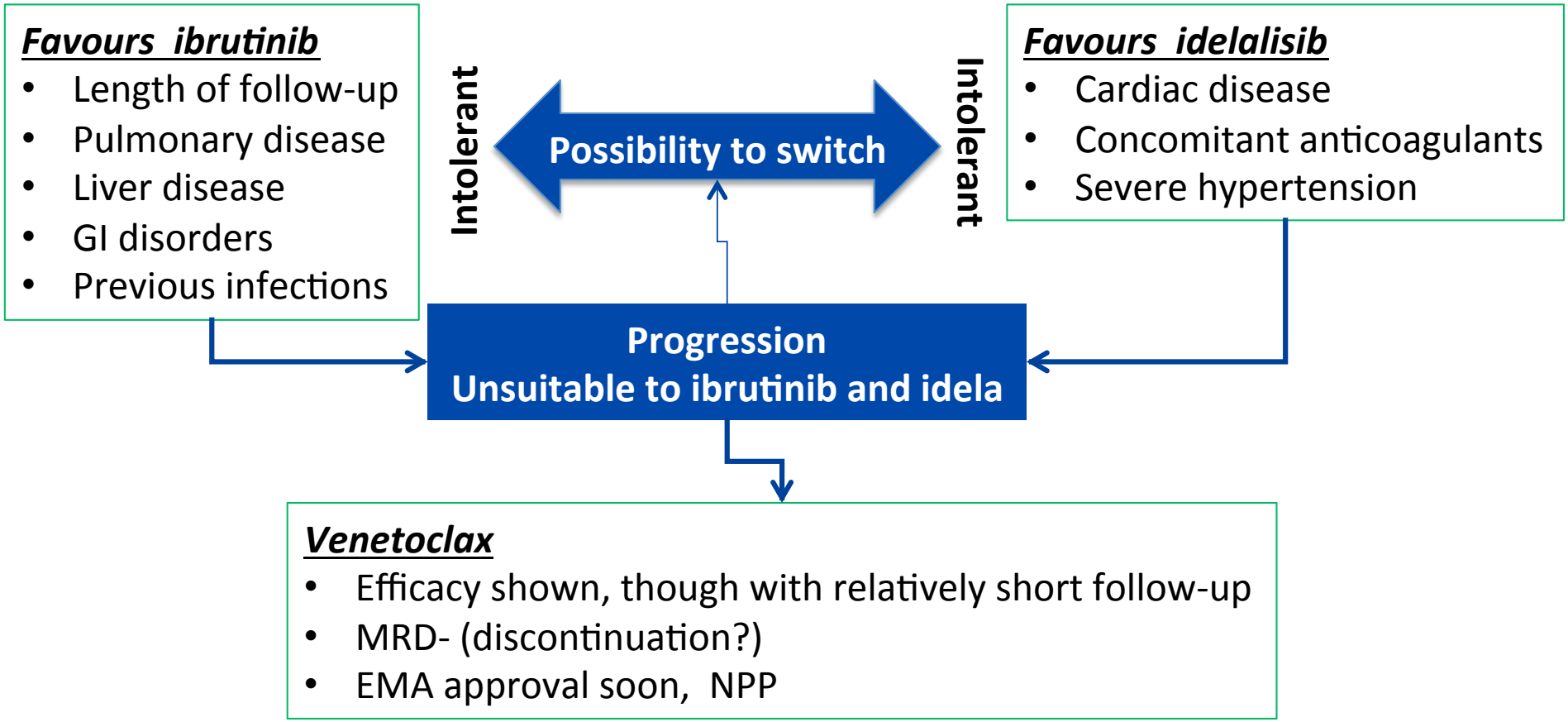
| | Ibrutinib Arm n=43 | | Idelalisib Arm n=21 | |
|---|---|---|---|---|
| | Assessed by | | Assessed by | |
| Best response, n (%) | Investigator | IRC | Investigator | IRC |
| ORR | 26 (61) | 30 (70) | 7 (33) | 10 (48) |
| CR / CRi | 2 (5) / 0 | 0 / 1 (2) | 1 (5) / 1 (5) | 0 / 0 |
| nPR | 2 (5) | 0 | 0 | 0 |
| PR | 22 (51) | 29 (67) | 5 (24) | 10 (47) |
| Stable disease | 12 (28) | - | 12 (57) | - |
| Disease progression | 1 (2) | - | 1 (5) | - |
| Non-responder | - | 13 (30) | - | 11 (52) |



# Which kinase targeted treatment in clinical practice in Italy today?

There are no solid scientific data allowing for a comparison to be made between drugs

**Yet a choice has to be made….**




GI: gastrointestinal; NPP: named patient program