
# LEUCEMIA LINFATICA CRONICA

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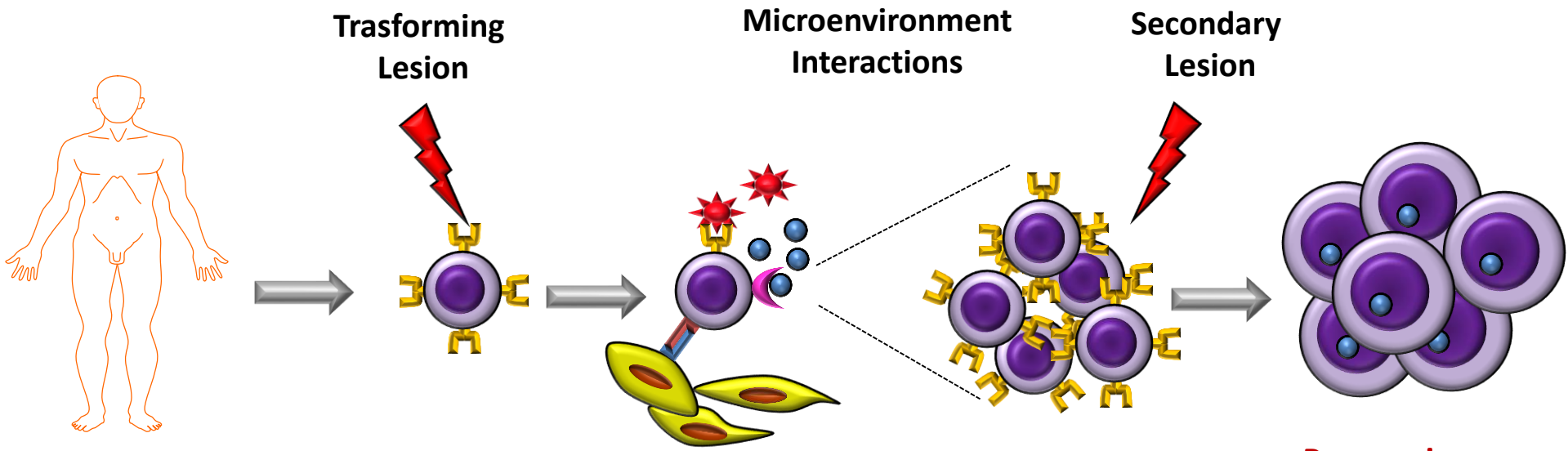
**Novara**

# Outline

- **CLL biology and pathogenesis**
- Prognostication and prediction
- Chemoimmunotherapy
- Novel agents

# Pathogenesis of CLL




**Predisposition**

Polygenic
*IRF4*
Other

**Initiation**

BCR
del13q
+12
*MYD88*

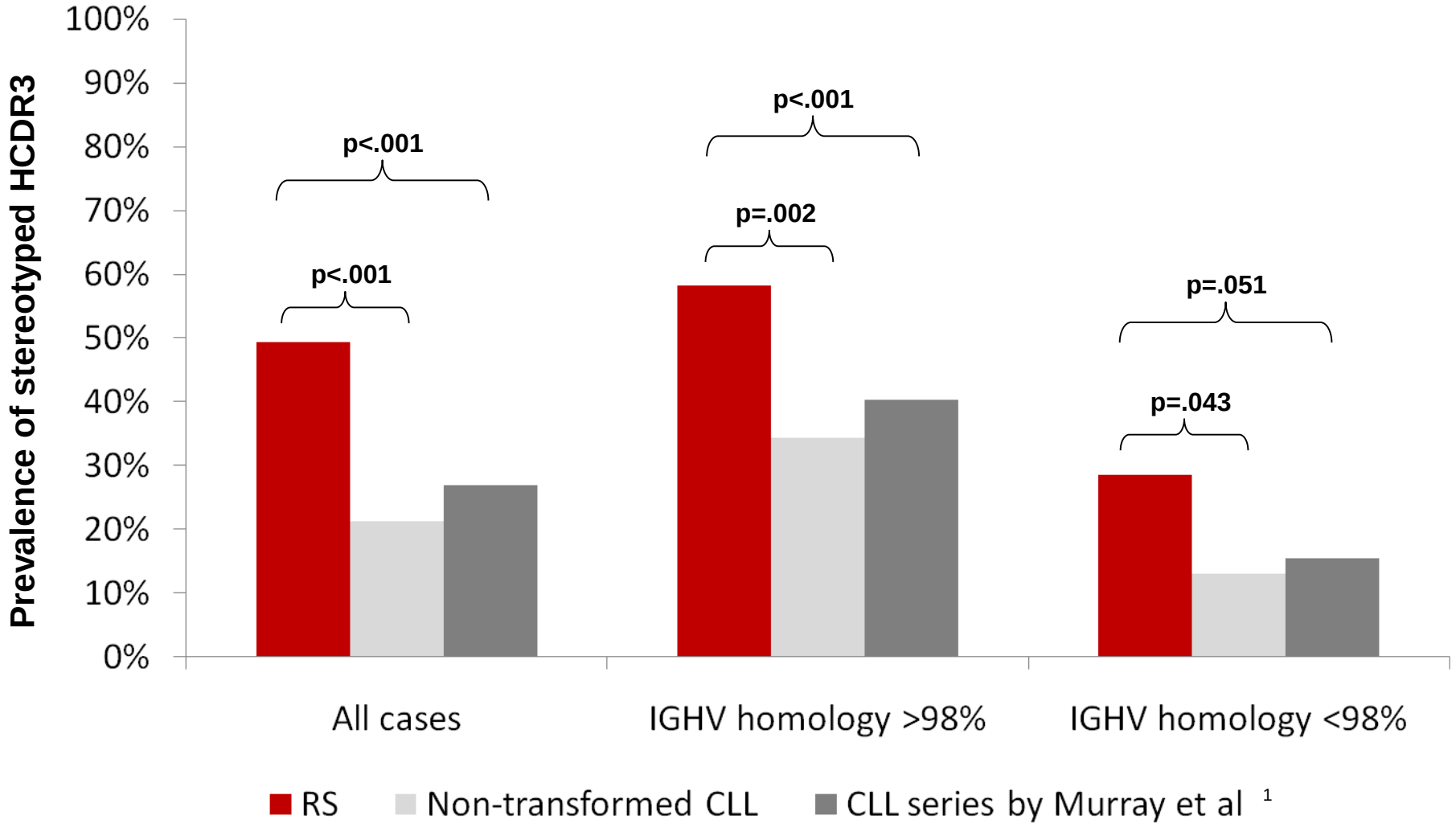
**Promotion/Accumulation**

Signaling pathways
BCR
NF-kB
TLR
CD38
VLA-4 integrins
NOTCH
CXCR4

**Progression**
**Chemorefractoriness**
**Transformation**

*TP53*
*NOTCH1*
*SF3B1*
*BIRC3*
*ATM*
*MYC*
*CDKN2A*

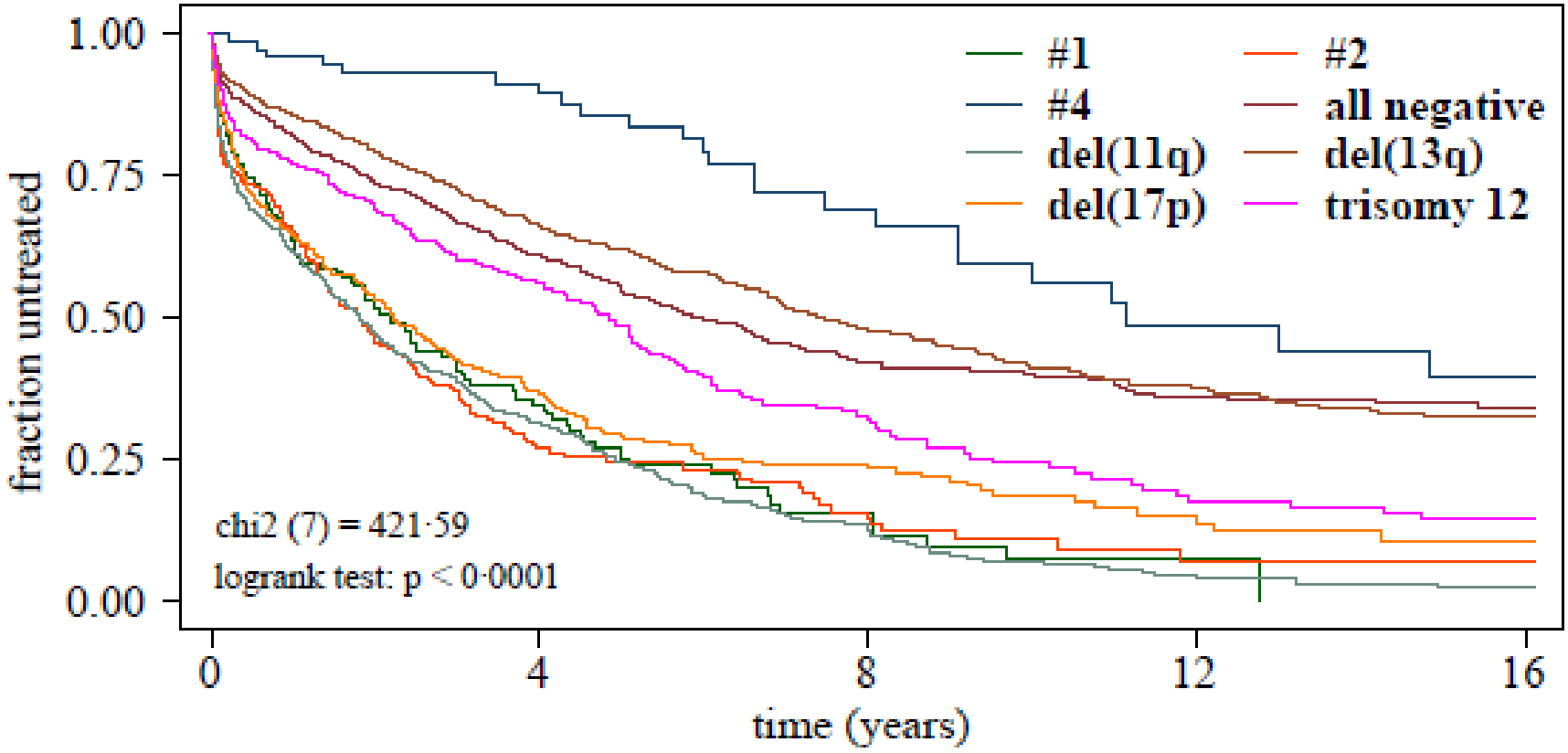
# CLL and RS carry stereotyped HCDR3 at high frequency




**Rossi et al, Clin Cancer Res 2009**

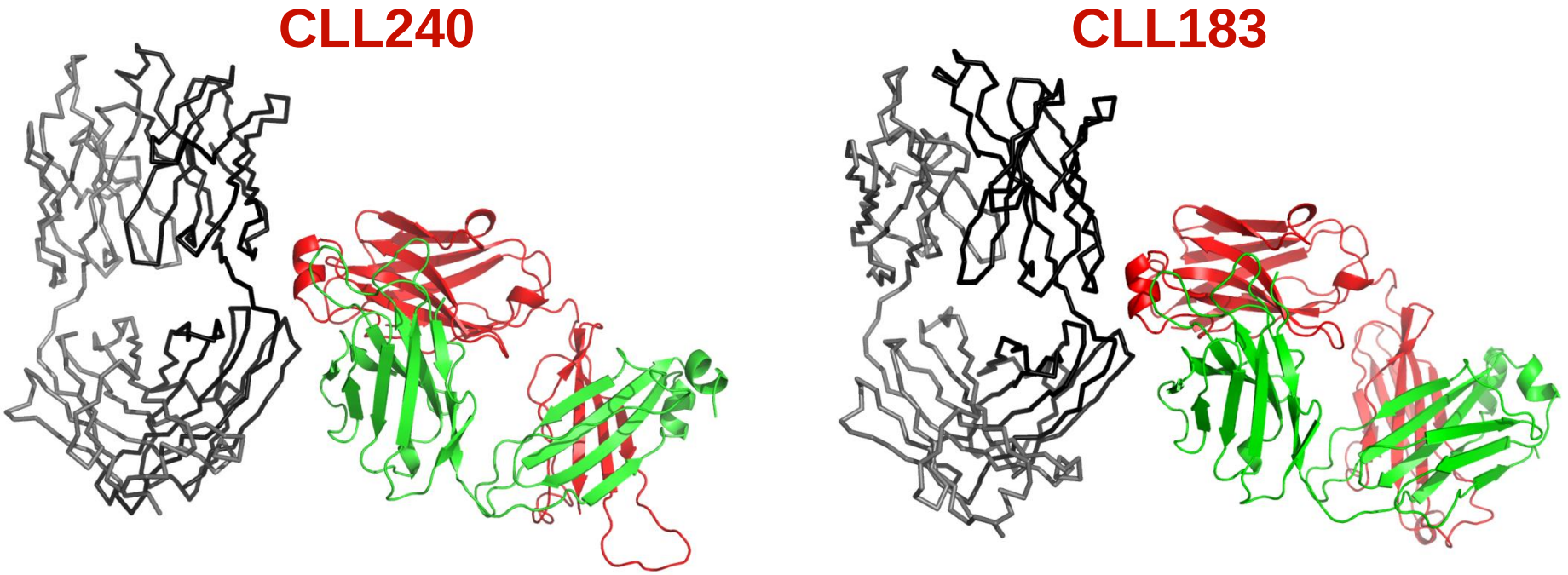
[1]Murray et al, Blood 2008

# Stereotyped subsets have a distinct clinical course




*Baliakas et al. Lancet Haematology 2014*

# Subset 4: self recognition of CLL Fab




**Interaction with the V-C hinge (VH FR1 and CH1 domains)**

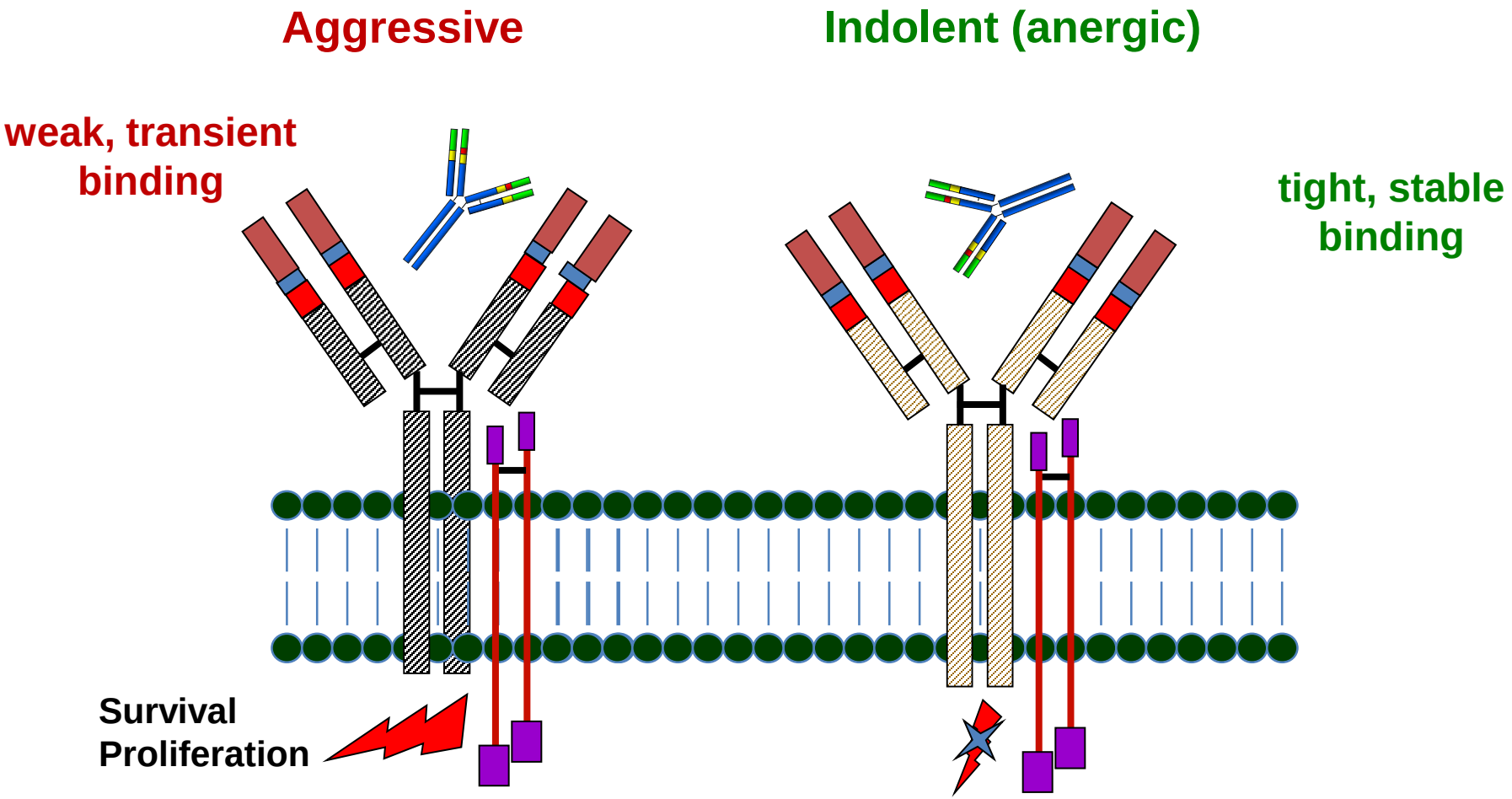
- First description of homotypic association process in BcRs that resembles antibody-antigen recognition and leads to intracellular signaling in CLL cells.

- BcR IGs from CLL cases with different prognosis bind homotypically via their combining sites to specific, diverse epitopes to initiate intracellular signalling

*Gounari et al, EHA-21 abstract #116, 2016*
*Minici, Gounari et al, submitted, 2016*

*Courtesy of P. Ghia*

# BCR signalling in CLL is heterogeneous




Tight, persistent binding was noted in cases with indolent disease whereas weaker interactions characterized the aggressive progressive cases

*Gounari et al, EHA-21 abstract #116, 2016*

*Courtesy of P. Ghia*

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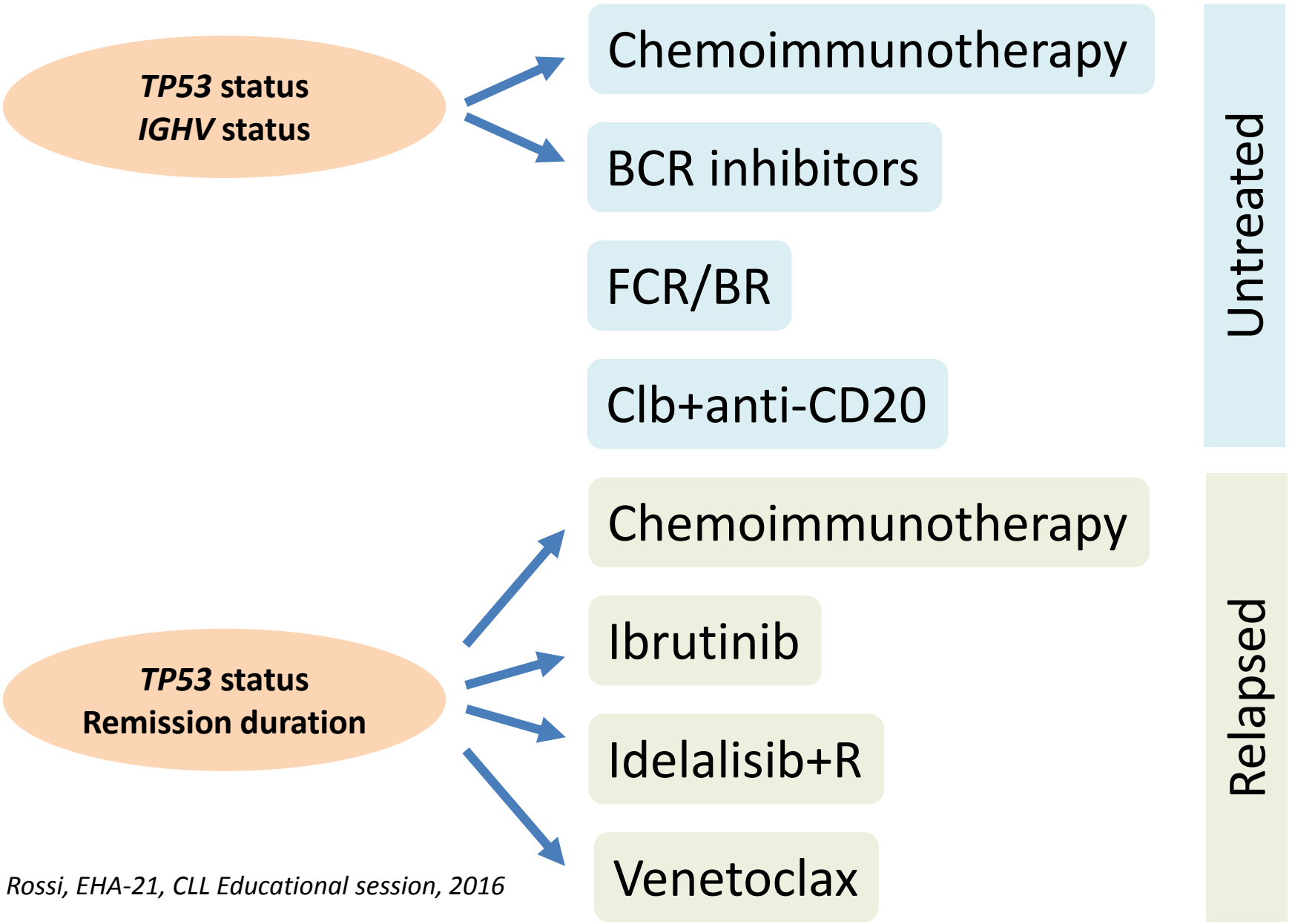
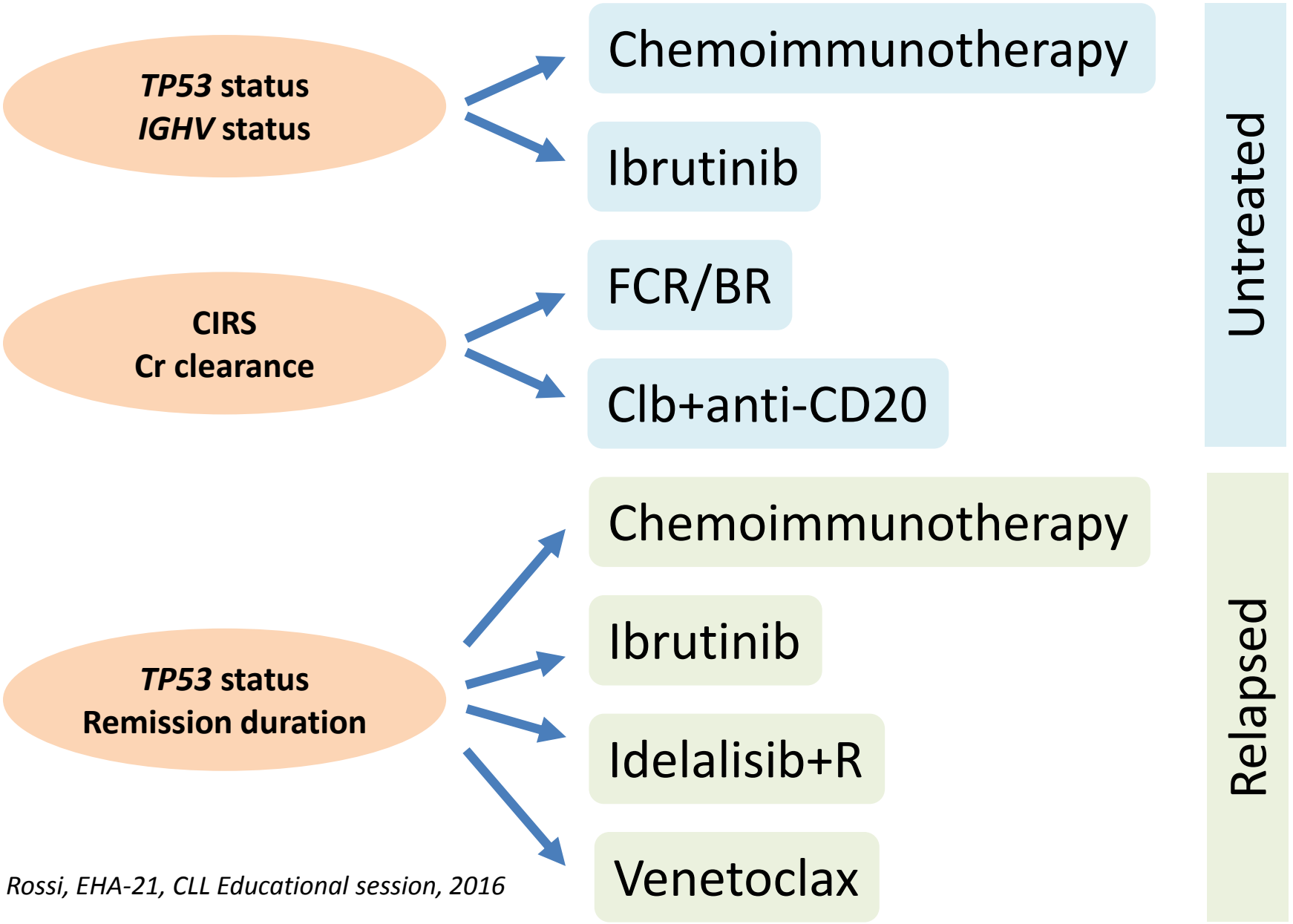
# Can treatment decision be informed by biomarkers?




*Rossi, EHA-21, CLL Educational session, 2016*

# Can treatment decision be informed by biomarkers?




*Rossi, EHA-21, CLL Educational session, 2016*

# Comorbidities in the novel agents era

| RESONATE 2 | Ibrutinib (n = 136) | Chlorambucil (n = 133) |
|---|---|---|
| **Median age** | 73y (65-89) | 72y (65-90) |
| **CIRS score >6** | 31% | 33% |
| **Creatinine clearance < 60 mL/min** | 44% | 50% |
| **Discontinuation due to AE** | **9%** | **23%** |

Burger J et al, New Engl J Med 2016

Comorbidities might support the choiche of one novel agents when multiple options are available[1,2]:

- **Pulmonary, gut, liver disease**
- **Warfarin use**
- **Renal failure**

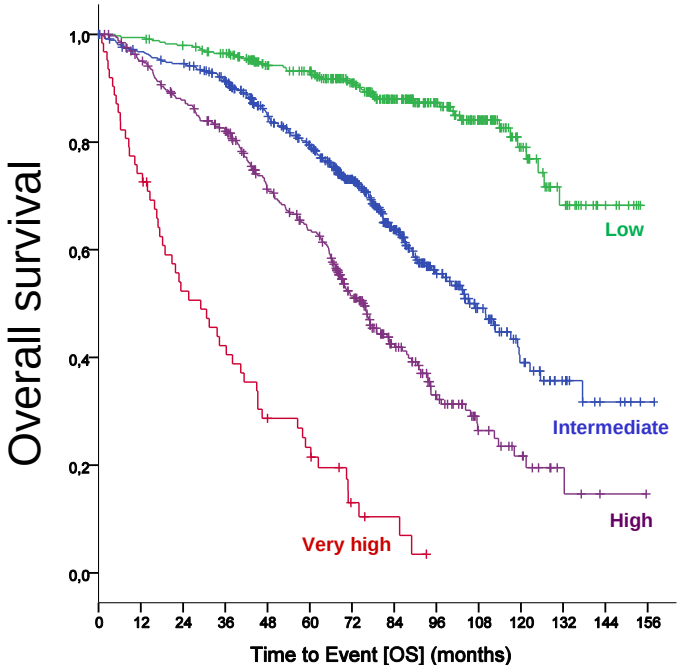
1. No formal counterindication
2. Low level of evidence
   - Populations underepresented in trials
   - Expert opinions

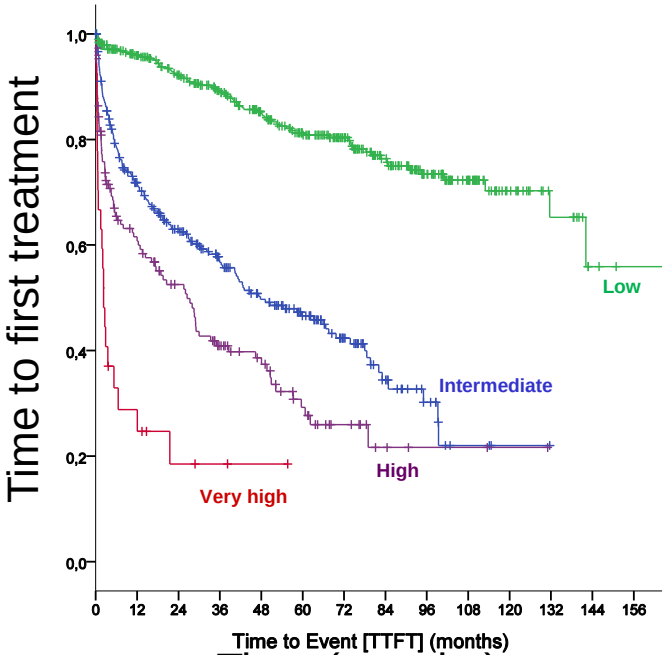
*Rossi, EHA-21, CLL Educational session, 2016*

# Comprehensive approaches incorporating clinical, serum, genetic, and molecular markers into a single risk score: CLL-IPI

| Variable | Adverse factor | Coeff. | HR | Grading |
|---|---|---|---|---|
| ***TP53* (17p)** | deleted and/or mutated | **1.442** | **4.2** | **4** |
| ***IGHV* status** | Unmutated | **0.941** | **2.6** | **2** |
| **B2M, mg/L** | > 3.5 | **0.665** | **2.0** | **2** |
| **Clinical stage** | Binet B/C **or** Rai I-IV | **0.499** | **1.6** | **1** |
| **Age** | > 65 years | **0.555** | **1.7** | **1** |
| **Prognostic Score** | | | | **0 – 10** |

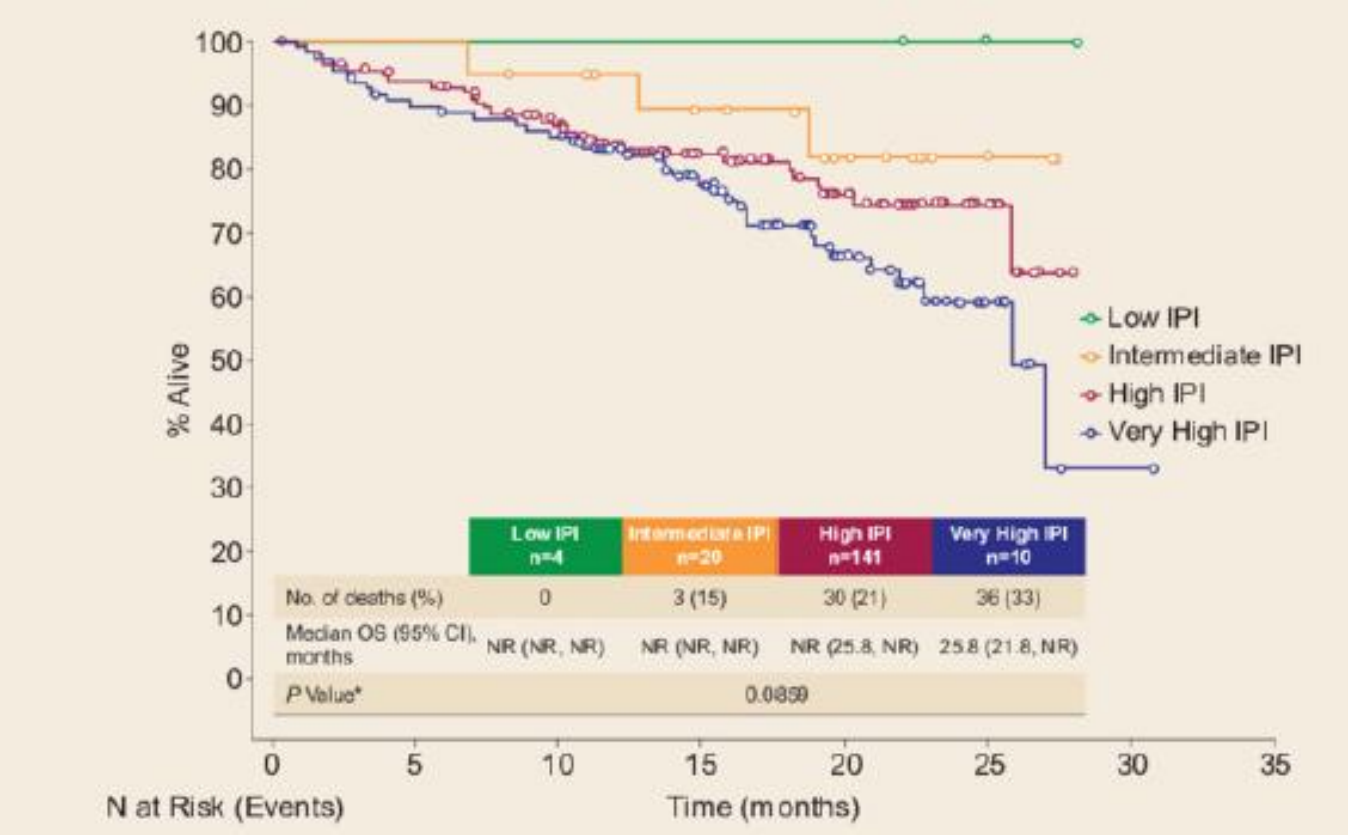
| Risk group | Score | Patients N (%) | 5-year OS, % |
|---|---|---|---|
| **Low** | **0 – 1** | 340 (29) | 93.2 |
| **Intermediate** | **2 – 3** | 464 (39) | 79.4 |
| **High** | **4 – 6** | 326 (27) | 63.6 |
| **Very High** | **7 – 10** | 62 (5) | 23.3 |




Kutsch N BJ, J Clin Oncol 2015;33(suppl). Abstract 7002; Wierda W, J Clin Oncol 2011;29:4088-4095; Pflug N, Blood 2014;124:49-62

# CLL-IPI score and prognostic factor analysis in R/R CLL in patients treated with idelalisib




Soumerai et al. EHA 2016, #P214.

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# Preliminary safety data from the phase 3b GREEN study of obinutuzumab (G) alone or combined with chemotherapy for previously untreated or relapsed/refractory chronic lymphocytic leukemia (CLL)

V Leblond,[1] M-S Dilhuydy,[2] R Foà,[3] W Knauf,[4] M Montillo,[5] S Robinson,[6] S Stilgenbauer,[7] E Gresko,[8] S Lasserre,[8] F Bosch[9]

*[1]AP-HP Hôpital Pitié-Salpêtrière, UPMC, Paris, France; [2]Hôpital du Haut-Lévèque, Centre Hospitalier Universitaire de Bordeaux, Bordeaux, France; [3]'Sapienza' University, Rome, Italy; [4]Onkologische Gemeinshaftspraxis, Frankfurt, Germany; [5]Niguarda Ca' Granda Hospital, Niguarda Cancer Center, Milan, Italy; [6]QEII Health Sciences Centre, Halifax, NS, Canada; [7]University of Ulm, Ulm, Germany; [8]F. Hoffmann-La Roche Ltd, Basel, Switzerland; [9]University Hospital Vall d'Hebron, Barcelona, Spain*

# GREEN: open-label, single-arm safety study

- 1L and R/R CLL pts requiring treatment
- Aged ≥18 yrs with documented CLL, ECOG PS 0–2 and adequate hematologic function
  - fit: CIRS ≤6 and CrCl ≥70mL/min
  - unfit: CIRS >6 and/or CrCl <70mL/min
- Treatments: G-FC (fit); G-Clb (unfit); G-B, G-mono* (either)
  - all treatments in six 28-day cycles
  - G dose = 1000mg (D1, 8, 15 of C1 + D1 of C2–6)
  - first dose of G split over 2 days (25/975mg or 100/900mg)
  - additional premedication with corticosteroids for selected pt cohorts
- Current analysis includes 825 pts (1L, 485; R/R, 340)
  - data cut-off for analysis = 26 August 2015

*Pts refractory to previous G monotherapy could only receive G with chemotherapy

B, bendamustine; CIRS, Cumulative Illness Rating Scale; FC, fludarabine, cyclophosphamide

# GREEN: most common grade 3–5 AEs by treatment group* and preferred term

| *n (%)* | *All (N=825)* | *G alone (n=106)* | *G-FC (n=159)* | *G-Clb (n=97)* | *G-B (n=463)* |
|---|---|---|---|---|---|
| Neutropenia | 369 (44.7) | 26 (24.5) | 93 (58.5) | 41 (42.3) | 209 (45.1) |
| TCP | 131 (15.9) | 11 (10.4) | 34 (21.4) | 19 (19.6) | 67 (14.5) |
| Anemia | 74 (9.0) | 5 (4.7) | 16 (10.1) | 6 (6.2) | 47 (10.2) |
| Febrile neutropenia | 57 (6.9) | 4 (3.8) | 15 (9.4) | 2 (2.1) | 36 (7.8) |
| Leukopenia | 51 (6.2) | 3 (2.8) | 17 (10.7) | 3 (3.1) | 28 (6.0) |
| TLS | 49 (5.9) | 5 (4.7) | 6 (3.8) | 3 (3.1) | 35 (7.6) |
| Pneumonia | 40 (4.8) | 5 (4.7) | 3 (1.9) | 9 (9.3) | 23 (5.0) |
| Lymphopenia | 38 (4.6) | 0 | 8 (5.0) | 0 | 30 (6.5) |
| Hypotension | 21 (2.5) | 6 (5.7) | 2 (1.3) | 6 (6.2) | 7 (1.5) |

*AEs reported by ≥5% of patients in any group; TCP, thrombocytopenia; TLS, tumor lysis syndrome

# GREEN: incidence of TLS by treatment group and patient fitness*

| | *All (N=825)* | *G alone (n=106)* | *G-FC (n=159)* | *G-Clb (n=97)* | *G-B (n=463)* | *G-B fit (n=232)* | *G-B unfit (n=231)* * |
|---|---|---|---|---|---|---|---|
| Any TLS, n (%) | 51 (6.2) | 6 (5.7) | 7 (4.4) | 3 (3.1) | 35 (7.6) | 12 (5.2) | 23 (10.0) |
| CIRS >6, n | 16 | 3 | 0 | 2 | 11 | 0 | 11 |
| CrCl <70mL/ min, n | 24 | 2 | 1 | 2 | 19 | 1 | 18 |

* Two fatal TLS cases in the G-B group

# GREEN: conclusions

- Safety data from the current analysis are in line with the known safety profile of G ± chemo in similar populations
  - the most frequent grade 3–5 AEs were hematologic disorders, primarily neutropenia
  - TLS reported in 51 (6.2%) pts
    - most common in unfit G-B pts (10.0% vs 5.2% in fit G-B)
    - two fatal cases; both 1L G-B pts and both considered at risk for TLS due to high tumor load and / or renal impairment at baseline*
- Differences in AE rates between treatment groups should be interpreted with caution due to non-randomized design

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Labor Kiel

laboratorium
medische
immunologie

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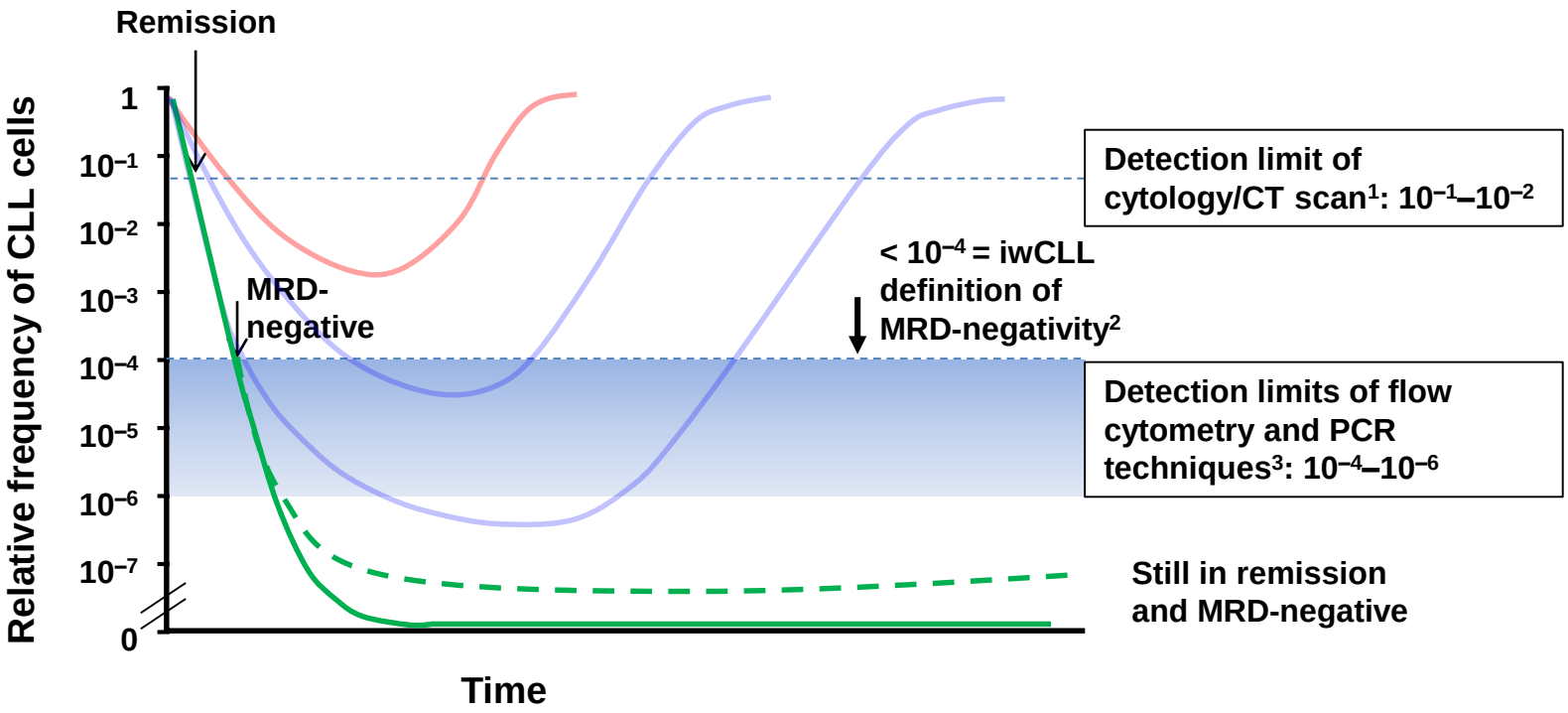
# QUANTITATIVE MRD IS PROGNOSTIC FOR PROGRESSION-FREE & OVERALL SURVIVAL IN ELDERLY PATIENTS RECEIVING CHLORAMBUCIL ALONE OR WITH OBINUTUZUMAB/RITUXIMAB: A PROSPECTIVE ANALYSIS OF THE CLL11 STUDY

**Matthias Ritgen***, **Anton W Langerak***, Valentin Goede, Jasmin Bahlo, Sandra Kluth, Kirsten Fischer, Michael Steurer, Marek Trněný́, Stephen Mulligan, Ulrich Mey, Kerstin Trunzer, Kathryn Humphrey, Günter Fingerle-Rowson, Stephan Stilgenbauer, Sebastian Böttcher, Monika Bruggemann, Michael Hallek, Michael Kneba, Jacques JM van Dongen

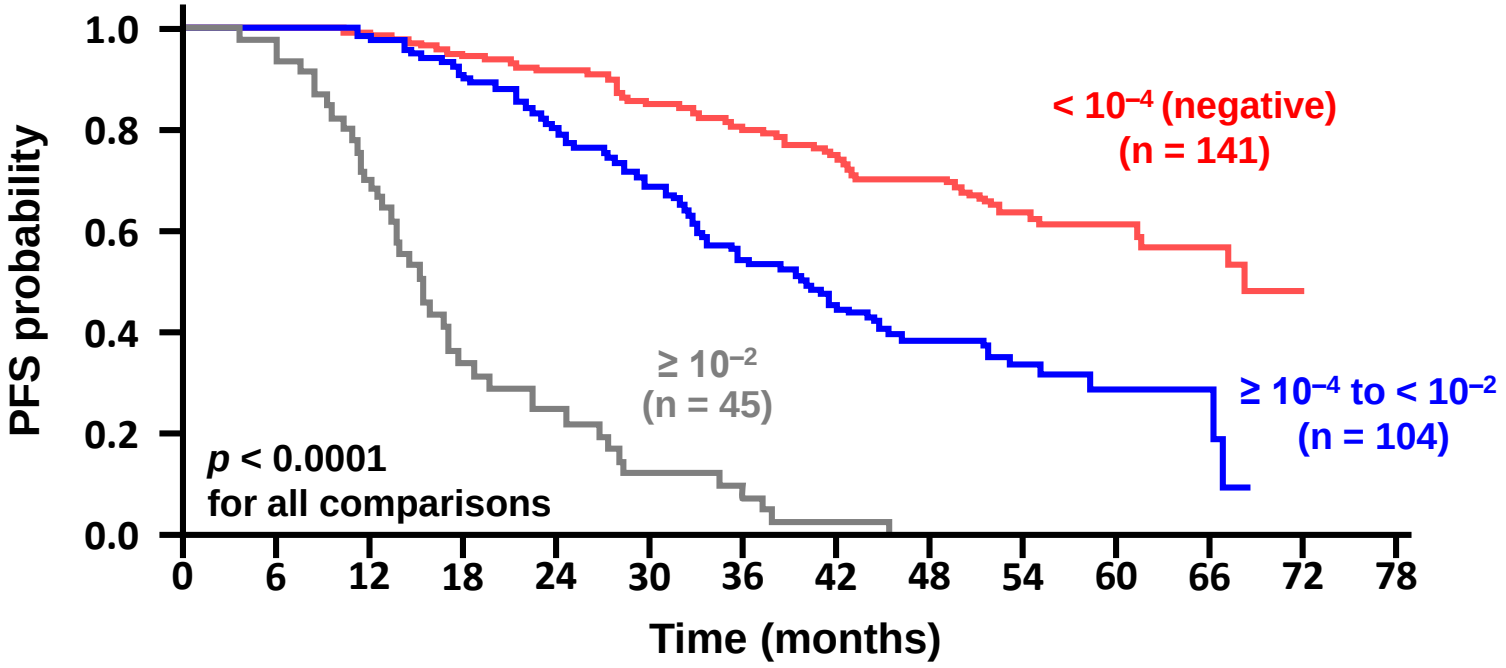
# MRD can indicate depth of remission and predict relapse




1 Böttcher S, *et al*. *Hematol Clin N Am* 2013; 27:267–288;
2. Hallek M, *et al. Blood* 2008; 111:5446–5456;
3. Moreno C, *et al. Best Pract Res Clin Haematol* 2010; 23:97–107.

# Clinical significance of MRD in CLL8

- Patients in CLL8 were grouped by MRD level (blood) at initial response assessment
- Patients achieving MRD-negative status had the best outcome, regardless of treatment
- The extent of MRD reduction was important for outcome




MRD by 4-color flow cytometry, validated against ASO-RQ-PCR

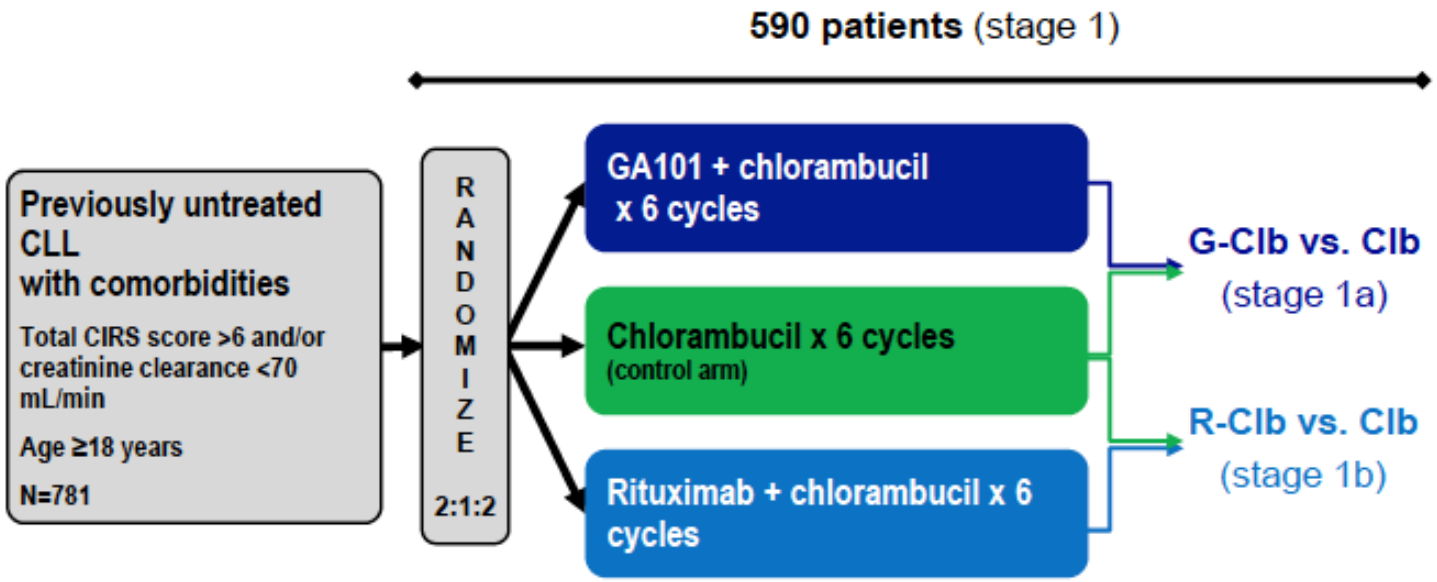
Böttcher S, *et al. J Clin Oncol* 2012; 30:980–988.

Hämatologie Labor Kiel

laboratorium medische immunologie

DEUTSCHE STUDIENGRUPPE

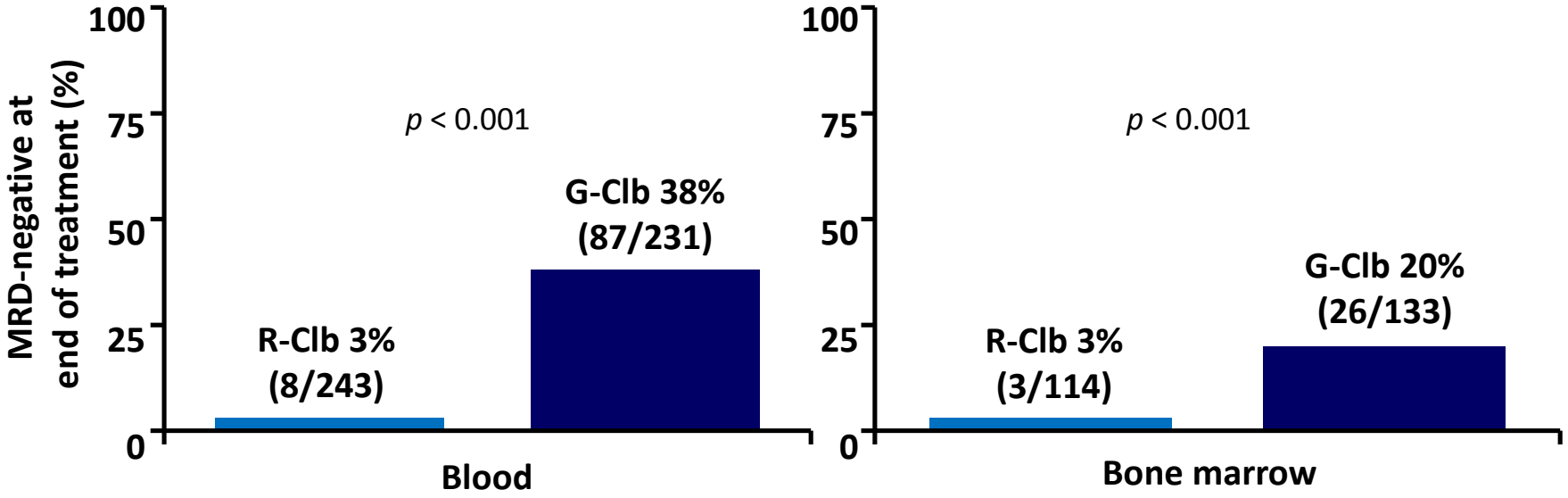
# CLL11: Study design




- GA101: 1000 mg days 1, 8, and 15 cycle 1; day 1 cycles 2–6, every 28 days
- Rituximab: 375 mg/m² day 1 cycle 1, 500 mg/m² day 1 cycles 2–6, every 28 days
- Chlorambucil: 0.5 mg/kg day 1 and day 15 cycle 1–6, every 28 days
- Patients with progressive disease in the Clb arm were allowed to cross over to G-Clb

# CLL11 stage II: MRD at the end of treatment

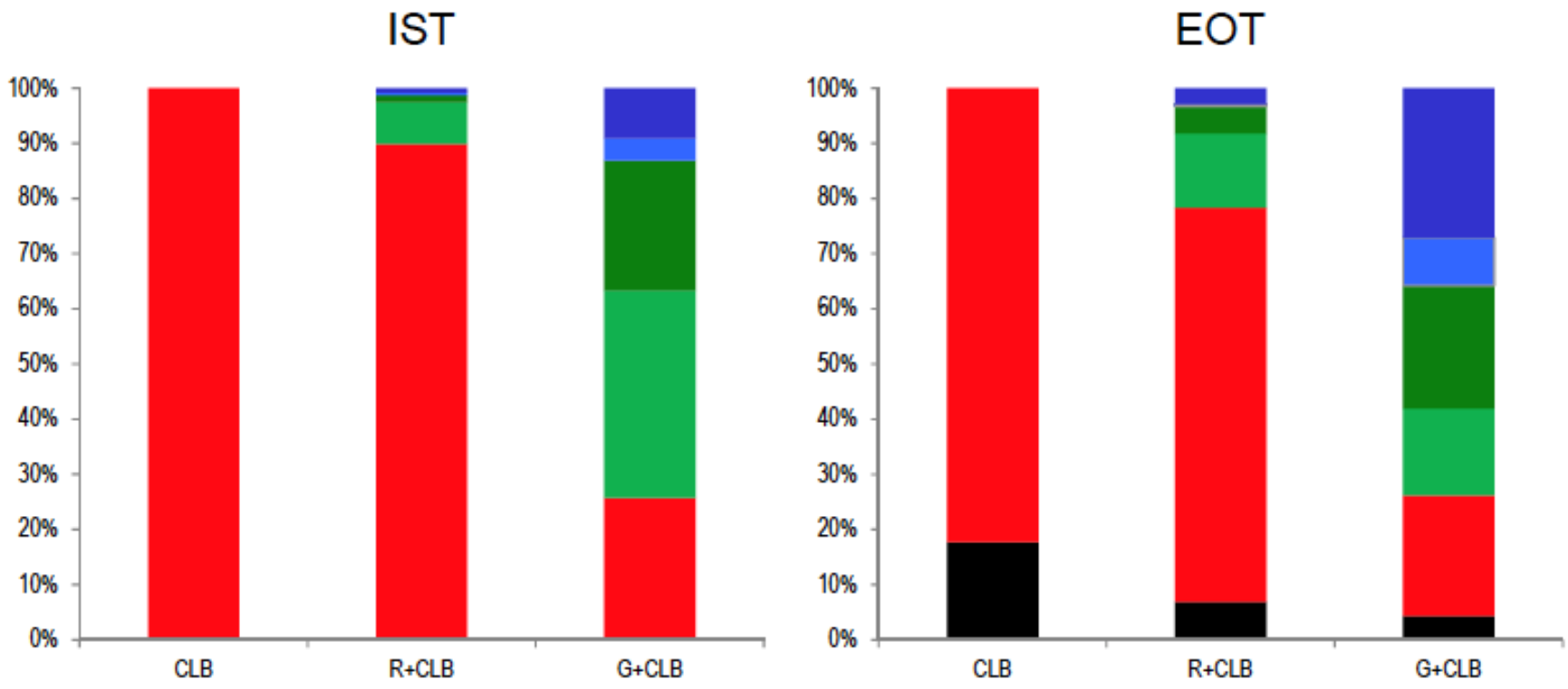
- 38% of patients in the G-Clb arm were MRD-negative in peripheral blood and 20% in the BM at final response assessment, compared with 3% in the R-Clb arm




- MRD by ASO-RQ-PCR at final response assessment
- BM samples were usually only taken from patients thought to be in CR
- Patients who progressed or died prior to MRD measurement were counted as MRD-positive

Goede V, *et al. N Engl J Med* 2014; 370:1101–1110.

# MRD response according to treatment arm (PB)




| MRD negative | MRD intermediate | MRD positive |
|---|---|---|
| $\leq 10^{-5}$ | $10^{-3}$ - $10^{-4}$ | $\geq 10^{-2}$ |
| $10^{-4}$ - $10^{-5}$ | $10^{-2}$ - $10^{-3}$ | PD/death |

IST = Interim staging; EOT, end of treatment

# MRD result (EOT) according to treatment

Stage 1a + 1b

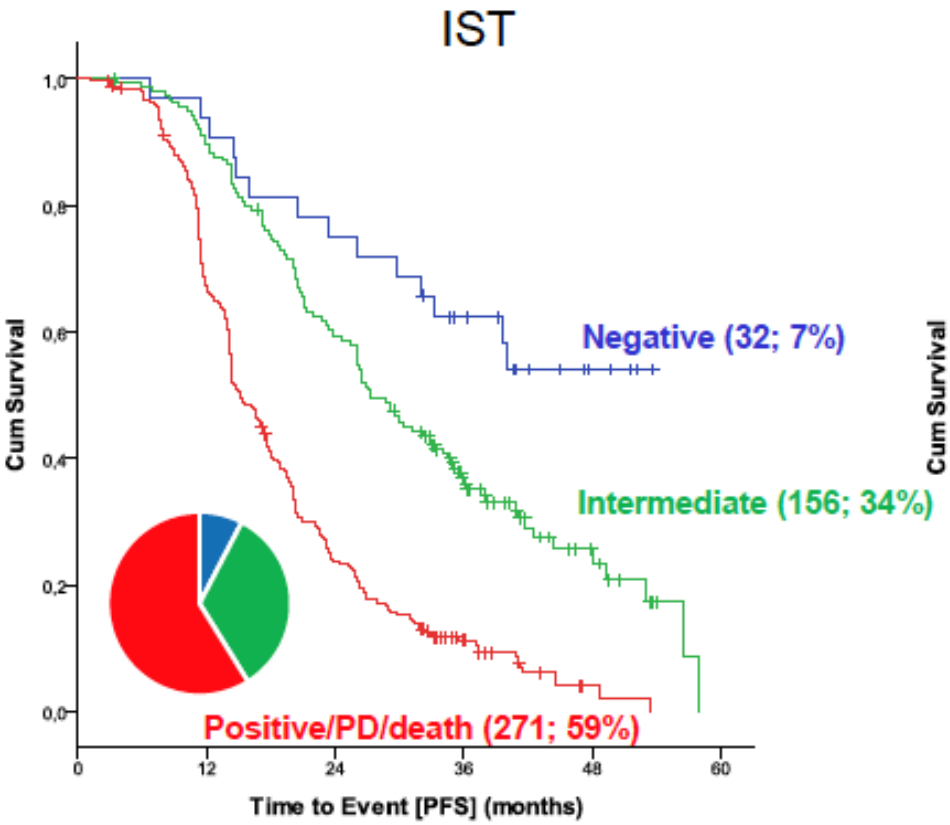
| | G+Clb | Clb | p | Clb | R+Clb | p |
|---|---|---|---|---|---|---|
| MRD category, N (%) PB | | | | | | |
| Negative | 63 (39.4) | 0 (0.0) | | 0 (0.0) | 4 (2.4) | |
| Intermediate | 55 (34.4) | 0 (0.0) | < 0.001 | 0 (0.0) | 30 (17.9) | < 0.001 |
| Positive/PD/death | 42 (26.3) | 90 (100.0) | | 90 (100.0) | 135 (79.9) | |
| Missing cases, N (%) | 78 (32.8) | 28 (23.7) | | 28 (23.7) | 64 (27.5) | |

Stage 2

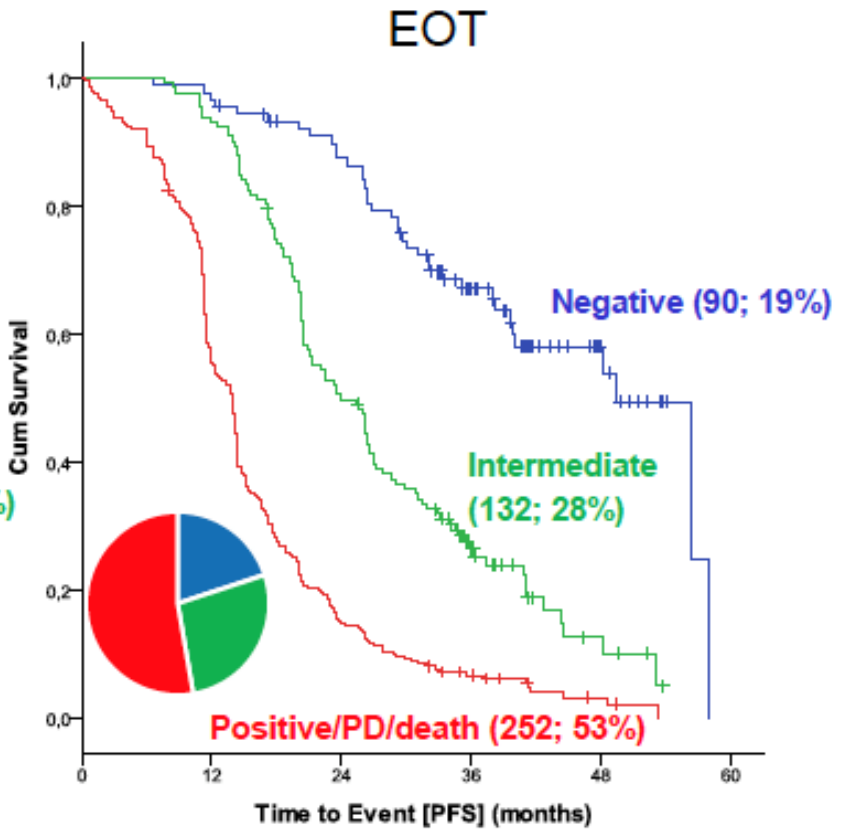
| | G+Clb | R+Clb | p value |
|---|---|---|---|
| **MRD category, N (%) PB** | | | |
| **Negative** | 82 (35.8) | 8 (3.3) | |
| **Intermediate** | 87 (38.0) | 45 (18.4) | < 0.001 |
| **Positive/PD/death** | 60 (26.2) | 192 (78.4) | |
| **MRD category, N (%) BM** | | | |
| **Negative** | 24 (18.2) | 3 (2.6) | |
| **Intermediate** | 46 (34.8) | 11 (9.6) | < 0.001 |
| **Positive/PD/death** | 62 (47.0) | 101 (87.8) | |

# PFS according to MRD status at IST and EOT

Stage 2 – peripheral blood




p < 0.001 (log-rank)

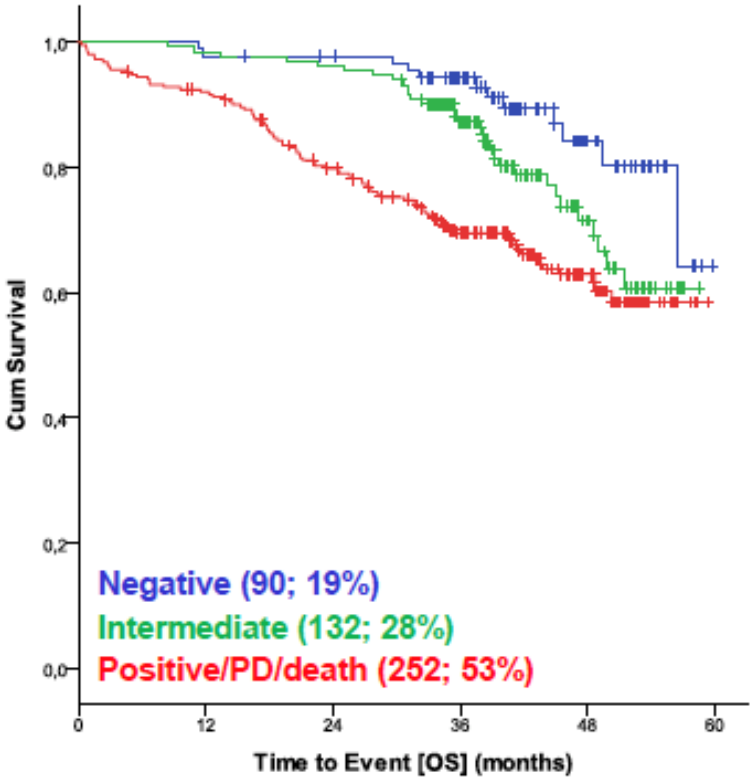



p < 0.001 (log-rank)

Data cut off: May 2015

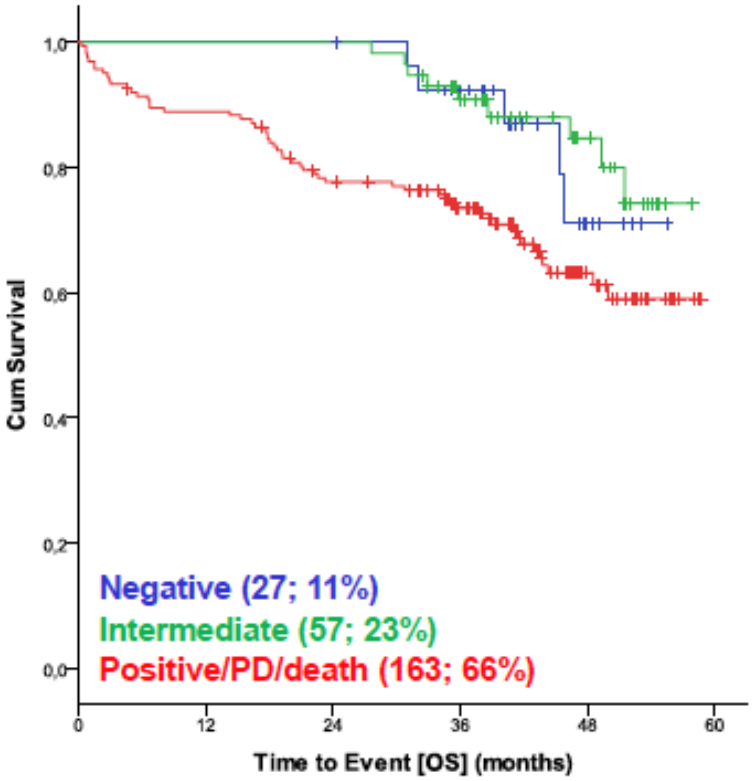
# Stage 2, OS according to MRD

PB (n=474)




p < 0.001 (log-rank)

BM (n=247)




p < 0.001 (log-rank)

# Conclusions CLL11 MRD

- MRD assessment in Clb-based Immuno-Chemotherapy is informative and can define prognostic risk groups
- Adding Obinutuzumab to Clb treatment increases MRD negativity rate compared to Clb alone or combination of R-Clb
- In both combination arms, MRD responders at IST can improve MRD status by further treatment cycles
- In the G-Clb arm, maximal MRD response seems to be reached at IST
- MRD is the most important independent prognostic factor for PFS and OS in multivariate analysis
- In this cohort, BM does not seem to be better than PB for the prognosis of progression risk

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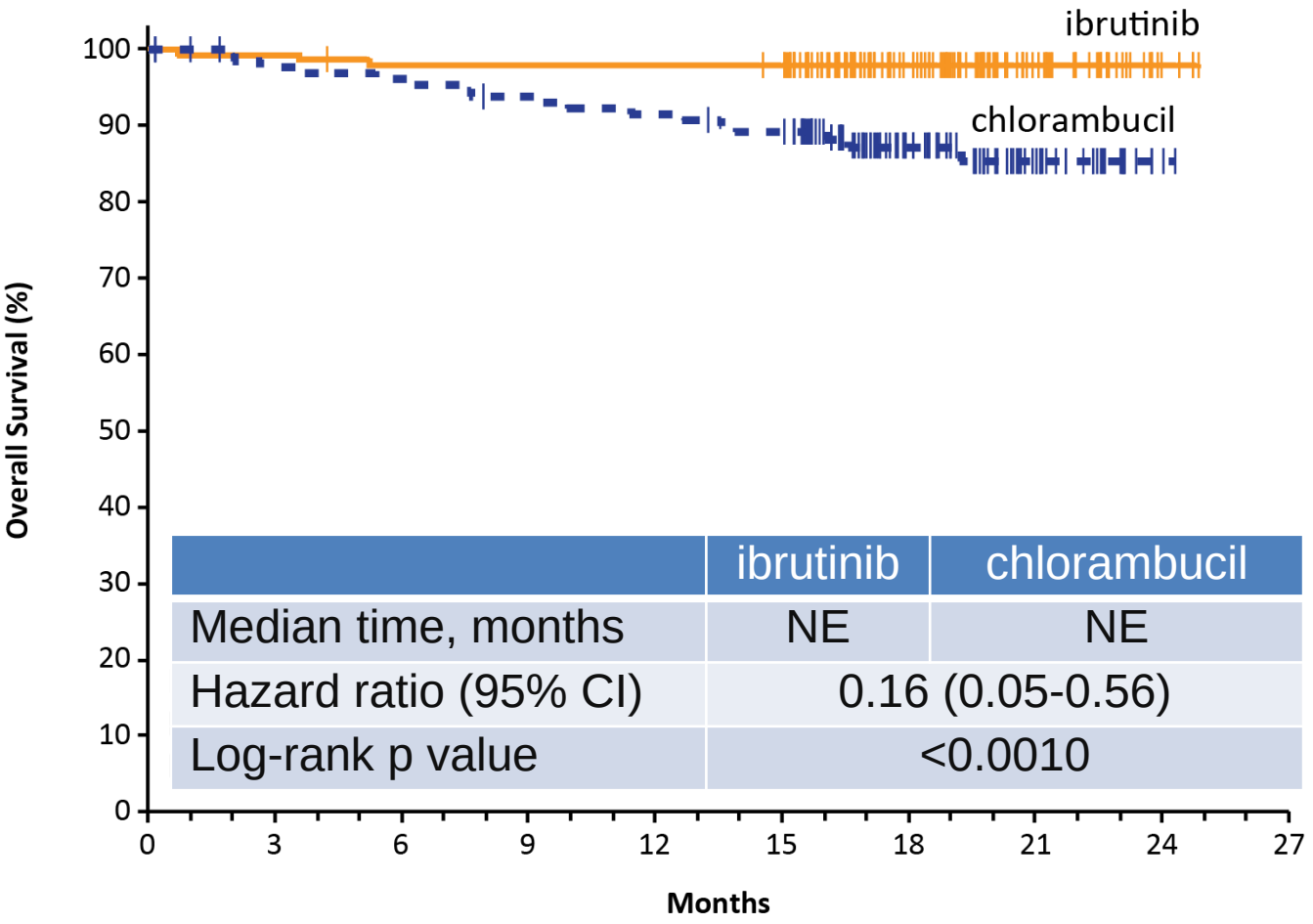
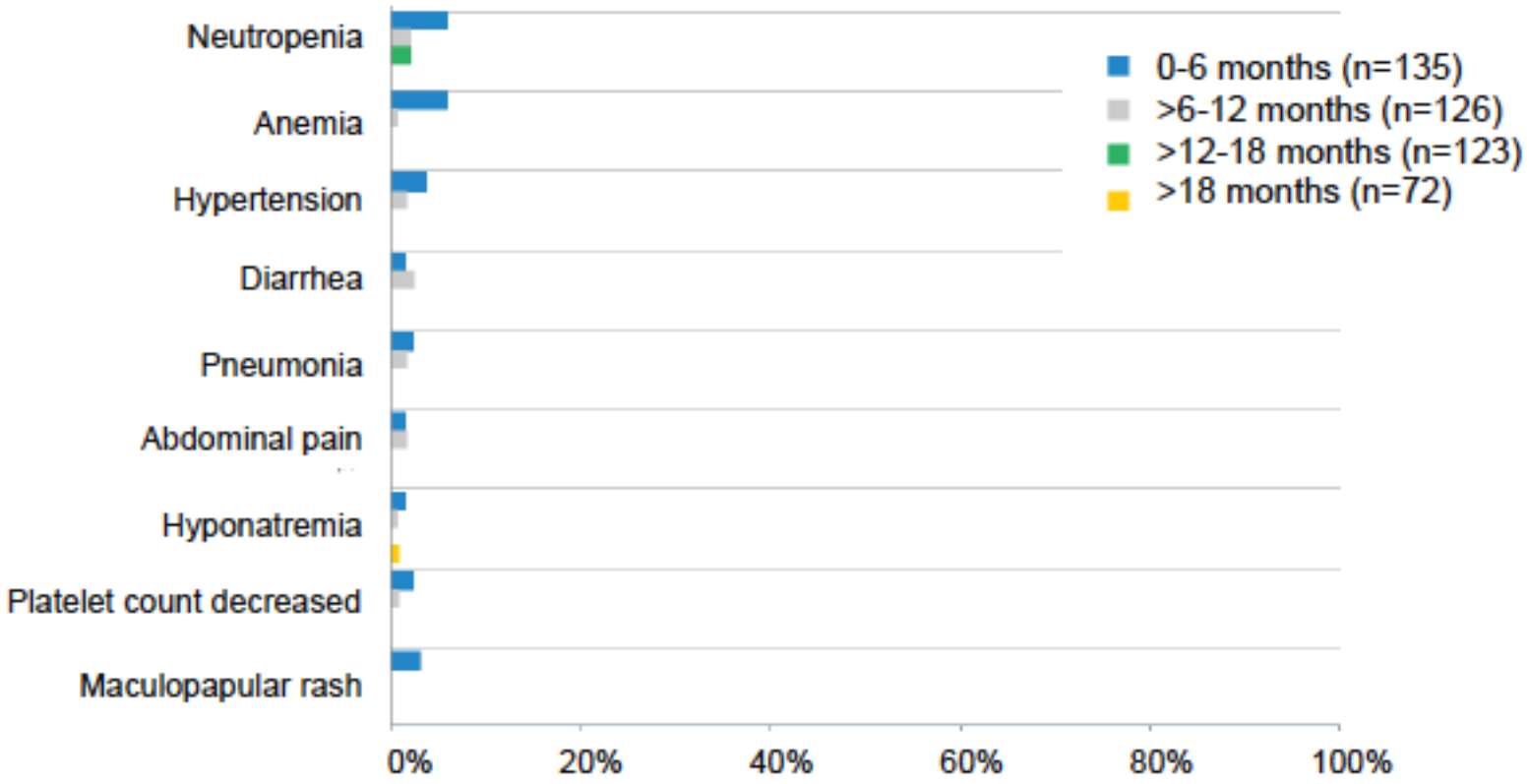
# RESONATE-2: OVERALL SURVIVAL




| | ibrutinib | chlorambucil |
|---|---|---|
| Median time, months | NE | NE |
| Hazard ratio (95% CI) | 0.16 (0.05-0.56) | |
| Log-rank p value | <0.0010 | |

Tedeschi et al., ASH 2015 (abstract 495, oral presentation)
Burger et al., N Engl J Med. 2015 373:2425-2437

# RESONATE-2:
# Onset of Grade ≥3 AEs (≥3% of patients) over time with ibrutinib

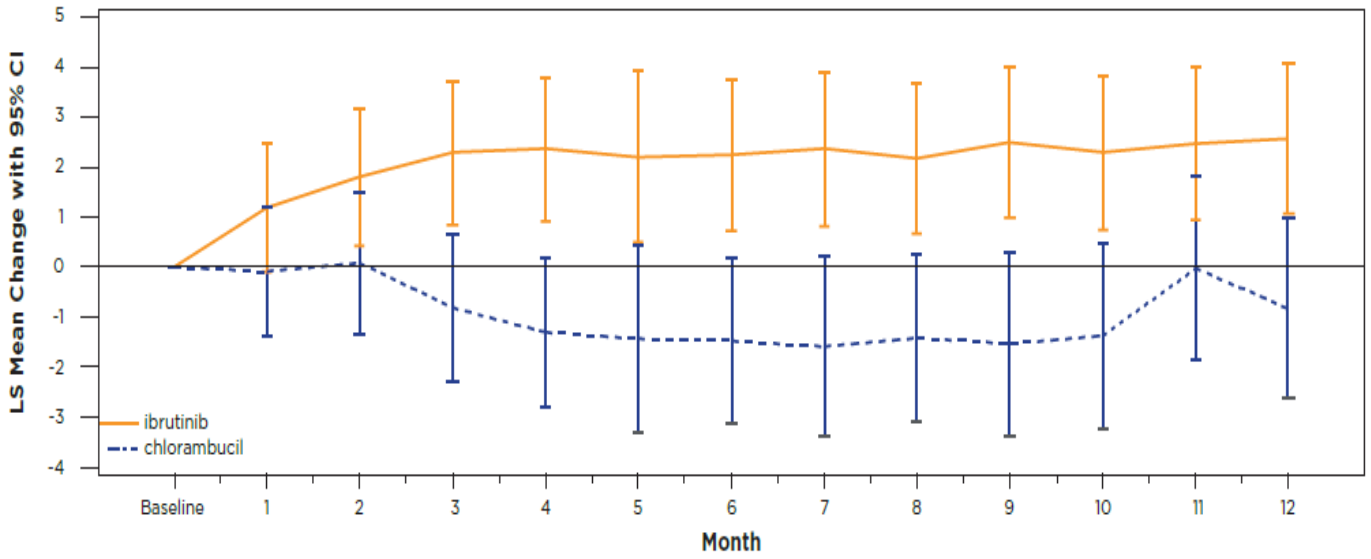



*Ghia et al., EHA 2016, #P217*

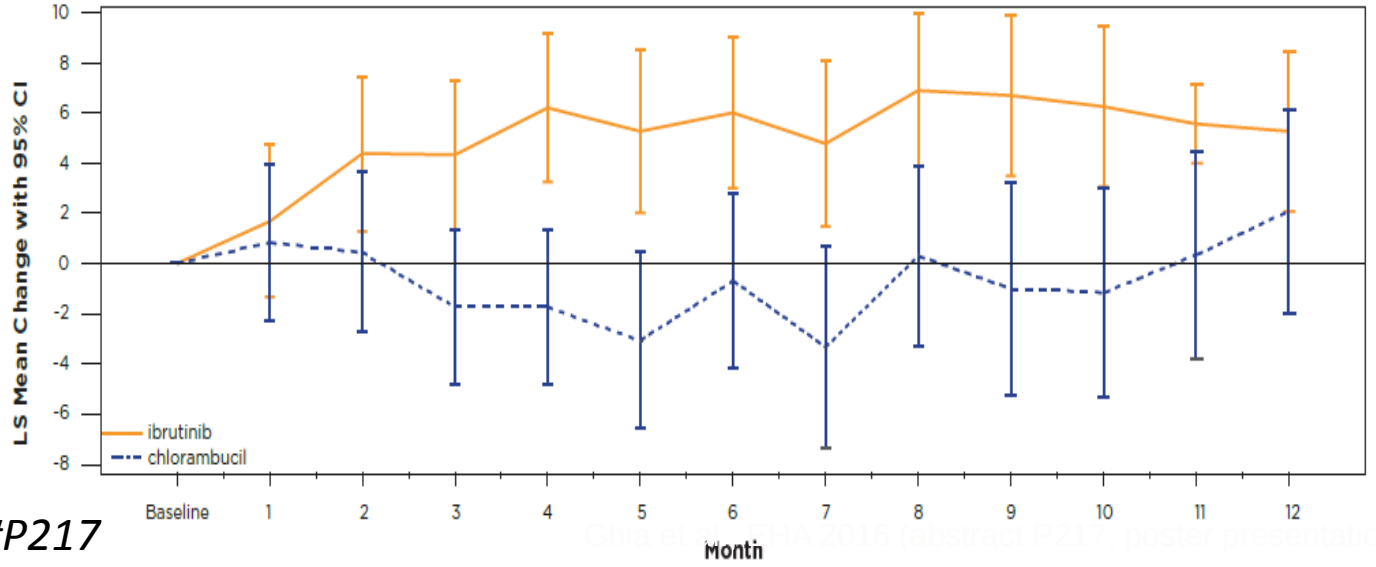
# RESONATE-2: QoL

Change in patient-reported QOL measures over time

FACIT-Fatigue Score* Over Time



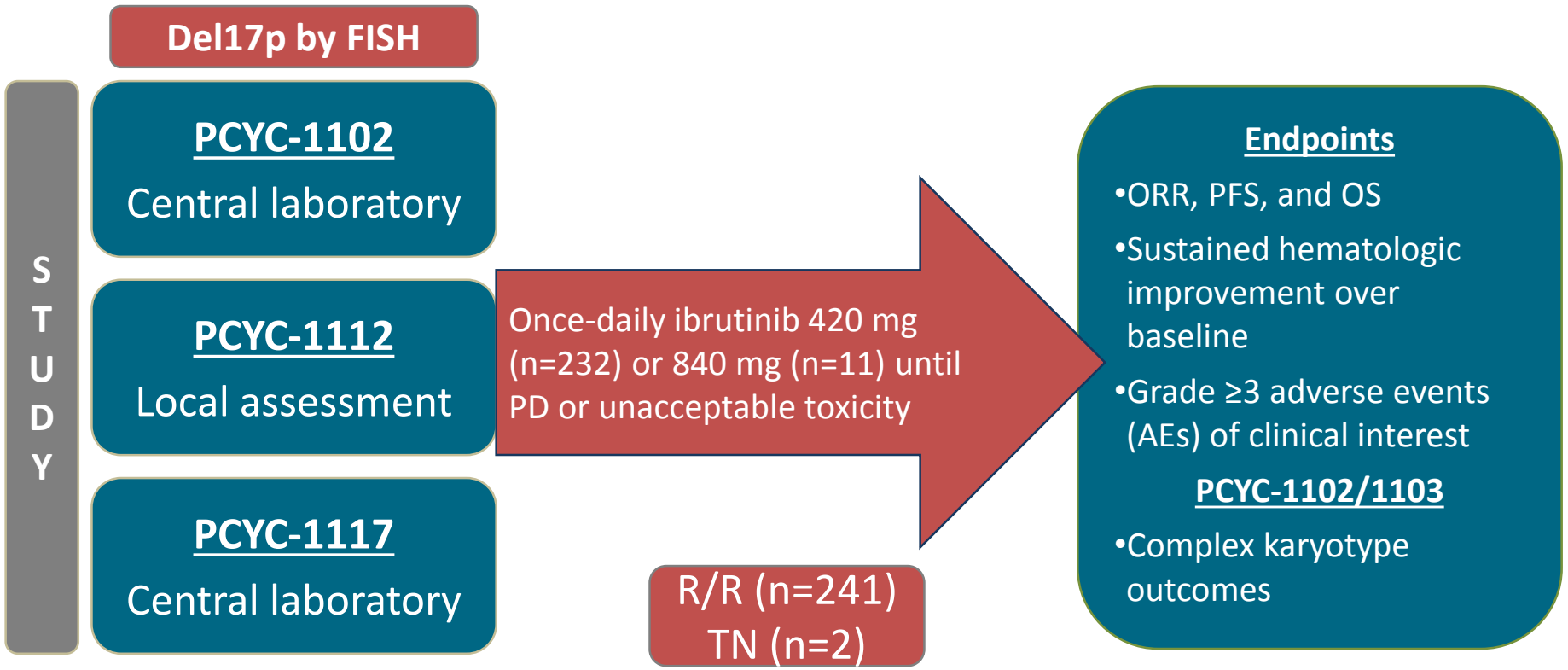

EORTC QLQ-C30 Global Health Status Score* Over Time




*Ghia et al., EHA 2016, #P217*

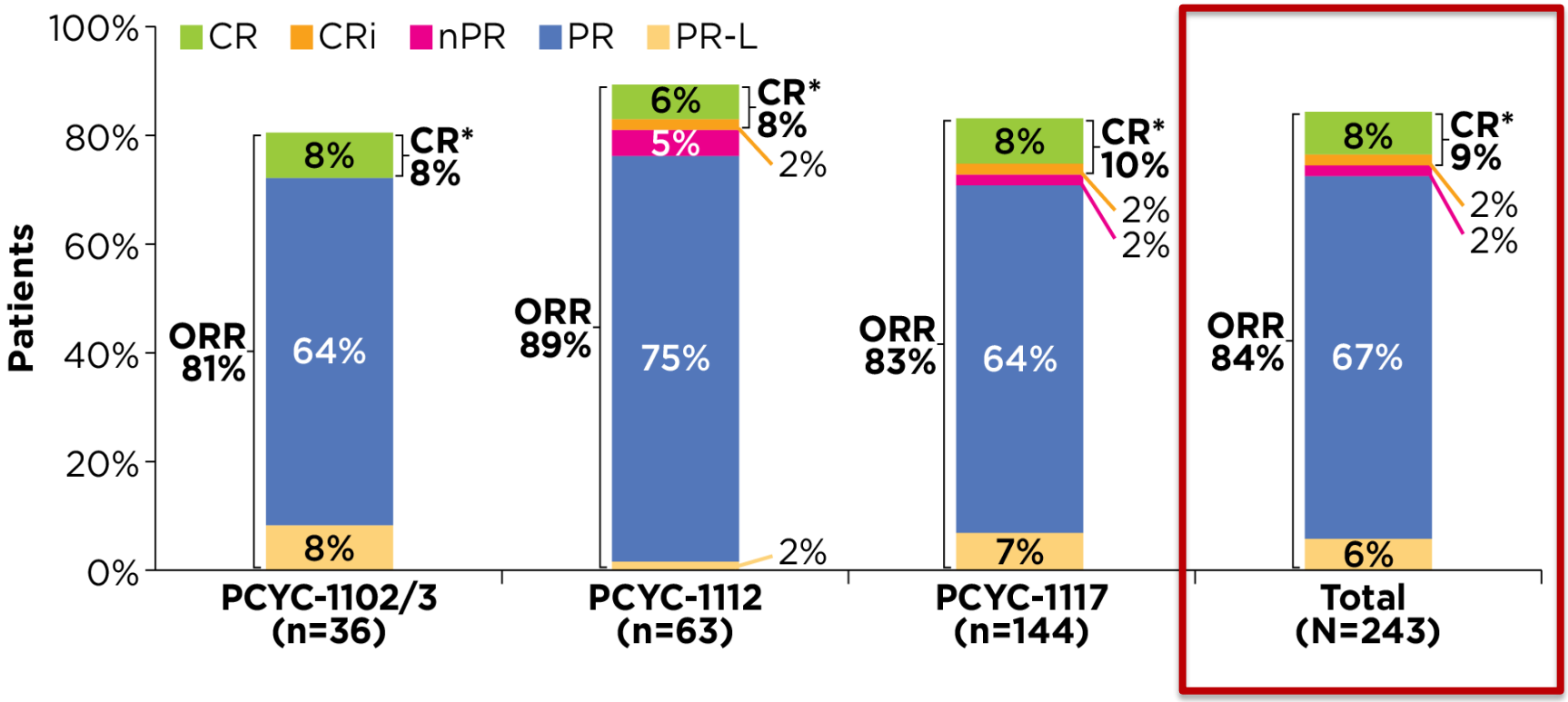
Ghia et al., EHA 2016 (abstract P217, poster presentation)

# A cross-study analysis of treatment outcomes in patients with deletion 17p CLL treated with ibrutinib



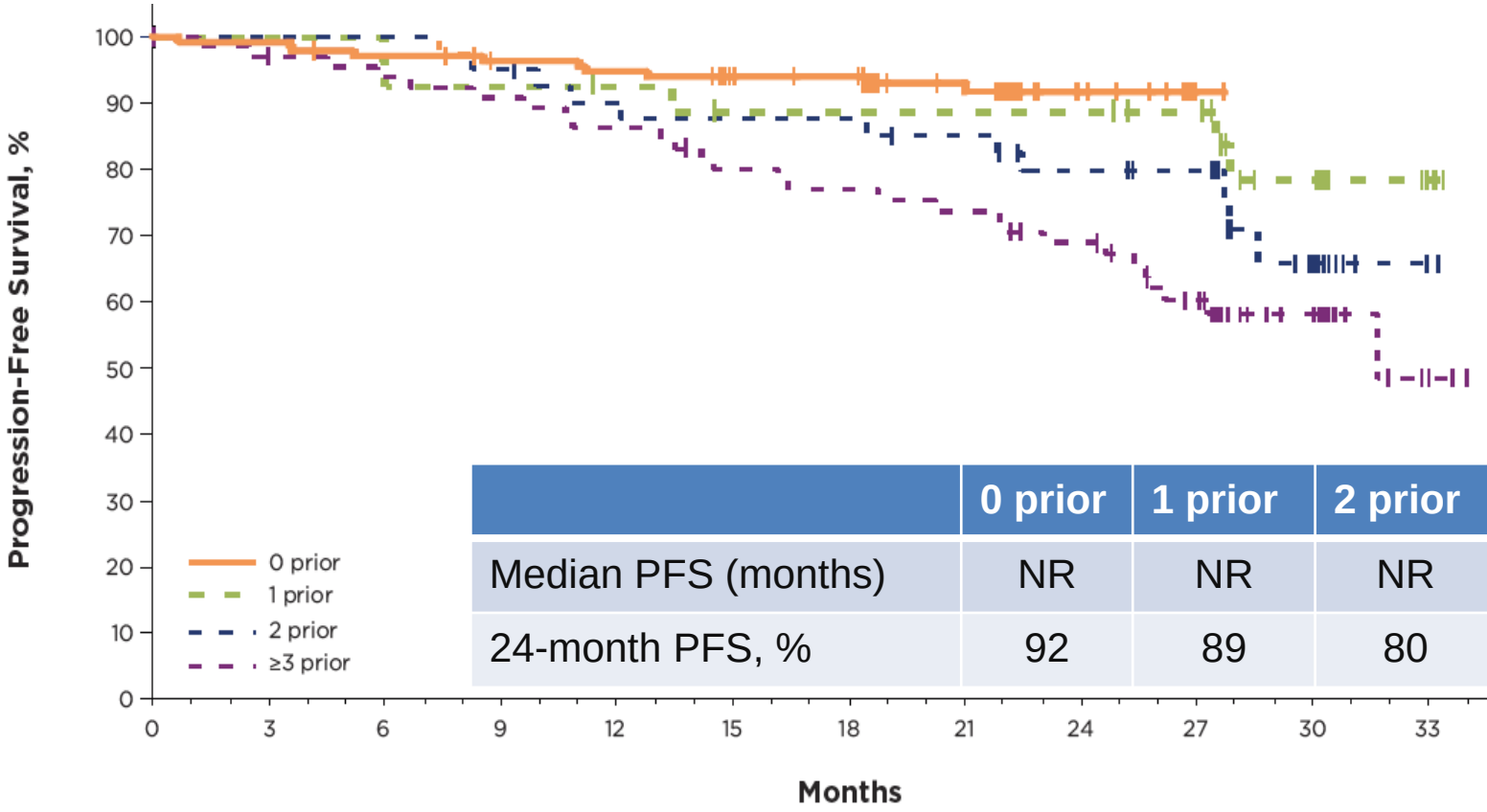

*Jones J, et al. EHA 2016, #S429*

# Cross-study analysis: Overall response rate




*Jones J, et al. EHA 2016, #S429*

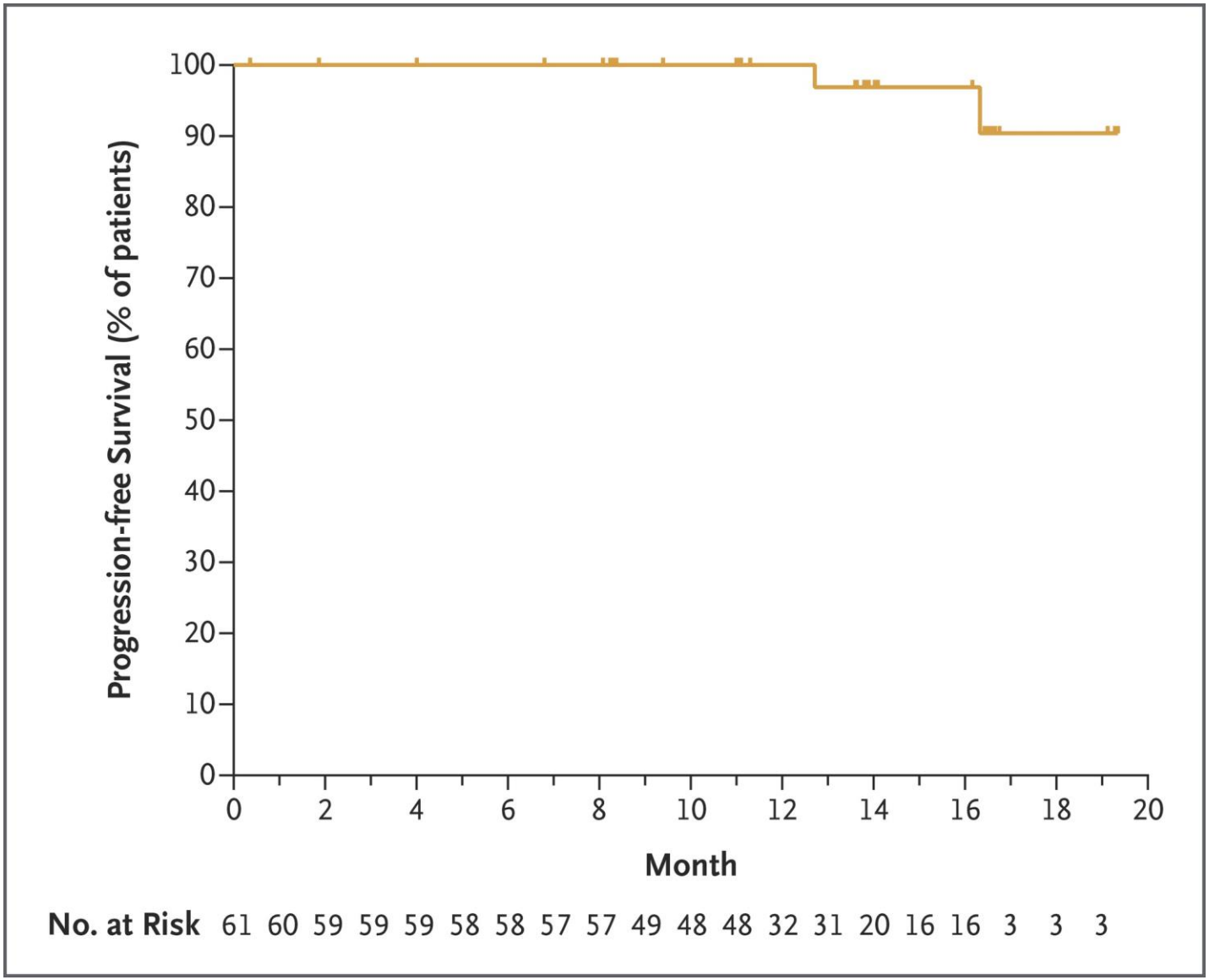
# Outcomes with ibrutinib by line of therapy
# PFS with prior lines of therapy




| | 0 prior | 1 prior | 2 prior | ≥ 3 prior |
|---|---|---|---|---|
| Median PFS (months) | NR | NR | NR | 31.7 |
| 24-month PFS, % | 92 | 89 | 80 | 69 |

*Hillmen et al., EHA 2016, #P596*

# Acalabrutinib in R/R CLL




Byrd JC et al. N Engl J Med 2016;374:323-332

# Acalabrutinib in previously-untreated CLL: Efficacy

| Best response n (%) | N=72 |
|---|---|
| PR | 63 (87.5) |
| PRL | 7 (9.7) |
| SD | 2 (2.8) |
| PD | 0 |
| ORR (CR+Cri+PR), n (%) | 63 (87.5) |
| 95% | 77.6-94.1 |
| ORR (CR+Cri+PR+PRL), n (%) | 70 (97.2) |
| 95% | 90.3-99.7 |

*Wierda W et al., EHA 2016, #S431*

# Acalabrutinib in previously-untreated CLL: Toxicity

| AE, % | n = 74 | |
|---|---|---|
| | Any Grade | Grade ≥ 3 |
| Any AE | 100.0 | 23.0 |
| Any treatment-related AE | 64.9 | 5.4 |
| Any serious AE | 20.3 | 16.2 |
| Any treatment-related serious AE | 2.7 | 2.7 |
| AEs occurring in ≥ 15% of pts | | |
| ▪ Headache | 40.5 | 1.4 |
| ▪ Diarrhea | 35.1 | 0 |
| ▪ Arthralgia | 21.6 | 1.4 |
| ▪ Nausea | 17.6 | 2.7 |
| ▪ Increased weight | 17.6 | 1.4 |
| ▪ Contusion | 17.6 | 0 |
| ▪ Rash | 16.2 | 1.4 |

*Wierda W et al., EHA 2016, #S431*

# Idelalisib in Combination with Rituximab in Chronic Lymphocytic Leukemia (CLL) / Small Lymphocytic Lymphoma (SLL): Real-World Experience Through an Early Access Program in Europe and Australia

Julia J. Li,[1] Alan S.M. Yong,[1] Chuck Smith,[1] Julio Delgado[2]

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# Results: Safety and Efficacy

## Safety

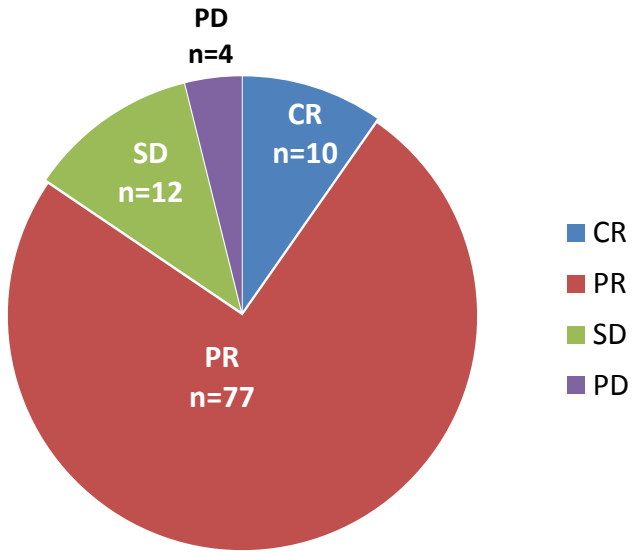
- Median follow up was 122 days (range, 31-391)

| SAEs, n (%) | TN (n=47) | R/R (n=171) | Total (N=218) |
|---|---|---|---|
| Patients with SAE | 9 (19) | 17 (10) | 26 (12) |
| Rash | 3 (6.4) | 3 (1.8) | 6 (2.8) |
| Pneumonia | 1 (2.1) | 4 (2.3) | 5 (2.3) |
| Liver test abnormality | 2 (4.3) | 3 (1.8) | 5 (2.3) |
| Pneumonitis | 1 (2.1) | 4 (2.3) | 5 (2.3) |
| Diarrhea/colitis | 2 (4.3) | 2 (1.2) | 4 (1.8) |
| Neutropenia | 1 (2.1) | 2 (1.2) | 3 (1.4) |
| Cellulitis | 0 | 2 (1.2) | 2 (0.9) |
| Acute kidney injury | 0 | 2 (1.2) | 2 (0.9) |
| Cardiac disorder | 0 | 2 (1.2) | 2 (0.9) |

- SAEs were consistent with those previously reported in clinical studies

## Efficacy

- Of 218 enrolled in 2015, 175 were evaluable for investigator-assessed response:
  - ORR: 103/175 (59%)



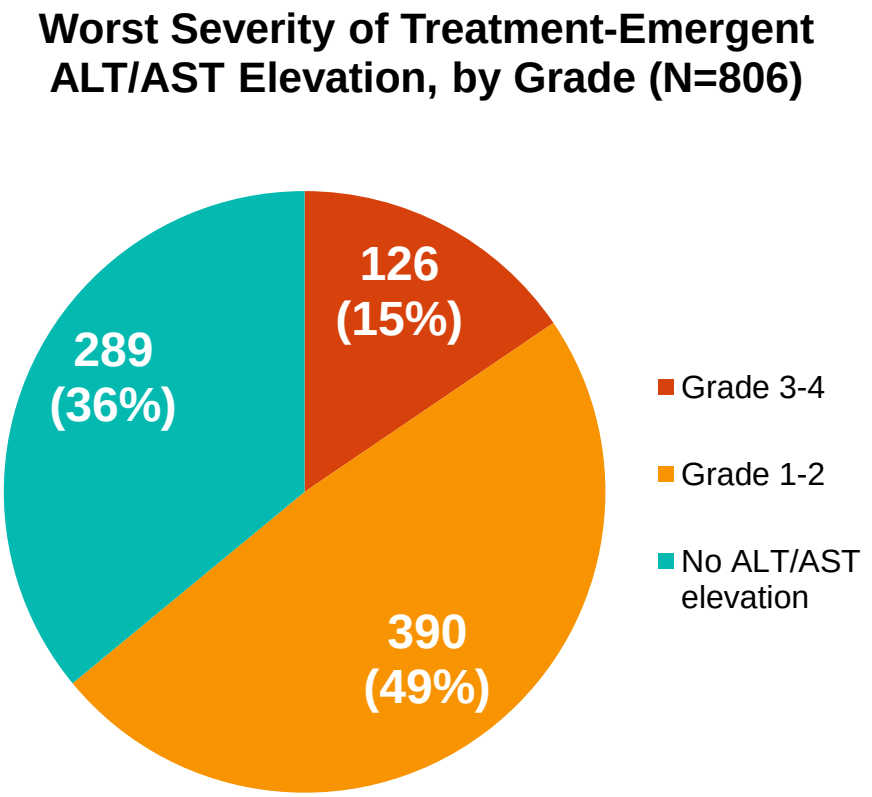

- Median OS was not reached
  - Deaths were reported for 8 patients, all with R/R disease

CR, complete response; PD, progressive disease; PR, partial response; R/R, relapsed/refractory; SAE, serious adverse event; SD, stable disease.

# Conclusions

- Patients included in the EAP had similar demographic characteristics to those of patients previously reported in clinical trials
- To date, available results indicate an acceptable tolerability profile for IDL+R in a real-world setting for patients with R/R CLL/SLL
- SAEs were similar to those previously described (rash, pneumonia, liver test abnormalities, pneumonitis, diarrhea/colitis, and neutropenia)

# Management of Transaminase Elevations Associated with Idelalisib
## ALT/AST Elevations by Severity Grade




- Transient ALT/AST elevation was observed for the majority of patients:
  - Treatment-Emergent ALT/AST Elevation:
    - Any grade: 516/806 (64%)
    - Grade ≥3: 125/806 (16%)
    - Grade ≥3 resolved[†]:115/125 (92%)
    - Rechallenged: 62/115 (54%)
  - Median times to onset and resolution of:
    - 1st event:
      - Onset: 7.9 weeks
      - Resolution: 4.1 weeks
    - 1st recurrent event after IDL rechallenge:
      - Onset: 1 week
      - Resolution: 2.1 weeks

Ghia, EHA 2016, P226

‡

# Results: Characteristics Associated with ALT/AST Elevations

**Distribution of Baseline Demographics and Clinical Characteristics, by Most Severe Post-Baseline Grade ALT/AST Elevation**

| Variable, n (%) | | Grade 0 (n=289) | Grade 1-2 (n=390) | Grade 3-4 (n=126) | *P*-value |
|---|---|---|---|---|---|
| Age Group | <65 years (n=311)<br>≥65 years (n=494) | 99 (31.8<br>190 (38.5) | 151 (48.6)<br>239 (48.4) | 61 (19.6)<br>64 (13.2) | 0.0024 |
| Rai Stage | 0-I (n-131)<br>II (n=129)<br>III (n=101)<br>IV (n=298) | 36 (27.5)<br>39 (30.2)<br>44 (43.6)<br>111 (37.2) | 65 (49.6)<br>59 (45.7)<br>43 (42.6)<br>157 (52.7) | 30 (22.9)<br>31 (24.0)<br>13 (13.9)<br>30 (10.1) | <0.0001 |
| Baseline Neutropenia | No (n=704)<br>Yes (n=213) | 201 (34.1)<br>88 (41.3) | 284 (48.2)<br>103 (48.4) | 104 (17.7)<br>22 (10.3) | <0.0001 |
| # Prior Regimens | 0 (n=105)<br>1-2 (n=300)<br>3-4 (n=236)<br>>4 (n=164) | 43 (41.0)<br>96 (32.0)<br>91 (38.6)<br>59 (36.0) | 39 (37.1)<br>143 (47.7)<br>100 (49.2)<br>75 (56.1) | 23 (21.9)<br>61 (20.3)<br>29 (12.3<br>13 (7.9) | 0.0010 |

- Increased incidence of grade ≥3 ALT/AST elevation was associated with:
  - Age <65 years, Rai stage 0-II disease, normal baseline ANC, and having received no more than two prior treatment regimens
- Increased incidence of grade ≥3 ALT/AST elevation was not associated with:
  - Race group, Karnofsky score, Ann Arbor stage (patients with iNHL), or IDL regimen (monotherapy vs combination therapy)

Ghia, EHA 2016, P226

# ALT/AST Elevations in Idelalisib treatment: Conclusions

- In this safety analysis:

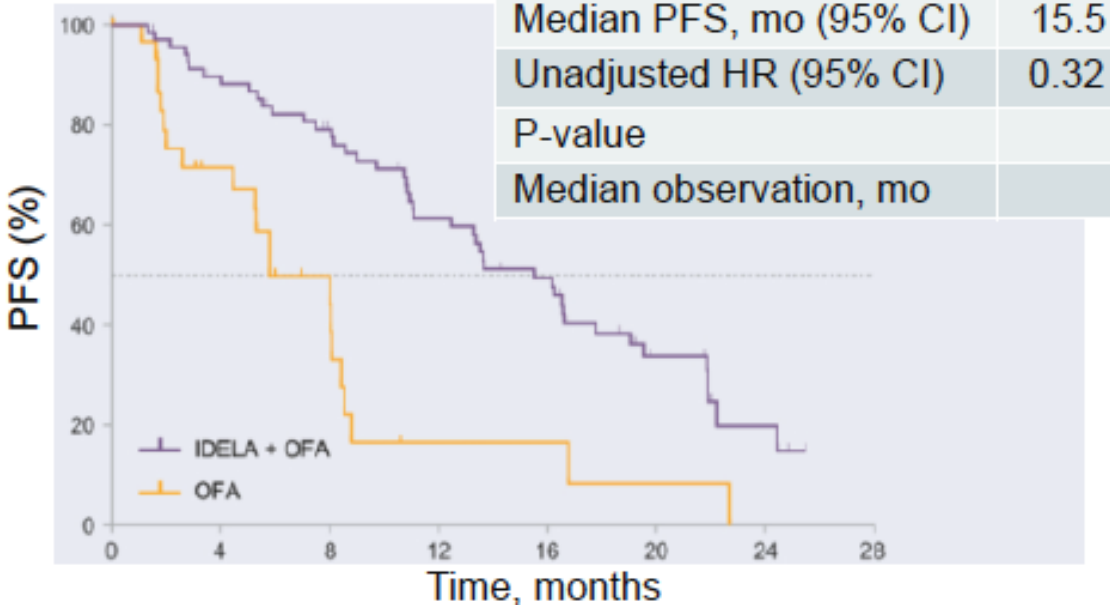
  - Most patients with grade ≥3 ALT/AST elevation managed with IDL dose-interruption and subsequent rechallenge had no event recurrence

  - Although risk factors for transaminase elevations associated with IDL treatment are largely undefined, certain patient-, disease-, and treatment-related characteristics generally associated with a more robust immune function were associated with an increased incidence of grade ≥3 ALT/AST elevation

- These data support the management of treatment-emergent ALT/AST elevation with IDL dose-interruption at grade 3 and subsequent rechallenge at the discretion of the treating physician

# Updated results from Phase 3 idelalisib and ofatumumab: PFS

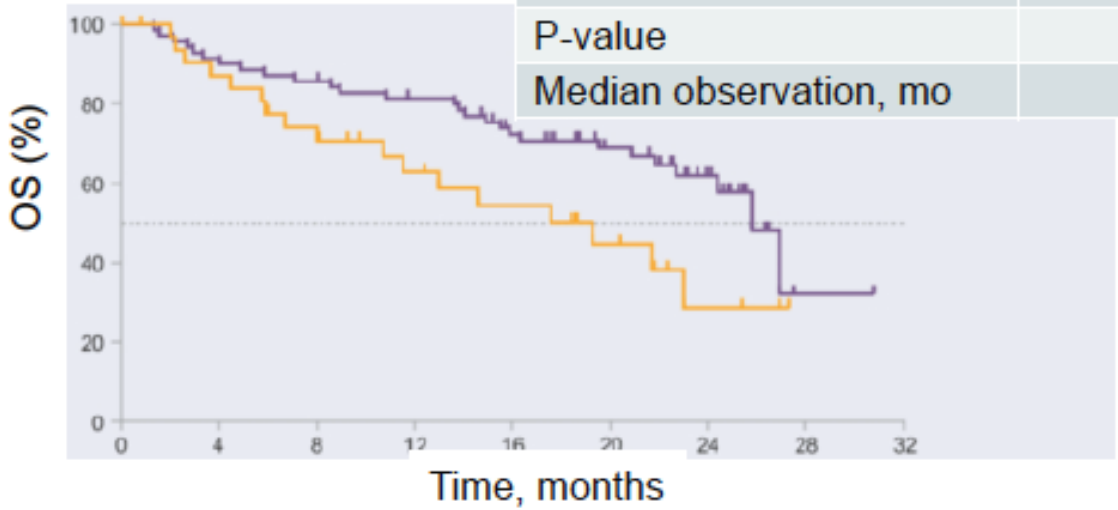
| | Idelalisib (n=174) | Ofatumumab (n=87) |
|---|---|---|
| Events, n (%) | 45 (64) | 21 (64) |
| Median PFS, mo (95% CI) | 15.5 (11.1, 19.1) | 5.8 (4.5, 8.4) |
| Unadjusted HR (95% CI) | 0.32 (0.18, 0.55) | |
| P-value | <0.001 | |
| Median observation, mo | 12.9 | 4.5 |




*Robak et al., EHA 2016, #P213*

# Updated results from Phase 3 idelalisib and ofatumumab: OS

| | Idelalisib (n=70) | Ofatumumab (n=33) |
|---|---|---|
| Deaths, n (%) | 27 (39) | 17 (52) |
| Median OS, mo (95% CI) | 25.8 (22.7, NR) | 19.3 (10.7, NR) |
| Unadjusted HR (95% CI) | 0.52 (0.28, 0.96) | |
| P-value | <0.03 | |
| Median observation, mo | 19.7 | 11.5 |




*Robak et al., EHA 2016, #P213*

# Venetoclax in CLL relapsed/refractory to ibrutinib or idelalisib

| | 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) |

- Venetoclax monotherapy demonstrated ORR of 70% in the ibrutinib arm and 48% in the idelalisib arm
- Venetoclax exhibited a tolerable safety profile; 1 patient with lab TLS and 1 with lab changes managed without clinical sequelae

Coutre et al., EHA 2016, #P559

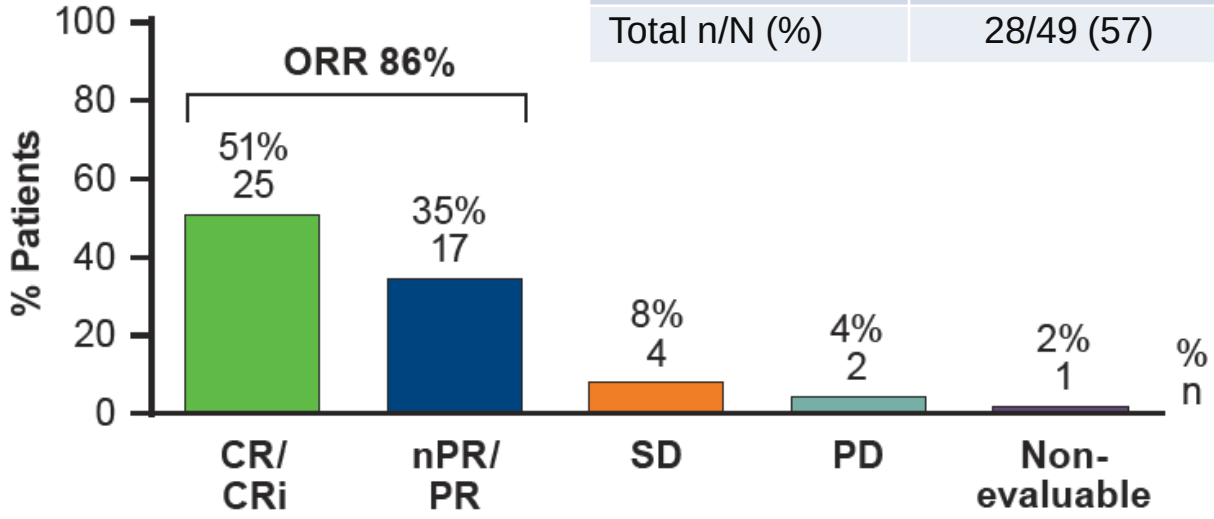
# Open issues & Questions

- Biomarkers in CLL: which and when are they *required*?
- Which role for MRD evaluation in the *clinical practice* of CLL?
- Do comorbidities have an impact in selecting the novel agents for CLL treatment?
- Side effects of new CLL drugs: any open issue for their management?

# Venetoclax plus rituximab: best objective response

**Best observed bone marrow MRD evaluation**

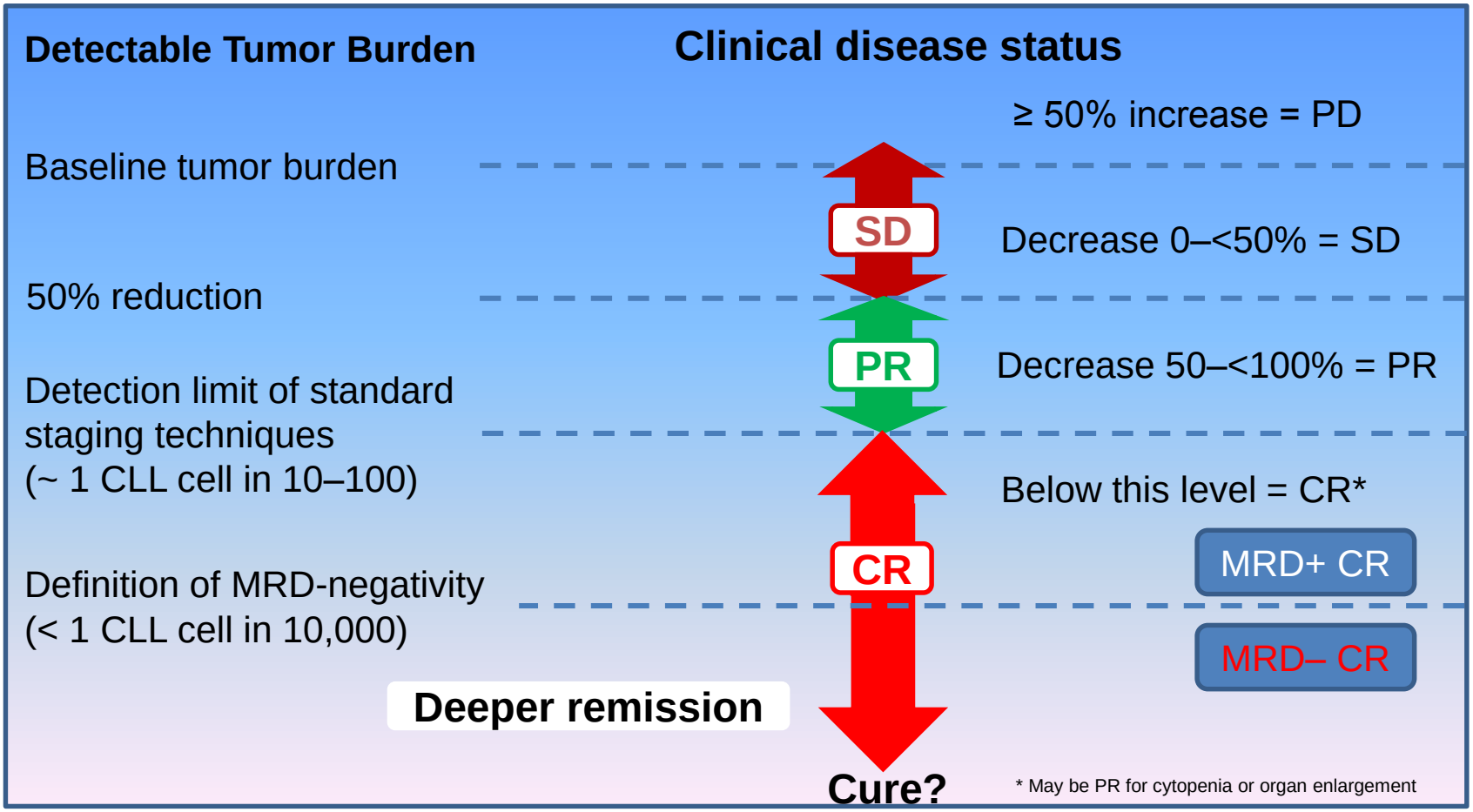
| Response classification | MRD-negative | MRD-positive | Not evaluable |
|---|---|---|---|
| CR/Cri (n=25) | 20 | 5 | 0 |
| nPR/PR (n=17) | 8 | 8 | 1 |
| Other (n=7) | 0 | 1 | 6 |
| Total n/N (%) | 28/49 (57) | 14/49 (29) | 7/49 (16) |




*Brander et al., EHA 2016, #P223*

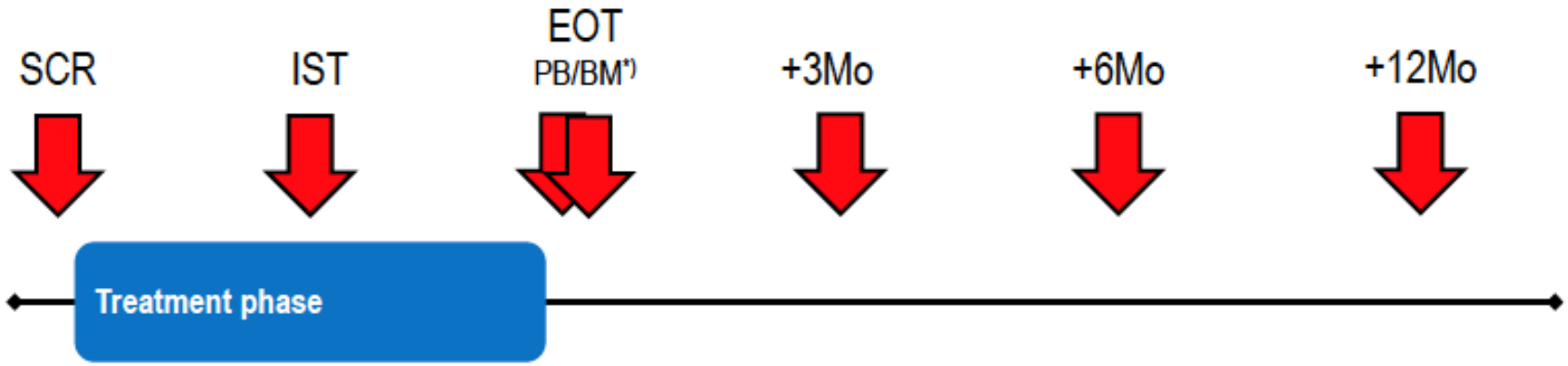
# MRD-negativity may indicate deeper remission

**MRD-negative patients have fewer CLL cells after treatment**




Hallek M, *et al. Blood* 2008; 111:5446–5456.

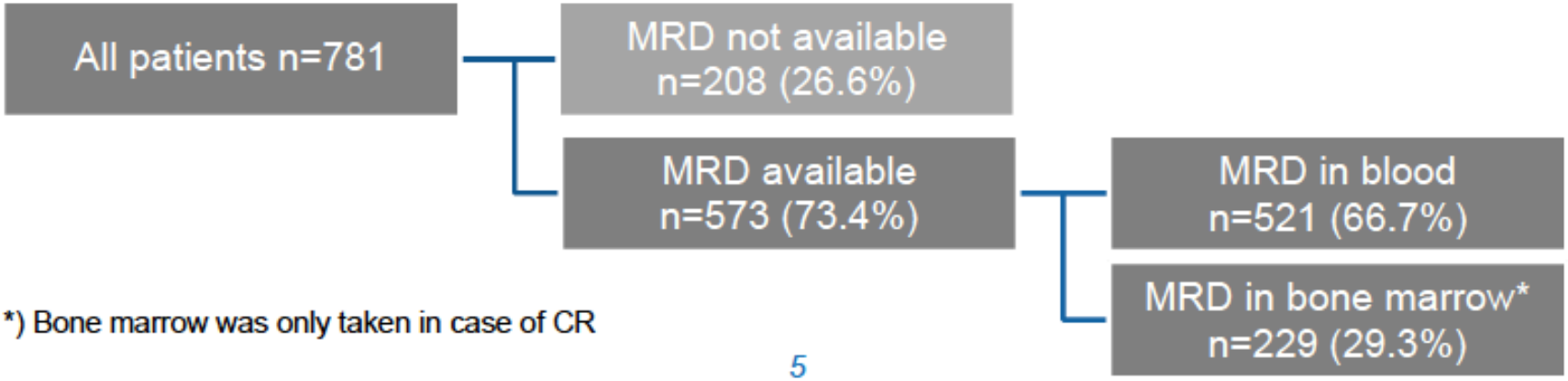
# CLL11: MRD assessment by IGH RQ-PCR




**Two laboratories (Kiel/Rotterdam)**

Categorizing according established MRD risk groups (Böttcher et al GCLLSG CLL8-trial)

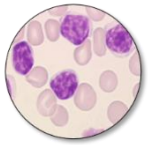
- MRD-positive group: MRD above $10^{-2}$
- MRD-intermediate: MRD between $10^{-2}$ and $10^{-4}$
- MRD-negative: MRD below $10^{-4}$



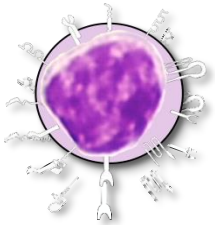

*) Bone marrow was only taken in case of CR

# (Bio)marker: variable that associates with disease outcome

**Host Factors:** ***Age***, ***Comorbidities, …***

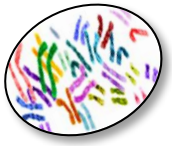


**Disease Markers:** ***Stage***, ***LDT***, *etc*

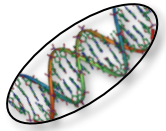


**Ag expression:** *CD38, Zap70,* ***CD49d****, etc*

**Serology:** ***β2M****, TK, LDH, sCD23, etc*



**Genetics:** ***del17p***, ***TP53 mutation***, *del11q22, del13q14, trisomy 12, NOTCH1 mutation, SFRB1 mutation, etc*



**Biology Markers:** ***IGVH-sequence***, *BCR-structure*

*Rossi, EHA-21, CLL Educational session, 2016*

# Markers that identify unfit patients

| | |
|---|---|
| **MDACC** | ↑ myelosuppression/dose reductions in patients >60 yrs[1]<br>↑ early treatment discontinuations in patients ≥70 yrs[2] |
| **CLL8** | ↑ hematological toxicity in patients ≥65 yrs[3]<br>↑ adverse events in pts with increased CIRS[4] |
| **CLL10** | ↑ infections in patients >65 yrs[5] |
| **REACH** | ↑ adverse events in patients with decreased CrCl[6] |

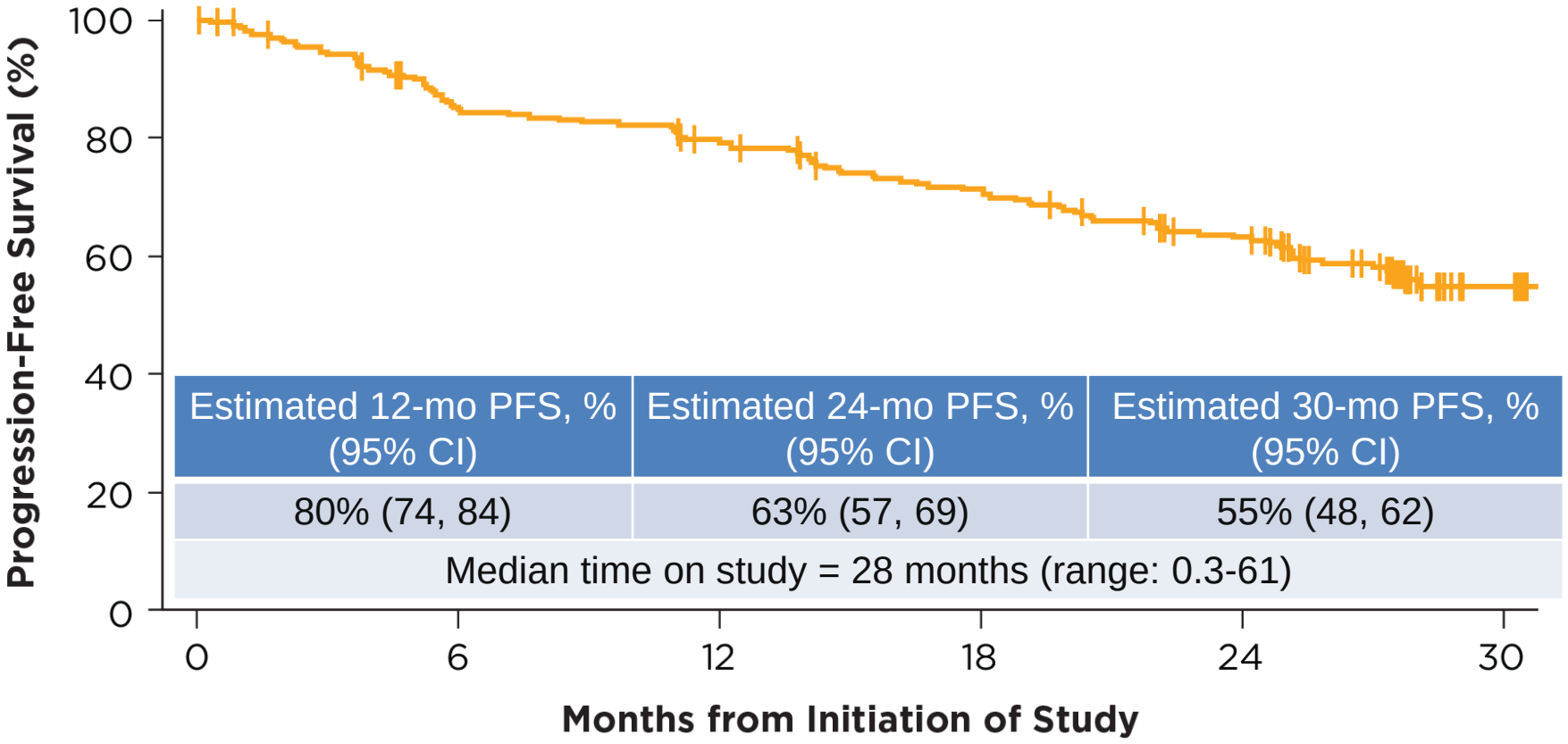
In routine practice, the following criteria characterize patients considered **less fit for FCR**:

- Older age (e.g. ≥**70 years**)
- Higher comorbidity burden (e.g. **CIRS >6**)
- Poor performance status (e.g. **ECOG >1**)
- Impaired renal function (e.g. **CrCl <70 mL/min**)

CrCl, creatinine clearance;
CIRS, cumulative illness rating scale;
ECOG, eastern cooperative oncology group

[1]Keating *et al. J Clin Oncol.* 2005; [2]T Ferrajoli A, *et al*. Leuk Lymphoma. 2005: S86; [3]Hallek *et al. Lancet.* 2010 ; [4]Goede *et al. Haematologica (EHA meeting abstracts). 2012*; [5]Eichhorst *et al. Blood.* 2014 (ASH meeting abstracts) ; [6]Robak *et al. J Clin Oncol.* 2010

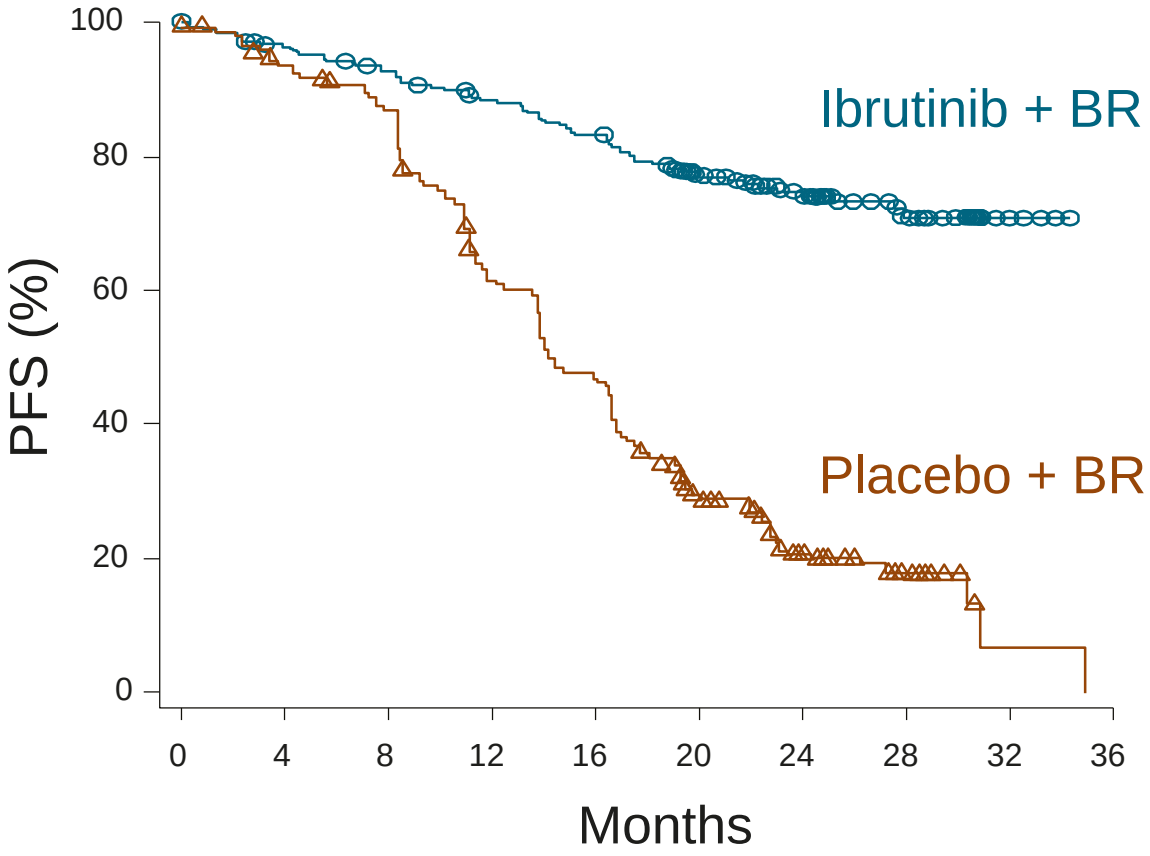
# Cross-study analysis: PFS




| Estimated 12-mo PFS, % (95% CI) | Estimated 24-mo PFS, % (95% CI) | Estimated 30-mo PFS, % (95% CI) |
|---|---|---|
| 80% (74, 84) | 63% (57, 69) | 55% (48, 62) |
| Median time on study = 28 months (range: 0.3-61) | | |

*Jones J, et al. EHA 2016, #S429*

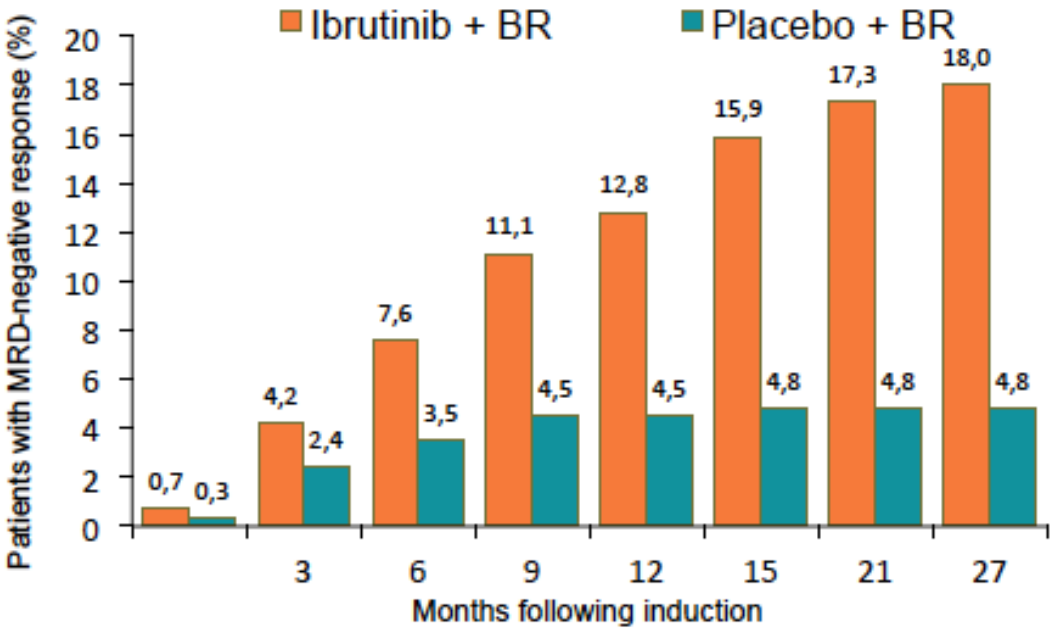
# HELIOS: Investigator-assessed PFS
# Median follow-up, 25.4 months




| | Ibrutinib + BR | Placebo + BR |
|---|---|---|
| Median PFS (months) | NR | 14.2 |
| HR | 0.199 | |
| 95% CI | 0.15-0.26 | |
| Log rank p value | < 0.0001 | |

*Fraser et al, EHA 2016, #S430*

# HELIOS (2-year follow-up): MRD-negative response over time




Among patients who exhibited a MRD-negative response (< 0.01%), those on ibrutinib + BR have not yet reached the median PFS, compared with a median PFS of 22.1 months (95% CI, 13.9-NE) for placebo + BR

*Fraser et al, EHA 2016, #S430*