# Mohamed A. Kharfan-Dabaja, MD, MBA

## CLL & CML

Relevant financial relationships in the past twelve months by presenter or spouse/partner.

Speakers Bureau: Alexion Pharmaceuticals, Incyte Corp, Seattle Genetics

The speaker will directly disclosure the use of products for which are not labeled (e.g., off label use) or if the product is still investigational.

MAYO CLINIC

# CLL and CML

**Mohamed A. Kharfan-Dabaja, MD, MBA, FACP**
Director, Blood and Marrow Transplantation and Cellular Therapies
Mayo Clinic
Jacksonville, FL

**15th Annual Miami Cancer Meeting, April 29, 2018**

# Outline

- **CLL**
  - Disease-risk stratification
    - Genomics
  - Ibrutinib-5 years later!
  - Novel ibrutinib-based combinations
  - *BCL2* inhibition-Murano Study update (ASH 2017)
  - Role of allogeneic HCT and CAR-T
- **CML**
  - CML, 17 years after Imatinib approval on May 2001
  - Updates on Dasision and ENESTnd
  - TKI discontinuation and treatment-free remission

# Cumulative Index Rating Scale (CIRS)

Frailty

- *No Go: Supportive therapy*
  - CIRS >12
- *Slow Go: Reduced-intensity treatment*
  - CIRS 7-12
- *Go Go: Standard treatment*
  - CIRS 0-6
  - Physically fit
  - No significant comorbidities (CIRS 3/4)
  - Excellent renal function
  - Regardless of age



*CIRS = Cumulative Index Rating Scale*
*Salvi et al, 2008; Eichhorst et al, 2009*

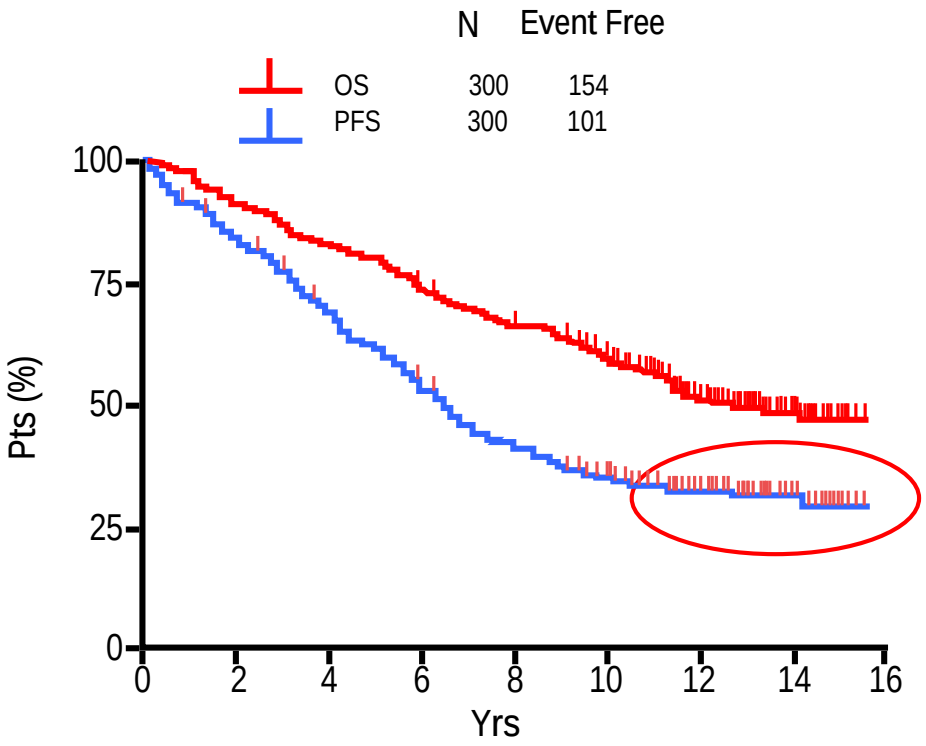
# CLL: Incidence of genetic lesions

| Incidence of Genetic Lesion, % | Treatment naïve CLL[1] (n = 452) | CLL8[2] Frontline FC vs FCR (n = 635) | CLL3X[3,4] High-Risk AlloSCT (n = 80) | CLL2H[5,6] F-Refractory Alemtuzumab (n = 97) |
|---|---|---|---|---|
| TP53$^{mut}$ | 5.3 | 11.5 | 30.0 | 39.0 |
| NOTCH1$^{mut}$ | 12.6 | 10.0 | 14.0 | 13.4 |
| SF3B1$^{mut}$ | 8.6 | 18.4 | 26.0 | 17.5 |
| IGHV UM | 32.8 | 63.0 | 96.0 | 79.0 |
| del(17p) | 5.3 | 8.4 | 18.1 | 30.1 |
| del(11q) | 16.0 | 24.6 | 36.1 | 19.4 |

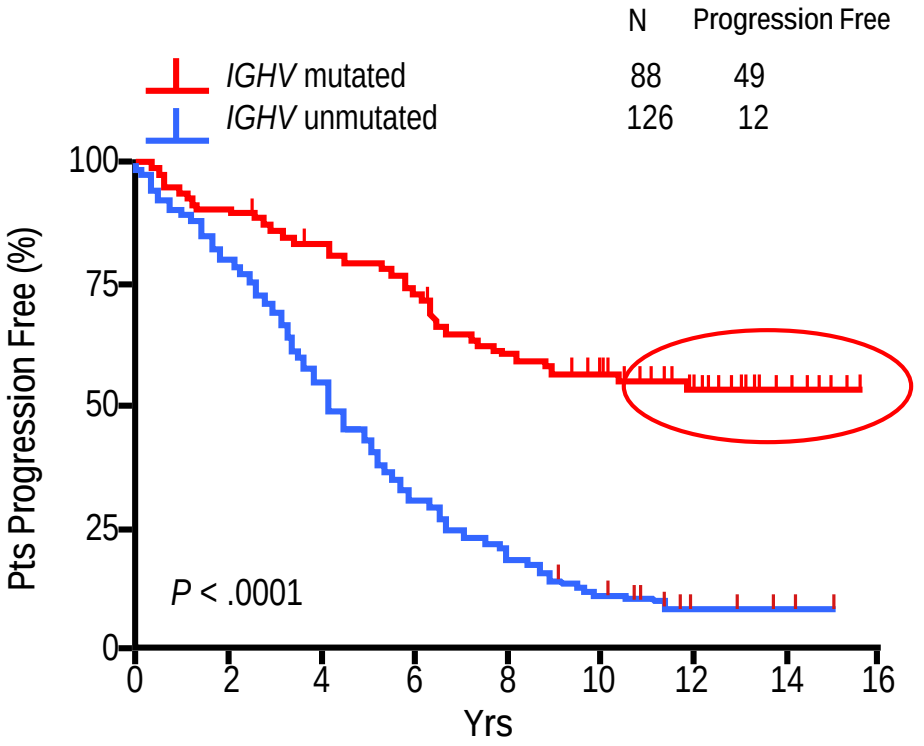
1. Puente XS, et al. Nature. 2015;526:519-524; 2. Stilgenbauer S, et al. Blood. 2014;123:3247-3254; 3. Dreger P, et al. ASH 2012. Abstract 966; 4. Dreger P, et al. Blood. 2013;121:3284-3288; 5. Schnaiter A, et al. Blood. 2013;122:1266-1270; 6. Schneiter A, et al. ASH 2012. Abstract 710.

# FCR300 Phase 2 Trial: plateau in PFS with FCR as initial therapy for CLL

- **With extended follow-up, PFS shows plateau at years 10-11**



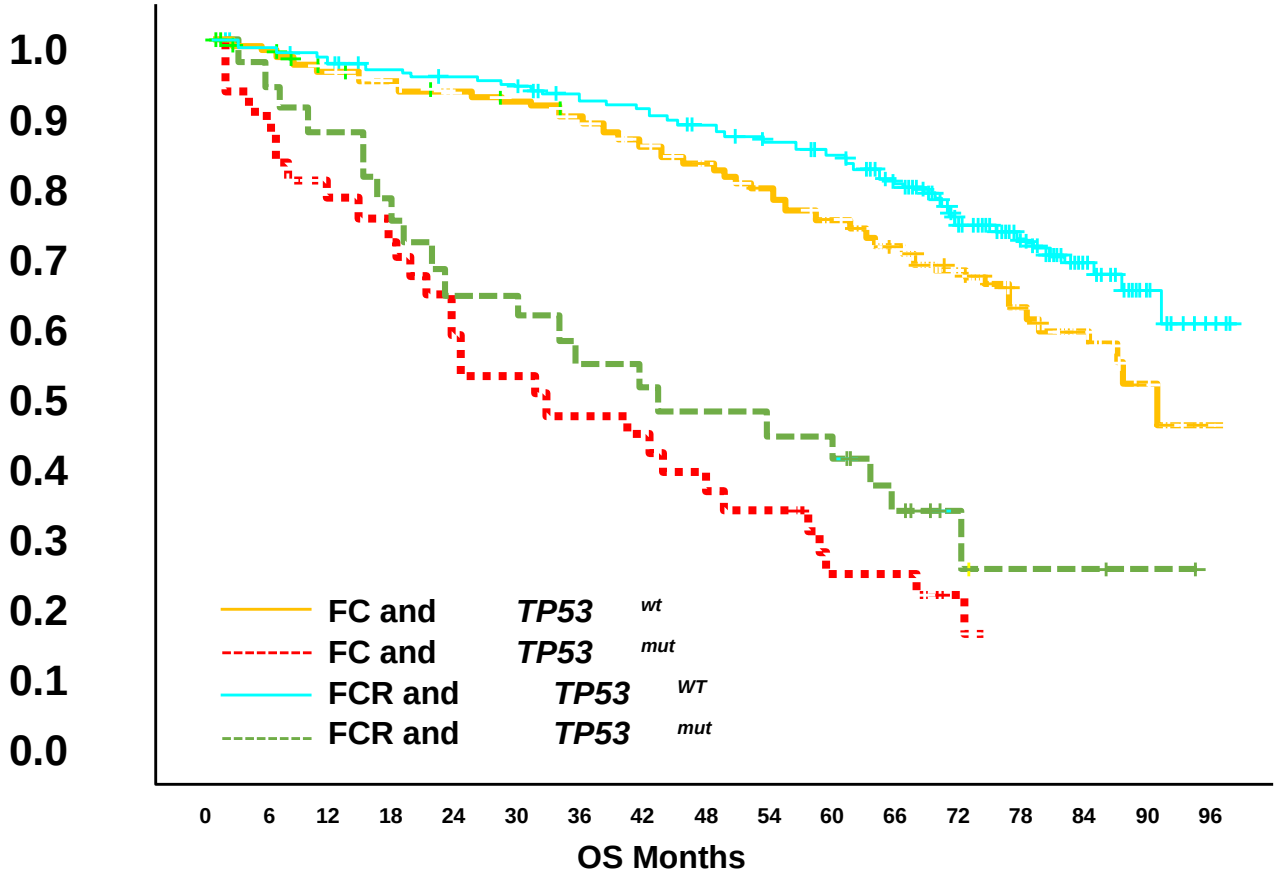

- **FCR has limited efficacy in unmutated *IGHV***






*Thompson PA, et al. Blood. 2016;127:303-309*

# del(17p)/*TP53mut* inferior outcomes CLL8 (FCR vs FC): *TP53* mutation on OS





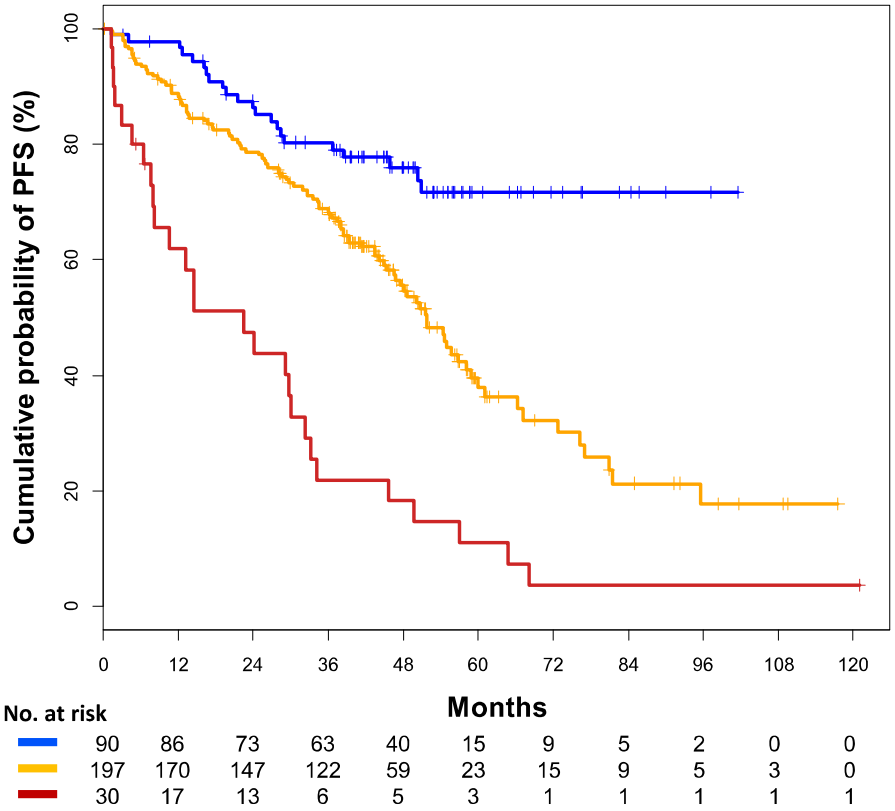

*Stilgenbauer S, et al. Blood. 2014;123(21):3247-54*

# FCR in untreated CLL

| | 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 of the PFS curves**

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




Low-risk group (*IGHV* mutated) Intermediate-risk group (*IGHV* unmutated and/or 11q deletion) High-risk group (17p deletion)



*Rossi et al. Blood. 2015;126(16):1921-24*

# CLL-International Prognostic Index CLL-IPI

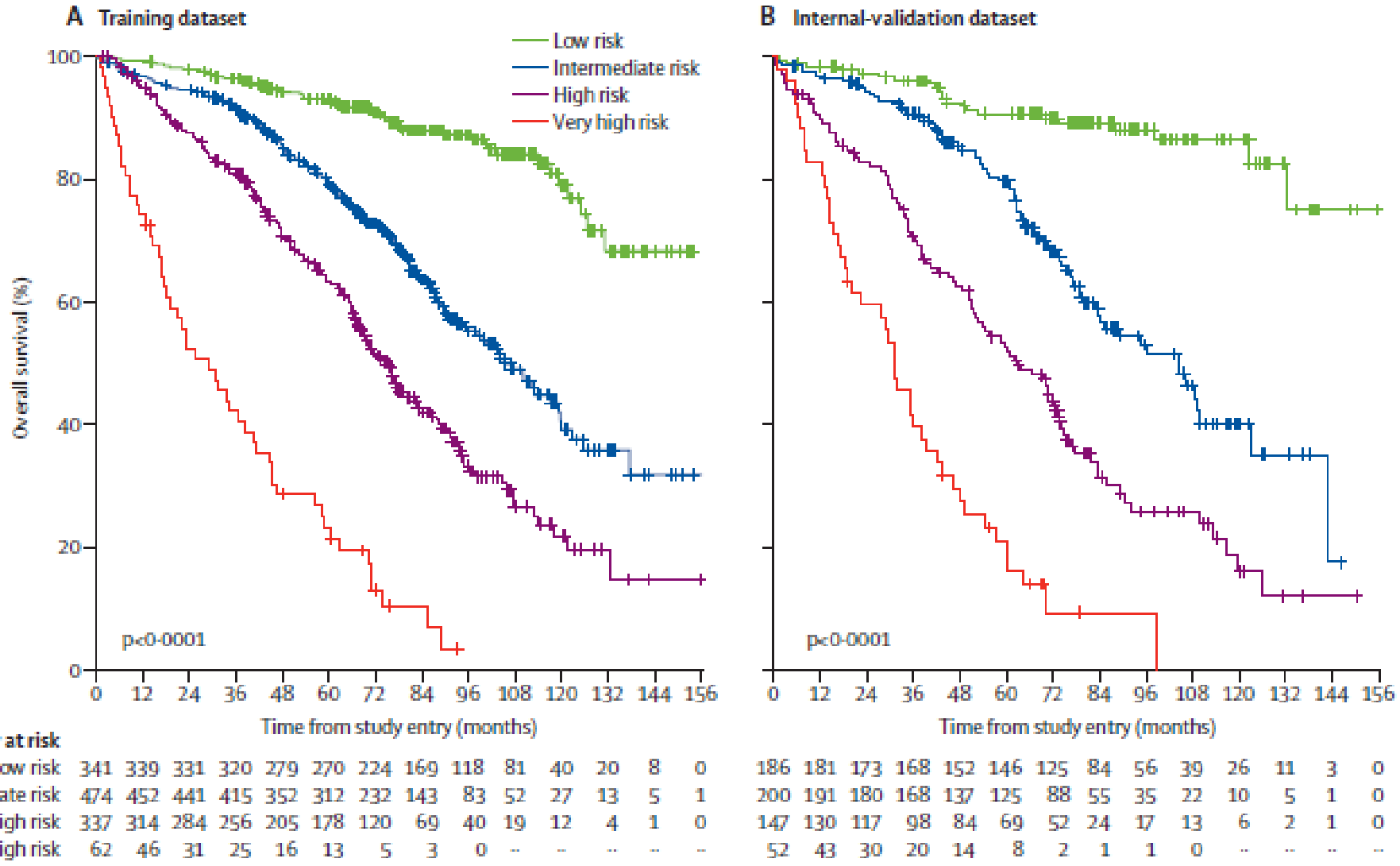
| Variable | Adverse Factor | Grading |
|---|---|---|
| *TP53*/17p | Mutated/deleted | 4 |
| *IGHV* status | Unmutated | 2 |
| β2 microglobulin | > 3.5 mg/L | 2 |
| Clinical stage | Binet B/C or Rai II-IV | 1 |
| Age | > 65 years | 1 |
| Prognostic score | | 0-10 |

| Risk Group | Score |
|---|---|
| Low | 0-1 |
| Intermediate | 2-3 |
| High | 4-6 |
| Very High | 7-10 |



*Kutsch N, et al. ASCO Annual Meeting Abstracts. 2015. Abstract 7002*
*Lancet Oncol 2016; 17: 779–90*

# CLL-IPI: risk groups & outcomes

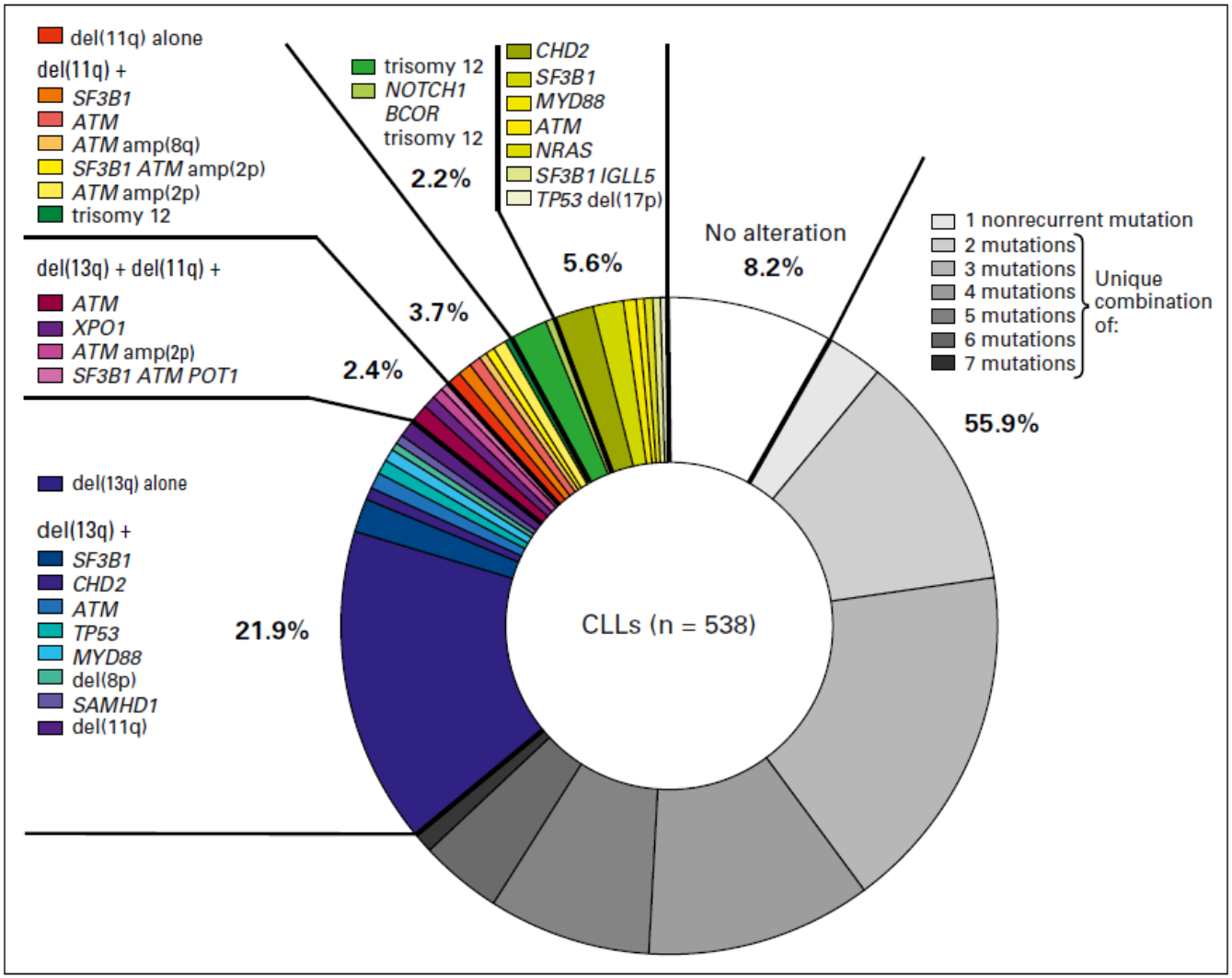



MAYO CLINIC

*Lancet Oncol.2016; 17: 779–90*

# Genomics

# CLL prognostic genomic landscape






*Lazarian G, et al. J Clin Oncol. 2017; 35: 984-93*

Clinical Cancer Research

# Survival of Del17p CLL Depends on Genomic Complexity and Somatic Mutation

Lijian Yu[1,2], Haesook T. Kim[3], Siddha N. Kasar[1,2], Parul Benien[4], Wei Du[4], Kevin Hoang[1], Andrew Aw[5], Bethany Tesar[1], Reina Improgo[1,2], Stacey M. Fernandes[1], Saranya Radhakrishnan[4], Josephine L. Klitgaard[1,2], Charles Lee[6], Gad Getz[7,8], Sunita R. Setlur[2,4], and Jennifer R. Brown[1,2]

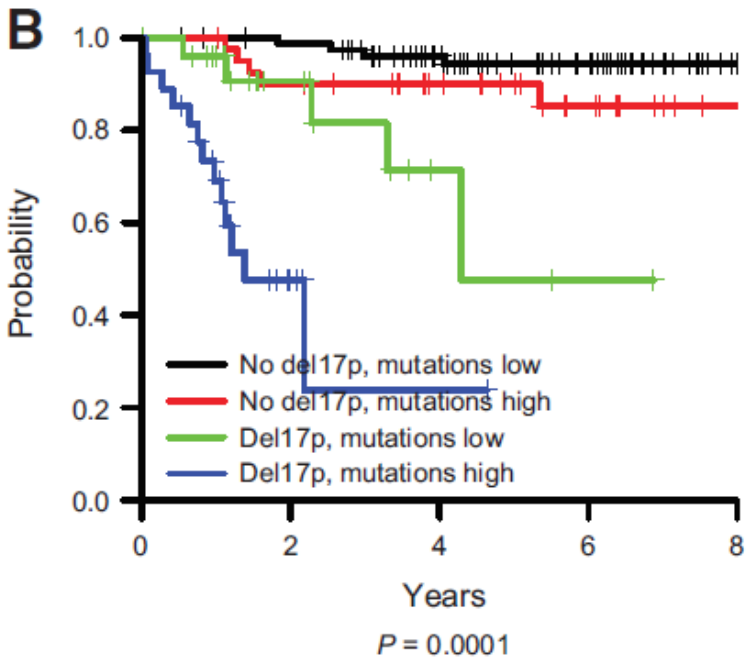
**Table 1.** Patient characteristics and summary of CNAs and somatic mutations

| | All | wt 17p | del(17p) | *P* |
|---|---|---|---|---|
| *N* | 277 (100%) | 208 (75%) | 69 (25%) | |
| Male | 163 (59%) | 118 (57%) | 45 (65%) | 0.26 |
| Age of onset | 55 (32–86) | 54 (32–78) | 61 (38–86) | 2.2e−05 |
| Treated before sampling | 74 (27%) | 39 (19%) | 35 (51%) | 6.4e−07 |
| *IGHV* mutated | 135 (52%) | 125 (64%) | 10 (16%) | 1.2e−11 |
| Complex karyotype | 42 (32%) | 20 (21%) | 22 (61%) | 4.03e−05 |
| FISH cytogenetics | | | | |
| 13q14 loss | 170 (61%) | 139 (67%) | 31 (45%) | 1.9E−4 |
| 11q loss | 37 (13%) | 29 (14%) | 8 (12%) | 0.55 |
| Trisomy 12 | 36 (13%) | 25 (12%) | 11 (16%) | 0.54 |
| Profiled by WES[a] | 176 (100%) | 123 (70%) | 53 (30%) | |
| Total mutations | 19 (0–94) | 18 (0–94) | 21 (7–68) | 0.0048 |
| Nonsynonymous mutations | 14 (0–70) | 13 (0–70) | 16 (5–54) | 0.0055 |
| Synonymous mutations | 4 (0–24) | 4 (0–24) | 4 (1–14) | 0.14 |
| Subclonal mutations | 9 (0–89) | 9 (0–89) | 8 (2–35) | 0.9 |
| Clonal mutations | 9 (0–34) | 7 (0–24) | 12 (0–34) | 5.8E−4 |
| Profiled by SNP[a] | 200 (100%) | 145 (72%) | 55 (28%) | |
| # of CNAs | 1 (0–36) | 1 (0–16) | 7 (0–36) | 1.5e−16 |
| # of losses | 1 (0–35) | 1 (0–16) | 6 (0–35) | 5e−15 |
| # of gains | 0 (0–19) | 0 (0–3) | 1 (0–19) | 3.3e−08 |
| Lost Mb | 3 (0–530) | 1.2 (0–88) | 97 (0–530) | 2.9e−18 |
| Gained Mb | 0 (0–340) | 0 (0–260) | 5.9 (0–340) | 9.9e−6 |
| 8p loss | 21 (10%) | 6 (4%) | 15 (27%) | 1.1e−05 |
| 3p loss | 15 (8%) | 0 (0%) | 15 (27%) | 8.1e−10 |
| 4p loss | 14 (7%) | 2 (1%) | 12 (22%) | 4.1e−06 |
| 9p loss | 15 (8%) | 2 (1%) | 13 (24%) | 1.1e−06 |
| Loss in 3p, 4p, or 9p | 31 (16%) | 3 (2%) | 28 (51%) | 8.6e−16 |

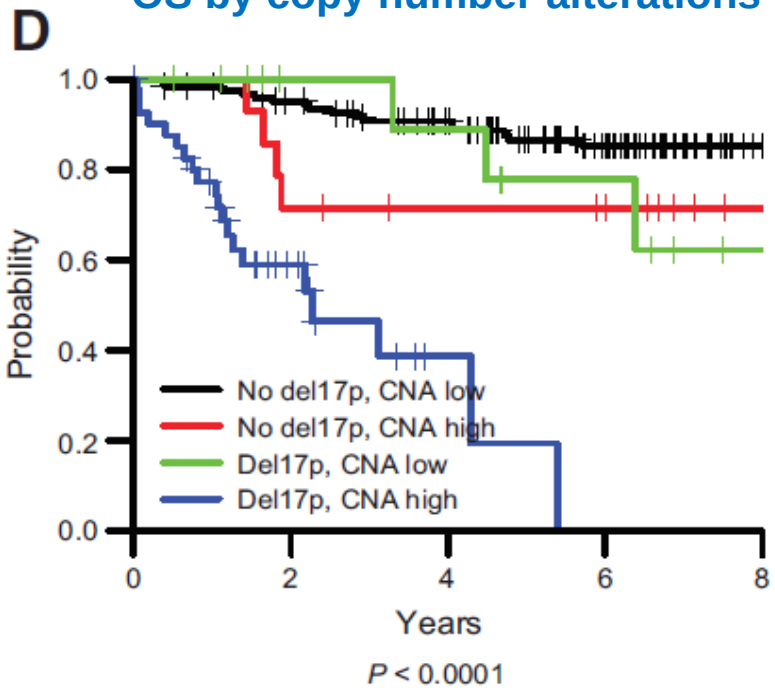
[a]Median values and ranges are presented for the WES and SNP analysis.

# Overall survival

## OS by number of mutations



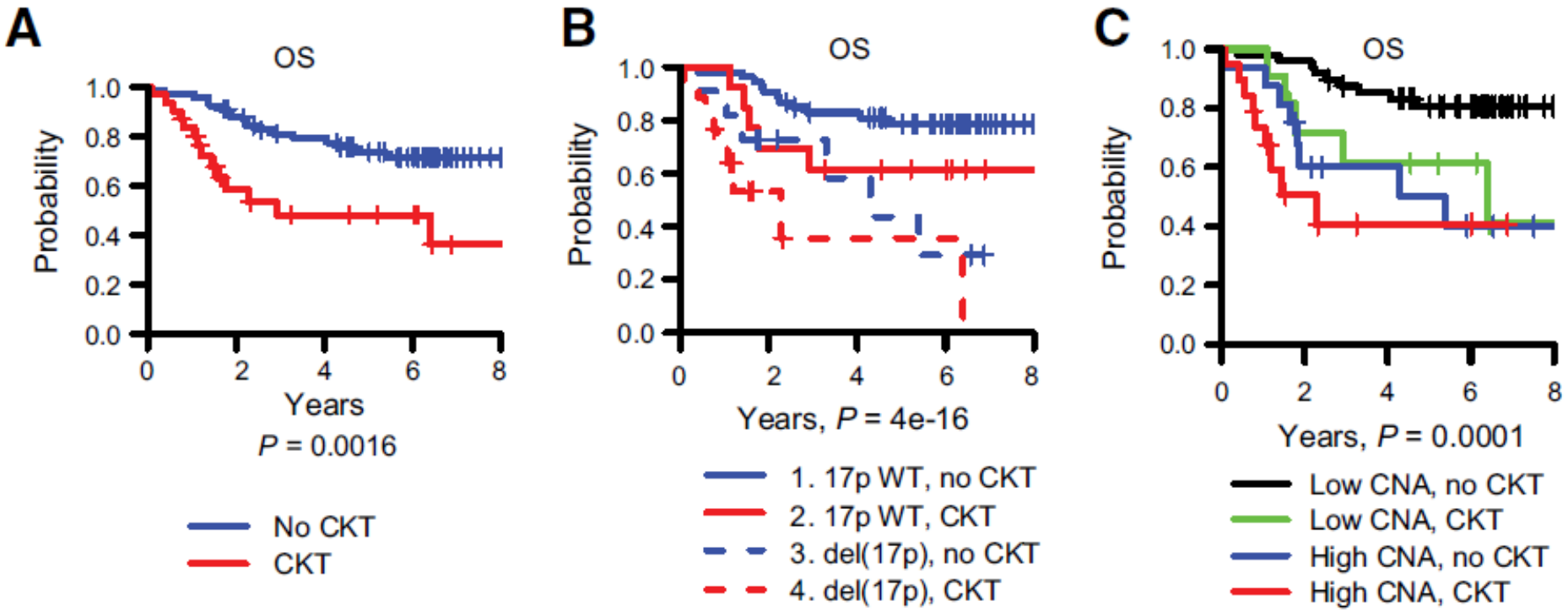

## OS by copy number alterations






*Yu L, et al. Clin Cancer Res. 2016; 23: 735-45*

# OS: complex karyotype






*Yu L, et al. Clin Cancer Res. 2016; 23: 735-45*

# Ibrutinib: 5 years later!

blood®

Prepublished online February 2, 2018;
doi:10.1182/blood-2017-10-810044 originally published online
February 2, 2018

**Single-Agent Ibrutinib in Treatment-Naïve and Relapsed/Refractory Chronic Lymphocytic Leukemia: A 5-Year Experience**

Susan O'Brien, Richard R. Furman, Steven Coutre, Ian W. Flinn, Jan A. Burger, Kristie Blum, Jeff Sharman, William Wierda, Jeffrey Jones, Weiqiang Zhao, Nyla A. Heerema, Amy J. Johnson, Ying Luan, Danelle F. James, Alvina D. Chu and John C. Byrd



# Ibrutinib: 5 years later!

**Table 1. Baseline characteristics of all treated patients**

| | TN ≥65 years (n=31) | R/R (n=101) | All patients (N=132) |
|---|---|---|---|
| **Median age, years (range)** | 71 (65–84) | 64 (37–82) | 68 (37–84) |
| Age ≥70 years, n (%) | 23 (74) | 34 (34) | 57 (43) |
| **ECOG performance status, n (%)** | | | |
| 0 | 23 (74) | 43 (43) | 66 (50) |
| 1 | 8 (26) | 54 (53) | 62 (47) |
| 2 | 0 (0) | 4 (4) | 4 (3) |
| **Rai stage, n (%)** | | | |
| 0-II | 13 (42) | 38 (38) | 51 (39) |
| III-IV | 17 (55) | 58 (57) | 75 (57) |
| Unknown | 1 (3) | 5 (5) | 6 (5) |
| **Bulky disease (lymph nodes), n (%)** | | | |
| ≥5 cm in diameter | 6 (19) | 55 (54) | 61 (46) |
| ≥10 cm in diameter | 0 | 15 (15) | 15 (11) |
| **Unmutated *IGHV* gene, n (%)** | 15 (48) | 79 (78) | 94 (71) |
| **Cytogenetic abnormalities, n (%)** | | | |
| del(17p) | 2 (6) | 34 (34) | 36 (27) |
| del(11q) | 1 (3) | 35 (35) | 36 (27) |
| Trisomy 12 | 8 (26) | 12 (12) | 20 (15) |
| del(13q) | 17 (55) | 47 (47) | 64 (49) |
| Complex karyotype | 4 (13) | 37 (37) | 41 (31) |
| **$\beta_2$-microglobulin level >3.5 mg/L, n (%)** | 4 (13) | 37 (37) | 41 (31) |
| **Median no. of prior therapy, n (range)** | — | 4 (1–12) | — |
| 1–2 prior therapies, n (%) | — | 27 (27) | — |
| 3 prior therapies, n (%) | — | 14 (14) | — |
| ≥4 prior therapies, n (%) | — | 60 (59) | — |
| **Types of prior systemic therapy, n (%)** | | | |
| Chemotherapy | — | 101 (100) | — |
| Nucleoside analog | — | 97 (96) | — |
| Alkylator (including bendamustine) | — | 92 (91) | — |
| Anti-CD20–based regimen | — | 99 (98) | — |
| Anti-CD20–based chemoimmunotherapy | — | 97 (96) | — |
| Alemtuzumab–based regimen | — | 23 (23) | — |
| Idelalisib | — | 6 (6) | |

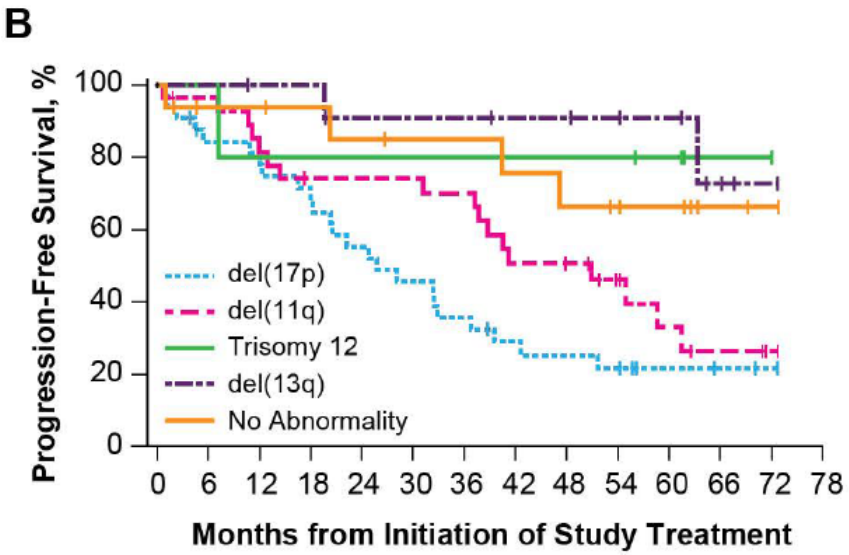
*O'Brien et al. Blood. 2018 . [Epub ahead of print]*

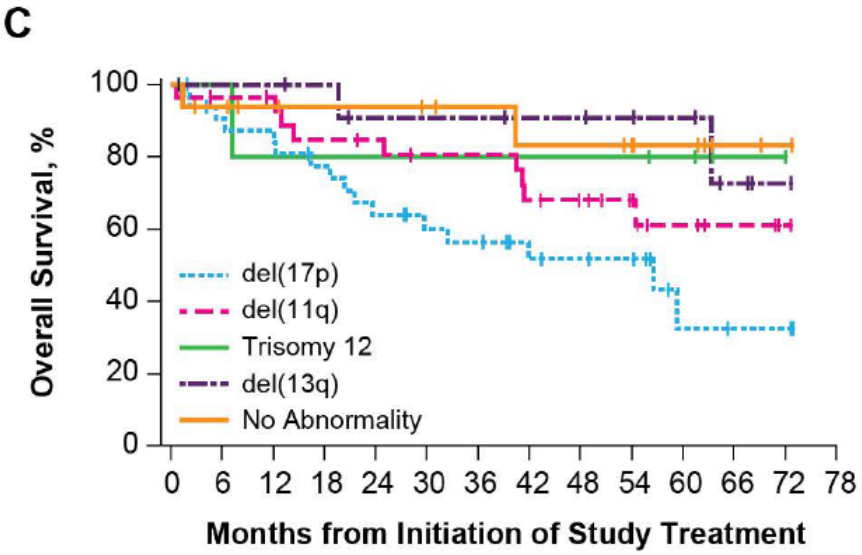


# Survival outcomes in relapsed/refractory pts

## Chromosomal abnormalities by *FISH*




*O'Brien et al. Blood. 2018 . [Epub ahead of print]*

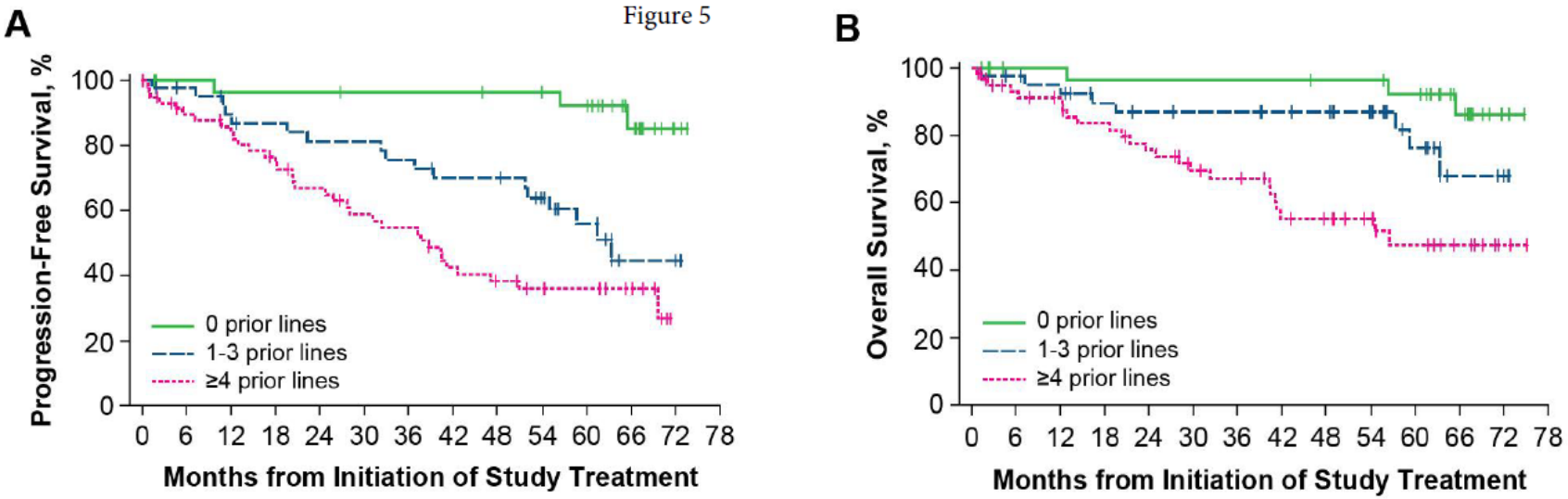


# Survival outcomes in relapsed/refractory pts

## Lines of prior therapy

Figure 5




*O'Brien et al. Blood. 2018 . [Epub ahead of print]*

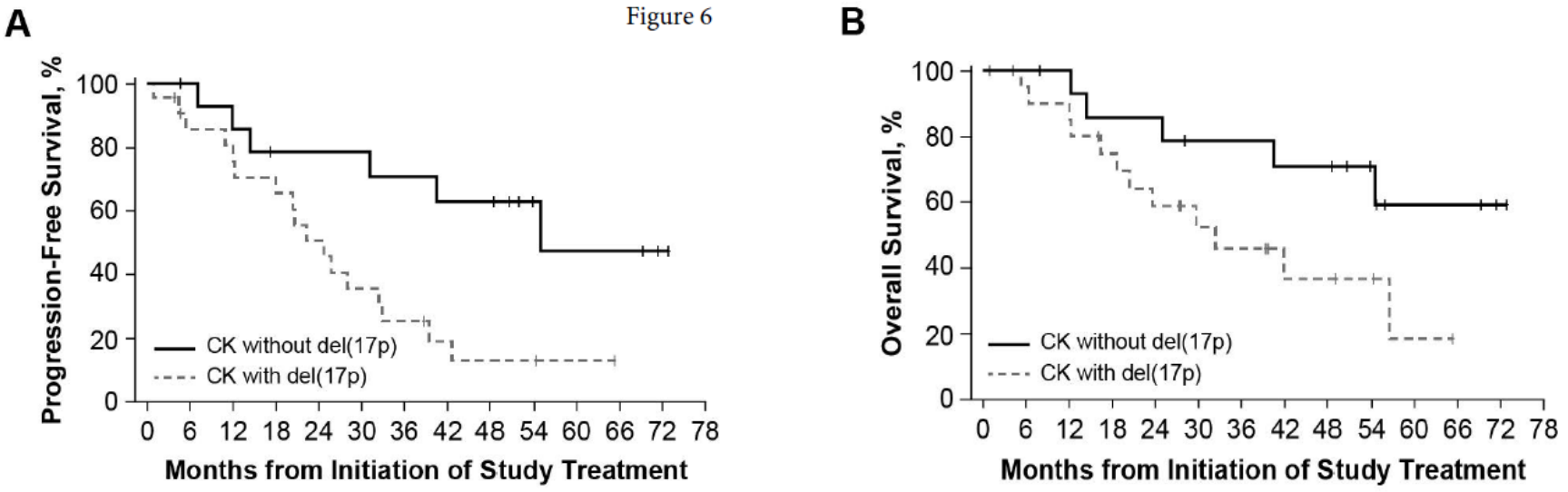


# Survival outcomes in relapsed/refractory pts

## Complex karyotype with or without del17p

Figure 6




*O'Brien et al. Blood. 2018 . [Epub ahead of print]*



# ASH 2017

## Mato AR, et al.

## Abstract 4315: Disease and Patient Characteristics, Patterns of Care, Toxicities, and Outcomes of Chronic Lymphocytic Leukemia (CLL) Patients Treated with Venetoclax: A Multicenter Study of 204 Patients

# ASH 2017-Mato AR, et al. Abs # 4315

- N= 204 (98% relapsed/refractory CLL)
  - Median age=67 (37-91)
  - Median prior therapies=**3** (0-11)
  - Del17p=**44%** (*TP53 mut*=41%)
  - Complex karytotype=**33%** (≥ 3abn)
  - Prior cellular therapy (CAR-T or transplantation)=5%
  - Prior kinase inhibitors=**64%**
    - ≥ 2 kinase inhibitors=15%
  - *BTK* mutated= 27% (51 tested)
  - *PLCγ2* mutated=10% (49 tested)

# Mato AR, et al. (ASH 2017), Venetoclax

- Median F/U (10 mos)
  - 72 venetoclax-treated pts discontinued therapy
    - CLL progression=47%
    - Richter transformation=21%
    - Toxicity=11%
    - Others=21%

## Multivariate analysis

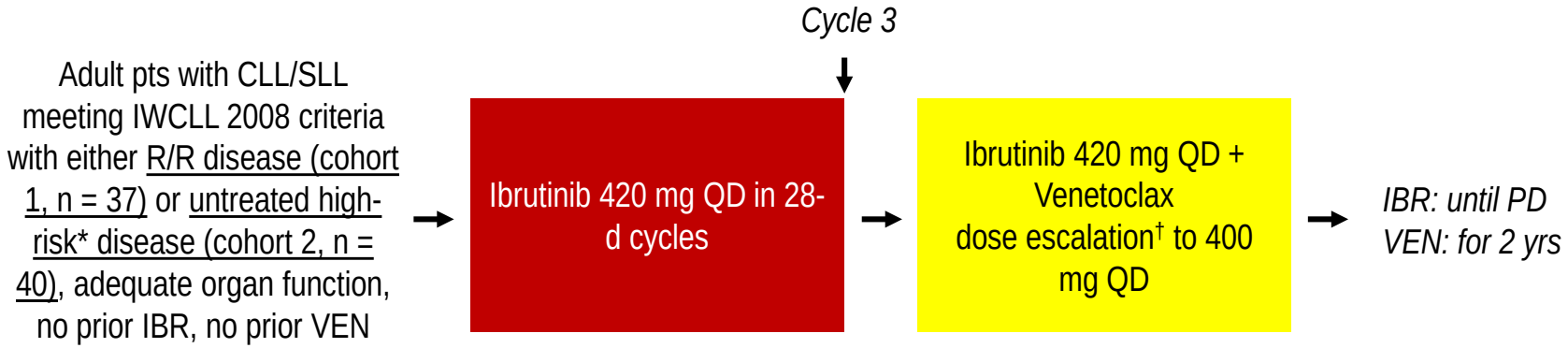
| Pre-venetoclax risk factors for inferior PFS | Hazard ratio (95%CI) | P-value |
|---|---|---|
| **Prior kinase inhibitor exposure** | **3.7 (1.9-7.5)** | **<0.001** |
| Prior cellular therapy | 4.6 (2.0-10.7) | <0.001 |
| *TP53* interruption | 2.8 (1.6-5.2) | <0.001 |
| Complex karyotype | 1.9 (1.04-3.4) | 0.04 |

# Venetoclax plus ibrutinib

# Venetoclax + Ibrutinib in CLL: study design

- Investigator-initiated, single-arm, multicohort phase II trial (all pts initiating tx: N = 116; current analysis: n = 77)




***≥ 1 of following high-risk characteristics: ≥ 65 yrs of age; del(11q); del(17p) or mutated *TP53*; unmutated *IGHV*.**

†Venetoclax weekly dose escalation (all doses QD): 20 mg, 50 mg, 100 mg, 200 mg, 400 mg.

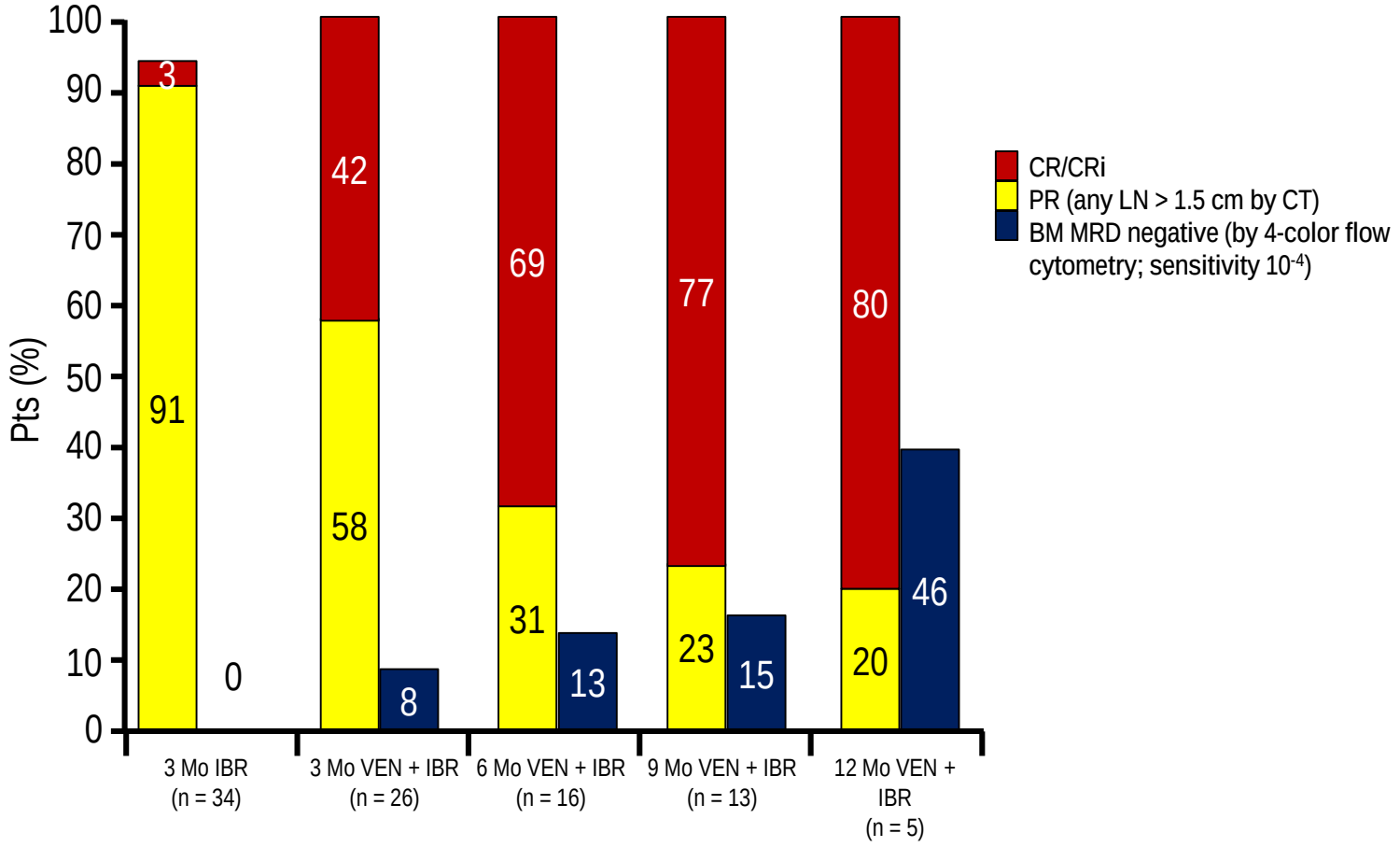
Response assessment by blood, BM, CT every 3 mos during Yr 1, every 6 mos during Yr 2, then every 6-12 mos thereafter.

- **Primary endpoint: CR/CRi per IWCLL 2008 criteria**
- **Other endpoints: OS, TLS risk categorization at BL vs post-IBR, safety**



*Jain N, et al. ASH 2017. Abstract 429. ClinicalTrials.gov. NCT02756897.*

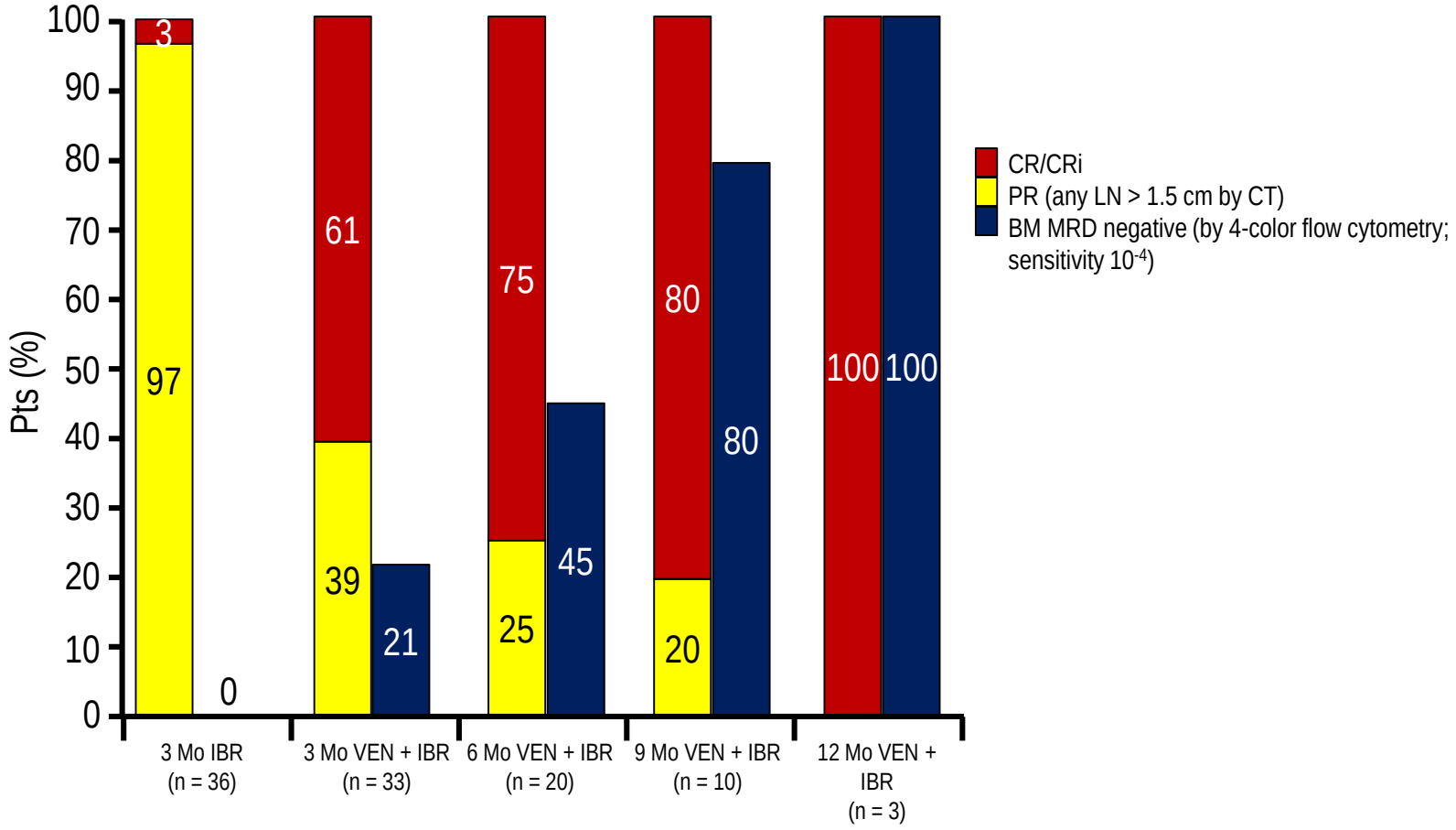
# Venetoclax + Ibrutinib in CLL: response in R/R CLL/SLL (Cohort 1)






*Jain N, et al. ASH 2017. Abstract 429*

# Venetoclax + Ibrutinib in CLL: response in untreated high-risk CLL/SLL (Cohort 2)






*Jain N, et al. ASH 2017. Abstract 429*

# Venetoclax + Ibrutinib in CLL: safety

- 2/3 of infections observed in ibrutinib monotherapy phase

| AE | n = 77 |
|---|---|
| Grade 3/4 hematologic AE,* % | |
| ▪ Neutropenia | 44 |
| ▪ Thrombocytopenia | 4 |
| Atrial fibrillation, n (%) | 10 (13) |
| Infections, n (%) | |
| ▪ Neutropenic fever† | 6 (8) |
| ▪ Pneumonia | 1 (2) |
| ▪ Cellulitis | 1 (2) |
| ▪ Septic arthritis | 1 (2) |

*Most grade 3/4 hematologic AEs occurred during VEN + IBR (neutropenia, 70%; thrombocytopenia, 100%). †Associated with aspergillosis (n = 1), anaplasmosis (n = 1), Vibrio (n = 1), or culture negative (n = 3).

- No clinical TLS observed; laboratory TLS observed in 2 pts
- TLS risk categorization downgraded (BL vs post-IBR) in 54% of pts

| TLS Risk Category,‡ n (%) | Baseline | Post-IBR |
|---|---|---|
| High | 18 (26) | 2 (3) |
| Medium | 38 (54) | 29 (41) |
| Low | 14 (20) | 39 (56) |

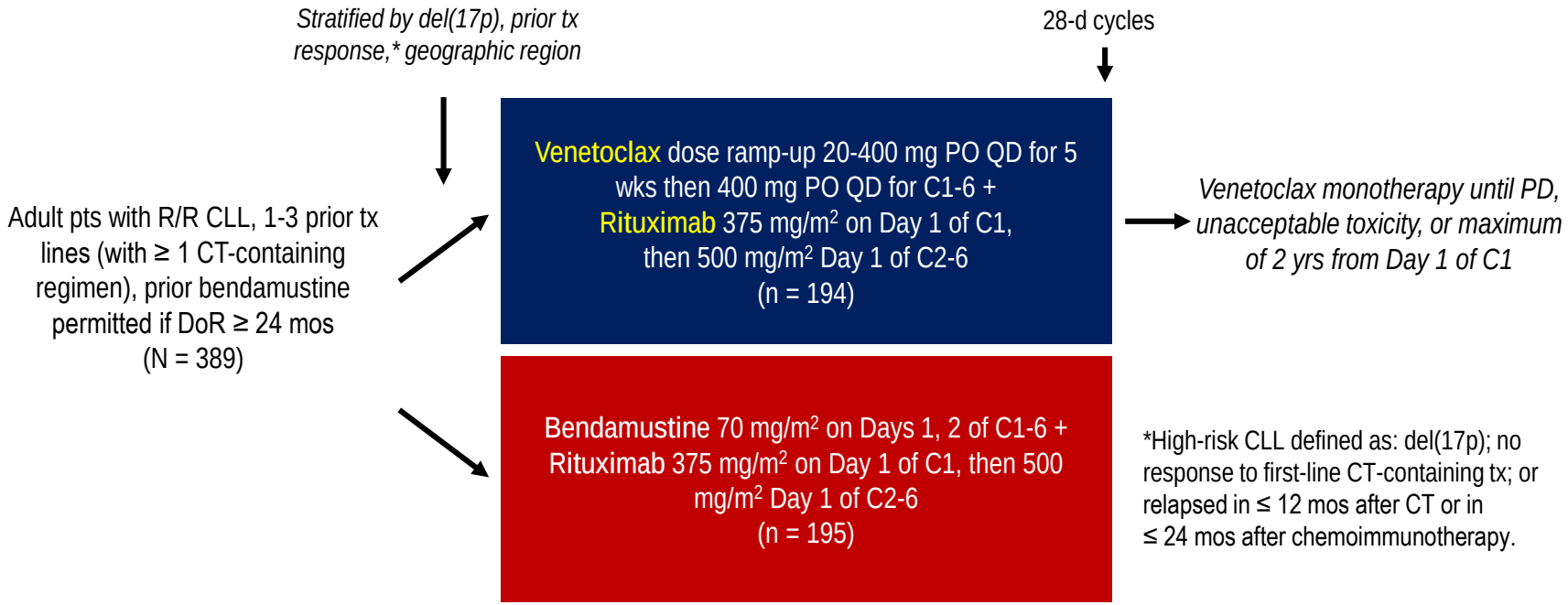
‡Assessed in 70 pts.



*Jain N, et al. ASH 2017. Abstract 429*

# MURANO interim analysis: study design

- Multicenter, randomized, open-label phase III trial

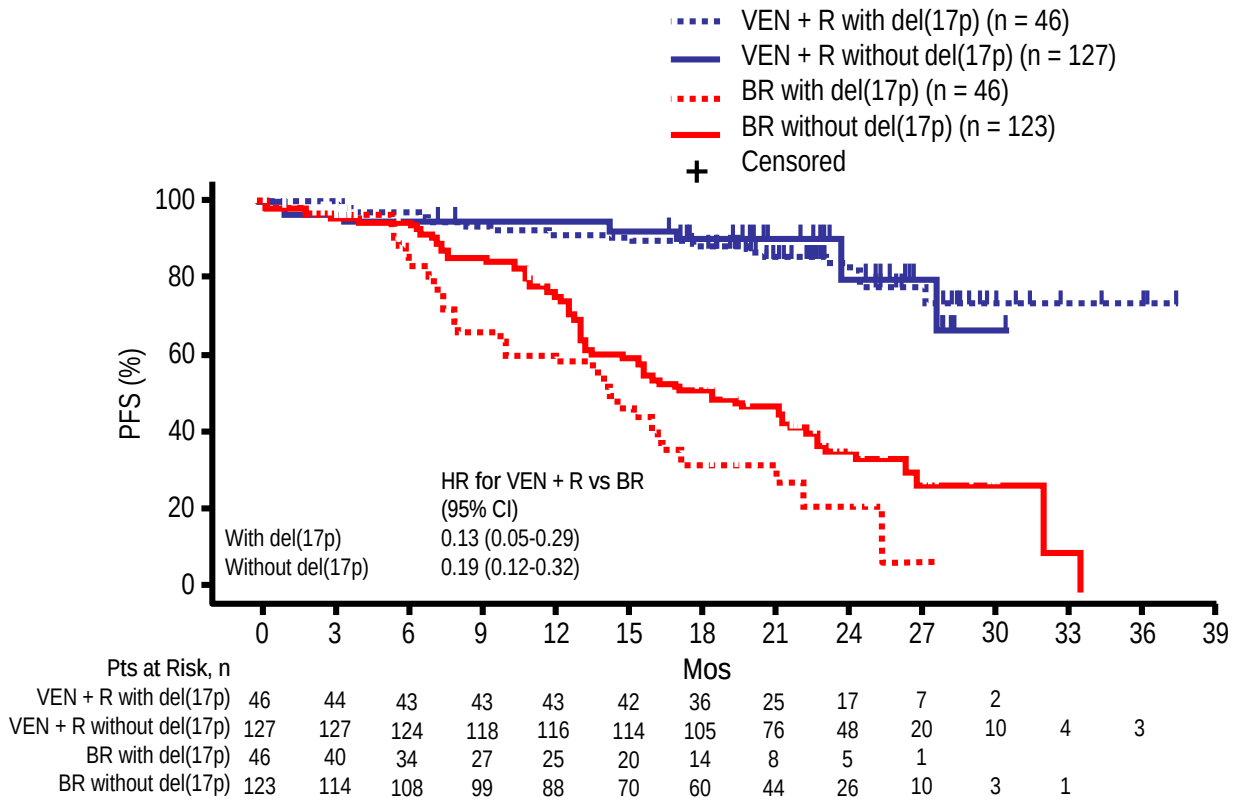



- **Primary endpoint: investigator-assessed PFS**
- Secondary endpoints: IRC-assessed PFS and MRD negativity, IRC-assessed CR → ORR → OS (hierarchical testing), safety



*Seymour JF, et al. ASH 2017. Abstract LBA-2. ClinicalTrials.gov. NCT02005471*

# MURANO interim analysis: investigator-assessed PFS by Del17p




- Venetoclax + rituximab consistently favored across subgroups stratified by del(17p) status, *TP53* status, baseline *IGHV* status, no. prior tx, refractory vs relapse to last tx

*Seymour JF, et al. ASH 2017. Abstract LBA-2*

# ASBMT 2016 recommendations

Biol Blood Marrow Transplant 22 (2016) 2117–2125

Biology of Blood and Marrow Transplantation

journal homepage: www.bbmt.org

Guideline

## Clinical Practice Recommendations for Use of Allogeneic Hematopoietic Cell Transplantation in Chronic Lymphocytic Leukemia on Behalf of the Guidelines Committee of the American Society for Blood and Marrow Transplantation

Mohamed A. Kharfan-Dabaja [1,2,*], Ambuj Kumar [3], Mehdi Hamadani [4], Stephan Stilgenbauer [5], Paolo Ghia [6], Claudio Anasetti [1,2], Peter Dreger [7], Emili Montserrat [8], Miguel-Angel Perales [9], Edwin P. Alyea [10], Farrukh T. Awan [11], Ernesto Ayala [1,2], Jacqueline C. Barrientos [12], Jennifer R. Brown [10], Januario E. Castro [13], Richard R. Furman [14], John Gribben [15], Brian T. Hill [16], Mohamad Mohty [17], Carol Moreno [18], Susan O'Brien [19], Steven Z. Pavletic [20], Javier Pinilla-Ibarz [2,21], Nishitha M. Reddy [22], Mohamed Sorror [23], Christopher Bredeson [24], Paul Carpenter [23], Bipin N. Savani [22]

# ASBMT 2016

- Different from EBMT 2007, the **ASBMT** guidelines included:
  - A mix of transplant and non-transplant physicians
  - Experts from USA (**20**), Canada (1), and Europe
    - Germany (2)
    - Italy (1)
    - Spain (2)
    - United Kingdom (1)
    - France (1)



*Kharfan-Dabaja MA, et al. Biol Blood Marrow Transplant. 2016; 22: 2117*

# ASBMT 2016: indications for allogeneic HCT for high risk CLL

**Table 3**
Summary of Indications for Allo-HCT in High-Risk CLL at Time of Transplant Evaluation

| | Clinical Scenarios | Strength of Recommendation |
|---|---|---|
| High-risk CLL at time of transplant evaluation | The panel **does not recommend** offering an allogeneic HCT in the front-line consolidation setting | Strong |
| | The panel **does not recommend** offering an allogeneic HCT for patients who relapse after front-line therapy and demonstrate sensitive disease after second line therapy (not BCR inhibitors) | Weak |
| | The panel **recommends** allogeneic HCT for patients who relapse after front-line therapy, demonstrate refractory disease after second-line (not BCR inhibitors), but show an objective response to BCR inhibitors or to a clinical trial | Strong |
| | The panel **recommends** allogeneic HCT for patients who relapse after front-line therapy, demonstrate refractory disease after second-line therapy including BCR inhibitors (not BCL-2 inhibitors), but show an objective response to BCL-2 inhibitors, namely venetoclax, or to a clinical trial | Strong |
| | The panel **recommends** allogeneic HCT when there is lack of response or there is progression after BCL-2 inhibitors, namely venetoclax | Strong |
| Richter transformation | The panel **recommends** allogeneic HCT for patients with Richter transformation after achieving an objective response to anthracycline-based chemotherapy | Strong |
| Purine analogue relapsed and/or refractory disease | The panel **considers** purine analogue relapsed and/or refractory disease high-risk disease but **not** an indication for immediate allogeneic HCT | Strong |

High-risk is defined as the presence of Del17p and/or *TP53* mutations and/or complex karyotype.



*Kharfan-Dabaja MA, et al. Biol Blood Marrow Transplant. 2016; 22: 2117*

# CAR-T

- Presently, CLL in not an approved indication for CAR-T cell therapy

- Encouraging data in the setting of
  - Richter Transformation
  - Patients relapsing after multiple lines of therapy

VOLUME 35 · NUMBER 26 · SEPTEMBER 10, 2017

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

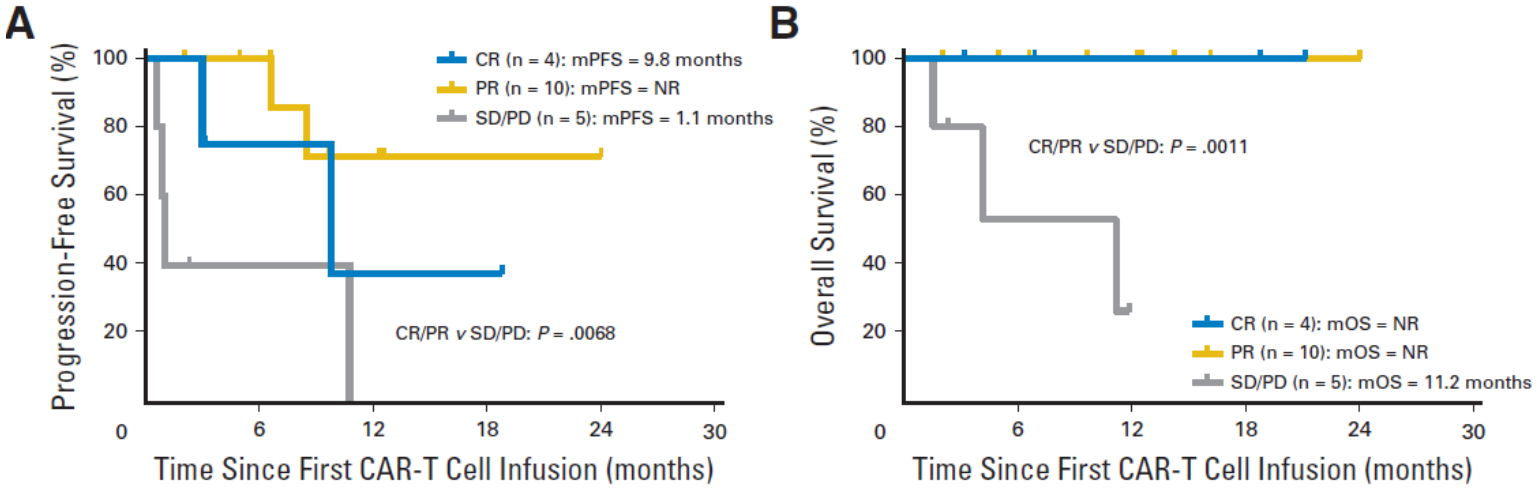
# Durable Molecular Remissions in Chronic Lymphocytic Leukemia Treated With CD19-Specific Chimeric Antigen Receptor–Modified T Cells After Failure of Ibrutinib

*Cameron J. Turtle, Kevin A. Hay, Laïla-Aïcha Hanafi, Daniel Li, Sindhu Cherian, Xueyan Chen, Brent Wood, Arletta Lozanski, John C. Byrd, Shelly Heimfeld, Stanley R. Riddell, and David G. Maloney*

**Table 1.** Patient Characteristics

| No. | Histology | Age (years) | Prior Therapies (No.) | Progression on Ibrutinib | Intolerant to Ibrutinib | Time on Ibrutinib (months) | Venetoclax | Complex Karyotype | Del 17p | Marrow Abnormal B Cells (% leukocytes) | Blood Abnormal B Cells (% leukocytes) | Absolute Lymphocyte Count (× 1,000 cells/μL) | Tumor Cross-sectional area ($mm^2$) | Maximum SUV |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | CLL/Richter's | 65 | 9 | Yes | No | 12 | No | No | Yes | 0.0 | 0.0 | 0.70 | NE | 12.9 |
| 2 | CLL/PLL | 54 | 3 | No | No | 0.75 | No | Yes | Yes | 21.9 | 10.6 | 0.88 | 1,223 | 3.4 |
| 3 | CLL/Richter's | 64 | 9 | Yes | No | 10 | No | No | Yes | 77.0 | 29.0 | 6.59 | 2,018 | NA |
| 4 | CLL | 59 | 7 | No | Yes | 1 | No | Yes | No | 78.8 | 75.1 | 0.41 | 4,276 | NA |
| 5 | CLL | 55 | 7 | Yes | No | 17 | Refractory | Yes | No | 89.8 | 23.0 | 0.81 | 20,406 | 9.1 |
| 6 | CLL | 61 | 6 | Yes | No | 11 | No | No | Yes | 77.7 | 92.0 | 66.63 | NE | NA |
| 7 | CLL | 63 | 7 | No | No | 3 | Refractory | No | Yes | 32.2 | 31.2 | 6.24 | 1,140 | NA |
| 8 | CLL | 62 | 5 | Yes | No | 14 | No | Yes | Yes | 66.4 | 39.7 | 8.93 | 3,867 | NA |
| 9 | CLL | 53 | 5 | Yes | No | 13 | No | Yes | Yes | 79.3 | 22.3 | 0.62 | 2,909 | 4.3 |
| 10 | CLL/Richter's | 68 | 4 | Yes | No | 16 | No | Yes | No | 3.5 | 0.2 | 0.66 | 1,683 | 27.5 |
| 11 | CLL | 53 | 5 | Yes | No | 34 | No | Yes | Yes | 64.5 | 26.1 | 1.04 | 4,753 | 10.9 |
| 12 | CLL | 70 | 5 | No | Yes | 5 | No | No | Yes | 55.4 | 62 | 5.08 | 1,490 | NA |
| 13 | CLL/Richter's | 47 | 3 | Yes | No | 13 | No | No | Yes | 6.7 | 0.1 | 1.28 | 11,057 | 10.1 |
| 14 | CLL/IPCs | 40 | 4 | Yes | No | 14 | No | Yes | Yes | 84.2 | 67.0 | 30.11 | 5,833 | 4.9 |
| 15 | CLL | 73 | 3 | Yes | No | 4 | No | No | Yes | 0.4 | 0.0 | 1.11 | 3,229 | 3.7 |
| 16 | CLL | 61 | 4 | No | Yes | 0.75 | No | Yes | No | 31.8 | 2.3 | 1.13 | 8,223 | NA |
| 17 | SLL/Richter's | 70 | 6 | Yes | No | 8 | No | No | No | 0.0 | 0.0 | 0.88 | 546 | 17.8 |
| 18 | CLL | 58 | 7 | Yes | No | 26 | Refractory | Yes | No | 96.0 | 84.9 | 10.68 | 2,482 | NA |
| 19 | CLL | 50 | 6 | Yes | No | 22 | Refractory | Yes | Yes | 90.0 | 79.0 | 22.62 | 3,223 | NA |
| 20 | CLL | 64 | 5 | Yes | No | 19 | No | Yes | No | 78.0 | 28.9 | 3.19 | 4,349 | NA |
| 21 | CLL/IPCs | 53 | 5 | Yes | No | 39 | No | Yes | No | 41.1 | 21.7 | 3.29 | 1,235 | 5.1 |
| 22 | CLL | 62 | 7 | Yes | No | 9 | Refractory | Yes | No | 40.0 | 0.03 | 1.02 | 3,093 | 11.5 |
| 23 | CLL | 66 | 4 | Yes | No | 26 | No | Yes | No | 58.6 | 13.1 | 2.49 | 2,400 | 3.8 |
| 24 | CLL | 58 | 7 | Yes | No | 19 | Refractory | Yes | Yes | 81.0 | 90.1 | 31.79 | 6,071 | 5.0 |

Abbreviations: CLL, chronic lymphocytic leukemia; IPCs, increased proliferation centers; NA, not applicable; NE, not evaluated (pretherapy imaging did not permit high-resolution tumor measurement); PLL, prolymphocytic leukemia; Richter's, Richter's transformation; SLL, small lymphocytic lymphoma; SUV, standardized uptake value.



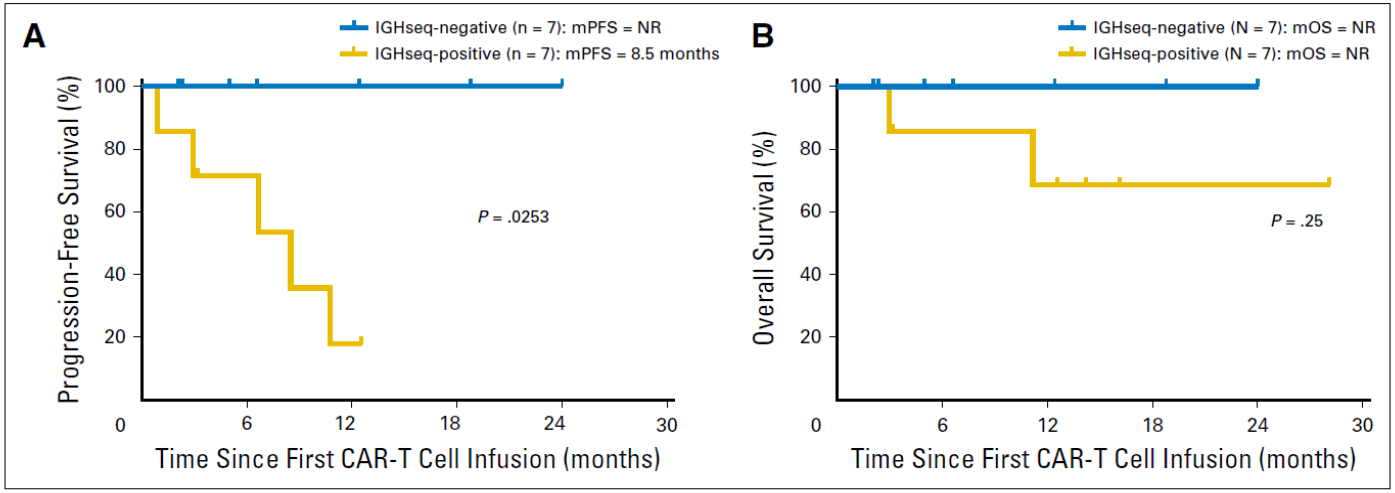
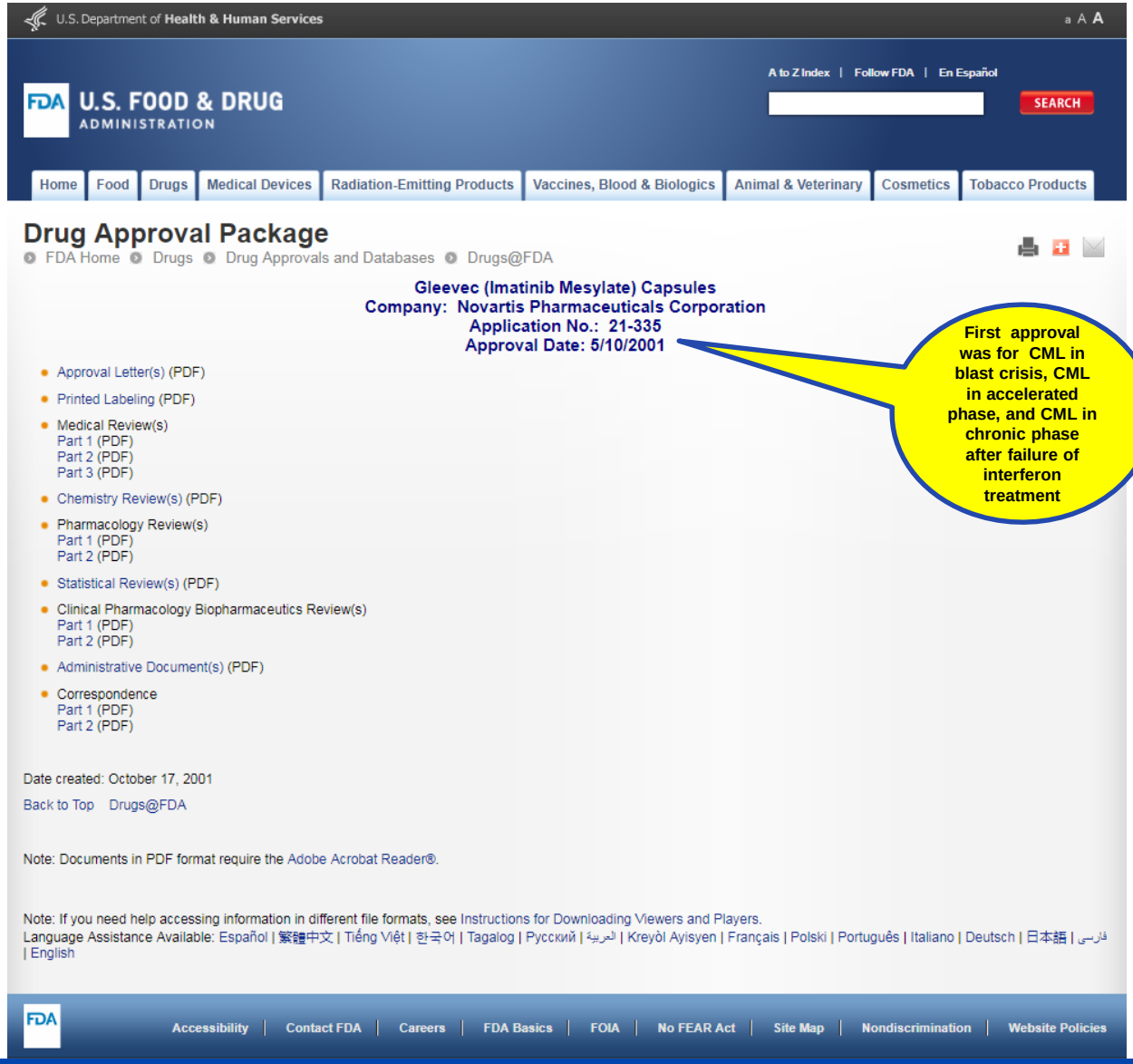
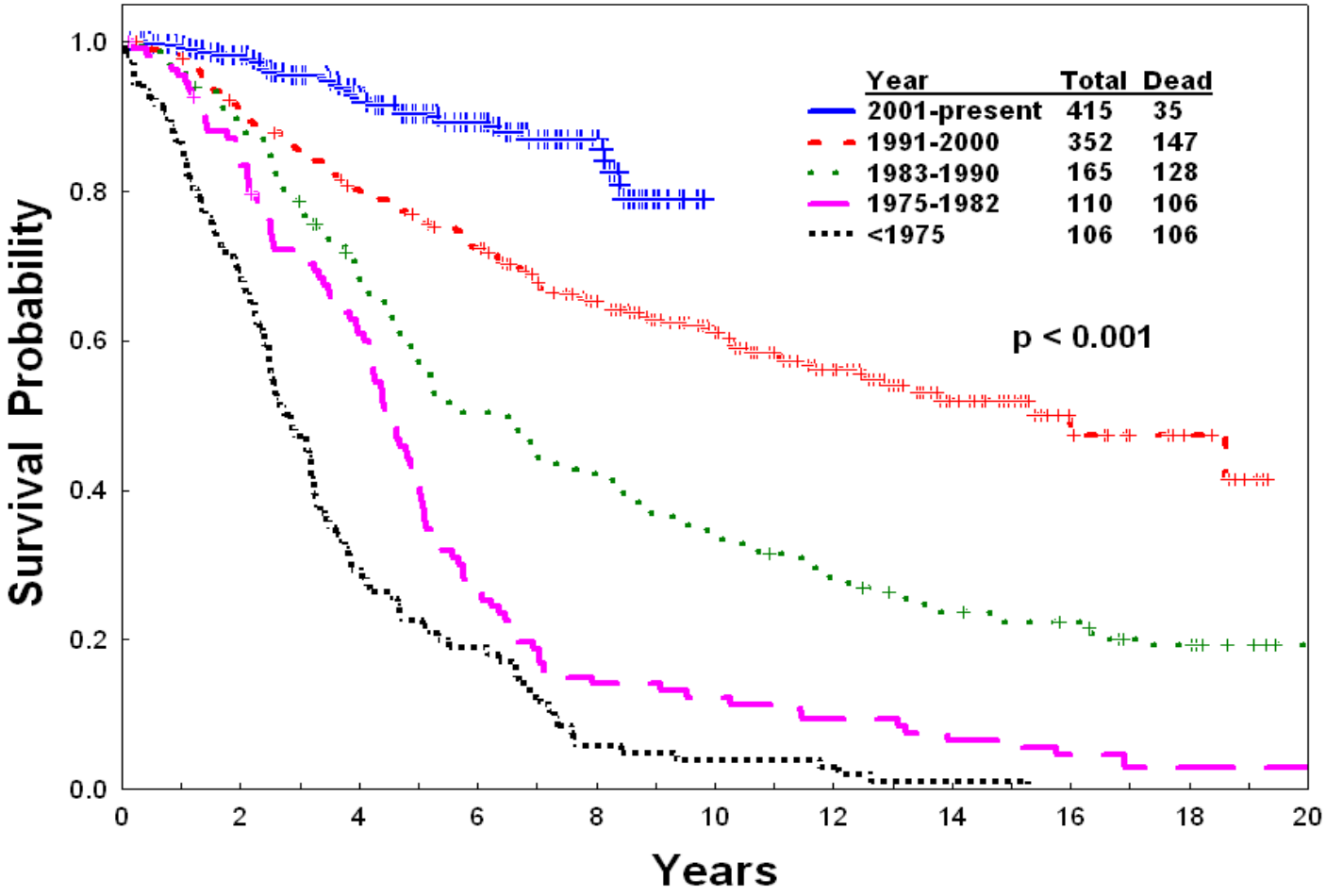




**Fig 4.** (A) Progression-free survival and (B) overall survival in patients who cleared disease from bone marrow 4 weeks after CAR-T cell infusion by flow cytometry and had no detectable malignant IGH copies (IGHseq-negative) compared with those who had detectable malignant IGH copies (IGHseq-positive). mOS, median OS; mPFS, median PFS; NR, not reached.

# CML


U.S. Department of Health & Human Services
a A A
A to Z Index | Follow FDA | En Español
U.S. FOOD & DRUG ADMINISTRATION
SEARCH
Home | Food | Drugs | Medical Devices | Radiation-Emitting Products | Vaccines, Blood & Biologics | Animal & Veterinary | Cosmetics | Tobacco Products
Drug Approval Package
FDA Home Drugs Drug Approvals and Databases Drugs@FDA
Gleevec (Imatinib Mesylate) Capsules
Company: Novartis Pharmaceuticals Corporation
Application No.: 21-335
Approval Date: 5/10/2001
Approval Letter(s) (PDF)
Printed Labeling (PDF)
Medical Review(s)
Part 1 (PDF)
Part 2 (PDF)
Part 3 (PDF)
Chemistry Review(s) (PDF)
Pharmacology Review(s)
Part 1 (PDF)
Part 2 (PDF)
Statistical Review(s) (PDF)
Clinical Pharmacology Biopharmaceutics Review(s)
Part 1 (PDF)
Part 2 (PDF)
Administrative Document(s) (PDF)
Correspondence
Part 1 (PDF)
Part 2 (PDF)
First approval was for CML in blast crisis, CML in accelerated phase, and CML in chronic phase after failure of interferon treatment
Date created: October 17, 2001
Back to Top Drugs@FDA
Note: Documents in PDF format require the Adobe Acrobat Reader®.
Note: If you need help accessing information in different file formats, see Instructions for Downloading Viewers and Players.
Language Assistance Available: Español | 繁體中文 | Tiếng Việt | 한국어 | Tagalog | Русский | العربية | Kreyòl Ayisyen | Français | Polski | Português | Italiano | Deutsch | 日本語 | فارسی | English
Accessibility | Contact FDA | Careers | FDA Basics | FOIA | No FEAR Act | Site Map | Nondiscrimination | Website Policies

# Survival in early chronic phase CML




*Kantarjian et al. Blood 2012; 119: 1981-7*

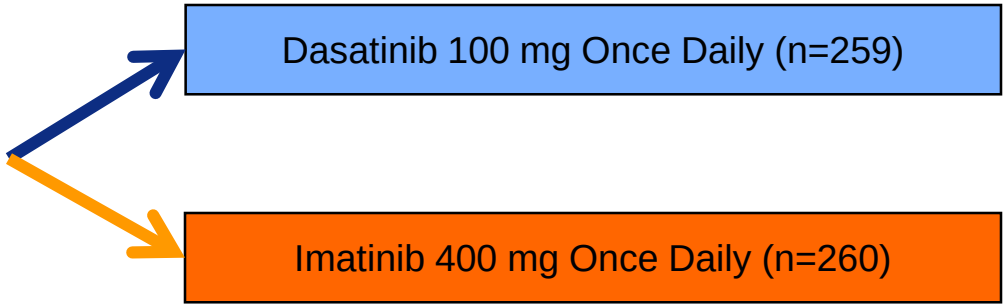


# DASISION
# randomized phase 3 trial

- n=519
- 108 centers
- 26 countries

Randomization




| Study Endpoints | |
|---|---|
| **Primary endpoint** | **Confirmed CCyR by 12 months** |
| **Secondary endpoints** | • **Major molecular response at any time**<br>• **Time to a confirmed complete cytogenetic response**<br>• **Time to a major molecular response** |
| **Other endpoints** | • **Rate of complete cytogenetic response observed at least once**<br>• **Rate of major molecular response by 12 months**<br>• **Progression-free survival**<br>• **Overall survival** |

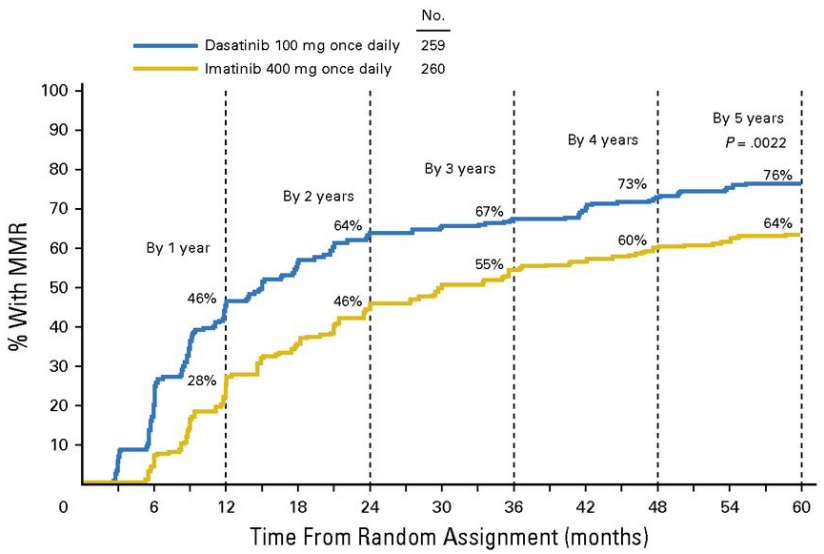


*Kantarjian H, et al. N Engl J Med 2010;362:2260-70*

# DASISION 5-year cum. response rates

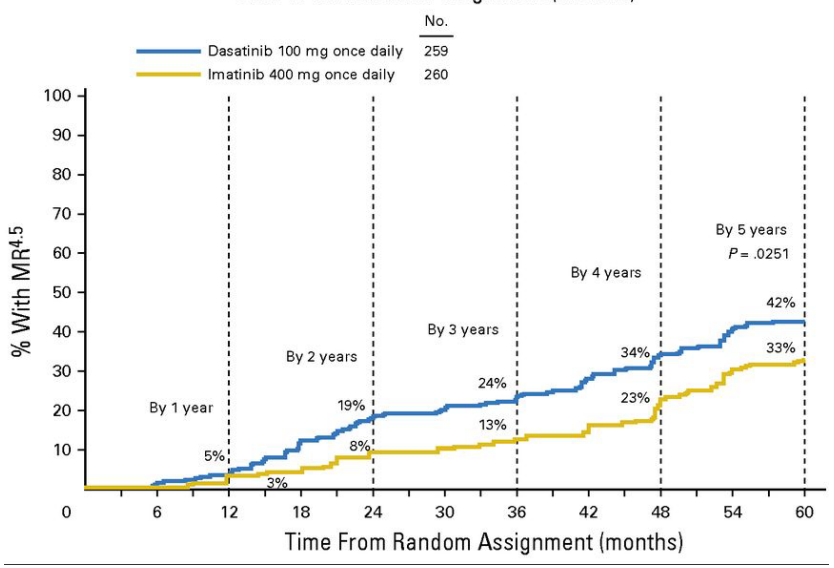
**MMR at 12 Months**
Dasatinib 46%
Imatinib 28%

**MMR at 5-years**
Dasatinib 76%
Imatinib 64%




**MR4.5 at 12 Months**
Dasatinib 5%
Imatinib 3%

**MR4.5 at 5-years**
Dasatinib 42%
Imatinib 33%






*Cortes et al. J Clin Oncol. 2016;34:2333-40*

# ENESTnd
# randomized phase 3 trial

- n=846
- 217 centers
- 35 countries

RANDOMIZED*

Nilotinib 300 mg BID (n=282)

Nilotinib 400 mg BID (n=281)

Imatinib 400 mg Daily (n=283)

**Stratification by Sokal risk score*

| Study Endpoints | |
|---|---|
| **Primary endpoint** | **MMR at 12 months** |
| **Secondary endpoints** | **Durable MMR at 24 months** |
| **Other endpoints** | • Rate of CCyR by 12 months<br>• Progression to accelerated or blast phase CML<br>• CML-related deaths |



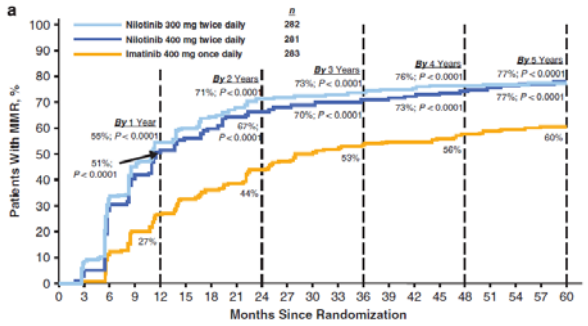
*Kantarjian H, et al. N Engl J Med 2010;362:2260-70*

*Saglio G, et al. N Engl J. Med 2010;362:2251-2259*

# ENESTnd 5-Year cum. response rates

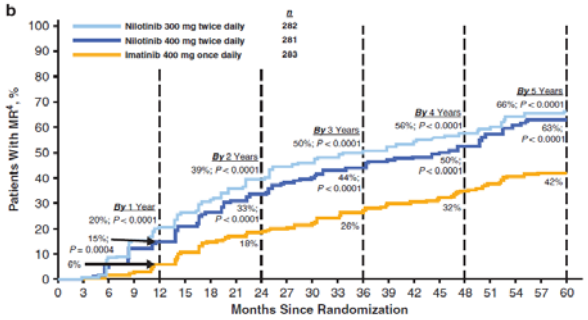
**MMR**
**12 Months** (p<0.0001)
Imatinib 27%
Nilotinib 55%

**5 Years** (p<0.0001)
Imatinib 60%
Nilotinib 77%



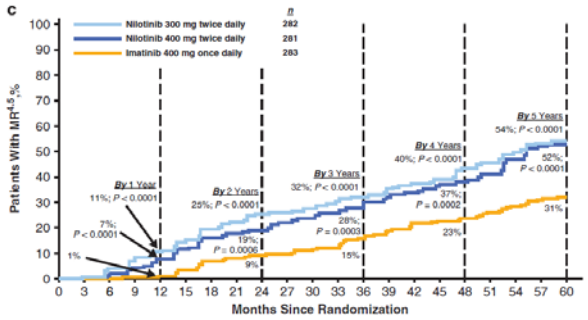

**MR4.0**
**12 Months** (p<0.0001)
Imatinib 6%
Nilotinib 20%

**5 Years** (p<0.0001)
Imatinib 42%
Nilotinib 66%




**MR4.5**
**12 Months** (p<0.0001)
Imatinib 1%
Nilotinib 11%

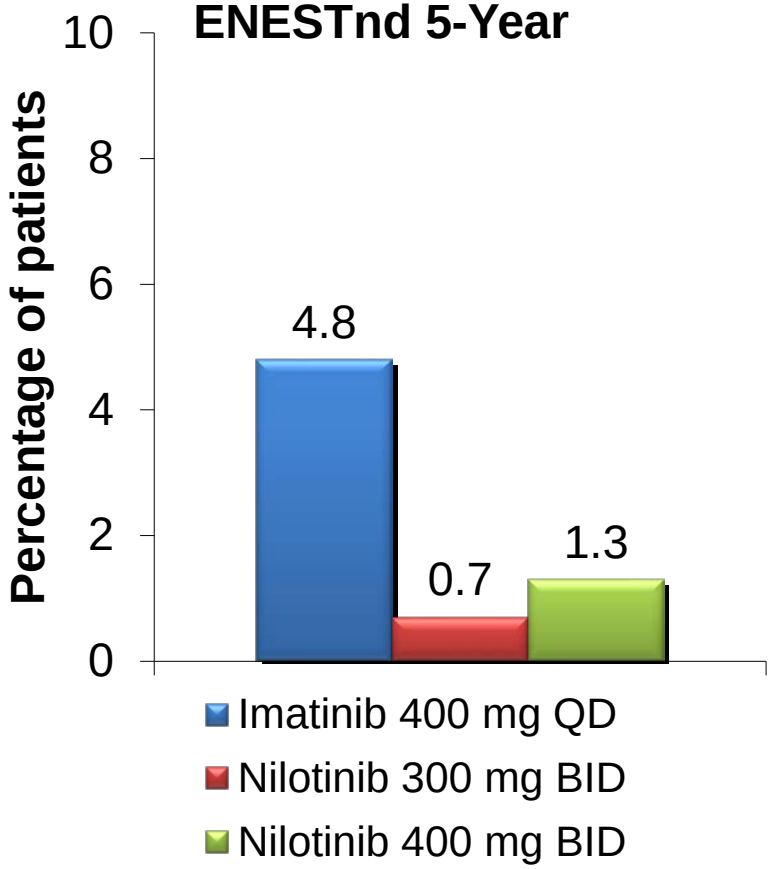
**5 Years** (p<0.0001)
Imatinib 31%
Nilotinib 54%

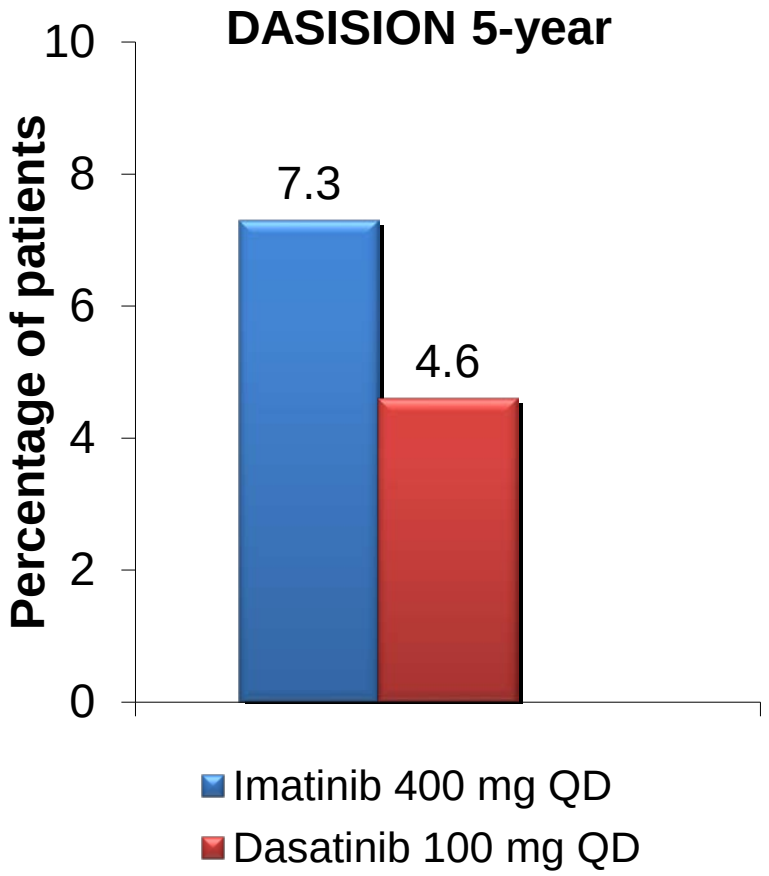





*Hochhaus, et al. Leukemia .2016; 30:1044-54*

# Transformation to AP/BP CML

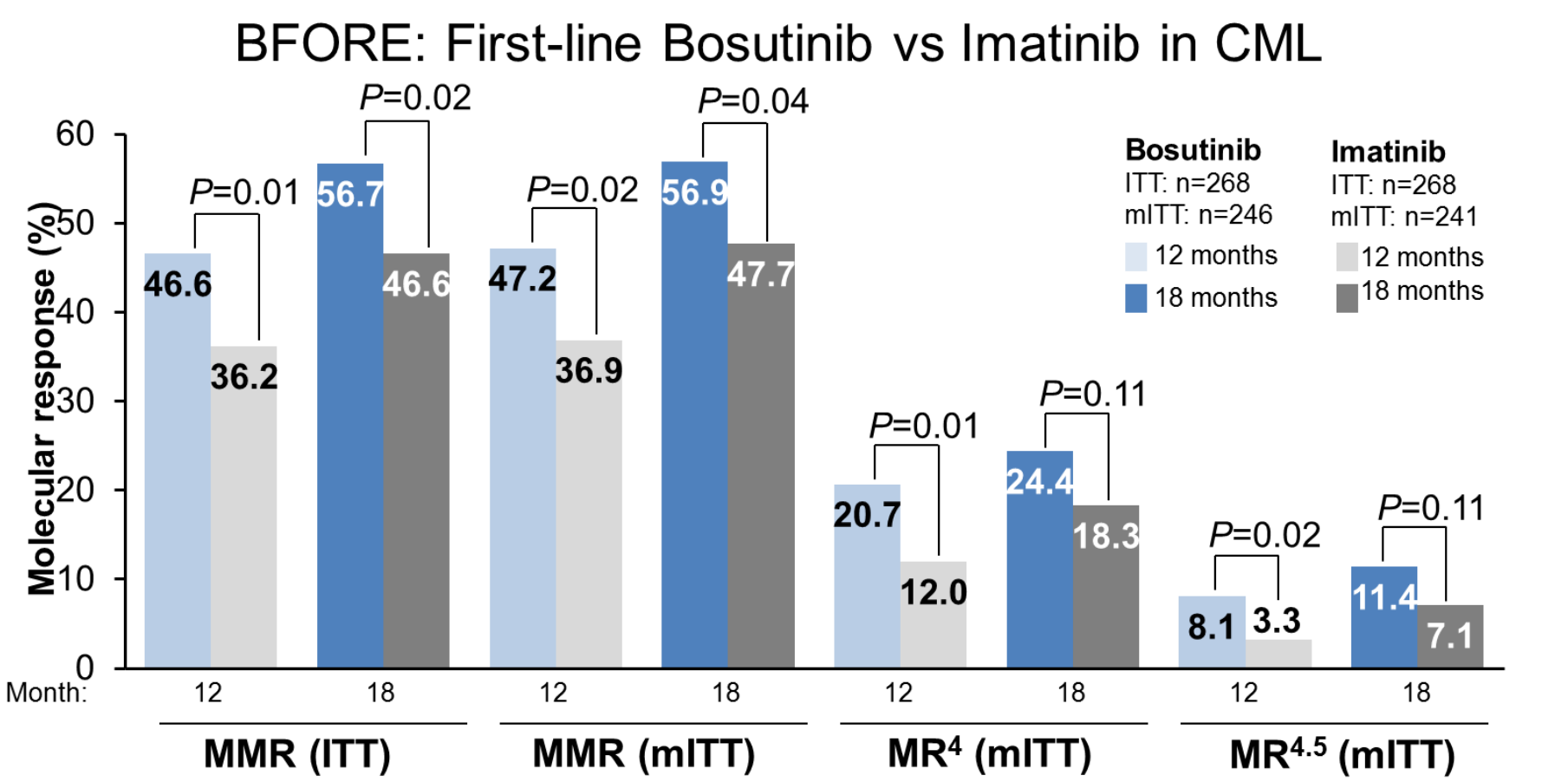





*Hochhaus A et al. Leukemia.2016 ;30:1044-54*
*Cortes J et al. J Clin Oncol. 2016;34:2333-40*

# Molecular response at 12 and 18 months




CML=chronic myeloid leukemia; ITT=intent-to-treat; mITT=modified intent-to-treat; MR=molecular response; MMR=major molecular response

**$MR^4$ (ITT), %**

| | Bosutinib | Imatinib | *P* |
|---|---|---|---|
| 12mo | 20.5 | 11.6 | <0.01 |
| 18mo | 24.6 | 18.3 | 0.08 |

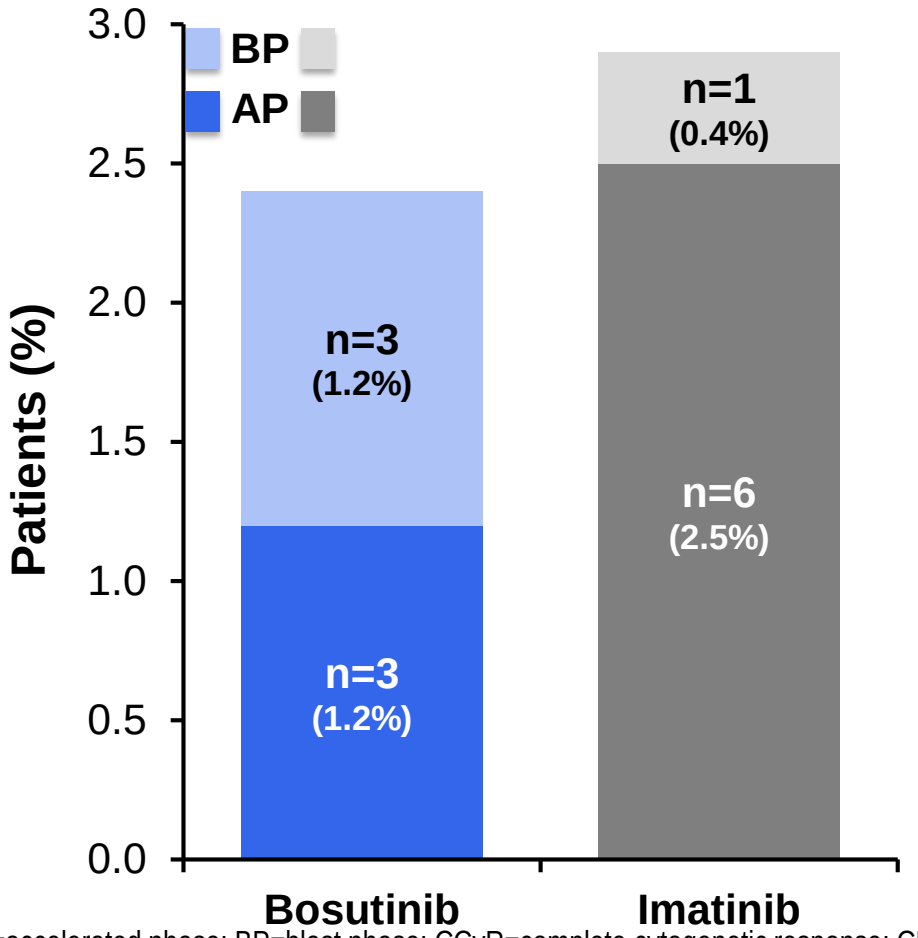
**$MR^{4.5}$ (ITT), %**

| | Bosutinib | Imatinib | *P* |
|---|---|---|---|
| 12mo | 7.5 | 3.0 | 0.02 |
| 18mo | 11.9 | 8.2 | 0.16 |



# AP/BP transformation at 18 months
# BFORE: first-line Bosutinib vs Imatinib in CML




- 6 (2.4%) pts in bosutinib arm and 7 (2.9%) on imatinib progressed to AP/BP during 1st 18 months of Rx
  - 6 of these patients (bosutinib: n=3; imatinib: n=3) met AP criteria within 2 wks based on basophil count
  - All 6 continued on study drug; 4 achieved MMR and 1 achieved CCyR
- There were no additional transformations in ITT population

AP=accelerated phase; BP=blast phase; CCyR=complete cytogenetic response; CI=confidence interval; CML=chronic myeloid leukemia; ITT=intent-to-treat; mITT=modified intent-to-treat; MMR=major molecular response



*Gambacorti-Passerini C, ASH Annual Meeting. 2017*

## RESPONSE MILESTONES[f,g]

| *BCR-ABL1* (IS) | 3 months | 6 months | 12 months | >12 months |
|---|---|---|---|---|
| >10%[h] | YELLOW | RED | | |
| 1%–10% | GREEN | | YELLOW | RED |
| 0.1%–<1% | GREEN | | | YELLOW |
| <0.1% | GREEN | | | |

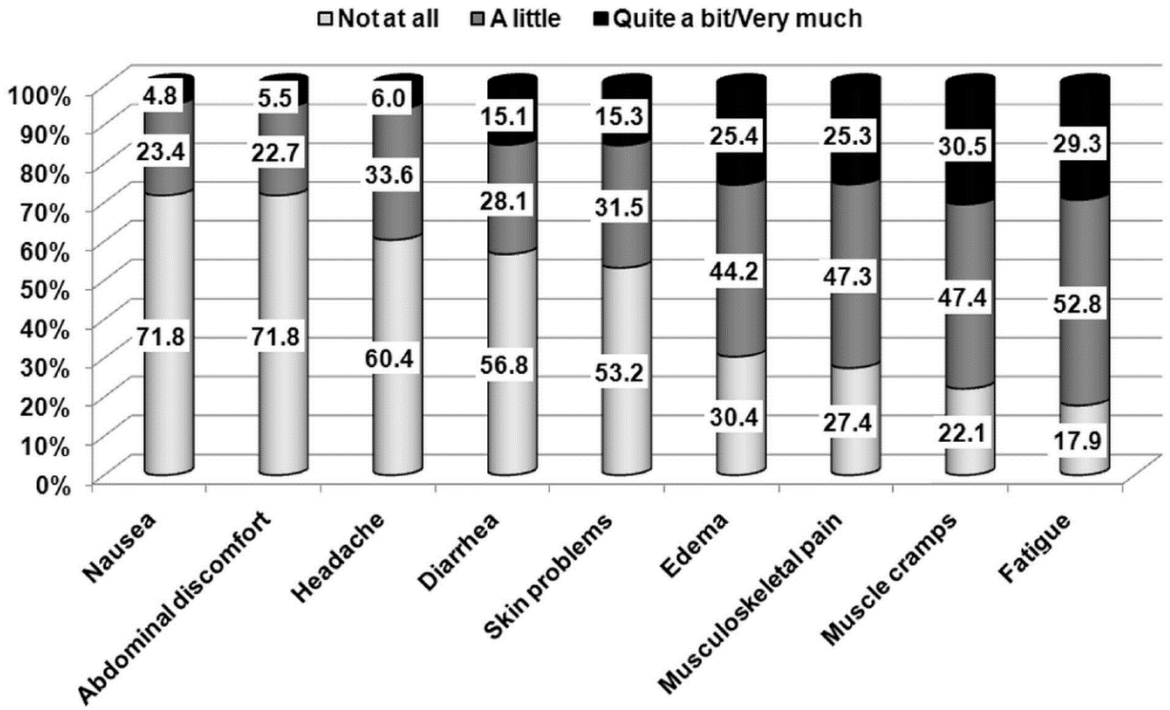
| | CLINICAL CONSIDERATIONS | SECOND-LINE AND SUBSEQUENT TREATMENT OPTIONS |
|---|---|---|
| RED | • Evaluate patient compliance and drug interations<br>• Mutational analysis | Switch to alternate TKI (CML-5)<br>and Evaluate for HCT (CML-6) |
| YELLOW | • Evaluate patient compliance and drug interactions<br>• Mutational analysis | Switch to alternate TKI (CML-5)<br>or Continue same TKI (CML-G)[i]<br>or Dose escalation of imatinib (to a max of 800 mg)<br>and Evaluate for HCT (CML-6) |
| GREEN | • Monitor response (CML-D) and side effet s | Continue same TKI (CML-G)[i] |

# Why to consider stopping Rx?

- TKI therapy associated with reduced QOL
- High cost to patients and society
- Potential for long-term toxicity
  - Cardiovascular
  - Pulmonary
  - Thyroid dysfunction
- Children and adolescents:
  - Substantial growth abnormalities
  - Effect on pregnancy/fertility
- **Some patients may not require lifelong TKIs**

# Health-related quality of life in chronic myeloid leukemia patients receiving long-term therapy with imatinib compared with the general population

Fabio Efficace,[1] Michele Baccarani,[2] Massimo Breccia,[3] Giuliana Alimena,[3] Gianantonio Rosti,[2] Francesco Cottone,[1] Giorgio Lambertenghi Deliliers,[4] Claudia Baratè,[5] Antonella Russo Rossi,[6] Giuseppe Fioritoni,[7] Luigia Luciano,[8] Diamante Turri,[9] Bruno Martino,[10] Francesco Di Raimondo,[11] Melissa Dabusti,[12] Micaela Bergamaschi,[13] Pietro Leoni,[14] Maria Pina Simula,[15] Luciano Levato,[16] Stefano Ulisciani,[17] Dino Veneri,[18] Simona Sica,[19] Alessandro Rambaldi,[20] Marco Vignetti,[1] and Franco Mandelli,[1] for GIMEMA



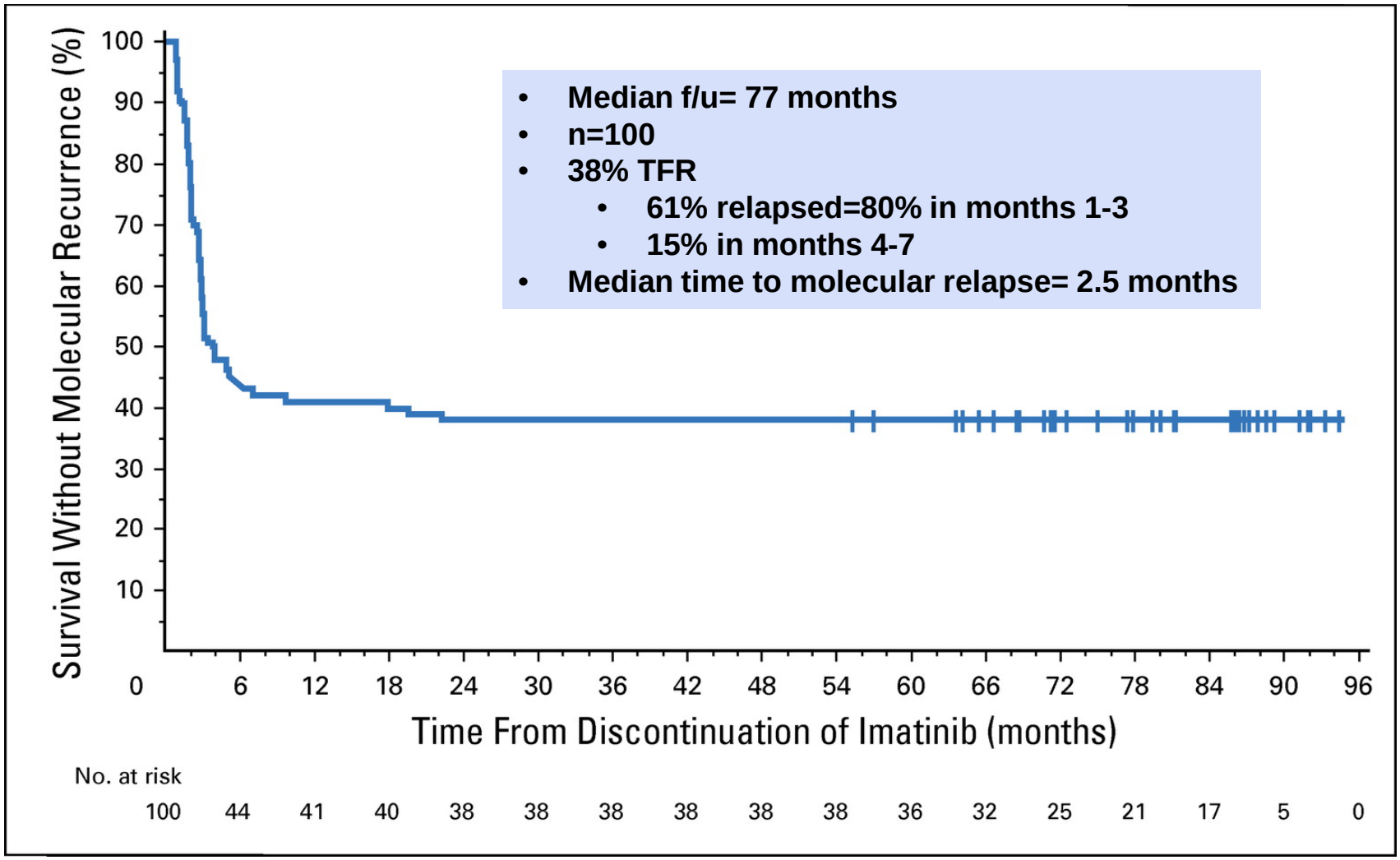



*Efficace F, et al. 2011; Blood. 118:4554-60*

# TKI discontinuation and treatment- free remission (TFR)

- The French **STIM1** TFR trial was first to address possibility of TKI discontinuation
  - 100 pts with undetectable BCR-ABL d/c'ed imatinib and were monitored off treatment until evidence of molecular relapse
  - *Proof-of-principle that attempting TKI discontinuation was safe in selected pts*
- Subsequent studies have confirmed feasibility of TFR
  - Association between longer imatinib duration and maintenance of TFR, although a minimum treatment duration prior to TFR has not been determined

# Long-term F/U from STIM

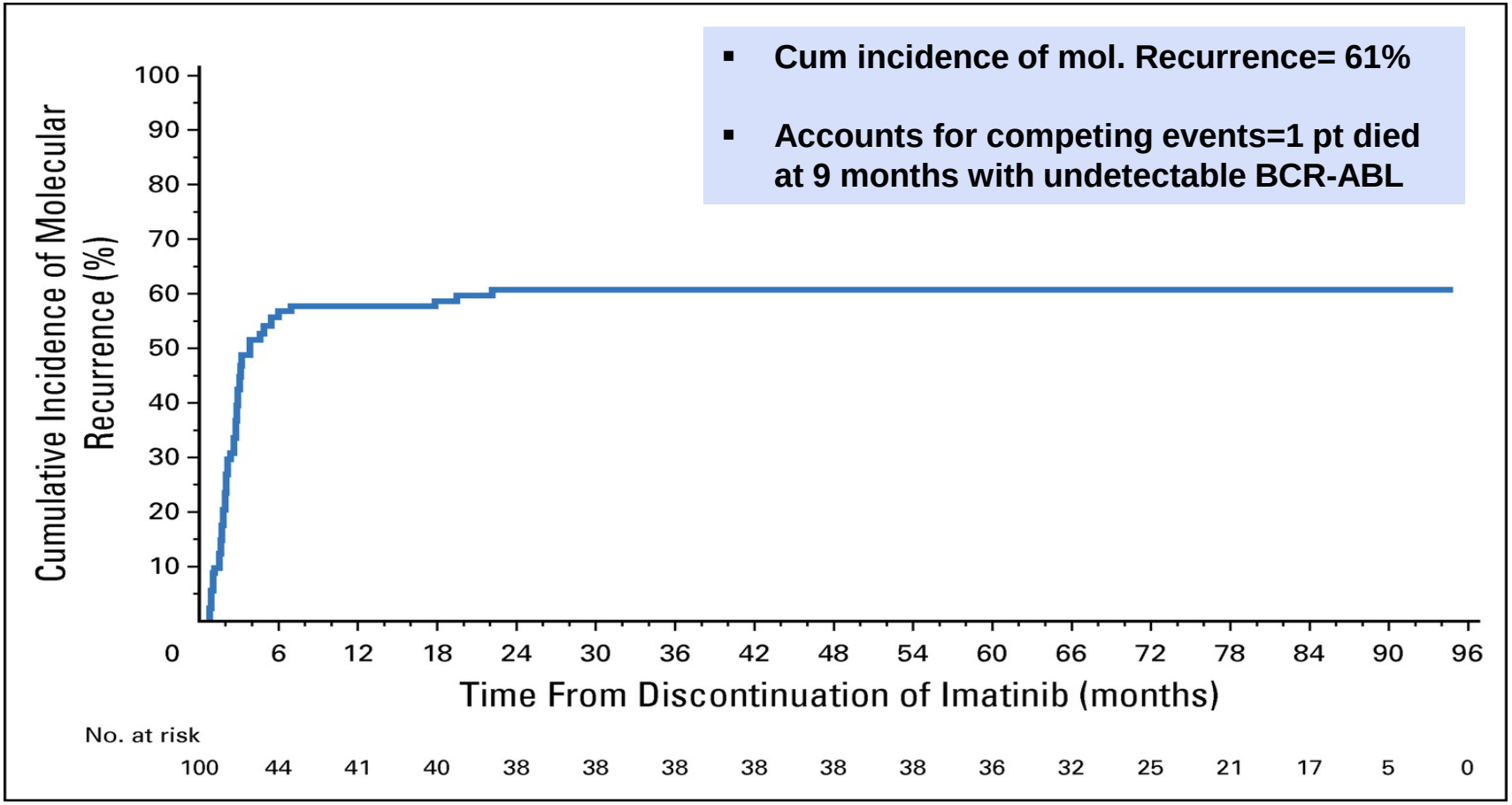



- Median f/u= 77 months
- n=100
- 38% TFR
  - 61% relapsed=80% in months 1-3
  - 15% in months 4-7
- Median time to molecular relapse= 2.5 months



*Etienne G. J Clin Oncol. 2017; 35: 298-305*

# Cum incidence of molecular recurrence on STIM




- **Cum incidence of mol. Recurrence= 61%**
- **Accounts for competing events=1 pt died at 9 months with undetectable BCR-ABL**

MAYO CLINIC

*Etienne G. J Clin Oncol. 2017; 35: 298-305*

# Outcomes in pts With molecular relapse

**Table 2.** MR Patient's Disposition, Treatment, and Molecular Status at the Last Date of Follow-Up

| Patient Disposition and Treatment | Patients (n = 61) No. | Patients (n = 61) % | No. of Molecular Responses at Last Available Evaluation: ≥ $MR^{4.5}$ | ≥ MMR to < $MR^{4.5}$ | < MMR |
|---|---|---|---|---|---|
| Alive with TKI therapy | 43 | 70.5 | 34 | 6 | 3 |
| Imatinib | 31 | 50.8 | 28 | 2 | 1 |
| Dasatinib | 7 | 11.4 | 3 | 3 | 1 |
| Nilotinib | 4 | 6.5 | 3 | 1 | 0 |
| Bosutinib | 1 | 1.6 | 0 | 1 | 0 |
| Alive without TKI therapy | 14 | 22.9 | 10 | 3 | 1 |
| Second or third TKI discontinuation* | 9 | 14.7 | 8 | 1 | 0 |
| Discontinuation for TKI-related AE | 2 | 3.2 | 0 | 1 | 1 |
| Without any TKI resumption | 3 | 4.9 | 2 | 1 | 0 |
| Death | 4† | 6.5 | 2 | 2 | 0 |

Abbreviations: AE, adverse event; MMR, major molecular response; MR, molecular response; $MR^{4.5}$, molecular response 4.5-log; TKI, tyrosine kinase inhibitor.
*Twenty-one patients who had achieved a second sustained undetectable molecular residual disease (UMRD) of at least 1 year had a second treatment discontinuation as previously described.[21] Of those patients, 13 had MR leading to treatment resumption, and eight were free from MR with a median follow-up of 11.6 months (range, 0.9 to 21.4 months) after second imatinib discontinuation and without TKIs at last follow-up. Among the 13 MR patients, four achieved a third sustained UMRD and one experienced a third treatment discontinuation without molecular recurrence at the last date of follow-up.
†One patient died as a result of pleural mesothelioma while receiving imatinib. The remaining three patients discontinued TKI therapy because of worsening concomitant disease leading to death (one patient case each of cerebral hemorrhage, metastatic gastric adenocarcinoma, and acute renal failure).

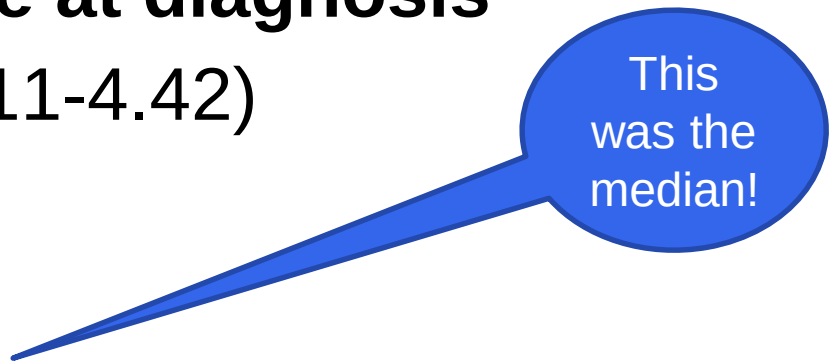
- 57/61 relapsed pts restarted TKIs
- 55 achieved 2nd undetectable status – **median time 4.3 months**
- None progressed to AP/BP
- 14 alive and off TKIs – **10 in MR4.5**
- 4 deaths – none were CML related



*Etienne G. J Clin Oncol. 2017; 35: 298-305*

# Multivariate analysis from STIM

- **Two factors predictive of molecular relapse**
  1. **High-risk Sokal score at diagnosis**
     - HR=2.22 (95%CI=1.11-4.42)
     - **P=0.024**




  2. **Imatinib duration ≥58.8 months prior to discontinuation**
     - HR=0.54 (95%CI=0.32-0.92)
     - **P=0.024**



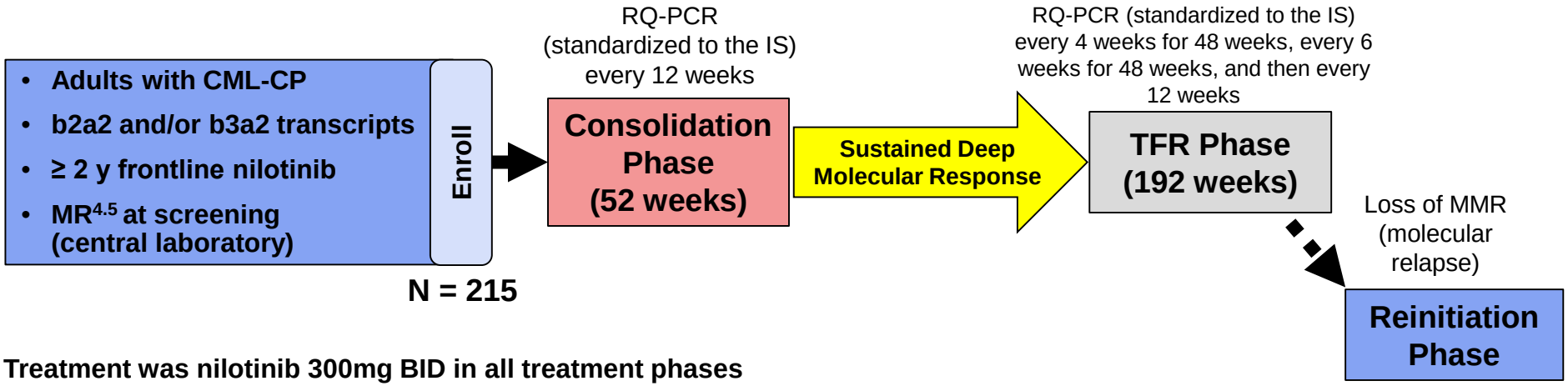
*Etienne G. J Clin Oncol. 2017; 35: 298-305*

# ENEST freedom

| Enrollment and Inclusion Criteria | |
|---|---|
| Total enrollment | n=215 |
| Minimum treatment duration required prior to discontinuation | ≥3 years frontline nilotinib |
| Minimum response required prior to discontinuation | Sustained $MR^{4.5}$ for at least 1 year |

- **37.9% of nilotinib 300mg BID treated patients on ENESTnd met the inclusion criteria for attempting TFR on ENESTfreedom**

## Study Design



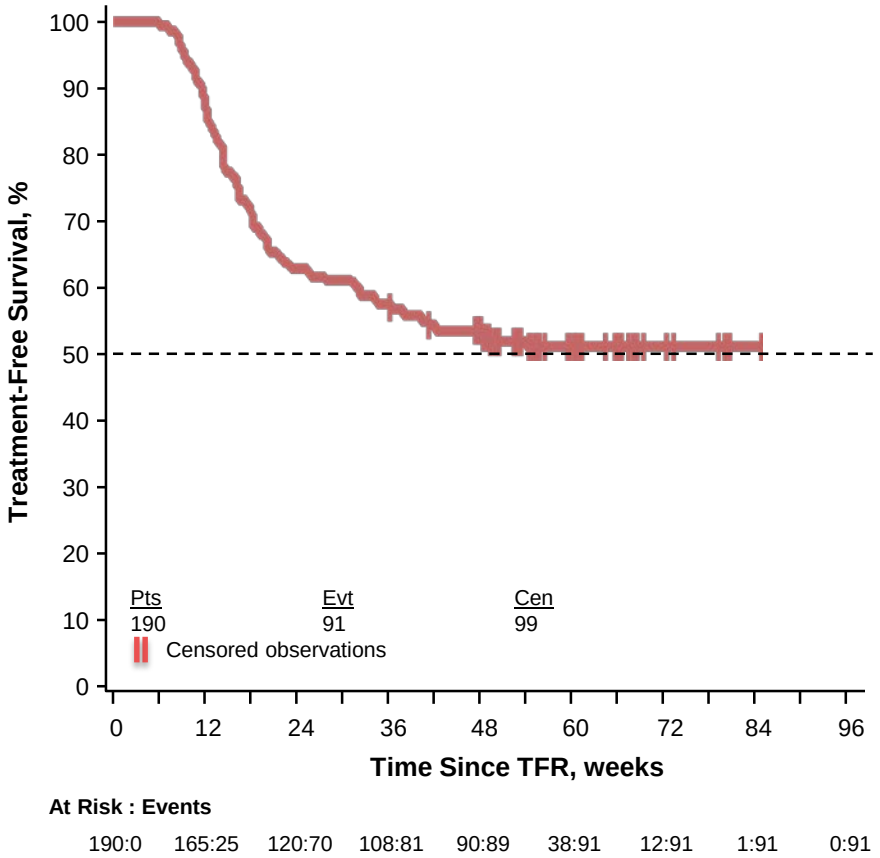

**Treatment was nilotinib 300mg BID in all treatment phases**



*Hochhaus A. ASCO Annual Meeting 2016. Abstract #7001*

# Treatment-free survival

## Kaplan-Meier estimated treatment-free survival[a]



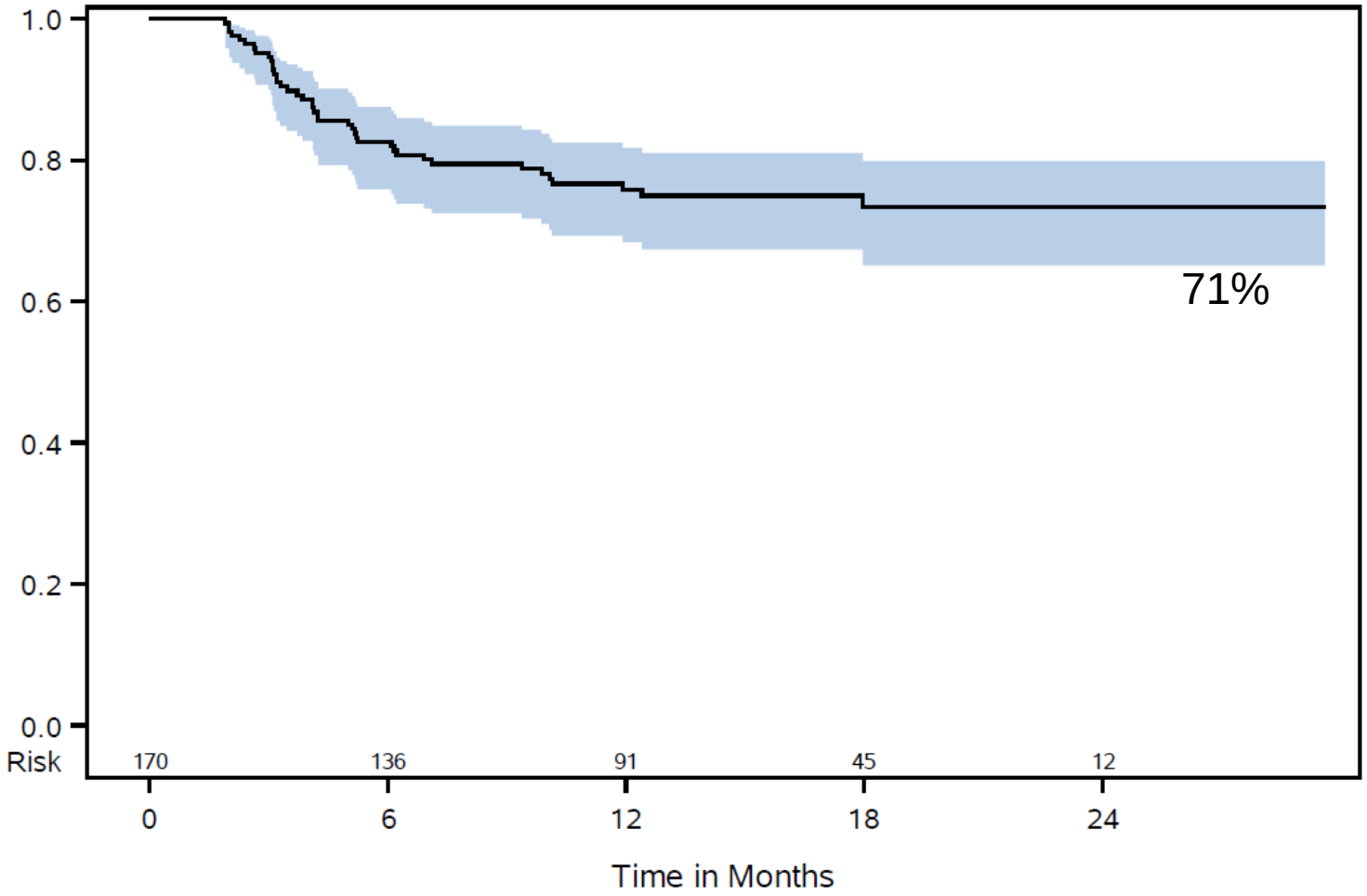

- **190 patients entered the TFR phase**
- **51.6% of patients (95% CI, 44.1-58.9%) remained in TFR after 48 weeks**

[a] Defined as the time from the start of TFR until the earliest of any of the following: loss of MMR, reinitiation of nilotinib for any reason, progression to accelerated phase/blast crisis, or death due to any cause.


# The LAST study is a national study examining discontinuation in the US

**Patients were enrolled from December 2014 through December 2016**

# Molecular recurrence-free survival




Molecular recurrence-free survival: 71% (based on study criteria)
Treatment free remission: 65% restarted drug

# When to restart?

| Trial | Trigger to Restart TKI |
|---|---|
| **STIM1** | Loss of MMR or confirmed ≥1-log increase in BCR-ABL |
| **STIM2** | Loss of MMR or ≥1-log increase in BCR-ABL |
| **TWISTER** | Loss of MMR or two consecutive positive PCR values |
| **A-STIM** | Loss of MMR |
| **LAST** | Loss of MMR |
| **EURO-SKI** | Loss of MMR |
| **KIDS** | Confirmed loss of MMR |
| **ENEST freedom** | Loss of MMR |



*Ross DM, et al. ASH Annual Meeting abstracts 2013; Mahon FX, et al. ASH Annual Meeting abstracts 2013; Mahon FX, et al. ASH Annual Meeting abstracts 2016; Atallah et al. ESH 2015; Choi SY et al. ASH Annual Meeting abstracts 2013; Rousselot P et al JCO 2013*

# TKI withdrawal syndrome

- Diffuse musculoskeletal pain and joint pain
- ~30% after stopping TKIs
- Median duration ~6 months



*Lee et al. Haematologica. 2016 Jun;101(6):717-23.*
*Richter et al. J Clin Oncol. 2014;32(25):2821–2823.*

# Closing remarks

- **CLL**
  - Treatment approach based on disease-risk and patient's fitness
  - Del17p plus complex karyotype is very high-risk
  - Genomics will be incorporated into future algorithms

- **CML**
  - Most pts with chronic phase CML do well with current therapy(ies)
  - Stopping TKIs is ready for prime time
    - Multi-team approach is a key component to the success and safety of TFR

# Thank you