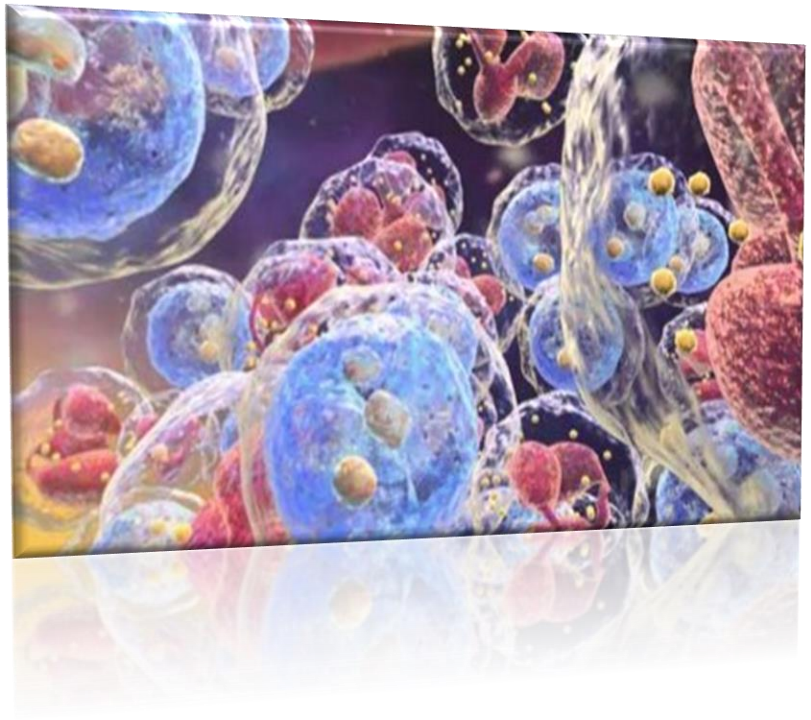


# Updates in CML and CLL

Alexis M. Cruz Chacon MD

Hematology and Medical Oncology

Adult Blood and Marrow Transplantation

AUXILIO TRASPLANTE MEDULA ÓSEA

AUXILIO CENTRO DE CÁNCER

HEMATOLOGY & ONCOLOGY

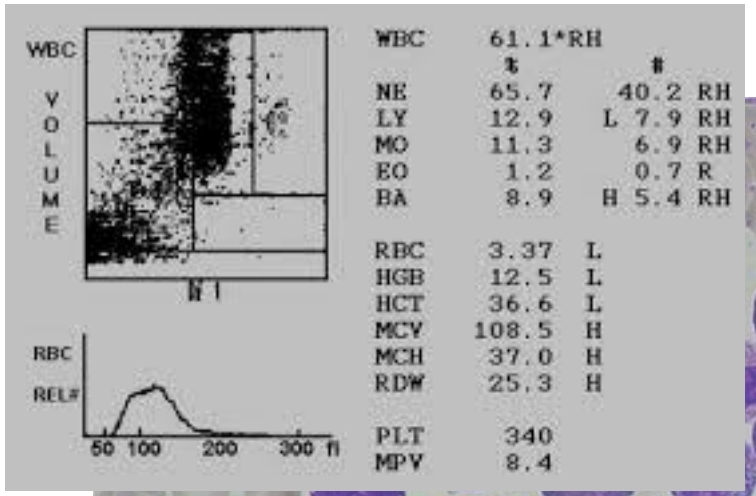
San Juan City Hospital
VA Caribbean Healthcare System

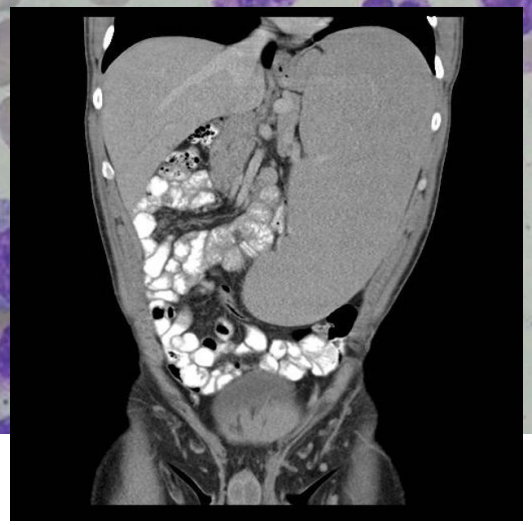
# Disclosures

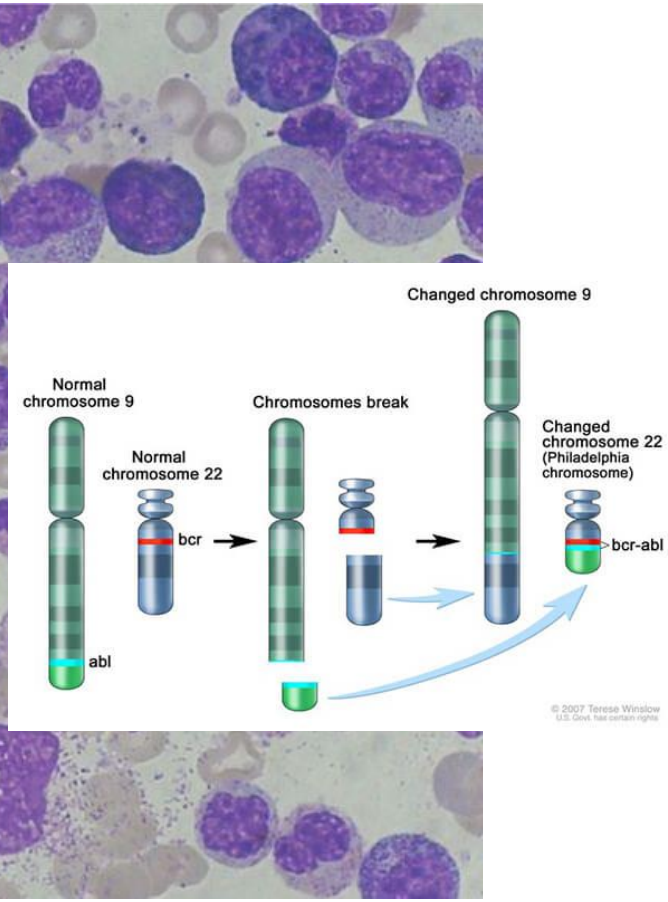
- Alexis M. Cruz-Chacon, MD has disclosed the following relevant financial relationships:
  - ***Speaker*****:** Celgene, Bristol-Myers Squibb, Takeda
  - ***Consultant/Advisor*****:** Bristol-Myers Squibb, Abbie, Merck

# Chronic Myelogenous Leukemia

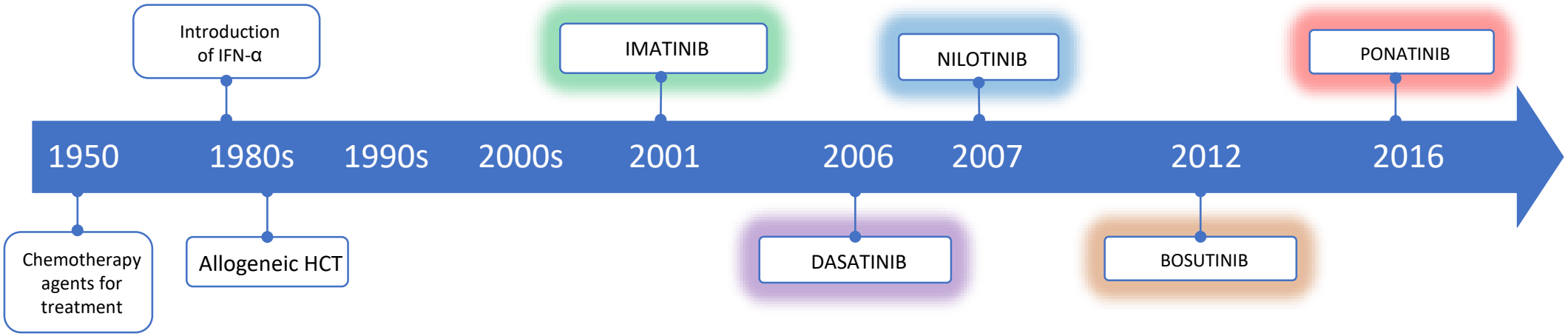
- Myeloproliferative disorder
  - Myeloid proliferation
- Philadelphia chromosome – t(9;22)
  - Results in fusion gene BCR-ABL with enhanced proliferation signaling
- Fatal disease
  - Conversion to resistant AML in 5 years
- Treatment options before year 2000
  - Chemotherapy
  - Interferon-alpha
  - **Only curative therapy was allogeneic HCT**






# CML in the Post-Imatinib Era

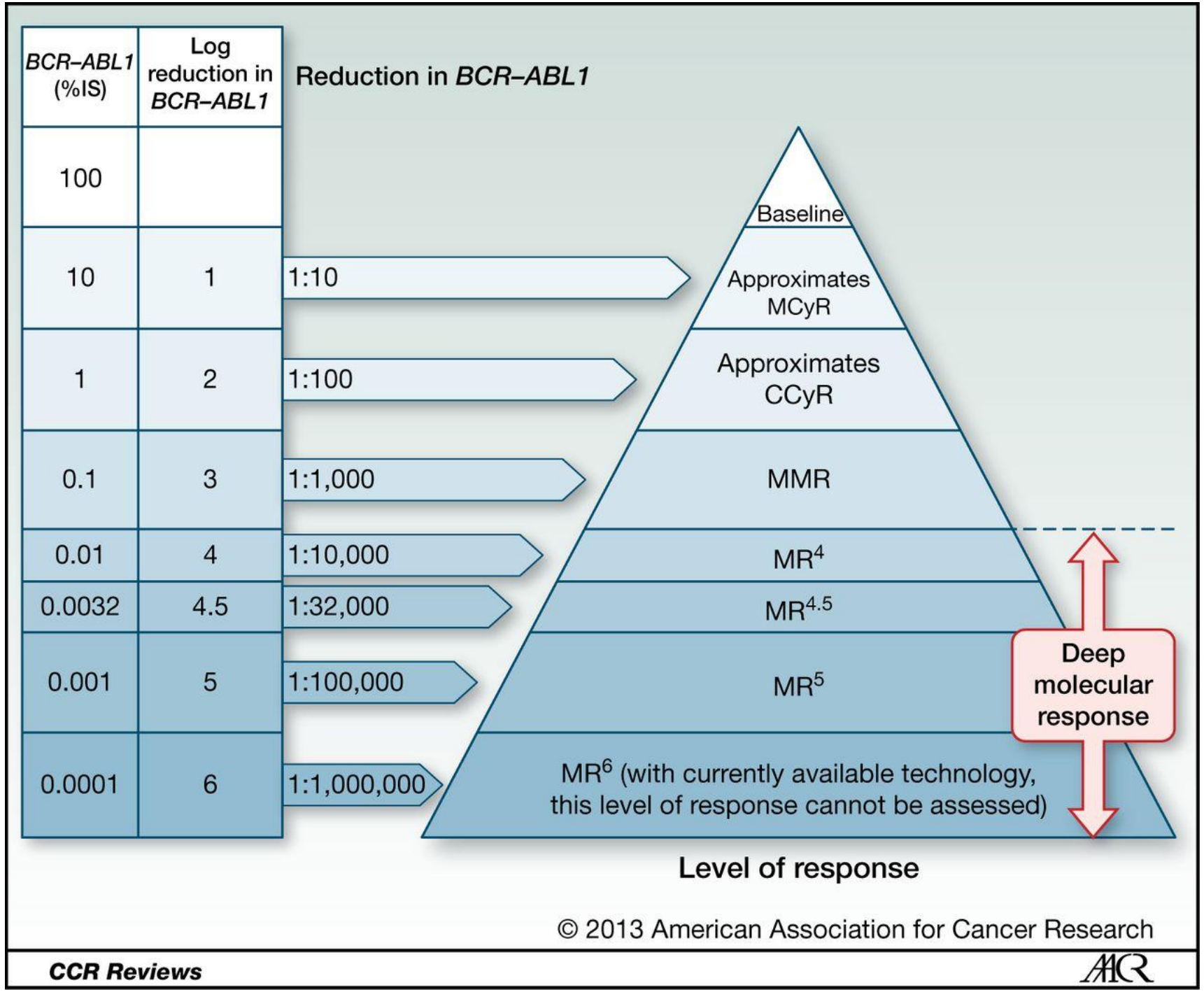



## Targeted BCR-ABL Inhibition Revolutionized Therapy for CML

# Pivotal phase III trials of approved tyrosine kinase inhibitors for the frontline treatment of CML

| Trial | Treatment | CCyR (%) | MMR (%) | BCR-ABL < 10% at 3 months (%) | EFS/PFS (%) | OS (%) | Longest follow-up (years) |
|---|---|---|---|---|---|---|---|
| | | At 10 years | | | At 10 years | | |
| IRIS | Imatinib ($n = 304$) | 83 | 93 | NR | 80 | 83 | 11 |
| | | At 2 years | At 5 years | | At 5 years | | |
| DASISION | Dasatinib ($n = 259$) | 86 | 76 | 84 | 85 | 91 | 5 |
| | Imatinib ($n = 260$) | 82 | 64 | 64 | 86 | 90 | |
| | | At 2 years | At 5 years | | At 5 years | At 6 years | |
| ENESTnd | Nilotinib 300 mg ($n = 282$) | 87 | 77 | 91 | 95 | 92 | 6 |
| | Nilotinib 400 mg ($n = 281$) | 85 | 77 | 89 | 97 | 96 | |
| | Imatinib ($n = 283$) | 77 | 60 | 67 | 93 | 91 | |
| | | At 12 months | | | At 12 months | | |
| BEFORE | Bosutinib 400 mg ($n = 268$) | 77 | 47 | 75 | 96 | 99.9 | 18 months |
| | Imatinib ($n = 268$) | 66 | 37 | 57 | 94 | 99.7 | |

NR, Not reported.


BCR–ABL1 (%IS)
Log reduction in BCR–ABL1
Reduction in BCR–ABL1
100
10
1
1:10
1
2
1:100
0.1
3
1:1,000
0.01
4
1:10,000
0.0032
4.5
1:32,000
0.001
5
1:100,000
0.0001
6
1:1,000,000
Baseline
Approximates MCyR
Approximates CCyR
MMR
MR4
MR4.5
MR5
MR6 (with currently available technology, this level of response cannot be assessed)
Deep molecular response
Level of response
© 2013 American Association for Cancer Research
CCR Reviews
AACR

National Comprehensive Cancer Network®

# NCCN Guidelines Version 4.2018
# Chronic Myeloid Leukemia

**RESPONSE MILESTONES[c,e]**

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

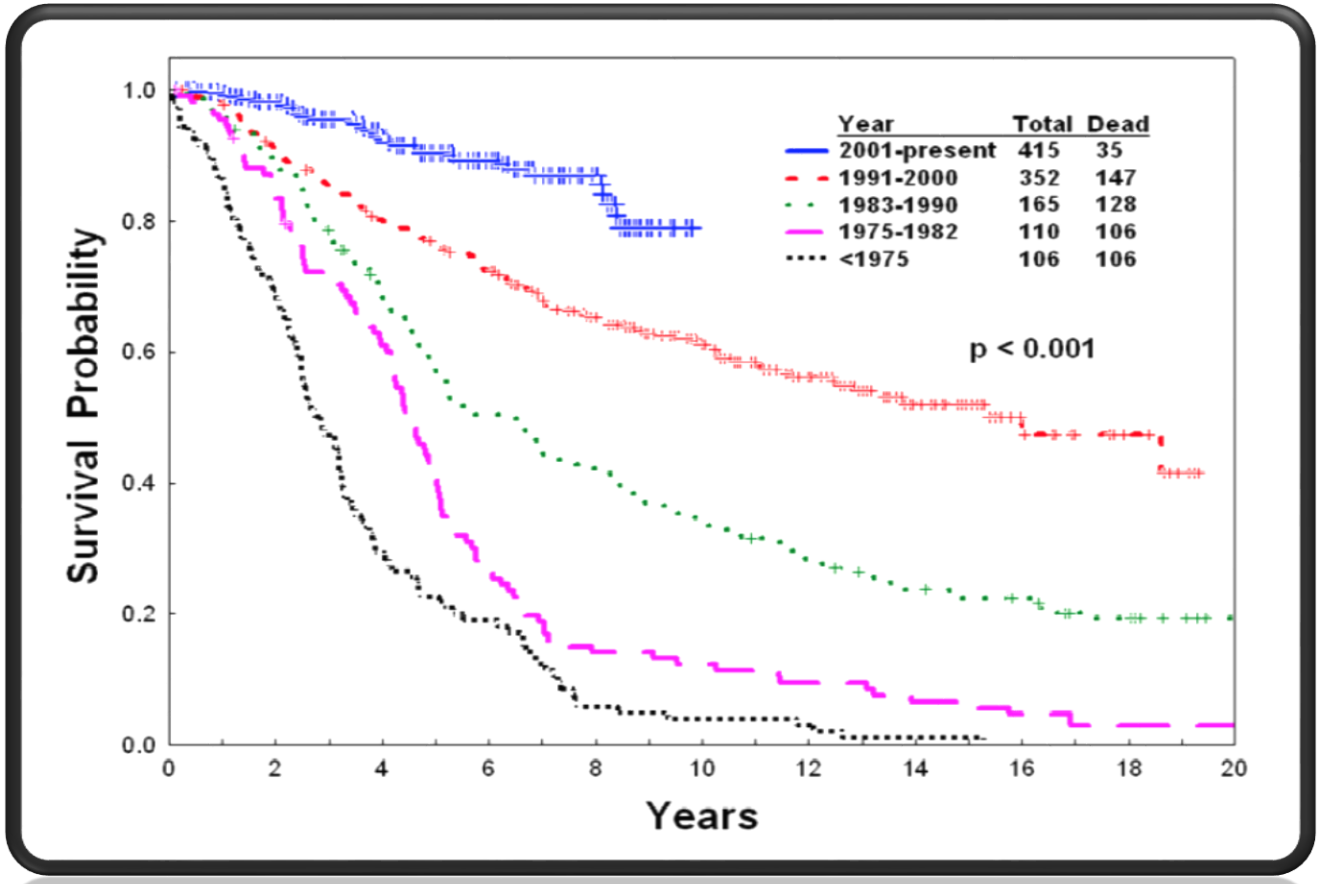
| | CLINICAL CONSIDERATIONS | SECOND-LINE AND SUBSEQUENT TREATMENT OPTIONS |
|---|---|---|
| RED | • Evaluate patient compliance and drug interactions<br>• Mutational analysis | Switch to alternate TKI (CML-5)<br>and Evaluate for HCT (CML-6) |
| YELLOW | • Evaluate patient compliance and drug interactions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

blood

Prepublished online January 6, 2012;
doi:10.1182/blood-2011-08-358135

**Improved survival in chronic myeloid leukemia since the introduction of imatinib therapy: a single-institution historical experience**

Hagop Kantarjian, Susan O'Brien, Elias Jabbour, Guillermo Garcia-Manero, Alfonso Quintas-Cardama, Jenny Shan, Mary Beth Rios, Farhad Ravandi, Stefan Faderl, Tapan Kadia, Gautam Borthakur, Xuelin Huang, Richard Champlin, Moshe Talpaz and Jorge Cortes




Discontinue therapy?

# EURO-SKI: Defining Cutoffs for Tyrosine Kinase Inhibitor Cessation in Patients With Chronic Myeloid Leukemia

# EURO-SKI: Background

- 40% to 55% of CML pts have achieved TFR after long-term TKI treatment with durable deep MR
  - Most pts (85% to 90%) experience molecular relapse within 6 mos of discontinuing TKI
  - Restarting TKI treatment regains MR in almost all pts (90% to 95%)

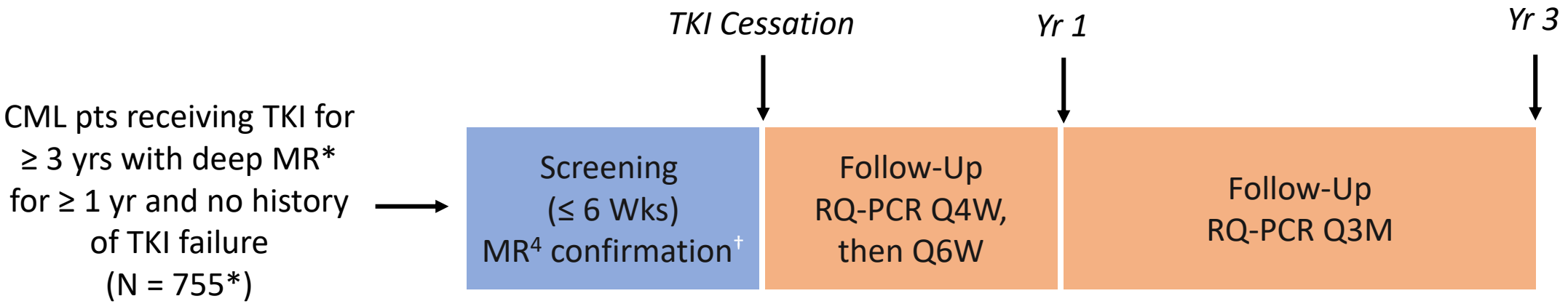
- Data on prognostic indicators of sustained TFR incomplete or inconsistent
  - Imatinib data: TKI treatment duration ≥ 5-6 yrs and deep MR (≥ 3 yrs) associated with sustained TFR following TKI cessation in CML pts[1,2]
  - No data on prognostic markers for dasatinib or nilotinib cessation

- EURO-SKI designed to establish stopping criteria for TKIs in CML pts[3]

1. Mahon FX, et al. Lancet Oncol. 2010;1029-1035. 2. Etienne G, et al. J Clin Oncol. 2017;35:298-305.
3. Sauselle S, et al. ASH 2017. Abstract 313.

# EURO-SKI: Study Design

- Observational cohort study




*In primary analysis of 868 preregistered pts.
†$MR^4$, defined as detectable BCR-ABL ≤ 0.01%, or undetectable BCR-ABL in samples with ≥ 10,000 ABL or ≥ 24,000 GUS transcripts, respectively.

- Primary endpoint: molecular recurrence (BCR-ABL > 0.1%, ie, loss of MMR)

Sauselle S, et al. ASH 2017. Abstract 313.

Slide credit clinicaloptions.com

# EURO-SKI: Pt Population

- N = 821 pts recruited
  - Male: 52%
  - Median age: 60 yrs (range: 19-90)

- N = 755 included in MRFS analysis
  - MMR loss after TKI cessation: n = 371 (49%)
  - TKI restarted in MMR: n = 13 pts
  - Death in MMR: n = 4 pts

Sauselle S, et al. ASH 2017. Abstract 313.

Slide credit clinicaloptions.com

# EURO-SKI: Molecular Recurrence-Free Survival

| Month | Pts at Risk, n | MRFS, % (95% CI) |
|---|---|---|
| 6 | 457 | 61 (58-65) |
| 12 | 396 | 55 (51-58) |
| 18 | 333 | 52 (49-56) |
| 24 | 219 | 50 (47-54) |
| 36 | 31 | 47 (43-51) |

Sauselle S, et al. ASH 2017. Abstract 313.

# EURO-SKI: Cutoffs for MMR at 6 Mos

- Cutoffs for 6-mo probability of MMR loss (minimal *P* value approach)
  - TKI (imatinib) cutoff: 5.8 yrs
    - MMR loss if discontinued at ≤ 5.8 yrs: 57% (95% CI: 48% to 64%)
    - MMR loss if discontinued at > 5.8 yrs: 34% (95% CI: 29% to 39%)
  - $MR^4$ cutoff: 3.1 yrs
    - MMR loss if $MR^4$ duration ≤ 3.1 yrs: 56% (95% CI: 47% to 64%)
    - MMR loss if $MR^4$ duration > 3.1 yrs: 38% (95% CI: 33% to 44%)

Sauselle S, et al. ASH 2017. Abstract 313.

# EURO-SKI: Conclusions

- Study defined stopping criteria for TKI cessation in CML pts who achieve durable deep MR
- Preferred cutoffs for 6-mo probability of MMR loss
  - TKI duration: 5.8 yrs
  - $MR^4$ duration: 3.1 yrs
- Probability of treatment-free remission increased almost linearly per each additional year of first-line imatinib and duration of $MR^4$

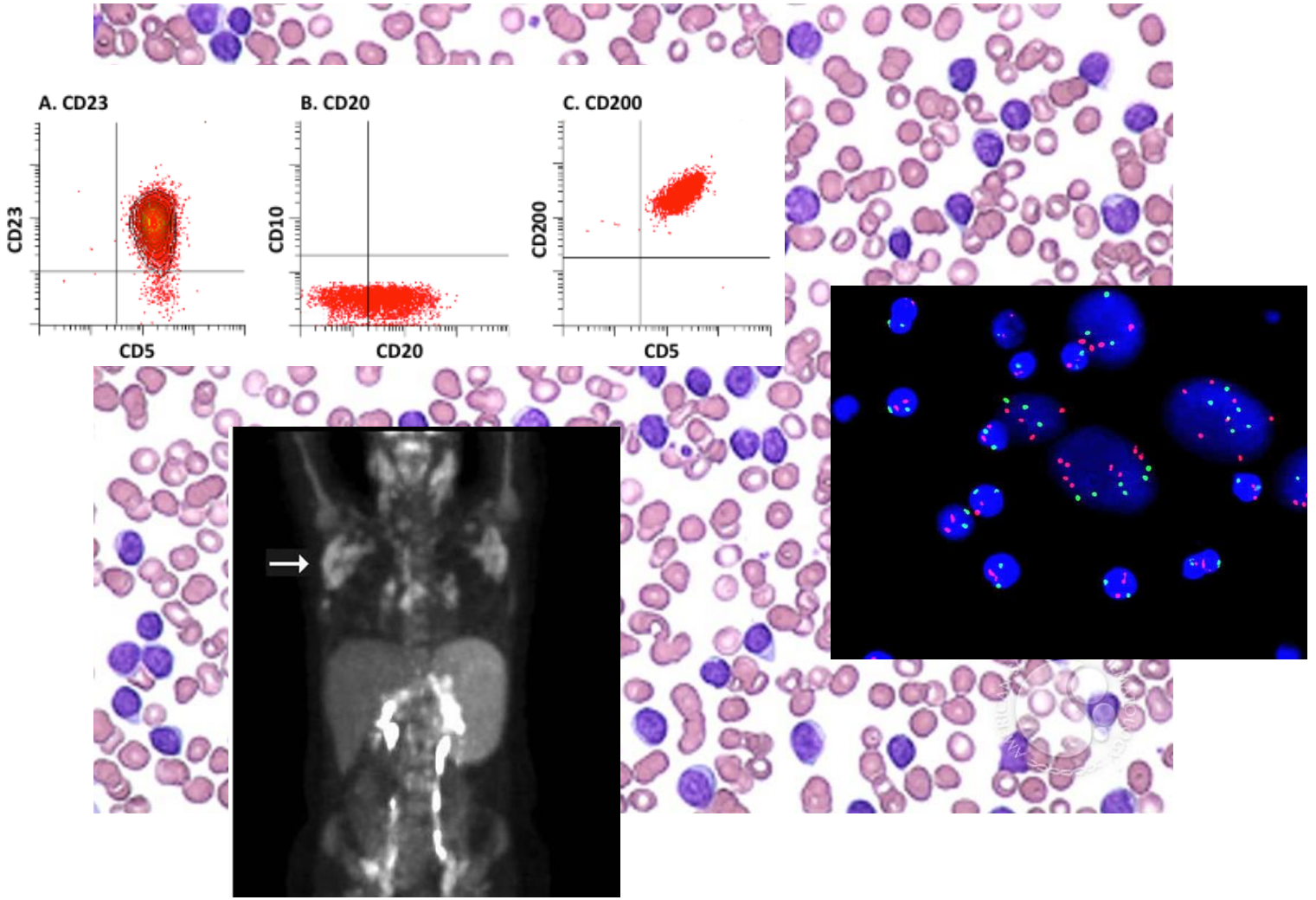
Sauselle S, et al. ASH 2017. Abstract 313.

# When consider to STOP therapy…

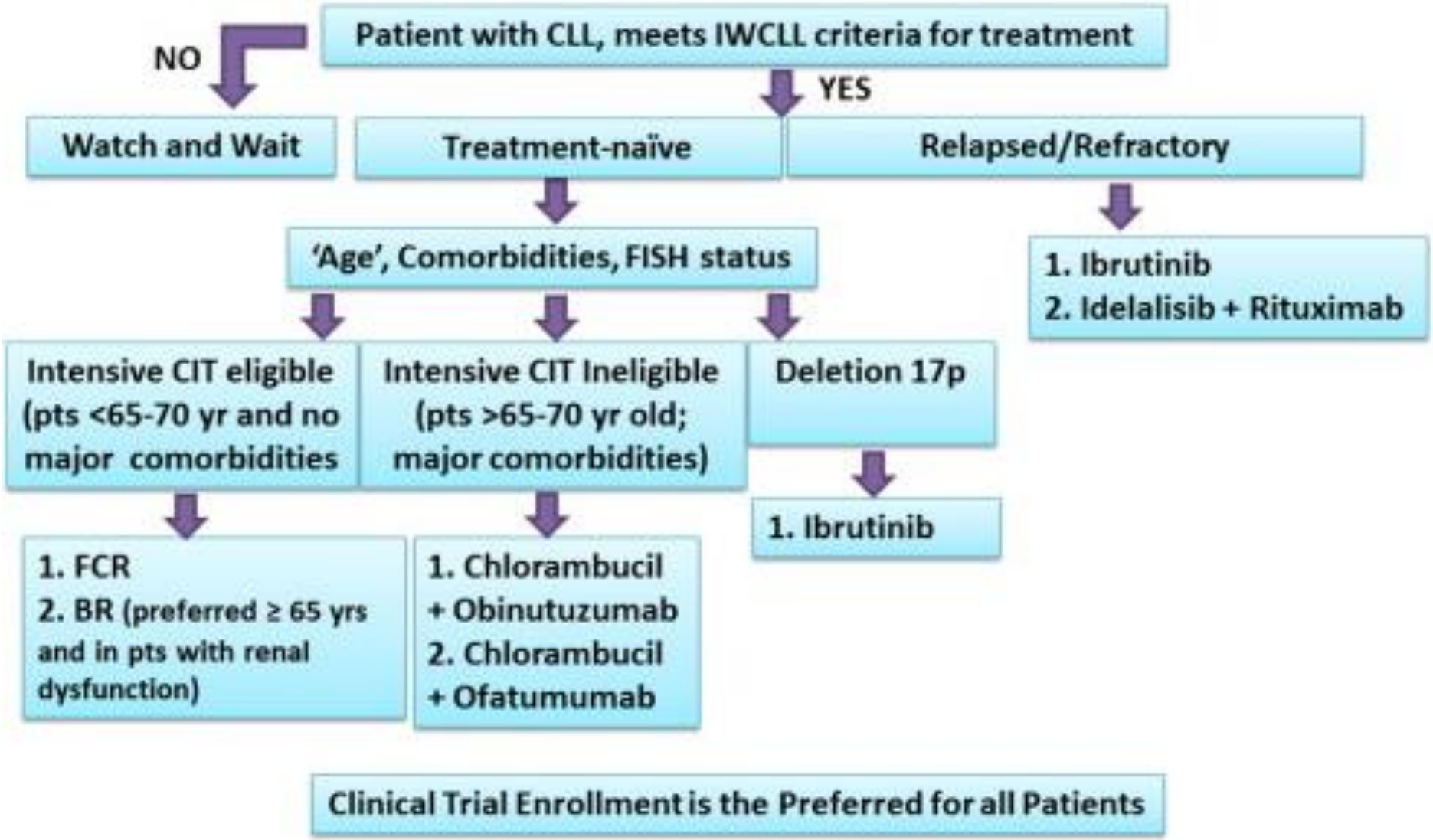
| Parameter | Discontinuation of TKI | |
|---|---|---|
| | Yes | No |
| Sokal risk | Low-intermediate | High |
| BCR-ABL1 transcripts | Quantifiable (e13a2 or e14a2) | Not quantifiable |
| CML stage | Chronic | Accelerated/blast phase |
| Response to first TKI | Optimal | Failure |
| Duration of all TKIs therapy | >6–8 years | <3 years |
| Depth of molecular response | CMR (MR4.5) | Less than MR4 |
| Duration of molecular response | >3+ years | < 3 years |
| Monitoring availability | Ideal (every 2 months in years 1–2) | Poor; noncompliant |

# Chronic Lymphocytic Leukemia

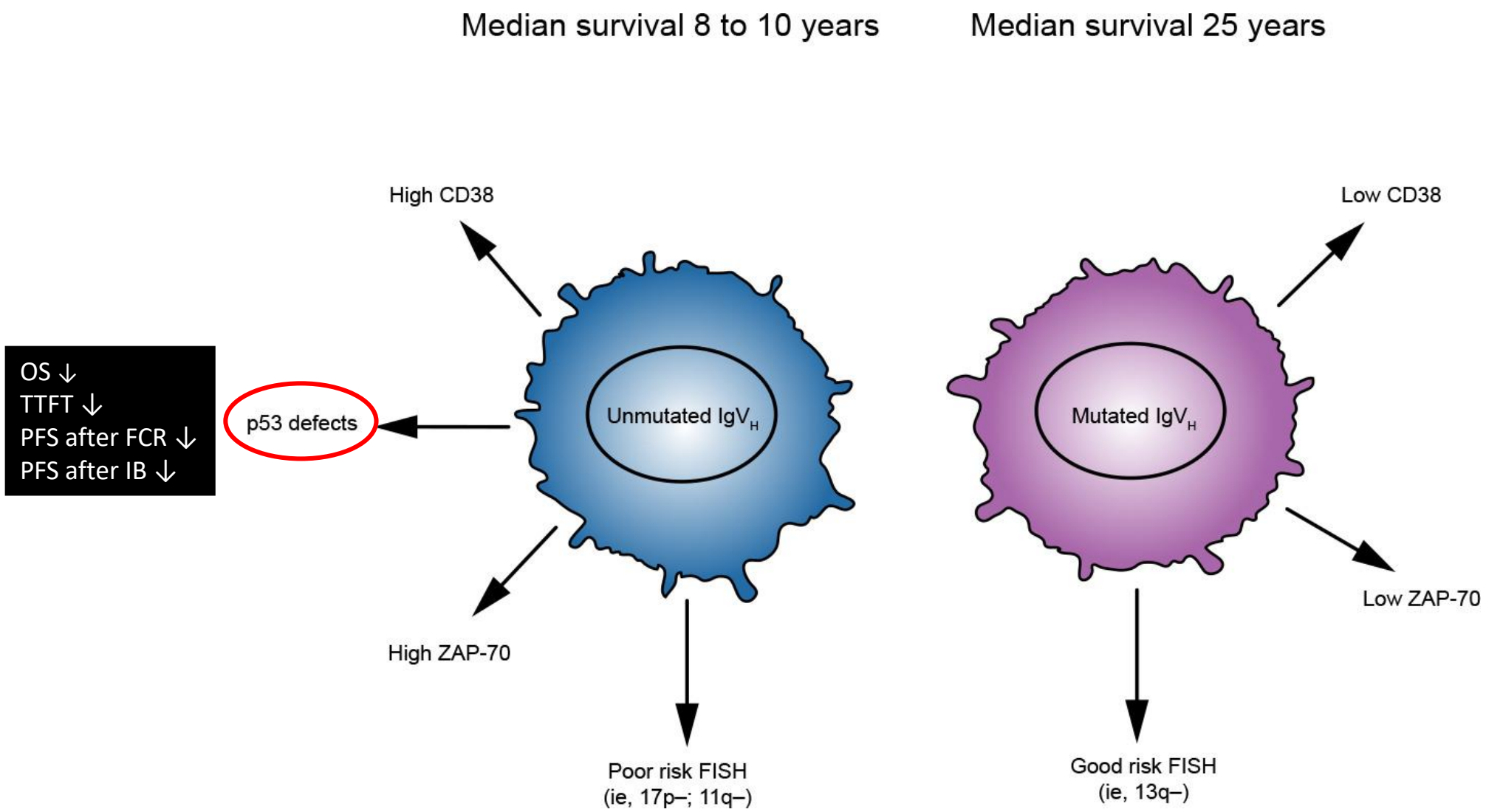
- Most common leukemia in adults
  - Median age at diagnosis 67-72 years
- Older population
  - Median age at diagnosis 67-72 years
  - Comorbidities
- Standard therapy: FCR (CLL8 study)
  - High frequency of grade 3-4 toxicity
  - Unsuitable for elderly population
- Other First line treatment options:
  - Bendamustine + rituximab
  - Obinutuzumab + chlorambucil
  - Ibrutinib



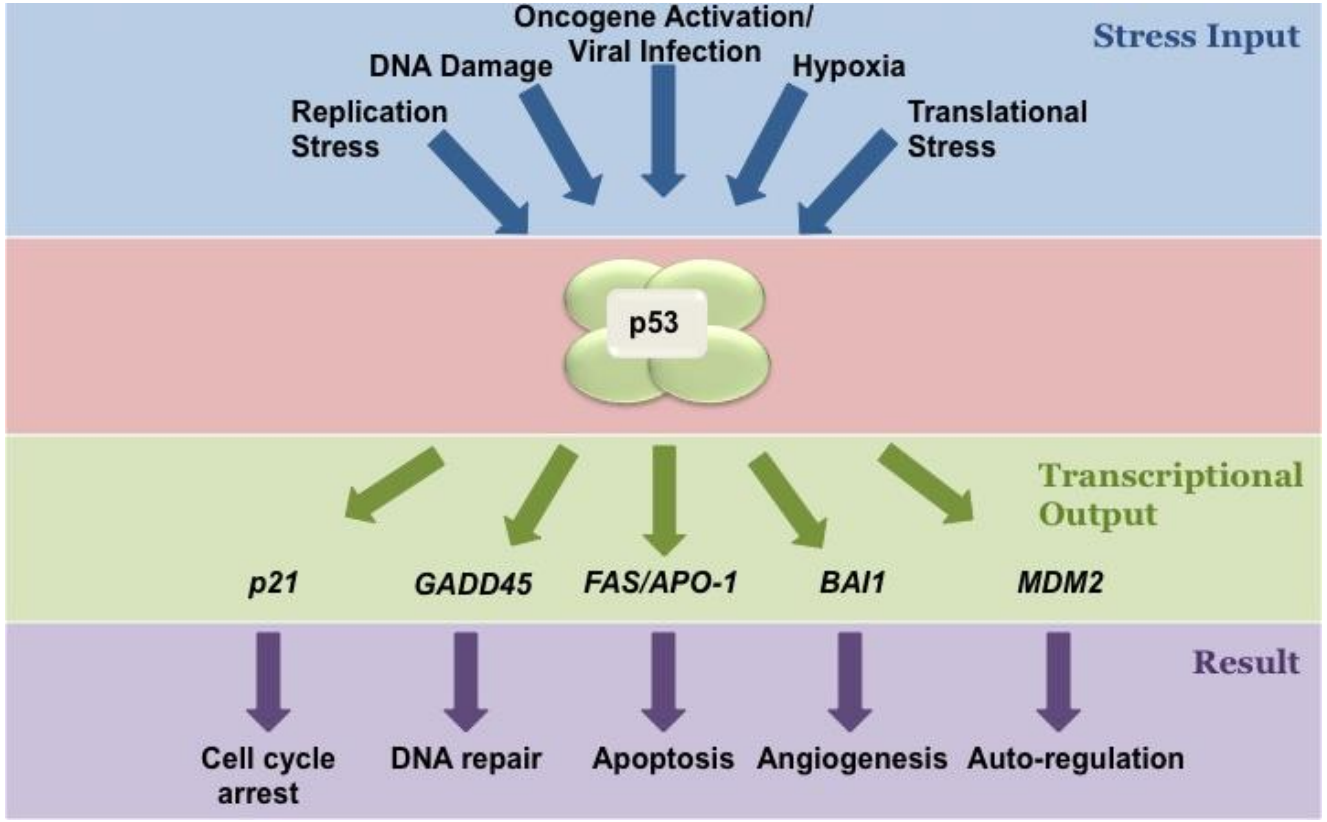
# Current Standard Treatment for CLL

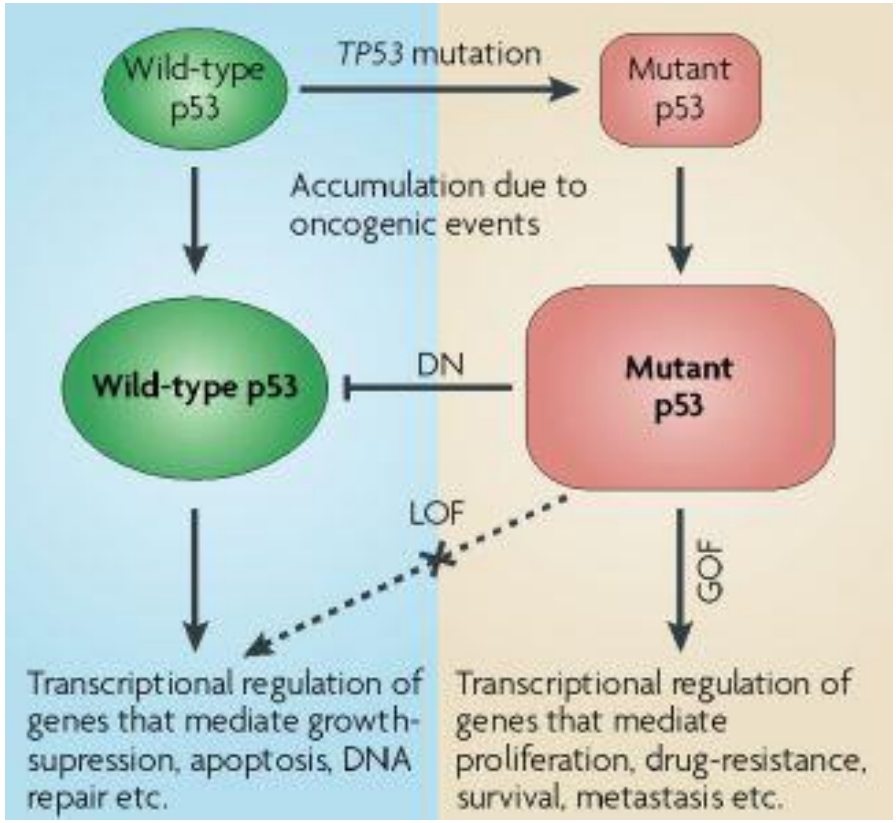


# Prognostic factors in CLL

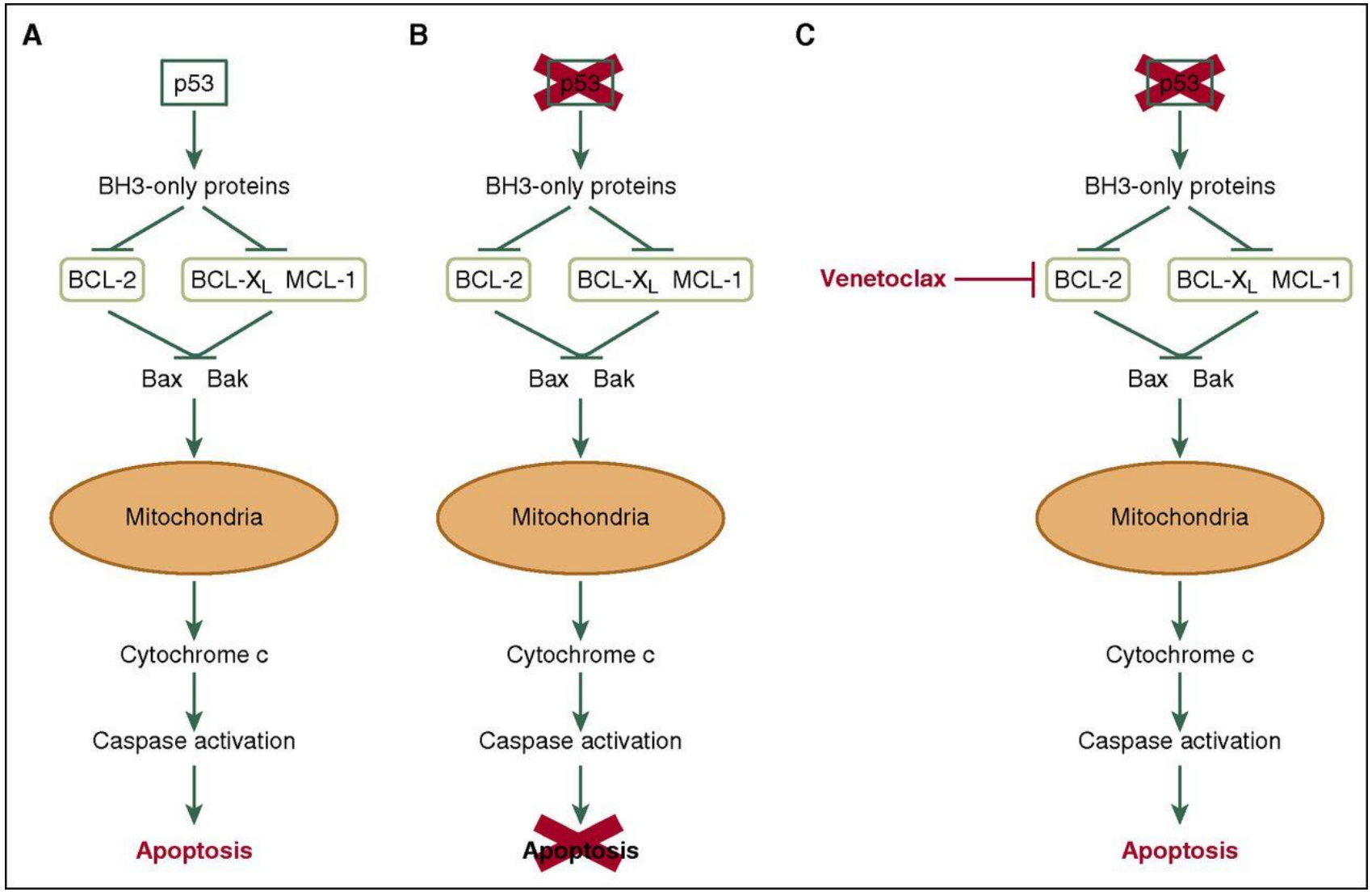


# p53 Tumor Suppressor Gene: A Master Regulator



# Venetoclax induces apoptosis of CLL cells independently of p53



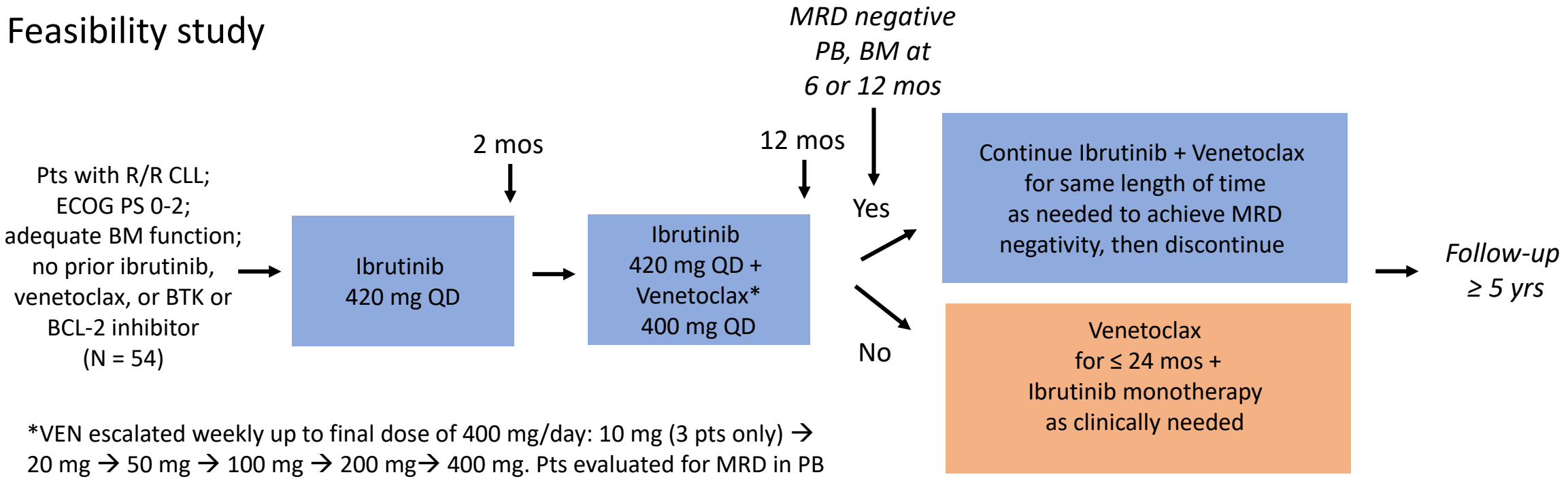
# CLARITY: Feasibility Study of Combination Ibrutinib + Venetoclax in R/R CLL

# Ibrutinib + Venetoclax in R/R CLL (CLARITY): Background

- MRD is associated with improved outcomes in CLL[1]
- CLL pathophysiology driven by cell proliferation with high Ki-67 expression plus apoptosis with BCL-2 expression[2]
- Ibrutinib: BTK inhibitor; FDA approved as monotherapy in CLL ± del(17p)[3]
  - Improved PFS, OS in R/R CLL but does not lead to disease eradication[4,5]
- Venetoclax: BCL-2 inhibitor; FDA approved in CLL pts with del(17p) who have been treated with at least 1 prior therapy[6]
  - Dramatic activity in CLL with TLS, high rates of MRD negativity[5,7]
- Current feasibility study evaluated safety, efficacy of ibrutinib + venetoclax in pts with R/R CLL[8]

# CLARITY: Study Design

- Feasibility study




*VEN escalated weekly up to final dose of 400 mg/day: 10 mg (3 pts only) → 20 mg → 50 mg → 100 mg → 200 mg→ 400 mg. Pts evaluated for MRD in PB every 3 mos, in BM (along with CT) at BL and at 6, 12, 24 mos of IBR + VEN. MRD negativity = < 0.01% CLL cells. IBR + VEN stopped at 14 mos if 8-mo BM MRD negative; at 26 mos if 14-mo BM MRD negative. VEN stopped, IBR continued at 26 mos if BM MRD positive. Datalock: 12/1/17.

- Primary endpoint: MRD eradication in BM after 12 mos of IBR + VEN
- Key secondary endpoints: MRD eradication in BM after 6, 24 mos of IBR + VEN, response, PFS, OS, safety

Hillmen P, et al. ASH 2017. Abstract 428.

Slide credit: clinicaloptions.com

# CLARITY: MRD in PB Over Time for Pts Receiving ≥ 2 Mos of Ibrutinib + Venetoclax

| Median MRD in PB, cells x $10^9$/L (IQR) for Pts Reaching ≥ Mo 4* | IBR + VEN (n = 46) |
|---|---|
| At screening (n = 46) | 54.5 (13-92) |
| Day 0 (before therapy initiation; n = 46) | 43.5 (10.3-94) |
| Wk 8 (end of IBR monotherapy; n = 46) | 60 (14-150) |
| Wk 12 (end of VEN escalation; n = 45) | 1.1 (0.23-6.25) |
| Mo 4 (after 8 wks of IBR + VEN; n = 46) | 0.019 (0.0028-0.21) |
| Mo 5 (after 12 wks of IBR + VEN; n = 45) | 0.012 (0.0011-0.1) |
| Mo 8 (after 6 mos of IBR + VEN; n = 37) | 0.001 (0-0.025) |

*Corresponds to 2 mos of IBR + VEN.

Hillmen P, et al. ASH 2017. Abstract 428.

# CLARITY: Responses With 6 Mos of Ibrutinib + Venetoclax

| Response at Mo 8, n (%) | CR | CRi | PR | ORR |
|---|---|---|---|---|
| All pts reaching this time point (n = 38)* | 15 (39) | 3 (8) | 20 (53) | 38 (100) |
| Prior FCR or BR with relapse < 36 mos (n = 17) | 9 (53) | 2 (12) | 6 (35) | 17 (100) |
| Prior idelalisib (n = 7) | 3 (43) | 0 | 4 (57) | 7 (100) |

*Pts who received ≥ 6 mos of IBR + VEN and had clinical response assessment by iwCLL, BM, and CT scan.

Hillmen P, et al. ASH 2017. Abstract 428.

Slide credit: clinicaloptions.com

# CLARITY: BM MRD With 6 Mos of Ibrutinib + Venetoclax

| Response at Mo 8, n/N (%) | MRD-Negative PB | MRD-Negative BM | Trephine Normal |
|---|---|---|---|
| All pts reaching this timepoint (n = 38)* | 15/38 (37) | 12/38 (32) | 32/38 (84) |
| Prior FCR or BR with relapse < 36 mos (n = 17) | 9/17 (52) | 7/17 (41) | 16/17 (94) |
| Prior idelalisib (n = 7) | 4/7 (57) | 3/7 (43) | 7/7 (100) |

*Pts who received ≥ 6 mos of IBR + VEN and had BM or PB MRD < 0.01% CLL ($10^{-4}$) cells by flow cytometry.

- MRD negativity in PB and BM increased over time with IBR + VEN combination therapy up to 6 mos

Hillmen P, et al. ASH 2017. Abstract 428.

Slide credit: clinicaloptions.com

# CLARITY: Conclusions

- In 54 pts with R/R CLL, combination therapy with ibrutinib + venetoclax was well tolerated with predictable, mostly low-grade AEs
  - Only 1 case of TLS
- 100% of pts had an objective response after 6 mos of combination therapy
  - Nearly one half (47%) in CR or CRi
  - Nearly one third (32%) with MRD negative BM
- Investigators report that results from CLARITY in R/R CLL informed modification of phase III NCRI FLAIR study to include ibrutinib + venetoclax as first-line therapy in newly diagnosed CLL

Hillmen P, et al. ASH 2017. Abstract 428.

Slide credit: clinicaloptions.com

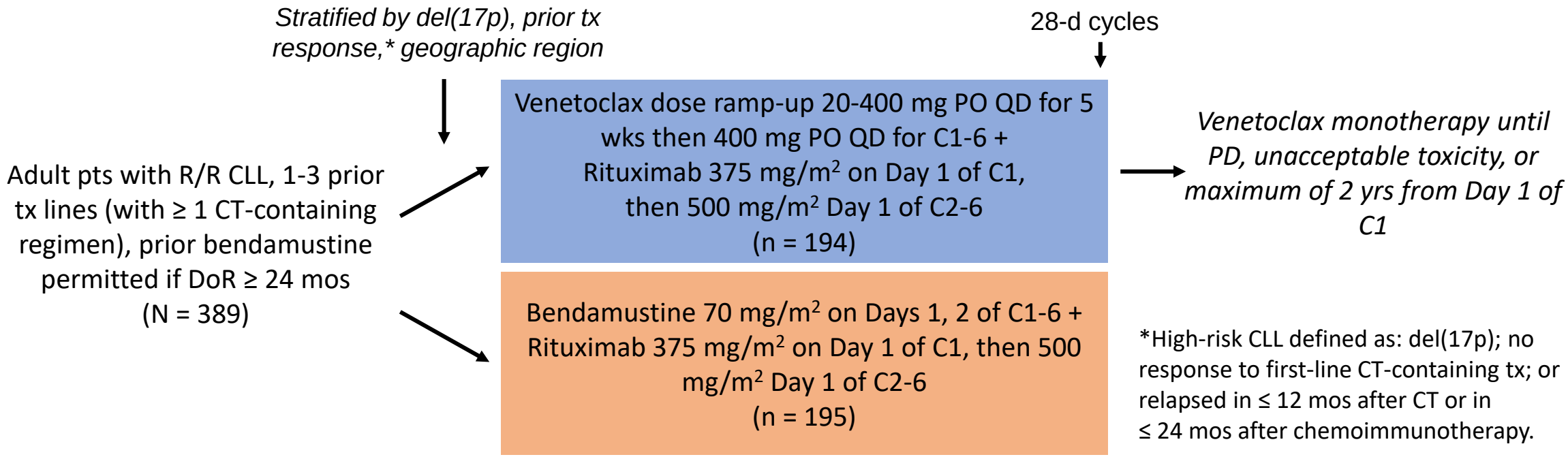
# MURANO Interim Analysis: Venetoclax + Rituximab vs Bendamustine + Rituximab in Patients With Relapsed/Refractory CLL

# Venetoclax + Rituximab in R/R CLL (MURANO Interim Analysis): Background

- Bendamustine + rituximab associated with limited efficacy in R/R CLL
  - Phase II trial reported mPFS of 15.2 mos and ORR of 59% (CR: 9%) in R/R CLL[1]
- Venetoclax: BCL-2 inhibitor approved for R/R CLL pts with del(17p)[2]
  - Single-agent venetoclax active (ORR: 79%) in R/R CLL, including in pts with del(17p)[3,4]
  - Common AEs: TLS, neutropenia, infections[2-4]
- Phase Ib study of venetoclax + rituximab in R/R CLL/SLL reported ORR in 42/49 (86%) pts (CR: 51%, negative MRD: 57%)[5]
  - Disease control maintained in 11 pts with MRD-negativity off therapy
- Current preplanned interim analysis evaluated efficacy, safety of time-limited venetoclax + rituximab vs bendamustine + rituximab in pts with R/R CLL[6]
  - After ~ 140 investigator-assessed PFS events (75% of total data)

# MURANO Interim Analysis: Study Design

- Multicenter, randomized, open-label phase III trial



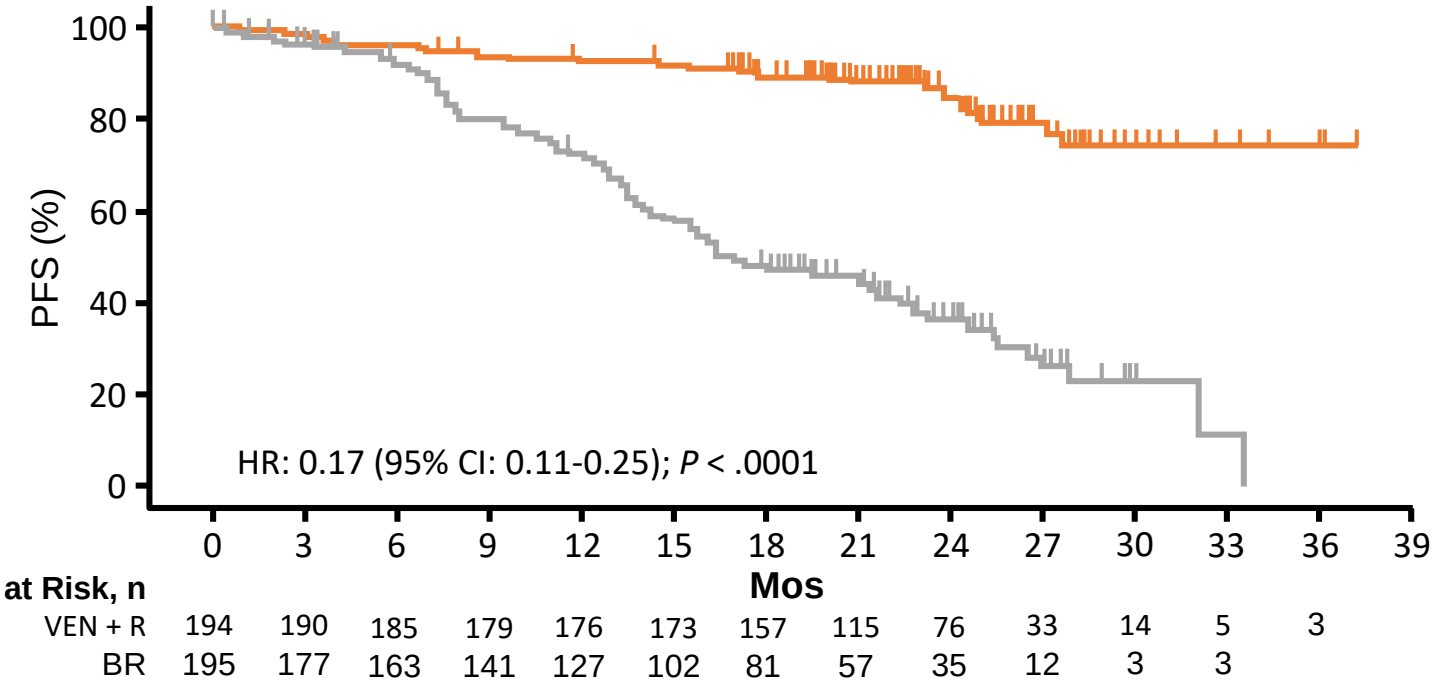

- Primary endpoint: investigator-assessed PFS
- Secondary endpoints: IRC-assessed PFS and MRD negativity, IRC-assessed CR → ORR → OS (hierarchical testing), safety

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

Slide credit: clinicaloptions.com

# MURANO Interim Analysis: Investigator-Assessed PFS (Primary Endpoint)

| | Pts, n | mPFS, Mos | 1-yr PFS, % | 2-yr PFS, % |
|---|---|---|---|---|
| VEN + R | 194 | NR | 92.7 | 84.9 |
| BR | 195 | 17 | 72.5 | 36.3 |

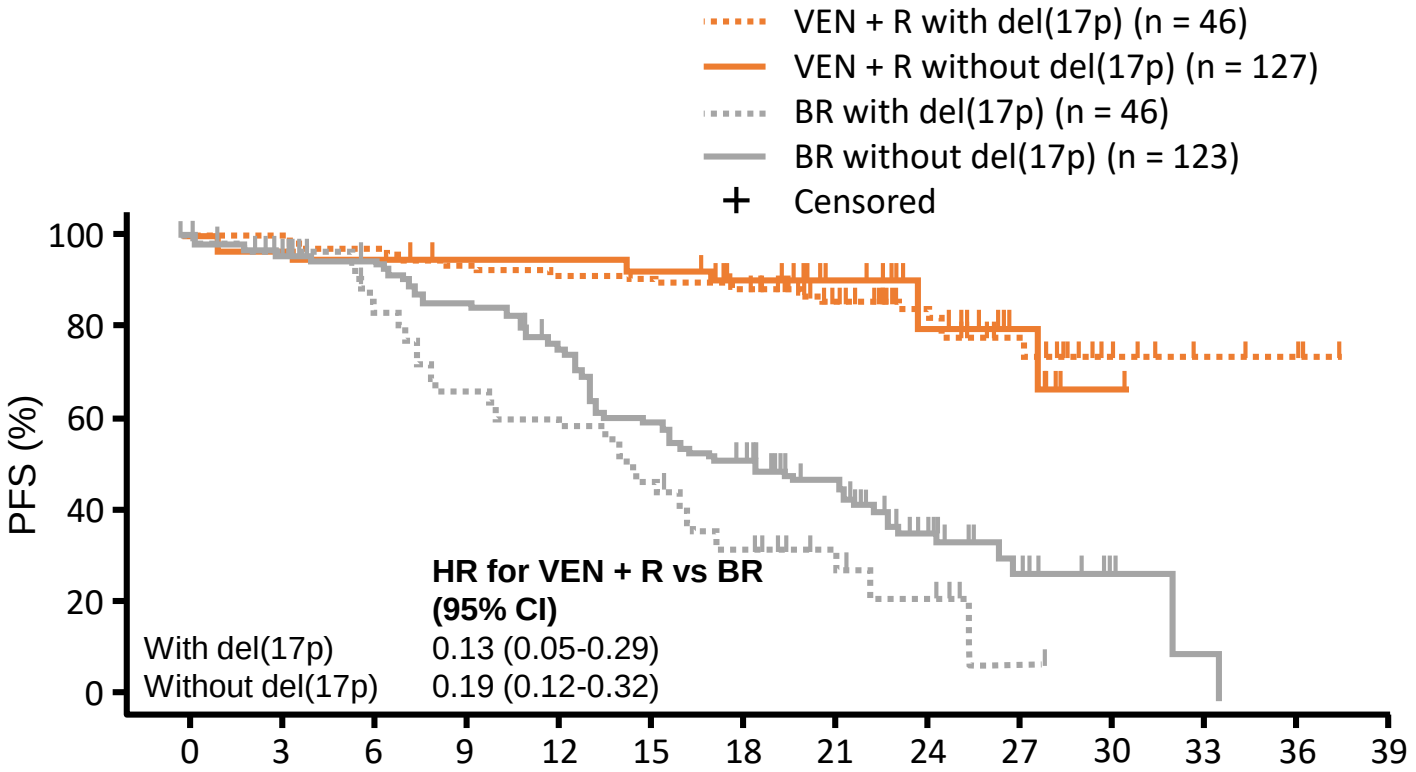



- Median f/u: 23.8 mos (0-37.4)
  - Completed 2-yrs without progression, n = 65; pts with ≥ 3-mo f/u, n = 12
- IRC-assessed PFS concordant with investigator assessment
  - mPFS for VEN + R vs BR: NR vs 18.1 mos (HR: 0.19; 95% CI: 0.13-0.28; *P* < .0001)

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

Slide credit: clinicaloptions.com

# MURANO Interim Analysis: Investigator-Assessed PFS by Del(17p) Status




**Pts at Risk, n**

| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| VEN + R with del(17p) | 46 | 44 | 43 | 43 | 43 | 42 | 36 | 25 | 17 | 7 | 2 | | |
| VEN + R without del(17p) | 127 | 127 | 124 | 118 | 116 | 114 | 105 | 76 | 48 | 20 | 10 | 4 | 3 |
| BR with del(17p) | 46 | 40 | 34 | 27 | 25 | 20 | 14 | 8 | 5 | 1 | | | |
| BR without del(17p) | 123 | 114 | 108 | 99 | 88 | 70 | 60 | 44 | 26 | 10 | 3 | 1 | |

- 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.

Slide credit: clinicaloptions.com

# MURANO Interim Analysis: Response, Survival

| Response, % | VEN + R (n = 194) | BR (n = 195) | P Value |
|---|---|---|---|
| Per INV | | | |
| ▪ ORR* | 93.3 | 67.7 | < .0001† |
| ▪ CR‡ | 26.8 | 8.2 | < .0001† |
| ▪ PR§ | 66.5 | 59.5 | -- |
| ▪ SD | 2.1 | 22.6 | -- |
| Per IRC | | | |
| ▪ ORR* | 92.3 | 72.3 | < .0001† |
| ▪ CR‡ | 8.2 | 3.6 | .0814 |
| ▪ PR§ | 84.0 | 68.7 | -- |
| ▪ SD | 7.2 | 23.6 | -- |

*ORR: CR + initial CR + PR + nodular PR. †Descriptive.
‡CR: CR/initial CR. §PR: PR/nodular PR.

- Discrepant investigator-assessed CRs in VEN + R arm, n = 42
  - n = 28 attributed to residual CT scan nodes 16-30 mm diameter, 88% with PB MRD negativity
- Survival significantly improved with VEN + R vs BR
  - Median OS: NR vs NR (HR: 0.48; 95% CI: 0.25-0.90; *P* = .0186)

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

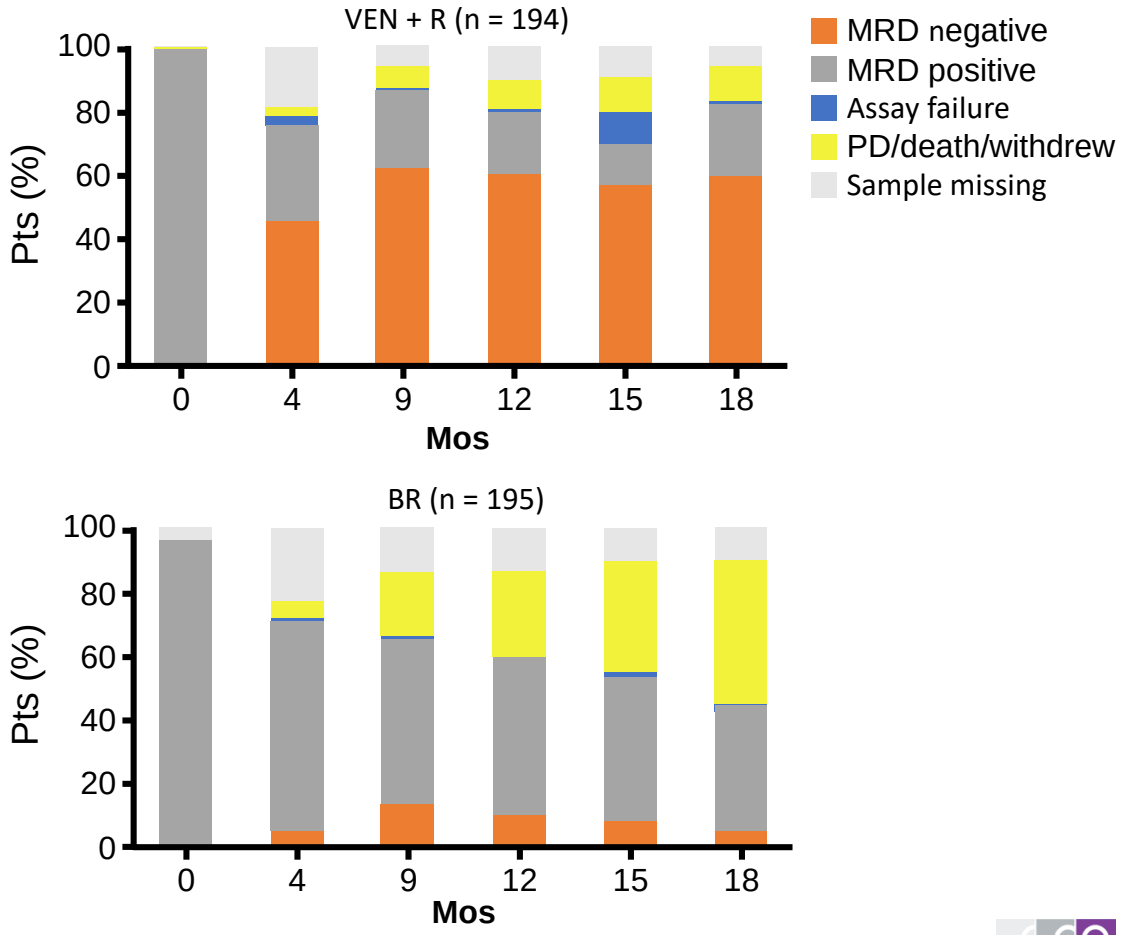
Slide credit: clinicaloptions.com

# MURANO Interim Analysis: MRD Negativity

- Higher rates of blood MRD negativity achieved and maintained with VEN + R vs BR

| MRD Negativity,* (n) % | VEN + R (n = 194) | BR (n = 195) |
|---|---|---|
| BL | 0 | 0 |
| 4 mos | 88 (45) | 11 (6) |
| 9 mos† | 121 (62) | 26 (13) |
| 12 mos | 117 (60) | 20 (10) |
| 15 mos | 110 (57) | 19 (9) |
| 18 mos | 116 (60) | 10 (5) |

*MRD negative: < 1 CLL cell/10,000 leukocytes ($10^{-4}$). Centrally assessed every 3 mos after end of combination therapy or at response by multicolor flow cytometry and/or ASO-PCR; only 1 positive assay needed to report as MRD positive. ITT analysis with missing MRD data or failed assay reported as MRD positive.
†End of combination therapy.

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# MURANO Interim Analysis: Safety

| AE, n (%) | VEN + R (n = 194) | BR (n = 188) |
|---|---|---|
| Pts with ≥ 1 any-grade AE | 194 (100) | 185 (98) |
| Serious AE | 90 (46) | 81 (43) |
| Grade 3/4 | 159 (82) | 132 (70) |
| Grade 5 | 10 (5)* | 11 (6)† |

*Pneumonia, n = 3; n = 1 each for following: sepsis, cardiac failure, MI, sudden cardiac death, CRC, status epilepticus, acute respiratory failure. †Sepsis, n = 2; lung CA, n = 2; n = 1 each for following: Listeria sepsis, Scedosporium infection, lymphoma, hemorrhagic stroke, pulmonary embolism, AML, sudden death.

- Single-agent VEN grade 3/4 AEs: neutropenia, 11%; anemia, 3%; thrombocytopenia, 2%; pneumonia, 2%

| Grade 3/4 AE With ≥ 2% Diff. Between Arms,* n (%) | VEN + R (n = 194) | BR (n = 188) |
|---|---|---|
| Neutropenia | 112 (58) | 73 (39) |
| Anemia | 21 (11) | 26 (14) |
| Thrombocytopenia | 11 (6) | 19 (10) |
| Febrile neutropenia | 7 (4) | 18 (10) |
| Pneumonia | 10 (5) | 15 (8) |
| Infusion-related reaction | 3 (2) | 10 (5) |
| TLS | 6 (3) | 2 (1) |
| Hypotension | 0 | 5 (3) |
| Hyperglycemia | 4 (2) | 0 |
| Hypogammaglobulinemia | 4 (2) | 0 |

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# MURANO Interim Analysis: Conclusions

- In a preplanned interim analysis, VEN + R significantly increased median PFS vs BR in pts with R/R CLL across subgroups and independent of del(17p) status
  - Overall median PFS: NR vs 17 mos (HR: 0.17; *P* < .0001)
- VEN + R demonstrated improved ORR with durable improvements in PB MRD negativity vs BR
  - ORR: 93.3% vs 67.7%
  - PB MRD negativity at Mo 18: 60% vs 5%
- No new safety signals observed
  - TLS in 3% of pts receiving VEN + R
- Investigators conclude that VEN + R represents a standard tx option in R/R CLL

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# THANKS