Chronic Lymphocytic Leukemia
Chronic Myeloid Leukemia

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Disclosures

Institutional research funding

Abbvie, Acerta, Gilead, Janssen, Pharmacyclics, Takeda

Data Safety Monitoring Committee

Beigene

Clinical Trial Steering Committee

Acerta

Consultancy

Abbvie, Adaptive, Astellas, Astra Zeneca, Genentech, Gilead, Janssen, Pharmacyclics

Honoraria

Janssen, Pharmacyclics

(CME accredited) Imedex, Medscape

Travel Expenses

Abbvie, Beigene, Genentech, Janssen, Pharmacyclics

Expert Witness

Genentech

Questions we will address - CLL

- What upfront regimens should we consider?
  - Chemoimmunotherapy?
  - Ibrutinib?
  - Acalabrutinib
  - Venetoclax/obinutuzumab
- What are our best options for a previously treated patient?
  - Ibrutinib
  - Acalabrutinib
  - Venetoclax/rituximab
- What combination regimens appear promising?

Previously Untreated

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CHEMOIMMUNOTHERAPY

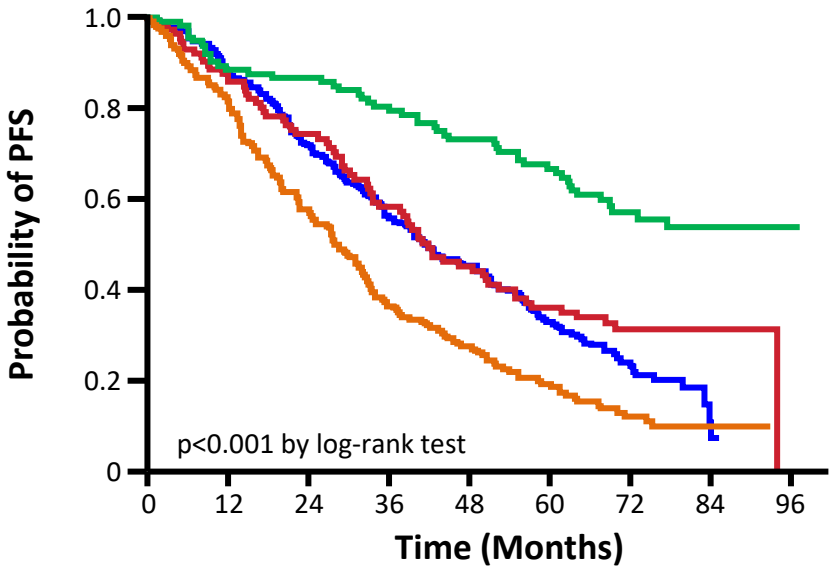
Long term remissions with FCR

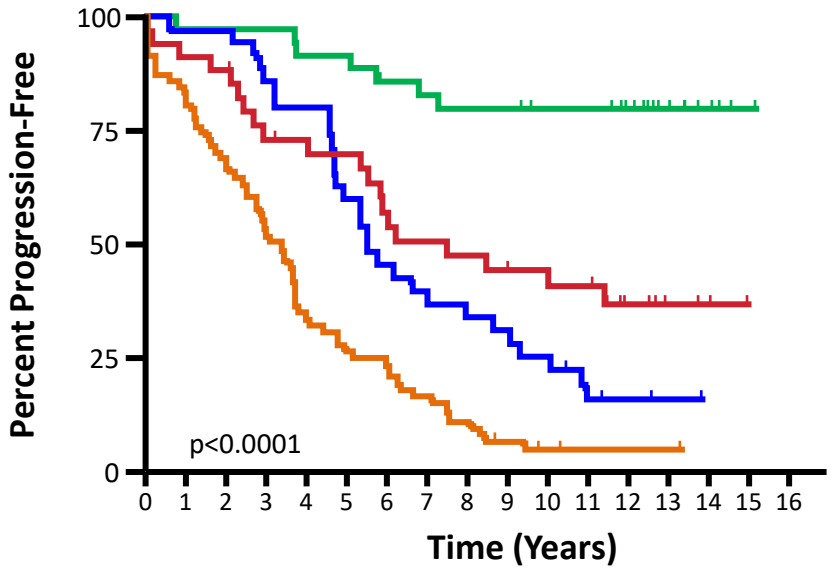
CLL8[1]

	N
FCR IGHV-M patients	113
FC IGHV-M patients	117
FCR IGHV-UM patients	197
FC IGHV-UM patients	195

MDACC[2]

	N
IGHV-M, MRD neg	35
IGHV-M, MRD pos	34
IGHV-UM, MRD neg	35
IGHV-UM, MRD pos	66





1. Fischer K, et al. Blood 2016; 127:208–215.
2. Thompson PA, et al. Blood 2016; 127:303–309.

IBRUTINIB

Update From the E1912 Trial Comparing Ibrutinib & Rituximab to FCR in Younger Patients with Previously Untreated Chronic Lymphocytic Leukemia (CLL)

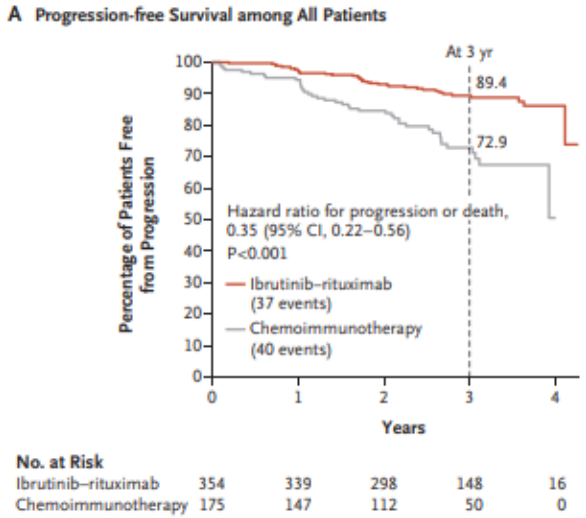
Tait Shanafelt, Xin Victoria Wang, Neil E. Kay, Susan O'Brien, Jacqueline Barrientos , Curt Hanson, Harry Erba, Rich Stone, Mark Litzow, Marty Tallman

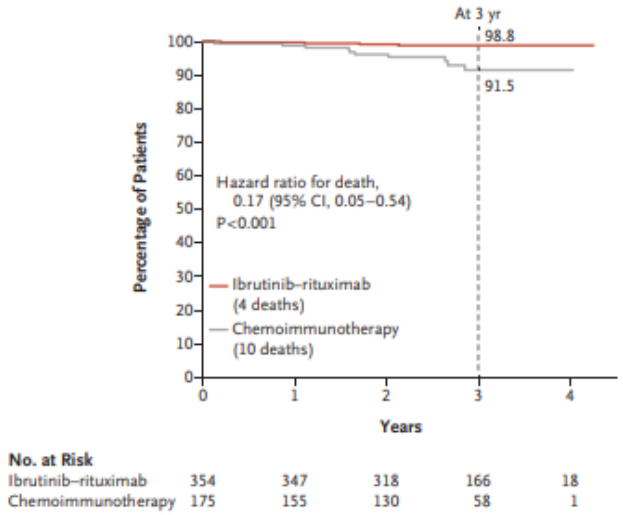
Shanafelt et al. ASH 2019. Abstract 33. NCT02048813.

Initial Results E1912: ASH 2018

- Patients age < 70 previously untreated patients, requiring treatment for CLL
  - 2:1 randomization to either ibrutinib + rituximab vs. FCR
- With median follow-up of 34 months, both progression-free survival (PFS) and overall survival (OS) favored ibrutinib-based therapy.

- A statistically significant improvement in OS was also observed for IR relative to FCR, but the number of deaths on both arms was limited.

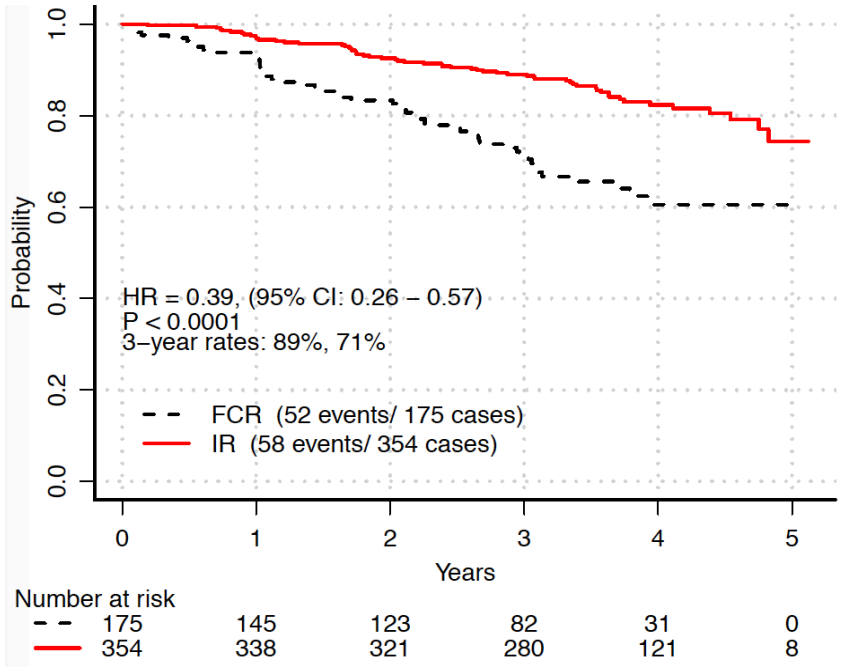




Shanafelt, et al NEJM 2019 381:432

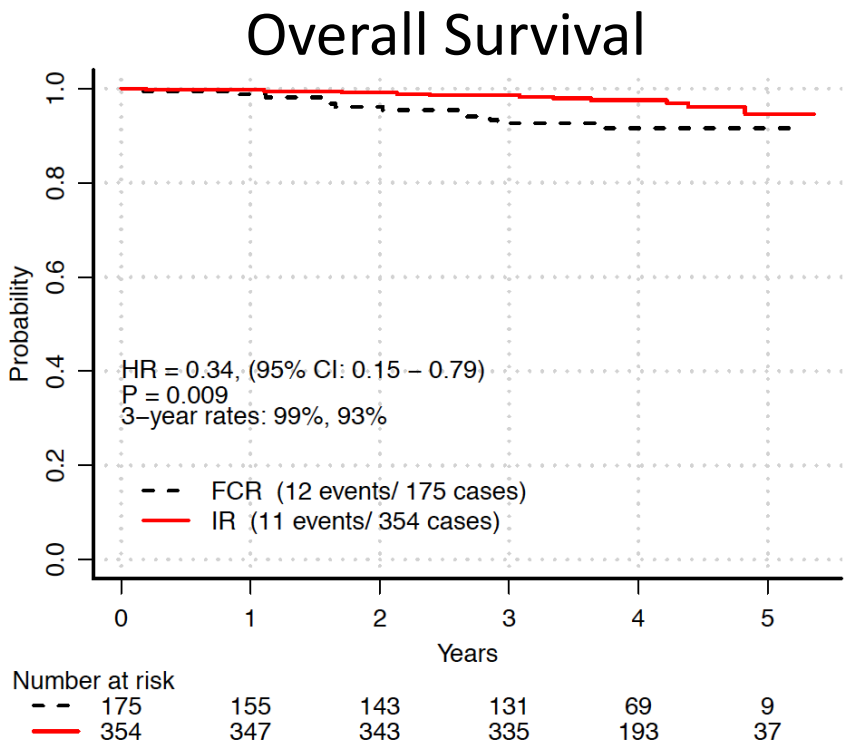
Updated Results E1912
ASH 2019 with median f/u time 45 mos

Progression Free Survival



Shanafelt et al. ASH 2019. Abstract 33. NCT02048813.

Updated Results E1912: ASH 2019



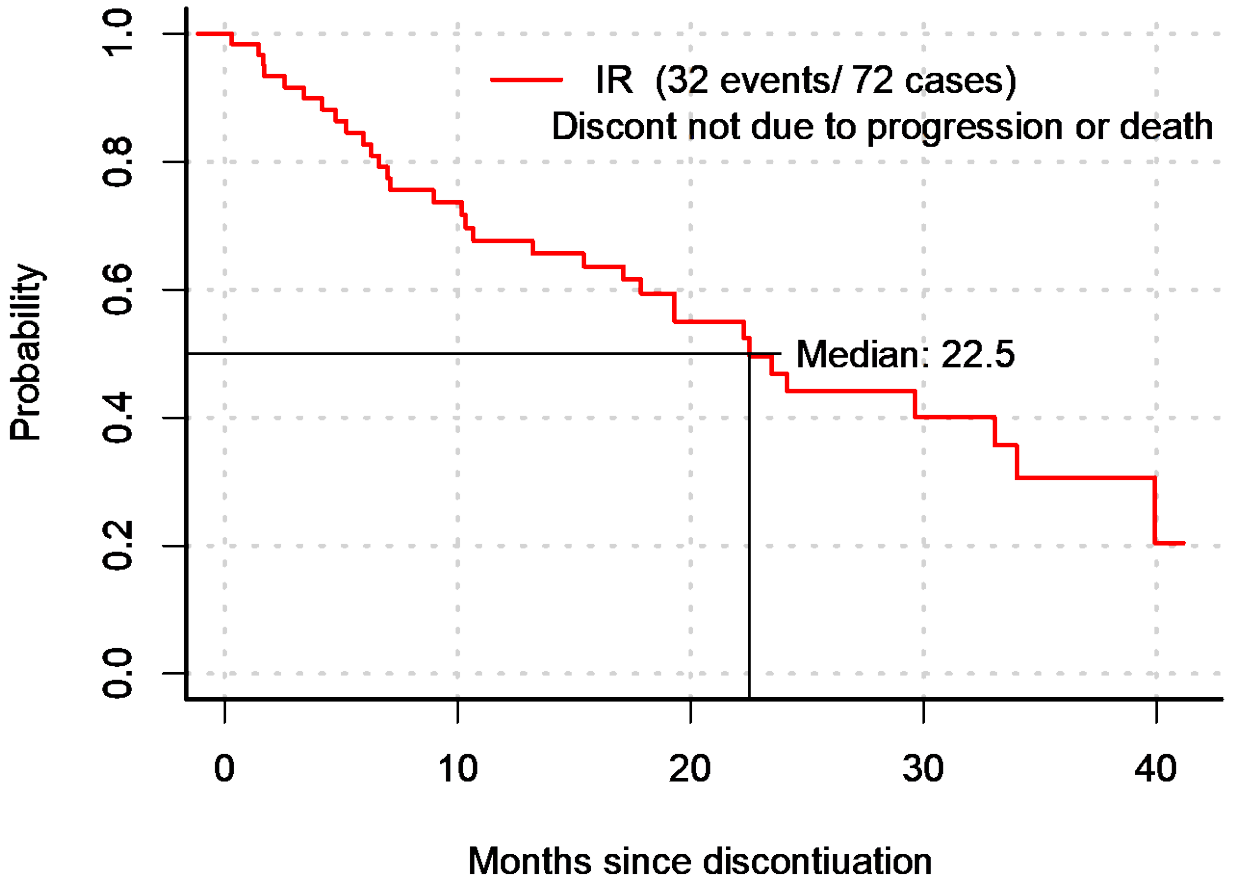
Shanafelt et al. ASH 2019. Abstract 33. NCT02048813.

Reasons for Ibrutinib Discontinuation

Reason for Discontinuation	All Patients Who Started IR N=352	Patients Discontinuing Treatment N= 95
Progression or death	23 (7%)	23 (24%)
Adverse event	48 (14%)	48 (51%)
Other reason*	24 (7%)	24 (25%)

*Other health conditions, patient preference, lost to follow-up

Progression Free Survival Post Discontinuation of Ibrutinib



N=72

Median time of therapy 15.1 months

Shanafelt et al. ASH 2019. Abstract 33. NCT02048813.

Grade 3-5 Treatment Related Adverse Events Throughout Observation

Adverse Event	IR (n=352, %)	FCR (n=158, %)	P-value
Anemia	4.3	**15.8**	<0.001
Arthralgia	**5.1**	0.6	0.011
Diarrhea	**2.6**	0.6	0.185
Hemolysis	0	**2.5**	0.009
Hypertension	**8.5**	1.9	0.003
Neutrophil count decreased	27	**43**	<0.001
Platelet count decreased	3.1	**15.8**	<0.001
Febrile neutropenia	2.3	**15.8**	<0.001
Infection	7.1	8.9	0.477
Sepsis	0.6	**3.2**	0.032
Other infections	7.1	6.3	0.851
Cardiac	**5.4**	0	0.001
Atrial fibrillation	**2.8**	0	0.036
Other cardiac	**3.4**	0	0.022
Any Grade 3 or higher AE	**69.6**	**80.4**	**0.013**

Shanafelt et al. ASH 2019. Abstract 33. NCT02048813.

Conclusions

- Ibrutinib and rituximab provides superior PFS and OS compared to FCR for patients with previously untreated CLL
- With a median follow-up of 48 months, 73% of IR patients remain on treatment
- Only 7% of ibrutinib treated patients progressed while on therapy
- Patients who discontinued ibrutinib prior to PD or death did not progress for a median of 23 months after last dose of ibrutinib.

Shanafelt et al. ASH 2019. Abstract 33. NCT02048813.

ACALABRUTINIB

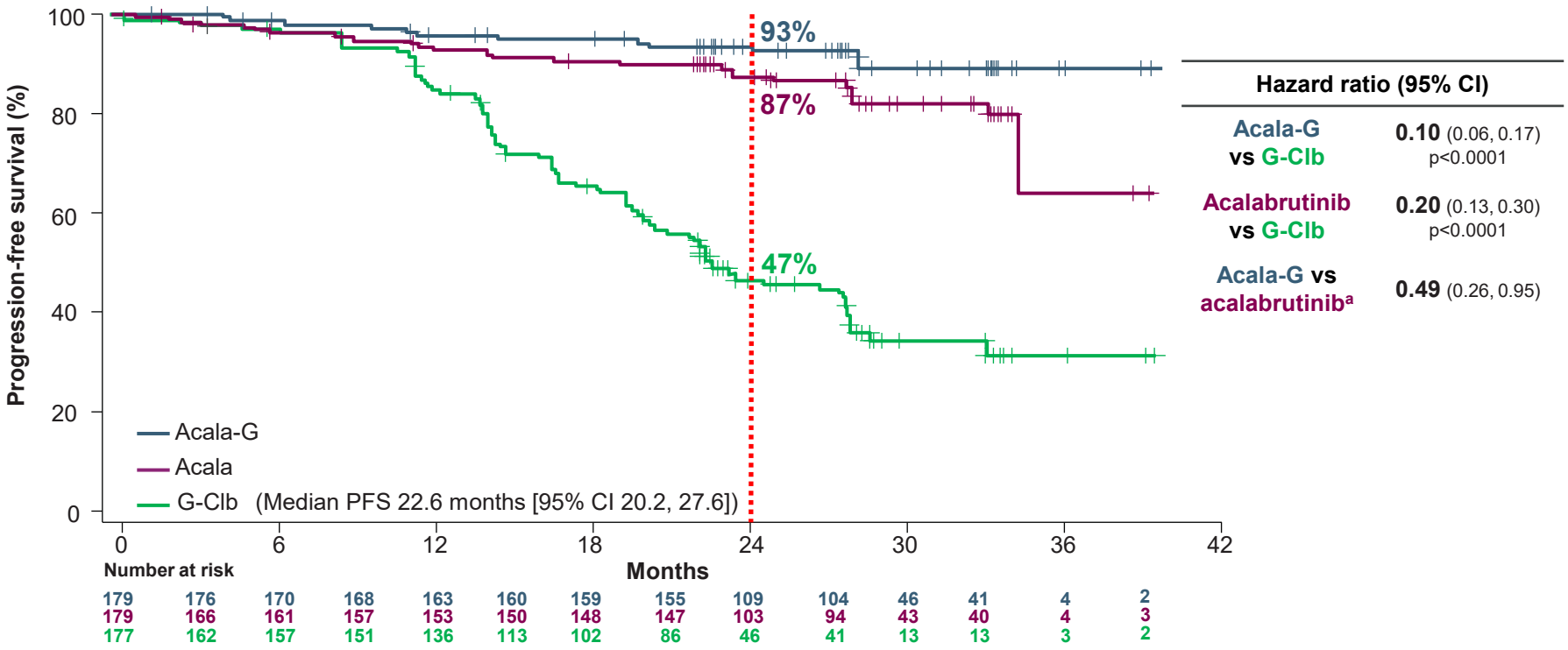
Phase 3 Study of Acalabrutinib Combined With Obinutuzumab or Alone vs Obinutuzumab Plus Chlorambucil in Patients With Treatment-Naive Chronic Lymphocytic Leukemia: Results From ELEVATE TN

Jeff P. Sharman, Versha Banerji, Laura Maria Fogliatto, Yair Herishanu, Talha Munir, Renata Walewska, George Follows, Karin Karlsson, Paolo Ghia, Gillian Corbett, Patricia Walker, Miklos Egyed, Wojciech Jurczak, Gilles Salles, Ann Janssens, Florence Cymbalista, William Wierda, Steven Coutre, John M. Pagel, Alan P. Skarbnik, Manali Kamdar, Jennifer A. Woyach, Raquel Izumi, Veerendra Munugalavadla, Priti Patel, Min Hui Wang, Sofia Wong, and John C. Byrd

Sharman et al. ASH 2019. Abstract 31. NCT02475681.

IRC-Assessed Progression-Free Survival

Median follow-up 28.3 months



Kaplan-Meier estimates performed by IRC and all analyses for the intention-to-treat population. No. of events: Acala-G, 14 (7.8%); Acala, 26 (14.5%); G-Clb, 93 (52.5%)

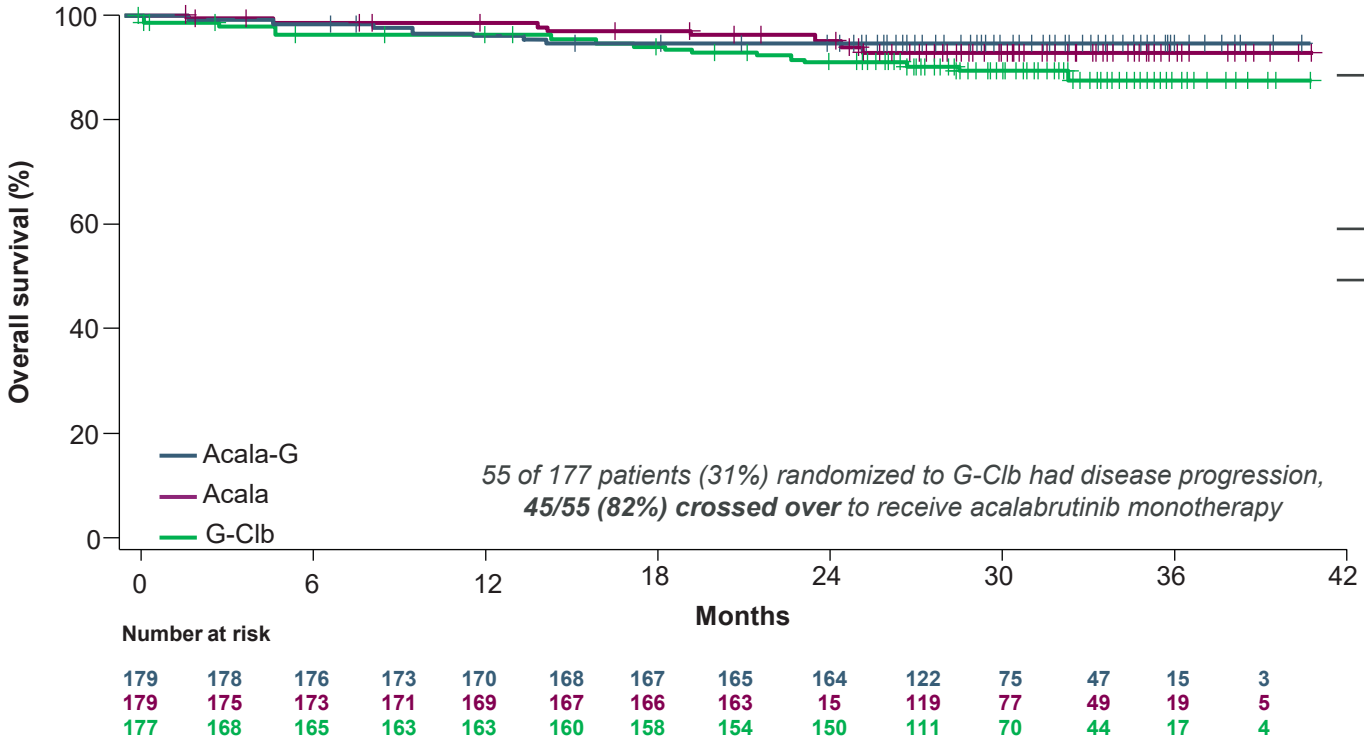
[a]*Post hoc* analysis.

Richter's transformation occurred in: Acala-G n=1, Acala n=5, G-Clb n=1

Sharman et al. ASH 2019. Abstract 31. NCT02475681.

Overall Survival

Median follow-up 28.3 months



Deaths	N (%)
Acala-G	9 (5.0)
Acala	11 (6.1)
G-Clb	17 (9.6)
Hazard ratio (95% CI)	
Acala-G vs G-Clb	**0.47** (0.21, 1.06) p=0.0577
Acalabrutinib vs G-Clb	**0.60** (0.28, 1.27) p=0.1556

Sharman et al. ASH 2019. Abstract 31. NCT02475681.

Most Common AEs (≥15% Patients) in Any Treatment Arm

	Acala-G N=178		Acalabrutinb N=179		G-Clb N=169	
AEs, n (%)	Any	Grade ≥3	Any	Grade ≥3	Any	Grade ≥3
Headache	71 (39.9)	2 (1.1)	66 (36.9)	2 (1.1)	20 (11.8)	0
Diarrhea	69 (38.8)	8 (4.5)	62 (34.6)	1 (0.6)	36 (21.3)	3 (1.8)
Neutropenia	56 (31.5)	53 (29.8)	19 (10.6)	17 (9.5)	76 (45.0)	70 (41.4)
Fatigue	50 (28.1)	3 (1.7)	33 (18.4)	2 (1.1)	29 (17.2)	1 (0.6)
Contusion	42 (23.6)	0	27 (15.1)	0	7 (4.1)	7 (4.1)
Arthralgia	39 (21.9)	2 (1.1)	28 (15.6)	1 (0.6)	8 (4.7)	2 (1.2)
Cough	39 (21.9)	0	33 (18.4)	1 (0.6)	15 (8.9)	0
URTI	38 (21.3)	4 (2.2)	33 (18.4)	0	14 (8.3)	1 (0.6)
Nausea	36 (20.2)	0	40 (22.3)	0	53 (31.4)	0
Dizziness	32 (18.0)	0	21 (11.7)	0	10 (5.9)	0
IRR	24 (13.5)	4 (2.2)	0	0	67 (39.6)	9 (5.3)
Pyrexia	23 (12.9)	0	12 (6.7)	1 (0.6)	35 (20.7)	1 (0.6)

AEs reported are from the treatment-emergent period (first dose through to 30 days after the last dose of study drug or the first date starting a new CLL therapy, whichever is earliest)
IRR, infusion-related reaction; URTI, upper respiratory tract infection

Sharman et al. ASH 2019. Abstract 31. NCT02475681.

Events of Clinical Interest for Acalabrutinib

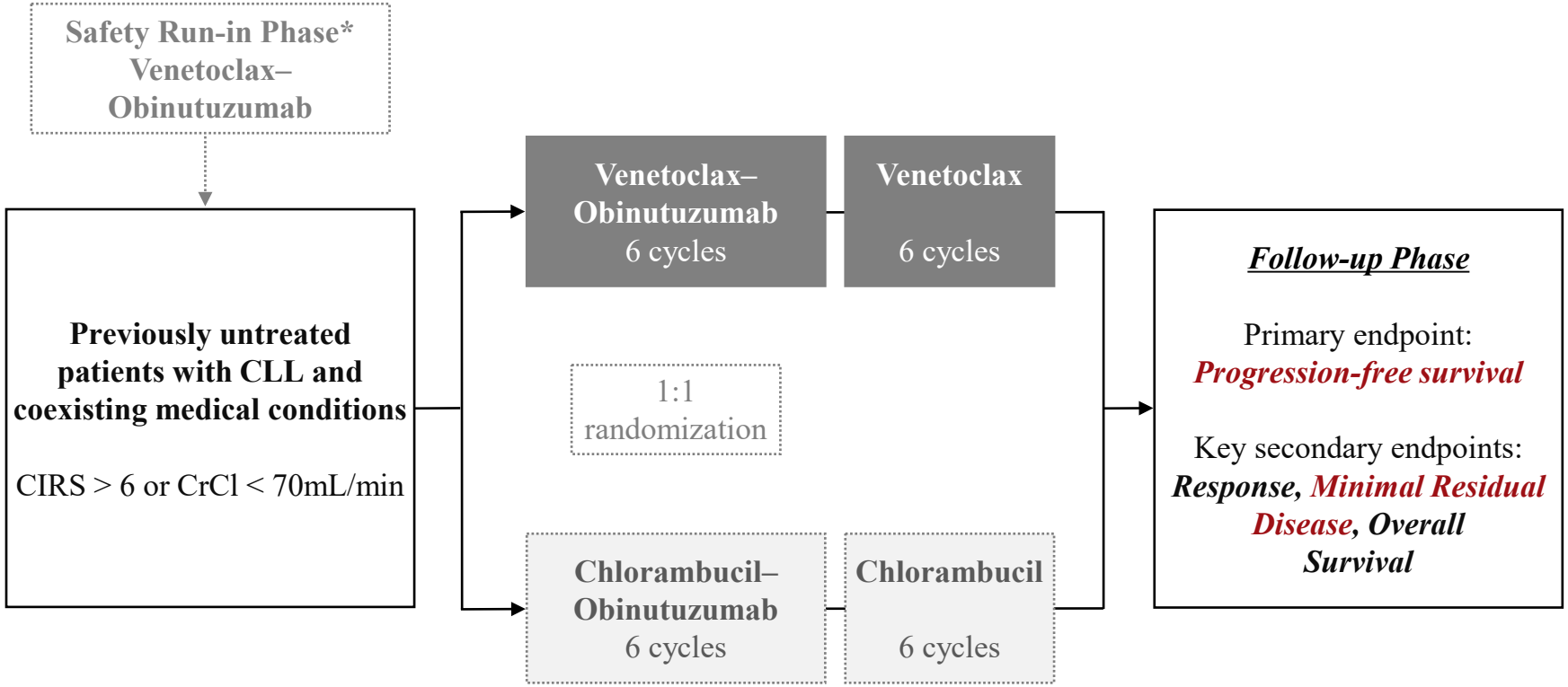
AEs, n (%)	Acala-G N=178		Acalabrutinib N=179		G-Clb N=169	
	Any	Grade ≥3	Any	Grade ≥3	Any	Grade ≥3
Atrial fibrillation	6 (3.4)	1 (0.6)	7 (3.9)	0	1 (0.6)	0
Hypertension	13 (7.3)	5 (2.8)	8 (4.5)	4 (2.2)	6 (3.6)	5 (3.0)
Bleeding	76 (42.7)	3 (1.7)	70 (39.1)	3 (1.7)	20 (11.8)	0
Major bleeding[a]	5 (2.8)[b]	3 (1.7)	3 (1.7)[c]	3 (1.7)	2 (1.2)[d]	0
Infections	123 (69.1)	37 (20.8)	117 (65.4)	25 (14.0)	74 (43.8)	14 (8.3)
Second primary malignancies, excluding NMSC	10 (5.6)[e]	6 (3.4)	5 (2.8)[f]	2 (1.1)	3 (1.8)[g]	2 (1.2)

There were no reported events of ventricular tachyarrhythmias
[a]Defined as any serious or grade ≥3 hemorrhagic event, or any grade hemorrhagic event in the central nervous system. [b]Includes gastric ulcer hemorrhage, gastrointestinal hemorrhage, hematemesis, postprocedural hemorrhage, and subdural hemorrhage. [c]Includes hemarthrosis, postprocedural hematoma, and retinal hemorrhage. [d]Includes subdural hemorrhage and hemoptysis. [e]Includes non-small cell lung cancer (n=2), squamous cell carcinoma (n=2), basosquamous carcinoma, bladder transitional cell carcinoma, breast cancer, gastric cancer stage IV, metastases to bone, prostate cancer, and renal cell carcinoma (all n=1). [f]Includes prostate cancer (n=2), glioblastoma, malignant melanoma in situ, transitional cell carcinoma (all n=1). [g]Includes prostate cancer, acute myelomonocytic leukemia, and lung adenocarcinoma (all n=1)
NMSC, nonmelanoma skin cancer

Sharman et al. ASH 2019. Abstract 31. NCT02475681.

VENETOCLAX/OBINUTUZUMAB

CLL14 Trial Design

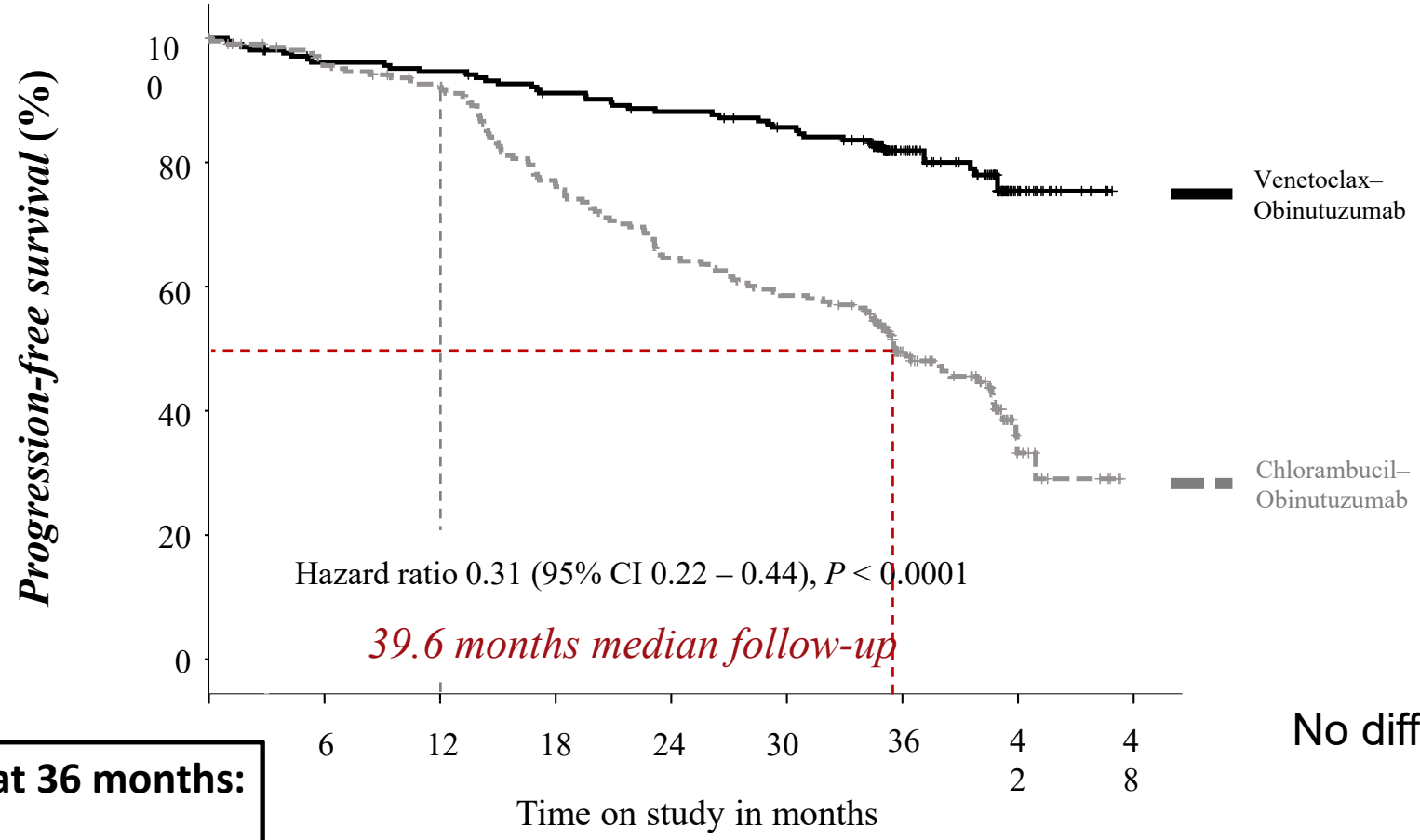


* Fischer K et al. Venetoclax and Obinutuzumab in chronic lymphocytic leukemia, Blood 11 May 2017

Fischer et al. N Engl J Med. 2019 Jun 6;380(23):2225-2236

Fischer et al. ASH 2019. Abstract 36. NCT02242942.

VO improves PFS compared to chlorambucil based treatment



PFS at 36 months:

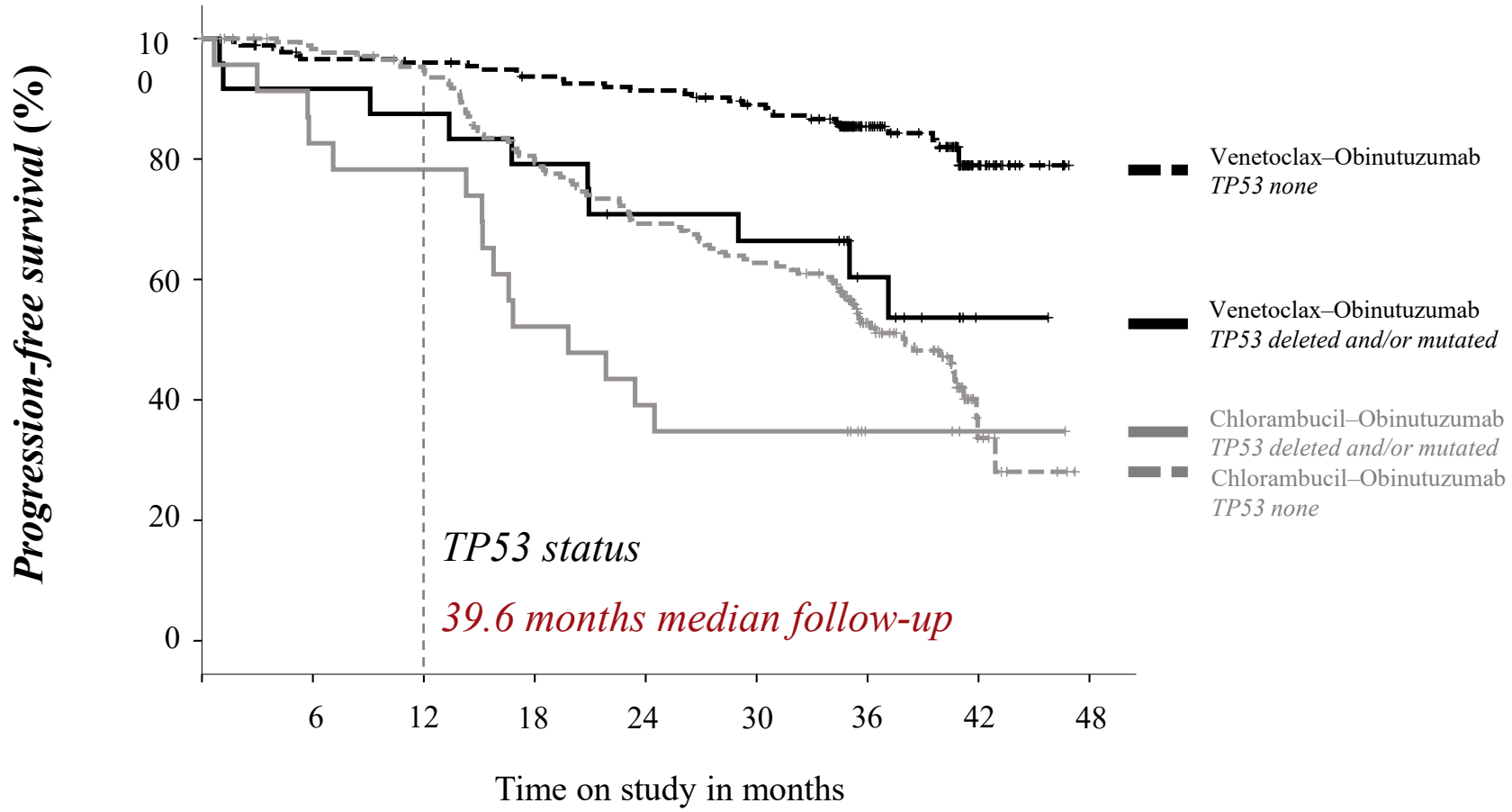
VO: 82%

Chlorambucil: 50%

No difference in OS

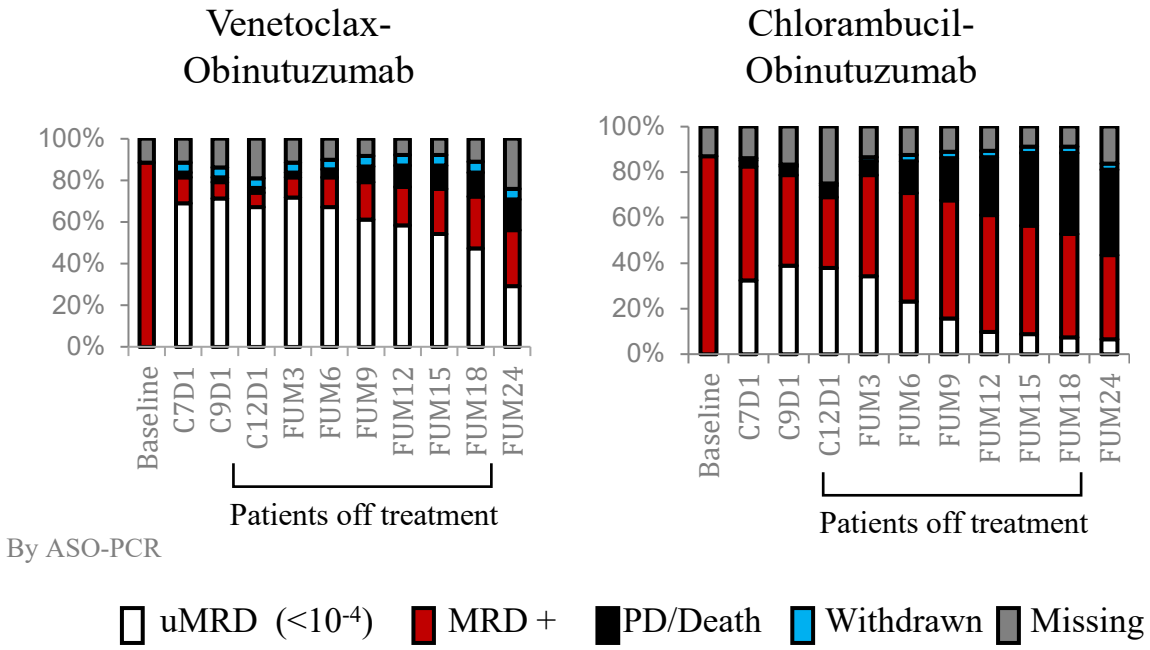
Fischer et al. ASH 2019. Abstract 36. NCT02242942.

Patients with TP53 mutations/deletions have inferior PFS

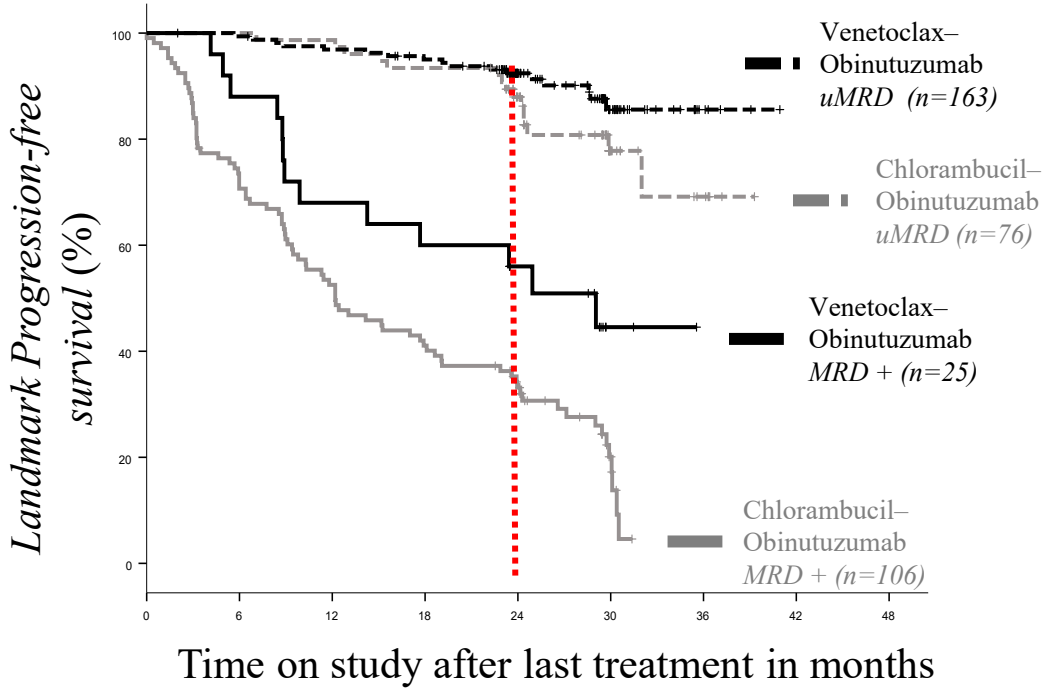


Fischer et al. ASH 2019. Abstract 36. NCT02242942.

MRD Rates and Effect on PFS



uMRD 76% (PB), 57% (BM) 3 mo after treatment (Concordance 86.8%)



Fischer et al. ASH 2019. Abstract 36. NCT02242942.

FIXED-DURATION *venetoclax and obinutuzumab …*

…continues to provide a superior outcome compared with chlorambucil and obinutuzumab

- regarding **PFS** across all relevant subgroups (including the IGHV mutated subgroup)
- but no difference in OS yet observed

…achieves high rates of undetectable MRD at EOT

- translating into sustained PFS benefits
- with more than 90% of these patients showing durable responses 24 months after EOT that appear to be sustained beyond this
- confirming the prognostic value of MRD in targeted combination therapy

Fischer et al. ASH 2019. Abstract 36. NCT02242942.

Previously Treated

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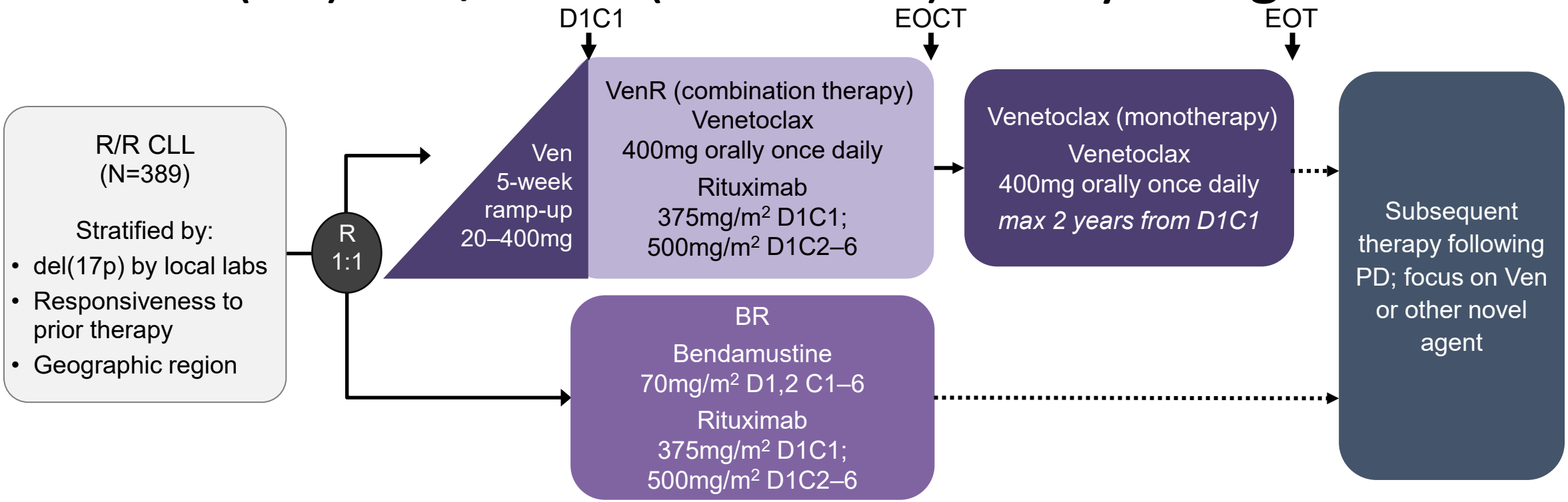
Four-year analysis of MURANO study confirms sustained benefit of time-limited venetoclax–rituximab (VenR) in relapsed/refractory (R/R) chronic lymphocytic leukemia (CLL)

John F Seymour,[1] Thomas J Kipps,[2] Barbara F Eichhorst,[3] Peter Hillmen,[4] James D'Rozario,[5] Sarit Assouline,[6] Carolyn Owen,[7] Tadeusz Robak,[8] Javier de la Serna,[9] Ulrich Jaeger,[10] Guillaume Cartron,[11] Marco Montillo,[12] Nicole Lamanna,[13] Su Young Kim,[14] Jenny Wu,[15] Yanwen Jiang,[15] Jue Wang,[15] Marcus Lefebure,[16] Michelle Boyer,[16] Kathryn Humphrey,[17] and Arnon P Kater[18]

[1]Royal Melbourne Hospital, Peter MacCallum Cancer Centre and University of Melbourne, Melbourne, Australia; [2]UCSD Moores Cancer Center, San Diego, CA, USA; [3]University of Cologne, Department I of Internal Medicine and Center of Integrated Oncology Aachen, Bonn, Cologne, Dusseldorf; German CLL Study Group, Cologne, Germany; [4]St. James's University Hospital, Leeds, United Kingdom; [5]The John Curtin School of Medical Research, Australian National University, Canberra, ACT, Australia; [6]Segal Cancer Center, Lady Davis Institute, Jewish General Hospital, Montreal, Canada; [7]University of Calgary, Calgary, AB, Canada; [8]Medical University of Lodz, Copernicus Memorial Hospital, Lodz, Poland; [9]Hospital Universitario 12 de Octubre, Madrid, Spain; [10]Dept. of Medicine I, Division of Hematology and Hemostaseology, Medical University of Vienna, Vienna, Austria; [11]Centre Hospitalier Universitaire de Montpellier, Montpellier, France; [12]Department of Hematology, Niguarda Cancer Center, ASST Grande Ospedale Metropolitano Niguarda, Milano, Italy; [13]Herbert Irving Comprehensive Cancer Center, Columbia University Medical Center, New York, NY, USA; [14]AbbVie Inc., North Chicago, USA; [15]Genentech, Inc., South San Francisco, CA, USA; [16]Clinical Science, Roche Products Limited, Welwyn Garden City, United Kingdom; [17]Roche Products Limited, Welwyn Garden City, United Kingdom; [18]Amsterdam University Medical Centers, Hovon CLL Working Group, Netherlands

Seymour, et al ASH 2019 Abstract 355.

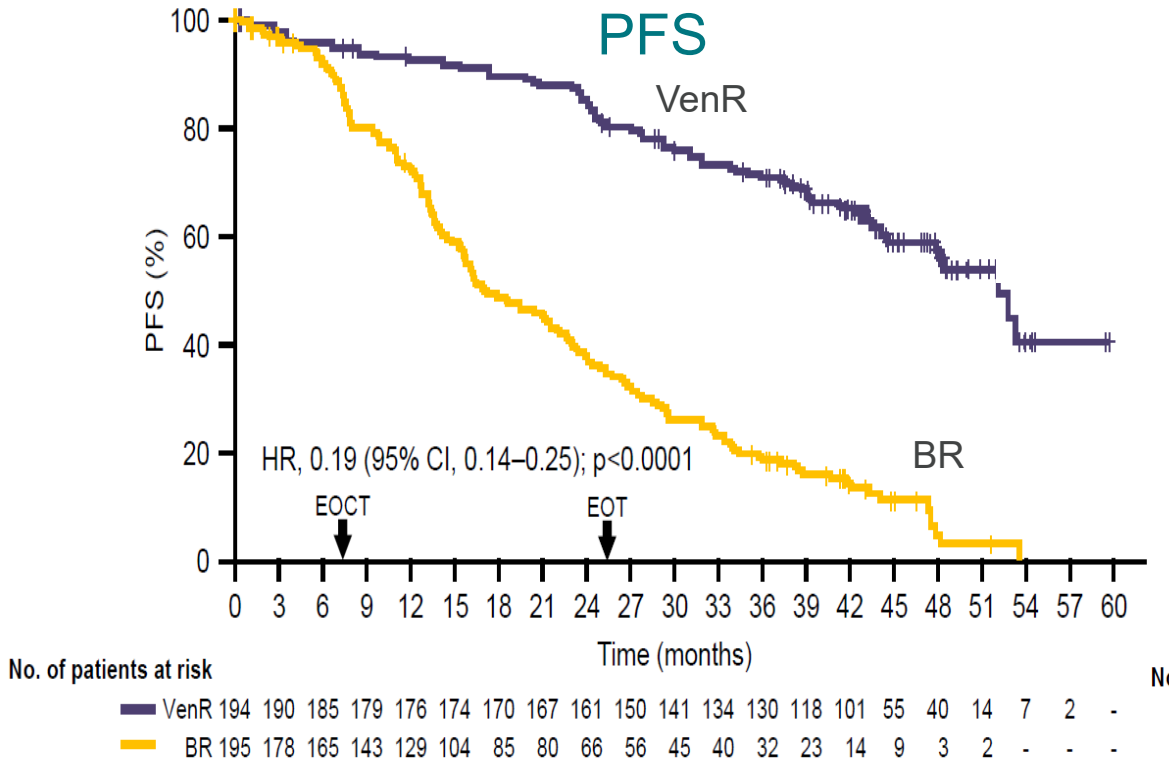
Venetoclax-rituximab (VenR) vs bendamustine-rituximab (BR) in R/R CLL (MURANO): study design

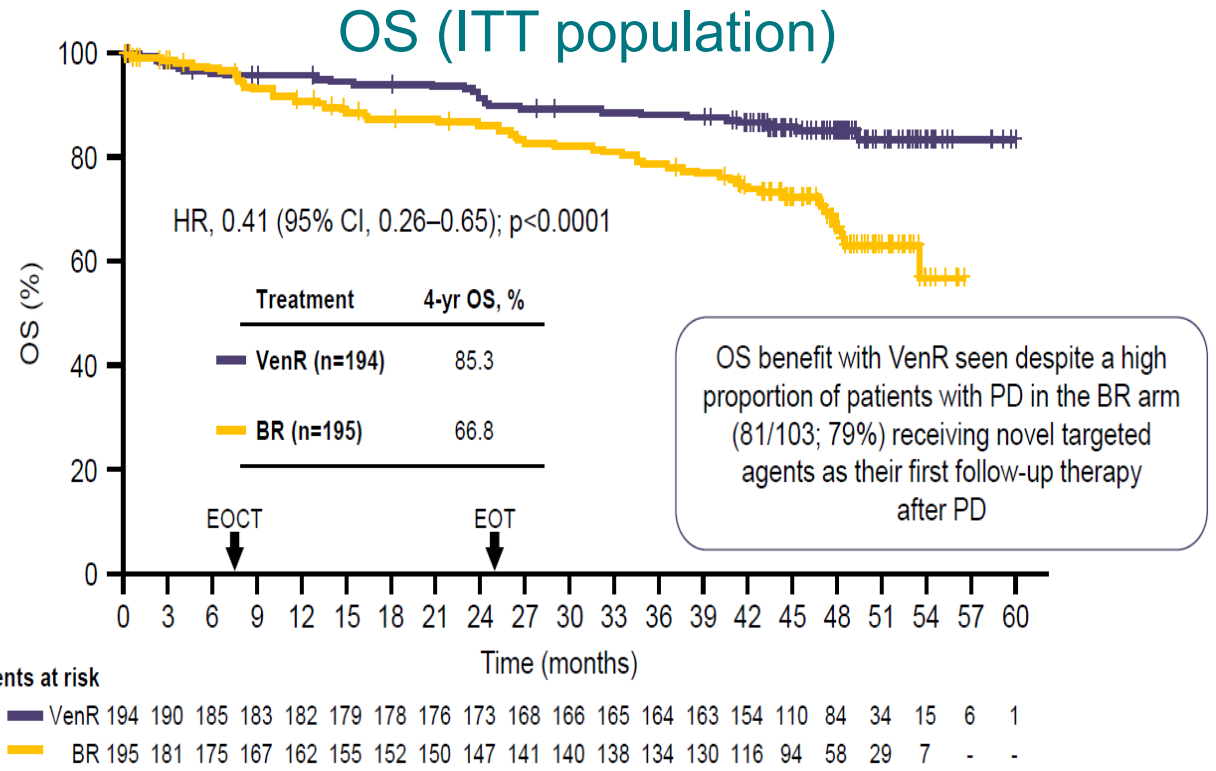


- Primary endpoint: investigator-assessed PFS
- Secondary endpoint: rates of clearance of MRD
- Clinical response and MRD* in PB during Ven monotherapy and follow-up visits were assessed every 3 months for 3 years, then every 6 months thereafter, or until PD

Seymour et al., ASH 2019; abstract 355

Four-year analysis of venetoclax-rituximab (VenR) vs bendamustine-rituximab (BR) in R/R CLL (MURANO)





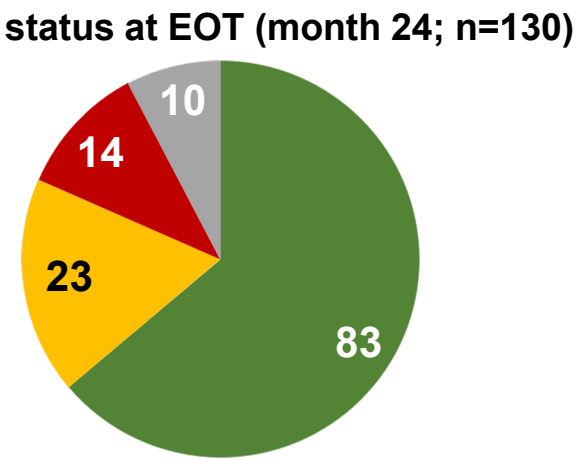
OS benefit with VenR seen despite a high proportion of patients with PD in the BR arm (81/103; 79%) receiving novel targeted agents as their first follow-up therapy after PD

Treatment	4-year PFS, % (95% CI)
VenR (n=194)	57.3 (49.4-65.3)
BR (n=195)	4.6 (0.1-9.2)

Seymour et al., ASH 2019; abstract 355

Most patients had uMRD in PB upon completion of Ven monotherapy (EOT)

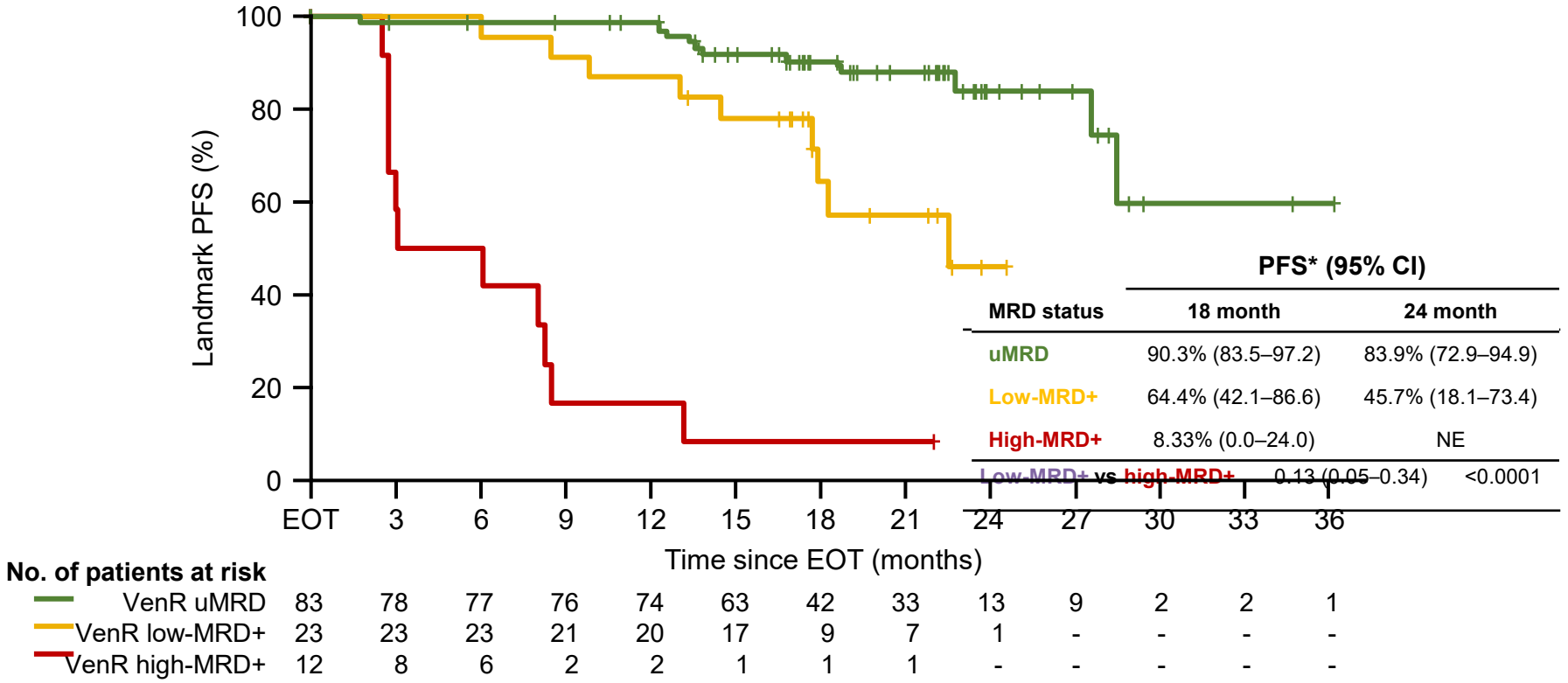
- In total, 130/194 patients completed 2 years of Ven therapy
- With a median 22 months off therapy (range 1–25 months), **35 progression events had occurred in 130 patients who completed 2 years of Ven**



Status off-therapy, n (%)	uMRD ($<10^{-4}$) n=83	Low-MRD+ (10^{-4}–10^{-2}) n=23	High-MRD+ ($>10^{-2}$) n=14	Unknown n=10
Progression-free	72 (86.7)	14 (60.9)	1 (7.1)	8 (80.0)
PD	11 (13.3)	9 (39.1)	13 (92.9)	2 (20.0)

Seymour, et al ASH 2019 Abstract 355.

PFS was longest in patients in the VenR arm with uMRD at EOT



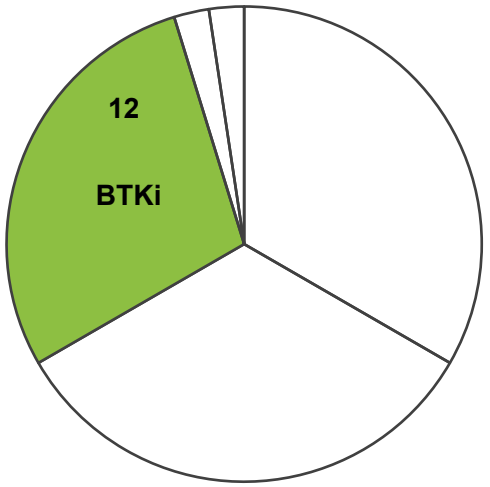
PFS* (95% CI)

MRD status	18 month	24 month
uMRD	90.3% (83.5–97.2)	83.9% (72.9–94.9)
Low-MRD+	64.4% (42.1–86.6)	45.7% (18.1–73.4)
High-MRD+	8.33% (0.0–24.0)	NE
Low-MRD+ vs high-MRD+	0.13 (0.05–0.34)	<0.0001

Seymour, et al ASH 2019 Abstract 355.

Ibrutinib post venetoclax

- 12 patients treated with ibrutinib after venetoclax:
  - 9/12 patients completed MURANO therapy regimen
  - 2/12 discontinued treatment early due to AE, but had meaningful treatment-free intervals of 857 and 874 days
  - 1/12 progressed on active venetoclax therapy



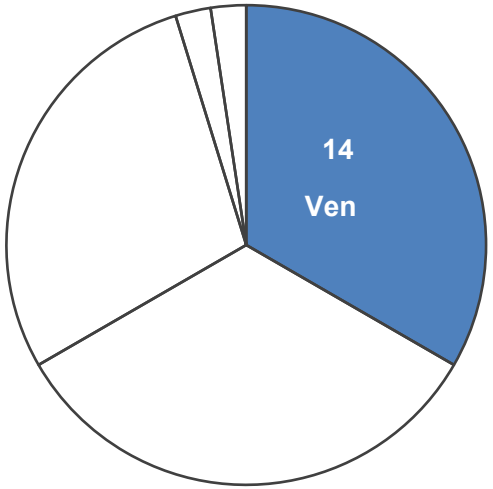
Time on Ibr	Best response to Ibr	Reason for discontinuation
190*	PR	
215	PR	New treatment (idelalisib + R)
250	Not available	Death (PD)
359*	PR	
364*	PR	
374*	PR	
431*	PR	
458	PR	Death (PD)
470*	PR	
665*	CR	
683*	Not available	
1304	PR	PD

Response rate Ibr post-Ven:
10/10 (100%)
(in evaluable patients)

Seymour, et al ASH 2019 Abstract 355.

Venetoclax re-treatment after trial

- 14 patients treated with venetoclax post trial
  - 13/14 patients completed MURANO therapy regimen
  - 1/14 discontinued treatment early
  - 4/14 achieved CR as best response on MURANO

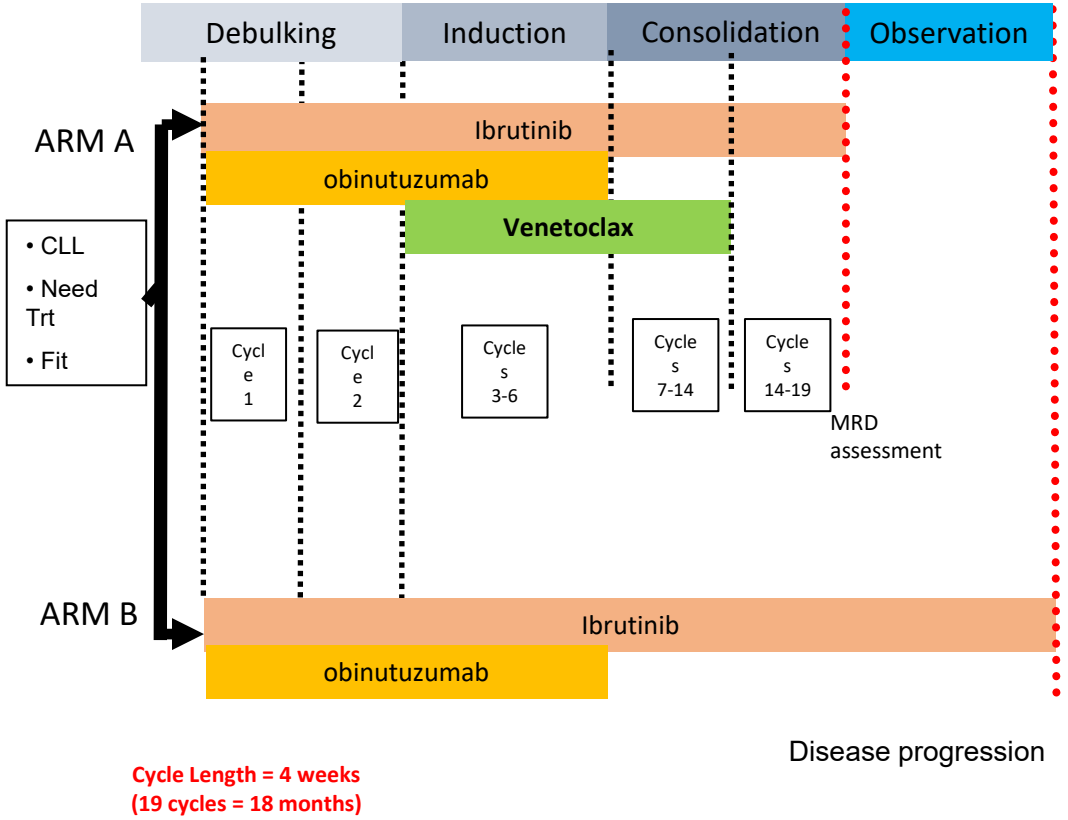


	Time on Ven-based regimen	Best response to Ven-based regimen	Reason for discontinuation
Ven	20	NR	Grade 3 diarrhea
	281*	Not available	
	504	PR	PD
VenR	221*	PR	
	59	PR	New treatment (Ibr)
Ven + Ibr	867*	PR	
VenR (MURANO regimen)	49	PD	Death (PD)
	160*	Not available	
	175*	Not available	
	243	PD	PD
	252*	PR	
	259*	PR	
	261*	SD	
	270*	SD	

Response rate Ven post-Ven: 6/11 (55%) (in evaluable patients)

Seymour, et al ASH 2019 Abstract 355.

EA9161 Trial



Primary endpoint:

- PFS

Secondary endpoint:

- MRD neg rates
- Time off therapy
- Clonal evolution
- Ibrutinib resist
- Richter's transformation
- Cost
- QOL

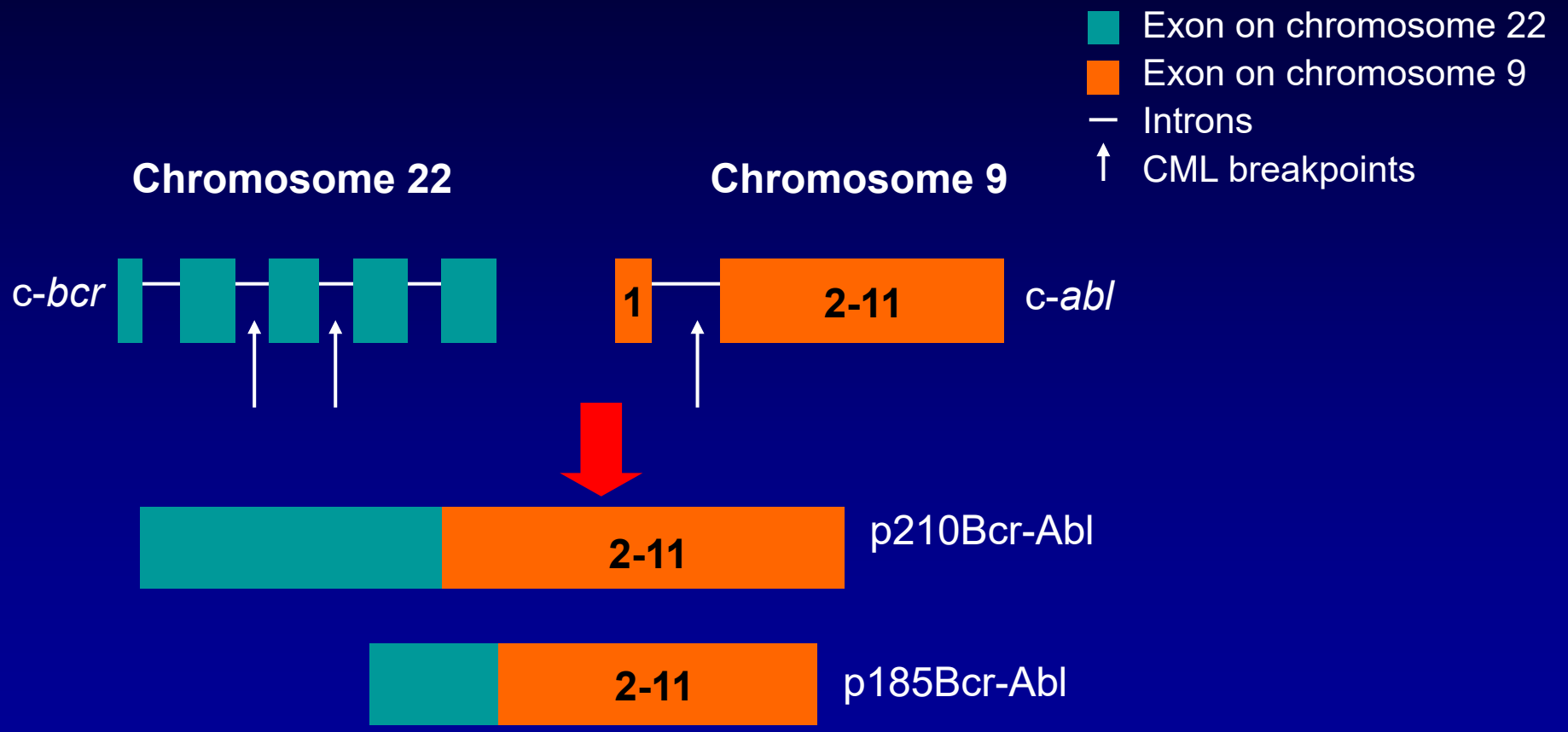
Current Accrual: 307

NCT03701282

Questions we will address - CML

- How to monitor response?
- Can therapy be stopped?
- New therapies?

The Ph Chromosome and the *bcr-abl* Gene: *bcr-abl* Gene Structure

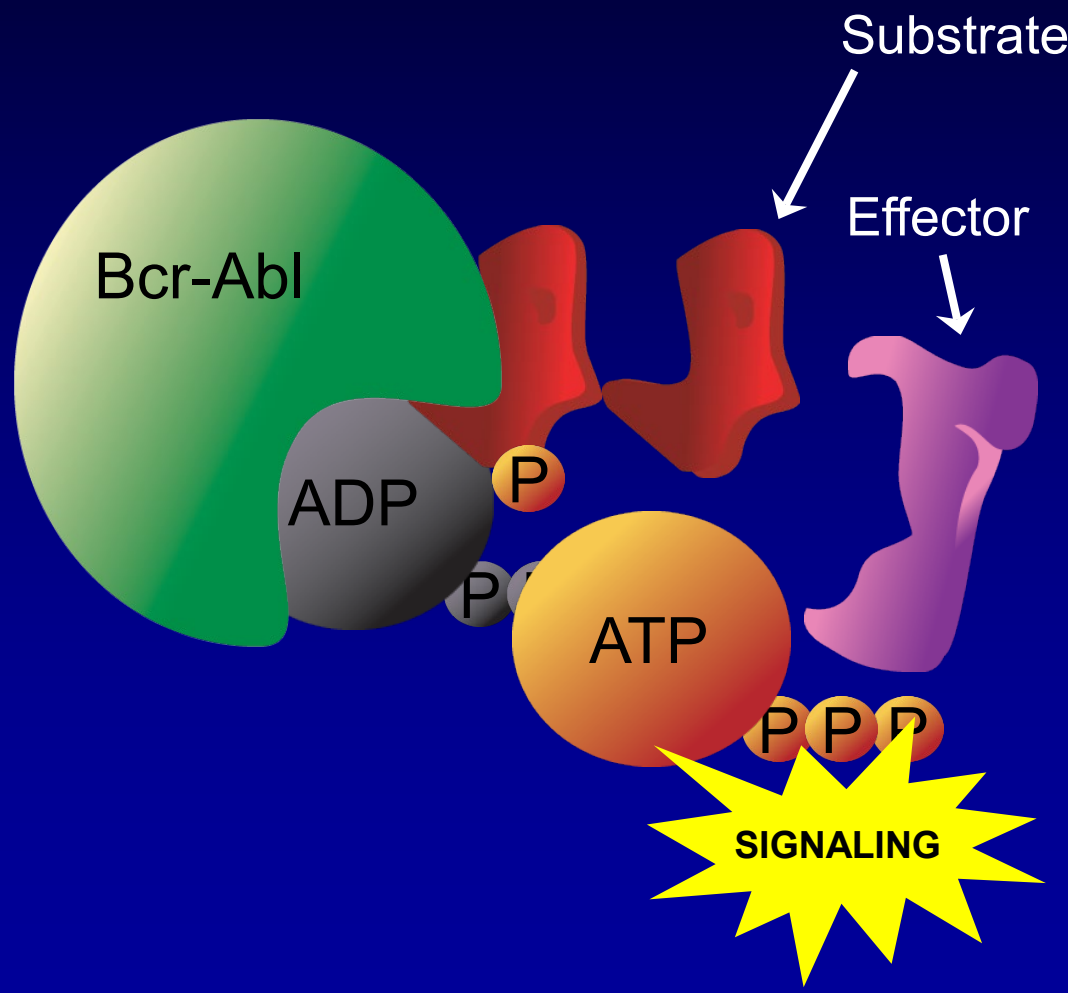


Melo. *Blood*. 1996;88:2375.
Pasternak et al. *J Cancer Res Clin Oncol*. 1998;124:643.

Normal Bcr-Abl Signaling

The kinase domain activates a substrate protein, eg, PI3 kinase, by phosphorylation

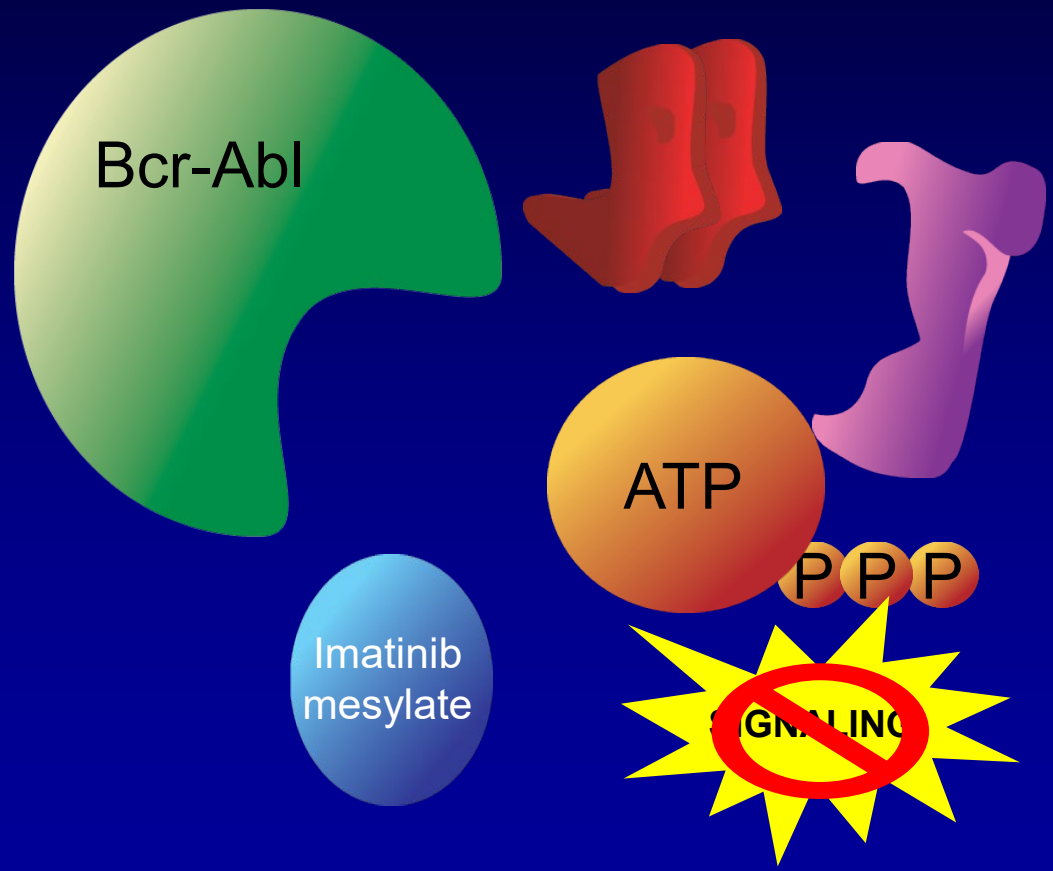
This activated substrate initiates a signaling cascade culminating in cell proliferation and survival



Savage and Antman. *N Engl J Med.* 2002;346:683
Scheijen and Griffin. *Oncogene.* 2002;21:3314.

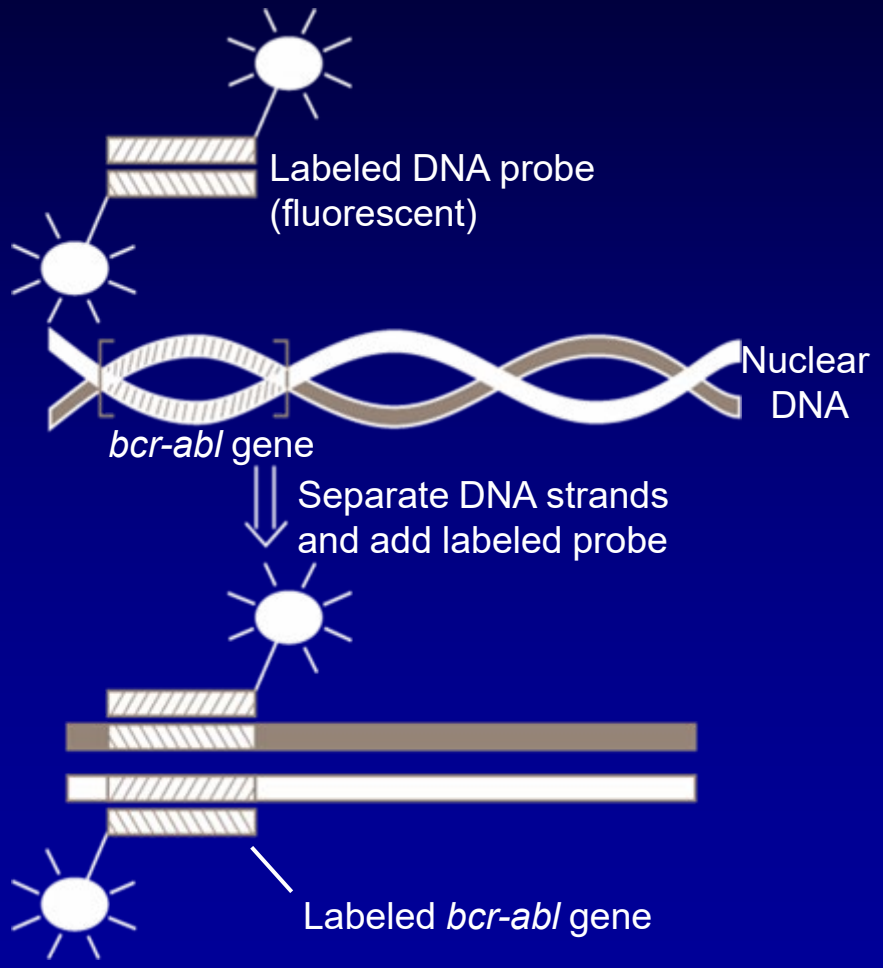
Imatinib Mesylate: Mechanism of Action

- Imatinib mesylate occupies the ATP binding pocket of the Abl kinase domain
- This prevents substrate phosphorylation and signaling
- A lack of signaling inhibits proliferation and survival



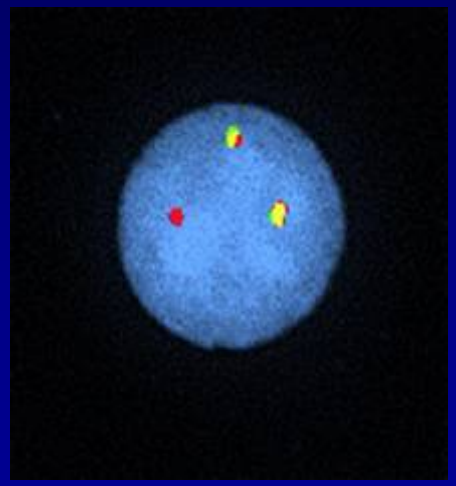
Savage and Antman. *N Engl J Med.* 2002;346:683.

Molecular Methods for Detecting *bcr-abl*

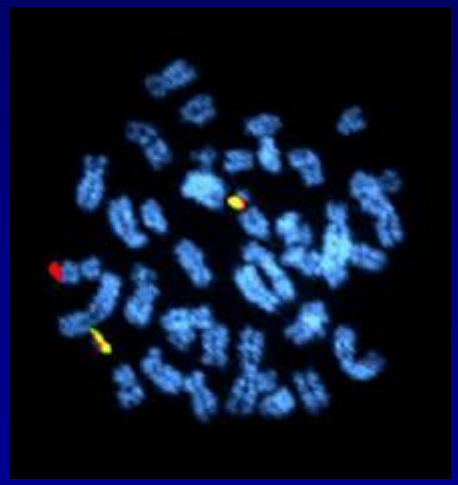


FISH

Interphase



Metaphase



Courtesy of Charles L. Sawyers, MD, UCLA.
Wang et al. *Genes Chromosomes Cancer*. 2001;32:97

Effects of a selective inhibitor of the Abl tyrosine kinase on the growth of Bcr-Abl positive cells

BRIAN J. DRUKER[1], SHU TAMURA[1], ELISABETH BUCHDUNGER[2], SAYURI OHNO[1], GERALD M. SEGAL[1], SHANE FANNING[1], JÜRG ZIMMERMANN[2] & NICHOLAS B. LYDON[2]

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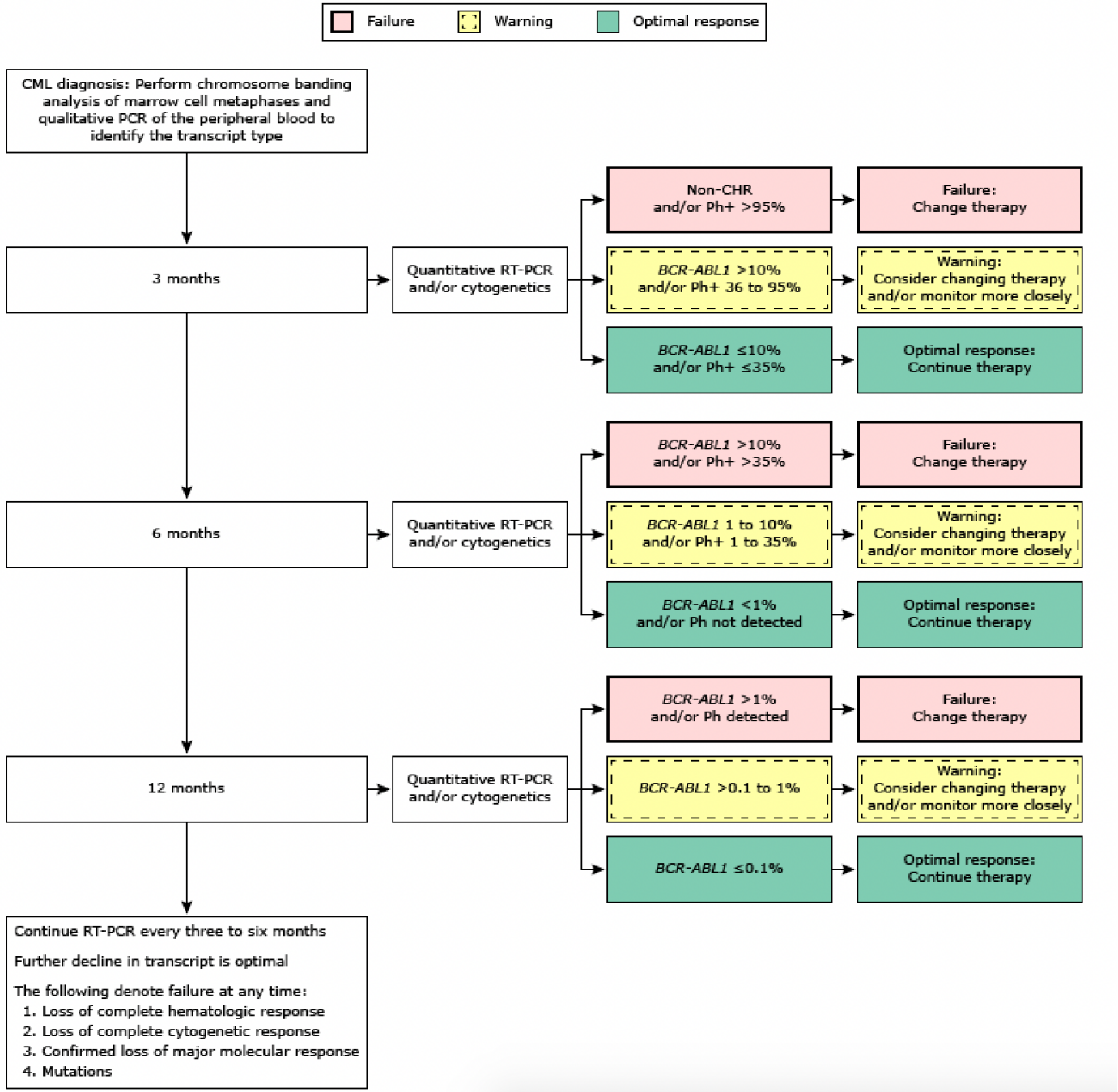
Correspondence should be addressed to B.J.D.

Setting the Goals of Therapy: Types of Response in Chronic Phase CML

- Hematologic response
  - Normalization of white cell counts as measured by standard CBC
- Cytogenetic response
  - Decrease in Ph-chromosome–positive cells as measured by karyotyping or FISH
- Molecular response
  - Decrease in the amount of Bcr-Abl transcripts as measured by quantitative PCR
    - Complete molecular response: no evidence of bcr-abl transcripts
    - Major molecular response: ≥3 logarithms (1000-fold) reduction of Bcr-Abl transcripts vs standardized baseline (IRIS trial)

Goal of therapy is to achieve MMR

- qRT-PCR @ 3mo, 6mo, and 12mo
- BM exam not typically needed



Original Article

Long-Term Outcomes of Imatinib Treatment for Chronic Myeloid Leukemia

Andreas Hochhaus, M.D., Richard A. Larson, M.D., François Guilhot, M.D., Jerald P. Radich, M.D., Susan Branford, Ph.D., Timothy P. Hughes, M.D., Michele Baccarani, M.D., Michael W. Deininger, M.D., Ph.D., Francisco Cervantes, M.D., Satoko Fujihara, Ph.D., Christine-Elke Ortmann, M.Sc., Hans D. Menssen, M.D., Hagop Kantarjian, M.D., Stephen G. O'Brien, M.D., Ph.D., Brian J. Druker, M.D., for the IRIS Investigators

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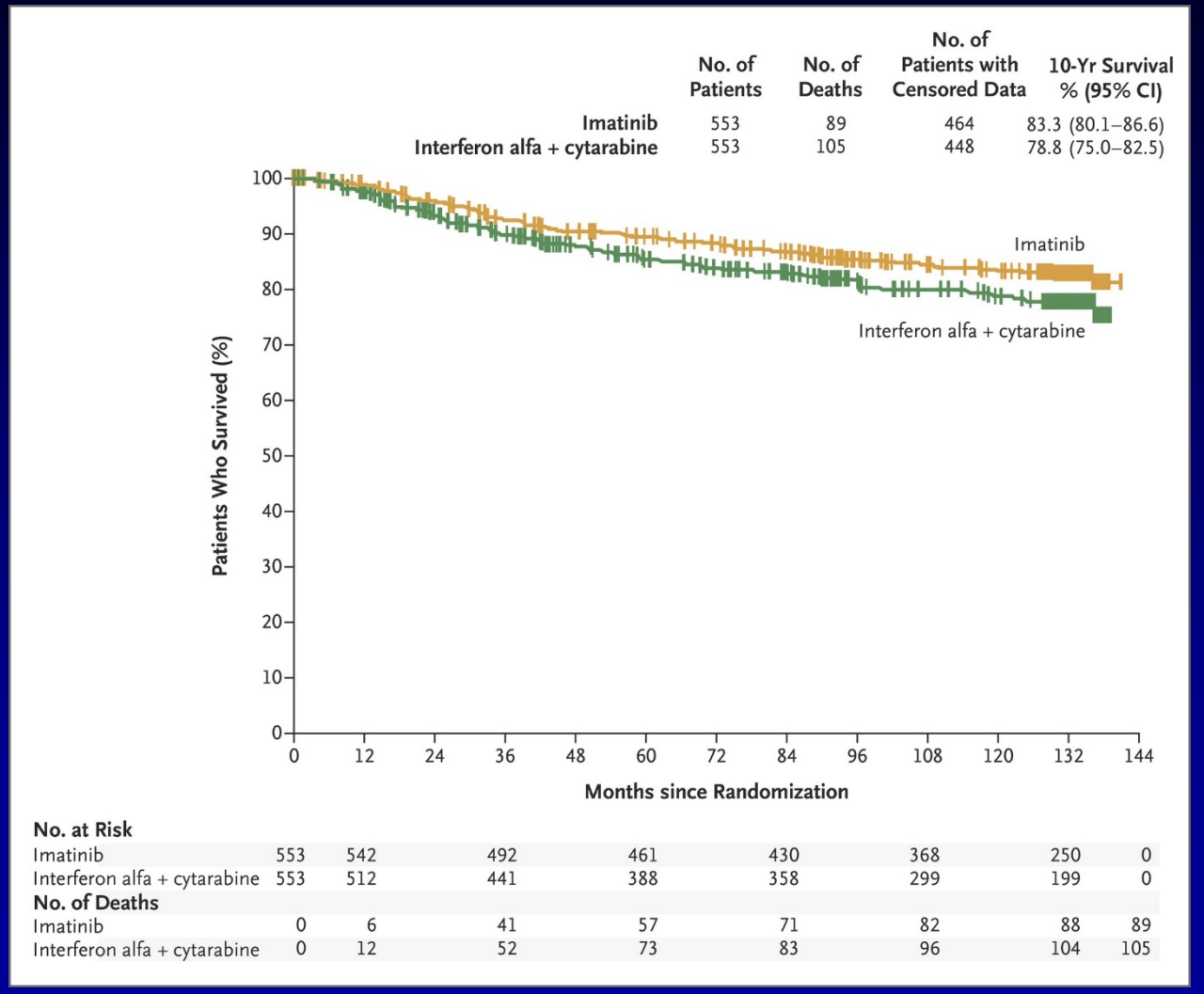
Volume 376(10):917-927
March 9, 2017

Overall Survival Rates at 10 Years



Hochhaus A et al. N Engl J Med 2017;376:917-927

Landmark Analysis of Outcomes at 10 Years According to Molecular Response Levels at 12 Months and 18 Months in Patients Treated with First-Line Imatinib Therapy Who Could Be Evaluated.

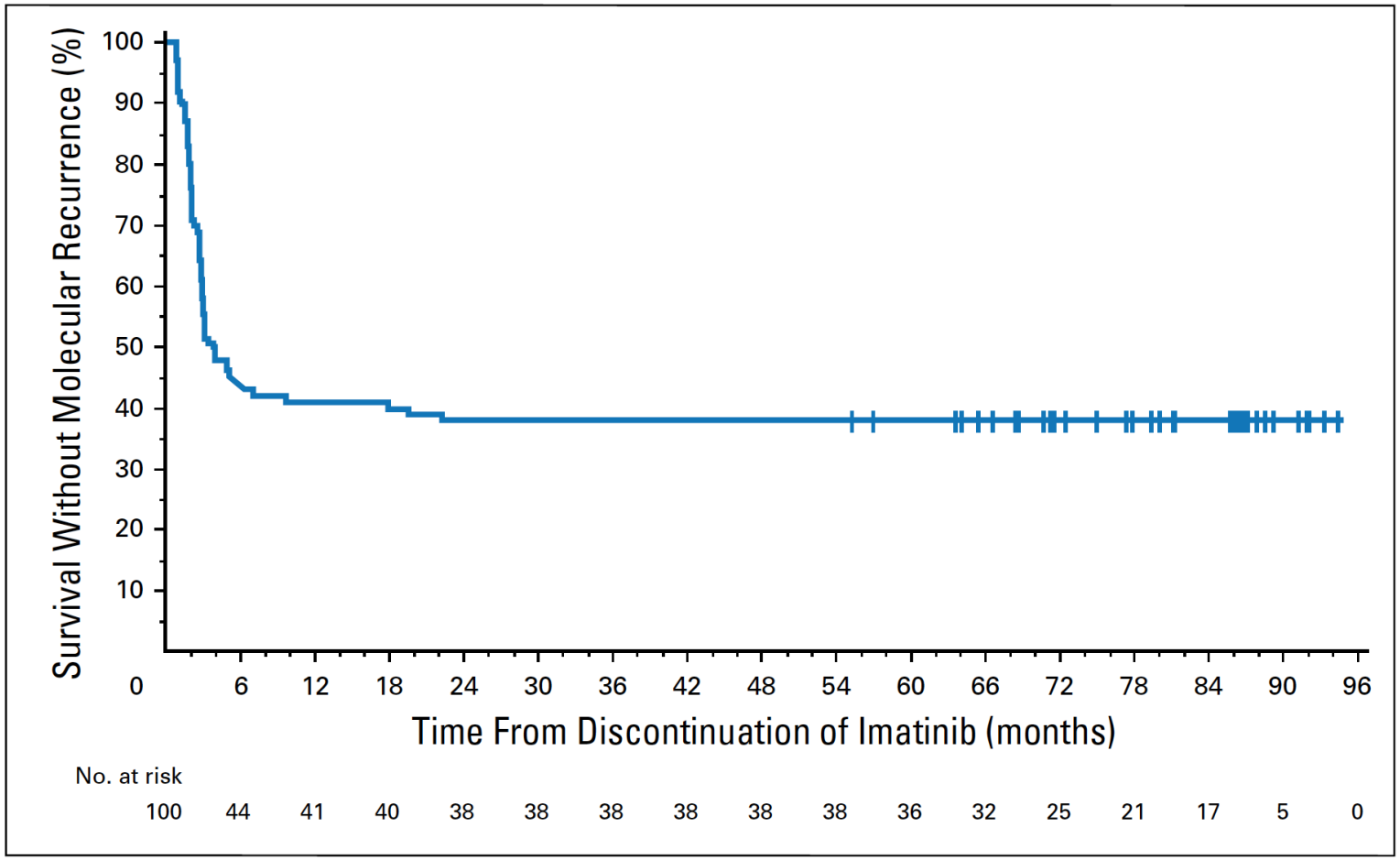
Table 4. Landmark Analysis of Outcomes at 10 Years According to Molecular Response Levels at 12 Months and 18 Months in Patients Treated with First-Line Imatinib Therapy Who Could Be Evaluated.*

Variable	Major Molecular Response or Better	Lack of Major Molecular Response	P Value
At 12 mo			
No. of patients who could be evaluated	153	151	
Death — no. (%)	15 (9.8)	22 (14.6)	
Not related to CML	11 (7.2)	7 (4.6)	
Related to CML	4 (2.6)	15 (9.9)	
Estimated 10-yr overall survival — % (95% CI)	91.1 (86.5–95.7)	85.3 (79.5–91.1)	0.15
Estimated 10-yr freedom from CML-related death — % (95% CI)	97.8 (95.4–100)	89.4 (84.3–94.5)	0.007
At 18 mo			
No. of patients who could be evaluated	164	89	
Death — no. (%)	12 (7.3)	13 (14.6)	
Not related to CML	12 (7.3)	4 (4.5)	
Related to CML	0	9 (10.1)	
Estimated 10-yr overall survival — % (95% CI)	93.0 (89.0–97.0)	85.6 (77.9–93.2)	0.04
Estimated 10-yr freedom from CML-related death — % (95% CI)	100 (100–100)	90.5 (84.1–96.8)	<0.001

* A total of 305 patients were considered able to be evaluated for molecular response at 12 months; however, 1 patient discontinued study treatment at 11 months (the patient was considered able to be evaluated for molecular response at 12 months on the basis of an 11-month assessment) and was therefore excluded from the 12-month landmark analysis. Patients who died or who had data censored before each landmark analysis were excluded from that landmark analysis. The deaths reported here are those that occurred in patients with the indicated level of molecular response at 12 months or 18 months who died at some point after 12 months or 18 months, respectively. Two-sided P values were calculated with the use of the log-rank test. CML denotes chronic myeloid leukemia.

Hochhaus A et al. N Engl J Med 2017;376:917-927

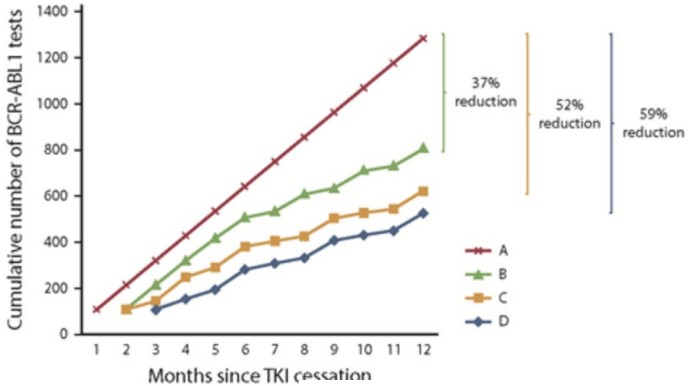
STOP Trial – Longterm Results

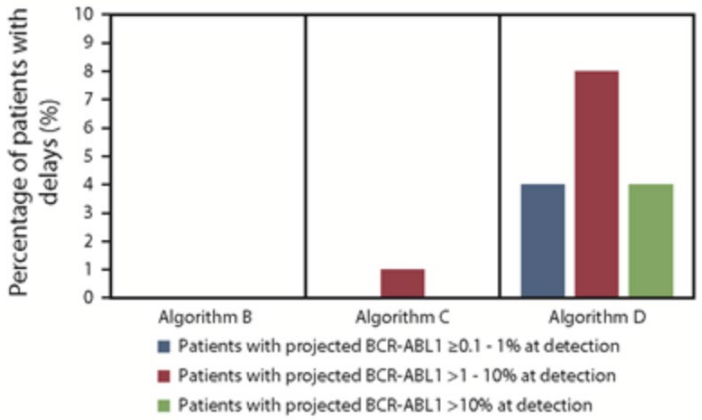


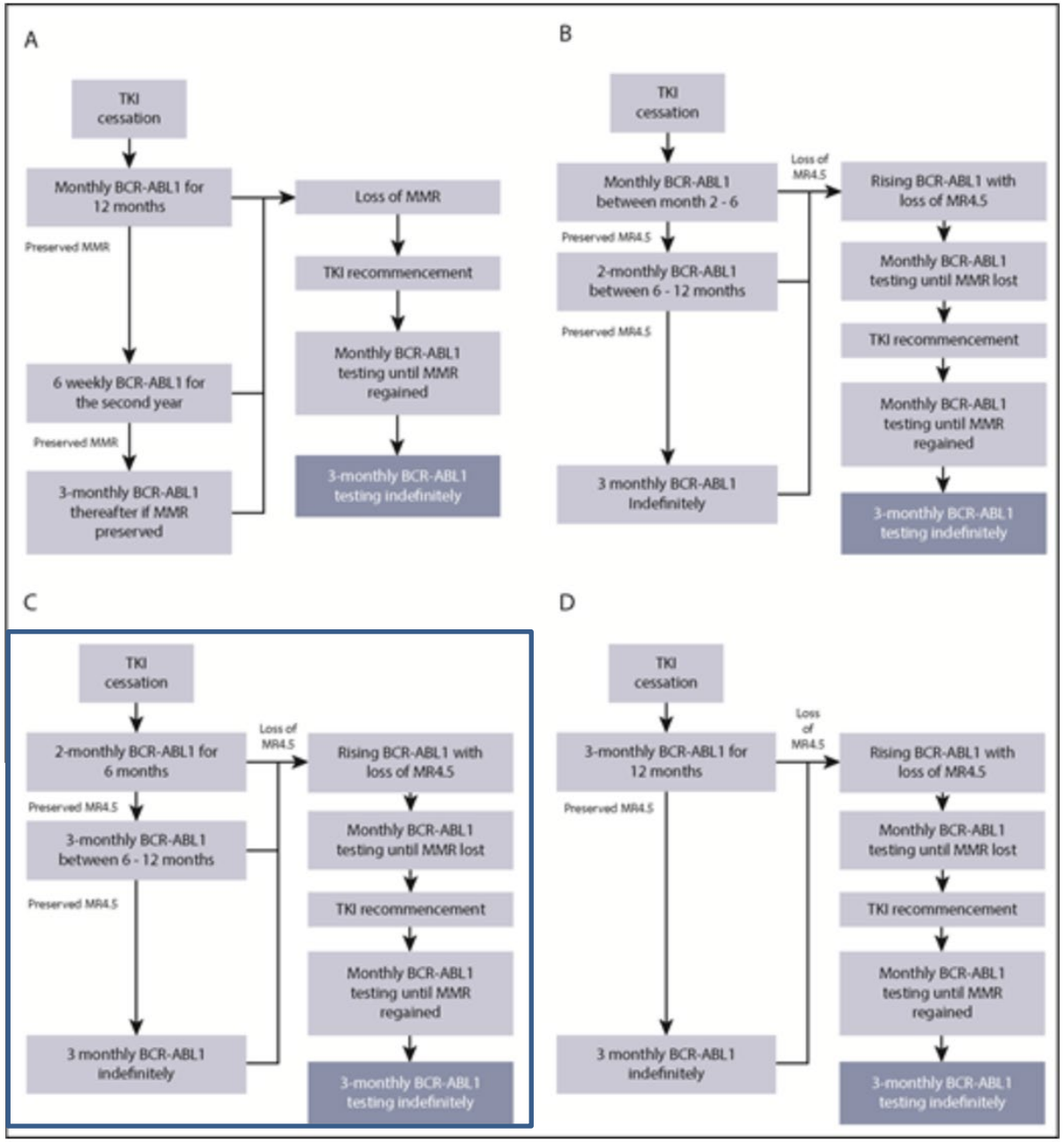
J Clin Oncol 2017 35:298-305.

Monitoring after TKI cessation

- qRT-PCR bcr-abl Q2mo for 6mo, then Q3mo between 6-12mo, then Q3mo
- If remains negative, continue Q3mo for 2-3 years?







Original Article

Asciminib in Chronic Myeloid Leukemia after ABL Kinase Inhibitor Failure

Timothy P. Hughes, M.D., Michael J. Mauro, M.D., Jorge E. Cortes, M.D., Hironobu Minami, M.D., Delphine Rea, M.D., Daniel J. DeAngelo, M.D., Ph.D., Massimo Breccia, M.D., Yeow-Tee Goh, M.D., Moshe Talpaz, M.D., Andreas Hochhaus, M.D., Philipp le Coutre, M.D., Oliver Ottmann, M.D., Michael C. Heinrich, M.D., Juan L. Steegmann, M.D., Ph.D., Michael W.N. Deininger, M.D., Ph.D., Jeroen J.W.M. Janssen, M.D., Ph.D., Francois-Xavier Mahon, M.D., Yosuke Minami, M.D., Ph.D., David Yeung, M.D., David M. Ross, M.B., B.S., Ph.D., Martin S. Tallman, M.D., Jae H. Park, M.D., Brian J. Druker, M.D., David Hynds, M.S., Yuyan Duan, Ph.D., Christophe Meille, Ph.D., Florence Hourcade-Potelleret, Ph.D., K. Gary Vanasse, M.D., Fabian Lang, M.D., and Dong-Wook Kim, M.D., Ph.D.

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The NEW ENGLAND JOURNAL of MEDICINE

Hematologic, Cytogenetic, and Molecular Responses with Asciminib

- CHR 92%
- MMR @ 12mo 36%
- Active in T315I mutated patients

Table 3. Hematologic, Cytogenetic, and Molecular Responses with Asciminib (Combined Once-Daily and Twice-Daily Schedules).*

Variable	Chronic-Phase CML						Accelerated-Phase CML					
	No T315I Mutation			T315I Mutation			No T315I Mutation			T315I Mutation		
	Overall (N=113)†	Response Achieved	Response Maintained	Overall (N=28)†	Response Achieved	Response Maintained	Overall (N=4)†	Response Achieved	Response Maintained	Overall (N=5)†	Response Achieved	Response Maintained
Median follow-up (range) — wk	72 (0.1–167)			37 (0.7–167)			46 (15–72)			16 (6–120)		
Patients remaining in the study — no. (%)	88 (78)			19 (68)			2 (50)			1 (20)		
Complete hematologic response — no./total no. (%)‡		34/37 (92)			14/16 (88)			3/3 (100)			4/5 (80)	
Major cytogenetic response — no./total no. (%)‡§	85/110 (77)	24/40 (60)	61/70 (87)	15/25 (60)	11/20 (55)	4/5 (80)	0/4	0/2	0/2	1/5 (20)	1/4 (25)	0/1
Complete cytogenetic response — no./total no. (%)‡§	77/110 (70)	31/57 (54)	46/53 (87)	11/25 (44)	9/22 (41)	2/3 (67)	0/4	0/2	0/2	1/5 (20)	1/4 (25)	0/1
Major molecular response — no./total no. (%)‡¶												
In all patients												
By 6 mo	37/99 (37)	19/80 (24)	18/19 (95)	5/20 (25)	4/19 (21)	1/1 (100)	0/4	0/3	0/1	1/5 (20)	1/5 (20)	0
By 12 mo	44/91 (48)	26/72 (36)	18/19 (95)	5/18 (28)	4/17 (24)	1/1 (100)	0/4	0/3	0/1	1/5 (20)	1/5 (20)	0
In patients with ≤2 previous TKIs‖												
By 6 mo	13/25 (52)	5/15 (33)	8/10 (80)	4/10 (40)	3/9 (33)	1/1 (100)	0/1	0/1	0			
By 12 mo	15/25 (60)	7/15 (47)	8/10 (80)	4/9 (44)	3/8 (38)	1/1 (100)	0/1	0/1	0			
In patients with >2 previous TKIs**												
By 6 mo	24/74 (32)	14/64 (22)	10/10 (100)	1/10 (10)	1/10 (10)	0	0/3	0/2	0/1	1/5 (20)	1/5 (20)	0
By 12 mo	29/66 (44)	19/56 (34)	10/10 (100)	1/9 (11)	1/9 (11)	0	0/3	0/2	0/1	1/5 (20)	1/5 (20)	0
In patients with resistance to or unacceptable side effects from ponatinib††												
By 6 mo	7/17 (41)	3/13 (23)	4/4 (100)	1/7 (14)	1/7 (14)	0/0				0/2	0/2	
By 12 mo	8/14 (57)	4/10 (40)	4/4 (100)	1/6 (17)	1/6 (17)	0/0				0/2	0/2	

* For definitions of hematologic, cytogenetic, and molecular responses, see the Methods section in the Supplementary Appendix.
† Shown is the number of patients who received at least one dose of asciminib.
‡ The total number is the number of patients who could be evaluated.
§ Data on cytogenetic responses are based on patients who presented with Philadelphia chromosome–positive CML at baseline. Calculation of the number of patients in whom a major cytogenetic response or complete cytogenetic response was achieved is based on patients not in the respective response category at baseline.
¶ Molecular-response assessment is reported only for patients with the b2a2 or b3a2 transcripts; 7 patients had atypical *BCR-ABL1* transcripts and were not included in the response assessment.
‖ The numbers of patients who received at least one dose of asciminib were as follows: 34 with chronic-phase CML without a T315I mutation, 12 with chronic-phase CML with a T315I mutation, and 1 with accelerated-phase CML without a T315I mutation.
** The numbers of patients who received at least one dose of asciminib were as follows: 79 with chronic-phase CML without a T315I mutation, 16 with chronic-phase CML with a T315I mutation, 3 with accelerated-phase CML without a T315I mutation, and 5 with accelerated-phase CML with a T315I mutation.
†† The numbers of patients who received at least one dose of asciminib were as follows: 18 with chronic-phase CML without a T315I mutation, 11 with chronic-phase CML with a T315I mutation, and 2 with accelerated-phase CML with a T315I mutation.

Hughes TP et al. N Engl J Med 2019;381:2315-2326

Acknowledgements

- Slides kindly provided by:
  - Kristen Fischer, Nitin Jain, John Seymour, Tait Shanenfelt, Jeff Sharman