Evolving Therapeutic Algorithms for Patients with Treatment-Naïve Chronic Lymphocytic Leukemia

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NCCN National Comprehensive Cancer Network®

NCI CCC A Comprehensive Cancer Center Designated by the National Cancer Institute

Disclosures

- Consulting
  - Genentech, Roche, Celgene, AbbVie, Kite, Janssen, Pharmacyclics, AstraZeneca, Juno, BeiGene, TG Therapeutics, MorphoSys
- Research Funding
  - Genentech, ADCT, Acerta, Celgene, BeiGene

Case Presentation: Dr Khan

49-year-old man

- IGHV-mutated, del(17p)- and TP53-unmutated CLL
- Patient wanted to receive ibrutinib, but at that time it was not available outside of a clinical trial
- FCR on a clinical trial versus ibrutinib/rituximab
  - Developed C. difficile colitis, hospitalized for pancytopenia

Case Presentation: Dr Peswani

78-year-old man

- Presents with fever, WBC 180,000, Hb 8, PLT 70,000 and a diffuse maculopapular rash
- Diagnosis: Chronic lymphocytic leukemia; IGHV-unmutated, normal cytogenetics
- Biopsy of maculopapular rash confirms CLL involvement

National Comprehensive Cancer Network®

NCCN Guidelines Version 3.2020

Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma

Updates in Version 3.2020 of the NCCN Guidelines for CLL/SLL from Version 2.2020 include:

CSLL-D 1 of 6

CLL/SLL without del(17p)/TP53 mutation

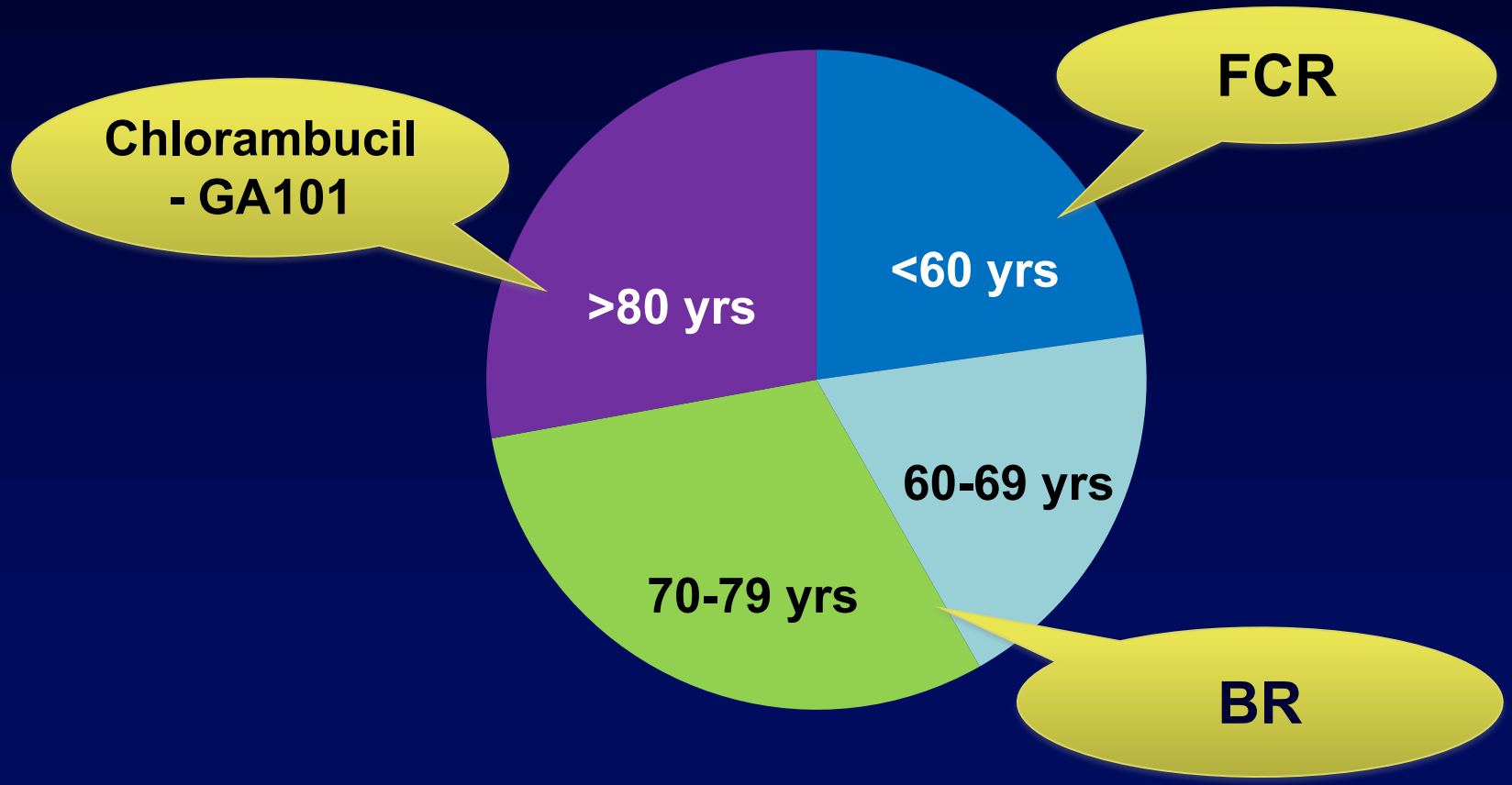
- **First-line therapy for both, "Frail patient with significant comorbidity..." and "Patients aged <65 y without significant comorbidities"**
  - **"Acalabrutinib ± obinutuzumab" was added as a category 2A, preferred recommendation.**

CSLL-D 3 of 6

CLL/SLL with del(17p)/TP53 mutation

- **First-line therapy, "Acalabrutinib ± obinutuzumab" was added as a category 2A, preferred recommendation.**

A simplistic (and outdated) approach to CLL



Shanafelt T. *ASH Education Book.* 2013;2013:158-167.

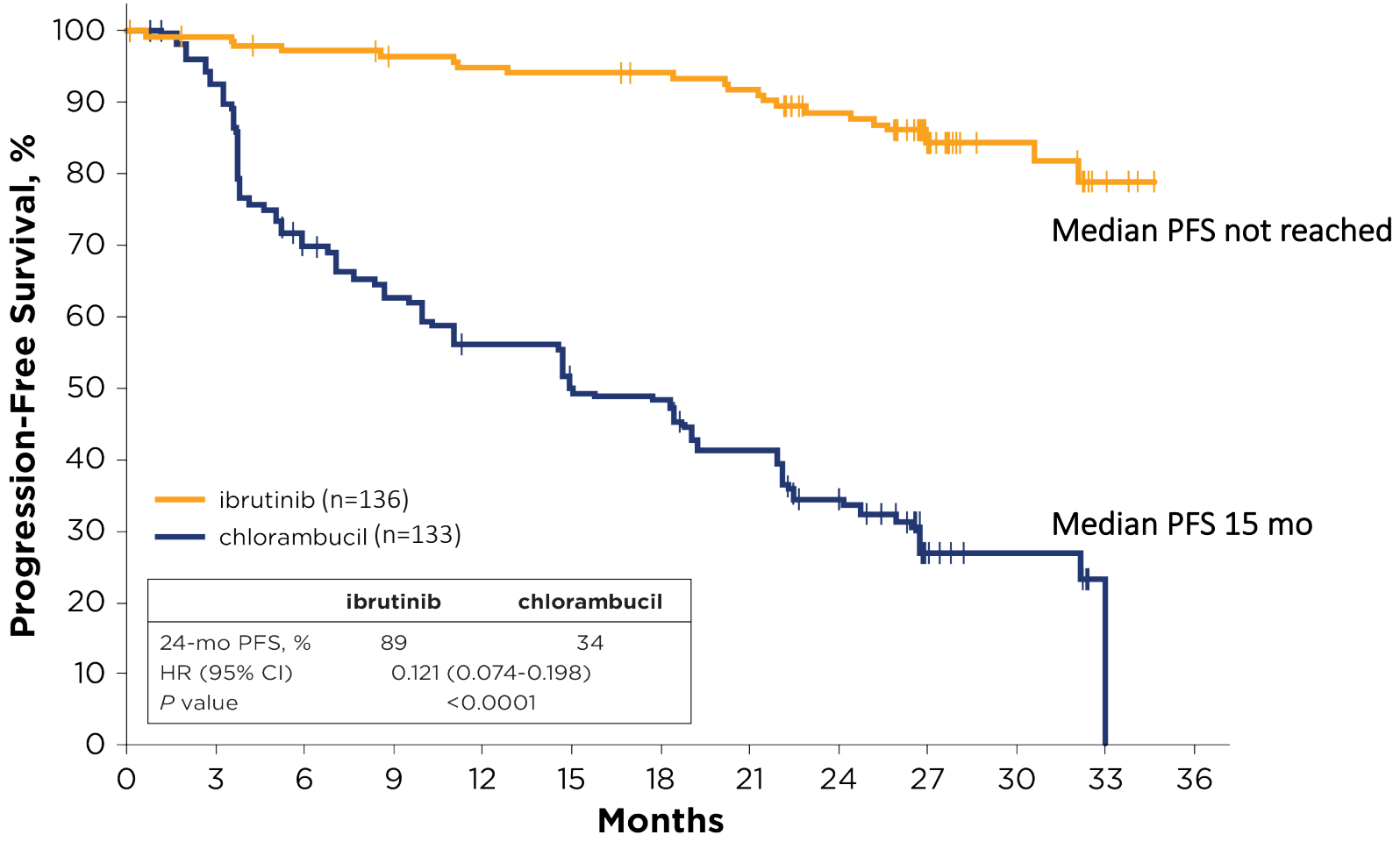
ORIGINAL ARTICLE

Ibrutinib as Initial Therapy for Patients with Chronic Lymphocytic Leukemia

J.A. Burger, A. Tedeschi, P.M. Barr, T. Robak, C. Owen, P. Ghia, O. Bairey, P. Hillmen, N.L. Bartlett, J. Li, D. Simpson, S. Grosicki, S. Devereux, H. McCarthy, S. Coutre, H. Quach, G. Gaidano, Z. Maslyak, D.A. Stevens, A. Janssens, F. Offner, J. Mayer, M. O'Dwyer, A. Hellmann, A. Schuh, T. Siddiqi, A. Polliack, C.S. Tam, D. Suri, M. Cheng, F. Clow, L. Styles, D.F. James, and T.J. Kipps, for the RESONATE-2 Investigators*

- Published Dec 17th, 2015 NEJM.
- March 2016 - Ibrutinib receives broad frontline indication in CLL.

Ibrutinib Prolonged PFS Over Chlorambucil



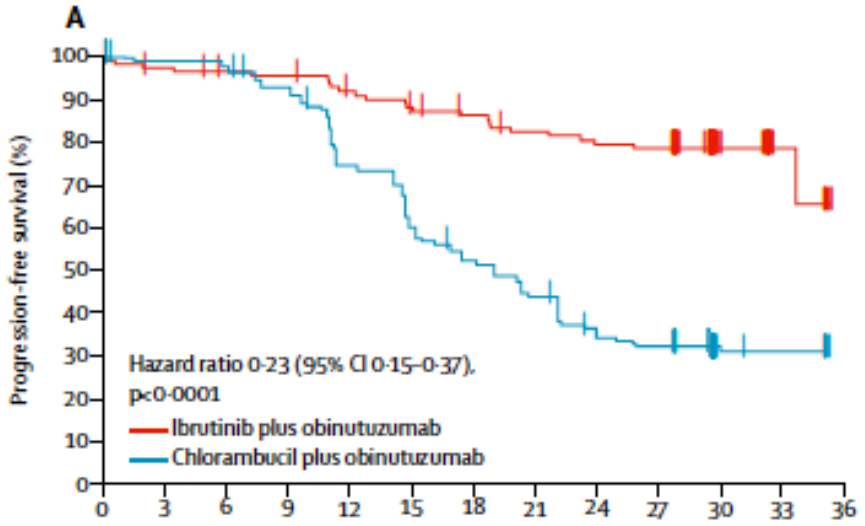
- 88% reduction in the risk of progression or death for patients randomized to ibrutinib
- Subgroup analysis of PFS revealed benefit was observed across all sub-groups

Barr, ASH 2016, Abstract 234.

Ibrutinib defeats some “worthy” opponents in 2019

Ibrutinib plus obinutuzumab versus chlorambucil plus obinutuzumab in first-line treatment of chronic lymphocytic leukaemia (iLLUMINATE): a multicentre, randomised, open-label, phase 3 trial

Carol Moreno, Richard Greil, Fatih Demirkan, Alessandra Tedeschi, Bertrand Anz, Loree Larratt, Martin Simkovic, Olga Samoilova, Jan Novak, Dina Ben-Yehuda, Vladimir Strugov, Devinder Gill, John G Gribben, Emily Hsu, Chih-Jian Lih, Cathy Zhou, Fong Clow, Danelle F James, Lori Styles, Ian W Flinn



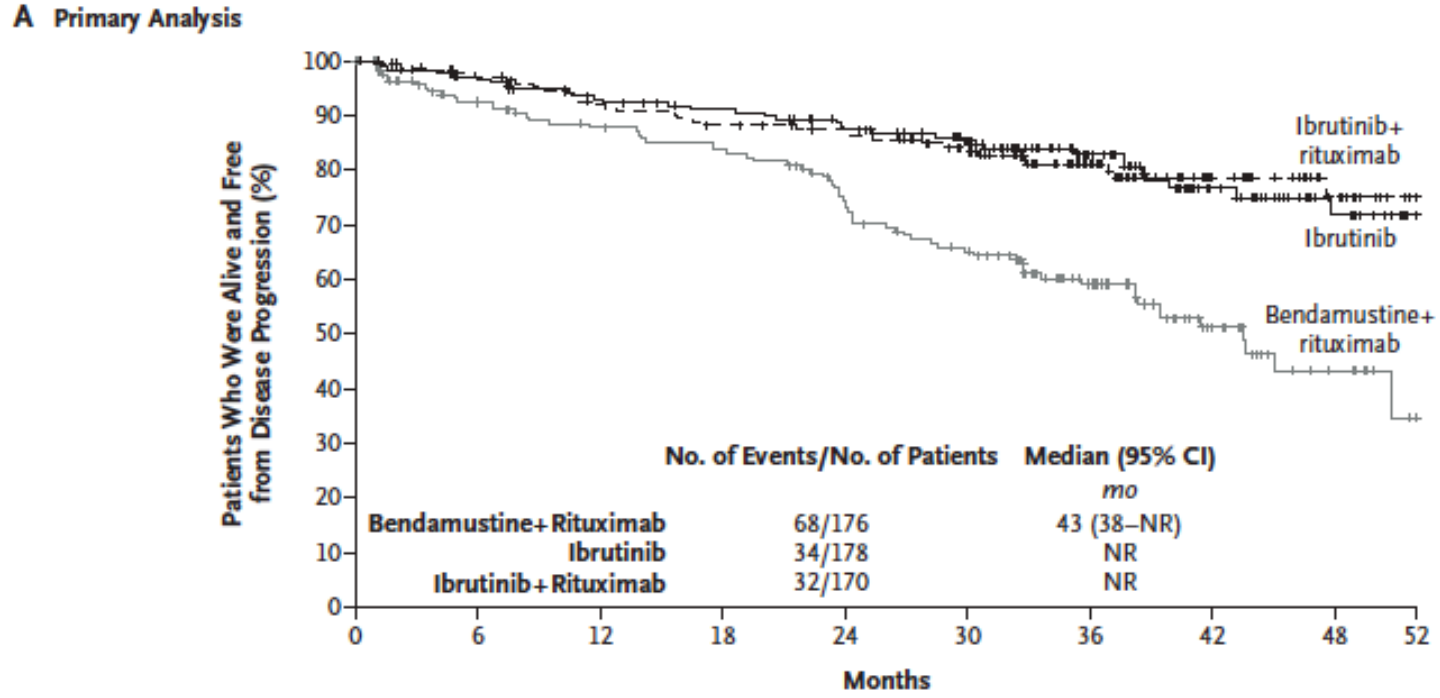
Number at risk (number censored)													
Ibrutinib plus obinutuzumab	113	109	106	105	99	94	90	85	82	81	28	6	0
	(0)	(1)	(3)	(3)	(5)	(6)	(8)	(9)	(9)	(9)	(62)	(84)	(89)
Chlorambucil plus obinutuzumab	116	111	109	102	81	67	56	47	35	33	6	5	0
	(0)	(4)	(4)	(6)	(7)	(7)	(8)	(8)	(10)	(10)	(36)	(37)	(42)

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Ibrutinib Regimens versus Chemoimmunotherapy in Older Patients with Untreated CLL

J.A. Woyach, A.S. Ruppert, N.A. Heerema, W. Zhao, A.M. Booth, W. Ding, N.L. Bartlett, D.M. Brander, P.M. Barr, K.A. Rogers, S.A. Parikh, S. Coutre, A. Hurria,* J.R. Brown, G. Lozanski, J.S. Blachly, H.G. Ozer, B. Major-Elechi, B. Fruth, S. Nattam, R.A. Larson, H. Erba, M. Litzow, C. Owen, C. Kuzma, J.S. Abramson, R.F. Little, S.E. Smith, R.M. Stone, S.J. Mandrekar, and J.C. Byrd



Subgroup	No. of Patients	No. of Events	Hazard Ratio for Disease Progression or Death (95% CI)
All patients			
Ibrutinib vs. bendamustine+rituximab	365	105	0.37 (0.25–0.56)
Ibrutinib+rituximab vs. bendamustine+rituximab	365	106	0.40 (0.27–0.60)
Ibrutinib+rituximab vs. ibrutinib	364	69	1.06 (0.66–1.70)

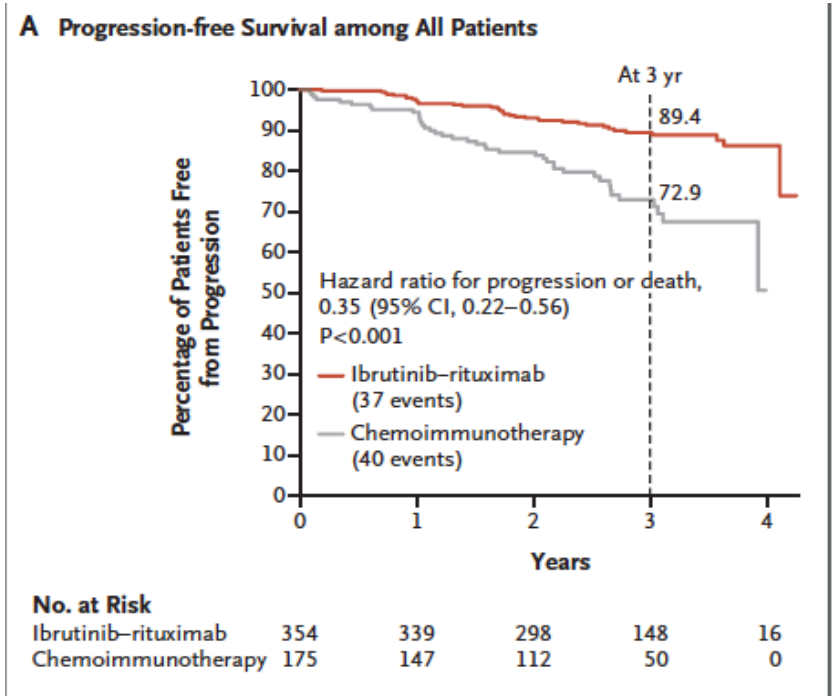
N Engl J Med 2018;379(26):2517-28.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Ibrutinib–Rituximab or Chemoimmunotherapy for Chronic Lymphocytic Leukemia

T.D. Shanafelt, X.V. Wang, N.E. Kay, C.A. Hanson, S. O'Brien, J. Barrientos, D.F. Jelinek, E. Braggio, J.F. Leis, C.C. Zhang, S.E. Coutre, P.M. Barr, A.F. Cashen, A.R. Mato, A.K. Singh, M.P. Mullane, R.F. Little, H. Erba, R.M. Stone, M. Litzow, and M. Tallman



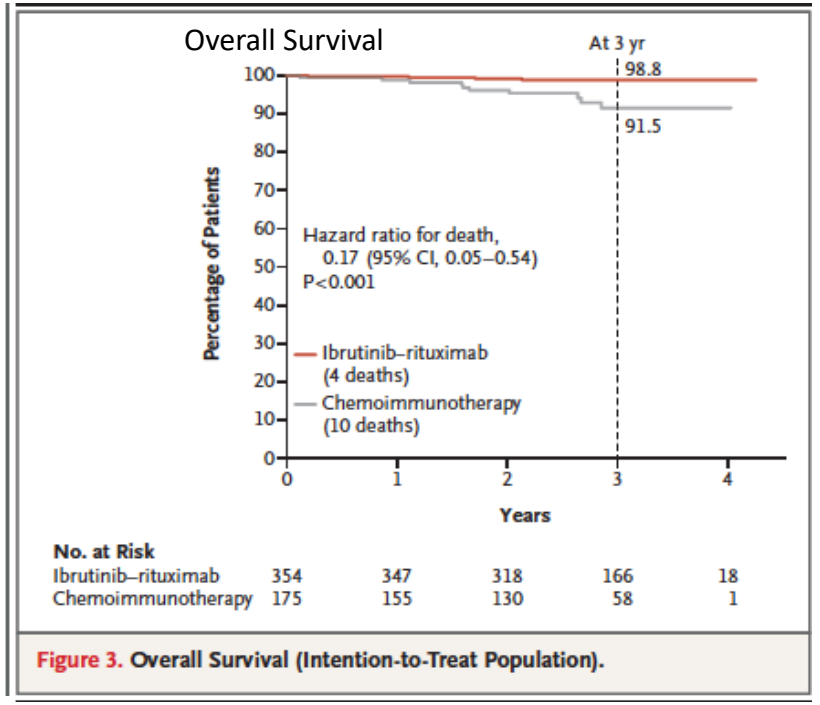


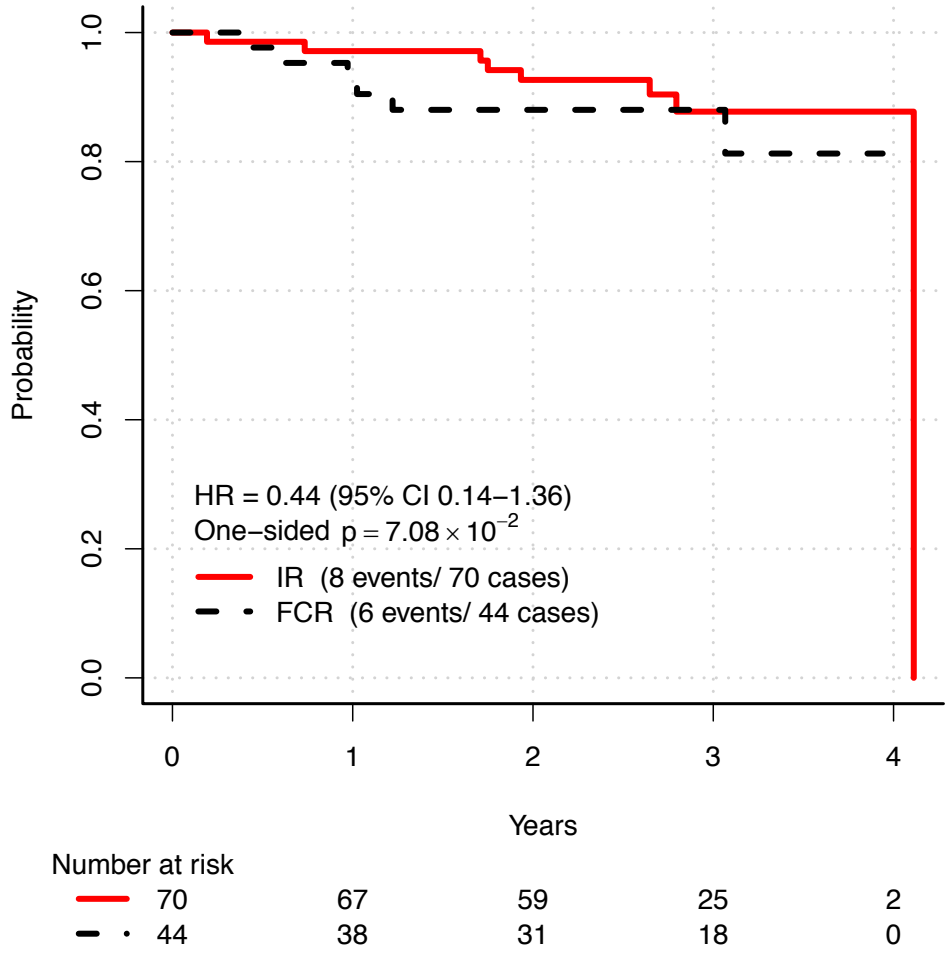
Figure 3. Overall Survival (Intention-to-Treat Population).

N Engl J Med 2019;381(5):432-43.

Ibrutinib frontline treatment considerations

- PRO
  - Ibrutinib efficacy excellent with longer term follow up – why not simply give that to everyone as initial therapy?
  - No need to worry about age, mutational status, 17p
  - No new safety signals emerging
- CON
  - Ibrutinib remissions tend be “shallow”
  - Low CR rate
  - Need continuous therapy
  - Cost

Additional Considerations



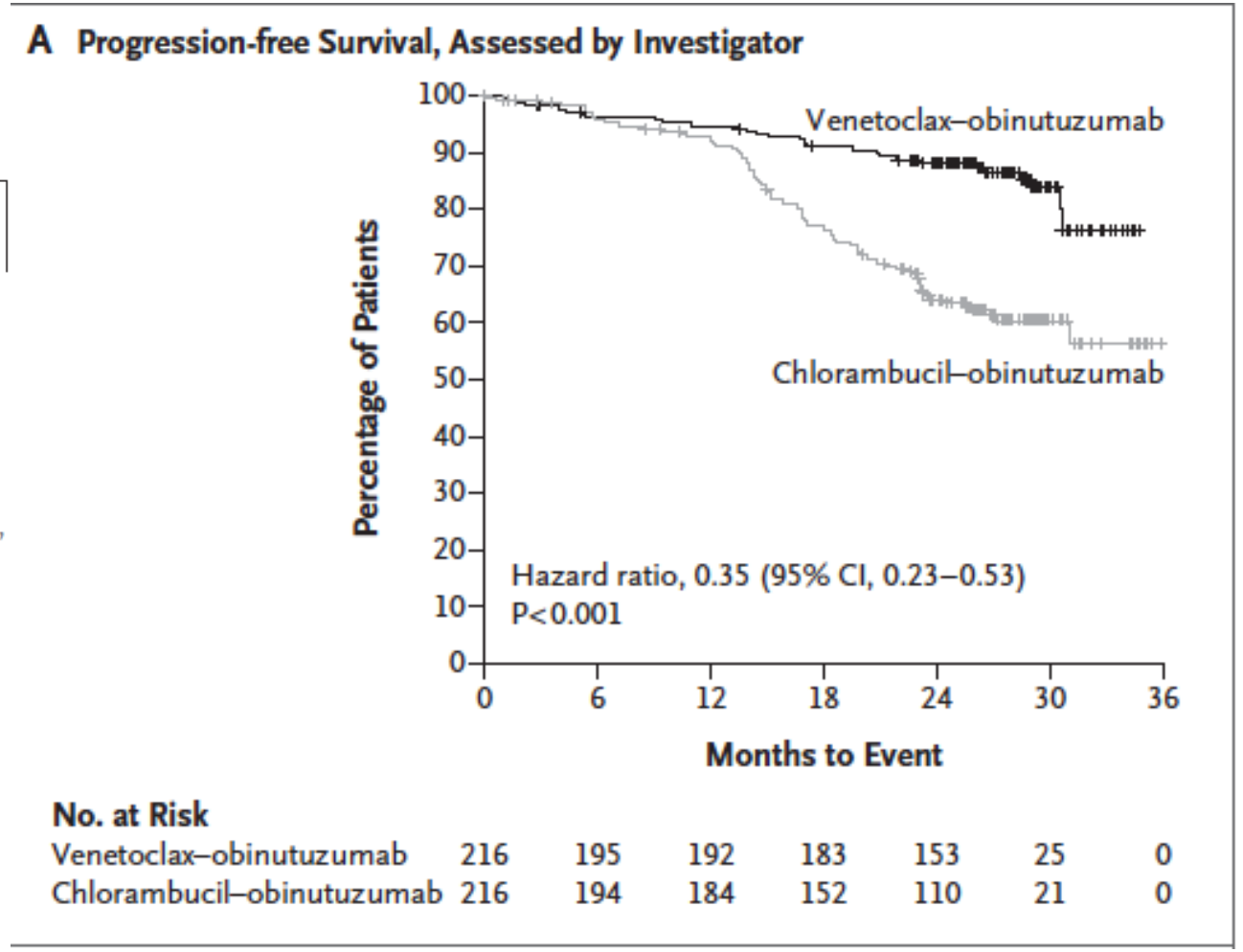
- BR and FCR perform similarly to ibrutinib in IgVH mutated patients
- Ibrutinib advantage larger in IgVH unmutated patients (easier decision)

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Venetoclax and Obinutuzumab in Patients with CLL and Coexisting Conditions

K. Fischer, O. Al-Sawaf, J. Bahlo, A.-M. Fink, M. Tandon, M. Dixon, S. Robrecht, S. Warburton, K. Humphrey, O. Samoylova, A.M. Liberati, J. Pinilla-Ibarz, S. Opat, L. Sivcheva, K. Le Dû, L.M. Fogliatto, C.U. Niemann, R. Weinkove, S. Robinson, T.J. Kipps, S. Boettcher, E. Tausch, R. Humerickhouse, B. Eichhorst, C.-M. Wendtner, A.W. Langerak, K.-A. Kreuzer, M. Ritgen, V. Goede, S. Stilgenbauer, M. Mobasher, and M. Hallek



N Engl J Med 2019;380(23):2225-36.

Competition for ibrutinib in frontline

- Venetoclax plus Obinutuzumab is time limited
  - O administered for 6 months
  - V administered for 12 months
- FDA approval May 2019
- NCCN preferred front line regimens:
  - Ibrutinib
  - Venetoclax-Obinutuzumab

Venetoclax

- Toxicity profile different from other targeted agents: TLS risks

Figure 1. **Intrapatient dose ramp-up scheme for CLL patients initiating venetoclax**

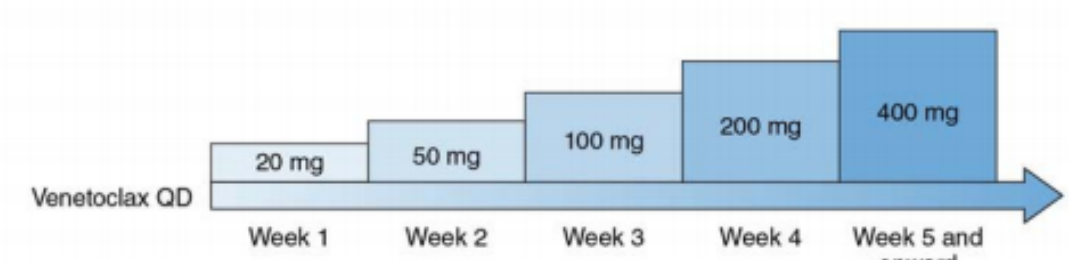


Figure 2. **Tumor lysis syndrome risk stratification, prophylaxis, and monitoring for CLL patients initiating venetoclax**

LOW RISK Nodal mass <5 cm and ALC <25,000 K/μL	**MEDIUM RISK** Nodal mass ≥5 cm and <10 cm or ALC ≥25,000 K/μL	**HIGH RISK** Nodal mass ≥10 cm or Nodal mass ≥5 cm but <10 cm and ALC ≥25,000 K/μL
Oral hydration (1.5-2L), allopurinol	Oral hydration (1.5-2L), consider IV hydration, allopurinol	Oral hydration (1.5-2L) and IV hydration (150-200 mL/hr as tolerated), allopurinol, consider rasburicase if elevated baseline uric acid
Outpatient administration	–Outpatient administration –Consider inpatient if CrCl <80 mL/min	–Inpatient administration for initial dose of 20 mg and 50 mg –Outpatient administration for subsequent dose escalations
Labs pre-dose, then 6-8 and 24 hours post-dose after initial dose of 20 mg and 50 mg	Labs pre-dose, then 6-8 and 24 hours post-dose after initial dose of 20 mg and 50 mg	**Inpatient:** Labs pre-dose, then 4, 8, 12, and 24 hours post-dose **Outpatient:** Labs pre-dose, then 6-8 and 24 hours post-dose

Blood. 2017;130(9):1081

Comparison of toxicities

Ibrutinib

- **bleeding risks**
  - phase I/II Studies: ICH: 2%
  - Follow up (3yr): 7% gr 3
- **cardiovascular risks**
  - afib: range up to 16%
  - HTN
- **other**
  - GI/diarrhea
  - Rash/skin
  - arthralgia/arthritis
  - Infections
  - edema

Venetoclax

- **tumor lysis**
  - Can be rapid
  - dose ramp up & hospitalization needs
- **cytopenias (gr ¾)**
  - neutropenia (41%)
  - anemia (12%)
  - thrombocytopenia (12%)
- **other (all grades)**
  - diarrhea
  - nausea
  - fatigue

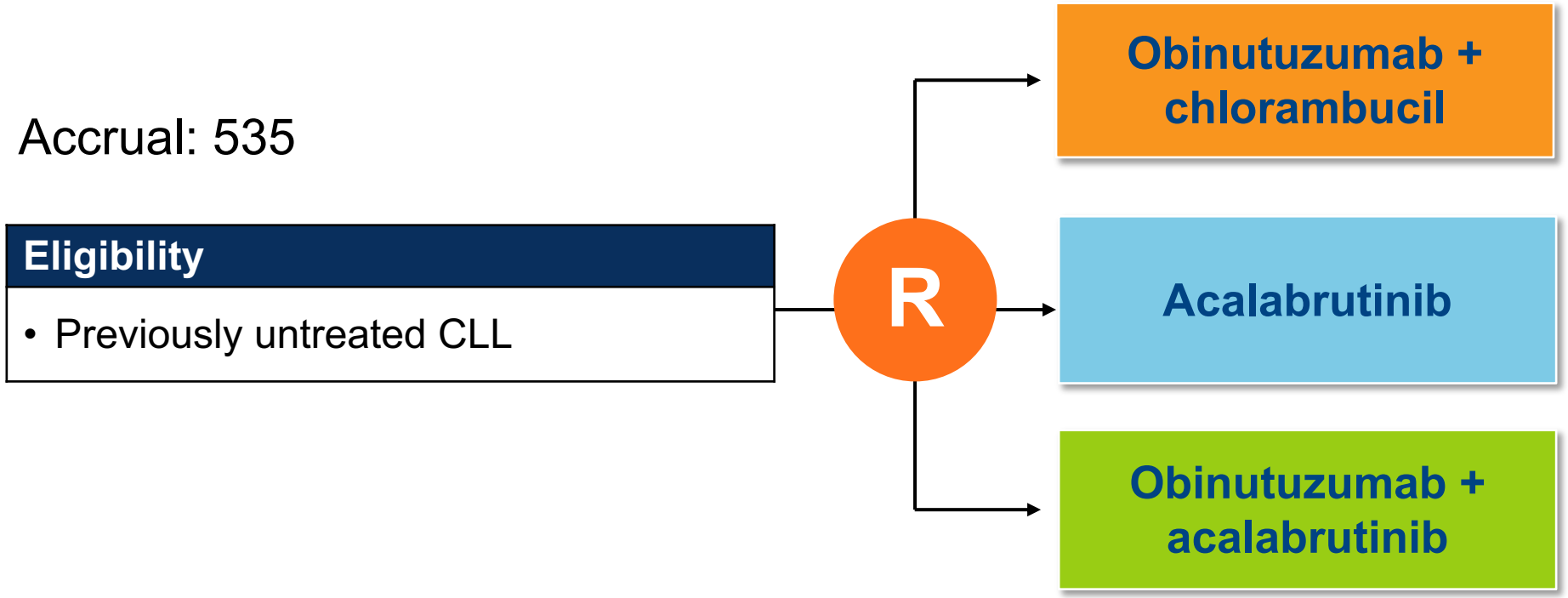
CLL patient requiring frontline Rx

1. 17p del/p53 mutation
   - Ibrutinib or VO
     - Would you stop V after 12 months?
2. IgVH unmutated (any age)
   - VO or ibrutinib
3. IgVH mutated
   - young and fit (<65)
     - VO or ibrutinib
     - Consider FCR
   - age 65-80
     - VO or ibrutinib
     - Consider BR
   - older > 80
     - VO or ibrutinib
     - Consider chlorambucil-obinutuzumab

Remaining questions

1. If you choose ibrutinib, should you give concurrent rituximab?
   - Alliance study suggests: NO
2. What about obinutuzumab?
   - Ibrutinib plus obinutuzumab approved (iLLUMINATE)
   - To be presented at ASH 2019: ELEVATE (abstract #31)
     - Acalabrutinib vs. Acala plus Obinutuzumab vs. Chlor-Obinutuzumab
3. Is ibrutinib the BTKi of choice?
   - Acalabrutinib received CLL approval in Nov 2019
     - Both frontline and R/R
4. Can we get away with time limited therapy?

ELEVATE-TN CLL: Phase III Trial Schema



Primary endpoint: Progression-free survival

www.clinicaltrials.gov. (NCT02475681) Accessed September 2019.

FDA Approval of Acalabrutinib in CLL

On November 21, 2019, the Food and Drug Administration approved acalabrutinib for adults with chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL). Approval was based on two randomized, actively controlled trials in patients with CLL: ELEVATE-TN (NCT02475681) and ASCEND (NCT02970318).

ELEVATE-TN randomized 535 patients with previously untreated CLL to one of three arms: acalabrutinib monotherapy, acalabrutinib plus obinutuzumab, or obinutuzumab plus chlorambucil. With a median follow-up of 28.3 months, PFS was significantly improved in both acalabrutinib arms. Compared to the obinutuzumab plus chlorambucil arm, the HR for PFS was 0.10 ($p < 0.0001$) with acalabrutinib plus obinutuzumab and 0.20 ($p < 0.0001$) with single agent acalabrutinib.

https://www.fda.gov/drugs/resources-information-approved-drugs/project-orbis-fda-approves-acalabrutinib-cll-and-sll

EA9161 Schema

Stratifications
Age: <65 yr vs ≥ 65 yr and <70 yr
PS: 0, 1, vs 2
Stage: 0, 1, or 2 vs 3, 4
Del11q22.3 vs others

Randomize

Arm A
Ibrutinib: Cycles 1-19:d1-28 420mg PO daily
Obinutuzumab: C1 **:** D1:100 mg IV, D2:900 mg IV, D8: 1000 mg IV, D15: 1000 mg IV; C2-6: D1 1000 mg IV
Venetoclax: C3 D1-7 20mg PO daily D8-14 50mg PO daily D15-21 100mg PO daily; D22-28 200 mg PO daily;
C4-14: D1-28 400mg PO daily

Arm B
Ibrutinib: Cycles 1-19+:d1-28 420mg PO daily
Obinutuzumab: C1 **:** D1:100 mg IV, D2:900 mg IV, D8: 1000 mg IV, D15: 1000 mg IV; C2-6: D1 1000 mg IV

Ongoing trials focusing on time limited therapy