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Chronic Lymphocytic Leukemia

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SITEMAN CANCER CENTER

BARNES-JEWISH Hospital BJC HealthCare | Washington University in St. Louis SCHOOL OF MEDICINE

NCCN National Comprehensive Cancer Network®

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

Disclosures

Consulting Agreements	AbbVie Inc, Acerta Pharma — A member of the AstraZeneca Group, AstraZeneca Pharmaceuticals LP, BeiGene, Celgene Corporation, Genentech, Pharmacyclics LLC, an AbbVie Company, Roche Laboratories Inc

Case presentation: Dr Cole

58-year-old man with Rai Stage 0 CLL

- Initially observed for several years
- WBC increased from 17,000 to 150,000; Hgb decreased from 13 to 11
- Patient increasingly concerned about WBC with nonspecific symptoms (Disease? Anxiety?)
- Patient advised to continue observation but wishes to be treated

Case presentation: Dr Sinha

72-year-old woman with CLL

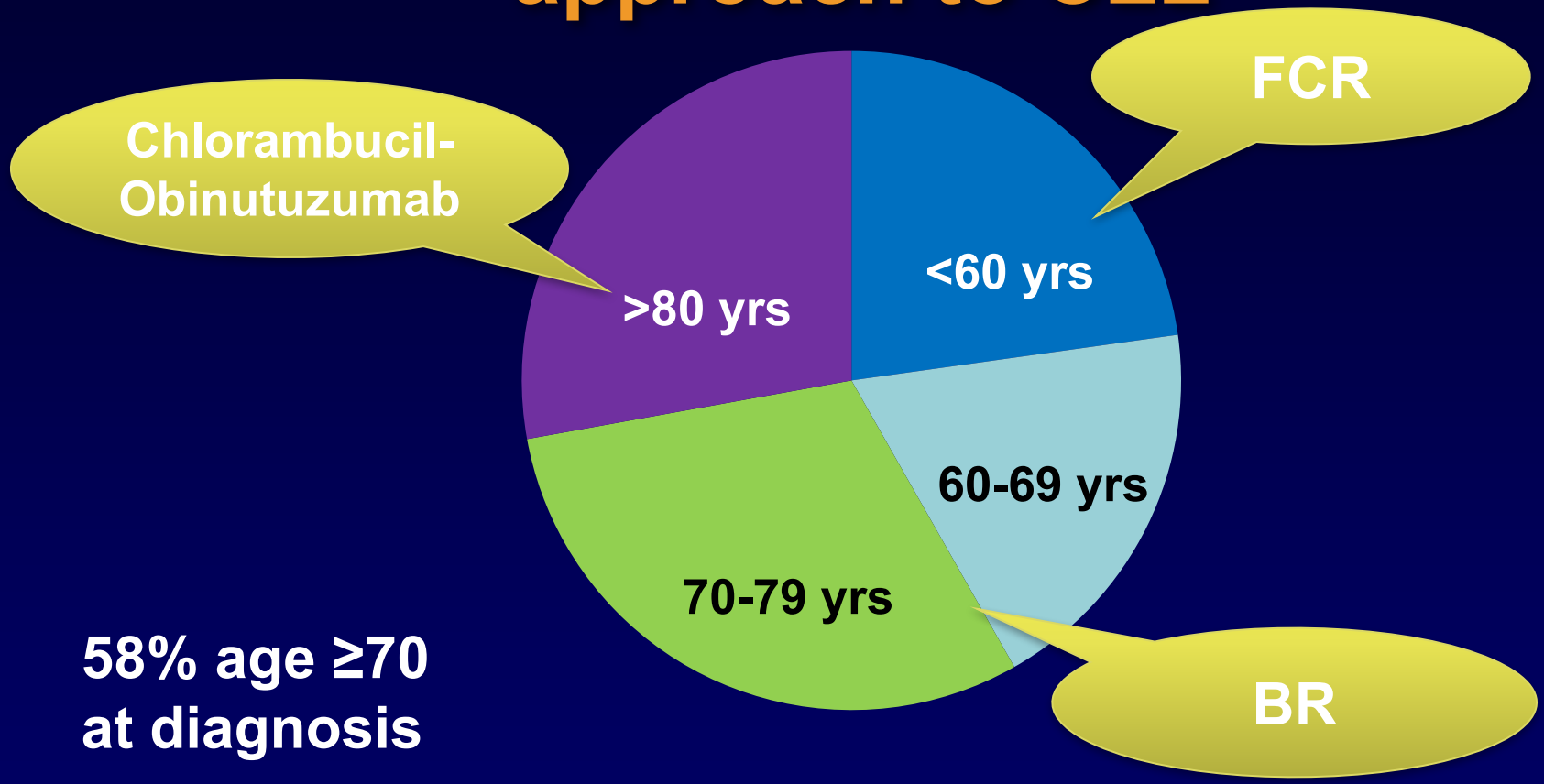
- IGHV mutated, del(17p) negative, TP53 unmutated
- Responded to treatment with ibrutinib for 3 years
- No significant tolerability issues
- Now presents with disease progression

Case presentation: Dr Rupard

54-year-old man with CLL

- IGHV unmutated, del(17p) negative, TP53 unmutated
- Front-line bendamustine/rituximab → disease progression after 3 months
- Ibrutinib started with good response
- CVA → started on clopidogrel and aspirin

A simplistic (and outdated) approach to CLL

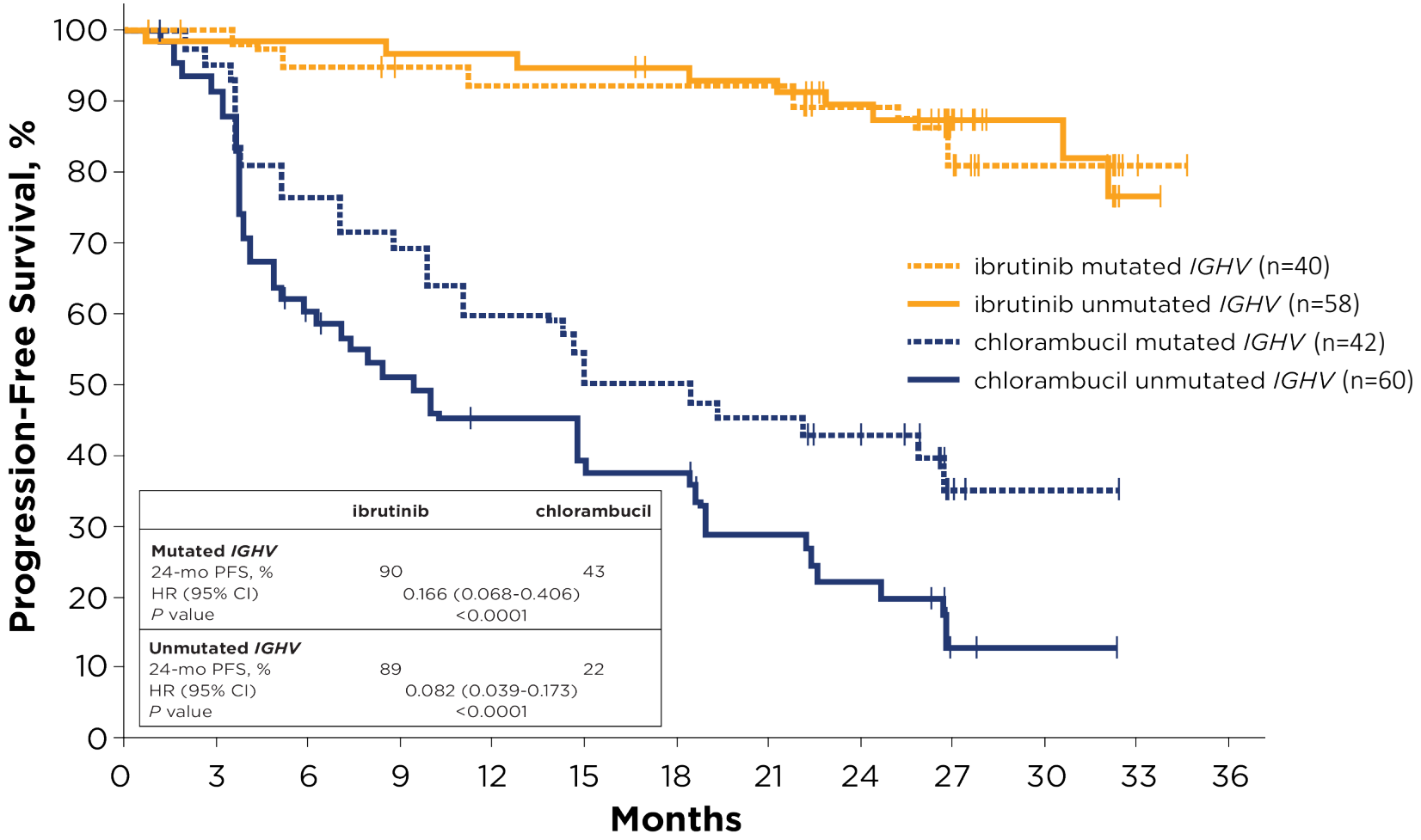


58% age ≥70 at diagnosis

Age at CLL Diagnosis
Olmsted County MN, 2000-2010

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

Ibrutinib Significantly Improved PFS in Patients Regardless of *IGHV* Status



- Ibrutinib led to 83% and 92% reduction in the risk of progression or death in patients with mutated and unmutated *IGHV*, respectively, compared to chemotherapy

ASH 2016, Updated Efficacy/Safety RESONATE-2; Barr et al.

Front-line management of CLL

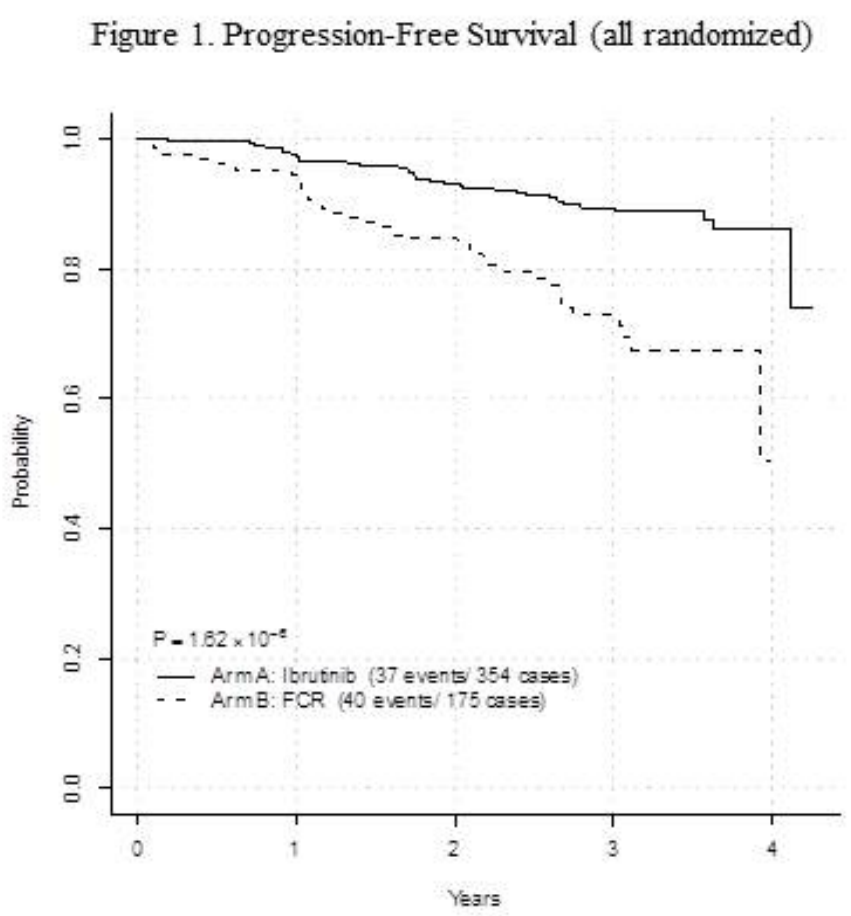
- One must take a more sophisticated approach to CLL now
  - Consider IgVH mutational status (particularly in younger patients)
  - Consider cytogenetic risk profile (CLL FISH panel)
    - 13q, trisomy 12, 11q, 17p
- Consider ibrutinib as a front-line option for any patient regardless of age or risk profile
  - A complicated discussion with patient
  - Lacking truly long-term outcome data with ibrutinib
  - Lacking "good" comparative data
- Until now…

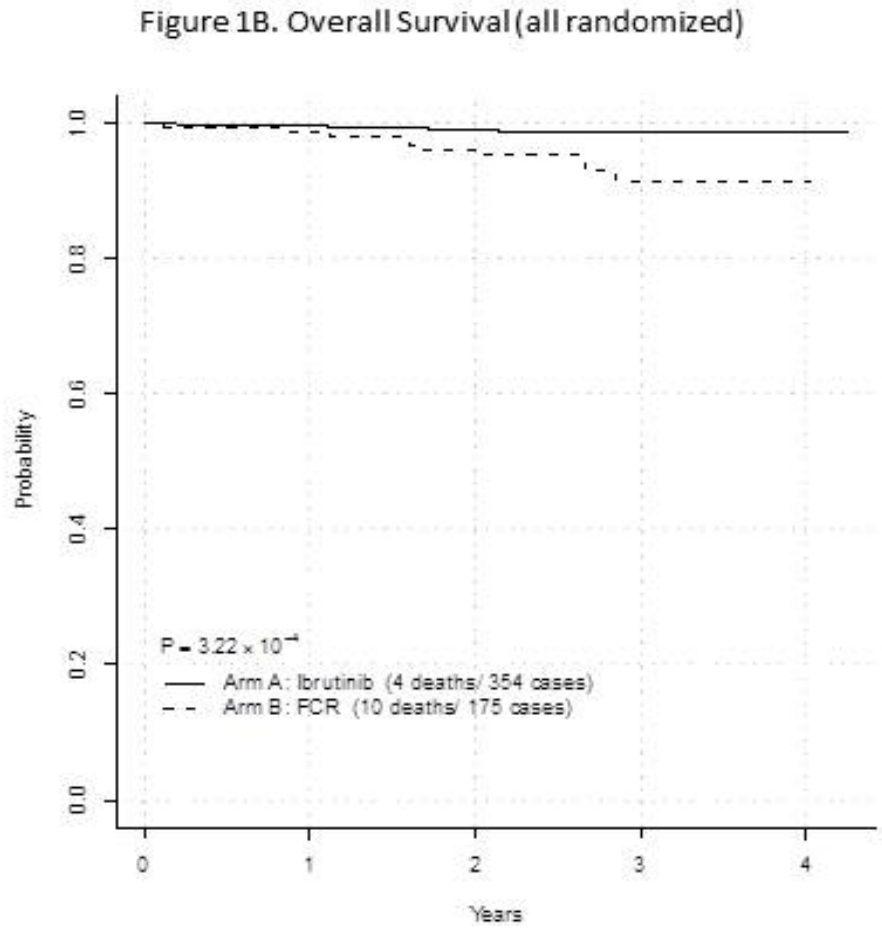
New at ASH 2018

- E1912
  - Ibrutinib-Rituximab vs. FCR in young fit
    - Late-Breaking Abstract #4, Tue am
- A041202
  - Ibrutinib vs. IR vs. BR in older CLL
    - Abstract #6, Plenary Session Sun pm
- iLLUMINATE
  - Ibrutinib-Obinutuzumab vs. Chl-Obin in older CLL
    - Abstract #691, CLL Oral Mon am

E1912 (Ibrutinib-Rituximab vs. FCR)

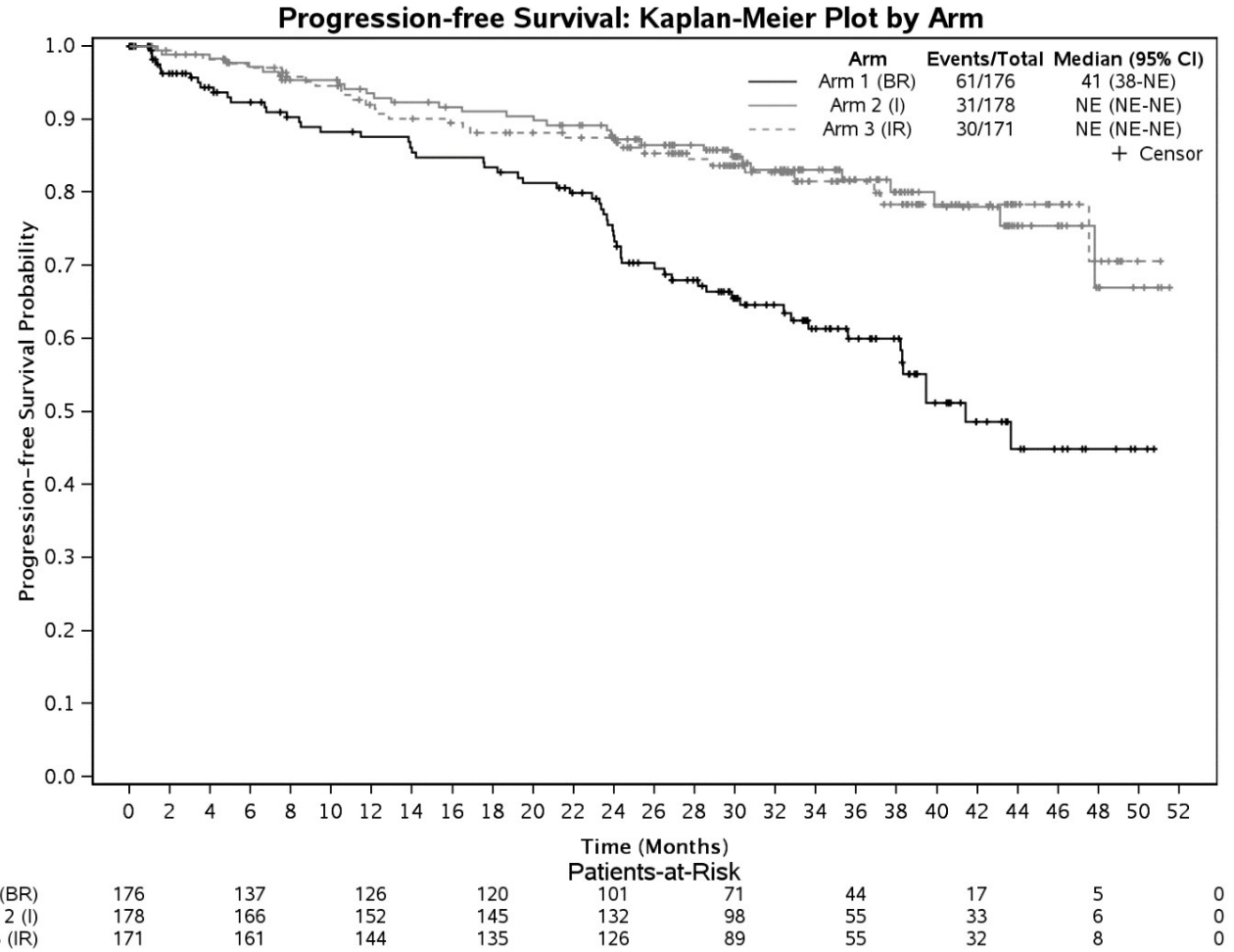
- Enrolled 529 treatment naïve CLL up to age 70
- Excluded 17p del
- Median follow-up 33 months
- PFS favors IR (HR .35)
- OS favors IR (HR .16)
- Benefit not observed in IgVH mutated patients





A041202: I vs. IR vs. BR

- 547 patients randomized
  - Crossover allowed
- Median age 71
- Median f/u 32 months
- PFS
  - BR median 41 months
  - I superior to BR (HR .4)
  - I = IR
- No OS difference
- The Grade 5 AE rate on the ibrutinib arms was 7.8% and 7.7%, and 2.8% on the BR arm.



iLLUMINATE: IO vs. Chl-O

- 229 patients randomized
  - Crossover allowed
- Median age 71
- Median f/u 31 months
- PFS
  - Chl-O median 19 months
  - IO superior (HR .26)
- No OS difference

Figure 1. PFS as assessed by IRC in the intention-to-treat population

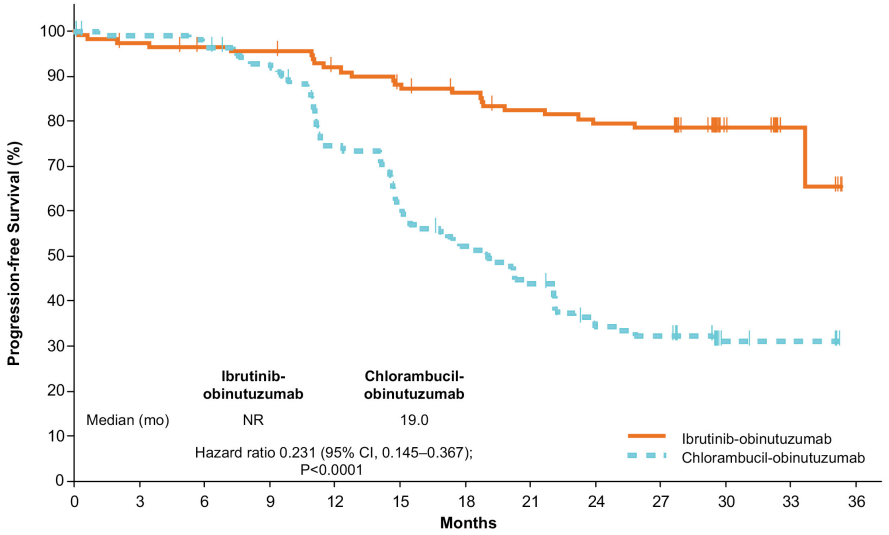
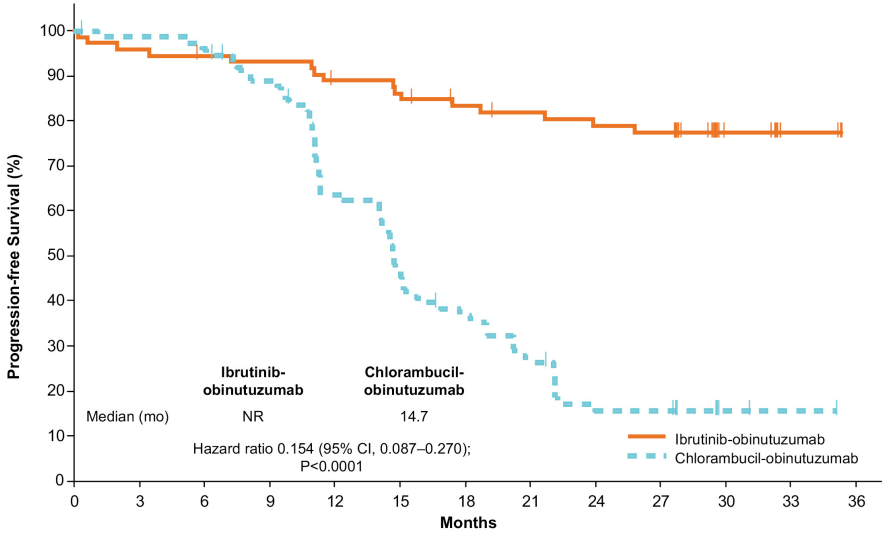


Figure 2. PFS in high-risk population with del(17p)/*TP53* mutation, del(11q), and/or unmutated *IGHV*



Discussion Points

- OS advantage in E1912 is provocative
  - Is ibrutinib substantially more efficacious than FCR?
  - If yes, why no OS advantage vs. BR or Chl-O?
  - Perhaps OS difference is due to toxic deaths from FCR
    - Trial allowed up to age 70
    - Will need to examine data carefully
- Evaluate each trial by mutated vs. unmutated IgVH
  - BR median PFS 41 months
    - Bound to be shorter in unmutated. Longer in mutated.
  - Chlorambucil-obinutuzumab median PFS 19 months
    - Would only use in very elderly/infirm

CLL patient requiring front-line Rx

- Any age with 17p del
  - Ibrutinib
- Young (< 65) and fit
  - mutated IgVH: FCR ≥ ibrutinib?
  - unmutated IgVH: Ibrutinib > FCR
- Less young (age 65-80)
  - mutated IgVH: BR ≥ ibrutinib?
  - unmutated IgVH: Ibrutinib > BR
- Older (> 80)
  - Ibrutinib > chl-obinutuzumab

Acalabrutinib for CLL

- 99 patients
- Treatment naïve
- Median age 64
- ORR 97%
  - Complete response 5%
- Afib 6%
- Discontinuation rate 5%

ASH 2018;Abstract 692

Figure 1. Progression-Free Survival

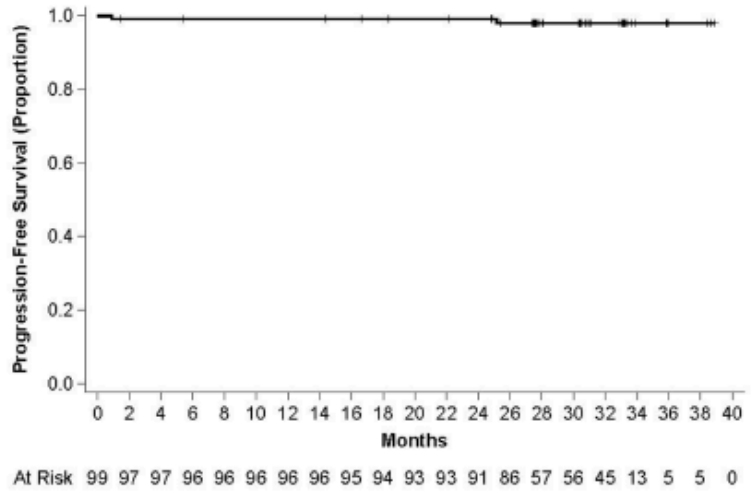
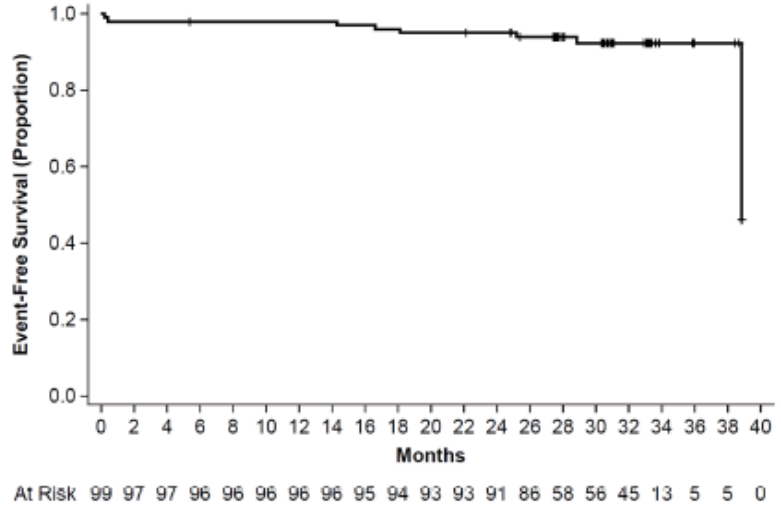


Figure 2. Event-Free Survival

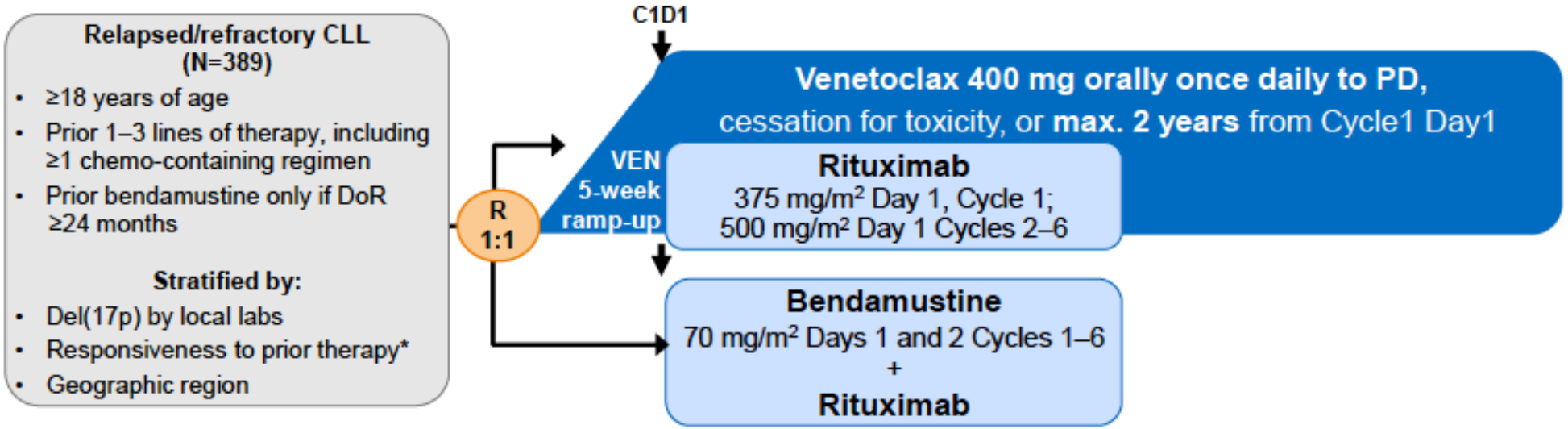


Relapsed CLL

- Ibrutinib FDA approved for R/R CLL in 2/14
  - ORR 90%, 3-yr PFS ~60% (Byrd et al, Blood 2015)
- Idelalisib-Rituximab approved for R/R CLL in 7/14
  - ORR 81%, 1-yr PFS ~60% (Furman et al, NEJM 2014)
- Venetoclax approved for R/R CLL with del(17p) in 5/16
  - ORR 79%, 1-yr PFS 72% (Stilgenbauer et al, Lancet Oncol 2016)
- Duvelisib approved for R/R CLL 9/18
  - ORR 74%, median PFS 13.3 months
- Venetoclax-Rituximab approved for R/R CLL in 6/18
  - MURANO trial
  - Fixed duration therapy

Venetoclax in CLL

MURANO Study Design

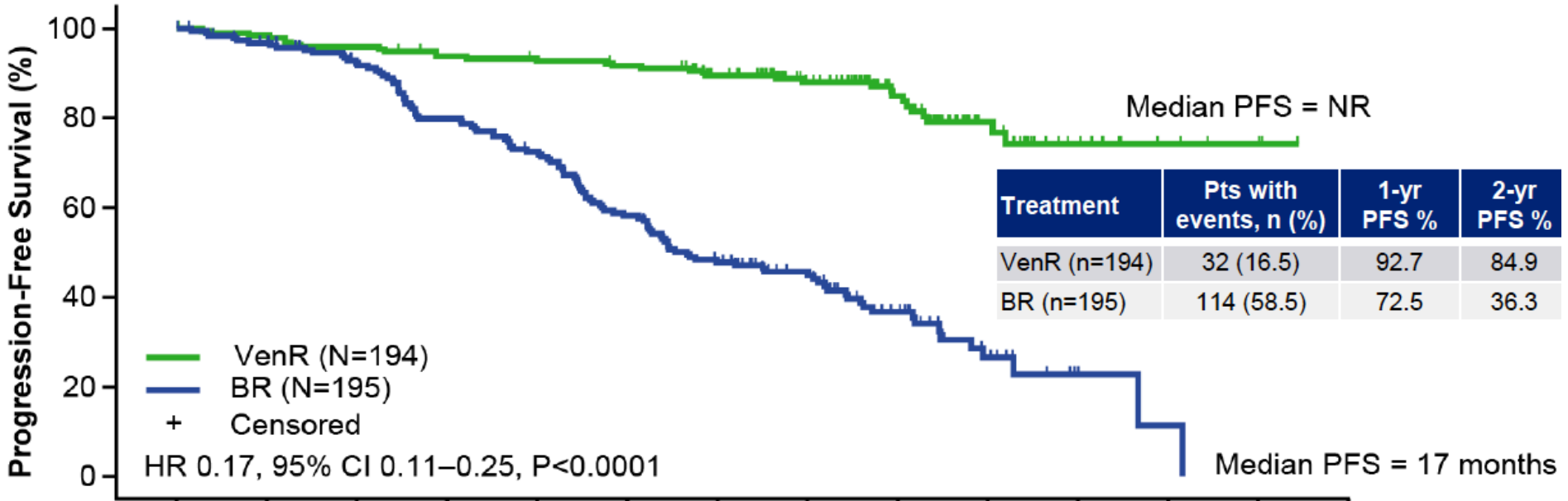


Primary Endpoint	INV-assessed PFS
Major Secondary Endpoints	• IRC-CR ⇒ IRC-ORR ⇒ OS (hierarchical testing) • IRC-assessed PFS and MRD-negativity
Key Safety Endpoints	Overall safety profile, focusing on serious adverse events and Grade ≥3 adverse events
Interim Analysis	Approximately 140 INV-assessed PFS events (75% of total information)

NCT02005471
*High-risk CLL – any of following features: del(17p) or no response to front-line chemotherapy-containing regimen or relapsed ≤12 months after chemotherapy or within ≤24 months after chemoimmunotherapy.

Seymour et al, NEJM April 2018

Investigator-Assessed PFS Superior for VenR vs. BR



Treatment	Pts with events, n (%)	1-yr PFS %	2-yr PFS %
VenR (n=194)	32 (16.5)	92.7	84.9
BR (n=195)	114 (58.5)	72.5	36.3

No. of patients at risk:

VenR	194	190	185	179	176	173	157	115	76	33	14	5	3
BR	195	177	163	141	127	102	81	57	35	12	3	1	

- Median (range) duration of follow-up, 23.8 (0.0–37.4) months: Venetoclax + rituximab, 24.8 months; bendamustine + rituximab, 22.1 months

As of 8 May 2017

MURANO: Select Grade 3/4 Adverse Events

	Venetoclax-Rituximab (n = 194)	Bendamustine-Rituximab (n = 188)
Grade 3/4 adverse event	82.0%	70.2%
Neutropenia	57.7%	38.8%
Infections and infestations	17.5%	21.8%
Anemia	10.8%	13.8%
Thrombocytopenia	5.7%	10.1%
Febrile neutropenia	3.6%	9.6%
Pneumonia	5.2%	8.0%
Infusion-related reaction	1.5%	5.3%
Tumor lysis syndrome	3.1%	1.1%

Seymour JF et al. *N Engl J Med* 2018;378(12):1107-20.

ACE-CL-001: Updated Efficacy and Safety of Acalabrutinib Monotherapy in Patients with R/R CLL

	All patients (n = 134)	Del(11)(q22.3) (n = 21)	Del(17)(p13.1) (n = 27)
ORR	85%	86%	85%
18-month DOR	85%	100%	71%
18-month PFS	88%	100%	78%

Adverse events (n = 134)	All grades	Grade 3-4
Headache	46%	NR
Diarrhea	43%	NR
Upper respiratory tract infection	28%	NR
Contusion	22%	NR
Neutropenia	NR	11%
Pneumonia	NR	10%
Hypertension	11%	3%
Atrial fibrillation	3%	2%

Byrd JC et al. *Proc ASH* 2017;Abstract 498.

FDA approvals with targeted agents

Agent	Target	FL	MZL	CLL	MCL
Bortezomib	proteasome				X
Lenalidomide	cereblon				X
Idelalisib	PI3k δ	X		X	
Copanlisib	PI3k α, δ	X			
Duvelisib	PI3k γ, δ	X		X	
Ibrutinib	BTK		X	X*	X
Acalabrutinib	BTK				X
Venetoclax	BCL-2			X	

*Approved in front-line and R/R setting.

All other approvals for R/R disease.

CLL in the Future

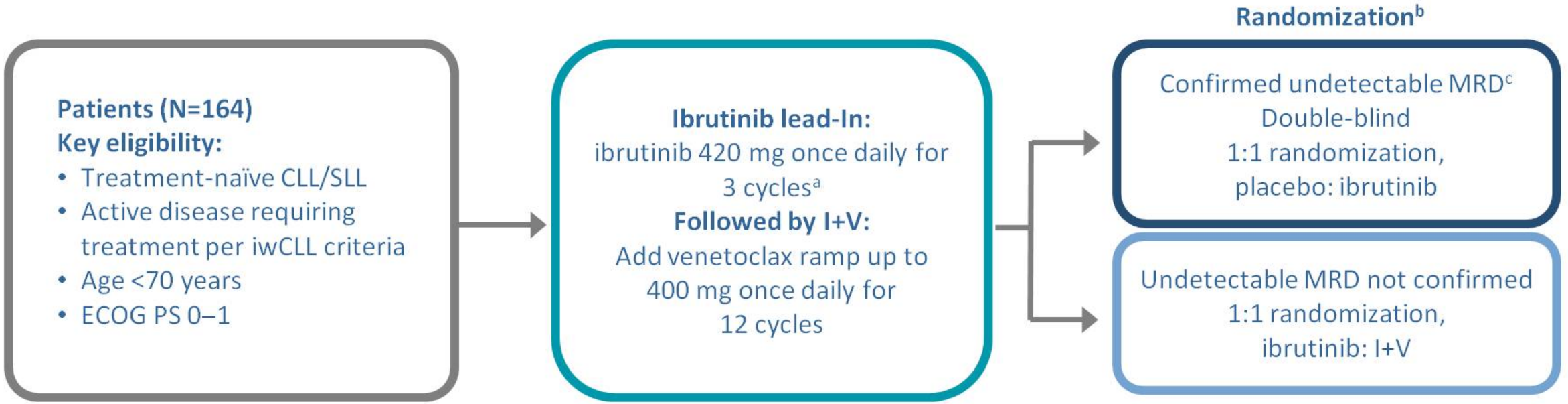
- Need to sort out the contribution and toxicity of agents in combination therapy
  - Ibrutinib + obinutuzumab (#691, Moreno et al)
  - Ibrutinib + venetoclax (#183, Hillmen et al)
  - Ibrutinib + venetoclax (#186, Jain et al)
  - Ibrutinib + obinutuzumab + venetoclax (#693, Rogers et al)
- Test new BTK inhibitors
  - Acalabrutinib (#692, Byrd et al)

CLL in the Future

- Time-limited therapy should become a major goal
  - Venetoclax plus rituximab (#184, Seymour et al)

- MRD assessments to permit rational discontinuation of treatment
  - Venetoclax plus rituximab (#183, Brander et al)
  - CAPTIVATE study (Wierda et al, ASCO 2018)

Phase 2 CAPTIVATE Study Design (NCT02910583)



[a]1 cycle = 28 days.
[b]Stratified by *IGHV* mutation status.
[c]Confirmed undetectable MRD for randomization defined as undetectable MRD serially over at least 3 cycles in peripheral blood (PB), and undetectable MRD in both PB and BM.

Study Populations:

- MRD cohort (N=164): exposure and safety analysis
  - Safety Run-in: first 14 patients completed C15 treatment (12 cycles of I+V); no dose-limiting toxicities (DLT) or clinical TLS during first 6 weeks of I+V combination
  - Prespecified analysis of the first 30 patients who completed C9 treatment (6 cycles of I+V) for MRD evaluation
- Fixed Duration cohort (N=159): separate cohort; analysis not shown