Selection and Sequencing Therapy for Relapsed/Refractory CLL

Julie M. Vose, M.D., M.B.A.

Chief, University of Nebraska Medical Center

Relapsed/Refractory CLL: Case 1

- 61 y/o female who was diagnosed with CLL 10 years ago
- 6 years ago she developed anemia requiring therapy
  - IGHV Mutated, FISH: del 13q
- She received FCR X 6 cycles with a CR
- Now she has rising lymphocytosis with new anemia (Hgb 8.5 gm/dl) and mild thrombocytopenia (plts 80,000/ul)
  - FISH still del 13q
- Many options left for therapy and combinations:
  - BTKi, Venetoclax, anti-CD20s, etc

NCCN Guidelines 4.2021

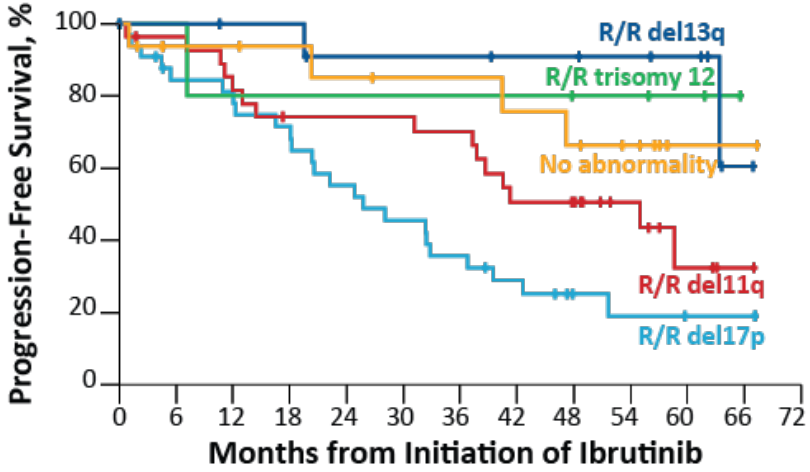
SUGGESTED TREATMENT REGIMENS[a,b,c,d]
CLL/SLL without del(17p)/*TP53* mutation
(alphabetical by category)

SECOND-LINE AND SUBSEQUENT THERAPY[e]			
Frail patient with significant comorbidity OR Patients aged ≥65 y and younger patients with significant comorbidities (CrCl <70 mL/min)	**Preferred regimens** • Acalabrutinib[f,n] (category 1) • Ibrutinib[f] (category 1) • Venetoclax[f,g] + rituximab (category 1) • Duvelisib[f] • Idelalisib[f] + rituximab[o]	**Other recommended regimens** • Alemtuzumab[p] ± rituximab • Chlorambucil + rituximab • Reduced-dose FCR[j,k] • HDMP + rituximab • Idelalisib[f] • Lenalidomide[q] ± rituximab • Obinutuzumab • Ofatumumab	• Reduced-dose PCR • Venetoclax[f,g] • Zanubrutinib (for patients with intolerance or contraindication to other BTKi)[n] • Dose-dense rituximab (category 2B) • Bendamustine + rituximab[r] (category 2B) • Bendamustine, rituximab + ibrutinib[f,r] (category 2B) • Bendamustine, rituximab + idelalisib[f,r] (category 3)
Patients aged <65 y without significant comorbidities	**Preferred regimens** • Acalabrutinib[f,n] (category 1) • Ibrutinib[f] (category 1) • Venetoclax[f,g] + rituximab (category 1) • Duvelisib[f] • Idelalisib[f] + rituximab[o]	**Other recommended regimens** • Alemtuzumab[p] ± rituximab • Bendamustine + rituximab • FC[j,k] + ofatumumab • FCR[j,k] • HDMP + rituximab • Idelalisib[f] • Lenalidomide[q] ± rituximab • Obinutuzumab • Ofatumumab	• PCR • Venetoclax[f,g] • Zanubrutinib (for patients with intolerance or contraindication to other BTKi)[n] • Bendamustine, rituximab + ibrutinib[f] (category 2B) • Bendamustine, rituximab + idelalisib[f] (category 2B)

POST SECOND-LINE CHEMOIMMUNOTHERAPY MAINTENANCE THERAPY (for complete or partial response after second-line therapy)
Other recommended regimens
• Lenalidomide[m] • Ofatumumab (category 2B)

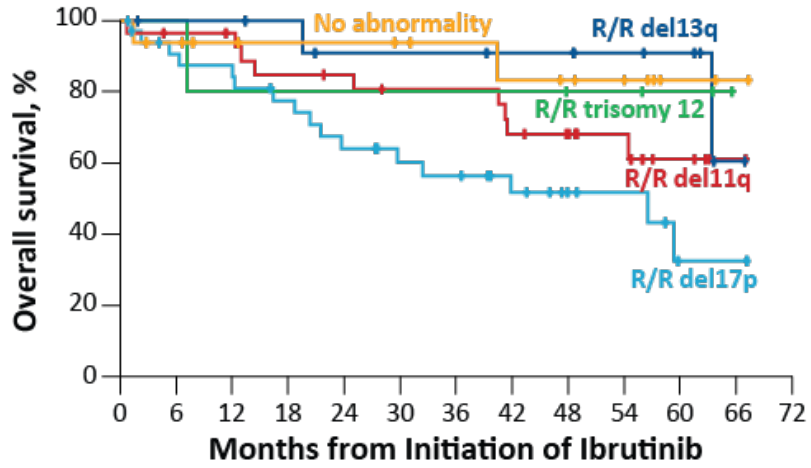
Single- Agent Ibrutinib is Effective in R/R CLL – A 5-Year Experience

Progression-Free Survival (median 55 mo.)



	Median PFS	5-year PFS
Del17p (n=34)	26 mo	19%
Del11q (n=28)	55 mo	33%
Trisomy 12 (n=5)	NR	80%
Del13q (n=13)	NR	91%
No abnormality** (n=16)	NR	66%

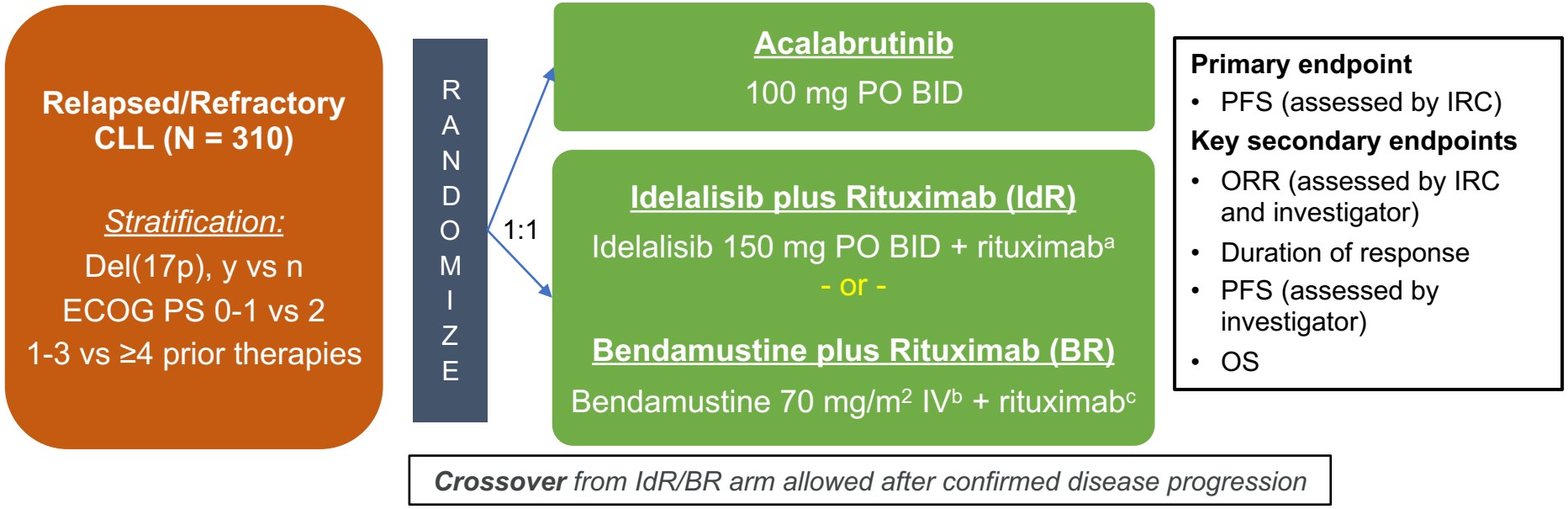
Overall Survival



	Median OS	5-year OS
Del17p (n=34)	57 mo	32%
Del11q (n=28)	NR	61%
Trisomy 12 (n=5)	NR	80%
Del13q (n=13)	NR	91%
No abnormality** (n=16)	NR	83%

O'Brien et al., *Blood*, 2018

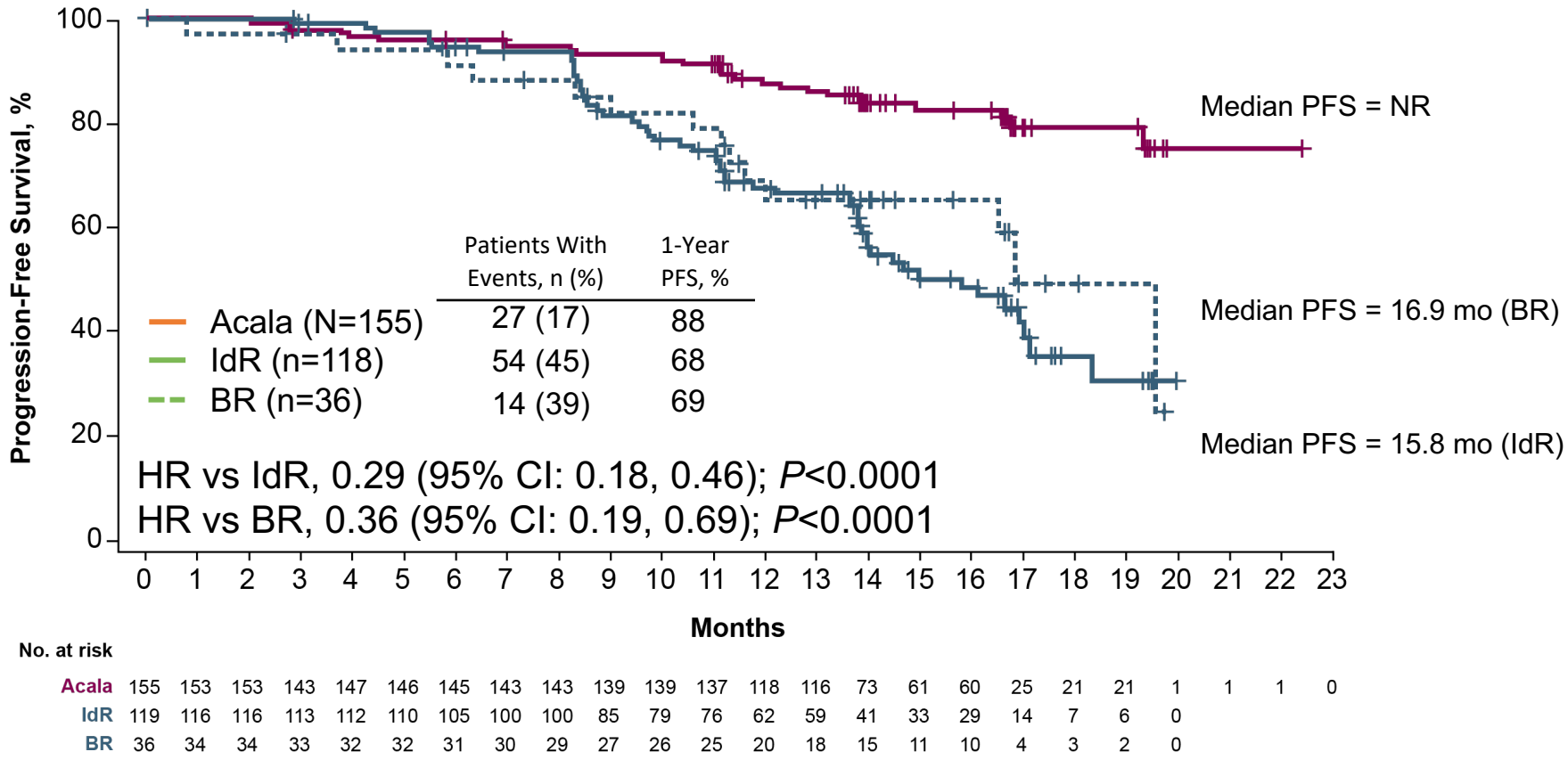
ASCEND Study Design (ACE-CL-309)



- Interim analysis was planned after occurrence of ~79 PFS events (2/3 of primary event goal)

Ghia et al., *J Clin Oncol 2020*

ASCEND: IRC-Assessed PFS Superior for Acalabrutinib vs IdR or BR

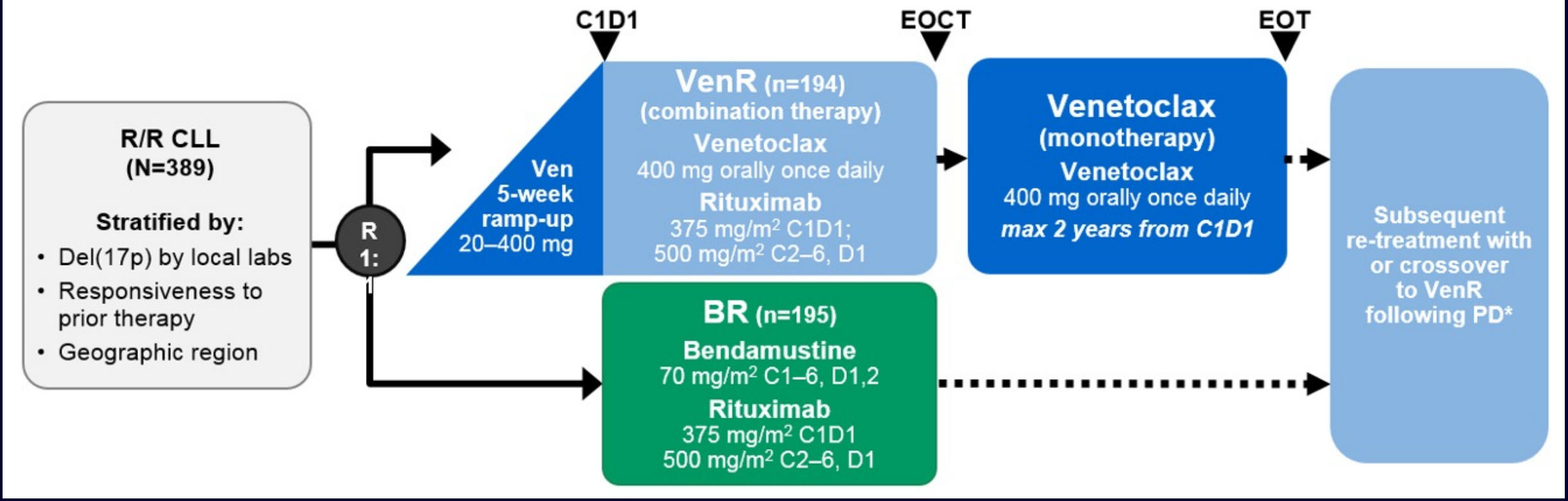


Acala = acalabrutinib; BR = bendamustine plus rituximab; HR = hazard ratio; IdR = idelalisib plus rituximab; IRC = independent review committee; NR = not reached; PFS = progression-free survival.

Ghia et al., *J Clin Oncol 2020*

MURANO Study (NCT02005471)

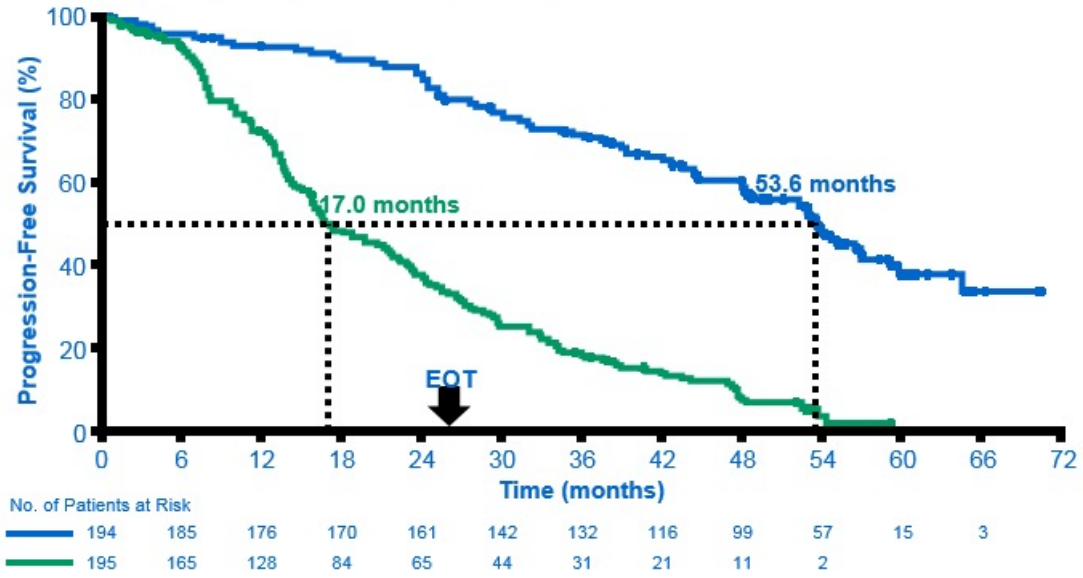
Global, phase III, open-label, randomized study[a]



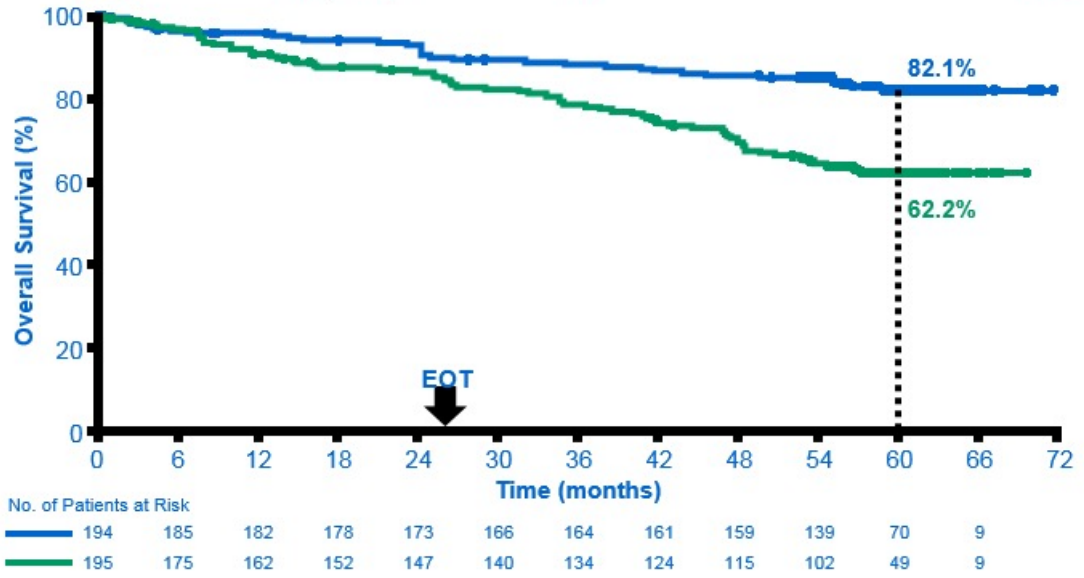
At 48 months of follow-up, deep responses with uMRD were associated with favorable PFS[b]
*Investigator-assessed PD according to International Workshop on Chronic
a. Seymour JF, et al. *N Engl J Med*. 2018;378:1107-1120; b. Kater AP, et al. *J Clin Oncol*. 2020;38:4042-4054.

MURANO: PFS and OS benefits with VenR over BR were sustained 3 years after EOT

	Median PFS (95% CI), months	HR* (95% CI)	5-yr PFS (%)
VenR (N=194)	**53.6** (48.4, 57.0)	**0.19** (0.15, 0.26) Stratified P-value <0.0001†	37.8
BR (N=195)	**17.0** (15.5, 21.7)		NE



	Median OS (95% CI), months	HR‡ (95% CI)	5-yr OS (%)
VenR (N=194)	NE	**0.40** (0.26, 0.62) Stratified P-value <0.0001†	82.1
BR (N=195)	NE		62.2



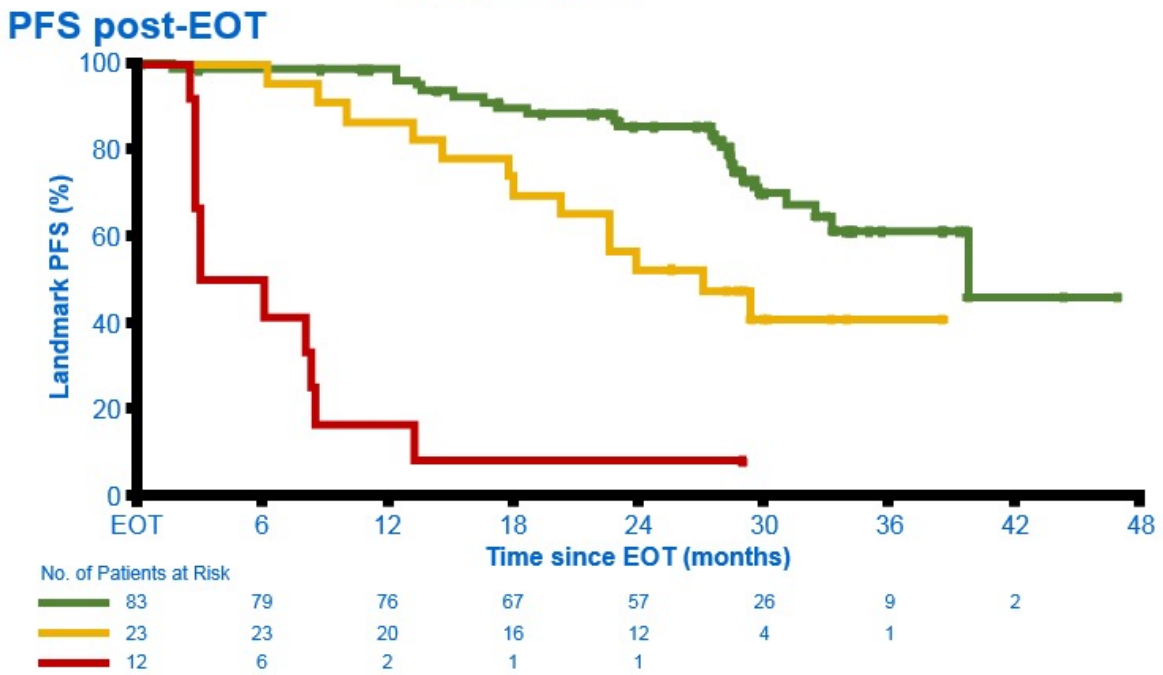
- With this 5-year update we can now accurately define the median PFS of VenR-treated patients
- No new safety signals were identified 3 years after EOT with longer follow up and patients are outside of the adverse event reporting window

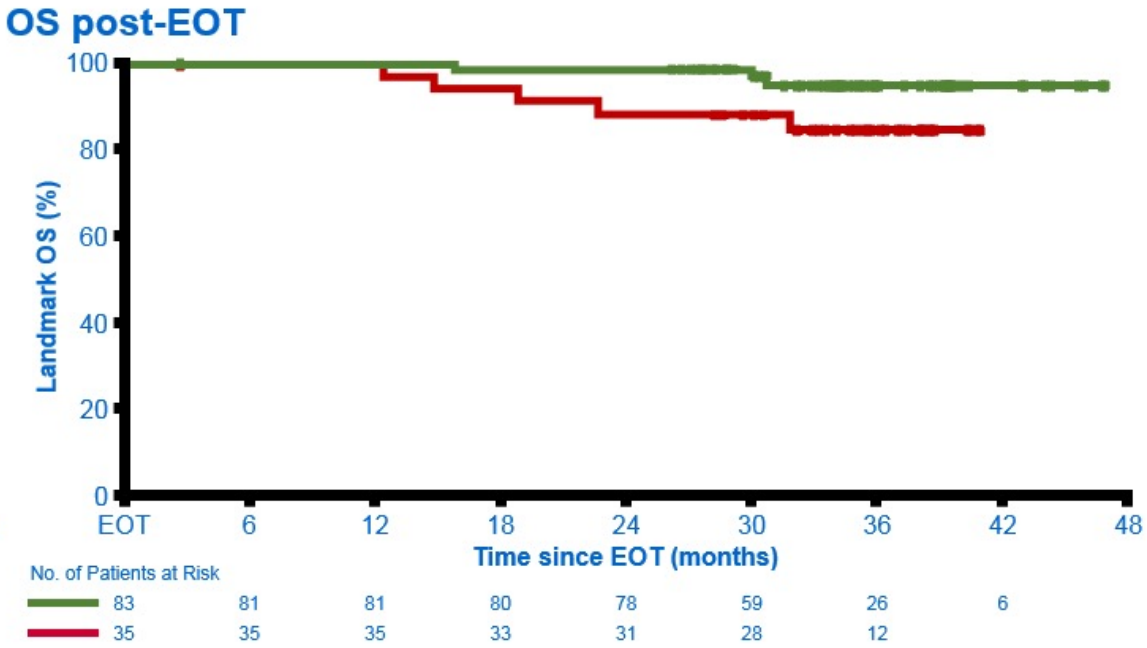
*Unstratified HR=0.21;‡Unstratified HR=0.42; †P-values are descriptive only; +, censored
BR, bendamustine-rituximab; CI, confidence interval; EOT, end of treatment; HR, hazard ratio; NE, not evaluable; OS, overall survival; PFS, progression-free survival; VenR, venetoclax-rituximab; yr, year

MURANO: uMRD at EOT is associated with improved outcomes post-EOT in the VenR arm

	PFS (95% CI) since EOT	
Category	24 month	36 month
uMRD ($<10^{-4}$)* (N=83)	85.4% (77.4, 93.4)	61.3% (47.3, 75.2)
Low-MRD+ (10^{-4}–10^{-2}) (N=23)	52.2% (31.8, 72.6)	40.7% (19.2, 62.2)
High-MRD+ ($>10^{-2}$) (N=12)	8.3% (0.0, 24.0)	NE
	HR (95% CI)	P-value
uMRD vs Low-MRD+	0.40 (0.18, 0.91)	0.0246
uMRD vs High-MRD+	0.02 (<0.01, 0.18)	<0.0001
Low-MRD+ vs High-MRD+	0.32 (0.10, 0.99)	0.0410

	OS (95% CI) since EOT	
Category	24 month	36 month
uMRD ($<10^{-4}$)* (N=83)	98.8% (96.4, 100.0)	95.3% (90.0, 100.0)
MRD ($\geq 10^{-4}$) (N=35)	88.6% (78.0, 99.1)	85.0% (72.8, 97.2)
	HR (95% CI)	P-value
uMRD vs MRD	NS	NS





CI, confidence interval; EOT, end of treatment; NE, not evaluable; NS, not significant; OS, overall survival; PFS, progression-free survival; (u)MRD, (undetectable) minimal residual disease; VenR, venetoclax-rituximab

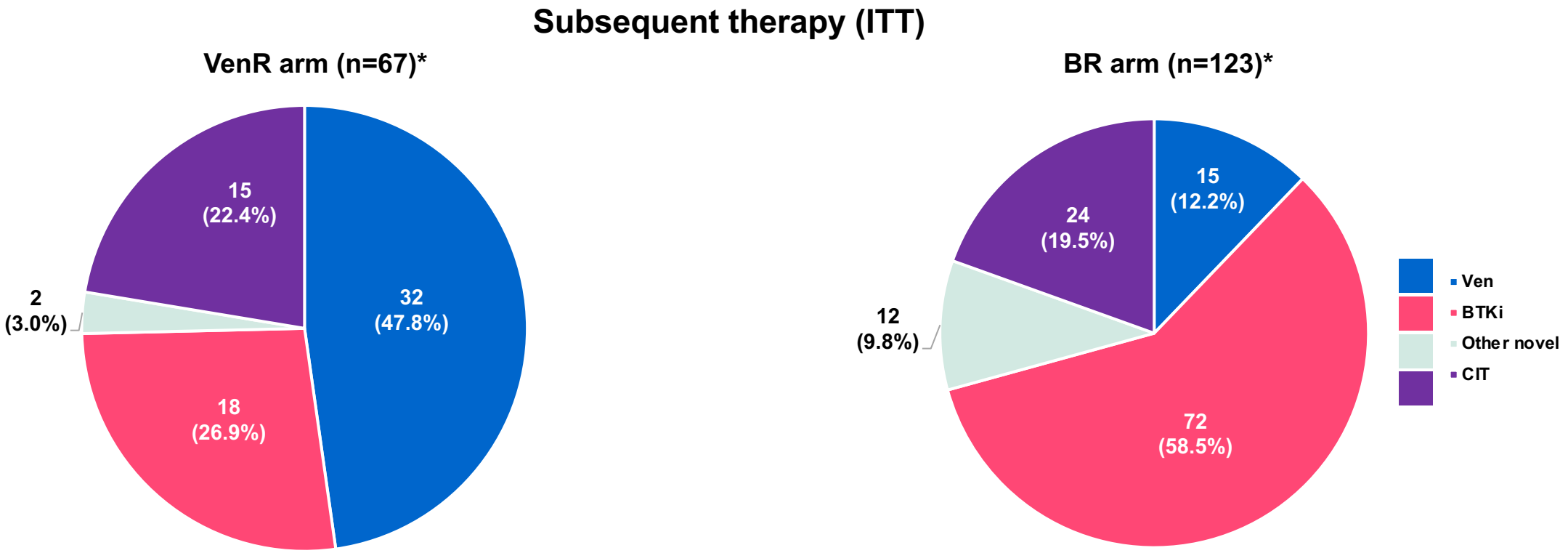
Poster No. 3139

Efficacy of Subsequent Novel Targeted Therapies, Including Repeated Venetoclax-Rituximab (VenR), in Patients With Relapsed/Refractory Chronic Lymphocytic Leukemia (R/R CLL) Previously Treated With Fixed-duration VenR in the MURANO Study

Rosemary Harrup*[1], Carolyn Owen[2], James D'Rozario[3], Tadeusz Robak[4], Arnon P. Kater[5], Marco Montillo[6], Javier de la Serna[7], Marek Trneny[8], Su Y. Kim[9], Edward Bataillard[10], Marcus Lefebure[10], Michelle Boyer[10], John F. Seymour[11]

ASH 2020, abstract 3139

Subsequent therapies

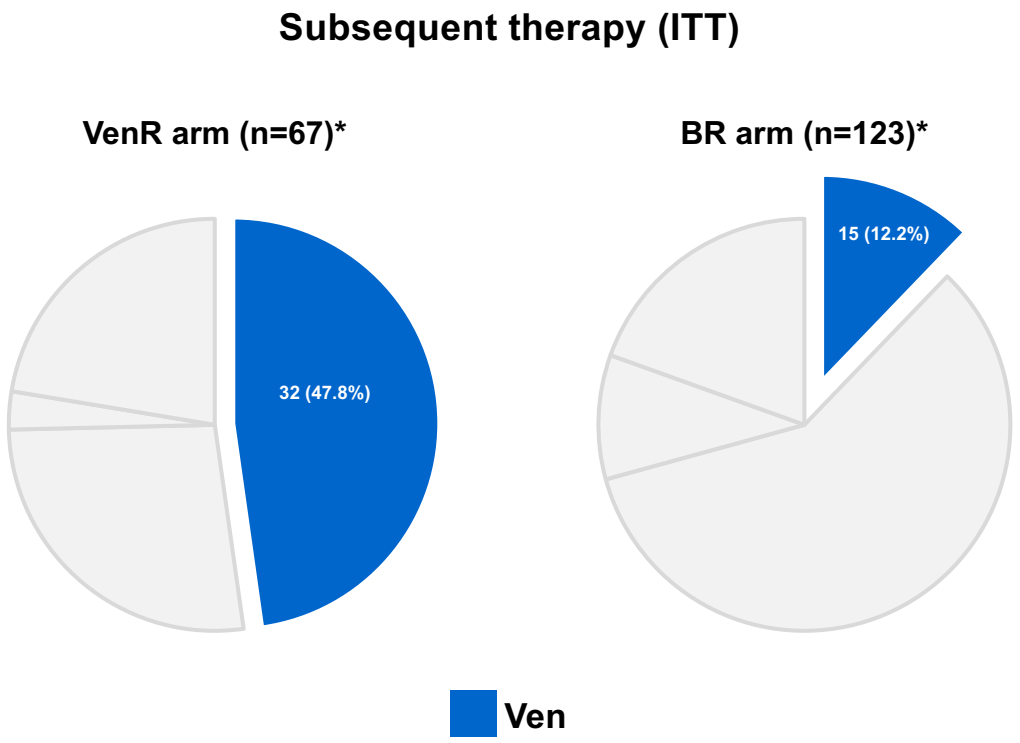


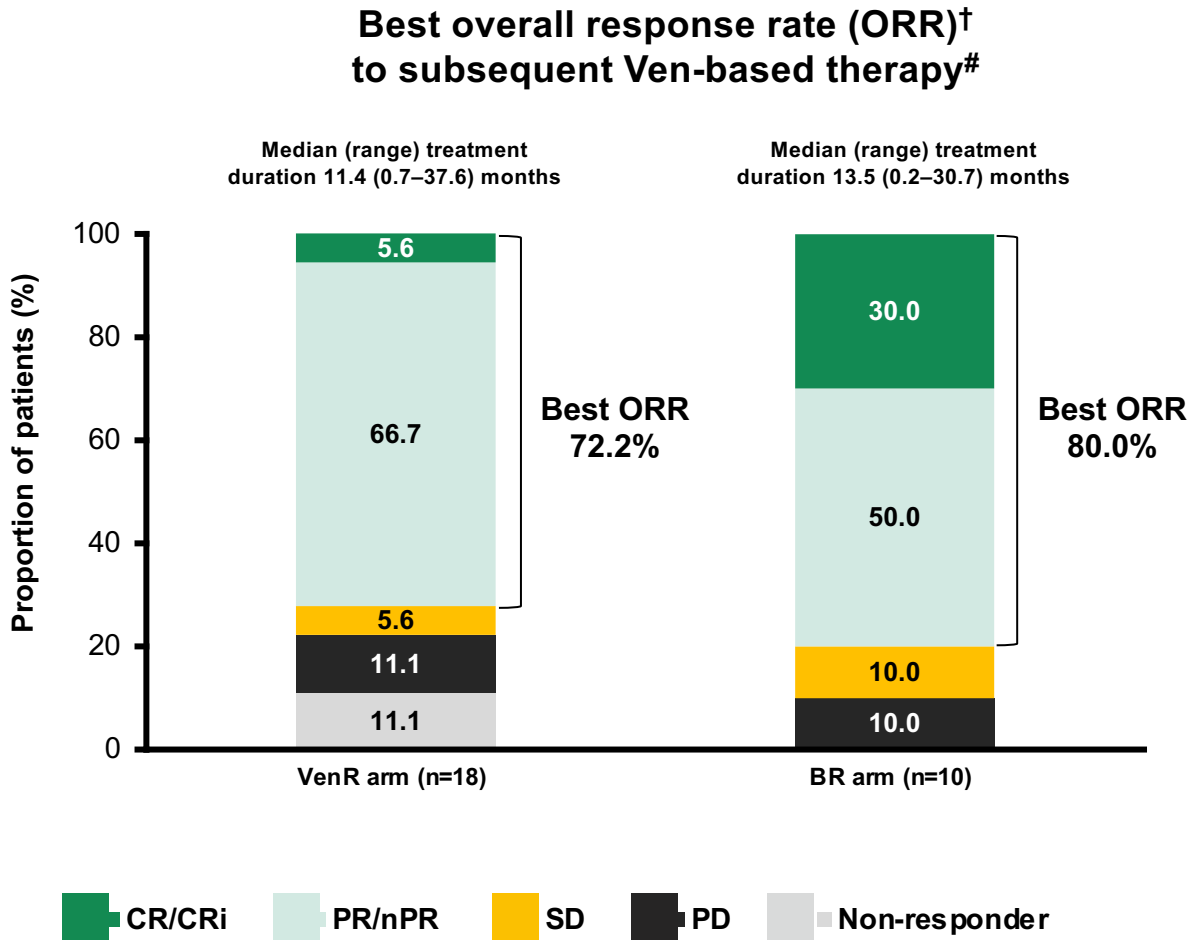
*Patients treated

BR, bendamustine-rituximab; BTKi, Bruton tyrosine kinase inhibitor; CIT, chemoimmunotherapy; ITT, intent-to-treat; Ven, venetoclax; VenR, venetoclax-rituximab

Harrup, et al: ASH 2020, abst 3139

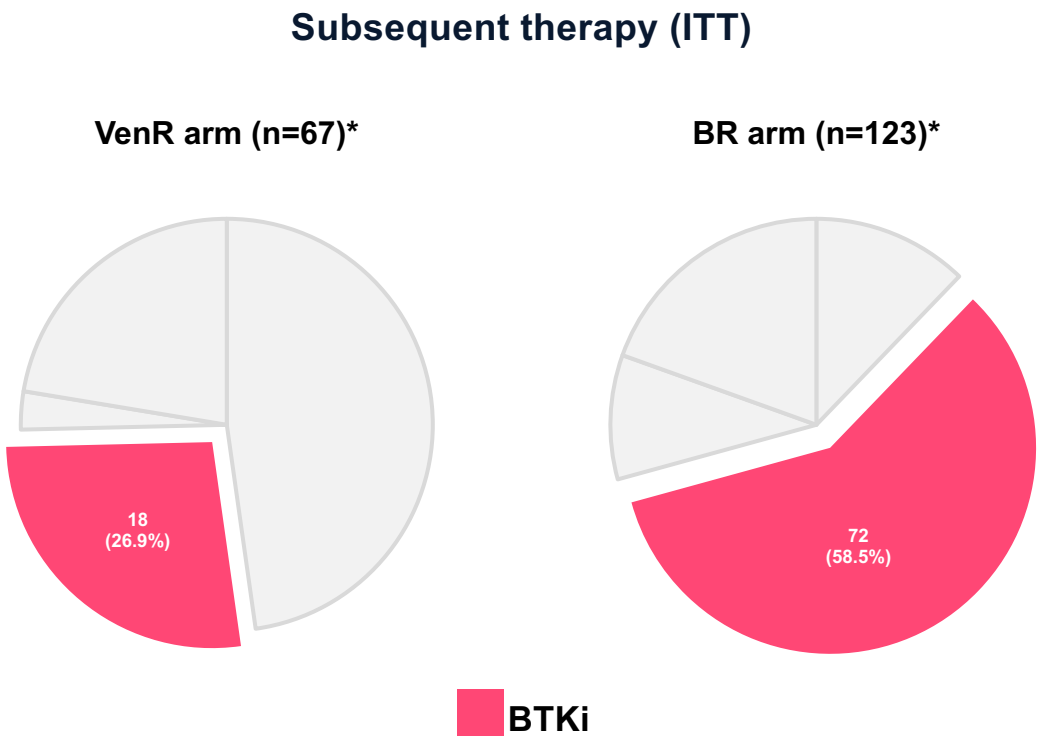
Response rates to subsequent Ven-based therapy were high

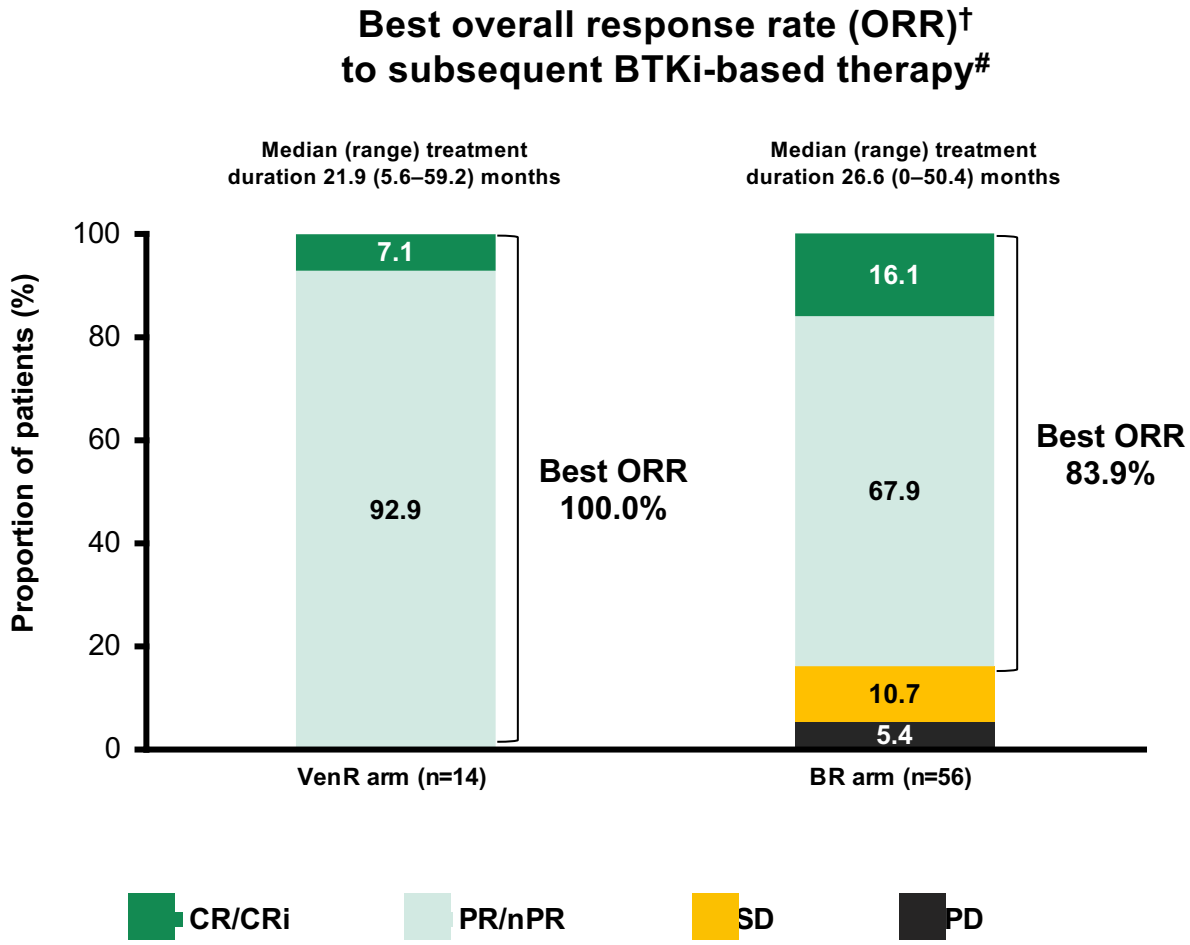




Harrup, et al: ASH 2020, 3139

Response rates to subsequent BTKi-based therapy were high





Harrup, et al: ASH 2020, abst 3139

Response to subsequent therapies following venetoclax discontinuation

Post-Ven Therapy	BTKi	BTKi	BTKi	PI3Ki	CAR-T	Anti-CD20 abs
Agents	Ibrutinib Acalabrutinib	Ibrutinib Acalabrutinib Non-covalent BTKi	Ibrutinib Acalabrutinib Non-covalent BTKi	Idelalisib Duvelisib	Anti-CD19	Rituximab Obinutuzumab Ofatumumab
Pre-Ven Exposure	BTKi-naïve	BTKi-exposed BTKi-resistant	BTKi-exposed BTKi-intolerant	PI3Ki-naïve BTKi-exposed	BTKi-exposed	
Patient Number	44	20	10	17	18	19
ORR	83.9%	53%	70%	46.9%	66.6%	32%
CR	9%	6.6%	20%	5.9%	33.3%	16%
PR	56.8%	26.4%	30%	35.2%	33.3%	16%
PR-L	18.1%	20%	20%	5.8%	0%	0%
SD	11.6%	20%	-	23.7%	5.7%	32%
PD	4.5%	27%	30%	29.4%	27.7%	37%

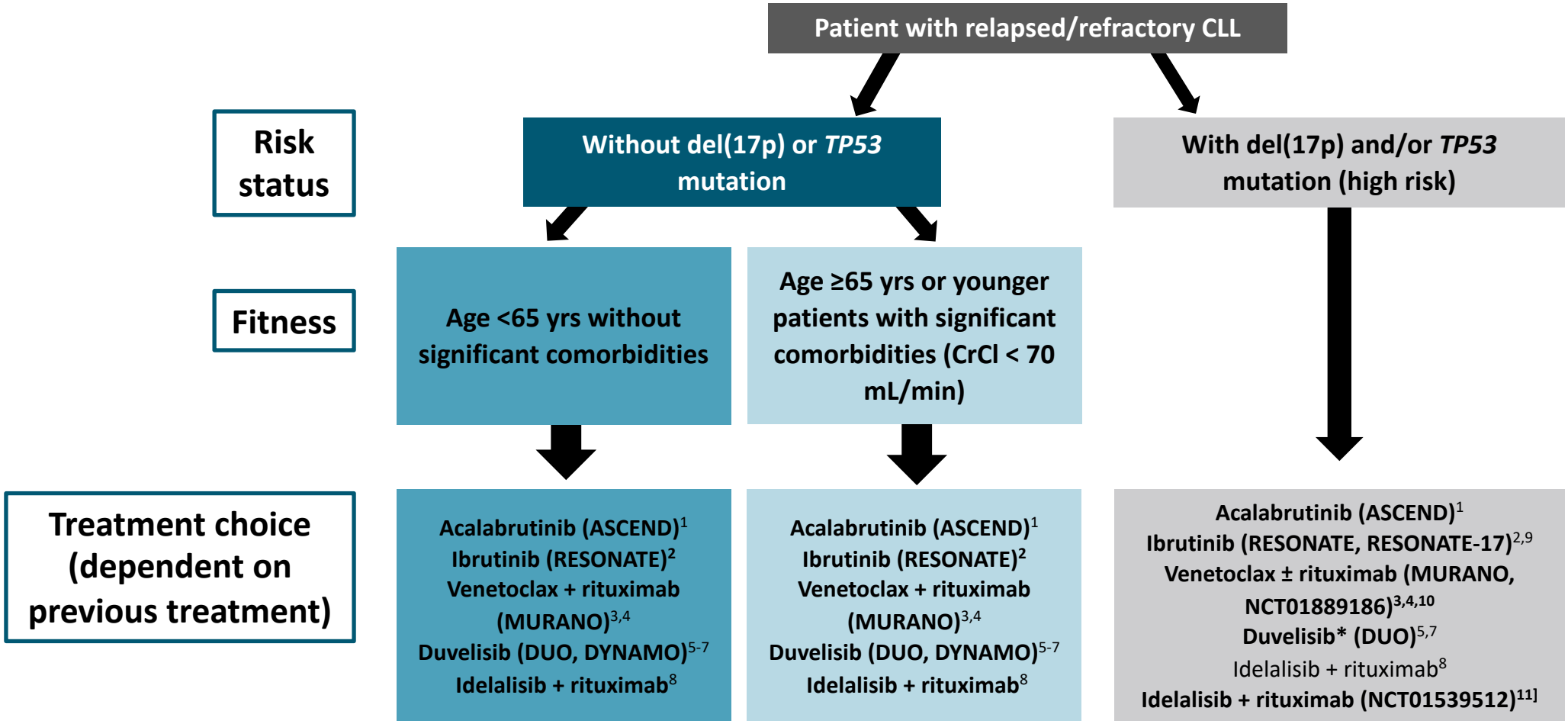
ORR BTKi (naïve) vs. BTKi (exposed, resistant), p=.001

Harrup, et al: ASH 2020, abst 3139

Relapsed/Refractory CLL: Case 2

- 75 y/o male who was diagnosed with CLL 11 years ago
- 7 years ago, he developed anemia and lymphadenopathy requiring therapy
  - IGHV Mutated, FISH: del 11q-
- He received Ibrutinib 420 mg/day – good tolerance
- 3 years ago, he had rising lymphocytosis with new anemia (Hgb 9.0 gm/dl) and lymphadenopathy - (FISH: del 11q -)
- He received Venetoclax/Rituximab –
  - but now progressed (FISH del 11q- with new del 17p-)
- Options left for therapy and combinations:
  - ? PI3K inhibitors, other BTK inhibitors, other anti-CD20 antibody combinations, clinical trials – CAR-T cells?

Treatment Recommendations for Relapsed/Refractory CLL



1. Ghia. JCO. 2020;38:2849. 2. Munir. Am J Hematol. 2019;94:1353. 3. Kater. JCO. 2019;37:269. 4. Kater. JCO. 2020;38:4042. 5. Flinn. Blood. 2018;132:2446. 6. Flinn. JCO. 2019;37:912. 7. Davids. Clin Cancer Res. 2020;26:2096. 8. Furman. NEJM. 2014;370:997. 9. O'Brien. Lancet Oncol. 2016;17:1409. 10. Stilgenbauer. JCO. 2018;36:1973. 11. Sharman. JCO. 2019;37:1391.

PI3K inhibitors Currently Approved for Hematologic Cancers

Idelalisib

PI3K delta Inhibitor

FDA

Indicated for relapsed CLL after failing 2 prior therapies

Duvelisib

PI3K dual delta/gamma Inhibitor

FDA

Indicated for the treatment of relapsed CLL after failing 2 prior therapies.

Copanlisib

PI3 kinase alfa Inhibitor

FDA

Not FDA approved for relapsed CLL treatment

Umbralisib

Dual PI3K and CK1e (casein kinase 1epsilon) Inhibitor

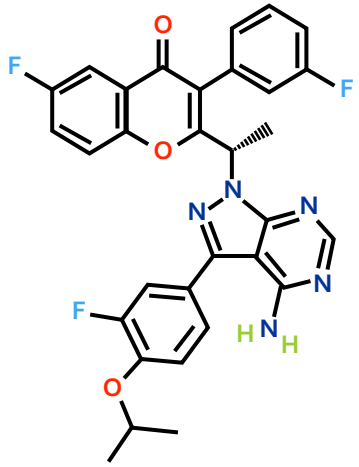
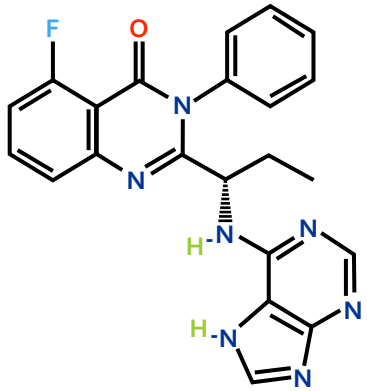
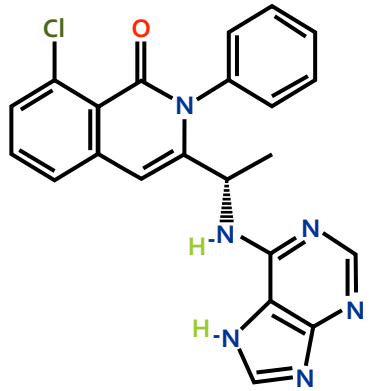
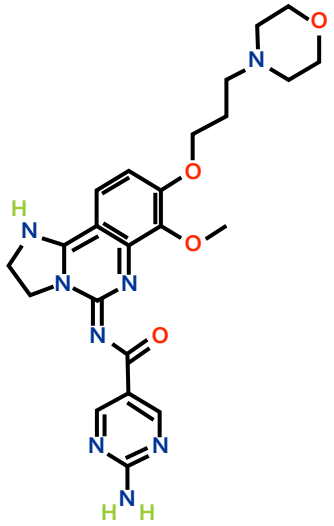
FDA – not yet approved for R/R CLL

Phase 3 Study of Umbralisib Combined With Ublituximab vs Obinutuzumab Plus Chlorambucil in Patients With Chronic Lymphocytic Leukemia: Results From UNITY-CLL

John G. Gribben, MD DSc[1], Wojciech Jurczak, MD, PhD[2], Ryan W. Jacobs, MD[3], Sebastian Grosicki, MD, PhD[4], Krzysztof Giannopoulos, MD, PhD[5], Tomasz Wrobel, MD PhD[6], Syed F. Zafar, MD[7], Jennifer L. Cultrera, MD[8], Suman Kambhampati, MD[9], Alexey Danilov, MD[10], John M. Burke, MD[11], Jerome Goldschmidt, MD[12], Douglas F. Beach, MD[13], Scott F. Huntington, MD, MPH[14], Javier Pinilla Ibarz, MD, PhD[15], Jeff P Sharman, MD[16], Tanya Siddiqi, MD[17], Danielle M. Brander, MD[18], John M. Pagel, MD PhD[19], Kathryn S. Kolibaba, MD[20], Monika Dlugosz-Danecka, MD, PhD[2], Nilanjan Ghosh, MD, PhD[3], Peter Sportelli, BS[21], Hari P. Miskin, MSc[21], Owen A. O'Connor, MD, PhD[21], Michael S. Weiss[21] and Ian W. Flinn, MD, PhD[22]

[1]Centre for Haemato-Oncology, Barts Cancer Institute, Queen Mary University of London, London, United Kingdom; [2]Maria Sklodowska-Curie National Research Institute of Oncology, Krakow, Poland; [3]Department of Hematology, Lymphoma Division, Levine Cancer Institute, Charlotte, NC; [4]Department of Hematology and Cancer Prevention, School of Public Health, Silesian Medical University, Katowice, Poland; [5]Medical Univ. of Lublin, Lublin, Poland; [6]Department of Hematology, Wroclaw Medical University, Wroclaw, Poland; [7]Florida Cancer Specialists South / Sarah Cannon Research Institute, Fort Myers, FL; [8]Florida Cancer Specialists North / Sarah Cannon Research Institute, St. Petersburg, FL; [9]Sarah Cannon Research Institute At Research Medical Ctr, Kansas City, MO; [10]Knight Cancer Institute, Oregon Health & Science University, Duarte, CA; [11]US Oncology Hematology Research Program, Rocky Mountain Cancer Centers, Aurora, CO; [12]Blue Ridge Cancer Centers / US Oncology Research, Blacksburg, VA; [13]Pennsylvania Hospital, Philadelphia, PA; [14]Yale Cancer Center, New Haven, CT; [15]Department of Immunology, Moffitt Cancer Center, Tampa, FL; [16]Willamette Valley Cancer Institute and US Oncology Research, Eugene, OR; [17]Department of Hematology and Hematopoietic Cell Transplantation, City of Hope National Medical Center, Duarte, CA; [18]Duke Cancer Institute, Duke University Health System, Durham, NC; [19]Swedish Cancer Institute, Seattle, WA; [20]Compass Oncology / US Oncology Research, Vancouver, WA; [21]TG Therapeutics, Inc., New York, NY; [22]Sarah Cannon Research Institute/Tennessee Oncology, Nashville, TN

Umbralisib Is a Dual Inhibitor of PI3Kδ and CK1ε

Umbralisib[1]	Idelalisib[1]	Duvelisib[1]	Copanlisib[2]
			

Isoform	K_d (nM)			
PI3kα	>10000	600	40	0.04
PI3Kβ	>10000	19	0.89	1.5
PI3Kγ	1400	9.1	0.21	0.31
PI3Kδ	6.2	1.2	0.047	0.068
CK1ε	180	>30,000	>30,000	>6,000

- Umbralisib is an oral, once daily, dual inhibitor of PI3Kδ and CK1ε
- Umbralisib has >1000-fold greater selectivity for PI3Kδ compared to α and β isoforms[3]
- Umbralisib is also **>200-fold** more selective for PI3Kδ relative to **PI3Kγ**

PI3k: phosphoinositide 3-kinase; CK1ε: casein kinase 1ε.

1. Burris HA, et al. *Lancet Oncol.* 2018;19(4):486-496. 2. Data on File [TGR 001]. TG Therapeutics, Inc, New York City, NY.

UNITY-CLL Study Design (UTX-TGR-304)

Focus is on primary analysis:U2 vs O+Chl (n=421)

Patients (N=421)
- Treatment-naïve or relapsed/refractory CLL
- Requiring treatment per iwCLL criteria
- Adequate organ function
- ECOG PS ≤2

Stratification
- del(17p): present vs absent
- Treatment status: treatment-naive vs previously treated

RANDOMIZE 1:1

Umbralisib[a] + Ublituximab[b] (U2)
[a]800 mg PO QD
[b]900 mg IV on D1/2, 8, 15 of Cycle 1, D1 of Cycles 2 – 6, D1 Q3 cycles

Obinutuzumab[c] + Chlorambucil[d] (O+Chl)
[c]1000 mg IV on D1/2, 8, 15 of Cycle 1, D1 of cycles 2 – 6
[d]0.5 mg/kg PO on D1 and D15 Cycles 1 – 6

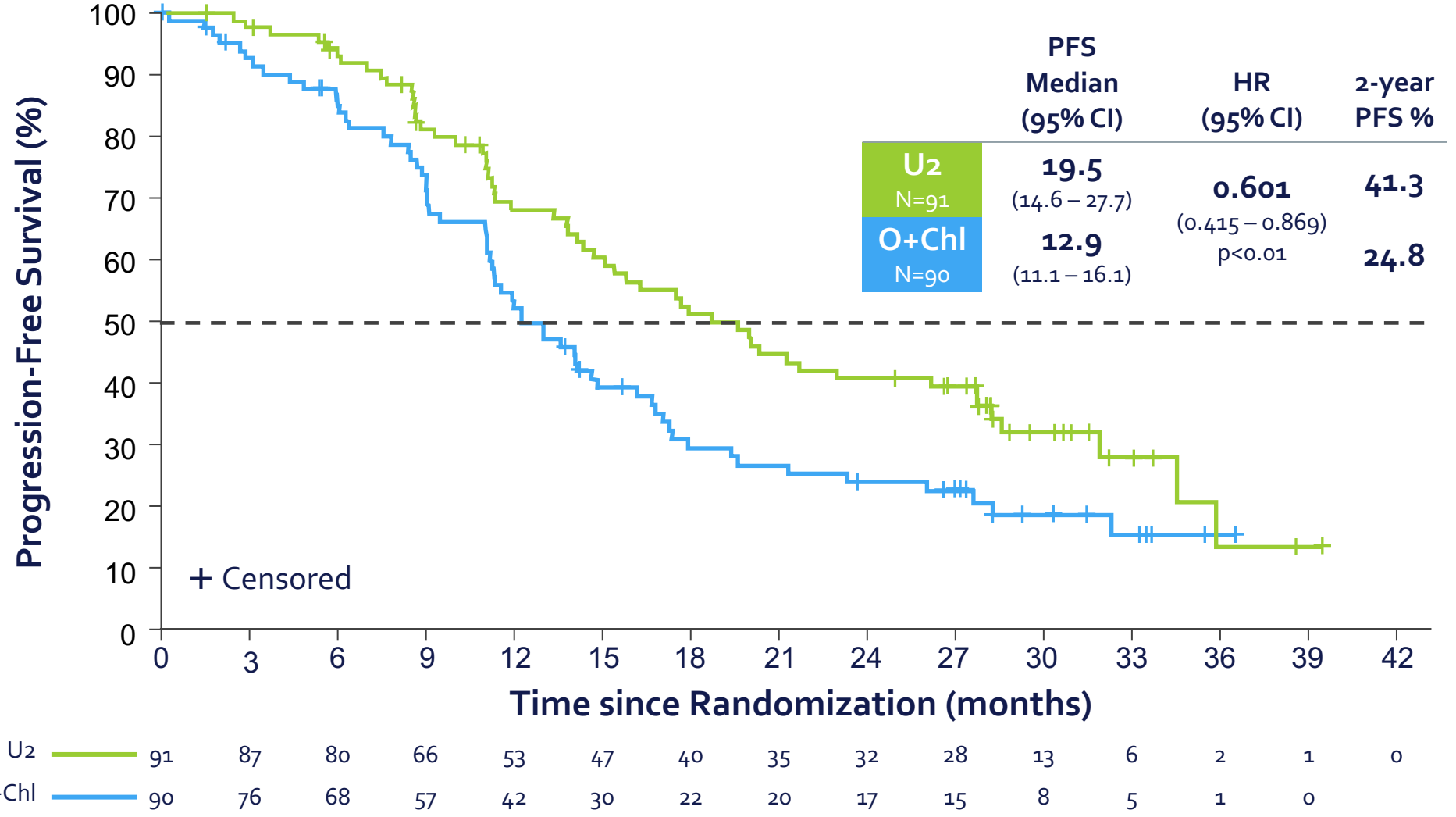
Primary endpoint
- IRC-assessed PFS U2 vs O+Chl

Secondary endpoints
- IRC-assessed:
  - ORR, CR, DOR
- uMRD (central)
- Safety

- Interim analyses for PFS were performed at:
  - 50% IRC-assessed PFS events to assess futility only
  - 75% IRC-assessed PFS events to evaluate superiority of U2 vs O+Chl

CR: complete response; DOR: duration of response; DSMB: data safety monitoring board; ECOG PS: Eastern Cooperative Oncology Group performance status; IRC: independent review committee; IV: intravenously; ORR: overall response rate; PFS: progression-free survival, PO: orally; Q3: every 3; QD: daily; uMRD: undetectable minimal residual disease; D1/2 signifies split doses ublituximab (150 mg / 750 mg) obinutuzumab (100 mg /900 mg); cycles were 28 days. U2 combination continued until progressive disease, unacceptable toxicity, or withdrawal of consent.

UNITY-CLL: IRC-Assessed Progression-Free Survival Previously Treated Population



CI: confidence interval; HR: hazard ratio; IRC: independent review committee; O+Chl: obinutuzumab + chlorambucil; PFS: progression-free survival; U2: umbralisib + ublituximab

UNITY-CLL: Events of Clinical Interest – PI3K specific

AEs, n (%)	U2 N=206		O+Chl N=200	
	Any	Grade ≥3	Any	Grade ≥3
ALT elevation	35 (17.0)	17 (8.3)	9 (4.5)	2 (1.0)
AST elevation	28 (13.6)	11 (5.3)	9 (4.5)	4 (2.0)
Colitis (non-infectious)[a]	10 (4.9)	4 (1.9)	0	0
Colitis (infectious)[a]	1 (0.5)	1 (0.5)	1 (0.5)	1 (0.5)
Pneumonitis	6 (2.9)	1 (0.5)	1 (0.5)	0
Rash[a]	26 (12.6)	5 (2.4)	10 (5.0)	1 (0.5)
Opportunistic Infections[a]	29 (14.1)	12 (5.8)	11 (5.5)	3 (1.5)

[a]Group includes multiple MedDRA terms. AE: adverse event; O+Chl: obinutuzumab + chlorambucil; U2: umbralisib + ublituximab.

ALPINE: Phase III Randomized Trial of Zanubrutinib vs Ibrutinib in Relapsed/Refractory CLL or SLL – 1º Outcome

	Zanubrutinib (n = 207), n (%)	Ibrutinib (n = 208), n (%)
Primary endpoint: ORR (PR + CR)	162 **(78.3)** 95% CI: 72.0, 83.7	130 **(62.5)** 95% CI: 55.5, 69.1
	Superiority 2-sided *p* = 0.0006 compared with prespecified alpha of 0.0099	
CR/CRi	4 (1.9)	3 (1.4)
nPR	1 (0.5)	0
PR	157 (75.8)	127 (61.1)
ORR (PR-L + PR + CR)	*183 (88.4)*	*169 (81.3)*
PR-L	21 (10.1)	39 (18.8)
SD	17 (8.2)	28 (13.5)
PD	1 (0.5)	2 (1.0)
Discontinued or new therapy prior to first assessment	6 (2.9)	9 (4.3)
	Del(17p) (n = 24), n (%)	**Del(17p) (n = 26), n (%)**
ORR (PC + CR)	20 (83.3)	14 (53.8)

CI, confidence interval; CR, complete response; CRi, complete response with incomplete bone marrow recovery; nPR, nodular partial response; ORR, overall response rate; PD, progressive disease; PR, partial response; PR-L, partial response with lymphocytosis; SD, stable disease

Hillmen P et al. EHA 2021;Abstract LB1900.

Take-Home Messages on R/R CLL in 2021

- Continuous novel agent monotherapy remains a viable approach
- Prospective data support continuous venetoclax monotherapy in patients progressing on ibrutinib
- Venetoclax + R is a 2-year time-limited therapy with durable benefit post CIT
- Many new promising strategies are on the horizon, including ven + BTKi, ven + PI3Ki, BTKi + PI3Ki, and reversible BTKi to overcome irreversible BTKi resistance
- Cellular therapies (BMT and CAR-T) should be considered in later therapy lines especially for fit patient with *TP53* aberrant disease
- Active participation in clinical trials remains critical