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MEETING SUMMARY
ASH 2019, Orlando, USA

Dr. Alexey V. Danilov, MD, PhD
OHSU Knight Cancer Institute, Portland, USA

HIGHLIGHTS ON CHRONIC LYMPHOCYTIC LEUKAEMIA

December 2019

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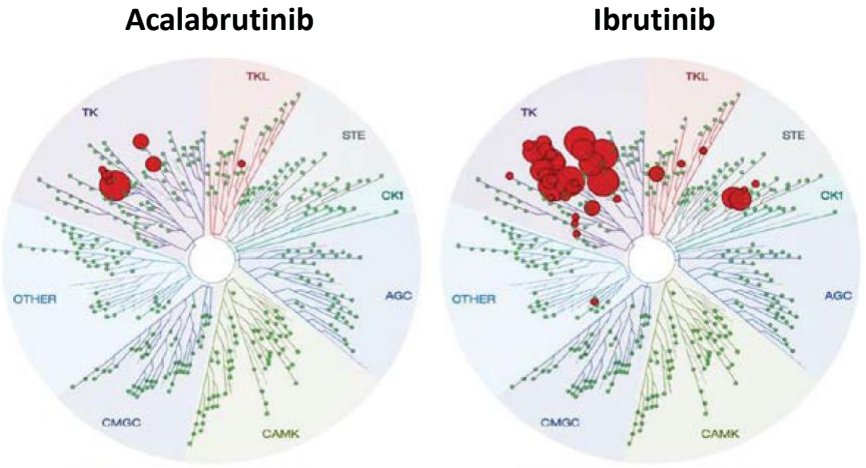
TREATMENT-NAIVE SETTING ACALABRUTINIB TRIALS

BACKGROUND: ACALABRUTINIB

- **Acalabrutinib** is a highly selective, covalent irreversible BTK inhibitor with minimal activity against other kinases[1]
  - Acalabrutinib is more selective for BTK with less off-target kinase inhibition compared with ibrutinib *in vitro*[2]

Kinase Selectivity Profiling at 1 μM



Larger red circles represent stronger inhibition

BTK, Bruton tyrosine kinase

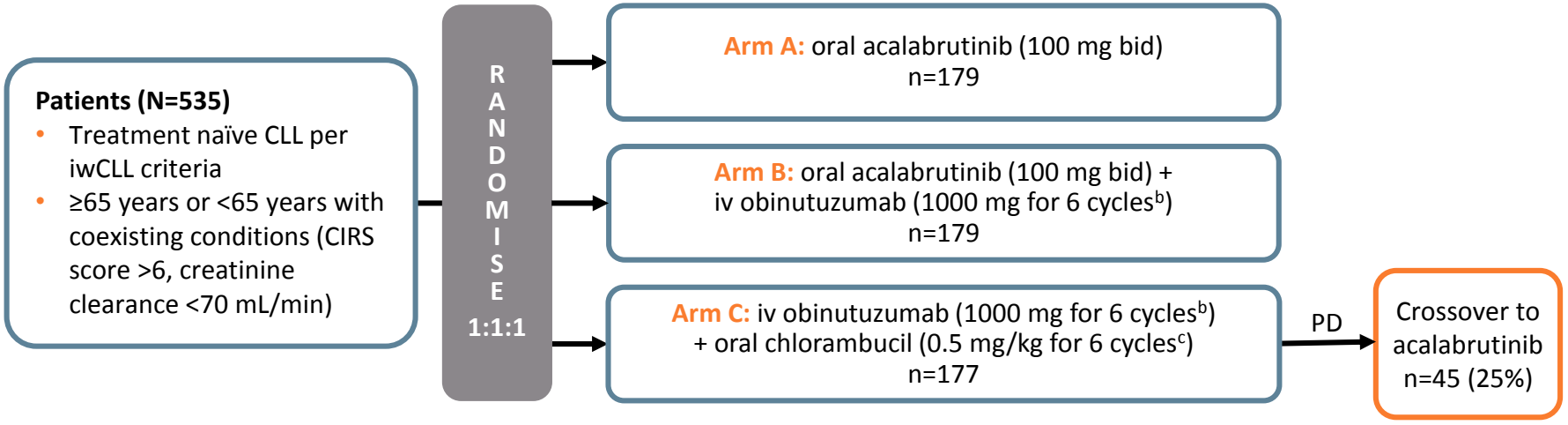
1. Sharman JP, et al. ASH 2019 Abstract #31. 2. Barf T, et al. J Pharmacol Exp Ther 2017; 363:240-52

ELEVATE TN: PHASE 3 STUDY OF ACALABRUTINIB COMBINED WITH OBINUTUZUMAB OR ALONE VS OBINUTUZUMAB PLUS CHLORAMBUCIL IN PATIENTS WITH TREATMENT-NAIVE CLL

Sharman JP, et al. ASH 2019 Abstract #31

ELEVATE TN
STUDY DESIGN

- ELEVATE TN is a multicentre, **open-label phase 3 study**



Stratification: del(17p) status, ECOG PS (≤1 vs 2), geographic region

Primary endpoint: PFS[a] in Arm B vs Arm C
Secondary endpoints: PFS[a] with Arm A vs Arm C, ORR[a], OS, safety

[a] IRC-assessed
[b] 1000 mg on Days 1, 2 (split 100/900), 8, and 15 of Cycle 2, and Day 1 of subsequent 28-day cycles
[c] 0.5 mg/kg on Days 1 and 15 of each 28-day cycle

bid, twice daily; BTK, Bruton tyrosine kinase; CIRS, Cumulative Illness Rating Scale; CLL, chronic lymphocytic leukaemia; ECOG PS, Eastern Cooperative Oncology Group performance status; IRC, independent review committee; iv, intravenous; iwCLL, International Workshop on Chronic Lymphocytic Leukemia; ORR, overall response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival

1. Sharman JP, et al. ASH 2019 Abstract #31. 2. https://clinicaltrials.gov/ct2/show/NCT02475681

ELEVATE TN
INTERIM EFFICACY RESULTS

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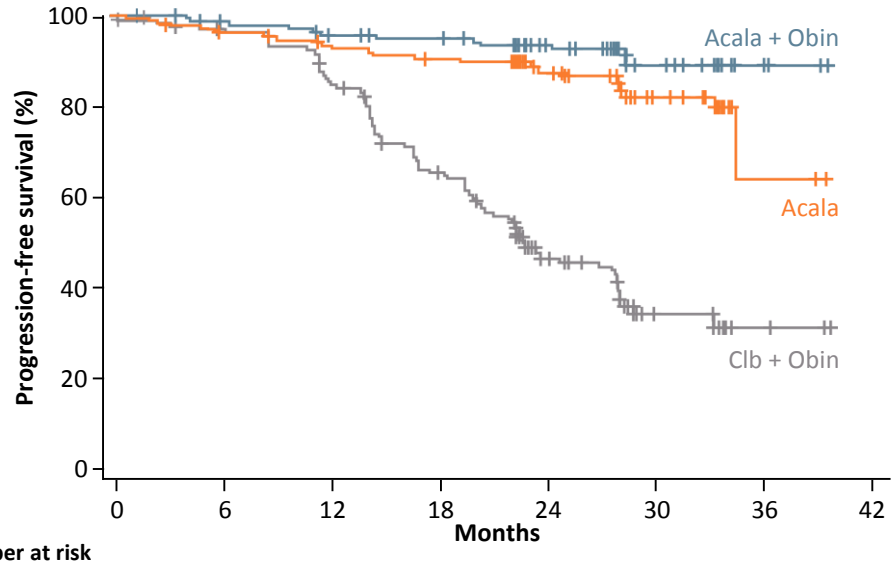
Acalabrutinib + obinutuzumab **reduced the risk of progression or death by 90%** vs obinutuzumab + chlorambucil



	Arm A: acalabrutinib	Arm B: acalabrutinib + obinutuzumab	Arm C: obinutuzumab + chlorambucil
Median follow up, months		28	
Median PFS, months	NR	NR	22.6
HR (95% CI); p value vs Arm C	0.20 (0.13-0.31); p<0.0001	0.10 (0.06-0.18); p<0.0001	
Estimated 30-month PFS, %	82	90	34
Estimated 30-month OS, %	94	95	90
ORR, % (95% CI)	85	94 (89.3-96.5)	79 (71.9-83.9)
p value vs Arm C		p<0.0001	
CR, %	0.6	13	5

Acala, acalabrutinib; CI, confidence interval; Clb, chlorambucil; CR, complete response; HR, hazard ratio; NR, not reached; Obin, obinutuzumab; ORR, overall response rate; OS, overall survival; PFS, progression-free survival

Sharman JP, et al. ASH 2019 Abstract #31

ELEVATE TN
INTERIM SAFETY RESULTS

- AEs were **similar between the acalabrutinib-containing arms**
- **AEs of interest** (acalabrutinib-containing arms vs obinutuzumab + chlorambucil)
  - Any grade atrial fibrillation: 3-4% vs 1%
  - Bleeding
    - Any grade: 39-43% vs 12%
    - Grade ≥3: 2% vs 0%
  - Grade ≥3 hypertension: 2-3% vs 3%

AEs (any grade in ≥30% or grade ≥3 in ≥5% of patients in any arm)

	Acalabrutinib + Obinutuzumab (n=178)		Acalabrutinib (n=179)		Obinutuzumab + Chlorambucil (n=169)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Any, n (%)	171 (96)	125 (70)	170 (95)	89 (50)	167 (99)	118 (70)
Serious, n (%)	69 (39)	58 (33)	57 (32)	53 (30)	37 (22)	33 (20)
Common AEs, n (%)						
Headache	71 (40)	2 (1)	66 (37)	2 (1)	20 (12)	0
Diarrhea	69 (39)	8 (4)	62 (35)	1 (1)	36 (21)	3 (2)
Neutropenia	56 (31)	53 (30)	19 (11)	17 (9)	76 (45)	70 (41)
Nausea	36 (20)	0	40 (22)	0	53 (31)	0
Infusion-related reaction	24 (13)	4 (2)	0	0	67 (40)	9 (5)
Thrombocytopenia	23 (13)	15 (8)	13 (7)	5 (3)	24 (14)	20 (12)
Anemia	21 (12)	10 (6)	25 (14)	12 (7)	20 (12)	12 (7)
Pneumonia	19 (11)	10 (6)	13 (7)	4 (2)	5 (3)	3 (2)
Tumor lysis syndrome[a]	3 (2)	2 (1)	0	0	15 (9)	13 (8)
Febrile neutropenia	3 (2)	3 (2)	2 (1)	2 (1)	9 (5)	9 (5)

[a] By clinical assessment
AE, adverse event
Sharman JP, et al. ASH 2019 Abstract #31

ELEVATE TN
DISCUSSION

- Acalabrutinib + obinutuzumab and acalabrutinib monotherapy **significantly improved PFS** vs obinutuzumab + chlorambucil, with **tolerable safety** in patients with treatment-naive CLL
- Despite cross over for disease progression in the obinutuzumab + chlorambucil arm, a **trend toward improved OS** was observed in both acalabrutinib arms, though **longer follow-up is needed**

CLL, chronic lymphocytic leukaemia; OS, overall survival; PFS, progression-free survival

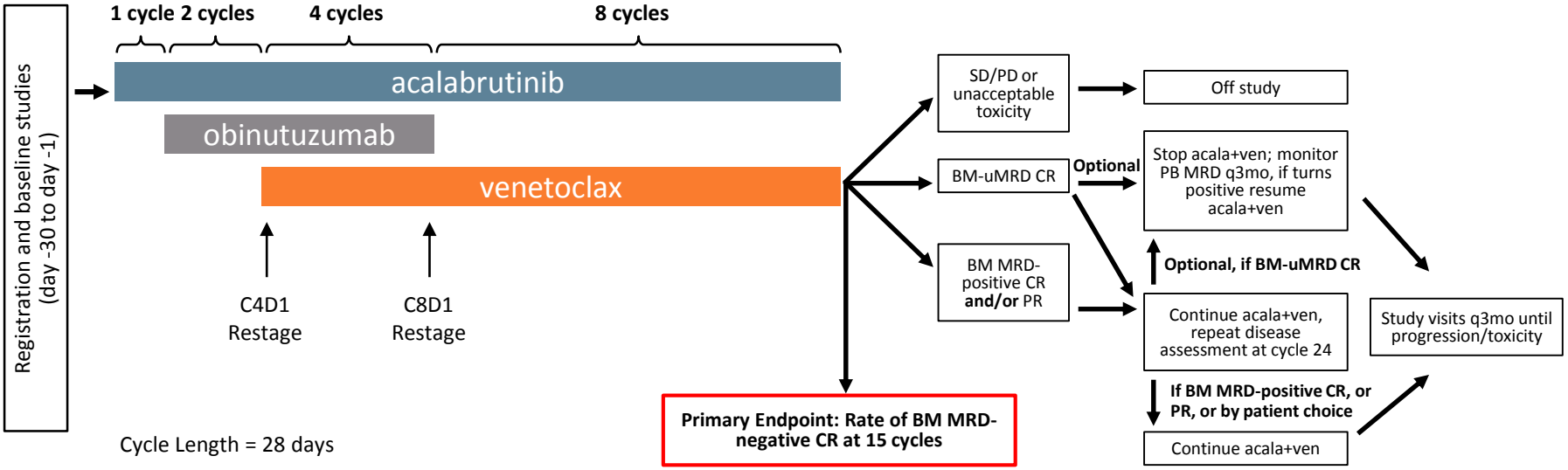
Sharman JP, et al. ASH 2019 Abstract #31

PRELIMINARY SAFETY AND EFFICACY RESULTS FROM A PHASE 2 STUDY OF ACALABRUTINIB, VENETOCLAX AND OBINUTUZUMAB IN PATIENTS WITH PREVIOUSLY UNTREATED CLL

Lampson BL, et al. ASH 2019 Abstract #32

STUDY DESIGN

- Ongoing **open-label, single arm, phase 2** investigator-initiated study
- Hypothesis: a time-limited triplet combination of **acalabrutinib, venetoclax and obinutuzumab (AVO)** could achieve a high rate of BM-uMRD with good tolerability in previously untreated patients with CLL, without restriction by prognostic marker status
  - Requiring treatment by iwCLL criteria, ECOG PS ≤2, creatinine clearance ≥50ml/min, absolute neutrophil count ≥500/mm^3, platelets ≥30,000/mm^3



acala, acalabrutinib; BM-uMRD, undetectable minimal residual disease in the bone marrow; C, cycle; CLL, chronic lymphocytic leukaemia; CR, complete response; D, day; ECOG PS, Eastern Cooperative Oncology Group performance status; iwCLL, International Workshop on Chronic Lymphocytic Leukemia; MRD, minimal residual disease in the peripheral blood; PD, progressive disease; PR, partial response; q3mo, every 3 months; SD, stable disease; ven, venetoclax

Lampson BL, et al. ASH 2019 Abstract #32

INTERIM RESULTS

EFFICACY

Enrolment is completed (N=37)

Efficacy in patients who completed cycle 8 restaging, n (%)	n=24
ORR	24 (100)
CR	5 (25)
PR	18 (75)
uMRD	
PB-uMRD	65%
BM-uMRD	12 (50)
BM-uMRD CR	3 (13)
ORR in TP53-aberrant patients	n=8
CR	2 (25)
PR	6 (75)
BM-uMRD	3 (38)

SAFETY

Safety (N=37), %	Total	Grade 1/2	Grade ≥3
Most frequent AEs			
Fatigue	81	78	3
Headache	76	73	3
Bruising	43	43	0
Most frequent grade 3/4 AEs			
Neutropenia	68	36	32
AEs of special interest			
Infusion-related reactions	22	19	3
Laboratory TLS	5	0	5
Atrial fibrillation	3	0	3
Haemorrhage	0	0	0
Febrile neutropenia	0	0	0

AE, adverse event; BM-uMRD, undetectable minimal residual disease in the bone marrow; CR, complete response; ORR, overall response rate; PB-uMRD, undetectable minimal residual disease in the peripheral blood; PR, partial response; TLS, tumour lysis syndrome; TP53, tumour protein 53; uMRD, undetectable minimal residual disease

Lampson BL, et al. ASH 2019 Abstract #32

DISCUSSION

- Preliminary data suggest that even at an early response evaluation after 8 cycles of therapy (including only 4 months of venetoclax), **first-line AVO leads to a high proportion of BM-uMRD and CR**, including patients with TP53-aberrant disease
- The **AE profile is favourable**, with a low rate of infusion reactions and no significant cardiac or bleeding toxicities
- AVO will be studied head-to-head against chemoimmunotherapy and the venetoclax and obinutuzumab doublet in the **phase 3 CL-311 trial** (NCT03836261), which is currently enrolling

AE, adverse event; AVO, acalabrutinib, venetoclax and obinutuzumab; BM-uMRD, undetectable minimal residual disease in the bone marrow; CR, complete response; TP53, tumour protein 53

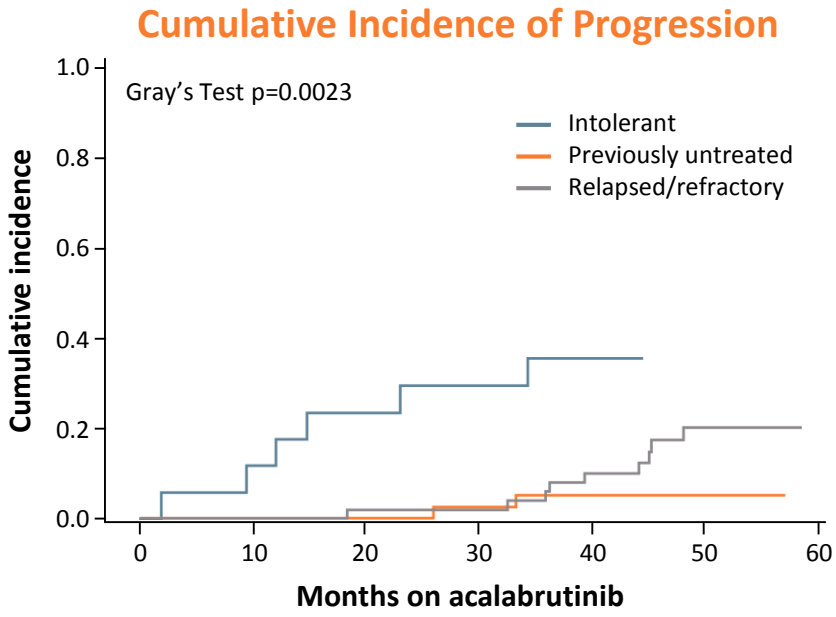
Lampson BL, et al. ASH 2019 Abstract #32

RESISTANCE TO ACALABRUTINIB IN CLL IS MEDIATED PRIMARILY BY *BTK* MUTATIONS

Woyach J, et al. ASH 2019 Abstract #504

CLL RELAPSE ON ACALABRUTINIB IS MEDIATED BY MUTATIONS IN BTK

- Deep sequencing in a phase 1b/2 study showed CLL relapse on acalabrutinib is mediated predominantly by **mutations in BTK similar to ibrutinib**
  - While not unexpected, this is significant as resistant patterns could be different given the more selective nature of acalabrutinib as well as potentially higher BTK occupancy over time due to twice daily dosing
- Monitoring for BTK resistance offers the opportunity to intervene clinically before symptomatic disease



BTK, Bruton tyrosine kinase; CLL, chronic lymphocytic leukaemia
Woyach J, et al. ASH 2019 Abstract #504

DISCUSSION AND INTERPRETATION

CLINICAL INTERPRETATION
FIRST-LINE ACALABRUTINIB IN CLL

- The first-line acalabrutinib data in CLL follow the ASCEND data, which established efficacy of acalabrutinib in patients with R/R CLL.[1-4]
  - **Acalabrutinib** therefore becomes an **additional therapeutic option for patients with CLL in both settings**
- The PFS benefit of added obinutuzumab is provocative but will require confirmation with longer follow-up
- Acalabrutinib **safety data is encouraging**, with low frequency of hypertension and atrial fibrillation, and will inform the BTK inhibitor choice
- Similar to ibrutinib, **resistance** to acalabrutinib in CLL is explained by mutations in BTK, thus allowing monitoring to predict clinical relapses[3]
- Acalabrutinib-based triplet **combinations** are highly efficacious[2]
  - Ongoing large studies will clarify their future role

1. Sharman JP, et al. ASH 2019 Abstract #31. 2. Lampson BL, et al. ASH 2019 Abstract #32. 3. Woyach J, et al. ASH 2019 Abstract #504. 4. Ghia P, et al. EHA 2019 Abstract #LB2606

BTK, Bruton tyrosine kinase; CLL, chronic lymphocytic leukaemia; PFS, progression-free survival; R/R, relapsed/refractory

R/R SETTING
VENETOCLAX-RITUXIMAB

FOUR-YEAR ANALYSIS OF MURANO STUDY CONFIRMS SUSTAINED BENEFIT OF TIME-LIMITED VenR IN R/R CLL

Seymour JF, et al. ASH 2019 Abstract #355

MURANO
BACKGROUND AND STUDY DESIGN

- MURANO is a **randomised phase 3 study** comparing fixed-duration venetoclax + rituximab (VenR) vs standard bendamustine + rituximab (BR) in R/R CLL[1]
  - Patients were randomised to:
    - 6 cycles of VenR followed by venetoclax 400 mg once daily for 2 years

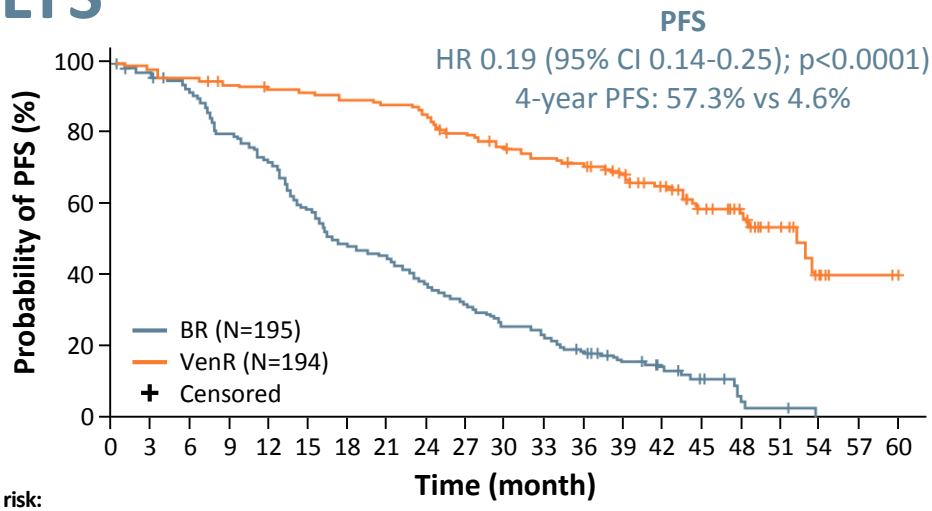
      OR
    - 6 cycles of BR

- In MURANO, VenR has previously shown **superior PFS** versus BR[2]
  - Continued PFS benefit was seen with longer follow-up and after all patients had completed therapy[3]
  - At **ASH 2019**, data at a **median follow-up of 48 months** were presented, when all patients had been off venetoclax treatment for a median of 22 months[1]

BR, bendamustine-rituximab; CLL, chronic lymphocytic leukaemia; PFS, progression-free survival; R/R, relapsed/refractory; VenR, venetoclax + rituximab

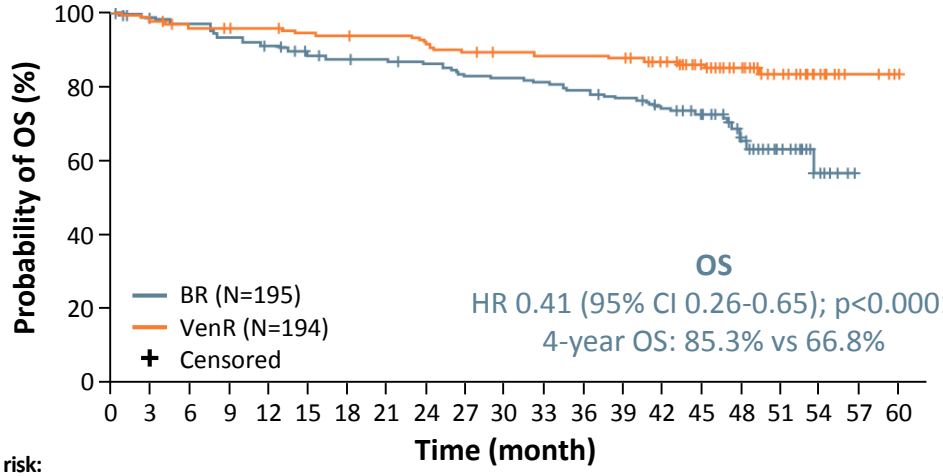
1. Seymour JF, et al. ASH 2019 Abstract #355. 2. Seymour JF, et al. N Engl J Med 2018;378:1107-1120. 3. Kater AP, et al. J Clin Oncol 2019;37:269-277

MURANO RESULTS



No. of patients at risk:

BR	195	178	165	143	129	104	85	80	66	56	45	40	32	23	14	9	3	2
VenR	194	190	185	179	176	174	170	167	161	150	141	134	130	118	101	55	40	14	7	2



No. of patients at risk:

BR	195	181	175	167	162	155	152	150	147	141	140	138	134	130	116	94	58	29	7
VenR	194	190	185	183	182	179	178	176	173	168	166	165	164	163	154	110	84	34	15	6	1

Sustained PFS and OS benefit with VenR over BR

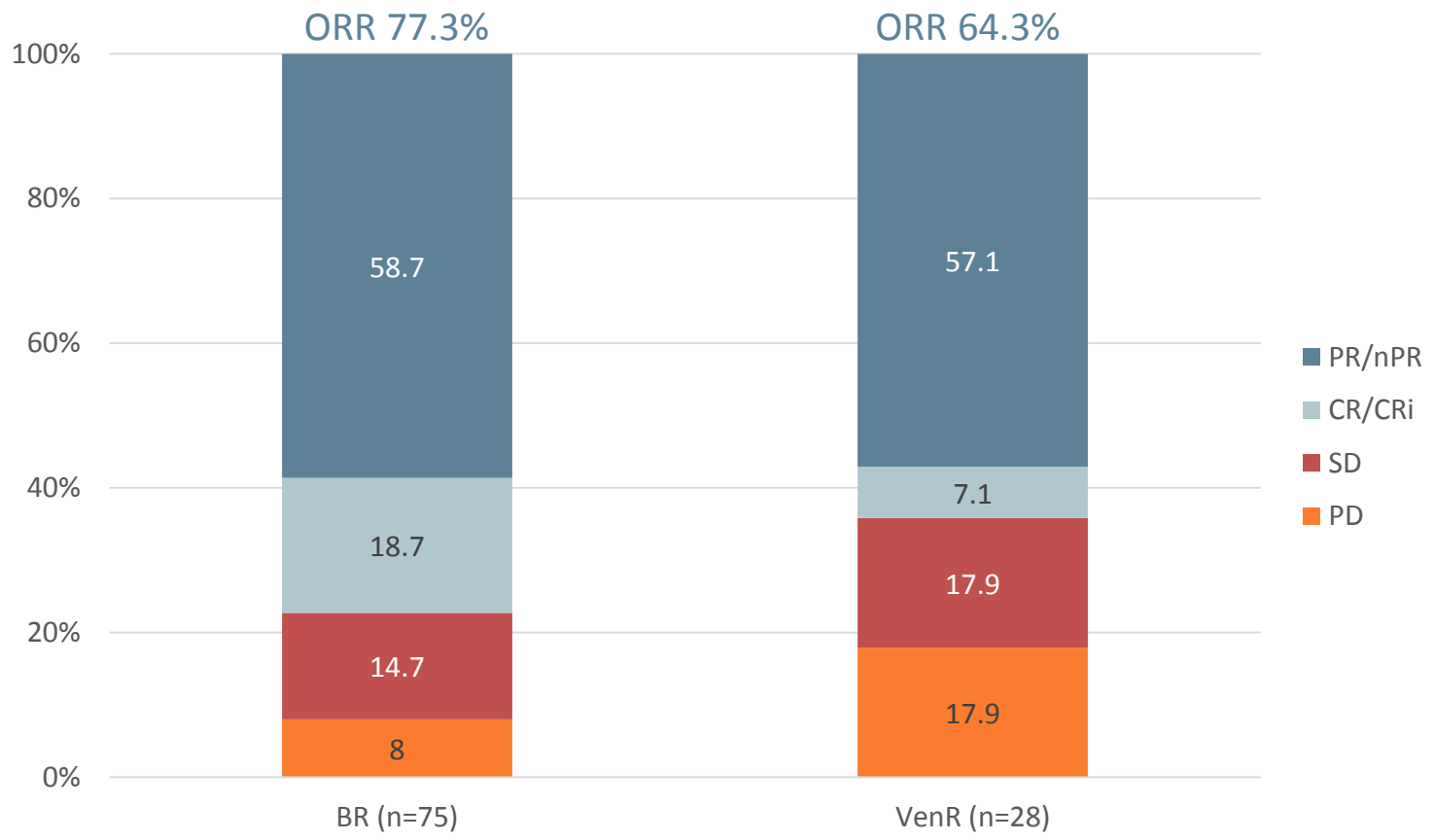
Despite 73% of BR patients receiving treatment after progression, including novel targeted agents (79%)

BR, bendamustine-rituximab; CI, confidence interval; HR, hazard ratio; OS, overall survival; PFS, progression-free survival; VenR, venetoclax + rituximab

Seymour JF, et al. ASH 2019 Abstract #355

MURANO RESULTS

Best response in patients who received novel therapy after progression



BR, bendamustine-rituximab; CR, complete response; CRi, complete response with incomplete blood count recovery; NA, not available; NE, not evaluable; nPR, nodular partial response; ORR, overall response rate; PD, progressive disease; PR, partial response; SD, stable disease; VenR, venetoclax + rituximab

Seymour JF, et al. ASH 2019 Abstract #355

MURANO
DISCUSSION AND INTERPRETATION

- Four-year data from MURANO demonstrate **sustained PFS and OS benefits** with VenR versus BR
  - 24-month post-treatment cessation PFS was 68% in patients completing 2 years of venetoclax
  - Patients who attained PB-uMRD showed particularly durable responses
- These data provide further support for the application of **time-limited VenR in R/R CLL**

- **Given the OS benefit associated with use of VenR, use of chemoimmunotherapy should be limited and well justified in patients with R/R CLL**
- **It is of paramount importance to now study the outcomes of retreatment with VenR**

BR, bendamustine-rituximab; CLL, chronic lymphocytic leukaemia; OS, overall survival; PB-uMRD, undetectable minimal residual disease in the peripheral blood; PFS, progression-free survival; R/R, relapsed/refractory; VenR, venetoclax + rituximab

Seymour JF, et al. ASH 2019 Abstract #355

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LYMPHOMA CONNECT
Bodenackerstrasse 17
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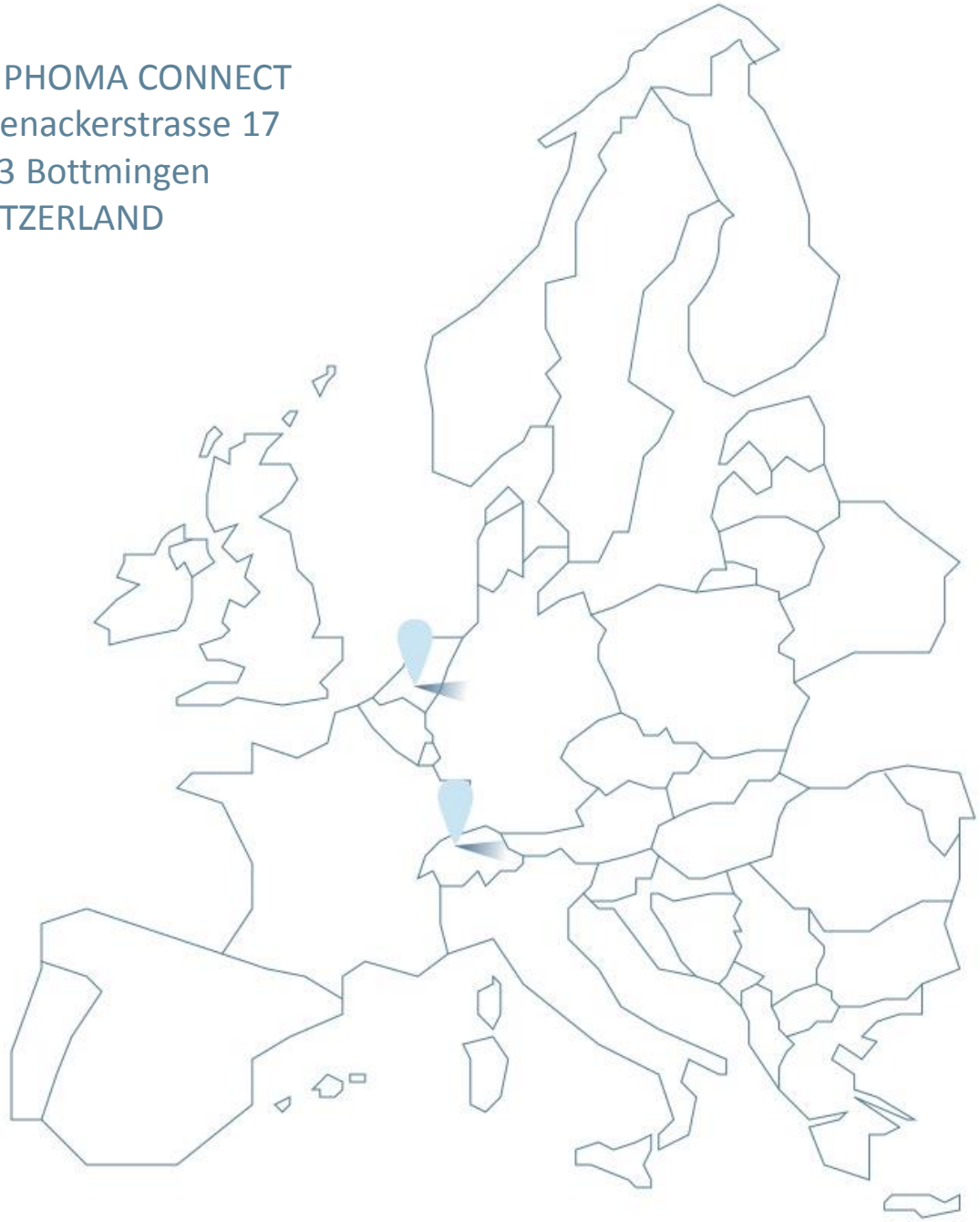

Dr. Antoine Lacombe
Pharm D, MBA
Phone: +41 79 529 42 79
antoine.lacombe@cor2ed.com

Dr. Froukje Sosef
MD
Phone: +31 6 2324 3636
froukje.sosef@cor2ed.com