Inibitori di BCL2: meccanismo di azione e nuove prospettive terapeutiche

Massimo Massaia

SC Ematologia - AO S. Croce e Carle – Cuneo, Italy

Laboratorio di Immunologia dei Tumori del Sangue, CeRMS Torino, Italy

Corso teorico-pratico per la gestione ottimale dei pazienti affetti da Linfoma Mantellare, Linfoma Follicolare e Leucemia Linfatica Cronica
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AO S.Croce e Carle
Cuneo

Università di Torino
MBC
Molecular Biotechnology Center

CeRMS
Centro di Ricerca in Medicina Sperimentale

Contents:

Contents:

- See glossary for abbreviations.

Evasion of Apoptosis, or Cell Death, is One Hallmark of Cancer

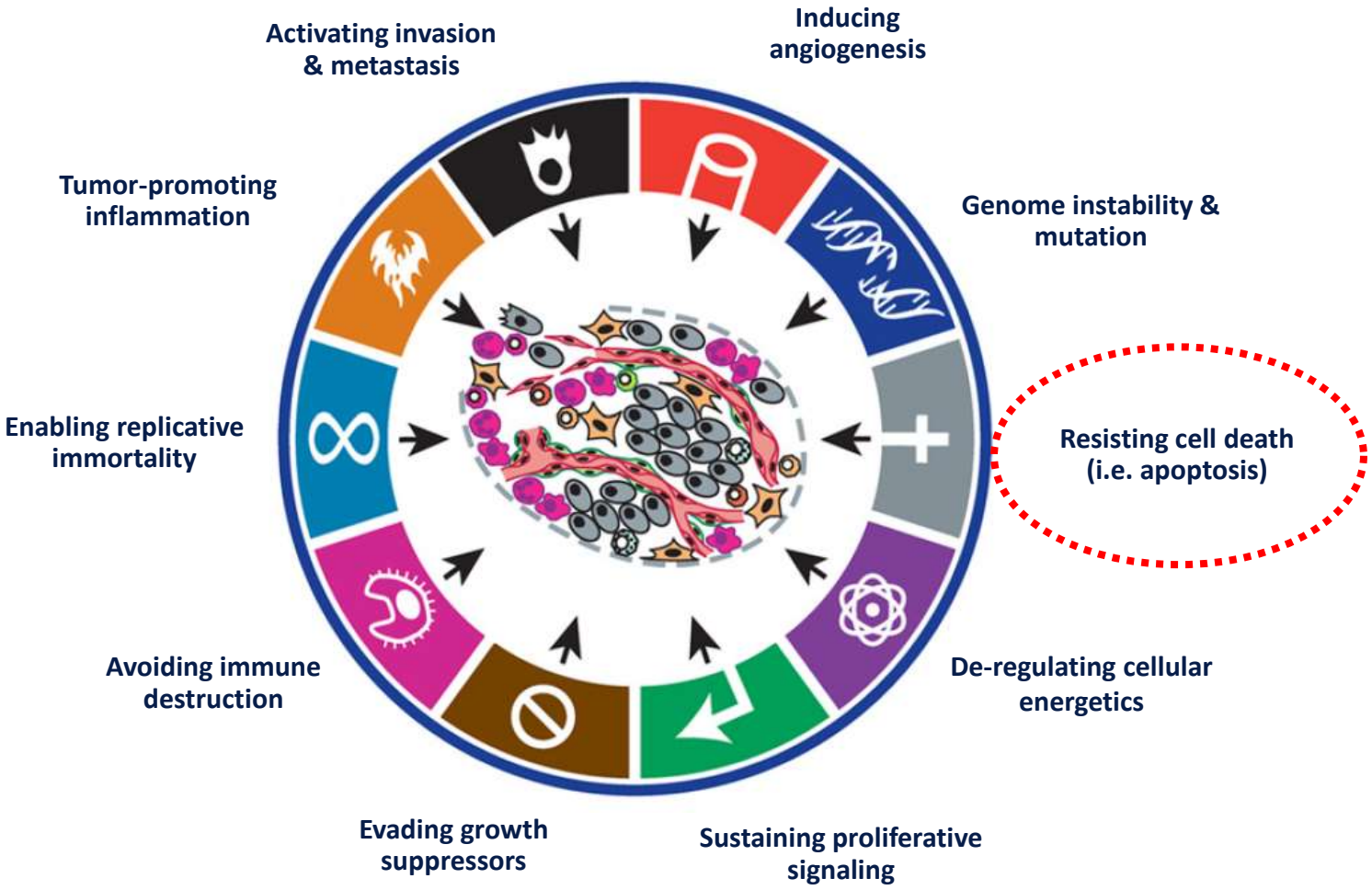
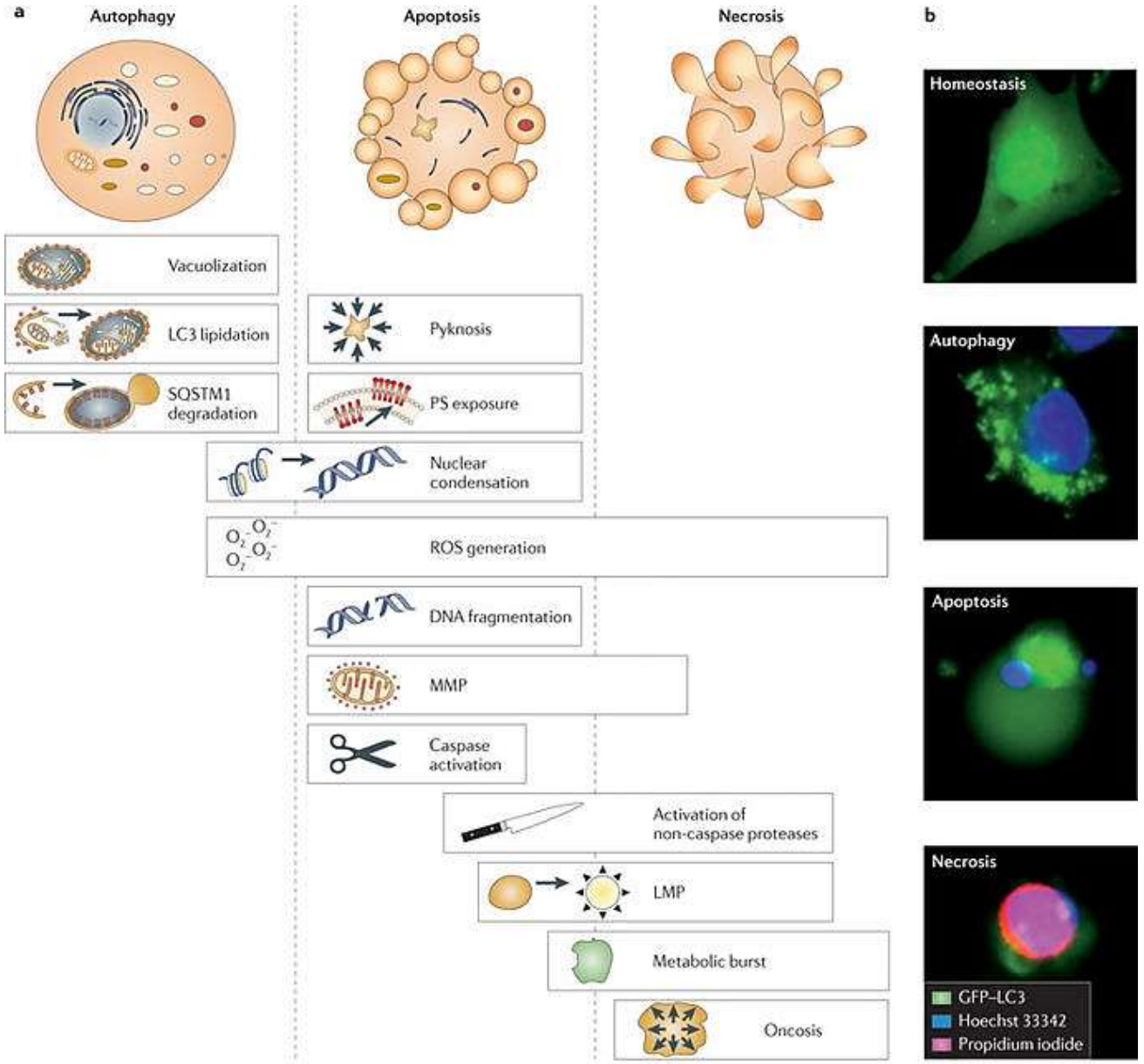


Figure adapted from Hanahan D & Weinberg RA. *Cell* 2011; 144:646–674.

Different cell death modalities



Kepp O et al., *Nat Rev Drug Discov*. 2011 Mar;10(3):221-37

Cell Death

Apoptosis

Programmed cell death. Death cycle is **programmed** by the cell itself

Autophagy

'Self-eating' Catabolic process involving lysosomes.

Necrosis

'Death' caused by external factors like trauma or toxins. **Not programmed.**

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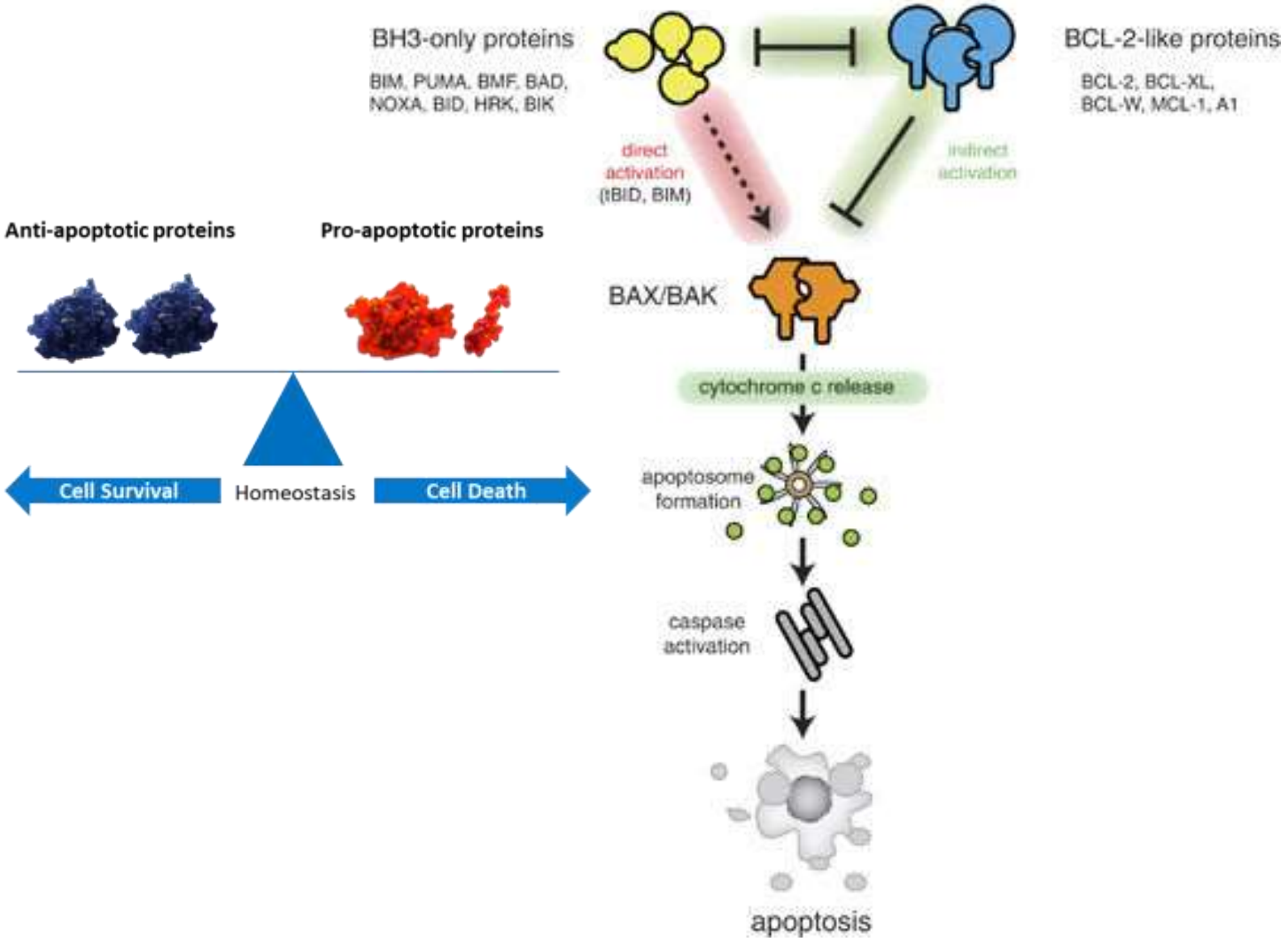
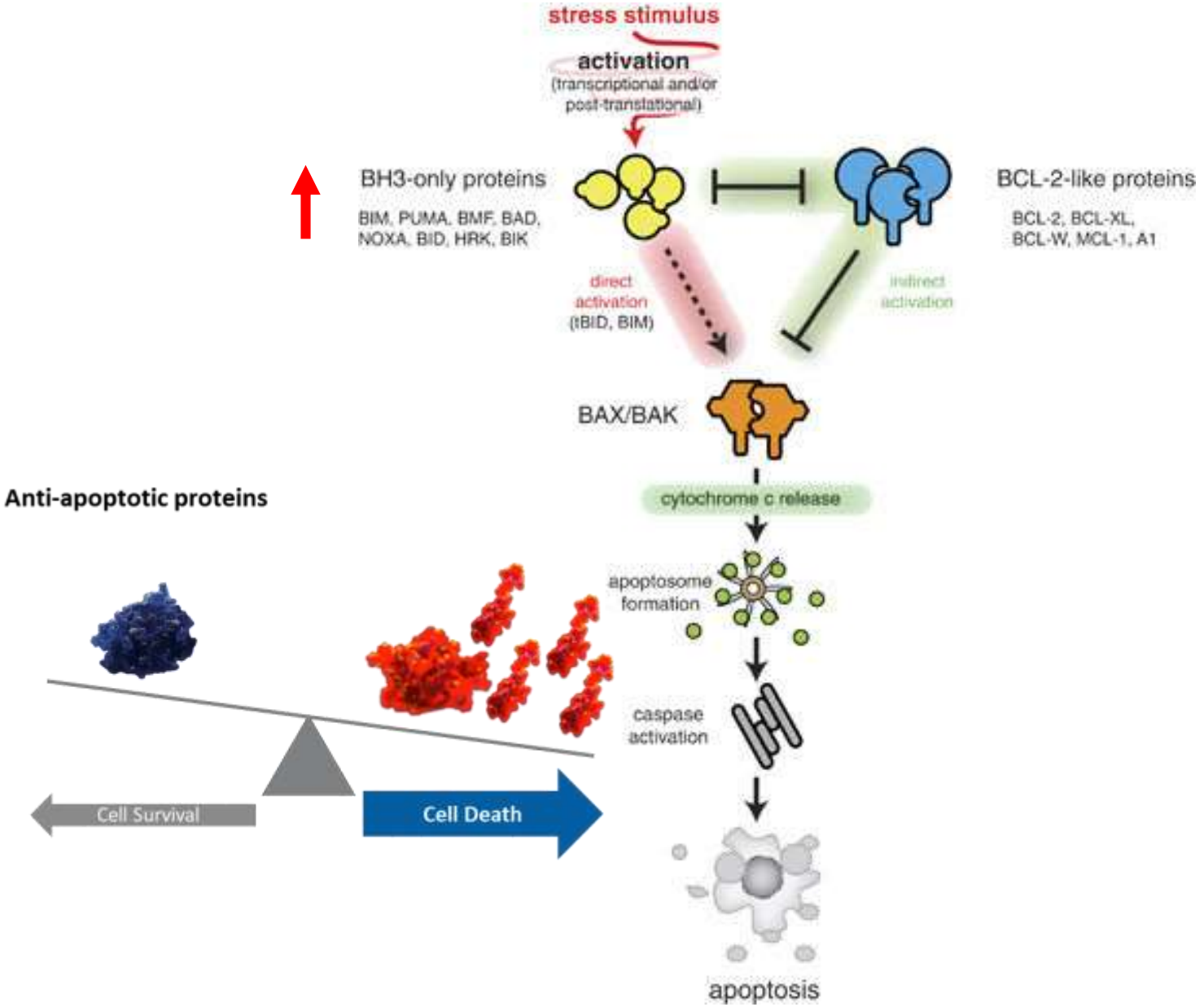
Regulation of apoptosis by BCL-2 family members



adapted from Delbridge AR et al., *Cell Death Differ*. 2015 Jul;22(7):1071-8

Regulation of apoptosis by BCL-2 family members



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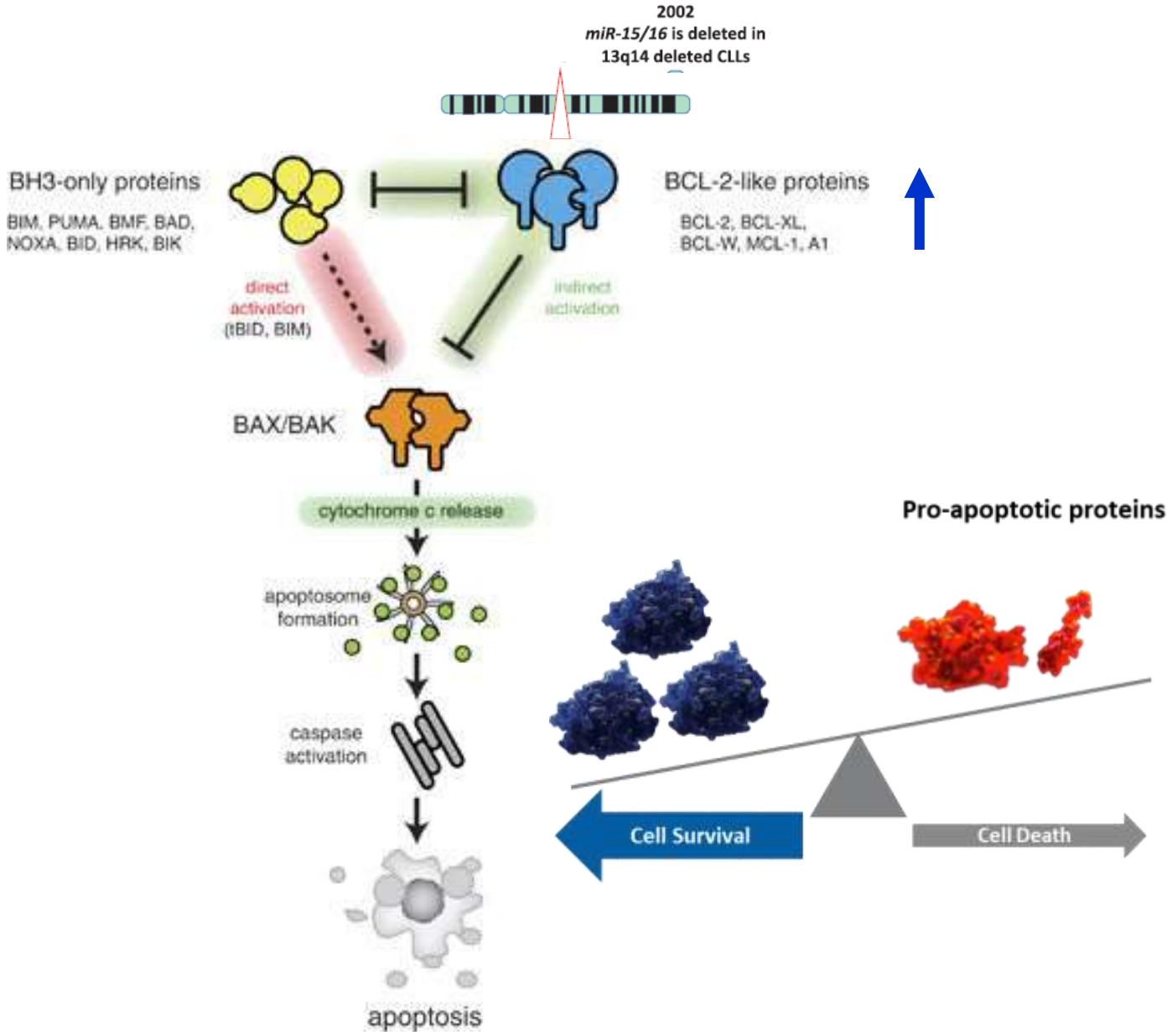
Regulation of apoptosis by BCL-2 family members

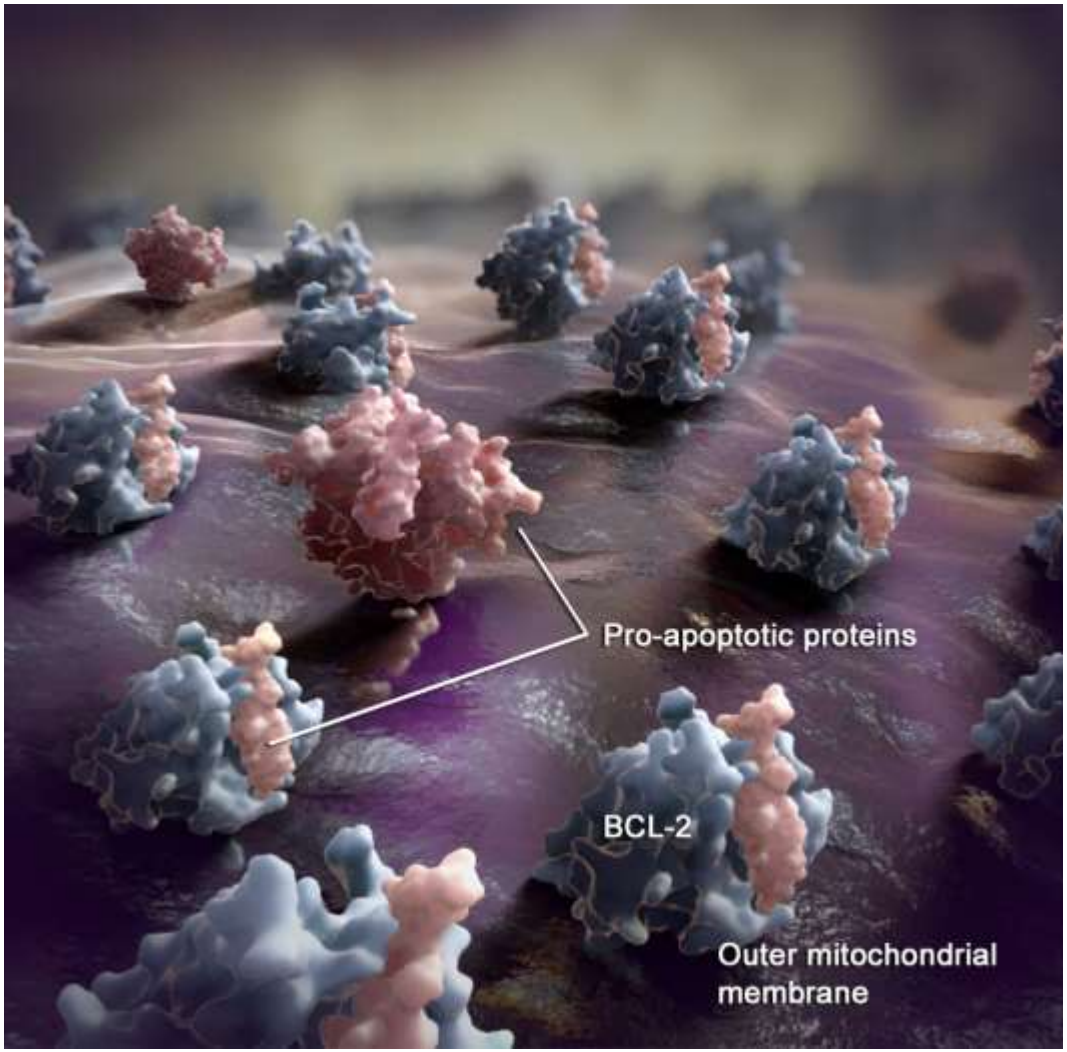


adapted from Delbridge AR et al., *Cell Death Differ*. 2015 Jul;22(7):1071-8

Contents:

- See glossary for abbreviations.

Increased Bcl-2 expression in malignant cells

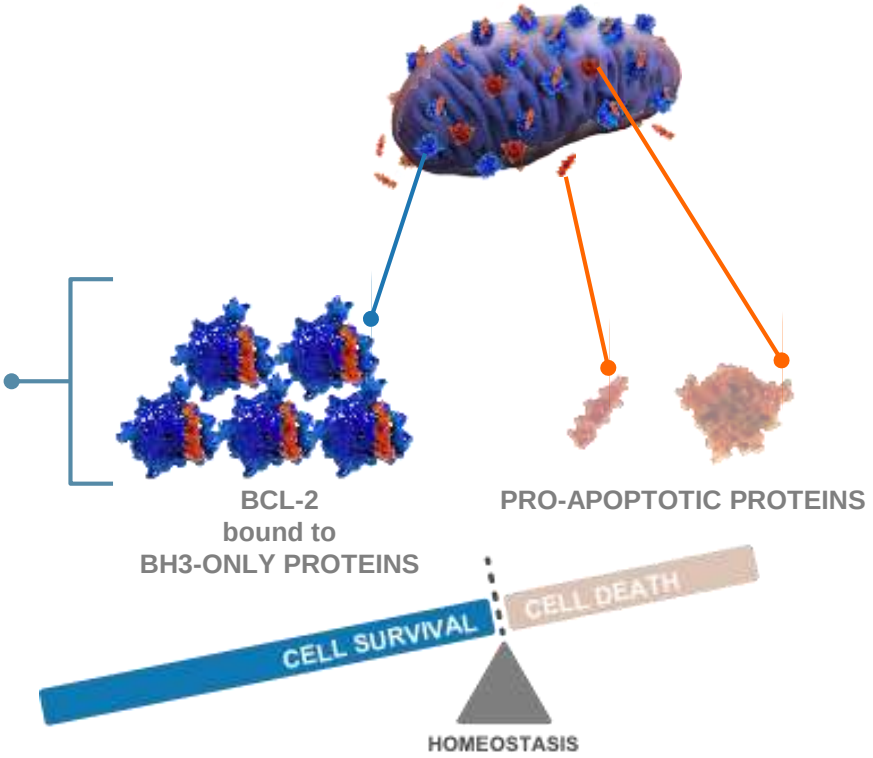


1.Souers AJ et al. *Nat Med*. 2013;19(2):202-208.
2.Certo M et al. *Cancer Cell*. 2006;9(5):351-365.

The Overexpression of BCL-2 Protein Allows Malignant Cells to Evade Apoptosis[3]

- BCL-2 binds and sequesters a surplus of pro-apoptotic proteins[3]

BCL-2
Implicated in tumorigenesis,[1,3,6–7] and increased resistance to chemotherapy[13–16]



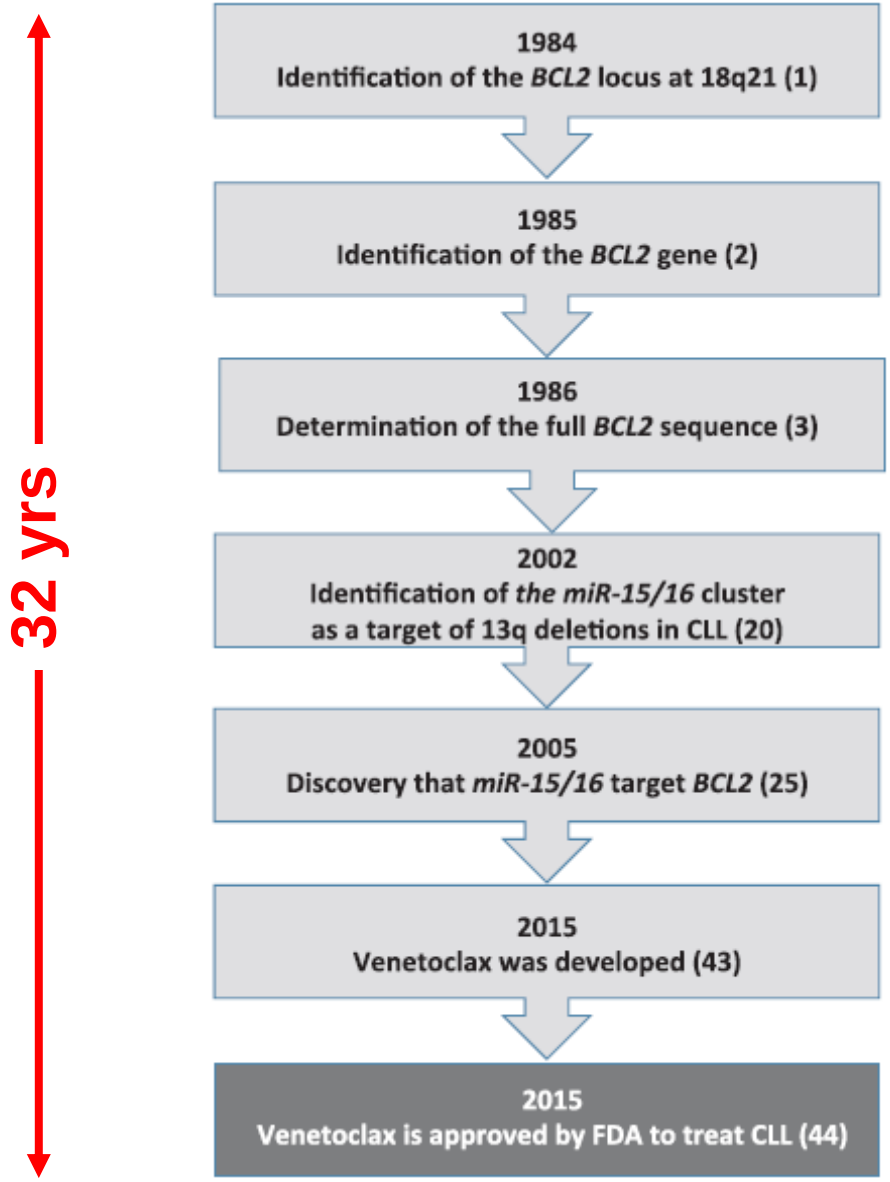
Increased expression of BCL-2 enables survival of malignant cells[8–12]

- 1. Cory S, *et al. Oncogene* 2003; **22:**8590–8607; 2. Hanahan D & Weinberg RA. *Cell* 2000; **100:**57–70; 3. Plati J, *et al. Integr Biol (Camb)* 2011; **3:**279–296; 4. Fulda S. *Int J Cell Biol* 2010; **2010:**370835; 5. Del Gaizo Moore V, *et al. J Clin Invest* 2007; **117:**112–121; 6. Adams JM & Cory S. *Oncogene* 2007; **26:**1324–1337;
7. Reed JC. *Blood* 2008; **111:**3322–3330; 8. Choi J, *et al. Cancer Res* 2005; **65:**5554–5560; 9. Takaoka A, *et al. Oncogene* 1997; **14:**2971–2977; 10. Biroccio A, *et al. FASEB J* 2000; **14:**652–660; 11. Warner KA, *et al. Neoplasia* 2008; **10:**131–139; 12. Vanasse GJ, *et al. Mol Cancer Res* 2004; **2:**620–631; 13. Schmitt CA, *et al. Nat Med* 2000; **6:**1029–1035; 14. Wacheck V, *et al. Oligonucleotides* 2003; **13:**393–400;
- 15. Mohammad RM, *et al. Clin Cancer Res* 2007; **13:**2226–2235; 16. O'Brien S, *et al. J Clin Oncol* 2007; **25:**1114–1120.

Contents:

- See glossary for abbreviations.

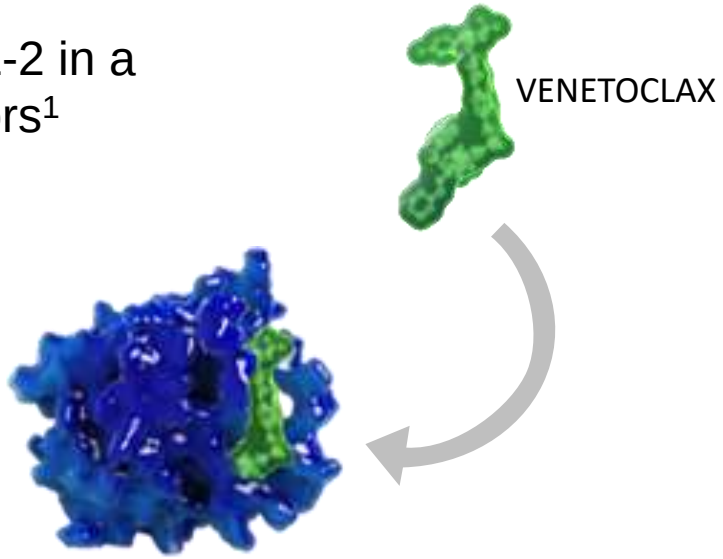
Timeline from BCL2 discovery to the development of specific BCL2 inhibitors



Pekarski T et al. *Cell Death Differ. 2017 Oct 6 [Epub ahead of print]*

Venetoclax Is a Selective Inhibitor of BCL-2[1]

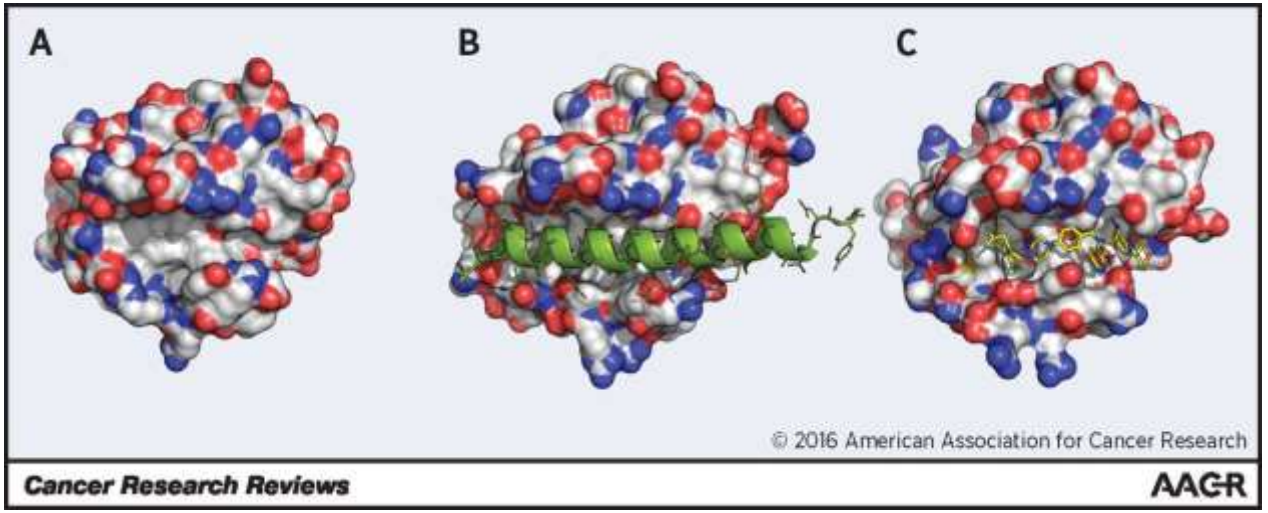
- Venetoclax (ABT-199/GDC-0199) is a selective, orally available, small-molecule BCL-2 inhibitor that helps to restore apoptosis independent of *TP53* functional status[1,2]
- Venetoclax is structurally designed to bind BCL-2 in a manner analogous to native pro-apoptotic factors[1]



- 1. Souers AJ, *et al. Nat Med* 2013; **19:**202–208;
  2. Anderson MA, *et al. Blood* 2013; **122:**1304.

Characteristics of small molecules that target BCL-2

Compound	Targets	Affinity
BCL-2 inhibitors		
ABT-737	BCL-2, BCL-X_L and BCL-W	Subnanomolar to nanomolar
Navitoclax (also known as ABT-263)	BCL-2, BCL-X_L and BCL-W	Subnanomolar to nanomolar
BM-1197	BCL-2 and BCL-X_L	Subnanomolar
S44563	BCL-2 and BCL-X_L	Nanomolar
BCL2-32	BCL-2 and BCL-X_L	Nanomolar
AZD4320	BCL-2 and BCL-X_L	≤1 nM
Venetoclax (also known as ABT-199)	BCL-2	Subnanomolar
S55746 (also known as BCL201)	BCL-2	Nanomolar



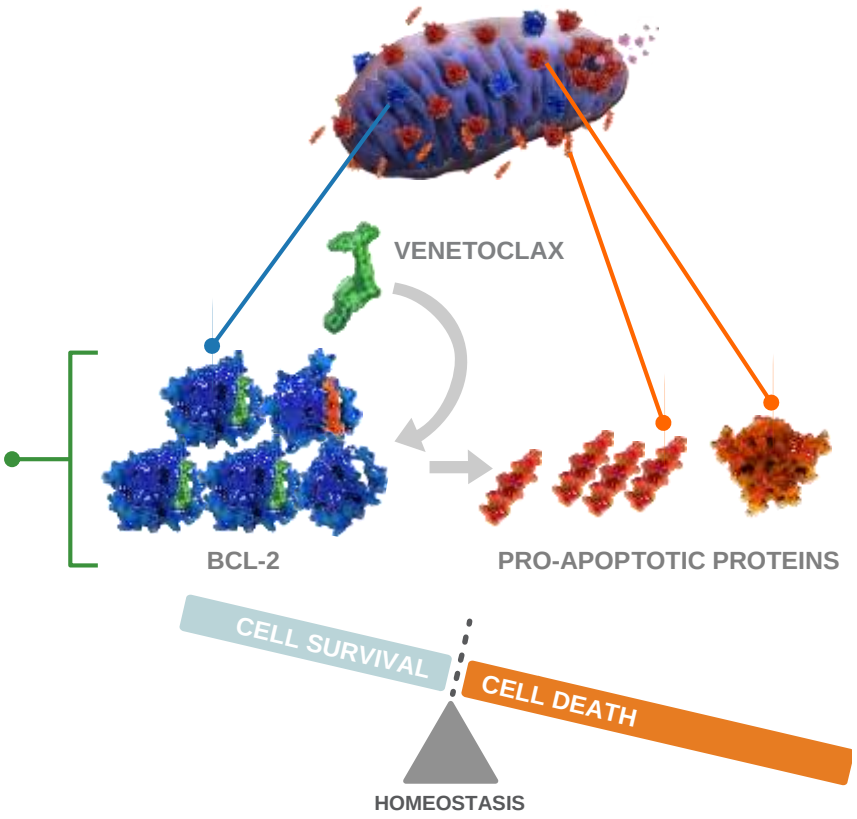
Croce CM et al., *Cancer Res.* 2016; 76(20):5914-20

Ashkenazi A et al., *Nat Rev Drug Discov*. 2017 Apr;16(4):273-284

Venetoclax Restores Apoptosis by Helping to Release Sequestered Pro-Apoptotic Proteins[1–4]

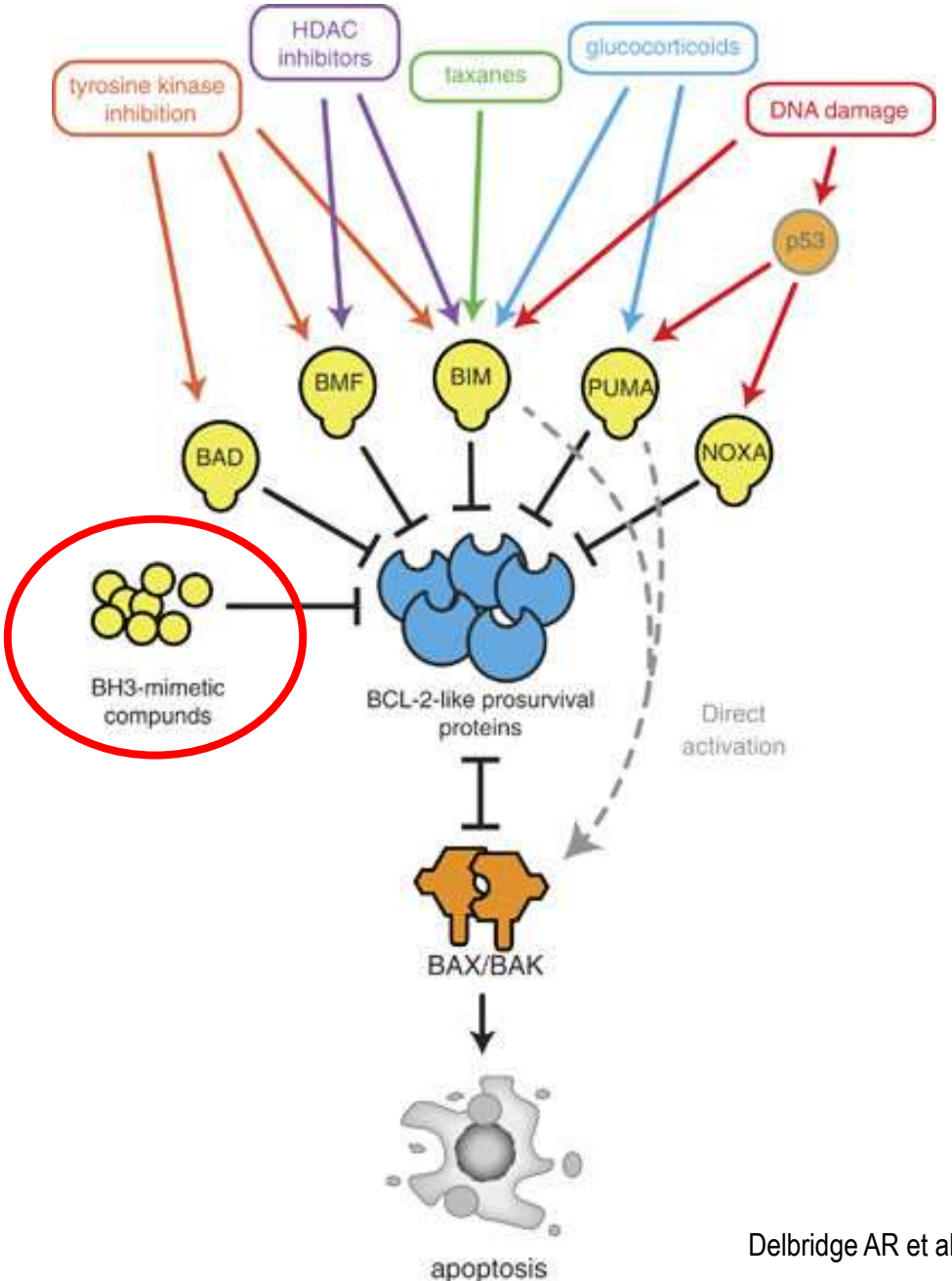
- Venetoclax inhibits BCL-2 and can contribute to releasing the store of pro-apoptotic proteins, helping tip the balance in favor of cell death[1–3]

Venetoclax can induce cell death irrespective of *TP53* function because the effects of BCL-2 inhibition are thought to be independent of this pathway[4]



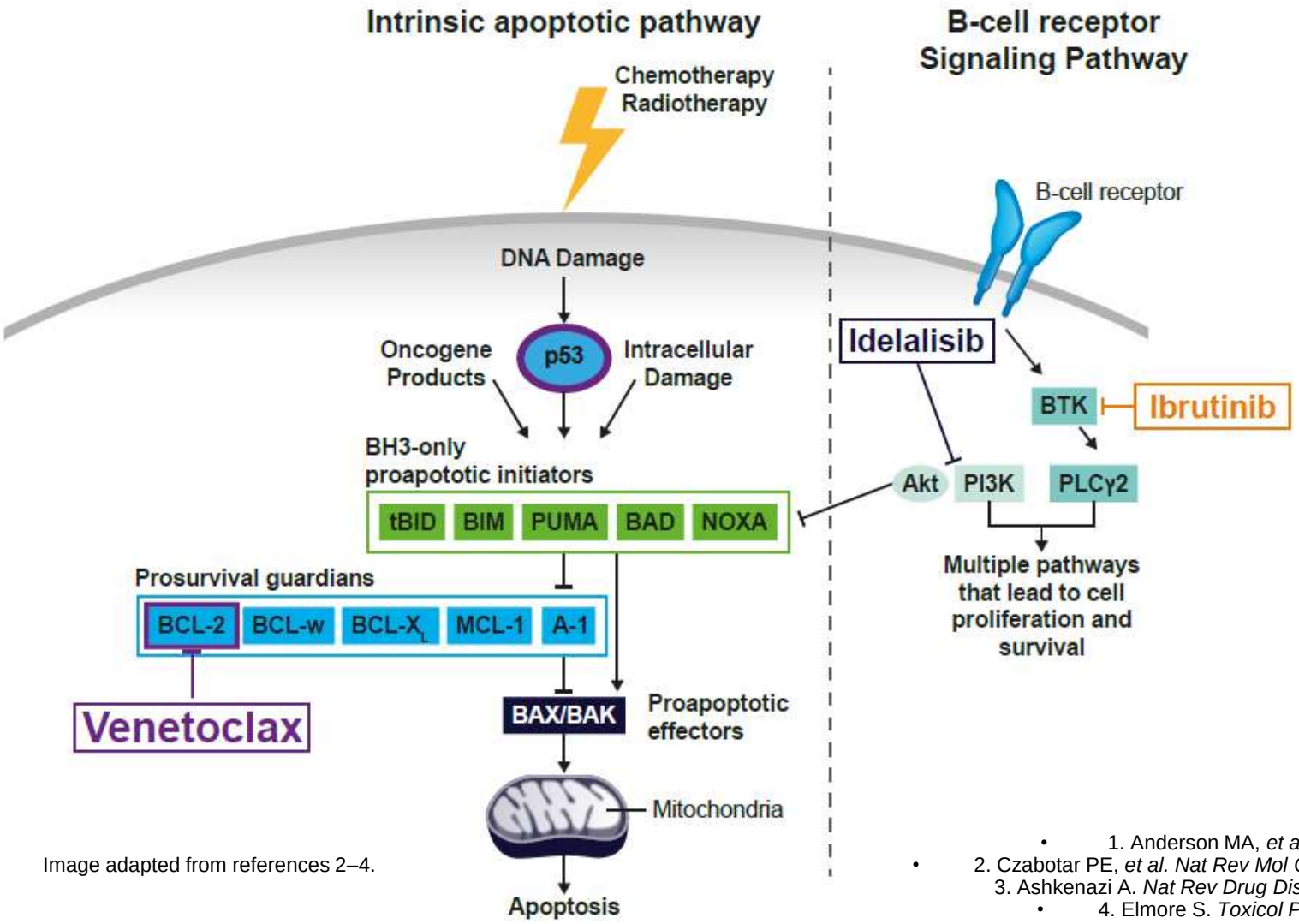
- 1. Cory S, *et al. Oncogene* 2003; **22:**8590–8607; 2. Plati J, *et al. Integr Biol (Camb)* 2011; **3:**279–296; 3. Deng J, *et al. Cancer Cell* 2007; **12:**171–185; 4. Certo M, *et al. Cancer Cell* 2006; **9:**351–365.

BH3-mimetics bypass the requirement for upstream initiators



Delbridge AR et al., *Cell Death Differ*. 2015 Jul;22(7):1071-8

Venetoclax Restores Apoptosis Independently of p53 and the BCR Pathway



- Image adapted from references 2–4.

- 1. Anderson MA, *et al. Blood* 2013; **122:**1304;
- 2. Czabotar PE, *et al. Nat Rev Mol Cell Biol* 2014; **15:**49–63;
- 3. Ashkenazi A. *Nat Rev Drug Discov* 2008; **7:**1001–1012;
- 4. Elmore S. *Toxicol Pathol* 2007; **35:**495–516.

Next Steps:

- Venetoclax + anti-CD20 (Rituximab/Obinutuzumab)
- Venetoclax + BTKi
- Venetoclax + BTKi + anti-CD20

Move forward:

- from rel/ref to TN patients

Venetoclax plus rituximab in rel/ref CLL: a phase 1b study (49 pts)

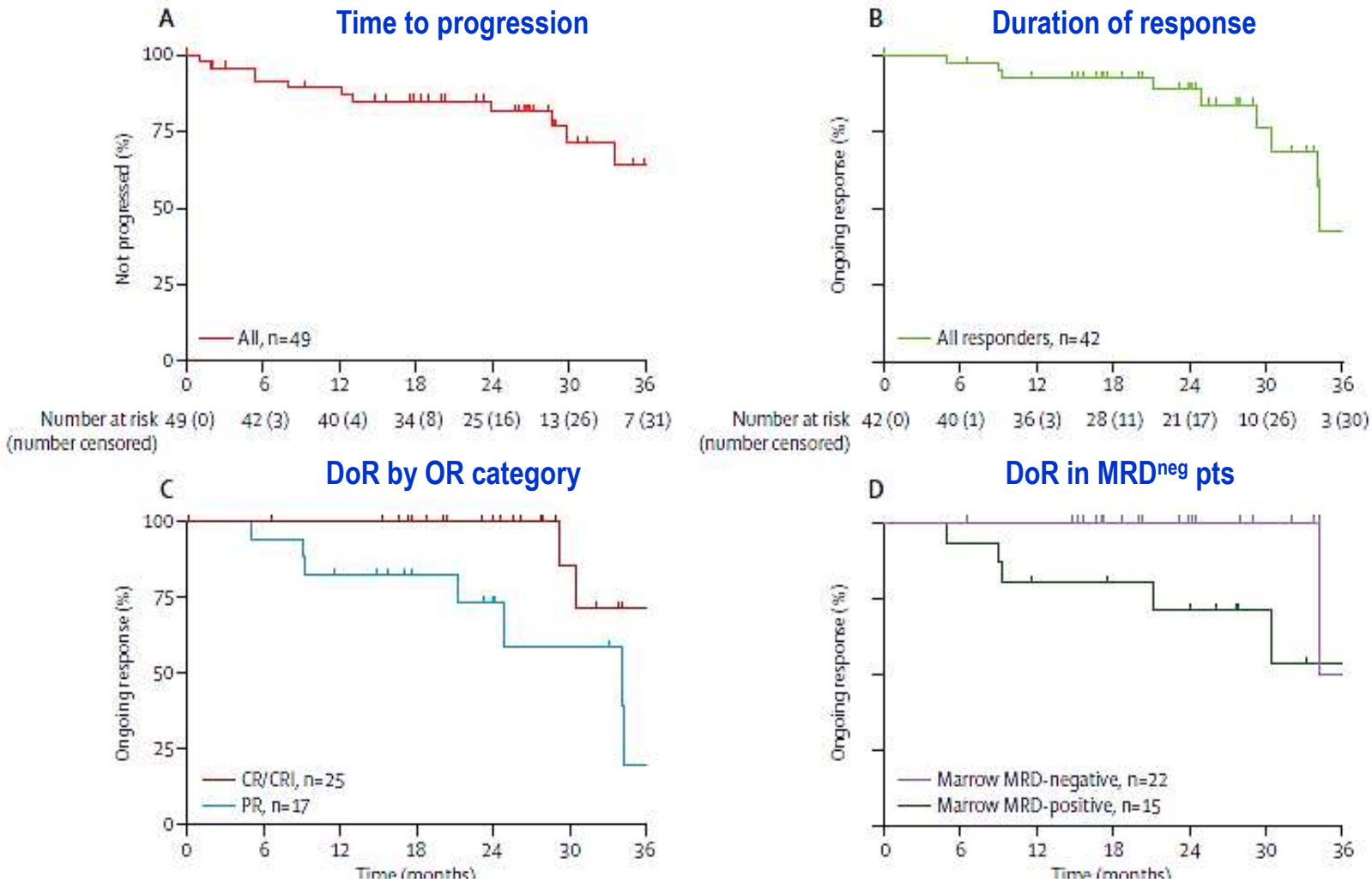
	200 mg (n=6)	300 mg (n=10)	400 mg (n=8)	500 mg (n=7)	600 mg (n=10)	Safety expansion, 400 mg (n=8)	Total (n=49)
Overall response	6 (100%)	8 (80%)	6 (75%)	6 (86%)	9 (90%)	7 (88%)	42 (86%), 95% CI 73–94
Complete response or complete response with incomplete marrow recovery	2 (33%)	5 (50%)	6 (75%)	4 (57%)	5 (50%)	3 (38%)	25 (51%), 95% CI 36–66
Nodular partial response or partial response	4 (67%)	3 (30%)	0	2 (29%)	4 (40%)	4 (50%)	17 (35%), 95% CI 22–50
Stable disease	0	1 (10%)	1 (13%)	1 (14%)	1 (10%)	0	4 (8%)
Progressive disease	0	1 (10%)	0	0	0	1 (13%)	2 (4%)
Not assessed*	0	0	1 (13%)	0	0	0	1 (2%)
Negative marrow minimal residual disease response	3 (50%)	3 (30%)	6 (75%)	4 (57%)	7 (70%)	5 (62%)	28 (57%)

Data are n (%) or n (%), 95% CI. *Patient had fatal tumour lysis syndrome on day 1.

Table 3: Response by dose level

Seymour JF et al., *Lancet Oncol*. 2017 Feb;18(2):230-240.

Venetoclax plus rituximab in rel/ref CLL: a phase 1b study



2 year estimates for progression-free survival and ongoing response were 82% and 89%

Seymour JF et al., *Lancet Oncol*. 2017 Feb;18(2):230-240.

Venetoclax Plus Rituximab is Superior to Bendamustine Plus Rituximab in Patients with Relapsed / Refractory Chronic Lymphocytic Leukemia – Results from Pre-Planned Interim Analysis of the Randomized Phase 3 MURANO Study

Adapted from the Seymour presentation at ASH on December 12, 2017

John F. Seymour[1], Thomas Kipps[2], Barbara Eichhorst[3], Peter Hillmen[4], James D'Rozario[5], Sarit Assouline[6], Carolyn Owen[7], John Gerecitano[8], Tadeusz Robak[9], Javier De la Serna[10], Ulrich Jaeger[11], Guillaume Cartron[12], Marco Montillo[13], Rod Humerickhouse[14], Elizabeth A. Punnoose[15], Yan Li[15], Michelle Boyer[16], Kathryn Humphrey[16], Mehrdad Mobasher[15], Arnon P. Kater[17]

[1]Peter MaCallum Cancer Centre, Royal Melbourne Hospital, and University of Melbourne, Australia; [2]University of California School of Medicine, San Diego, CA, USA; [3]Bonn University Hospital Cologne, Germany; [4]St. James University Hospital, Leeds, UK; [5]The John Curtin School of Medical Research, Australian National University, Canberra, Australia; [6]Segal Cancer Center, Lady Davis Institute, Jewish General Hospital, Montreal, QC, Canada; [7]Departments of Medicine and Oncology, University of Calgary, Alberta, Canada; [8]Memorial Sloan Kettering Cancer Center, New York City, NY; [9]Department of Hematology, Medical University of Lodz and Copernicus Memorial Hospital, Lodz, Poland; [10]Hospital Universitario 12 de Octubre, Madrid Spain; [11]Medical University of Vienna, Dept. of Medicine I, Division of Hematology and Hemostaseology, Vienna, Austria; [12]Department of Hematology CHU Montpellier, France; [13]Department of Onco-Hematology, Division of Hematology, Niguarda Ca' Granda Hospital, Milan, Italy; [14]AbbVie, Inc., Chicago, IL; [15]Genentech, Inc, South San Francisco, CA; [16]F. Hoffmann-La Roche, Ltd. Welwyn Garden City, United Kingdom; [17]Academic Medical Center, HOVON CLL working group, Amsterdam, The Netherlands.

The American Society of Hematology – 59th Annual Meeting and Exposition
Atlanta, Georgia ● December 9–12, 2017

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Venetoclax–Rituximab in Relapsed or Refractory Chronic Lymphocytic Leukemia

J.F. Seymour, T.J. Kipps, B. Eichhorst, P. Hillmen, J. D'Rozario, S. Assouline, C. Owen, J. Gerecitano, T. Robak, J. De la Serna, U. Jaeger, G. Cartron, M. Montillo, R. Humerickhouse, E.A. Punnoose, Y. Li, M. Boyer, K. Humphrey, M. Mobasher, and A.P. Kater

Seymour JF et al., *N Engl J Med*. 2018 Mar 22;378(12):1107-1120

MURANO Study Design

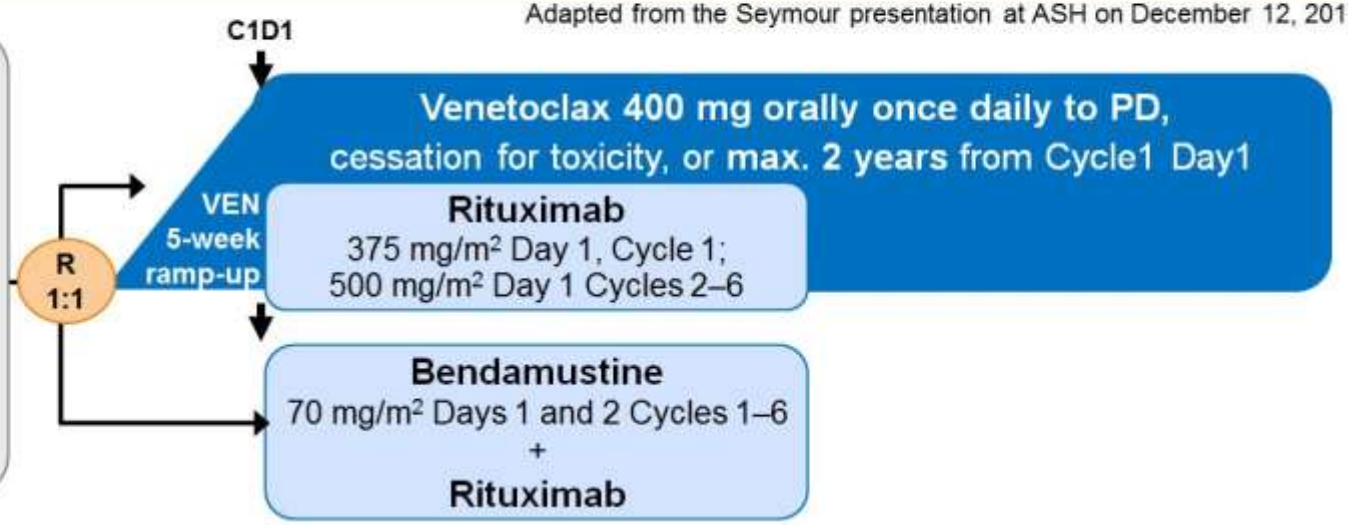
Adapted from the Seymour presentation at ASH on December 12, 2017

Relapsed/refractory CLL (N=389)

- ≥18 years of age
- Prior 1–3 lines of therapy, including ≥1 chemo-containing regimen
- Prior bendamustine only if DoR ≥24 months

Stratified by:

- Del(17p) by local labs
- Responsiveness to prior therapy*
- Geographic region



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.

Patient Demographics and Disease Characteristics Balanced Between Arms

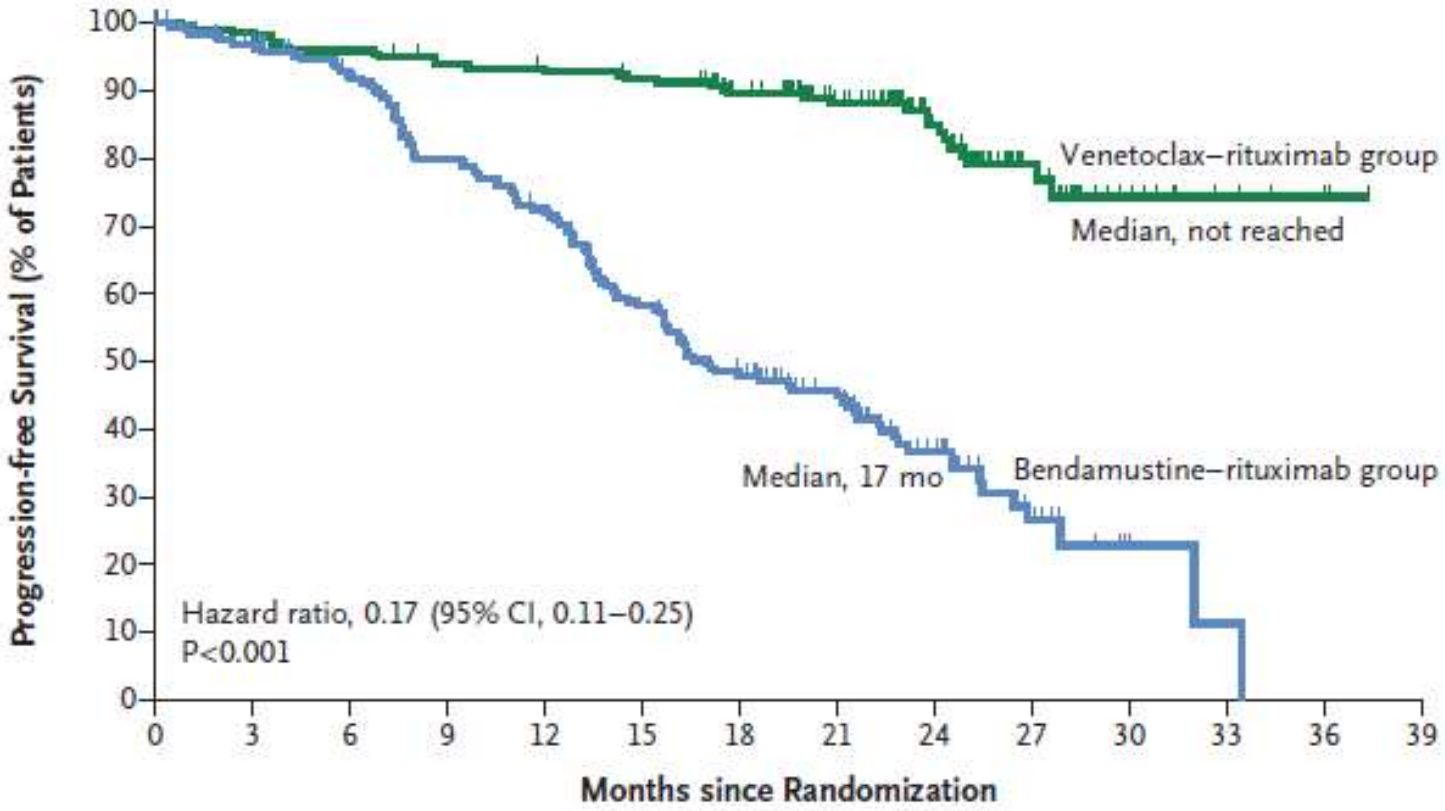
Status	Venetoclax + Rituximab (N=194)	Bendamustine + Rituximab (N=195)
Age, median (range), years	64.5 (28–83)	66.0 (22–85)
Lymphocyte count ($\times 10^9$/L), median (range)	43.1 (0.3–703)	54.7 (0.3–536)
Del(17p)*, n/N (%)	46/173 (27)	46/169 (27)
Unmutated IGHV*, n/N (%)	123/180 (68)	123/180 (68)
Mutated *TP53**, n/N (%)	48/192 (25)	51/184 (28)
Number of prior therapies, n (%)		
1	111 (57)	117 (60)
2	57 (29)	43 (22)
3	22 (11)	34 (17)
>3	4 (2)	1 (1)
Prior therapies, n (%)		
Alkylating agent	182 (93)	185 (95)
Purine analog	157 (81)	158 (81)
Anti-CD20 antibody	153 (78)	148 (76)
B-cell receptor pathway inhibitors	5 (3)	3 (2)

*Central lab

Adapted from the Seymour presentation at ASH on December 12, 2017

As of 8 May 2017

A Progression-free Survival



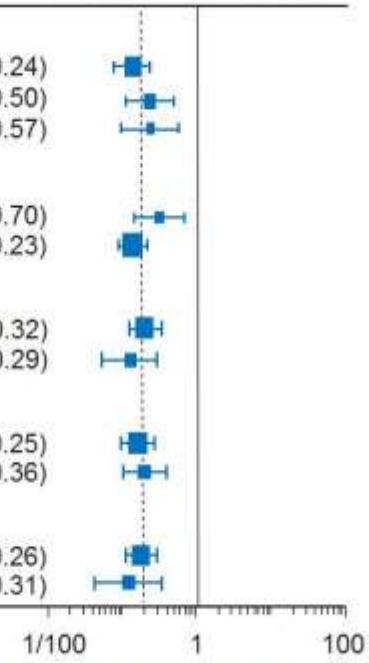
No. at Risk

Venetoclax–rituximab group	194	190	185	179	176	173	157	115	76	33	14	5	3
Bendamustine–rituximab group	195	177	163	141	127	102	81	57	35	12	3	1	

Seymour JF et al., *N Engl J Med*. 2018 Mar 22;378(12):1107-1120

Treatment Effect With VenR Consistent Across Subgroups; Investigator-assessed PFS

Subgroups	Total N	Venetoclax + Rituximab (N=194) n	Venetoclax + Rituximab (N=194) Median (Months)	Bendamustine + Rituximab (N=195) n	Bendamustine + Rituximab (N=195) Median (Months)	Hazard Ratio	95% Wald CI
Number of prior therapies							
1	228	111	NR	117	16.6	0.14	(0.08–0.24)
2	100	57	NR	43	21.2	0.24	(0.11–0.50)
≥3	61	26	NR	35	10.5	0.24	(0.10–0.57)
Refractory vs. relapse to most recent prior therapy							
Refractory	59	30	NR	29	13.6	0.32	(0.15–0.70)
Relapse	330	164	NR	166	18.6	0.14	(0.09–0.23)
del(17p) status*							
Absent	250	127	NR	123	21.4	0.19	(0.12–0.32)
Present	92	46	NR	46	15.4	0.13	(0.05–0.29)
TP53* mutational status							
Unmutated	277	144	NR	133	21.2	0.15	(0.09–0.25)
Mutated	99	48	NR	51	12.9	0.19	(0.10–0.36)
Baseline IGHV mutational status*							
Unmutated	246	123	NR	123	15.7	0.16	(0.10–0.26)
Mutated	104	53	NR	51	22.9	0.11	(0.04–0.31)



*Central lab

Adapted from the Seymour presentation at ASH on December 12, 2017

Overall HR = 0.17

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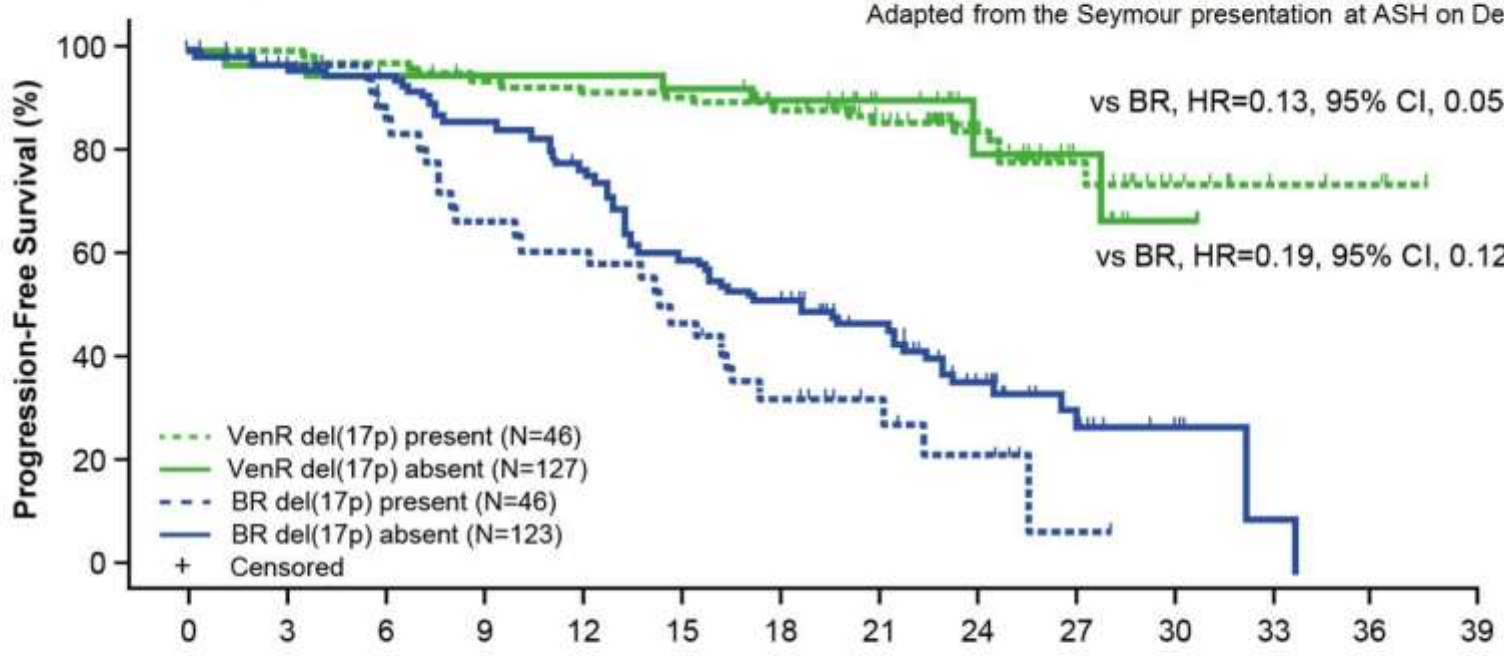
Investigator-assessed PFS Superior for VenR vs. BR Among Patients With and Without del(17p)

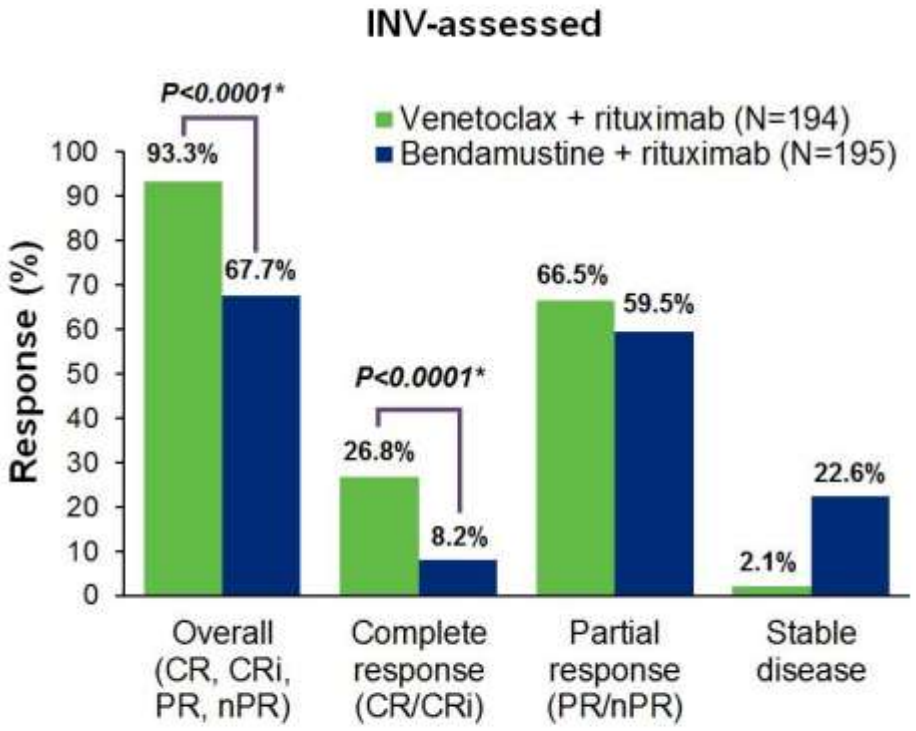
Adapted from the Seymour presentation at ASH on December 12, 2017

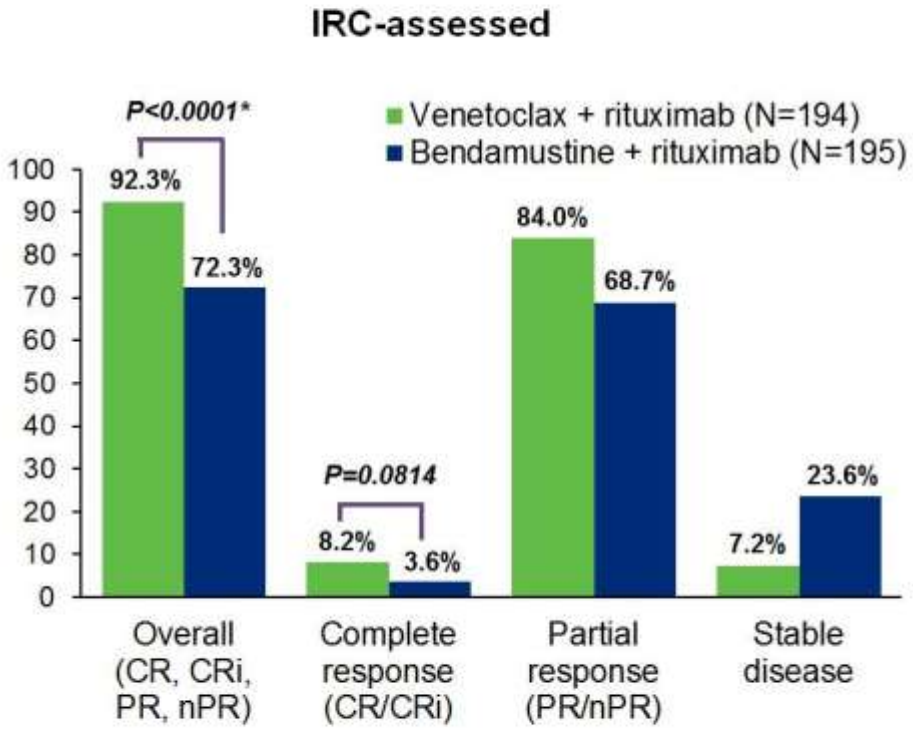


No. of patients at risk:													
VenR del(17p) present	46	44	43	43	43	42	36	25	17	7	2		
VenR del(17p) absent	127	127	124	118	116	114	105	76	48	20	10	4	3
BR del(17p) present	46	40	34	27	25	20	14	8	5	1			
BR del(17p) absent	123	114	108	99	88	70	60	44	26	10	3	1	

As of 8 May 2017

Improved Response Rates for VenR vs. BR





Adapted from the Seymour presentation at ASH on December 12, 2017

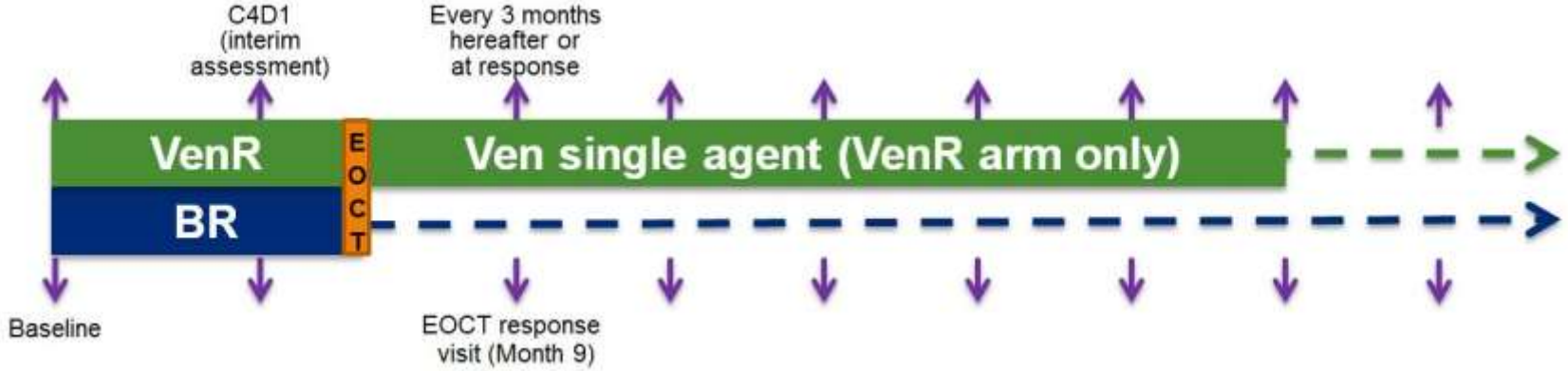
* Descriptive P-values.

Of 42 INV-assessed CRs discrepant in VenR arm, 28 due to residual CT scan nodes 16–30 mm diameter; 88% of these were PB MRD negative

As of 8 May 2017

Minimal Residual Disease in Peripheral Blood

- MRD negativity: <1 CLL cell per 10 000 leukocytes (10^{-4})[1]
- Sample collection times identical in both arms; represented by purple arrows

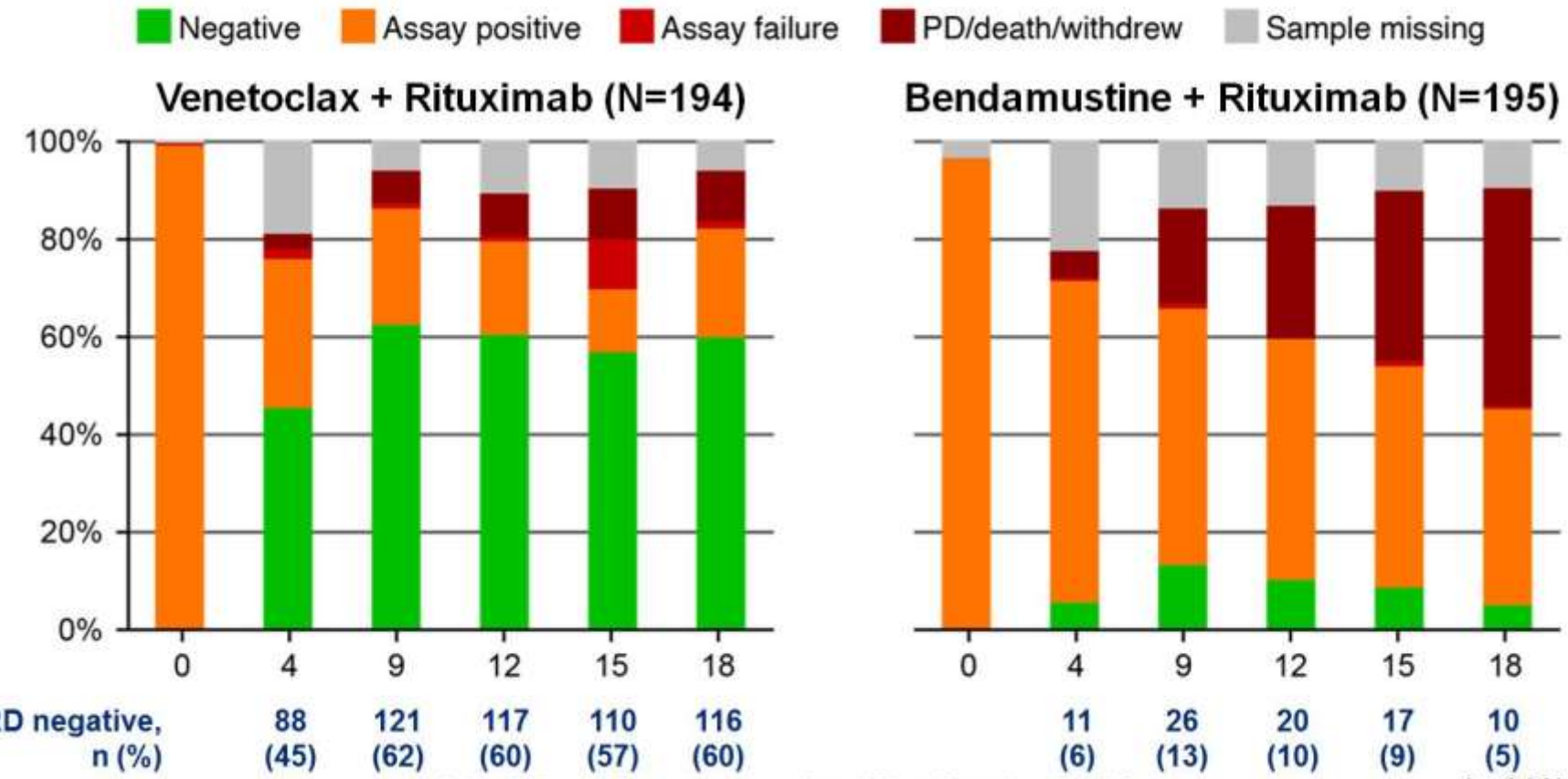


- MRD was centrally assessed by ASO-PCR[1] and/or multicolor flow cytometry[2]
- MRD-negativity is reported conservatively:
  - MRD positive by **either** ASO-PCR or by flow cytometry is reported as positive
  - Analysis is by ITT population. Missing MRD data or assay failure is reported as MRD positive

Adapted from the Seymour presentation at ASH on December 12, 2017
ASO-PCR, allele-specific-oligonucleotide polymerase chain reaction; EOCT, end of combination treatment; ITT, intent-to-treat.

1. Van der Velden VH, et al. Leukemia 2007;1(4):604-11
2. Rawstron AC, et al. Leukemia 2013;27:142-9

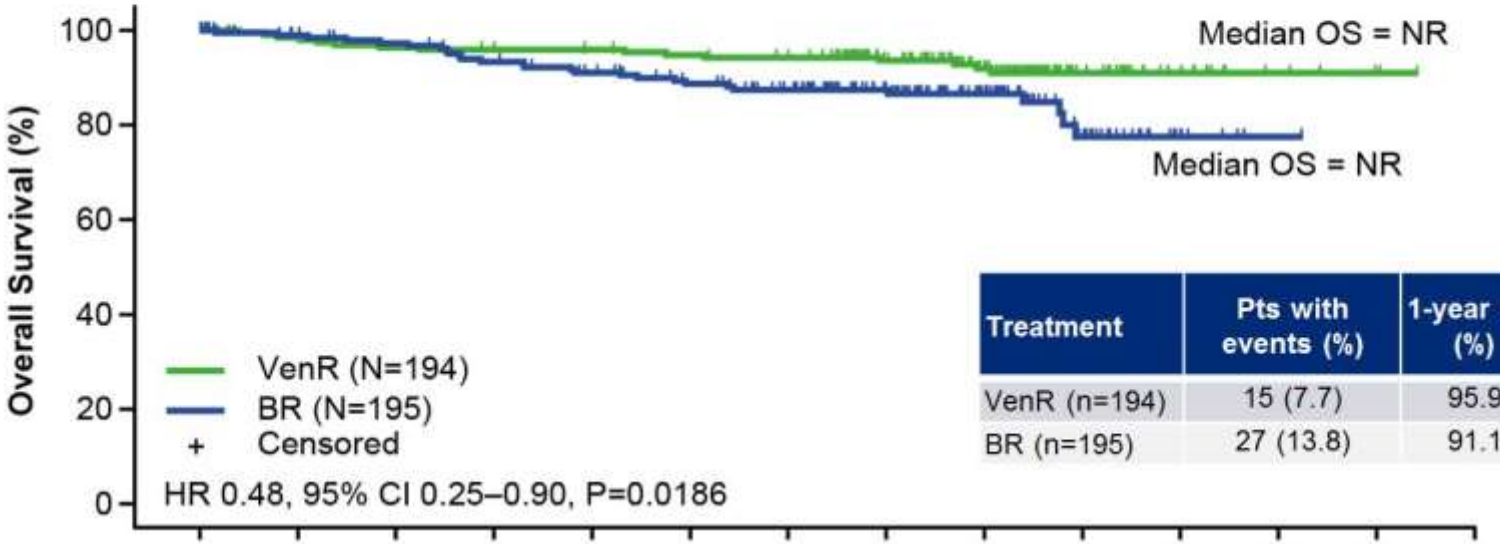
High Peripheral Blood MRD Negativity Rate Maintained Over Time for VenR vs. BR



Adapted from the Seymour presentation at ASH on December 12, 2017

As of 8 May 2017

Clinically Meaningful Improvement in Overall Survival for VenR vs. BR



Treatment	Pts with events (%)	1-year OS (%)	2-year OS (%)
VenR (n=194)	15 (7.7)	95.9	91.9
BR (n=195)	27 (13.8)	91.1	86.6

No. of patients at risk:

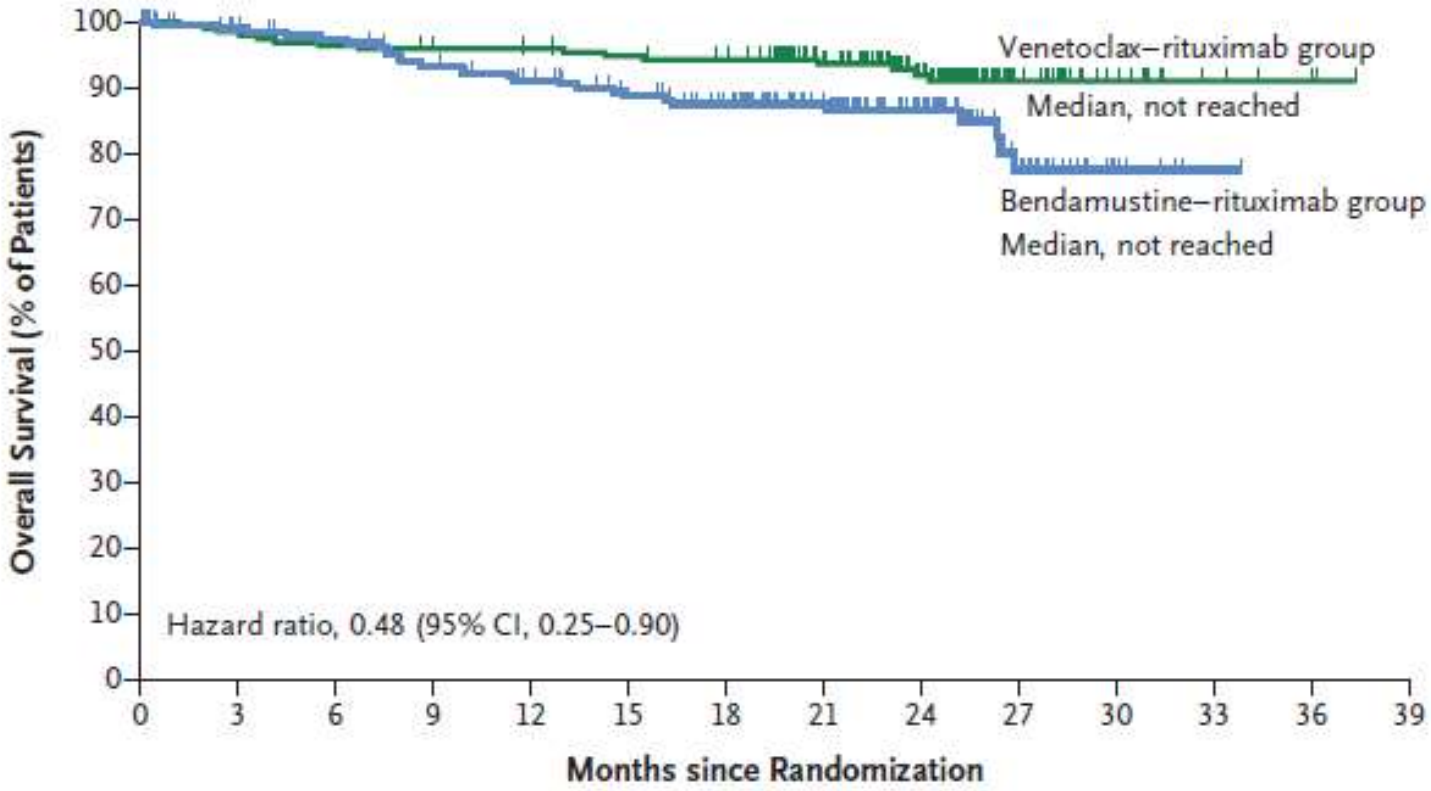
VenR	194	190	185	183	181	178	175	142	102	36	15	5	3
BR	195	181	175	166	158	146	134	102	66	29	8	2	

Descriptive p-values
Pre-specified boundary, P=0.0001.

Adapted from the Seymour presentation at ASH on December 12, 2017

As of 8 May 2017

B **Overall Survival**



No. at Risk

Venetoclax–rituximab group	194	190	185	183	181	178	175	142	102	36	15	5	3
Bendamustine–rituximab group	195	181	175	166	158	146	134	102	66	29	8	2	

Seymour JF et al., *N Engl J Med*. 2018 Mar 22;378(12):1107-1120

Safety Overview

Note: *AE Reporting Period Longer with VenR vs. BR*

Adverse Event (AE) Type, n (%)	Venetoclax + Rituximab (N=194)	Bendamustine + Rituximab (N=188)
Patients with ≥1 AE (all grades)	194 (100)	185 (98)
Serious AEs	90 (46)	81 (43)
Grade 3–4 AEs	159 (82)	132 (70)
Grade 5 AEs	10 (5)*	11 (6)†

*Pneumonia (n=3; 2 in setting of PD/Richter transformation, 1 with thrombocytopenia, leading to death); and sepsis, cardiac failure, myocardial infarction, sudden cardiac death, colorectal cancer, status epilepticus, and acute respiratory failure (all n=1).

†Sepsis (n=2), lung cancer (n=2), and Listeria sepsis, Scedosporium infection, lymphoma, hemorrhagic stroke, pulmonary embolism, AML and sudden death (all n=1).

Adapted from the Seymour presentation at ASH on December 12, 2017

Adverse event reporting period: up to 90 days after end of bendamustine treatment (maximum 6 months); up to 28 days after end of venetoclax treatment (maximum 2 years).

As of 8 May 2017

Grade 3–4 AEs; ≥2% Difference in Incidence Between Arms

Note: *AE Reporting Period Longer with VenR vs. BR*

AEs, n (%)	Venetoclax + Rituximab (N=194)	Bendamustine + Rituximab (N=188)
Neutropenia	112 (58)	73 (39)
Anemia	21 (11)	26 (14)
Thrombocytopenia	11 (6)	19 (10)
Febrile Neutropenia	7 (4)	18 (10)
Pneumonia	10 (5)	15 (8)
Infusion-Related Reaction	3 (2)	10 (5)
Tumor Lysis Syndrome	6 (3)	2 (1)
Hypotension	0	5 (3)
Hyperglycemia	4 (2)	0
Hypogammaglobulinemia	4 (2)	0

Adapted from the Seymour presentation at ASH on December 12, 2017

Adverse event reporting period: up to 90 days after end of bendamustine treatment (maximum 6 months); up to 28 days after end of venetoclax treatment (maximum 2 years).

As of 8 May 2017

Conclusions

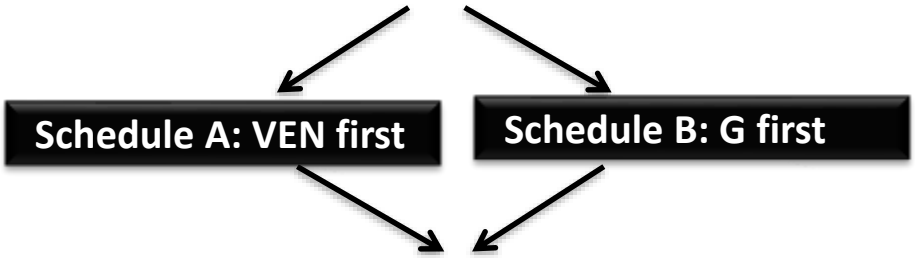
- In MURANO, venetoclax plus rituximab:
  - Superior to bendamustine plus rituximab in prolonging PFS in adults with relapsed/refractory CLL
    - Effects consistent across subgroups, regardless of del(17p) status
  - Superior ORR and rate of peripheral blood MRD negativity
    - Maintained over time
  - Clinically meaningful improvement in overall survival
- Safety consistent with known safety profile in patients with relapsed/refractory CLL
- Venetoclax plus rituximab should be considered as a standard therapeutic option in patients with relapsed/refractory CLL

Phase 1b Venetoclax + Obinutuzumab in TN-CLL: Study Design

Key eligibility criteria
- Treatment-naïve CLL
- ECOG PS 0-1
- Adequate organ function

Primary objective: MTD, Safety, and tolerability
Secondary objective: Efficacy
Exploratory: MRD

Cycle 1: VEN 400 mg (ramp up per US label);
G 100 mg D1, 900 mg D2, 1000 mg D8,15 (28-day cycle)



6 cycles of VEN+G, followed by 6 cycles of VEN monotherapy
(VEN could be extended after 1 yr depending on CLL status)

Baseline Characteristics	1L CLL (N=32)
Median age; years (range)	63 (47-73)
Male; n (%)	20 (63)
TLS risk; n (%)	
Medium	23 (72)
High	7 (22)
Schedule A (VEN first); n	6
Schedule B (G first); n	26
β2M ≥3.5 mg/mL, n/N (%)	19/32 (59)

Baseline Characteristics	1L CLL (N=32)
Cytogenetic assessment available, n/N (%)	
Del(17p)	5/29 (17)
Del(11q)	6/29 (21)
Trisomy 12	6/29 (21)
Del (13q)	11/29 (38)
TP53 mutation, n/N (%)	5/26 (19)
IGHV unmutated, n/N (%)	16/27 (57)
CD38+, n/N (%)	12/25 (48)

Flinn et al. ASH 2017. Abstract #430.

Phase 1b Venetoclax + Obinutuzumab in TN-CLL: Safety

- All pts experienced ≥1 AE
- 4 Gr 3-4 infections were reported: appendicitis, diverticulitis, enterobacter bacteremia, and respiratory infection
- Clinical TLS was not observed; 1 laboratory TLS was observed with G (prior to VEN administration)
- 1 patient discontinued treatment due to AE (Grade 3 diarrhea)
- As of data cut-off, no deaths occurred in 1L CLL pts

Adverse events, n (%)	Total (N=32)
AEs of Any Grade in >25% pts	
Nausea	22 (69)
Infusion-relate reaction	21 (66)
Neutropenia	21 (66)
Diarrhea	18 (56)
Pyrexia	15 (47)
Fatigue	14 (44)
Thrombocytopenia	13 (41)
Headache	12 (38)
Chills	11 (34)
Vomiting	11 (34)
Cough	10 (31)
Flushing	10 (31)
Anemia	9 (28)
Dyspnea	9 (28)
Grade 3-4 AEs in ≥ 2 pts	
Neutropenia	17 (53)
Thrombocytopenia	5 (16)
Febrile neutropenia	4 (13)

Flinn et al. ASH 2017. Abstract #430.

Phase 1b Venetoclax + Obinutuzumab in TN-CLL: Efficacy

- With median time on study of 18.5 mo, all 32 pts responded to the treatment
- ORR 100%; CR/CRi 72% and PR 28%
  - High CR rates (60-100%) across subgroups (del17p, del11q, trisomy 12, del13q, *IGHV* status, no abnormalities)
- 4/7 patients with PR and BM MRD- classified as PD due to residual lymphadenopathy
- 3 patients had disease progression:
  - 2 with Richter transformation: HL in one patient with del(17p) at screening, and DLBCL in a patient with trisomy 12 and IGHV unmutated at baseline
  - 1 patient with PD: had del(11q), del(17p), and IGHV unmutated at baseline

MRD Negativity, %	N=32
PB MRD Negativity (< 10^{-4})	
Best MRD negativity	100
3 mos after last G	91
9 mos after last G	91
12 mos after last G	72
≥3 mos after end of all Tx	70
BM MRD Negativity (< 10^{-4})	
All 1L patients	75
CR/CRi	74 (n=23)
PR	78 (n=9)

PFS	All 1L Patients
Median	NR
12-month, %	100
15-month, % (95% CI)	93.8 (85.4 – 100)
18-month, % (95% CI)	90.5 (80.3 – 100)

Flinn et al. ASH 2017. Abstract #430.

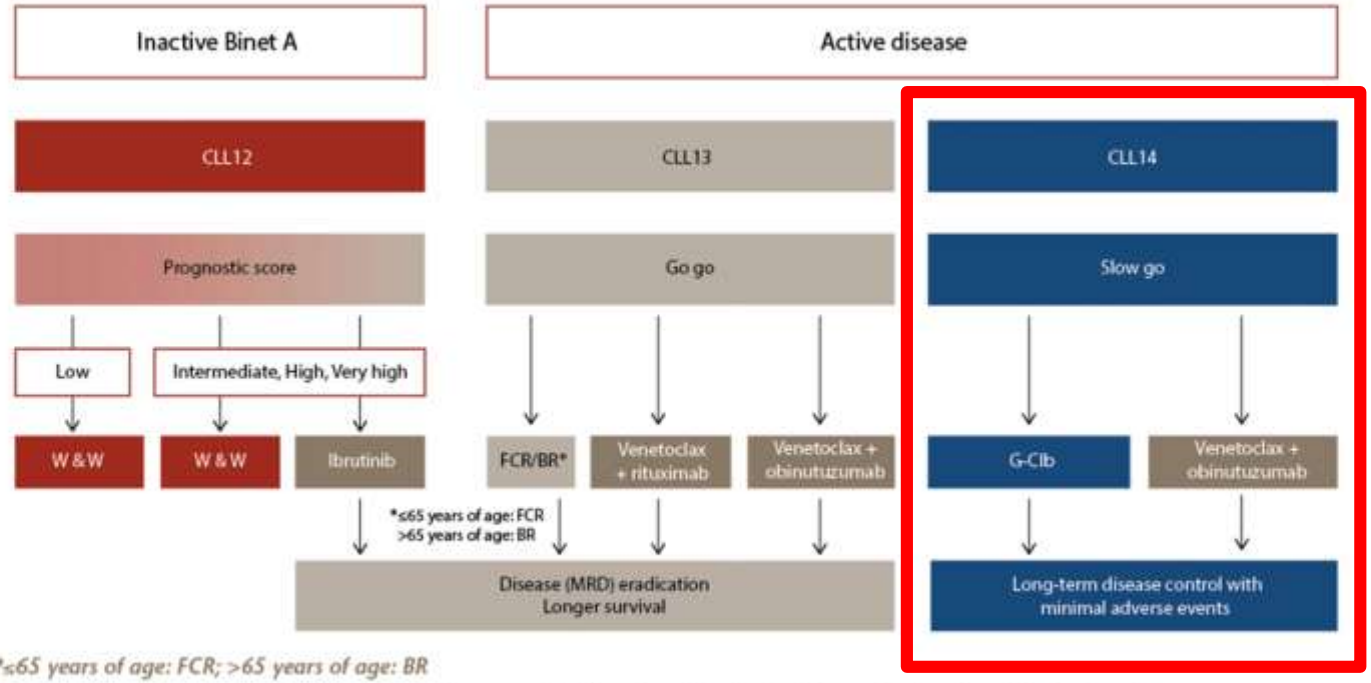
Phase 1b Venetoclax + Obinutuzumab in TN-CLL: Conclusions

- In this phase 1b GP28331 study of VEN + G, all 1L CLL patients treated with VEN + G achieved a response, with high CR rates across subgroups
- High rates of BM MRD- were observed regardless of response status
- Undetectable PB MRD- rates were maintained post-treatment
- VEN + G has acceptable/manageable safety profile: no clinical TLS, no deaths, no synergistic toxicity (consistent with known safety profiles of VEN and G)
- High CR rates, MRD- and preliminary PFS predict durable clinical outcomes for 1L CLL patients treated with VEN + G for 1-year fixed duration

Flinn et al. ASH 2017. Abstract #430.

DEUTSCHE STUDIENGRUPPE

DCLLSG



*≤65 years of age: FCR; >65 years of age: BR

BR = bendamustine, rituximab; CLL = chronic lymphocytic leukemia; FCR = fludarabine, cyclophosphamide, rituximab; G-Clb = obinutuzumab, chlorambucil; GCLLSG = German CLL Study Group; MRD = minimal residual disease; W & W = watch and wait

Safety and Efficacy of Venetoclax and Obinutuzumab in Untreated CLL and Coexisting Medical Conditions: Final Results of the Run-in Phase of the Randomized CLL14 Trial (BO25323)(13 pts)

Total CIRS-score > 6 or creatinine clearance: 30 - 70 mL/min

Age ≥ 18 years

At month 15, 11 of 12 patients were evaluable for final response assessment.

All patients responded to therapy.

CR occurred in 7 of the 12 patients including one CRi.

Ten of 12 patients had no detectable ($<10^{-4}$) MRD in PB and one patient was assessed intermediate ($\geq 10^{-4} < 10^{-2}$).

At month 15, there were no events of disease progression or deaths, translating into an estimated progression-free survival of of 100%.

Fischer K et al., *Blood*. 2017 Mar 21 [Epub ahead of print]

Ibrutinib + Venetoclax in R/R CLL – Initial Results: Study Design, Baseline,Disposition

Bloodwise TAP CLARITY Study

Key eligibility criteria
- Relapsed within 3 y of FCR or BR *or*
- Had del17p and had failed ≥1 line of therapy

8 wks of IBR (420mg/day), followed by the addition of VEN, which is ramped up from 10-400mg/day over 5 weeks

Primary endpoint: MRD eradication in the marrow after 12 mo of IBR+VEN

Secondary endpoints: MRD eradication from the marrow after 6 and 24 mo of IBR+VEN; safety

Baseline (n=54)	
Median prior therapies, no (range)	1 (1-6)
FCR or BR, %	81
Relapse ≤3 years of BR or FCR, %	44
Idelalisib, %	20
Unmutated *IGHV, %*	74
Del(17p), % (n=51)	20
Del(11q), % (n=51)	25

- 4 patients stopped IBR before adding VEN due to toxicity
- 50 patients recruited to combination part of the trial
- 49 patients successfully passed through VEN escalation phase
- 46 patients received ≥8 weeks of IBR+VEN

Hillmen et al. ASH 2017. Abstract #428

Ibrutinib + Venetoclax in R/R CLL: Safety and Efficacy

Grade 3/4 adverse event, n	N=54
Any grade 3/4 AE	54
Neutropenia	22
Gastrointestinal disorders	7
Infections and infestations	7

- 1 patient had TLS (at 200 mg dose of VEN) – increasing phosphate and creatinine
  - Managed by delaying VEN, rapid re-escalation with no further TLS

Time point		n	Median MRD in PB (x 10^9/l)	25th centile (x 10^9/l)	75th centile (x 10^9/l)
Screening		46	54.5	13	92
Day 0	Pre-IBR	46	43.5	10.3	94
Week 8	Pre-VEN	46	60	14	150
Week 12	End of VEN escalation	45	1.1	0.23	6.25
Month 4	After 8 weeks of VEN + IBR	46	0.019	0.0028	0.21
Month 5	After 12 weeks of VEN + IBR	45	0.012	0.0011	0.1
Month 8	After 6 month VEN + IBR	37	0.001	0	0.025

Hillmen et al. ASH 2017. Abstract #428

Ibrutinib + Venetoclax in R/R CLL: Efficacy

- 38 patients had ≥6 months of IBR+VEN (efficacy evaluable; BM and CT-scan)

	n	CR, %	CRi, %	PR, %	ORR, %
All patients*	38	39	8	53	100
FCR/BR relapsed <36 months[1]	17	53	12	35	100
Prior idelalisib[2]	7	43	0	57	100

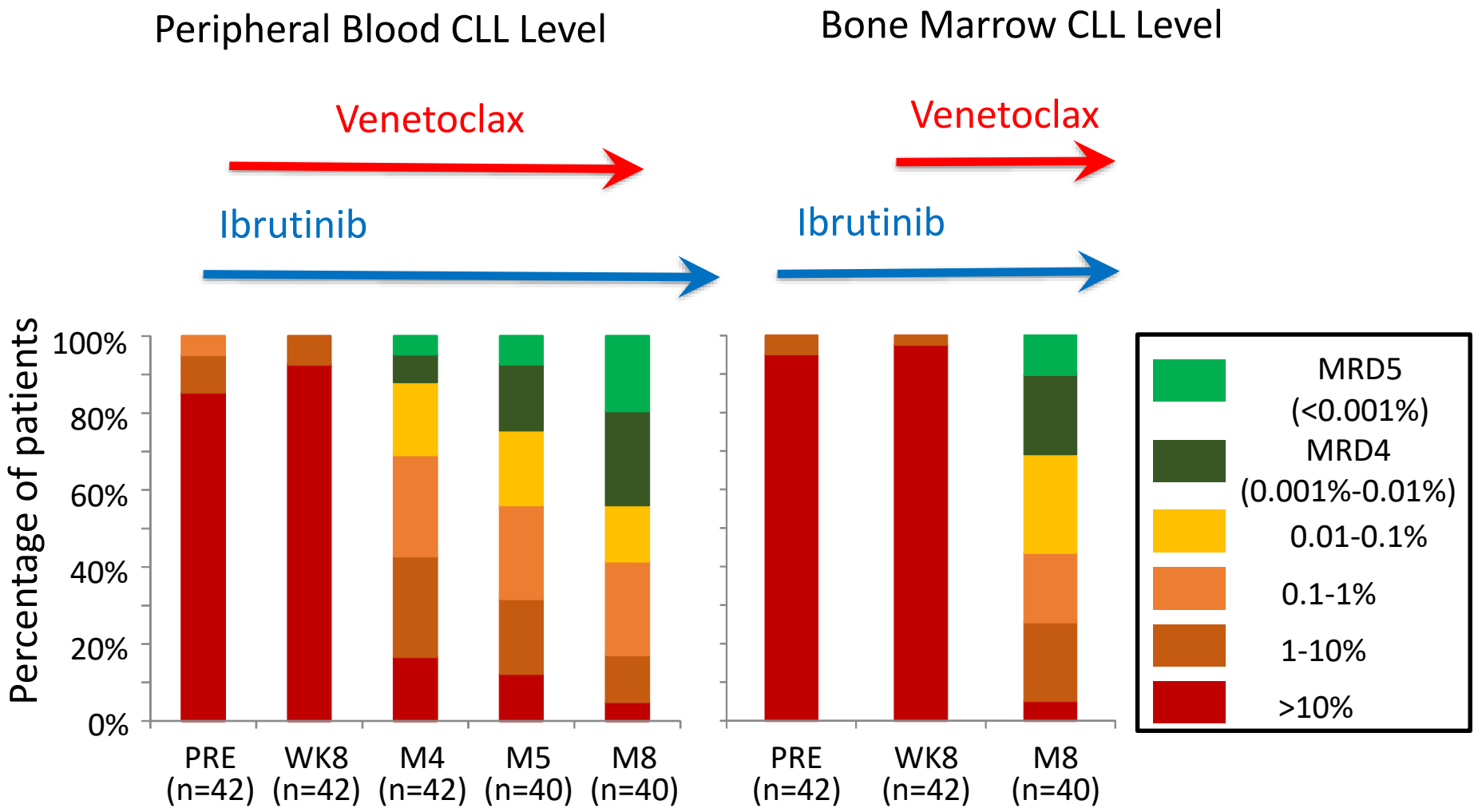
*% calculated over total number of patients assessed for response (38 patients)
[1]% calculated over total patients who had FCR/BR and relapsed <36 months and were assessed for response
[2]% calculated over total number of patients who had idelalisib before joining study and were assessed for response

- MRD PB or BM <0.01% CLL cells (10^{-4}) by flow cytometry

At month 8	n	PB MRD$^-$, %	BM MRD$^-$, %	Trephine normal, %
All patients	38	37	32	84
FCR/BR relapsed <36 months	17	52	41	94
Prior idelalisib	7	57	43	100

Hillmen et al. ASH 2017. Abstract #428

PB & BM MRD level by time-point (up to 6 months I+V)



Hillmen et al. ASH 2017. Abstract #428

Ibrutinib + Venetoclax in R/R CLL: Conclusions

- The combination of IBR with VEN is well tolerated in R/R CLL, with only one experiencing biochemical TLS and predictable AEs (GI or neutropenia most common)
- All patients have an objective response and 18/38 (47%) were in CR/CRi after 6 months of IBR + VEN; 32% were MRD- in BM at that time
- Based on these results, the phase III NCRI FLAIR trial has been modified to include IBR + VEN in frontline CLL

Phase 2 Venetoclax + Ibrutinib TN High-Risk CLL and R/R CLL: Study Design and Baseline

Eligibility criteria
- age ≥18 yrs
- ECOG PS ≤2,
- Adequate renal function
- No hepatic impairment

Primary endpoint
- achievement of CR/CRi

Cohort 1 (relapsed/refractory CLL);

Cohort 2 (untreated pts with at least one high-risk feature: del(17p), mutated TP53, del(11q), unmutated IGHV, ≥65 yrs)

IBR monotherapy 420mg daily for the first 3 months, followed by addition of VEN (weekly dose escalation to 400 mg daily). IBR may be continued indefinitely; VEN for a total of 2 yrs.

Baseline, n (%) or median [range]	Cohort 1 (n=37)	Cohort 2 (n=40)
Age, yrs	59 [32-76]	65 [25-82]
Gender, M	30 (81)	30 (75)
Prior Therapies	1 [1-4]	-
Del(17q)	11 (30)	7 (18)
Del(11q)	14 (38)	10 (25)
Del(13q)	5 (14)	5 (12)
Trisomy 12	5 (14)	5 (12)
Negative FISH	2 (5)	5 (12)

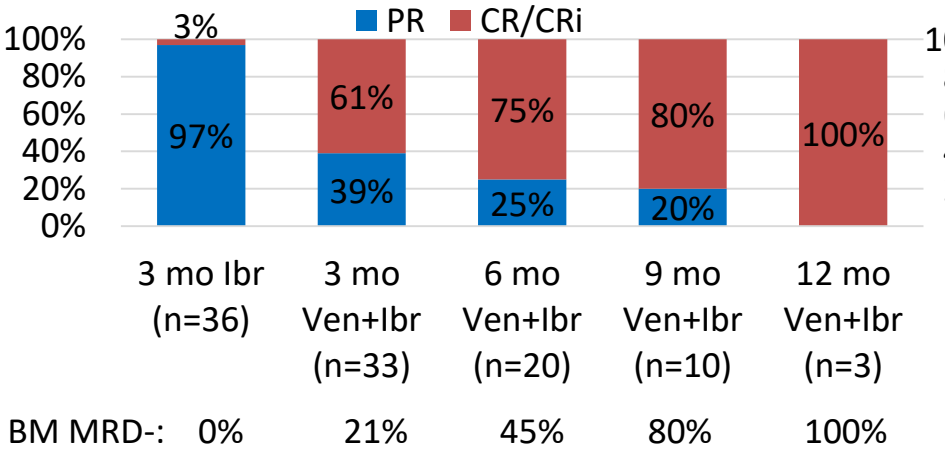
Baseline, N (%)	Cohort 1	Cohort 2
IGHV	n=31	n=37
Unmutated	27 (87)	30 (81)
Mutated	4 (13)	7 (19)
Cytogenetics	n=29	n=39
Complex	5 (17)	6 (15)
Diploid	10 (34)	16 (41)
Mutations	n=32	n=40
TP53	10 (31)	7 (18)
NOTCH1	3 (9)	14 925)
SF3B1	7 (22)	11 (28)

Jain et al. ASH 2017. Abstract #429.

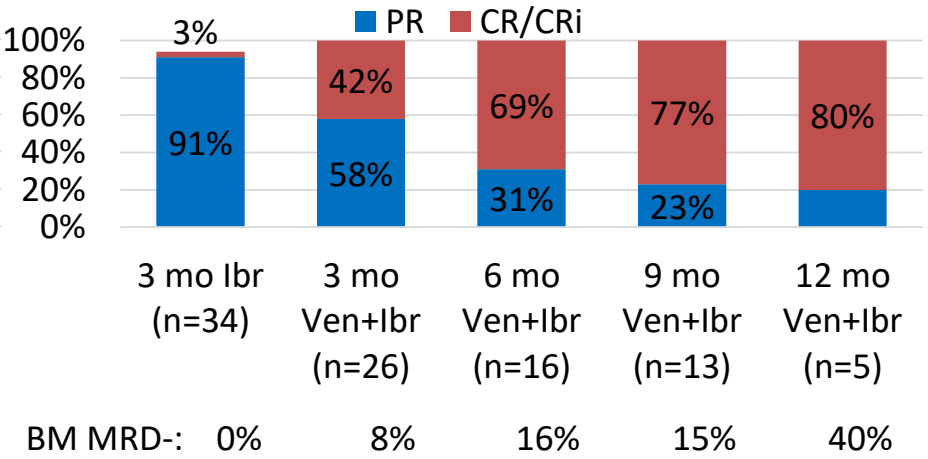
Phase 2 Venetoclax + Ibrutinib TN High-Risk CLL and R/R CLL: Results

- Median follow-up is 7.5 months (range, 0.6-12.1)
- A total of 15 pts have come off study
  - ➢ 7 during the IBR monotherapy; 8 after starting VEN
  - ➢ 70 patients started venetoclax (34 R/R, 35 TN)

Firstline:



R/R Cohort:



Jain et al. ASH 2017. Abstract #429.

Phase 2 Venetoclax + Ibrutinib TN High-Risk CLL and R/R CLL: Results

- 54% had down-grading of TLS risk category
- 2 pts had lab TLS, no clinical TLS
- 44% grade 3/4 neutropenia;
- 4% grade 3/4 thrombocytopenia
  - ➢ 70% grade 3/4 neutropenia and all grade 3/4 thrombocytopenia occurred during Ven+Ibr
- Infections: neutropenic fever (8%), pneumonia, cellulitis, septic arthritis (each 2%)
  - ➢ 2/3 of infections occurred during Ibr monotherapy phase
- 13% atrial fibrillation
- Dose reduction:
  - 36% ibrutinib
  - 26% venetoclax

TLS risk (n=70)	Baseline	Post IBR
High	18 (26)	2 (3)
Medium	38 (54)	29 (41)
Low	14 (20)	39 (56)

Jain et al. ASH 2017. Abstract #429.

Phase 2 Venetoclax + Ibrutinib TN High-Risk CLL and R/R CLL: Conclusions

- Combination of Ven+Ibr provides a safe and effective non-chemo treatment for CLL
- 54% of patients had down-grading of TLS risk category with use of ibrutinib
- Responses continue to improve with time with many patients achieving BM MRD- remission

Phase 1b/2: Obinutuzumab, Ibrutinib, and Venetoclax in CLL - Treatment Naive Cohort: Study Design and Baseline

Inclusion criteria
- TN, symptomatic CLL
- ECOG PS ≤1
- Preserved end-organ and BM function

Exclusion criteria
- Uncontrolled autoimmune thrombocytopenia or anemia
- Clinically apparent Richter's Transformation
- CNS involvement by leukemia
- Use of Warfarin or potent CYP3A4 inhibitors or inducers ≤ 7 days prior to study treatment

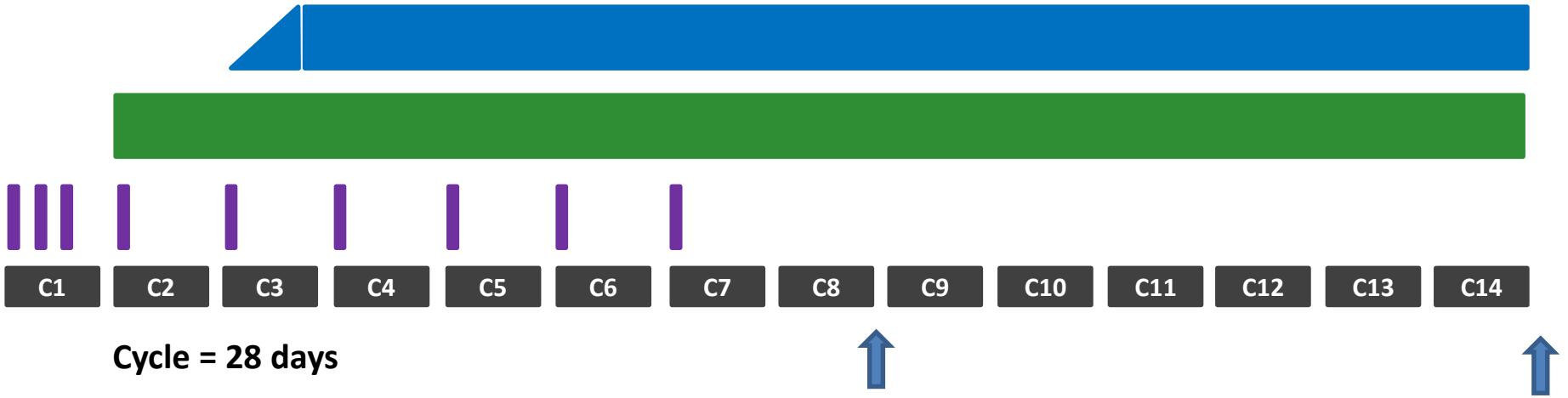
Fourteen 28-day cycles OBI+IBR+VEN started sequentially over the first 3 cycles
- C1: OBI (D1: 100mg, D2: 900mg, D8,D15: 1,000mg, C2-8 D1: 1,000mg)
- C2: add IBR in C2 (C2-14 D1-28: 420mg)
- C3: add VEN in C3 with dose escalation according to its US label

Primary objective: MRD (-) CR after C14 are expected in May 2018

Baseline Characteristics, %	N=25	Baseline Characteristics, %	N=25
Median age, yrs (range)	59 (24-77)	**Unmutated IGHV**	71
Male	60	**Complex karyotype**	24
Del(11)q	20	**Trisomy 12**	12
Del(17)p	12	**TLS Risk high**	28
Del(13)q	20	**TLS Risk medium**	72
		TLS Risk low	0

Rogers et al. ASH 2017. Abstract #431

Treatment Schema



Obinutuzumab 1000 mg IV

Ibrutinib 420 mg daily PO

Venetoclax (cohort dose) mg daily PO

Response assessed (CT + BMBx)
– After Cycle 8
– 2 months beyond end Cycle 14

- Drugs initiated sequentially to limit risk for tumor lysis syndrome (TLS)
- All patients discontinue treatment after Cycle 14
- Sequential cohorts of 3 underwent dose escalation to target venetoclax dose in Cycle 3 to establish MTD of venetoclax in combination

Phase 1b/2: Obinutuzumab, Ibrutinib, and Venetoclax in CLL - Treatment Naive Cohort: Disposition and Efficacy

- With median follow-up of 14.7 mo (range, 7.4-16.1), 22 patients remain on study
  - 1 discontinued treatment after C7 at the discretion of the treating physician
  - 1 after C10 for patient preference
  - 1 after C10 for AEs of neutropenia and colitis (deceased)
- 12 patients completed combination treatment

Responses post-C8, n (%)	N=25	MRD (–) Both*
ORR	24 (96)	14/24 (58%)
CR	5 (20)	8/13 (46)
CRi	8 (32)	
PR	11 (46)	6/11 (55)
SD	0	
PD	0	
NR	1 (4)	

- CRi due to cytopenias with (4/8) or without (4/8) hypocellular marrow
- 6/11 PR patients met count and marrow requirements for CR but had LN >1.5 cm
- All but 1 patients had no morphologic evidence of CLL in bone marrow

*4-color flow cytometry on PB and BM.

Rogers et al. ASH 2017. Abstract #431

Phase 1b/2: Obinutuzumab, Ibrutinib, and Venetoclax in CLL - Treatment Naive Cohort: Safety

Grade 1/2 Tx-Related	%
Infusion related reaction	76
Nausea	60
Bruising	48
Oral mucositis	48
Dyspepsia	48
Hypertension	44
Diarrhea	44
Fatigue	40
Maculo-papular rash	40
Myalgia	36
Arthralgia	32
Hyperuricemia	32
Weight gain	32
Bilirubin increased	28
Chills	28
Hypocalcemia	28

Grade 3/4 Tx-Related	%
Hypertension	36
Dyspepsia	4
Arthralgia	4
Hyperuricemia	4
AST increased	4
ALT increased	4
Atrial fibrillation	4
Colitis	4
Pneumonia	4
Menorrhagia	4
Sepsis	4

- No cases of clinical or laboratory TLS
- Hematologic AEs were the most frequently reported AEs
- No cases of neutropenic fever

Hematologic Tx-Related AEs, %	Grade 1/2	Grade 3/4	Any Grade
Thrombocytopenia	48	36	84
Lymphopenia*	44	32	76
Neutropenia	28	48	76
Leukopenia*	40	36	76
Lymphocytosis*	20	4	24
Anemia	16	0	16

*Anticipated therapeutic drug effect

Rogers et al. ASH 2017. Abstract #431

Phase 1b/2 Obinutuzumab, Ibrutinib, and Venetoclax in CLL - Treatment Naive Cohort: Conclusions

- OBIN, IBR, and VEN can be safety administered in combination as 1L treatment for CLL; majority of AEs were hematologic, high-grade AEs were rare
- This combination has high initial response rates (96% ORR)
- Combination therapy is extremely effective at eliminating detectable CLL
- Results from the primary endpoint are expected in May 2018
- Further follow-up is required to determine PFS

Future ONCOLOGY

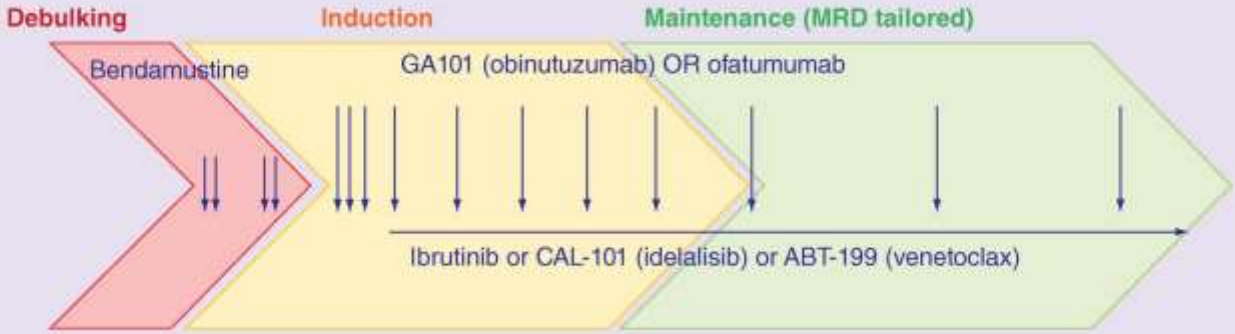
Clinical Trial Protocol

CLL2-BXX Phase II trials: sequential, targeted treatment for eradication of minimal residual disease in chronic lymphocytic leukemia

- CLL2-BIG: bendamustine, followed by ibrutinib and GA101 (obinutuzumab);
- CLL2-BAG: bendamustine, followed by ABT-199 (venetoclax) and GA101 (obinutuzumab);
- CLL2-BCG: bendamustine, followed by CAL-101 (idelalisib) and GA101 (obinutuzumab);
- CLL2-BIO: bendamustine, followed by ibrutinib and ofatumumab.

Cramer P et al., *Future Oncol*. 2018 Mar;14(6):499-513.

CLL2-BXX studies



Debulking (two cycles with a duration of 28 days): bendamustine

Should be omitted in case of:
Contraindications for the usage of bendamustine (known hypersensitivity to bendamustine, refractoriness to bendamustine or chemotherapy-induced bone marrow damage) or if not necessary due to low tumor burden (ALC ≤25,000/µl and absence of bulky disease with lymph nodes ≤5 cm in the longest diameter)

Bendamustine:	Cycles 1–2: d1 & 2: 70mg/m^2 iv.

Induction (six cycles with a duration of 28 days): CD20 antibody & kinase inhibitor/bcl-2 antagonist

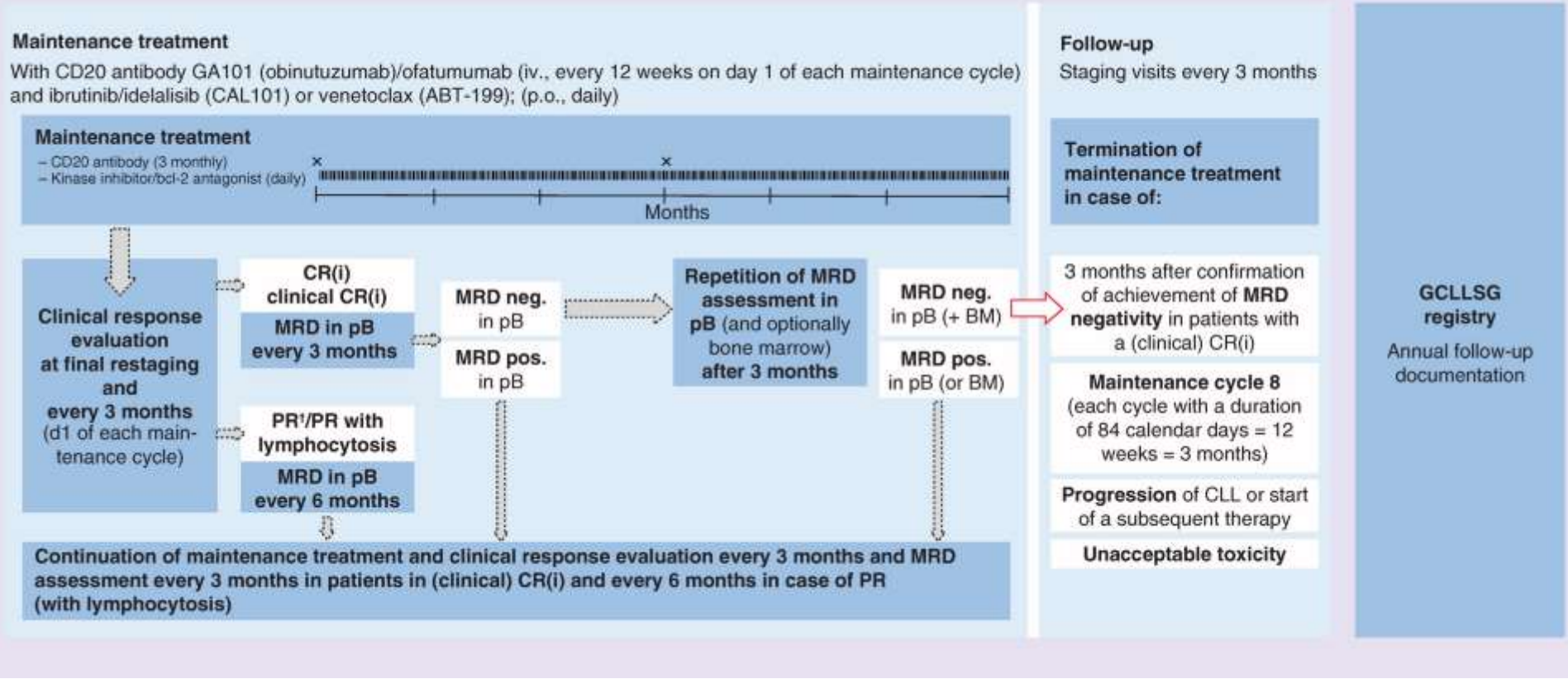
GA101 (obinutuzumab, Gazyvaro©):	Cycle 1: d1: 100 mg iv., d1 (or 2): 900 mg, d8 & 15: 1000 mg, Cycles 2–6: d1: 1000 mg iv.
Ofatumumab (Azerra©):	Cycle 1: d1: 300 mg iv., d8 & 15: 1000 mg, Cycles 2–6: d1: 1000 mg iv.
Ibrutinib (Imbruvica©):	Cycles 2–6: d1–28: 420 mg p.o. 1x/d
CAL-101 (idelalisib, Zydelig©):	Cycles 2–6: d1–28: 150 mg p.o. 2x/d
ABT-199 (venetoclax, Venclyxto©):	Cycle 2: d1–7: 20 mg p.o., d8–14: 50 mg, d15–21: 100 mg, d22–28: 200–mg p.o., cycles 3–6: d1–28: 400 mg p.o. 1x/d

Maintenance (two to eight cycles with a duration of 84 days): CD20 antibody & kinase inhibitor/bcl-2 antagonist

Will be continued until (whichever occurs first):
3 months after achievement of (clinical) CR/CRI and MRD negativity (confirmed by two measurements), completion of 24 months of maintenance (eight cycles each with a duration of 84 calendar days), progression of CLL, start of new CLL treatment, or unacceptable toxicity

GA101 (obinutuzumab, Gazyvaro©):	Cycle 1–8: d1: 1000 mg iv.
Ofatumumab (Azerra©):	Cycle 1–8: d1: 1000 mg iv.
Ibrutinib (Imbruvica©):	Cycles 1–8: d1–84: 420 mg p.o. 1x/d
CAL-101 (idelalisib, Zydelig©):	Cycles 1–8: d1–84: 150 mg p.o. 2x/d
ABT-199 (venetoclax, Venclyxto©):	Cycles 1–8: d1–84: 400 mg p.o. 1x/d

Cramer P et al., *Future Oncol.* 2018 Mar;14(6):499-513.



Cramer P et al., *Future Oncol*. 2018 Mar;14(6):499-513.

Emerging therapeutic landscapes (2018-?)

R/R: Ven + Ritux
Ven + Ibru

TN: Ven + Ritux
Ven + Obi
Ven + Ibru
Ven + Ibru + Obi
B + XXX + maint