
Venetoclax
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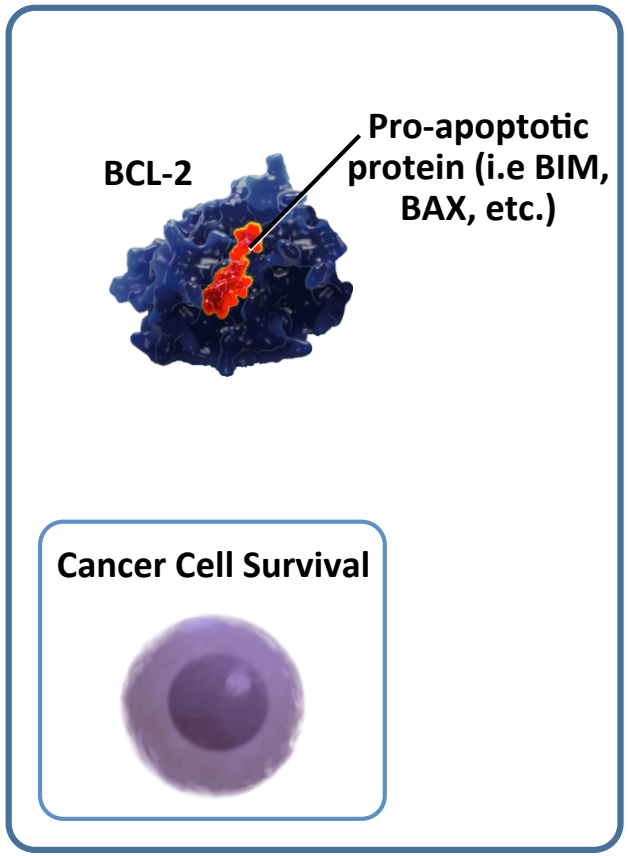
13th November 2017

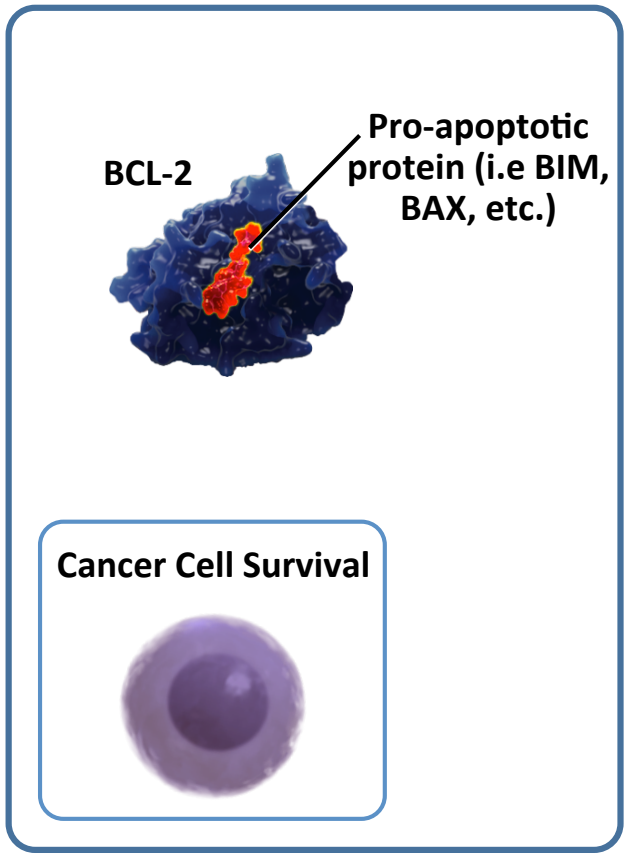
Restoration of apoptosis through BCL-2 inhibition

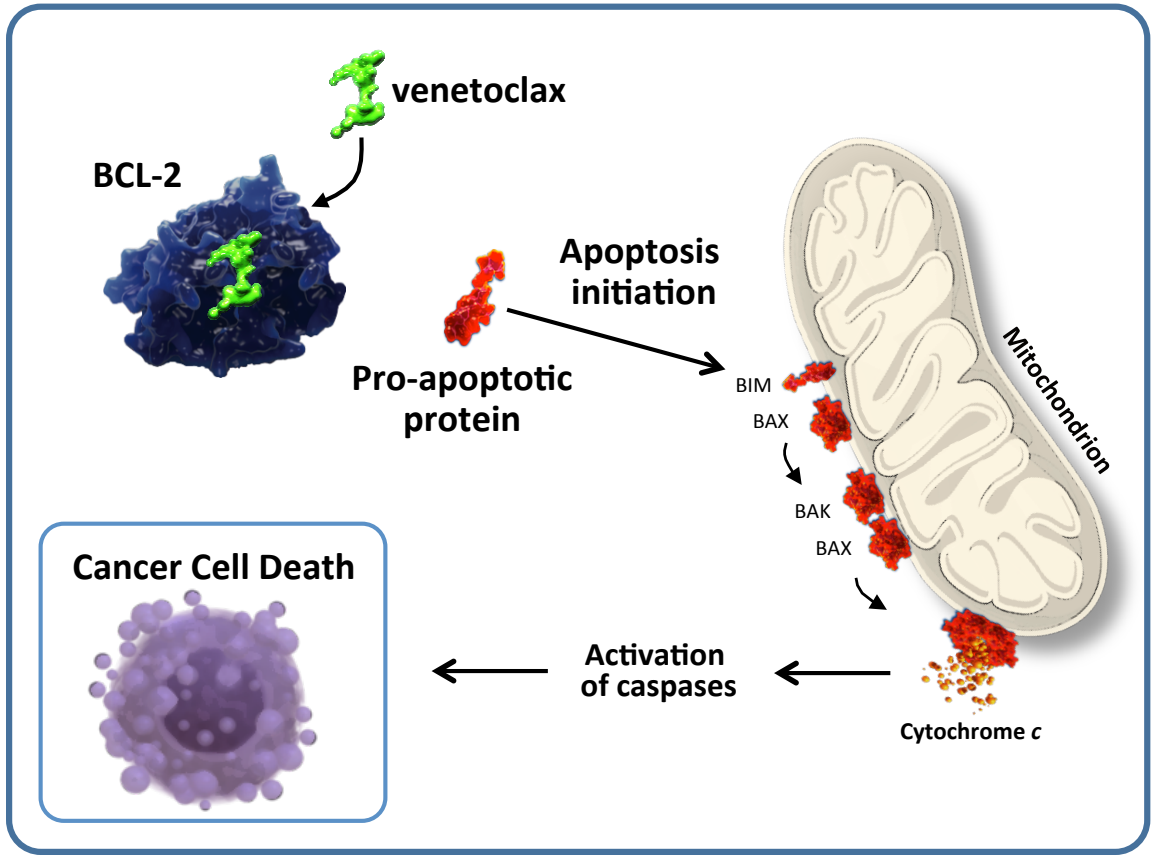


BCL-2 overexpression allows cancer cells to evade apoptosis by sequestering pro-apoptotic proteins.[1-3]

1. Leverson JD, et al. *Cancer*. 2015;7(279). 2. Czabotar, et al. *Nature Reviews* 2014;15:49-63. 3. Plati J, Bucur O, Khosravi-Far R. *Integr Biol (Camb)* 2011;3:279–296. 4. Certo M, et al. *Cancer Cell*. 2006;9(5):351-65. 5. Souers AJ, et al. *Nat Med*. 2013;19(2):202-8. 6. Del Gaizo Moore V et al. *J Clin Invest*. 2007;117(1):112-21.

Restoration of apoptosis through BCL-2 inhibition





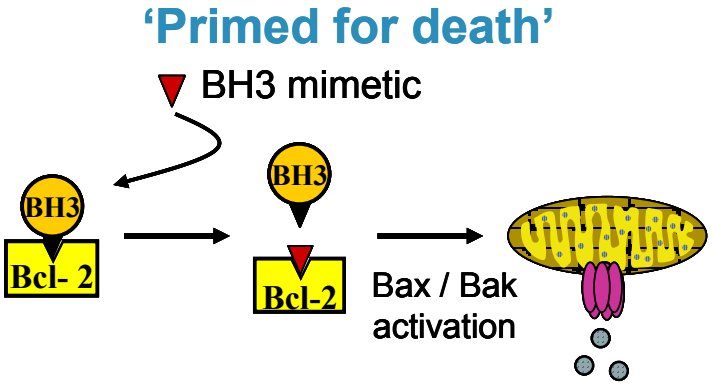
BCL-2 overexpression allows cancer cells to evade apoptosis by sequestering pro-apoptotic proteins.[1-3]

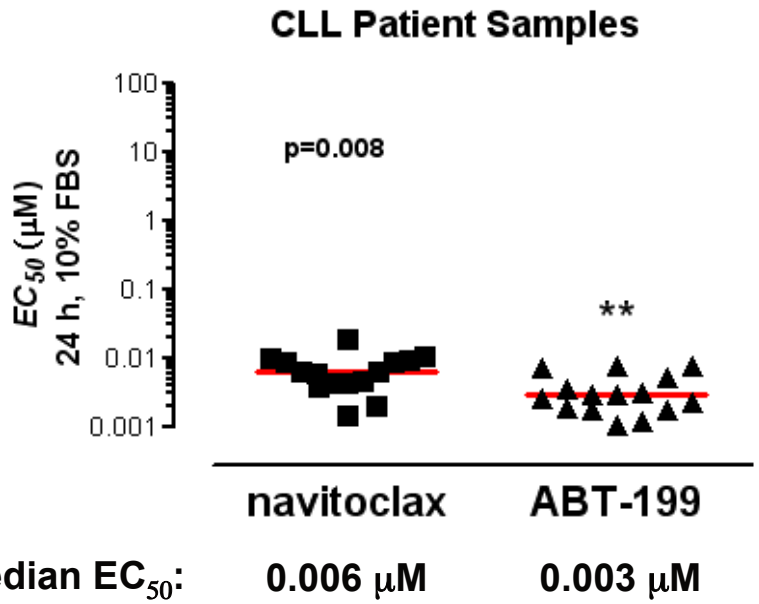
Venetoclax binds selectively to BCL-2, freeing pro-apoptotic proteins that initiate programmed cell death (apoptosis).[4-6]

1. Leverson JD, et al. *Cancer*. 2015;7(279). 2. Czabotar, et al. *Nature Reviews* 2014;15:49-63. 3. Plati J, Bucur O, Khosravi-Far R. *Integr Biol (Camb)* 2011;3:279–296. 4. Certo M, et al. *Cancer Cell*. 2006;9(5):351-65. 5. Souers AJ, et al. *Nat Med*. 2013;19(2):202-8. 6. Del Gaizo Moore V et al. *J Clin Invest*. 2007;117(1):112-21.

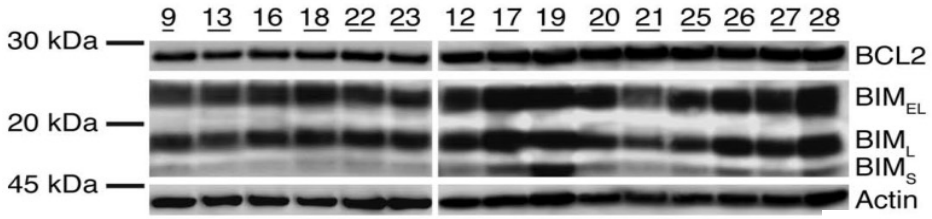
CLL Cell Survival is Dependent on Bcl-2 'primed for death'

- Uniformly high Bcl-2 & Bim expression
- Bcl-2:Bim complex at mitochondria
- Bcl-2 inhibition induces rapid apoptosis
- ABT-199 potently kills primary CLL patient samples (n=15)

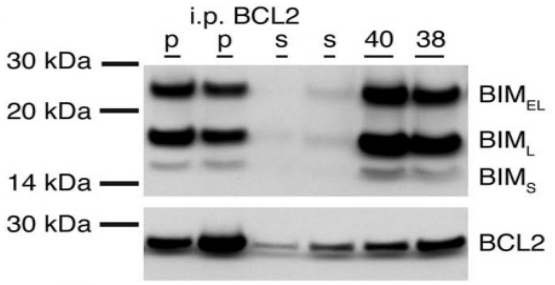




Souers et al, Nat Med 2013



Del Gaizo Moore, et.al. *J. Clin. Invest.* 117, 112, (2007)



M13-982 Trial: Venetoclax in 17p deleted CLL

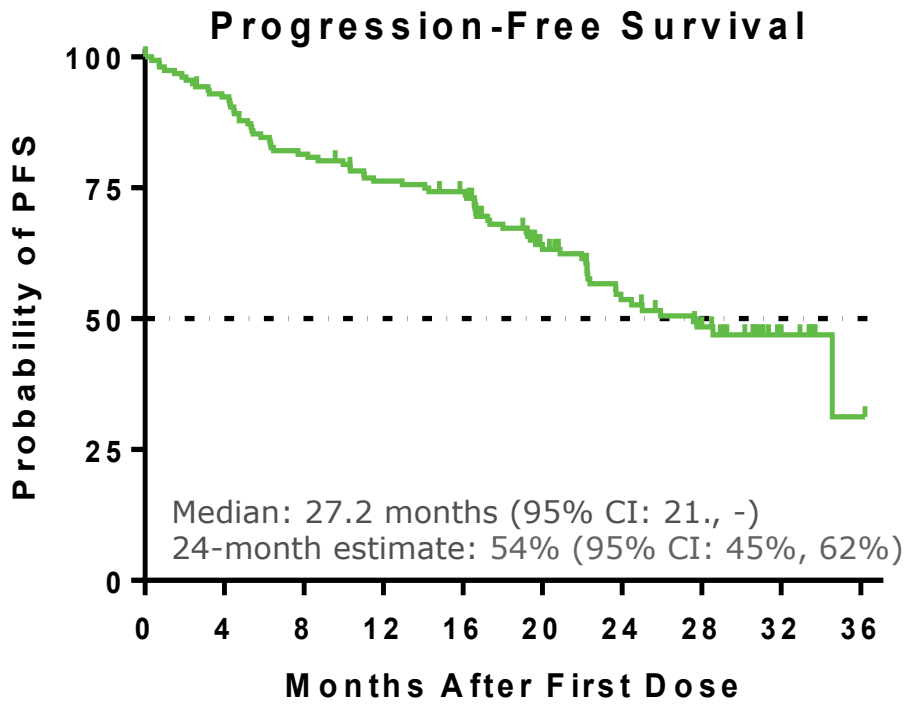
	All Patients N=158
Age, median (range), years	67 (29 – 85)
Number of prior therapies, median (range)	2 (0 – 10)
Fludarabine-containing regimen, n (%) Fludarabine refractory	60 (38) 45 (32)
Prior B-cell pathway receptor inhibitor	18 (11)
TLS risk category,* n (%) Low Medium High	 36 (23) 60 (38) 62 (39)
ALC, median (range), x 10^9/L ≥25 x 10^9/L, n (%)	25 (.3 – 399) 79 (50)
Bulky nodes, n (%) ≥5 cm ≥10 cm	 76 (48) 21 (13)
Unmutated *IGVH*, n/N (%)	45/58 (78)
TP53 mutation, n/N (%)	55/77 (71)
Chromosome 11q deletion, n/N (%)	38/157 (24)
Serum β-2 microglobulin, median (range), μg/mL	3.6 (1.3 – 31)

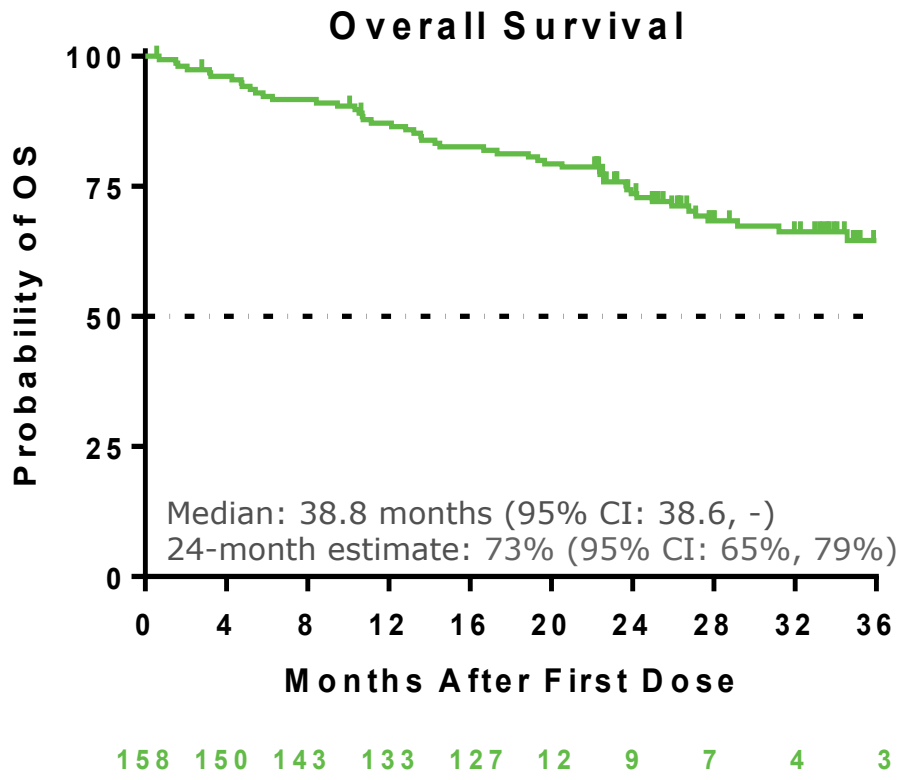
*TLS risk categories are defined as follows: Low – all lymph nodes <5 cm and ALC <25 x10^9/L, Medium – any lymph node ≥5 cm to <10 cm or ALC >25 x10^9/L, High – any lymph node >10 cm OR any lymph node ≥5 cm and ALC >25 x10^9/L.

Stilgenbauer S et al. *Lancet Oncol* 2016;17:768–778.; EHA 2017

M13-982 Trial: Venetoclax in 17p deleted CLL

Outcome on Venetoclax Monotherapy





As of 4Apr2017

Stilgenbauer S et al. *Lancet Oncol* 2016;17:768–778.; EHA 2017

M13-982 Trial: Venetoclax in 17p deleted CLL

Best MRD Status

	Flow Cytometry and/or NGS*
Peripheral blood	
No. of patients	101
MRD negative	40
MRD positive	61
Bone marrow	
No. of patients	74
MRD negative	18
MRD positive	56

*Specimens assayed by flow cytometry and/or NGS. Discordant results at the same visit were called MRD positive.

- 30% (48/158) patients demonstrated blood MRD negativity by flow cytometry and confirmed by NGS in 21/29 who had an evaluable matched time point specimens

As of 4Apr2017

Stilgenbauer S et al. *Lancet Oncol* 2016;17:768–778.; EHA 2017

M13-982 Trial: Venetoclax in 17p deleted CLL

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	CR/CRi	nPR	PR
Total peripheral blood negative	20	1	19
Peripheral blood negative and bone marrow negative	14	0	4‡
Peripheral blood negative but bone marrow positive†	3	0	4
Peripheral blood negative but bone marrow not assessed	3	1	11

†BM MRD assessment occurred concurrent with 1 or after 2 PB negative assessments.
‡Sites of residual disease in PR patients

- Splenomegaly
- 18 mm lymph node
- 20 mm lymph node
- 19 mm lymph node and hepatomegaly

- 47% (7/15) of patients without BM assessment demonstrated sustained peripheral blood MRD negativity (≥24 weeks) (4% [7/158] of all patients), and the remaining patients either had no other blood assessments (n=3;1 CR, 1 nPR, 1 PR) or became MRD positive at a subsequent assessment (n=5; 1 CR, 4 PR)

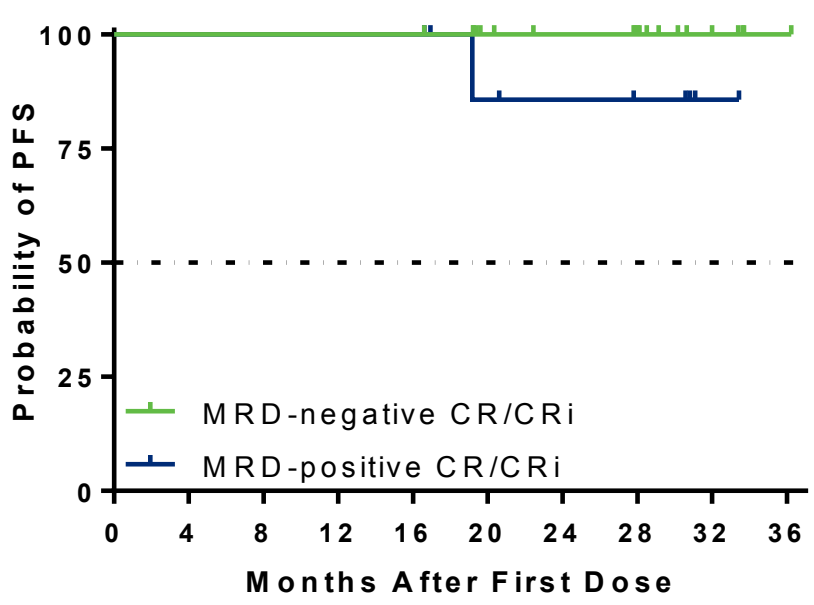
As of 4Apr2017

Stilgenbauer S et al. *Lancet Oncol* 2016;17:768–778.; EHA 2017[8]

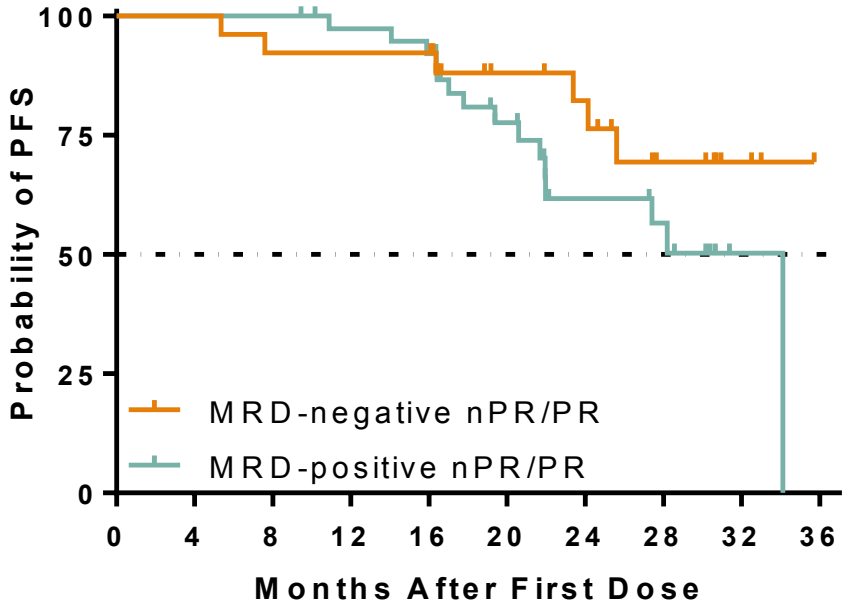
M13-982 Trial: Venetoclax in 17p deleted CLL

MRD in Peripheral Blood and PFS

- 24-month PFS estimates of MRD in blood by flow cytometry:
  - MRD-negative CR/CRi: 100% (n=22)
  - MRD-positive CR/CRi: 86% (n=9)
  - MRD-negative nPR/PR: 83% (n=26)
  - MRD-positive nPR/PR: 62% (n=40)



Pts at risk										
	22	22	22	22	22	18	16	14	6	2
	9	9	9	9	9	7	6	5	2	1

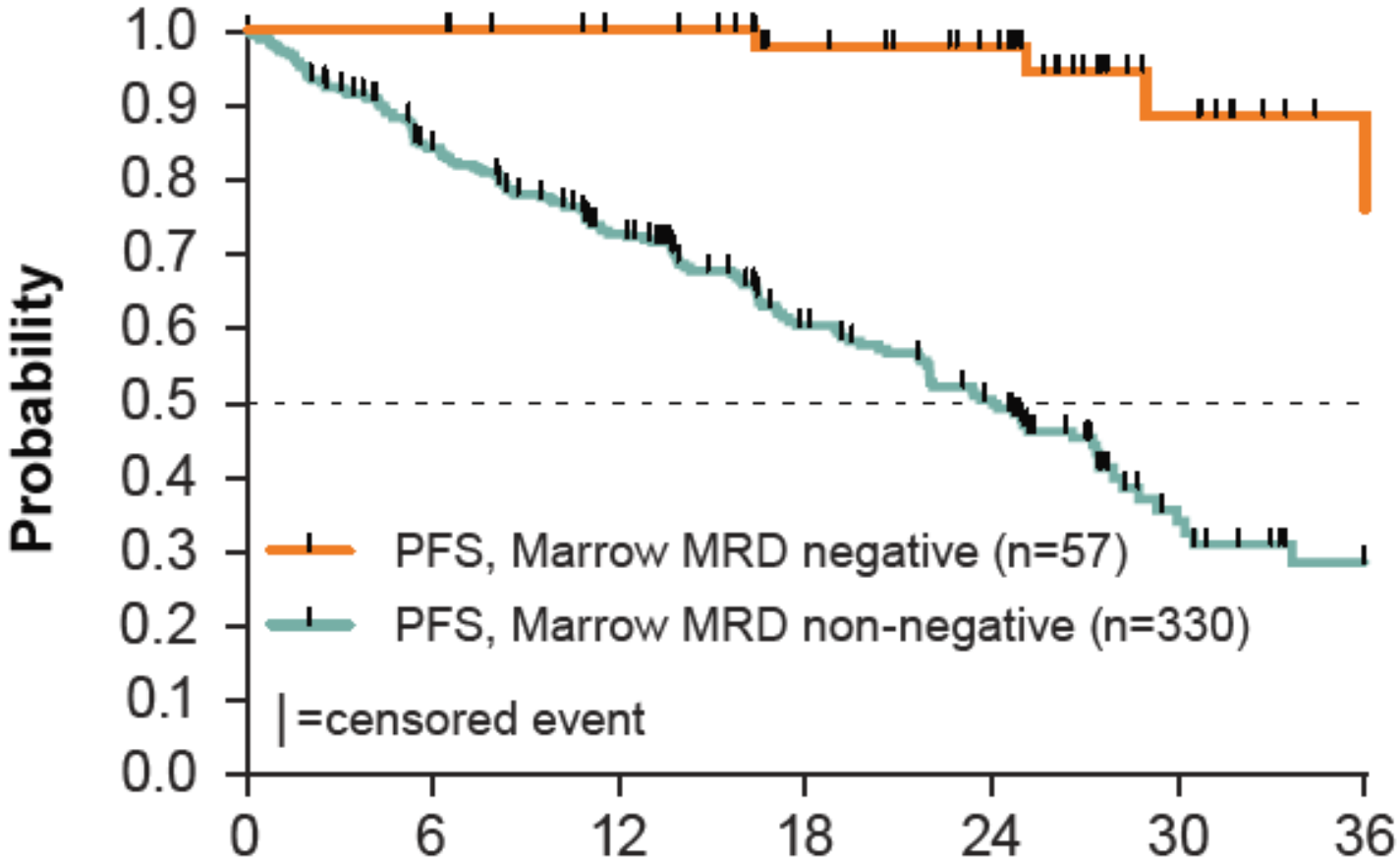


Pts at risk									
	26	26	25	25	25	19	15	9	4
	40	40	40	38	36	23	14	10	2

As of 4Apr2017

Stilgenbauer S et al. *Lancet Oncol* 2016;17:768–778.; EHA 2017[9]

Pooled Multi-trial Analysis of Venetoclax Efficacy in R/R CLL: PFS by Marrow MRD Status

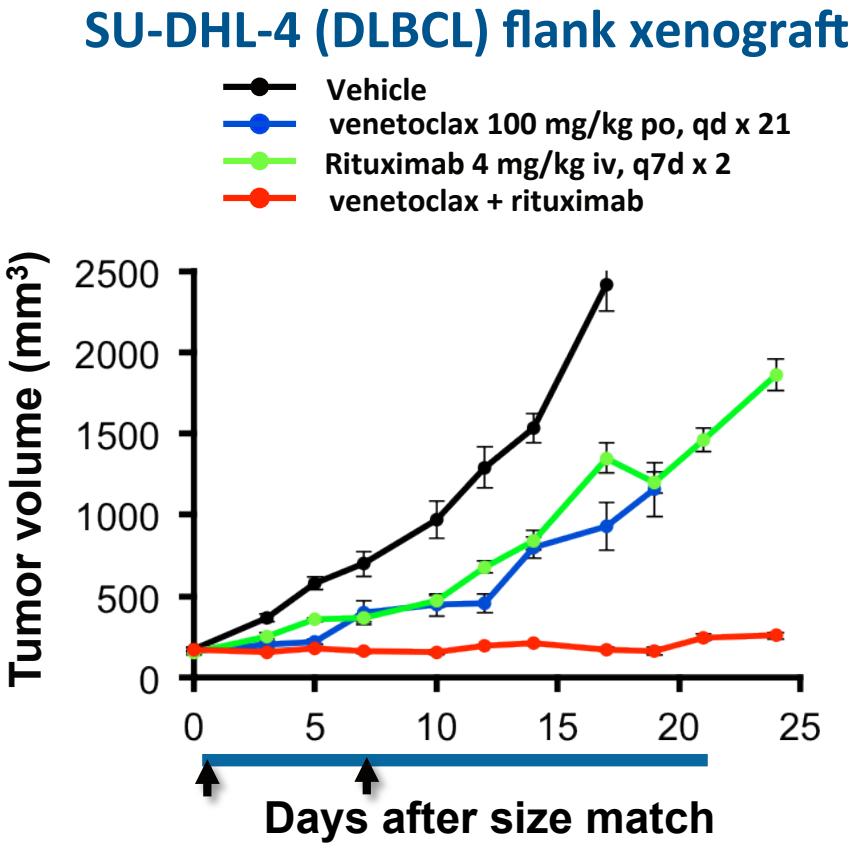


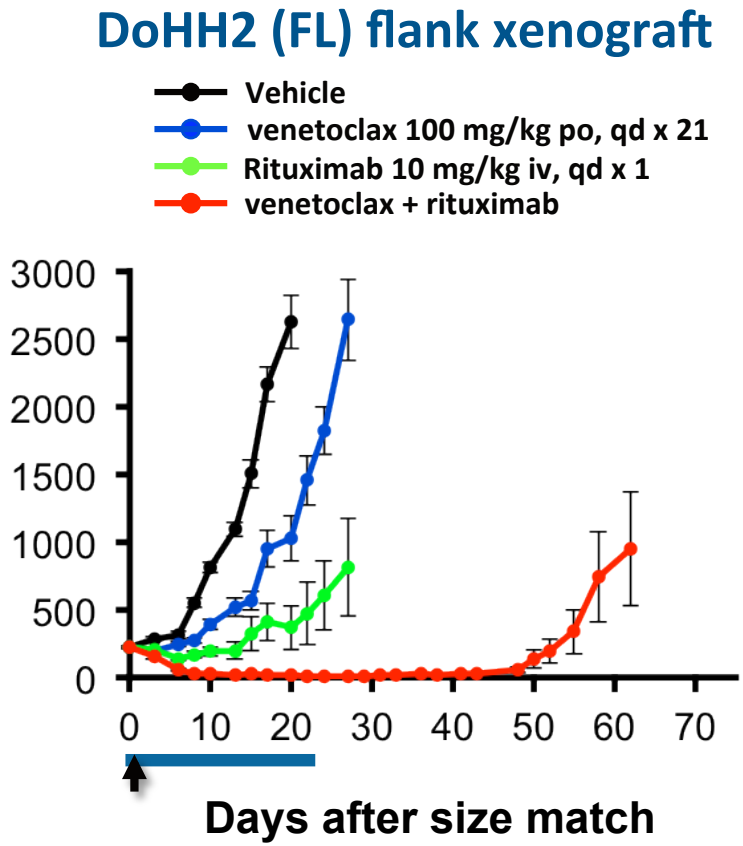
Pts at risk							
PFS (MRD negative)	57	57	50	41	35	15	7
PFS (MRD non-negative)	330	262	197	117	85	22	11

Roberts et al. ASH 2016. Abstract #3230.

Venetoclax Combines with Rituximab *in vivo*

- SU-DHL-4 and DoHH2 harbor t(14;18) translocation





Souers *et al.* (2013). Nature Medicine

Deep and Durable Responses Following Venetoclax (ABT-199 / GDC-0199) Combined with Rituximab in Patients with Relapsed / Refractory Chronic Lymphocytic Leukemia: Results from a Phase 1b Study

Shuo Ma[1], Danielle Brander[2], John F. Seymour[3], Thomas J. Kipps[4], Jacqueline C. Barrientos[5], Matthew S. Davids[6], Mary Ann Anderson[7], Michael Choi[4], Constantine Tam[3], Tanita Mason-Bright[8], Betty Prine[8], Wijith Munasinghe[8], Ming Zhu[8], Su Young Kim[8], Rod A. Humerickhouse[8], Andrew W. Roberts[7]

[1]Northwestern University, USA; [2]Duke University Medical Center, USA; [3]Peter MacCallum Cancer Centre, Australia; [4]University of California San Diego, USA; [5]Hofstra North Shore-LIJ School of Medicine, USA; [6]Dana-Farber Cancer Institute, USA; [7]Royal Melbourne Hospital and Walter and Eliza Hall Institute of Medical Research, Australia; [8]AbbVie, USA

Adapted from Ma et al. Oral Presentation at ASH 2015, Orlando, Florida.

Patient Characteristics

Characteristics	N = 49
Median age, years [range]	68 [50–88]
Male sex, n (%)	30 (61)
Diagnosis CLL / SLL	48 / 1
Lymphocyte count (x 10^9/L), median [range] > 5 x 10^9/L, n (%)	18.6 [0.3–207.1] 32 (65)
Bulky nodes, n (%) > 5 cm	 22 (45)
Prior therapies – median [range] ≥ 3, n (%)	2 [1–5] 21 (43)
Rituximab-containing, n (%) - Rituximab Refractory [a]	45 (90) 14 (29)
Fludarabine-containing, n (%) - Fludarabine Refractory [a]	28 (57) 9 (18)
del17p and/or TP53 mutation, n/N (%)	15/45 (33)
Unmutated *IGVH*, n/N (%)	19/27 (70)

[a] Progressed on therapy or within 6 months of therapy

As of October 28, 2015

Adapted from Ma et al. Oral Presentation at ASH 2015, Orlando, Florida.

Objective Responses

Best Objective Response, n (%)	All Patients n=49
Overall Response	42 (86)
Complete response, CR (includes 7 CRi)	23 (47)
Partial response, PR (includes 1 nPR)	19 (39)
Stable disease	4 (8)
Disease progression	2 (4)
Death (TLS) [a]	1 (2)

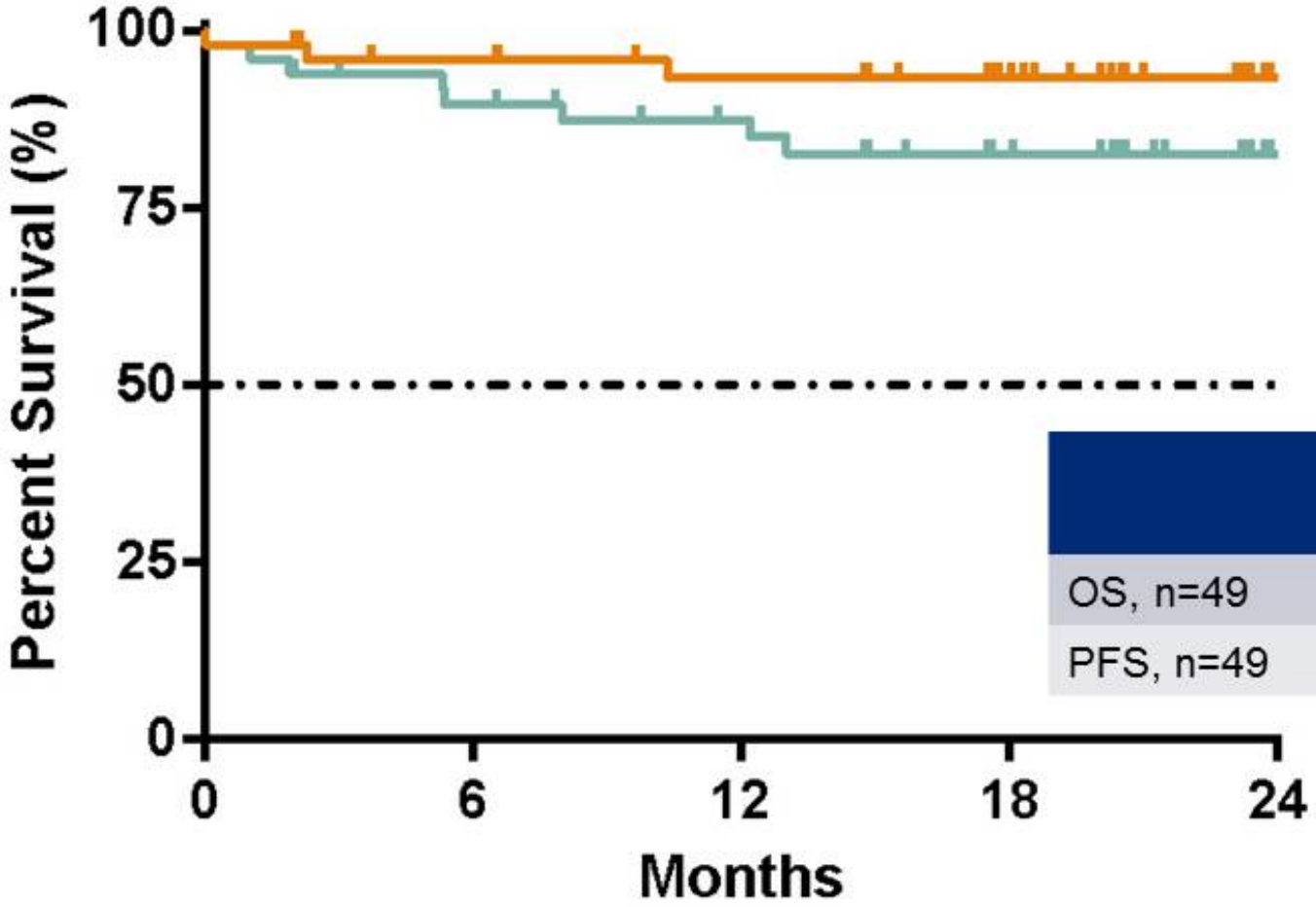
[a] Fatal TLS event previously reported; no other fatal TLS events occurred after May 2013 protocol amendment

- The median time on study is 21 months (<1 – 37) for all patients
  - 37 patients remain on study with a median time of 23 (15 – 37) months
  - 12 discontinued (6 due to PD including 5 Richter's; 3 due to AE; 3 withdrew consent)

Adapted from Ma et al. Oral Presentation at ASH 2015, Orlando, Florida.

As of October 28, 2015

Progression Free Survival and Overall Survival



	24-month estimate (95% CI)
OS, n=49	94% (81, 98)
PFS, n=49	83% (68, 90)

Patients at risk:	49	44	40	32	16
Patients at risk:	49	42	37	28	16

Adapted from Ma et al. Oral Presentation at ASH 2015, Orlando, Florida.

As of October 28, 2015

Bone Marrow Minimal Residual Disease (MRD)

MRD was assessed using local institutional methods and sensitivity $\leq 10^{-4}$

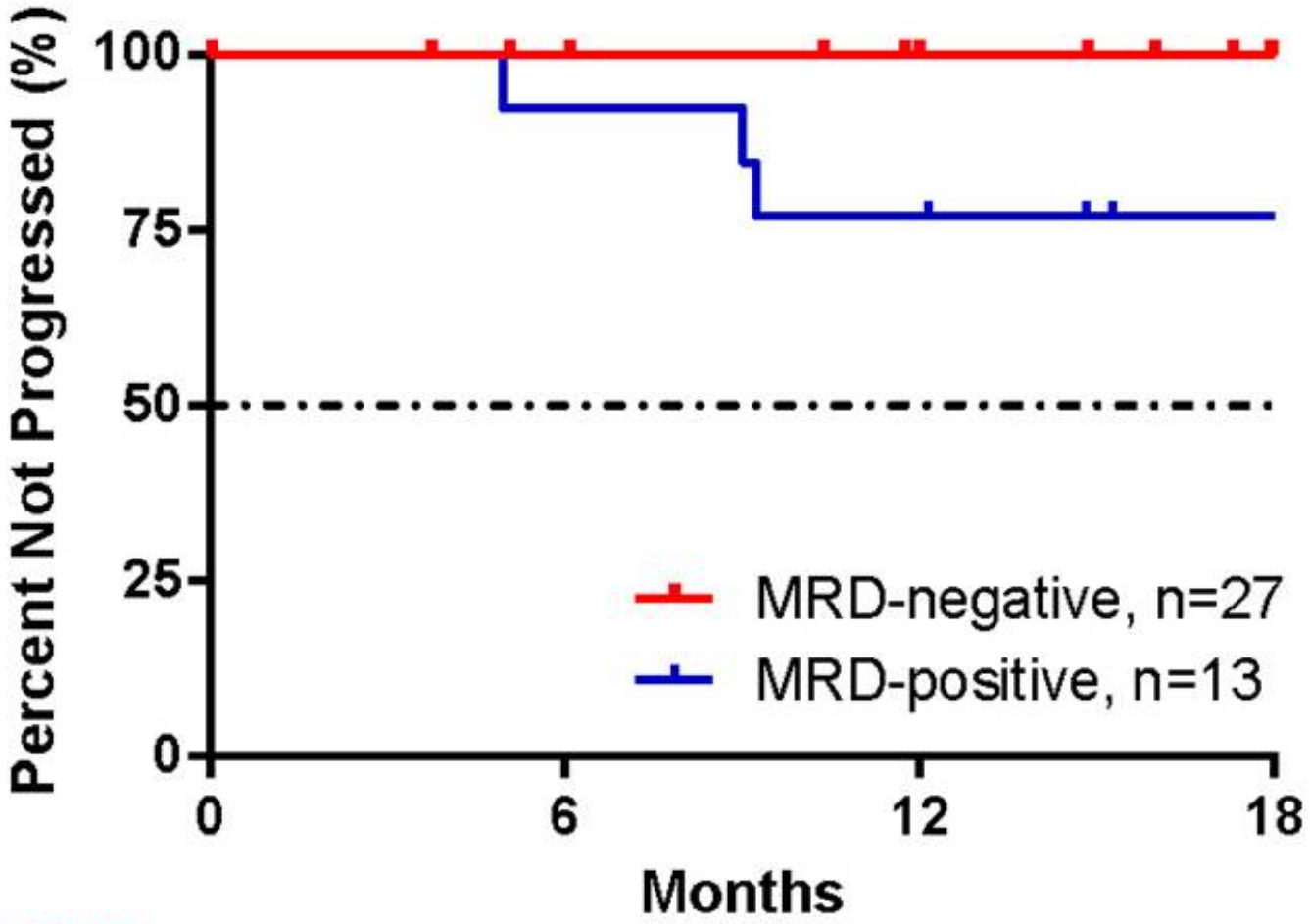
Response Classification	MRD-negative	MRD-positive	Not evaluable
CR (n=23)	17	5	1 [a]
PR (n=19)	10	8	1 [a]
Other (n=7)	0	1 [b]	6 [c]
Total, n/N (%)	27/49 (55)	14/49 (29)	8/49 (16)

[a] Samples inadequate for assessment
[b] SD
[c] no sample

Adapted from Ma et al. Oral Presentation at ASH 2015, Orlando, Florida.

As of October 28, 2015

Duration of Response Based on MRD Status

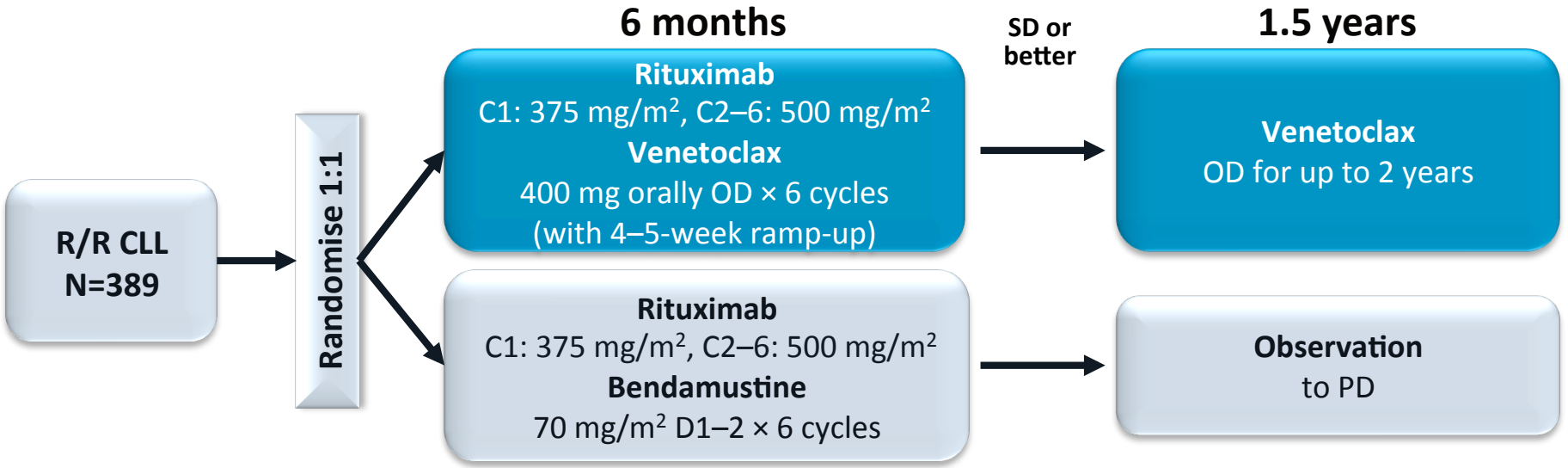


Patients at risk:	27	24	21	14
Patients at risk:	13	12	9	6

Duration of response is calculated from earliest response to last visit
MRD-negative includes 17 CR and 10 PR

Adapted from Ma et al. Oral Presentation at ASH 2015, Orlando, Florida.

MURANO: Phase 3 trial of rituximab + venetoclax for 2 years in R/R CLL



Key eligibility criteria:

- R/R CLL
- ECOG PS ≤1
- Received 1–3 prior lines of therapy
- No prior alloSCT

Primary endpoint:

- Investigator-assessed PFS

Secondary endpoints:

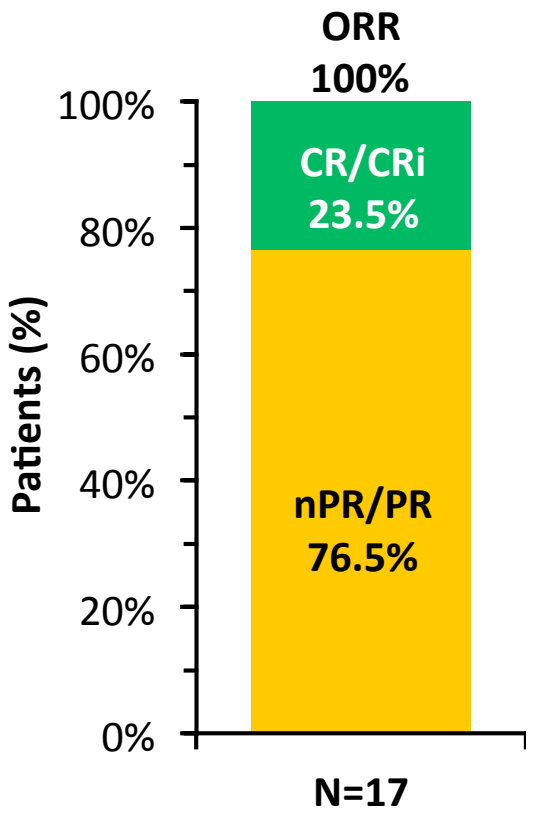
- IRC-assessed PFS
- PFS in patients with del(17p)
- Investigator- and IRC-assessed best ORR, and overall OR, CR, CRi, nPR, PR rate
- OS
- EFS, DoR, TTNT
- MRD rate
- Lymphocyte count
- PK
- Safety
- Patient-reported outcomes

alloSCT, allogeneic stem cell transplantation; DoR, duration of response; IRC, independent review committee.

ClinicalTrials.gov. Available at: https://clinicaltrials.gov/ct2/show/NCT02005471 (accessed May 2017).

Venetoclax + obinutuzumab in R/R or 1L CLL: Phase 1b GP28331 study

Response rates (investigator assessment)



Safety	N=32
Any-grade AEs ≥10 patients	
Any infectious AE	16 (50)
Diarrhoea	16 (50)
Infusion-related reaction	13 (40.6)
Nausea	12 (37.5)
Neutropenia	12 (37.5)
Fatigue	10 (31.1)
Hyperphosphatemia	10 (31.1)
Grade 3 AEs ≥2 patients	
Neutropenia	11 (34.4)
Infectious AEs	6 (18.8)
TLS*	4 (12.5)
Hyperphosphatemia	3 (9.4)
Neutrophil count decreased	3 (9.4)
Anaemia	2 (6.3)
Febrile neutropenia	2 (6.3)
Grade 4 AEs ≥2 patients	
Neutropenia	4 (12.5)
SAEs ≥2 patients	
Hyperphosphatemia	3 (9.4)
TLS*	2 (6.3)
Pyrexia	2 (6.3)

* No cases of clinical TLS occurred.

Flinn I, *et al. Blood* 2015; **126:**Abstract 494.

CLL14 - Venetoclax + Obinutuzumab (G) in TN CLL with Coexisting Medical Conditions: Study Design

Key eligibility criteria

- TN CLL requiring treatment
- CIRS >6 and/or CrCl <70 mL/min

6 cycles G (cycle 1: 100 mg day 1, 900 mg day 2, 1000 mg days 8 and 15; cycles 2-6: 1000 mg day 1) + venetoclax (starting day 22 of cycle 1, gradual weekly ramp-up 20 mg to 400 mg)

followed by 6 cycles single-agent venetoclax

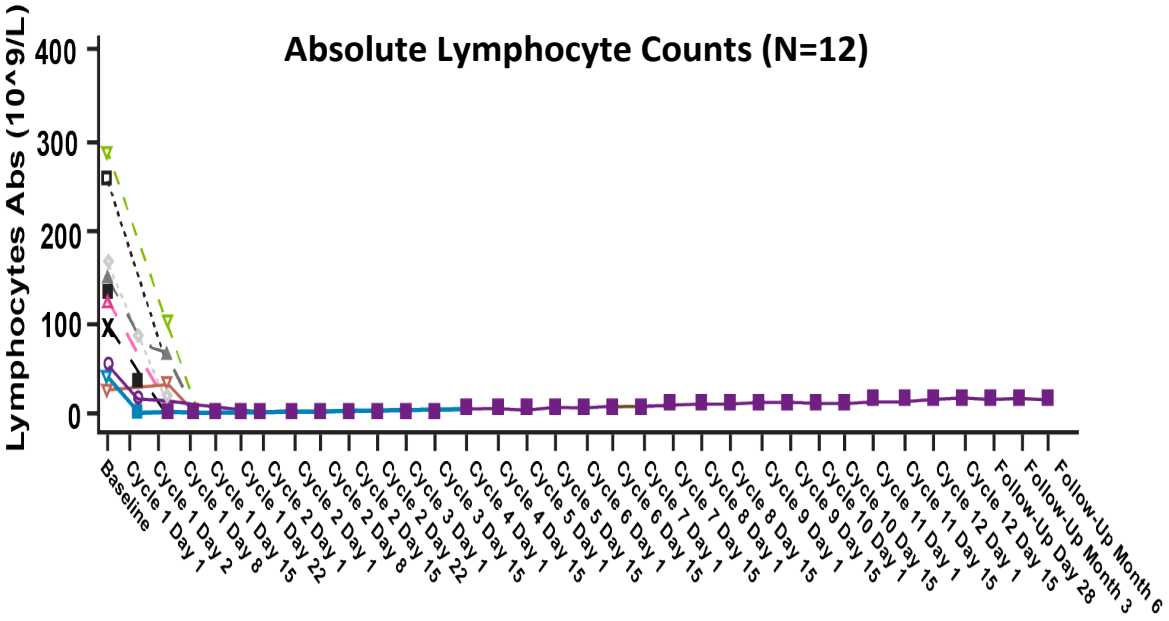
Study designed stopping: 1 treatment-related death or 1 grade 4 AE related to clinical TLS despite protocol-specified prophylaxis

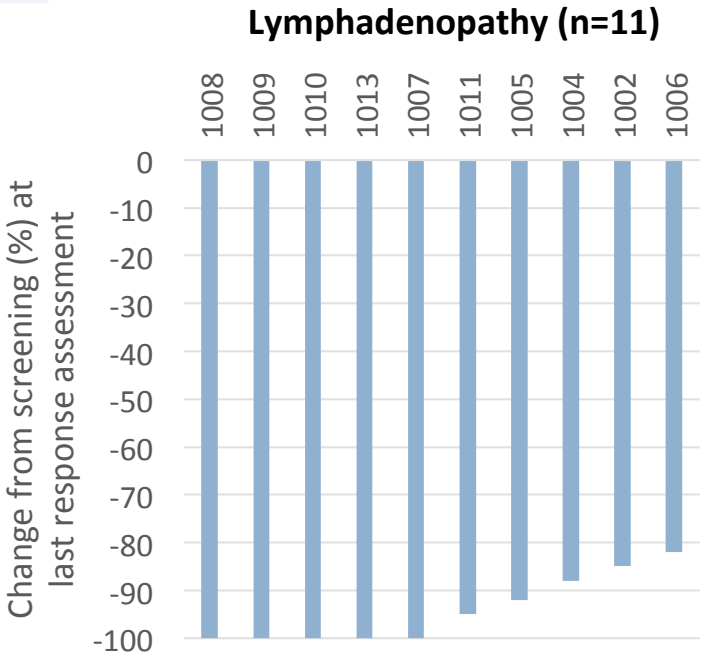
Final response to treatment including MRD in peripheral blood assessed per iwCLL guidelines 4 months after treatment end

Fischer et al. Blood 2017 129:2702-2705

CLL14 - Venetoclax + Obinutuzumab (G) in TN CLL with Coexisting Medical Conditions: Efficacy

Response Rates at Month 15	
Overall Response Rate, %	(N=12)
Complete Response	58
Partial Response	42
Minimal residual disease in peripheral blood, %	(N=11)
Negative ($<10^{-4}$)	91
Intermediate ($\geq 10^{-4}$ and $<10^{-2}$)	9

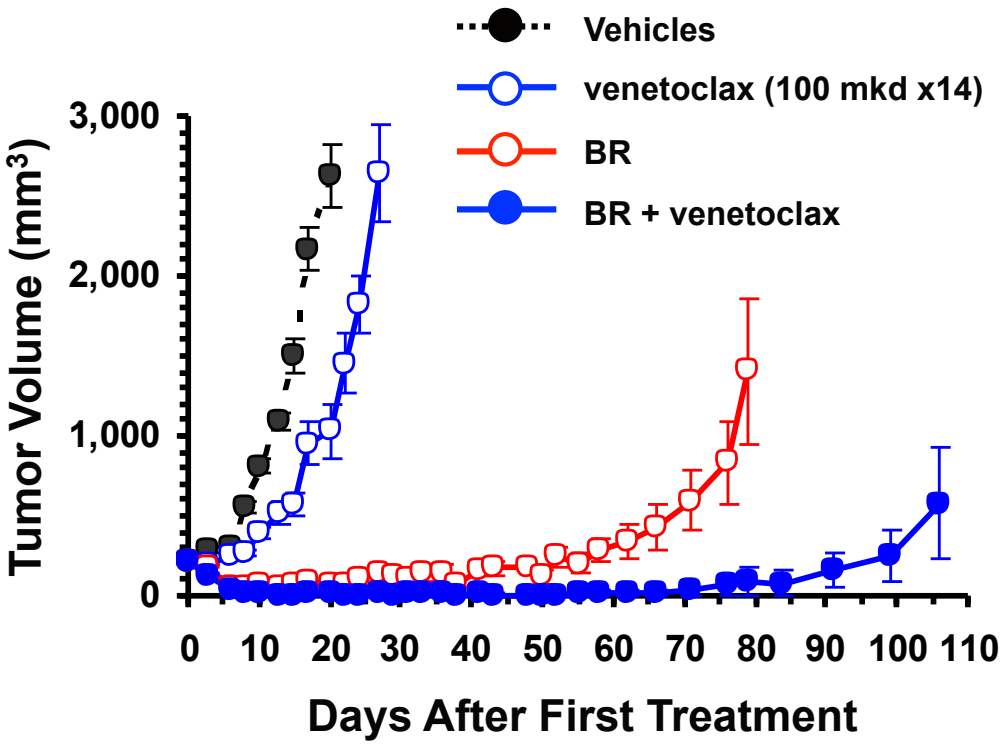




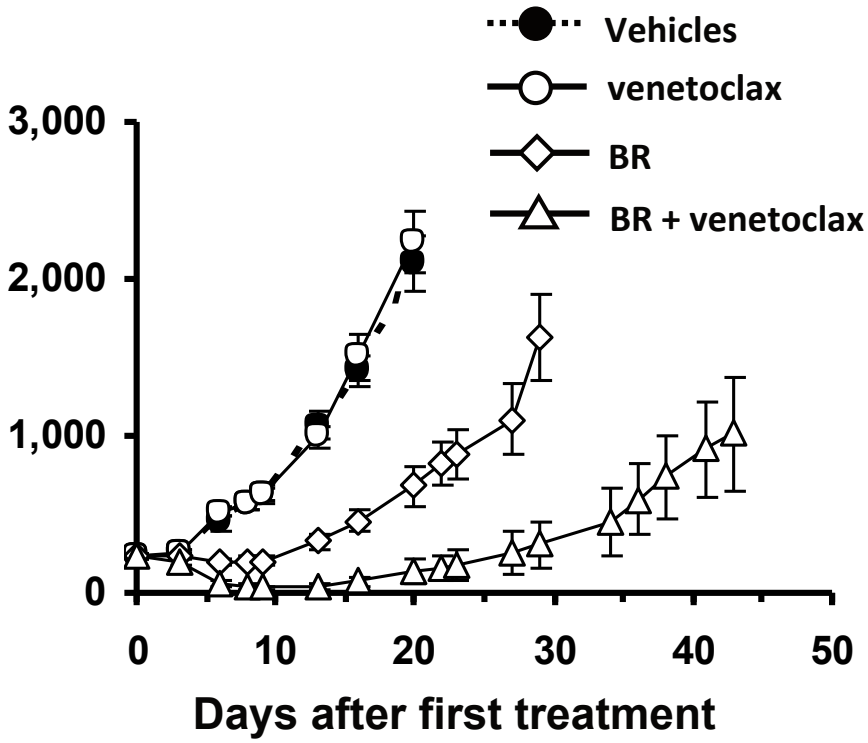
Fischer et al. Blood 2017 129:2702-2705

Venetoclax Combines with Bendamustine-R *in vivo*

DoHH2 (FL) Xenograft



Granta-519 (MCL) Xenograft



B- (bendamustine) 25 mg/kg (IV) qdx1
R- (rituximab) 10 mg/kg (IV) qdx1

Souers *et al.* (2013). Nature Medicine

Phase Ib Study (GO28440) of Venetoclax with Bendamustine/Rituximab or Bendamustine/ Obinutuzumab in Patients with Relapsed/ Refractory or Previously Untreated Chronic Lymphocytic Leukemia

Stephan Stilgenbauer, Franck Morschhauser, Clemens Wendtner, Guillaume Cartron, Michael Hallek, Barbara Eichhorst, Mark Kozloff, Thomas Giever, Gerard Lozanski, Elizabeth Punnoose, Jue Wang, James Hilger, Mehrdad Mobasher and Gilles Salles

ASH December 2016
Blood 2016 128:4393;

Table 3: Group Efficacy by Investigator Assessment and MRD Status (Best Response)

	VEN+BR		VEN+BG
n (%)	**R/R (100–400mg) (n=30)**	**1L (400 mg) (n=17)**	**1L (400 mg) (n=8)**
Yet to reach endpoint	3	3	1
Response evaluable	**27**	**14**	**7**
ORR	**26 (96)**	**14 (100)**	**7 (100)**
CR/CRi	7 (26)	6 (43)	3 (43)
nPR/PR	19 (70)	8 (57)	4 (57)
SD	0	0	0
PD	0	0	0
Off study before response evaluation*	1 (4)	0	0
MRD assessed†	21 (70)	9 (53)	4 (50)
Undetectable MRD‡	16 (76)	6 (67)	2 (50)
Detectable MRD	5 (24)	1 (11)	0
Undetermined§	0	2 (22)	2 (50)

*Pt was taken off study before response assessment was conducted due to transformation of disease

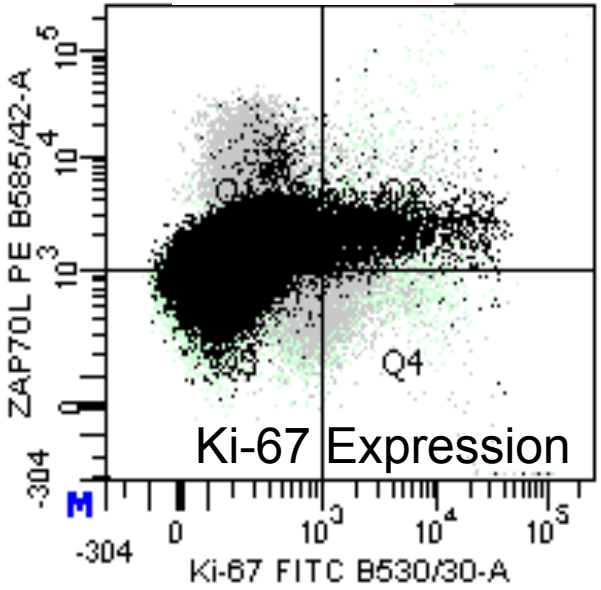
†Assay using flow cytometry

‡Undetectable defined as less than 20 CLL cells per 200,000 leukocytes (10^{-4} sensitivity)

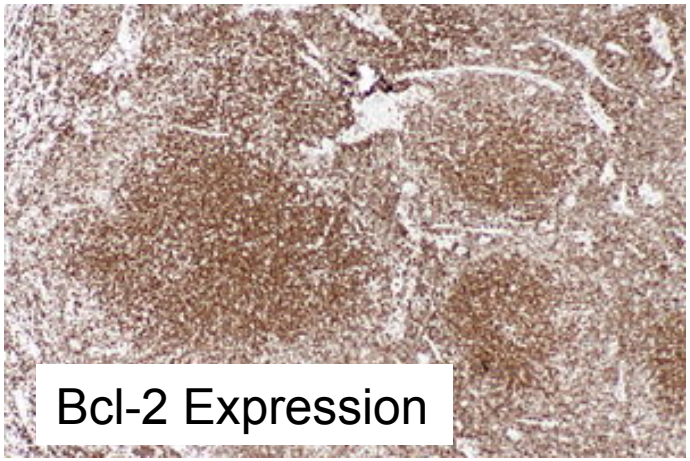
§Undetermined defined as sample with MRD level less than 10^{-4} but where less than 200,000 leukocytes were assessed (insufficient sensitivity at 10^{-4})

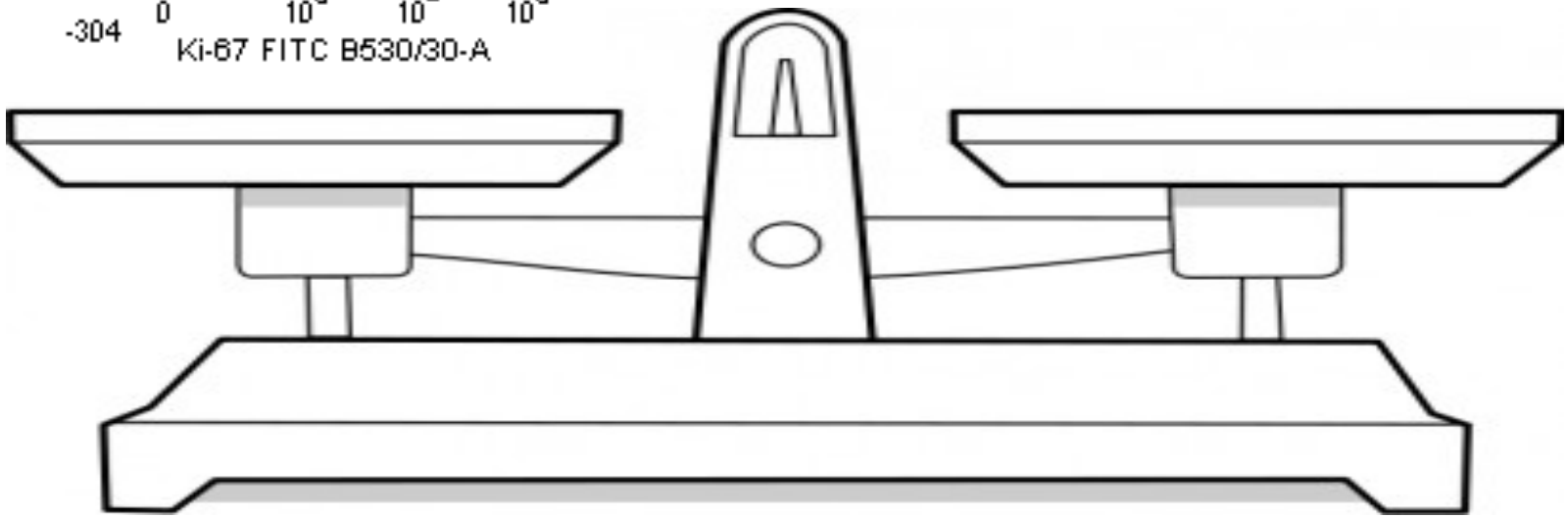
Pathophysiology of CLL: Proliferation vs Apoptosis

Proliferation

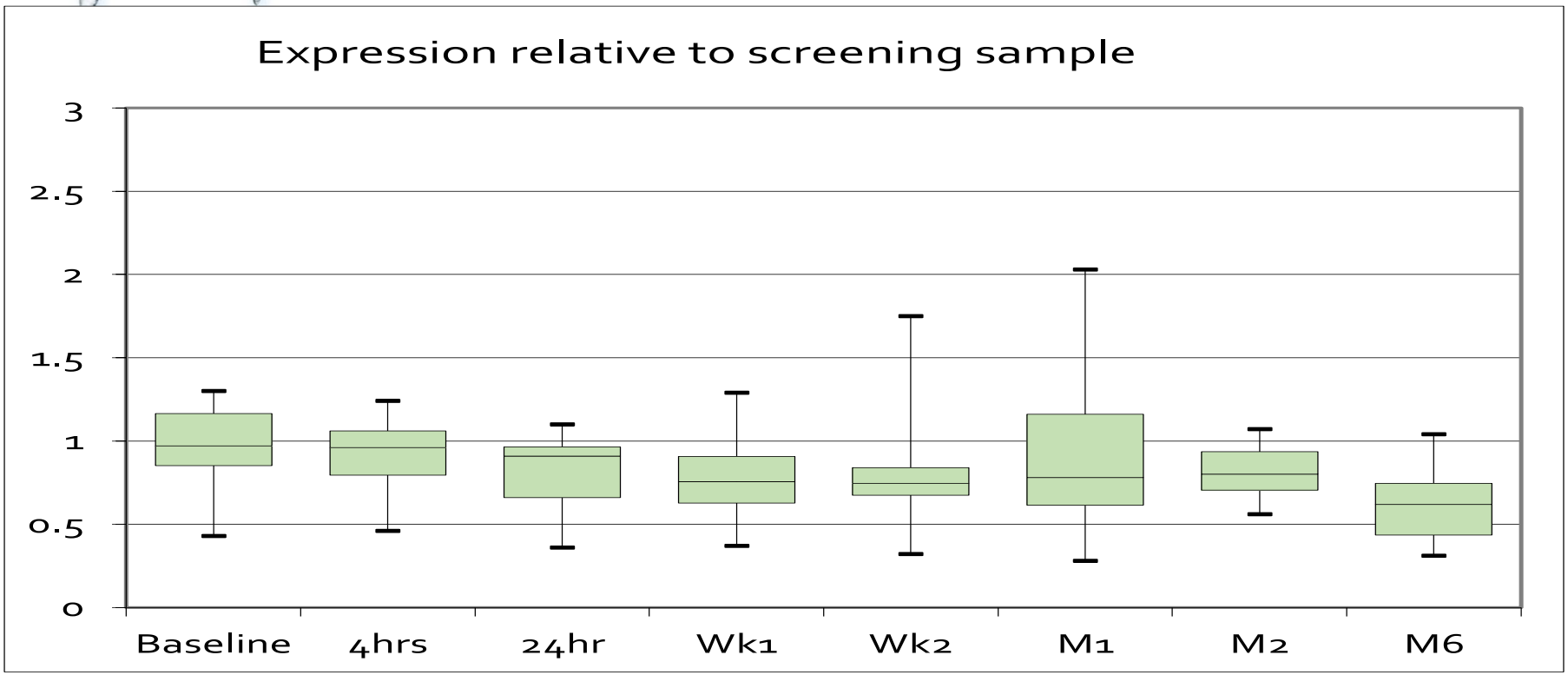


Apoptosis





Persistently strong BCL2 expression during ibrutinib treatment



Bloodwise
Beating blood cancer since 1960

TAP

Munir *et al.*, April 2016, BSH/ISH, Glasgow

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Assessment of venetoCLAx in combination with ibRutInib plus ABT-199 in relapsed/ refracTory chronic lymphocYtic leukaemia

- Feasibility study to investigate the combination of ibrutinib and venetoclax (ABT-199) in relapsed refractory CLL.
- MRD response as the primary outcome measure to determine whether ibrutinib + venetoclax (ABT-199) shows sufficient evidence of activity and safety.
- Results from this trial will inform a potential modification of Flair

50 patients with relapsed/refractory CLL who are ibrutinib naïve

CLARITY Treatment Schedule

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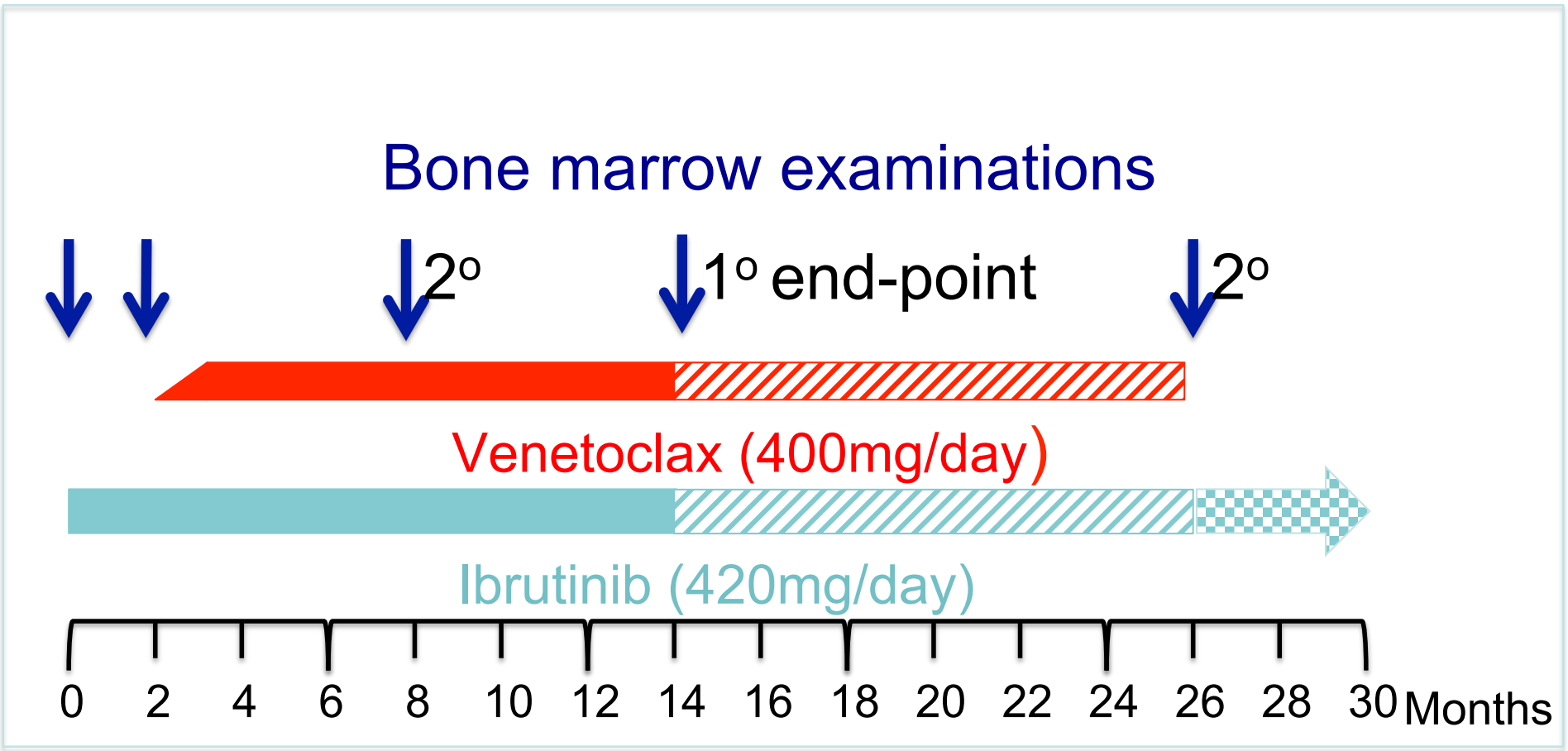

- VEN and IBR stop at 14 months if 8 month BM is MRD negative
- VEN and IBR stop at 26 months if 14 month BM is MRD negative
- IBR alone continues if 26 month BM is MRD positive

Hillmen *et al.*, Poster, IWCLL & Oral EHA, 2017

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Patient characteristics

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Characteristic	Patients (n = 45)
Gender (Male/Female)	32 (71%) / 13 (29%)
Age (Median [Range])	64yo (31 – 83)
Binet Stage (A/B/C)	9 (25%) / 12 (33%) / 15 (42%)
Lymph nodes (>5cm)	4 (9%)
ECOG (0/1/2)	25 (60%) / 14 (33%) / 3 (7%)
Prior therapies (median [range])	2 (1 to 6)
V_H mutation (mutated/unmutated/ VH3-21)	8 (19%) / 32 (74%) / 3 (7%)
17p del	8 (20%)
11q del	10 (24%)
17p or 11q del	18 (44%)

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Toxicity

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	Grade				
Category	**1 and 2**	**3**	**4**	**NK**	**Total**
Blood and lymphatic system disorders	7	2	0	0	9
Cardiac disorders	9	1	0	1	11
Ear and labyrinth disorders	3	0	0	0	3
Eye disorders	14	1	0	0	15
Gastrointestinal disorders	**182**	6	0	4	**192**
General disorders and administration site conditions	59	2	0	0	61
Hepatobiliary disorders	1	0	0	1	2
Immune system disorders	4	0	0	0	4
Infections and infestations	32	6	0	1	39
Injury, poisoning and procedural complications	25	1	0	1	27
Investigations	8	15	6	0	29
Metabolism and nutrition disorders	10	2	0	0	12
Musculoskeletal and connective tissue disorders	**68**	0	0	0	**68**
Nervous system disorders	39	1	0	0	40
Psychiatric disorders	9	0	0	0	9
Renal and urinary disorders	8	0	0	0	8
Reproductive system and breast disorders	2	0	0	0	2
Respiratory, thoracic and mediastinal disorders	35	1	1	0	37
Skin and subcutaneous tissue disorders	**47**	1	0	2	**50**
Surgical and medical procedures	1	0	0	0	1
Vascular disorders	11	1	0	0	12
Total	574	40	7	10	631

Date of data snap shot: 19-Sep-2017

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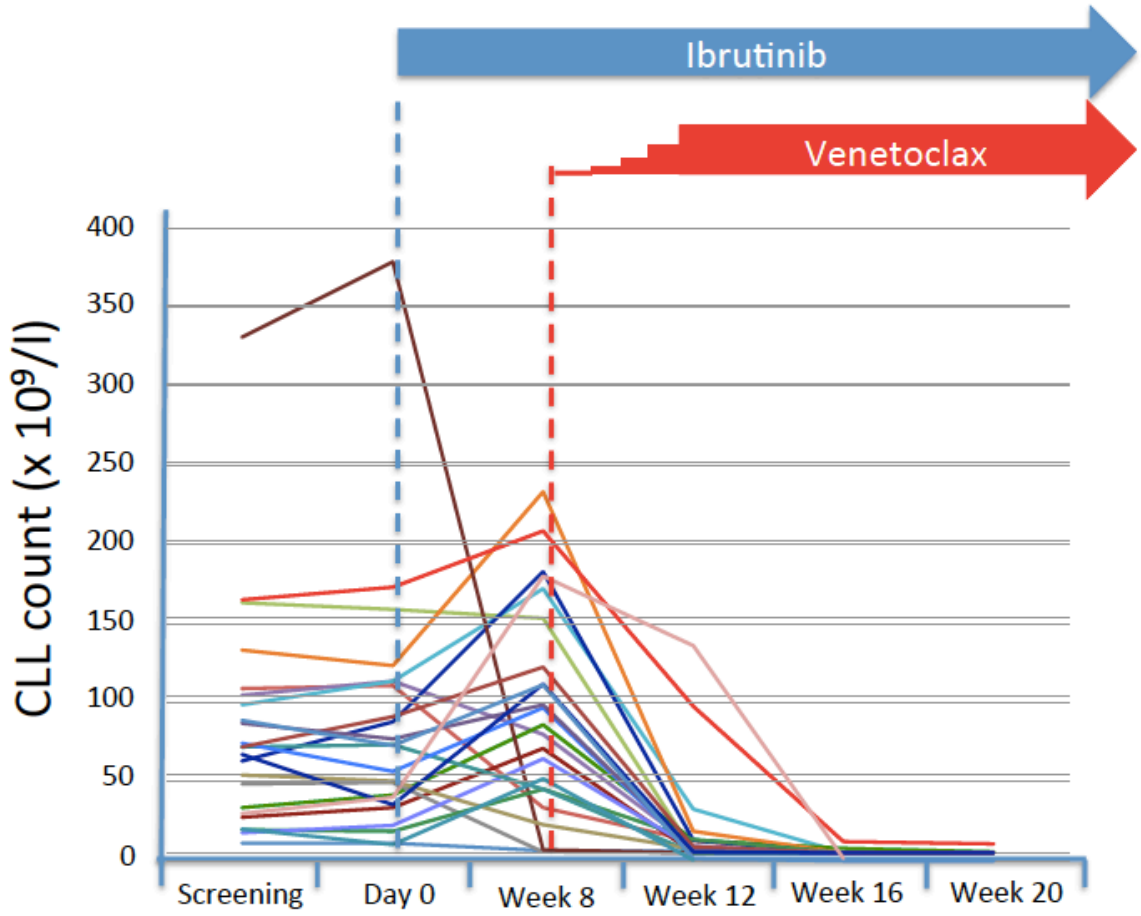
Blood CLL Responses - linear scale

Fall in PB CLL count in 18 patients starting at >10 x 10^9/l CLL cells



CLL count increased during IBR monotherapy at 420mg/day from a median of:
50 x 10^9 /l (range: 0 to 330) to
55 x 10^9 /l (range: 0 to 237)

CLL count then falls during the first 8 weeks of combined IBR with VEN from a median of **55 x 10^9 /l** to **0.017 x 10^9 /l** (range; 0 to 3.1).

The rate of fall is rapid in all patients with a median of 3 log reduction in CLL level after 8 weeks of combined therapy.

Hillmen *et al.*, Poster, IWCLL & Oral EHA, 2017

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Initial Results of Ibrutinib Plus Venetoclax in Relapsed, Refractory CLL (Bloodwise TAP CLARITY Study): High Rates of Overall Response, Complete Remission and MRD Eradication after 6 Months of Combination Therapy

Peter Hillmen, MBChB, PhD[1,2], Talha Munir, MBBS[2*], Andy Rawstron, PhD[2*], Kristian Brock, MSc, BSc[3*], Samuel Munoz Vicente, MSc[3*], Francesca Yates, PhD[3*], Rebecca Bishop, BSc[3*], Christopher Fegan, MD[4*], Donald Macdonald[5*], Alison McCaig, PhD[6*], Anna Schuh, MD, PhD[7], Andrew Pettitt, FRCPath, PhD[8*], John G. Gribben[9], Stephen Devereux, MD[10], Adrian Bloor[11*], Christopher P Fox, MBChB PhD[12*] and Francesco Forconi, MD, PhD[13*]

Oral presentation, 12.15am, Sunday 10th December, ASH 2017

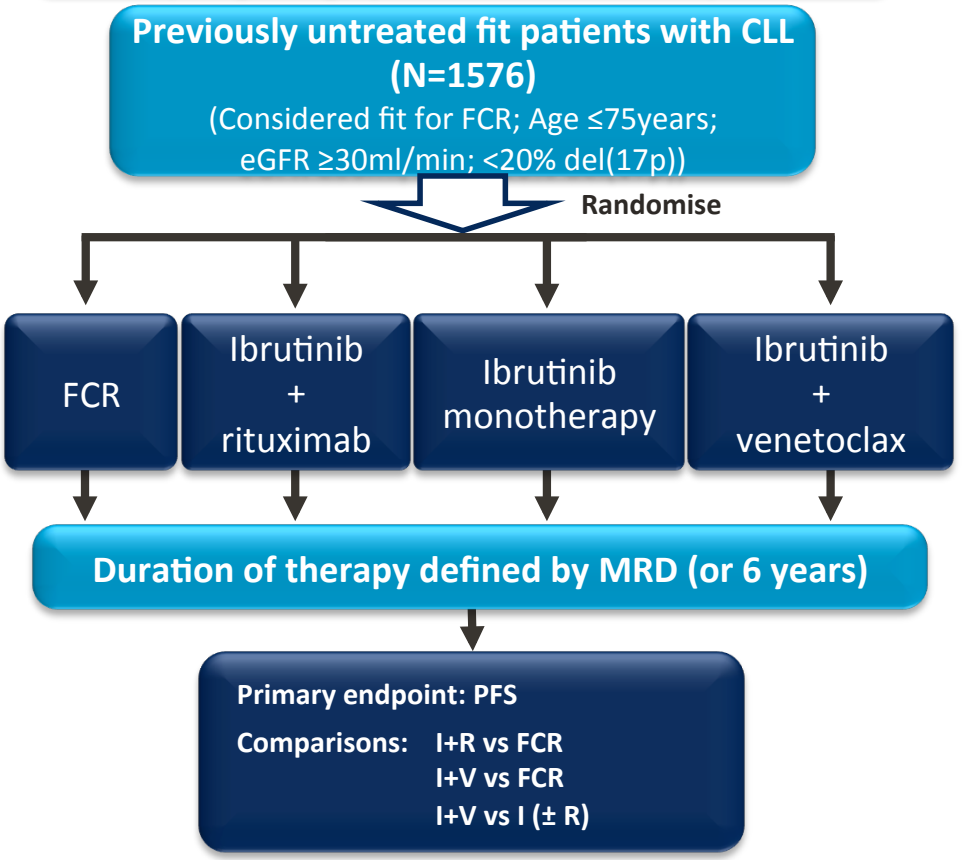
Modified the NCRI *Flair* Trial –opened July 2017

Bloodwise TAP CLARITY trial: Peripheral blood CLL responses[1]

Time point	Median, × 10^9/L (range)
Pre-treatment	50 (0–330)
End of 8 weeks' ibrutinib monotherapy	55 (0–237)
After 8 weeks' venetoclax + ibrutinib	0.017 (0–3.1)

- One case of laboratory TLS observed
  - Resolved with venetoclax + ibrutinib dose interruption
- To date, 5 SAEs and 22 AEs of special interest have been observed, including:
  - Lung infection (n=3)
  - Neutropenia (n=11)

UK NCRI FLAIR trial (ongoing, planned N=1576)[2,3]



1. Hillmen P, *et al. Haematologica* 2017; Abstract 2810;
2. EudraCT. Available at: https://www.clinicaltrialsregister.eu/ctr-search/trial/2013-001944-76/GB (accessed June 2017);
3. Derby-Burton Local Cancer Network. Available at: http://www.derbyhospitals.nhs.uk/EasysiteWeb/getresource.axd?AssetID=288688&type=full&servicetype=Attachment (accessed June 2017).

Phase 1b Results of a Phase 1/2 Study of Obinutuzumab, Ibrutinib, and Venetoclax (GIV) in Patients With R/R CLL: Study Design

Key eligibility criteria

- CLL relapsed after or refractory to ≥1 prior therapy
- Requiring treatment
- No patients with chronic viral hepatitis infection, HIV, uncontrolled autoimmune cytopenia, active RT, or known C481 BTK mutation or PD during treatment with a C481-binding BTK inhibitor

Obinutuzumab 1000 mg X 7 cycles

Ibrutinib 420 mg/day, starting in cycle 2

Venetoclax was dose escalated in cycle 3 in 3x3 cohorts (100, 200, 400 mg) to a maximum planned dose of 400 mg/day

Drugs initiated sequentially to limit risk of TLS

All patients discontinue after cycle 14

Response assessment according to IWCLL 2008 criteria, including BM biopsy with 4-color immunophenotyping of marrow and PB for MRD, occurs after cycle 8 and 2 months beyond end of cycle 14

Jones et al. ASH 2016. Abstract #639.

Phase 1b Results of a Phase 1/2 Study of Obinutuzumab, Ibrutinib, and Venetoclax (GIV) in Patients With R/R CLL: Baseline and Efficacy

Baseline Characteristics, n (%)		(N=12)
Median age, years (range)		57 (42-70)
Male sex, n (%)		11 (92)
Prior therapies, median (range)		1 (1-7)
β-2 microglobulin, median (range)		3.3 (2.2-6.8)
Unmutated *IGHV,* n (%)		11 (92)
Zap70 unmethylated, n (%)		7 (58)
Del(17p), n (%)		1 (8)
Del(11q), n (%)		8 (67)
Complex karyotype		5 (42)
TLS risk	Low	1 (8)
	Intermediate	7 (58)
	High	4 (33)

- 11 patients remain on therapy and 1 has completed 14 cycles and is pending final response assessment
- 10 patients have reached response assessment at cycle 9 of therapy
  - All 10 have achieved objective response (8 PR, 2 CR)
  - 7/10 MRD-negative in PB
  - 4/10 MRD-negative in BM

Jones et al. ASH 2016. Abstract #639.

Phase 1b Results of a Phase 1/2 Study of Obinutuzumab, Ibrutinib, and Venetoclax (GIV) in Patients With R/R CLL: Safety

Most common Grade 1/2 AEs, %	N=12
Bruising	100
Hypocalcemia	75
Infusion-related reaction	75
Diarrhea	75
Hyperuricemia	75
Hypertension	67
Headache	58
Arthralgia	58
Dizziness	58
Myalgia	58

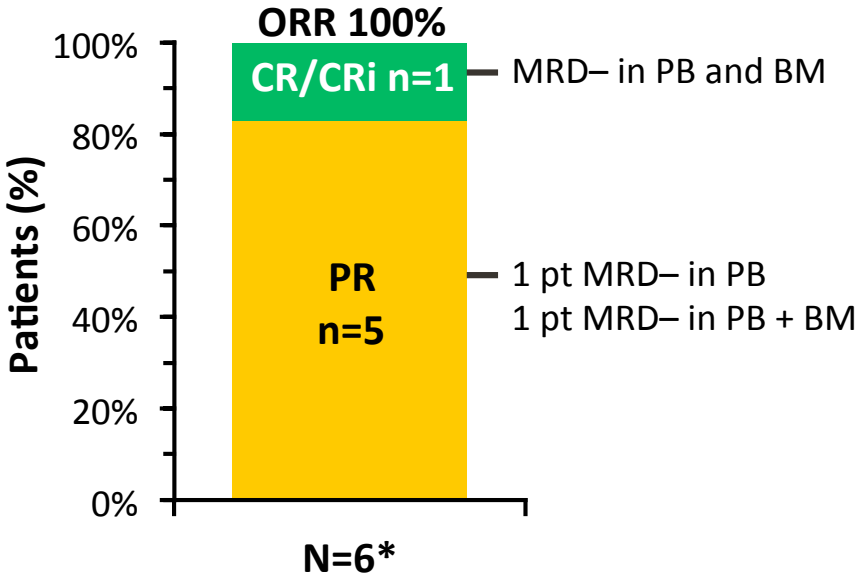
Hematologic AEs, %	Grade 1/2	Grade 3+	All Grades
WBC count decreased	58	33	92
Neutrophil count decreased	42	58	100
Lymphocyte count decreased	42	42	83
Platelet count decreased	58	17	75
Anemia	17	0	17

- Neutropenia common, but no grade 3/4 infections observed
  - 8 cases of grade 1 infection, no neutropenia fever
- 5 patients received ≥1 dose of G-CSF
  - 1 patient with baseline neutropenia received >4 doses

Jones et al. ASH 2016. Abstract #639.

Ongoing trials with obinutuzumab + ibrutinib + venetoclax (GIVe)

Phase 1b/2 study of GIVe in R/R CLL (N=12 to date)[1]



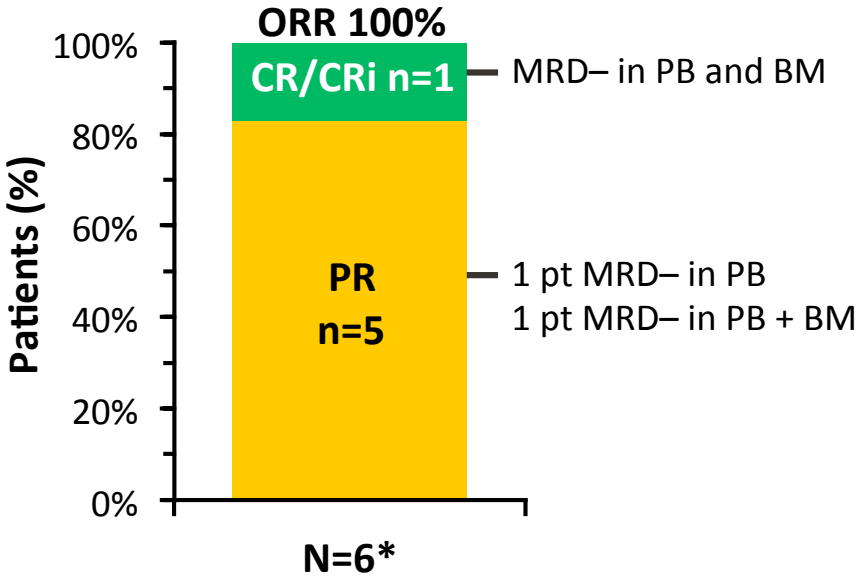
- Most common grade ≥3 AEs: neutropenia (50%), lymphopenia (33%), hypertension (25%), and fatigue (17%)
- No cases of clinical or lab TLS were observed

PB, peripheral blood.
* 6 patients have reached response assessment after completing 8 cycles of therapy;
† <65 years of age; ‡ >65 years of age.

1. Jones J, *et al. Blood* 2016; **128:**Abstract 639;
2. ClinicalTrials.gov. Available at: https://clinicaltrials.gov/ct2/show/NCT02950051 (accessed April 2017).

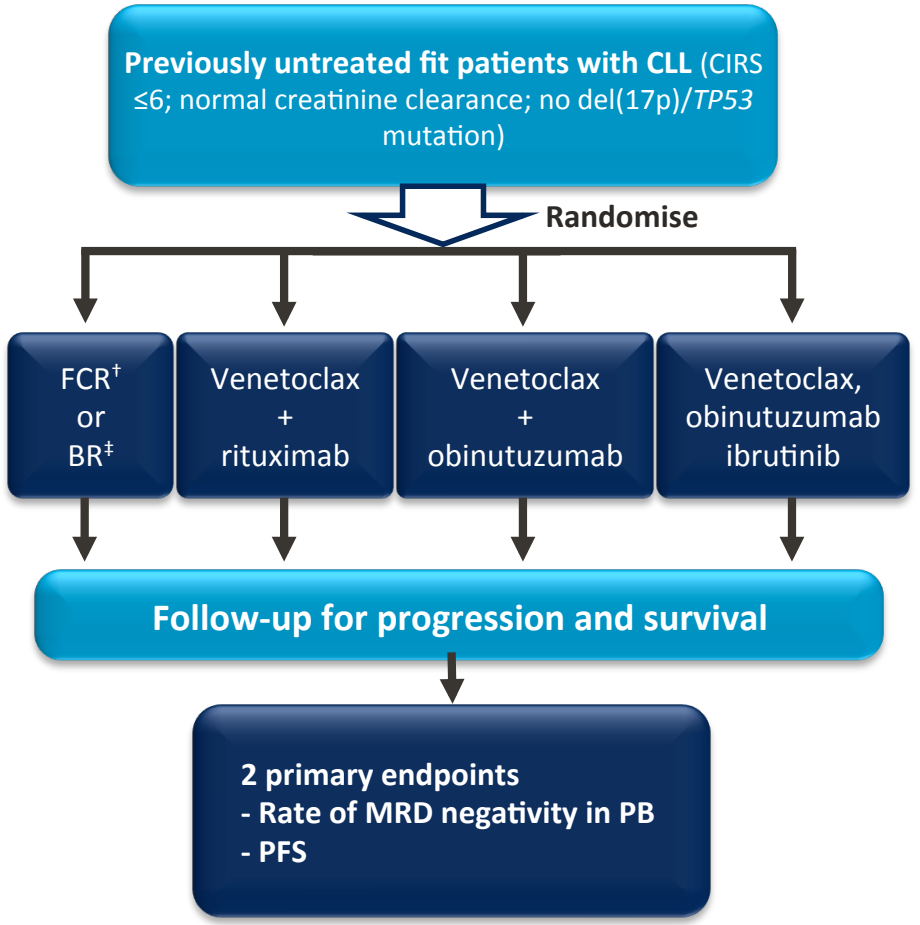
Ongoing trials with obinutuzumab + ibrutinib + venetoclax (GIVe)

Phase 1b/2 study of GIVe in R/R CLL (N=12 to date)[1]



- Most common grade ≥3 AEs: neutropenia (50%), lymphopenia (33%), hypertension (25%), and fatigue (17%)
- No cases of clinical or lab TLS were observed

GCLLSG CLL13 trial (ongoing, planned N=920)



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Conclusions: Venetoclax in CLL

Impressive single agent activity

- Minority of patients achieving MRD negative remissions
- Possibility of stopping therapy
- Well tolerated except for tumour lysis syndrome

Extremely promising activity in combination

- Apparent synergy with antibodies (rituximab and obinutuzumab) and chemoimmunotherapy (BR)
- Combinations with ibrutinib ± obinutuzumab in Phase II and Phase III trials
- Higher MRD eradication rates are reported