VENETOCLAX (ABT 199)

Simon Rule

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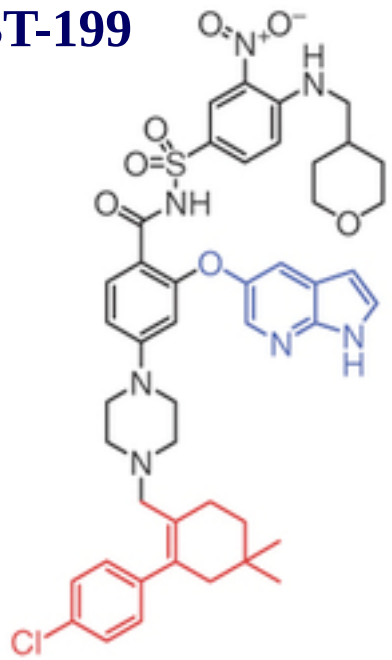
ABT-199 Venetoclax

- ABT-199 is a selective, potent, orally bioavailable, small molecule Bcl-2 inhibitor
- ABT-199 binds with high affinity to Bcl-2 and with substantially lower affinity to other Bcl-2 proteins (Bcl- x_L, Bcl-w and MCL-1)
- ABT-199 has shown preclinical activity in a wide range of hematologic malignancies as a single agent

ABT-199 / Venetoclax : a potent and selective Bcl-2 inhibitor

ABT-199



ABT-199 Affinity

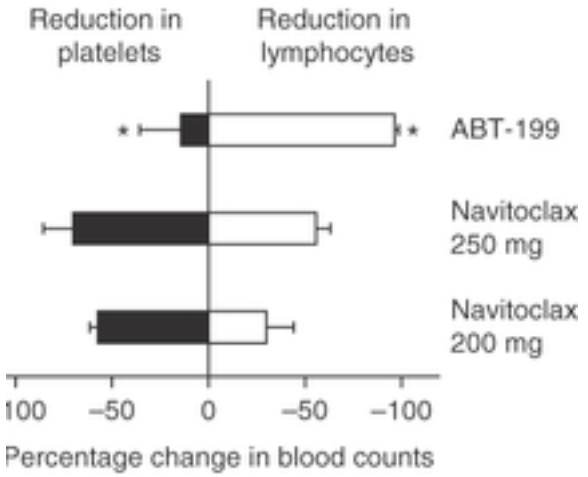
Bcl-2 < 0.01 nM

Bcl-x_L = 48nM

Bcl-w = 245nM

Mcl-1 >444nM

LLC patients



Souers et al Nature Medecine 2013

ABT-199

Phase I First-in-Human Study of Venetoclax in Patients With Relapsed or Refractory Non-Hodgkin Lymphoma

Matthew S. Davids, Andrew W. Roberts, John F. Seymour, John M. Pagel, Brad S. Kahl, William G. Wierda, Soham Puvvada, Thomas J. Kipps, Mary Ann Anderson, Ahmed Hamed Salem, Martin Dunbar, Ming Zhu, Franklin Peale, Jeremy A. Ross, Lori Gressick, Monali Desai, Su Young Kim, Maria Verdugo, Rod A. Humerickhouse, Gary B. Gordon, and John F. Gerecitano

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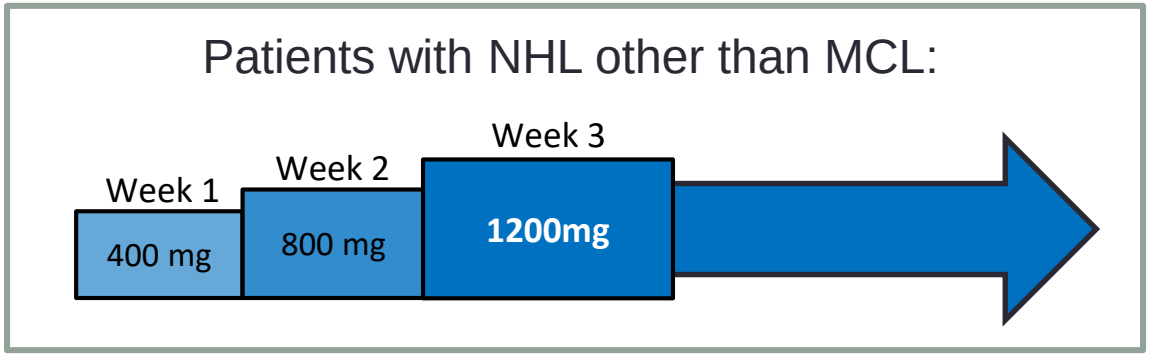
ORIGINAL REPORT

Venetoclax Escalation Strategy

- 70 patients with R/R NHL (multiple histology subtypes) were enrolled in dose-escalation cohorts (target daily dose: 200 – 1200mg)
- 15 patients with FL and 21 with DLBCL were enrolled in a safety expansion cohort (target daily dose: 1200 mg)



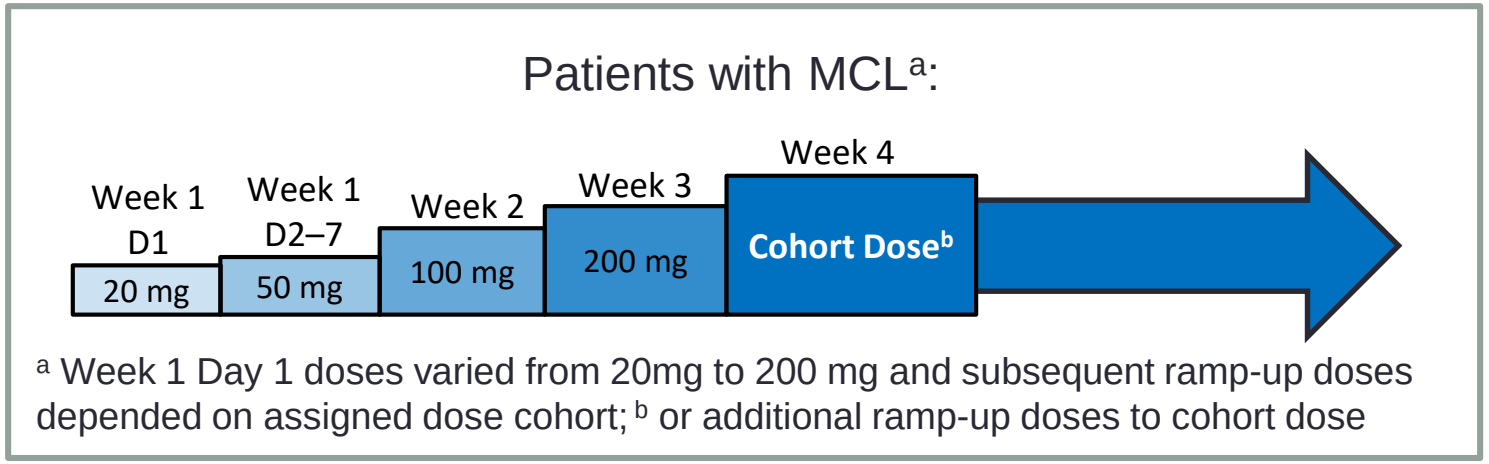


Table 1. Patient Demographic and Clinical Characteristics (N = 106)

Characteristic	No. (%)							
	All Patients	MCL (n = 28)	FL (n = 29)	DLBCL* (n = 34)	DLBCL-RT (n = 7)	WM (n = 4)	MZL (n = 3)	Other† (n = 1)
Age (years)								
Median	66	72	64	67	73	67	63	56
Range	25-86	35-85	46-75	25-86	57-77	58-73	63-67	56-56
Previous therapies								
Median	3	3	3	3	3	4	4	2
Range	1-10	1-7	1-10	1-8	2-7	3-5	2-6	2-2
Prior ASCT	16	7	2	6	0	1	0	0
Bulky nodes (cm)								
> 5	48 (45)	14 (50)	8 (28)	17 (50)	5 (71)	2 (50)	0	1 (100)
> 10	14 (13)	3 (11)	2 (7)	6 (18)	2 (29)	2 (50)	0	0
LDH > upper limit of normal	45 (42)	7 (25)	10 (34)	20 (59)	7 (100)	0	0	1 (100)
High BCL-2 expression‡	41 of 46	13 of 14	14 of 15	9 of 12	1 of 1	3 of 3	1 of 1	0

Abbreviations: ASCT, autologous stem-cell transplantation; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; LDH, lactate dehydrogenase; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma; RT, Richter transformation; WM, Waldenström macroglobulinemia.

*Includes patients with primary mediastinal B-cell lymphoma (n = 2).

†One patient with multiple myeloma (a histology allowed before an early study amendment) had early disease progression and discontinued study after 21 days.

‡Proportion of patients with high B-cell leukemia/lymphoma-2 expression by immunohistochemistry (> 50% lymphoma cells scored 2+ or 3+) among those with adequate samples for analysis.

Treatment-Emergent Adverse Events

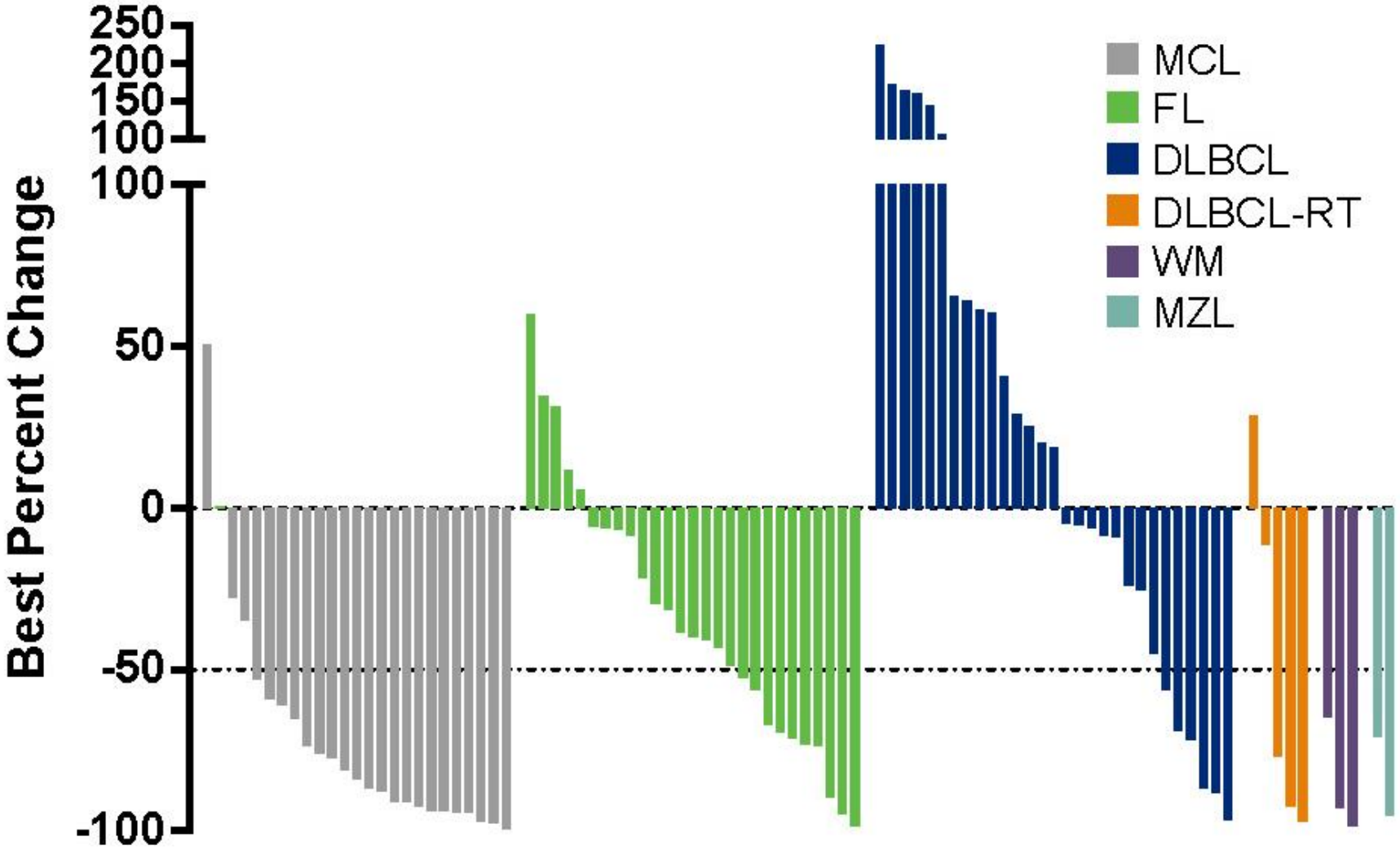
All Grade AEs (in ≥ 15% patients), n (%)	N=106
Any AE	103 (97)
Nausea	51 (48)
Diarrhea	47 (44)
Fatigue	43 (41)
Decreased appetite	22 (21)
Vomiting	22 (21)
Anemia	19 (18)
Constipation	19 (18)
Headache	19 (18)
Neutropenia	19 (18)
Cough	18 (17)
Back pain	17 (16)
Upper respiratory tract infection	16 (15)

Grade 3/4 AEs (in ≥ 5% patients), n (%)	N=106
Any Grade 3/4 AE	57 (54)
Anemia	17 (16)
Neutropenia	13 (12)
Thrombocytopenia	10 (9)
Fatigue	6 (6)

Serious Adverse Events (in ≥2 patients), n (%)	N=106
Any SAE	35 (33)
Diarrhea	3 (3)
Hyponatremia	3 (3)
Influenza	3 (3)

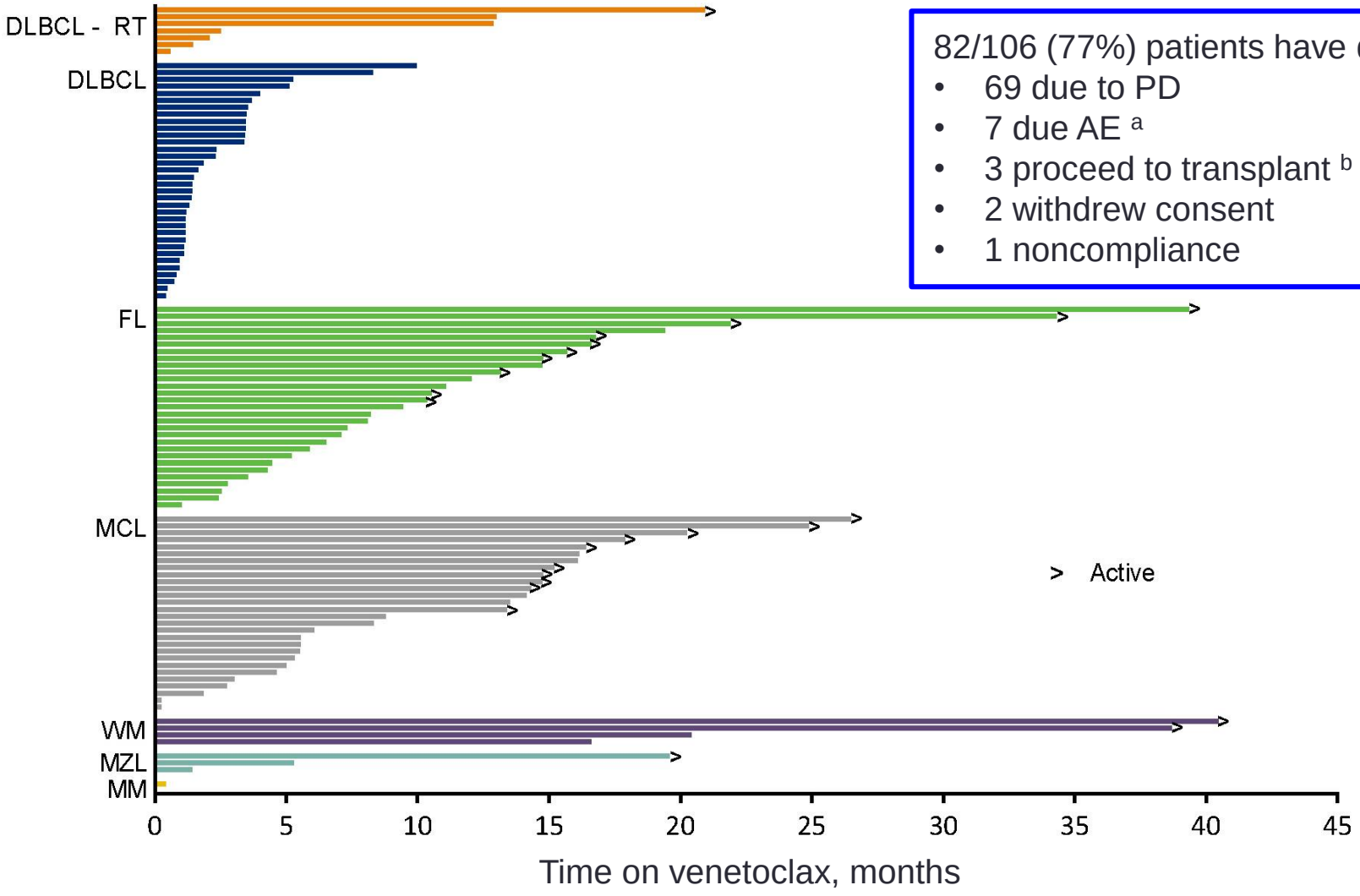
As of September 15, 2015

Best Percent Change From Baseline in Nodal Mass by CT Scan



As of September 15, 2015

Current Status



82/106 (77%) patients have discontinued

- 69 due to PD
- 7 due AE [a]
- 3 proceed to transplant [b]
- 2 withdrew consent
- 1 noncompliance

[a] 1 each sepsis, anemia, rheumatoid arthritis, type 2 respiratory failure, thrombocytopenia, toxic myopathy, diarrhea/nausea

[b] Two after achieving PR and one after achieving CR

As of September 15, 2015

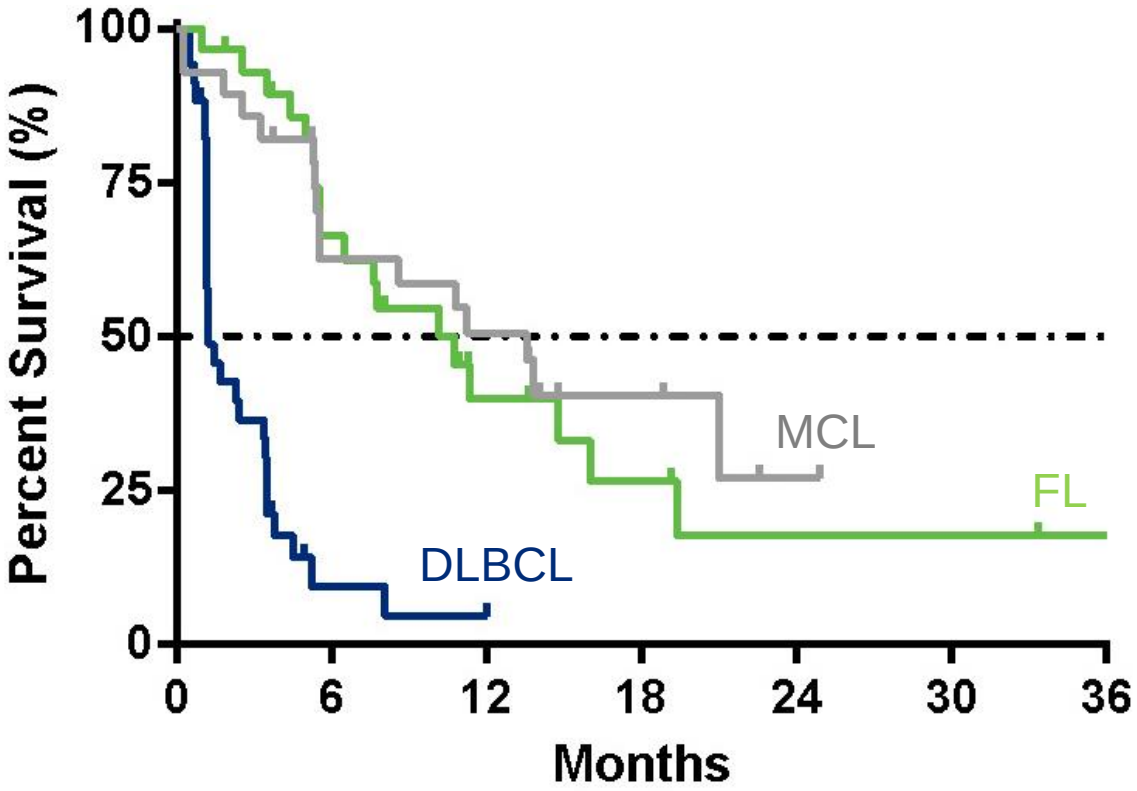
Objective Responses by Histology – All Doses

Best Objective Response, n (%)	All N=106	MCL n=28	FL n=29	DLBCL n=34	DLBCL-RT n=7	WM n=4	MZL n=3
Overall Response	**47 (44)**	**21 (75)**	**11 (38)**	**6 (18)**	**3 (43)**	**4 (100)**	**2 (67)**
CR	14 (13)	6 (21)	4 (14)	4 (12)	0	0	0
PR	33 (31)	15 (54)	7 (24)	2 (6)	3 (43)	4 (100)	2 (67)
SD	32 (30)	5 (18)	17 (59)	8 (24)	2 (29)	0	0
PD	23 (22)	1 (4)	1 (4)	19 (56)	1 (14)	0	0

- 4 patients discontinued prior to assessment
- n=1 with MM had PD

As of September 15, 2015

Progression-Free Survival by Histology Subtype



MCL:	28	16	12	4	1		
FL:	29	17	7	4	2	1	1
DLBCL:	34	2					

	Median PFS, Months (95% CI)
All, n=106	17 (14, 22)
MCL, n=28	14 (ND)
FL, n=29	11 (6, 19)
DLBCL, n=34	1 (1, 3)

As of September 15, 2015

Venetoclax, bendamustine, and rituximab in patients with relapsed or refractory NHL: a phase Ib dose-finding study

S. de Vos[1*], L. J. Swinnen[2], D. Wang[3], E. Reid[4], N. Fowler[5], J. Cordero[6], M. Dunbar[6], S. H. Enschede[6], C. Nolan[6], A. M. Petrich[6], J. A. Ross[6], A. H. Salem[6,7], M. Verdugo[6], S. Agarwal[6], L. Zhou[6], M. Kozloff[8], L. J. Nastoupil[5] & C. R. Flowers[9]

Annals of Oncology 00: 1–7, 2018
doi:10.1093/annonc/mdy256
Published online 28 July 2018

Table 1. Patient demographics and clinical characteristics

Characteristics	Total *N* = 60
Age, median (range), years	62 (29–90)
Male, *n* (%)	40 (67)
Histology, *n* (%)	
Follicular lymphoma	32 (53)
Diffuse large B-cell lymphoma	22 (37)
Marginal zone B-cell lymphoma	6 (10)
Prior therapies, *n*, median (range)	3 (1–8)
Rituximab or R-based chemotherapy, *n* (%)	60 (100)
Bendamustine or BR, *n* (%)	15 (25)
Refractory to prior therapy, *n* (%)	32 (52)
Bulky nodes, *n* (%)	
>5 cm	33 (55)
>10 cm	6 (10)

De Vos *et al.* Ann Oncol 2018

Table 4. Exploratory antitumor activity

Response by subtype, *n* (%)	**DLBCL *n* = 22**	**FL *n* = 32**	**MZL *n* = 6**	**Total *N* = 60**
Objective response (CR+PR)	**9 (41)**	**24 (75)**	**6 (100)**	**39 (65)**
CR	3 (14)	12 (38)	3 (50)	18 (30)
Partial response	6 (27)	12 (38)	3 (50)	21 (35)
Stable disease	4 (18)	2 (6)	0	6 (10)
Progressive disease	9 (41)	3 (9)	0	12 (20)
Discontinued without assessment	0	3 (9)	0	3 (5)
Response by schedule, *n* (%)	**Arm A (3/28-day VEN [+BR]) *n*=8**	**Arm B (7/28-day VEN [+BR]) *n*=13**	**Arm C (28-day VEN [+BR]) *n*=39**	**Total *N*=60**
Objective response (CR+PR)	**5 (63)**	**10 (77)**	**24 (62)**	**39 (65)**
CR	2 (25)	3 (23)	13 (33)	18 (30)
Partial response	3 (38)	7 (54)	11 (28)	21 (35)
Stable disease	2 (25)	0	4 (10)	6 (10)
Progressive disease	1 (13)	2 (15)	9 (23)	12 (20)
Discontinued without assessment	0	1 (8)	2 (5)	3 (5)

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Table 2. Treatment-emergent adverse events

All-grade TEAEs (≥20% total patients), *n* (%)	Arm A (3/28-day VEN [+BR]) *n* = 8	Arm B (7/28-day VEN [+BR]) *n* = 13	Arm C (28-day VEN [+BR]) *n* = 39	Total *N* = 60
Grade 3/4 TEAEs (≥5% total patients), *n* (%)				
Any grade 3/4 TEAE	4 (50)	12 (92)	34 (87)	50 (83)
Neutropenia	3 (38)	10 (77)	23 (59)	36 (60)
Lymphocyte count decrease	0	6 (46)	17 (44)	23 (38)
White blood cell count decrease	0	3 (23)	10 (26)	13 (22)
Leukopenia	1 (13)	4 (31)	7 (18)	12 (20)
Thrombocytopenia	2 (25)	1 (8)	14 (36)	17 (28)
Anemia	2 (25)	2 (15)	6 (15)	10 (17)
Febrile neutropenia	1 (13)	1 (8)	3 (8)	5 (8)
CD4 lymphocytes decrease	0	0	4 (10)	4 (7)
Dyspnea	0	2 (15)	1 (3)	3 (5)
Fatigue	0	1 (8)	2 (5)	3 (5)
Hypokalemia	0	1 (8)	2 (5)	3 (5)
Hypophosphatemia	0	1 (8)	2 (5)	3 (5)
Lymphopenia	0	1 (8)	2 (5)	3 (5)
Nausea	0	0	3 (8)	3 (5)

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Conclusions: This study established the safety profile of venetoclax in combination with BR, and results demonstrated tolerability and preliminary efficacy of the combination. Additional follow-up is needed to better determine the future role of BR plus venetoclax in the treatment of relapsed/refractory B-cell NHL.

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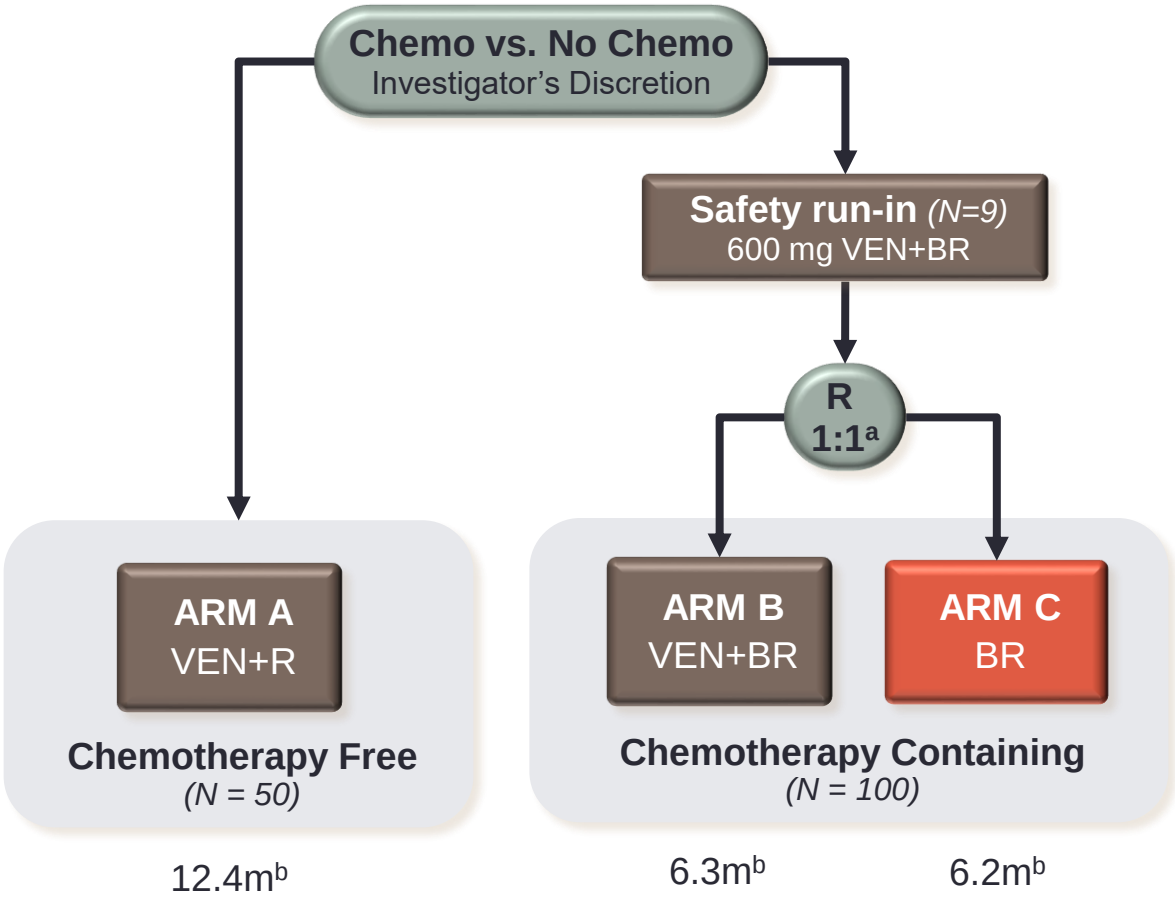
CONTRALTO Phase 2 Study Design

VEN + R and randomized VEN + BR vs BR alone in patients with R/R FL, Grade 1–3a



a Stratified: DOR to prior tx (≤12m vs. >12m) Disease burden (high vs. low)

b median months on study so far (ongoing)

Key inclusion criteria

- Age ≥18 yrs
- Confirmed R/R FL (Gr 1–3a)
- Treated with ≥1 line of prior therapy for FL
- Adequate marrow, coagulation, renal, and hepatic function
- No history of bendamustine-refractory disease
- No CNS lymphoma

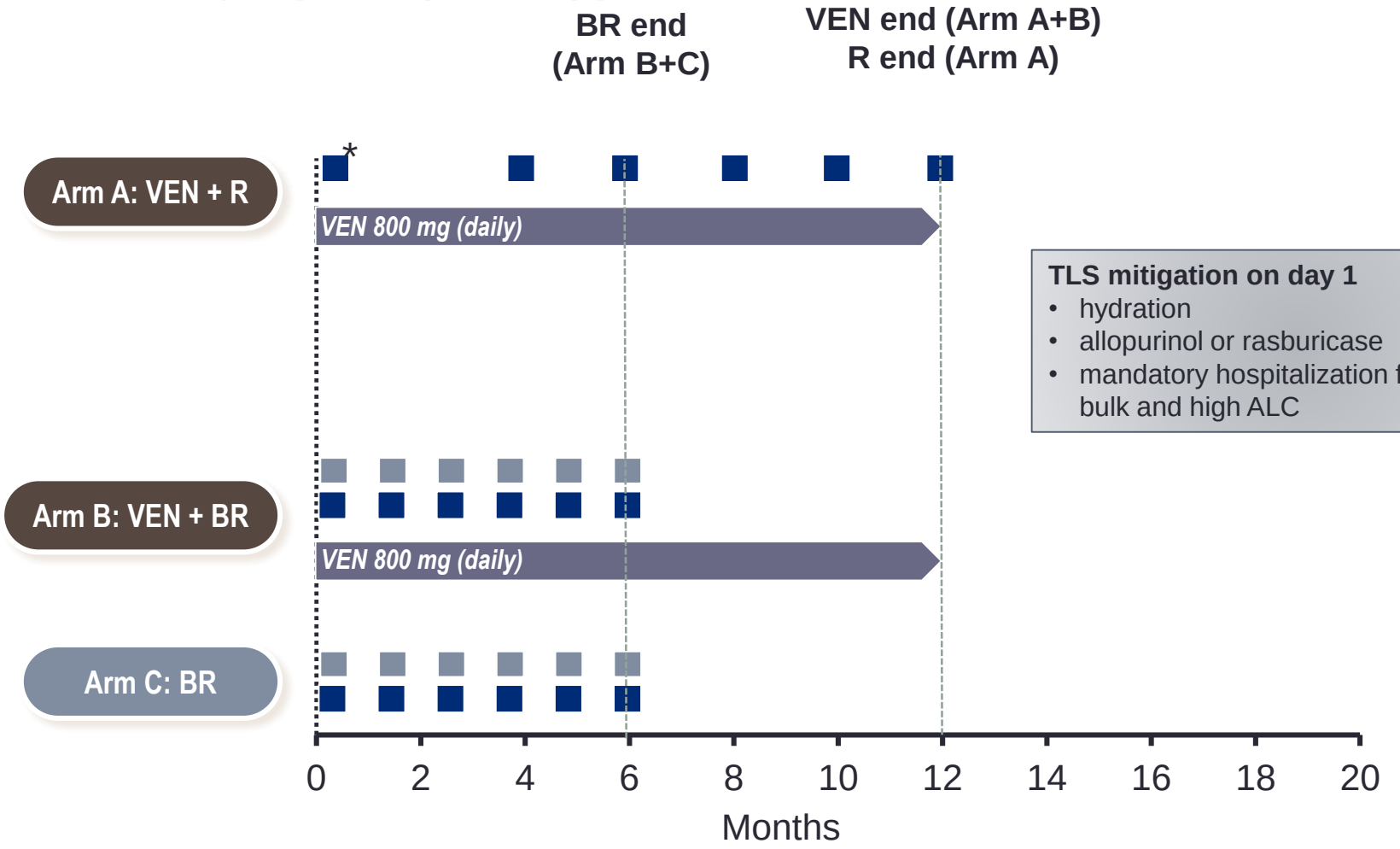
Primary Endpoint

- PET-CR rate by IRC at end of induction (Cheson 2014)

Secondary Endpoints

- CR rate (PET and CT) by investigator at end of induction and 1 year
- ORR
- PFS
- Safety

Dosing Schedule by Arm and Time on Study (Ongoing)



TLS mitigation on day 1

- hydration
- allopurinol or rasburicase
- mandatory hospitalization for pts with bulk and high ALC

Venetoclax	Daily over period indicated	800 mg daily
Rituximab	D1 of period indicated	375 mg/m^2
Bendamustine	D1 + D2 of period indicated	90 mg/m^2

Blue circles represent the median, and the lines are for the associated range
*R administered on Days 1, 8, 15 and 22.
28-day cycles

VEN + R Safety

All AE > 10%, n (%)	*(N=52)*
Diarrhea	21 (40)
IRR	15 (29)
Neutropenia	15 (29)
Nausea	14 (27)
Fatigue	13 (25)
Thrombocytopenia	8 (15)
Vomiting	7 (14)
Abdominal Pain	7 (14)
G3–4 > 5%, n (%)	
Neutropenia	13 (25)
Thrombocytopenia	5 (10)
Diarrhea	3 (6)

Lab tumor lysis syndrome was seen in 1 pt and was manageable

6 deaths on study

- 2 PD
- 1 each of: pulmonary hemorrhage, colitis, myocardial infarction, and unknown cause

Pts with adverse events leading to stopping drug: 5 (10%) total

- VEN: 5 (10%) pts
- R: 2 (4%) of pts

VEN + R: Efficacy

Response rates by PET-CT by investigator at 6-month (primary),[1] n (%)	VEN + R (N=53)	VEN + R Refractory (N=40)	VEN + R Non Refractory (N=13)
ORR	**16 (30)**	**11 (28)**	**5 (38)**
CMR	7 (13)	5 (13)	2 (15)
PMR	9 (17)	6 (15)	3 (23)
No metabolic response	2 (4)	3 (8)	0
Progressive disease	24 (45)	19 (48)	5 (38)
Response data unavailable	**11 (21)**	**8 (20)**	**3 (23)**
Best response[2] by PET-CT or CT by investigator, n (%)			
ORR	**20 (38)**	**13 (33)**	**7 (54)**
CR	11 (21)	9 (23)	2 (15)
PR	9(17)	4 (10)	5 (38)
Stable disease	8 (15)	6 (15)	2 (15)
Progressive disease	18 (34)	16 (40)	2 (15)
Response data unavailable	**7 (13)**	**5 (13)**	**2 (15)**

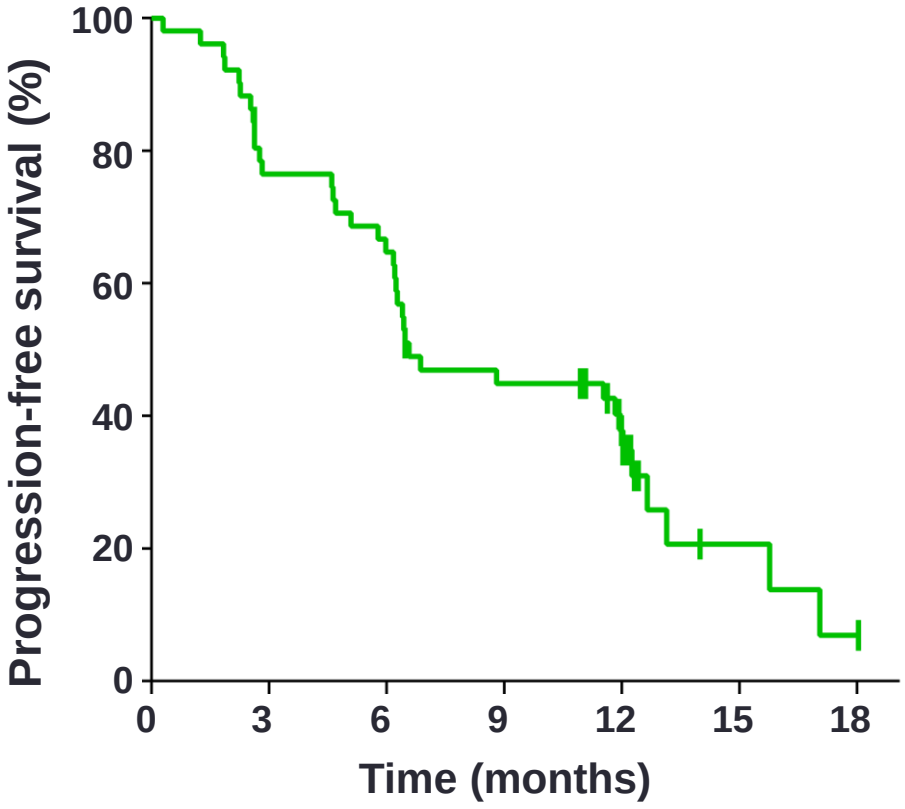
[1] Primary responses evaluated 6-8 weeks after: C6D1 or date of drug discontinuation (whichever was earlier)

[2] Best responses evaluated from randomization to the end of the study. CT used if PET was unavailable.

VEN + BR vs. BR: Efficacy

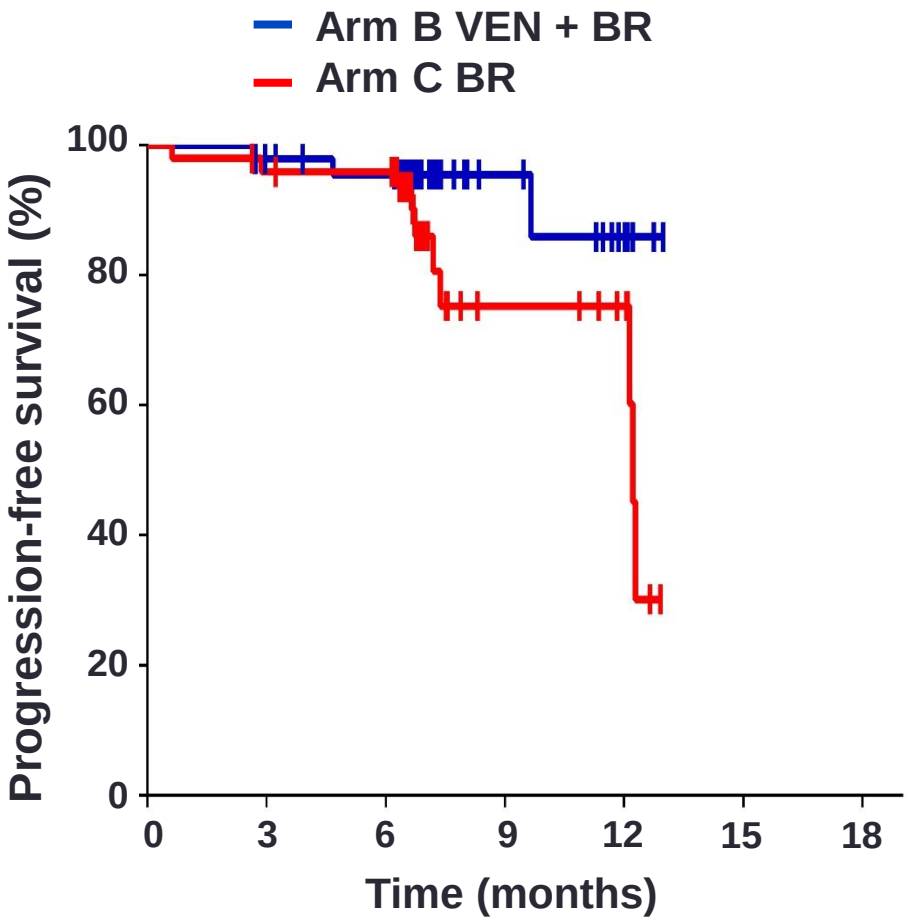
Response rates by PET-CT by investigator at 6-month (primary),[1] n (%)	Arm B VEN + BR (N=51)	Arm C BR (N=51)
ORR	**38 (75)**	**39 (77)**
CMR	32 (63)	31 (61)
PMR	6 (12)	8 (16)
No metabolic response	0	0
Progressive disease	2 (4)	6 (12)
Response data unavailable	**11 (22)**	**6 (12)**
Best response[2] by PET-CT or CT by investigator, n (%)		
ORR	**46 (90)**	**45 (88)**
CR	**36 (71)**	**34 (67)**
PR	**10 (20)**	**11 (22)**
Stable disease	1 (2)	0
Progressive disease	1 (2)	4 (8)
Response data unavailable	**3 (6)**	**2 (4)**

[1] Primary responses evaluated 6-8 weeks after: C6D1 or date of drug discontinuation (whichever was earlier)
[2] Best responses evaluated from randomization to the end of the study. CT used if PET was unavailable.



Pts at risk:

(50) (39) (33) (22) (13) (3) (1)



Pts at risk:

Arm B VEN + BR (48) (42) (39) (11) (5) - -

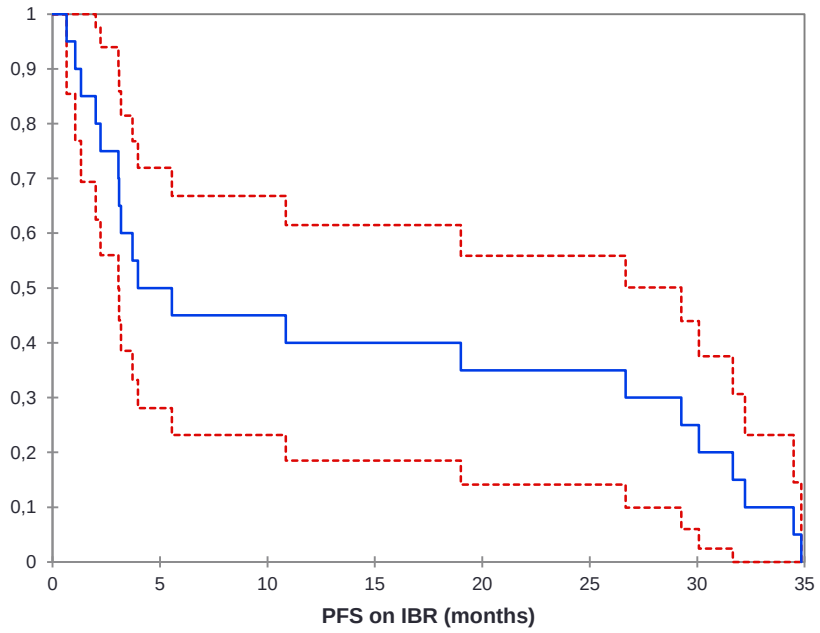
Arm C BR (49) (47) (45) (10) (7) - -

EFFICACY OF VENETOCLAX MONOTHERAPY IN PATIENTS WITH RELAPSED, REFRACTORY MANTLE CELL LYMPHOMA POST BTK INHIBITION THERAPY.

T.A. Eyre, H. S. Walter, S. Iyengar, G. Follows, C.P. Fox, N. Morley, M.J.S. Dyer & G. P. Collins.

Results – prior therapies: BTKi

median PFS to BTKi of 4.8 months (95% CI 3.1-29.2 months)



All patients (N=20)	n (%)
Response rate to prior BTK inhibitor	ORR 11/20 (55%)
	CR 3 (15%)
	PR 8 (40%)
	SD 4 (20%)
	PD 5 (25%)
Duration of exposure to BTK inhibitor (months; range)	4.8 months
	(range 0.7 – 34.8 months)
Reason for BTK inhibitor discontinuation	
Progressive disease	17
Stable disease	1
Toxicity	2

ibrutinib (n=17), ibrutinib with donor lymphocyte infusion (n=1), tirabrutinib (n=2)

Response to Venetoclax

- 20 patients evaluable for response assessment
- Median follow up from start of venetoclax: 5.1 months.
- ORR 60% (CR 20%, PR 40%)
- Median 3.75 x 28-day cycles (range 0.5-13).
- ORR according to prior BTKi response:
  - primary BTKi resistance (n = 9): ORR 44.4% *vs* response to prior BTKi (n = 11): ORR 72.7%

Treatment post Venetoclax	n (%)
Allogenic stem cell transplantation-> PEP-C	1
R-BAC	2[a]
R-Bendamustine	2
Lenalidomide-based+/-R	2
Ibrutinib	2
Nil	12

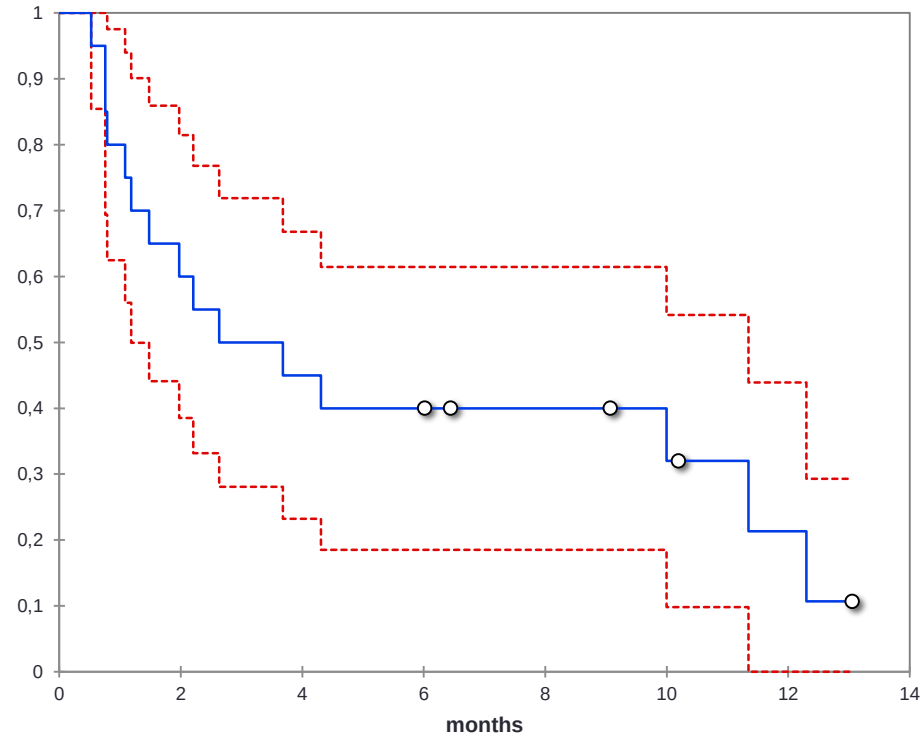
a) 1 patient R-BAC given with aim to bridge to allogenic SCT (developed secondary AML)

Blastoid (n = 4)

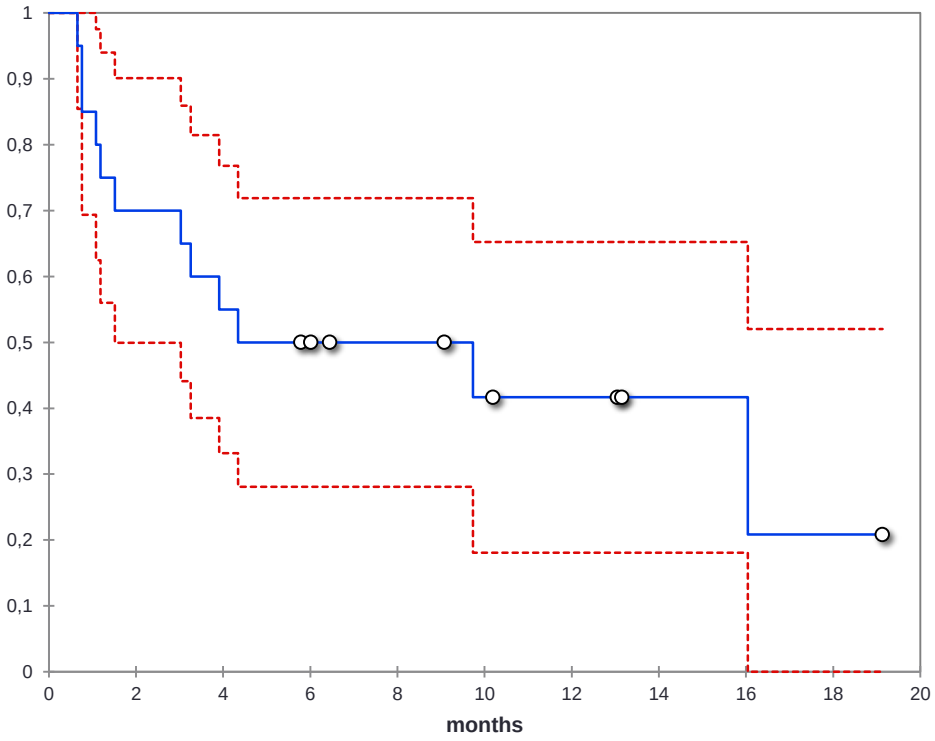
- Diagnosis to VEN (yrs): 2.1, 0.8, 0.9, 1.3
- Ki67%: 90%, 80%, 80%, 75%
- ORR: PD, PD, PD, CRu
- Cycles: 1.5, 1.5, 2, 1.25

Survival following venetoclax monotherapy

Progression free survival
Median 3.2 months (95% CI 1.2 - 11.3 months)

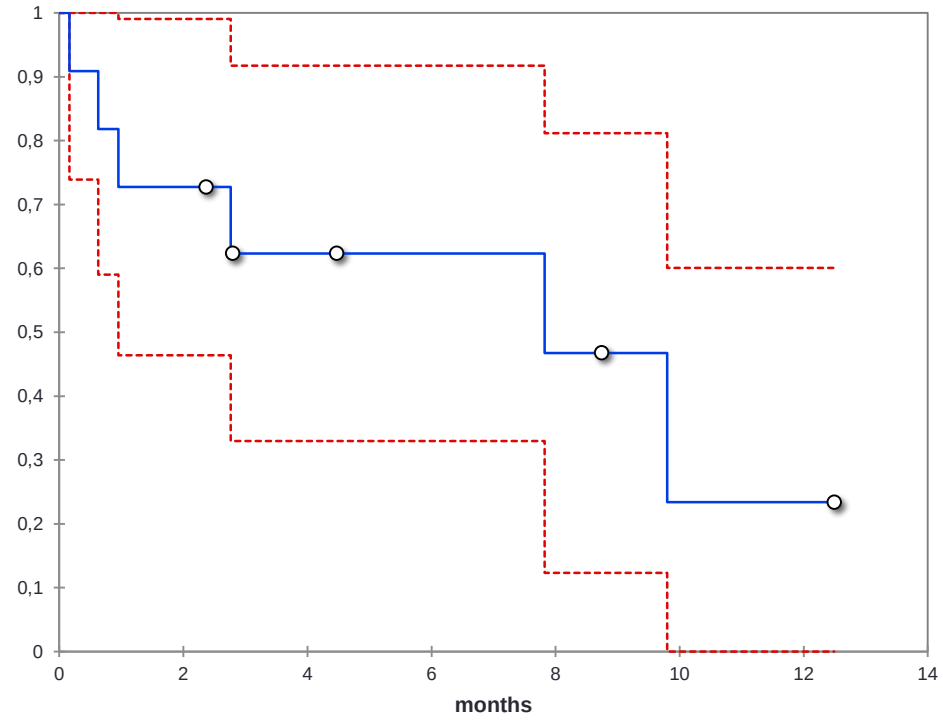


Overall survival
Median 9.4 months (95% CI 1.5 months - NR)

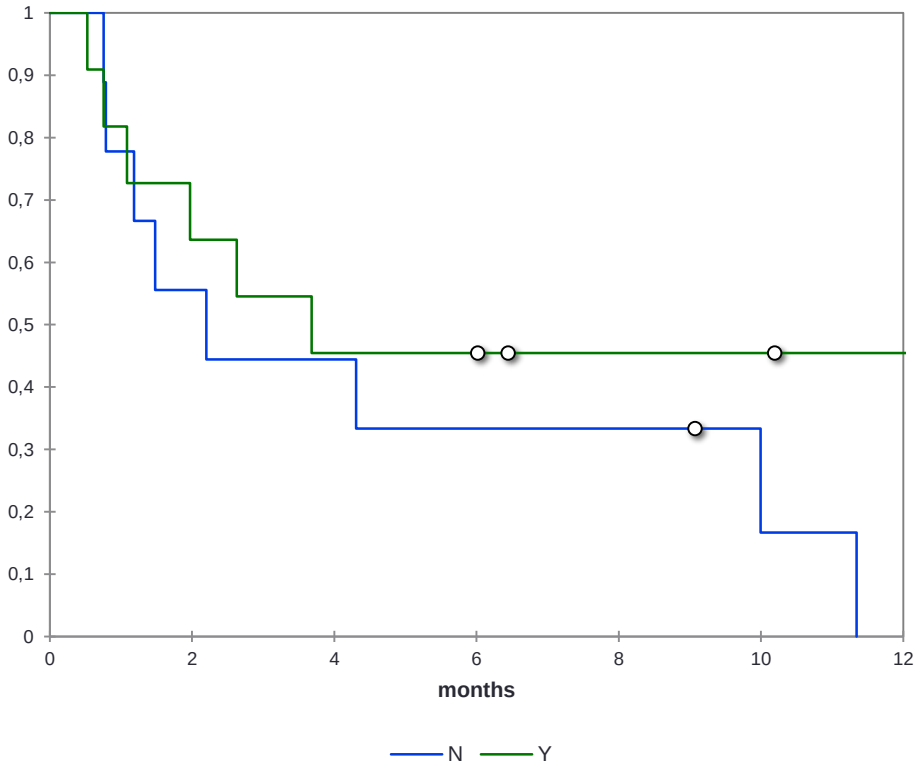


DOR and PFS according to Ibrutinib response

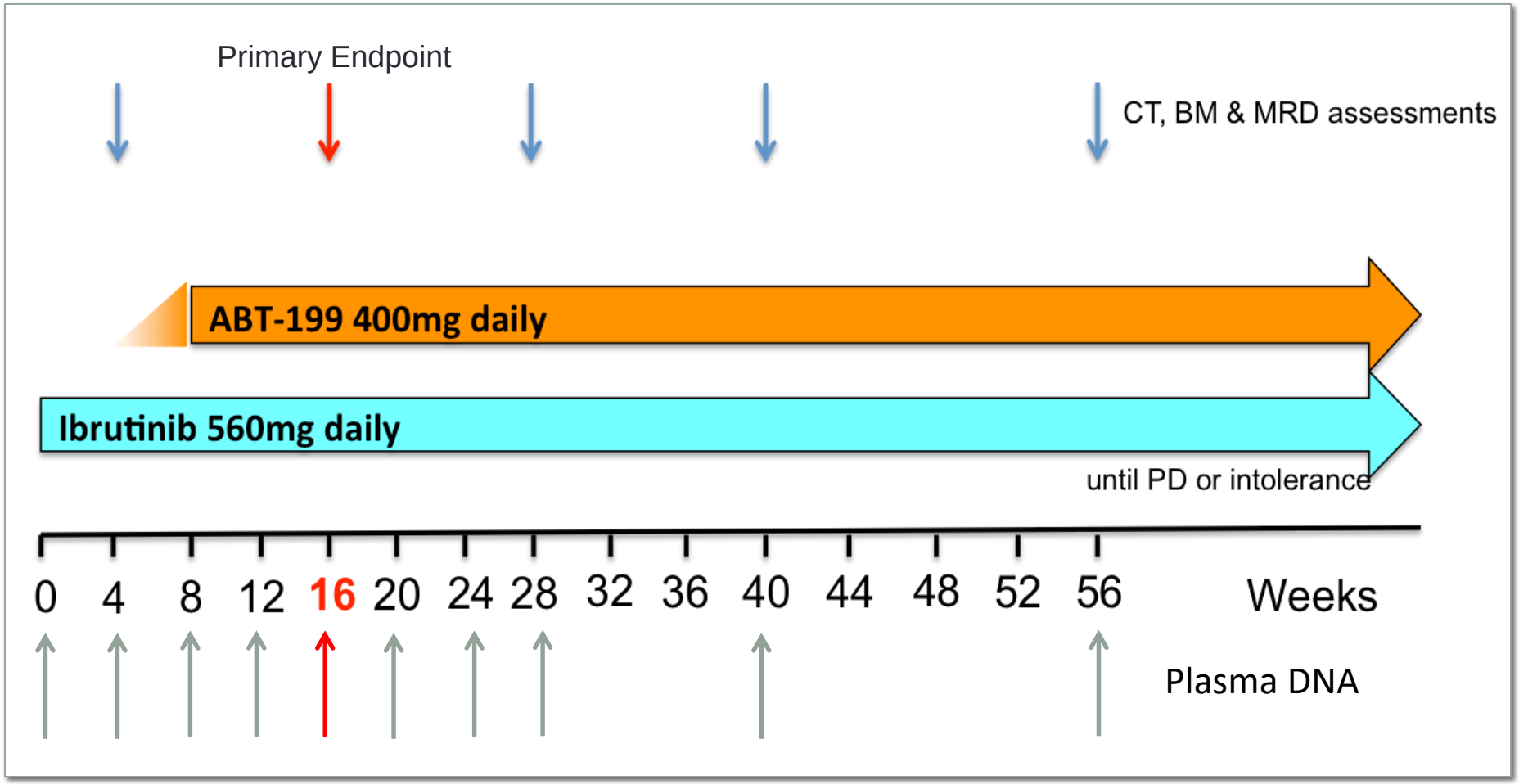
Duration of response
Median 7.8 months (95% CI 1.0 months - NR)



PFS according to prior Ibrutinib response
p = 0.296



AIM (ABT-199 & Ibrutinib in MCL) Study Schema



Tam et al. N Engl J Med 2018 378(13);1211-1223

Baseline Patient Characteristics

Baseline Characteristic (N = 24)	Value	
Age (years), median (range)	68	(47 – 81)
Male	21	88%
ECOG 0 – 1 ECOG 2	19 5	79% 21%
B-symptoms	4	17%
Largest bulk 5 to 10 cm Largest bulk > 10cm	4 7	17% 29%
MIPI Low MIPI Intermediate MIPI High	2 3 19	8% 13% 79%
No prior therapy for MCL	1	4%
Previously treated for MCL - Lines of prior therapy, median (range) - Prior autologous stem cell transplantation - No response (<PR) to last treatment	23 2 7 11	96% (1 – 6) 29% 48%

Adverse Events Irrespective of Causality

(AE ≥ 20% and/or Grade 3+ listed)

Adverse Event	All Grades		Grade 3+	
Diarrhoea	20	83%	1	4%
Fatigue	18	75%	0	
Nausea and/or Vomiting	16	67%	0	
Upper Respiratory Tract Infection	10	42%	0	
Gastro-oesophageal Reflux	8	33%	0	
Neutropenia	8	33%	8	33%*
Cough	7	29%	0	
Dyspnoea	6	25%	1	4%
Anaemia	5	21%	2	8%
Bruising	5	21%	0	
Peripheral Neuropathy	5	21%	0	
Thrombocytopenia	5	21%	4	17%*
Pneumonia	3	13%	2	8%
Atrial Fibrillation	2	8%	2	8%
Tumour Lysis Syndrome	2	8%	2	8%

Other Grade 3+ AE (1 each): Heart Failure, Haematuria, Insomnia, Pleural Effusion, Amnesia, Ascites, Ischaemic Heart Disease, Colitis, Dehydration, Hyperglycaemia, Hypertension, Hypotension, Neck Pain, Otitis Externa, Thromboembolic Event, Vasovagal Reaction

*G4 neutropenia = 17%; G4 thrombocytopenia = 8%

AIM Study: Response Rates (PET)

	Week 16, CT only	Week 16, PET/CT
Complete Response (CR)	10 (42%)	15 (63%)
CR, unconfirmed	4 (17%)	-
Partial Response (PR)	4 (17%)	2 (8%)
Stable Disease (SD)	1 (4%)	1 (4%)
Progressive disease (PD)	3 (13%)	4 (17%)
Not Evaluable	2 (8%)	2 (8%)

Wk 16

OR = 71%

CR = 63%

Patients were restaged at week 16 using CT, PET, double endoscopy (if baseline involvement), and BMAT with MRD studies.

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Wk 16

OR = 71%

CR = 63%

50% TP53 aberrations
Half achieved CR

Patients were restaged at week 16 using CT, PET, double endoscopy (if baseline involvement), and BMAT with MRD studies.

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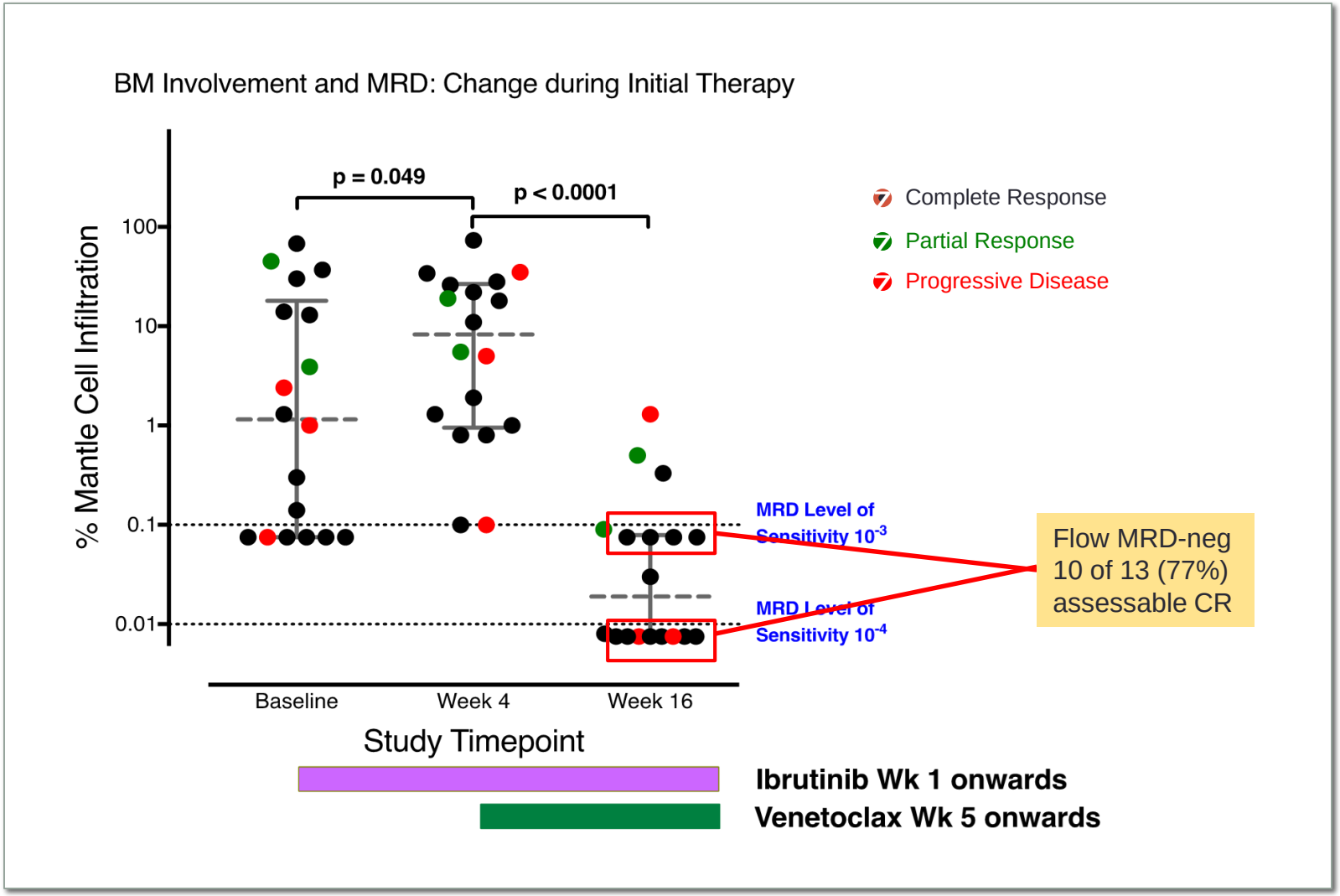
AIM Study : Marrow Flow MRD Kinetics*



* 3 patients had no marrow involvement

Tam et al. N Engl J Med 2018 378(13);1211-1223

OAsIs

A phase I trial of Obinutuzumab, ABT-199 plus Ibrutinib in Relapsed / Refractory Mantle Cell Lymphoma patients

PI (UK): Pr Rule Simon
PI (France): Pr Le Gouill Steven
Study Coordinator: S. Cussonneau (France)
and Study coordinator for UK:

Countries : France and UK
Sites :
2 in France (Nantes and Bordeaux)
2 in UK (Plymouth and Southampton)

Patients : 33 (step A : 9 patients, step B: 24 patients)

With Financial support from Roche
With support from Abbott, Janssen and Genentech

What's happening?

- 38 studies in ClinicalTrials.gov

- SYMPATICO – Randomised Ibru +/- V in MCL (287)
- BR+IV in RR MCL (MSK)
- R-BAC+V (elderly MCL up front)
- V+DA-EPOCH
- V+BEAM