Efficacy of venetoclax monotherapy in patients with relapsed, refractory mantle cell lymphoma after Bruton tyrosine kinase inhibitor therapy

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doi:10.3324/haematol.2018.198812

Table S1: Dose ramp up schedule on VEN-MONO (n = 19)

Final dose intention	Ramp up schedule	Highest dose reached
200 mg OD	weekly ramp up 20mg, 50mg, 100mg	100 mg OD (stopped early: sepsis)
400 mg OD	weekly ramp up: 20mg, 50mg, 100mg, 200mg, 400mg	400 mg OD
400 mg OD	weekly ramp up: 20mg, 50mg, 100mg, 200mg, 400mg	400 mg OD
800 mg OD	weekly ramp up: 20mg, 50mg, 100mg, 200mg, 400mg, 800mg	800 mg OD
800 mg OD	weekly ramp up 20mg, 50mg, 100mg, 200mg, 400mg, 800mg	800 mg OD
800 mg OD	weekly ramp up: 50mg, 100mg, 200mg, 400mg, 800mg	800 mg OD
800 mg OD	weekly ramp up: 50mg, 100mg 3 days, 200mg 10 days, 400mg	400 mg OD (stopped early: PD)
800 mg OD	weekly ramp up: 20mg, 50mg, 100mg, 200mg, 400mg, 600mg, 800mg	800 mg OD
800 mg OD	weekly ramp up: 20mg, 50mg, 100mg, 200mg, 400mg	400 mg OD but reduced to 200 mg OD due to G2 neutropenia
800 mg OD	weekly ramp up: starting at 100mg, 200mg, 400mg, 800mg	800 mg OD
1200 mg OD	weekly ramp up: 20mg, 50mg, 100mg, 200mg, 400mg, 800mg, 1200mg	1200 mg OD but reduced to 600 mg OD due to G2 fatigue and G3 LRTI
1200 mg OD	weekly ramp up: 20mg, 50mg, 100mg, 200mg, 400mg, 800mg, 1200mg	1200 mg OD but reduced to 800 mg OD due to G2 diarrhoea and G2 nausea
1200 mg OD	weekly ramp up: 20mg, 50mg, 100mg, 200mg, 400mg, 800mg, 1200mg	1200 mg OD but reduced to 800mg OD due to G2 diarrhoea
1200 mg OD	weekly ramp up: 20mg, 50mg, 100mg, 200mg	200 mg OD (stopped early: PD)
1200 mg OD	weekly ramp up 20mg, 50mg, 100mg, 200mg, 400mg, 800mg, 1200mg	1200 mg OD
1200 mg OD	weekly ramp up: 20mg, 50mg	50 mg OD (stopped early: PD)
1200 mg OD	weekly ramp up: 50mg, 100mg, 200mg, 400mg, 800mg, 1200mg	1200 mg OD
1200 mg OD	weekly ramp up: 50mg 4 days, 100mg 3 days, 200mg 3 days, 400mg 3 days, 800mg 2 days, 1200mg 3 days	1200 mg OD
1200 mg OD	weekly ramp up: 20mg, 50mg, 200mg, 400mg, 800mg, 1200mg	1200 mg OD but reduced to 600 mg OD due to G2 diarrhoea

	Starting dose (mg)	Episodes of biochemical TLS meeting Howard Criteria	Dosing ramp up	Dose at which Howard criteria occurred	Anti-urate	Outcome	Worst biochemical abnormalities (ranges given where available)
Patient 1	100 mg OD	2	100mg; stopped after single dose. Held for 5 days and restarted at 100mg then weekly escalation (200mg; 400mg; 800mg). Recurrent TLS at 800mg.	100 mg 800 mg	Rasburicase and IV fluids on both occasions	1) Dose held for 5 days then rechallenged and successfully escalated 2) Dose held for 24 hours then rechallenged at 400mg and successfully escalated	1) PO4 3.01 (0.65-1.05), Adj Ca 1.95, K+ 5.9, Urate <0.03 (had receive rasburicase) 2) PO4 2.43 (0.65-1.05), Urate 0.68 (0.21-0.42), Adj Ca 2.11 (2.10-2.60), K+ 4.0 (3.5-5)
Patient 2	50 mg OD	1	Weekly ramp up: 50mg, 100mg; 200mg; 400mg. Final dose 400mg.	50 mg	rasburicase and IV fluids; haemodialysis	Dose ramp up in weekly fashion. Haemodialysis for metabolic acidosis at full dose but not clearly due to TLS at that time. Did not hold venetoclax dosing.	PO4 1.84 Adj Ca 1.95 K+ 6.3 Urate 0.36 (subsequently <0.03 with rasburicase)
Patient 3	50 mg OD	1	50mg for 1 day then interrupted for 2 days then 6 days then weekly ramp up: 100mg; 200mg; 400mg, 800mg; 1200mg.	50 mg	rasburicase and IV fluids	Dose held for 2 days. Resolved and successfully restarted and dose ramped up.	PO4 1.75 (0.8-1.5) Adj Ca 2.06 (2.2-2.6) K+ 5.2 (3.5-5.3) Urate <30 and subsequently 109 despite rasburicase given pre (200 to 430)
Patient 4	20mg OD	1	Weekly ramp up: 20mg; 50mg, 100mg; 200mg; 400mg; 800mg. Single episode after 9 day omission (moderate neutropenia and line sepsis) on 400mg when restarted at same dose.	800 mg	Rasburicase and IV fluids	There was no TLS seen at all in initial ramp up phase. The single episode of lab TLS occurred after a 9 day Venetoclax omission. All settled spontaneously and reloaded starting at 20mg with no recurrent TLS.	PO4 3.1 (0.8-1.5) Adj Ca 1.76 (2.2-2.6) K+ 5.8 Urate 559 (200-430)

Table S2: Summary data for Laboratory TLS events (n = 4)

Table S3: Adverse Events on VEN-MONO

All patients (n=20)	n (%)
Dose reductions from target dose required	5 (25%)
Reasons: Grade 2 fatigue (n = 1), Grade 2 diarrhoea (n = 2), Grade 2 diarrhoea alongside grade 2 nausea (n = 1), grade 2 neutropenia (n = 1)	
Grade 4 sepsis	1 (5%)
Grade 3 pneumonia	3 (15%)
Grade 2 diarrhoea	3 (15%)
Grade 2 fatigue	2 (10%)
Grade 2 headache	2 (10%)
Grade 2 neutropenia	2 (10%)
Grade 2 nausea	2 (10%)
Grade 2 raised gamma GT	1 (5%)
Grade 1 anaemia	1 (5%)
Biochemical Tumour lysis	5 (25%)
Clinical Tumour lysis syndrome	0 (0%)
No adverse effects reported	12 (60%)

Supplementary Table S4: Treatment post VEN-MONO

Allogenic stem cell transplantation	1
R-BAC a) 1 patient R-BAC given with aim to bridge to allogenic SCT; developed secondary AML in remission	2[a]
R-Bendamustine	2
Lenalidomide-based+/-R	2
Ibrutinib	2
Nil	12

ASCT in CR1	R-M	Line BTK given	Time on IBR (months)	Reason for Cessation of IBR	ORR to BTKi	Prior lines	Diagnosis to VEN (years)	Stage	Age at VEN	Extranodal	LDH raised	WCC	ECOG PS	s-MIPI	Histology	Ki67%	Cycles	Biochem TLS	Best ORR to VEN	Toxicity	Treatment post VEN	Dose reduction (MG)	Follow up (months) *= progression
Y	N	3	30.1	PD	CR	4	10.1	4	69	periorbital mass	N	4.2	2	3	NK	N/A	2	N	N/A	Nil	Nil	Nil	2.0*
N	N	3	3.1	PD	PD	3	11.0	3	56	Nil	N	10.0	0	3	small cell	30%	9	N	N/A	G2 fatigue. G3 Pneumonia x 2.	Nil	600	9.1
Y	N	2	2.2	PD	PD	2	2.1	4	56	BM	Y	3.2	1	3	blastoid	90%	1.5	Y	PD	G2 diarrhoea G2 Nausea	LEN-Dex 1 cycle	Nil	1.5*
N	N	3	34.5	PD	PR	3	5.6	4	80	BM	N	4.8	1	3	classical	40%	12	N	PR	G2 diarrhoea	IBR -> BR ongoing	600	12.3*
N	N	2	3.1	Toxicity (grade 4 low PLTs)	PD	4	1.4	4	43	Liver, BM	Y	7.6	2	4	classical	10%	5	N	SD	Nil	R-BAC then developed secondary AML	Nil	4.3*
N	N	**5**	5.6	PD	PR	5	9.0	4	57	BM	N	10.1	0	4	classical	N/A	6	N	PR	Nil	Nil	Nil	6.0
Y	N	2	10.8	PD	CR	4	8.6	4	67	Lung	Y	5.7	0	5	small cell	80%	0.5	N	PD	Nil	Nil	Nil	0.8*
N	N	2	3.2	PD	PD	2	0.8	4	70	BM	Y	1.8	3	5	blastoid	80%	1.5	Y	PD	Nil	R-BAC x 1 cycle	Nil	0.8*
N	Y	**4**	0.7	Toxicity (grade 4 SDH)	SD	4	4.7	3	69	Nil	Y	NK	3	6+	pleomorphic	N/A	10.5	N	PR	Nil	IBR	Nil	10.0*
N	N	**5**	31.7	PD	PR	5	8.3	4	66	Breast	Y	10.5	1	6	small cell	N/A	6.5	N	CRu	G2 Headache; G2 Nausea; G2 Neutropenia; G1 Anaemia; G1 low PLTs; G2 raised GGT	Nil	Nil	6.4
N	N	3	32.2	PD	PR	3	5.2	4	70	BM	N	26.2	3	7	pleomorphic	N/A	10	N	PR	Nil	Nil	Nil	10.2
N	N	2	34.8	PD	PR	2	4.6	4	79	BM	Y	8.1	0	7	NK	45%	3.5	N	PD	Nil	LEN-R ongoing	Nil	2.6*
Y	N	2	3.7	PD	PR	2	1.6	4	57	BM	Y	145.0	3	8	small cell	N/A	1	N	PR	G4 Sepsis	Nil	Nil	1.1*
Y	N	2	1.1	PD	SD	2	2.8	4	56	BM	Y	193.9	1	7	pleomorphic	N/A	1	Y	PD	Nil	Nil	Nil	0.8*
N	N	3	26.7	PD	PR	3	4.5	4	77	Lung, Pleura	Y	4.1	3	7	NK	N/A	1	N	PD	Nil	Nil	Nil	0.5*

Y	N	2	4.0	PD	SD	2	1.3	4	60	BM	Y	269	2	8	small cell	45%	9	Y	CR	Nil	Allograft -> relapse -> PEP-C ongoing	Nil	11.3*
N	Y	2	1.3	PD	PD	2	0.9	1	73	Nil	Y	10.5	1	8	blastoid	80%	2	N	PD	Nil	BR	Nil	2.2*
N	N	2	2.0	SD	SD	2	1.3	4	79	Skin	Y	18.4	1	9	Blastoid	75%	1.25	N	Cru	G2 fatigue. G2 Neutropenia	Nil	Nil	1.2*
N	N	3	29.3	PD	CR	3	5.9	4	84	BM	Y	65.5	1	9	Small cell	N/A	13	N	PR	G2 diarrhoea	Nil	600	13.1
N	N	**5**	19.0	PD	PR	5	8.2	4	72	BM	Y	19.6	2	10	small cell	15%	4	Y	PR	Nil	Nil	Nil	3.7*

Table S5: Summary data for all patients

Supplementary Figure 1A-D