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Title Page

Efficacy of venetoclax monotherapy in patients with relapsed, refractory mantle cell lymphoma post BTK inhibitor therapy.

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LETTER

Mantle cell lymphoma (MCL) is an aggressive B-cell malignancy, accounting for 6% of non-Hodgkin lymphoma (NHL) and which remains incurable with standard therapy. Despite the approval of bortezomib[1], temsirolimus[2], lenalidomide[3], ibrutinib[4] and acalabrutinib[5], patients with relapsed, refractory (R/R) MCL have a survival of 2 years.

Although ibrutinib monotherapy provides significant efficacy (overall response rate (ORR) 68% (complete response (CR) 21%; partial response (PR) 47%)) and tolerability in R/R MCL, patients ultimately relapse (median PFS 13.9 months) following Bruton's tyrosine kinase inhibition (BTKi).

There are minimal outcome data in patients progressing post-BTKi and the optimal approach is not established. Recent retrospective analyses have reviewed several agents (including traditional chemotherapy, lenalidomide, bortezomib, and Pi3Ki) in this setting. These collated data[6] displayed an ORR 20-48% and a short progression-free survival (PFS) and overall survival (OS)[7,8].

Cheah and colleagues analyzed immunochemotherapy given post-ibrutinib (n=31). The ORR was 32% (CR 19%). The median OS was 8.4 months and median DOR was 6 months[7]. Martin and colleagues assessed therapy post-ibrutinib (n=73). The ORR was 26% (CR 7%) resulting in a median PFS of 1.9 months and median OS 5.8 months[9]. MCL-004 assessed a lenalidomide-based approach post-ibrutinib (PD 88%; toxicity 9%). The ORR to prior ibrutinib was 45%. Thirteen received lenalidomide, 11 lenalidomide-rituximab and 34 lenalidomide plus other therapy. The ORR was 29% and median DOR was 20 weeks.

Outside of MCL-004, no specific regimen has assessed >15 BTKi-resistant patients. Existing therapies do not overcome unfavourable tumour biology in this setting and novel combinations with differing targeted mechanisms are required.

BCL2 is overexpressed in MCL due to BCL2 loci amplification[10], defective protein degradation *via* lack of E3 ubiquitin ligase FBXO10, and transcriptional upregulation *via* BTK-mediated canonical NF-κB activation[11].

Venetoclax is a potent, selective, oral BCL2 inhibitor (BCL2i). A recent phase 1 trial of venetoclax monotherapy (VEN-MONO) in NHL included 28 R/R MCL[12]. Within the whole cohort, toxicity was minimal and the ORR was 75% in MCL (21% CR). The median PFS was 14 months with 800mg o.d. representing a safe dose sufficient to achieve durable remissions. Whilst these results are impressive, no patients had received prior BTKi. To our knowledge, there are no data outlining VEN-MONO efficacy outside of this initial publication and no data published post-BTKi. We retrospectively collected data on 20 R/R MCL patients treated with off-label, free-of-charge VEN-MONO (03/2016-05/2018) via a UK-wide compassionate use programme supported by Abbvie. Data were collected from hospital records by the treating physician and included: response to prior lines including BTKi, duration on and reasons for stopping BTKi. Pre-venetoclax data collected included Ann Arbor stage, simplified prognostic index (sMIPI), histological subtype and Ki67% where available. Response was assessed by PET-CT or CT alone (Cheson 2014 criteria). 1 patient with heavy marrow infiltration at baseline was re-assessed with repeat marrow evaluation. 2 patients with marked lymphocytosis and splenomegaly were included in the ORR analysis as response was clearly assessable. 3 patients were evaluated clinically and therefore excluded from ORR analysis but included in the survival analysis. Induction immunochemotherapy included high-dose cytarabine (HDAraC) HDAraC/maxi-CHOP-R (cyclophosphamide, doxorubicin, vincristine, prednisolone, rituximab) and autologous stem-cell transplantation (ASCT) consolidation[13]. This pathway was considered a single treatment line. Rituximab maintenance following immunochemotherapy +/- ASCT was also included within first treatment. Following consent within a compassionate use programme, patients received VEN-MONO in a weekly ramp-up phase starting at 20-100mg o.d. to a maximum intended dose of 200-1200mg

o.d. until progressive disease (PD), toxicity, death, physician or patient choice. Detailed dosing were available for 19/20 patients (Table S1). The final intended dose was 800mg o.d. for 7/19 (37%) patients and 1200mg o.d. for 9/19 (47%) patients. The final intended dose was reached in 14/19 (74%) patients. Intended dose was not obtained because of neutropenia (n=1), sepsis (n=1), and PD (n=3). 5 patients who reached final intended dose required a subsequent dose reduction (Table S1).

Adverse event (AE) data, the incidence of tumour lysis syndrome (TLS), and anti-urate therapy were collected. AE grading were collected according to CTCAEv4.03. Follow-up was censored at the most recent hospital visit or death. Non-responsive MCL was defined as stable disease (SD) or PD. Data were censored in 05/2018. PFS, OS and DOR were calculated in standard fashion. Statistical analyses were performed in XLSTAT.

The median age was 69 (range 43-84) years with a typical male predominance (85%) (Table 1). Patients received a median of 3 prior therapies (range 2-5). 40% received a HDAraC-based induction regimen, with 30% receiving ASCT in first remission. At relapse (first or subsequent), all received a BTKi (ibrutinib (n=17), ibrutinib with donor lymphocyte infusion (n=1), tirabrutinib (n=2)). ORR to BTKi was 55% (CR 15%), with a median PFS of only (range 0.7-34.9) 4.8 months. Eighteen patients stopped BTKi due to PD and 2 for toxicity (grade (G)4 thrombocytopenia; G4 subdural haemorrhage). Post-BTKi, four relapsed with blastoid MCL (Table 2). Prior to VEN-MONO, 95% had stage III/IV disease. 50% (9/18) were high-risk according to s-MIPI. Median Ki67% was 45% (11 biopsies assessed).

VEN-MONO was well tolerated. There was no clinical TLS and 4 transient, asymptomatic biochemical TLS; managed with successful temporary cessation and re-challenge (Table S2). Three patients required dose reductions to 600mg o.d. due to AEs (G2 fatigue (n=1), G2 diarrhoea (n=2)). There were 17 AEs reported including pneumonia (G3; n=3), sepsis (G4; n=1), fatigue (G2; n=2), neutropenia (G2; n=2) and diarrhoea (G2; n=3) (Table S3). Patients received allopurinol (45%), rasburicase (30%) or both (25%) as prophylaxis (Table 2).

The ORR to VEN-MONO was 53% (18% CR; 35% PR). The median time to response on venetoclax was 48 (range: 14-204) days. The median PFS was 3.2 months (95% CI 1.2-11.3 months) and the median OS was 9.4 months (95% CI 1.5 months-not reached (NR)) (Figure 1A-B). The median DOR was 8.1 (95% CI 2.8-9.8) months and the PFS was significantly improved in venetoclax responders (median 10.7 months (95% CI 3.7-12.3)) *versus* non-responders (median 1.1 months (95% CI 0.8-2.6); p=0.002) (Figure 1C; Supplementary Figure 1A). Although the initial ORR to venetoclax varied according to prior BTKi response (primary resistance to BTKi (n=8): ORR 38% *versus* response to BTKi (n=9): ORR 67%) (p=0.24)), this did not translate to an improved PFS (data not shown). Duration on ibrutinib (<4 vs. >4 months) did also not predict for PFS to VEN-MONO (p=0.13) (Figure 1D). The s-MIPI pre-venetoclax also did not predict PFS (p=0.714) (Supplementary Figure 1B). The PFS for the 2 patients that stopped ibrutinib due to toxicity were 4.3 months (best response: SD) and 10.0 months (best response: PR) respectively.

Patients who received only 2 prior lines pre-VEN-MONO had a paradoxically shorter PFS (median 1.3 months (95% CI 0.8-2.6)) compared to more heavily pre-treated (>2 prior lines) (median 10.0 months (95% CI 3.7-NR); p=0.042). Similar results were seen when comparing patients with a time from initial MCL diagnosis to start of venetoclax of >4.5 years (median 10.0 months (95% CI 2.6-NR)) *versus* <4.5 years (median 1.3 months (95% CI 0.8-4.3); p=0.027) (Supplementary Figure 1C-D). As such, *less* heavily pre-treated patients were enriched for those with a considerably shorter time from MCL diagnosis to venetoclax commencement and therefore likely represented those with more aggressive disease biology. 4 patients with blastoid disease had a short time from diagnosis to VEN-MONO (0.8-2.1 years), possessed high Ki67% (75-90%), had a ORR of 25%, and all progressed by 2 months. Eight patients received treatment post-VEN-MONO (Table S4). One patient received an alloSCT following response to VEN-MONO but subsequently relapsed.

To date, 12 patients have died; 9 from PD, 2 from the combination of PD and infection, and 1 patient from secondary acute myeloid leukaemia whilst in remission post R-BAC (Table S5).

We present initial real-world data outlining the efficacy of VEN-MONO in a patient cohort with aggressive MCL who had failed BTKi. The ORR and median PFS to BTKi is markedly inferior to the pivotal trials with ibrutinib[4] and acalabrutinib[5], suggesting our cohort possessed particularly adverse clinical and biological features. We provide the first evidence of VEN-MONO tolerability and efficacy in MCL the post-BTKi setting. An ORR 53% (CR 18%) is encouraging and compares favorably with other treatments in this setting; however the median PFS was short. VEN-MONO responses in BTKi resistance provides extension of the proof-of-principle initially obtained in chronic lymphocytic leukemia that BH3 mimetics have activity in BTKi-resistant lymphoproliferative disease[14]. Subgroup analysis was limited by small numbers but prior BTKi response or duration did not predict PFS.

Weaknesses in our study include the intrinsic biases associated with retrospective data reporting, the lack of centralized pathology review, formalized radiological reporting, and prospective AE reporting.

VEN-MONO provides an encouraging initial ORR in R/R MCL post-BTKi with minimal toxicity and therefore provides further evidence for its place investigating rational novel combinations in this setting. Specific clinical benefit was gained in responding patients but the overall PFS was disappointing. Synergy between BTKi and BCL2i has been demonstrated in BTK-sensitive and resistant MCL cells *in-vitro* and *in-vivo*[11] and early clinical data combining ibrutinib-venetoclax (n=24) suggest safety, high complete metabolic responses (71%) and high MRD-negativity (67% marrow; 8-colour flow cytometry)[15]

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Table 1: Baseline characteristics: prior therapies

All patients (N=20)	n (%)
Gender	
Male	17 (85%)
Female	3 (15%)
First line therapy	
CHOP+/-R or CHOP-like	6
Fludarabine-based+/-R	4[a]
MAXI-CHOP/HDAC+/-R	8
Other	2[b]
a) Included FMC RIC alloSCT in CR1	
b) R-VCAP, R-chlorambucil	
ASCT Consolidation in 1st remission	
Yes	6 (30%)
No	14 (70%)
Rituximab Maintenance in 1st remission	
Post immunochemotherapy	2 (10%)
Post ASCT	0 (0%)
Neither	18 (90%)
Duration of exposure to BTK inhibitor (months; range)	4.77 months
	(range 0.66 – 34.85 months)
Response rate to prior BTK inhibitor	ORR 11/20 (55%)
	CR 3 (15%)
	PR 8 (40%)
	SD 4 (20%)
	PD 5 (25%)
Reason for BTK inhibitor discontinuation (n = 20)	
Progressive disease	17
Stable disease	1
Toxicity	2

Abbreviations: CHOP (cyclophosphamide, doxorubicin, vincristine, prednisolone), R (rituximab), HDAC (high dose cytarabine), RIC (reduced intensity conditioning), FMC (fludarabine, melphalan, alemtuzumab (campath)), AlloSCT (allogenic stem cell transplantation), VCAP (bortezomib (velcade), cyclophosphamide, doxorubicin, prednisolone), ASCT (autologous stem cell transplantation), BTK (bruton tyrosine kinase)

Table 2: Baseline characteristics: pre-VEN-MONO

Age prior to Venetoclax use	Median 69 (43-84) years
Prior lines of therapy pre-Venetoclax	Median 3 prior lines (range 2-5)
Stage 1-2	1
Stage 3-4	19
Extranodal disease Y / N a) bone marrow n = 12; liver n = 1; skin n = 2; pleural/pulmonary n = 2	Y 17 / N 3[a]
LDH > ULN	15
ECOG PS 0-1	11
ECOG PS 2-4	9
sMIPI 0-3	4
sMIPI 4-6	5
sMIPI 7-9	11
Ki67% b) 11 biopsies assessed for Ki67% pre-venetoclax	Median 45% (range 10-90%)[b]
Histology	Small cell 7
	Classical 3
	Pleomorphic 3
	Blastoid 4
	Not known 3
Anti-Urate Agent used	
Allopurinol	9 (45%)
Rasburicase	6 (30%)
Both	5 (25%)
Neither	0 (0%)

Abbreviations: LDH (lactate dehydrogenase), ECOG PS (eastern cooperative oncology group performance status), R (rituximab), BAC (bendamustine, cytarabine), SCT (stem cell transplantation), AML (acute myeloid leukaemia).

Figure Legend

Overall Title: Survival outcome of patients with relapsed, refractory MCL on venetoclax monotherapy

Figure 1A – Progression free survival of all patients

Figure 1B – Overall survival of all patients

Figure 1C – Duration of response

Figure 1D – Progression free survival according to duration on ibrutinib

Figure 1A-D

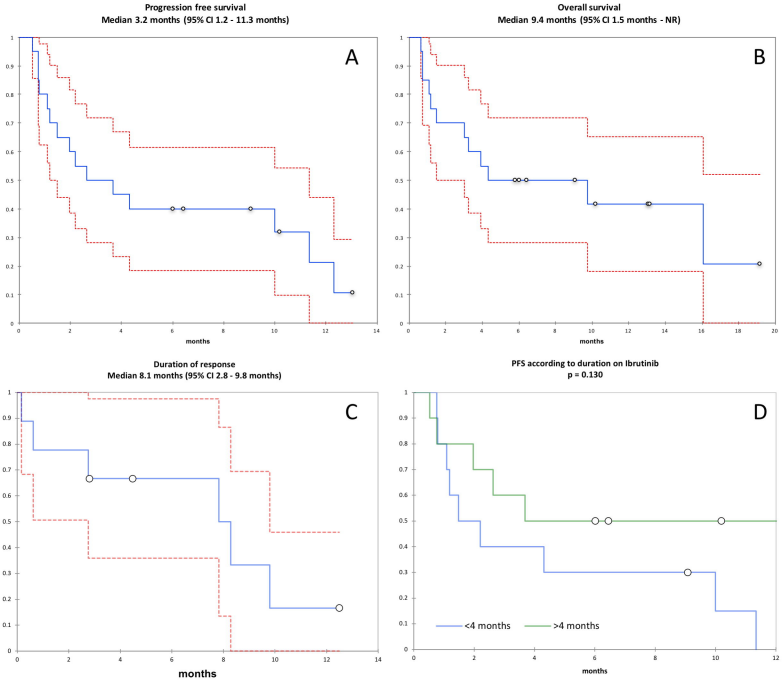
Progression free survival
Median 3.2 months (95% CI 1.2 - 11.3 months)
A
months
Overall survival
Median 9.4 months (95% CI 1.5 months - NR)
B
months
Duration of response
Median 8.1 months (95% CI 2.8 - 9.8 months)
C
months
PFS according to duration on Ibrutinib
p = 0.130
D
<4 months
>4 months
months

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