Supplementary Appendix

Figure 1

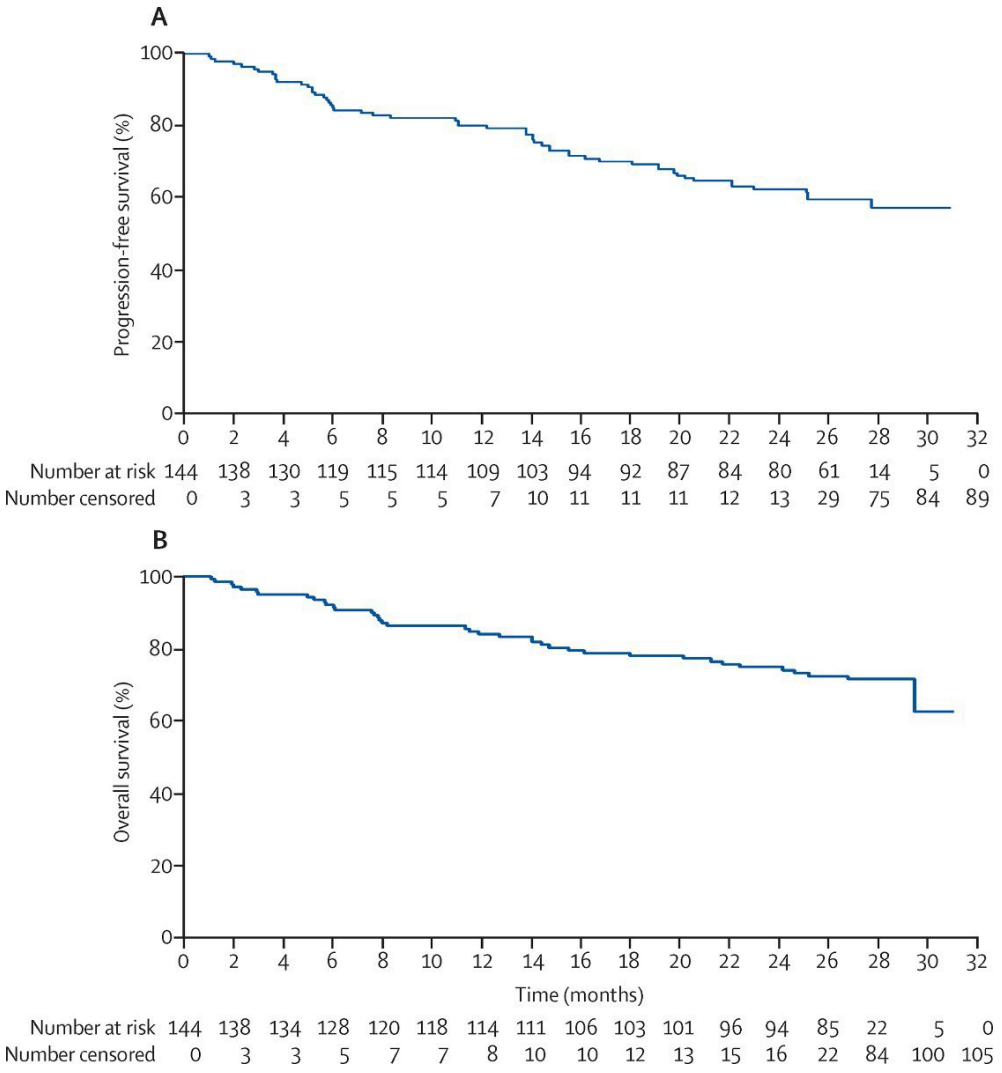

Figure 1: Progression-free survival (A) and overall survival (B) in patients with 17p deletion chronic lymphocytic leukaemia treated with ibrutinib

Note: Reprinted from *Lancet Oncol*, 15, O'Brien S, Furman RR, Coutre SE, et al, Ibrutinib as initial therapy for elderly patients with chronic lymphocytic leukaemia or small lymphocytic lymphoma: an open-label, multicentre, phase 1B/2 trial, 48–58, copyright 2014, with permission from Elsevier.[19]

Figure 2

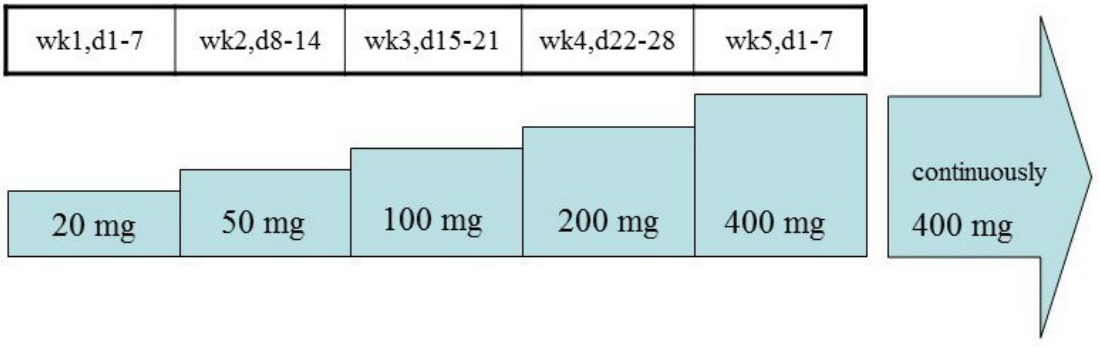

Figure 2: Dose escalation of venetoclax over five weeks as given in the phase 2 trial protocol and in the phase 1 expansion cohort. This ramp-up scheme is still used in CLL current trials while dosing venetoclax.

Table 1: Baseline characteristics of the patients in the phase 1 trial

Characteristics	Dose-Escalation Cohort (n = 56)	Expansion Cohort (n = 60)	All patients (N=116)
Age			
median (range)- yr	67 (36-86)	66 (42-84)	66 (36-86)
> 70yr – number (%)	20 (36)	14 (23)	34 (29)
Sex – no. (%)			
Male	41 (73)	48 (80)	89 (70)
Female	15 (27)	12 (20)	27 (23)
Diagnosis – no. (%)			
CLL	49 (88)	53 (88)	102 (88)
SLL	7 (12)	7 (12)	14 (12)
Rai Stage III or IV – no (%)	28 (50)	39 (65)	67 (58)
Median no of previous therapies (range)[X]	4 (1-10)	3 (1-11)	3 (1-11)
Resistance to most recent therapy – no. (%)[XX]	23 (41)	22 (37)	45 (39)
Previous fludarabine-based therapy – no (%)			
Any previous fludarabine	51 (91)	49 (82)	100 (86)
Resistance to fludarabine	28 (50)	42 (70)	70 (60)
ECOG Performance Status – no. (%)**			
Grade 0	29 (52)	27 (45)	56 (48)
Grade 1	27 (48)	31 (52)	58 (50)
Missing Data	0	2 (3)	2 (2)
Peripheral-Blood Lymphocytosis			
Absolute Lym count > 5000 per mm³ - no. (%)	31 (55)	35 (58)	66 (57)
Median count per mm³ (range)	27,000 (5,400 – 204,500)	25,100 (5,200 – 259,000)	27,500 (5,200 – 259,000)
Bulky nodes – o. (%)			
> 5 cm	29 (52)	38 (63)	67 (58)
> 10 cm	10 (18)	12 (20)	22 (19)
Interphase cytogenetic abnormality – no/total no. with CLL*			
chromosome 17p deletion	19/49 (39)	12/53 (23)	31/102 (30)
chromosome 11q deletion	13/49 (27)	15/53 (28)	28/102 (27)
no chr 17p/11q deletion	16/49 (33)	27/53 (51)	43/102 (42)
data missing or intermediate	7/49 (14)	3/53 (6)	10/102 (10)
IGHV mutation status – no./total no. with CLL (%)**			
unmutated	26/49 (53)	20/53 (38)	46/102 (45)
mutated	6/49 (12)	11/53 (21)	17/102 (17)
data missing	17/49 (35)	22/53 (42)	39/102 (38)

[X] A total of 116 patients (100%) received anti-CD20 antibodies, 110 (95%) received alkylating agents, and 103 (89%) received purine analogues.
[XX] Resistance was defined as either a lack of at least a partial response or disease progression while receiving therapy or within 6 months after the completion of therapy. Nineteen patients with resistance to fludarabine were also resistant to the combination of fludarabine, cyclophosphamide, and rituximab.
* A total of 11 patients — 7 in the dose-escalation cohort and 4 in the expansion cohort — had both chromosome 17p and chromosome 11q deletions.
** ECOG denotes Eastern Cooperative Oncology Group, and IGHV immunoglobulin heavy-chain variable region.

Note: From *N Engl J Med*, Roberts AW, Davids MS, Pagel JM, et al, Targeting BCL2 with venetoclax in relapsed chronic lymphocytic leukemia, 374, 311–322, Copyright ©2016 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.[48]

Table 2: Baseline characteristics of the patients in the pivotal phase 2 trial[52]

	Venetoclax (n = 107)
Age (years)	67 (37 – 85)
> 65 years	61 (57%)
< 65 years	46 (43%)
Sex	
Female	37 (35%)
Male	70 (65%)
Previous treatments*	
Median number of previous treatments	2 (1-4)
Bendamustine	54 (50%)
Bendamustine refractory	38 (70%)
Fludarabine	78 (73%)
Fludarabine refractory	34 (44%)
Bendamustine or fludarabine refractory	62 (58%)
Idelalisib	1 (1%)
Ibrutinib	3 (3%)
Other B-cell receptor inhibitors	1 (1%)
ECOG performance status	
0	42 (39%)
1	56 (52%)
2	9 (8%)
Rai stage at study entry	
Stage III	19 (18%)
Stage IV	32 (30%)
Other	56 (52%)
Binet stage at study entry	
Binet A-B	65 (61%)
Binet C	42 (39%)
Disease-related complications	
Neutropenia	24 (22%)
Anemia	22 (21%)
Thrombocytopenia	16 (15%)
Absolute lymphocyte count	
> $25x10^9$ cell per L	54 (51%)
< $25x10^9$ cell per L	53 (50%)
Median ($x10^9$)	25.8 (7.9 – 89.9)
Bulky disease	
One or more nodes > 5cm	57 (53%)
No nodes > 5cm	50 (47%)
Tumor lysis syndrome risk category†	
Low	19 (18%)
Medium	43 (40%)
High	45 (42%)
TP53 mutation‡	
Yes	60 (72%)

No	17 (21%)
Intermediate	6 (7%)
Missing	24 (22%)
IGHV mutation	
Yes	7 (19%)
No	30 (81%)
Missing	70 (65%)
Serum β-2 microglobulin	
< 3mg/L	4 (24%)
> 3mg/L	13 (77%)
Missing	90 (84%)
11q deletion	
Deleted	30 (28%)
Not deleted	77 (72%)

Reprinted from *Lancet Oncol*, 17, Stilgenbauer S, Eichhorst B, Schetelig J, et al, Venetoclax in relapsed or refractory chronic lymphocytic leukaemia with 17p deletion: a multicentre, open-label, phase 2 study, 768–778, copyright (2016), with permission from Elsevier.[52]
Data are n (%) or median (IQR) unless otherwise noted. Percentages might not add up to 100% because of rounding. ECOG=Eastern Cooperative Oncology Group. *Refractory status was defi ned as no response or disease progression within 6 months of treatment; ten patients were refractory to both fl udarabine and bendamustine. †Description of tumour lysis syndrome risk categories in appendix. ‡Investigator reported.

Table 3: A choice of current clinical combination trials in CLL.

Drugs	Indication CLL	Phase	Status	Location	Identifier	Sponsor
Venetoclax + rituximab	r/r	I	ongoing	USA, Australia	NCT01682616	AbbVie
Venetoclax + obinutuzumab	1st line, CIRS>6	III	ongoing	Multinational	NCT02242942 (CLL14)	Roche/Genentech
Venetoclax + ibrutinib	r/r or 1st line 17p-	II	recruiting	USA (Texas)	NCT02756897	AbbVie
Bendamustine → venetoclax + obinutuzumab	1st line or r/r	II	ongoing	Germany	NCT02401503(CLL2BAG)	German CLL Study Group
Venetoclax + ibrutinib + obinutuzumab	1st line or r/r	Ib/II	recruiting	USA	NCT02427451	Jeffrey Jones
Venetoclax + ibrutinib + obinutuzumab	1st line, 17p-	II	recruiting	Germany	NCT02758665 (CLL2GIVe)	German CLL Study Group

Table 4: A choice of current clinical combination trials of hematologic malignancies and solid tumors.

Drugs	Indication	Phase	Status	Location	Identifier	Sponsor
Venetoclax + decitabine or azacytidine	AML	I	recruiting	multinational	NCT02203773	AbbVie
Venetoclax + ibrutinib + obinutuzumab	MCL	I/II	recruiting	France/UK	NCT02558816(OAsIs)	Nantes University Hospital
Venetoclax + bortezomib + dexamethasone	MM	I	recruiting	USA, France, Australia	NCT01794507	AbbVie
Venetoclax + tamoxifen	Breast cancer	I		Australia	ISRCTN98335443	AbbVie