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Ibrutinib Plus Venetoclax in Relapsed, Refractory CLL: Updated results of the Bloodwise TAP CLARITY Study

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Study End-Points

Primary end-point :

- Minimal Residual Disease (MRD) eradication (<0.01% CLL cells) in the marrow after 12 months of IBR+VEN.

Secondary end-points:

- MRD eradication (<0.01% CLL cells) in the marrow after 6 & 24 months of IBR+VEN
- Response rate, Progression-free survival (PFS) and Overall survival (OS)
- Toxicity of combination therapy (AE's and SAE's)

Key Exploratory end-points:

- Phosphoprotein and Bcl-2 protein expression.
- Investigation of the apoptotic pathway
- Depletion of MRD below 10^{-5} and 10^{-6} using high sensitivity flow cytometry and HTS

Key Entry Criteria

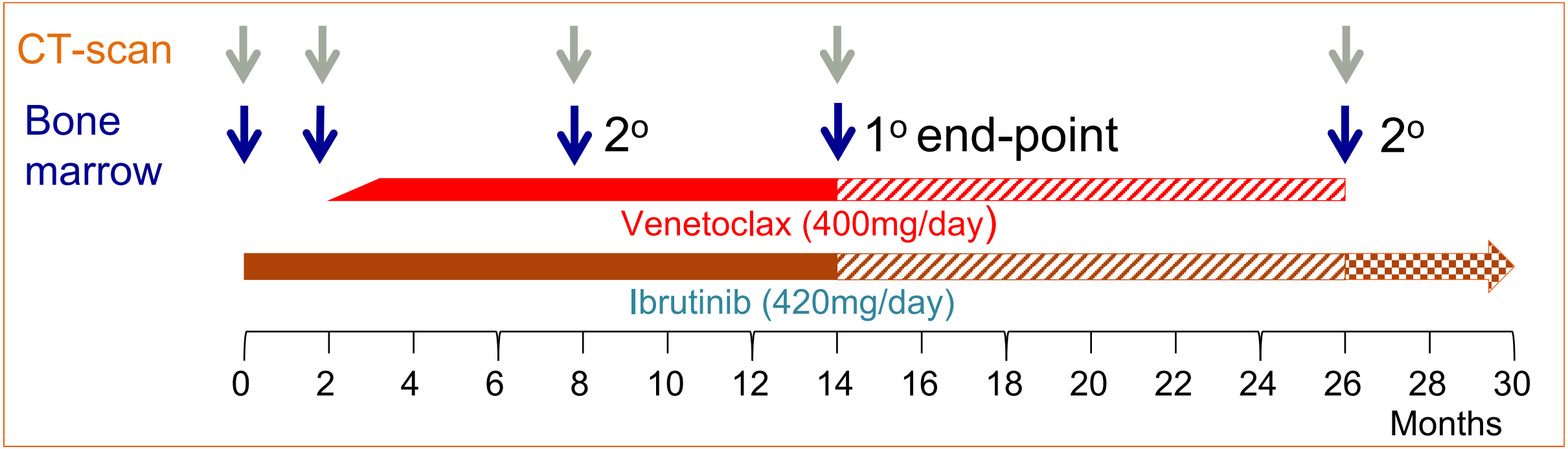
Key Inclusion Criteria:

- CLL requiring therapy according to IWCLL criteria
- Refractory/relapsed CLL defined as any of the following:
  - Patients with CLL with 17p del after at least one previous therapy.
- ECOG performance status (PS) of 0, 1, or 2
- Adequate bone marrow function (Plt >75; Neut >1.0) unless due to marrow involvement

Key Exclusion Criteria:

- Richter's transformation or CNS involvement by CLL
- Previous treatment with ibrutinib, venetoclax or an alternative Btk or Bcl-2 inhibitor
- Active autoimmune haemolysis or immune mediated thrombocytopenia

Treatment Schedule and Stopping Rules



Stopping rules: Duration of therapy is double time to MRD4 negative

1) MRD negative (<0.01%) at M8 stop I+V at M14
2) MRD negative (<0.01%) at M14 or M26 stop I+V at M26
3) MRD positive (≥0.01%) at M26 continue ibrutinib monotherapy

Patient characteristics

Characteristic	Patients (n = 54)
Gender (Male/Female)	37 (69%) / 17 (31%)
Age (Median [Range])	64 (31 – 83)
Current Binet Stage (A / B / C / NK)	12 (22%) / 18 (33%) / 22 (41%) / 2 (4%)
Lymph nodes ("bulky" ≥ 5cm)	4 (8%)
ECOG (0/1/2/NK)	32 (59%) / 18 (33%) / 3 (6%) / 1 (2%)
V_H (mutated/unmutated/VH3-21/failed)	10 (19%) / 40 (74%) / 3 (6%) / 1 (2%)
17p del	10/50 (20%)
11q del (not 17p del)	13/51 (25%)
Prior therapies (median [range])	1 (1 to 6)
• previous FCR or BR	44/54 (82%)
→ relapse within 3 years of BR or FCR	22/44 (50%)
• previous idelalisib	11/54 (20%)

NK, not known

- 4 patients stopped ibrutinib before adding venetoclax due to toxicity

Study Patient number	Toxicity category/event
11	Infections and infestations
25	Brain abscess
34	Vascular disorder
50	Gastrointestinal disorder, renal disorder, general disorder, injury

- 50 patients recruited to combination part of trial
- 50 patients successfully passed through venetoclax escalation phase

Date of data lock: 05 September 2019

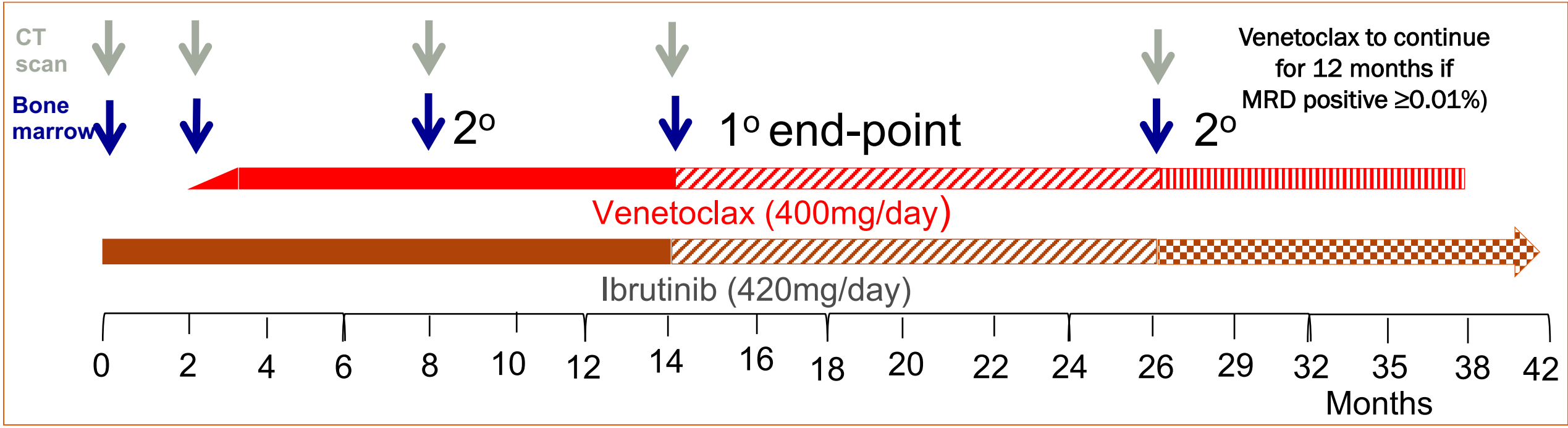
Primary end-point: undetectable MRD4 (<0.01%) in BM after 12 months I+V

All at Month 14	PB MRD negative	BM MRD negative	Trephine normal
All patients	29/50 (58%)	20/50 (40%)	39/48 (81%)
FCR/BR rel <36 months	14/20 (70%)	9/20 (45%)	18/19 (95%)
Prior idelalisib	6/9 (67%)	5/9 (56%)	7/9 (78%)

50/50 patients have reached at least Month 14 and have had a bone marrow MRD PB or BM <0.01% CLL cells (10^{-4}) by flow cytometry

Using statistical significance (alpha) of 2.5% and statistical power of 95.5%, the A'Hern design requires at least 10 of 50 patients to achieve MRD-eradication in the marrow to reach the pre-defined efficacy threshold for the combined treatment.
Assumptions: Ibr+Ven 30% MRD eradication; Ibr monotherapy <10% MRD eradication

Treatment Schedule and Stopping Rules



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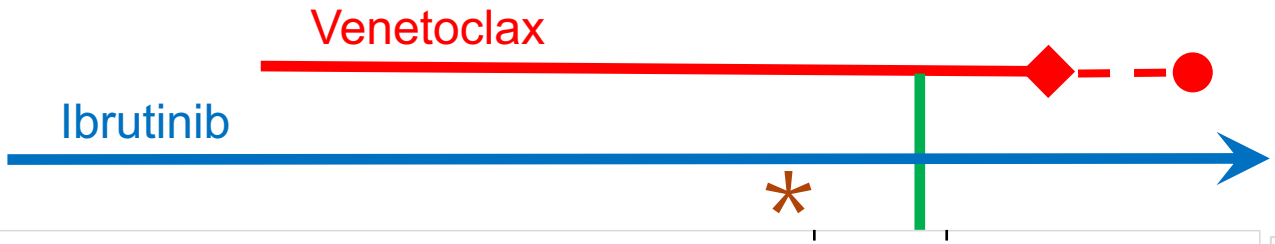
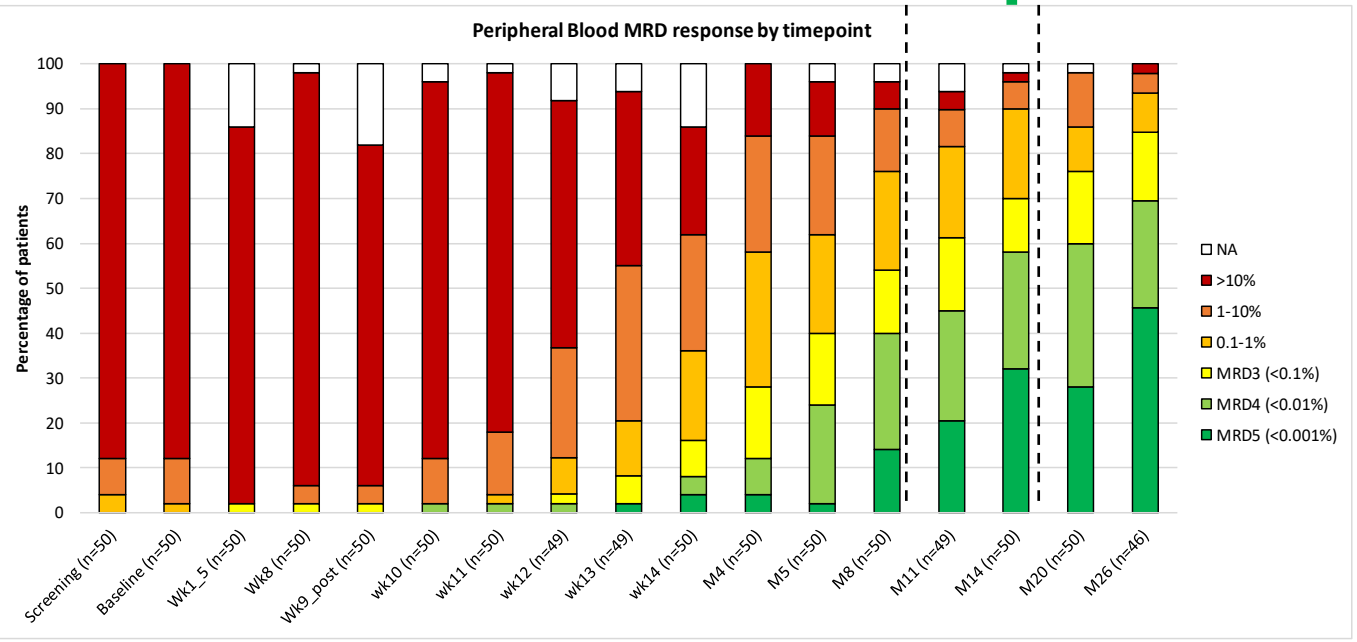
3) MRD positive (≥0.01%) at M26 continue ibrutinib monotherapy
4) MRD positive (≥0.01%) at M26 can continue venetoclax for 12 months (Amendment)

MRD level by time-point (up to Month 26)

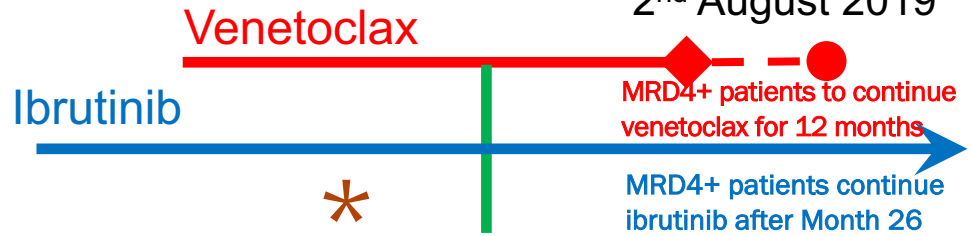
Peripheral Blood

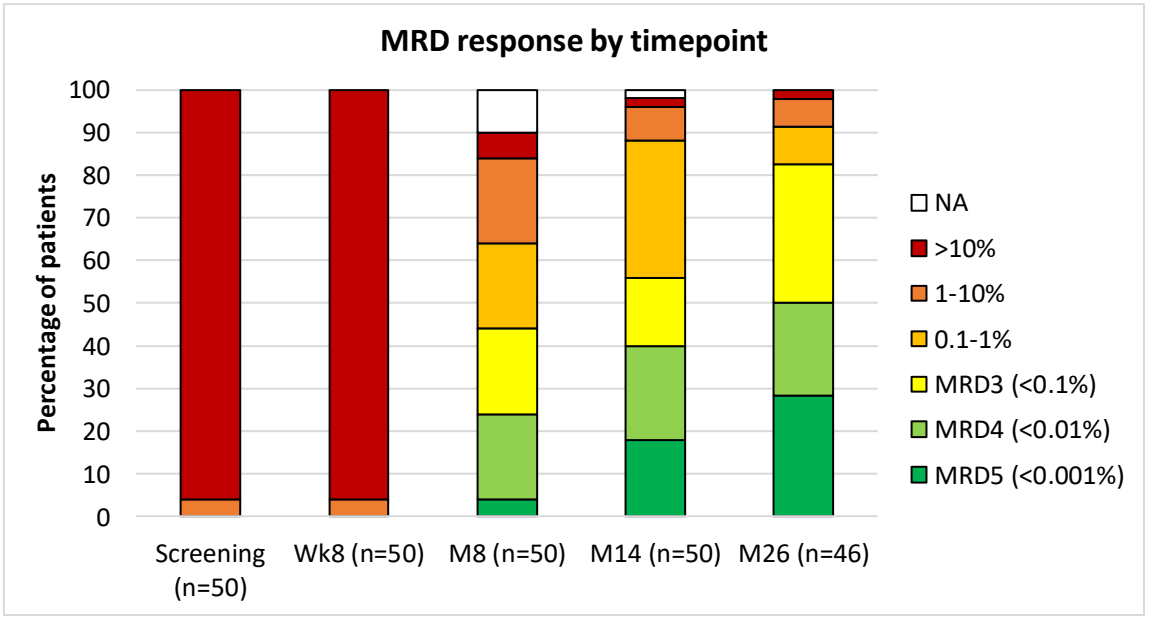




Bone Marrow

Date of data lock:
2nd August 2019





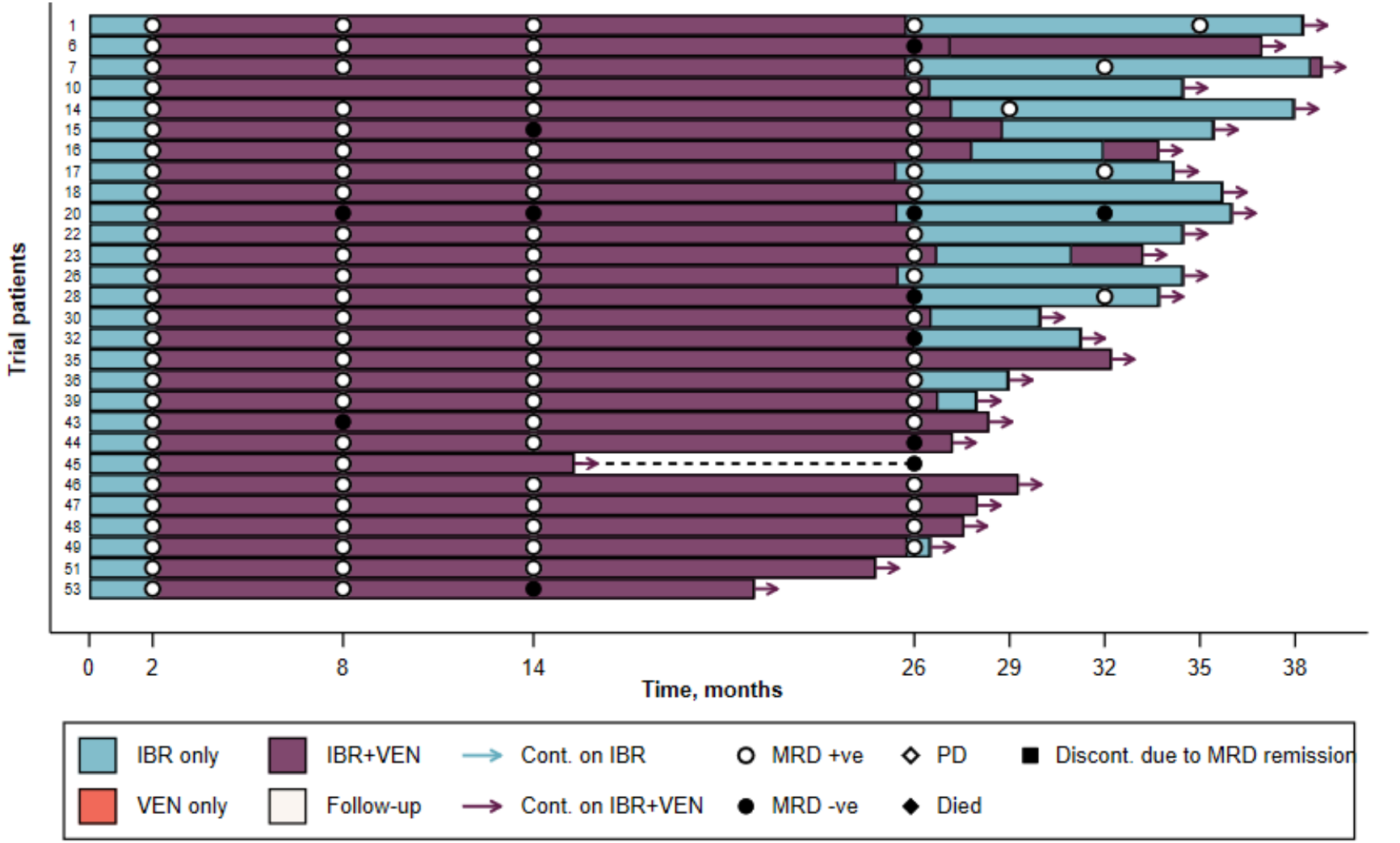
*PB & BM MRD negative pts at Month 8 & 14 stop I+V → All 16/17 reaching M26 remain MRD negative to date

Undetectable MRD4 (<0.01% and (<0.001%) in PB and BM after 24 months I+V

All at Month 26	PB MRD negative <0.01%	BM MRD negative <0.01%	PB MRD negative <0.001%	BM MRD Negative <0.001%
All evaluable patients	32/46 (70%)	23/46 (50%)	21/46 (46%)	13/46 (28%)

50/50 patients have reached at least Month 14 and have had a bone marrow MRD PB or BM <0.01% CLL cells (10^{-4}) by flow cytometry

Patients receiving I + V currently at Month 26 (n=28)

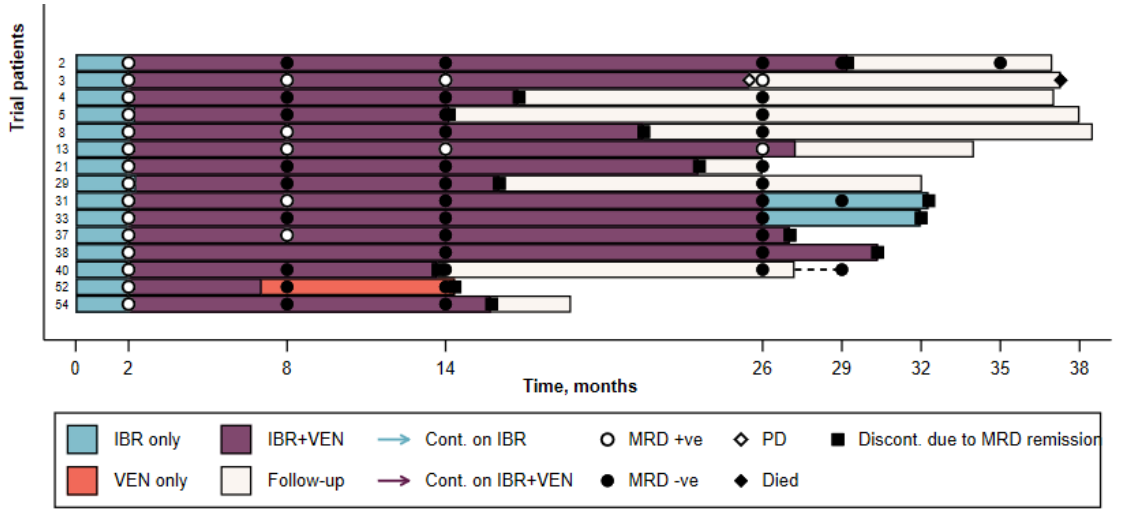


Note: This graph represents the data available in the database on 05-Sep-2019.
Information on venetoclax pauses is still being collected and so some additional patients may have discontinued/paused venetoclax earlier than has been presented here.

Drug discontinuations at Month 26

Ibrutinib + Venetoclax discontinuations

n= 15



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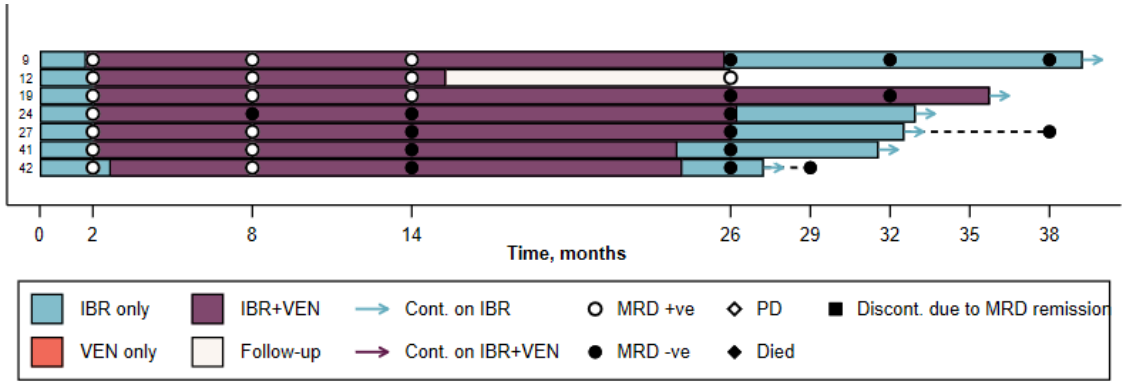
Venetoclax discontinuation

n= 7



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IWCLL Responses
Month 14 (12 months I+V)

	No.	CR	CRi	PR	ORR
All patients	50	23 (46%)	5 (10%)	20 (40%)	48 (96%)
FCR/BR relapsed <36 months[1]	20	8 (40%)	2 (10%)	9 (45%)	19 (95%)
Prior idelalisib[2]	9	3 (33%)	1 (11%)	4 (44%)	8 (89%)

[1] Percentages calculated over the total number of patients who had FCR/BR and relapsed <36 months and have been assessed for response

[2] Percentages calculated over the total number of patients who had Idelalisib before joining the study and have been assessed for response

Date of data lock: 05 September 2019

Toxicity – AEs of interest

Toxicity	Grade 1&2, events (patients)	Grade 3, events (patients)	Grade 4, events (patients)	Any Grade, events (patients)
Atrial fibrillation / flutter	3 (3)	3 (2)	0 (0)	6 (5)
Blood Blister(s) / Bleeding	12 (8)	2 (2)	0 (0)	14 (10)
Bruising	37 (20)	0 (0)	0 (0)	37 (20)
Esophageal Hemorrhage	1 (1)	0 (0)	0 (0)	1 (1)
Eye Haemorrhage	5 (4)	1 (1)	0 (0)	6 (5)
Febrile Neutropenia	1 (1)	0 (0)	0 (0)	1 (1)
Haematoma (Retroperitoneal)	0 (0)	1 (1)	0 (0)	1 (1)
Neutrophil Count Decreased	3 (3)	24 (11)	10 (5)	37 (13)
Pleural Hemorrhage	1 (1)	0 (0)	0 (0)	1 (1)
Retroperitoneal Haematoma*	0 (0)	1 (1)	0 (0)	1 (1)
Tumor Lysis Syndrome	0 (0)	1 (1)	0 (0)	1 (1)

* The two events are thought to be the same event & are being queried

Single case of tumour lysis syndrome (at 200mg dose) – increasing phosphate and creatinine. Managed by delaying venetoclax. Rapidly re-escalated with no further TLS

Recommendation in protocol to give G-CSF to keep the neutrophil count above 1 x 10^9/L.

Date of data lock: 05 September 2019

Case of disease progression

- Single case of Richter's transformation (Not biopsy proven)
- Diagnosed 2011. Treated with FCR x 6 to PR in 2013
- Progressive disease 2016. FISH del(13q14), IGHV 97.6% homology to germline VH3-21
- Achieved MRD +ve CR on CLARITY study

- May 2018- Progressive nodal disease. PET-CT highly suspicious of transformation. R-CHOP x 6 to transient PR with relapse in Nov 2018. Palliative Etoposide and steroids.
- April 2019- CNS progression. Died May 2019.

PR Partial response
FCR Fludarabine, Cyclophosphamide, Rituximab

Conclusions

Combination of ibrutinib (IBR) with venetoclax (VEN) is well tolerated in relapsed, refractory CLL

- with one case of laboratory TLS
- Adverse event reported mostly grade 1 or 2- with GI or neutropenia most common AE.

48/50 (96%) patients have an objective response and 28/50 (56%) are in CR or CRi after 12 months combined IBR+VEN

- 20/50 (40%) are MRD negative (<0.01%) in marrow after 12 months IBR+VEN
- 23/46 (50%) and 32/46 (70%) achieve MRD4 (<0.01%) in marrow and peripheral blood respectively after 24 months IBR+VEN.

The Phase III NCRI FLAIR Trial has been modified to include IBR+VEN in front-line CLL

Only one case of disease progression with Richter's transformation

Acknowledgements

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