3rd POSTGRADUATE CLL CONFERENCE Bologna
Royal Hotel Carlton, 14-15 November 2022

The Best potential combination - BTKi plus venetoclax

Zanubrutinib plus Venetoclax

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- **ZANUBRUTINIB IN COMBINATION WITH VENETOCLAX FOR PATIENTS WITH TN CLL/SLL**
  EARLY RESULTS FROM ARM D OF THE SEQUOIA (BGB-3111-304) TRIAL

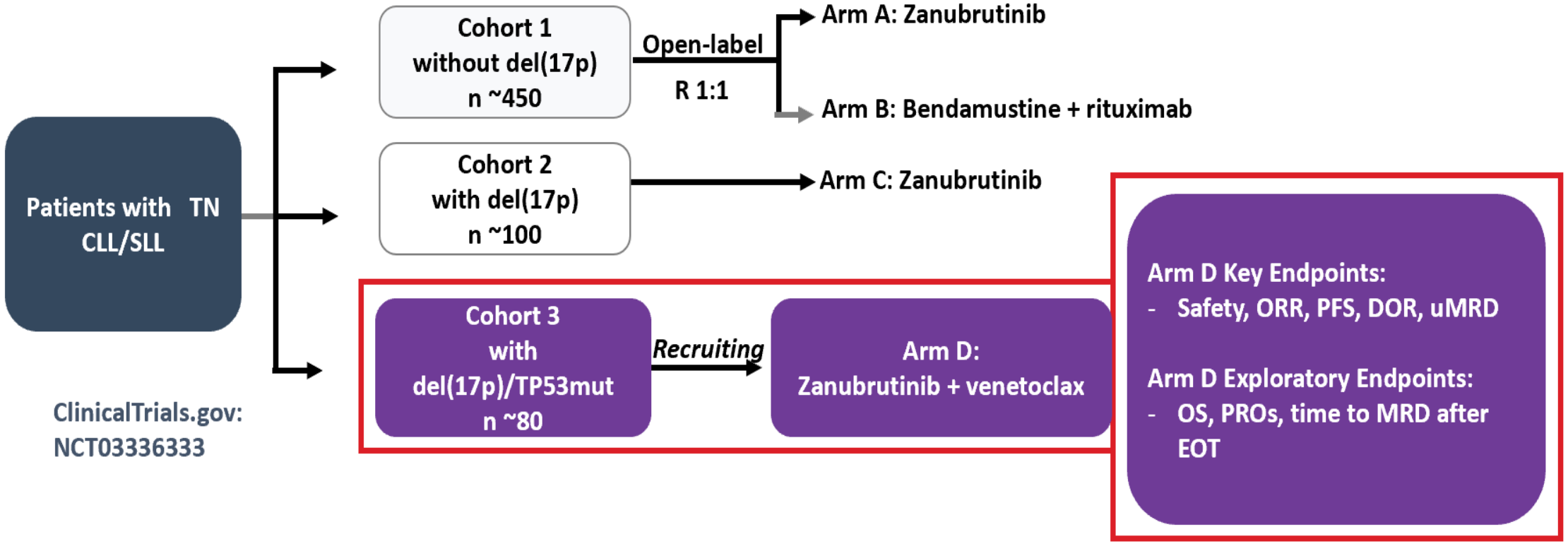
Tedeschi et al, ASH 2021

- **ZANUBRUTINIB, OBINUTUZUMAB, AND VENETOCLAX WITH MRD-DRIVEN DISCONTINUATION IN PREVIOUSLY UNTREATED PATIENTS WITH CLL/SLL**
  A MULTICENTER, SINGLE-ARM, PHASE 2 TRIAL (BOVEN STUDY)

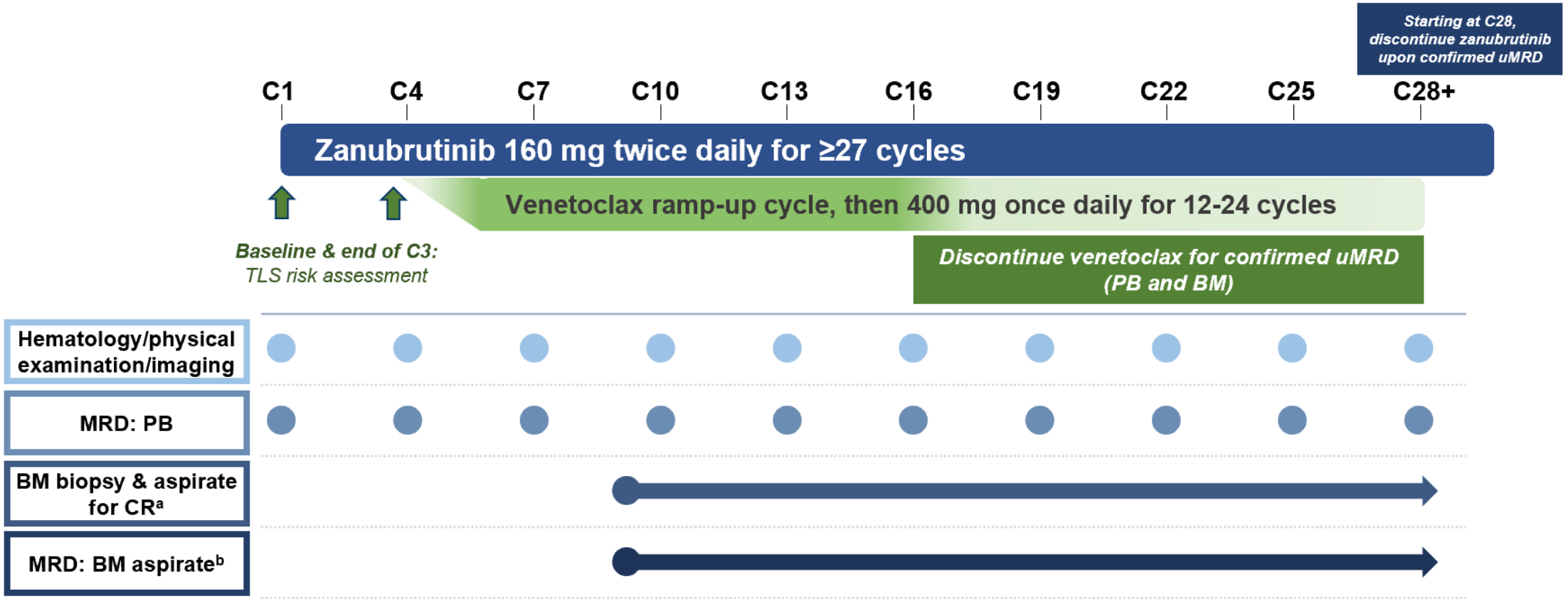
Soumerai a et al, Lancet Hematol 2021

ZANUBRUTINIB IN COMBINATION WITH VENETOCLAX FOR PTS WITH TN CLL/SLL WITH DEL(17P): EARLY RESULTS FROM ARM D OF THE SEQUOIA (BGB-3111-304) TRIAL

Sequoia Trial Study Design:



SEQUOIA (BGB-3111-304)
Arm D Treatment Regimen and Response Assessment Schedule



BM, bone marrow; C, cycle; CLL, chronic lymphocytic leukemia; CR, complete response; CRi, CR with incomplete bone marrow recovery; MRD, measurable residual disease; PB, peripheral blood; TLS, tumor lysis syndrome; uMRD, undetectable measurable residual disease (<1 CLL cell in 10,000 leukocytes at 10^{-4} sensitivity by 8-color flow cytometry).

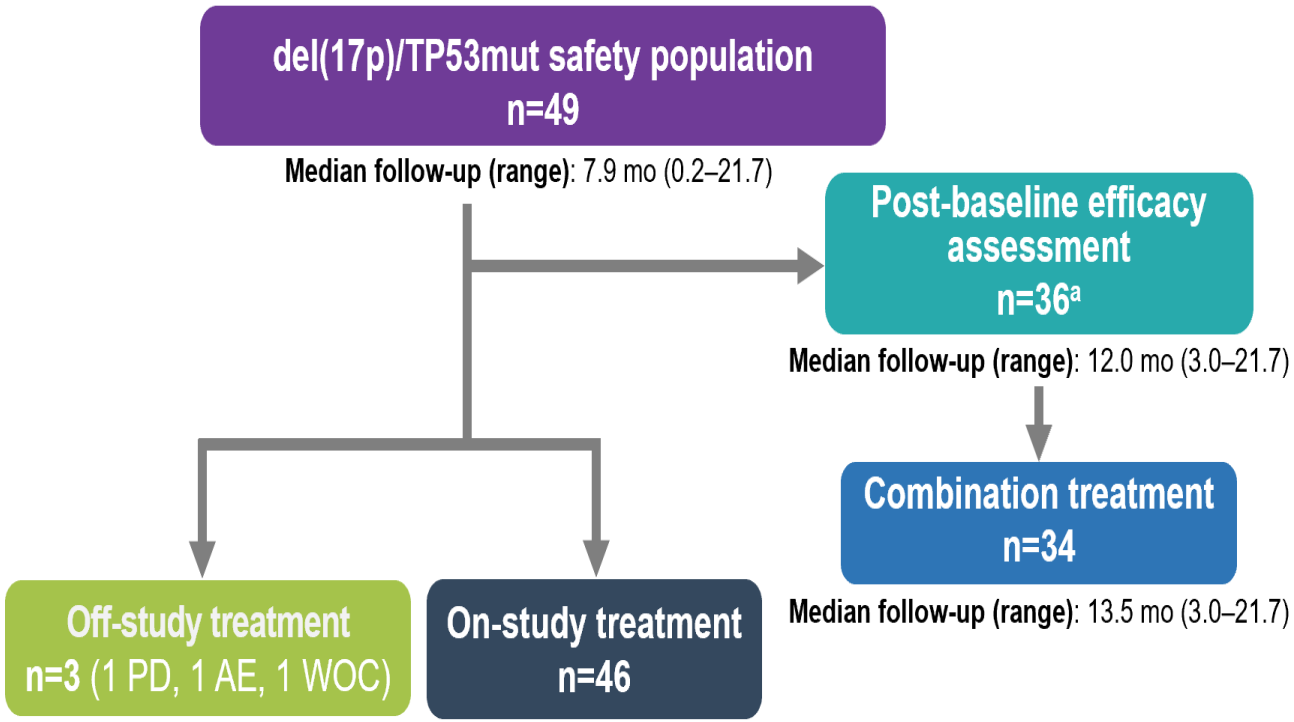
[a]Bone marrow biopsy and aspirate are required to confirm a suspected CR/CRi, starting after cycle 9 and then annually if needed.

[b]Patients with confirmed CR/CRi and 2 consecutive peripheral blood MRD tests plus 2 consecutive BM aspirate MRD tests with results that meet uMRD requirements for dose stopping.

SEQUOIA (BGB-3111-304)
Arm D: Patient disposition and characteristics

Characteristics	n=49
Age, median (range), y	65.0 (25–86)
Male, n (%)	27 (55.1)
ECOG PS ≥1, n (%)	26 (53.1)
Months since diagnosis, median (Q1-Q3)	19.8 (5.7–38.1)
SLL, n (%)	3 (6.1)
Binet stage C for patients with CLL, n/N (%)	22/46 (47.8)
Bulky disease, n (%) Any target lesion LDi ≥5 cm Any target lesion LDi ≥10 cm	 20 (40.8) 3 (6.1)
del(17p) by central lab FISH, n (%) Positive Negative (eligible by local lab TP53 mutation)	 46 (93.9) 3 (6.1)
del(17p) percent of abnormal nuclei, median	77.5
Retrospective TP53 mutation,[a] n/N (%)	34/37 (91.9)
IGHV mutational status, n (%) Unmutated Mutated	 43 (87.8) 6 (12.2)
Complex karyotype,[b] n/N (%) Non-complex (0–2 abnormalities) Complex (3 or more abnormalities) Complex (5 or more abnormalities)	 4/24 (16.7) 20/24 (83.3) 17/24 (70.8)

[a]Ongoing analysis by next-generation sequencing. [b]Ongoing analysis.



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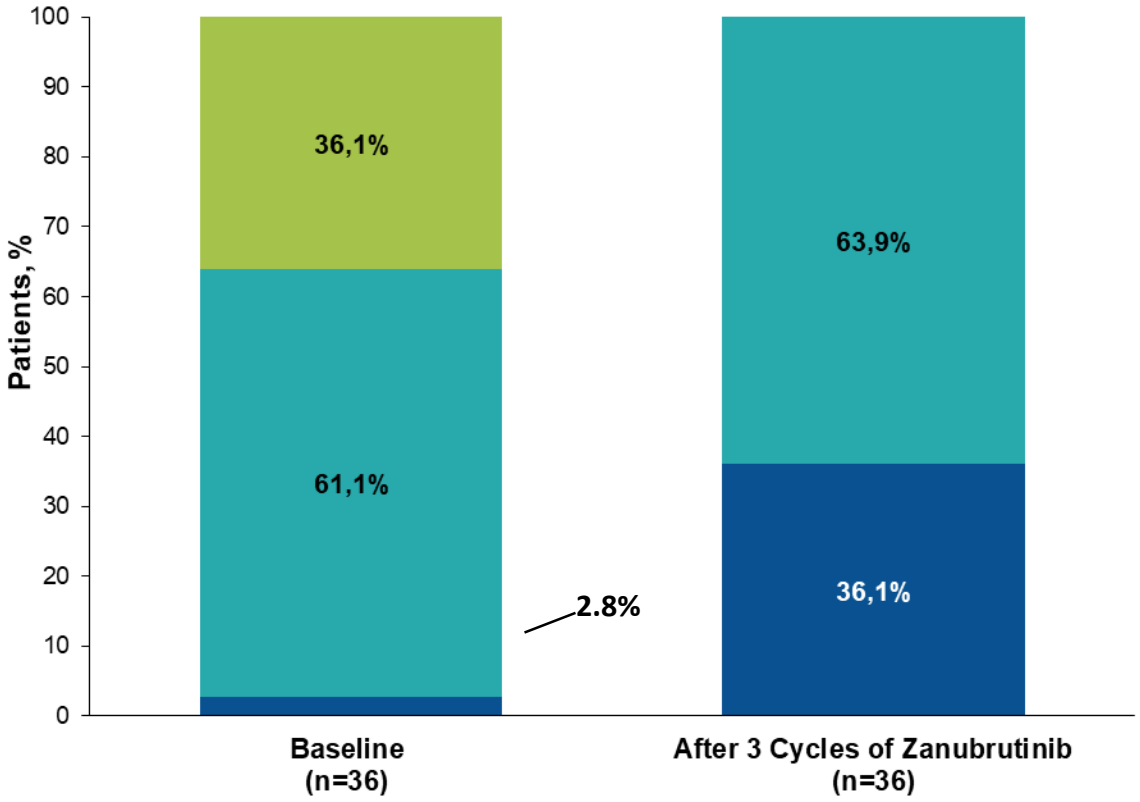
Zanubrutinib 3-Cycle Lead-in Decreases Risk of TLS



- No clinical TLS has been reported

TLS high risk: Presence of any LN ≥10 cm with the largest diameter by radiographic assessment OR presence of both ALC ≥25×10^9/L and one LN ≥5 cm

TLS medium risk: Presence of all measurable LNs with the largest diameter ≥5 cm and <10 cm by radiographic assessment OR ALC ≥25×10^9/L

TLS low risk: Presence of all measurable LNs with the largest diameter <5 cm by radiographic assessment AND ALC <25×10^9/L

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Adverse Event Summary

n (%)	All Patients (n=49)	Patients on combination treatment (n=34)
Any AE	40 (81.6)	29 (85.3)
Grade ≥3 AE	16 (32.7)	13 (38.2)
Serious AE	4[a] (8.2)	3[c] (8.8)
Fatal AE	1[b] (2.0)	0 (0.0)
AE leading to dose interruption	10 (20.4)	10 (29.4)
AE leading to dose reduction	0 (0.0)	0 (0.0)
AE leading to treatment discontinuation	1[b] (2.0)	0 (0.0)

AE, adverse event.
[a]Serious AEs included anemia, drug hypersensitivity, COVID-19 pneumonia, thoracic vertebral fracture, and lung carcinoma. [b]Lung carcinoma (unrelated) leading to discontinuation of zanubrutinib and death prior to initiating venetoclax treatment. [c]Serious AEs included anemia, COVID-19 pneumonia, and drug hypersensitivity.

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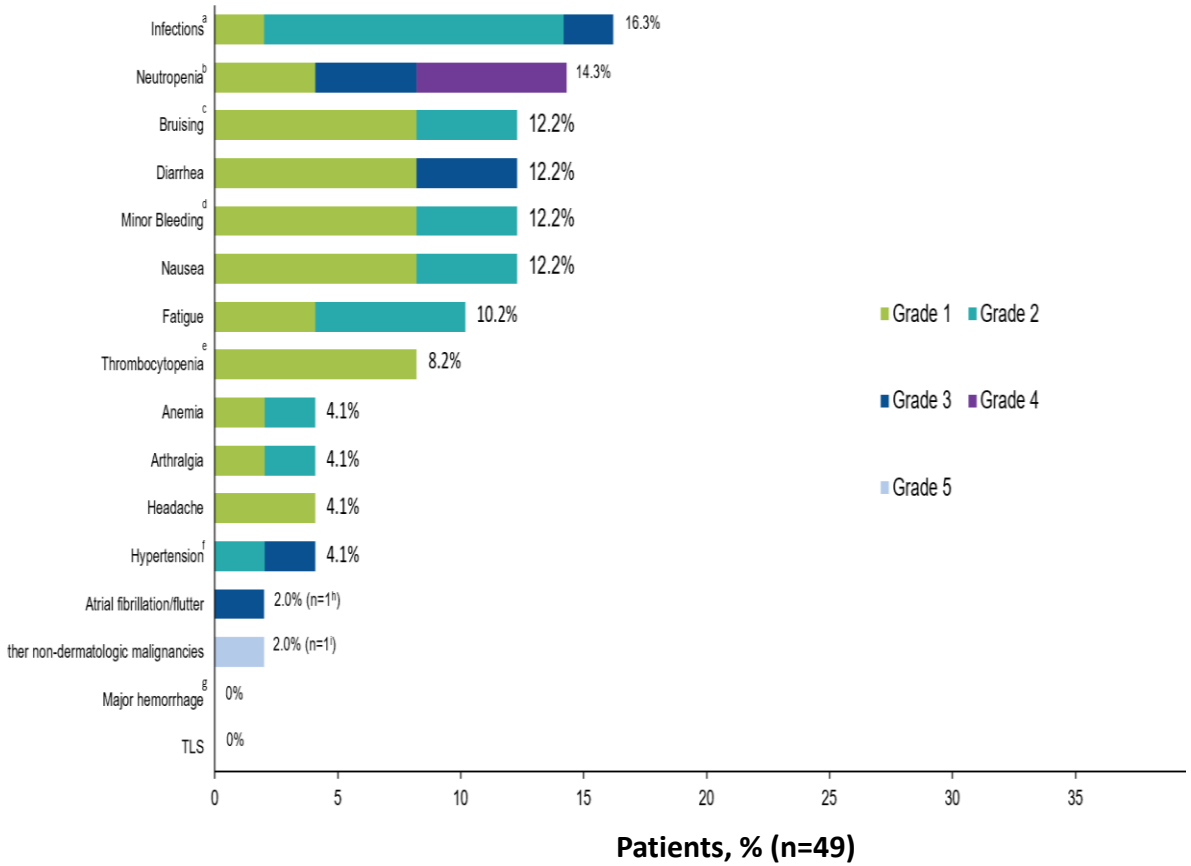
Adverse Events

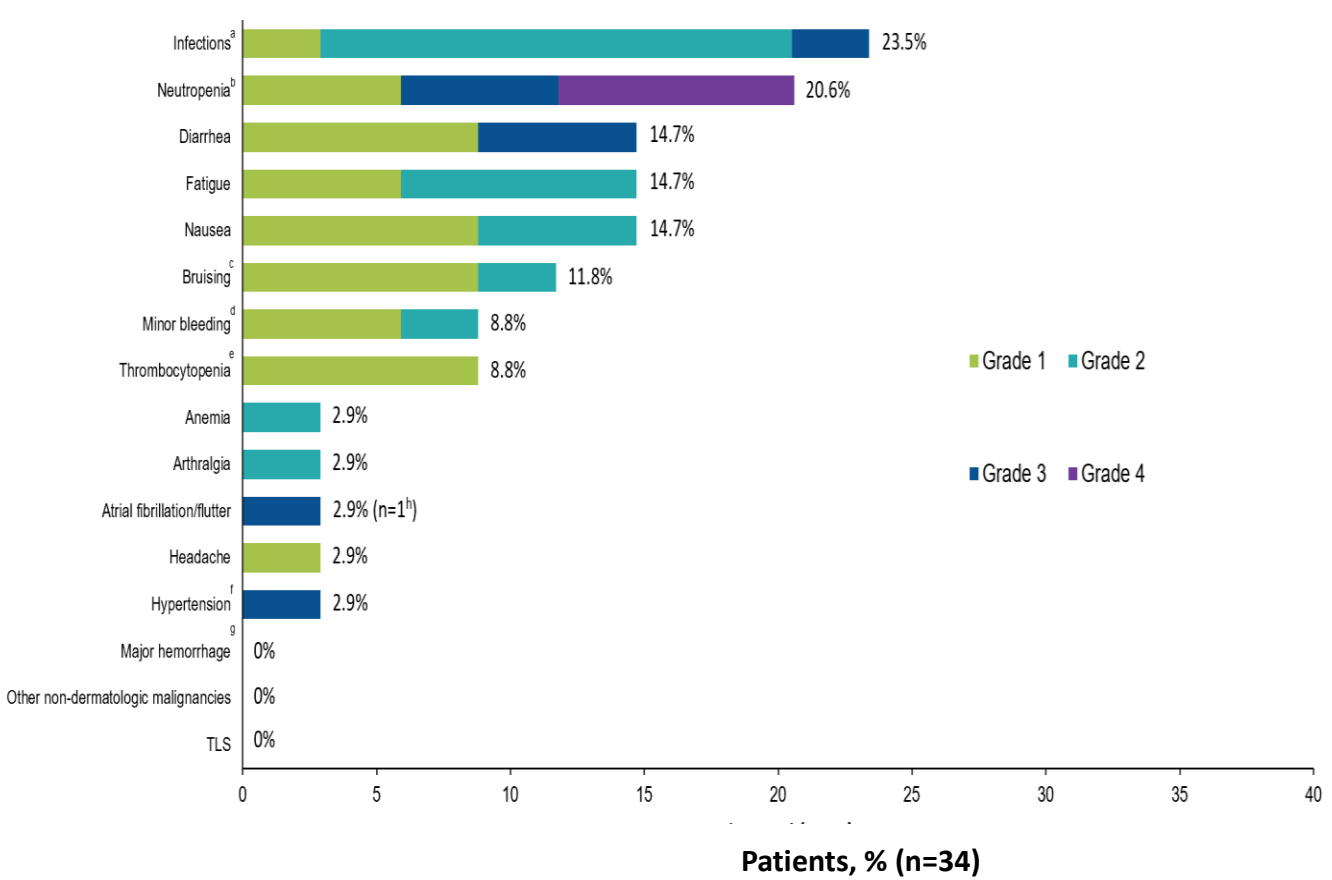
AE of Interest in All Patients *(follow-up 7.9 m)*



Patients, % (n=49)

Note: Pooled term analysis. Median follow-up: 7.9 months.
TLS, tumor lysis syndrome.
[a]All infection terms pooled. [b]Neutropenia, neutrophil count decreased, or febrile neutropenia. [c]Purpura, contusion, ecchymosis or increased tendency to bruise. [d]Pooled term of bleeding not included in bruising, petechiae, or major bleeding. [e]Thrombocytopenia or platelet count decreased. [f]Hypertension, blood pressure increased, or hypertensive crisis. [g]Grade ≥3 hemorrhage, serious hemorrhage, and central nervous system hemorrhage of any grade were pooled. [h]One patient experienced atrial fibrillation that was worsened from a pre-existing condition. [i]Lung carcinoma (unrelated) leading to discontinuation of zanubrutinib and death prior to initiating venetoclax treatment.

AE of Interest in pts Receiving Combination Treatment *(follow-up 13.5 m)*



Patients, % (n=34)

Note: Pooled term analysis; median follow-up: 13.5 months.
TLS, tumor lysis syndrome.
[a]All infection terms pooled. [b]Neutropenia, neutrophil count decreased, or febrile neutropenia. [c]Purpura, contusion, ecchymosis or increased tendency to bruise. [d]Pooled term of bleeding not included in bruising, petechiae, or major bleeding. [e]Thrombocytopenia or platelet count decreased. [f]Hypertension, blood pressure increased, or hypertensive crisis. [g]Grade ≥3 hemorrhage, serious hemorrhage, and central nervous system hemorrhage of any grade were pooled. [h]One patient experienced atrial fibrillation that was worsened from a pre-existing condition.

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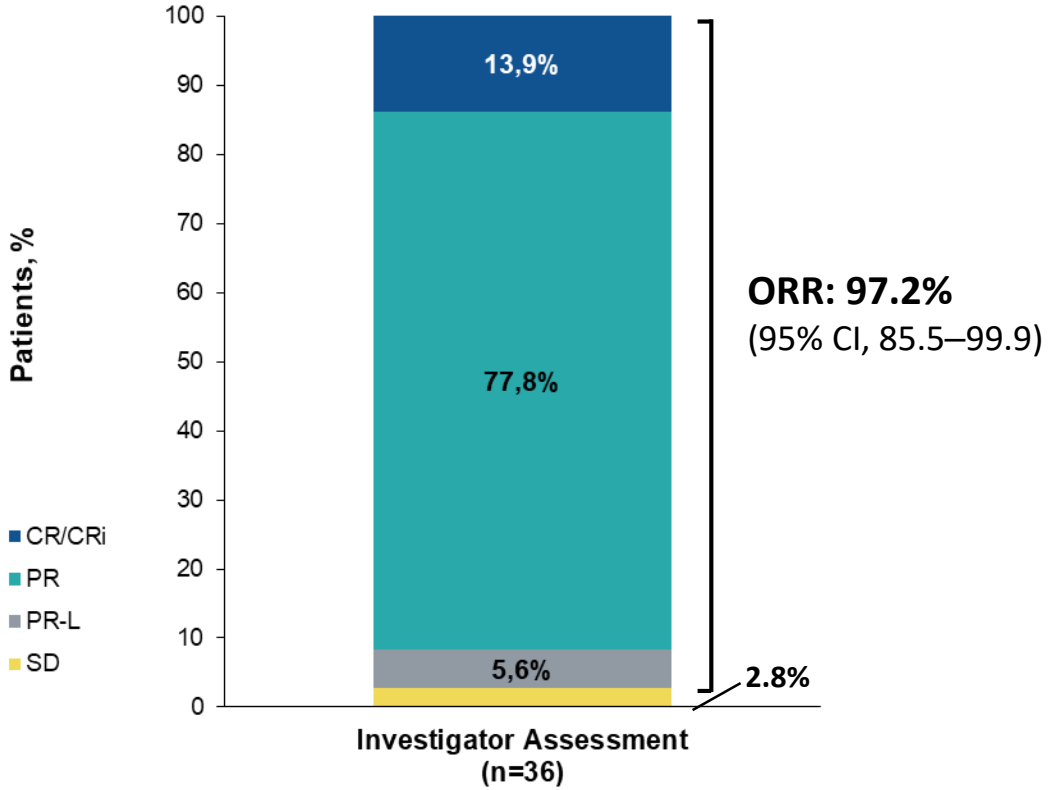
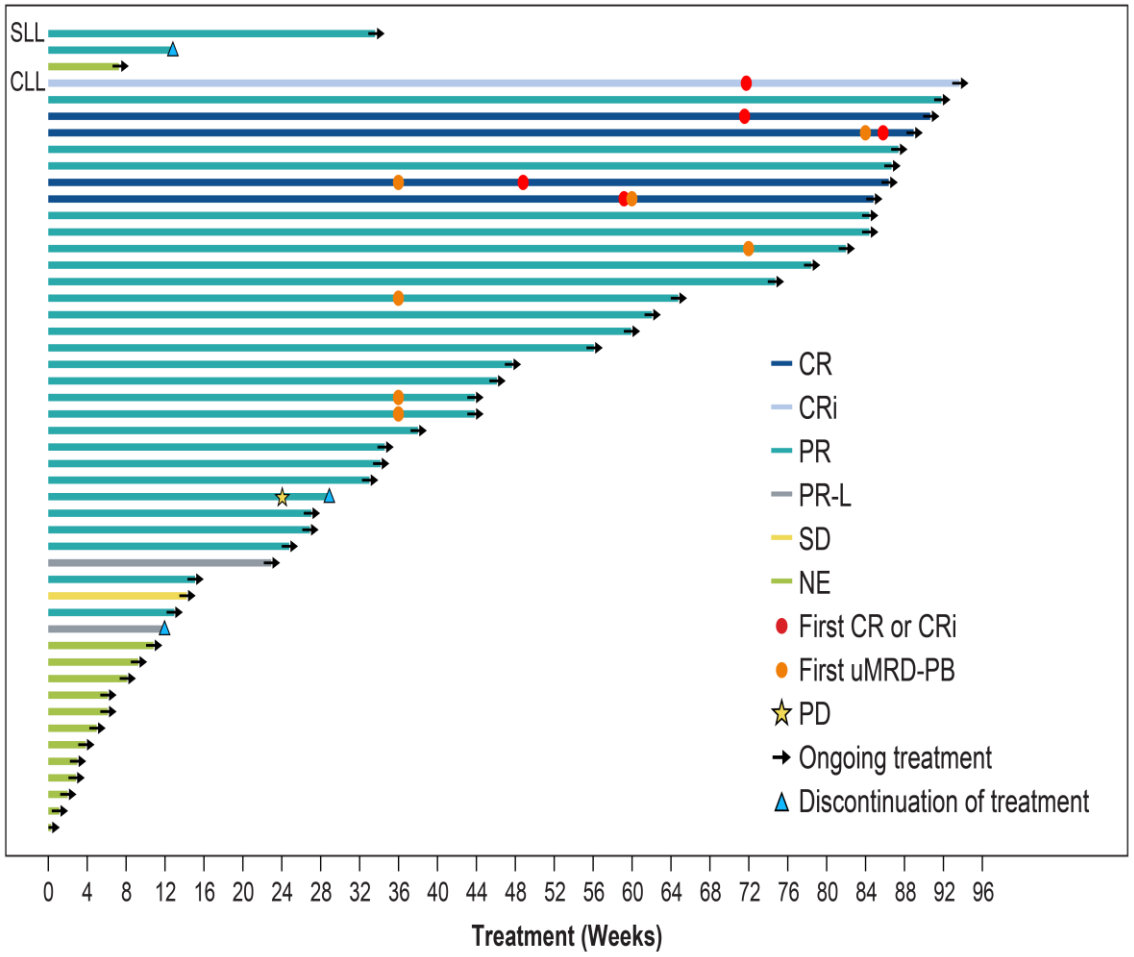
Overall Response Rate and treatment disposition by patient Follow-up

Responses



ORR: 97.2%
(95% CI, 85.5–99.9)

Treatment Disposition by Patient



- **36 pts had post-baseline response evaluations by the data cutoff date**
- **Of 36 pts:**
  14 were treated with the combination therapy for at least 12 m
  - **5/14 (36%) pts performed BM to assess CR, all 5 pts achieved CR/CRi**
  - **4 additional pts in this subgroup met criteria for CR/CRi but did not perform BM assessment some due to COVID-19 restrictions**

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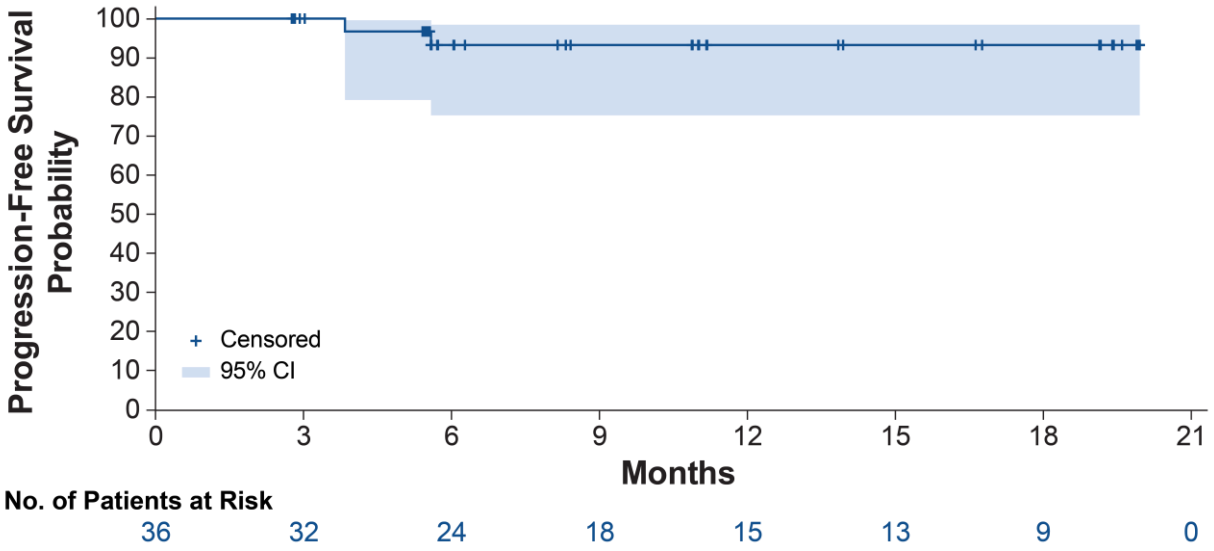
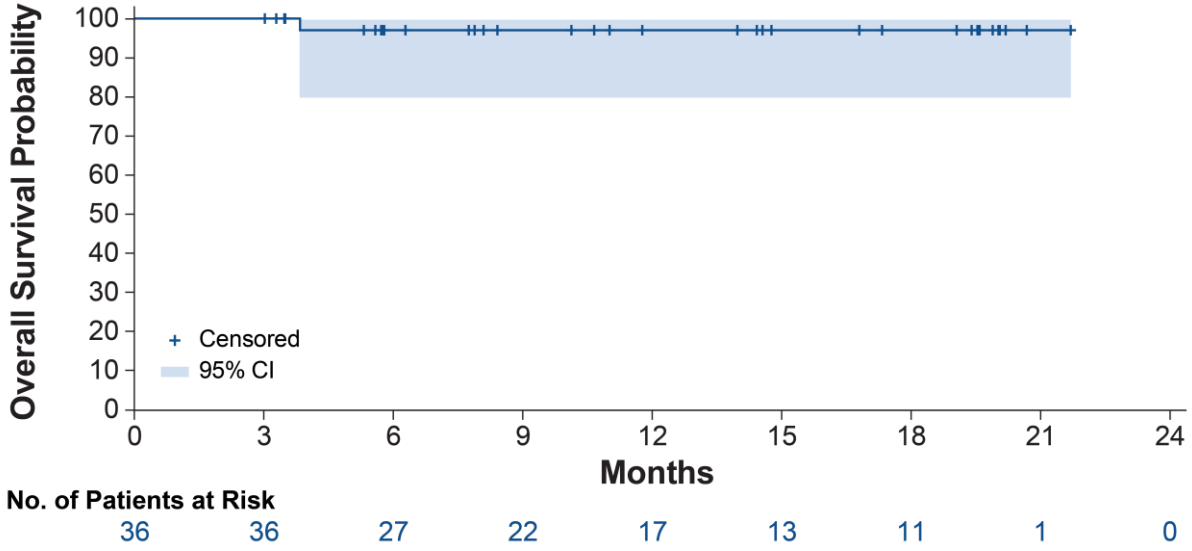
Progression-Free Survival and Overall Survival

Median Follow-Up (Range): 12.0 Months (3.0–21.7)

Progression-Free Survival



Overall Survival



- One patient had PD as assessed by investigator
  - PD based on enlargement of one non-target lesion, while all other compartments responded
  - No Richter transformation reported
  - No PLCG2, BTK, or BCL-2 gene mutations identified in post-PD sample
- One death due to lung carcinoma prior to initiating venetoclax treatment
- No reported sudden death

BCL-2, B-cell lymphoma-2; BTK, Bruton tyrosine kinase; PD, progressive disease; PLCG2, phospholipase C gamma 2.

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Zanubrutinib, obinutuzumab, and venetoclax with MRD-driven discontinuation in previously untreated patients with CLL/SLL

A MULTICENTER, SINGLE-ARM, PHASE 2 TRIAL (BOVEN STUDY)

PHASE 2

Study Identifier: BOven, NCT03824483

Primary Endpoint: uMRD*

Key Secondary Endpoints: time to uMRD from treatment initiation, recommended duration of therapy, discontinuation following uMRD, durability of clinical benefit after treatment discontinuation

KEY ELIGIBILITY CRITERIA

- Aged ≥18 years
- ECOG PS 0-2
- Diagnosis of CLL/SLL
- Treatment naïve (excluding local radiation and corticosteroids)
- Requiring treatment according to 2018 iwCLL guidelines
- Adequate organ and hematological function

SCREENING →

TREATMENT

Cycles: 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8-24

Zanubrutinib 160 mg PO BID
D1 C1 until PD or trial completion

Obinutuzumab 1000 mg IV
D1 C1: 1000 mg†
D8 and D15 C1 1000 mg
D1 C2–8 1000 mg

Venetoclax 400 mg PO QD
5-week ramp-up initiated from D1 C3

uMRD ASSESSMENT

Beginning on D1 of C7 and then every other cycle, patients with PB uMRD (cutoff: $<10^{-4}$) underwent BMB and aspiration within 14 days to assess MRD status

If patients had BM uMRD, PB MRD testing was repeated after 2 additional cycles

Patients with confirmed uMRD discontinued therapy

FOLLOW-UP

Safety and survival

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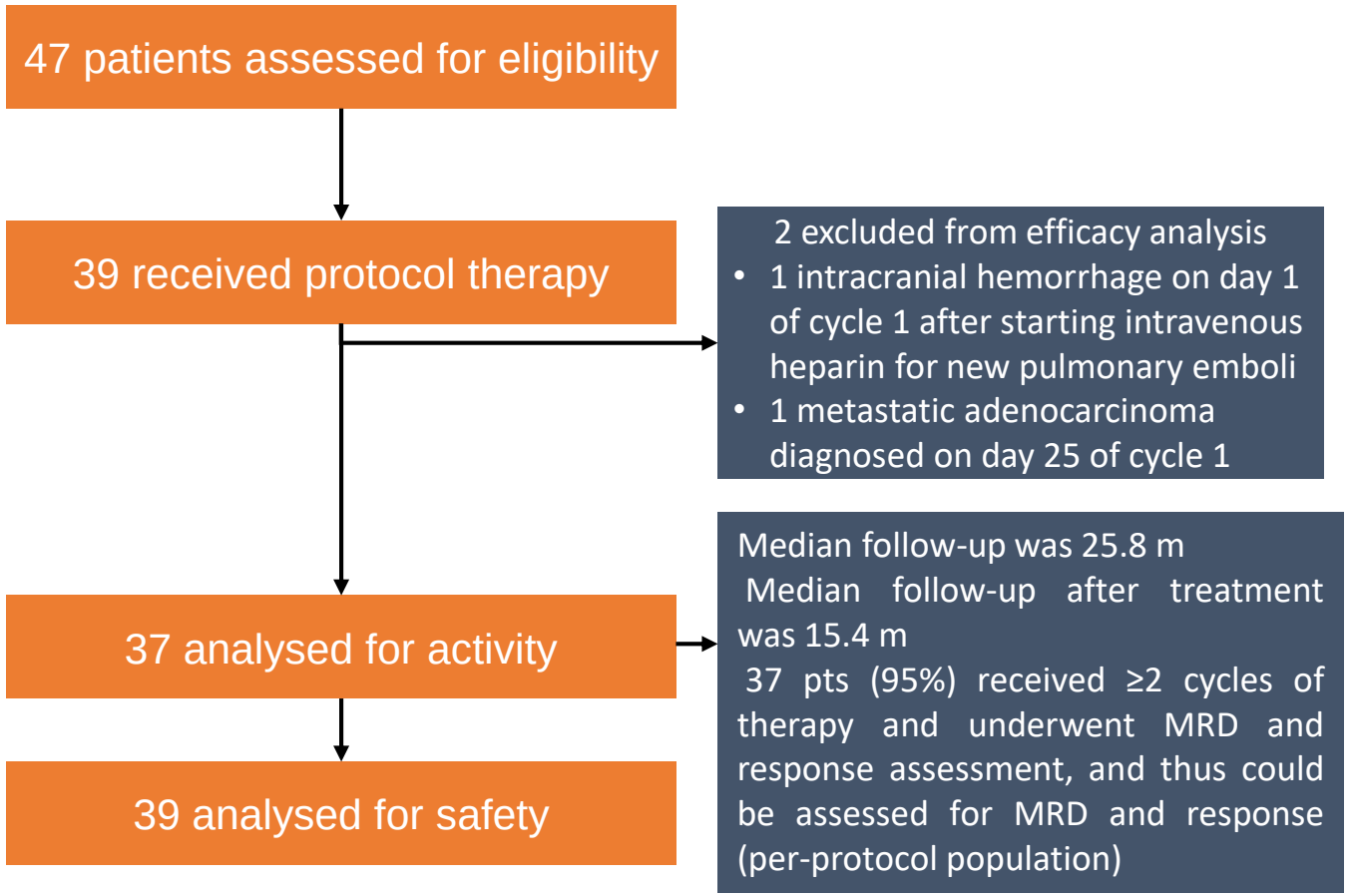
Patient disposition and characteristics

Patient disposition



Patient charcateristics

Charcateristics	Patients (n=39)
Age	62 (52-70)
Sex	
Female/Male	9 (23%)/30 (77%)
IGHV unmutated	28 (72%)
High-risk or very-high-risk CLL-IPI	26 (67%)
17p deletion or TP53 mutation	5 (13%)
17p deletion	2/39 (5%)
TP53 mutation	5/38 (13%)
FISH:	
11q deletion	6 (15%)
Normal	17 (44%)
Trisomy 12	5 (13%)
13q deletion	9 (23%)

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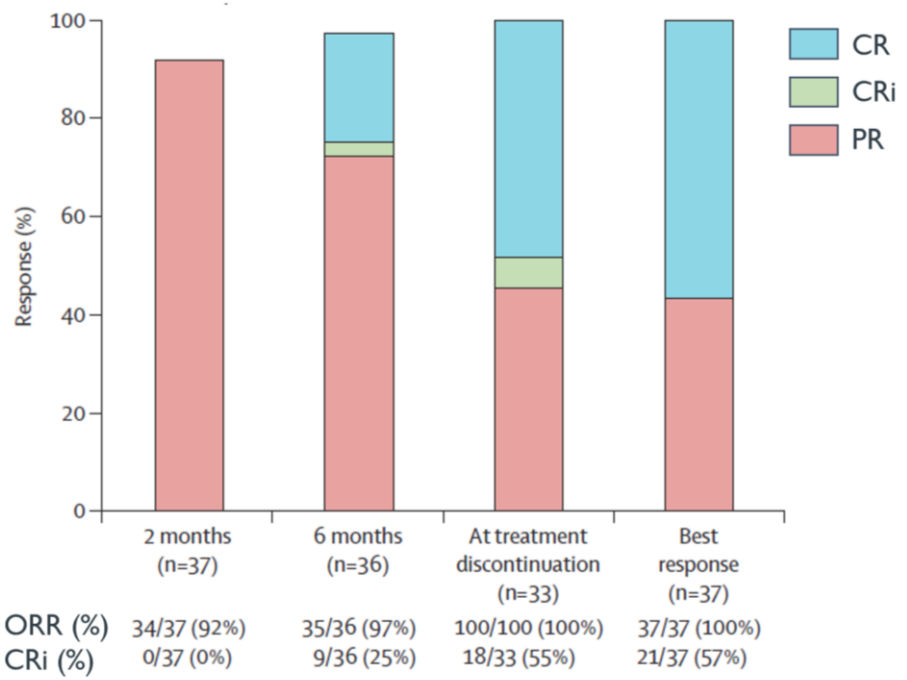
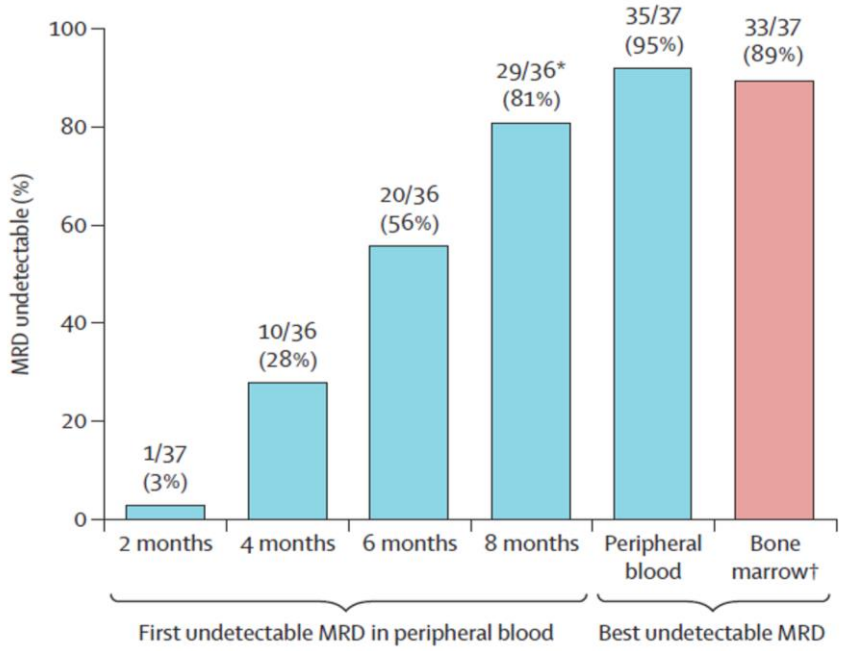
Responses

Response in Evaluable Patients by iwCLL Criteria



- **37 (100%) patients had an overall response**
- **21 (57%) had a CR or CRi**

Minimal Residual Disease by Flow Cytometry



Primary endpoint was met:

- **uMRD in both PB and BM occurred in 33 (89%) pts (95% CI 75–97)**
- **Median time to BM uMRD was 8 months (IQR 6–10)**

Peripheral Blood	Bone Marrow
Flow Cytometry: 35 uMRD immunosequencing-established: - 35 uMRD at $<10^{-4}$ - 33 (94%) had uMRD at $<10^{-5}$	Flow Cytometry: 33 uMRD immunosequencing-established on 30: - 80% uMRD at $<10^{-4}$ - 40% uMRD at $<10^{-5}$ - 3% uMRD at $<10^{-6}$

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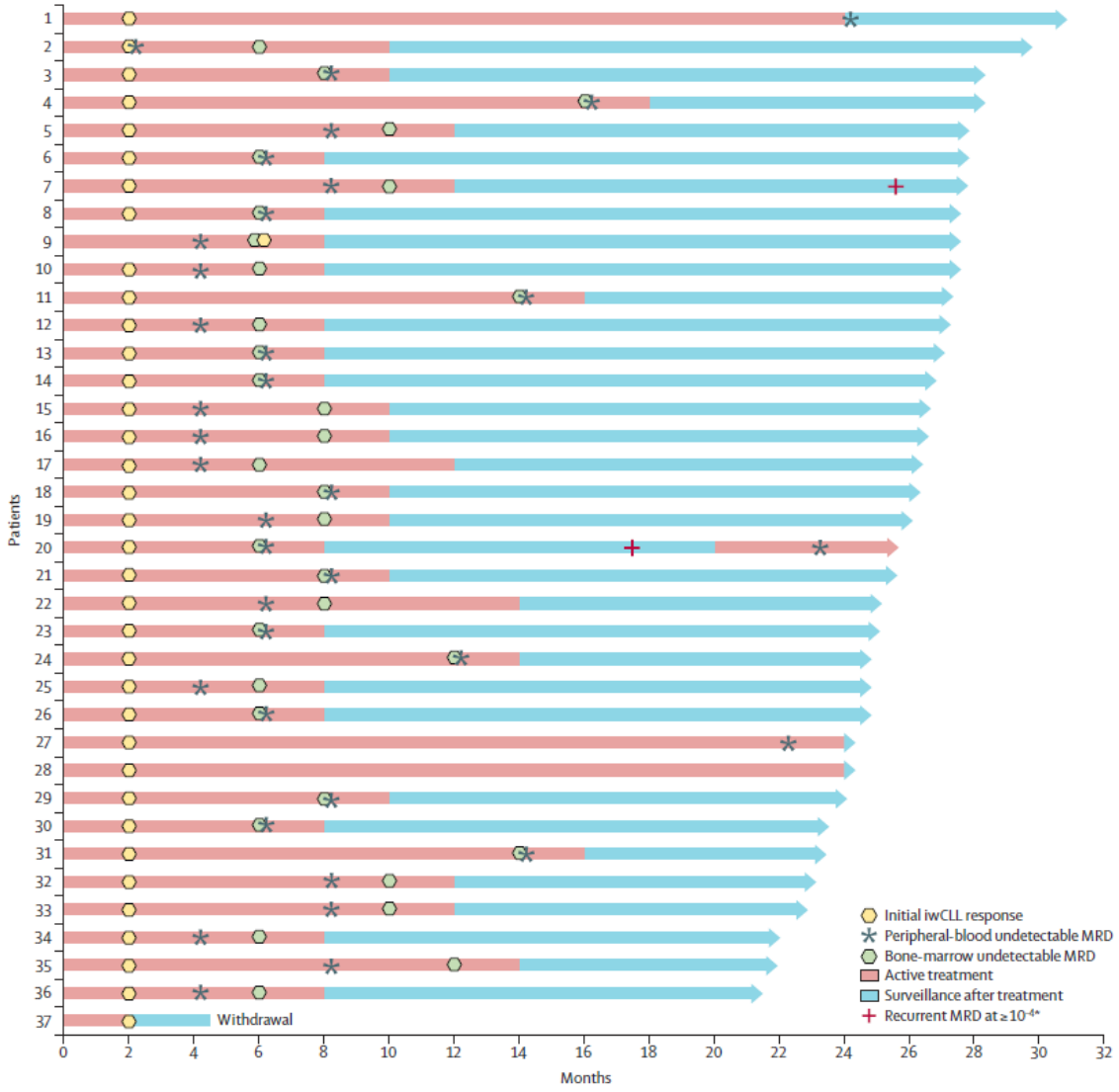
Patient Level Outcomes



33 (89%) pts (95% CI 75–97) reached the prespecified MRD endpoint and discontinued therapy after a median of 10 cycles (IQR 8–12)

- **-18 of whom (55%; 95% CI 36-72) had iwCLL CR / CRi**
- **-15 of whom (45%; 95% CI 28-64) had iwCLL PR**

3 (8%) ps completed 24 cycles and stopped therapy with detectable BM MRD

1 (3%) patient withdrew consent with ongoing MRD detectable PR after 2 cycles of therapy

2/33 patients had recurrent detectable MRD as established by flow cytometry

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ADVERSE EVENTS

- **Grade ≥3 AEs that occurred in ≥5% of patients were:**
  - **Neutropenia (5 [18%])**
  - **Thrombocytopenia (3 [8%])**
  - **Rash (3 [8%])**
  - **Lung infection (3 [8%])**
  - **Infusion-related reaction (2 [5%])**
- **9 (23%) patients received G-CSF for grade 3–4 (5 patients) or grade 2 neutropenia (4 patients)**
- **1 grade 1 atrial-fibrillation event occurred in a patient with previous paroxysmal atrial fibrillation**

- **1 death occurred due to intracranial hemorrhage on day 1 of cycle 1 after initiating intravenous heparin for pulmonary emboli, following one dose of zanubrutinib and day 1 of split-dose Obinutuzumab No additional grade 3 or worse bleeding or bruising occurred**
- **1 death occurred in a patient who was diagnosed with metastatic adenocarcinoma on day 25 of cycle 1 and opted for hospice**

dose reduction for toxicity: 4 pts

-3 required dose reduction of zanubrutinib and venetoclax for grade 2 diarrhea after 5.9 m, 6.4 m, and 8.2 m

-1 patient required dose reduction of venetoclax for grade 3 lung infection after 5.9 m

Summary

- **Zanubrutinib plus venetoclax ± Obinutuzumab appeared well tolerated with no reported clinical TLS, and relatively low incidences of neutropenia, diarrhea, and nausea**
- **Sequoia arm D study (zanubrutinib venetoclax first line: del17p/TP53mut):**
  - **high response rate in a very high-risk del(17p)/TP53 mutant CLL/SLL patient population**
  - **responses appeared to deepen in patients treated with the combination for longer periods**
  - **More mature follow-up is needed to fully assess depth of response**
- **BOVEN study (zanubrutinib, obinutuzumab, and venetoclax first line)**
  - **The primary endpoint of the trial was met 33 (89%) patients attaining uMRD both PB and BM**
  - **All of whom met the prespecified uMRD endpoint treatment-discontinuation criterion and stopped therapy after a median of 10 months of treatment**

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