Zanubrutinib (BGB-3111) in Combination with Obinutuzumab in Patients with Chronic Lymphocytic Leukemia and Follicular Lymphoma

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Conflict of Interest Disclosure – Constantine S Tam; Oral #75

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Introduction

- The first generation BTK inhibitor ibrutinib has limited activity as monotherapy in relapsed/refractory (R/R) Follicular Lymphoma (Phase 2 DAWN study, n=110, median F/up 27.7 months)[1]
  - Overall response rate (ORR) = 20.9%
  - Complete response rate (CR) = 11%
  - Median progression-free survival (PFS) = 4.6 months

- While ibrutinib has activity in CLL/SLL, the addition of rituximab to ibrutinib has not improved PFS[2]
  - Ibrutinib inhibits ITK-mediated anti-CD20-induced antibody-dependent cell-mediated cytotoxicity[3] which may diminish efficacy in combination with anti-CD20s

CLL/SLL - chronic lymphocytic leukemia/small lymphocytic lymphoma, FL – follicular lymphoma.

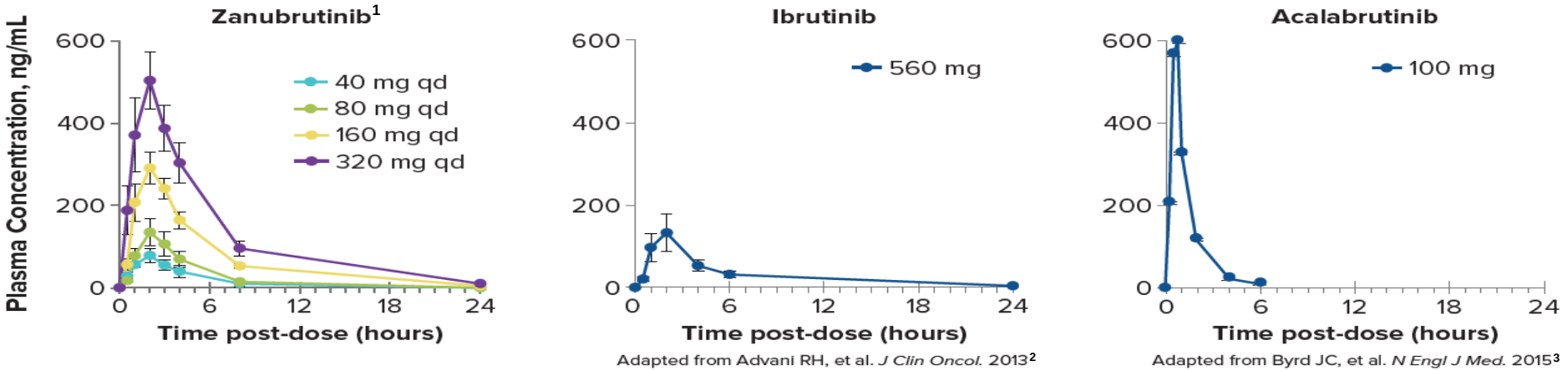
1. Gopal AK, *J Clin Oncol.* 2018; 36:2405-12; 2. Burger JA Blood. 2019 Mar 7;133(10):1011-1019; ; 3. Kohrt HE. Blood. 2014 Mar 20; 123(12): 1957-1960;

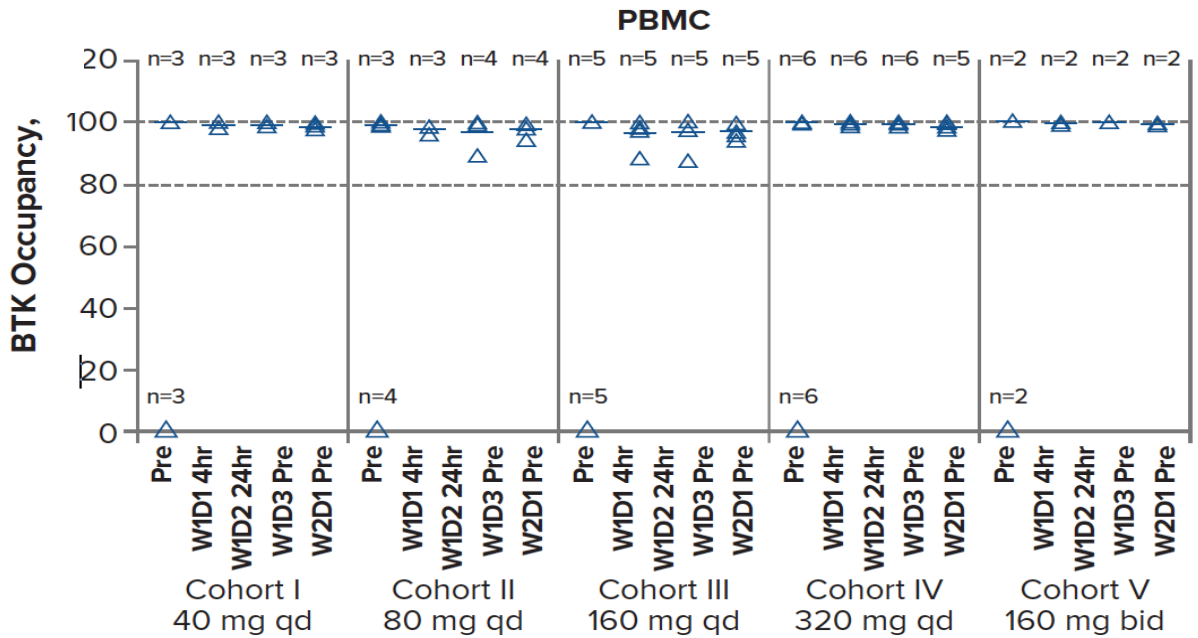
Zanubrutinib

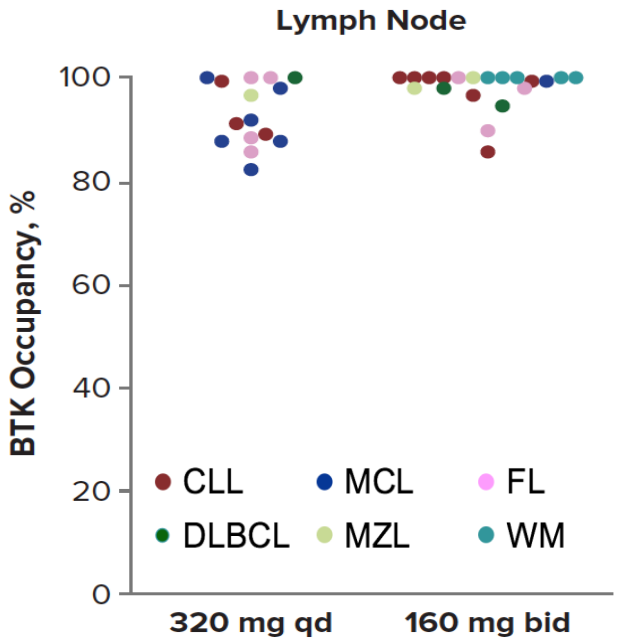
- Zanubrutinib (BGB-3111) is an investigational next-generation BTK inhibitor designed to maximize BTK occupancy and minimize off-target inhibition of TEC- and EGFR-family kinases
  - Zanubrutinib has minimal inhibitory effects against ITK and does not inhibit ITK-mediated anti-CD20-induced antibody-dependent cell-mediated cytotoxicity[1]
- Zanubrutinib has a favorable drug-drug interaction profile
  - Co-administration with strong or moderate CYP3A inhibitors (including agents such as azole anti-fungals, important in the management of patients with leukemia/lymphoma) is permitted at a reduced dose
  - Co-administration of proton pump inhibitors or other gastric acid-reducing agents does not affect zanubrutinib exposure
  - Patients have been allowed to receive anticoagulant and antiplatelet agents on zanubrutinib trials

1. Li N, et al. *Cancer Res*. 2015;75:2597

Zanubrutinib: Pharmacokinetics and Target Occupancy







Note: these data are from 3 separate analyses and differences in studies should be considered.

1. Tam CS, et al. *Blood*. 2015;126:832 [oral presentation]. 2. Advani RH, et al. *J Clin Oncol.* 2013;31:88-94. 3. Byrd JC, et al. *N Engl J Med*. 2016;374:323-332.

Phase 1b study of zanubrutinib + obinutuzumab in patients with B-cell malignancies

Indication-specific expansion cohorts

DOSE ESCALATION

Cohort	Zanubrutinib[a] (D1-28/28-D cycles)	Obinutuzumab	Patients Dosed
1a	**320 mg qd**	Cycle 1 D2: 100 mg Cycle 1 D3: 900 mg Cycle 1 D9 and D16: 1000 mg Cycles 2-6 D1: 1000 mg	**4**
1b	**160 mg bid**		**5**

Eligibility:

- WHO defined B-cell lymphoid malignancy
- ≥1 prior therapy (relapsed cohorts only); no available higher priority treatment
- ECOG performance status 0-2
- ANC >1000/µL, platelets >40,000/µL[b]
- Adequate renal and hepatic function; no significant cardiac disease[c]

End Points:

- Primary for expansion: response rate and duration by standard International Working Group Criteria
- Key secondary: safety of the combination
- Exploratory: assessment of MRD in patients with CLL/SLL

DOSE EXPANSION

Population	Disease	Planned n
TN	**CLL/SLL**	**20**
R/R	**CLL**	**20**
R/R	**non-GCB DLBCL**	**20**
R/R	**FL, MCL, MZL, and WM**	**20**
R/R	**FL**	**40**

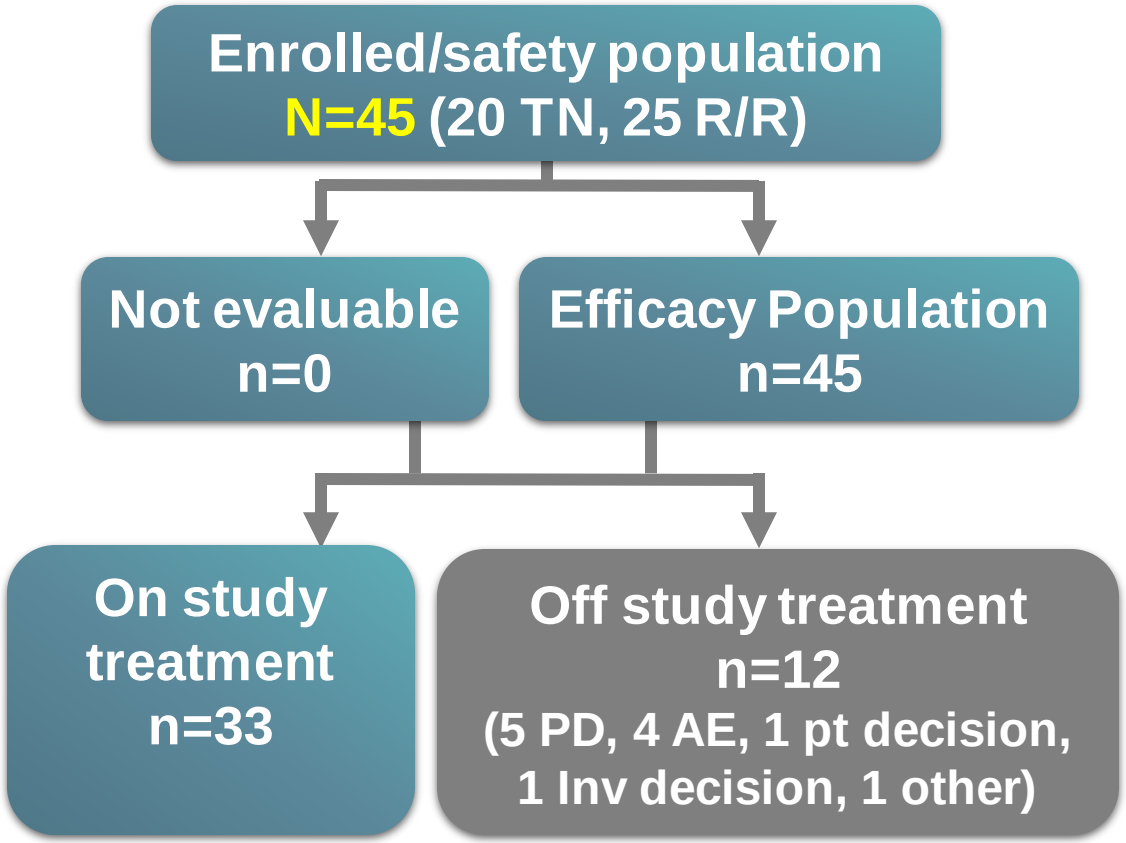
NCT02569476

[a]Zanubrutinib treatment continued until progression, death, or unacceptable toxicity. [b]Growth factor/transfusion allowed. [c]Anticoagulation allowed.
ANC, absolute neutrophil count; bid, twice daily; CLL/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma; D, day; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; GCB, germinal center B-cell-like; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma; qd, once daily; R/R, relapsed/refractory; TN, treatment-naïve; WHO, World Health Organization; WM, Waldenström macroglobulinemia.

Patient disposition (as of 28 February, 2019)

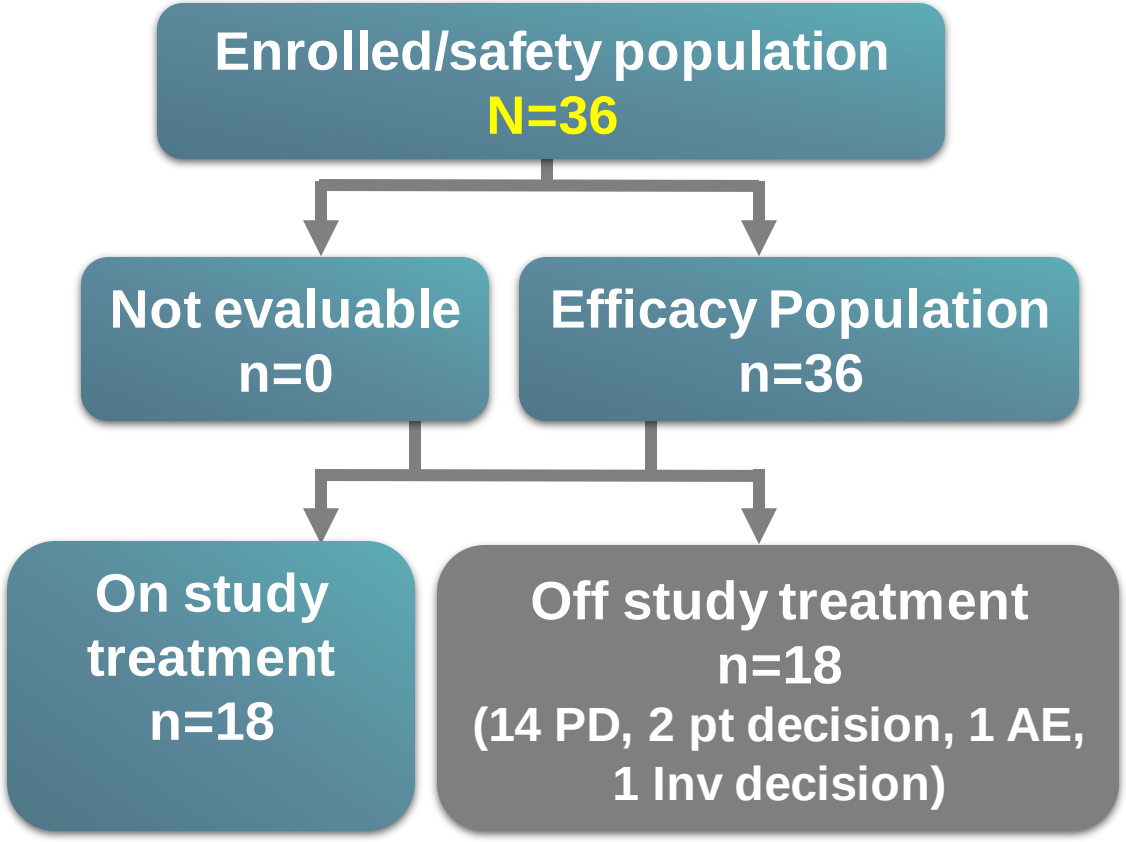
CLL/SLL

- Median follow up 28.9 mo (range, 7.9-36.9)



R/R FL

- Median follow up 20.1 mo (range, 2.3-37.2)



AE, adverse event; Inv, Investigator; PD, progressive disease; pt, patient; R/R, relapsed/refractory; TN, treatment-naïve.

Patient and disease characteristics

Characteristic	CLL/SLL (n = 45)	FL (n = 36)
Age, median (range), y	68 (38-82)	58.5 (34-86)
ECOG PS, n (%)		
0	20 (44.4)	28 (77.8)
1	24 (53.3)	6 (16.7)
2	1 (2.2)	2 (5.6)
Prior treatment status		
Treatment-naïve, n (%)	20 (44.4)	0
Relapsed/refractory, n (%)	25 (55.6)	36 (100)
Prior therapies for RR populations, median (range)	1 (1-4)	2 (1-9)
Bulky Disease, n (%)		
Node >5 cm	15 (33.3)	17 (47.2)
Node >10 cm	0	4 (11.1)
Molecular risk factors [n = 39, n (%)]		
Del(17p)/p53 mutation	16 (41.0)	N/A
Del(11q)	10 (25.6)	N/A
Unmutated *IGHV*	19 (48.7)	N/A
Complex karyotype	9 (23.1)	N/A

CLL/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma; ECOG PS, Eastern Cooperative Oncology Group performance status; FL, follicular lymphoma; *IGHV*, immunoglobulin heavy-chain variable region gene; N/A, not applicable.

Safety summary

Event, n (%)	CLL/SLL (n = 45)	R/R FL (n = 36)
Patients with any AE	45 (100.0)	35 (97.2)
Patients with any treatment related AE	43 (95.6)	30 (83.3)
Patients with ≥1 grade ≥3 AE	33 (73.3)	19 (52.8)
Patients with AEs leading to treatment discontinuation	4 (8.9)[a]	3 (8.3)[b]
Patients with AE leading to death	1 (2.2)[c]	0

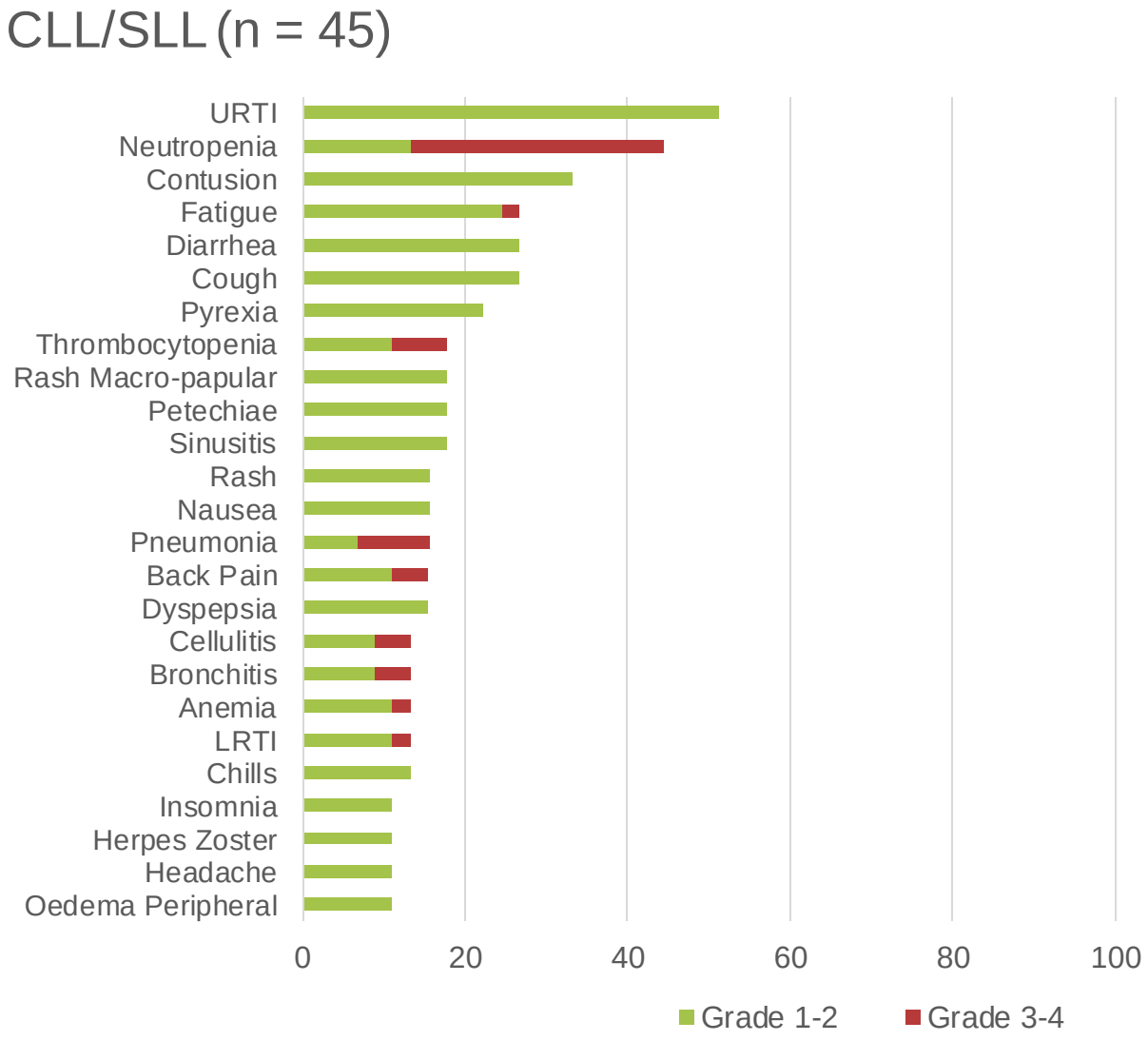
AE, adverse event; CLL/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma; FL, follicular lymphoma; R/R, relapsed/refractory; SAE, serious AE.

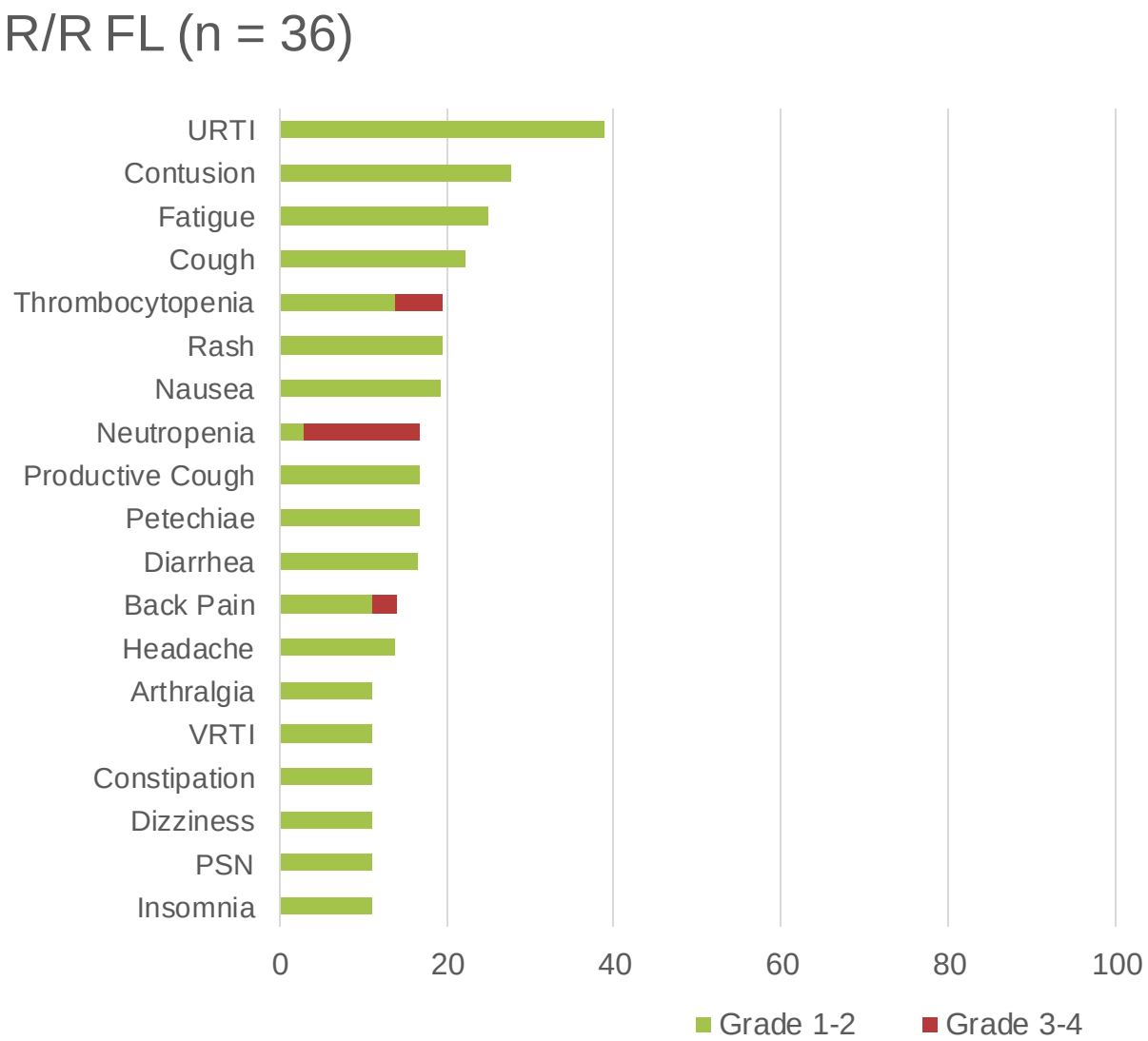
[a]CLL/SLL: patient with a history of squamous cell carcinoma discontinued due to squamous cell carcinoma, disseminated cryptococcal infection, pneumonia, and neoplasm.

[b]R/R FL: lethargy, ascites, and back pain.

[c]Squamous cell carcinoma in patient with a history of squamous cell carcinoma.

Most common (>10%) adverse events in patients with CLL/SLL and R/R FL were primarily low grade





LRTI, lower respiratory tract infection; PSN, peripheral sensory neuropathy; URTI, upper respiratory tract infection; VRTI, viral respiratory tract infection.

Adverse events of interest

Event, n (%)	CLL/SLL (n = 45)		R/R FL (n = 36)	
	All Grade	Grade ≥3	All Grade	Grade ≥3
Diarrhea	12 (26.7)	0	6 (16.7)	0
Major hemorrhage[a]	0	0	1 (2.8)[b]	0
Atrial fibrillation	0	0	0	0
Hypertension	4 (8.9)	3 (6.7)	3 (8.3)	3 (8.3)
Infusion-related reactions	11 (24.4)	1 (2.2)	5 (13.9)	0
Infections	39 (86.7)	17 (37.8)	24 (66.7)	7 (19.4)

CLL/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma; FL, follicular lymphoma; R/R, relapsed/refractory.
[a]Grade ≥3 hemorrhage or SAE or central nervous system hemorrhage of any grade.
[b]Patient with epistaxis, admitted overnight for observation due to rural location.

Disease response

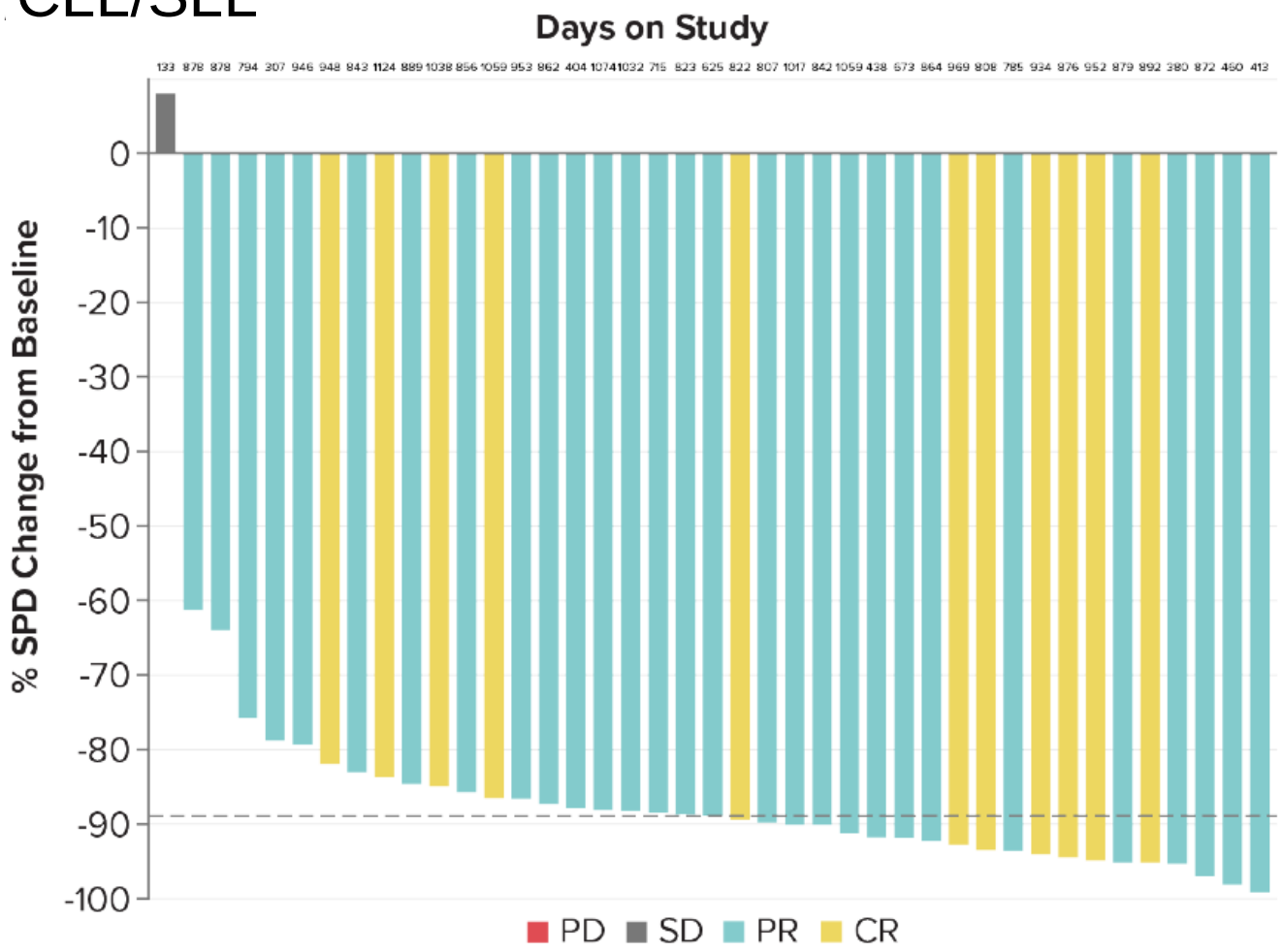
	TN CLL/SLL (n = 20)	R/R CLL/SLL (n = 25)	R/R FL (n = 36)
Follow-up median (range), mo	28.8 (13.9 - 34.8)	28.9 (7.9 – 36.9)	20.1 (2.3-37.2)
Best Response, n (%)			
ORR	**20 (100.0)**	**23 (92.0)**	**26 (72.2)**
CR*	6 (30.0)	7 (28.0)	14 (38.9)
PR	14 (70.0)	16 (64.0)	12 (33.3)
SD	0	2 (8.0)	6 (16.7)
PD	0	0	4 (11.1)
ORR for Del(17p) or p53	6 (100)	8 (80)	n/a

*3 of 6 tested in PB were MRD negative at <10-4.

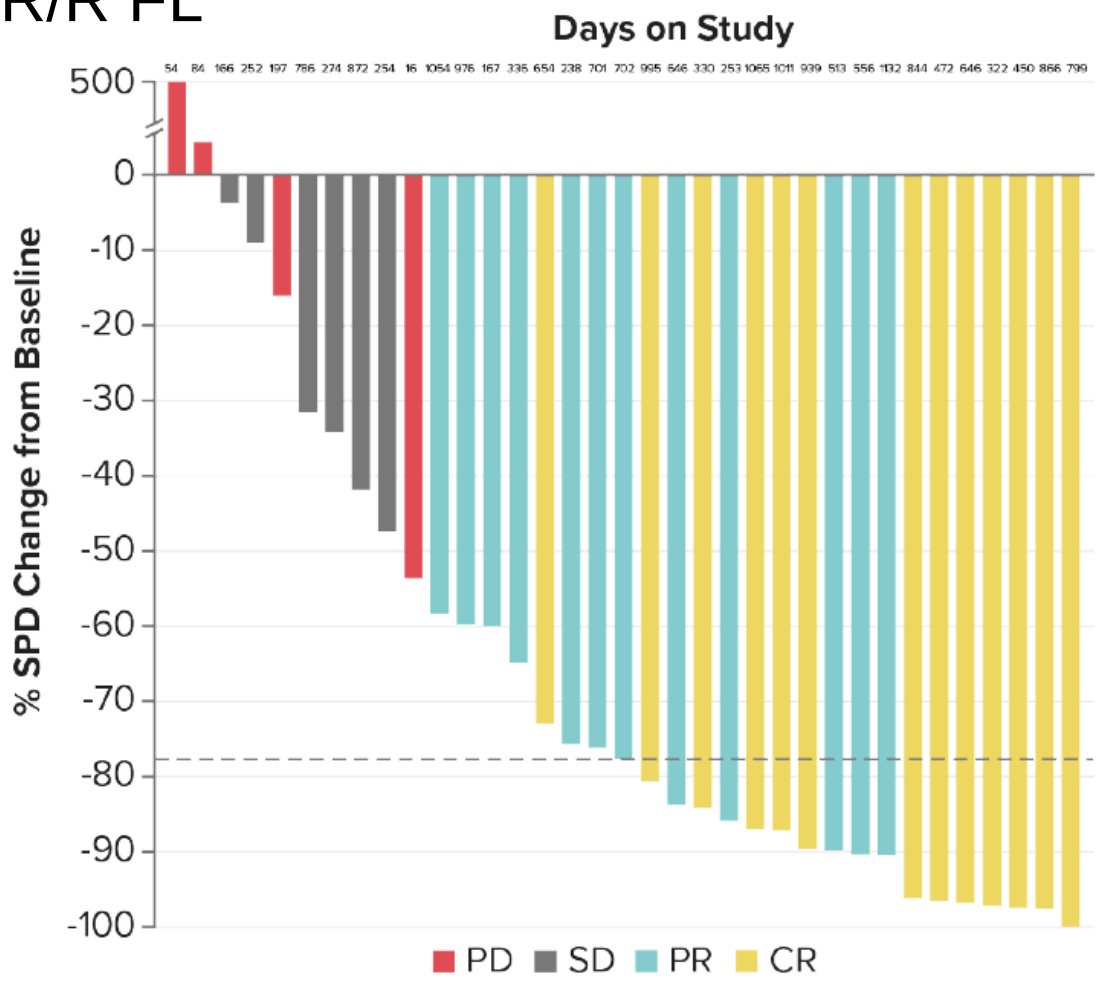
CLL/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma; CR, complete response; FL, follicular lymphoma; ORR, overal response rate; PD, progressive disease; PR, partial response; R/R, relapsed/refractory; SD, stable disease; TN, treatment-naïve.

Maximum improvement in SPD in patients with target lesions for

CLL/SLL



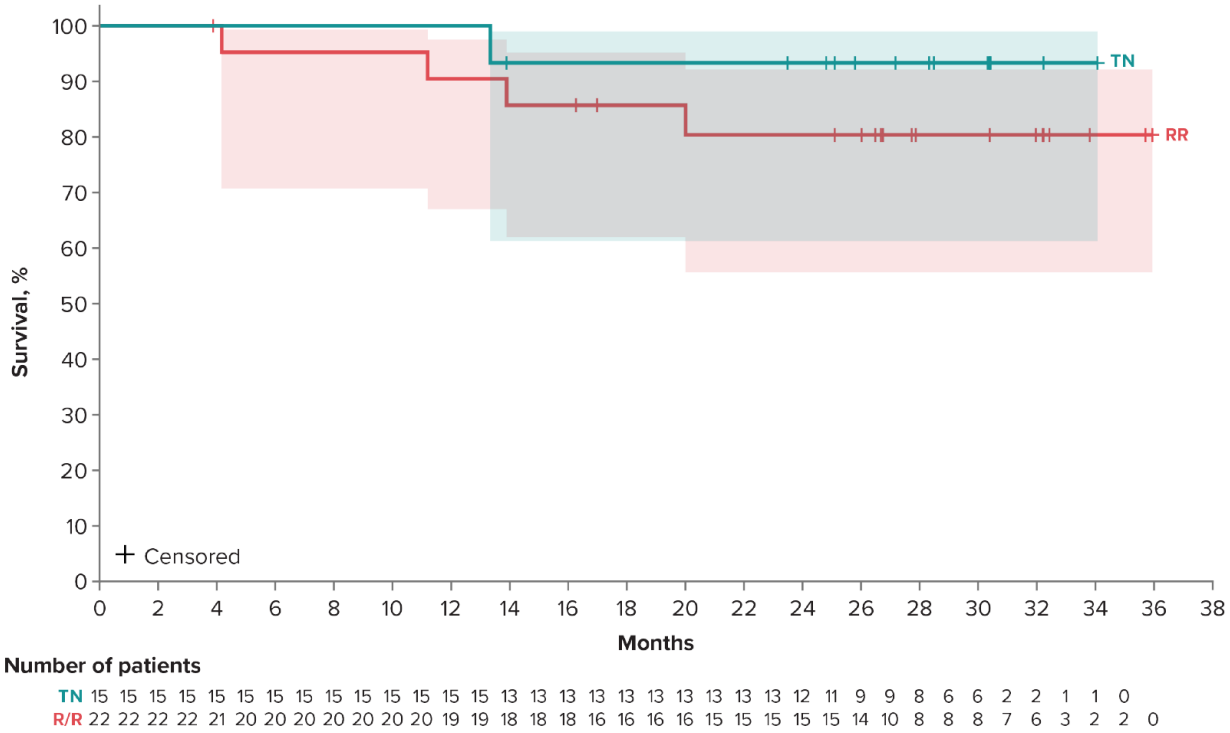
R/R FL



CLL/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma; CR, complete response; FL, follicular lymphoma; PD, progressive disease; PR, partial response; R/R, relapsed/refractory; SD, stable disease; SPD, sum of the perpendicular diameter.

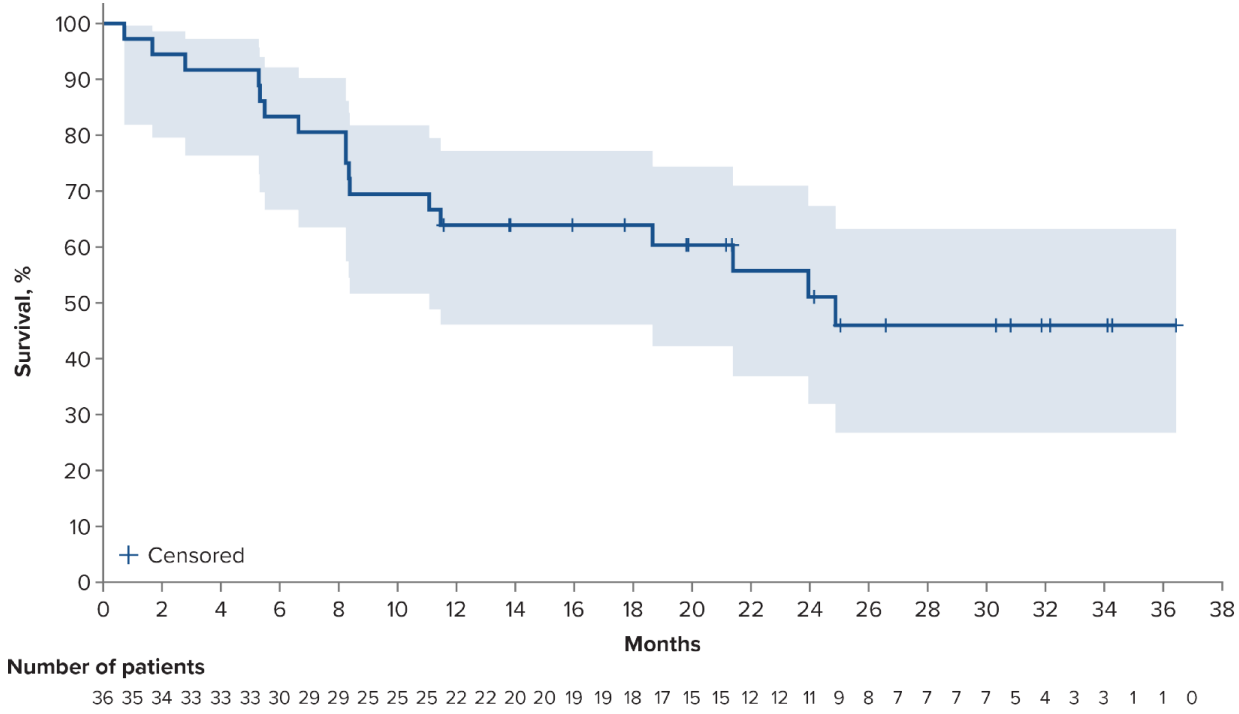
Progression-free survival

CLL/SLL (median f/up 28.8 months)



Median PFS not reached
33 (73.3%) remain on treatment

R/R FL (median f/up 20.1 months)



Median PFS 24.9 mo (range, 0.7-36.4)
18 (50.0%) remain on treatment

PFS defined as time to first PD or death
CLL: Patients without PD or death are censored at the latest date of response assessment, radiographic scan, targeted physical examination (liver, spleen, or lymph node), B symptoms assessment, and local hematology lab assessment (hemoglobin, platelet, neutrophil, or lymphocyte).
SLL: pts without PD or death are censored at the latest date of response assessment, radiographic scan, and targeted physical examination (liver, spleen, or lymph node).
R/R FL: PFS defined as time to first PD or death. Patients without PD or death are censored at the latest date of response assessment, radiographic scan, and targeted physical examination (liver, spleen, or lymph node).
CLL/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma; FL, follicular lymphoma; PD, progressive disease; PFS, progression-free survival; R/R, relapsed/refractory; TN, treatment naïve.

Conclusions

- Updated results from the phase 1b trial suggest that BTK inhibitor zanubrutinib (BGB-3111) and the anti-CD20 mAb obinutuzumab were generally well-tolerated, when given in combination in patients with CLL/SLL and R/R FL
- Few serious infusion reactions observed
- Compared with the expected rates with BTK inhibitor or anti-CD20 mAb monotherapy, the combination shows:
  - Favorable CR rates in CLL/SLL
  - Favorable frequency and depth of response (ORR and CR rate) in R/R FL
- A global randomized registration trial for the combination of zanubrutinib and obinutuzumab in R/R FL is ongoing (NCT03332017)
- If approved, this combination could offer a chemotherapy-free option for select patients with R/R FL

BeiGene

ROSEWOOD
Phase 2 Relapsed/Refractory FL

Global randomized phase 2 now enrolling

Pivotal Phase 2 Study of Obinutuzumab ± Zanubrutinib in R/R FL

R/R FL (N=210)
- Grade 1, 2, or 3a
- ≥2 prior treatments
- Must have received prior anti-CD20 mAb and an alkylator
- Relapsed after or refractory to last treatment

R
2:1

Arm A
Zanubrutinib 160 mg bid until PD + **obinutuzumab** x 6 cycles then Q8W for up to 30 total months (n=140)

Arm B
Obinutuzumab x 6 cycles then Q8W for up to 30 total months (n=70)

Stratification factors:
- No. of prior lines of therapy (2-3 vs >3)
- Rituximab refractory status (yes vs no)
- China vs ex-China

Primary end point:
- ORR by IRC

Secondary end points:
- DOR
- PFS
- OS
- TTR

bid, twice daily; DOR, duration of response; FL, follicular lymphoma; IRC, Independent review committee; ORR, overall response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; Q8W, every 8 weeks; R, randomized; R/R, relapsed/refractory; TTR, time to response.

ClinicalTrials.Gov. https://clinicaltrials.gov/ct2/show/NCT03332017.

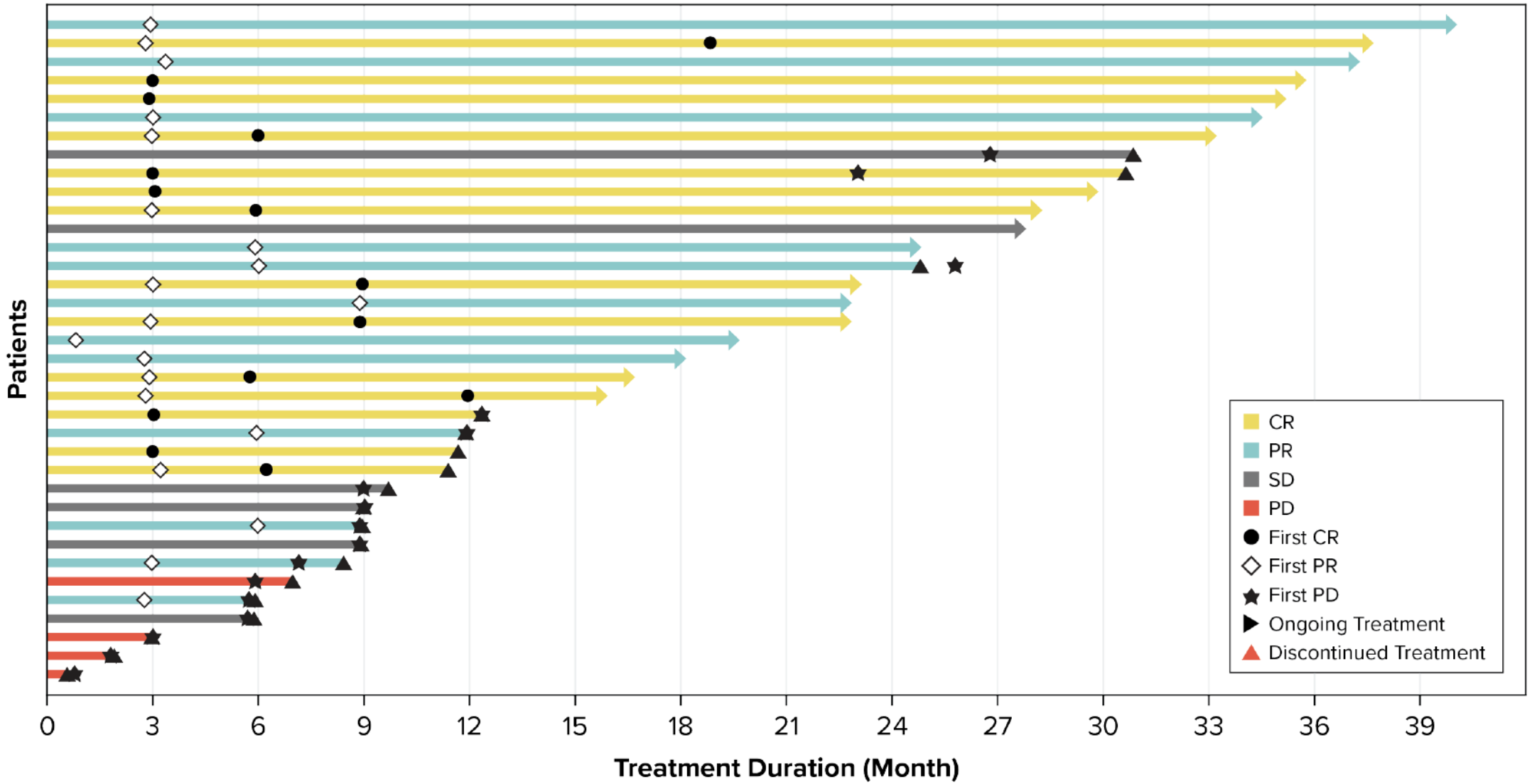
Back-up Slides

ORR by molecular subtype in patients with CLL/SLL

ORR in Evaluable Patients, n (%)	TN CLL/SLL	R/R CLL/SLL	All CLL/SLL
Del(17p) or p53	6 (100)	8 (80)	**14 (87.5)**
Del(11q)	2 (100)	8 (100)	**10 (100)**
Unmutated *IGHV*	7 (100)	11 (91.7)	**18 (94.7)**
Complex karyotype	4 (100)	3 (60.0)	**7 (77.8)**

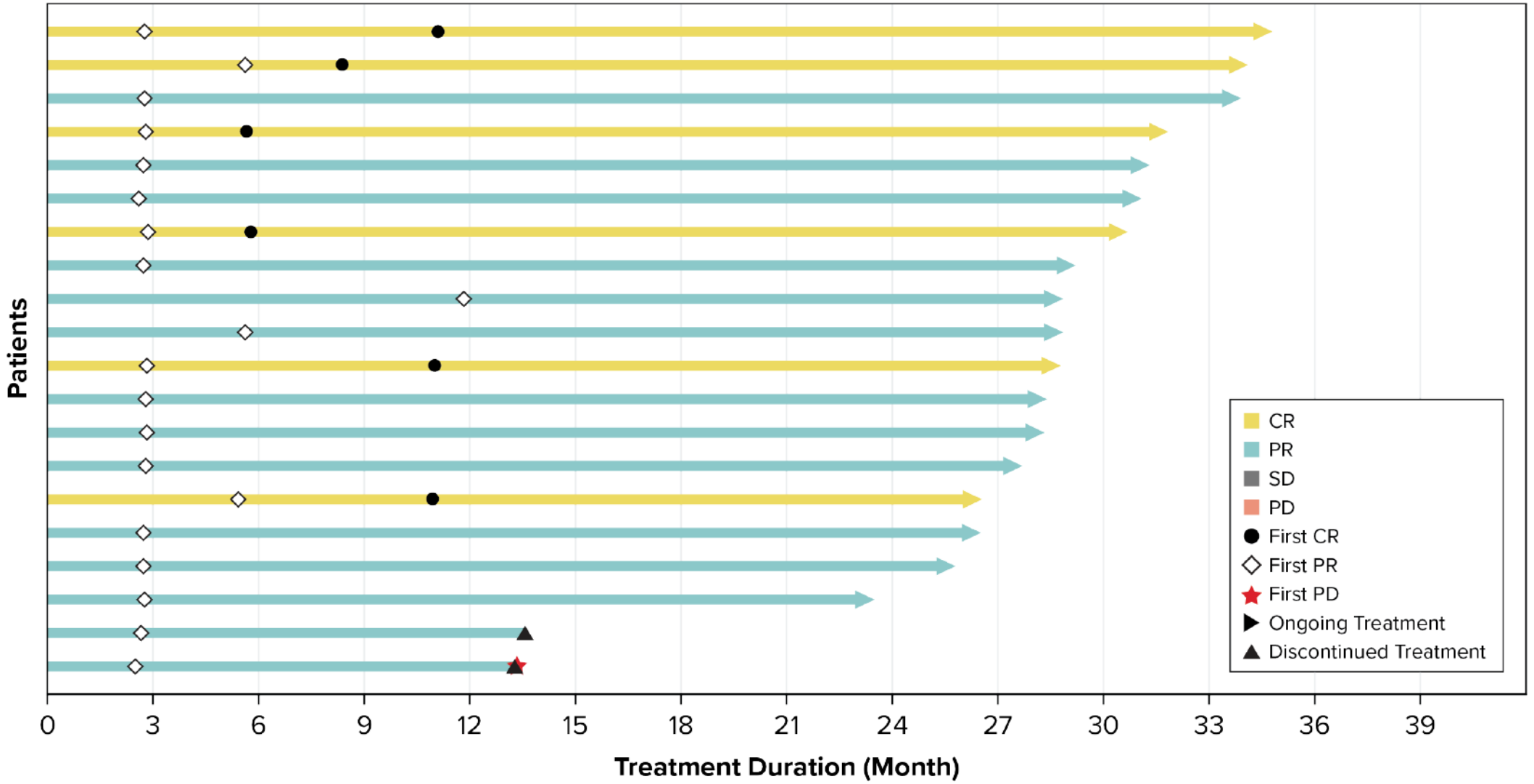
CLL/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma; ORR, overall response rate; R/R, relapsed/refractory; TN, treatment-naïve.

Swimmer's plot – R/R FL



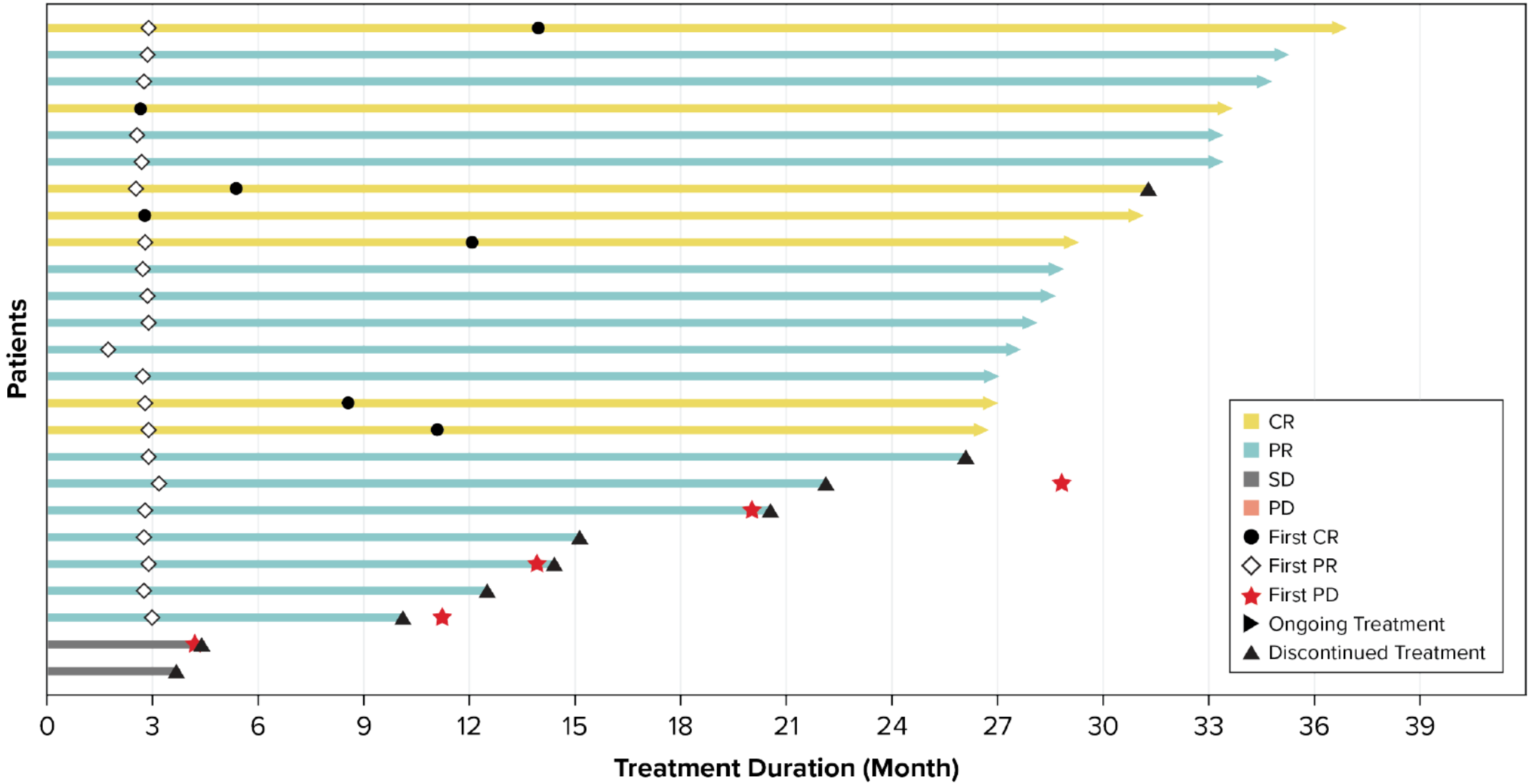
CR, complete response; FL, follicular lymphoma; PD, progressive disease; PR, partial response; R/R, relapsed/refractory; SD, stable disease.

Swimmer's plot – TN CLL/SLL



CLL/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma; CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease; TN, treatment naive.

Swimmer's plot – R/R CLL/SLL



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