Safety and Activity of the Highly Specific BTK Inhibitor Zanubrutinib (BGB-3111) in Patients with Indolent and Aggressive Non-Hodgkin's Lymphoma

Constantine S. Tam[1], David Simpson[2], Stephen Opat[3], Won Seog Kim[4], Michael Wang[5], Gavin Cull[6], Patrick B Johnston[7], Javier Munoz[8], WonSik Lee[9], Paula Marlton[10], David Gottlieb[11], Lai Wang[12], Jane Huang[12], James Hilger[12], Ling Xue[12], Sunhee Ro[12], and Judith Trotman[13]

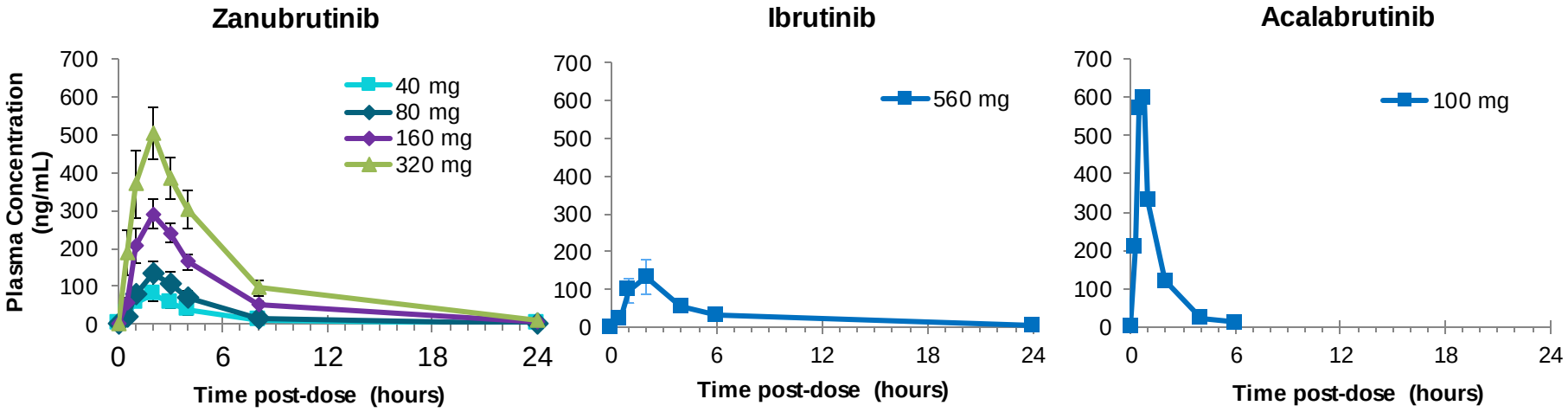
[1]Peter MacCallum Cancer Centre & St. Vincent's Hospital, Melbourne, Australia; [2]North Shore Hospital, Auckland, New Zealand; [3]Monash Medical Centre, Monash Health, Clayton, Australia; [4]Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea, Republic of (South); [5]Department of Stem Cell Transplantation and Cellular Therapy, The University of Texas MD Anderson Cancer Center, Houston, TX; [6]Department of Haematology, Sir Charles Gairdner Hospital, Nedlands, Australia; [7]Division of Hematology, Mayo Clinic, Rochester, MN; [8]Banner MD Anderson Cancer Center, Gilbert, AZ; [9]Inje University Busan Paik Hospital, Busan, Korea, Republic of (South); [10]Princess Alexandra Hospital, University of Queensland School of Medicine, Brisbane, Australia; [11]Westmead Hospital, Westmead Institute of Medical Research University of Sydney, Sydney, Australia; [12]BeiGene, San Mateo, CA; [13]Concord Repatriation General Hospital, Sydney, Australia

Zanubrutinib (BGB-3111): High BTK Selectivity

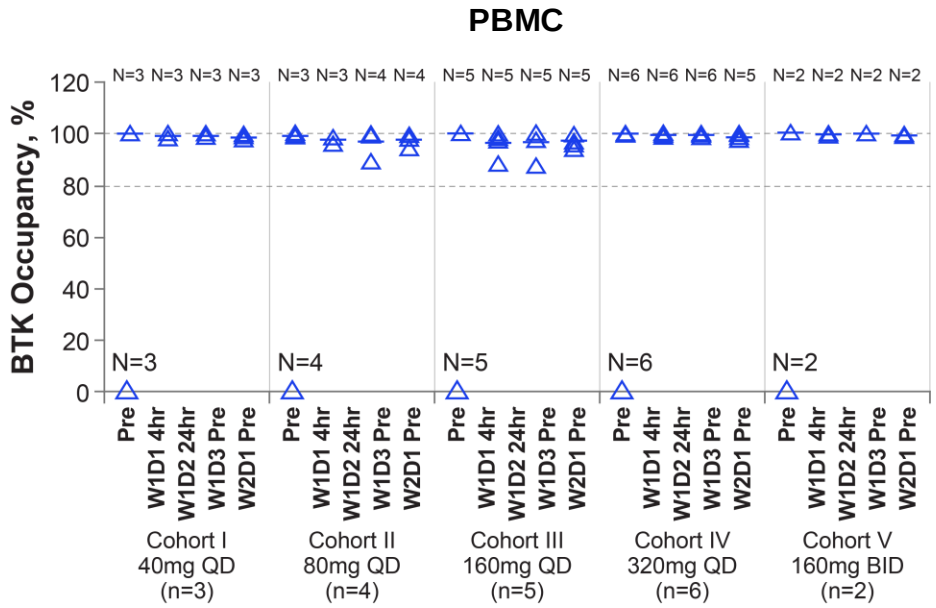
Targets	Assays	Ibrutinib IC_{50} (nM)	Zanubrutinib IC_{50} (nM)	Ratio (Zanubrutinib:Ibrutinib)
BTK	BTK-pY223 Cellular Assay	3.5	1.8	0.5
	Rec-1 Proliferation	0.34	0.36	1.1
	BTK Occupation Cellular Assay	2.3	2.2	1.0
	BTK Biochemical Assay	0.20	0.22	1.1
EGFR	p-EGFR HTRF Cellular Assay	101	606	6.0
	A431 Proliferation	323	3210	9.9
ITK	ITK Occupancy Cellular Assay	189	3265	17
	p-$PLC_{\gamma 1}$ Cellular Assay	77	3433	45
	IL-2 Production Cellular Assay	260	2536	9.8
	ITK Biochemical Assay	0.9	30	33
JAK3	JAK3 Biochemical Assay	3.9	200	51
HER2	HER2 Biochemical Assay	9.4	661	70
TEC	TEC Biochemical Assay	0.8	1.9	2.4

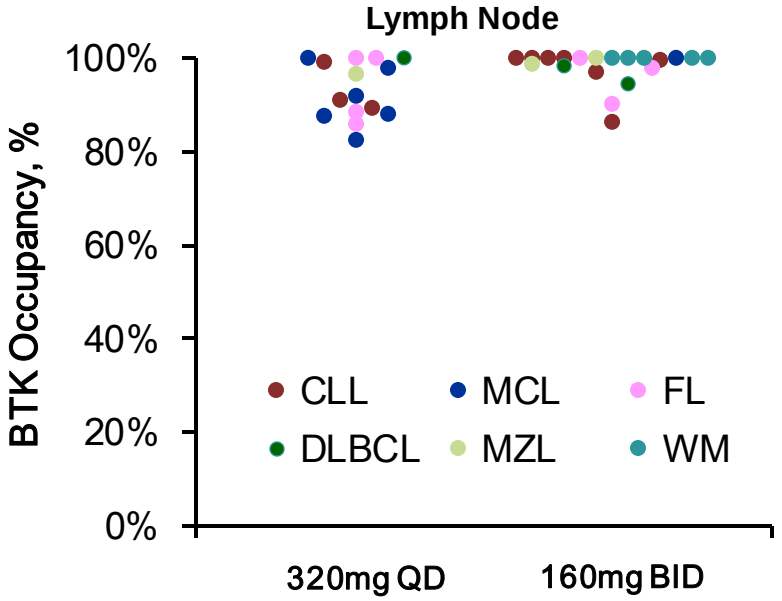
BTK, Bruton's tyrosine kinase; EGFR, epidermal growth factor receptor; IC50, drug concentration causing 50% inhibition of the desired activity; ITK, interleukin-2 inducible T-cell kinase; JAK3, Janus kinase 3.

Zanubrutinib: Favorable Pharmacokinetics, Biopsy Proven Continuous Nodal BTK inhibition



Adapted from Advani, et al, *J Clin Oncol*, 2013[9]





Introduction

- A recent update of clinical data suggested a high frequency of durable responses in patients with CLL/SLL and Waldenstrøm's macroglobulinemia, with low overall treatment discontinuation rates[1,2]
- Here we present early safety and efficacy data for patients with other NHL subtypes:
  - **Aggressive lymphoma** including R/R DLBCL and MCL
  - **Indolent lymphoma** including FL and MZL

BID, twice daily; CLL/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma; PBMC, peripheral blood mononuclear cells; R/R, relapsed/refractory.

1. Seymour et al. ICML 2017. 2. Trotman et al. ICML 2017.

Trial Design: First-in-Human, Open-label, Multicenter, Phase 1b Study of Zanubrutinib in Patients With B-cell Malignancies

DOSE ESCALATION

Dose		Enrolled (indolent, aggressive)
40 mg	QD	4 (0, 1)
80 mg	QD	5 (0, 1)
160 mg	QD	6 (0, 2)
320 mg	QD	6 (0, 1)
160 mg	BID	4 (0, 2)

RP2D

320 mg QD

or

160 mg BID

DOSE EXPANSION

Population	RP2D Dose	Disease	Planned
R/R	BID, QD	MCL, MZL, FL, GCB DLBCL	40
R/R	BID	Non-GCB DLBCL	40
R/R	BID	CLL/SLL	70
R/R	BID	WM	20
R/R	QD	CLL/SLL	20
R/R, TN	BID, QD	WM	50
R/R	BID, QD	MCL	20
TN	BID, QD	CLL/SLL	20
TN	BID, QD	MCL	20
R/R	BID, QD	HCL	10
R/R	BID	iNHL	40
R/R	BID	Richter Transform.	15
R/R or intolerant	BID	BTK-R/R WM	15

Eligibility:

- World Health Organization-defined B-cell malignancy
- No available higher priority treatment
- Eastern Cooperative Oncology Group 0-2
- ANC >1,000/µL, platelets >100,000/µL*
- Adequate renal and hepatic function
- No significant cardiac disease†

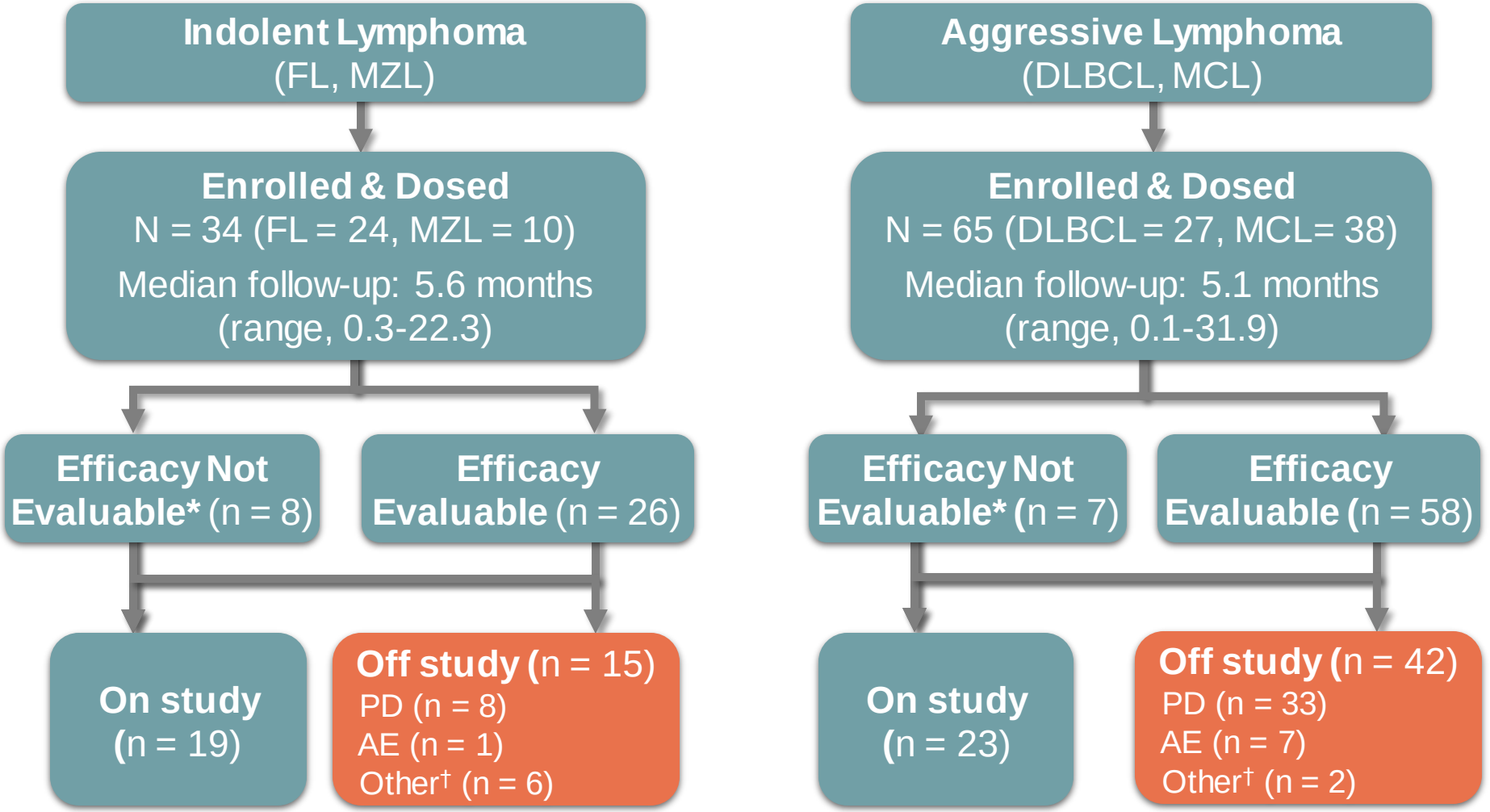
*Growth factor/transfusion allowed. †Anti-coagulation allowed.
BID, twice daily; CLL/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; GCB, germinal center B-cell–like; HCL, hairy cell leukemia; iNHL, indolent non-Hodgkin lymphoma; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma; Pop, population; RP2D, recommended phase 2 dose; QD, once daily; WM, Waldenström macroglobulinemia.

Endpoints

- **Primary endpoints**
  - Safety including AEs and SAEs per the National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.03, based on physical examination and laboratory measurements
  - Recommended phase 2 dose

- **Select secondary endpoints**
  - Pharmacokinetics
  - Efficacy, including overall response rate, progression-free survival, overall survival, and duration of response

NHL Patient Disposition as of 15-SEP-2017



AE, adverse event; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; FU, follow-up; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma; PD, progressive disease.

*On study < 12 weeks without coming off study; †Other = withdrawal of consent, "other", non-compliance.

Patient Characteristics

Characteristic	Indolent (FL, MZL) n = 34	Aggressive (DLBCL, MCL) n = 65	Total N = 99
Age, years, median (range)	65 (41-79)	70 (20-86)	68 (20-86)
ECOG Performance Status, (%)			
0	16 (47)	28 (43)	44 (44)
1	15 (44)	29 (45)	44 (44)
2	3 (9)	8 (12)	11 (11)
Prior treatment status			
Treatment-naïve, n (%)	0	2 (3)	2 (2)
Relapsed/refractory, n (%)	34 (100)	63 (97)	97 (98)
Number of prior therapies, median (range)	2 (1-8)	2 (1-10)	2 (1-10)
Bulky disease,* n (%)	0	3 (5)	3 (3)
Stage at Study Entry (per disease type)			
I	2 (6)	2 (3)	4 (4)
II	3 (9)	7 (11)	10 (10)
III	7 (21)	12 (18)	19 (19)
IV	22 (65)	43 (66)	65 (66)
LDH at baseline, median (range) in µkat/L	4.1 (2.2-23.1)	4.4 (2-77.6)	4.2 (2-77.6)
DLBCL: GCB vs. non-GCB†	-	4 vs. 23	-

* Any lymph node >10 cm in maximum diameter. †Defined by Hans algorithm.

DLBCL, diffuse large B-cell lymphoma; ECOG, Eastern Cooperative Oncology Group; GCB, germinal center B-cell like; LDH, lactate dehydrogenase; LN, lesion.

Indolent Lymphoma (FL, MZL; n = 34): Most Frequent Adverse Events

Adverse Event	All Grade, n (%)	Grade 3-5, n (%)
Petechiae/purpura/contusion	8 (24)	0
Upper respiratory tract infection	7 (21)	0
Nausea	6 (18)	1 (3)
Pyrexia	5 (15)	0
Anemia	4 (12)	3 (9)
Headache	4 (12)	0
Rash	4 (12)	0
Urinary tract infection	3 (9)	2 (6)
Abdominal pain	3 (9)	2* (6)
Neutropenia	3 (9)	3 (9)

*1 Grade 5 event in the setting of progressive disease

Aggressive Lymphoma (DLBCL, MCL; n = 65): Most Frequent Adverse Events

Adverse Event	All Grade, n (%)	Grade 3-5, n (%)
Petechiae/purpura/contusion	16 (25)	0
Diarrhea	15 (23)	1 (2)
Constipation	14 (22)	0
Fatigue	12 (18)	0
Upper respiratory tract infection	12 (18)	1 (2)
Anemia	11 (17)	7 (11)
Cough	10 (15)	0
Pyrexia	10 (15)	2 (3)
Thrombocytopenia	10 (15)	6 (9)
Neutropenia	8 (12)	6 (9)
Pneumonia	6 (9)	4 (6)*

*1 Grade 5 event in the setting or progressive disease

Selected Adverse Events

Event, n (%)	Indolent (FL, MZL) n = 34	Aggressive (DLBCL, MCL) n = 65
Patients with ≥1 AE Grade ≥3	13 (38)	39 (60)
Patients with ≥1 serious AE	11 (32)	26 (40)
Events leading to treatment discontinuation	2 (6)	8 (12)
Fatal AE	1* (3)	6† (9)
AE of special interest		
Petechiae/purpura/contusion	8 (24)	16 (25)
Diarrhea	2 (6)	15 (23)
Hypertension	1 (3)	5 (8)
Severe hemorrhage‡	1 (3)	2 (3)
Atrial fibrillation	0	2 (3)

*Abdominal pain in the context of progressive disease.

†n=2 pneumonia, n=1 congestive cardiac failure, cerebral infarction, multi-organ failure, septic shock, unknown causes. Pneumonia and septic shock from same patient. All in the context of progressive disease except for cardiac failure and cerebral infarction

‡≥G3: gastrointestinal hemorrhage, hematuria, renal hematoma.

Follicular and Marginal Zone Lymphomas: Best Responses

Response (based on CT for majority of pts)	FL n = 17	MZL n = 9	Indolent Total N = 26
Median efficacy follow-up, mo (range)	7.8 (1.9-22.3)	7 (2.8-22)	7.5 (1.9-22.3)
Best Response, n (%)			
ORR	**7 (41)**	**7 (78)**	**14 (54)**
CR	3 (18)	0	3 (12)
PR	4 (24)	7 (78)	11 (42)
SD	7 (41)	2 (22)	9 (35)
PD	1 (6)	0	1 (4)
NE*	2 (12)	0	2 (8)

CR, complete response; NE, not evaluable; ORR, overall response rate; PD, progressive disease; PR, partial response; PR-L, partial response with lymphocytosis; SD, stable disease.
* Both due to withdrawal of consent.

DLBCL and Mantle Cell Lymphoma: Best Responses

Response (based on CT for majority of pts)	DLBCL* n = 26	MCL*** n = 32	Aggressive Total N = 58
Median efficacy follow-up, mo (range)	4.2 (0.1-24)	9.5 (0.8-31.9)	5.6 (0.1-31.9)
Best Response, n (%)			
ORR	**8 (31)**	**28 (88)**	**36 (62)**
CR	4 (15)	8 (25)	12 (21)
PR	4 (15)	20 (63)	24 (41)
SD	4 (15)	1 (3)	5 (9)
PD	13 (50)	1 (3)	14 (24)
NE**	1 (4)	2 (6)	3 (5)

CR, complete response; NE, not evaluable; ORR, overall response rate; PD, progressive disease; PR, partial response; PR-L, partial response with lymphocytosis; SD, stable disease.

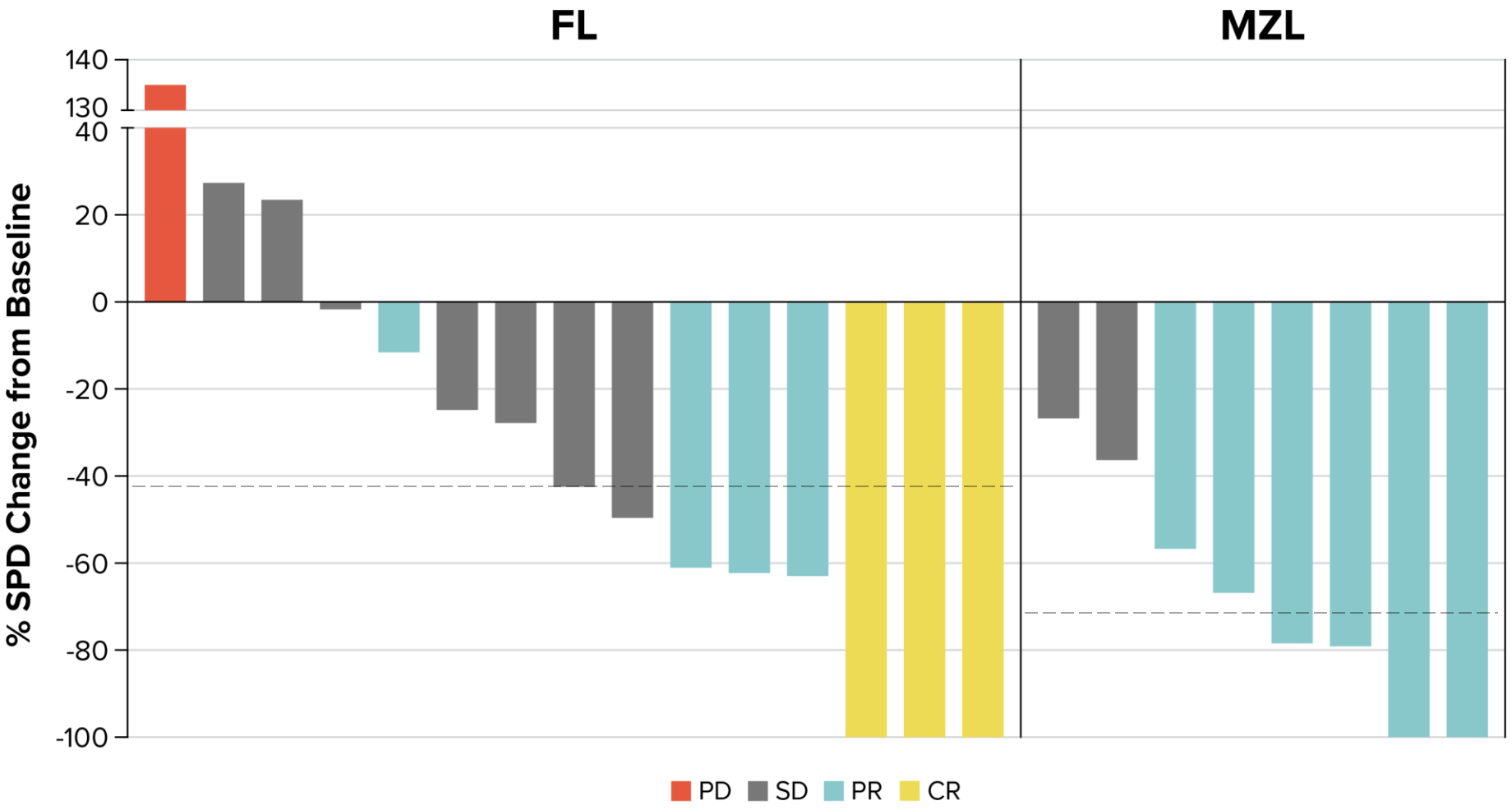
*ORR was 25% (1 of 4) and 32% (7 of 22) for GCB and non-CGB, respectively.

** n = 1 DLBCL withdrew consent, n = 2 MCL off study for adverse event before response assessment

*****In mantle cell patients treated with minimum of 320 mg/d ORR is 93% and CR is 28%**

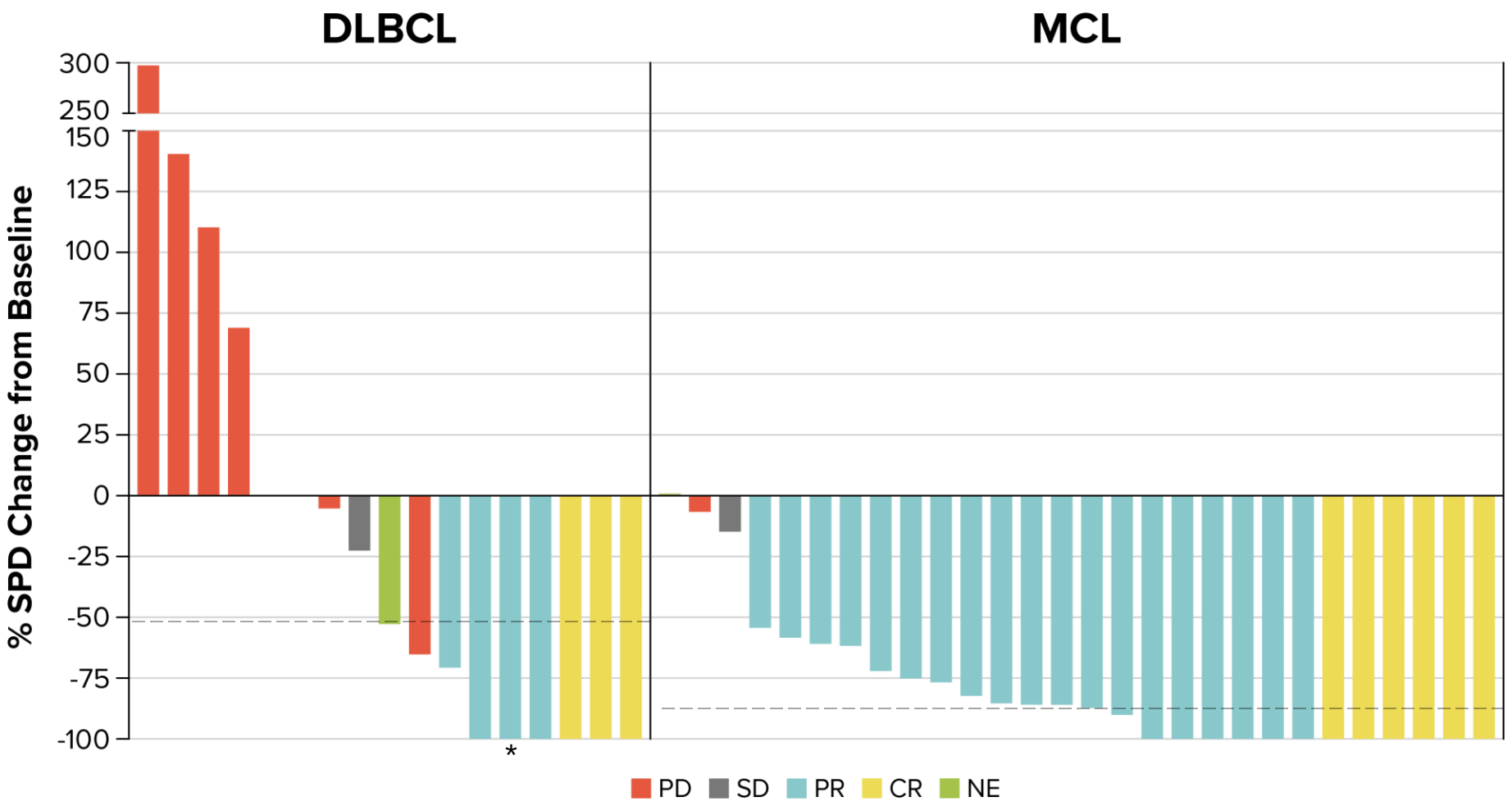
PET scanning not mandated for trial

Indolent Lymphoma (FL, MZL): SPD Response



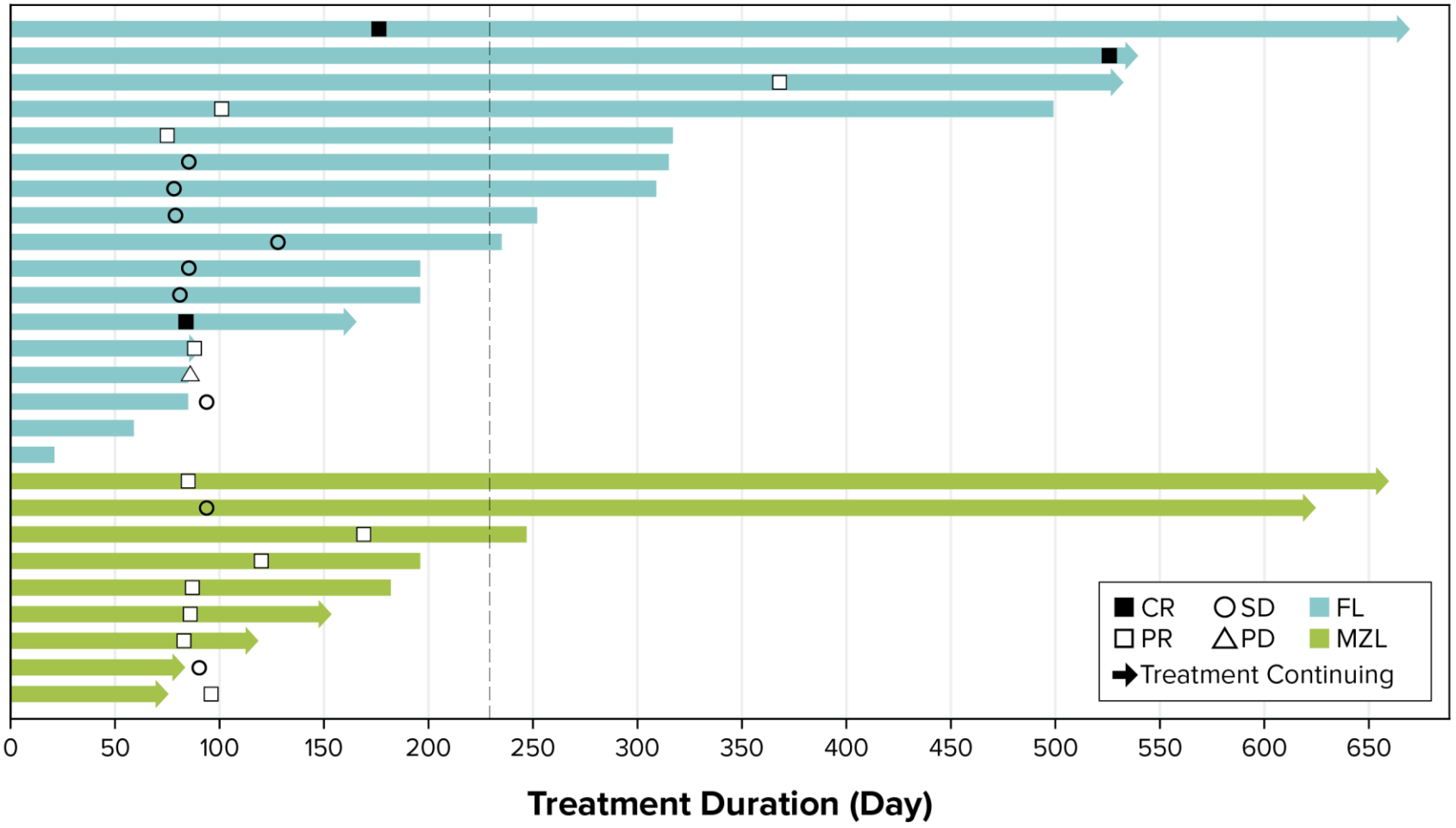
Note: 1 subject had no measurable lesions at baseline, 2 subjects did not have a post baseline scan.
Dashed lines = median reduction in SPD (-42% for FL, -73% for MZL).
SPD, sum of the products of lymph node diameters by CT scan.

Aggressive Lymphoma (DLBCL, MCL): SPD Response



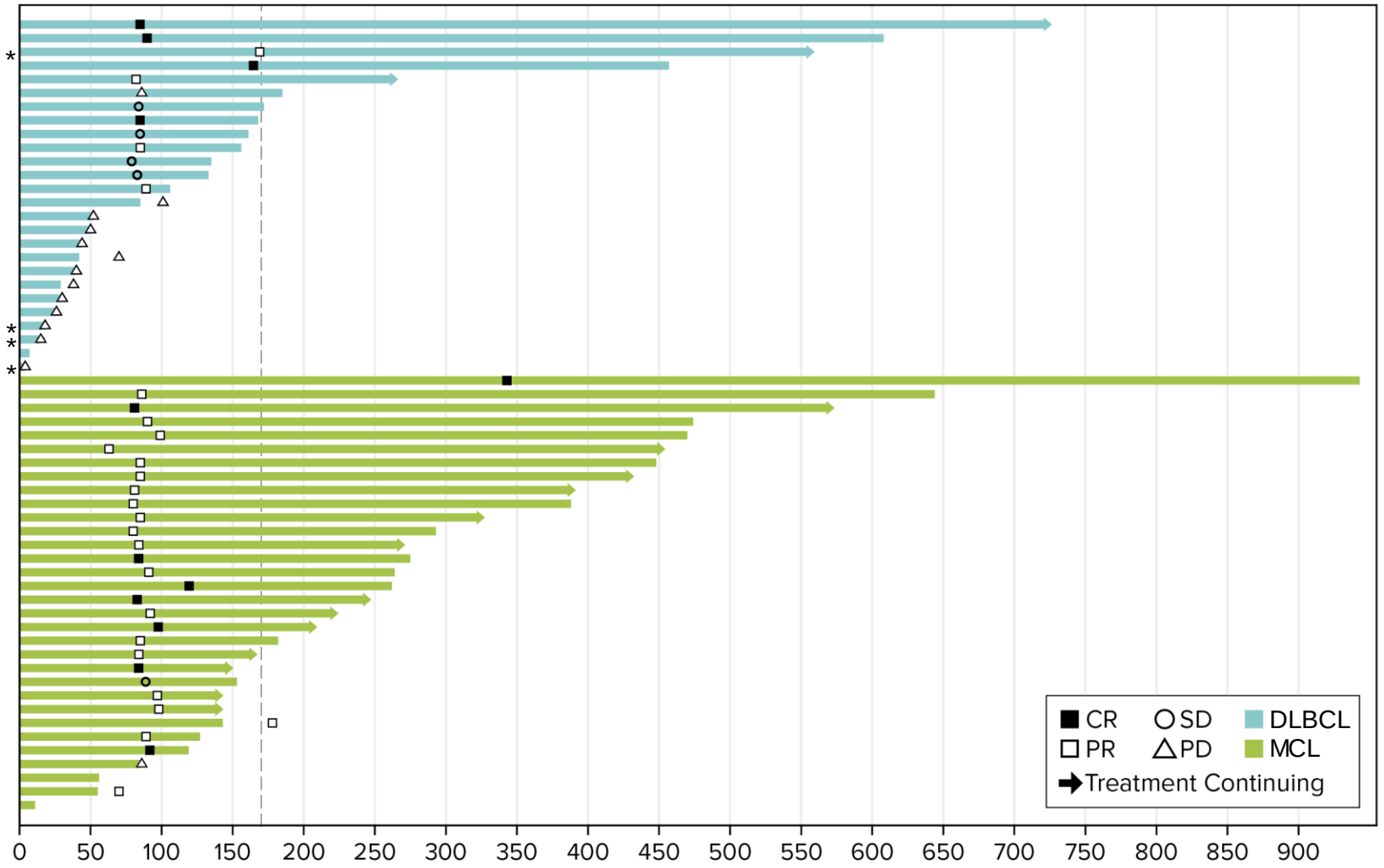
*Patient had GBC-DLBCL.
Note: 4 subjects had no measurable lesions at baseline, 9 subjects did not have a post baseline scan.
Dashed lines = median reduction in SPD (-53% for DLBCL, -87% for MCL).
SPD, sum of the products of lymph node diameters by CT scan.

Indolent Lymphoma (FL, MZL): Swim Lane



Note: symbols indicate best response.
Dashed line = median follow-up (7.5 months)

Aggressive Lymphoma (DLBCL, MCL): Swim Lane

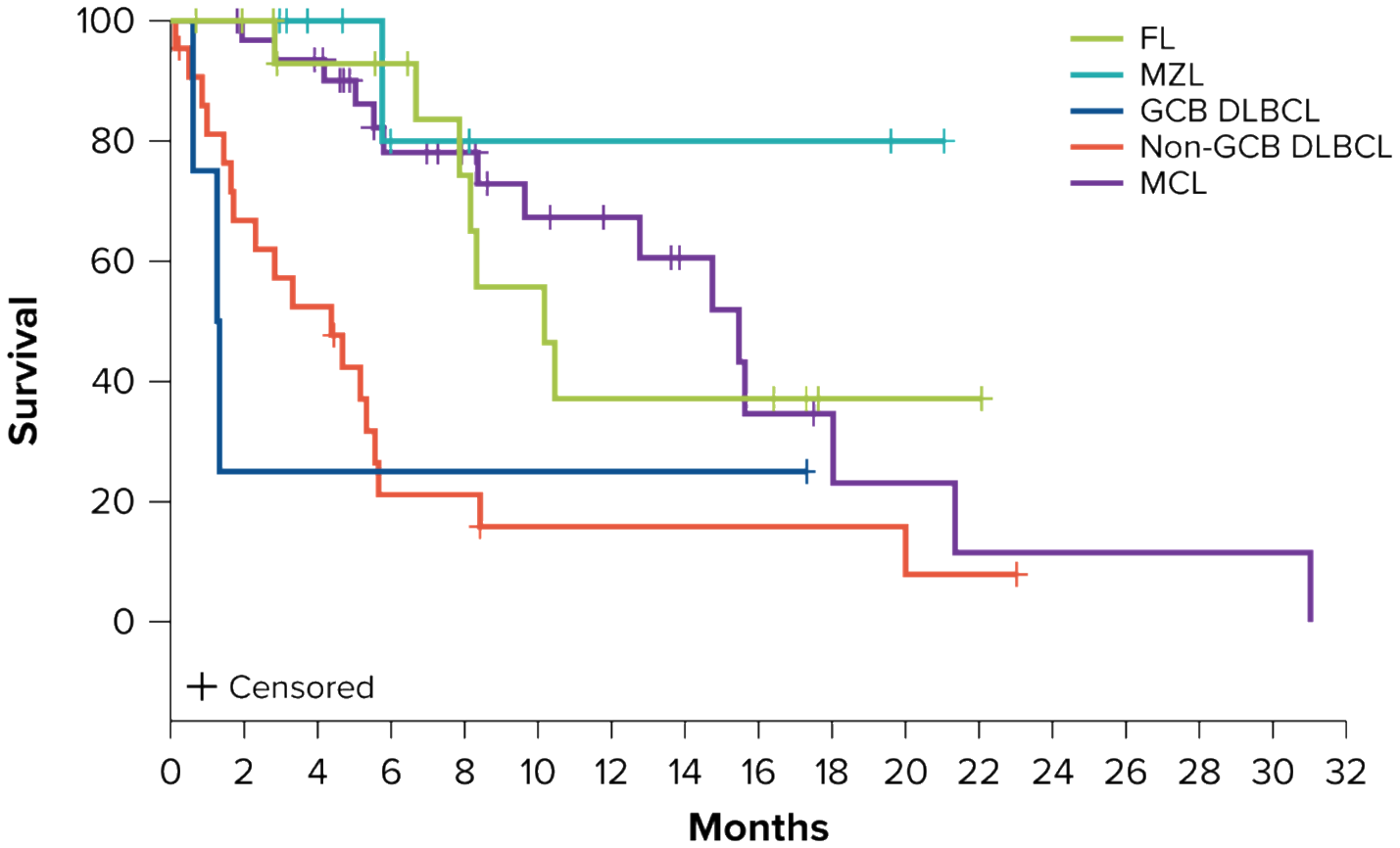


*Patients had GCB-DLBCL.

Note: symbols indicate best response.

Dashed line = median follow-up (5.6 months)

Progression-Free Survival



At risk (n)

FL	17	15	12	11	8	6	4	4	4	1	1	1	0				
MZL	9	9	6	3	3	2	2	2	2	2	1	0					
GCB DLBCL	4	1	1	1	1	1	1	1	1	0							
Non-GCB DLBCL	22	14	11	4	4	2	2	2	2	2	2	1	0				
MCL	32	30	28	19	16	12	10	7	4	3	2	1	1	1	1	1	0

Conclusions

- Zanubrutinib (BGB-3111) is well tolerated in multiple NHL subtypes
  - Adverse events led to discontinuation in 10% of patients overall
  - Encouraging activity across multiple aggressive and indolent NHL subtypes
  - ORR of 88% (28/32 pts) in MCL and 78% (7/9 pts) in MZL
  - Durable responses observed across a variety of histologies
- Supports ongoing development of zanubrutinib
  - Monotherapy: in registrational trials in WM and CLL
  - Combination: in registrational trial in FL in combination with obinutuzumab (Poster #1745, Saturday December 9)
  - Additional Phase 3 trials planned

Acknowledgments

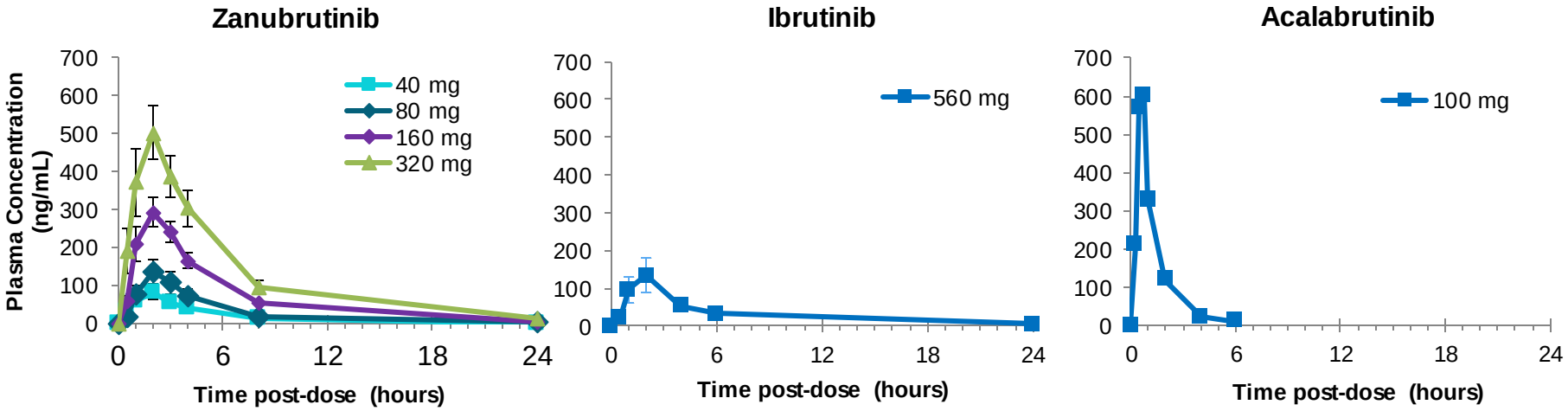
- We would like to thank the investigators, site support staff and especially the patients for participating in this study
- This study was sponsored by BeiGene. Editorial support was provided by Bio Connections LLC and funded by BeiGene

BACK-UP

Original style

Introduction

- Bruton's tyrosine kinase (BTK) plays a critical role in B-cell receptor signaling, which mediates B-cell proliferation, migration, and adhesion[1-3]
  - The BCR pathway is an established therapeutic target in multiple subtypes of non-Hodgkin's lymphoma (NHL)[4,5]
- Based on preclinical data, zanubrutinib is a potent, highly specific, and irreversible BTK inhibitor, with greater selectivity for BTK vs. other TEC- and EGFR-family kinases and demonstrates favorable pharmacokinetic and pharmacodynamic properties



Adapted from Advani, et al, *J Clin Oncol*, 2013[9]

1. Rickert RC. *Nat Rev Immunol.* 2013;13:578-591. 2. Choe H, Ruan J. *Oncology (Williston Park).* 2016;30:847-858. 3. Aalipour A, Advani RH. *Br J Haematol.* 2013;163:436-443. 4. ten Hacken E, Burger JA. *Clin Cancer Res.* 2014;20:548-556. 5. Krysiak K, et al. *Blood.* 2017;129:473-483.

Original style

Introduction

Zanubrutinib Kinase Selectivity

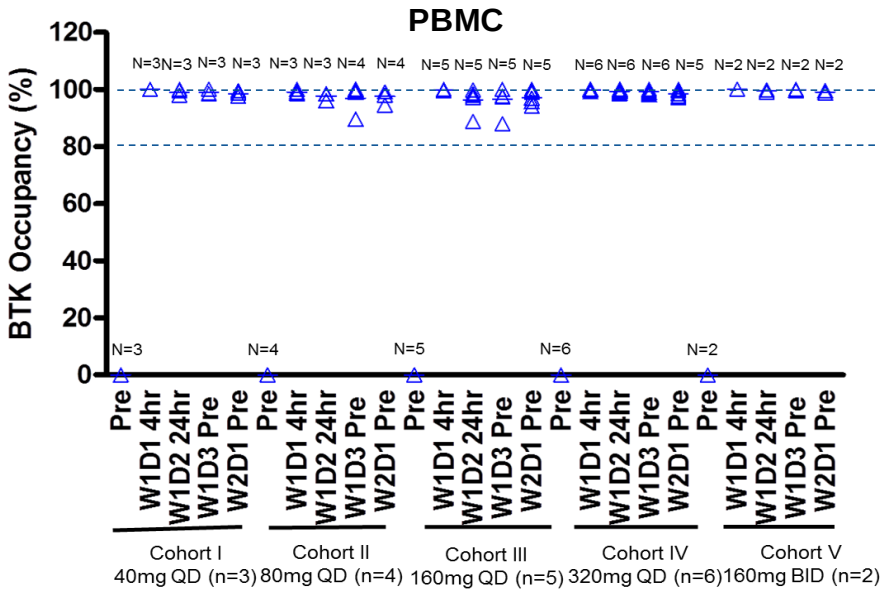
Targets	Assays	Ibrutinib IC_{50} (nM)	Zanubrutinib IC_{50} (nM)	Ratio (Zanubrutinib:Ibrutinib)
BTK	BTK-pY223 Cellular Assay	3.5	1.8	0.5
	Rec-1 Proliferation	0.34	0.36	1.1
	BTK Occupation Cellular Assay	2.3	2.2	1.0
	BTK Biochemical Assay	0.20	0.22	1.1
EGFR	p-EGFR HTRF Cellular Assay	101	606	6.0
	A431 Proliferation	323	3210	9.9
ITK	ITK Occupancy Cellular Assay	189	3265	17
	p-$PLC_{\gamma 1}$ Cellular Assay	77	3433	45
	IL-2 Production Cellular Assay	260	2536	9.8
	ITK Biochemical Assay	0.9	30	33
JAK3	JAK3 Biochemical Assay	3.9	200	51
HER2	HER2 Biochemical Assay	9.4	661	70
TEC	TEC Biochemical Assay	0.8	1.9	2.4

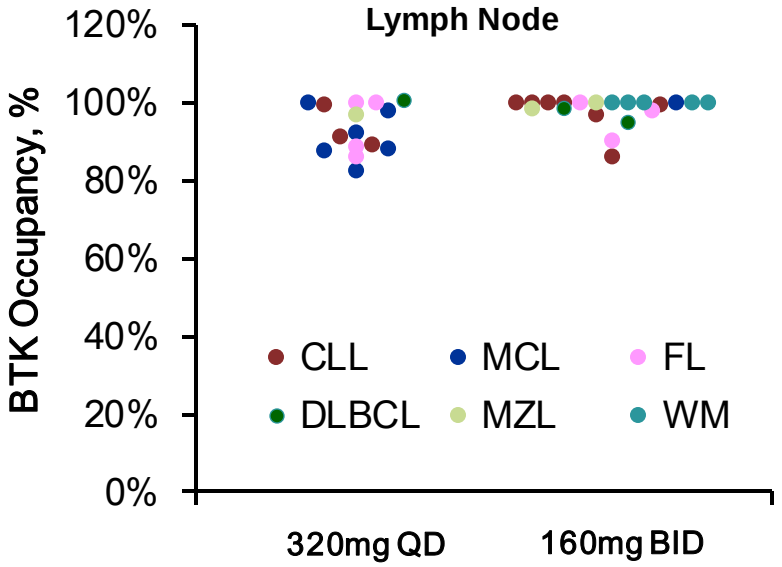
BTK, Bruton's tyrosine kinase; EGFR, epidermal growth factor receptor; IC50, drug concentration causing 50% inhibition of the desired activity; ITK, interleukin-2 inducible T-cell kinase; JAK3, Janus kinase 3.

Original style

Introduction

- Zanubrutinib achieves complete and sustained BTK occupancy in peripheral blood mononuclear cells and lymph nodes in patients treated at 160 mg BID in a phase 1 trial[1]





- A recent update of clinical data suggests durable responses in patients with CLL/SLL and Waldenstrøm's macroblobulinemia[2,3]
- Here we present early safety and efficacy data for patients with other NHL subtypes:
  - **Aggressive lymphoma** including R/R DLBCL and MCL
  - **Indolent lymphoma** including FL and MZL

BID, twice daily; CLL/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma; PBMC, peripheral blood mononuclear cells; R/R, relapsed/refractory.

1. Tam CS, et al. ASH 2016. 2. Seymour et al. ICML 2017. 3. Trotman et al. ICML 2017.

Dose Escalation and Recommended Phase 2 Dose

- A total of 25 patients with B-cell malignancies were enrolled in the dose-escalation phase
  - No dose-limiting toxicities were experienced
- No maximum-tolerated dose was reached during dose escalation
- The RP2D was established as either 320 mg QD or 160 mg BID, and both doses were used during dose expansion

BID, twice daily; QD, once daily; RP2D, recommended phase 2 dose.

Fatal (Grade 5) Adverse Events

Adverse Event , n (%)	Indolent (n = 34)	Aggressive (n = 65)
Any fatal AE	**1 (3)**	**6 (9)**
Bronchopneumonia/pneumonia	0	2* (4)
Congestive cardiac failure	0	1 (2)
Cerebral infarction	0	1 (2)
Multi-organ failure	0	1 (2)
Septic shock	0	1* (2)
Unknown causes	0	1 (2)
Abdominal pain	1 (3)	0

* Same patient had pneumonia and septic shock.

Reasons for Study & Treatment Discontinuation

Event, n (%)	Indolent (FL, MZL) n = 34	Aggressive (DLBCL, MCL), n = 65
Pts that have discontinued *study*	**15 (44.1)**	**42 (64.6)**
Progression of Disease	8 (23.5)	33 (50.8)
Adverse events (any)	1 (2.9)	7 (10.8)
Patient Withdrawal	3 (8.8)	2 (3.1)
Other	3 (8.8)	0
Pts with AEs leading to *treatment* discontinuation	**2 (5.9)**	**8 (12.3)**
Nausea	1 (2.9)	0
Blood creatinine increased	1 (2.9)	0
Cerebral infarction	0	1 (1.5)
Cognitive disorder	0	1 (1.5)
Congestive heart failure	0	1 (1.5)
Pyrexia	0	1 (1.5)
Pneumonia	0	1 (1.5)
Renal hematoma	0	1 (1.5)
Decreased appetite	0	1 (1.5)
Joint effusion	0	1 (1.5)
Myalgia	0	1 (1.5)
Myelodysplastic syndromes	0	1 (1.5)
Acute kidney injury	0	1 (1.5)

Reasons for Study & Treatment Discontinuation

	Indolent (FL, MZL) n = 34	Aggressive (DLBCL, MCL), n = 65
Pts that have discontinued *study*	**15 (44.1)**	**42 (64.6)**
Progression of Disease	8 (23.5)	33 (50.8)
Adverse events (any)	1 (2.9)	7 (10.8)
Patient Withdrawal	3 (8.8)	2 (3.1)
Other	3 (8.8)	0
Pts with AEs leading to *treatment* discontinuation	**2 (5.9)**	**8 (12.3)**

Aggressive Lymphoma (DLBCL, MCL; n = 65): Most Frequent Adverse Events (All Grade >15% or Grade 3-5 >5%)

Adverse Event	All Grade, n (%)	Grade 3-5, n (%)
Petechiae/purpura/contusion	16 (24.6)	0
Diarrhea	15 (23.1)	1 (1.5)
Constipation	14 (21.5)	0
Fatigue	12 (18.5)	0
Upper respiratory tract infection	12 (18.5)	1 (1.5)
Anemia	11 (16.9)	7 (10.8)
Cough	10 (15.4)	0
Pyrexia	10 (15.4)	2 (3.1)
Back pain	9 (13.8)	2 (3.1)
Thrombocytopenia	10 (10.8)	6 (9.2)
Pruritus	9 (13.8)	0
Dyspnea	8 (12.3)	1 (1.5)
Hematuria	8 (12.3)	0
Neutropenia	8 (12.3)	6 (9.2)
Decreased appetite	7 (10.8)	0
Nausea	7 (10.8)	0
Peripheral edema	7 (10.8)	0
Pneumonia	6 (9.2)	4 (6.2)

Serious Adverse Events

Indolent (FL, MZL)	n = 34
Any SAE, n (%)	**11 (32.4)**
All events, n*	18
Any drug-related SAE, n (%)	**4 (11.8)**
Diarrhea	1 (2.9)
Nausea	1 (2.9)
Urinary tract infection	1 (2.9)
Creatinine increase	1 (2.9)

*All n = 1.

Aggressive (DLBCL, MCL)	n = 65
Any SAE	**26 (40)**
All events, n*	48
Events in >1 patient, n (%)	
Pneumonia	6 (9.2)
Hypercalcemia	2 (3.1)
Any drug-related SAE	**3 (4.6)**
Pneumonia	1 (1.5)
Peripheral edema	1 (1.5)
Joint effusion	1 (1.5)
Pneumonitis	1 (1.5)

*For 41 events, n = 1.

Indolent Lymphoma: Patient Characteristics

Characteristic	FL n = 24	MZL n = 10	Indolent Total n = 34
Age, years, median (range)	63.5 (41-73)	70 (52-79)	65 (41-79)
ECOG Performance Status, (%) 0 1 2	 13 (54.2) 9 (37.5) 2 (8.3)	 3 (30.0) 6 (60.0) 1 (10.0)	 16 (47.1) 15 (44.1) 3 (8.8)
Follow-up, months, median (range)	4.6 (1.0-22.3)	6.2 (0.3-22.0)	5.6 (0.3-22.3)
Prior treatment status Treatment-naïve, n (%) Relapsed/refractory, n (%) Number of prior therapies, median (range)	 0 24 (100) 3 (1-8)	 0 10 (100) 1.5 (1-4)	 0 34 (100) 2 (1-8)
Bulky disease,* n (%)	0	0	0
Stage at Study Entry (per disease type) I II III IV	 1 (4.2) 3 (12.5) 6 (25.0) 14 (58.3)	 1 (10.0) 0 1 (10.0) 8 (80.0)	 2 (5.9) 3 (8.8) 7 (20.6) 22 (64.7)
LDH at baseline, median (range)	4.1 (2.5-23.1)	3.3 (2.2-7.2)	4.1 (2.2-23.1)

* Any lymph node >10 cm in maximum diameter.

ECOG, Eastern Cooperative Oncology Group; GCB, germinal center B-cell like; LDH, lactate dehydrogenase.

Aggressive Lymphoma: Patient Characteristics

Characteristic	DLBCL n = 27	MCL n = 38	Aggressive Total, n = 65
Age, years, median (range)	66 (20-85)	71 (42-86)	70 (20-86)
ECOG Performance Status, (%)			
0	9 (33.3)	19 (50.0)	28 (43.1)
1	13 (48.1)	16 (42.1)	29 (44.6)
2	5 (18.5)	3 (7.9)	8 (12.3)
Follow-up, months, median (range)	4.0 (0.1-24.0)	7.9 (0.1-31.9)	5.1 (0.1-31.9)
Prior treatment status			
Treatment-naïve, n (%)	0	2 (5.3)	2 (3.1)
Relapsed/refractory, n (%)	27 (100)	36 (94.7)	63 (96.9)
Number of prior therapies, median (range)	3 (1-10)	2 (1-4)	1 (0-10)
Bulky disease,* n (%)	0	3 (7.9)	3 (4.6)
Stage at Study Entry (per disease type)			
I	1 (3.7)	1 (2.6)	2 (3.1)
II	4 (14.8)	3 (7.9)	7 (10.8)
III	9 (33.3)	3 (7.9)	12 (18.5)
IV	13 (48.1)	30 (78.9)	43 (66.2)
LDH at baseline, median (range)	5.2 (2.5-77.6)	4.3 (2.0-13.1)	4.4 (2.0-77.6)
DLBCL: GCB vs. non-GCB	4 vs. 23	-	4 vs. 23

* Any lymph node >10 cm in maximum diameter.

DLBCL, diffuse large B-cell lymphoma; ECOG, Eastern Cooperative Oncology Group; GCB, germinal center B-cell like; LDH, lactate dehydrogenase; LN, lesion.

Follicular Lymphoma (n = 24): Most Frequent Adverse Events

Adverse Event	All Grade, n (%)	Grade 3-5, n (%)
Petechiae/purpura/contusion	5 (20.8)	0
Anemia	4 (16.7)	3 (12.5)
URTI	4 (16.7)	0
Neutropenia	3 (12.5)	3 (12.5)
Cough	3 (12.5)	0
Dyspnea	3 (12.5)	0
Nausea	3 (12.5)	1 (4.2)
Pyrexia	3 (12.5)	0
Urinary tract infection	3 (12.5)	2 (5.9)

Marginal Zone Lymphoma (n = 10): Most Frequent Adverse Events

Adverse Event	All Grade, n (%)	Grade 3-5, n (%)
Nausea	3 (30.0)	0
Petechiae/purpura/contusion	3 (30.0)	0
URTI	3 (30.0)	0
Diarrhea	2 (20.0)	1 (10.0)
Headache	2 (20.0)	0
Pyrexia	2 (20.0)	0
Rash	2 (20.0)	0
Hypertension	1 (10.0)	1 (10.0)
Non-cardiac chest pain	1 (10.0)	1 (10.0)

DLBCL (n = 27): Most Frequent Adverse Events

Adverse Event	All Grade, n (%)	Grade 3-5, n (%)
Pyrexia	7 (25.9)	1 (3.7)
Cough	6 (22.2)	0
Anemia	5 (18.5)	3 (11.1)
Back pain	5 (18.5)	0
Constipation	5 (18.5)	0
Dyspnea	5 (18.5)	1 (3.7)
Fatigue	5 (18.5)	0
Nausea	5 (18.5)	1 (3.7)
Pruritus	5 (18.5)	0
Thrombocytopenia	4 (14.8)	4 (14.8)
Neutropenia	4 (14.8)	3 (11.1)
Arthralgia	4 (14.8)	0
Decreased appetite	4 (14.8)	1 (3.7)
Pneumonia	4 (14.8)	2 (7.4)
Diarrhea	3 (11.1)	0
Hematuria	3 (11.1)	0
Petechiae/Purpura/Contusion	3 (11.1)	0
Upper respiratory tract infection	3 (11.1)	0
Urinary tract infection	3 (11.1)	0

Mantle Cell Lymphoma (n = 38): Most Frequent Adverse Events

Adverse Event	All Grade, n (%)	Grade 3-5, n (%)
Petechiae/purpura/contusion	13 (34.2)	0
Diarrhea	12 (31.6)	1 (2.6)
Constipation	9 (23.7)	0
Upper respiratory tract infection	9 (23.7)	1 (2.6)
Fatigue	7 (18.4)	0
Anemia	6 (15.8)	4 (10.5)
Thrombocytopenia	6 (15.8)	2 (5.3)
Hematuria	5 (13.2)	0
Peripheral edema	5 (13.2)	2 (5.3)
Neutropenia	4 (10.5)	3 (7.9)
Back pain	4 (10.5)	2 (5.3)
Cough	4 (10.5)	0
Dyspepsia	4 (10.5)	0
Dyspnea exertional	4 (10.5)	0
Epistaxis	4 (10.5)	0
Pruritus	4 (10.5)	0
Rash	4 (10.5)	0
Myalgia	3 (7.9)	2 (5.3)
Acute kidney injury	2 (5.3)	2 (5.3)
Pneumonia	2 (5.3)	2 (5.3)

Fatal (Grade 5) Adverse Events

Adverse Event , n (%)	FL (n = 24)	MZL (n = 10)	DLBCL (n = 27)	MCL (n = 38)
Any fatal AE	**1 (4.2)**	**0**	**3 (11.1)**	**3 (7.9)**
Bronchopneumonia	0	0	0	1 (2.6)
Pneumonia	0	0	1* (1.5)	0
Congestive cardiac failure	0	0	0	1 (2.6)
Cerebral infarction	0	0	0	1 (2.6)
Multi-organ failure	0	0	1 (1.5)	0
Septic shock	0	0	1* (1.5)	0
Unknown causes	0	0	1 (1.5)	0
Abdominal pain	1 (4.2)	0	0	0

* From the same patient.

Indolent Lymphoma: Serious Adverse Events

Follicular Lymphoma	n = 24
Any SAE, n (%)	**9 (37.5)**
All events, n*	15
Any drug-related SAE, n (%)	**3 (12.5)**
Nausea	1 (4.2)
Urinary tract infection	1 (4.2)
Blood creatinine increase	1 (4.2)

*All n = 1.

Marginal Zone Lymphoma	n = 10
Any SAE, n (%)	**2 (20.0)**
All events, n*	3
Any drug-related SAE, n (%)	**1 (10.0)**
Diarrhea	1 (10.0)

*All n = 1.

Aggressive Lymphoma: Serious Adverse Events

DLBCL	n = 27
Any SAE, n (%)	**16 (59.3)**
All events, n*	21
Events in >1 patient, n (%)	
Pneumonia	4 (14.8)
Hypercalcemia	2 (7.4)
Any drug-related SAE, n (%)	**2 (7.4)**
Pneumonia	1 (3.7)
Pneumonitis	1 (3.7)

*For 15 events, n = 1.

Mantle Cell Lymphoma	n = 38
Any SAE, n (%)	**10 (26.3)**
All events, n*	26
Events in >1 patient, n (%)	
Pneumonia	2 (5.3)
Any drug-related SAE, n (%)	**1 (2.6)**
Peripheral edema	1 (2.6)
Joint effusion	1 (2.6)

*For 24 events, n = 1.

Indolent Lymphoma: Reasons for Permanent Treatment Discontinuation

Event, n (%)	FL n = 24	MZL n = 10	Indolent (FL, MZL) n = 34
Pts that have discontinued *study*	**12 (50.0)**	**3 (30.0)**	**15 (44.1)**
Progression of Disease	7 (29.2)	1 (10.0)	8 (23.5)
Adverse events (any)	0	1 (10.0)	1 (2.9)
Patient Withdrawal	2 (8.3)	1 (10.0)	3 (8.8)
Other	3 (12.5)	0	3 (8.8)
Pts with AEs leading to *treatment* discontinuation	**2 (8.3)**	**0**	**2 (5.9)**
Nausea	1 (4.2)	0	1 (2.9)
Blood creatinine increased	1 (4.2)	0	1 (2.9)

Aggressive Lymphoma: Reasons for Permanent Treatment Discontinuation

Event, n (%)	DLBCL n = 27	MCL n = 38	Aggressive (DLBCL, MCL), n = 65
Pts that have discontinued *study*	**23 (85.2)**	**19 (50.0)**	**42 (64.6)**
Progression of Disease	21 (77.8)	12 (31.6)	33 (50.8)
Adverse events (any)	0	7 (18.4)	7 (10.8)
Patient Withdrawal	2 (7.4)	0	2 (3.1)
Other	0	0	0
Pts with AEs leading to *treatment* discontinuation	**1 (3.7)**	**7 (18.4)**	**8 (12.3)**
Pyrexia	1 (3.7)	0	1 (1.5)
Decreased appetite	1 (3.7)	0	1 (1.5)
Cerebral infarction	0	1 (2.6)	1 (1.5)
Cognitive disorder	0	1 (2.6)	1 (1.5)
Congestive heart failure	0	1 (2.6)	1 (1.5)
Pneumonia	0	1 (2.6)	1 (1.5)
Renal hematoma	0	1 (2.6)	1 (1.5)
Joint effusion	0	1 (2.6)	1 (1.5)
Myalgia	0	1 (2.6)	1 (1.5)
Myelodysplastic syndromes	0	1 (2.6)	1 (1.5)
Acute kidney injury	0	1 (2.6)	1 (1.5)

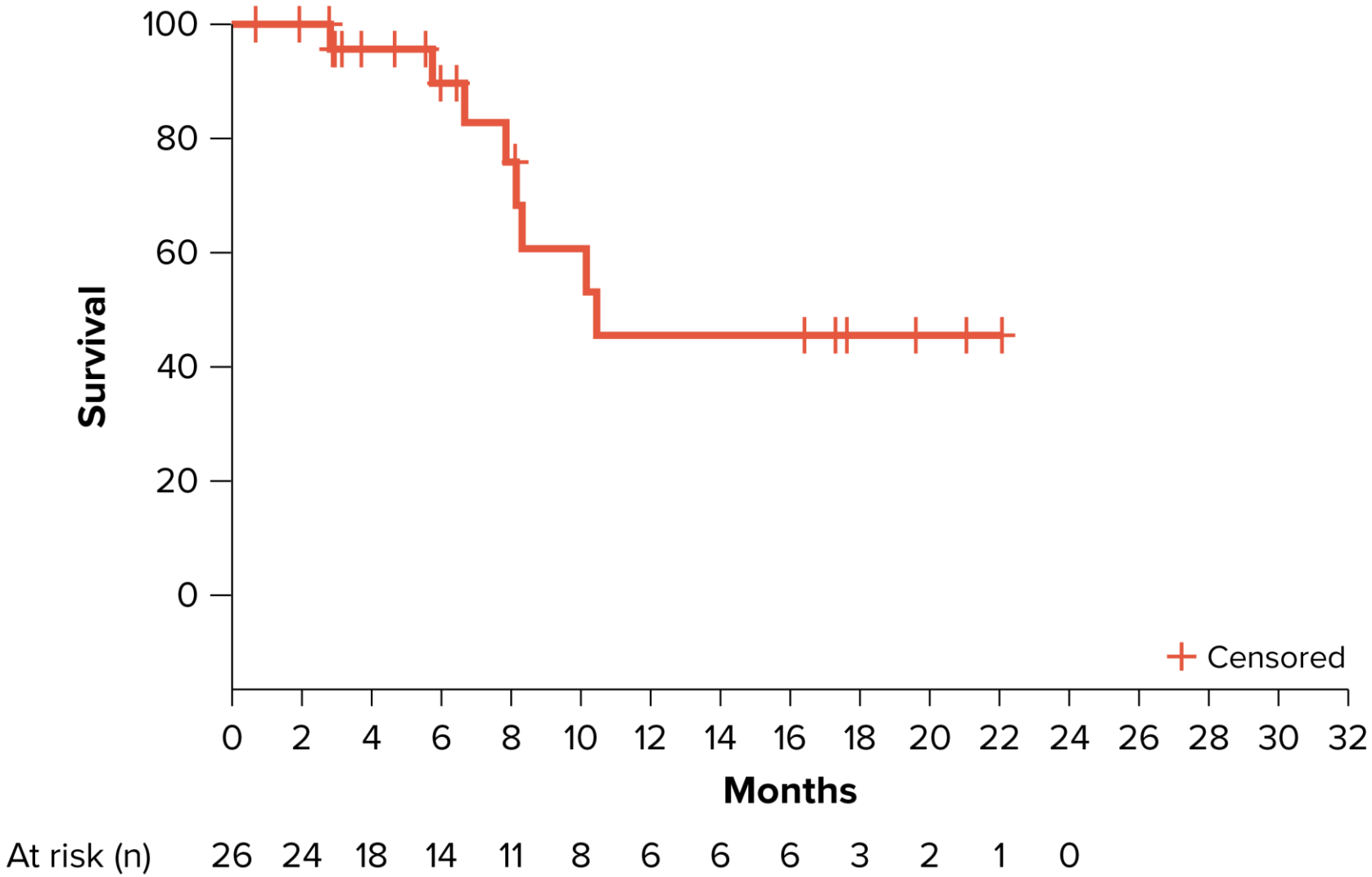
Best Responses

Response	Indolent (FL, MZL) n = 26	Aggressive (DLBCL, MCL) n = 58	Total N = 84
Median efficacy follow-up, mo (range)	7.5 (1.9-22.3)	5.6 (0.1-31.9)	6.9 (0.1-31.9)
Best Response, n (%)			
ORR	**14 (53.8)**	**36 (62.1)**	**50 (59.5)**
CR	3 (11.5)	12 (20.7)	15 (17.9)
PR	11 (42.3)	24 (41.4)	35 (41.7)
SD	9 (34.6)	5 (8.6)	14 (16.7)
PD	1 (3.8)	14 (24.1)	15 (17.9)
NE*	2 (7.7)	3 (5.2)	5 (6.0)

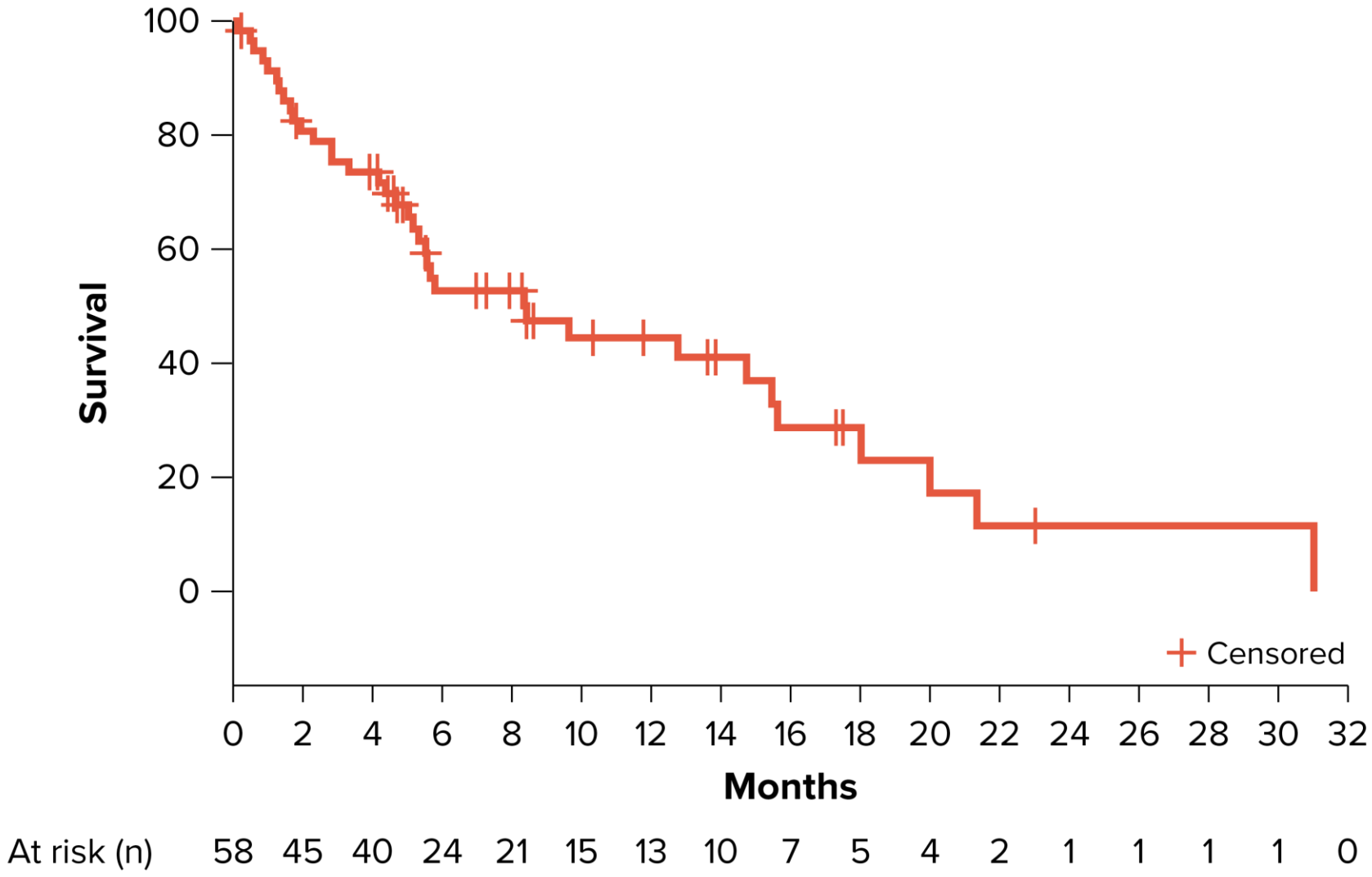
CR, complete response; NE, not evaluable; ORR, overall response rate; PD, progressive disease; PR, partial response; PR-L, partial response with lymphocytosis; SD, stable disease.

* Patient discontinued for reason other than PD before 1st response assessment, or response assessment was NE, or scheduled response assessment was not done

Indolent Lymphoma (FL, MZL): Progression-Free Survival



Aggressive Lymphoma (DLBCL, MCL): Progression-Free Survival



Progression-Free Survival