Valemetostat

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Conflicts Of Interest

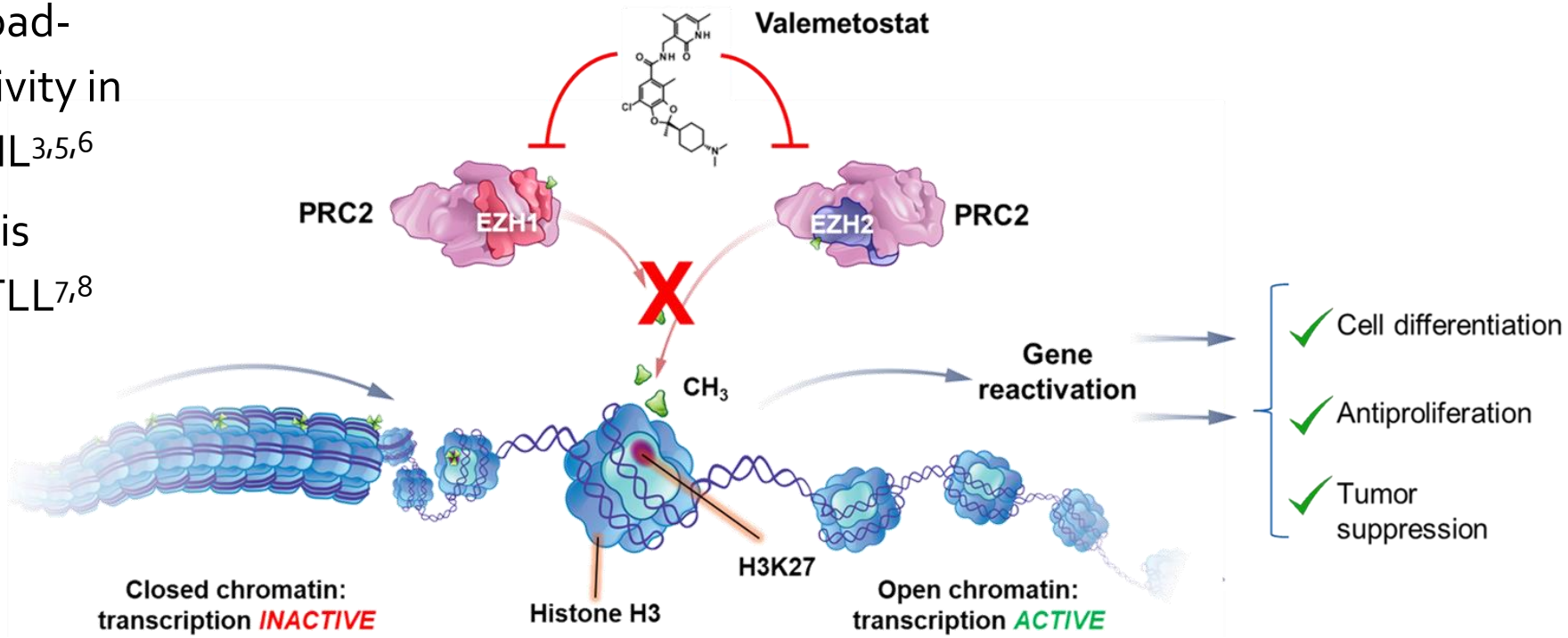
In the past 12 months, I have the following relationships:

Consulting:
Abcuro, Inc., Corvus, Daiichi Sankyo, Kyowa Hakko Kirin, March, ONO Pharmaceuticals, Seattle Genetics, SecuraBio, Takeda, and Yingli Pharma Limited.

Research support: Affimed, C4 Therapeutics, Daiichi Sankyo, Kyowa Hakko Kirin,Takeda, Seattle Genetics, Trillium Therapeutics, and SecuraBio

Valemetostat

- EZH2 and EZH1 catalyze the trimethylation of histone H3 at lysine 27 (H3K27me3), leading to transcriptional repression[1,2]
- Valemetostat tosylate (valemetostat) is a novel, potent, and selective dual inhibitor of EZH2 and EZH1 that suppresses aberrant H3K27me3, thereby promoting antitumorigenic processes[2-4]
    - Valemetostat shows broad-spectrum antitumor activity in preclinical models of NHL[3,5,6]
- Valemetostat monotherapy is approved in Japan for R/R ATLL[7,8]



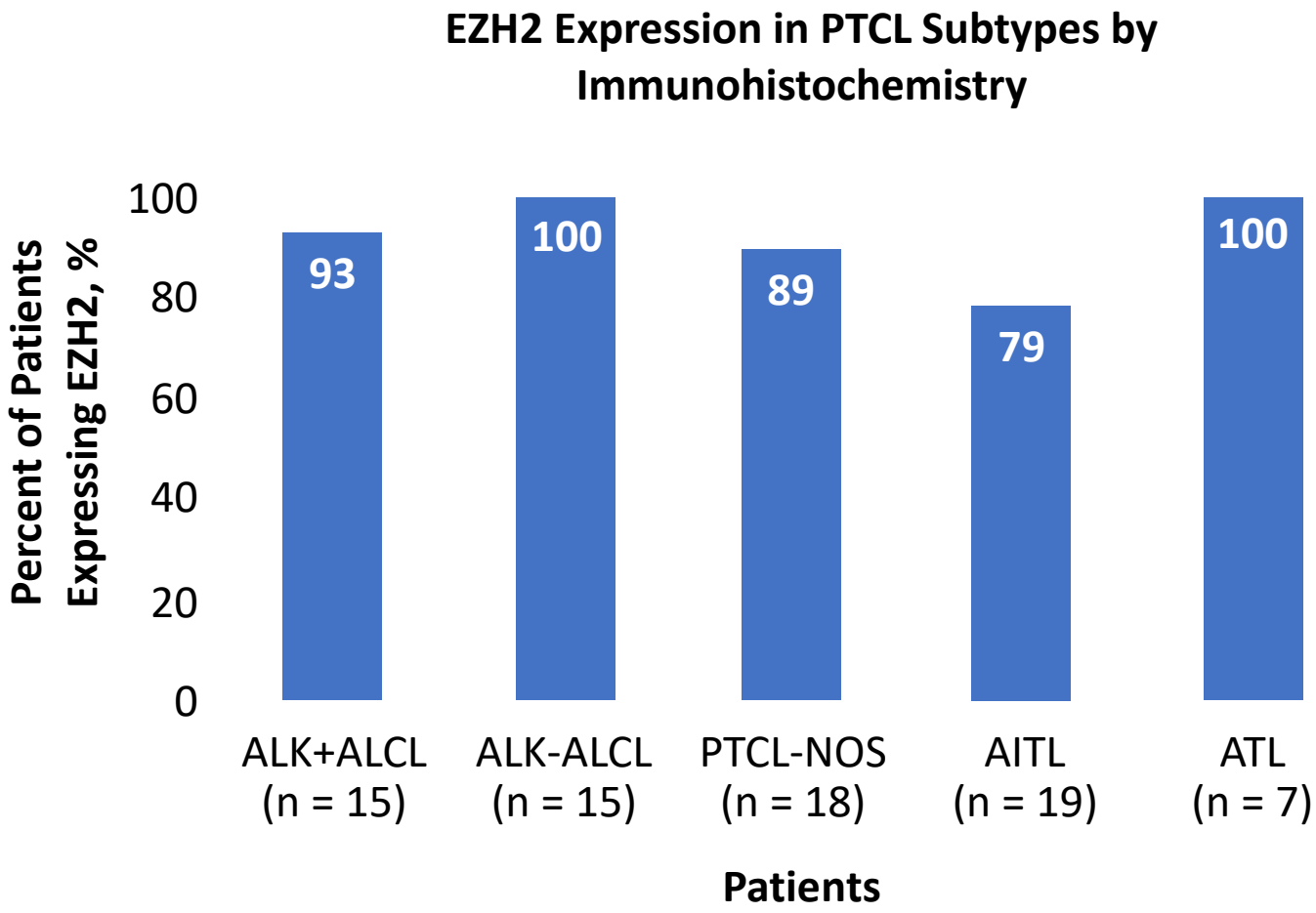
- 1. Herviou L, et al. *Oncotarget* 2016;7:2284–2296. 2. Nakagawa M, Kitabayashi I. *Cancer Sci* 2018;109:2342–2348. 3. Yamagishi M, et al. *Cell Rep* 2019;29:2321–2337e7. 4. Fujikawa D, et al. *Blood* 2016;127:1790–1802. 5. Hama Y, et al. *Blood* 2019;134(Suppl 1):4642. 6. Honma D, et al. *Cancer Sci* 2017;108:2069–2078. 7. Izutsu K, et al. *Blood* 2023;141:1159–1168. 8. EZHARMIA® (valemetostat tosilate). [package insert]. Tokyo, Japan: Daiichi Sankyo; 2022.

Valemetostat

- PTCL-cell lymphoma
  - Phase 1
  - Phase 2
- ATL
- BCL

Variation in EZH2 Expression Across PTCL Subtypes

- EZH2 is overexpressed in PTCL
- Expression of EZH2 correlates with a high tumor proliferation rate
- Can be associated with more aggressive disease and poor prognosis
- Gain of function mutations in TCL rare



Shi. Leukemia & Lymphoma. 2015;56:2087. Zhang. Oncol Letters. 2019;18:1415.

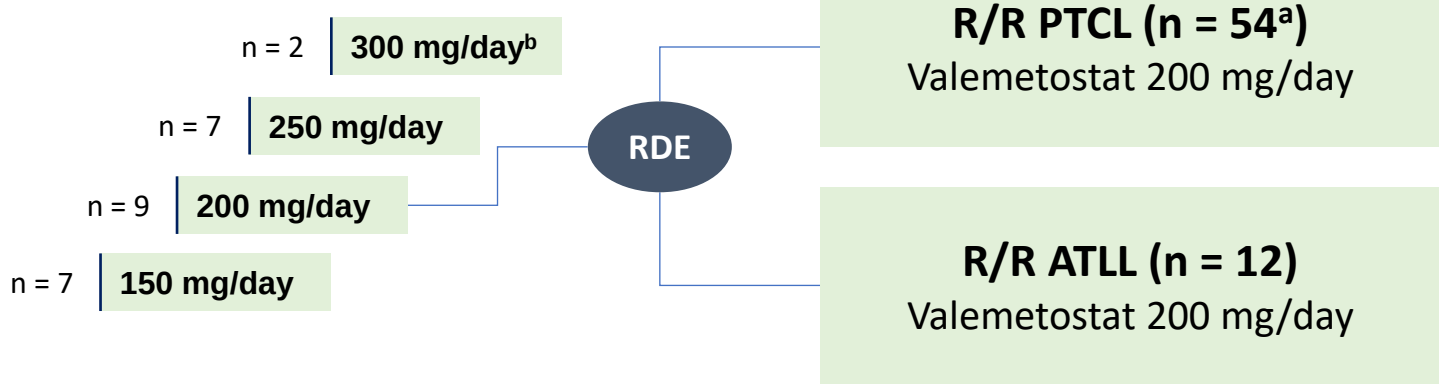
DS3201-A-J101: Multicenter, single-arm, phase 1 dose-escalation and expansion trial of valemetostat in R/R B- or T-NHLs

Key inclusion criteria

- T- or B-cell NHL
- R/R to ≥ 1 prior line of therapy
- Age ≥ 20 (Japan) or ≥ 18 (US) y
- ECOG PS score 0 or 1

Part 1:
Dose escalation (N = 25)
B-NHL (n = 19) & T-NHL (n = 6)

R/R NHL (all-comers)



Part 2:
Dose expansion (N = 66[a])
T-NHL: PTCL and ATLL

R/R PTCL (n = 54[a])
Valemetostat 200 mg/day

R/R ATLL (n = 12)
Valemetostat 200 mg/day

Primary endpoints: Safety (including DLTs, TEAEs), RP2D, PK parameters

Secondary endpoints: MTD, efficacy

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Characteristic	Total (n = 71)	PTCL (n = 57)	ATLL (n = 14)
Age, years, median (range)	68 (26–83)	68 (26–83)	66.5 (37–78)
Sex, n (%)			
Male	43 (61)	35 (61)	8 (57)
Female	28 (39)	22 (39)	6 (43)
Country of enrollment, n (%)			
Japan	27 (38)	18 (32)	9 (64)
US	44 (62)	39 (68)	5 (36)
ECOG PS score, n (%)			
0	29 (41)	21 (37)	8 (57)
1	41 (58)	36 (63)	5 (36)
≥ 2	1 (1)[a]	0	1 (7)[a]

Characteristic	Total (n = 71)	PTCL (n = 57)	ATLL (n = 14)
T-NHL type, n (%)			
PTCL	57 (80)	57 (100)	0
ALCL[b]	2 (3)	2 (4)	0
AITL	23 (32)	23 (40)	0
PTCL, NOS	26 (37)	26 (46)	0
Other T-cell lymphoma[c]	6 (8)	6 (11)	0
ATLL	14 (20)	0	14 (100)
Acute	7 (10)	0	7 (50)
Lymphomatous	7 (10)	0	7 (50)
Prior lines of therapy, median (range)	2 (1–8)	2 (1–8)	2.5 (1–8)
Prior HCT, n (%)	18 (25)	16 (28)	2 (14)
Allogeneic	4 (6)	2 (4)	2 (14)
Autologous	14 (20)	14 (25)	0

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Clinical response

Response	PTCL (n = 55[a,b])	PTCL subtype		ATLL[c] (n = 14)
		AITL (n = 22)	PTCL, NOS (n = 26)	
Best overall response, n (%)				
CR[d]	17 (31)	10 (45)	7 (27)	4 (29)
PR	13 (24)	4 (18)	6 (23)	5 (36)
SD	4 (7)	1 (5)	3 (12)	1 (7)
PD	15 (27)	5 (23)	8 (31)	3 (21)
NE	1 (2)	1 (5)	0	0
ND	5 (9)	1 (5)	2 (8)	1 (7)
ORR,[e] % (n/N)	**55 (30/55)**	**64 (14/22)**	**50 (13/26)**	**64 (9/14)**
[95% CI][f]	[40.6, 68.0]	[40.7, 82.8]	[29.9, 70.1]	[35.1, 87.2]

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TRAEs leading to dose modifications

- Dose interruption in ≥ 2 patients: CMV infection (3 patients), dysgeusia (3), platelet count decreased (3), pneumonitis (2), neutrophil count decreased (2)
- Dose reduction: platelet count decreased (2 patients), anemia (1), colitis (1), diarrhea (1)
- Treatment discontinuation in PTCL: AML (1 patient) , MDS (1), colitis (1), acute kidney injury (1)
  - One patient in the B-NHL cohort receiving valemetostat 150 mg/day had *Pneumocystis jirovecii* pneumonia that led to treatment discontinuation

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VALENTINE-PTCL01: global, multicenter, open-label, single-arm, phase 2 trial of valemetostat in R/R PTCLs

Eligibility Criteria

- ≥ 18 years
- Confirmed PTCL diagnosis (WHO 2016 classification[1])
- ECOG PS score ≤ 2
- ≥ 1 prior line of systemic therapy
  - Patients with ALCL received prior brentuximab vedotin treatment

R/R PTCL
N = 133
N = 119 with PTCL histology confirmed by central pathology

Valemetostat
200 mg/day
Continuous 28-day cycles until PD or unacceptable toxicity

Primary endpoint: ORR (CT-based BICR assessment; ≥ 10 months follow-up[b])

Key secondary endpoints: DOR, DOCR, CR rate, PR rate, PFS (CT-based BICR assessment and investigator assessment), OS, safety and tolerability

Key exploratory endpoint: PET-CT–based clinical response (BICR)

Lugano 2014 response criteria[2]

Baseline Demographics and Disease Characteristics

Characteristic	PTCL (N = 133)
Median age, years (range)	69.0 (22–85)
Sex, n (%)	
Male	91 (68.4)
Female	42 (31.6)
ECOG PS score, n (%)	
0	58 (43.6)
1	65 (48.9)
2	9 (6.8)
3	1 (0.8)
Median prior lines of therapy (range)	2.0 (1–12)
1	36 (27.1)
2	36 (27.1)
3	29 (21.8)
≥ 4	32 (24.1)
Prior HCT, n (%)	35 (26.3)
Autologous	32 (24.1)
Allogeneic	5 (3.8)

PTCL subtypes, n (%) (WHO 2016 classification; central review)	PTCL (N = 133)
TFH phenotype	
AITL	42 (31.6)
Nodal PTCL with TFH phenotype	8 (6.0)
FTL	3 (2.3)
PTCL-NOS	41 (30.8)
ALCL	
ALK^+	7 (5.3)
ALK^-	2 (1.5)
MEITL	1 (0.8)
$CD8^+$ PCAECTCL	1 (0.8)
PCGTL	1 (0.8)
Other TCL[a]	13 (9.8)
Non-TCL or undetermined[b]	6 (4.5)
Missing[c]	8 (6.0)

Efficacy analysis set

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Clinical Response (BICR Assessment)

CT–based assessment

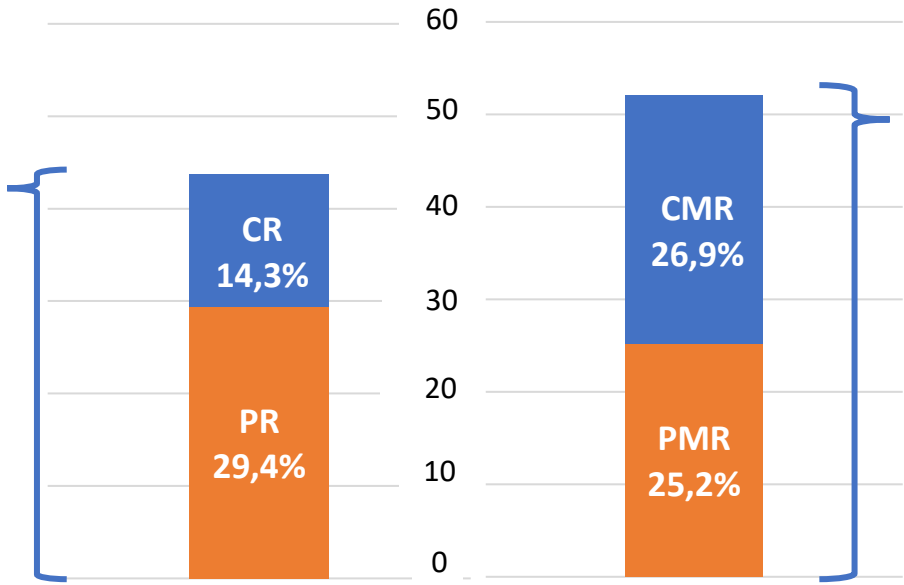
(Primary endpoint)

ORR was **43.7**%
(n = 52; 95% CI, 34.6–53.1)

17 patients **(14.3%)** achieved a **CR**

35 patients **(29.4%)** achieved a **PR**

Efficacy-evaluable population (N = 119)



PET-CT–based assessment

(Exploratory endpoint)

ORR was **52.1%**
(n = 62; 95% CI, 42.8–61.3)

32 patients **(26.9%)** achieved a **CMR**

30 patients **(25.2%)** achieved a **PMR**

- Ten (8.4%) patients treated with valemetostat proceeded to allo-HCT, including 8 patients (6.7%) with a CR[a] and 2 patients with an unknown response
  - The median time from first dose of valemetostat to subsequent allo-HCT was 6.9 months

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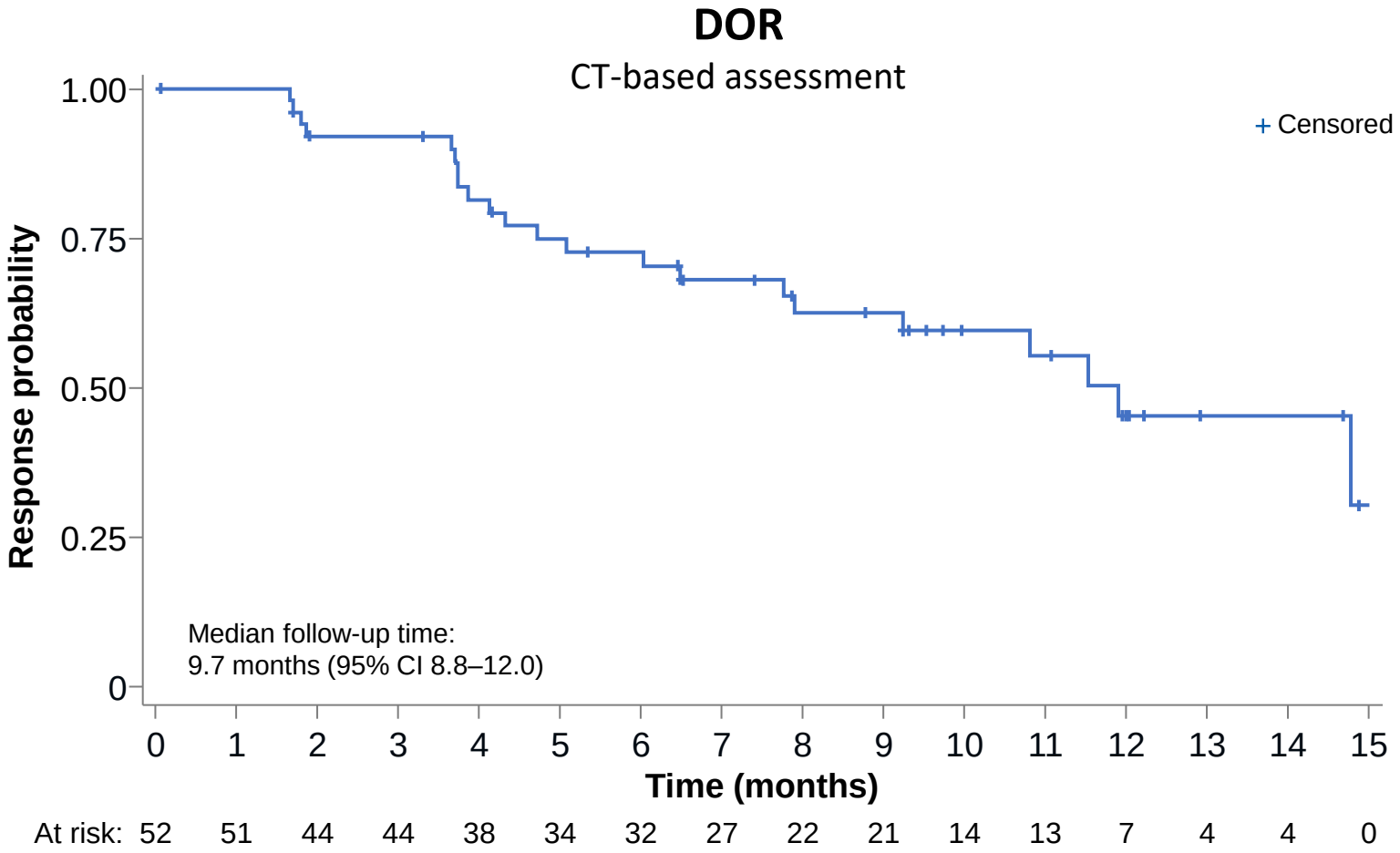
Duration of Response (CT-Based BICR Assessment)

- Median **TTR** was **8.1 weeks** (range, 5–37) and median **DOR** was **11.9 months** (95% CI, 7.8 months to NE)



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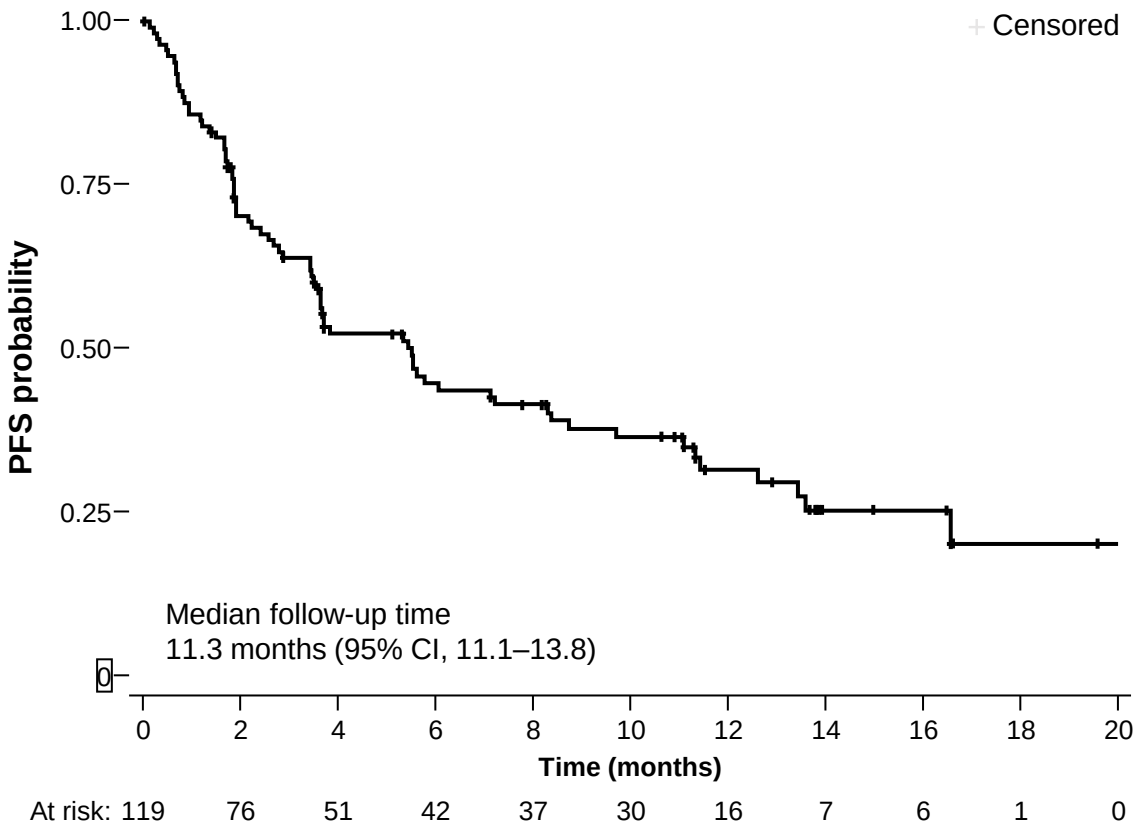
Progression-Free Survival and Overall Survival

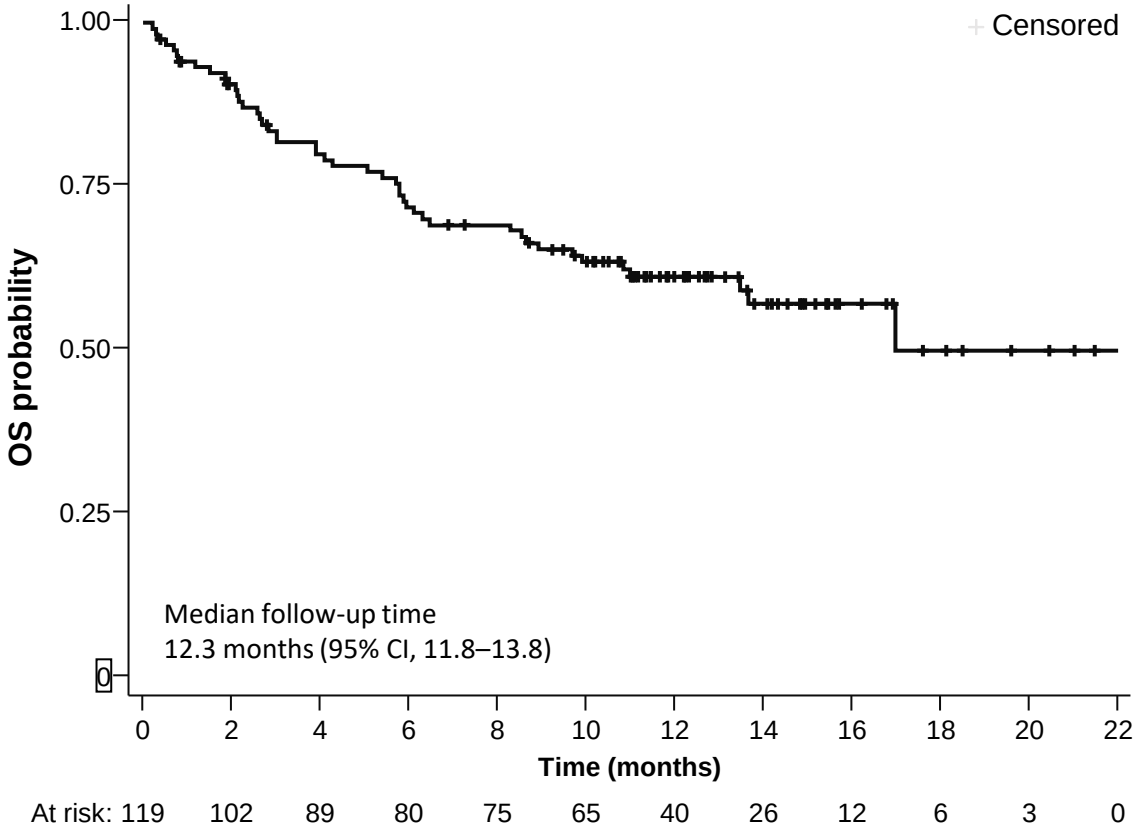
PFS[a]

Median 5.5 months (95% CI, 3.5–8.3)
(N = 119)



OS

Median 17 months (95% CI, 13.5 months to NE)
(N = 119)



Data cutoff: May 5, 2023.

[a] PFS evaluated by BICR CT-based assessment.

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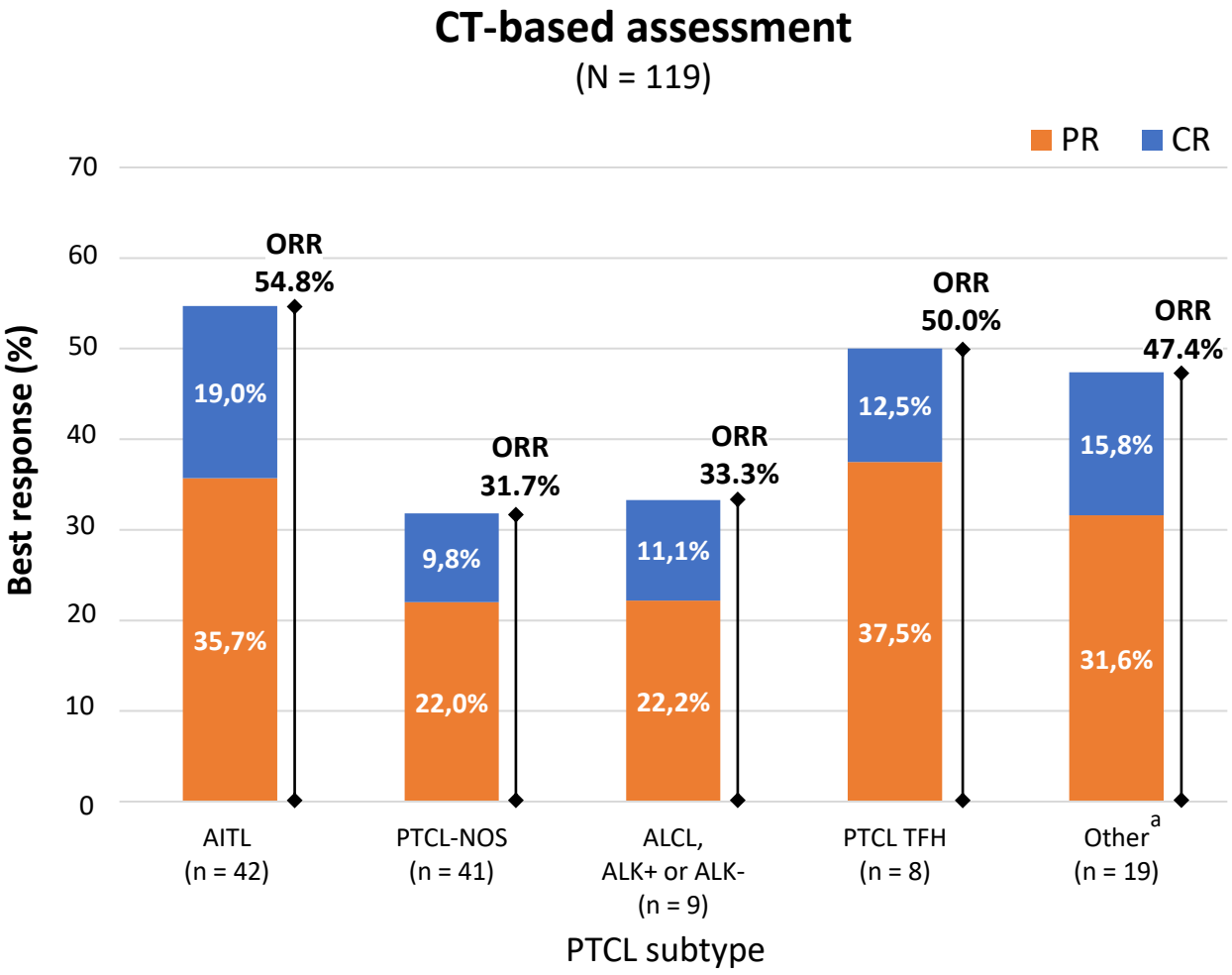
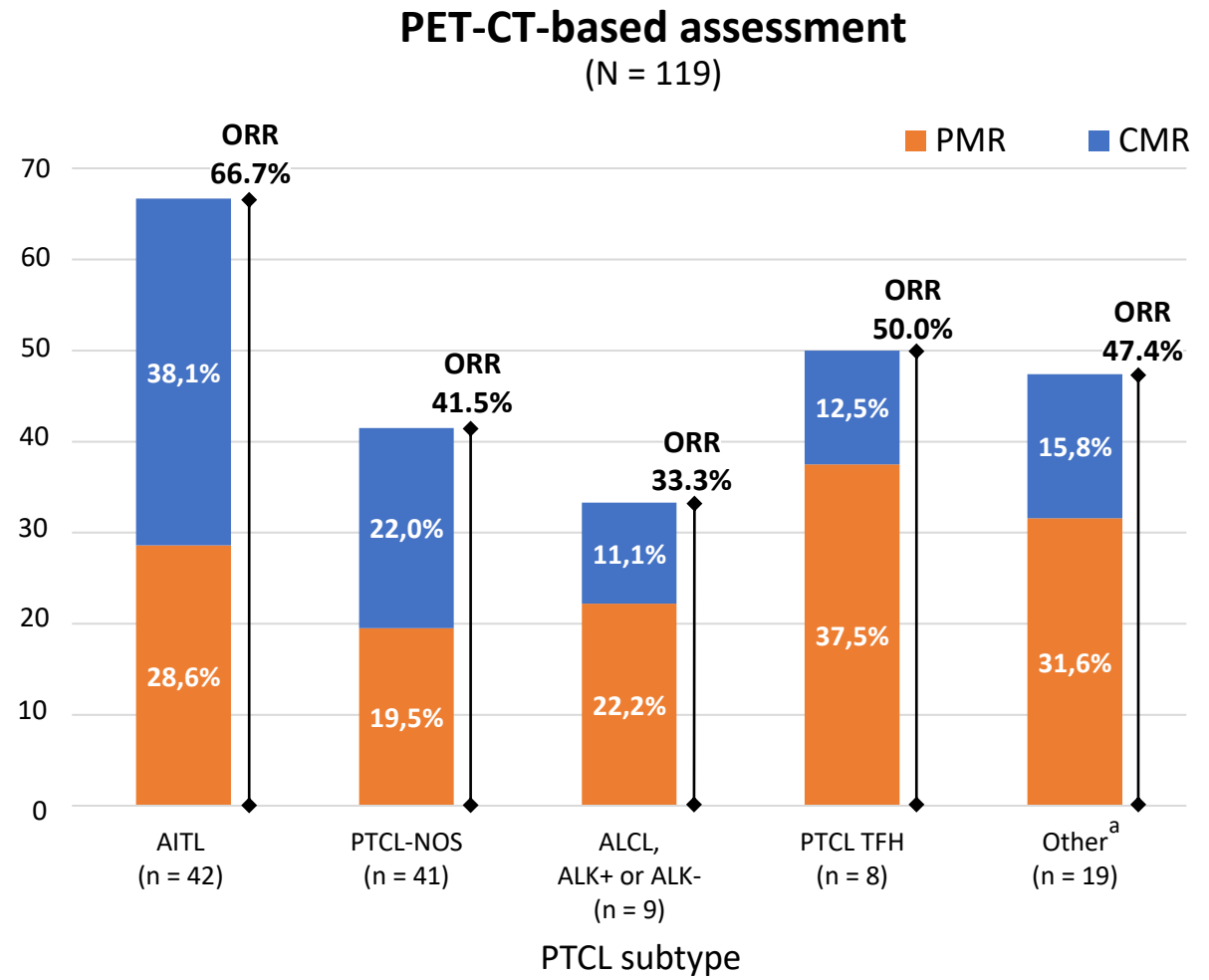
Responses were observed across all PTCL subtypes





Data cutoff: May 5, 2023.

[a] Other TCLs include 3 patients with FTL, 1 with PCGTL, 1 with CD8+ PCAECTCL, 1 with MEITL, and 13 with other eligible, but undetermined PTCL subtypes.

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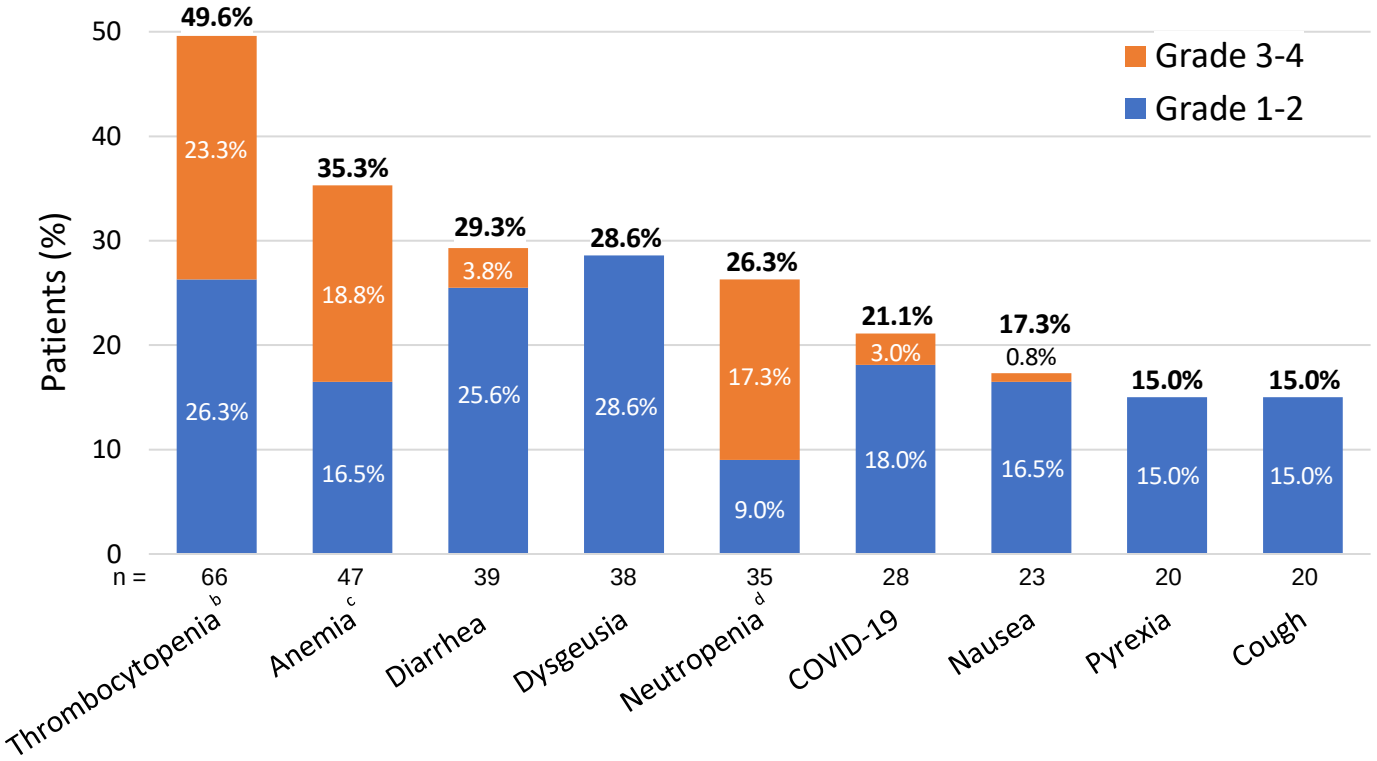
Common TEAEs (Occurring in ≥ 15% of Patients) and Dose Modifications

- Cytopenias were common, and were manageable with dose modifications and/or supportive therapies such as transfusions and G-CSF
  - Thrombocytopenia was the most frequent any grade (49.6%) and grade ≥ 3 (23.3%) TEAE
  - The median time to first onset of platelet count < 50×10^9/L was 18 days from the first dose and the median time to recovery was 12 days
- 2 patients developed secondary AML and discontinued treatment



TEAEs leading to dose modifications[a] (N = 133)

Preferred term	Treatment discontinuation %	Dose reduction %	Dose interruption %
Any TEAE	**9.8**	**15.8**	**49.6**
Thrombocyt[b]	2.3	5.3	16.5
Anemia[c]	0	3.8	9.8
COVID-19	0	1.5	8.3
Neutropenia[d]	0	2.3	5.3

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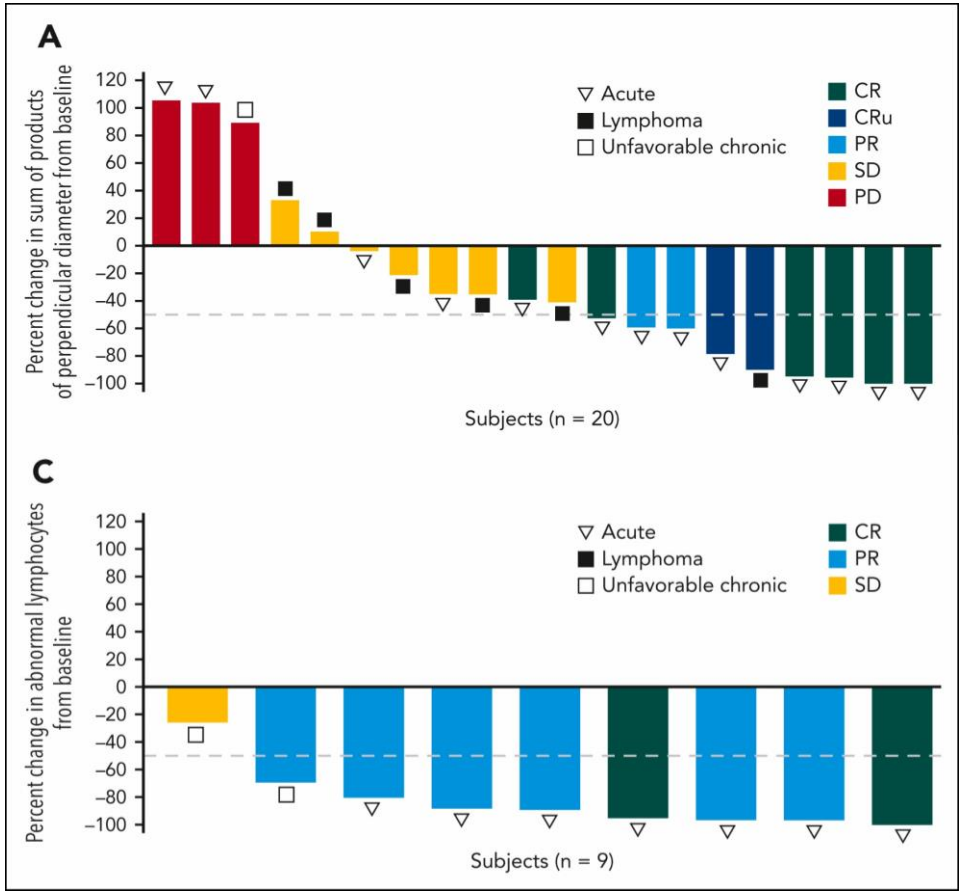
An open-label, single-arm phase 2 trial of valemetostat for relapsed or refractory adult T-cell leukemia/lymphoma

Population	N	ORR, n (%)	CR, n (%)	CRu, n (%)	PR, n (%)
All patients	**25**	**12 (48.0)**	**5 (20.0)**	**0**	**7 (28.0)**
ATL subtype					
Acute	16	10 (62.5)	5 (31.3)	0	5 (31.3)
Lymphoma	6	1 (16.7)	0	0	1 (16.7)
Unfavorable chronic	3	1 (33.3)	0	0	1 (33.3)



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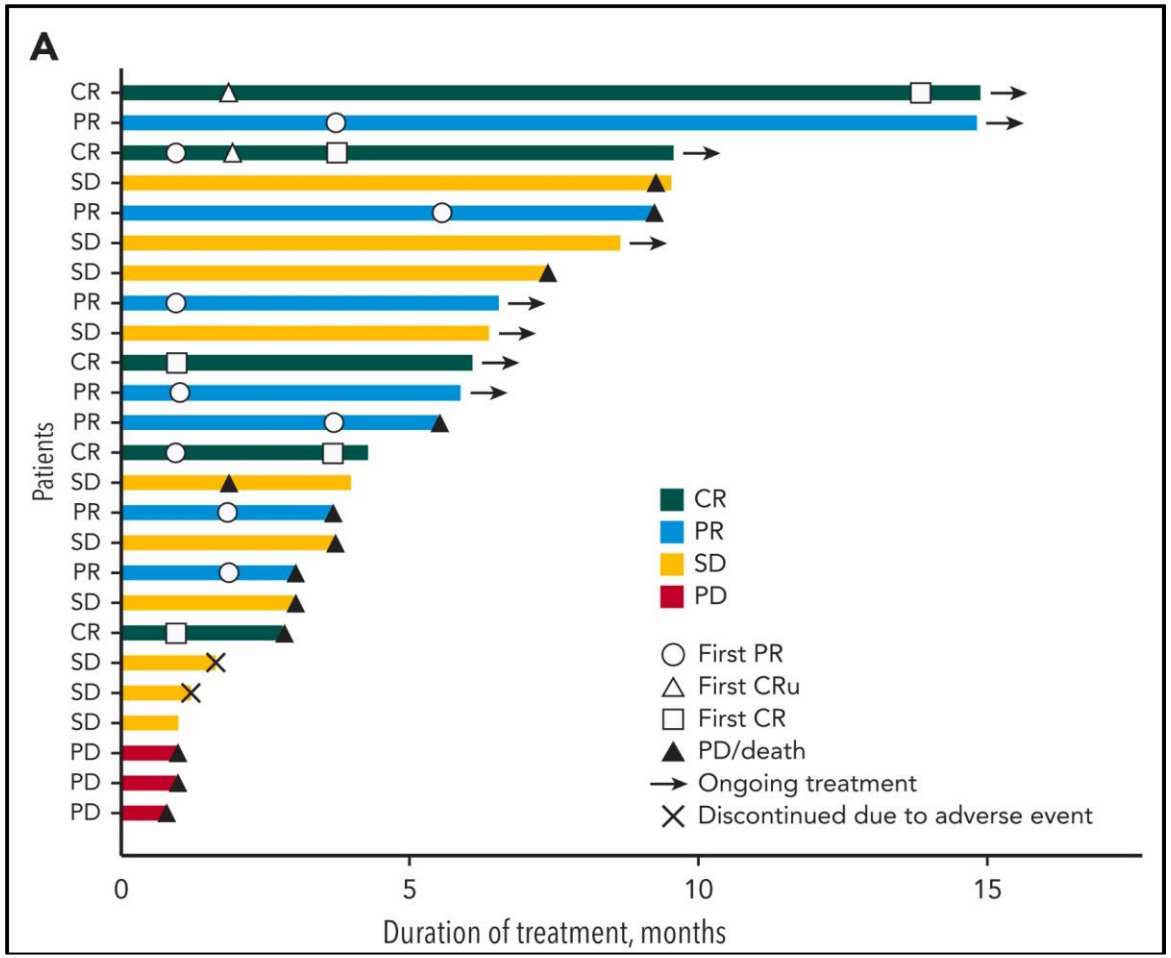
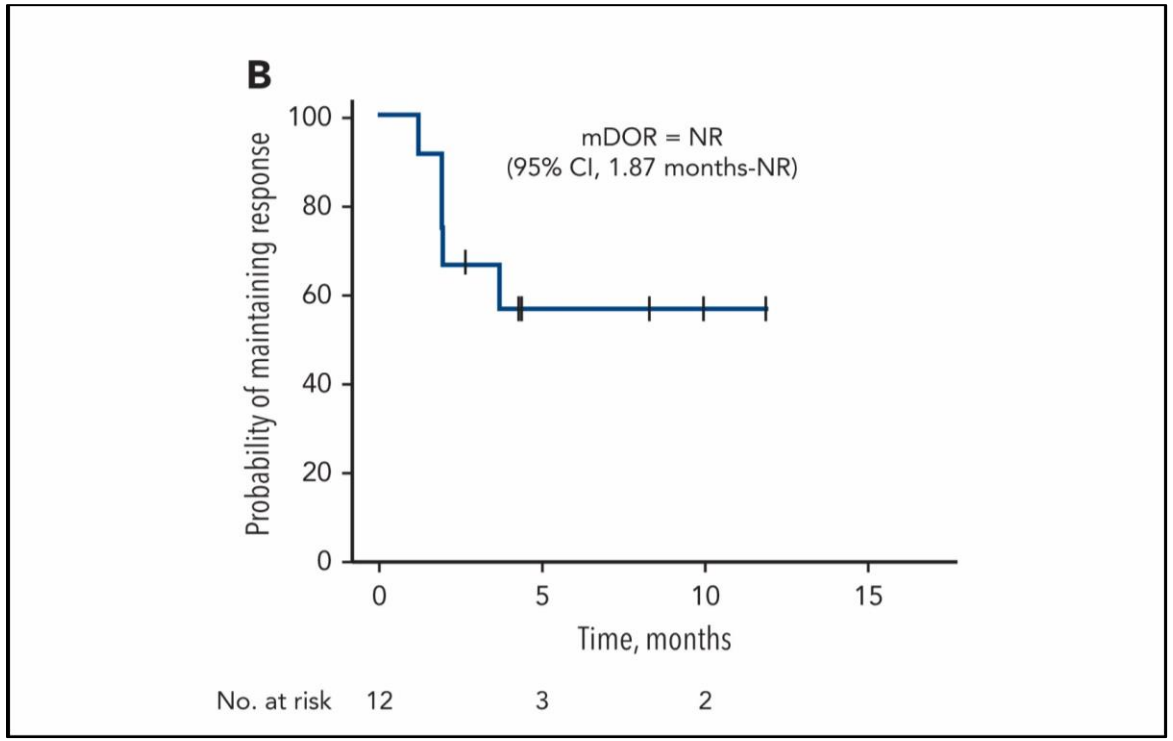




Izutsu, K et al. , Blood, 2023.

Results: Clinical responses in patients with R/R B-NHLs

- The ORR in patients with R/R B-NHL was 47% (9/19; 95% confidence interval [CI], 24.4–71.1)
  - Clinical responses
  - DLBCL. 3/7 patients; CR 1
  - FL 4/7 patients; CR 1

Response	All B-NHL (N = 19)
Best overall response, n (%)	
CR	2 (11)
PR	7 (37)
SD	8 (42)
PD	2 (11)
ORR,[a] % (n/N)	**47 (9/19)**
[95% CI][b]	[24.4, 71.1]
DOR,[c] median, months	18.4
[95% CI][b]	[5.3, NR]
Follow-up time,[d] median, months	49.2
[95% CI][e]	[0.03, 64.0]

Izutsu K, et al. ASH 2023. 1731

Conclusions

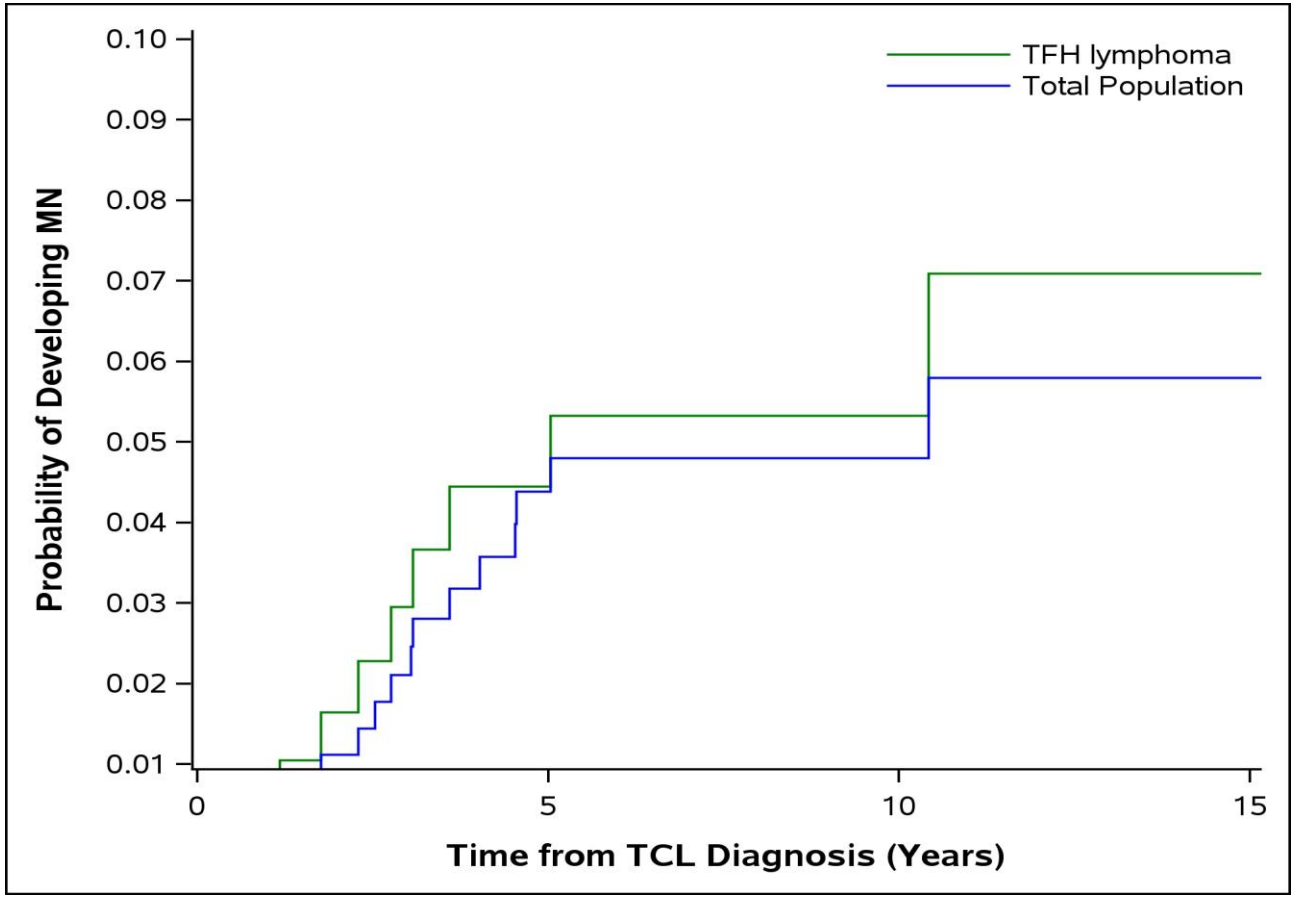
- Valemetostat demonstrated a high response rate and durable responses in patients with R/R PTCL and ATLL, who have limited treatment options
  - Responses were observed across all PTCL subtypes
  - In PTCL 10 (8.4%) patients treated with valemetostat proceeded to allo-HCT
  - Approved for R/R ATLL in Japan
  - Small dataset in BCL
- Valemetostat demonstrated an acceptable safety profile in patients with R/R PTCL
  - The most common any grade/grade ≥ 3 TEAEs were cytopenias, and most TEAEs were manageable with patients rarely discontinuing treatment
- The VALENTINE-PTCL01 study demonstrated that valemetostat monotherapy is tolerable, and provides a clinically meaningful benefit for patients with R/R PTCL

Cumulative Incidence of Myeloid Neoplasms in Patients with T-cell Lymphomas

Years since lymphoma diagnosis	Total Population (PTCL-NOS + TFH)	TFH Lymphoma
2	0.0112 (0.0042-0.0298)	0.0164 (0.00531-0.0508)
5	0.0439 (0.0256-0.0751)	0.0445 (0.0213-0.0927)
10	0.0480 (0.0286-0.0806)	0.0533 (0.0267-0.1061)
15	0.0580 (0.0337-0.0997)	0.0709 (0.0350-0.1437)

* TFH lymphoma includes:
- AITL
- Nodal TFH, NOS
- Nodal TFH, follicular type

CI of MN in pts. with TCL (PTCL-NOS/TFH lymphoma).



Stuver, R et al ASH 2023