Efficacy and Safety of Valemetostat Monotherapy in Patients With Relapsed or Refractory Peripheral T-Cell Lymphomas: Primary Results of the Phase 2 VALENTINE-PTCL01 Study

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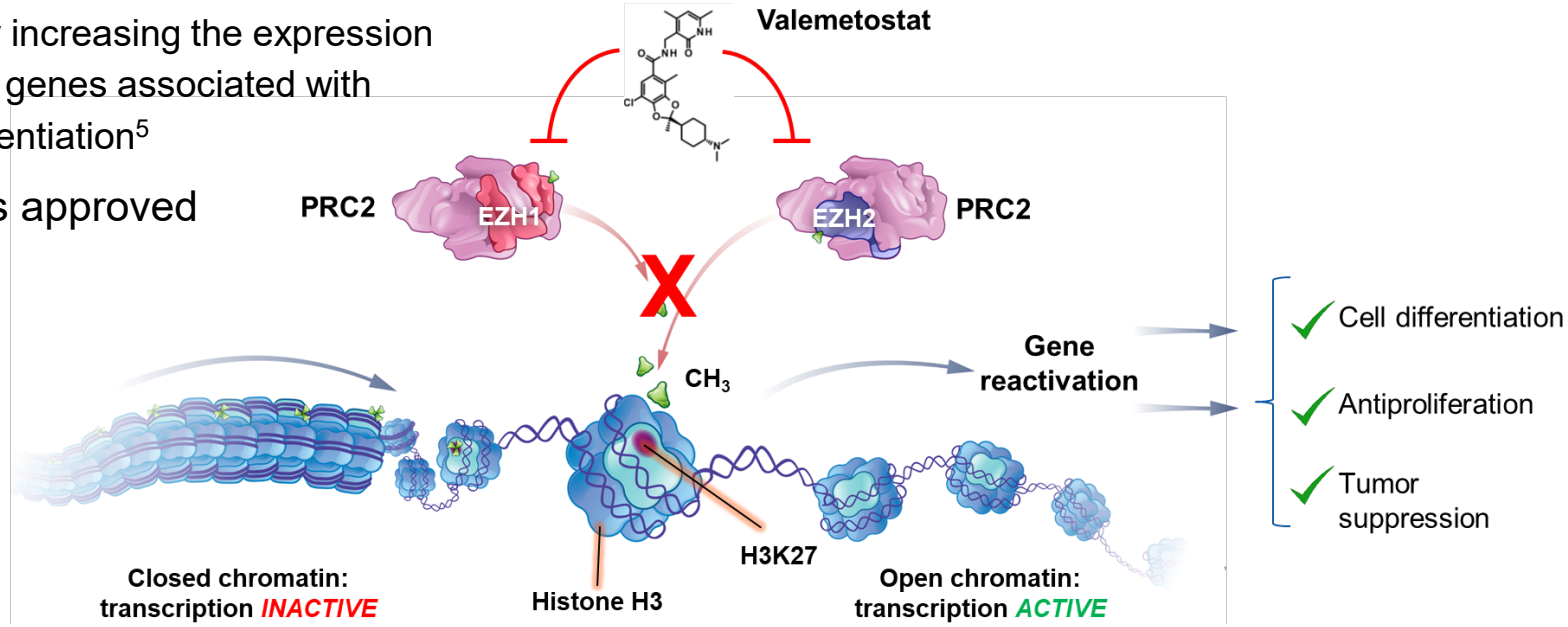
Abstract #302

PTCL and Valemetostat: Background

- PTCLs account for approximately 10% of NHLs in Western countries and approximately 20% of lymphomas in Eastern Asia[1,2]
- Patients with PTCL often have a poor prognosis, with unfavorable OS and PFS[3]
- EZH2 overexpression drives the development and progression of many types of cancer, including PTCL[4]
  - *EZH2* mutations are rare in PTCL
- Valemetostat tosylate is a novel, potent, and selective dual inhibitor of EZH2 and EZH1
  - Valemetostat prevents H3K27me3, thereby increasing the expression of genes silenced by H3K27me3, including genes associated with the regulation of cell proliferation and differentiation[5]
- Valemetostat monotherapy (200 mg/day) is approved in Japan for R/R ATLL[6,7]



ATLL, adult T-cell leukemia/lymphoma; EZH, enhancer of zeste homolog; H3K27me3, tri-methylation of lysine 27 on histone H3 protein; NHL, non-Hodgkin lymphoma; OS, overall survival; PFS, progression-free survival; PRC2, polycomb repressive complex 2; PTCL, peripheral T-cell lymphoma; R/R, relapsed/refractory.

1. Vose J, et al. *J Clin Oncol* 2008;26:4124–4130. 2. Ling L, et al. *Br J Haematol* 2017;178:772–780. 3. Sibon D, et al. *Cancers* 2022;14:2332. 4. Herviou L, et al. *Oncotarget* 2016;7:2284–2296. 5. Yamagishi M, et al. *Cell Rep* 2019;29:2321–2337.e7. 6. EZHARMIA® (valemetostat tosilate). [package insert]. Tokyo, Japan: Daiichi Sankyo; 2022. 7. Izutsu K, et al. *Blood* 2023;141:1159–1168.

Study Design

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

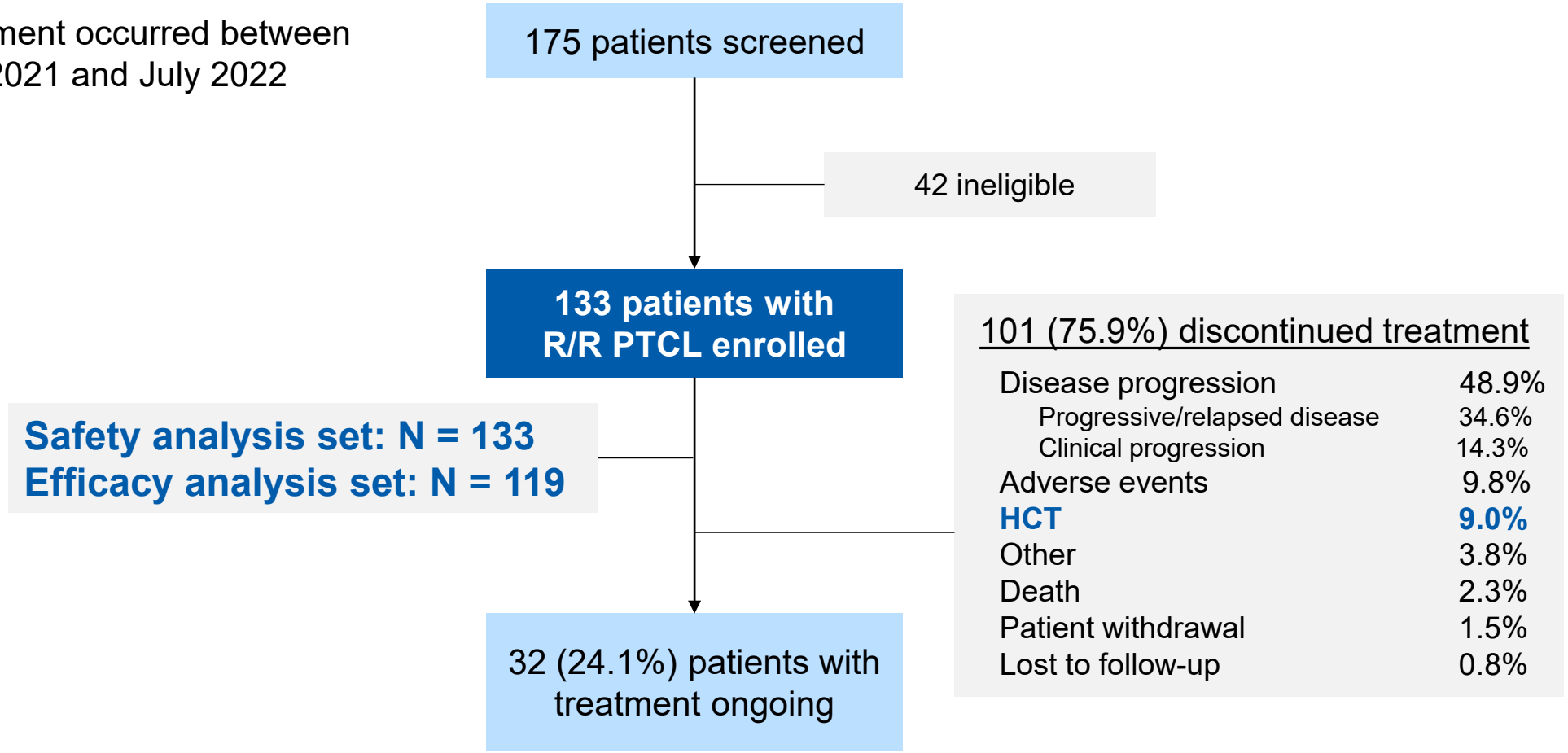
Key exploratory endpoint: PET-CT–based clinical response (BICR)

Lugano 2014 response criteria[2]

[a] PTCL subtypes included AITL, FTL, PTCL-TFH, PTCL-NOS, ALCL ($ALK^{+/-}$), EATL, MEITL, HSTL, PCGTL, or $CD8^+$ PCAECyTCL; subtypes were determined prior to the initiation of study drug according to 2016 WHO classification.
[b] Primary analysis was planned at least 10 months after the first dose of the last enrolled patient.
AITL, angioimmunoblastic T-cell lymphoma; ALCL, anaplastic large cell lymphoma; ALK, anaplastic lymphoma kinase; BICR, blinded independent central review; CD, cluster of differentiation; $CD8^+$ PCAECTCL, primary cutaneous $CD8^+$ aggressive epidermotropic cytotoxic T-cell lymphoma; CR, complete response; CT, computed tomography; DOCR, duration of complete response; DOR, duration of response; EATL, enteropathy-associated T-cell lymphoma; ECOG, Eastern Cooperative Oncology Group; FTL, follicular T-cell lymphoma; HSTL, hepatosplenic T-cell lymphoma; MEITL, monomorphic epitheliotropic intestinal T-cell lymphoma; NOS, not otherwise specified; ORR, objective response rate; PCGTL, primary cutaneous gamma delta T-cell lymphoma; PD, progressive disease; PET, positron emission tomography; PR, partial response; PS, performance status; TCL, T-cell lymphoma; TFH, T follicular helper; WHO, World Health Organization.1. Swerdlow SH, et al. *Blood* 2016;127:2375–2390. *2.* Cheson BD, et al. *J Clin Oncol* 2014;32:3059–3068.

Enrollment and Disposition

- Enrollment occurred between June 2021 and July 2022



- Primary data cutoff occurred 10 months after first dose of the last enrolled patient
- Median (range) valemetostat treatment duration at data cutoff: 18.0 weeks (0.3–93.4)

Data cutoff: May 5, 2023.
HCT, hematopoietic cell transplantation.

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

Data cutoff: May 5, 2023.
[a] Includes patients with eligible but undetermined subtypes.
[b] Includes patients with undetermined eligibility due to the limited sample tumor tissue.
[c] Includes patients with either no sample or a sample insufficient for review.

Clinical Response (BICR Assessment)

CT–based assessment

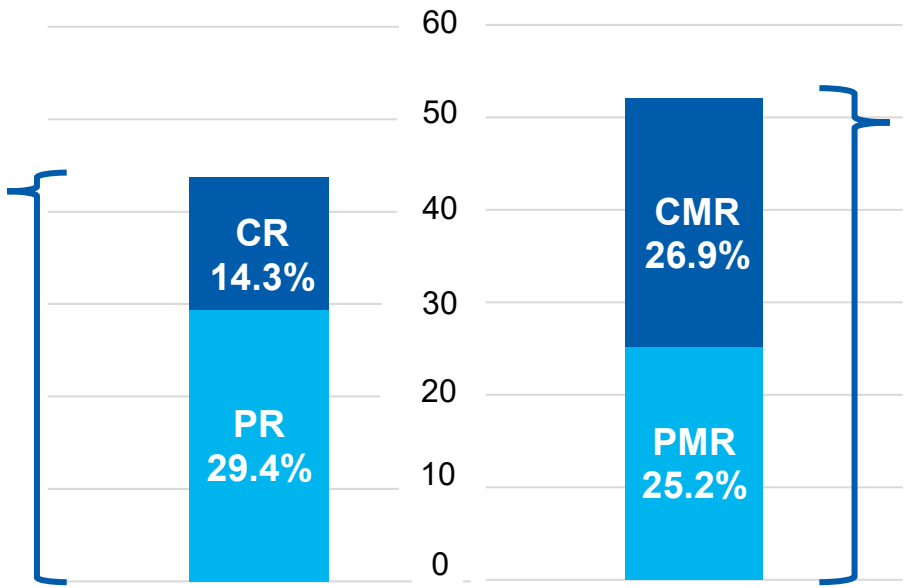
(Primary endpoint)

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**

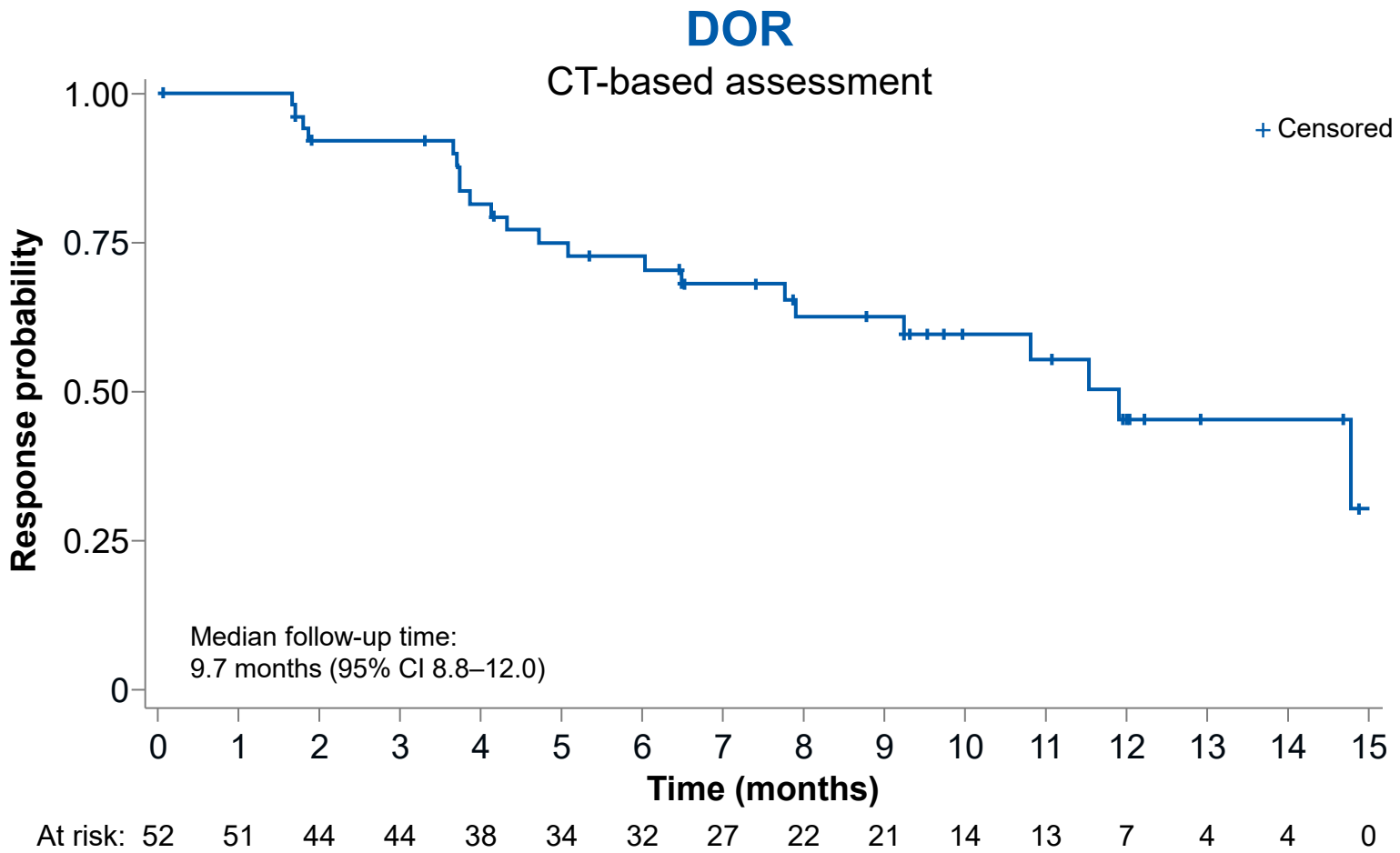
30 patients **(25.2%)** achieved a **PMR**

- 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

Data cutoff: May 5, 2023.
[a] Responses evaluated by investigator assessment.
allo-HCT, allogeneic HCT; CI, confidence interval; CMR, complete metabolic response; PMR, partial metabolic response.

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)

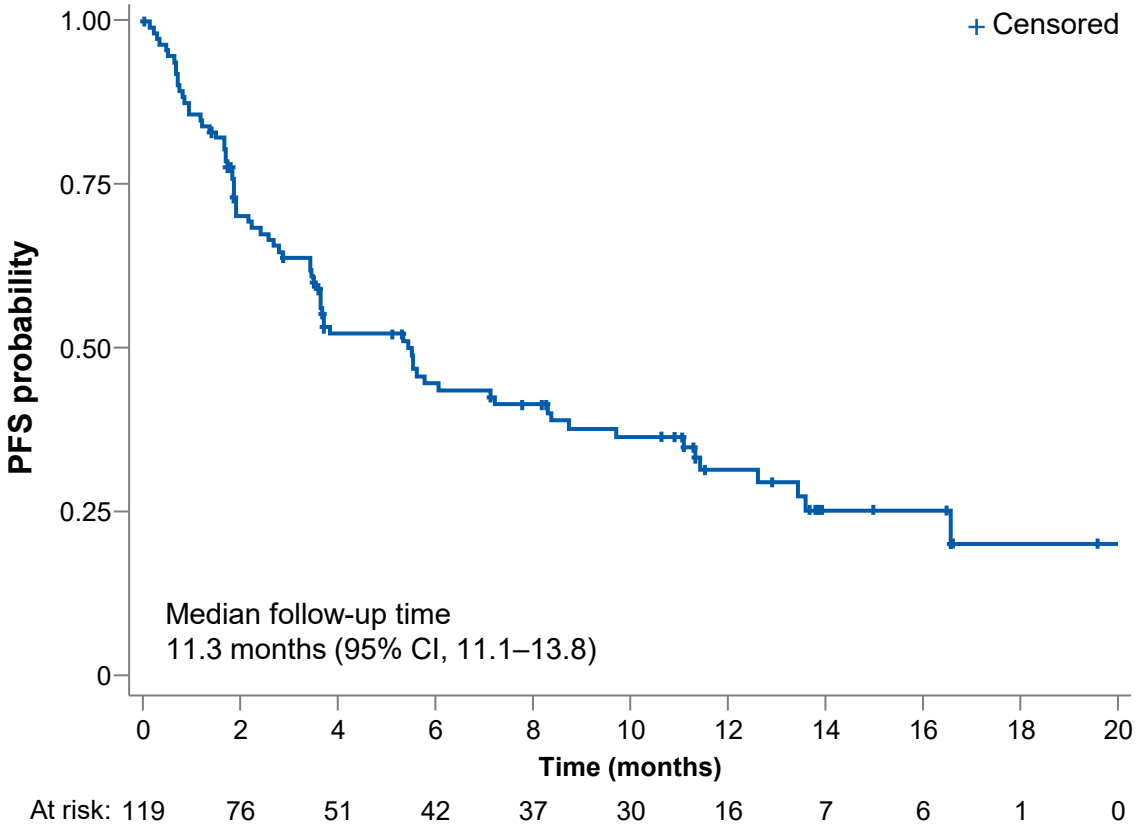


Data cutoff: May 5, 2023.
NE, not evaluable; TTR, time to response.

Progression-Free Survival and Overall Survival

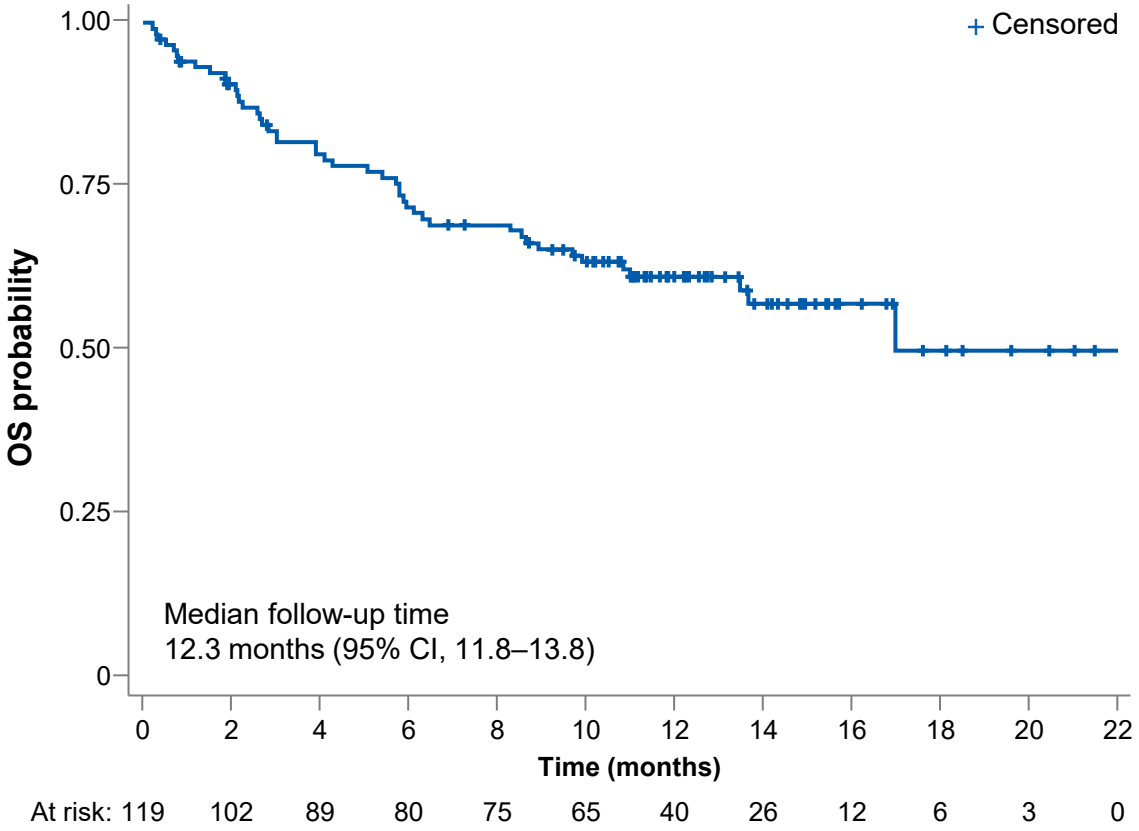
PFS[a]

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)



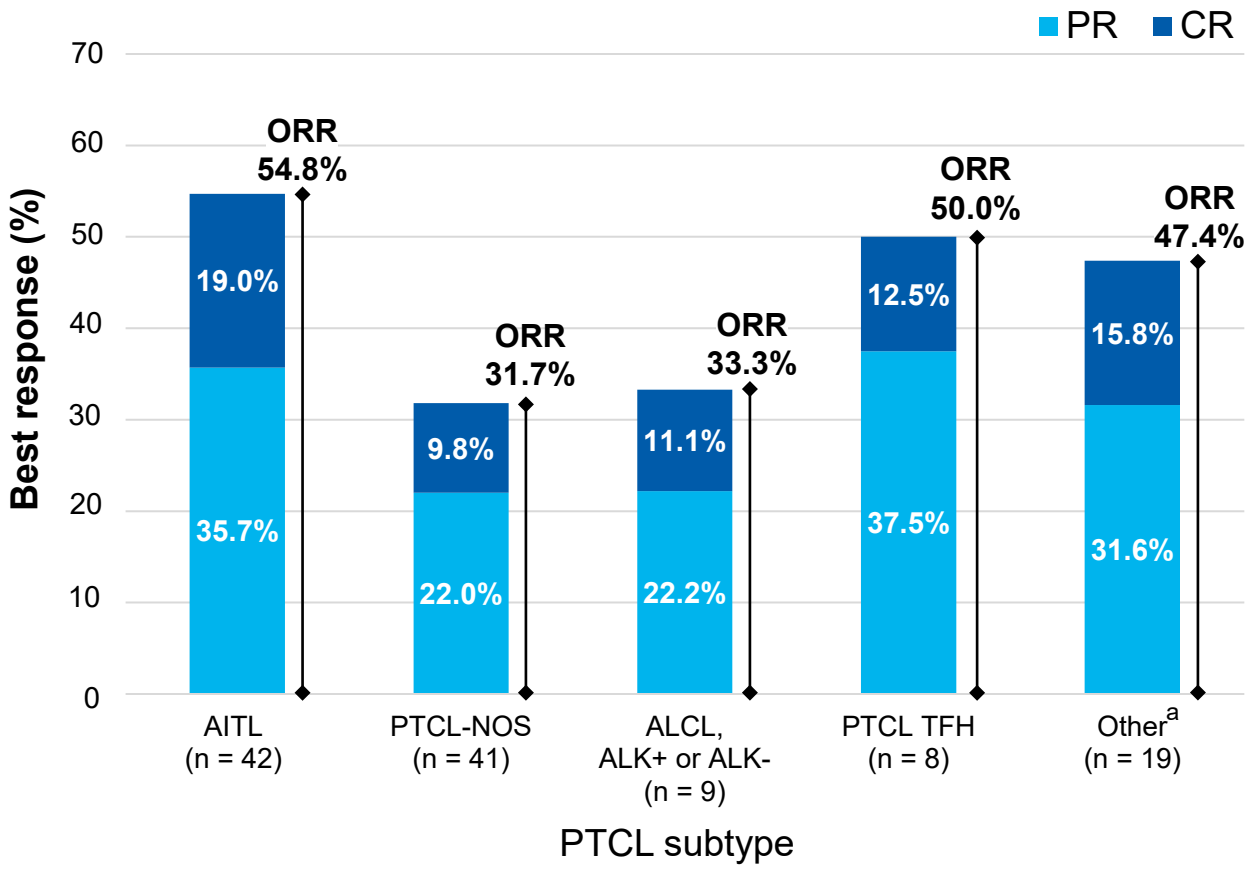
Data cutoff: May 5, 2023.
[a] PFS evaluated by BICR CT-based assessment.

Clinical Response by PTCL Subtype (BICR Assessment)

Responses were observed across all PTCL subtypes

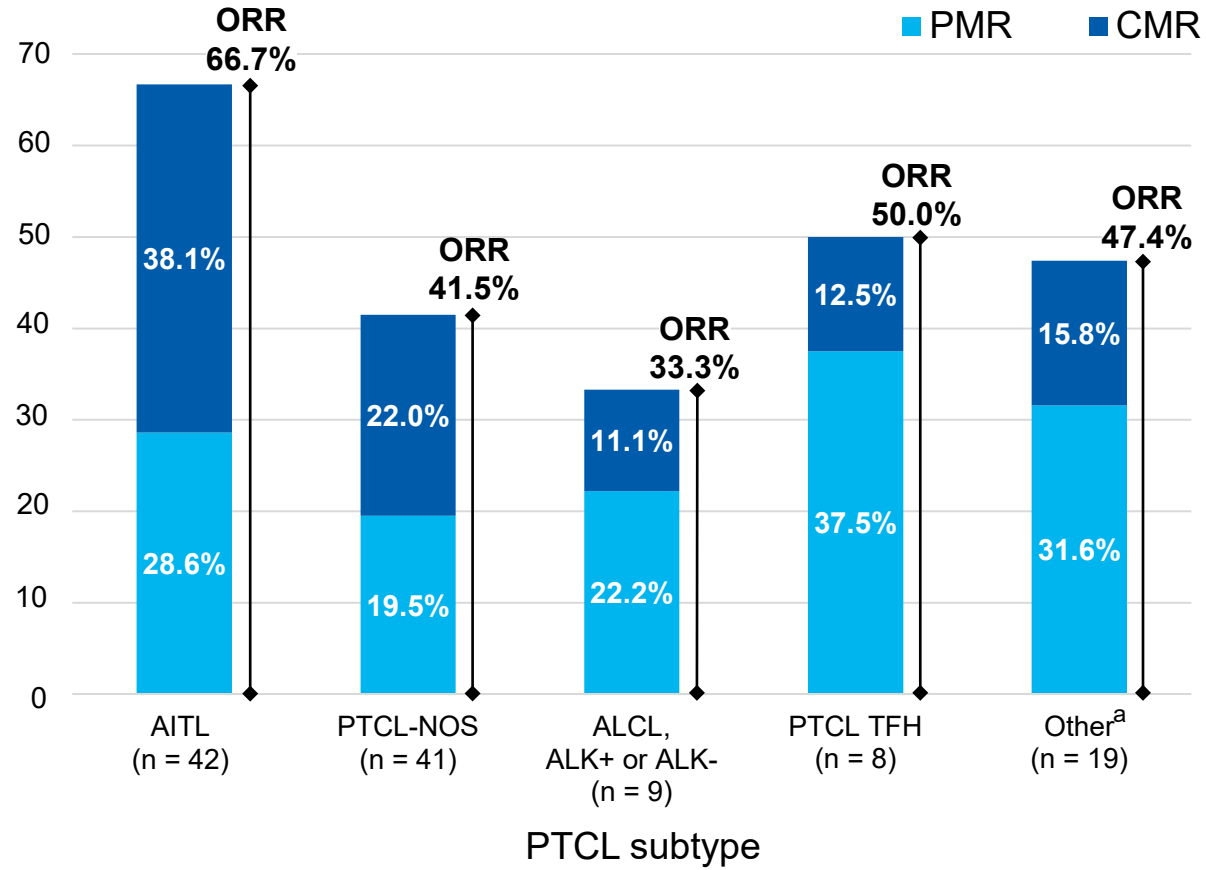
CT-based assessment

(N = 119)



PET-CT-based assessment

(N = 119)



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.

Overall Safety

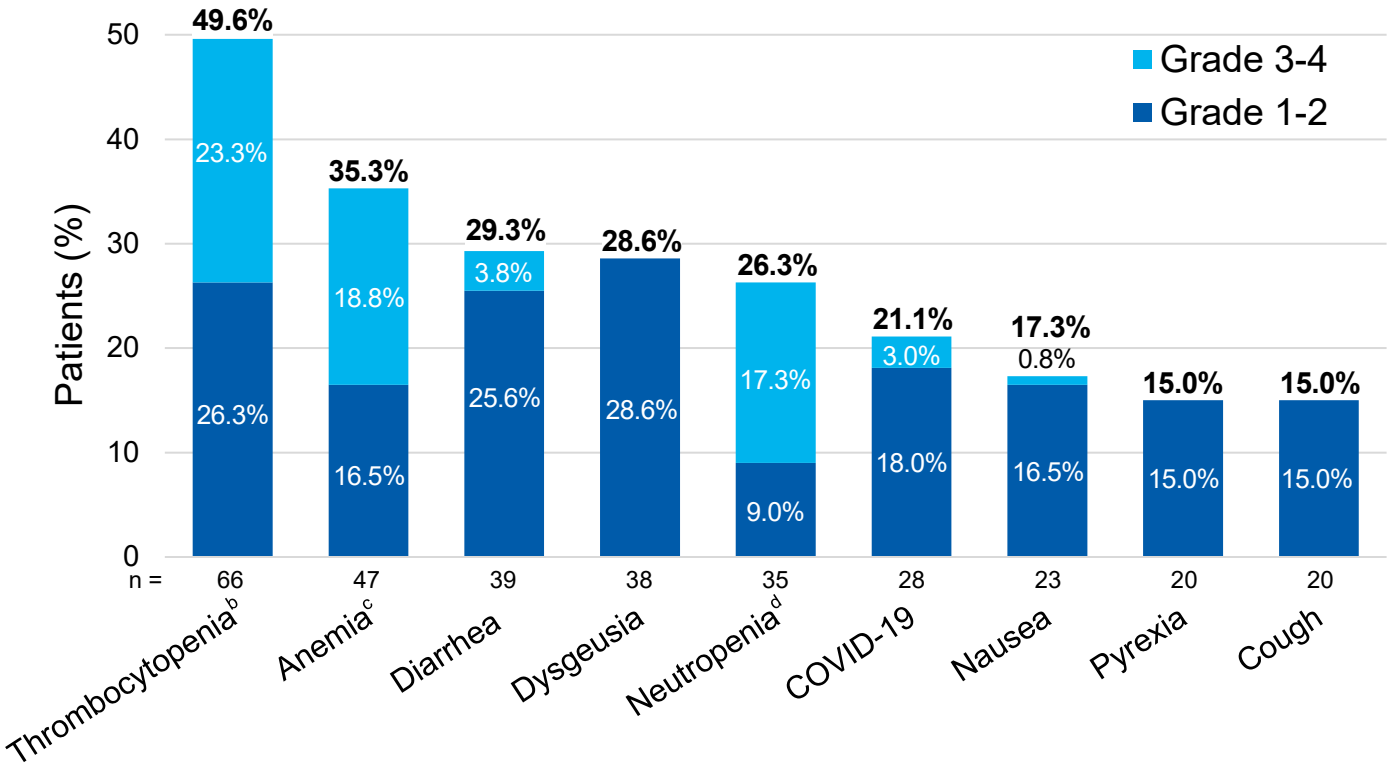
TEAE/TRAE summary, %	PTCL (N = 133)
TEAEs	96.2
TRAEs	79.7
Grade ≥ 3 TEAEs	57.9
Grade ≥ 3 TRAEs	36.8
Serious TEAEs	39.8
Serious TRAEs	6.8

TEAE/TRAE summary, %	PTCL (N = 133)
TEAEs leading to death	11.3
TRAEs leading to death	0
TEAEs leading to discontinuation	9.8
TRAEs leading to discontinuation	6.8
TEAEs leading to dose reduction	15.8
TRAEs leading to dose reduction	12.0
TEAEs leading to dose interruption	49.6
TRAEs leading to dose interruption	31.6

Data cutoff: May 5, 2023.
TEAEs, treatment-emergent adverse events; TRAEs, treatment-related adverse events.

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**
Thrombocytopenia[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

Data cutoff: May 5, 2023.
[a] TEAEs included that led to treatment interruption in ≥ 5% of patients. [b] Thrombocytopenia includes platelet count decrease. [c] Anemia includes hemoglobin decrease, and red blood cell count decrease.
[d] Neutropenia includes neutrophil count decrease.
AML, acute myeloid leukemia; G-CSF, granulocyte colony stimulating factor.

Conclusions

- Valemetostat demonstrated a high response rate and durable responses in patients with R/R PTCL, who have limited treatment options
  - Responses were observed across all PTCL subtypes
  - 10 (8.4%) patients treated with valemetostat proceeded to allo-HCT
- 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

Data cutoff: May 5, 2023.

Acknowledgements

- The authors thank the patients, families, and caregivers for their participation, and the study staff for their contributions
- This study is sponsored by Daiichi Sankyo Co., Ltd
- Editorial support was provided by Declan Grewcock, PhD, of Excerpta Medica, funded by Daiichi Sankyo Co., Ltd, and in accordance with Good Publication Practice (GPP) guidelines
- The authors thank the following investigators for contributing to patient enrolment and study design

Ana Marín-Niebla
Antonio Pinto
Bradley Haverkos
Carlo Gambacorti-Passerini
Daisuke Ennishi
Francine Foss
Franck Morschhauser
Graham Collins
Guillermo Rodríguez Garcia
Hirokazu Nagai
Jasmine Zain
Jia Ruan
Junya Kuroda
Loic Ysebaert
Miles Prince
Ming-Chung Wang
Nabila Bennani-Baiti
Nobuhiko Yamauchi
Pier Luigi Porcu
Ranjana Advani
Tai-Chung Huang
Tatyana Feldman
Thomas Weber
Tsai-Yun Chen
Weiyun Ai
Won Seog Kim

- Thank you also to central pathologist, Jose Cabecadas