Valemetostat Monotherapy in Patients with Relapsed or Refractory Peripheral T-Cell Lymphomas: Efficacy by Prior Lines of Treatment and Last Treatment Outcome from the VALENTINE-PTCL01 Study

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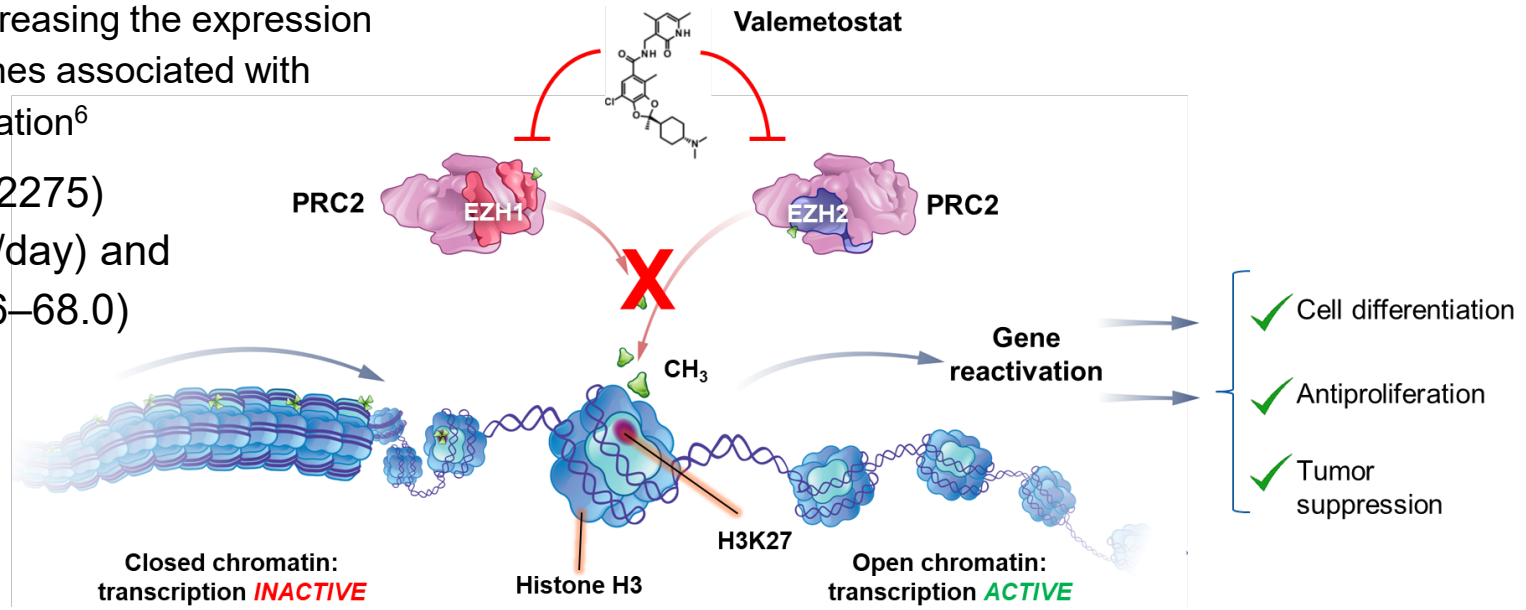
Abstract #S247

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 R/R 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* gene mutations are rare in PTCL[5]
- 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[6]
- The previous, phase 1, J101 study (NCT02732275) established the RDE of valemetostat (200 mg/day) and reported an ORR of 55% (30/55; 95% CI, 40.6–68.0) in patients with R/R PTCL, including 17 (31%) patients achieving a CR[7]
- Valemetostat monotherapy (200 mg/day) is approved in Japan for R/R ATLL[8,9]



ATLL, adult T-cell leukemia/lymphoma; CI, confidence interval; CR, complete response; EZH, enhancer of zeste homolog; H3K27, histone H3 at lysine 27; H3K27me3, trimethylation of H3K27; NHL, non-Hodgkin lymphoma; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PRC2, polycomb repressive complex 2; PTCL, peripheral T-cell lymphoma; RDE, recommended dose for expansion; 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. Schümann FL, et al. *Biomedicines* 2021;9:1842. 6. Yamagishi M, et al. *Cell Rep* 2019;29:2321–2337.e7. 7. Jacobsen E, et al. *Blood* 2023;142:303. 8. EZHARMIA® (valemetostat tosilate). [package insert]. Tokyo, Japan: Daiichi Sankyo; 2022. 9. 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,2])

Key secondary endpoints: DOR, DOCR, CR rate, PR rate, PFS, OS, safety and tolerability

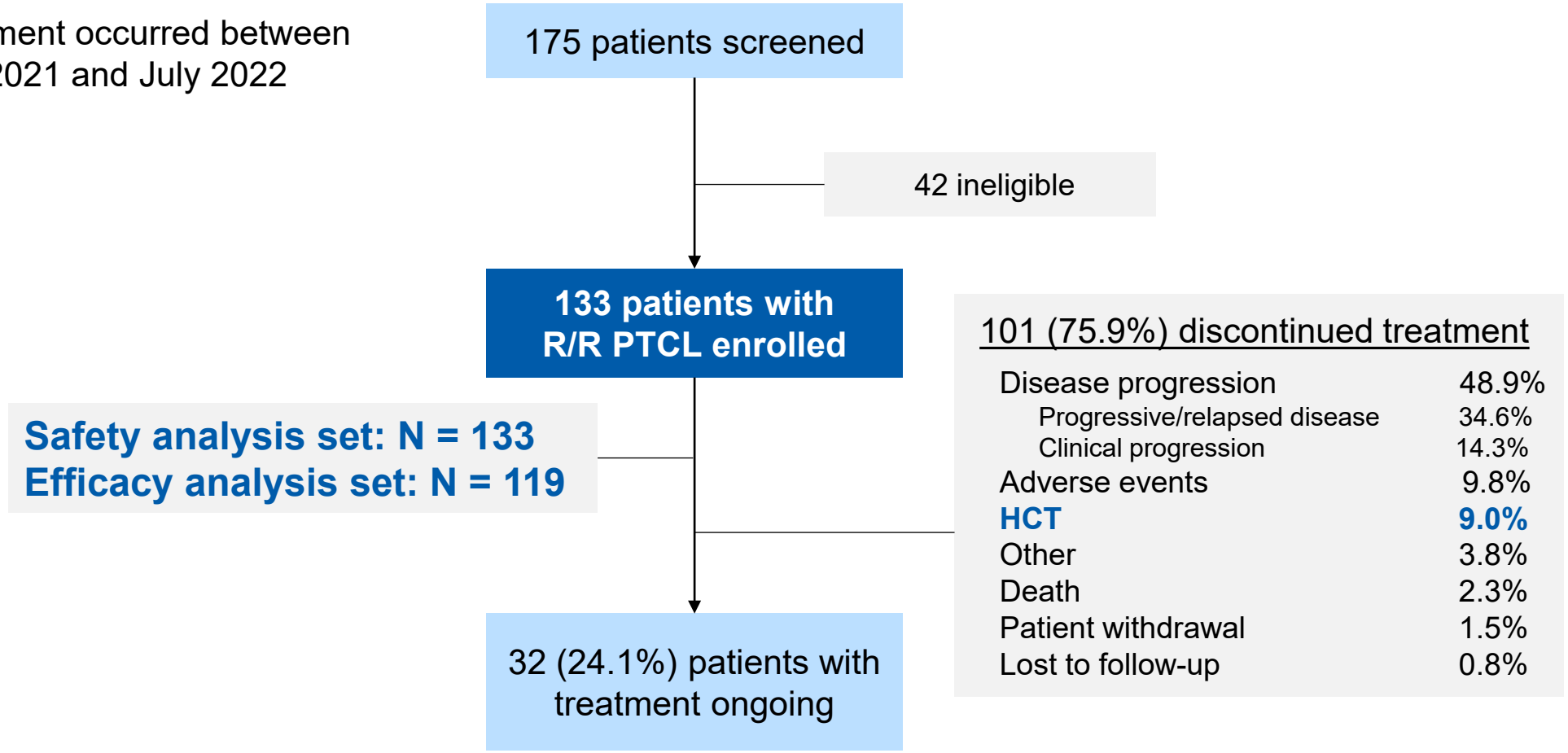
Key exploratory endpoint: PET-CT–based clinical response (BICR)

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 PS, Eastern Cooperative Oncology Group performance status; 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. Median follow-up 9.7 months.
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)
Response to last treatment, n (%)	
Relapsed	39 (29.3)
Refractory	80 (60.2)
Not assessable or unknown	14 (10.5)

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

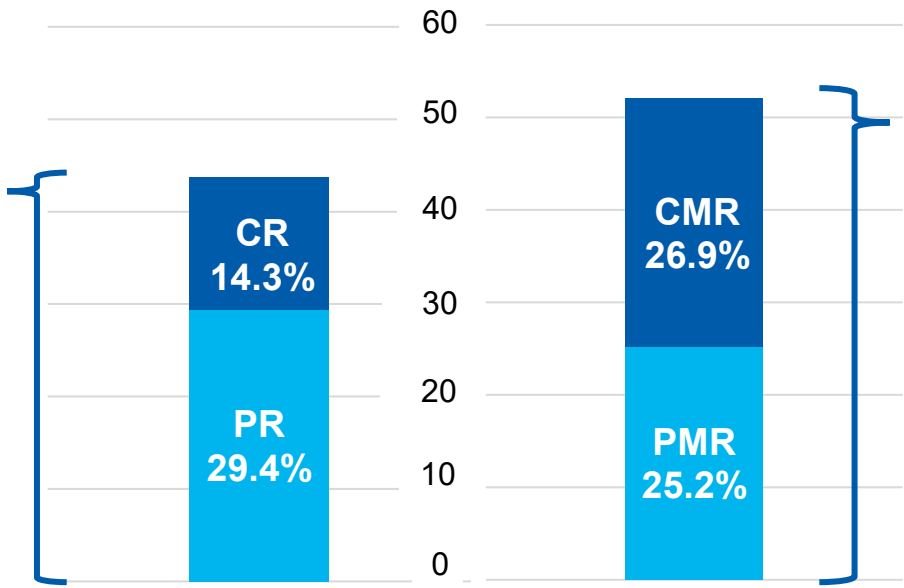
(Primary endpoint)

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**

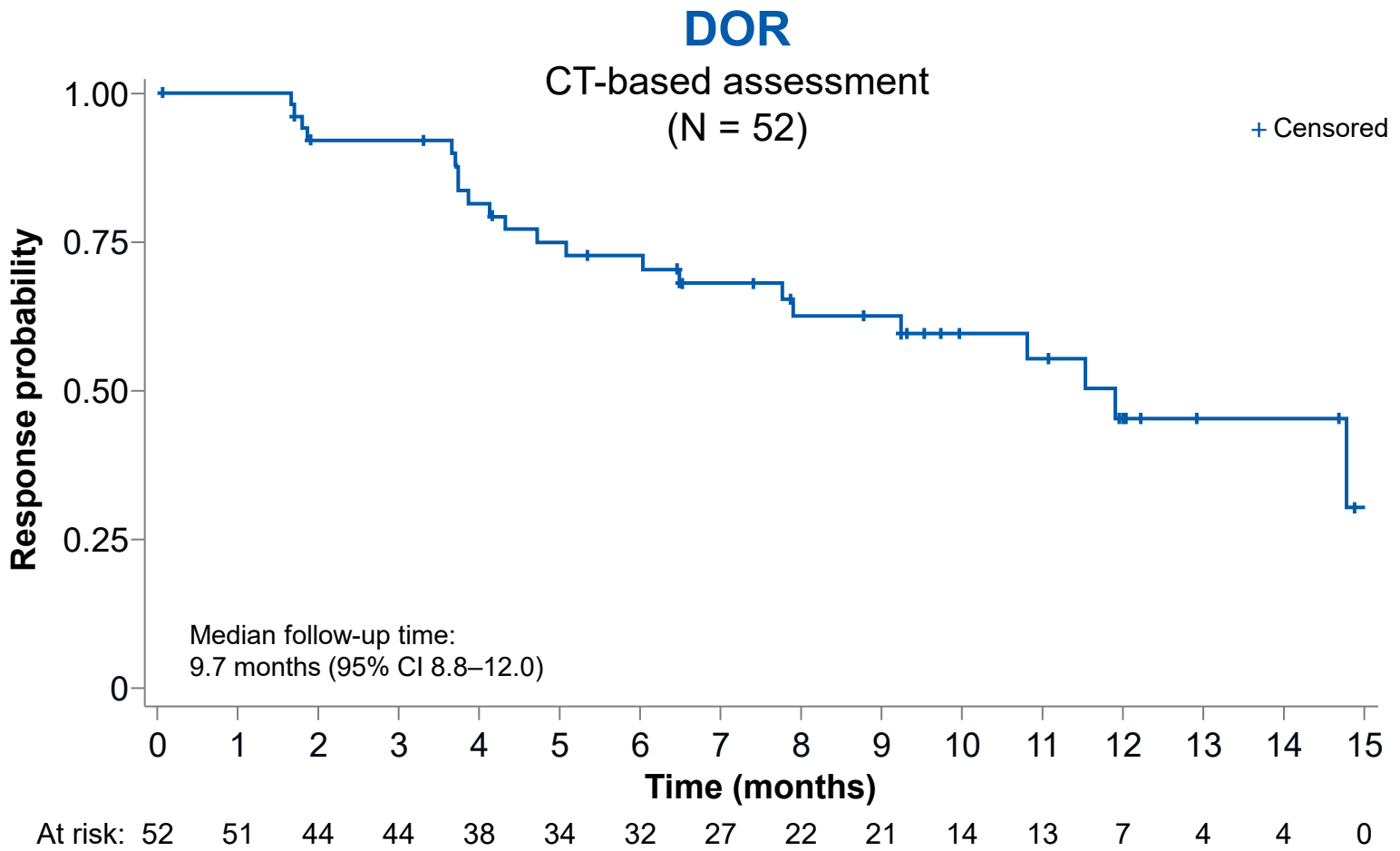
30 patients **(25.2%)** achieved a **PMR**

- **Ten (8.4%) patients treated with valemetostat proceeded to allo-HCT, including 6 (5.0%) with a CR[a]**
- The median time from first dose of valemetostat to subsequent allo-HCT was 6.7 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)

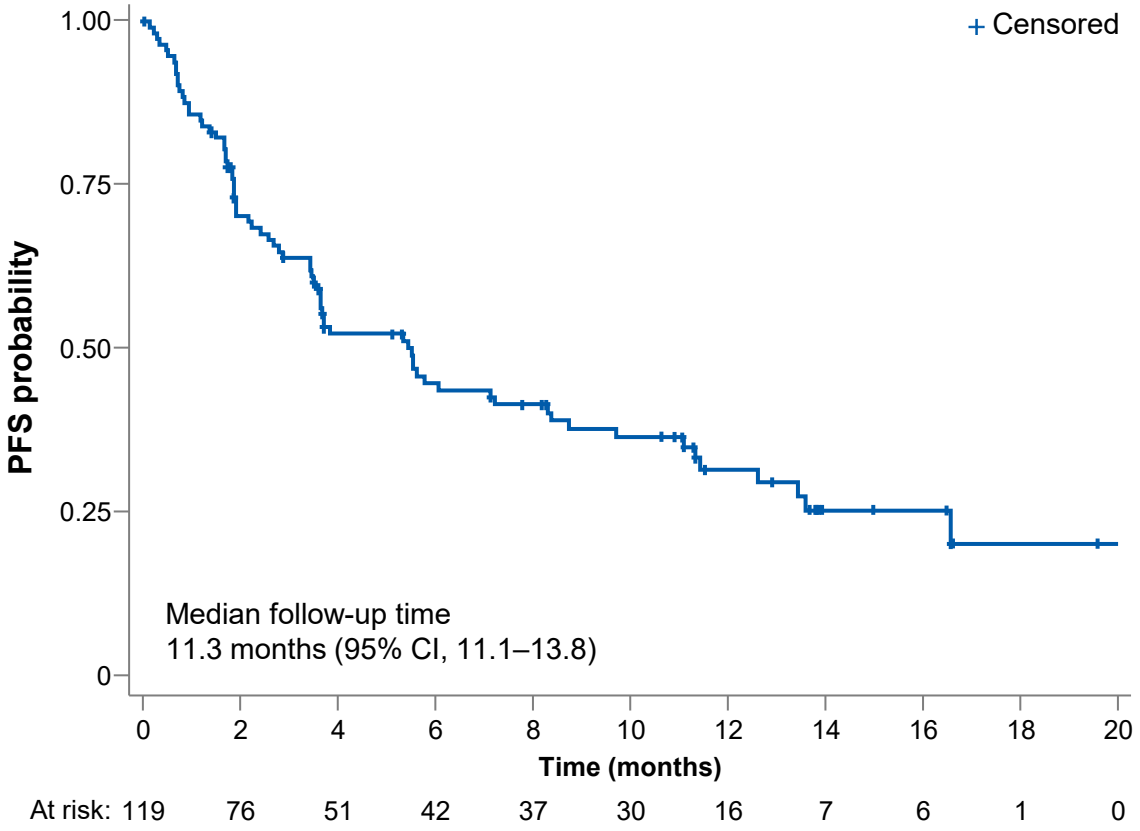


Data cutoff: May 5, 2023.
NE, not evaluable; TTR, time to response.

Progression-Free Survival and Overall Survival

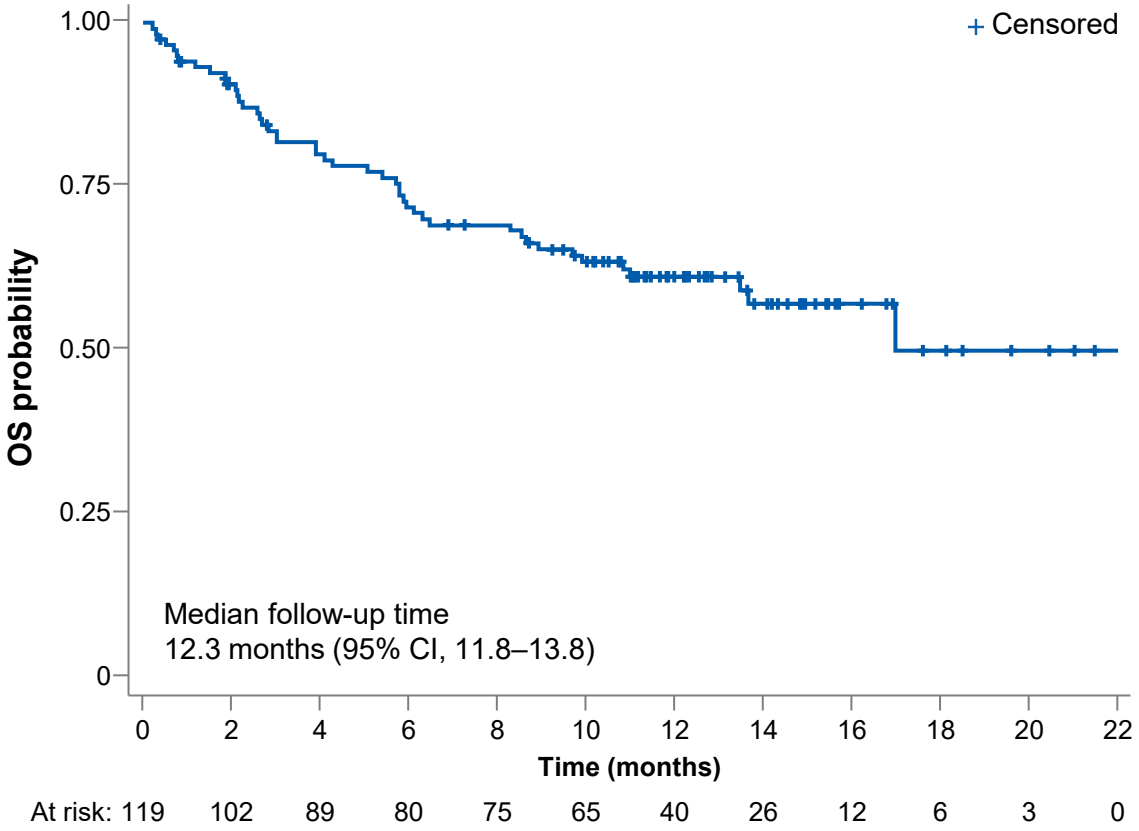
PFS[a]

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



OS

(N = 119)
Median 17.0 months (95% CI, 13.5 months to NE)

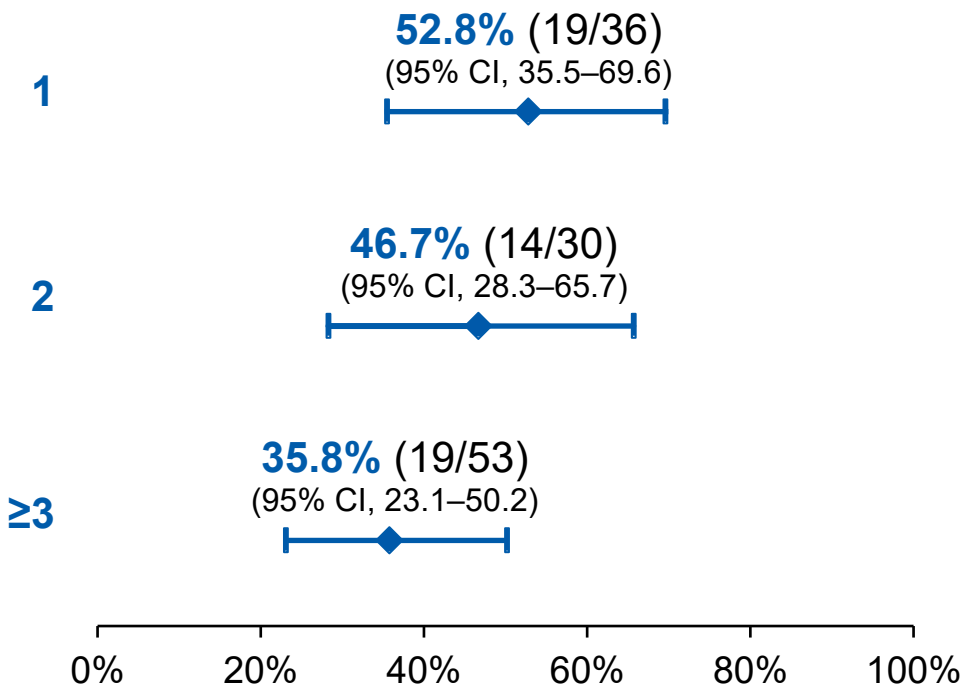


Data cutoff: May 5, 2023.
[a] PFS evaluated by BICR CT-based assessment.

Response by Prior Number of Treatments and Last Treatment Outcome

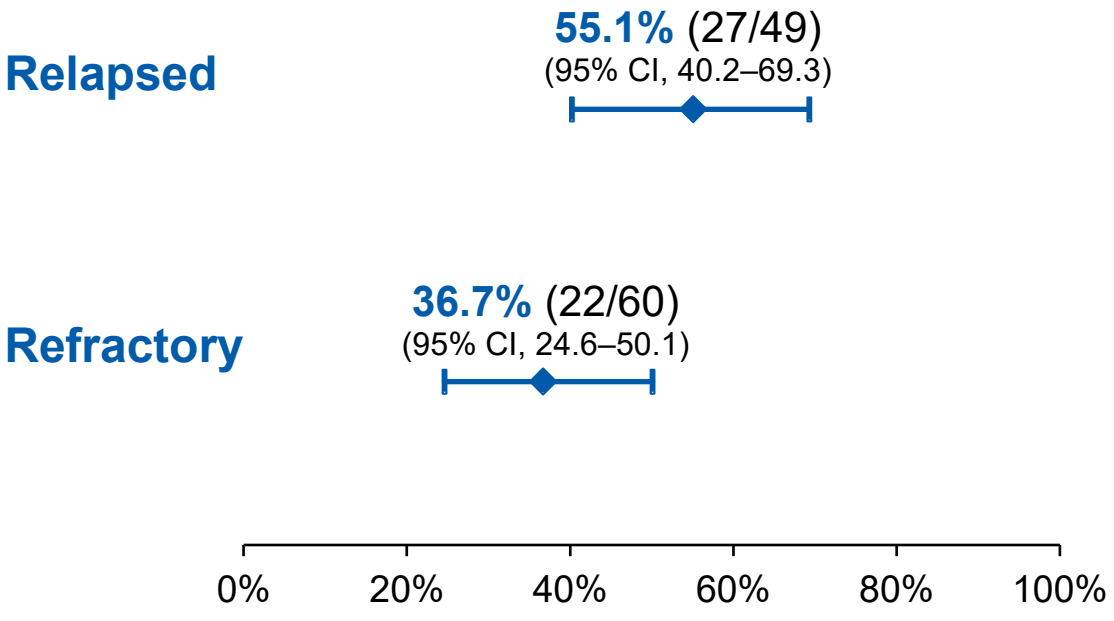
ORR by # of prior LOT

- **ORRs** for patients with **1, 2,** and **≥3 prior LOT** were **52.8%, 46.7%,** and **35.8%,** respectively



ORR by prior LOT outcome[a]

- Patients who **relapsed** following their last LOT had a nominally **higher ORR** than with those who were **refractory**[b] to their last LOT

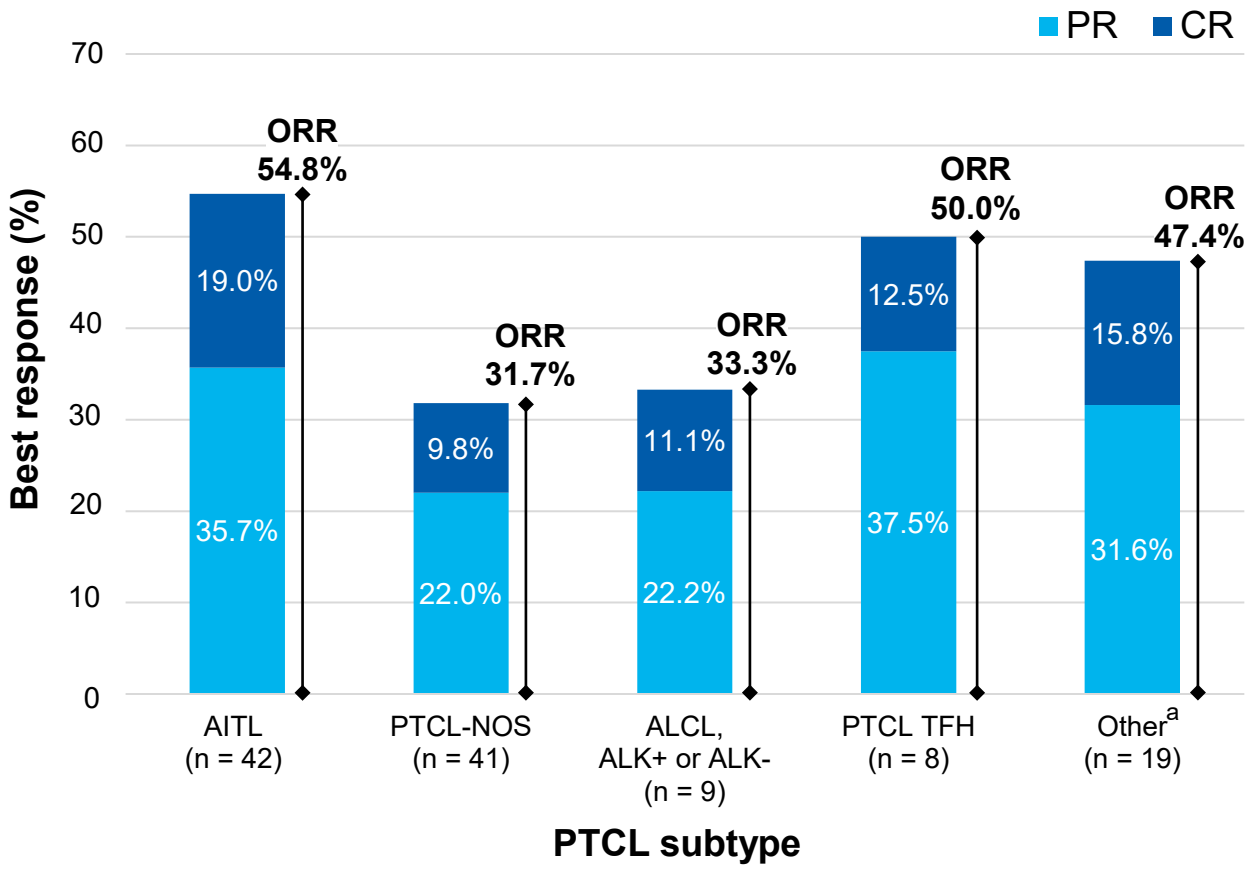


Data cutoff: May 5, 2023.
Responses evaluated by CT-based BICR assessment. [a] If the best response of the last prior line of therapy was 'not assessable' or 'unknown', the patient was excluded.[b] Refractory includes patients who had only one prior LOT and did not achieve CR, and patients who had ≥ one prior LOT and did not achieve CR or PR in their latest LOT. Relapsed (including Progressed) includes patients that had CR as best response in their latest LOT and relapsed, and patients who had ≥ one prior LOT and had PR as best response in their latest LOT and subsequently progressed.
LOT, line of therapy.

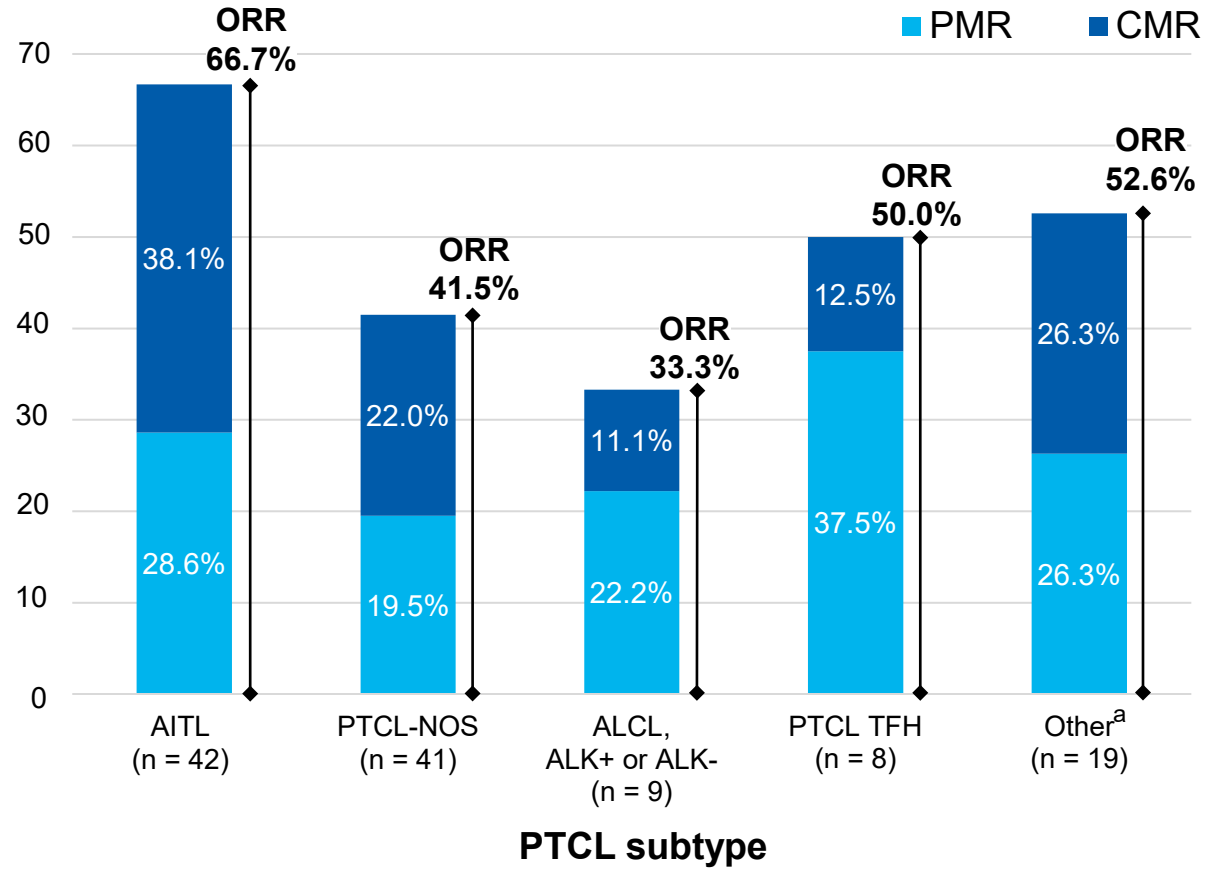
Clinical Response by PTCL Subtype (BICR Assessment)

Responses were observed across 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

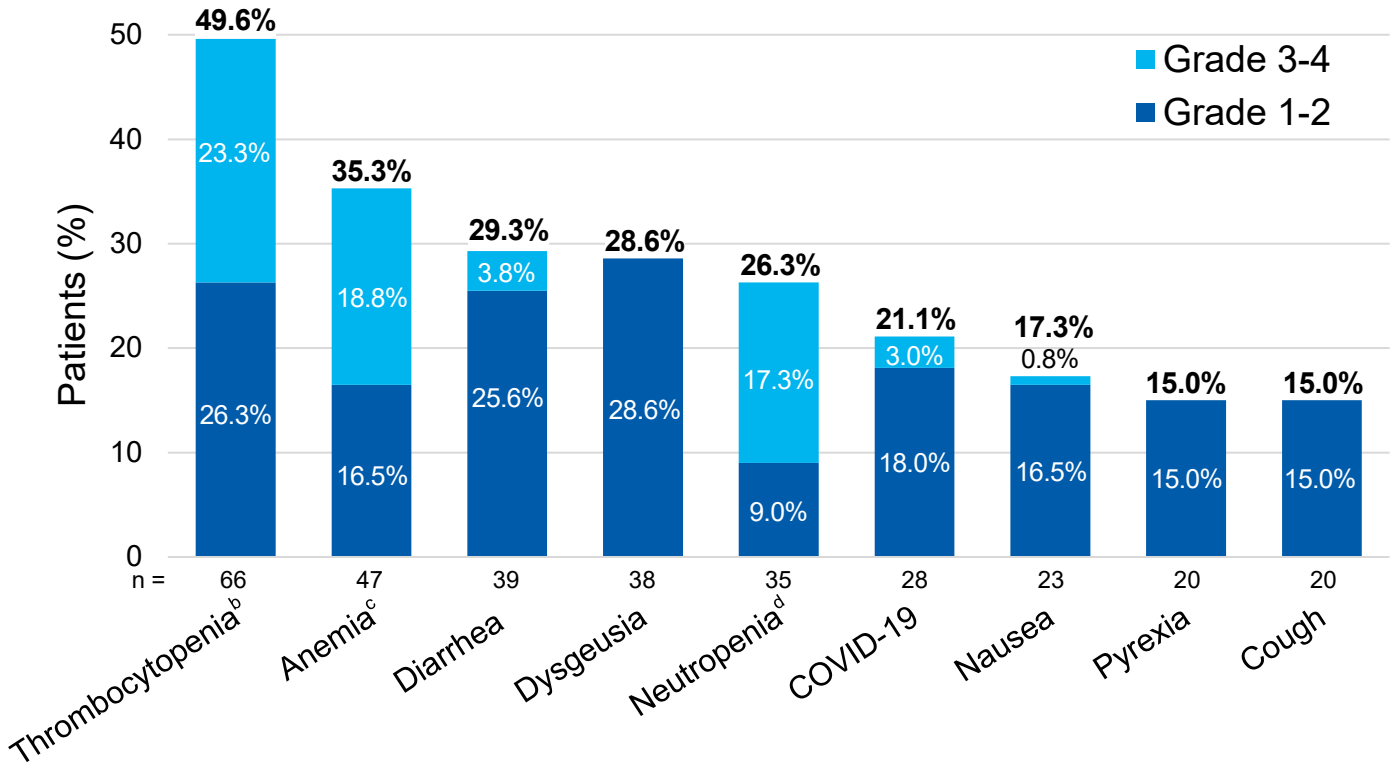
TEAE/TRAE summary, %	PTCL (N = 133)
Any TEAE	96.2
Any TRAE	79.7
Grade ≥ 3 TEAE	57.9
Grade ≥ 3 TRAE	36.8
Serious TEAE	39.8
Serious TRAE	6.8

TEAE/TRAE summary, %	PTCL (N = 133)
TEAE leading to death	11.3
TRAE leading to death	0
TEAE leading to discontinuation	9.8
TRAE leading to discontinuation	6.8
TEAE leading to dose reduction	15.8
TRAE leading to dose reduction	12.0
TEAE leading to dose interruption	49.6
TRAE 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 but manageable with dose modifications and 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 decreased. [c] Anemia includes hemoglobin decreased, and red blood cell count decreased.
[d] Neutropenia includes neutrophil count decreased.
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
  - By PET-CT assessment, over 25% of patients achieved a CMR
  - Responses were observed across all PTCL subtypes enrolled
  - Ten (8.4%) patients treated with valemetostat proceeded to allo-HCT
- Clinical responses were observed in patients who relapsed or were refractory to their last LOT, and regardless of the number of prior treatments, including those heavily pretreated
- Valemetostat demonstrated an acceptable safety profile in patients with R/R PTCL
  - The most common any grade/grade ≥ 3 TEAEs were cytopenias
  - TEAEs were typically manageable and did not frequently require treatment discontinuation
- 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.

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