Valemetostat for Relapsed or Refractory Peripheral T-Cell Lymphomas: Primary Results from a Phase 1 Trial

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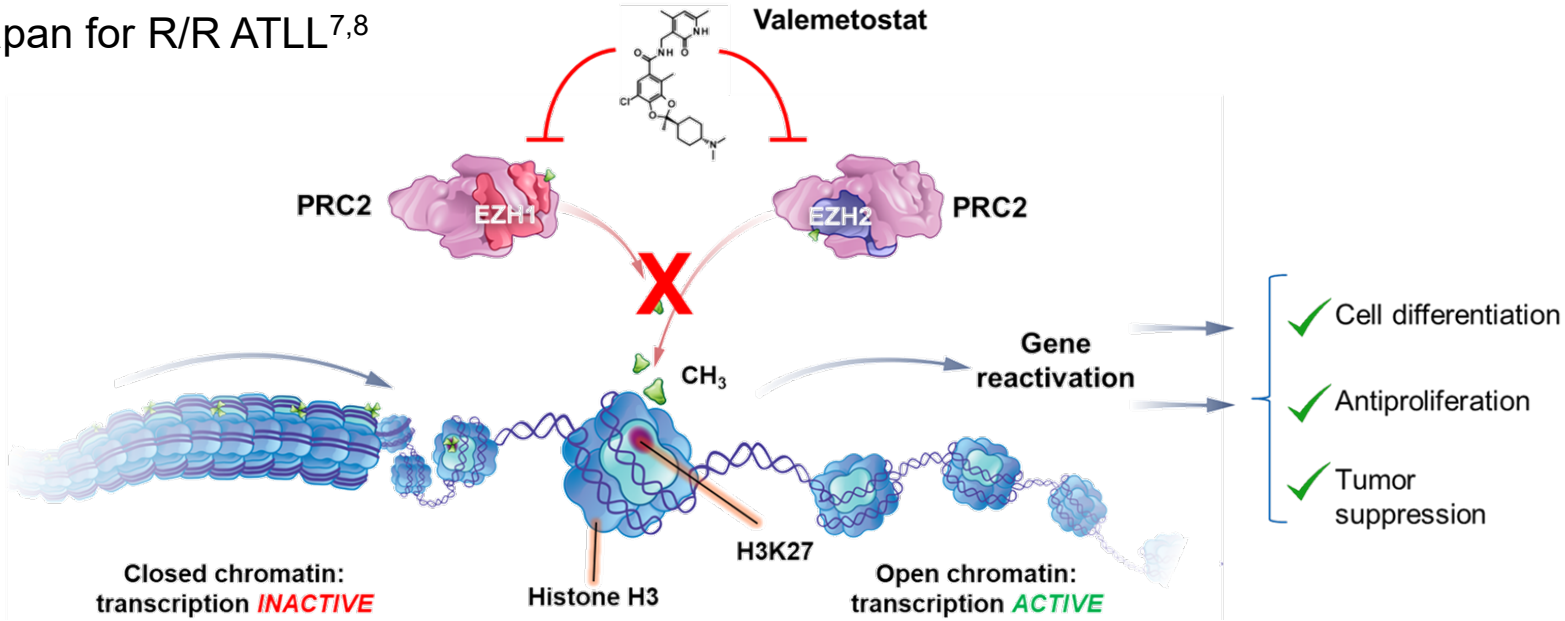
Abstract #303

Valemetostat

- Treatment options are limited and prognosis is often poor for patients with R/R T-NHLs, including PTCL and ATLL
- 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]



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

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.

Study design

DS3201-A-J101 (“J101”; NCT02732275): 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)

- n = 2 | **300 mg/day[b]**
- n = 7 | **250 mg/day**
- n = 9 | **200 mg/day**
- n = 7 | **150 mg/day**

RDE

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

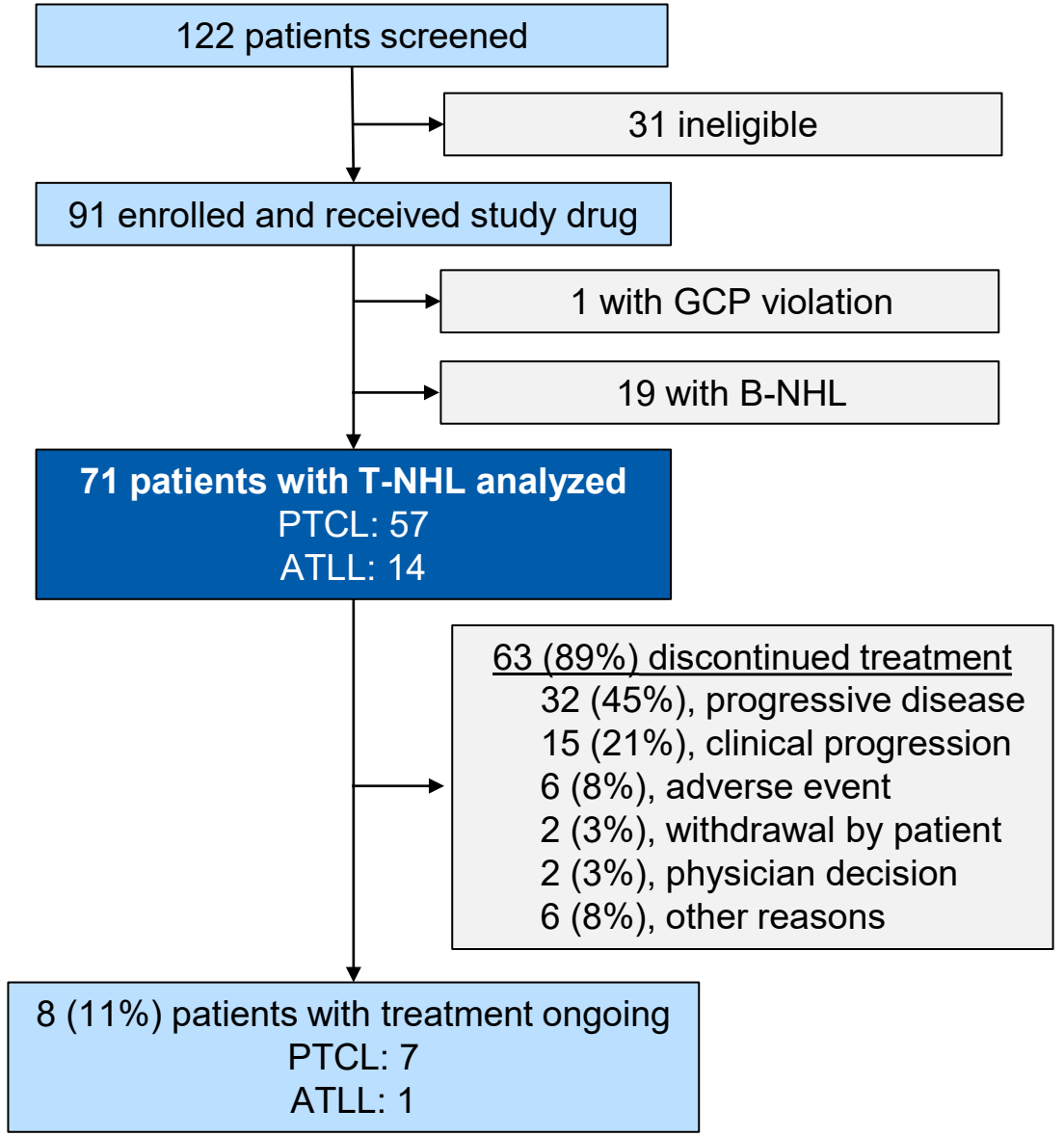
Primary endpoints: Safety (including DLTs, TEAEs), RP2D, PK parameters

Secondary endpoints: MTD, efficacy

[a] Number includes 1 patient excluded from all analyses due to a GCP violation.
[b] 2 of 2 patients in the 300 mg/day cohort experienced DLTs: 1 patient had grade 3 anemia requiring transfusion and grade 4 platelet count decreased, and another patient had grade 4 platelet count decreased.
B-NHL, B-cell non-Hodgkin lymphoma; DLT, dose-limiting toxicity; ECOG, Eastern Cooperative Oncology Group; GCP, good clinical practice; MTD, maximum tolerated dose; PK, pharmacokinetic; PO, by mouth; PS, performance status; QD, once daily; RDE, recommended dose for expansion; RP2D, recommended phase 2 dose; TEAE, treatment-emergent adverse event; y, years.

J101 T-NHL cohort: Enrollment and disposition

- Patients were enrolled from April 2016 through June 2021
- Data from 71 patients from the J101 trial with T-NHLs were analyzed
  - The trial included 57 patients with PTCL and 14 patients with ATLL
  - Patients with T-NHLs received doses of 150 mg/day or 200 mg/day
    - PTCL: 150 mg/day, n = 2; 200 mg/day, n = 55
    - ATLL: 150 mg/day, n = 2; 200 mg/day, n = 12
- Median treatment duration at data cutoff (Dec 31, 2022) was 3.7 months (range, 0.03–44.4)



Baseline demographic and disease characteristics

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

Data cutoff: December 31, 2022.

[a] One patient had an eligible ECOG PS score (≤ 2) at the time of screening, but then had a score of 4 at baseline.

[b] Includes 1 patient with ALK^- ALCL and 1 patient whose ALK status was unknown.

[c] Includes patients with SPTCL; (n = 2), ENKTCL (nasal type; n = 1), hepatosplenic T-cell lymphoma (n = 1), nodal PTCL with TFH phenotype (n = 1), and primary cutaneous gamma-delta T-cell lymphoma (n = 1).

AITL, angioimmunoblastic T-cell lymphoma; ALCL, anaplastic large-cell lymphoma; ALK, anaplastic lymphoma kinase; ENKTCL, extranodal NK/T-cell lymphoma HCT, hematopoietic cell transplantation; NK, natural killer; NOS, not otherwise specified; SPTCL, subcutaneous panniculitis-like T-cell lymphoma; TFH, T follicular helper.

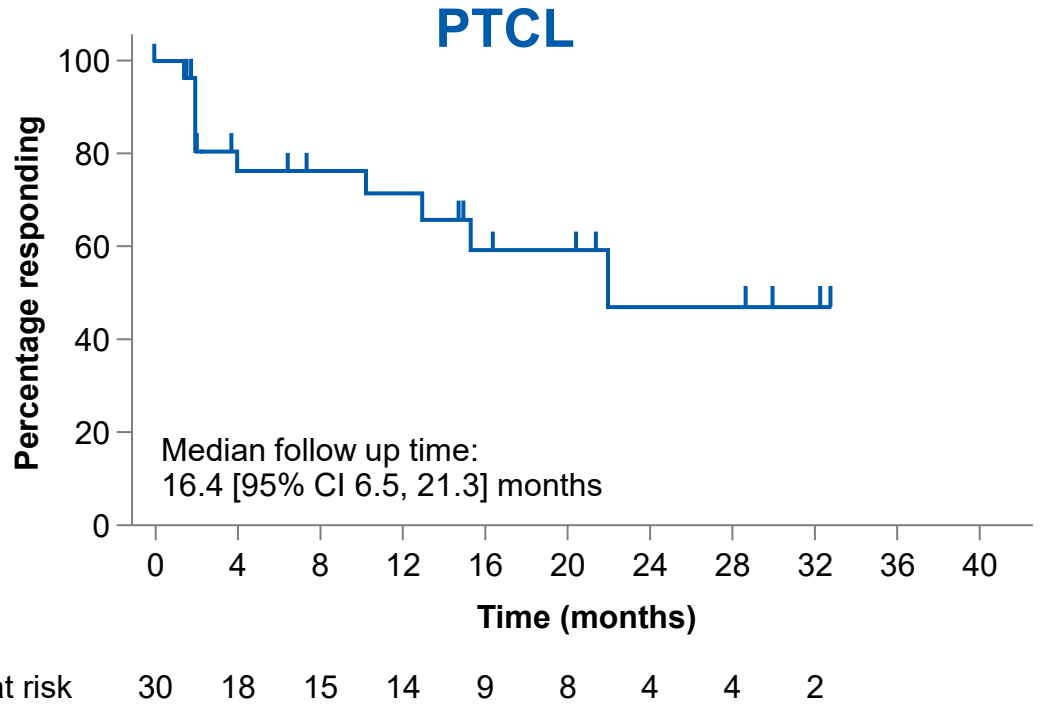
Clinical response

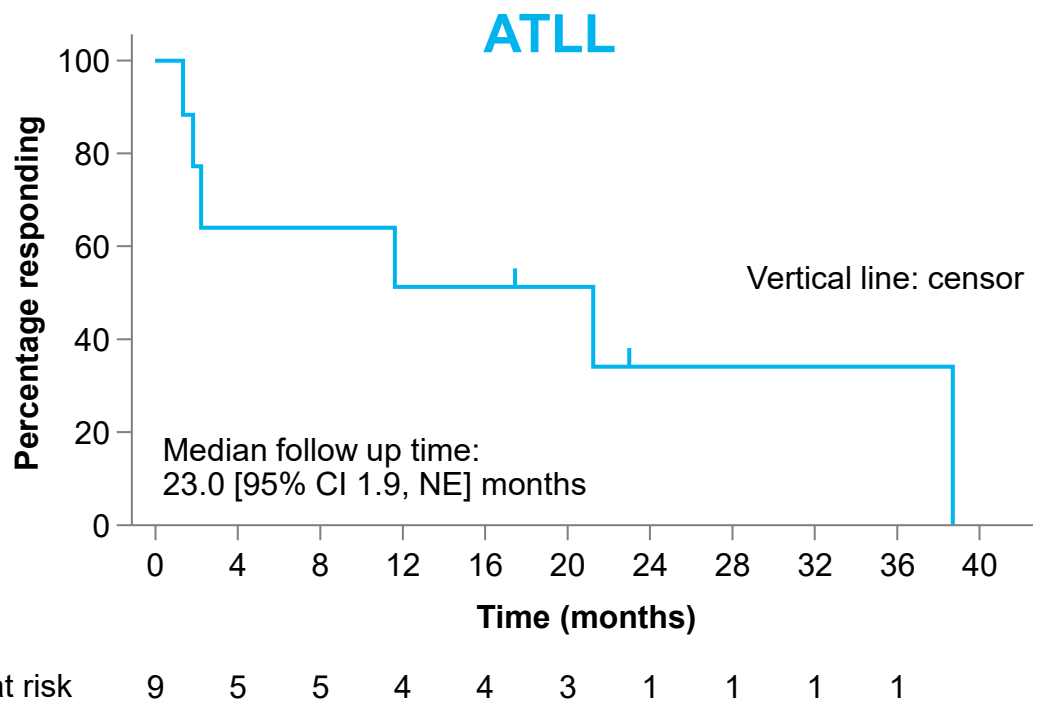
Response	PTCL (n = 55[a,b])	PTCL subtype		ATLL[c] (n = 14)
		AITL (n = 22)	PTCL, NOS (n = 26)	
Best overall response, n (%)				
CR[d]	17 (31)	10 (45)	7 (27)	4 (29)
PR	13 (24)	4 (18)	6 (23)	5 (36)
SD	4 (7)	1 (5)	3 (12)	1 (7)
PD	15 (27)	5 (23)	8 (31)	3 (21)
NE	1 (2)	1 (5)	0	0
ND	5 (9)	1 (5)	2 (8)	1 (7)
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]

Data cutoff: December 31, 2022.
[a] 2 patients without measurable disease at baseline were excluded from response analyses.
[b] Includes patients who received 150 mg/day (n = 2) and 200 mg/day (n = 53).
[c] Includes patients who received 150 mg/day (n = 2) and 200 mg/day (n = 12).
[d] CR includes CRu for ATLL.
[e] Clinical response defined per 2007 International Working Group response criteria for PTCL or modified ATLL 2009 response criteria; ORR was the proportion of patients achieving CR or PR.
[f] 95% CI based on the Clopper–Pearson method.
CI, confidence interval; CR, complete response; CRu, uncertified CR; ND, not done; NE, not evaluable; ORR, overall response rate; PD, progressive disease; PR, partial response; SD, stable disease.

Duration of response

- Median DOR was 21.9 [95% CI 10.2, NE] months for PTCL and was 21.2 [1.4, 38.7] months for ATLL
- Median times to response were 1.8 (range, 1.0–5.6) and 1.9 (1.7–19.4) months, respectively

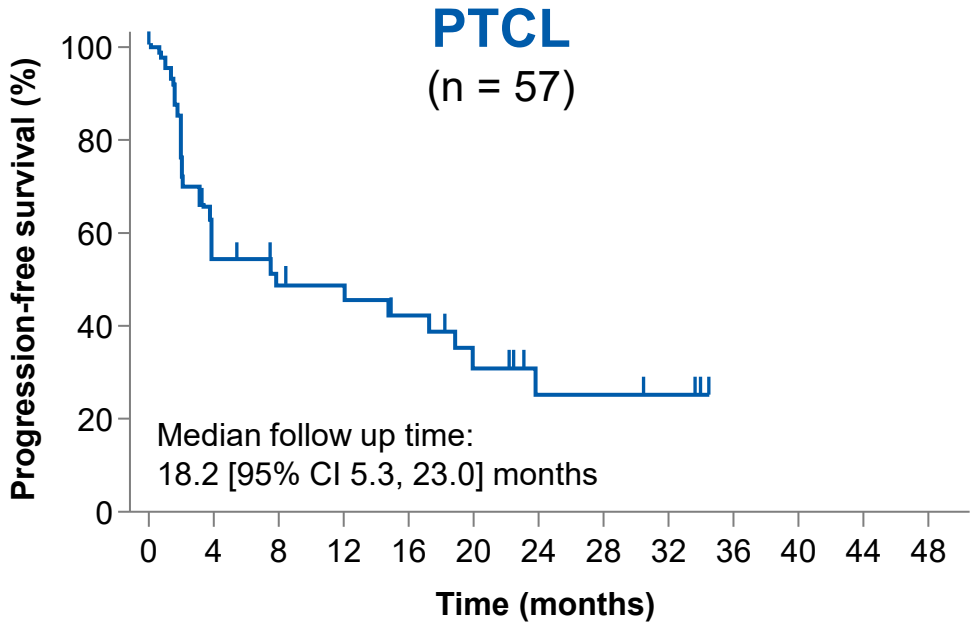




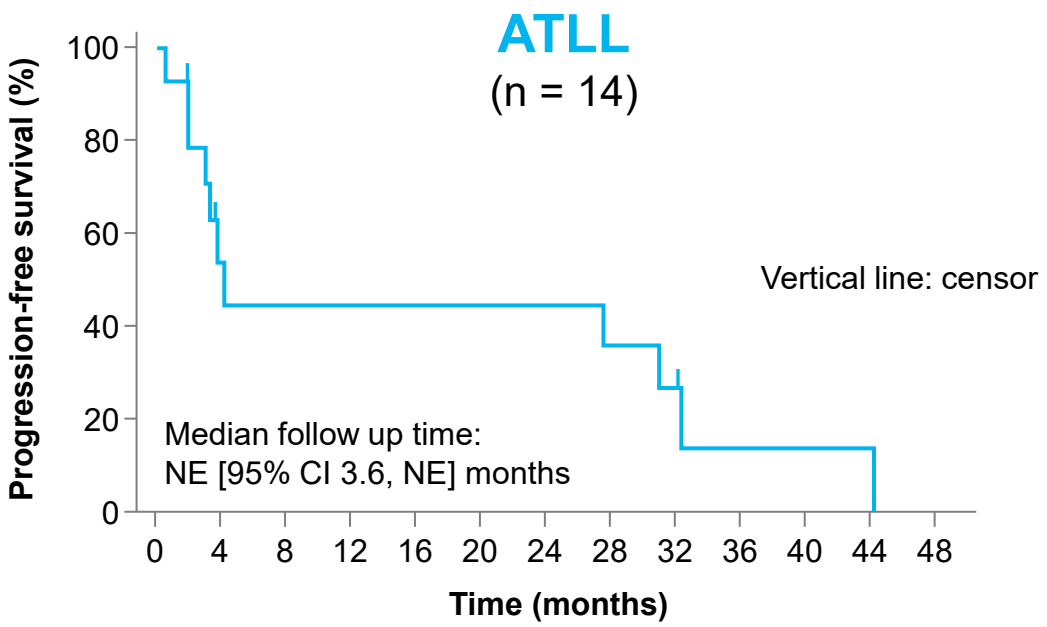
Data cutoff: Dec 31, 2022.
Median follow-up for each cohort was estimated using the reverse-Kaplan-Meier method.
DOR, duration of response; NE, not estimable.

Progression-free survival

- Median PFS for PTCL and ATLL was 7.7 [95% CI 3.6, 19.8] and 4.1 [1.9, 32.2] months, respectively



No. at risk 57 21 17 14 12 8 4 4 3

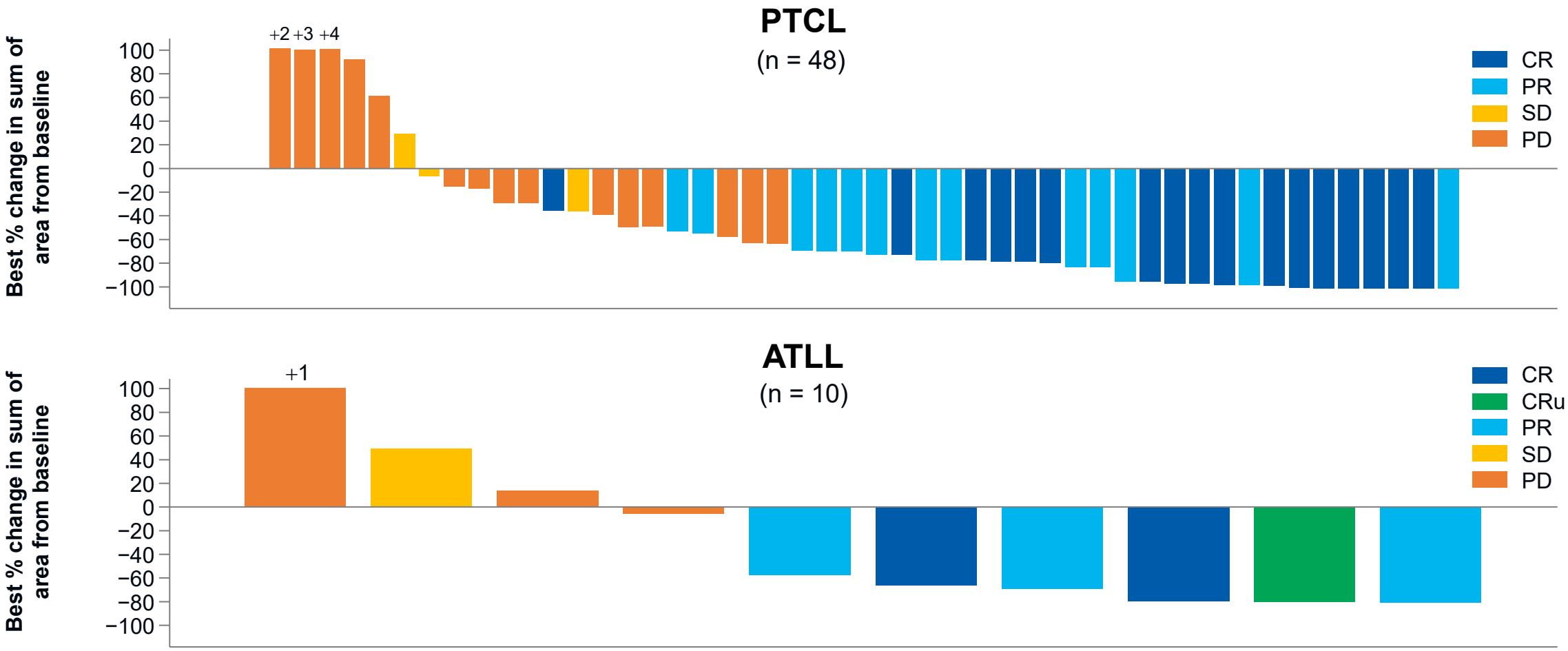


No. at risk 14 6 5 5 5 5 5 4 3 1 1 1

Data cutoff: Dec 31, 2022.
PFS, progression-free survival.

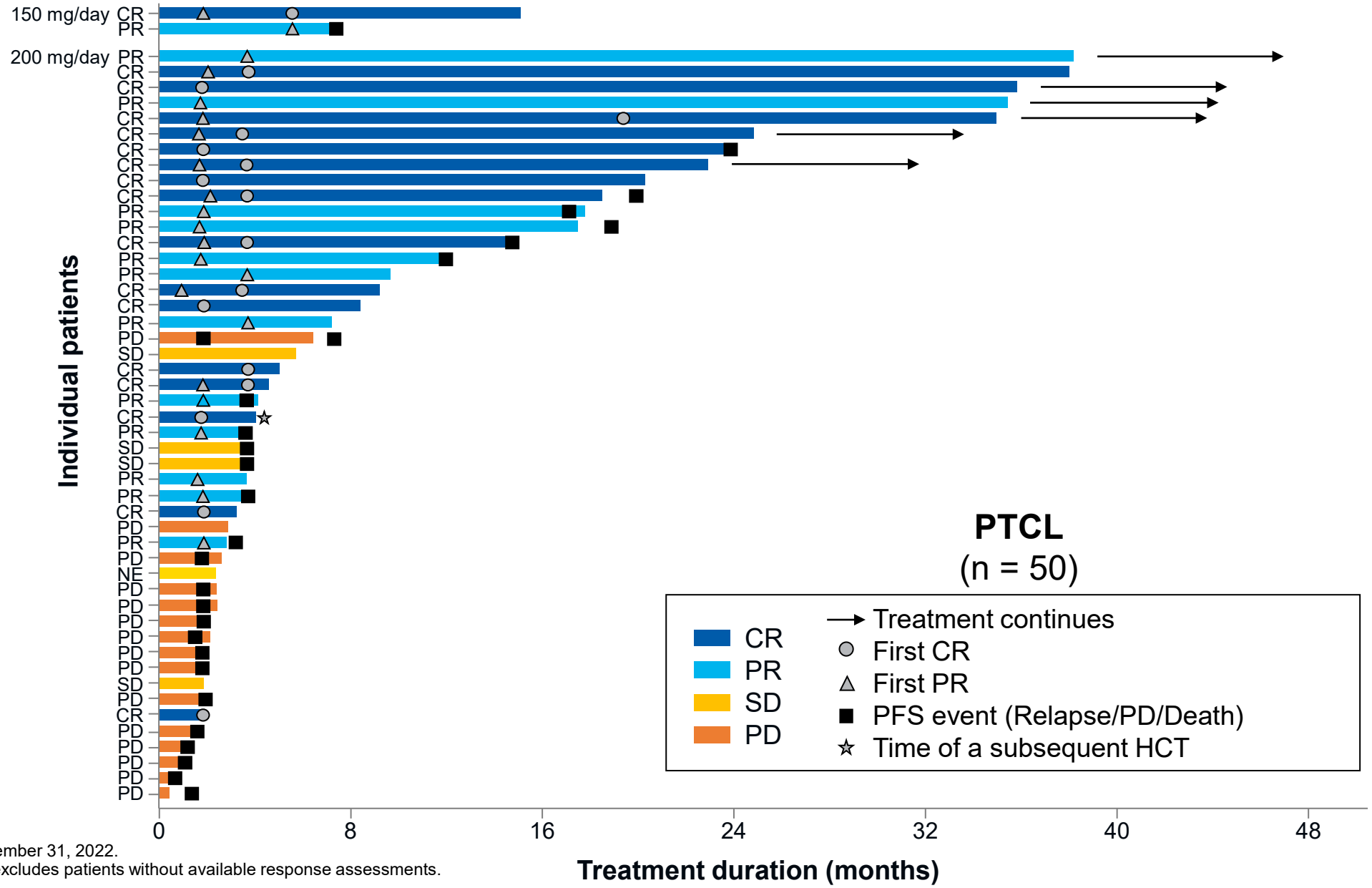
Change in target lesions from baseline

- 32 (67%) patients with PTCL and 6 (60%) patients with ATLL experienced a maximum reduction of > 50% from baseline in measurable target lesions



Data cutoff: Dec 31, 2022.
Analysis includes all patients with measurable lesions at baseline and at least 1 valid post-baseline assessment.

Exposure duration and clinical responses



Data cutoff: December 31, 2022.
Swimmer's plot excludes patients without available response assessments.

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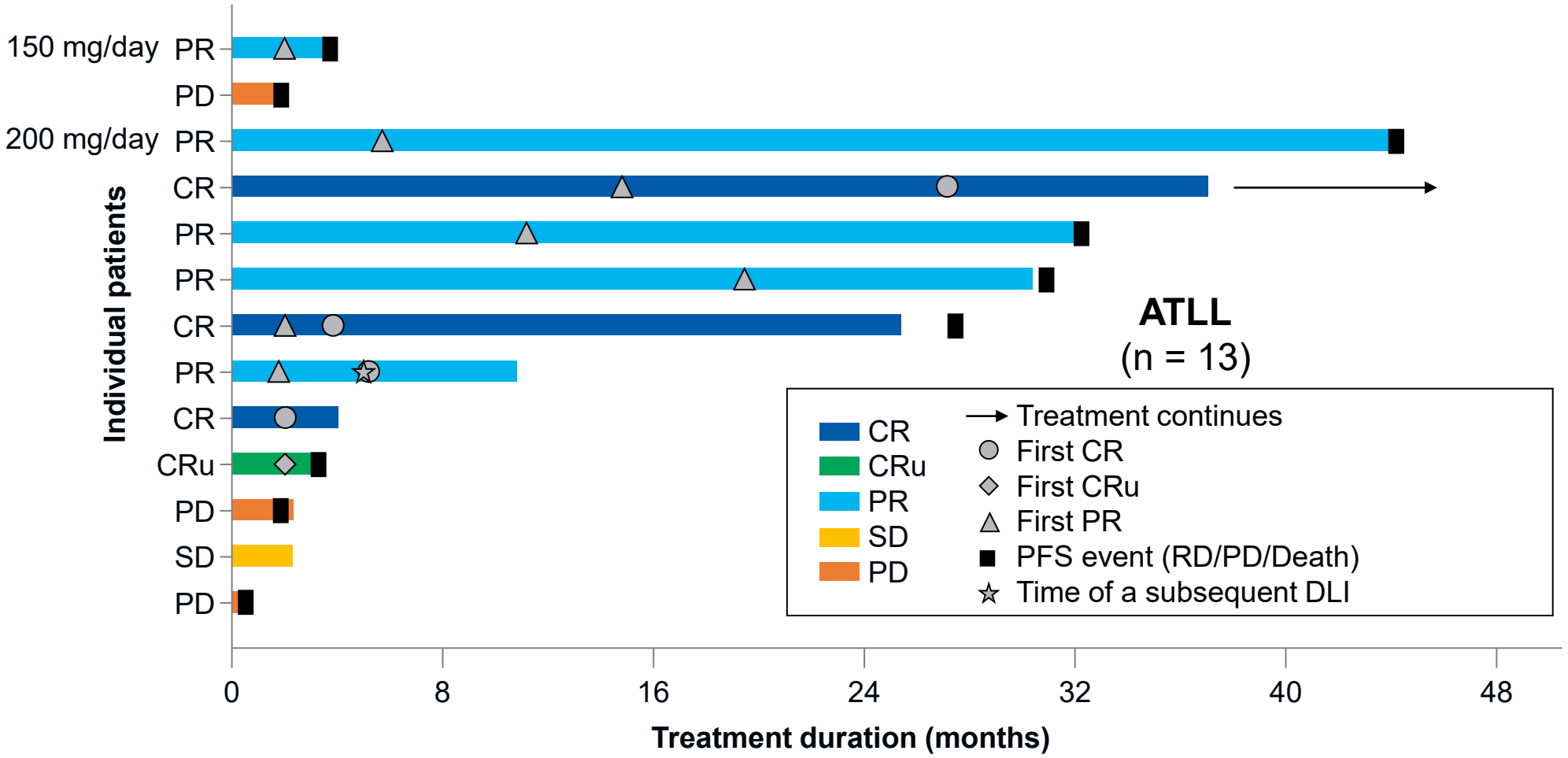
Exposure duration and clinical responses



Data cutoff: Dec 31, 2022.
Swimmer's plot excludes patients without available response assessments.

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Safety summary

TEAE/TRAE summary, n (%)	PTCL (N = 57[a])	ATLL (N = 14[b])
TEAEs	57 (100)	14 (100)
TRAEs	47 (82)	12 (86)
Grade ≥ 3 TEAEs	39 (68)	12 (86)
Grade ≥ 3 TRAEs	23 (40)	8 (57)
Serious TEAEs	29 (51)	7 (50)
Serious TRAEs	8 (14)	2 (14)

TEAE/TRAE summary, n (%)	PTCL (N = 57[a])	ATLL (N = 14[b])
TEAEs leading to death	0	0
TRAEs leading to death	0	0
TEAEs leading to discontinuation	6 (11)	0
TRAEs leading to discontinuation	4 (7)	0
TEAEs leading to dose reduction	4 (7)	1 (7)
TRAEs leading to dose reduction	4 (7)	1 (7)
TEAEs leading to dose interruption	30 (53)	4 (29)
TRAEs leading to dose interruption	15 (26)	3 (21)

Data cutoff: December 31, 2022.
[a] Includes patients who received 150 mg/day (n = 2) and 200 mg/day (n = 55).
[b] Includes patients who received 150 mg/day (n = 2) and 200 mg/day (n = 12).
TRAE, treatment-related treatment-emergent adverse event.

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

AML, acute myeloid leukemia; CMV, cytomegalovirus; MDS, myelodysplastic syndromes.

Most common TEAEs in patients with T-NHL

- Cytopenias were frequent; the most common TEAE was platelet count decreased

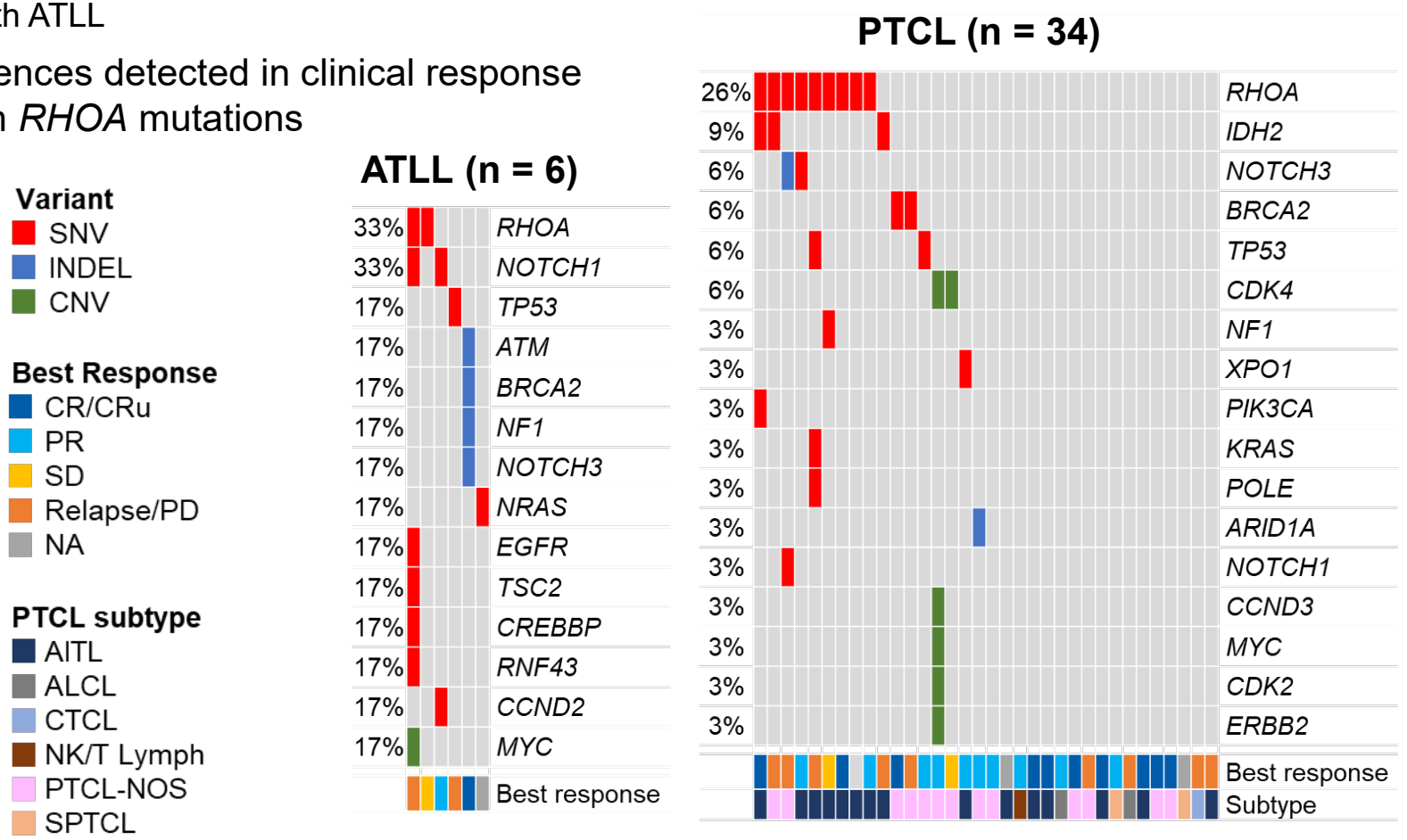
Preferred term, n (%)	TEAEs				TRAEs			
	PTCL (N = 57[a])		ATLL (N = 14[b])		PTCL (N = 57[a])		ATLL (N = 14[b])	
	All grades	Grade ≥ 3	All grades	Grade ≥ 3	All grades	Grade ≥ 3	All grades	Grade ≥ 3
Platelet count decreased[c]	32 (56)	13 (23)	9 (64)	4 (29)	25 (44)	7 (12)	8 (57)	3 (21)
Dysgeusia	25 (44)	0	8 (57)	0	24 (42)	0	8 (57)	0
Anemia[d]	23 (40)	10 (18)	5 (36)	2 (14)	14 (25)	3 (5)	4 (29)	1 (7)
Neutrophil count decreased[e]	16 (28)	11 (19)	7 (50)	6 (43)	12 (21)	7 (12)	6 (43)	5 (36)
Alopecia	16 (28)	0	6 (43)	0	15 (26)	0	6 (43)	0
Diarrhea	16 (28)	1 (2)	3 (21)	0	15 (26)	1 (2)	1 (7)	0
WBC count decreased[f]	14 (25)	7 (12)	4 (29)	3 (21)	11 (19)	4 (7)	4 (29)	3 (21)
Nausea	15 (26)	0	3 (21)	0	12 (21)	0	3 (21)	0
Fatigue[g]	13 (23)	3 (5)	3 (21)	0	8 (14)	3 (5)	1 (7)	0

Data cutoff: December 31, 2022.
[a] Includes patients who received 150 mg/day (n = 2) and 200 mg/day (n = 55). [b] Includes patients who received 150 mg/day (n = 2) and 200 mg/day (n = 12).
[c] Platelet count decreased includes MedDRA preferred terms Thrombocytopenia and Platelet count decreased.
[d] Anemia includes Anemia, Hemoglobin decreased, and Red blood cell count decreased. [e] Neutrophil count decreased includes Neutropenia and Neutrophil count decreased.
[f] WBC count decreased includes Leukopenia and White blood cell count decreased. [g] Fatigue includes Asthenia and Fatigue.
MedRA, Medical Dictionary for Regulatory Activities; WBC, white blood cell.

Jacobsen E, et al. ASH 2023 #303

Gene mutations at baseline

- Mutational analyses were performed using the Oncomine™ Comprehensive Assay (v3) covering 161 cancer genes
- The most frequently mutated gene was *RHOA*, which was detected in 11 of 40 patients
  - 9 of 34 patients with PTCL (AITL: n = 7; PTCL, NOS: n = 2)
  - 2 of 6 patients with ATLL
- No significant differences detected in clinical response among patients with *RHOA* mutations



Data cutoff: Dec 31, 2022.
CNV, copy number variation; CTCL, cutaneous T-cell lymphoma; INDEL, insertion-deletion; RHOA, ras homolog family member A; SNV, single nucleotide variant.

Conclusions

- These results indicate that valemetostat monotherapy showed encouraging efficacy in R/R PTCL and R/R ATLL
  - Valemetostat monotherapy induced durable responses, with median DOR of > 21 months in both R/R PTCL and R/R ATLL
- TEAEs were generally manageable in R/R PTCL and R/R ATLL
- Results for patients in this trial with R/R B-NHLs are described in an abstract by Izutsu et al (abstract #1731) at this congress
- Ongoing trials of valemetostat in patients with R/R PTCLs include the phase 2 monotherapy VALENTINE-PTCL01 trial (NCT04703192; Horwitz et al #302)

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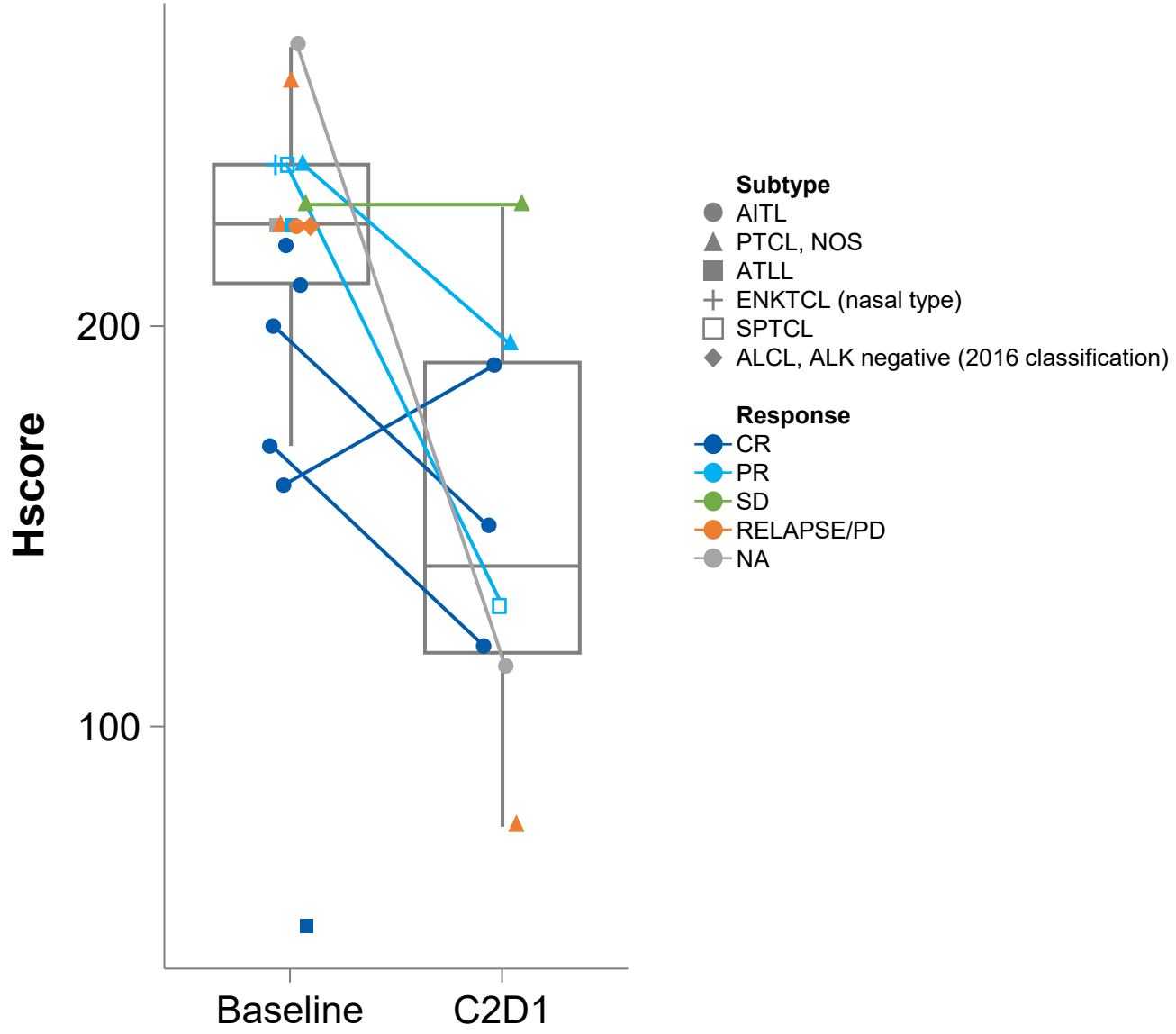
  - Kisato Nosaka
  - Jia Ruan
  - Atae Usunomiya
  - Jie Wang
  - Jasmine Zain

[a] Investigators are listed in alphabetical order of surname.

Backup slides

H3K27me3 levels during valemetostat treatment

- In most patients, H3K27me3 levels in tumor cells likely decreased on C2D1 compared with baseline



Data cutoff: December 31, 2022.
[a] Valemetostat was administered in continuous 28-day cycles.
C2D1, Cycle 2 Day 1.