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Long-term efficacy and safety of tucidinostat in patients with relapsed or refractory peripheral T-cell lymphoma: final analysis of phase IIb results

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Contributions

SR, WSK, KA, IC, KoI, NT, DM, KuT, JK, JA, MH, YK, HK, TU, DeHY, KjI , KiI, JSK, HGL, HM, HSE, MK, JHL, JSL, WSL, HN, TS, DoHY, SY participated in the study, treated patients, and provided data; SR, MG, HO and KeT were involved in the manuscript development; MG, HO and KeT were involved in the study design, data collection and

analysis and data interpretation; All authors were involved in the review of the contents and approved the submitted version of the manuscript.

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SR receives honoraria (Chugai, Ono and Janssen). WSK receives research funding (Sanofi, Beigene, Boryong, Roche, Kyowa Kirin, Donga). KA receives research funding (Solasia, Novartis, Janssen, Otsuka, IQVIA, Zenyaku, Chugai, Astellas) and honoraria (Kyowa Kirin, Takeda, Chugai, Meiji Seika, Eisai, Mochida). KoI receives research funding (AstraZeneca, Yakult, Abbvie, Kyowa Kirin, Incyte, Ono, Celgene/BMS, Daiichi Sankyo, Novartis, Chugai, Bayer, Beigene, Pfizer, Genmab, Janssen, LOXO Oncology) and honoraria (Janssen, Ono). NT receives research funding (Chugai, Kyowa Kirin, Daiichi Sankyo, Teijin). DM is a consultant (Amgen, Biopharma, Celgene, Kyowa Kirin, Novartis, Chugai, Ono, Takeda, Janssen, Sanofi, Otsuka, BMS, Astellas, Eisai, AbbVie, Taiho, MSD) and receives research funding (Ono, Celgene, Nippon Shinyaku, Janssen, Mundipharma, Eisai, Chugai, Kyowa Kirin, MSD, Zenyaku, Sanofi, SymBio, Takeda, AbbVie, BMS, AstraZeneca). KuT is a consultant (Daiichi Sankyo, Ono, HUYABIO, Yakult, Meiji Seika, Solasia) and receives research funding (Daiichi Sankyo, BMS, HUYABIO, Chugai, Bayer, Eisai, Kyowa Kirin, Regeneron Pharmaceuticals, Inc.) and honoraria (Celgene, Chugai, Eisai, Kyowa Kirin, Takeda). JK receives research funding (Ono, BMS, Eisai, Takeda) and honoraria (BMS, Ono, Eisai, Takeda). YK is a consultant (BMS Korea, Novartis Korea, Janssen Korea), has a Leadership position (Genome Opinion) and receives honoraria (Janssen Korea, Novartis Korea, BMS Korea) and has stock or stock options (Genome Opinion, Curocell). KjI receives honoraria (Chugai, Kyowa Kirin, Daiichi Sankyo, Meiji Seika, BMS) and research funding (Ono, Incyte, Kyowa Kirin, Daiichi Sankyo). KiI is a consultant (SAWAI, Micron, Kyowa Kirin) and receives research funding (Novartis, AbbVie, SymBio, Otsuka, Pfizer, Takeda, Kyowa Kirin) and honoraria (Takeda, BMS, Ono, Novartis, Chugai, Eisai, Janssen). HM receives research funding (Asahikasei, Astellas, Bayer, Behringer, BMS, Chugai, CSL Behring, Daiichi Sankyo, Sumitomo Dainippon, Eisai, Kyowa Kirin, Lilly, Merck Serono, Mitsubishi Tanabe, MSD, Nippon Kayaku, Nippon Shinyaku, Ono, Otsuka, Sanofi, Shionogi, Takeda, Taiho, Teijin, Tsumura) and honoraria (AbbVie, Bayer, BMS, Chugai, Daiichi Sankyo, Eisai, Genomic Health, Kyowa Kirin, Lilly, Meiji Seika, Merck Serono, MSD, Nihon Servier, Novartis, Ono, Otsuka, Pfizer, Sanofi, Sumitomo Dainippon, Taiho, Takeda), and others as clinical trial (AstraZeneca, Bayer, BMS, Chugai, Daiichi Sankyo, MSD, Ono, Pfizer, Taiho, Amgen, Novartis, Incyte). HN receives research funding

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Data sharing statement

Individual participant data will not be shared, because informed consents were not obtained for the data sharing, and protocol will also not be shared, due to sponsor policy.

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Letter to the Editor

Tucidinostat (formerly known as chidamide) is an orally bioavailable, novel benzamide class of histone deacetylase (HDAC) inhibitor that modifies the epigenetic mechanism by selectively blocking HDAC1, 2, 3, and 10[1,2]. We conducted a multicenter Phase IIb study to investigate the efficacy and safety of tucidinostat in Japanese and South Korean patients with relapsed or refractory (R/R) peripheral T-cell lymphoma (PTCL) in accordance with Good Clinical Practice, International Council for Harmonization guidelines. The study was approved by Ethics Committees at each site and an informed consent was obtained from each patient (clinicaltrials gov. Identifier: NCT02953652). The primary analysis was performed in March 2019 when the last subject completed second tumor assessment. As previously reported[3], the objective response rate (ORR) was 46% (95% confidence interval [CI]: 30.9, 61.0). The responses were observed across various PTCL subtypes, and most of the adverse events (AEs) were manageable by supportive care and dose modification[3].

Long term follow-up was performed to evaluate the efficacy of tucidinostat, particularly overall survival (OS), because the median follow-up period was 8.3 months in the primary analysis with eight patients (15%, 8/55) still on treatment and 28 patients (51%, 28/55) on survival follow-up. In this letter, we report the results of final analysis after an additional three-year follow-up from the data cut-off for primary analysis. This final analysis demonstrated that tucidinostat oral administration led to clinically meaningful improvement in OS for patients with R/R PTCL.

The study design and methodology were described in a previous report[3]. In brief, patients were included if they were aged 20 or older with a histologically diagnosed PTCL according to the 2008 World Health Organization Classification[4], and had a history of at least one prior systemic chemotherapy. The revised criteria (Lugano Classification in 2014[5]) were used for computed tomography-based treatment response assessment.

Between March 2017 and November 2018, a total of 74 patients were enrolled and the study was ended in February 2022. Of these, 55 patients were treated with tucidinostat (40 mg twice a week [BIW]) and included in the final analysis. Patients had been treated with a median of two (range, 1 to 9) prior systemic therapies. The median number of 28-day treatment cycles administered was 2.9 (range, 0.36 - 48.07). The incidence of dose reduction and dose interruption of tucidinostat were 52.7% (29/55), and 72.7% (40/55), respectively. The median relative dose intensity achieved was 0.72 (range, 0.42 - 1.05).

Seven patients (13%) received tucidinostat for more than 1 year with the longest treatment period of 44 months **(Figure 1)**. At the study end, three patients were still receiving tucidinostat. Among them, one patient decided not to receive more treatment, and the remaining two patients continued treatment with marketed tucidinostat instead of clinical trial tucidinostat tablets. The remaining 52 patients discontinued tucidinostat due to progressive disease (PD) (n=27), AEs (n=18), consent withdrawal (n=6), and non-compliance (n=1).

For the final analysis, efficacy was assessed in a per protocol set population (n=46), defined as subjects who met all eligibility criteria and had completed cycle 1 or discontinued tucidinostat during cycle 1 due to clinical PD, as assessed by an Independent Overall Efficacy Review Committee. The primary endpoint ORR was 46 % (95% CI: 30.9, 61.0). However, four patients who had achieved partial response (PR) at the time of primary analysis subsequently achieved complete response (CR). Thus, the CR rate increased from 11% (5/46) in primary analysis to 20% (9/46) in this final analysis. Disease subtypes of these additional four patients were PTCL-not otherwise specified (PTCL-NOS) (n=3) and angioimmunoblastic T-cell lymphoma (AITL) (n=1). It is noteworthy that PRs in these patients were durable, and the durability eventually led to CR after more than 18 months (18.4, 18.4, 18.4, 33.1 months) of continuous treatment. Overall, two of the later CR patients had sustained CR. Details of clinical courses for each of the four patients are depicted in **Supplementary Figure 1 (A-D)**.

At the conclusion of the study, with a median follow-up duration of 19.1 months, the median duration of response (DOR) was 25.7 months (95% CI: 5.4, Not reached [NR]) among 21 responders (**Figure 2A**). Ten patients (refractory [n=4], relapsed [n=6]) had a DOR ≥12 months, including three patients who assessed as PRs. In addition, six patients (refractory [n=3], relapsed [n=3]) continued to receive tucidinostat for more than 24 months, including two patients who were assessed as PRs; disease subtypes of these patients were PTCL-NOS (n=3), AITL (n=2) and enteropathy-associated T-cell lymphoma (EATL) (n=1). At the end of study, three patients (PTCL-NOS [n=2] and AITL [n=1]), remained CR and one patient remained PR (EATL) (n=1).

The median progression-free survival (PFS) was 5.5 months (95% CI: 2.9, 24.0) (**Figure 2B**). The median OS was 33.6 months (95% CI: 16.5, NR) (**Figure 2C**). To assess the impact of tumor response obtained by tucidinostat treatment on OS, survival curves by response status were created using the method of Simon & Makuch[6]. In this approach, the response status (response/non-response) was regarded as a time-dependent

covariate and OS was evaluated in each response status. The median OS was 12.6 months (6.6, 16.5) in non-response status and not reached (52.7, NR) in response status (**Supplementary Figure 2A**).

Regarding PTCL disease subtypes, the median OS for patients with AITL (52.7 months, 95% CI: 20.1, NR) was longer than for patients with PTCL-NOS (19.6 months, 95% CI: 10.1, NR) (**Supplementary Figure 2B**). For AITL (n=8), seven patients received post-study lymphoma treatment, and one patient discontinued tucidinostat due to AE; however, CR had been maintained for 43 months after the discontinuation without need for further lymphoma treatment in this case. For PTCL-NOS (n=34), 20 patients received post-study lymphoma treatment; seven patients withdrew consent and post-study treatment status was unknown, and four patients did not receive post study lymphoma treatment, three of whom died and one was alive without need for further lymphoma treatment. The remaining three patients had still on tucidinostat treatment at the study end.

In addition to the favorable efficacy, tucidinostat showed a manageable safety profile. In this study, seven patients had tucidinostat treatment for more than 12 cycles, with the longest treatment of 48 cycles, almost 4 years. Among them, five had dose reduced to 20 mg BIW to manage AEs. However, two patients were able to receive 40 mg BIW without dose reduction. The most common AEs (all grades) were thrombocytopenia, neutropenia, leukopenia, anemia, diarrhea, and lymphopenia (**Supplementary Table 1**). The incidence of Grade ≥3 AEs emerging in ≥20% of patients (N=55) only slightly increased for the AEs of thrombocytopenia (55%, +2 patients), neutropenia (38%), lymphopenia (24%), and leukopenia (20%). The number of patients reporting Grade ≥3 AEs was highest in Cycles 1 and 2 (**Figure 3)**. While the safety profiles of tucidinostat supported long-term therapy, patients treated with tucidinostat should be carefully monitored, and appropriate dose modification is essential.

With a three-year extended follow-up, additional responder was not reported because most of the non-responders had discontinued treatment before data cutoff for primary analysis. However, four patients deepened response from PR at primary analysis to CR at this final analysis. Although follow-up was still short to evaluate durability of response or survival, longer DOR and OS were observed in the final analysis. In the preceding Chinese phase II study[7], tucidinostat showed the median PFS, DOR, and OS of 2.1, 9.9, and 21.4 months, respectively, all of which seem longer in our study. We

speculate that these differences may be due to differences in doses of tucidinostat and the patient characteristics. In particular, more patients in our study (36%) had only received one prior line of treatment in contrast to the Chinese study (20%), suggesting that more patients with favorable features were enrolled in our study.

There was a trend of longer OS in patients with AITL compared to other subtypes with tucidinostat treatment. This is consistent with the higher response rates for HDAC inhibitors for AITL[7,8], although the underlying mechanisms are unknown. However, it should be interpreted with caution because of the small numbers of AITL patients and the heterogeneity of the post-study lymphoma treatment. Furthermore, the responses appeared more durable in some patients with PTCL-NOS and EATL. Two patients with PTCL-NOS, and one patient with EATL (75 year-old male with refractory disease after the first line therapy, history of Celiac disease was not reported at baseline) had DOR ≥36 months. The notion that PTCL subtypes may influence the disease responsiveness to HDAC inhibitors was supported by several studies[9,10].

Because only the information of therapy immediately after tucidinostat discontinuation was collected in this study, there was not sufficient data regarding the efficacy of the post-study lymphoma treatment(s) or the number of patients who subsequently underwent autologous stem cell transplantation (SCT) and/or allogeneic SCT. Thus, the impact of subsequent salvage therapy on OS could not be assessed.

In summary, this final analysis with three-year extended follow-up provided additional evidence of the efficacy of tucidinostat with durable responses in a subset of patients and an improvement in OS for Japanese and South Korean patients with R/R PTCL. The safety profiles remained consistent with those observed in the primary analysis[3], and no new safety signals were observed during the additional follow-up period.

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Figure Legends

Figure 1. Swimmer plot showing treatment exposure and responses over time by response in 46 patients.

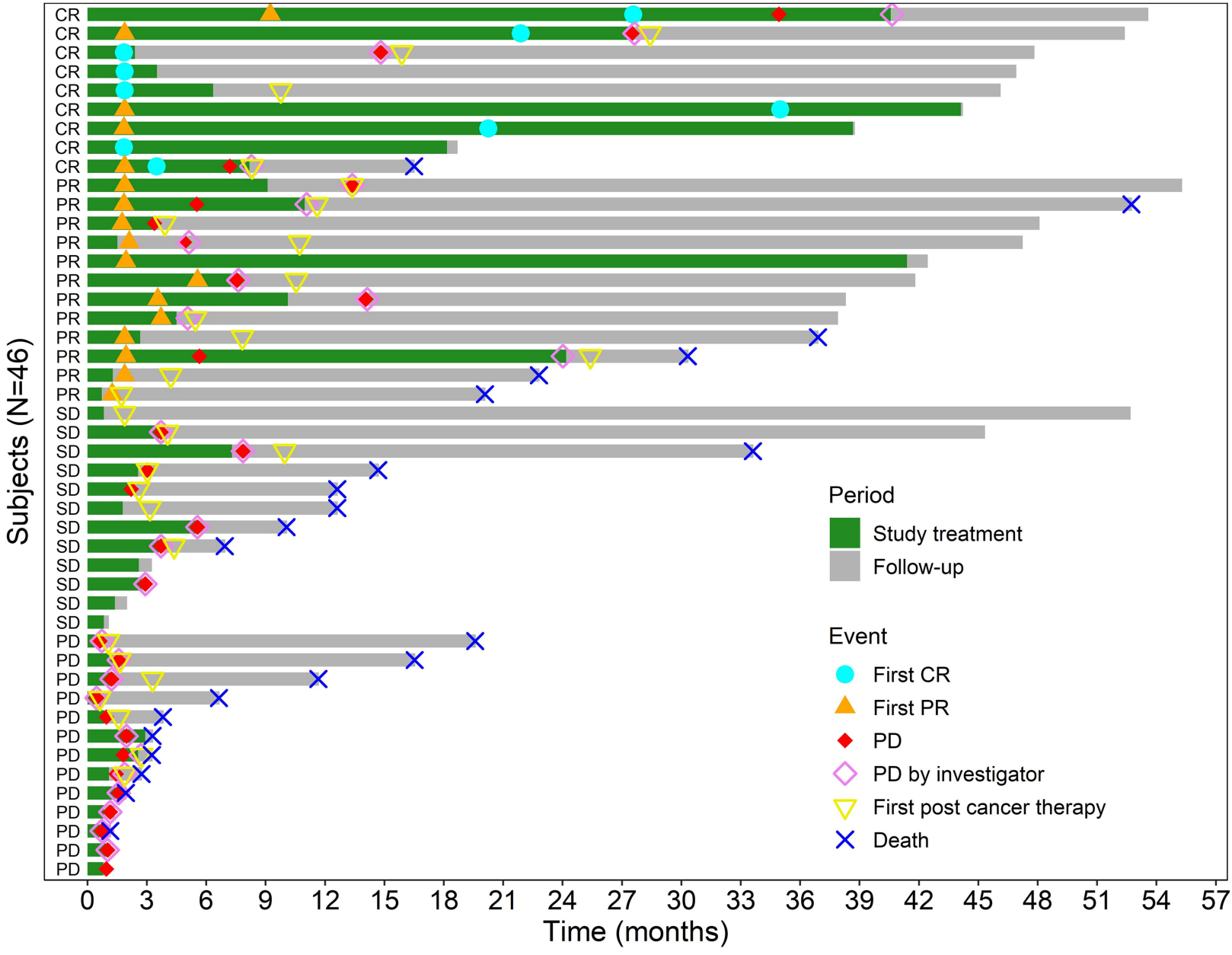
Figure 2. Duration of response, Progression-Free Survival and Overall Survival

(A) Kaplan-Meier plot of Duration of Response

(B) Kaplan-Meier plot of Progression-Free Survival

(C) Kaplan-Meier plot of Overall Survival

Figure 3. Incidence of grade ≥3 Adverse Events by treatment cycle. Cycles in which no grade ≥ 3 Adverse Events were reported are not included.


Subjects (N=46)
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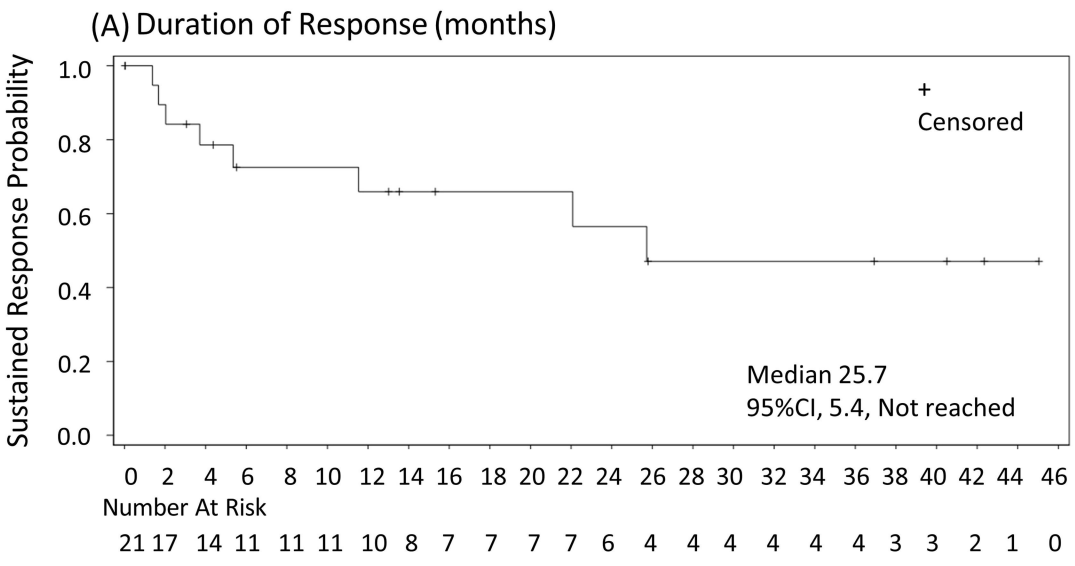
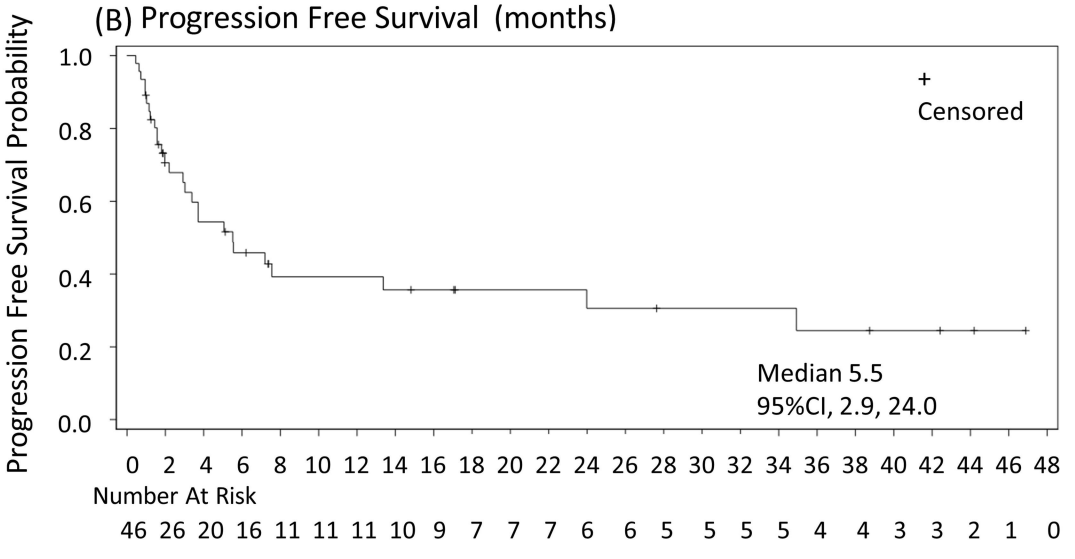
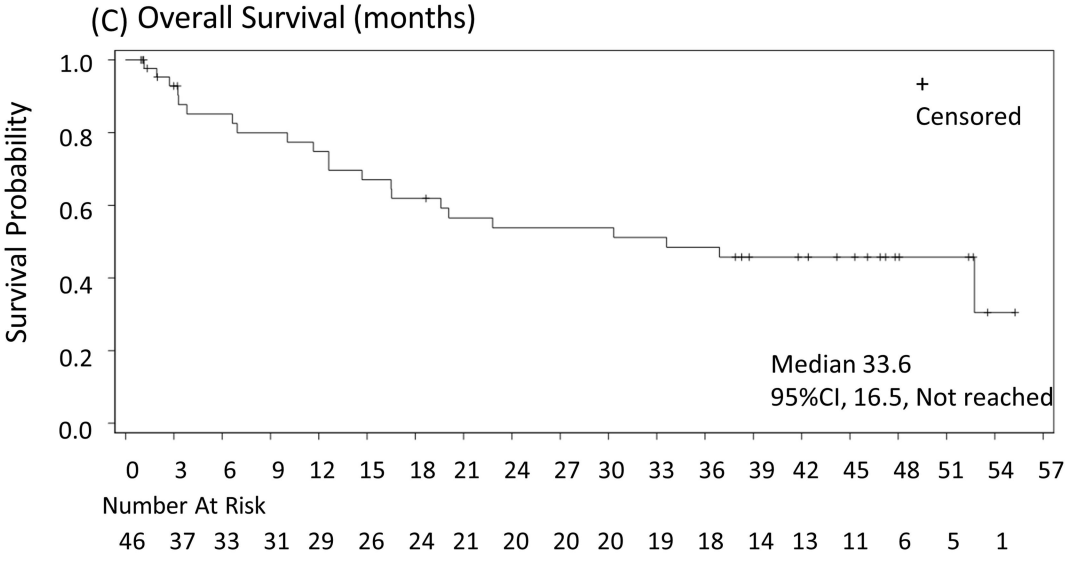
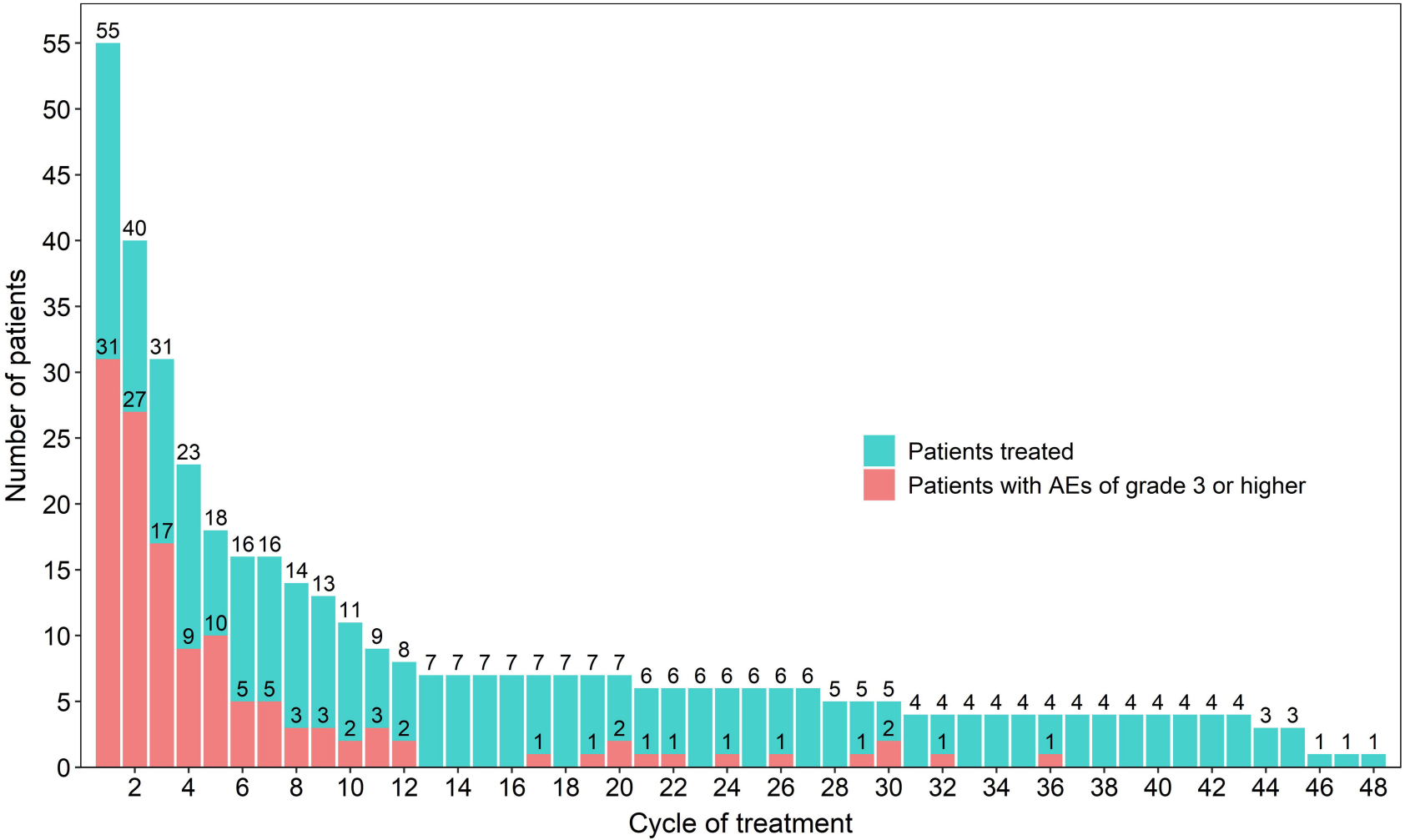
0
3
6
9
12
15
18
21
24
27
30
33
36
39
42
45
48
51
54
57
Time (months)
Period
Study treatment
Follow-up
Event
First CR
First PR
PD
PD by investigator
First post cancer therapy
Death


(A) Duration of Response (months)
Sustained Response Probability
1.0
0.8
0.6
0.4
0.2
0.0
+
Censored
Median 25.7
95%CI, 5.4, Not reached
0 2 4 6 8 10 12 14 16 18 20 22 24 26 28 30 32 34 36 38 40 42 44 46
Number At Risk
21 17 14 11 11 11 10 8 7 7 7 7 6 4 4 4 4 4 4 3 3 2 1 0

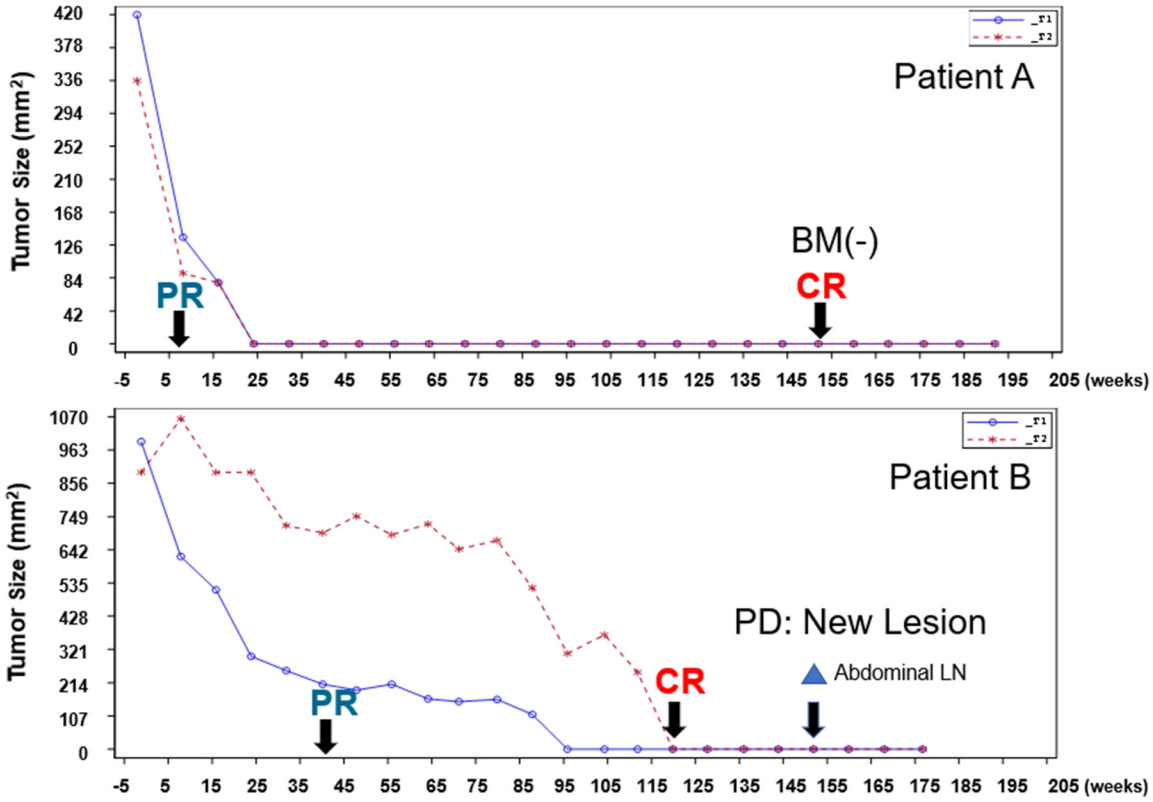

(B) Progression Free Survival (months)
Progression Free Survival Probability
1.0
0.8
0.6
0.4
0.2
0.0
+
Censored
Median 5.5
95%CI, 2.9, 24.0
0 2 4 6 8 10 12 14 16 18 20 22 24 26 28 30 32 34 36 38 40 42 44 46 48
Number At Risk
46 26 20 16 11 11 11 10 9 7 7 7 6 6 5 5 5 5 4 4 3 3 2 1 0

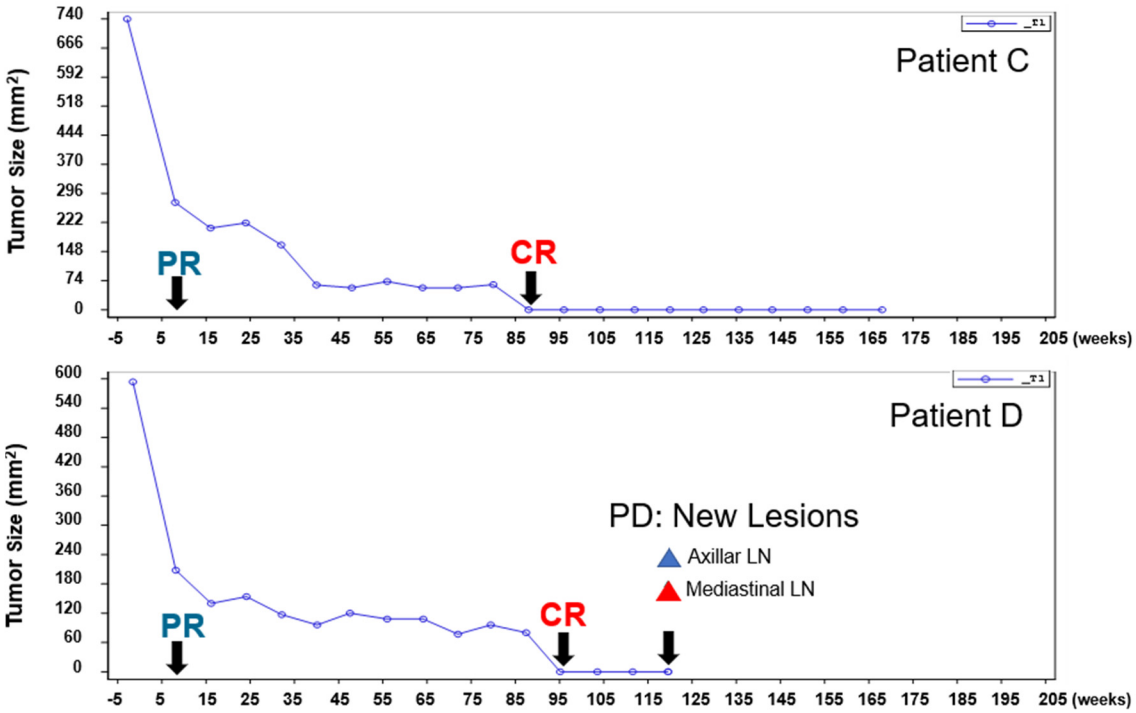

(C) Overall Survival (months)
Survival Probability
1.0
0.8
0.6
0.4
0.2
0.0
+
Censored
Median 33.6
95%CI, 16.5, Not reached
0 3 6 9 12 15 18 21 24 27 30 33 36 39 42 45 48 51 54 57
Number At Risk
46 37 33 31 29 26 24 21 20 20 20 19 18 14 13 11 6 5 1


Number of patients
Cycle of treatment
Patients treated
Patients with AEs of grade 3 or higher
55 40 31 23 18 16 16 14 13 11 9 8 7 7 7 7 7 7 7 7 6 6 6 6 6 6 6 5 5 5 4 4 4 4 4 4 4 4 4 4 4 4 3 3 1 1 1
31 27 17 9 10 5 5 3 3 2 3 2 1 1 2 1 1 1 1 1 2 1 1
0 5 10 15 20 25 30 35 40 45 50 55
2 4 6 8 10 12 14 16 18 20 22 24 26 28 30 32 34 36 38 40 42 44 46 48

Supplementary Figure 1.

Tumor change by individual subject who achieved CR after the primary analysis

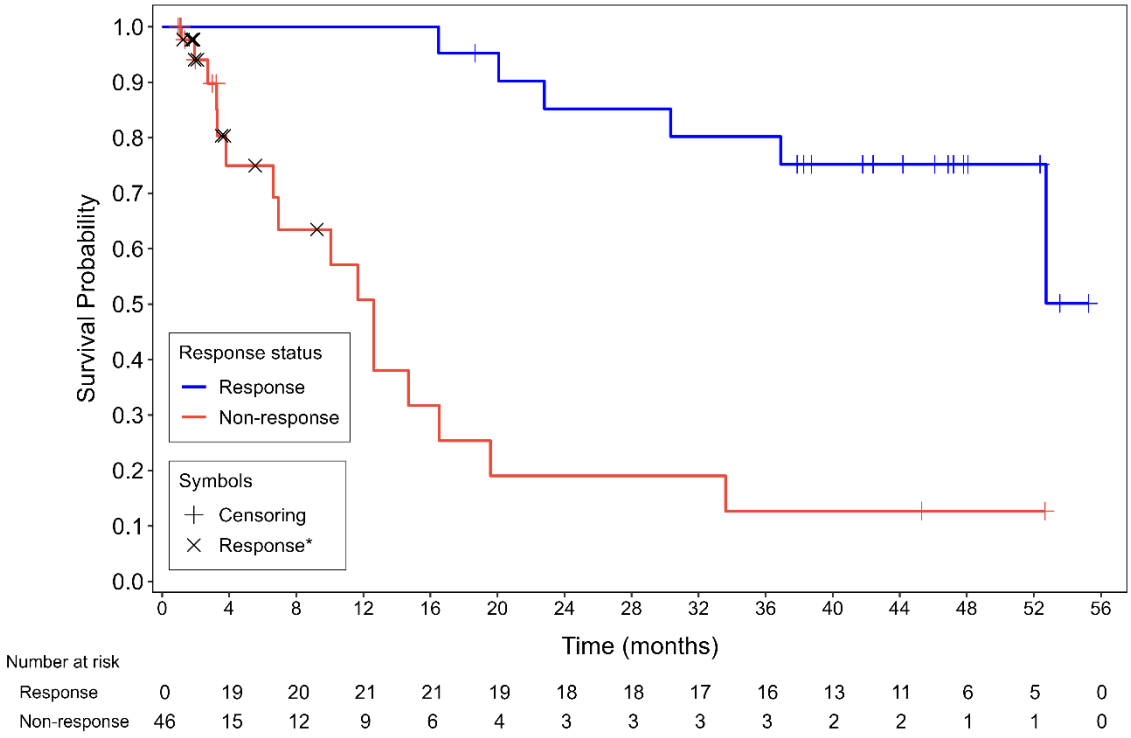




BM = Bone Marrow, CR = complete response, LN = lymph node, PD = progreesion disease, PR = partial response, T = target

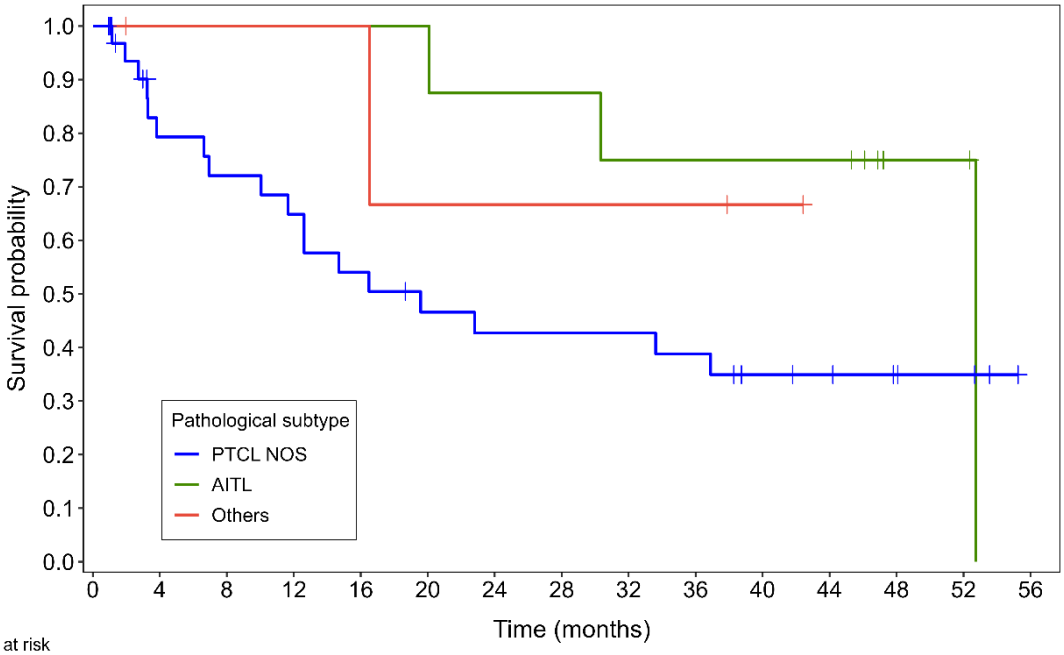
Supplementary Figure 2.

(A) Simon- Makuch estimates of overall survival by response status These survival curves were drawn by designating objective response as a time-dependent covariate to remove a bias (guarantee-time bias) related to differences in time to response and to take into consideration that the patient’s response status may change over time.



*The symbol X represents the time point at which a patient's response status changed from “non-response” to “response.”

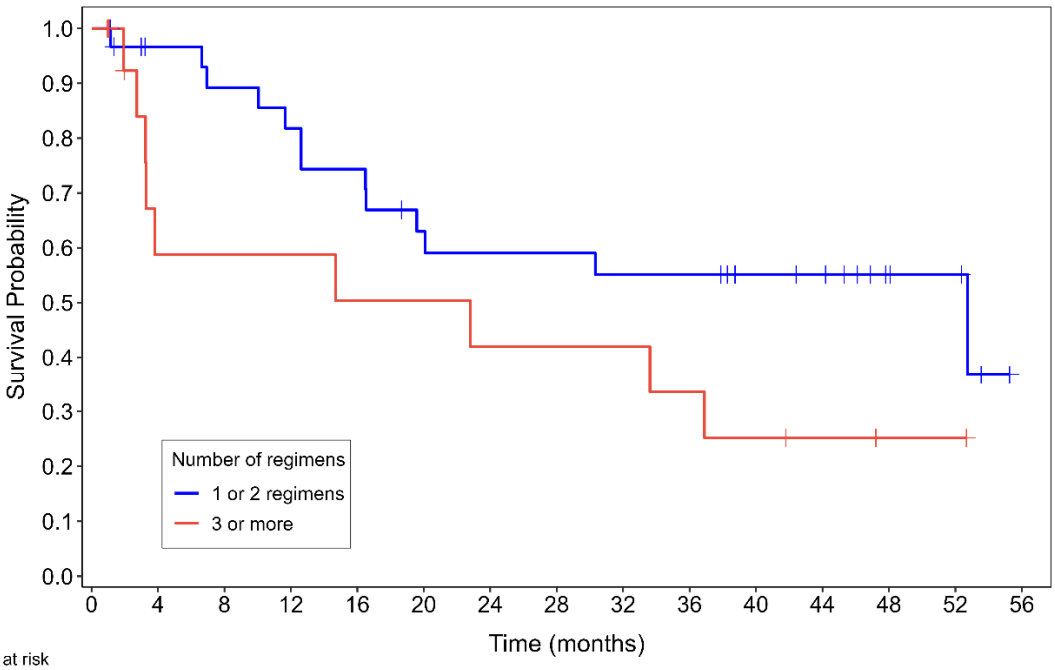
(B) Kaplan-Meier plot of Overall Survival by PTCL subtype



Number at risk

PTCL NOS	34	22	20	18	15	12	11	11	11	10	7	6	4	3	0
AITL	8	8	8	8	8	8	7	7	6	6	6	6	2	2	0
Others	4	3	3	3	3	2	2	2	2	2	1	0	0	0	0

(C) Kaplan-Meier plot of Overall Survival by prior therapy number



Number at risk

1 or 2 regimens	31	26	24	22	20	16	15	15	14	14	11	10	5	4	0
3 or more	15	7	7	7	6	6	5	5	5	4	3	2	1	1	0

Supplementary Table 1.

AEs regardless of causal relationship to tucidinostat observed in ≥10% of patients (n=55).

Adverse event	Any Grade, n (%)	≥ Grade 3, n (%)
Number of patients with at least one AE	55 (100)	48 (87)
Thrombocytopenia	46 (84)	30 (55)
Neutropenia	32 (58)	21 (38)
Leukopenia	25 (46)	11 (20)
Anemia	19 (35)	10 (18)
Diarrhea	19 (35)	1 (2)
Lymphopenia	17 (31)	13 (24)
Decreased appetite	14 (26)	2 (4)
Nausea	12 (22)	0 (0)
Pyrexia	13 (24)	0 (0)
Blood alkaline phosphatase increased	8 (15)	1 (2)
Gamma-glutamyltransferase increased	8 (15)	3 (6)
Malaise	9 (16)	0 (0)
Aspartate aminotransferase increased	7 (13)	0 (0)
Cough	7 (13)	0 (0)

Adverse event	Any Grade, n (%)	≥ Grade 3, n (%)
Headache	7 (13)	0 (0)
Weight decreased	7 (13)	1 (2)
Fatigue	6 (11)	0 (0)
Alanine aminotransferase increased	6 (11)	0 (0)
Back pain	6 (11)	0 (0)
Muscle spasms	6 (11)	0 (0)

Abbreviations: n: number of subjects; AE: adverse event.

Anemia: Anemia/Hemoglobin decreased

Leukopenia: Leukopenia/White blood cell count decreased

Lymphopenia: Lymphocyte count decreased/Lymphopenia

Neutropenia: Neutropenia/Neutrophil count decreased/Granulocytopenia

Thrombocytopenia: Thrombocytopenia/Platelet count decreased