

## Supplementary Information

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*Treating relapsed/refractory mature T- and NK-cell neoplasms with tislelizumab: a multicenter open label phase 2 study*

### Supplemental Methods

#### Study patients

Eligible patients were adult males and females with R/R mature T- and NK-cell neoplasms (histologically confirmed based on the World Health Organization 2016 classification).<sup>1</sup>

Eligible patients had measurable disease per the Lugano criteria<sup>2</sup> (cohorts 1 and 2) or the International Society of Cutaneous Lymphoma (ISCL)/European Organization of Research and Treatment of Cancer (EORTC) criteria<sup>3</sup> (cohort 3). Patients were allocated to one of the three cohorts based on their histologic diagnosis. Cohort 1 included patients with relapsed/refractory (R/R) extranodal NK-/T-cell lymphomas (nasal or non-nasal type); patients with aggressive NK leukemia were excluded. Cohort 2 was comprised of patients with R/R mature T-cell neoplasms limited to peripheral T-cell lymphoma not otherwise specified (cohort 2a), angioimmunoblastic T-cell lymphoma (cohort 2b), and angioimmunoblastic T-cell lymphoma (cohort 2c). Cohort 3 included patients with R/R T-cell lymphomas, limited to mycosis fungoides or Sézary syndrome of stage IB or higher. All patients had previously received at least one appropriate systemic therapy (e.g., a non-anthracycline-based regimen such as L-asparaginase-based therapy for patients in cohort 1 or combination chemotherapy for patients in cohort 2) and had disease progression during or after completion of the most recent therapy or refractory disease. Radiation therapy alone was not considered a prior systemic therapy. Patients with R/R anaplastic large cell lymphoma

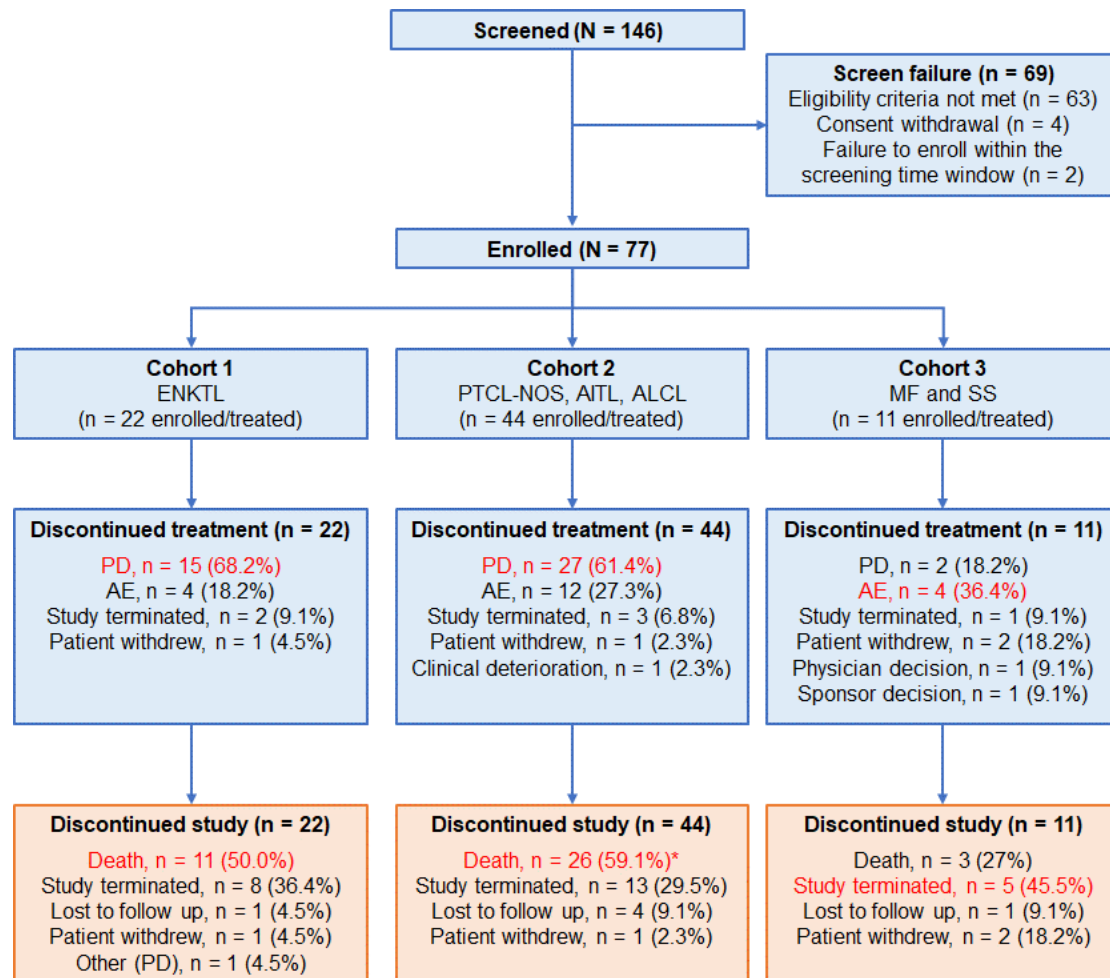
(ALCL) were required to have received prior treatment with brentuximab vedotin, provided it was available in their country. Refractory disease was defined as failure to achieve complete response (CR) or partial response (PR) to the most recent therapy, provided that the most recent therapy was an appropriate systemic therapy for mature T-cell or NK-cell lymphoma. Patients were not eligible for the study if they were eligible for autologous or allogeneic stem cell transplantation (unless the patient had refused transplantation), had undergone prior allogeneic hematopoietic stem cell transplantation or organ transplantation, or had received autologous stem cell transplantation within 6 months prior to the first dose of study drug. Patients had adequate organ function, did not have active autoimmune disease, had no known active infection with hepatitis B or C, HIV, or human T-cell lymphotropic virus, and had life expectancy  $\geq 6$  months.

## REFERENCES

1. Swerdlow SH, Campo E, Pileri SA, et al. The 2016 revision of the World Health Organization classification of lymphoid neoplasms. *Blood*. 2016;127(20):2375-2390.
2. Cheson BD, Fisher RI, Barrington SF, et al. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. *J Clin Oncol*. 2014;32(27):3059-3068.
3. Cheson BD, Ansell S, Schwartz L, et al. Refinement of the Lugano Classification lymphoma response criteria in the era of immunomodulatory therapy. *Blood*. 2016;128(21):2489-2496.

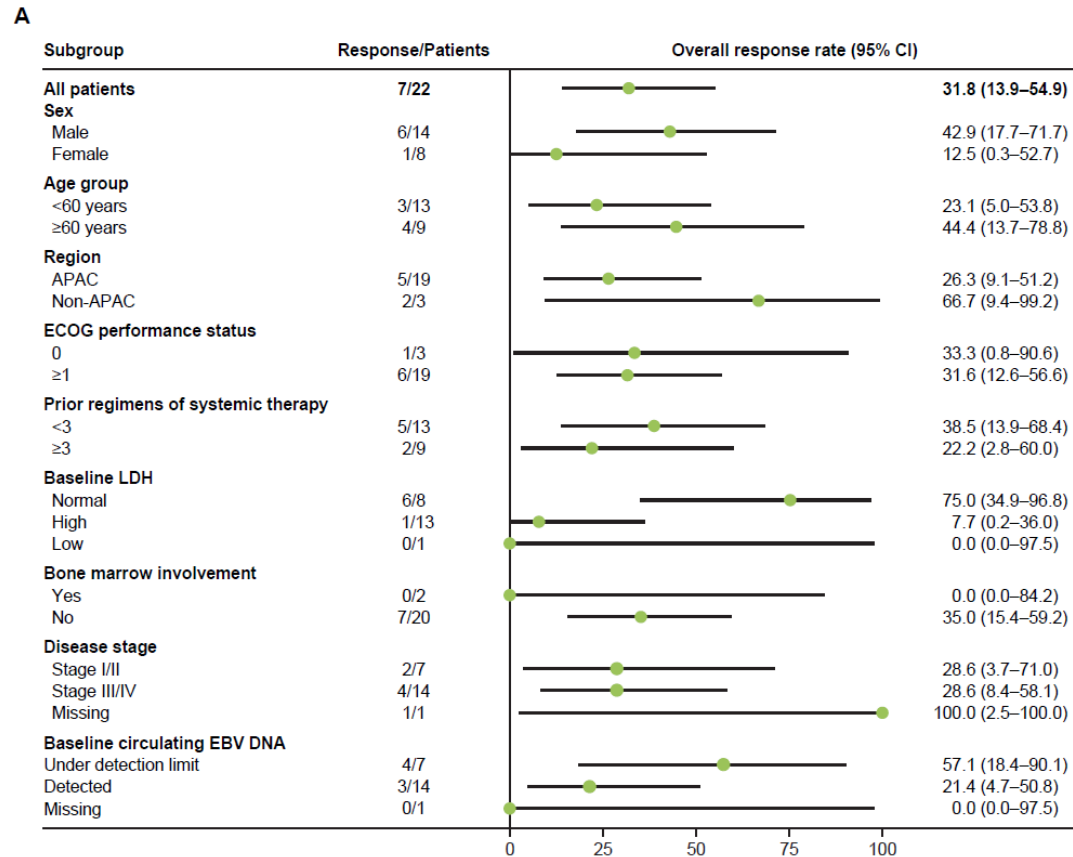
## Supplemental Figure

**Figure S1. Patient disposition and reasons for discontinuation**

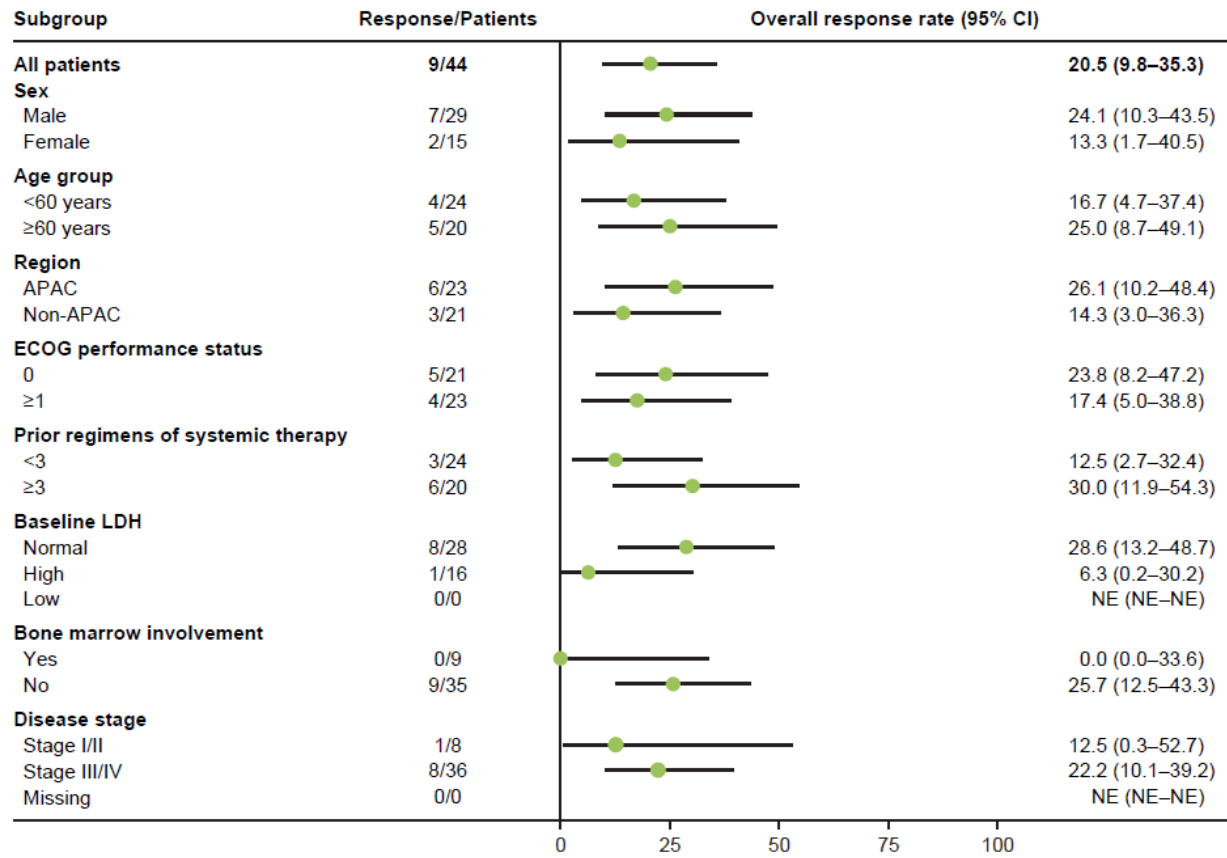


\*One patient died due to COVID-19. Note: Patients who were still benefiting from the study treatment at study termination were transferred to a long-term extension study (clinicaltrials.gov NCT04164199; EudraCT 2019-002554-23) to receive continued therapy until disease progression, intolerable toxicities, or voluntary withdrawal. Abbreviations: AE, adverse event; AITL, angioimmunoblastic T-cell lymphoma; ALCL, anaplastic large cell lymphoma; ENKTL, extranodal natural killer-/T-cell lymphoma; MF, mycosis fungoides; PD, progressive disease; PTCL-NOS, peripheral T-cell lymphoma-not otherwise specified; SS, Sézary syndrome.

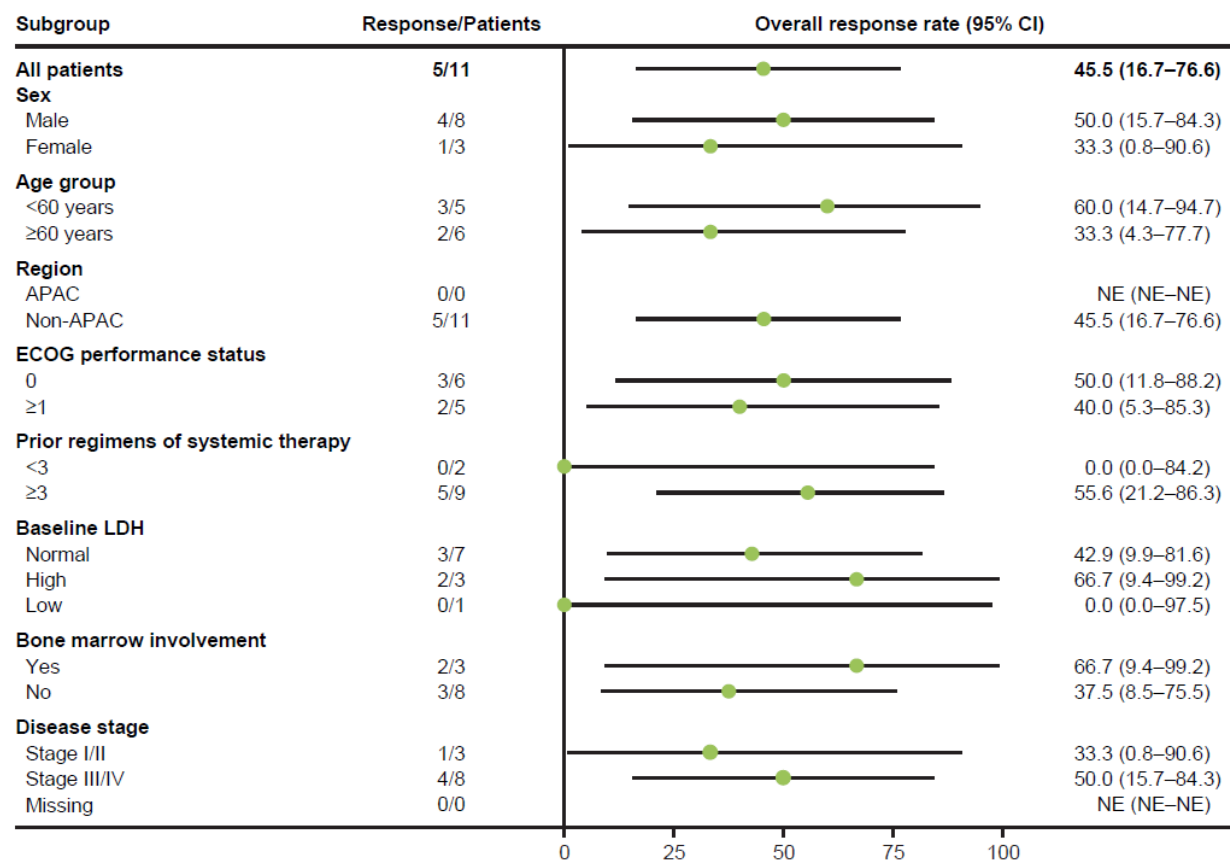
**Figure S2. Subgroup analyses of the primary endpoint (ORR) for (A) cohort 1 [ENKTL], (B) cohort 2 [PCTLs], and (C) cohort 3 [MF or SS]**



**B**

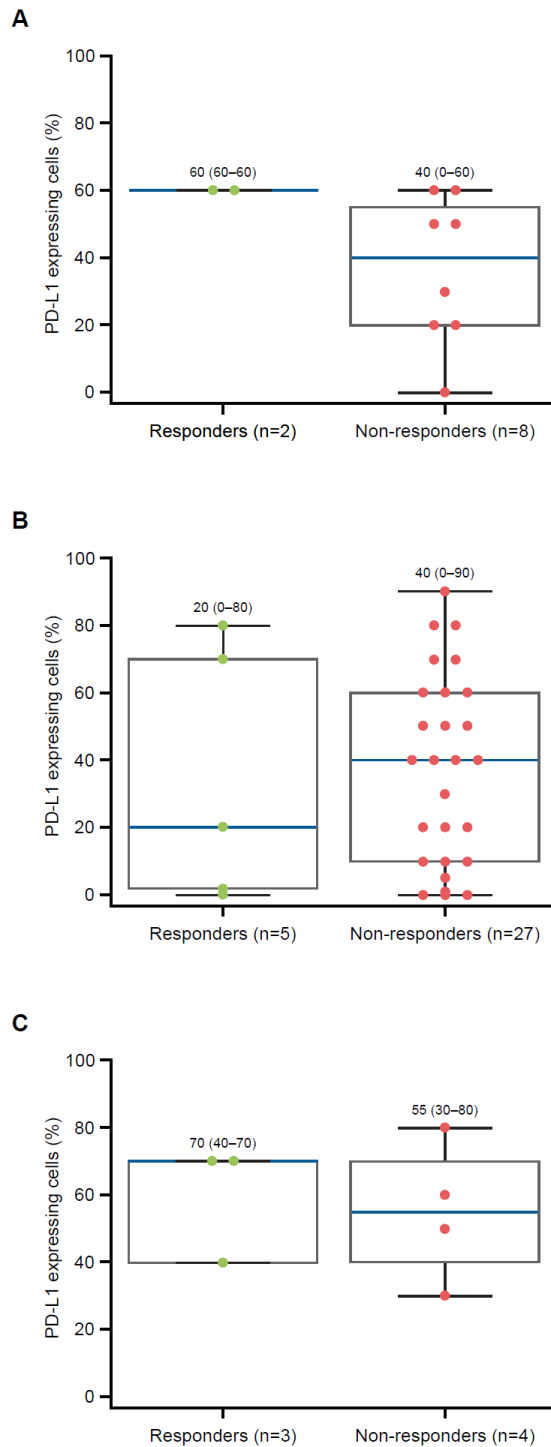


C



Abbreviations: APAC, Asia-Pacific; CI, confidence interval; EBV, Epstein-Barr virus; ECOG, Eastern Cooperative Oncology Group performance status; LDH, lactate dehydrogenase; NE, not evaluable; ORR, overall response rate.

**Figure S3. PD-L1 expression by response status in (A) cohort 1 [ENKTL], (B) cohort 2 [PCTLs], and (C) cohort 3 [MF or SS].** Only patients with available PD-L1 expression level data are included. PD-L1 expression level was assessed by immunohistochemistry and defined as the percentage of cells expressing PD-L1 (including tumor cells and tumor-infiltrating immune cells). Median (range) is shown.



**Figure S4. Circulating EBV DNA in (A) cohort 1 [ENKTL] and (B) cohort 2 [PCTLs].**

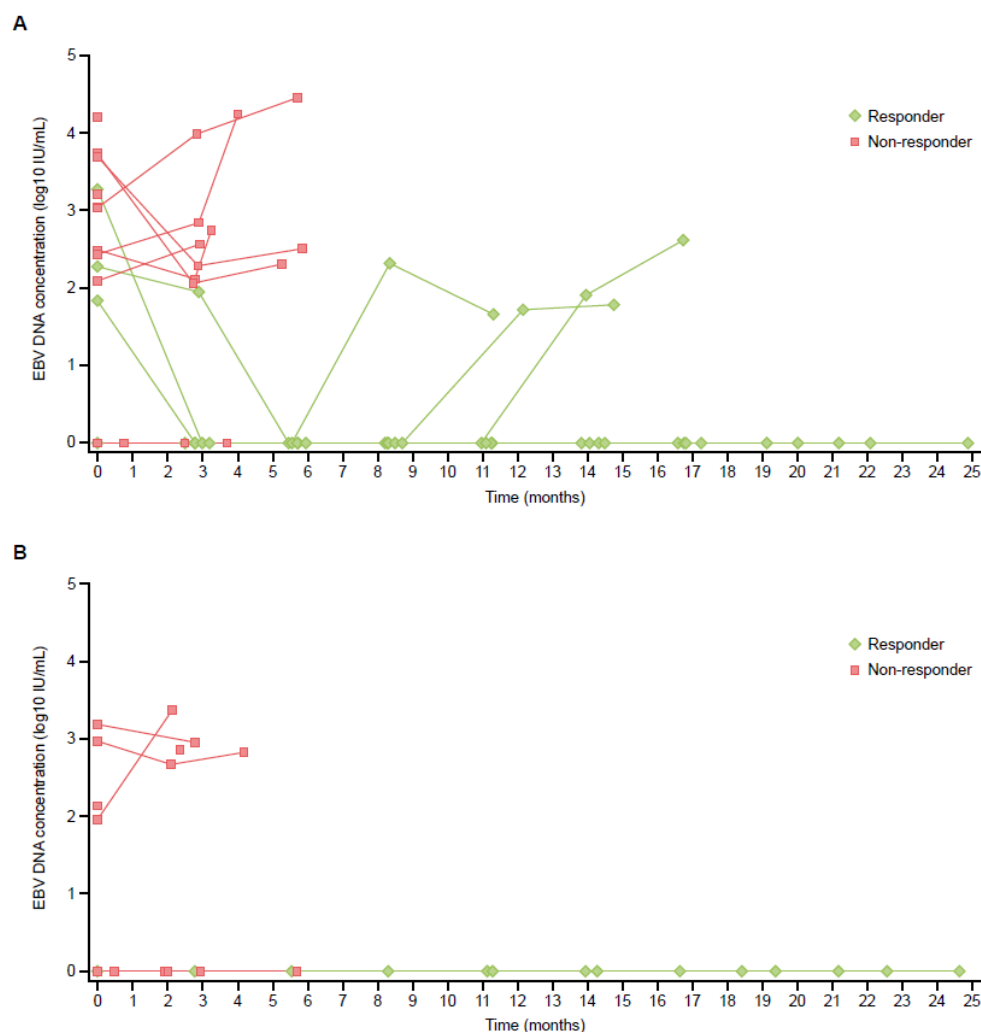
In cohorts 1 and 2, EBV expression was assessed at screening using EBV-encoding RNA *in situ* hybridization, and after this, circulating EBV DNA was scheduled to be measured every 4 cycles during treatment (in patients who were EBV positive at screening) using quantitative polymerase chain reaction.

(A) In cohort 1, all the patients were EBV encoding RNA positive at baseline.

Baseline circulating EBV DNA was detectable in 14 patients (three responders), undetectable in seven patients (four responders) and missing in one patient.

(B) In cohort 2, 14 patients were EBV encoding RNA positive at baseline. Baseline circulating EBV DNA was detectable in five patients (no responders) and undetectable in 13 patients (five responders).

Note: The lower limit of the circulating EBV DNA quantitation test was 1.6 log<sub>10</sub> IU/mL. Any value lower than 1.6 log<sub>10</sub> IU/mL was considered undetectable and counted as 0 log<sub>10</sub> IU/mL.





**Table S1. Most Frequent Prior Systemic Therapies by Category and Main Components**

<b>Treatment category*</b> <b>Main component</b>	<b>Cohort 1</b> <b>ENKTL</b> <b>(n = 22)</b>	<b>Cohort 2</b> <b>PTCL</b> <b>(n = 44)</b>	<b>Cohort 3</b> <b>MF or SS</b> <b>(n = 11)</b>	<b>Total</b> <b>(N = 77)</b>
Patients with any prior systemic therapy, n (%)	22 (100.0)	44 (100.0)	11 (100.0)	77 (100.0)
Most frequent prior systemic therapies (>20% in any cohort), n (%)				
Alkylating agents and related substances	20 (90.9)	44 (100.0)	7 (63.6)	71 (92.2)
Nitrogen mustard analogues	14 (63.6)	44 (100.0)	5 (45.5)	63 (81.8)
Cyclophosphamide	6 (27.3)	44 (100.0)	3 (27.3)	53 (68.8)
Ifosfamide	10 (45.5)	8 (18.2)	0 (0.0)	18 (23.4)
Platinum compounds	14 (63.6)	21 (47.7)	1 (9.1)	36 (46.8)
Cisplatin	7 (31.8)	15 (34.1)	1 (9.1)	23 (29.9)
Oxaliplatin	8 (36.4)	8 (18.2)	0 (0.0)	16 (20.8)
Plant alkaloids and other natural products	17 (77.3)	44 (100.0)	4 (36.4)	65 (84.4)
Vinca alkaloids and analogues	8 (36.4)	42 (95.5)	4 (36.4)	54 (70.1)
Vincristine	5 (22.7)	36 (81.8)	3 (27.3)	44 (57.1)
Podophyllotoxin derivatives	13 (59.1)	31 (70.5)	3 (27.3)	47 (61.0)
Etoposide	13 (59.1)	31 (70.5)	3 (27.3)	47 (61.0)
Cytotoxic antibiotics and related substances	5 (22.7)	41 (93.2)	7 (63.6)	53 (68.8)
Anthracyclines	5 (22.7)	41 (93.2)	7 (63.6)	53 (68.8)
Doxorubicin	2 (9.1)	28 (63.6)	7 (63.6)	37 (48.1)
Epirubicin	3 (13.6)	13 (29.5)	0 (0.0)	16 (20.8)
Antimetabolites	18 (81.8)	23 (52.3)	8 (72.7)	49 (63.6)
Pyrimidine analogues	14 (63.6)	23 (52.3)	7 (63.6)	44 (57.1)
Gemcitabine	14 (63.6)	18 (40.9)	7 (63.6)	39 (50.6)
Cytarabine	0 (0.0)	9 (20.5)	1 (9.1)	10 (13.0)
Folic acid analogues	10 (45.5)	4 (9.1)	1 (9.1)	15 (19.5)
Methotrexate	10 (45.5)	4 (9.1)	1 (9.1)	15 (19.5)
L-asparaginase	21 (95.5)	4 (9.1)	0 (0.0)	25 (32.5)
Pegaspargase	16 (72.7)	2 (4.5)	0 (0.0)	18 (23.4)
Asparaginase	8 (36.4)	2 (4.5)	0 (0.0)	10 (13.0)
Histone deacetylase (HDAC) inhibitors	3 (13.6)	13 (29.5)	3 (27.3)	19 (24.7)
Chidamide	3 (13.6)	9 (20.5)	0 (0.0)	12 (15.6)
Monoclonal antibodies	2 (9.1)	7 (15.9)	9 (81.8)	18 (23.4)
Brentuximab Vedotin	2 (9.1)	7 (15.9)	8 (72.7)	17 (22.1)
Retinoids for cancer treatment	0 (0.0)	1 (2.3)	5 (45.5)	6 (7.8)
Bexarotene	0 (0.0)	1 (2.3)	5 (45.5)	6 (7.8)
Corticosteroids for systemic use	20 (90.9)	42 (95.5)	4 (36.4)	66 (85.7)
Glucocorticoids	20 (90.9)	42 (95.5)	4 (36.4)	66 (85.7)
Dexamethasone	14 (63.6)	14 (31.8)	1 (9.1)	29 (37.7)
Prednisone	5 (22.7)	28 (63.6)	1 (9.1)	34 (44.2)
Prednisolone	2 (9.1)	13 (29.5)	2 (18.2)	17 (22.1)
Methylprednisolone	0 (0.0)	9 (20.5)	0 (0.0)	9 (11.7)
Immunostimulants	0 (0.0)	1 (2.3)	4 (36.4)	5 (6.5)
Interferons	0 (0.0)	1 (2.3)	4 (36.4)	5 (6.5)
Other dermatological preparations	0 (0.0)	0 (0.0)	4 (36.4)	4 (5.2)

\*Patients with two or more medications within a category or main component are counted only once within that category or main component. ENKTL, extranodal NK-/T-cell lymphomas; MF, mycosis fungoides; PTCL, peripheral T-cell lymphoma; SS, Sézary syndrome.

**Table S2. Most Frequent Subsequent Therapies by Category and Main Components**

<b>Treatment category*</b> <b>Main component</b>	<b>Cohort 1</b> <b>ENKTL</b> <b>(n = 22)</b>	<b>Cohort 2</b> <b>PTCL</b> <b>(n = 44)</b>	<b>Cohort 3</b> <b>MF or SS</b> <b>(n = 11)</b>	<b>Total</b> <b>(N = 77)</b>
Patients with any subsequent local treatment, n (%)	2 (9.1)	3 (6.8)	0 (0.0)	5 (6.5)
Radiotherapy	1 (4.5)	2 (4.5)	0 (0.0)	3 (3.9)
Other local treatment	1 (4.5)	1 (2.3)	0 (0.0)	2 (2.6)
Patients with any subsequent systemic therapy, n (%)	11 (50.0)	28 (63.6)	1 (9.1)	40 (51.9)
Most frequent Subsequent Systemic Therapies (>5% overall), n (%)				
Alkylating agents and related substances	3 (13.6)	17 (38.6)	0 (0.0)	20 (26.0)
Nitrogen mustard analogues	1 (4.5)	9 (20.5)	0 (0.0)	10 (13.0)
Platinum compounds	2 (9.1)	9 (20.5)	0 (0.0)	11 (14.3)
Antimetabolites	4 (18.2)	11 (25.0)	0 (0.0)	15 (19.5)
Pyrimidine analogues	2 (9.1)	10 (22.7)	0 (0.0)	12 (15.6)
Plant alkaloids and other natural products	3 (13.6)	8 (18.2)	0 (0.0)	11 (14.3)
Podophyllotoxin derivatives	3 (13.6)	7 (15.9)	0 (0.0)	10 (13.0)
Vinca alkaloids and analogues	1 (4.5)	5 (11.4)	0 (0.0)	6 (7.8)
Cytotoxic antibiotics and related substances	2 (9.1)	10 (22.7)	0 (0.0)	12 (15.6)
Anthracyclines	1 (4.5)	7 (15.9)	0 (0.0)	8 (10.4)
Anthraquinones	1 (4.5)	4 (9.1)	0 (0.0)	5 (6.5)
L-Asparaginase	4 (18.2)	1 (2.3)	0 (0.0)	5 (6.5)
Histone Deacetylase (HDAC) inhibitors	3 (13.6)	8 (18.2)	0 (0.0)	11 (14.3)
Monoclonal Antibodies	4 (18.2)	5 (11.4)	1 (9.1)	10 (13.0)
PD-1/L1 inhibitors	4 (18.2)	1 (2.3)	0 (0.0)	5 (6.5)
Other monoclonal antibodies	1 (4.5)	4 (9.1)	1 (9.1)	6 (7.8)
Protein kinase inhibitors	5 (22.7)	2 (4.5)	0 (0.0)	7 (9.1)
Other antineoplastic agents	1 (4.5)	9 (20.5)	0 (0.0)	10 (13.0)
Corticosteroids for systemic use	4 (18.2)	17 (38.6)	0 (0.0)	21 (27.3)

\*Patients with two or more medications within a category or main component are counted only once within that category or main component. ENKTL, extranodal NK-/T-cell lymphomas; MF, mycosis fungoides; PTCL, peripheral T-cell lymphoma; SS, Sézary syndrome.