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Organ Involvement in Adults with BPDCN is Associated with Sun Exposure History, TET2 and RAS Mutations, and Survival

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Abstract:
Blastic plasmacytoid dendritic cell neoplasm (BPDCN) can involve skin, bone marrow (BM), central nervous system (CNS), and non-CNS extramedullary sites. Preclinical models demonstrated clonal advantage of TET2-mutated plasmacytoid dendritic cells exposed to UV radiation. However, whether sun exposure, disease characteristics, and patient survival are clinically related is unclear. We classified 66 BPDCN patients based on organ involvement at diagnosis as skin only (n=19), systemic plus skin (n=33), or systemic only (n=14). BM involvement was absent, microscopic (<5%), or overt ({greater than or equal to}5%). UV exposure history was based on clinical and demographic data. Patients with skin only BPDCN were more frequently {greater than or equal to}75 years (47% vs. 19%, p=0.032) and had lower rates of complex karyotype (0 vs. 32%, p=0.022) and mutated NRAS (0 vs. 29%, p=0.044). Conversely, those in the systemic only group had lower UV exposure (23% vs. 59%, p=0.03) and fewer TET2 mutations (33% vs. 72%, p=0.051). With median follow-up of 42 months, the median overall survival (OS) was 23.5, 20.4, and 17.5 months for skin only, systemic plus skin, and systemic only, respectively. Patients with no BM involvement had better OS vs. overt BM involvement (median OS 27.3 vs. 15.0 months, p=0.033) and comparable to those with microscopic BM involvement (27.3 vs. 23.5 months, p=0.6). Overt BM involvement remained significant for OS in a multivariable analysis adjusted for baseline characteristics and treatment. In summary, BPDCN clinical characteristics are associated with disease genetics and survival. These data are useful to estimate prognosis for individual patients and may indicate informative subtyping of BPDCN.

Conflict of interest: COI declared - see note

COI notes: SS, JK, DSN, and CJF have no conflicts of interest; MRL receives research funding from Abbvie, Jazz Pharmaceuticals, and Novartis. NRL is a consultant and has received honoraria from Bayer, Seattle Genetics, Sanofi, Silverback, Fortress Biotech, and Synox Therapeutics. AAL is a Scholar of the Leukemia & Lymphoma Society. AAL. has received research funding from Abbvie and Stemline therapeutics, and consulting fees from Cimeio Therapeutics, IDRx, Jnana Therapeutics, ProteinQure, and Qiagen, and has equity as an advisor for Medzown.

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Key points:

- High UV exposure is associated with mutated *TET2* and skin involvement in BPDCN, whereas mutated *NRAS* is associated with systemic involvement.
- Overt BM involvement (≥5% BPCDN cells in the BM) at BPDCN diagnosis is independently associated with worse OS.

Abstract

Blastic plasmacytoid dendritic cell neoplasm (BPDCN) can involve skin, bone marrow (BM), central nervous system (CNS), and non-CNS extramedullary sites. Preclinical models demonstrated clonal advantage of *TET2*-mutated plasmacytoid dendritic cells exposed to UV radiation. However, whether sun exposure, disease characteristics, and patient survival are clinically related is unclear. We classified 66 BPDCN patients based on organ involvement at diagnosis as skin only (n=19), systemic plus skin (n=33), or systemic only (n=14). BM involvement was absent, microscopic (<5%), or overt (≥5%). UV exposure history was based on clinical and demographic data. Patients with skin only BPDCN were more frequently ≥75 years (47% *vs.* 19%, p=0.032) and had lower rates of complex karyotype (0 *vs.* 32%, p=0.022) and mutated *NRAS* (0 *vs.* 29%, p=0.044). Conversely, those in the systemic only group had lower UV exposure (23% *vs*. 59%, p=0.03) and fewer *TET2* mutations (33% *vs.* 72%, p=0.051). With median follow-up of 42 months, the median overall survival (OS) was 23.5, 20.4, and 17.5 months for skin only, systemic plus skin, and systemic only, respectively. Patients with no BM involvement had better OS *vs.* overt BM involvement (median OS 27.3 *vs*. 15.0 months, p=0.033) and comparable to those with microscopic BM involvement (27.3 *vs.* 23.5 months, p=0.6). Overt BM involvement remained significant for OS in a multivariable analysis adjusted for baseline characteristics and treatment. In summary, BPDCN clinical characteristics are associated with disease genetics and survival. These data are useful to estimate prognosis for individual patients and may indicate informative subtyping of BPDCN.

Introduction

Blastic plasmacytoid dendritic cell neoplasm (BPDCN) is a rare, aggressive hematologic neoplasm that arises from malignant plasmacytoid dendritic cells (pDC) or their precursors (1, 2). Most (80-90%) patients present with characteristic, deep purple skin tumors or plaques.

Remarkably, despite being a hematologic cancer, half of patients with BPDCN have disease restricted to the skin at diagnosis, without detectable disease in the marrow, blood, or lymph nodes (3). Recent findings show that migration of pDC progenitors to and from the skin, where they may be exposed to ultraviolet light (UV), contributes to the development of BPDCN (4). Whether UV exposure influences likelihood of a cutaneous presentation of BPDCN, is associated with specific disease genetics, or influences prognosis is unknown.

In addition to skin, BPDCN can involve the bone marrow (BM), central nervous system (CNS), and non-CNS extramedullary disease (EMD) sites (5-7). Conflicting data exist as to whether the pattern of anatomic involvement affects prognosis. Specifically, the role of low burden, non-overt BM involvement (greater than zero but less than 5%, known as "microscopic" or "minimal" disease) remains unclear, as trials have only regarded ≥5% as evidence of BPDCN. Furthermore, BPDCN genetics have not been fully incorporated into prognostic models that include sites of disease (8-10).

To address these questions, we conducted a retrospective cohort study to characterize the associations between genetics, clinicopathological characteristics, and UV exposure in BPDCN, and to determine the impact of these disease features on clinical outcomes.

Methods

Patients

We retrospectively identified consecutive patients with biopsy proven BPDCN seen at the Dana-Farber Cancer Institute (DFCI) between 2006-2022. Patient, disease, and treatment characteristics were extracted from electronic medical records. Ultraviolet exposure was dichotomized as high *vs.* low through a comprehensive analysis of each patient's medical, occupational, and social histories by an independent investigator (C.J.F.), who was blinded to study outcomes. A patient was assigned to the high UV exposure category if s/he satisfied at least one of the following criteria: documented presence of severely sun-damaged skin by a dermatologist, history of blistering sunburns, documented employment or recreational activities necessitating a majority of time outdoors, or history of residing in geographical regions with substantially heightened sun exposure for greater than 10 cumulative years. Next generation sequencing (NGS) was performed on blood or BM at diagnosis (11). Bone marrow involvement at diagnosis was classified as overt (≥5% BPDCN cells on aspirate smear, flow cytometry, or core biopsy), microscopic (more than zero but <5% identifiable clonal BPDCN cells), or absent (no evidence of any BPDCN cells). Based on organ involvement at diagnosis, we classified 3 organ involvement groups: "systemic without skin" (absence of skin involvement, with either overt BM and/or EMD involvement), "skin only" (skin involvement, with no EMD and absent or microscopic bone marrow involvement), or "skin and systemic" (skin involvement, with either overt bone marrow involvement and/or EMD involvement) (**Supplemental Figure 1)**. Due to paucity of data on CNS involvement at diagnosis, particularly from earlier years before CNS

evaluation was standard in BPDCN, anatomic groups were classified irrespective of CNS involvement.

Outcomes

Overall survival (OS) was calculated from day 1 of treatment until death or last follow up. Responses were documented as the best response achieved per line of therapy and classified as complete remission (CR; <5% disease cells in the BM and no EMD, CNS, or skin involvement documented), partial response (PR; <5% disease cells in the BM and no EMD and CNS, improvement in skin lesion) or progressive disease (PD; overt BM disease or EMD or CNS disease, progression or new skin lesions).

Statistics

Categorical variables are presented by number and percentage and comparison were performed by Fisher's exact test. Continuous variables are presented by median and range or interquartile range (IQR) and comparisons were performed by Wilcoxon rank-sum test or Kruskal-Wallis tests. All survival data and duration of response (DOR) were calculated with the Kaplan-Meier method and reported as medians plus 95% confidence interval (CI). Survival comparisons were made by the log-rank test. Cumulative incidence of relapse (CIR) was performed with death as competing risk and comparisons were conducted by the Gray's test. CIR and DOR were only calculated for patients who achieved CR after the first line of therapy. Uni- and multivariable Cox regression models were fit for association with OS, with allogeneic hematopoietic stem cell transplantation (alloSCT) as a time-varying covariate. Mutated genes were univariate model candidates if prevalent in ≥10% of patients. All analyses were conducted using R, version 4.3.

This study was conducted with the approval of the institutional review board at the Dana-Farber Cancer Institute.

Results

Patients

Overall, we included 66 patients (median age 68 years [IQR 61-76]), who were predominantly male (n=57, 86%) (**Table 1**). Disease distribution at diagnosis involved skin (n=52, 79%), BM (n=50, 76%; 39 [59%] with overt involvement, 11 [17%] with microscopic involvement) and EMD (n=30, 45%). Based on the aforementioned criteria, patients were classified into three diagnostic organ groups: skin only (n=19, 29%), skin plus systemic (n=33, 50%), and systemic only (n=14, 21%) (**Figure 1)**. Ten patients (15%) had prior myeloid disease, most commonly myelodysplastic syndrome (MDS), with no statistically significant difference in prior MDS between organ groups (skin only n=5, 26%; skin plus systemic n=2, 6%; systemic only n=3, 21%, p=0.1). Eleven patients (17%) had prior non-melanoma skin cancer and the same number (n=11, 17%) had another solid tumor. Ultraviolet exposure history was assessable for 59/66 patients (89%), of which 30/59 (51%) were classified as high UV exposure. Among patients with

known karyotype, normal and complex karyotypes at diagnosis were seen in 34/50 (68%) and 12/50 (24%), respectively. *TET2* was the most commonly mutated gene found in the BM/blood at diagnosis (31/48 [65%] of patients with molecular data available) (**Figure 2A)**. The median time interval from first symptom to diagnosis was 61 days (IQR 35-134), and 30 days (IQR 20-46) from diagnosis to day 1 of treatment. The first therapeutic regimen was tagraxofusp (n=30, 45%), AML-based (n=12, 18%) or ALL-based (n=12, 18%) chemotherapy regimens, or other (n=12, 18%). Overall, patients received a median of two lines of therapy (range 0-6).

Clinicopathological associations with organ involvement group at diagnosis

Patients in the skin only group (n=19) *vs.* any systemic involvement (n=47, comprised of systemic only and systemic plus skin groups) were more frequently ≥75 years (9/19 [47%] *vs.* 9/47 [19%], p=0.032), had lower rates of complex karyotype (0 *vs.* 12 [32%], p=0.022), and had lower rates of activated signaling mutations (*NRAS, KRAS*, *FLT3*, *CBL*, *CKIT*, *SH2B3*; 1 [8%] *vs.* 14 [40%], p=0.04), mainly driven by lower *NRAS* (zero in skin only *vs.* 10 [29%] with any systemic, p=0.044, **Figure 2B**). In contrast, those with any skin involvement (n=52, comprised of skin only and systemic plus skin groups) had higher rates of UV exposure (27 [59%] *vs*. 3 [23%], p=0.03) and *TET2* mutations (28 [72%] *vs.* 3 [33%], p=0.051) compared to those with no skin involvement (**Figure 2C**).

To determine whether patients with overt BM (n=39; ≥5%) differ from those with microscopic BM (n=11, >0 but <5%) involvement, we compared those patients' baseline characteristics (**Supplemental Table 1**). Patients with overt BM disease had shorter period between diagnosis and treatment (median 25 days [IQR 15-37] *vs.* 45 days [IQR 34-69], p=0.019), higher rates of complex karyotype (40% *vs.* 0%, p=0.036), and lower rates of normal karyotype (50% *vs.* 100%, p=0.007).

Frequent involvement of the CNS in patients with BPDCN was increasingly recognized in recent years; thus, systematic evaluation of the CNS at diagnosis was not performed in all patients throughout the entire study period. However, among the 16 patients who were diagnosed in 2021 and later, 15 had CNS evaluation at diagnosis; 3/15 (20%) were positive. Among the 58 patients who had at least one CNS evaluation by lumbar puncture at any time, 16 (28%) had evidence for BPDCN cells in the cerebrospinal fluid. The rates of CNS disease at any timepoint were higher among those with systemic only disease at presentation (7/13, 54%) compared with those who had any skin involvement: either skin only (3/17, 18%) or systemic plus skin (6/28, 21%), p=0.031.

Response, relapse, and alloSCT

Complete remission (CR) and partial remission (PR) after first treatment were achieved in 35 (57%) and 13 (21%) patients, respectively. After a median of 6.1 (IQR 2.4-8.1) months from first CR achievement, 22/35 (63%) who had achieved CR relapsed (**Table 2**), with skin as the most common relapse site (n=13/21 evaluated patients, 62%), followed by overt BM (n=12, 57%), EMD (n=5, 24%), and CNS (n=3, 14%) (**Figure 3A**). Although CRs were also achieved after

subsequent lines of therapy (CR achievement post 2nd line: 18/35; post 3rd line: 7/20; post 4th line 2/12; post 5th line: 2/4; post 6th line: 2/3, **Table 2**), those responses were not durable and most patients relapsed, with skin consistently as the most common organ involved in relapse (**Figure 3A**).

To evaluate whether the pattern of relapse differs after alloSCT, we evaluated all transplanted patients. Overall, 35 (53%) patients received alloSCT, most commonly in CR1 (n=28/35 [80%] transplanted), with reduced intensity conditioning in 54% and a matched unrelated donor in 46% (**Supplemental Table 2)**. After a median of 5.9 months (IQR 2.8-17.7) post-alloSCT, relapse occurred in 14/35 (40%) of transplanted patients. Similar to the aforementioned relapse pattern, skin was also the most common relapse site post-alloSCT (n=8, 57%), followed by overt BM (n=5, 36%), EMD (n=3, 21%), and CNS (n=3, 21%) (**Figure 3B**).

When evaluated by organ involvement groups, both 1st treatment CR rates (skin only 50%; systemic only 57%; systemic plus skin 61%, p=0.7) and relapse rates (skin only 50%; systemic only 75%; systemic plus skin 63%, p=0.6) were comparable. The CR rates with tagraxofusp vs. other treatments were numerically lower in those with skin disease (30% vs. 83%, p=0.12) and in those with systemic disease (41% vs. 71%, p=0.063), but these results did not reach statistical significance. When we evaluated on the pattern of post-CR relapse by organ groups, the diagnostic group tended to predict organ group at relapse: those who were classified as skin only at diagnosis tended to relapse as skin only (5/8 [63%]); those classified as systemic only at diagnosis relapsed as systemic only (4/9 [44%]) or systemic plus skin (3/9 [33%]); and those with systemic plus skin had a more heterogenous pattern of relapse (**Figure 3C**).

Survival

After a median follow-up of 41.6 months (95% CI 28-81), the median OS was 18.2 months (95% CI 13-24). When evaluated by organ involvement group, the median OS was 23.5 months (95% CI 13.4-NA) in the skin only group, 20.4 months (95% CI 10.6-25.6) in the skin plus systemic group (p=0.3 compared to skin only group) and 17.5 months (95% CI 9.0-22.1) in the systemic only group (p=0.066 vs. skin only group) (**Figure 4A**). When we evaluated survival by type of bone marrow involvement (none vs. microscopic vs. overt), those with no BM involvement (median OS 27.3 months [95% CI 16.9-NA]) had better OS compared with overt BM involvement (median OS 15.0 months [95% CI 9.9-22.1], p=0.033), and comparable to those with microscopic BM involvement (median OS 23.5 months [95% CI 12.8-NA], p=0.6) (**Figure 4B**).

In a multivariable analysis, age <60 years (vs. 60-75 years) was associated with improved OS (HR 0.35 [95% CI 0.13-0.94], p=0.038), whereas BM involvement ≥5% (but not >0 to <5% involvement) was independently associated with worse OS (HR 2.65 [95% CI 1.1-6.36], p=0.029, **Table 3**). When we conducted univariable and multivariable analyses in patients who were transplant-eligible by age (≤75 years, n=48), we found that alloSCT as a time-varying covariate was associated with better OS (HR 0.4 [95% CI 0.17-0.94, p=0.036]. In contrast,

similar to the entire cohort, overt BM involvement at diagnosis was associated with worse survival even in those receiving alloSCT (HR 3.34 [95% CI 0.97-11.5], p=0.055) (**Supplemental Table 3**).

To evaluate for an interaction between organ groups at diagnosis, treatment modality (tagraxofusp vs. others), and outcome, we conducted treatment analyses separately in the skin only group (n=19) and in those with any systemic involvement (n=47). There were no statistically significant differences in OS, DOR, or CIR rates between tagraxofusp vs. other treatments in either in the skin only group or in those with any systemic involvement. (**Supplemental Table 4**).

Discussion

BPDCN is a rare, aggressive malignant neoplasm that arises from pDCs and characteristically involves the skin but also frequently involves BM, extramedullary disease sites, and CNS (12). Recent evidence suggests a role for UV exposure in BPDCN pathogenesis (4). However, the correlation between clinicopathological characteristics, UV exposure, organ involvement at presentation and their effect on outcomes is unclear.

We demonstrate here for the first time an association between skin involvement at diagnosis, high UV exposure and *TET2* mutations. Our findings are consistent with the recently demonstrated link between UV exposure and selection for *TET2* mutated plasmacytoid dendritic cells in BPDCN development, as well as previous findings on the association of *TET2* with BPDCN (13-16). Furthermore, the high prevalence of skin involvement among *TET2*-mutated BPDCN patients exposed to UV denotes that UV exposure is not only associated with the development of BPDCN but may also affect its presentation. We also showed that patients with skin only involvement at diagnosis were older. As mutated *TET2* is considered a common age-dependent clonal hematopoiesis mutation with increasing frequency at older age (11) and older patients have UV exposure accumulation throughout their life (17, 18), our findings are consistent with UV exposure and mutated *TET2* as a combined aging-associated mechanism of BPDCN oncogenesis in older patients, particularly in those presenting with skin only disease. As skin involvement is also seen in other myeloid neoplasms (19), future research might evaluate the role of UV radiation in these cases well. On the other hand, systemic involvement was associated with *NRAS* mutations and higher rates of complex karyotype. It is not clear whether systemic patients have distinct disease pathogenesis compared to those with skin disease, or rather if acquisition of certain mutations such as in *RAS* or chromosomal abnormalities direct the difference in organ involvement (20). Furthermore, BPDCN-associated somatic mutations, including in *TET2* and RNA splicing factors, have been implicated in impaired tumor cell cytokine production and dendritic activation phenotypes when compared to normal pDCs (21, 22). How these various BPDCN genotype-phenotype associations at the cellular level may be

related to the features of organ involvement and clinical outcomes revealed in this study are important areas for future research.

We found that overt BM involvement (≥5% BPDCN cells in the bone marrow at diagnosis) but not microscopic involvement (defined as presence of BPDCN cells <5% in the bone marrow) is independently associated with worse OS when adjusted in a multivariable model. In addition, when classified by diagnostic organ groups, there was worse survival among those in the systemic only group vs. skin only group. The effect of organ involvement on prognosis was evaluated in several previous studies with conflicting results (3, 8, 23). The difference may relate, in part, to modest cohort size or variable definitions of organ involvement or other clinicopathologic characteristics between studies. In our study the prognostic value of bone marrow involvement was retained even after adjustment for several other clinicopathologic characteristics, such as demographics, cytogenetics and tumor DNA sequencing, initial treatment, and alloSCT. The effect of overt marrow involvement should be integrated into future risk models and clinical trials evaluating treatment for BPDCN.

Similar to previous studies (24, 25), we demonstrated that skin is the most common site involved and is found in about 80% of patients at diagnosis. Here, we also showed that skin is the most common relapse site, both after 1st treatment, after subsequent lines of therapy, and after transplant. We also demonstrated that the diagnostic organ involvement patterns influence subsequent relapses sites. Despite this, given that some patients switched to a different organ involvement group at the time of relapse, these data emphasize the importance of assessing all possible disease compartments in all patients regardless of their prior organ involvement, including frequent meticulous skin evaluations. Further consideration regarding best approaches to achieve and verify complete clearance of the skin are warranted, as beyond visual inspection and palpation, it is not currently possible to determine integumentary MRD with certainty.

Our study has several limitations. First, its retrospective nature and heterogeneity of patients spanning almost 2 decades may contribute to bias, which we partially addressed using a regression analysis that included treatment modalities. In addition, although we know today that CNS involvement is far more common than once thought (7), we had incomplete data on CNS evaluation at the time of diagnosis and whether the patients received prophylactic intrathecal treatment. However, we integrated all available data and found an association between CNS involvement at any time and systemic only disease at diagnosis. Finally, samples for next-generation sequencing were derived only from bone marrow and/or blood; a different molecular pattern might be revealed by including genetic evaluation of other involved tissues, particularly the skin. However, as blood or BM remain the most common and feasible sites for NGS as part of routine clinical care in patients with leukemia including BPDCN, our findings are more likely to be utilized in the “real world” clinical setting.

In summary, in a cohort of 66 patients with BPDCN we found genotype-phenotype associations with disease presentation, and a correlation between organ involvement at diagnosis and subsequent relapses. We also demonstrated that overt bone marrow involvement is independently associated with worse OS, even after adjustment for multiple clinicopathologic and molecular characteristics. Future studies should integrate organ involvement into prognostic models for BPDCN and explore potential mechanisms that delineate distinct phenotypic presentations of the disease.

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Authorship contributions

SS and AAL designed the research; SS and CJF performed data extraction; SS, JK and DSN analyzed the data; SS and AAL wrote the initial draft. JK, CJF, MRL, DSN, NRL and AAL reviewed the manuscript and contributed to its final version. All authors reviewed the final version of the manuscript and agreed for submission.

Conflict of interest disclosure

SS, JK, DSN, and CJF have no conflicts of interest; MRL receives research funding from Abbvie, Jazz Pharmaceuticals, and Novartis. NRL is a consultant and has received honoraria from Bayer, Seattle Genetics, Sanofi, Silverback, Fortress Biotech, and Synox Therapeutics. AAL is a Scholar of the Leukemia & Lymphoma Society. AAL. has received research funding from Abbvie and Stemline therapeutics, and consulting fees from Cimeio Therapeutics, IDRx, Jnana Therapeutics, ProteinQure, and Qiagen, and has equity as an advisor for Medzown.

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Tables

	N (%) (N=66)
Sex (male)	57 (86)
Age (years, median, IQR)	68.3 (61.2, 75.5)
Age groups	
<60 years	15 (23)
60 to <75 years	33 (50)
≥75 years	18 (27)
Prior neoplasms	
Myeloid disease	10 (15)
Non-melanoma skin cancer	11 (17)
Other solid cancer	11 (17)
ECOG[1]	
0	43 (66)
1	21 (32)
2	1 (2)
UV exposure[2]	
High	30 (51)
Low	29 (49)
Cytogenetics[3]	
Complex karyotype	12 (24)
Normal karyotype	34 (68)
Other	4 (8)
First treatment	
Tagraxofusp	30 (45)
AML-like intensive chemotherapy regimen	12 (18)
ALL-like intensive chemotherapy regimen	12 (18)
Others	12 (19)
Selected time intervals	
Diagnosis to 1st treatment (days, median, IQR)	29.5 (20.0, 46.0)
First symptom to first treatment (days, median, IQR)	108 (64.2, 161.0)

Table 1. Patient characteristics.

IQR – interquartile range; ECOG – eastern cooperative oncology group; UV – ultraviolet; AML – acute myeloid leukemia; ALL – acute lymphoblastic leukemia.

[1] ECOG is missing for 1 patient.

[2] UV exposure data is missing for 7 patients.

[3] Cytogenetic data is missing for 16 patients.

	N, %					
Line of therapy	1st line	2nd line	3rd line	4th line	5th line	6th line
Treated	66	38[1]	21[2]	14[3]	4	3
Achieved CR	35 (53%)	18 (51%)	7 (35%)	2 (17%)	2 (50%)	2 (67%)
Relapsed after CR	22/35 (63%)	11/18 (61%)	6/7 (86%)	2/2 (100%)	1/2 (50%)	0/2 (0%)
Time from previous line (Months, IQR)	-------	3.4 (2.7-7.6)	3.1 (1.9,6.1)	3.9 (2.3-6.6)	1.4 (0.5-5.9)	2.7 (2.1-3.9)

Table 2. Complete remissions and post-CR relapse after each treatment.
CR – complete remission; IQR – interquartile range.

[1] 3 pts missing evaluation post 2nd line.
[2] 1 pt missing evaluation post 3rd line.
[3] 2 pts missing evaluation post 4th line.

Covariate	Univariable analysis (HR, CI 95%)	p-value	Multivariable analysis (HR, CI 95%)	p-value
Age (relative to 60 to <75 years)				
- <60 years	0.30 (0.12, 0.75)	0.0097	0.35 (0.13, 0.94)	0.038
- ≥75 years	1.87 (0.94, 3.68)	0.072	1.74 (0.78, 3.89)	0.17
Sex (relative to female)	1.83 (0.65, 5.13)	0.25		
Prior neoplasm				
- Prior myeloid neoplasm	1.25 (0.56, 2.83)	0.59		
- Prior solid cancer	0.63 (0.25, 1.60)	0.33		
ECOG (1 or 2 relative to 0)[1]	1.83 (0.97, 3.44)	0.061		
Cytogenetics[2]				
- Complex karyotype	1.16 (0.52, 2.57)	0.72		
- Normal karyotype	0.59 (0.29, 1.20)	0.15		
Organ involvement at diagnosis				
- Skin at diagnosis	0.58 (0.29, 1.13)	0.11		
- BM at diagnosis				
- Microscopic (<5% involvement)	1.36 (0.46, 4.06)	0.58	1.09 (0.35, 3.42)	0.89
- Overt (≥5% involvement)	2.40 (1.04, 5.54)	0.039	2.65 (1.10, 6.36)	0.029
- EMD at diagnosis	1.37 (0.75, 2.51)	0.31		
Molecular[3]				
- *ASXL1*	1.46 (0.71, 3.02)	0.30		
- *IDH2*	0.95 (0.33, 2.76)	0.93		
- *NRAS*	1.26 (0.53, 2.96)	0.60		
- *SRSF2*	1.71 (0.64, 4.57)	0.29		
- *TET2*	1.95 (0.89, 4.31)	0.097		
- *ZRSR2*	1.78 (0.67, 4.76)	0.25		
First treatment (SL401 relative to no SL401)	0.92 (0.50, 1.68)	0.78		
AlloSCT as time varying covariate	0.34 (0.17, 0.68)	0.0024	0.55 (0.24, 1.30)	0.17

Table 3. Univariable and multivariable Cox regression overall survival analysis.
HR – hazard ratio; CI confidence interval; ECOG – eastern cooperative oncology group; BM – bone marrow; EMD – extramedullary disease, not including central nervous system disease. AlloSCT – allogeneic hematopoietic stem cell transplantation.

[1] 1 patient was omitted from the univariable regression analysis for ECOG due to missing data

[2] 16 patients were omitted from the univariable regression analysis for complex karyotype and normal karyotype due to missing data

[3] 18 patients were omitted from the univariable regression analysis for molecular variables due to missing data

Figure legends

Figure 1. Patients' organ involvement and group allocation.

BM – bone marrow; EMD -extra-medullary disease, not including central nervous system.

* Defined as ≥5% in BM. Additional 11 patients had measurable residual disease (<5%) in bone marrow: 7 in the skin only group; 2 in the systemic plus skin group; 2 in the systemic only group.

Figure 2 – UV exposure, cytogenetics and molecular abnormalities by diagnostic organ groups.

A. Molecular and cytogenetic samples taken from bone marrow or blood at diagnosis.
B. Comparison between skin only group vs. any systemic involvement (defined as systemic only or systemic plus skin).
C. Comparison between systemic only group vs. any skin involvement (defined as skin only group or systemic plus skin).
UV -ultraviolet.

Figure 3 – Organ involvement at relapse.

A. Involvement by lines of therapy.
B. Involvement classified by diagnostic organ groups.
C. Involvement post alloSCT.
CR – complete remission; LAD – lymphadenopathy; CNS – central nervous system; alloSCT – allogeneic stem cell transplantation.

Figure 4 – Overall survival.

A. Stratified by diagnostic organ group.
B. Stratified by bone marrow involvement – none vs. microscopic (defined as >0 and < 5% of BPDCN cells) vs. overt (defined as ≥5% BPDCN cells in the bone marrow).
OS -overall survival; CI – confidence interval; BM – bone marrow; NA – not available; BPDCN – Blastic plasmacytoid dendritic cell neoplasm.

Figure 1

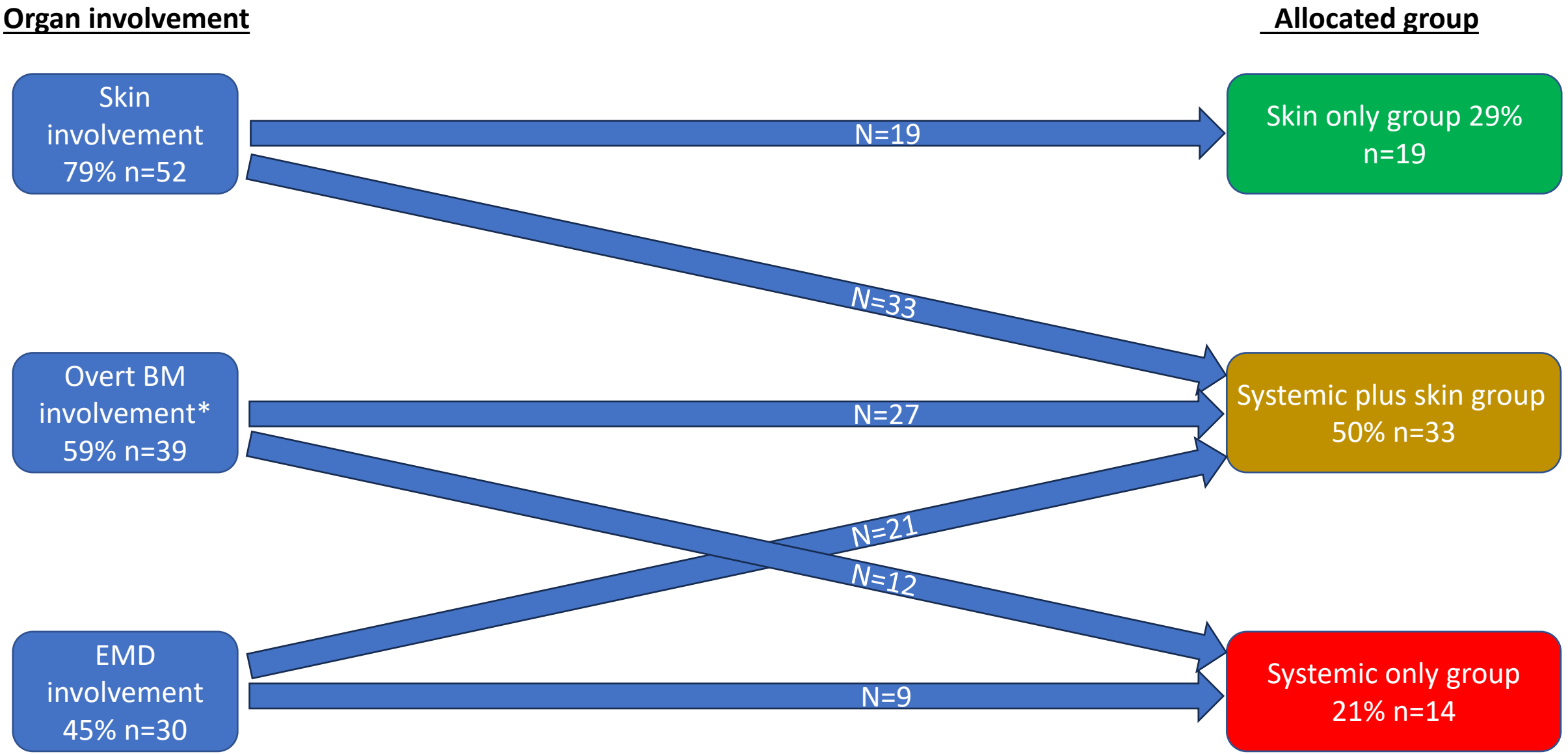


Figure 2

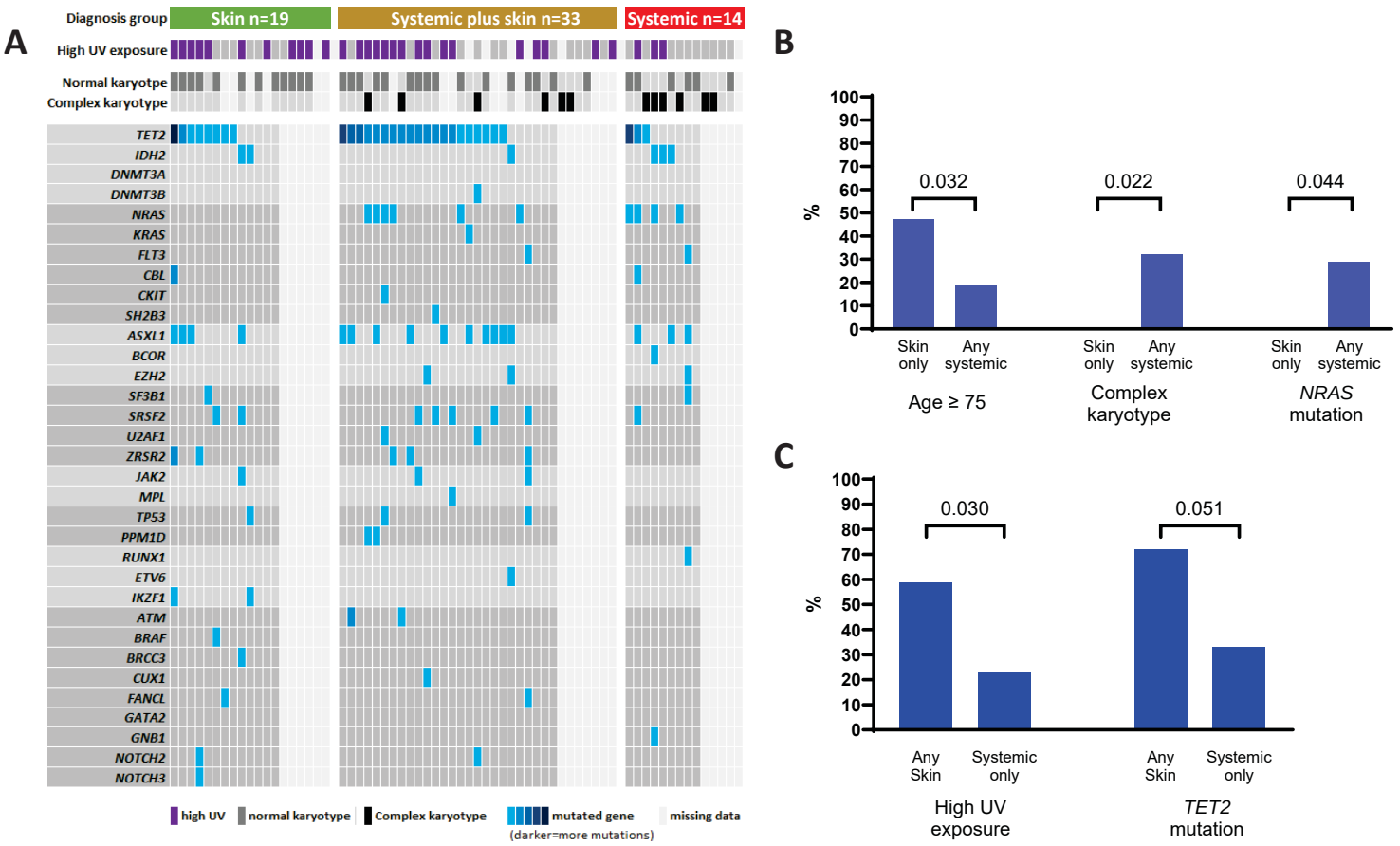
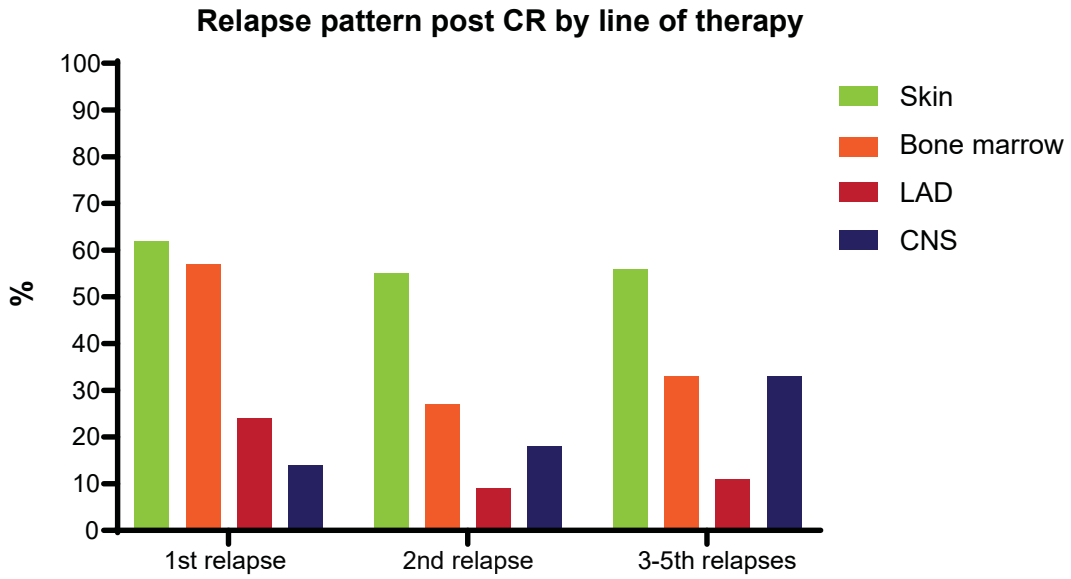


Figure 3

A



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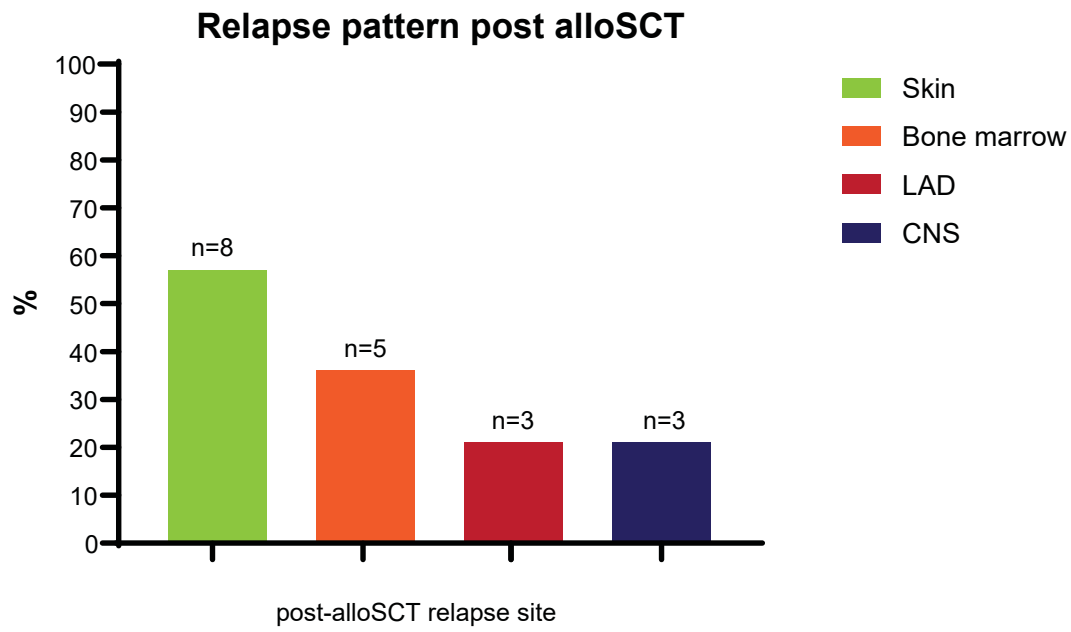

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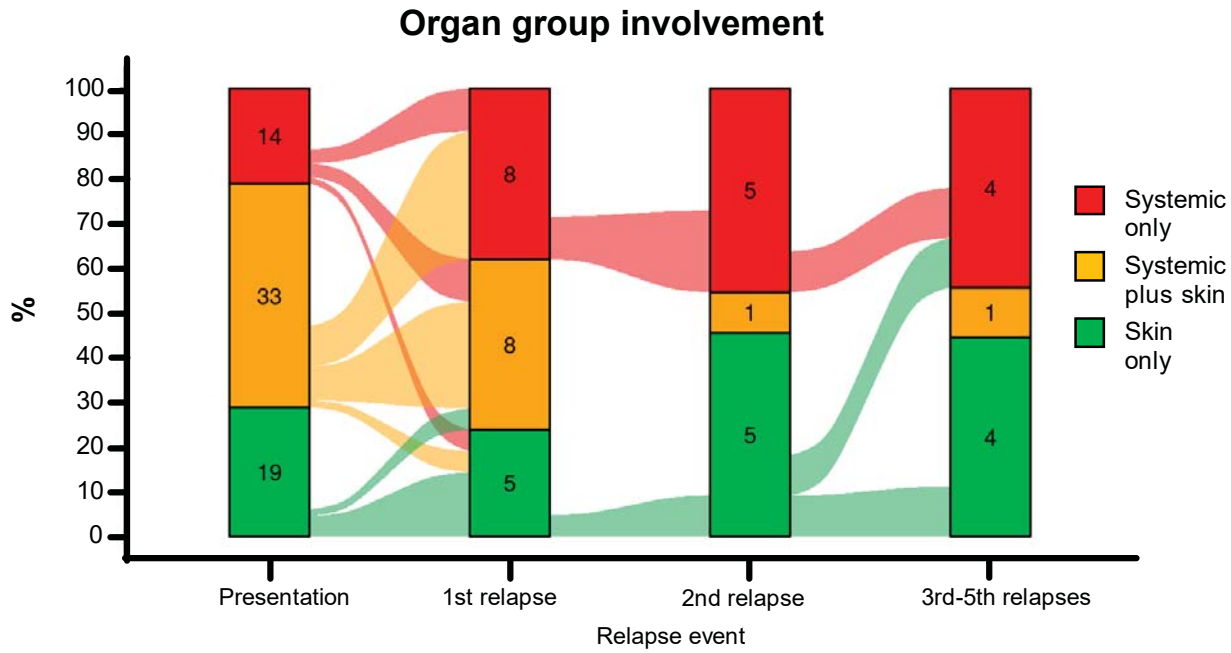

Figure 4