REGULAR ARTICLE

blood advances

TP53 mutations identify high-risk events for peripheral T-cell lymphoma treated with CHOP-based chemotherapy

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Key Points

- *TP53* mutations are frequent events in certain subtypes of PTCL.
- Patients with *TP53*-mutated PTCL experience high relapse rates when treated with curative-intent CHOP-based chemotherapy.

Nodal peripheral T-cell lymphomas (PTCL), the most common PTCLs, are generally treated with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP)-based curative-intent chemotherapy. Recent molecular data have assisted in prognosticating these PTCLs, but most reports lack detailed baseline clinical characteristics and treatment courses. We retrospectively evaluated cases of PTCL treated with CHOP-based chemotherapy that had tumors sequenced by the Memorial Sloan Kettering Integrated Mutational Profiling of Actionable Cancer Targets next-generation sequencing panel to identify variables correlating with inferior survival. We identified 132 patients who met these criteria. Clinical factors correlating with an increased risk of progression (by multivariate analysis) included advanced-stage disease and bone marrow involvement. The only somatic genetic aberrancies correlating with inferior progression-free survival (PFS) were *TP53* mutations and *TP53*/17p deletions. PFS remained inferior when stratifying by *TP53* mutation status, with a median PFS of 4.5 months for PTCL with a *TP53* mutation (n = 21) vs 10.5 months for PTCL without a *TP53* mutation (n = 111). No *TP53* aberrancy correlated with inferior overall survival (OS). Although rare (n = 9), *CDKN2A*-deleted PTCL correlated with inferior OS, with a median of 17.6 months vs 56.7 months for patients without *CDKN2A* deletions. This retrospective study suggests that patients with PTCL with *TP53* mutations experience inferior PFS when treated with curative-intent chemotherapy, warranting prospective confirmation.

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Genetic data are available at the cBioPortal for Cancer Genomics at https://www.cbioportal.org/study/summary?id=mtnn_msk_2022.

Deidentified data that are not publicly accessible or included in this article or data supplement are available upon request from the corresponding author, William T. Johnson (johnsow3@mskcc.org).

The full-text version of this article contains a data supplement.

Introduction

Comprising ~10% to 15% of all non-Hodgkin lymphoma cases, peripheral T-cell lymphoma (PTCL) encompasses more than 30 histological subtypes.[1,2] The relative frequency of each subtype is influenced by geographic region, but the most common PTCL, globally, remains nodal PTCL.[2] Nodal PTCLs include PTCL–not otherwise specified (PTCL-NOS), angioimmunoblastic T-cell lymphoma (AITL), other PTCL with a follicular T-helper cell phenotype (PTCL-TFH), and anaplastic large cell lymphoma (ALCL), including anaplastic lymphoma kinase (ALK)-positive and -negative disease.[1-3] Although pathologically and molecularly distinct, nodal PTCLs are most often treated similarly, with curative-intent cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP)-based chemotherapy for eligible patients.[3-8] In patients with $CD30^+$ PTCL, vincristine can be replaced by brentuximab vedotin (BV), based on the ECHELON-2 data showing improved survival compared with use of CHOP, although this advantage was predominantly driven by patients with ALCL.[9] For those with $CD30^-$ PTCL, etoposide can be added, which has been correlated with improved response rates and survival, particularly in patients aged ≤60 years.[4,10,11] For eligible patients who achieve remission, high-dose chemotherapy with autologous stem cell transplantation (ASCT) rescue can be offered, with ASCT showing a survival advantage in nonrandomized prospective trials, compared with historical control therapies, and in some retrospective analyses.[4,12-14]

Over the past decade, the genetic landscape and oncogenic underpinning of PTCL have been more clearly delineated and, to some extent, can aid in prognosticating and predicting the response to treatments.[15-21] However, although most studies define molecular risk factors for inferior overall survival (OS), they often omit comprehensive details on both first-line treatment and treatment at relapse. Moreover, few reports detail somatic genetic risk factors for refractory or relapsed disease when treated with curative-intent strategies. This makes it challenging to risk stratify patients who may benefit from alternative induction and consolidation strategies and to stratify patients in future first-line randomized control trials.

We sought to add to the existing PTCL genetic literature by incorporating baseline clinical characteristics and comprehensive treatment data for a cohort of patients treated with curative-intent CHOP-based chemotherapy and to combine these data with a clinically validated targeted next-generation sequencing (NGS) panel to identify features of patients at highest risk for relapsed or refractory disease.

Methods

Patient selection

The protocol for this retrospective study was approved by the institutional review board (IRB) at Memorial Sloan Kettering Cancer Center (MSK; IRB #22-025) and was written in compliance with the principles outlined in the Declaration of Helsinki. The online platform cBioPortal for Cancer Genomics was used to screen for all patients with PTCL who visited MSK from 1 April 2015 to 31 December 2020 and had NGS of tumor biopsies performed primarily via the Memorial Sloan Kettering Cancer Center Integrated Mutational Profiling of Actionable Cancer Targets (MSK-IMPACT; 1 included tumor was sequenced using a smaller 49-gene MSK-targeted sequencing panel at diagnosis).[22,23] MSK-IMPACT is a clinically validated, targeted NGS panel analyzing somatic alterations in up to 500 genes.[24] Using various iterations of this NGS platform, the mutational landscape of >10 000 tumors has been published, and MSK-IMPACT has become an integral part of the PTCL pathological work-up at MSK.[25]

MSK-IMPACT panels and sequencing results are provided in supplemental Table 1. In addition to the nodal PTCL subtypes, we also included enteropathy-associated T-cell lymphoma and monomorphic epitheliotropic T-cell lymphoma (MEITL) because they are treated similarly to nodal PTCL.

Subsequently, patients' electronic medical records were manually reviewed to confirm the diagnosis and first-line treatment regimen (regimens listed in Table 1). All diagnoses were confirmed by ≥1 hematopathologist at MSK. We included only adults aged ≥18 years. Patients were excluded if they were lost to follow-up during first-line treatment, underwent allogeneic stem cell transplantation (allo-SCT) in first remission, or had active central nervous system involvement at the time of diagnosis. We manually extracted electronic medical records data on baseline clinical characteristics, treatments, and survival for patients meeting all inclusion criteria, which included having an aforementioned histology, being treated with curative-intent CHOP-based chemotherapy (with or without ASCT in first remission), and having MSK-IMPACT performed on biopsied tumor tissue.

We anticipated that some patients with tumors sequenced via MSK-IMPACT were not patients of an MSK oncologist during first-line therapy, thus, potentially missing key clinical baseline prognostic data, and/or patients for whom MSK-IMPACT would have had been ordered only at the time of relapse, thereby inducing a selection bias. Accordingly, 3 cohorts were grouped for analysis: (1) the entire MSK-IMPACT–sequenced cohort meeting the inclusion criteria (entire cohort); (2) a cohort with complete clinical baseline prognostic data, including pretreatment laboratory data and baseline bone marrow (BM) biopsies (complete clinical data [CCD] cohort); and (3) the cohort that was managed by an MSK oncologist during the CHOP-based treatment and also had their pretreatment tumor biopsy sequenced at the time of CHOP-based treatment and/or before relapse, when applicable (prospective cohort).

MSK-IMPACT results from pretreatment biopsies were analyzed when available; sequencing results from progression biopsies (applicable only to the entire and CCD cohorts) were otherwise analyzed.

Statistical analysis

Progression-free survival (PFS) was calculated from the start of chemotherapy to progression or death. The OS was calculated from the start chemotherapy to the date of death, with data of living patients censored at the time of the last documented follow-up, with a data cutoff on 31 May 2021.

Univariate analysis was performed using a Cox proportional hazards regression analysis for PFS and OS. Characteristics with $P \leq .05$ in the univariate analyses were included in a multivariate analysis. Baseline clinical parameters were chosen based on previously described prognostic indicators in PTCL.[26,27] Characteristics also

Table 1. Baseline clinical characteristics and treatments of the 3 PTCL cohorts

	Entire cohort (N = 132)	CCD cohort (n = 87)	Prospective cohort (n = 72)	*P*
Demographics				
Median age, y (range)	65 (25-82)	63 (26-81)	66 (25-81)	.87
Male, n (%)	81 (61)	56 (64)	43 (60)	.83
Disease characteristics at diagnosis				
Histology, n (%)				
PTCL-NOS	36 (27)	28 (32)	15 (21)	.25
AITL	62 (47)	39 (45)	38 (53)	.59
PTCL-TFH	9 (7)	6 (7)	6 (8)	.92
ALK^- ALCL	15 (11)	8 (9)	7 (10)	.88
ALK^+ ALCL	6 (5)	2 (2)	2 (3)	.71
MEITL	4 (3)	4 (5)	4 (6)	.65
Stage, n (%)				
I/II*	22 (17)	15 (17)	14 (19)	.90
III/IV*	110 (83)	72 (83)	58 (81)	
BM involvement by morphological assessment, n (%)				
No	72 (55)	55 (63)	42 (58)	.99
Yes	39 (29)	32 (37)	23 (32)	
Unknown	21 (16)	0 (0)	7 (10)	
Extranodal disease other than BM involvement, n (%)				
No	81 (61)	52 (60)	44 (61)	.98
Yes	51 (39)	35 (40)	28 (39)	
LDH elevated, n (%)				
No	39 (30)	34 (39)	29 (40)	.91
Yes	58 (44)	53 (61)	39 (54)	
Unknown	35 (27)	0 (0)	4 (6)	
ECOG PS ≥2, n (%)				
No	112 (85)	77 (89)	62 (86)	.87
Yes	14 (11)	10 (11)	10 (14)	
Unknown	6 (5)	0 (0)	0 (0)	
IPI score, n (%)				
0-1	18 (14)	17 (20)	14 (19)	.99
2	30 (23)	28 (32)	22 (31)	
3	31 (24)	31 (36)	20 (28)	
4-5	15 (11)	11 (14)	11 (15)	
Incomplete data	38 (29)	0 (0)	5 (7)	
PIT score, n (%)				
0-1	44 (33)	44 (51)	30 (42)	.95
2	24 (18)	24 (28)	20 (28)	
3-4	19 (14)	19 (22)	11 (15)	
Incomplete data	45 (34)	0 (0)	11 (15)	
Treatments				
Chemotherapy regimen, n (%)				
CHOEP/EPOCH	59 (45)	38 (44)	31 (43)	.97
CHOP	40 (30)	23 (26)	19 (26)	
BV-CH(E)P	16 (12)	12 (14)	11 (15)	
CHOP-based + novel agent	17 (13)	14 (16)	11 (15)	

BV-CH(E)P, CHOP with brentuximab vedotin in place of vincristine with or without etoposide; CHOEP, CHOP with etoposide; ECOG PS, Eastern Cooperative Oncology Group performance status; LDH, lactate dehydrogenase.

*One patient with documented stage II disease and 8 patients with documented stage III disease based on imaging were missing baseline BM biopsies.

Table 1 (continued)

	Entire cohort (N = 132)	CCD cohort (n = 87)	Prospective cohort (n = 72)	P
ASCT in first remission, n (%)				
No	82 (62)	50 (57)	39 (54)	.52
Yes	50 (38)	37 (43)	33 (46)	
Maintenance therapy, n (%)				
No	119 (90)	75 (86)	60 (83)	.34
Yes	13 (10)	12 (14)	12 (17)	

BV-CH(E)P, CHOP with brentuximab vedotin in place of vincristine with or without etoposide; CHOEP, CHOP with etoposide; ECOG PS, Eastern Cooperative Oncology Group performance status; LDH, lactate dehydrogenase.

*One patient with documented stage II disease and 8 patients with documented stage III disease based on imaging were missing baseline BM biopsies.

included the use of etoposide, use of BV, receipt of consolidation ASCT in first remission, and/or receipt of maintenance therapy after CHOP-based chemotherapy with or without consolidative ASCT. Further characteristics included genetic aberrancies (mutations or copy number alterations [CNAs]) that occurred in ≥5% of the entire cohort.

Fisher's exact test and the Wilcoxon rank sum test were used for the descriptive statistical analyses of categorical data and continuous data, respectively. Comparisons between survival curves were performed using the log-rank test, and hazard ratios (HRs) were computed using the Cox proportional hazards model. Data analysis was generated using SAS software (Cary, NC). The oncoplot was developed using R and Complex Heatmap package (version 4.2.2), and the lollipop plot was generated using cBioPortal.

Results

Patient distribution into cohorts

A total of 396 patients with PTCL sequenced via MSK-IMPACT were identified through cBioPortal, of whom 179 (45%) had a confirmed histology of interest. Of these 179 patients, 141 (79%) were treated with a CHOP-based regimen. Nine patients were further excluded, leaving 132 patients comprising the entire cohort (Figure 1). There were 45 patients (34%) missing ≥1 baseline clinical prognostic parameter (Table 1). Missing baseline clinical variables included lactate dehydrogenase level (LDH), the most frequent and only missing variable in 24 patients (18%), followed by BM biopsies, the only missing variable in 10 patients (8%); both baseline LDH and BM biopsies were missing in 11 patients (8%). Thus, the CCD cohort consisted of 87 patients (66%; Figure 1).

Of the 87 patients in the CCD cohort, 26 (30%) were not included in the prospective cohort because they were not patients of MSK until after relapse or had MSK-IMPACT sequencing only after relapse. The prospective cohort consisted of 72 patients (55% of the entire cohort). There were 61 patients who were included in both the CCD cohort and the prospective cohort.

Baseline characteristics and treatments

Table 1 depicts the baseline characteristics of the entire cohort (N = 132), CCD cohort (n = 87), and prospective cohort (n = 72) (note that throughout the manuscript and supplement, uppercase N denotes the entire cohort, whereas lowercase n denotes all other groups). Among the entire cohort, the median age at diagnosis was 65 years (range, 25-82 years) with a male predominance (61%; n = 81). The most common histology was AITL, (47%; n = 62) followed by PTCL-NOS (27%; n = 36), ALK^- ALCL (11%; n = 15), PTCL-TFH (7%; n = 9), ALK^+ ALCL (5%; n = 6), and MEITL (3%; n = 4). The majority of patients had advanced-stage disease (83%; n = 110). Most patients in the CCD cohort had a low-intermediate to high-risk score on the international prognostic index (IPI; 81%; n = 70) and a prognostic index for T-cell lymphomas (PIT) score of ≥2 (49%; n = 43).[4,26-28]

The most common CHOP-based regimen was that containing etoposide, including both CHOP with etoposide (CHOEP) or etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin (EPOCH) (45%; n = 59) followed by CHOP (30%; n = 40) or a CHOP-based clinical trial with the addition of a novel investigational drug (13%; n = 17). BV-containing regimens were used in 16 patients (12%), including 9 of 21 patients with ALCL (43%). Of the total cohort, 50 patients (38%) received ASCT in first remission, and in the prospective cohort, 33 patients (46%) received ASCT in first remission, and 13 patients (10%) were treated on a maintenance therapy clinical trial protocol either after CHOP-based chemotherapy (n = 3) or after ASCT consolidation (n = 10).

There were no significant differences in any baseline clinical characteristic, chemotherapy regimen, or ASCT status among the 3 cohorts (Table 1).

MSK-IMPACT results

Of the entire cohort, samples used for sequencing were most often taken from a lymph node biopsy (70%; n = 93), whereas 8 (6%) had sequencing performed using a sample of leukemic blood or a biopsy of BM with disease involvement, and 31 (24%) came from other diseases sites. A patient-matched control was available in 103 (78%) cases, with those lacking a patient-matched control being matched to a pool of healthy donor control tissues (supplemental Table 1A).

Of the entire cohort, 87 patients (66%) had tumor samples sequenced upon initial diagnostic biopsy, 25 (19%) upon first relapse, and 20 (15%) beyond first relapse. For the CCD cohort, 64 patients (74%) had tumor samples sequenced upon initial diagnosis, 15 (17%) upon first relapse, and 8 (9%) beyond first relapse. By predetermined definition, all patients in the prospective cohort had sequencing performed using a diagnostic biopsy (supplemental Table 1A).

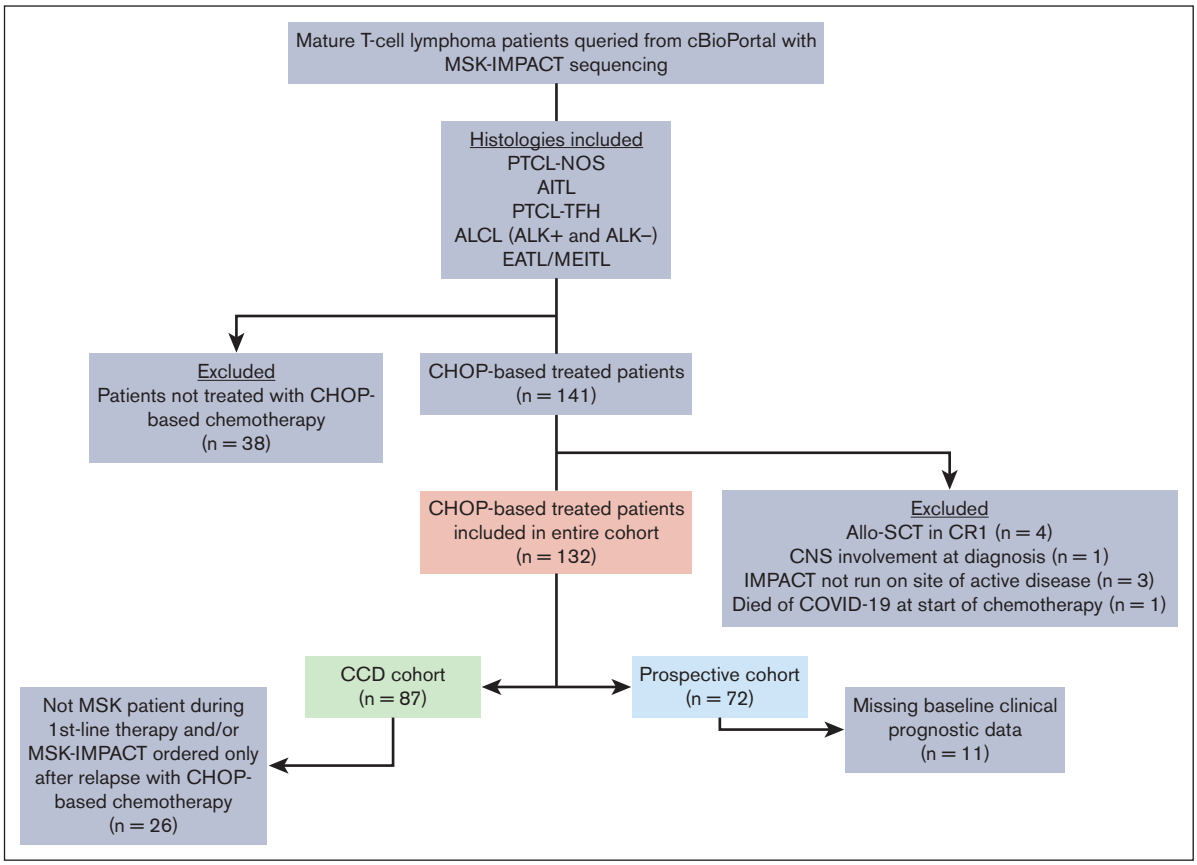

Figure 1. Flowchart of patient identification and distribution into respective cohorts. The entire cohort includes 132 patients with NGS of tumor samples. CCD was available for 87 patients, and 72 patients were managed by an MSK oncologist for their first-line treatment and had tumor NGS before or during CHOP-based treatment. CNS, central nervous system; CR1, first complete remission; EATL, enteropathy-associated T-cell lymphoma.

The most common mutations for the entire cohort were in *TET2* (52%; n = 69), *RHOA* (30%; n = 40), *DNMT3A* (19%; n = 25), *TP53* (16%; n = 21), and *IDH2* (11%; n = 15). The most common CNAs were *TP53* deletions (7%; n = 9) and *CDKN2A* deletions (7%; n = 9) (Figure 2; supplemental Table 1A-J).

Among the 36 cases of PTCL-NOS, the most common mutations were in *TP53* (28%; n = 10), and *TET2* (28%; n = 10), followed by *PLCG1* (17%; n = 6), *STAT5B* (11%; n = 4), and *KMT2D* mutations (11%; n = 4). *TP53* or 17p deletions (11%; n = 4) were also observed. No patient had an *IDH2* mutation, and 2 patients (6%) had *RHOA* mutations (Figure 2; supplemental Table 1B-C).

The most common aberrancy among the 62 cases of AITL were *TET2* mutations (82%; n = 51) followed by mutations in *RHOA* (53%; n = 33), *DNMT3A* (31%; n = 19), and *IDH2* (23%; n = 14). All *IDH2* mutations involved exon 4 at R172X. Of the 52 cases with *TET2* mutations, 36 (71%) had >1 mutation in *TET2*. Of the 33 *RHOA* mutations, 29 (88%) were *RHOA* G17V mutations. *TP53* mutations (3%; n = 2), *TP53* deletions (2%; n = 1), and *CDKN2A* deletions (2%; n = 1) were rare (Figure 2; supplemental Table 1D-E).

The most common aberrancy among the 9 cases of PTCL-TFH were *TET2* mutations (67%; n = 6) followed by mutations in *RHOA* (56%; n = 5), *DNMT3A* (44%; n = 4), *TP53* (22%; n = 2), and *TET3* (22%; n = 2) (Figure 2; supplemental Table 1F-G).

The most common aberrancy among the 15 cases of ALK$^-$ ALCL were *TP53* mutations (33%; n = 5), followed by *TP53* deletions (27%; n = 4), *STAT3* mutations (20%; n = 3), and *FAT1* mutations (20%; n = 3) (Figure 2; supplemental Table 1H-I). *TP63* and *DUSP22/IRF4* rearrangements were detected via other methodologies (fluorescence in-situ hybridization and/or RNA sequencing) in 3 (20%) and 2 (13%) cases, respectively, although not all cases of ALK$^-$ ALCL were evaluated for these structural variations via these other methodologies. No patient with either of these rearrangements had a *TP53* mutation.

Among this series of 132 cases, there were 6 cases of ALK$^+$ ALCL (5%) and 4 cases of MEITL (3%). Aside from ALK rearrangements, the most common aberrancies among the 6 cases of ALK$^+$ ALCL were *FAT1* mutations (33%; n = 2), whereas *TP53* mutations occurred in 1 case (17%) (Figure 2; supplemental Table 1H-I). Of the 4 cases of MEITL, 3 (75%) had *CDKN2A* aberrancies (mutation, n = 1; deletions, n = 2), 3 (75%) had *SETD2* mutations, and 1 (25%) had a *TP53* mutation (Figure 2; supplemental Table 1J-K).

Responses and survival

The overall response rate was 69% (62% complete response [CR], n = 82 and 7% partial response [PR], n = 9) for the entire cohort, 73% (67% CR and 6% PR) for the CCD cohort, and 80% (74% CR and 6% PR) for the prospective cohort. The median

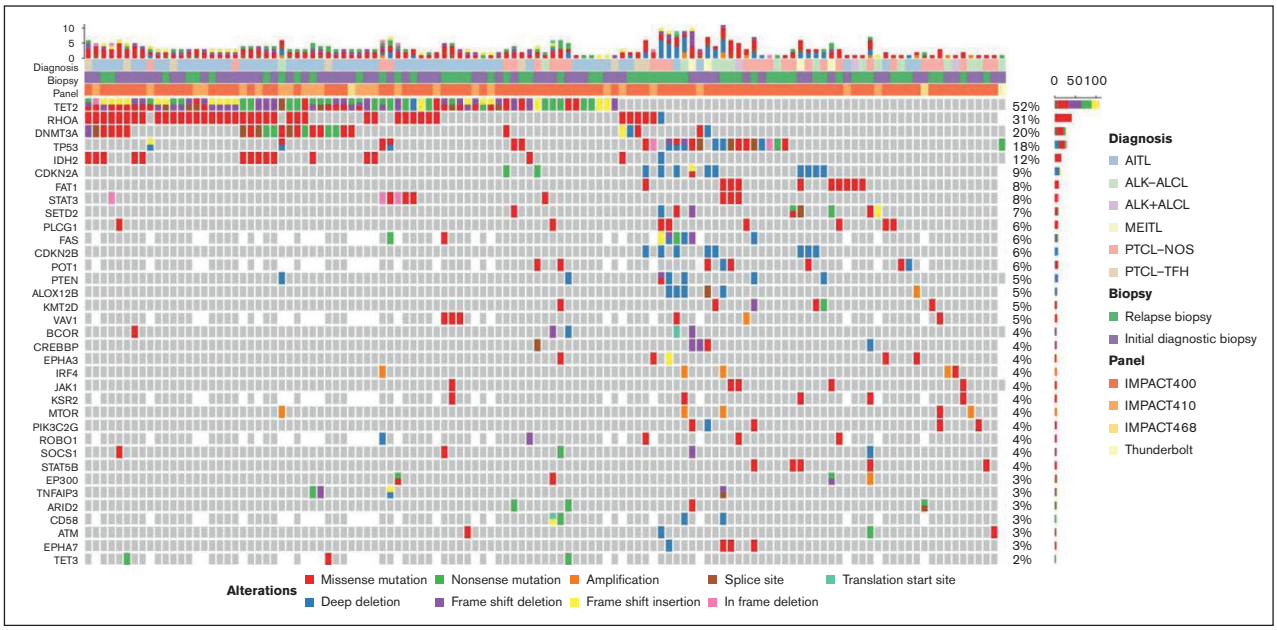

Figure 2. Oncoplot of the most frequent genetic aberrations in the entire cohort (N = 132). Each column represents a unique patient. The top row represents both the number and type of alterations detected in each biopsy. Each row represents the diagnosis, biopsy, sequencing panel, gene and type of mutation, and/or CNA. Gray tiles indicate wild type. Missing tiles represent a gene that is not included in that specific NGS panel. Percent frequencies in the far-right column represent both mutations and CNAs for that specific gene.

follow-ups among survivors were 26, 23, and 24 months for the entire cohort, CCD cohort, and prospective cohort, respectively (supplemental Table 2).

The median PFS was 9.4 months (95% confidence interval [CI], 7.3-13.9) for the entire cohort, 10.8 months (95% CI, 7.8-20.1) for the CCD cohort, and 19.1 months (95% CI, 10.8-40.7) for the prospective cohort. The 2-year PFS was 28% (95% CI, 21.0-38.0) for the entire cohort, 34% (95% CI, 25.0-47.0) for the CCD cohort, and 43% (95% CI, 32.0-58.0) for the prospective cohort. Compared with the entire cohort, the prospective cohort had a longer PFS ($P = .02$), but otherwise, PFS did not differ based on the cohort (Figure 3A; supplemental Table 2).

The median OS was 53.2 months (95% CI, 42.5-70.7) for the entire cohort, 56.7 months (95% CI, 44.6 to not reached [NR]) for the CCD cohort, and NR (95% CI, 45.9-NR) for the prospective cohort. The 2-year OS was 74% (95% CI, 66.0-82.0) for the entire cohort, 73% (95% CI, 63.0-84.0) for the CCD cohort, and 77% (95% CI, 66.0-88.0) for the prospective cohort (Figure 3B; supplemental Table 2). OS did not differ based on the cohort. PFS and OS did not differ based on the histology (supplemental Figure 1).

Clinical and genetic associations with survival

Factors affecting PFS in univariate analyses (Table 2) were examined in a multivariate analysis. For the 87 patients in the CCD cohort, the clinical parameters correlating with inferior PFS on multivariate analysis were advanced-stage disease (HR, 5.1; 95% CI, 1.1-22.5; $P = .03$) and BM involvement (HR, 3.0; 95% CI, 1.1-8.4; $P = .04$). Although higher IPI and PIT scores correlated with inferior PFS on univariate analysis, they lost significance upon multivariate analysis. No first-line treatment regimen correlated with PFS outcomes, but receipt of ASCT in first remission was associated with superior PFS (HR, 0.3; 95% CI, 0.1-0.5; $P < .001$). The only 2 genetic aberrancies correlating with inferior PFS on multivariate analysis were *TP53* mutations (HR, 3.1; 95% CI, 1.4-6.8; $P = .005$) and *TP53*/17p deletions (HR, 4.1; 95% CI, 1.1-15.0; $P = .03$; Table 2).

Factors affecting the OS in univariate analyses (Table 3) were examined in a multivariate analysis. The only baseline clinical parameter correlating with inferior OS on multivariate analysis was an Eastern Cooperative Oncology Group performance status score of ≥2 (HR, 19.2; 95% CI, 2.8-133.0; $P = .003$). ASCT receipt during the first remission remained significant for a superior OS upon multivariate analysis (HR, 0.1; 95% CI, 0.04-0.4; $P < .001$). The only genetic aberrancy correlating with inferior OS was the presence of a *CDKN2A* deletion (HR, 12.1; 95% CI, 2.8-52.0; $P < .001$). In contrast to PFS, *TP53* alterations did not correlate with inferior OS (Table 3).

Cohort-wide survival based on *TP53* and *CDKN2A* status

Cases harboring either a *TP53* mutation or a *TP53*/17p deletion in the CCD cohort correlated with inferior PFS on multivariate analysis. Therefore, we stratified the entire cohort based on the presence (16%; n = 21) or absence (84%; n = 111) of a *TP53* mutation (with or without a *TP53*/17p deletion). Of the 21 cases with *TP53* mutations, 15 (71%) did not have a concurrent *TP53*/17p deletion, and 6 (29%) had a concurrent *TP53*/17p deletion. Two cases (10%) had a concurrent *CDKN2A* deletion, 1 of which also had a concurrent *TP53*/17p deletion. A *TP53*/17p deletion without a concurrent *TP53* mutation was found in only 3 cases (2%) of the entire cohort.

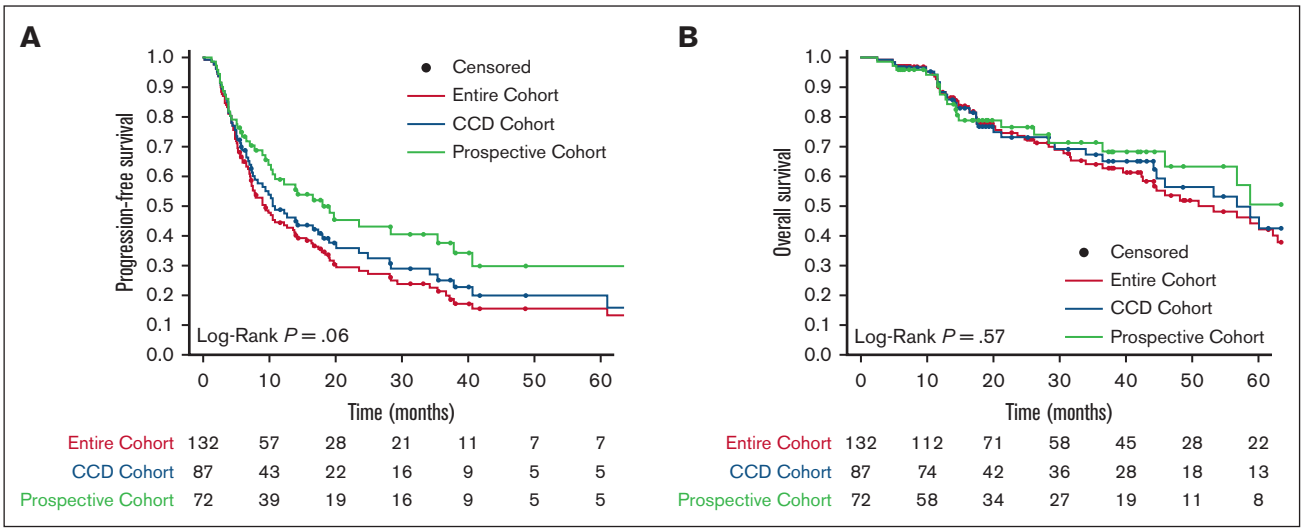

Figure 3. Kaplan-Meier survival curves for each cohort. (A) PFS and (B) OS of the entire cohort (red), CCD cohort (blue), and prospective cohort (green). The prospective cohort had superior PFS compared with the entire cohort ($P = .02$). There were no other significant differences in PFS or OS. Living patients were censored at time of last follow-up (filled circles). The number of patients at risk for each time point and cohort is shown.

Among the entire cohort of PTCL, patients with *TP53* mutations had inferior PFS, with a median PFS of 4.5 months (95% CI, 3.8-13.9) vs 10.5 months (95% CI, 7.8-18.1) for those without *TP53* mutations ($P < .001$) (Figure 4A; supplemental Table 3). The 2-year PFS was 10% (95% CI, 3.0-36.0) in *TP53*-mutated PTCL and 32% (95% CI, 24.0-43.0) in *TP53*-unmutated PTCL (supplemental Table 3). All PFS events for patients with *TP53*-mutated PTCL were due to relapsed or refractory disease. In the prospective cohort, the median PFS was 4.1 months (95% CI, 2.8-NR) for patients with *TP53*-mutated PTCL vs 19.7 months (95% CI, 10.8-72.3) for those with *TP53*-unmutated PTCL ($P = .02$; supplemental Figure 2A; supplemental Table 4).

There were no significant differences in the OS of patients with *TP53*-mutated PTCL compared with that of those with *TP53*-unmutated PTCL in either the entire or prospective cohorts. For the entire cohort, the median OS of patients with *TP53*-mutated PTCL was 48.2 months (95% CI, 29.2-NR) vs 53.2 months (95% CI, 42.3-71) for those with *TP53*-umutated PTCL (Figure 4B; supplemental Table 3). In the prospective cohort, the median OS was NR (95% CI, NA-NA) for patients with *TP53*-mutated PTCL vs 58.7 months (95% CI, 45.9-NR) for those with *TP53*-unmutated PTCL (supplemental Figure 2B; supplemental Table 4).

CDKN2A deletions correlated with inferior OS upon multivariate analysis in the CCD cohort. Therefore, we compared the OS of the entire cohort with that of the prospective cohort based on the presence (7%; n = 9) or absence (93%; n = 123) of *CDKN2A* deletions. Of the 9 cases with a *CDKN2A* deletion, 2 (22%) had a concurrent *TP53*/17p deletion, and 2 (22%) had a concurrent *TP53* mutation. For the entire cohort, *CDKN2A*-deleted PTCL correlated with an inferior OS, with a median of 17.6 months (95% CI, 12.8-NR) vs 56.7 months (95% CI, 44.6-101.0) for PTCL without *CDKN2A* deletions ($P = .004$; supplemental Figure 3B; supplemental Table 3). PFS trended but remained nonsignificant based on the presence or absence of *CDKN2A* deletions (supplemental Figure 3A; supplemental Table 3). There were only 4 cases (5%) with *CDKN2A* deletions in the prospective cohort (supplemental Table 4).

Consistent with prior reports, *TP53* mutations (3%; n = 2) and *CDKN2A* deletions (n = 0) were rare in AITL.[29] Therefore, we analyzed the survival rates of non-AITL PTCL (n = 70) based on the presence or absence of these alterations. Patients with *TP53*-mutated non-AITL PTCL experienced inferior PFS, with a median of 4.5 months (95% CI, 4.1-17.4) vs 7.8 months (95% CI, 7.1-20.1) for *TP53*-unmutated non-AITL PTCL ($P = .02$), with no difference in the OS (supplemental Figure 4; supplemental Table 5). Patients with non-AITL PTCL harboring *CDKN2A* deletions had inferior OS, with a median OS of 17.4 months (95% CI, 11.1-NR) for patients with *CDKN2A* deletions vs 48.2 months (95% CI, 42.5-NR) for those without such deletions ($P = .004$). There was no difference in the PFS based on the *CDKN2A* status (supplemental Figure 5; supplemental Table 5).

TP53/17p deletions were uncommon in the absence of a *TP53* mutation (2%; n = 3). There were no differences in PFS when both *TP53*/17p deletion and *TP53* mutation were present as compared with a *TP53* mutation alone (supplemental Figure 6).

Characteristics of *TP53*-mutated PTCL

We then compared the characteristics and treatment outcomes for patients with *TP53*-mutated PTCL vs *TP53*-unmutated PTCL (Table 4). *TP53* mutations were relatively enriched in PTCL-NOS (n = 10; $P = .03$) and relatively less frequent in AITL (n = 2; $P < .001$) compared with other histologies. There were no significant differences in age, disease stage, BM involvement, involvement of other extranodal sites, or IPI or PIT scores between patients with *TP53*-mutated and *TP53*-unmutated PTCL. There were also no differences in first-line treatment regimen or whether ASCT was received in first remission. There was a trend toward fewer CRs for patients with *TP53*-mutated PTCL ($P = .053$).

Similar proportions of patients with *TP53*-mutated and *TP53*-unmutated PTCL had sequencing performed using their initial diagnostic biopsy. *TP53* mutations were more likely to cooccur with *TP53* or 17p deletions ($P < .001$), whereas *TET2* and *RHOA*

Table 2. Variables correlating with inferior PFS in the CCD cohort (n = 87)

		Univariate analysis			Multivariate analysis		
Variable	**n (%)**	**HR**	**95% CI**	***P***	**HR**	**95% CI**	***P***
Age > 60 y	50 (57)	1.2	0.7-1.9	.56			
Stage III/IV	72 (83)	3.0	1.3-6.9	**.01**	5.1	1.1-22.5	**.03**
Performance: ECOG PS ≥ 2	10 (11)	1.9	0.9-3.7	.08			
LDH elevated	53 (61)	1.1	0.7-1.9	.69			
BM involvement (by morphological assessment)	32 (37)	2.3	1.4-3.9	**.002**	3.0	1.1-8.4	**.04**
Other extranodal sites of involvement	35 (40)	1.9	1.1-3.1	**.01**	1.5	0.7-3.3	.32
IPI score							
0-1	17 (20)	1.0					
2	28 (32)	2.1	0.9-4.7	.08	1.0	0.2-4.3	.98
3	30 (34)	2.9	1.3-6.5	**.009**	0.4	0.1-2.8	.35
4-5	12 (14)	2.8	1.1-7.0	**.03**	0.1	0.01-2.0	.15
PIT score							
0-1	44 (51)	1.0					
2	24 (28)	1.3	0.7-2.4	.37	1.3	0.4-3.8	.65
3-4	19 (22)	2.2	1.2-4.1	**.01**	2.4	0.3-17.0	.41
Histology							
PTCL-NOS	28 (32)	1.0					
PTCL-TFH	6 (7)	0.3	0.1-1.1	.08			
AITL	39 (45)	0.7	0.4-1.2	.14			
ALK^+ ALCL	2 (2)	0.3	0.04-2.3	.24			
ALK^- ALCL	8 (9)	0.4	0.1-1.2	.10			
MEITL	4 (5)	0.7	0.2-2.5	.61			
Use of etoposide-containing regimens	47 (54)	1.0	0.6-1.6	.91			
Use of BV-containing regimens	12 (14)	0.8	0.3-2.0	.65			
ASCT consolidation	37 (43)	0.3	0.2-0.6	**<.001**	0.3	0.1-0.5	**<.001**
Maintenance*	12 (14)	0.4	0.2-1.0	**.04**	0.4	0.1-1.0	.051
TP53 mutation	13 (15)	2.4	1.3-4.6	**.008**	3.1	1.4-6.8	**.005**
TP53 or 17p deletion	5 (6)	9.6	3.4-27.2	**<.001**	4.1	1.1-15.0	**.03**
CDKN2A deletion	7 (8)	2.2	0.9-5.1	.07			
TET2 mutation	48 (55)	0.9	0.5-1.5	.69			
DNMT3A mutation	17 (20)	1.4	0.8-2.5	.27			
DNMT3A exon 23 mutation	5 (6)	1.4	0.6-3.6	.44			
RHOA mutation	26 (30)	0.8	0.4-1.3	.34			
FAT1 mutation	4 (5)	1.1	0.3-3.4	.92			
STAT3 mutation	4 (5)	1.0	0.3-3.3	.94			
SETD2 mutation	5 (6)	0.5	0.2-1.6	.24			
IDH2 mutation	7 (8)	0.6	0.2-1.7	.33			
PCLG1 mutation	7 (8)	1.2	0.5-2.9	.76			
Total number of aberrancies	87 (100)	1.0	1.0-1.1	.07			

ECOG PS, Eastern Cooperative Oncology Group performance status; LDH, lactate dehydrogenase.
Bold indicates $P < .05$.
*Twelve patients received maintenance systemic therapy on a clinical trial either after chemotherapy or after ASCT.

mutations were enriched in patients with PTCL without *TP53*-mutations ($P = .03$ and $P = .04$, respectively). *TET2* and *TP53* mutations cooccurred in 6 cases. None of the 15 patients with an *IDH2* mutation had a concurrent *TP53* mutation. Cases with mutated *TP53* had a higher median number of total aberrancies per sample ($P = .008$; Table 4).

Lastly, for all cases of PTCL with a *TP53* mutation (16%; n = 21), we compared the median variant allele frequency of the *TP53* mutation to all other concurrent mutations within each patient's biopsy (Figure 5A). *TP53* mutations were the dominant mutation in 12 cases (57%), at or above the median of all mutations in 18 cases (86%). The majority of *TP53* mutations involved the DNA

Table 3. Variables correlating with inferior OS in the CCD cohort (n = 87)

		Univariate analysis			Multivariate analysis		
Variable	**n (%)**	**HR**	**95% CI**	***P***	**HR**	**95% CI**	***P***
Age > 60 y	50 (57)	1.3	0.6-2.7	.54			
Stage III/IV	72 (83)	2.7	0.6-11.4	.18			
Performance: ECOG PS ≥ 2	10 (11)	3.6	1.6-8.0	**.002**	19.2	2.8-133.0	**.003**
LDH elevated	53 (61)	2.4	1.1-5.7	**.04**	1.9	0.5-7.2	.33
BM involvement (by morphological assessment)	32 (37)	3.4	1.7-7.0	**<.001**	3.8	0.8-19.0	.10
Other extranodal sites of involvement	35 (40)	2.1	1.0-4.2	**.04**	1.0	0.2-4.5	.96
IPI score, n (%)							
0-1 (group 1)	17 (20)	1.0					
2 (group 2)	28 (32)	4.4	0.5-35.0	.16	7.8	0.8-73.0	.07
3 (group 3)	30 (34)	7.5	1.0-57.0	**.052**	2.1	0.1-28.0	.59
4-5 (group 4)	12 (14)	11.8	1.5-95.0	**.02**	0.4	0.01-21.0	.64
PIT score, n (%)							
0-1 (group 1)	44 (51)	1.0					
2 (group 2)	24 (28)	2.1	0.8-5.2.0	.13	0.8	0.2-3.5	.76
3-4 (group 3)	19 (22)	4.3	1.8-10.0	**<.001**	1.3	0.1-30.0	.87
Histology							
PTCL-NOS	28 (32)	1.0					
PTCL-TFH	6 (7)	1.0	0.2-4.3	.95			
AITL	39 (45)	0.8	0.4-1.8	.61			
ALK^+ ALCL	2 (2)	0.0	-	.99			
ALK^- ALCL	8 (9)	0.3	0.04-2.4	.26			
MEITL	4 (5)	0.9	0.1-7.1	.93			
Use of etoposide-containing regimens	47 (54)	0.7	0.3-1.3	.25			
Use of BV-containing regimens	12 (14)	1.9	0.6-6.5	.31			
ASCT consolidation	37 (43)	0.2	0.1-0.5	**<.001**	0.1	0.04-0.40	**< .001**
Maintenance therapy*	12 (14)	0.4	0.1-1.2	.09			
TP53 mutation	13 (15)	0.7	0.2-1.9	.45			
TP53 or 17p deletion	5 (6)	1.4	0.3-6.0	.63			
CDKN2A deletion	7 (8)	5.3	1.9-14.4	**.001**	12.1	2.8-52.0	**< .001**
TET2 mutation	48 (55)	1.3	0.6-2.7	.47			
DNMT3A mutation	17 (20)	1.6	0.7-3.6	.25			
DNMT3A exon 23 mutation	5 (6)	0.0	-	.99			
RHOA mutation	26 (30)	0.9	0.4-2.0	.79			
FAT1 mutation	4 (5)	1.9	0.4-8.1	.40			
STAT3 mutation	4 (5)	1.1	0.2-8.5	.90			
SETD2 mutation	5 (6)	0.0	-	.99			
IDH2 mutation	7 (8)	2.0	0.7-5.8	.19			
PCLG1 mutation	7 (8)	2.1	0.6-7.2	.22			
Total number of aberrancies	87 (100)	1.0	1.0-1.1	**.04**			

ECOG PS, Eastern Cooperative Oncology Group performance status; LDH, lactate dehydrogenase.
Bold indicates $P < .05$.
*Twelve patients received maintenance systemic therapy on a clinical trial either after chemotherapy or after ASCT.

binding domain (81%; n = 17) and were missense mutations (52%; n = 11; Figure 5B). All the *TP53* mutations had been reported previously as a cancer hotspot mutation and/or are documented in the OncoKB database as being likely oncogenic.[30,31]

Discussion

To the best of our knowledge, these data represent the largest cohort of patients with PTCL treated with curative-intent chemotherapy to undergo targeted NGS of their tumors using a clinically validated sequencing panel. We centered on histologies treated

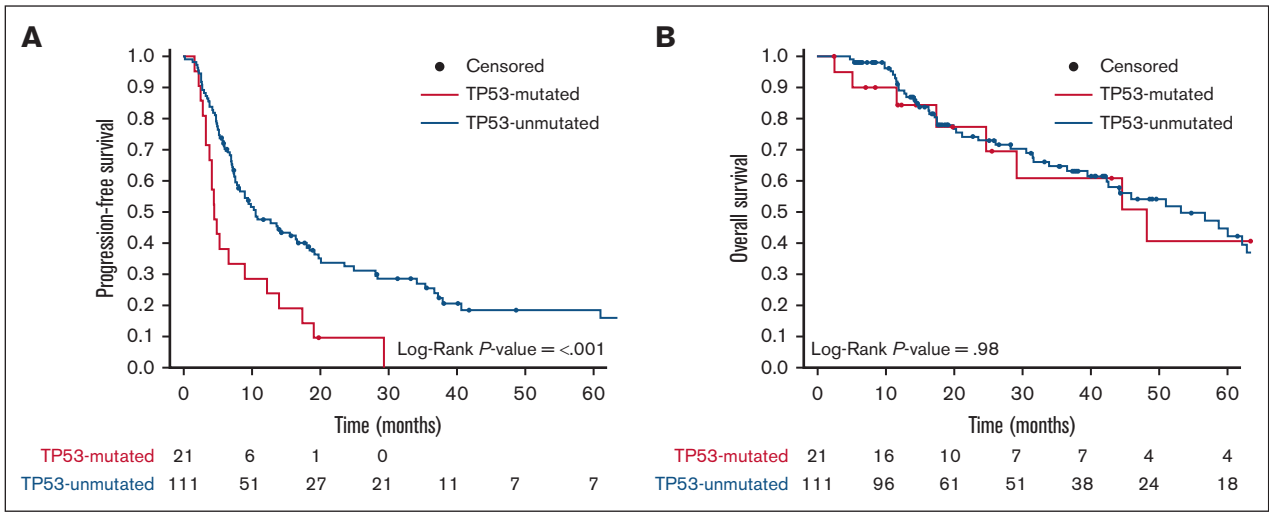

Figure 4. Kaplan-Meier survival curves for the entire cohort (N = 132) stratified based on the *TP53* mutation status. (A) PFS and (B) OS of patients with (*TP53*-mutated; red) or without (*TP53*-unmutated; blue) PTCL. Data of living patients were censored at the time of last follow-up (filled circles). The number of patients at risk for each time point and cohort is shown.

with CHOP-based regimens with the option of ASCT consolidation, when eligible. Upon multivariate analysis in the CCD cohort, *TP53* alterations were detected as the only genetic event that independently predicted inferior PFS; this result was observed in both the entire and prospective cohorts when stratified based on the presence or absence of a *TP53* mutation. In addition, *TP53*-mutated PTCL showed a trend toward a lower frequency of CRs compared with *TP53*-unmutated PTCL, suggesting inherent chemoresistance in these cases. This is consistent with the observations of patients with *TP53* alterations in other hematological malignancies in which *TP53* alterations associate with inferior outcomes when treated with both curative- and noncurative-intent therapies.[32-36]

The *TP53* mutations in our cohort were highly suggestive of a predominant clone based on the high allele frequency observed in all but 1 case. The relatively high prevalence of *TP53* mutations in PTCL-NOS (28%) and ALK$^-$ ALCL (33%) in this series was similar to prior reports. For example, 2 independent publications on PTCL-NOS reported the presence of *TP53* mutations in 28% and 19% of cases, respectively.[18,19] In a recent large series of patients with systemic ALCL (N = 82), *TP53* mutations occurred in 23% of ALK$^-$ and 11% of ALK$^+$ ALCL cases, respectively, and correlated with inferior PFS and OS.[16] *TP53* mutations in our series were rare in AITL (3%), consistent with prior reports.[29] Based on previous observations, *TP53* mutations occured in ~17% to 40% of PTCL-TFH cases[37,38] and 33% of MEITL cases.[39] Overall, our data on the prevalence of *TP53* mutations in PTCL are consistent with prior observations.

Interestingly, although patients with *TP53* mutations experienced inferior PFS, they had no impact on OS. We hypothesized that this could have been attributed to the inclusion of multiple histologies, access to multiple novel clinical trials implementing non-cytotoxic therapies, and/or variability in eligibility for curative-intent allogeneic stem cell transplant. However, only 3 (10%) patients with *TP53*-mutated PTCL underwent curative-intent allo-SCT after CHOP-based progression, and all 3 relapsed. One of these patients achieved a second CR with duvelisib plus romidepsin, was consolidated with donor lymphocyte infusion, and has remains disease-free for >5 years.[40] Nevertheless, despite the low number of patients with *TP53*-mutated PTCL who underwent a potentially curative allo-SCT, the median number of lines of therapy was 3 (range, 1-11), and 10 (48%) patients received ≥4 lines of therapy (data not shown). Moreover, 10 (48%) patients were treated on a least 1 clinical trial investigating novel therapies such as valemetostat, duvelisib, duvelisib plus romidepsin, ruxolitinib, or cerdulatinib; all of which have demonstrated relatively encouraging response rates and durability in a subset of patients.[40-44] This suggests novel agents may provide meaningful outcomes for *TP53*-mutated PTCL. A dedicated analysis on the outcomes of relapsed or refractory *TP53*-mutated PTCL compared with non-*TP53*-mutated PTCL is needed to better understand this patient population and determine the best treatment strategies.

Multivariate analyses in the CCD cohort and the entire cohort indicated that patients with *CDKN2A* deletions experienced inferior OS when compared to patients who did not harbor such deletions. Using various methodologies for CNA detection combined with other published datasets, a recent study reported a high frequency (46%) of these deletions in PTCL-NOS and their significant association with inferior PFS and OS.[15] *CDKN2A* deletions were rare in our cohort (7% of entire cohort and 8% in PTCL-NOS), possibly restricted by the threshold of CNA detection through exome sequencing and the clinical reporting of MSK-IMPACT limiting definitive conclusions based on our data alone.

Limitations to this retrospective study include the small numbers of patients with certain histologic subsets, patients for whom data on baseline clinical characteristics were missing, lack of uniform treatment for patients, lack of complete PTCL-TFH immunohistochemical markers in older cases, and the limitations of MSK-IMPACT methodologies in detecting CNAs and other structural variations. There are also limitations with targeted exon sequencing and the threshold for calling chromosome arm-level deletions and copy-neutral loss of heterozygosity with MSK-IMPACT. Given these limitations, caution is advised when interpreting these data for first-line treatment modifications and should not reflexively institute deviations in the current standard of care including enrollment onto first-line clinical trials.

Table 4. Characteristics and outcomes for patients with *TP53*-mutated vs *TP53*-unmutated PTCL

	TP53 mutated (n = 21)	*TP53* unmutated (n = 111)	*P*
Median age, y (range)	60 (46-79)	66 (25-82)	.39
Sex, n (%)			
Male	16 (76)	65 (59)	.15
Female	5 (24)	46 (41)	
Histology, n (% frequency per histology)			
PTCL-NOS	10/36 (28)	26/36 (72)	**.03**
AITL	2/62 (3)	60/62 (97)	**< .001**
PTCL-TFH	2/9 (22)	7/9 (78)	.63
ALK^{-} ALCL	5/15 (33)	10/15 (67)	.06
ALK^{+} ALCL	1/6 (17)	5/6 (83)	>.99
MEITL	1/4 (25)	3/4 (75)	.50
Stage, n (%)			
I/II*	5 (24)	17 (15)	.35
III/IV*	16 (76)	94 (85)	
BM involvement by (by morphological assessment), n (%)			
N	13 (62)	59 (53)	.17
Y	3 (14)	36 (32)	
Unconfirmed	5 (24)	16 (14)	
Other extranodal sites of involvement, n (%)			
N	12 (57)	69 (62)	.81
Y	9 (43)	42 (38)	
IPI score, n (%)			
0-1	2 (10)	17 (15)	.80
2	5 (24)	26 (23)	
3	5 (24)	25 (23)	
4-5	1 (5)	15 (14)	
Incomplete data	8 (38)	28 (25)	
PIT score, n (%)			
0-1	8 (38)	36 (32)	.79
2	3 (14)	21 (19)	
3-4	2 (10)	17 (15)	
Incomplete data	8 (38)	37 (33)	
First-line treatment, n (%)			
CHOP	4 (19)	36 (32)	.16
CHOEP/EPOCH	11 (52)	48 (43)	
BV-CH(E)P	5 (24)	11 (10)	
CHOP-based + novel agent	1 (5)	16 (14)	
Response to induction, n (%)			
CR	9 (43)	73 (66)	.053
<CR	12 (57)	38 (34)	
Received ASCT in first remission, n (%)			
Y	6 (29)	44 (40)	.17
N	15 (71)	67 (60)	
Outcomes after ASCT, n (%)			
PFS event	5/6 (83)	29/44 (66)	.65
Ongoing remission	1/6 (17)	15/44 (34)	

BV-CH(E)P, CHOP with brentuximab vedotin in place of vincristine with or without etoposide; CHOEP, CHOP with etoposide; N, no; Y, yes.
Bold indicates $P < .05$.
*One patient with documented stage II disease and 8 patients with documented stage III disease based on imaging were missing baseline BM biopsies.

Table 4 (continued)

	TP53 mutated (n = 21)	*TP53* unmutated (n = 111)	*P*
MSK-IMPACT sample sequencing time point, n (%)			
Diagnostic biopsy	10 (48)	77 (69)	.09
First relapse biopsy	5 (24)	20 (18)	
Beyond first relapse	6 (29)	14 (13)	
Other aberrancies, n (%)			
TP53 or 17p deletion	6 (29)	3 (3)	**<.001**
CDKN2A deletion or mutation	3 (14)	9 (8)	.41
DNMT3A mutation	2 (10)	23 (21)	.36
TET2 mutation	6 (29)	63 (57)	**.03**
RHOA	2 (10)	38 (34)	**.04**
IDH2	0 (0)	15 (13)	.13
Median number of aberrancies (range)	11 (1-48)	5 (0-33)	**.008**

BV-CH(E)P, CHOP with brentuximab vedotin in place of vincristine with or without etoposide; CHOEP, CHOP with etoposide; N, no; Y, yes.
Bold indicates $P < .05$.
*One patient with documented stage II disease and 8 patients with documented stage III disease based on imaging were missing baseline BM biopsies.

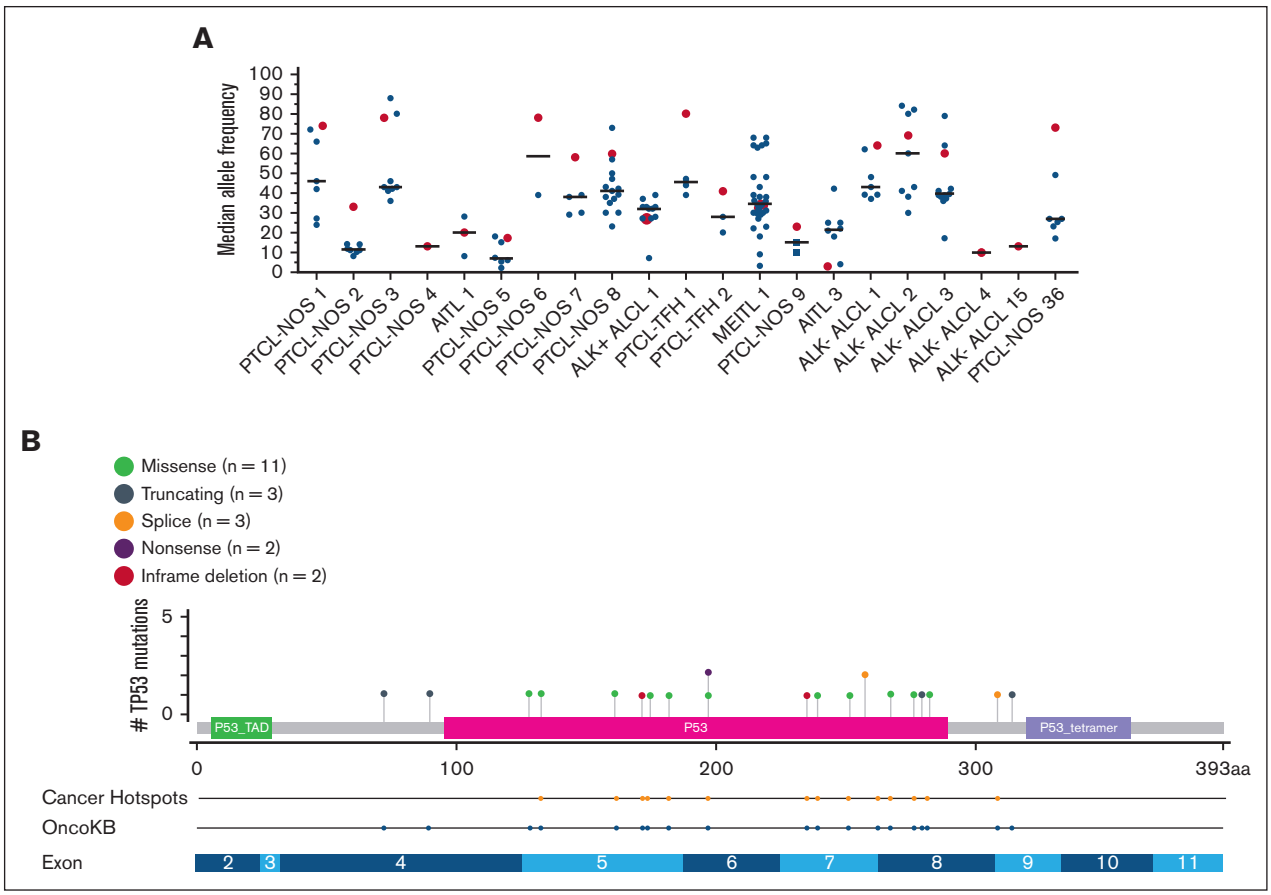

Figure 5. *TP53* median variant allele frequencies (MAFs) and mutation specifics among PTCL cases with a *TP53* mutation (n = 21). (A) MAF of *TP53* mutations as compared with all other gene mutations in each tumor sample (n = 21). Each of these 21 patients' biopsies are represented on the x-axis. Red symbols represent the MAF of the *TP53* mutation. Black symbols represent the MAF of any non-*TP53*–mutated gene found in the same biopsy. The solid lines represent the median MAF of all mutations occurring in the biopsy sample. (B) Lollipop plot of *TP53* mutations (n = 21). Each colored symbol represents a specific *TP53* mutation along the entire coding region. The green boxed region represents the transactivation domain (P53_TAD). The red boxed region represents the DNA binding domain (P53). The blue boxed region represents the tetramerization domain (P53_tetramer). The next 2 rows signify that all mutations are listed in the OncoKB database as likely oncogenic, and 15 have been reported as cancer hotspot mutations. The bottom row illustrates the exon structure of the *TP53* gene.

Despite some limitations, we found that 95% of patients (20 of 21) with *TP53*-mutated PTCL in our study had relapsed after, or were refractory to, curative-intent treatment with CHOP-based therapy. Other than *TP53* mutations, as described in this manuscript and in others, additional genetic markers including GATA-3 expression, *FAT1* mutations, and *CDKN2A* deletions in PTCL-NOS, *CD28* mutations in AITL, and *TP63* structural variations in ALK^{-} ALCL have been previously reported as indicators of a poor prognosis.[7,15,17,21,45] Whether *TP53* aberrancies or other genetic events require an alternative approach to therapeutic induction and/or consolidative strategies will require further research on a larger cohort of patients who are uniformly treated.

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Authorship

Contributions: W.T.J. designed the research study, collected the data, and wrote the manuscript; N. Ganesan performed the primary statistical analysis; Z.D.E.-P., A.J.M., and R.N.S. reviewed and assisted in the writing of the manuscript; C.R.M. collected the data; N. Galasso collected the data and assisted in the institutional review board submission process; T.C. collected the data; N.K. reviewed and assisted in the writing of the manuscript; U.A. reviewed the sequencing data, and reviewed and assisted in the writing of the manuscript; N.E.L. reviewed the pathology diagnoses; A.D.Z., M.L.P., M.J.M., A.N., A.M.H., P.H., P.C.C., D.J.S., A.M.I., C.L.B., A.K., C.N.O., C.S.S., L.F., J.K.L., S.A.V., and G.S. reviewed and assisted in the writing of the manuscript; A.D. reviewed the pathology diagnoses; N.D.S. assisted with data review from cBioPortal; M.E.A. reviewed the clinically reported genetic sequencing results; and S.M.H. provided oversight to the research study design and reviewed and assisted in writing the manuscript.

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