ALK-negative anaplastic large cell lymphoma with *DUSP22* rearrangement has distinctive disease characteristics with better progression-free survival: a LYSA study

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Abstract

ALK-negative anaplastic large cell lymphoma (ALCL) comprises subgroups harboring rearrangements of *DUSP22* (*DUSP22*-R) or *TP63* (*TP63*-R). Two studies reported 90% and 40% 5-year overall survival (OS) rates in 21 and 12 *DUSP22*-R/*TP63*-not rearranged (NR) patients, respectively, making the prognostic impact of *DUSP22*-R unclear. Here, 104 newly diagnosed ALK-negative ALCL patients (including 37 from first-line clinical trials) from the LYSA TENOMIC database were analyzed by break-apart fluorescence *in situ* hybridization assays for *DUSP22*-R and *TP63*-R. There were 47/104 (45%) *DUSP22*-R and 2/93 (2%) *TP63*-R cases, including one *DUSP22*-R/*TP63*-R case. *DUSP22*-R tumors more frequently showed CD3 expression (62% *vs*. 35%, *P*=0.01), and less commonly a cytotoxic phenotype (27% *vs*. 82%; *P*<0.001). At diagnosis, *DUSP22*-R ALCL patients more frequently had bone involvement (32% *vs*. 13%, *P*=0.03). The patient with *DUSP22*-R/*TP63*-R ALCL had a rapidly fatal outcome. After a median follow-up of 4.9 years, 5-year progression-free survival (PFS) and OS rates of 84 patients without *TP63*-R treated with curative-intent anthracycline-based chemotherapy were 41% and 53%, respectively. According to *DUSP22* status, 5-year PFS was 57% for 39 *DUSP22*-R *versus* 26% for 45 triple-negative (*DUSP22*-NR/*TP63*-NR/ALK-negative) patients (*P*=0.001). The corresponding 5-year OS rates were 65% and 41%, respectively (*P*=0.07). In multivariate analysis, performance status and *DUSP22* status significantly affected PFS, and distinguished four risk groups, with 4-year PFS and OS ranging from 17% to 73% and 21% to 77%, respectively. Performance status but not *DUSP22* status influenced OS. The use of brentuximab vedotin in relapsed/refractory patients improved OS independently of *DUSP22* status. Our findings support the biological and clinical distinctiveness of *DUSP22*-R ALK-negative ALCL. Its relevance to outcome in patients receiving frontline brentuximab vedotin remains to be determined.

Introduction

Anaplastic lymphoma kinase (ALK)-negative anaplastic large cell lymphoma (ALCL) is one of the four ALCL entities recognized in the current World Health Organization (WHO) classification of lymphoid neoplasms. It is a systemic disease entity defined as a CD30-positive T-cell neoplasm that is not reproducibly distinguishable on morphological grounds from ALK-positive ALCL but lacks ALK protein expression.[1] Before 2017, ALK-negative ALCL was listed as a provisional entity, because of overlapping features with CD30-positive peripheral T-cell lymphoma, not otherwise specified (PTCL-NOS), and the lack of established diagnostic criteria. Improved criteria for routine diagnostic practice, together with results from several studies suggesting distinguishing molecular features, led to the validation of ALK-negative ALCL as a definitive entity.[1,2]

Multiple studies over the past years have highlighted the heterogeneity of ALK-negative ALCL, and emphasized that this entity is not merely defined by the lack of *ALK* gene fusions, but comprises a heterogeneous genomic landscape including subgroups harboring *DUSP22* or *TP63* rearrangements (*DUSP22*-R or *TP63*-R) or lacking both (*DUSP22*-NR/*TP63*-NR/ALK-negative, referred to as triple-negative ALCL). Other recurrent alterations consist of somatic mutations of *JAK1*, *STAT3* or *MSC*, the expression of ERBB4-aberrant transcripts, or a deregulated BATF3/IL-2R module.[3-7] In particular, it has been shown that ALK-negative ALCL with *DUSP22*-R is characterized by a distinct gene expression signature, recurrent *MSC* mutations, lack of STAT3 activation and DNA hypomethylation.[6,8] For these reasons, the recently released International Consensus Classification of lymphoid neoplasms, but not as yet the 5th Edition of the WHO-HAEM classification, considers *DUSP22*-R ALCL as a distinct genomic subtype.[9,10]

With conventional therapy, 5-year overall survival (OS) of ALK-negative ALCL patients is approximately 50%.[11–15] It has been suggested that *DUSP22*-R could impact this survival rate. In the first clinical report from a multi-institution US study, the 5-year OS of 21 patients with *DUSP22*-R/*TP63*-NR ALK-negative ALCL was 90%. Later on, a similar favorable outcome was reported in five patients in a Danish study (5-year OS, 80%) and in four patients from Spain (5-year OS, 100%).[16,17] However, in another recent work from the British Columbia Cancer Agency (BCCA) database, the 5-year OS of 12 patients with *DUSP22*-R/*TP63*-NR ALK-negative ALCL was 40%.[18] Thus, the prognostic impact of *DUSP22*-R in ALK-negative ALCL is currently unclear. The National Comprehensive Cancer Network guidelines suggest that treatment of the *DUSP22*-R subgroup according to the ALK-positive ALCL algorithm may be considered.[19] However, this could lead to undertreating patients if the prognosis of *DUSP22*-R is not as favorable as expected.

In this retrospective study of 104 patients with ALK-negative ALCL from the TENOMIC database of the Lymphoma Study Association (LYSA), we analyzed the pathological characteristics, clinical features, and outcomes of patients according to *DUSP22* and *TP63* status.

Methods

Patients and samples

Patients with ALK-negative ALCL diagnosed between January 2001 and January 2020 were retrieved from the TENOMIC database, the translational T-cell lymphoma research consortium of the LYSA. Thirty-seven patients had been enrolled in first-line clinical trials (26 Ro-CHOP, 8 AATT, 3 ECHELON-2 studies), and six in the TOTAL study for relapsed/refractory patients, the results of which have been reported,[20-23] and nine patients were from a previous study.[24] Other patients had been treated in routine care. Inclusion criteria required availability of diagnostic tissue (or existing documentation of a *DUSP22* fluorescence *in situ* hybridization [FISH] result), and of clinical data including treatment and follow-up. Among the cases for which *DUSP22* FISH was performed secondarily, we recorded a failure in five cases. These cases have not been included in the series. Special attention was paid in order to exclude patients with primary cutaneous ALCL. Diagnostic histological slides were reviewed by at least two expert pathologists and clinical data were collected (details are provided in the *Online Supplementary Appendix*). The study was approved by the ethics committee of the TENOMIC program (Comité de Protection des Personnes Ile-de-France IX 08-009).

Fluorescence *in situ* hybridization

Break-apart FISH assays to explore rearrangements of *DUSP22*/*IRF4* and *TP63* were performed on formalin-fixed paraffin-embedded tissue sections, using laboratory-developed probes,[25] or commercial probes (Zyto*Light* SPEC *IRF4*, *DUSP22* Dual Color Break Apart Probe [ZytoVision GmbH, Bremerharven, Germany]; and *TP63* Split FISH Probe [Abnova, Taipei, Taiwan]), as previously described.[26] At least 50 tumor nuclei were evaluated. The cutoff to consider a rearrangement was ≥10% of rearranged nuclei. Copy gains or losses of the explored loci were recorded qualitatively for rearranged and non-rearranged alleles.

Statistical analyses

The statistical analyses are described in the *Online Supplementary Appendix*.

Results

Patients' and disease characteristics

In total, 104 ALK-negative ALCL patients newly diagnosed

between January 2001 and January 2020 were analyzed, including 37 patients from first-line clinical trials and 67 patients treated in routine care. Baseline patients' and disease characteristics did not differ significantly between patients included in first-line clinical trials and the others (*Online Supplementary Table S1*). At diagnosis, the median age of the 104 patients was 60 years (range, 39-86), 74% were male, 36% had a performance status (PS) ≥2, 72% had stage 3-4 disease, bone was the most frequently involved extranodal site, and the International Prognostic Index (IPI) score was equally distributed across the four risk groups (Table 1). Ten patients who had skin involvement had advanced stage disease and not just involvement of a draining lymph node. Most patients (97/104, 93%) were treated frontline with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP)/CHOP-like regimens, and seven patients received non-curative intent care.

The diagnostic samples were mostly lymph nodes (91/104 cases, 88%), and the majority were surgical biopsies. The other tissues examined were from the nasopharynx and tonsil (3/104), liver (3/104), mediastinum (1/104), and other extranodal organs (parotid, lung, intestine, maxillary sinus) (6/104). In all cases the tumor consisted of large cells strongly positive for CD30 and negative for ALK protein expression. Other immunophenotypic features are summarized in Table 2. Expression of pan-T-cell antigens was variably detected; the most commonly expressed was CD2 (66/87, 76%) followed by CD3 (49/104, 47%), CD5 (36/97, 37%) and CD7 (11/75, 15%). Expression of at least one cytotoxic molecule was demonstrated in 45/101 (45%) cases. Co-expression of EMA was common (41/87 cases, 47%). CD4 and CD8 were expressed in 72/97 (74%) and 11/89 (12%) cases, respectively. Phospho-STAT3 (pSTAT3) was positive in 21/44 (48%) samples.

Fluorescence *in situ* hybridization results

The *DUSP22* locus was rearranged in 47/104 cases (45%), with several distinct hybridization patterns observed (Figure 1). Among *DUSP22*-R cases, 38/47 (81%) showed a classical break-apart pattern, i.e. one normal fusion signal and one red and one green separated (split) signals representing the rearranged allele (Figure 1C); or variant classical patterns, comprising several pairs of separated red and green signals. This group included three cases in which two rearranged alleles were present in the absence of any non-rearranged allele, reflecting biallelic rearrangements (Figure 1D). The remaining 9/47 (19%) *DUSP22*-R cases featured "atypical" hybridization patterns, consisting of at least one isolated green (3') signal, in the absence of isolated red (5') signals (Figure 1E); in one of these cases, tight clusters of more than ten green signals were detected, in addition to fusion signals (Figure 1F); in another case, only one or two isolated green signals could be seen, without any detectable fusion signal.

FISH assay for *TP63* was contributive in 93/99 cases, indicating a failure rate of 6%, and could not be performed in five cases (no material available). The *TP63* locus was rearranged in 2/93 cases (2%), including one case with dual *DUSP22*-R and *TP63*-R. Both *TP63*-R cases showed a "classical" break-apart pattern, with a relatively small distance between the separated red and green signals of the rearranged allele (Figure 2), consistent with an inv(3)(q26q28) resulting in the *TBL1XR1::TP63* fusion, although dual fusion FISH probes were not tested to prove this. Among the samples lacking structural alterations of the explored loci, low-level (3 to 4) (Figure 1A) or high-level (≥5) copy gains of *DUSP22* were observed in the majority of cases (23/57 [40%] and 15/57 [26%], respectively), including three samples with tight clusters of up to 20 fusion signals, consistent with *DUSP22* locus amplification (Figure 1B). Copy gains of *TP63* were mostly of low level (47/91, 52%), with 4/91 samples (4%) showing up to five copies per nucleus.

Distinctive pathological and clinical features according to *DUSP22* status

A morphological spectrum was observed irrespective of *DUSP22* rearrangement, with marked overlap between the two genomic groups (*Online Supplementary Figure S1*). Although doughnut-type cells were essentially seen in the *DUSP22*-R subgroup, hallmark-type cells were otherwise seen as a prominent or more discrete component of the tumor cell population irrespective of the genomic status in most cases. Marked pleomorphism was seen in some cases of both *DUSP22*-R and *DUSP22*-NR.

Considering the immunophenotype of the neoplastic cells (Table 2), CD3 and CD2 were more often positive among *DUSP22*-R cases than in *DUSP22*-NR tumors (62% *vs*. 35%, P=0.01; and 87% *vs*. 67%, P=0.044 of the cases, respectively). The expression of other T-cell markers (CD4, CD5, CD7, CD8) was otherwise not significantly different between the two groups. Remarkably, the distribution of the tumors according to CD4 and CD8 expression was almost identical in the two subgroups, the usual profile being $CD4^+$ $CD8^-$ (71% and 67% of the cases in *DUSP22*-R and *DUSP22*-NR cases, respectively), followed by $CD4^-$ $CD8^-$ (19% of the cases in both subgroups) and $CD4^-$ $CD8^+$ (9% and 10% of the *DUSP22*-R and *DUSP22*-NR cases, respectively). Overall, there were only three $CD4^+$ $CD8^+$ cases. Conversely, the two genetic subgroups differed markedly in the frequency of expression of cytotoxic proteins, EMA and pSTAT3. Expression of TIA1, granzyme B or perforin was seen in 11-13% of the *DUSP22*-R group *versus* 40-63% of *DUSP22*-NR cases. Overall, considering the cases tested for all three cytotoxic markers, 8/30 (27%) of *DUSP22*-R cases *versus* 37/45 (82%) of *DUSP22*-NR cases (P<0.001) exhibited a cytotoxic profile, i.e. expressed at least one cytotoxic marker. Similarly, EMA was significantly less ex-

Table 1. Patients' and disease characteristics.

Clinical features at diagnosis	All patients	*DUSP22*-non rearranged ALK-negative ALCL	*DUSP22*-rearranged ALK-negative ALCL	*P*
Number	104	57	47	
Period of diagnosis	2001-2020	2001-2020	2004-2019	
Age, years				
Median (range)	60 (39-86)	61 (39-85)	60 (40-86)	
>60, N (%)	53/104 (51)	29/57 (51)	24/47 (51)	1
Male, N (%)	77/104 (74)	39/57 (68)	38/47 (81)	0.225
Performance status ≥2, N (%)	37/103 (36)	23/57 (40)	14/46 (30)	0.403
Staging at diagnosis, N (%)				0.701
PET	84/100 (84)	45/55 (82)	39/45 (87)	
CT	16/100 (16)	10/55 (18)	6/45 (13)	
Ann Arbor stage, N (%)				0.862 (for 1-2
1	8/104 (8)	3/57 (5)	5/47 (11)	*vs.* 3-4)
2	21/104 (20)	12/57 (21)	9/47 (19)	
3	20/104 (19)	16/57 (28)	4/47 (8)	
4	55/104 (53)	26/57 (46)	29/47 (62)	
Involved site (any), N (%)				
Bone	22/103 (21)	7/56 (13)	15/47 (32)	**0.031**
Liver	17/103 (17)	8/56 (14)	9/47 (19)	0.692
Bone marrow	13/103 (13)	7/56 (13)	6/47 (13)	1
Lung	13/103 (13)	5/56 (9)	8/47 (17)	0.350
Spleen	12/103 (12)	5/56 (9)	7/47 (15)	0.528
Soft tissue	12/103 (12)	10/56 (18)	2/47 (4)	0.067
Skin	10/103 (10)	3/56 (5)	7/47 (15)	0.196
Gastrointestinal tract	7/103 (7)	4/56 (7)	3/47 (6)	1
Parotid	4/103 (4)	1/56 (2)	3/47 (6)	0.490
Nasopharynx	3/103 (3)	1/56 (2)	2/47 (4)	0.877
Tonsil	2/103 (2)	1/56 (2)	1/47 (2)	1
Sinus	2/103 (2)	1/56 (2)	1/47 (2)	1
Thyroid	1/103 (1)	0/56 (0)	1/47 (2)	0.930
Adrenal	1/103 (1)	0/56 (0)	1/47 (2)	0.930
Blood	1/103 (1)	1/56 (2)	0/47 (0)	1
Ascites	1/103 (1)	0/56 (0)	1/47 (2)	0.930
Pleura	0/103 (0)	0/56 (0)	0/47 (0)	---
Extranodal site >1, N (%)	29/104 (28)	15/57 (26)	14/46 (30)	0.862
Elevated lactate dehydrogenase, N (%)	58/103 (56)	30/57 (53)	28/46 (61)	0.523
β2-microglobulin ≥3 mg/L, N (%)	24/55 (44)	17/34 (50)	7/21 (33)	0.352
IPI score, N (%)				0.358
0-1	29/103 (28)	13/57 (23)	16/46 (35)	
2	24/103 (23)	16/57 (28)	8/46 (17)	
3	26/103 (25)	16/57 (28)	10/46 (22)	
4-5	24/103 (23)	12/57 (21)	12/46 (26)	
Patients in first-line clinical trials, N (%)	37/104 (36)	24/57 (42)	13/47 (28)	0.185
Primary therapy, N (%)				0.292
CHOP	45/104 (43)	23/57 (40)	22/47 (47)	
CHOEP	24/104 (23)	13/57 (23)	11/47 (23)	
Romidepsin-CHOP	10/104 (10)	9/57 (16)	1/47 (2)	
BV-CH(E)P	6/104 (6)	3/57 (5)	3/47 (6)	
Mini-CHOP	7/104 (7)	2/57 (4)	5/47 (11)	
ACVBP	5/104 (5)	3/57 (5)	2/47 (4)	
Non-curative care	7/104 (7)	4/57 (7)	3/47 (6)	
Consolidative transplantation				0.218
AutoSCT	14/104 (13)	5/57 (9)	9/47 (19)	
AlloSCT	5/104 (5)	2/57 (4)	3/47 (6)	
Auto-mini-alloSCT tandem	1/104 (1)	1/57 (2)	0/47 (0)	

ALK: anaplastic lymphoma kinase; ALCL: anaplastic large cell lymphoma; PET: positron emission tomography; CT: computed tomography; IPI: International Prognostic Index; CHOP: cyclophosphamide, doxorubicin, vincristine, and prednisone; CHOEP: CHOP + etoposide; BV: brentuximab vedotin; CH(E)P: cyclophosphamide, doxorubicin, (etoposide), prednisone; ACVBP: doxorubicin, cyclophosphamide, vindesine, bleomycin, prednisone; autoSCT: autologous stem-cell transplantation; alloSCT: allogeneic stem-cell transplantation. Statistically significant value shown in bold.

Table 2. Immunophenotypic characteristics of the 104 tumors.

	All patients (N=104)	*DUSP22*-NR ALK-negative ALCL (N=57)	*DUSP22*-R ALK-negative ALCL (N=47)	*P*
CD30, N^+/N	104/104	57/57	47/47	1
ALK, N^+/N	0/104	0/57	0/47	1
T-cell antigens, N^+/N (%)				
CD3	49/104 (47)	20/57 (35)	29/47 (62)	**0.01**
CD5	35/97 (36)	17/53 (32)	19/44 (43)	0.296
CD2	66/87 (76)	33/49 (67)	33/38 (87)	**0.044**
CD7	11/75 (15)	7/40 (18)	4/35 (11)	0.528
CD4	72/97 (72)	38/50 (76)	34/47 (72)	0.817
CD8	11/89 (12)	5/45 (11)	6/44 (11)	0.758
CD4+ CD8-	60/87 (69)	28/42 (64)	32/45 (69)	0.817
CD4- CD8-	16/87 (18)	8/42 (19)	8/45 (18)	1
CD4- CD8+	8/87 (9)	4/42 (10)	4/45 (9)	1
CD4+ CD8+	3/87 (3)	2/42 (5)	1/45 (2)	0.608
EMA, N^+/N (%)	41/87 (47)	36/49 (73)	5/38 (13)	**<0.0001**
Cytotoxic markers, N^+/N (%)				
TIA1	21/78 (27)	16/40 (40)	5/38 (13)	**0.01**
Granzyme B	26/92 (28)	21/48 (44)	5/44 (11)	**0.001**
Perforin	31/76 (41)	27/43 (63)	4/33 (12)	**<0.0001**
Cytotoxic profile*	45/75 (60)	37/45 (82)	8/30 (27)	**<0.0001**
pSTAT3, N^+/N (%)	21/44 (48)	19/24 (79)	2/20 (10)	**<0.001**

*Taking into consideration only fully conclusive cases, either negative for the three cytotoxic molecules analyzed, or positive for at least one of them. NR: not rearranged; R: rearranged; ALK: anaplastic lymphoma kinase; ALCL: anaplastic large cell lymphoma. Statistically significant values shown in bold. N^+/N: number positive/number tested.

pressed in *DUSP22*-R cases, being positive in 13% *versus* 73% of *DUSP22*-NR cases ($P<0.001$). Phospho-STAT3 was positive in only 2/20 (10%) *DUSP22*-R samples *versus* 19/24 (79%) of *DUSP22*-NR cases ($P<0.001$).

Comparing the characteristics of *DUSP22*-R and *DUSP22*-NR patients (Table 1), there was no significant difference in median age or sex, and IPI score was equally distributed. The only statistically significant difference was bone involvement, which was more frequent in *DUSP22*-R cases (32% *vs*. 13%, $P=0.031$). The two groups of patients did not differ regarding involvement of other extranodal sites. Of note, the frequency of *DUSP22*-R was 35% (13/37) for patients included in clinical trials and 51% (34/67) for patients treated routinely ($P=0.185$) (*Online Supplementary Table S1*).

After a median follow-up of 5 years, the 5-year PFS and OS of the 104 patients were 36% and 50%, respectively (Figure 3A, B). According to *DUSP22* status, 5-year PFS was 48% *versus* 25% for 47 *DUSP22*-R and 57 *DUSP22*-NR patients, respectively ($P=0.025$) (Figure 3C), and 5-year OS was 58% *versus* 44% for *DUSP22*-R and *DUSP22*-NR patients, respectively ($P=0.2$) (Figure 3D).

Treatment response, survival, and prognostic factors

Analyses of treatment response, survival, and prognostic factors were restricted to patients for whom FISH information was complete, who had a confirmed *TP63*-NR status, and who were treated with curative intent with front-line anthracycline-based chemotherapy. This set consisted of 84 patients (39 *DUSP22*-R/*TP63*-NR and 45 triple-negative ALCL). The patients' and disease characteristics are shown in *Online Supplementary Table S2*, and their immunophenotypic characteristics are presented in *Online Supplementary Table S3*.

Four patients (1 *DUSP22*-R and 3 *DUSP22*-NR) were not evaluable for response because of early death (mainly due to infections). The overall response rate and the complete response rate were 75% and 67%, respectively, without significant difference between triple-negative and *DUSP22*-R/*TP63*-NR patients (*Online Supplementary Table S4*).

The median follow-up of the 84 patients was 4.9 years (range, 0.9 to 10 years). Their 2- and 5-year PFS rates were 45% (95% CI: 36%-57%) and 41% (95% CI: 31%-53%), respectively, and the 2- and 5-year OS rates were 67% (95% CI: 57%-78%) and 53% (95% CI: 42%-66%), respectively. PFS rates were significantly higher in *DUSP22*-R/*TP63*-NR patients than in triple-negative patients (2-year PFS, 67% *vs*. 26%; 5-year PFS, 57% *vs*. 26%, $P=0.001$) (Figure 4A). However, the OS rates were not significantly different between *DUSP22*-R/*TP63*-NR and triple-negative patients (2-year OS, 74% *vs*. 60%; 5-year OS, 65% *vs*. 41%, $P=0.07$)

(Figure 4B). Importantly, PFS and OS were similar for patients included or not in first-line clinical trials (*Online Supplementary Figure S2*).

Clinical and laboratory features were subjected to univariate analyses to evaluate their impact on PFS and OS (*Online Supplementary Table S5*). PS (Figure 4C, D), β2-microglobulin level, granzyme B and perforin expression significantly influenced PFS and OS, whereas *DUSP22* status and cytotoxic profile affected only PFS. Only PS (0-1 *vs.* ≥ 2) and *DUSP22*-R/*DUSP22*-NR status were retained for multivariate analysis because of missing data for the other factors. Both PS and *DUSP22* status significantly affected PFS, but only PS remained significant for OS (Table 3). These two variables delineated four risk groups (Figure 4E, F): *DUSP22*-R/*TP63*-NR and PS 0-1, with 4-year PFS and OS rates of 73% and 77%, respectively; *DUSP22*-R/*TP63*-NR and PS ≥2, with 4-year PFS and OS rates of 27% and 29%, respectively; triple-negative and PS 0-1, with 4-year PFS and OS rates of 33% and 62%, respectively; and triple-negative and PS ≥2, with 4-year PFS and OS rates of 17% and 21%, respectively (P<0.001 for PFS and P=0.001 for OS).

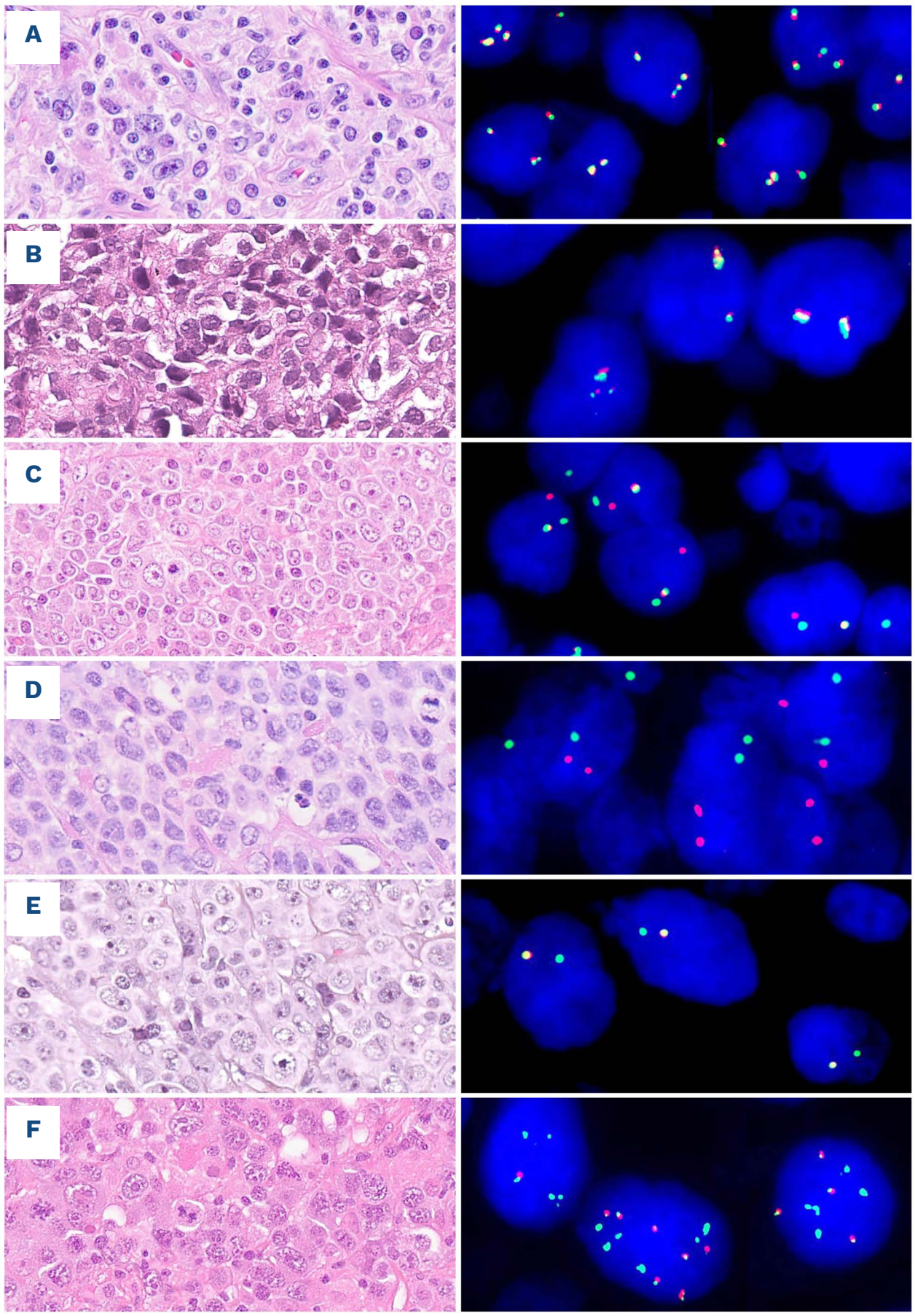

Figure 1. *DUSP22* fluorescence *in situ* hybridization patterns. The range of fluorescence *in situ* hybridization (FISH) patterns observed for the *DUSP22* locus (right column: Zyto*Light* SPEC *IRF4*, *DUSP22* Dual Color Break Apart Probe, ZytoVision) is illustrated, with the corresponding hematoxylin & eosin (H&E) images (left column). *DUSP22* non-rearranged cases (A, B) included a majority of samples showing copy gains (A: 3 to 4 fusion signals per nucleus), and a few characterized by an amplification of the *DUSP22* locus (B: tight clusters of fusion signals). Among *DUSP22*-rearranged cases (C-F), approximately 80% showed a classical break-apart pattern of the *DUSP22* locus or variants thereof (C: separated red and green signals for the rearranged allele, with an additional fusion signal representing the non-rearranged allele; D: biallelic rearrangements), while 20% featured various atypical break-apart patterns (E: rearrangement with deletion of the red 5' portion of the probe, resulting in an isolated green 3' signal, in addition to the non-rearranged allele; F: variant of the pattern shown in E, presenting tight clusters of green 3' signals, in addition to fusion signals representing the non-rearranged allele). All H&E images were taken at an original x400 magnification and the FISH images at x630.

Post-progression survival

Of the 84 patients, 43 (14 *DUSP22*-R and 29 triple-negative) progressed or relapsed after frontline treatment. From this event, the 4-year OS (OS2) was 29% (21% in *DUSP22*-R/*TP63*-NR *vs*. 34% in triple-negative patients, *P*=0.62) (Figure 5A). Information on salvage treatment was retrieved for 40/43 patients. The 4-year OS2 was 44% for the 27 patients who received brentuximab vedotin (BV) at relapse (only one patient had previously received frontline BV) *versus* 0% for the 13 patients who received standard treatment, mainly cytarabine-based regimens or bendamustine (*P*<0.001) (Figure 5B). Figure 5C illustrates OS2 according to *DUSP22* status and BV as salvage treatment. In multivariate analysis of these two parameters, only BV affected OS2 (*P*<0.001; HR=0.119, 95% CI: 0.041-0.343). Indeed, when restricting the OS2 analysis to the patients who received BV as salvage treatment, there was no significant difference according to *DUSP22* status (Figure 5D).

Characteristics of the two patients with *TP63*-rearranged ALK-negative anaplastic large cell lymphoma

The patient with the dual *TP63* and *DUSP22* rearrangement

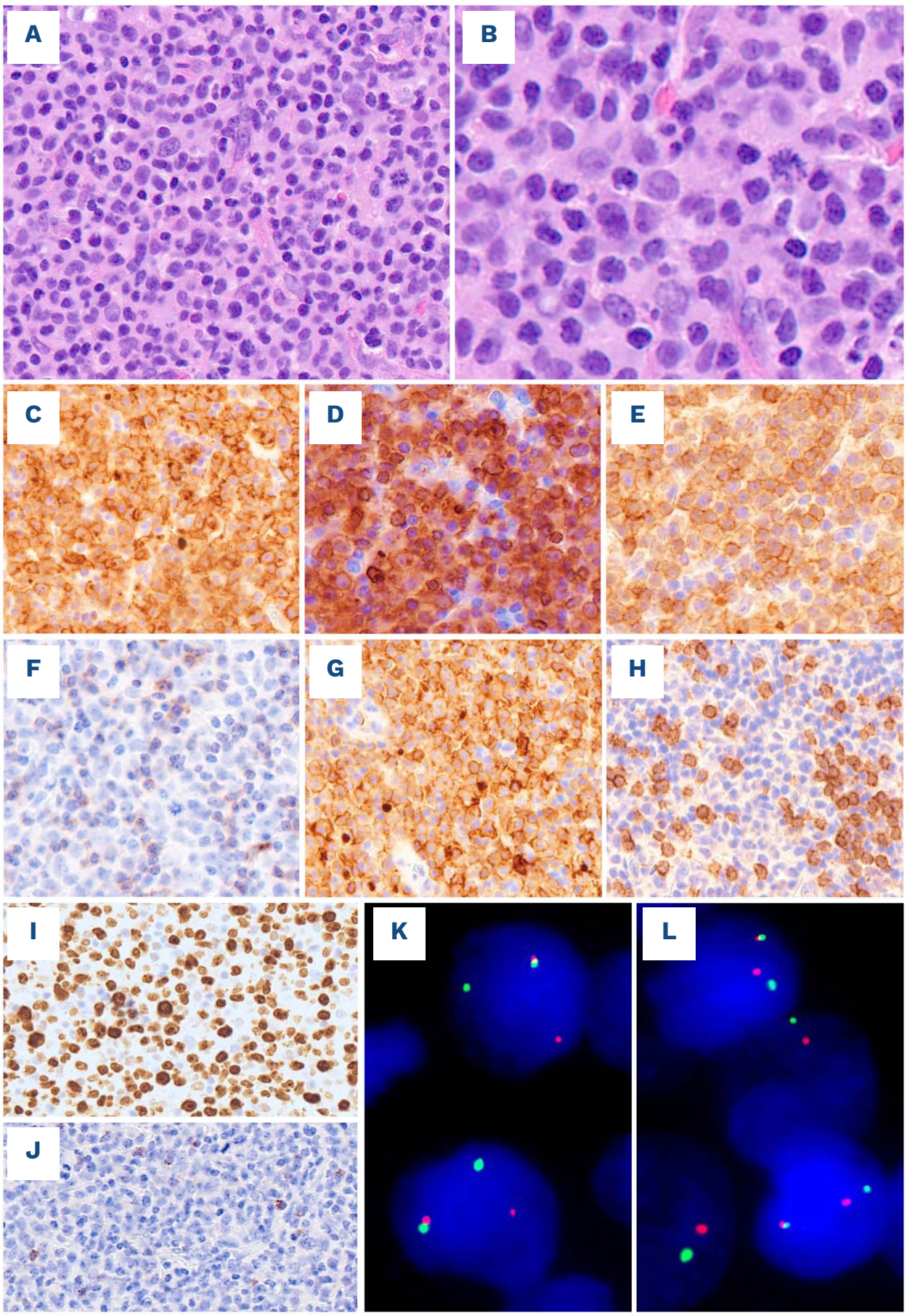

Figure 2. ALK-negative anaplastic large cell lymphoma with dual *TP63* and *DUSP22* rearrangement. (A, B) The tumor comprises cohesive sheets of atypical lymphoid cells including anaplastic-type “hallmark” cells (hematoxylin & eosin, original magnifications x400 and x800); (C-J) on immunohistochemical stains the neoplastic cells are strongly $CD30^{+}$ (C), $CD3^{+}$ (D), $CD5^{+}$ (E), $CD7^{-}$ (F), $CD4^{+}$ (G), $CD8^{-}$ (H), with a high Ki67 proliferation index (I) and negative for TIA-1 (J) (all immunoperoxidase; original magnification x400); (K-L) representative nuclei from the fluorescence *in situ* hybridization assays for *DUSP22* (K) and *TP63* rearrangement (L) showing a pattern indicative of a break for the two tested loci (original magnification x630).

was a 43-year-old man presenting with cervical lymphadenopathy and an IPI score of 0. The tumor consisted of diffuse sheets of medium-sized to large atypical lymphoid cells with frequently reniform or horseshoe-shaped nuclei (Figure 2). In addition to being positive for CD30, the tumor cells were CD3$^+$, CD4$^+$, CD5$^+$, CD7$^-$, CD8$^-$, EMA$^-$, TIA-1$^-$, granzyme B$^-$, perforin$^-$, pSTAT3$^-$ and p63$^+$. Re-biopsy at relapse 1 year later showed identical features.

The patient with an isolated *TP63* gene rearrangement was a 52-year-old woman with an IPI score of 2 (Ann Arbor stage 3 and elevated lactate dehydrogenase). A lymph node biopsy showed cohesive sheets of large cells with oval nuclei and prominent nucleoli, associated with diffuse interstitial fibrosis (*Online Supplementary Figure S3*). The neoplastic cells were strongly positive for CD30, CD2$^+$, CD3$^-$, CD4$^+$, CD5$^-$, CD8$^-$, TIA1$^+$, granzyme B$^+$, perforin$^+$ with nuclear p63 protein expression.

Both patients reached CR after CHOP (the *DUSP22*-R/*TP63*-R case) or CHOEP (CHOP with etoposide) (the *TP63*-R case) regimens and underwent consolidative autologous stem-cell transplantation. They both relapsed after transplantation: the patient with a dual rearrangement died from lymphoma 5 months after relapse, and the other remains in CR more than 2 years after salvage treat-

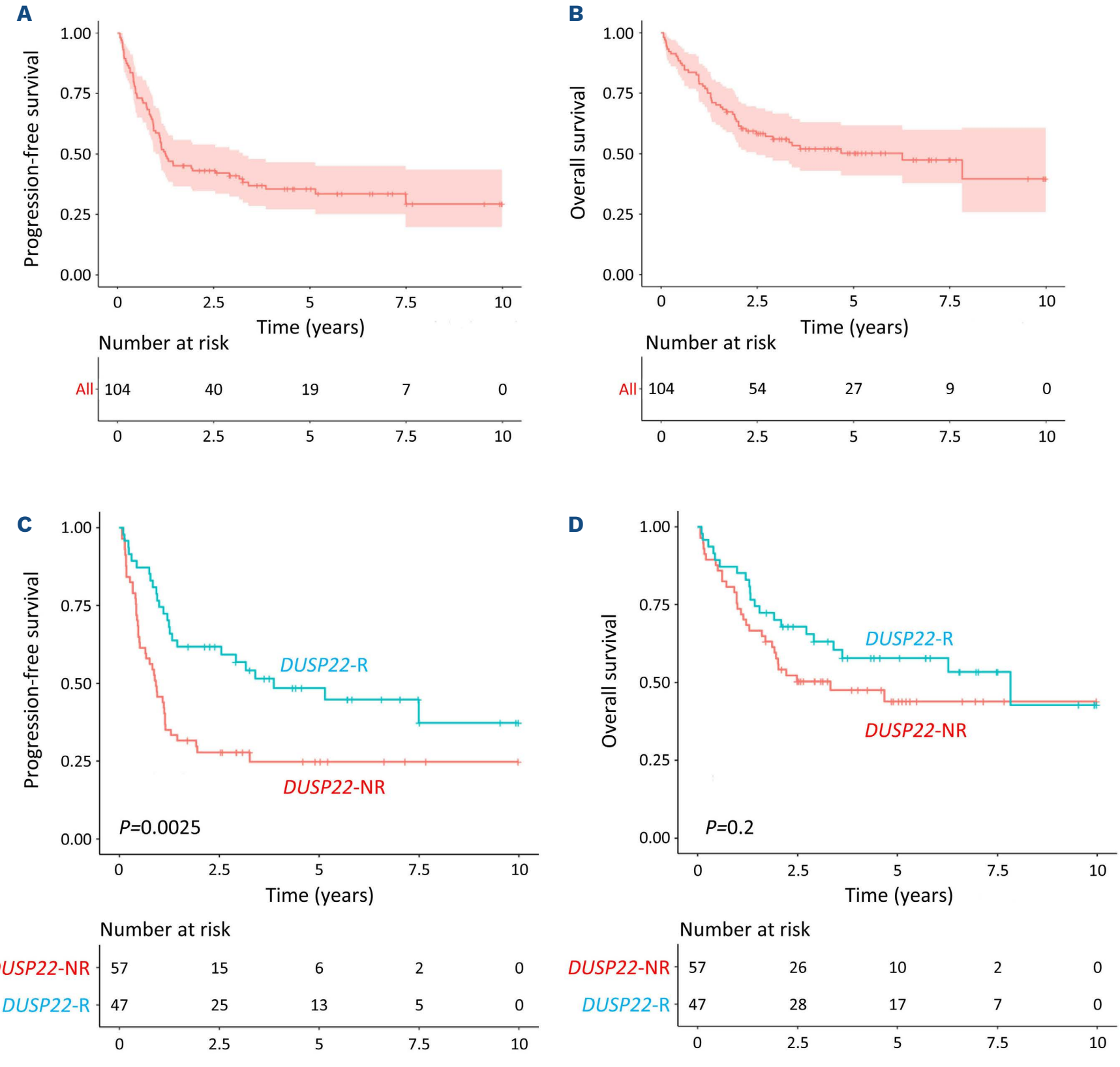

Figure 3. Survival of the 104 patients with ALK-negative anaplastic large cell lymphoma. (A) Progression-free survival and (B) overall survival of the whole cohort. (C) Progression-free survival and (D) overall survival according to *DUSP22* status. R: rearranged; NR: not rearranged.

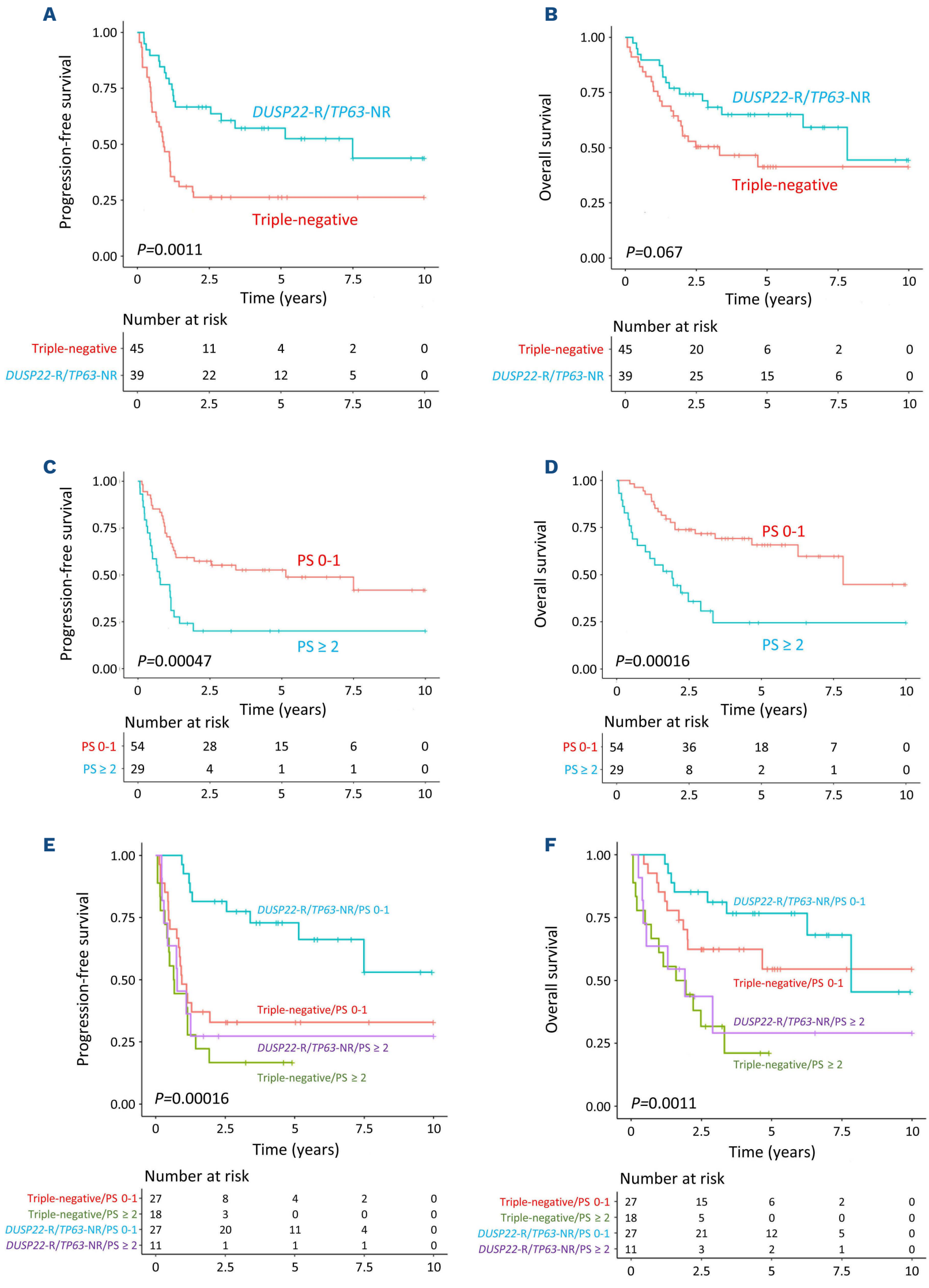

Figure 4. Survival of the 84 *TP63* -non-rearranged patients treated with anthracycline-based chemotherapy with curative intent. (A) Progression-free survival (PFS) and (B) overall survival (OS) according to *DUSP22* status. (C) PFS and (D) OS according to performance status. (E) PFS and (F) OS according to both factors. R: rearranged; NR: not rearranged; PS: performance status.

Table 3. Parameters influencing progression-free survival and overall survival in multivariate analyses in 83 patients.

Parameter	PFS			OS		
	P	HR	95% CI	*P*	HR	95% CI
PS ≥2	**0.005**	2.259	1.271-4.013	**<0.001**	3.024	1.593-5.741
DUSP22-NR	**0.008**	2.256	1.233-4.127	0.194	1.556	0.799-3.031

PFS: progression-free survival; OS: overall survival; HR: hazard ratio; 95% CI: 95% confidence interval; PS: performance status; NR: not rearranged.

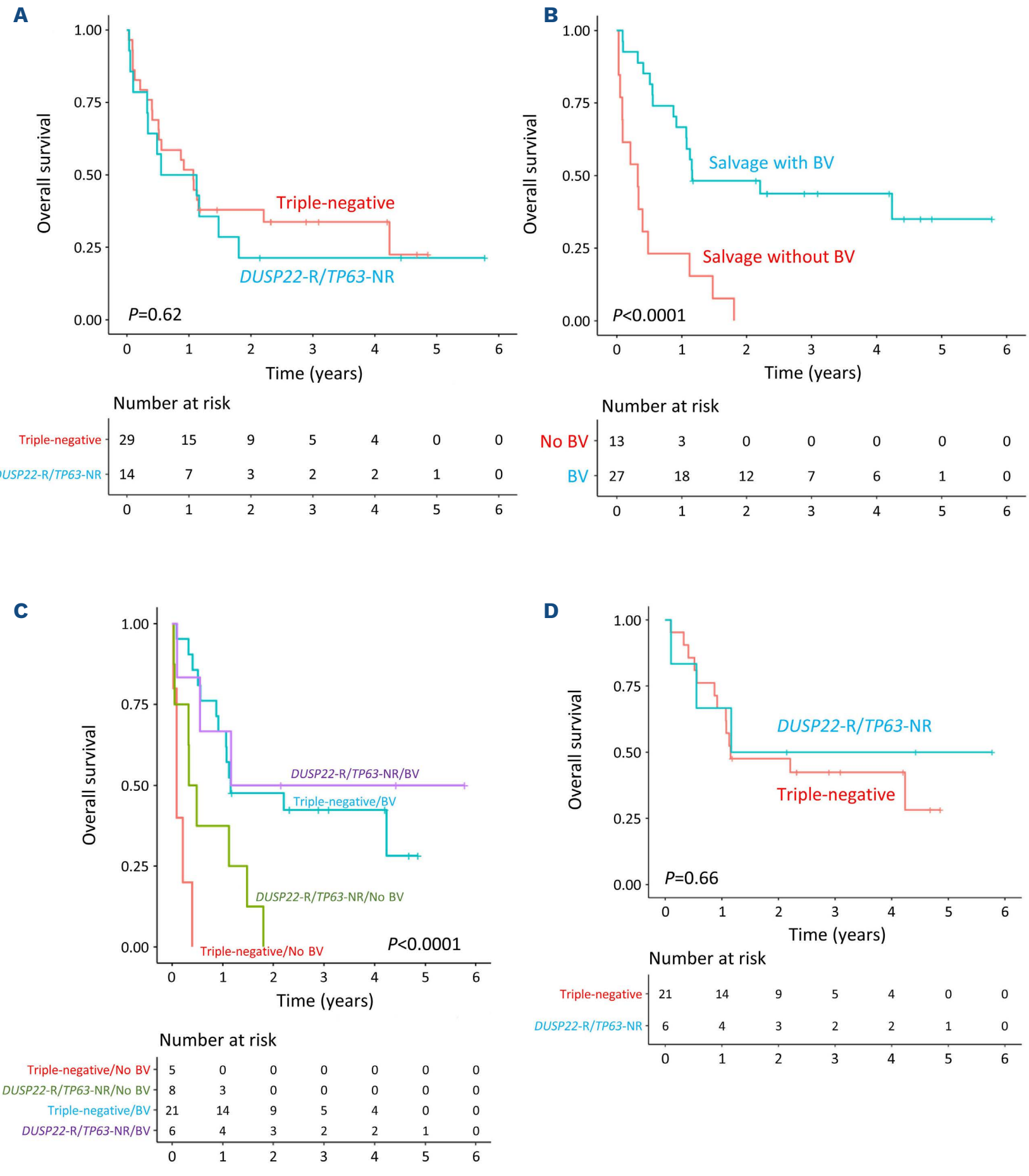

Figure 5. Post-progression overall survival (OS2). Overall survival following relapse/progression (A) according to *DUSP22* status, (B) according to brentuximab vedotin (BV) use at relapse/progression, (C) according to both parameters, and (D) when restricting the analysis to the patients who received BV as salvage treatment. R: rearranged; NR: not rearranged.

ment with BV + gemcitabine and allogeneic stem-cell transplantation.

Discussion

We report here the clinical and pathological findings of 104 patients with ALK-negative ALCL according to *DUSP22* status (47 *DUSP22*-R and 57 *DUSP22*-NR) and *TP63* status (2 *TP63*-R and 91 *TP63*-NR), including 39 *DUSP22*-R/*TP63*-NR and 45 triple-negative cases. This represents the largest such series published so far. The main conclusions of our study are: (i) *DUSP22*-R ALCL encompasses a spectrum of FISH patterns, has distinctive immunophenotypic features and more frequently involves bone; (ii) the 65% 5-year OS of *DUSP22*-R patients is intermediate between those previously documented in an US study (90%) and by the BCCA investigators (40%); (iii) both *DUSP22* status and PS have independent impacts on PFS; (iv) OS was mainly affected by PS; and (v) OS2 was markedly improved by the use of BV as salvage treatment, without *DUSP22* status having a significant influence on this post-progression survival.

With the comparison group (*DUSP22*-NR ALK-negative ALCL) consisting of 57 individuals, the *DUSP22*-R cases constituted 45% of our study population. Strikingly, this proportion is higher than in other studies from North America and Europe, in which the frequency of *DUSP22*-R has been reported to be between 18% and 30%.[3,16-18] However, the mode of recruitment of samples and patients precludes conclusions being drawn regarding the relative prevalence of ALK-negative ALCL genomic subgroups. Of note, the distribution of *DUSP22*-R/*DUSP22*-NR cases was different among the 37 patients enrolled in first-line clinical trials (13/37 [35%] *DUSP22*-R, including 6/26 [23%] in the Ro-CHOP study) *versus* the others collected through the TENOMIC network (34/67 [51%]). Since all cases of ALK-negative ALCL patients from the clinical trials were included in this study when possible, they represent an "unbiased" group of cases and their characteristics in terms of *DUSP22* status are much consistent with the existing literature, confirming the 30% prevalence of *DUSP22*-R in the multi-institution US study.[3]

There are several explanations for the relatively numerous *DUSP22*-R cases among the non-clinical trial patients in our study. The collection of patients' data and samples through TENOMIC primarily aims at collecting high-quality data and cases of medical and scientific interest, which may be influenced by specific topics of interest such as the current project on ALCL with *DUSP22*-R.[27] Moreover, the most active participants are referral centers with expert pathologists being consulted for unusual or difficult cases, or for ancillary techniques such as FISH. In addition, it is worth mentioning the use of cases from a former publication, among which a majority (7/9) harbored a *DUSP22*-R.[24] In fact, five of these cases, all *DUSP22*-R that had been coded as CD30-positive PTCL-NOS in that study because they did not fulfill the stringent immunophenotypic criteria originally used for the diagnosis of ALK-negative ALCL (i.e., requiring the expression of at least one cytotoxic molecule or EMA), became consistent with ALK-negative ALCL in the light of updated criteria developed later.

We found only 2/93 (2%) *TP63*-R cases in our series, which is at the lower end of previously reported frequencies (2-8%) in ALK-negative ALCL.[3,16,18] It might be argued that the exclusive use of a break-apart FISH probe to explore the *TP63* locus may have missed cases harboring a *TBL1XR1::TP63* intrachromosomal inversion, due to the small distance between the split signals in this context. Nonetheless, being aware of the risk of false negative results, the slides were examined very carefully, and we believe that the low prevalence of *TP63*-R truly reflects the biology of our cohort. On the other hand, cryptic *TP63* rearrangements cannot formally be excluded, as recently described.[28] These latter would however not have been detected in previously published series based on FISH assays.

A spectrum of *DUSP22* FISH patterns was observed (Figure 1). In addition to extra copies of the intact (non-rearranged) *DUSP22* locus, which could represent either specific gains or polysomy of chromosome 6, three *DUSP22*-NR cases featured a FISH pattern consistent with *DUSP22* locus amplification. This observation has not previously been reported, and its biological consequence is unclear. The *DUSP22* gene encodes a dual specificity phosphatase that functions as a tumor-suppressor gene by exerting an inhibitory effect on various signaling pathways.[29,30] While it has been shown that *DUSP22* gene rearrangements lead to the downregulation of the enzyme, it is questionable how an amplification could result in its silencing, unless the amplified allele encodes an altered, non-functional isoform. Alternatively, the pathogenic effect in such cases could be mediated by the amplification of another neighboring gene with an oncogenic function (e.g., *IRF4*).

Among *DUSP22*-R cases, we observed both the most classical break-apart FISH pattern and variants of it, including cases with biallelic rearrangements or extra copies of both the rearranged and non-rearranged alleles. Although details regarding the FISH patterns encountered are frequently missing in the literature (the result being commonly limited to binary information: rearranged or not), the classical break-apart pattern is the most frequently described one in the series and case reports published so far on *DUSP22*. In our cohort, however, approximately 20% of *DUSP22*-R cases were characterized by atypical hybridization patterns, featuring one or several extra copies of isolated green signals, suggesting a re-

arrangement with subsequent deletion of the 5' side of the locus (telomeric red probe) and preservation of its 3' side (centromeric green probe). This configuration, which reflects an unbalanced translocation, has been recurrently described in earlier series of cutaneous CD30$^+$ T-cell lymphoproliferations, when the gene believed to be involved in 6p25.3 locus rearrangements was *IRF4*, but it has been reported once in systemic ALK-negative ALCL.[31,32] Nonetheless, in a case of lymphomatoid papulosis characterized by a similar atypical *DUSP22* FISH pattern, Karai and colleagues could demonstrate by FISH that the partner locus of the translocation was at 7q32.3, similar to what has been described for the classical break-apart pattern.[29,33]

The immunohistochemistry results on our series are overall consistent with the range described in previous reports.[3,18,34] In addition, we documented CD4 and CD8 expression profiles which were evaluated in the majority of cases (87/104) and were remarkably similar irrespective of *DUSP22* status, being most commonly CD4$^+$ CD8$^-$ (67% of the cases) or CD4$^-$ CD8$^-$ (21% of the cases). In addition, our findings confirm significant differences between *DUSP22*-R and *DUSP22*-NR cases in terms of cytotoxic profile. Of note, while confirming the lack of cytotoxic phenotype as a characteristic feature of *DUSP22*-R cases, we also found that a significant minority of these (8/30, 27%) expressed one or several cytotoxic marker(s), which is a higher proportion than the approximately 10% in previously reported series.[3,18] EMA and pSTAT3 expression were also much less common in *DUSP22*-R cases, and there was less frequent CD3 positivity in *DUSP22*-NR ALCL.[3,8,18] The case with dual *DUSP22* and *TP63* rearrangements (Figure 2) was CD3$^+$ CD4$^+$ CD8$^-$ EMA$^-$ pSTAT3$^-$ and non-cytotoxic. Similar findings have been reported in the other ALK-negative ALCL cases with that rare genomic configuration, suggesting that the immunophenotype is likely driven by the *DUSP22* rearrangement in those tumors.[35,36]

We found that among ALCL patients treated with chemotherapy with curative intent, *DUSP22*-R was a significant determinant of improved PFS in both univariate and multivariate analyses, with 57% 5-year PFS in *DUSP22*-R/*TP63*-NR *versus* 26% in triple-negative patients. In comparison, in the BCCA study, the 5-year PFS of 11 *DUSP22*-R/*TP63*-NR patients treated with curative-intent chemotherapy was 44%.[18] PFS was not reported in the US study.[3] Unlike previous reports, the advantage in OS for our *DUSP22*-R/*TP63*-NR patients compared to triple-negative patients (5-year OS: 65% *vs*. 41%, respectively) did not reach statistical significance. We also found that PS affected PFS and was the prominent factor affecting OS in multivariate analysis in our series. Indeed, we identified a low-risk group characterized by *DUSP22*-R and PS of 0-1, with a 4-year PFS of 73% and 4-year OS of 77%. Conversely, patients with *DUSP22*-R and PS ≥2 had 4-year PFS and OS rates of 27% and 29%, respectively, demonstrating the major impact of PS on outcome. In a recent report from the International T-Cell Project, PS ≥2 was the factor with the strongest impact on PFS and OS in multivariate analysis with hazard ratios of 3.69 and 4.04, respectively, but genomic subtyping of these ALK-negative ALCL was not studied.[15]

BV has previously been shown to improve OS2 after progression/relapse of ALK-negative ALCL patients compared to historical controls.[37,38] Here, we also confirm that OS2 was markedly improved by salvage treatment with BV, which was the main prognostic factor in multivariate analysis. Interestingly, we found no significant difference in OS2 according to *DUSP22* status and an overall similarly good outcome in patients who received BV at relapse/progression in *DUSP22*-R/*TP63*-NR and triple-negative patients, suggesting that response to BV in relapsed/refractory patients is not influenced by *DUSP22* status.

PFS rather than OS may better capture the prognostic impact of *DUSP22*-R since it is not influenced by salvage treatment, while OS analysis is more complex to interpret and should take into account potential differences in salvage treatment. It turned out that, at relapse/progression, 21/26 (81%) triple-negative patients but only 6/14 (43%) *DUSP22*-R patients received BV. Therefore, this imbalance could contribute to the absence of a significant difference in OS between *DUSP22*-R and *DUSP22*-NR patients.

Despite limitations inherent to a retrospective study with unbalanced distribution of *DUSP22*-R/*DUSP22*-NR patients, incomplete *TP63* FISH data, and heterogeneity in first-line treatments, our findings support the biological and clinical distinctiveness of *DUSP22*-R ALK-negative ALCL. Moreover, our results confirm a better PFS of *DUSP22*-R/*TP63*-NR cases compared to triple-negative ALCL, but clearly inferior to that of a historical series of ALK-positive ALCL patients.[39] Of note, with the limitation of low statistical power of small groups, outcome did not differ according to first-line treatment (CHOP, CHOEP or BV-CH(E)P; *data not shown*), but only a small fraction of our patients received frontline BV. Given the benefit of BV-CHP over CHOP in ALK-negative ALCL in the ECHELON-2 trial with an improved 5-year PFS (but not OS), BV-CHP has become the standard of care for first-line treatment of ALK-negative ALCL.[22] However, since genomic subtyping was not reported, its potential impact on the PFS difference observed between the BV-CHP and CHOP arms is unknown. Future studies will be necessary to clarify this point and the impact of *DUSP22* status in newly diagnosed patients with ALK-negative ALCL treated with frontline BV.

Disclosures

No conflicts of interest to disclose.

Contributions

DS collected and reviewed clinical data, analyzed data, designed the research, and wrote the manuscript. BB performed morphological diagnoses and FISH studies, analyzed data and wrote the manuscript; ChrB, EB, DC, FL, KB, NK, GB, AC, GD, and OT reviewed and interpreted clinical data. EP performed morphological diagnoses and FISH analyses. VF supported material and data acquisition and collected data. ChlB and AD performed FISH analyses. FD, JB, CélB, and MP performed morphological diagnoses. JPJ analyzed data and supervised the statistical analyses; PG and LdL performed morphological diagnoses, designed and sustained the research, collected and analyzed data, and wrote the manuscript.

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Data-sharing statement

Anonymized data can be made available on request to the corresponding authors by independent researchers, with a collaborative agreement, through a standard process which includes an internal feasibility assessment and scientific review process by the LYSA.

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