


# Clinical and pathological characteristics of peripheral T-cell lymphomas in a Spanish population: a retrospective study

Socorro Maria Rodriguez-Pinilla,<sup>1</sup>   
 Eva Domingo-Domenech,<sup>2</sup> Finia  
 Climent,<sup>3</sup> Joaquin Sanchez,<sup>4</sup>  
 Carlos Perez Seoane,<sup>4</sup>  
 Javier Lopez Jimenez,<sup>5</sup>  
 Monica Garcia-Cosio,<sup>6</sup>  
 Dolores Caballero,<sup>7</sup>  
 Oscar Javier Blanco Muñoz,<sup>8</sup>  
 Cecilia Carpio,<sup>9</sup> Josep Castellvi,<sup>10</sup>  
 Antonio Martinez Pozo,<sup>11</sup>  
 Blanca Gonzalez Farre,<sup>12</sup>  
 Angeles Bendaña,<sup>13</sup> Carlos Aliste,<sup>13</sup>  
 Ana Julia Gonzalez,<sup>14</sup> Sonia Gonzalez de  
 Villambrosia,<sup>15</sup> Miguel A. Piris,<sup>16</sup>  
 Jose Gomez Codina,<sup>17</sup>  
 Empar Mayordomo-Aranda,<sup>17</sup>  
 Belen Navarro,<sup>18</sup> Carmen Bellas,<sup>19</sup>  
 Guillermo Rodriguez,<sup>20</sup> Juan Jose  
 Borrero,<sup>20</sup> Ana Ruiz-Zorrilla,<sup>21</sup>  
 Marta Grande,<sup>21</sup> Carmen Montoto<sup>21</sup> and  
 Raul Cordoba<sup>22</sup>

<sup>1</sup>Pathology Department, Hospital  
 Universitario Fundación Jiménez Díaz,  
 Madrid, CIBERONC, Madrid, <sup>2</sup>Hematology  
 Department, Institut Català d'Oncologia

L'Hospitalet de Llobregat (Barcelona),

<sup>3</sup>Pathology Department, Hospital  
 Universitari de Bellvitge. IDIBELL,  
 L'Hospitalet de Llobregat (Barcelona),  
 Barcelona, <sup>4</sup>Hematology Department and  
 Pathology Department, Hospital

Universitario Reina Sofía, Cordoba,

<sup>5</sup>Hematology Department, Hospital  
 Universitario Ramón y Cajal, Madrid,

<sup>6</sup>Anatomical Pathology Department,  
 Hospital Universitario Ramón y Cajal,  
 Madrid, CIBERONC, Madrid, <sup>7</sup>Hematology  
 Department, Hospitalario Universitario de  
 Salamanca (HUS/IBSAL) and

CIBERONC, Salamanca, <sup>8</sup>Pathology  
 Department, Complejo Asistencial  
 Universitario de Salamanca-IBSAL,

Salamanca, <sup>9</sup>Hematology Department,  
 Hospital Universitari Vall d'Hebron,

<sup>10</sup>Pathology Department, Hospital

## Abstract

We investigated the clinicopathological features and prognostic factors of patients with peripheral T-cell lymphoma (PTCL) in 13 sites across Spain. Relevant clinical antecedents, CD30 expression and staining pattern, prognostic indices using the International Prognostic Index and the Intergruppo Italiano Linfomi system, treatments, and clinical outcomes were examined. A sizeable proportion of 175 patients had a history of immune-related disorders (autoimmune 16%, viral infections 17%, chemo/radiotherapy-treated carcinomas 19%). The median progression-free survival (PFS) and overall survival (OS) were 7.9 and 15.8 months, respectively. Prognostic indices influenced PFS and OS, with a higher number of adverse factors resulting in shorter survival ( $P < 0.001$ ). Complete response (CR) to treatment was associated with better PFS (62.6 vs. 4 months;  $P < 0.001$ ) and longer OS (67.0 vs. 7.3 months;  $P < 0.001$ ) compared to no CR. CD30 was expressed across all subtypes; >15% of cells were positive in anaplastic lymphoma kinase-positive and -negative anaplastic large-cell lymphoma and extranodal natural killer PTCL groups. We observed PTCL distribution across subtypes based on haematopathological re-evaluation. Poor prognosis, effect of specific prognostic indices, relevance of histopathological subclassification, and response level to first-line treatment on outcomes were confirmed. Immune disorders amongst patients require further examination involving genetic studies and identification of associated immunosuppressive factors.

**Keywords:** peripheral T-cell lymphoma, anaplastic lymphoma kinase, anaplastic large-cell lymphoma, progression-free survival, overall survival, complete response.

Universitari Vall d'Hebron, <sup>11</sup>Pathology Department, Hospital Clínic, Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), CIBERONC, Universitat de Barcelona, <sup>12</sup>Hematopathology Unit, Hospital Clínic, Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), CIBERONC, Universitat de Barcelona, Barcelona, <sup>13</sup>Hematology Department, Complexo Hospitalario Universitario de Santiago de Compostela, La Coruña, <sup>14</sup>Hematology Department, Hospital Universitario Central de Asturias, Oviedo, <sup>15</sup>Hematology Department, Hospital Universitario Marqués de Valdecilla, Santander, <sup>16</sup>Hospital Universitario Fundación Jiménez Díaz, Madrid, CIBERONC, Madrid, <sup>17</sup>Medical Oncology Department, Hospital Universitari i Politècnic La Fe, Valencia, <sup>18</sup>Hematology Department, Hospital Universitario Puerta de Hierro, Madrid, CIBERONC, <sup>19</sup>Pathology Department, Hospital Universitario Puerta de Hierro, Madrid, CIBERONC, Madrid, <sup>20</sup>Anatomical Pathology Department, Hospital Universitario Virgen del Rocío, Instituto de Biomedicina de Sevilla (IBIS)/Universidad de Sevilla, Sevilla, <sup>21</sup>Medical Department, Takeda Farmacéutica España S.A, and <sup>22</sup>Hematology Department, Fundación Jiménez Díaz, Madrid, CIBERONC, Madrid, Spain

Received 19 February 2020; accepted for publication 21 April 2020

Correspondence: Raúl Córdoba, Hematology Department, Hospital Universitario Fundación Jiménez Díaz, Avenida Reyes Católicos 2. 28040, Madrid, Spain.  
E-mail: raul.cordoba@fjd.es

T-cell lymphomas (TCLs) are a heterogeneous group of lymphoid diseases that include nodal entities, extranodal lymphomas and T-cell leukaemia. The differences in cellular origin and the broad phenotypical and morphological spectrum make it difficult to subclassify TCLs. Despite the wide use of reference guidelines, including the World Health Organization (WHO) classification of lymphoid neoplasms,<sup>1,2</sup> accurate diagnosis requires expert haematopathologists and various clinical and molecular tests. Experienced pathologists may need to refer cases for central review to reach a final diagnosis.

Reports related to the International Non-Hodgkin Lymphoma (NHL) Prognostic Factors Project<sup>3</sup> have identified several features of TCLs, including outcome trends,<sup>4</sup> risk groups,<sup>5</sup> and potential therapeutic targets, such as CD30. CD30, originally identified as a Reed-Sternberg and Hodgkin cell-surface maker in classic Hodgkin lymphoma,<sup>6</sup> is expressed in several types of NHLs. CD30 expression also has prognostic value in diffuse large B-cell lymphoma.<sup>7,8</sup>

In Spain, there are insufficient epidemiological data regarding peripheral TCL (PTCL) and several years have passed since the publication of the available reports.<sup>9,10</sup> Our

present multicentre retrospective study aimed to characterise this patient setting in a descriptive manner and to remark on the issue of the potential diagnostic differences associated with a second (central) review of samples, by analysing PTCL cases from several Spanish centres using the 2016 WHO classification criteria. We studied the frequency, clinical and biological behaviours, and prognostic factors (including CD30 expression) of PTCL. Considering the low frequency and wide heterogeneity of PTCL, identifying histological subtypes through local diagnosis and expert central review has been assessed as a prognostic factor.

## Patients and methods

### Data collection

Medical records from 13 Spanish centres were searched to identify PTCL patients diagnosed between 1 January 2008 and 31 December 2013 using the 2008 WHO classification of lymphoid neoplasms.<sup>1</sup> The inclusion criteria included biopsy specimens from the initial diagnosis (node or 16–18 mm core biopsy in paraffin) and histologically confirmed PTCL, involving subtypes including extranodal natural killer (NK) TCL nasal type, enteropathy-associated TCL (EATCL), hepatosplenic TCL, PTCL not-otherwise-specified (PTCL-NOS), angioimmunoblastic TCL (AITL), anaplastic lymphoma kinase (ALK)-positive anaplastic large-cell lymphoma (ALK+ ALCL), or ALK-negative ALCL (ALK– ALCL). Clinical data included sex, age, relevant clinical history, Ann Arbor Stage, Eastern Cooperative Oncology Group Performance Status (ECOG PS), treatments, and outcomes [complete response (CR) or partial response (PR), stable disease or progression of disease (PD)]. In order to calculate progression-free survival (PFS), date of PD or date of death were recorded, and the latter of these was used to calculate overall survival (OS). The International Non-Hodgkin Lymphoma Prognostic Factors Project system<sup>3</sup> and the Intergruppo Italiano Linfomi system<sup>11</sup> were used to calculate the International Prognostic Index (IPI) and the Prognostic Index for TCL (PIT), respectively.

### Central review

Tissue microarrays were constructed using archival formalin-fixed and paraffin-embedded patient samples originating from the local pathology laboratory. Immunohistochemical staining and assessment were performed by an expert central pathology committee. Positive tumour cells were scored in percentage classes including programmed cell death protein 1 (PD1), lymphoid enhancer binding factor-1 (LEF1), Ki67, B-cell lymphoma 6 (BCL6), cluster of differentiation 10 (CD10), and percentage of Epstein–Barr virus (EBV)-encoded small nuclear RNAs (EBERs) cells. CD30 was considered positive with  $\geq 15\%$  tumour cells (no expression, negative  $>0$ –14%), while intensity of staining was estimated visually and scored as no expression (negative), weak, moderate and strong.

Expression of tumour protein p53 (p53) was included during the samples assessment<sup>12,13</sup> and was classified into: negative, positive (1–50%) and very positive ( $>50\%$ ). The expert committee also reviewed and re-classified and/or updated the PTCL specimens into subtypes according to the 2016 WHO criteria<sup>2</sup> and based on their evaluation and the available evidence, diagnoses were categorised into one of the following six subtypes: (i) PTCL-NOS, (ii) AITL plus nodal PTCL with T follicular helper (TFH) phenotype,<sup>14,15</sup> (iii) ALK+ ALCL, (iv) ALK– ALCL, (v) extranodal NK/T (including EBV-associated TCLs)<sup>2</sup> and (vi) intestinal TCL (including patients diagnosed with EATCL and those with monomorphic epitheliotrophic intestinal TCL).

### Statistics

Categorical variables are reported as percentages and analysed using binomial regression. Continuous variables are reported as mean  $\pm$  standard deviation (SD) or median (range). Follow-up was calculated based on overall observation time, on censoring times for surviving patients, and on reserve censoring by Kaplan–Meier curve analysis.<sup>16,17</sup> Time-to-event analyses (OS, PFS, and time-to-PD) were performed using the Kaplan–Meier method and the log-rank test. Estimated mean with 95% confidence interval (95% CI) was used when the median value was not reached. The Cox proportional hazards model allowed the assessment of the potential prognostic covariates for OS and PFS. Univariate and multivariate analyses are reported using hazard ratios (HRs) with 95% CIs. Factors with  $P \leq 0.1$  in univariate analyses were included in the multivariate analyses using two approaches: firstly excluding potential confounding factors that were already included in further variables, i.e. ECOG PS for the IPI score or bone marrow disease for the PIT score and, secondly, by excluding the IPI and PIT scores. Logistic regression models considering CR as ‘the event’ were presented as odds ratio (ORs) with 95% CIs. As previously, only potential confounding factors were taken into account in the multivariate logistic regression analyses. Differences were considered statistically significant at  $P < 0.05$ . All analyses were performed using the Statistical Package for the Social Sciences (SPSS®), version 22.0 (SPSS Inc., IBM Corp., Armonk, NY, USA).

### Ethical approval

All patients provided written informed consent prior to inclusion. The study protocol was approved by the ethics committees at all participating sites.

## RESULTS

### The study population and PTCL clinical features

A total of 198 patients were diagnosed with PTCL, and 175 patients fulfilled the eligibility criteria and were included in

the study Fig 1. PTCL subtypes were mostly found in males (63.4%). The median (range) age at first PTCL diagnosis was 62.8 (18.3–88.7) years Table I; however, the ALK+ ALCL group had the youngest median (range) age, at 31.6 (18.3–81.6) years, amongst all subtypes.

A relevant clinical history including previous neoplasms was reported in 18.9% of the enrolled patients, and most frequently in the extranodal NK/T group (25%). Viral infections were relatively frequent (17.7%), particularly hepatitis C virus (7.4%). Other autoimmune factors, including inflammatory or rheumatological disorders (16%), and immunosuppressive treatments were also reported Table I at PTCL diagnosis (4.6%) and at any other time (7.4%).

At diagnosis, most patients had advanced Ann Arbor Stages (III and IV). Bone marrow infiltration was confirmed in 32 patients (18.3%). Serum lactic acid dehydrogenase (LDH) levels were elevated in 92 (52.6%) patients and B symptoms were present in 95 (54.3%). Other PTCL clinical characteristics are detailed in Table II.

The median (range) follow-up interval was 12.4 (0.1–92.3) months in all patients (observation time), 42.3 (0.5–92.3) months amongst surviving patients (censoring times), and 53.0 (42.4–63.7) months by reverse censoring. Only three patients received palliative treatments, while 158 received curative treatment Fig 1. Cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) or CHOP-like regimens (69.7%) were most commonly used Table S1).

### Central review

The final diagnosis in 67.4% of patients involved no classification change after central review and update according to the 2016 WHO classification (Fig 2 and Table S2) PTCL-NOS diagnosis (30.9%) was less frequent after expert review (12%). The remaining cases included new subtypes of PTCL, such as nodal PTCL with TFH phenotype ( $n = 23$ ),

monomorphic epitheliotropic intestinal TCL ( $n = 5$ ), and others including T-cell prolymphocytic leukaemia ( $n = 1$ ). AITL+ TFH incidence showed a remarkable change after re-evaluation (30.9% vs. 44.6%, respectively), of note, no cases of EBV-associated TCL were centrally reported. The most clinically relevant differences between local and central diagnoses were observed in two cases involving diffuse B-cell NHL (one patient with plasmablastic differentiation), which were previously classified as PTCL-NOS (one) and ALK–ALCL (one), and two other cases where the diagnoses were updated to reactive lymphadenopathies (prior diagnosis was PTCL-NOS and intestinal PTCL, one patient each, samples from these patients were taken from nodes).

### Treatments

The best response ( $n = 125$ ) was observed at a median (range) interval of 4.0 (0–65.2) months after first-line therapy; CR, PR, stable disease, and PD were reported in 34.9% ( $n = 61$ ), 22.9% ( $n = 40$ ), nine, and 41 patients, respectively. The median (range) interval from the start of first-line treatment to relapse or PD was 6.0 (0.2–77.3) months.

In all, 90 patients received salvage therapy due to relapse or no CR; 38% received platinum-based regimens [etoposide, methylprednisolone, cytarabine, cisplatin (ESHAP) in 24 patients, and dexamethasone, cytarabine, cisplatin (DHAP) in six patients] (Table S3). Of these 90 patients, 41 had clinical benefit with salvage therapy (CR = 21, PR = 20, stable disease = 15). Autologous stem cell transplantation was used in 21 patients as part of their first-line therapy and in four as part of their salvage therapy, allogeneic stem cell transplantation was reported in five patients during first-line and in two after salvage therapy. A total of 40 patients received treatment beyond the second-line [27, a third-line treatment; and nine, a fourth-line treatment; with a median (range) of 3 (1–10) lines].

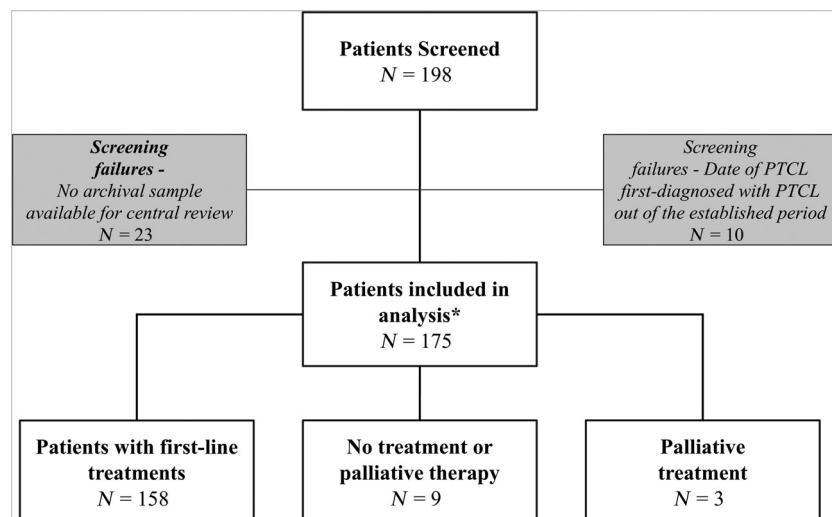


Fig 1. Study flow chart. \*One patient died before start of any treatment. Information on four other patients was not available at the time of data collection.

Table 1. Patient characteristics.

	Overall sample	AITL+ TFH	PTCL-NOS	PTCL extranodal NK/T	ALK+ ALCL	ALK- ALCL	Intestinal PTCL
Age at diagnosis, years, median (range)	62.8 (18.3-88.7)	65.7 (27.1-88.7)	69.1 (37.2-82.6)	63.2 (22.3-88.1)	31.6 (18.3-81.6)	63.8 (29.6-83.0)	54.1 (21.5-76.0)
N (%):							
Sex							
Male	111 (63.4)	48 (61.5)	14 (66.7)	13 (65.0)	11 (84.6)	16 (88.9)	7 (63.6)
Female	64 (36.6)	30 (38.5)	7 (33.3)	7 (35.0)	2 (15.4)	2 (11.1)	4 (36.4)
Relevant comorbidities							
Any	113 (64.6)	50 (64.1)	14 (66.7)	16 (80.0)	7 (53.9)	14 (77.8)	5 (45.5)
Arterial hypertension	41 (23.4)	18 (23.1)	8 (38.1)	4 (20.0)	2 (15.4)	5 (27.8)	1 (9.1)
Diabetes mellitus type II	22 (12.6)	10 (12.8)	3 (14.3)	2 (10.0)	2 (15.4)	4 (22.2)	1 (9.1)
Appendectomy	15 (8.6)	8 (10.3)	1 (4.8)	3 (15.0)	0 (0.0)	1 (5.6)	2 (18.2)
Dyslipidaemia	12 (6.9)	5 (6.4)	1 (4.8)	1 (5.0)	1 (7.7)	3 (16.7)	0 (0.0)
Hypercholesterolaemia	10 (5.7)	5 (6.4)	2 (9.5)	2 (10.0)	0 (0.0)	1 (5.6)	0 (0.0)
Previous neoplasia*							
Total	33 (18.9)	17 (21.8)	4 (19.1)	5 (25.0)	2 (15.4)	3 (16.7)	1 (9.1)
Genitourinary <sup>†</sup>	12 (6.9)	6 (7.7)	2 (9.5)	1 (5.0)	1 (7.7)	0 (0.0)	0 (0.0)
Not specified	6 (3.4)	2 (2.6)	1 (4.8)	1 (5.0)	1 (7.7)	1 (5.6)	0 (0.0)
Other lymphomas	5 (2.9)	4 (5.1)	0 (0.0)	1 (5.0)	0 (0.0)	0 (0.0)	0 (0.0)
Digestive	4 (2.3)	3 (3.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Breast	3 (1.7)	1 (1.3)	0 (0.0)	1 (5.0)	0 (0.0)	0 (0.0)	1 (9.1)
Skin no melanoma	3 (1.7)	2 (2.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Other tumours <sup>‡</sup>	6 (3.4)	2 (2.6)	1 (4.8)	1 (5.0)	0 (0.0)	2 (11.1)	0 (0.0)
Previous inflammatory, autoimmune or rheumatological disease	28 (16.0)	15 (19.2)	2 (9.5)	4 (20.0)	1 (7.7)	2 (11.1)	2 (18.2)
Solid organ recipient	7 (4.0)	3 (3.9)	1 (4.8)	0 (0.0)	1 (7.7)	1 (5.6)	1 (9.1)
Immunosuppressive treatment							
Viral infections <sup>§</sup>							
Anytime	13 (7.4)	6 (7.7)	2 (9.5)	0 (0.0)	1 (7.7)	1 (5.6)	2 (18.2)
At time of diagnosis	8 (4.6)	3 (3.9)	2 (9.5)	0 (0.0)	1 (7.7)	1 (5.6)	1 (9.1)
HIV	10 (5.7)	3 (3.9)	2 (9.5)	1 (5.0)	1 (7.7)	3 (16.7)	0 (0.0)
HBV	8 (4.6)	3 (3.9)	1 (4.8)	2 (10.0)	1 (7.7)	0 (0.0)	0 (0.0)
HCV	13 (7.4)	5 (6.4)	3 (14.3)	1 (5.0)	2 (15.4)	2 (11.1)	0 (0.0)
Previous exposure to radiation	14 (8.0)	5 (6.4)	3 (14.3)	3 (15.0)	1 (7.7)	1 (5.6)	1 (9.1)
Previous exposure to chemotherapy	19 (10.9)	6 (7.7)	3 (14.3)	5 (25.0)	1 (7.7)	2 (11.1)	0 (0.0)

AITL, angioimmunoblastic T-cell lymphoma; PTCL, peripheral T-cell lymphoma; NOS, not otherwise specified; ALK+ ALCL, anaplastic lymphoma kinase-positive anaplastic large-cell lymphoma; ALK- ALCL, ALK-negative ALCL; N, total number of patients; SD, standard deviation; HIV, human immunodeficiency virus; HBV, hepatitis B virus; HCV, hepatitis C virus.

\*Four patients reported >1 previous neoplasia (n = 1, digestive + genitourinary; n = 1, other lymphomas + skin no melanoma; n = 1, two genitourinary types including prostate and clear cell renal cancer; and n = 1, other lymphomas + skin no melanoma (2 different types: basal cell carcinoma and Bowen disease).

<sup>†</sup>Includes renal, bladder, and/or prostate cancer.

<sup>‡</sup>Includes myeloma (n = 2, one patient from the AITL + TFH group and one from the PTCL extranodal NK/T group), thyroid cancer (n = 1, AITL + TFH), lung (n = 1, ALK- ALCL), acute leukaemia (n = 1, PTCL-NOS) and head/neck cancer (n = 1, ALK- ALCL).

<sup>§</sup>17 patients with at least one type of viral infection (n = 5, HIV + HBV + HCV; n = 4, HIV + HCV; n = 3, HBV; and n = 1, HIV).

Table II. PTCL clinical features.

	Overall sample (N = 175)	AITL+ TFH (N = 78)	PTCL-NOS (N = 22)	PTCL extranodal NK/T (N = 20)	ALK+ ALCL (N = 13)	ALK- ALCL (N = 18)	Intestinal PTCL (N = 11)
Ann Arbor Stage, n (%)							
I-II	40 (22.9)	12 (15.4)	3 (14.3)	8 (40.0)	3 (23.1)	8 (44.4)	2 (18.2)
III-IV	128 (73.1)	63 (80.8)	18 (85.7)	11 (55.0)	10 (76.9)	10 (55.6)	7 (63.6)
N.A./U.K.	7 (4.0)	3 (3.8)	0 (0.0)	1 (5.0)	-	-	2 (18.2)
Extranodal disease, n (%)							
No	73 (41.7)	33 (42.3)	9 (42.9)	4 (20.0)	10 (76.9)	10 (55.6)	1 (9.09)
Yes	98 (56.0)	43 (55.1)	12 (57.1)	15 (75.0)	3 (23.1)	8 (44.4)	9 (81.8)
N.A./U.K.	4 (2.3)	2 (2.6)	0 (0.00)	1 (5.0)	-	-	1 (9.1)
Extranodal locations							
1	59 (60.2)	24 (55.8)	6 (50.0)	8 (53.3)	3 (100.0)	6 (75.0)	5 (55.6)
(extranodal disease n = 93;							
Median: 1; range 1-4), n (%)	29 (29.6)	13 (30.2)	4 (33.3)	5 (33.3)	-	2 (25.0)	3 (33.3)
2	3 (3.0)	1 (2.3)	1 (8.3)	0 (0.00)	-	-	1 (11.1)
3	3 (3.0)	2 (4.7)	0 (0.0)	1 (6.7)	-	-	-
4	4 (4.1)	3 (7.0)	1 (8.3)	1 (6.7)	-	-	-
N.A./U.K.							
Total	98 (100)	43 (100.0)	12 (100.0)	15 (100.0)	3 (100.0)	8 (100.0)	9 (100.0)
Bone marrow infiltration							
Yes	32 (18.3)	23 (29.5)	6 (27.3)	1 (5.0)	1 (7.7)	-	-
No	114 (65.1)	42 (53.8)	14 (63.6)	15 (75.0)	11 (84.6)	16 (88.9)	6 (54.5)
Not available/ U.K.	29 (16.6)	13 (16.7)	2 (9.1)	4 (20.0)	1 (7.7)	2 (11.1)	5 (45.5)
Procedure for diagnosis of							
bone marrow disease, n (%)							
Flow cytometry	15 (8.6) <sup>1</sup>	12 (15.4)	3 (14.3)	-	-	-	-
Histology	19 (10.9) <sup>1</sup>	16 (20.5)	2 (9.5)	-	-	-	-
Molecular Biology	4 (2.3) <sup>1</sup>	3 (3.9)	1 (4.8)	-	-	-	-
N.A./U.K.	137 (78.3) <sup>1</sup>	47 (60.3)	15 (71.4)	20 (100.0)	13 (100.0)	18 (100.0)	11 (100.0)
B Symptoms, n (%)							
Yes	95 (54.3)	35 (44.9)	10 (47.6)	4 (20.0)	7 (53.9)	8 (44.4)	1 (9.1)
No	69 (39.4)	38 (48.7)	11 (52.4)	14 (70.0)	6 (46.2)	9 (50.0)	8 (72.7)
N.A./U.K.	11 (6.3)	5 (6.4)	0 (0.0)	2 (10.0)	-	1 (5.6)	2 (18.2)
Bulky disease, (>10 cm)*, n (%)							
Yes	26 (14.9)	10 (12.8)	5 (23.8)	4 (20.0)	3 (23.1)	2 (11.1)	2 (18.2)
No	141 (80.6)	65 (83.3)	17 (77.3)	15 (75.0)	9 (69.2)	16 (88.9)	8 (72.7)
N.A./U.K.	8 (4.6)	3 (3.9)	0 (0.0)	1 (5.0)	1 (7.7)	-	1 (9.1)
PET at diagnosis (n = 175), n (%)							
Yes	62 (35.4)	31 (39.7)	6 (28.6)	7 (35.0)	8 (61.5)	6 (33.3)	3 (27.3)
No	102 (58.3)	42 (53.1)	16 (72.7)	11 (55.0)	-	11 (61.1)	7 (63.6)
N.A./U.K.	11 (6.3)	5 (6.4)	0 (0.0)	2 (10.0)	5 (38.5)	1 (5.6)	1 (9.1)
ECOG PS at PTCL							
diagnosis (n = 175), n (%)							
0-2	102 (58.3)	48 (61.5)	12 (57.1)	10 (50.0)	9 (69.2)	9 (50.0)	6 (54.5)
3-4	17 (9.7)	8 (10.3)	3 (14.3)	1 (5.0)	2 (15.4)	1 (5.6)	2 (18.2)
Low/ intermediate risk	55 (50.0)	23 (42.6)	4 (30.8)	5 (55.6)	9 (90.0)	6 (60.0)	2 (33.3)
Intermediate/ high risk	55 (50.0)	31 (57.4)	9 (69.2)	4 (44.4)	1 (10.0)	4 (40.0)	4 (66.7)
Total	110 (100.0)	54 (100.0)	13 (100.0)	9 (100.0)	10 (100.0)	10 (100.0)	6 (100.0)

Continues

Table II. (Continued)

	Overall sample (N = 175)	PTCL extranodal					Intestinal PTCL (N = 11)
		AITL+ TFH (N = 78)	PTCL-NOS (N = 22)	NK/T (N = 20)	ALK+ ALCL (N = 13)	ALK- ALCL (N = 18)	
PTCL* (n = 104), n (%)							
0-1 adverse factors	54 (51.9)	22 (44.9)	4 (30.8)	7 (77.8)	8 (80.0)	3 (30.0)	3 (60.0)
2-4 adverse factors	50 (48.1)	27 (55.1)	9 (69.2)	2 (22.2)	2 (20.0)	7 (70.0)	2 (40.0)
Total	104 (100.0)	49 (100.0)	13 (100.0)	9 (100.0)	10 (100.0)	10 (100.0)	5 (100.0)
Biomarkers							
p53							
Negative	113 (87.6)	71 (98.6)	15 (93.8)	6 (60.0)	9 (81.8)	7 (70.0)	3 (37.5)
Positive	16 (12.4)	1 (1.4)	1 (6.3)	4 (40.0)	2 (18.2)	3 (30.0)	5 (62.5)
Total	129 (100.0)	72 (100.0)	16 (100.0)	10 (100.0)	11 (100.0)	10 (100.0)	8 (100.0)
LDH							
Normal	68 (38.9)	31 (39.7)	5 (23.8)	8 (40.0)	6 (46.1)	6 (33.3)	4 (36.4)
High	92 (52.6)	44 (56.4)	13 (61.9)	9 (45.0)	5 (38.5)	10 (55.6)	5 (45.5)
N.A./U.K.	15 (8.6)	3 (3.8)	3 (14.3)	3 (15.0)	2 (15.4)	2 (11.1)	2 (18.2)
n	n = 155	n = 72	n = 16	n = 12	n = 11	n = 10	n = 9
CD30 expression	132	18.5 (21.0)	25.0 (34.8)	53.1 (41.0)	97.3 (6.5)	74.5 (32.0)	31.7 (46.6)
PD1	130	49.9 (33.2)	36.6 (41.4)	17.5 (33.3)	0.0 (0.0)	2.5 (7.1)	2.2 (6.7)
LEF1	131	62.2 (25.6)	39.7 (35.4)	11.0 (29.3)	11.8 (27.1)	44.4 (42.8)	18.9 (37.6)
Ki67	129	32.3 (25.3)	48.8 (24.4)	45.9 (32.7) <sup>†</sup>	66.8 (24.7)	55.0 (38.2)	26.3 (35.7)
BCL6	131	6.5 (6.7)	7.4 (17.2)	3.0 (5.7)	3.8 (5.9)	0.8 (1.7)	2.4 (5.0)
CD10	130	9.1 (17.8)	7.1 (20.2)	1.3 (3.1)	0.2 (0.6)	0.0 (0.0)	0.0 (0.0)
Double PDI-LEF1	131	39.7 (33.5)	14.4 (27.8)	7.7 (25.9)	0.0 (0.0)	0.0 (0.0)	10.6 (31.7)
% EBER-positive cells	133	7.2 (13.0)	12.3 (31.5)	75.0 (32.5)	0.0 (0.0)	0.3 (0.6) <sup>‡</sup>	0.1 (0.3)

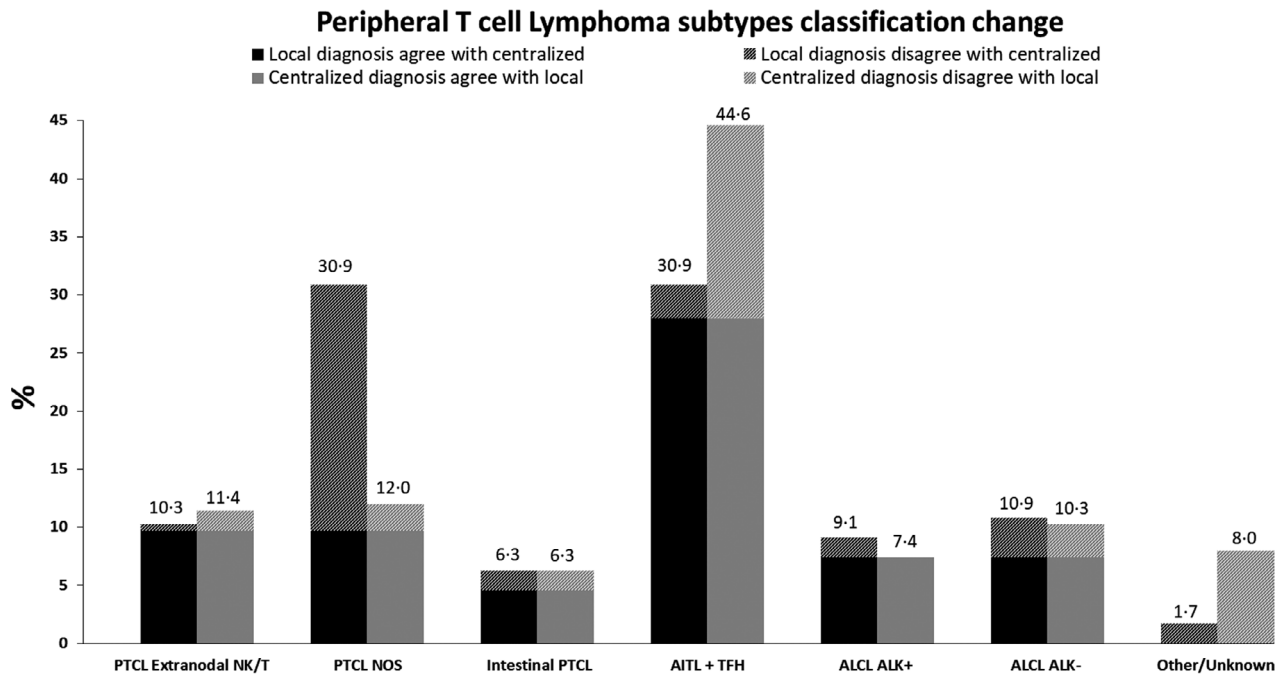
% based on total patients (n = 175).

AITL, angioimmunoblastic T-cell Lymphoma; PTCL, peripheral T-cell Lymphoma; NOS, not otherwise specified; ALK+ ALCL, anaplastic lymphoma kinase (ALK)-positive anaplastic large-cell lymphoma; ALK- ALCL, anaplastic lymphoma kinase (ALK)-negative anaplastic large-cell lymphoma; N, total number of patients; SD, standard deviation; HIV, Human immunodeficiency virus; BHV, hepatitis B virus; CHV, hepatitis C virus. N.A., Not available; U.K., Unknown; n.s., not statistically significant.

\*Location included NOS (42.3%), spleen (15.3%; among whom one patient with a 14 cm lesion and one with splenomegaly), retroperitoneal (11.5%; including one patient with mesenteric disease) and other locations (30.8%).

<sup>†</sup>Based on 11 patients.

<sup>‡</sup>IPI and PIT is presented based on the total number of patients with complete information to calculate both indices (n = 110 and n = 104, respectively).



**Cases in Local diagnosis that disagree with centralized classification:**

- PTCL Extranodal NK/T: Intestinal PTCL 0.6% (n=1).
- PTCL-NOS: PTCL Extranodal NK/T 1.7% (n=3), AITL+TFH 14.9% (n=26), ALCL ALK- 2.3% (n=4), Other/Unknown 2.3% (n=4).
- Intestinal PTCL: Other/Unknown 1.7% (n=3).
- AITL+TFH: PTCL NOS 0.6% (n=1), Other/Unknown 2.3% (n=4).
- ALCL ALK+: ALCL ALK- 0.6% (n=1), Other/Unknown 1.1% (n=2).
- ALCL ALK-: PTCL NOS 1.1% (n=2), Intestinal PTCL 0.6% (n=1), AITL+TFH 1.1% (n=2), Other/Unknown 0.6% (n=1).
- Other/Unknown: PTCL NOS 0.6% (n=1), Intestinal PTCL 0.6% (n=1), AITL+TFH 0.6% (n=1).

**Cases in Centralized diagnosis that disagree with local classification:**

- PTCL Extranodal NK/T: PTCL NOS 1.7% (n=3).
- PTCL NOS: AITL+TFH 0.6% (n=1), ALCL ALK- 1.1% (n=2), Others/Unknown 0.6% (n=1).
- Intestinal PTCL: PTCL Extranodal NK/T 0.6% (n=1), Enteropathy-type T/NKT cell Lymphoma 0.6% (n=1), ALCL ALK- 0.6% (n=1).
- AITL+TFH: PTCL NOS 14.9% (n=26), Peripheral T-cell Lymphoma follicular variant (f-PTCL) 0.6% (n=1), ALCL ALK- 1.1% (n=2).
- ALCL ALK-: PTCL NOS 2.3% (n=4), ALCL ALK+ 0.6% (n=1).
- Other/Unknown: PTCL NOS 2.3% (n=4), Intestinal PTCL 1.7% (n=3), AITL+TFH 2.3% (n=4), ALCL ALK+ 1.1% (n=2), ALCL ALK- 0.6% (n=1).

Fig 2. Peripheral T-cell Lymphoma subtypes and results from experts' central review. Two patients were reported with follicular T-cell lymphoma ( $n = 1$ ) and enteropathic T-cell lymphoma ( $n = 1$ ) by the local diagnosis. These subtypes were not considered in the central review due to the WHO classification update. Central review also confirmed new subtypes such as nodal PTCL with TFH phenotype ( $n = 23$ ) and other included in the graphic as 'Other entities' including monomorphic epitheliotropic intestinal T-cell lymphoma ( $n = 5$ ), T-cell prolymphocytic leukaemia ( $n = 1$ ), reactive lymphadenopathy ( $n = 2$ ), and diffuse B-cell lymphoma ( $n = 2$ , one with plasmablastic differentiation).

**Prognostic factors for outcome: PFS and OS**

The median PFS among 157 patients was 7.9 (95% CI 5.0–10.7) months. The intermediate/high-risk group had a significantly shorter PFS according to the IPI (6.3 months, 95% CI 3.7–8.8) than the low/intermediate-risk group (71.7 months, 95% CI 22.3–121.1;  $P < 0.001$ ) (Fig 3A). Similar findings were seen for patients with 0–1 PIT adverse factors, with a median PFS of 22.7 months (95% CI 0–82.3) vs. 6.7 months (95% CI 2.0–11.4) for PIT 2–4 ( $P < 0.001$ ) (Fig 3B).

A CR after first-line therapy was significantly associated with a better median PFS (62.6 months, 95% CI 20.2–105.1) compared with reaching PR (7.1 months, 95% CI 5.8–8.4) or stable disease (6.3 months, 95% CI 1.1–11.4;  $P < 0.001$ ) Fig 3C. When different PTCL subtypes were compared, patients with ALK+ ALCL showed a significantly better PFS

(22.7 months, 50% of patients had PD throughout the study period) than those with other subtypes ( $P < 0.001$ ), while intestinal forms of PTCL showed a poorer outcome (median PFS of 2.6 months, 95% CI, 1.1–4.0) Fig 3D.

The median OS for all the 175 patients was 15.8 months (95% CI 10.2–21.3). The most frequent causes of death ( $n = 114$ ) were PD (65.8%) and infections (18.4%).

Being classified into the intermediate/high-risk groups (IPI) and having 2–4 adverse factors (PIT) were both associated with shorter OS (median 7.9 months, 95% CI 3.9–11.9; and 13.9 months, 95% CI 8.8–18.9, respectively) compared with the lower-risk groups (IPI low/intermediate risk, median 59.4 months, 95% CI 49.0–70.4;  $P < 0.001$ ; and PIT 0–1 adverse factors, mean 57.5 months, 95% CI 46.5–68.6;  $P < 0.001$ ) (Fig 4A,B).

Reaching CR after first-line therapy was associated with longer OS (mean 67.0 months, 95% CI 58.2–75.9) vs.



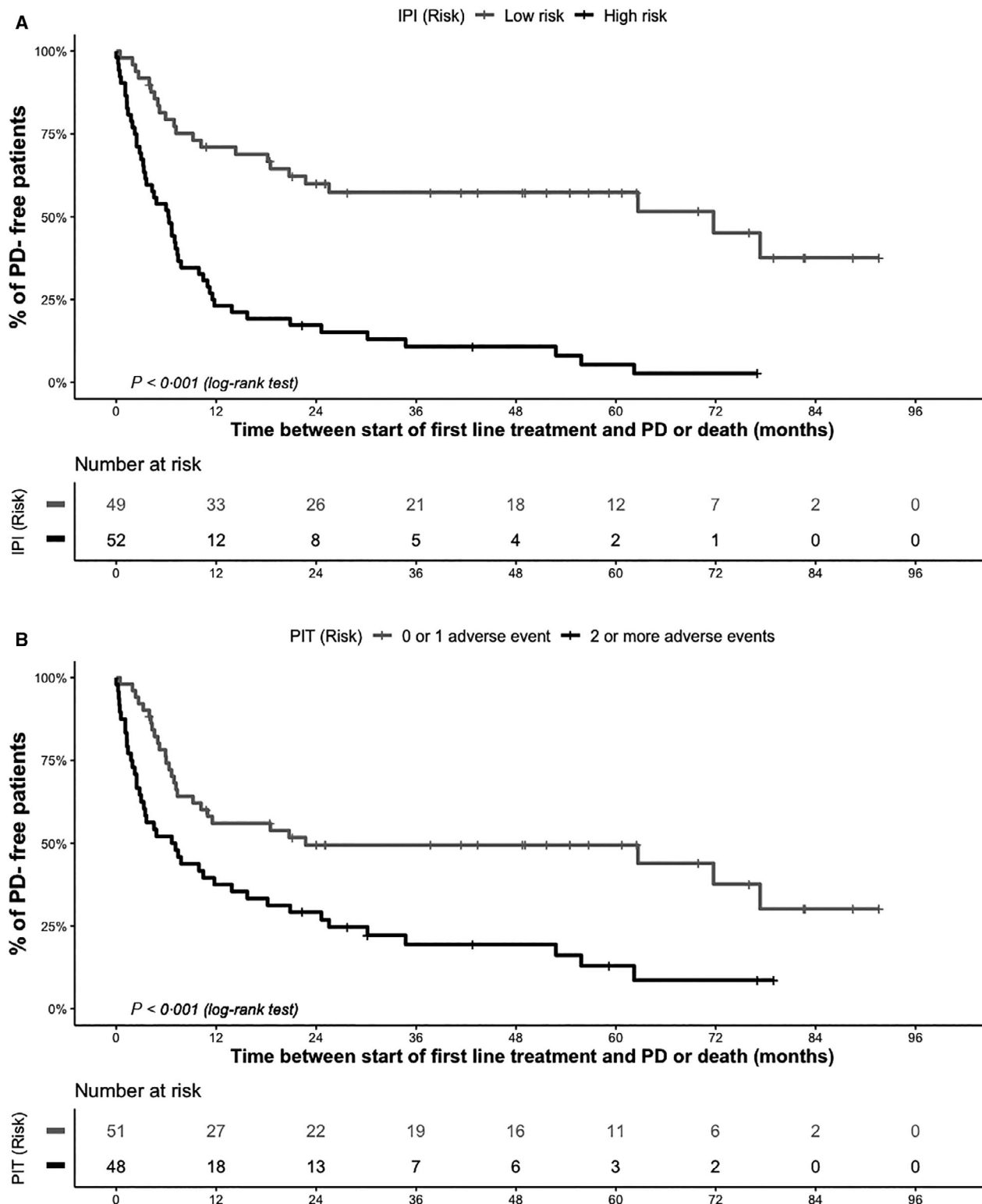


Fig 3. Progression-free survival (PFS) curves. (A) PFS according to IPI score groups; (B) PFS according to PIT groups; (C) PFS according to response intention-to-cure chemotherapy as first-line treatment; (D) PFS of clinically relevant diagnostic groups after central review.

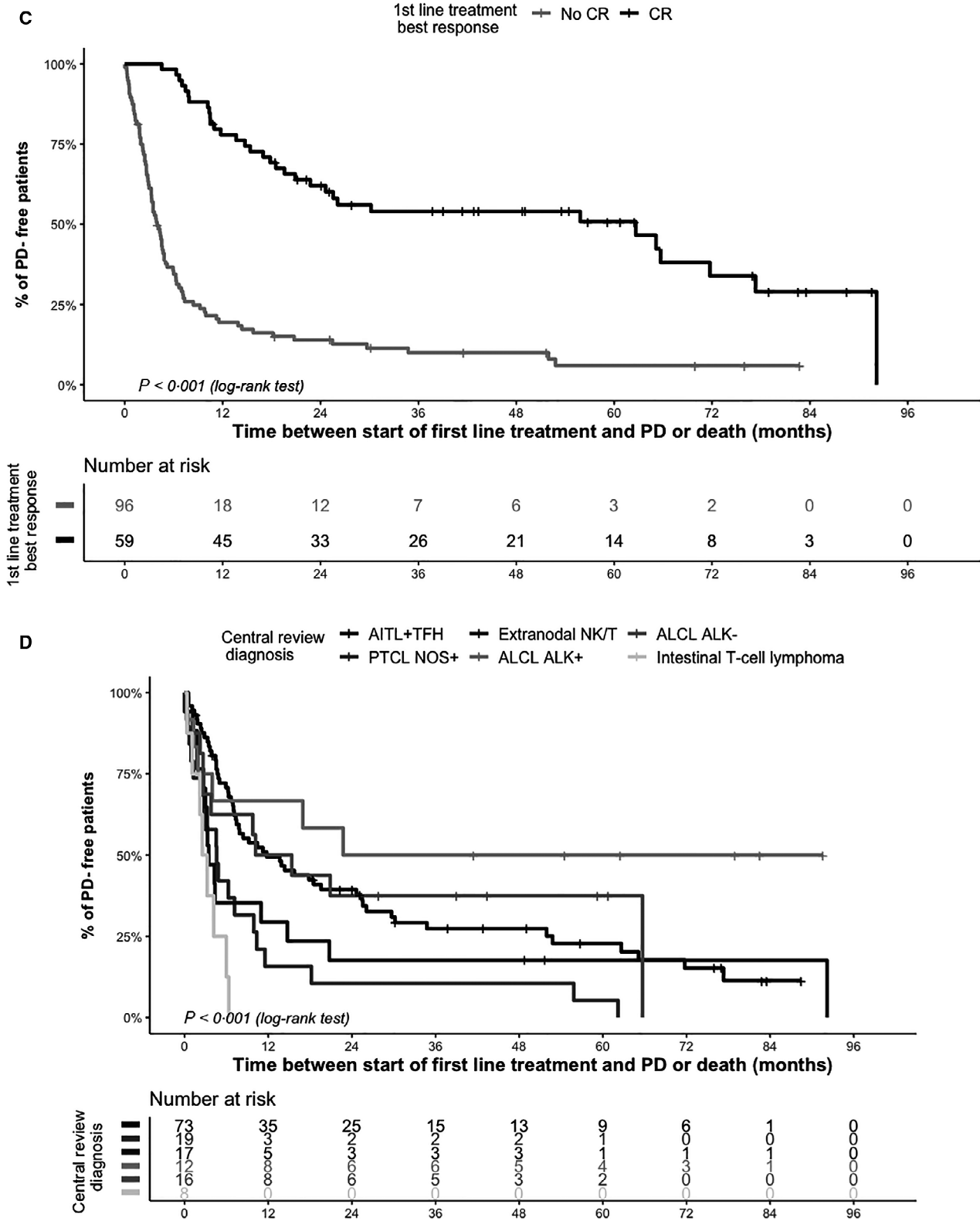


Fig 3. (Continued).

median 7.3 months, 95% CI 5.9–8.8;  $P < 0.001$ ) (Fig 4C). Histological subtypes associated with the shortest survival corresponded to those re-classified as intestinal PTCL (median 6.2 months, 95% CI 3.9–8.5) and extranodal NK/T PTCL (median 6.4 months, 95% CI 2.9–9.8;  $P < 0.001$ ) (Fig 4D).

Univariate and multivariate analyses for PFS Table III also confirmed that reaching a CR was overall associated with a lower risk of PD in multiple multivariate testing, early Ann Arbor Stages I–II, an ECOG PS 0–2 were also significant for PFS when IPI and PIT were excluded as factors. When OS was evaluated, the predictive factors for survival were: CR after the first PTCL treatment, low/intermediate risk based on IPI, and normal/low LDH values. Patients with very positive p53 showed a longer OS and a trend to significance with respect to those with negative results when excluding the IPI and PIT scores from the analysis; however, limited sample size compromises its interpretation.

#### *Prognostic factors for CR to first-line treatment*

Univariate logistic regression analysis for evaluating factors associated with CR after the first therapeutic approach revealed significant differences between the proportion of CR and non-CR patients, particularly for PTCL subtypes, including ALK+ ALCL (odds ratio [OR] 18, 95% CI 2.7–119.2;  $P = 0.003$ ), ALK– ALCL (OR 10.1, 95% CI 1.8–57.9;  $P = 0.009$ ), and angioimmunoblastic + TFH (OR 6.9, 95% CI 1.5–31.7;  $P = 0.014$ ); reference cohort, PTCL-NOS ( $P = 0.032$ ). Other factors with significant differences in univariate analysis regarding CR included: a younger age (OR 0.99, 95% CI 0.97–1.0;  $P = 0.093$ ), an IPI low/intermediate risk (OR 2.9, 95% CI 1.3–6.7;  $P = 0.01$ ), a negative p53 expression (OR 4.7, 95% CI 1.0–22.0;  $P = 0.050$ ), a low/normal LDH value (OR 2.8, 95% CI 1.4–5.5;  $P = 0.003$ ), Ann Arbor Stages I–II (OR 2.4, 95% CI 1.1–5.1;  $P = 0.025$ ), an absence of extranodal infiltration (OR 2.5, 95% CI 1.3–4.9;  $P = 0.006$ ) and no bone marrow disease (OR 2.7, 95% CI 1.1–6.5;  $P = 0.029$ ). Despite these results, when using multivariate analysis, only the ALK + ALCL subtype was statistically associated with high probability of CR by excluding the potential confounders as explained in the methods section (Fig 5A,B).

#### *CD30 expression*

CD30 expression was scored as positive (68/132 patients) for patients with >15% positive neoplastic cells. The intensity of CD30 expression was graded in positive patients from weak, 35/121 patients; moderate, 57/121 patients, or intense, 29/121 patients. An association between the IPI groups and CD30 expression was found, showing higher average and median values for the low/intermediate-risk groups [mean (SD) 36.4 (38.6) vs. 18.3 (26.6) for the high/intermediate groups;  $P = 0.004$ ]; also, a higher CD30 intensity was more

frequently reported in the low/intermediate-IPI group (Table S4). Neither CD30 expression ( $P = 0.082$ ) nor CD30 intensity ( $P = 0.361$ ) showed significant differences in the PIT groups. A comparison of CD30 expression across clinically relevant groups showed significant differences between median values, being particularly high for ALK+ ALCL (100%, range, 80–100%), ALK– ALCL (80%; range, 15–100%), and extranodal NK/T (70%; range, 0–100%) groups.

## DISCUSSION

Among the various lymphoid neoplasms, PTCL is associated with poor prognosis compared to B-cell lymphomas.<sup>18</sup> The rarity of this disease with limited data regarding outcomes and limited treatments has made it difficult to identify factors for classifying patients with high-risk disease. Analysis of epidemiological and baseline characteristics at diagnosis have led to relevant prognostic indices, including IPI and PIT. Here, the prognostic values of IPI and PIT for the identification of patients at a higher risk of PD or death were confirmed, as previously reported.<sup>10,19</sup> We showed that a large proportion of patients with PTCL had a previous medical history of immune-related conditions, including autoimmune diseases (16%), viral infections (17%), or previous chemo/radiotherapy for the treatment of other carcinomas (almost 19%), as described previously.<sup>20</sup> These findings warrant an in-depth study, along with relevant genetic studies and research, into associated immunosuppressive factors.

There were mixed results when considering the distribution amongst various PTCL subtypes.<sup>21,22</sup> Comparison of our present results to those of the International TCL Project<sup>21</sup> showed a higher frequency of PTCL-NOS (30.9% vs. 25.9%) and AITL (30.9% vs 18.5%), while Carson *et al.*<sup>23</sup> recently reported that 51.3% of patients with PTCL were diagnosed with PTCL-NOS. Undoubtedly, PTCL-NOS diagnosis requires careful consideration.<sup>24</sup> Its heterogeneous cytological and phenotypic characteristics may result in subjective biases and discrepancies in diagnosis between different pathologists despite the widespread use of immunophenotyping;<sup>21,25</sup> therefore, appropriate pathological review is recommended. In relation to the present study, updated classification criteria and central review by experienced haematopathologists could ensure high reproducibility of diagnoses. This approach also reduced the number of patients with PTCL without specific features, that is, in PTCL-NOS cases (from 54 cases to 21). However, TCL may show 'overlapping phenotypes' and its clinical course might lead to differences in diagnosis, especially in gamma-delta and EBV-related lymphomas. Therefore, access to the extranodal location of origin is also necessary to subclassify TCLs effectively.

Although almost 58% of the patients showed some response to first-line therapy (CR or PR), The PFS and OS were low (7.9 and 15.8 months, respectively). When we analysed the variables influencing PFS and OS, CR to first-line

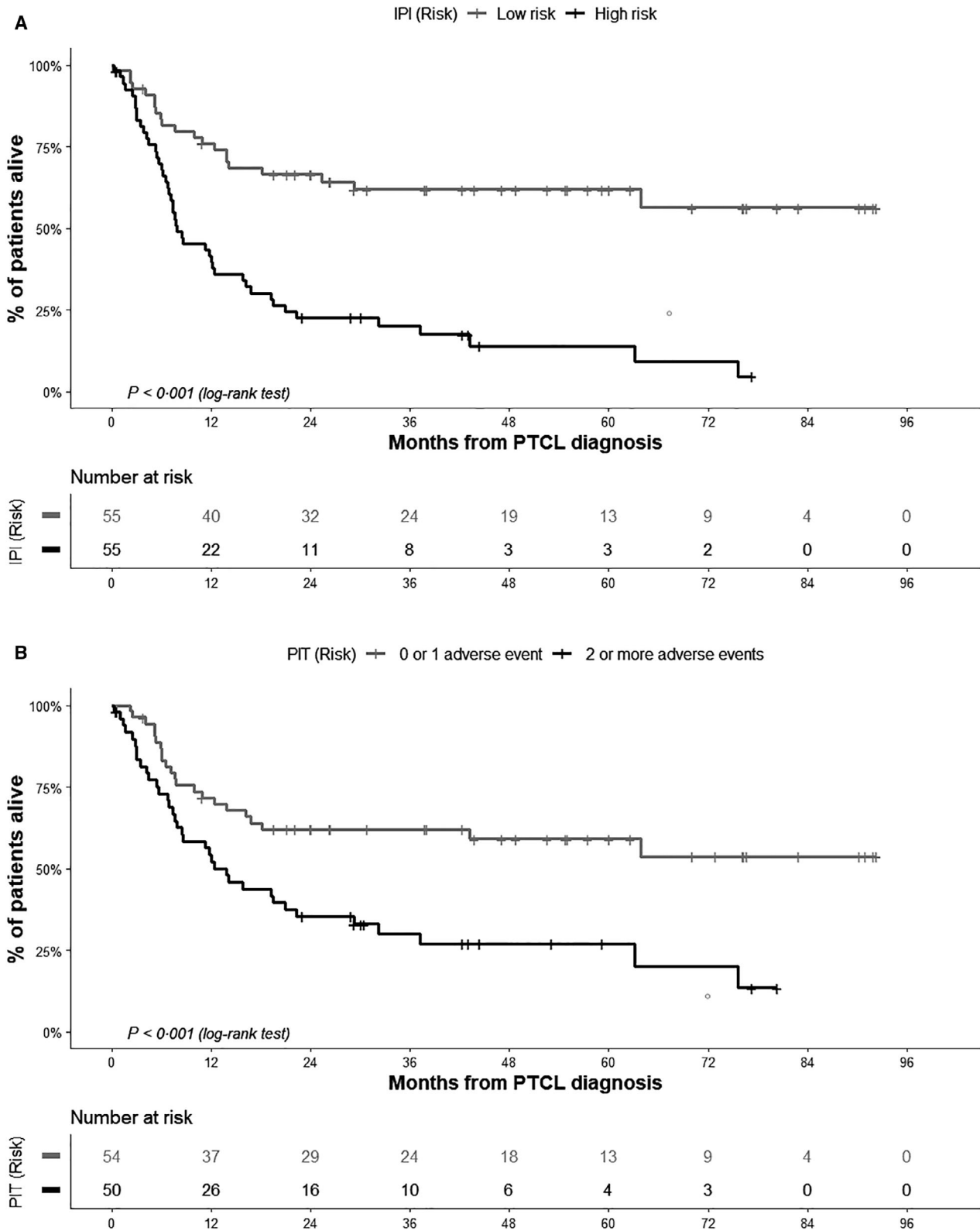


Fig 4. Overall survival (OS) curves. (A) OS according to IPI score groups; (B) OS according to PIT groups; (C) OS according to response intention-to-cure chemotherapy as first-line treatment; (D) OS of clinically relevant diagnostic groups after central review.

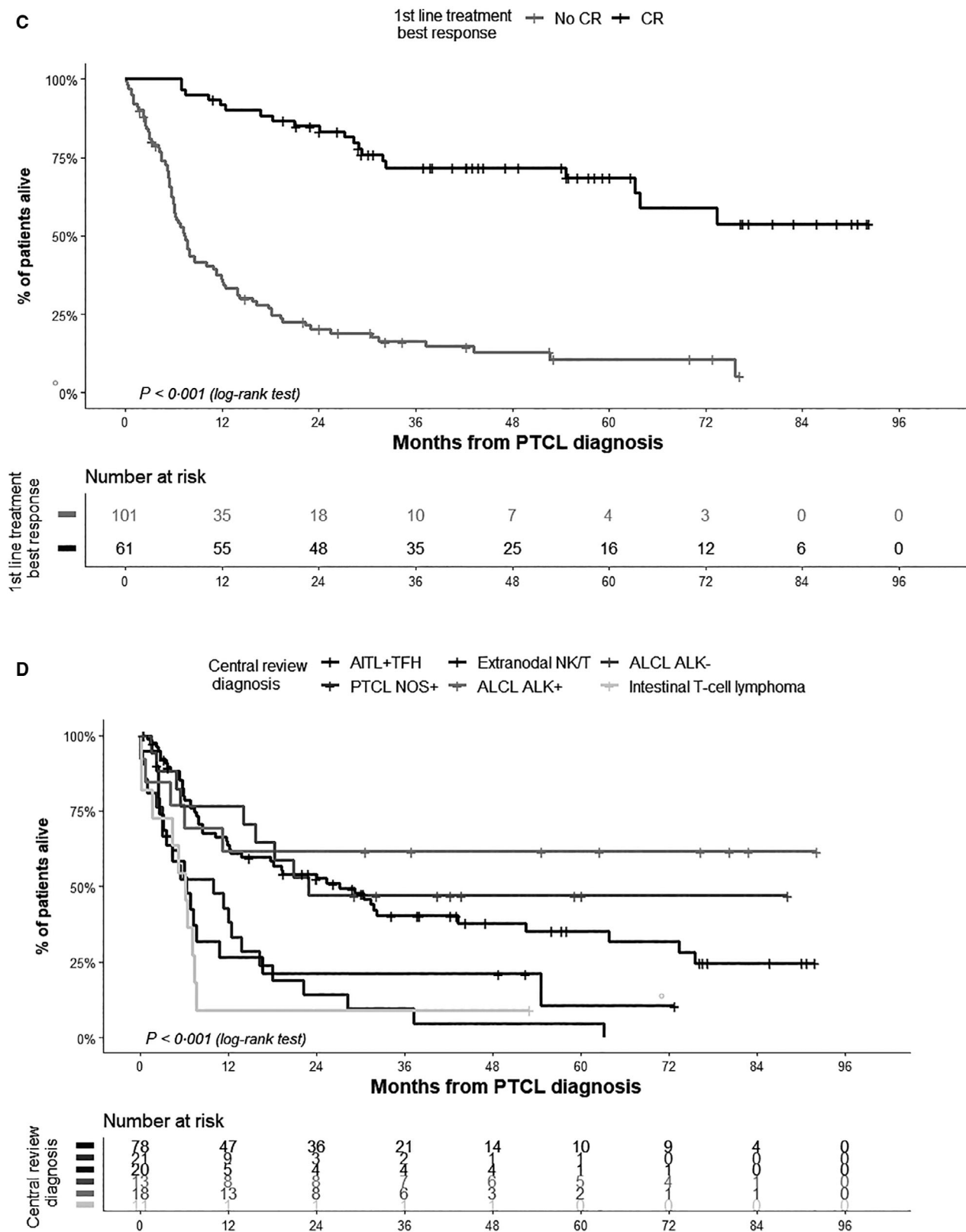


Fig 4. (Continued).

Table III. Multivariate Cox regression model for progression-free survival and overall survival.

Factors	Progression-free survival (PFS)					Overall survival (OS)					
	Univariate		Multivariate (1)			Univariate		Multivariate (2)			
	Median PFS, months (95% CI)	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	Median OS, months (95% CI)	HR (95% CI)	P	HR (95% CI)	
Age	7.8 (4.7–10.9)	1.01 (1.00–1.02)	0.071	–	–	–	13.9 (5.7–19.1)	1.02 (1.00–1.03)	<b>0.013</b>	–	n.s.
Central review diagnosis											
ALK+ ALCL*	22.7 (–)	Reference	<b>&lt;0.001</b>	–	n.s.	–	58.5 (32.3–81.8)	Reference	<b>&lt;0.001</b>	–	n.s.
Angioimmunoblastic + TFH	11.8 (4.2–19.3)	1.97 (0.84–4.60)	n.s.	–	–	–	27.1 (14.9–39.4)	1.89 (0.75–4.78)	n.s.	–	–
PTCL-NOS	4.6 (1.9–7.3)	4.42 (1.74–11.21)	0.002	–	–	–	10.0 (0.9–19.2)	5.13 (1.91–13.80)	0.001	–	–
Extranodal NK/T	3.5 (2.1–4.9)	15 (1.20–8.26)	0.019	–	–	–	6.4 (2.9–9.8)	4.22 (1.53–11.64)	0.005	–	–
PTCL											
ALK-negative	10.2 (0–21.1)	1.87 (0.69–5.08)	n.s.	–	–	–	47.8 (29.4–66.1)	1.55 (0.52–4.65)	n.s.	–	–
ALCL											
Intestinal PTCL	2.6 (1.1–4.0)	8.67 (2.91–25.90)	<0.001	–	–	–	6.2 (3.9–8.5)	6.52 (2.19–19.42)	<0.001	–	–
Ann Arbor Stage											
I–II*	25.6 (0–86.7)	Reference	<b>0.003</b>	–	–	Reference	54.6 (0–109.4)	–	n.s.	–	n.s.
III–IV	6.6 (5.3–8.0)	2.14 (1.28–3.55)	–	–	–	3.07 (1.23–7.61)*	11.9 (5.6–18.3)	–	–	–	–
Extranodal disease											
No	17.8 (8.8–26.8)	Reference	<b>0.025</b>	–	–	–	63.1 (6.9–119.4)	Reference	<b>&lt;0.001</b>	–	n.s.
Yes	6.4 (3.7–7.0)	1.69 (1.15–2.49)	0.007	–	–	–	8.5 (4.0–13.0)	2.13 (1.41–3.22)	<0.001	–	–
N.A./U.K.	6.3 (3.2–9.4)	1.80 (0.56–5.85)	n.s.	–	–	–	5.7 (0–11.7)	5.26 (1.83–15.10)	0.002	–	–
Bone marrow infiltration at PTCL diagnosis											
No*	10.5 (2.6–18.4)	Reference	<b>0.031</b>	–	n.s.	–	27.1 (14.6–39.7)	Reference	<b>&lt;0.001</b>	–	n.s.
Yes	7.3 (3.1–11.6)	1.30 (0.84–2.03)	n.s.	–	–	–	12.4 (0.8–24.0)	1.42 (0.89–2.28)	n.s.	–	–
N.A./U.K.	3.8 (3.0–4.6)	2.10 (1.19–3.71)	0.011	–	–	–	5.4 (2.3–8.4)	3.32 (2.00–5.50)	n.s.	–	–
ECOG PS											
0–2*	11.8 (4.1–19.5)	Reference	<b>&lt;0.001</b>	–	–	Reference	20.9 (2.5–39.4)	Reference	<b>&lt;0.001</b>	–	n.s.
3–4	1.8 (0.1–3.5)	3.39 (1.80–6.42)	–	–	–	7.64 (3.16–18.48)	3.5 (2.2–4.9)	3.96 (2.20–7.15)	–	–	–
Best response to first-line tx.											
Complete response (CR)*	62.6 (20.2–105.1)	Reference	<b>&lt;0.001</b>	Reference	<b>&lt;0.001</b>	Reference	67.0 (58.2–75.9)	Reference	<b>&lt;0.001</b>	Reference	<b>&lt;0.001</b>
No CR (PR and stable disease)	4.0 (3.1–4.9)	4.62 (3.00–7.12)	–	5.14 (2.61–10.13)	5.42 (2.60–11.28)	–	7.3 (5.9–8.8)	6.35 (3.78–10.67)	–	8.73 (2.93–25.98)	–

Continues

Table III. (Continued)

Factors	Progression-free survival (PFS)						Overall survival (OS)					
	Univariate			Multivariate (1)			Univariate			Multivariate (3)		
	Median PFS, months (95% CI)	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	Median OS, months (95% CI)	HR (95% CI)	P	HR (95% CI)	P	
IPI												
Low/intermediate risk	71.7 (22.3–121.1)	Reference	<0.001	Reference	<b>0.010</b>	–	59.5 (48.5–70.4)	Reference	<0.001	–	–	
(0–2 points)*												
Intermediate/high risk	6.3 (3.7–8.8)	3.81 (2.24–6.48)		2.89 (1.29–6.50)		–	7.9 (3.9–11.9)	3.31 (1.93–5.67)		–	–	
(3–5 points)												
PIT												
0/–1 adverse factors*	22.7 (0–82.3)	Reference	<b>0.002</b>	–	n.s.	–	57.5 (46.5–68.6)	Reference	<b>0.003</b>	–	–	
2–4 adverse factors	6.7 (2.0–11.4)	2.17 (1.32–3.58)		–		–	13.9 (8.8–19.0)	2.29 (1.32–3.99)		–	–	
LDH												
Low/normal LDH*	17.0 (8.0–25.9)	Reference	<b>0.024</b>	–	–	n.s.	52.6 (19.0–86.3)	Reference	<0.001	Reference	<b>0.036</b>	
High LDH	6.0 (3.7–8.3)	1.57 (1.06–2.33)		–		–	8.5 (4.8–12.2)	2.22 (1.44–3.41)		2.61 (1.07–6.38)		
p53												
Negative*	10.4 (4.9–15.8)	–	n.s.	–	–	–	19.3 (6.3–32.3)	Reference	<b>0.005</b>	–	n.s.	
Low positive	4.3 (2.2–6.4)	–		–		–	55.0 (19.3–90.7)	0.50 (0.12–2.05)	n.s.	–	–	
Very positive	4.2 (0.9–7.5)	–		–		–	5.3 (0.2–10.4)	3.24 (1.54–6.83)	0.002	–	–	

IPI groups: low risk 0–1 point, low/intermediate risk 2 points, high/intermediate risk 3 points and high risk 4–5 points. Multivariate PFS (1): including IPI/PIT but excluding factors involved in their calculation (age, LDH, ECOG PS, Ann Arbor Stage and extranodal disease), variables without significant result are not shown. Multivariate PFS (2): excluding IPI/PIT and including factors involved in their calculation (age, LDH, ECOG PS, Ann Arbor Stage and extranodal disease), variables without significant result are not shown. Multivariate OS (3): excluding IPI/PIT and including factors involved in their calculation (age, LDH, ECOG PS, Ann Arbor Stage and extranodal disease), variables without significant result are not shown. OS multivariate model including IPI/PIT but excluding factors involved in their calculation (age, LDH, ECOG PS, Ann Arbor Stage and extranodal disease), was also calculated (data not shown) and only best response to first-line treatment remained significant in the model, (HR 12.05, 95% CI 4.33–33.48;  $P < 0.001$ ). HR, hazard ratio; CI, confidence interval; ALK+ ALCL, anaplastic lymphoma kinase (ALK)-positive anaplastic large-cell lymphoma; PTCL, peripheral TCL; NOS, not otherwise specified; ALK– ALCL, ALK-negative anaplastic large-cell lymphoma; ECOG PS, Eastern Cooperative Oncology Group Performance Status; CR, complete response; PR, partial response; IPI, International prognostic index; PIT, Prognostic Index for TCL. n.s., not statistically significant; N.A., Not available; U.K., Unknown. Bold to highlight statistically significant values from reference categories. \*Reference category.

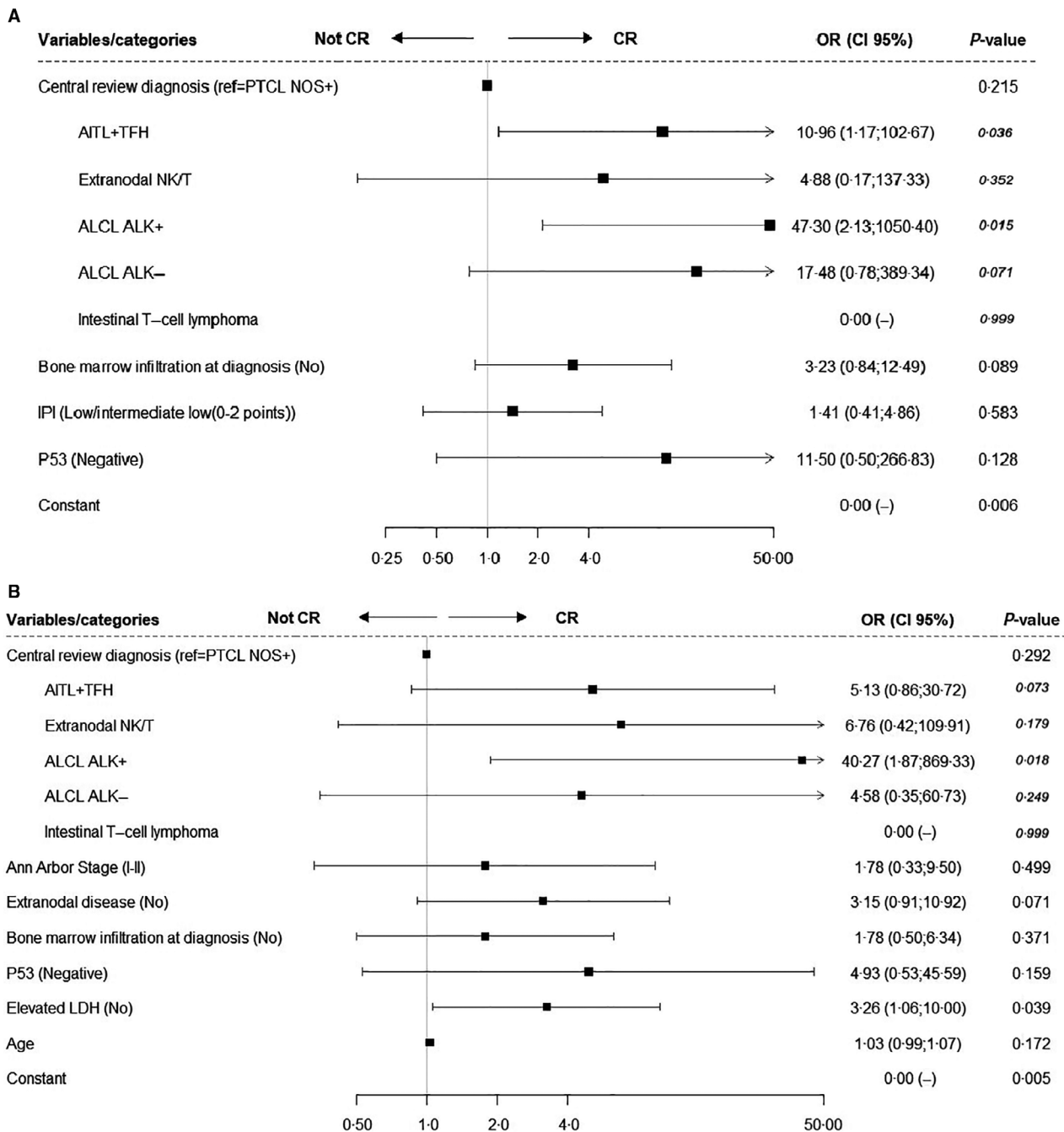


Fig 5. Multivariate logistic regression model for complete response (CR) to first-line treatment. (A) Multivariate logistic regression model on the probability of reaching CR to first-line treatment considering all factors with  $P < 0.1$  in the univariate analysis, and excluding factors already included in the IPI calculation. (B) Probability of reaching a CR factors used in the IPI calculation (excluding IPI). \*\*Reference factor. OR, odds ratio; CI, confidence interval; AITL, angioimmunoblastic T-cell Lymphoma; ALK+ ALCL, anaplastic lymphoma kinase (ALK)-positive anaplastic large-cell lymphoma; ALK- ALCL, ALK-negative ALCL; PTCL, peripheral T-cell lymphoma; NOS, not otherwise specified; ECOG PS, Eastern Cooperative Oncology Group Performance Status; IPI, International prognostic index; PIT, Prognostic Index for T-Cell Lymphoma.

treatment emerged as the strongest (and probably the only modifiable) prognostic factor, considering that the IPI and PIT scores derived from the results of combinations of patient characteristics during therapeutic decisions.

The frontline management in all these centres followed international recommendations<sup>26,27</sup> as in a previous report,<sup>23</sup> where 41.8% of patients were treated with doxorubicin-containing regimens (compared to CHOP and CHOP-like



treatments in 69.7% of our patients, irrespective of the PTCL subtype). Outcome is the most relevant issue in relation to treatment choice, in terms of response to treatment, only 34.9% of the patients reached CR after first-line treatment in our present investigation. There is evidently a need for new agents to improve the response after first-line treatment and positively affect the prognosis of these patients, even in those who initially attain remission.<sup>26</sup>

Finally, one of the most relevant findings in the present study has been that CD30 was expressed across all subtypes, even though higher median values (>15% of cells) were reported for ALCL (ALK+ and ALK-) and extranodal NK/T PTCL groups; CD30 could also be explored as a potential marker for effectively differentiate PTCL-NOS from its morphological variant,<sup>28,29</sup> the ALK- ALCL. Further, CD30 expression was lower among the higher-risk groups (based on the IPI or PIT scores), although the differences were not significant. Additional prospective studies with larger cohorts are needed to examine the role of this biomarker and to determine whether its expression can be clearly correlated with PTCL subtypes. Despite CD30 expression providing evidence to allow for targeting with specific therapies such as brentuximab vedotin that could be a potential first-line treatment for patients with PTCL,<sup>30,31</sup> in terms of our present study results, CD30 expression could not be considered for prognosis, but remains relevant as a therapeutic target.

The present study provides information on a large number of patients with PTCL in Spain and provides insights into different epidemiological and clinical features that can characterise PTCL subtypes. Despite these strengths, the present study had some limitations. The numbers of patients in some parts of the analysis were low because of missing data, which reduced the number of events considerably in some subcategories. Furthermore, additional tools are needed to better define patient profiles, which would likely result in improved treatment selection and subsequent outcomes.

## Acknowledgements

The authors would like to thank all sites that participated in the study, including Dr María Soledad Fernández (Hospital Universitario Central de Asturias, Oviedo Spain). All participating sites, including the The Biobanco del Complejo Hospitalario Universitario de Santiago de Compostela (C.H.U.S.) provided samples for this study. Medical writing and statistical analysis were performed by Cindy L. Larios MD, and Jordi Curto MSc, respectively, both from MFAR Clinical Research (Barcelona, Spain).

## Conflicts of interest

Socorro Maria Rodriguez-Pinilla, Fina Climent, Joaquin Sanchez, Carlos Perez Seoane, Monica Garcia-Cosio, Oscar Javier Blanco Muñoz, Josep Castellvi, Antonio Martinez Pozo,

Blanca Gonzalez Farre, Carlos Aliste, Ana Julia Gonzalez, Jose Gomez Codina, Empar Mayordomo-Aranda, Belen Navarro, Carmen Bellas, and Juan Jose Borrero have no conflicts of interest to declare. Eva Domingo-Domenech: consulting/advisory (C/A) role for Takeda. Research funding (RF) by Bristol-Myers Squibb (BMS) and Takeda. Travel, accommodations and expenses (TAE) by Takeda, Roche and Janssen. Javier Lopez Jimenez: RF by Gilead, Janssen, Abbvie and Roche. Speaker bureau (SB) for Gilead, Roche, Abbvie, Janssen, MSD and Takeda. Dolores Caballero: C/A for Gilead, Kire, Novartis, Celgene, Janssen; SB for Takeda and Jazz. Cecilia Carpio: SB for Takeda and Celgene; AB: SB for Roche. Sonia Gonzalez de Villambrosia: SB for Janssen and Roche. Miguel A. Piris: C/A for Celgene, Gilead, Janssen, Nanostring and Kyowa Kirin. RF by Gilead and Kura. Advisory board, lecture fees and RF for/by Millenium/Takeda. Guillermo Rodriguez: C/A for Roche, Janssen, Celgene and Takeda. Ana Ruiz-Zorrilla: Former employee of Takeda Farmacéutica España S.A at the time of study design, analyses of study results and manuscript writing. Marta Grande and Carmen Montoto are employees of Takeda Farmacéutica España S.A. Raul Cordoba: SB for Takeda.

## Funding

This study was sponsored by Takeda.

## Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

**Table S1.** Characteristics of first-line treatment for PTCL.

**Table S2.** Cross-reference table comparing local diagnosis and central review diagnosis.

**Table S3.** Treatment characteristics for salvage therapy.

**Table S4.** Prognostic factors and CD30.

## REFERENCES

1. Swerdlow SH, Campo E, Harris NL, Jaffe ES, Pileri SA, Stein H, *et al.*, editors. WHO classification of tumours of haematopoietic and lymphoid tissues. In: Bosman, FT, Jaffe, ES, Lakhani, SR & Ohgaki, H, editors. World Health Organization Classification of Tumours. Lyon, France: IARC; 2008.
2. Swerdlow SH, Campo E, Pileri SA, Harris NL, Stein H, Siebert R, *et al.* The 2016 revision of the World Health Organization classification of lymphoid neoplasms. *Blood*. 2016;**127**:2375–90.
3. The International Non-Hodgkin's Prognostic Factors Project. A predictive model for aggressive non-Hodgkin's lymphoma. The International Non-Hodgkin's Lymphoma Prognostic Factors Project. *N Engl J Med*. 1993;**329**:987–94.
4. Bellei M, Foss FM, Shustov AR, Horwitz SM, Marcheselli L, Kim WS, *et al.* The outcome of peripheral T-cell lymphoma patients failing first line therapy: a report from the prospective, international T-Cell project. *Haematologica*. 2018;**103**:1191–7.
5. Federico M, Bellei M, Marcheselli L, Schwartz M, Manni M, Tarantino V, *et al.* Peripheral T cell lymphoma, not otherwise specified (PTCL-NOS). A new prognostic model developed by the International T cell Project Network. *Br J Haematol*. 2018;**181**:760–9.

6. Dürkop H, Latza U, Hummel M, Eitelbach F, Seed B, Stein H. Molecular cloning and expression of a new member of the nerve growth factor receptor family that is characteristic for Hodgkin's disease. *Cell*. 1992;**68**:421–7.
7. Hu S, Xu-Monette ZY, Balasubramanyam A, Manyam GC, Visco C, Tzankov A, et al. CD30 expression defines a novel subgroup of diffuse large-B cell lymphoma with favorable prognosis and distinct gene expression signature: a report from the International DLBCL Rituximab-CHOP Consortium Program Study. *Blood*. 2013;**121**:2715–24.
8. Chen Z, Guan P, Shan T, Ye Y, Gao L, Wang Z, et al. CD30 expression and survival in extranodal NK/T-cell lymphoma: a systematic review and meta-analysis. *Oncotarget*. 2018;**9**:16547–56.
9. López-Guillermo A, Cid J, Salar A, López A, Montalbán C, Castrillo JM, et al. Peripheral T-cell lymphomas: initial features, natural history, and prognostic factors in a series of 174 patients diagnosed according to the R.E.A.L. classification. *Ann Oncol*. 1998;**9**:849–55.
10. Gutiérrez-García G, García-Herrera A, Cardesa T, Martínez A, Villamor N, Ghita G, et al. Comparison of four prognostic scores in peripheral T-cell lymphoma. *Ann Oncol*. 2011;**23**:397–404.
11. Gallamini A, Stelitano C, Calvi R, Bellei M, Mattei D, Vitolo U, et al. Intergruppo Italiano Linfomi. *Periph T Cell Lymphoma*. 2004;**103**:2474–9.
12. Huang HS, Liao CK, Liu TT, You HL, Wang MC, Huang WT. TP53 mutations in peripheral mature T and NK cell lymphomas: a whole-exome sequencing study with correlation to p53 expression. *Hum Pathol*. 2018;**80**:145–51.
13. Laribi K, Alani M, Truong C, Baugier de Materre A. Recent advances in the treatment of peripheral T-cell lymphoma. *Oncologist*. 2018;**23**:1039–53.
14. Manso R, González-Rincón JJ, Rodríguez-Justo M, Roncador G, Gómez S, Sánchez-Beato M, et al. Overlap at the molecular and immunohistochemical levels between angioimmunoblastic T-cell lymphoma and a subgroup of peripheral T-cell lymphomas without specific morphological features. *Oncotarget*. 2018;**9**:16124–33.
15. de Level L, Savilom E, Longtine J, Ferry JA, Harris NL. Peripheral T-cell lymphoma with follicular involvement and a CD4+/bcl-6+ phenotype. *Am J Surg Pathol*. 2001;**25**:395–400.
16. Schemper M, Smith TL. A note on quantifying follow-up studies of failure time. *Control Clin Trials*. 1996;**17**:343–6.
17. Altman DG, De Stabola BL, Love SB, Stepniwska KA. Review of survival analyses published in cancer journals. *Br J Cancer*. 1995;**72**:511–8.
18. Coiffier B, Brousse N, Peuchmaur M, Berger F, Gisselbrecht C, Bryon PA, et al. Peripheral T-cell lymphomas have a worse prognosis than B-cell lymphomas: a prospective study of 361 immunophenotyped patients treated with the LNH-84 regimen. Groupe d'Etude des Lymphomes Aggressives (GELA). *Ann Oncol*. 1990;**1**:45–50.
19. Savage KJ, Harris NL, Vose JM, Ullrich F, Jaffe ES, Connors JM, et al. International Peripheral T-Cell Lymphoma Project. ALK- anaplastic large-cell lymphoma is clinically and immunophenotypically different from both ALK+ ALCL and peripheral T-cell lymphoma, not otherwise specified: report from the International Peripheral T-Cell Lymphoma Project. *Blood*. 2008;**111**:5496–504.
20. Kleinstern G, Maurer MJ, Liebow M, Habermann TM, Koff JL, Allmer C, et al. History of autoimmune conditions and lymphoma prognosis. *Blood Cancer J*. 2018;**8**:73.
21. William BM, Armitage JO. International analysis of the frequency and outcomes of NK/T-cell lymphomas. *Best Pract Res Clin Haematol*. 2013;**26**:23–32.
22. Siaghani PJ, Song JY. Updates of peripheral T cell lymphoma based on the 2017 WHO classification. *Curr Hematol Malig Rep*. 2018;**13**:25–36.
23. Carson KR, Horwitz SM, Pinter-Brown LC, Rosen ST, Pro B, His ED, et al. A prospective cohort study of patients with peripheral T-cell lymphoma in the United States. *Cancer*. 2017;**123**:1174–83.
24. Machan S, Córdoba R, Carvajal N, Requena L, Piris MÁ, Facchetti F, et al. Atypical histiocytic lesion preceding a peripheral T-cell lymphoma involving the skin exhibiting the same molecular alterations. *Am J Dermatopathol*. 2019;**41**:148–54.
25. Herrera AF, Crosby-Thompson A, Friedberg JW, Abel GA, Czuczman MS, Gordon LI, et al. Comparison of referring and final pathology for patients with T-cell lymphoma in the National Comprehensive Cancer Network. *Cancer*. 2014;**120**:1993–9.
26. Horwitz SM, Zelenetz AD, Gordon LI, Wierda WG, Abramson JS, Advani RH, et al. NCCN Guidelines Insights: Non-Hodgkin's Lymphomas, Version 3.2016. *J Natl Compr Canc Netw*. 2016;**14**:1067–79.
27. d'Amore F, Gaulard P, Trümper L, Corradini P, Kim WS, Specht L, et al. Peripheral T-cell lymphomas: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2015;**26**(Suppl. 5):v108–15.
28. ten Berge RL, Oudejans JJ, Ossenkuppe GJ, Meijer CJ. ALK-negative systemic anaplastic large cell lymphoma: differential diagnostic and prognostic aspects: a review. *J Pathol*. 2003;**200**:4–15.
29. Medeiros LJ, Elenitoba-Johnson KS. Anaplastic large cell lymphoma. *Am J Clin Pathol*. 2007;**127**:707–22.
30. Bossard C, Dobay MP, Parrens M, Lamant L, Missiaglia E, Haioun C, et al. Immunohistochemistry as valuable tool to assess CD30 expression in peripheral T-cell lymphomas: high correlation with mRNA levels. *Blood*. 2014;**124**:2983–6.
31. Bisig B, Gaulard P, de Level L. New biomarkers in T-cell lymphomas. *Baillière's best practice & research. Clin Haematol*. 2012;**25**:13–28.