Supplementary material

MATERIALS AND METHODS

Epstein-Barr virus (EBV) status

EBV-status was determined by immunohistochemical staining to detect EBV latent membrane protein 1 (LMP-1), and/or *in situ* hybridization to detect EBV encoded small RNAs (EBER), as previously described for Danish[1] and Swedish[2] cases. cHL cases containing HRS cells positive for EBV gene products were designated as EBV-positive. Tumor EBV status was available for 385 (99%) patients (Table 1).

Statistical methods

Continuous variables were compared using the Spearman Rank Order Correlation test. To allow for further comparison with the IPS criteria, analyses were restricted to advanced stage patients (IIB-IV) and all the risk factors included in the IPS (age ≥45 years, albumin <40 g/L, WBC >15x10^9/L, hemoglobin <105 g/L, lymphocyte count <0.6x10^9/L, male gender and stage IV) were evaluated. In sensitivity analyses, the cohort was further restricted to only ABVD treated patients (to investigate the prognostic value in a homogenously treated group), and to patients with advanced stage (IIB-IV) or unfavorable limited stage (to investigate all high risk groups). In subgroup analyses, the pooled cohort of Danish and Swedish patients was stratified into a Danish and a Swedish cohort. In line with the definition by the German Hodgkin Study Group[3], unfavorable limited stage was defined as stage I or II with at least one of the following risk factors: large mediastinal tumor (>1/3 maximum transverse thoracic diameter); extranodal involvement; ≥3 lymph node areas

involved; B symptoms and erythrocyte sedimentation rate (ESR) >30 mm/h, or ESR >50 mm/h without B symptoms. We defined bulky tumor as tumor size ≥10 cm, in line with the definition by the German Hodgkin Study Group. In a sub analysis, PD-1 was considered as a continuous variable.

Evaluation of PD-1, PD-L1 and PD-L2 in the tumor microenvironment

To determine the validity of the digital software analysis, the proportions of PD-1, PD-L1 and PD-L2 positive leukocytes in cores from one TMA (cases, n=59) were also manually assessed. There were excellent correlations between manual and digital estimates of the proportions of PD-1 (Spearman rank order correlation R=0.88, p<0.001) and PD-L1 (Spearman rank order correlation R=0.82, p<0.001), and lower correlation for PD-L2 positive leukocytes (Spearman rank order correlation R=0.37, p=0.006) calculated by the software.

RESULTS

Event-free survival

PD-1, PD-L1 and PD-L2 in leukocytes

When year of diagnosis (1990-1998 *versus* 1999-2007) was added to the fully adjusted multivariate model, the results for PD-1 and PD-L1 remained the same; however, patients diagnosed 1990-1998 had an inferior EFS compared to patients diagnosed 1999-2007 in the fully adjusted multivariate model [HR=1.69 (95% CI 1.01-2.84)] (p=0.04).

There were no formal statistically significant interactions between high proportion of PD-1 positive leukocytes and high proportion of PD-L1 positive leukocytes (p=0.89), age (p=0.64),

WBC >15x10^9/L, (p=0.82), or advanced stage (p=0.55), or between high proportion of PD-L1 positive leukocytes and age (p=0.27), WBC >15x10^9/L (p=0.10), or advanced stage (p=0.69).

In fully adjusted multivariate analysis restricted to patients treated with ABVD, high PD-1 leukocyte expression was still significantly associated with shorter EFS [HR=2.00 (95% CI 1.13-3.55)] (p=0.02), while a high proportion of PD-L1 positive leukocytes was not associated with EFS [HR=1.49 (95% CI 0.83-2.68)] (p=0.18).

In an analysis restricted to patients with advanced stage and adjusted for risk factors included in the IPS criteria, a high proportion of PD-1 positive leukocytes was associated with shorter EFS, along with age ≥45 years and WBC >15x10^9/L (sTable 5). However, when PD-L1 was added to this model, neither PD-1 nor PD-L1 were significantly associated with inferior EFS, but the point estimates were both elevated to the level of 1.70 and 1.74, respectively. When the analysis was limited to patients with advanced stage (IIB-IV) as well as unfavorable limited stages, high PD-1 expression continued to be a significant negative prognostic factor for EFS [HR=2.26 (95% CI 1.22-4.21)] (p=0.01) while a high proportion of microenvironmental expression of PD-L1 was not associated with EFS [HR=1.26 (95% CI 0.67-2.38)] (p=0.48).

In subgroup analyses by country, patients with a high proportion of PD-1 positive leukocytes had a shorter EFS compared with patients with low proportion (sFigure 1), represented in univariate analyses by a HR of 3.17 (95% CI 1.36-7.38) (p=0.007) for Swedish patients, and a HR of 1.60 (95% CI 1.00-2.58) (p=0.052) for Danish patients. Patients with a high proportion of PD-L1 positive leukocytes had shorter EFS in Danish patients [HR=1.86 (95% CI 1.15-3.02)] (p=0.01), but not in Swedish patients [HR=1.50 (95% CI 0.58-3.89)] (p=0.41). In age-adjusted

analyses, a high proportion of PD-L1 positive leukocytes was associated with inferior EFS, represented by a HR of 1.74 (95% CI 1.07-2.84) (p=0.03), as well as inferior EFS in the fully adjusted multivariate model [HR=1.81 (95% CI 1.00-3.27)] (p=0.048) for Danish patients. The other country-specific estimates did not reach statistical significance in age-adjusted or full multivariate analyses. When the follow-up was restricted to the first 5 years (when most treatment failures occurred), the association of PD-1 with shorter EFS became slightly stronger in univariate analyses (Sweden: HR=3.76 (95% CI 1.51-9.35) (p=0.004); Denmark: HR=1.87 (95% CI 1.14-3.08) (p=0.01)). The association of PD-L1 with shorter EFS became slightly weaker in univariate analyses (Sweden: HR=1.48 (95% CI 0.51-4.27) (p=0.47); Denmark: HR=1.60 (95% CI 0.96-2.67) (p=0.07)).

When PD-1 was analyzed as a continuous variable, it proved to be associated with inferior EFS in univariate [HR=1.02 (95% CI 1.01-1.03)] (p=0.02), age-adjusted [HR=1.02 (95% CI 1.00-1.03)] (p=0.01), and fully adjusted multivariate analyses [HR=1.02 (95% CI 1.00-1.04)] (p=0.03). In addition, when analyzed on advanced stage patients adjusted for the IPS risk factors, PD-1 was also associated with inferior EFS [HR=1.02 (95% CI 1.00-1.04)] (p=0.03).

Overall survival

PD-1, PD-L1 and PD-L2 in leukocytes

When year of diagnosis (1990-1998 versus 1999-2007) was added to the fully adjusted multivariate model, the results for a high proportion PD-L1 positive leukocytes remained the same, however, patients diagnosed 1990-1998 had an inferior OS compared to patients diagnosed 1999-2007 in the fully adjusted multivariate model [HR=2.99 (95% CI 1.16-7.69)] (p=0.02).

There were no formal statistically significant interactions between high proportion of PD-L1 positive leukocytes and age (p=0.84), albumin <40g/L (p=0.90) and extranodal involvement (p=0.68).

In fully adjusted multivariate analysis restricted to patients treated with ABVD, a high proportion of PD-L1 positive leukocytes was associated with inferior OS with borderline significance [HR=3.21 (95% CI 0.98-10.49)] (p=0.053). When the analysis was limited to patients with advanced stage (IIB-IV) as well as unfavorable limited stages, a high proportion of PD-L1 positive leukocytes was not associated with OS [HR=2.18 (95% CI 0.69-6.90)] (p=0.19). A high proportion of PD-1 positive leukocytes did not predict OS among patients treated with ABVD, nor among patients with advanced or unfavorable limited stage in univariate analyses (Table 3). In an analysis restricted to patients with advanced stage and adjusted for risk factors included in the IPS criteria and country, a high proportion of PD-1 positive leukocytes as well as a high proportion of PD-L1 positive leukocytes had no impact on OS; only age ≥45 years and WBC >$15x10^9$/L were associated with inferior OS (sTable 6).

In subgroup analyses by country, patients with tumors with a high proportion of PD-L1 positive leukocytes was associated with inferior OS compared with patients with a low proportion, represented by a crude HR of 2.31 (95% CI 1.16-4.60) (p=0.02), age-adjusted HR of 2.01 (95% CI 1.00-4.02) (p=0.049), and a fully adjusted multivariate HR of 4.31 (95% CI 1.34-13.84) (p=0.01) for Danish patients. However, the other country-specific estimates regarding high proportion of PD-1 positive leukocytes and high proportion of PD-L1 positive

leukocytes did not reach statistical significance in univariate, age-adjusted or full multivariate analyses.

REFERENCES

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2. Hollander P, Rostgaard K, Smedby KE, et al. Autoimmune and Atopic Disorders and Risk of Classical Hodgkin Lymphoma. *Am J Epidemiol*. 2015;182(7):624-632.
3. Klimm B, Goergen H, Fuchs M, et al. Impact of risk factors on outcomes in early-stage Hodgkin's lymphoma: an analysis of international staging definitions. *Ann Oncol*. 2013;24(12):3070-3076.

Supplementary Table 1. Different cut-offs tested for **microenvironmental expression of PD-1, PD-L1 and PD-L2**, and **HRS expression of PD-L1 and PD-L2**, with the number of cases below, at or above each cut-off, hazard ratios with 95% confidence intervals and p-values for event-free survival (EFS) and overall survival (OS) estimated with Cox proportional hazards regression

	Cut-off (%)	Below cut-off (n)	At or above cut-off (n)	EFS	OS
PD-1	Median (2%)	209	178	**1.43: 1.02-2.01, 0.04**	0.89: 0.57-1.38, 0.59
	75th percentile (5%)	299	88	**1.65: 1.14-2.38, 0.008**	1.29: 0.79-2.11, 0.31
	10%	330	57	**1.91: 1.26-2.88, 0.002**	1.20: 0.66-2.17, 0.55
	15%	353	34	**2.12: 1.30-3.45, 0.003**	1.04: 0.48-2.26, 0.92
	20%	365	22	**2.12: 1.17-3.84, 0.013**	1.55: 0.68-3.58, 0.30
PD-L1 microenvironment	5%	102	280	**1.74: 1.14-2.68, 0.01**	**1.86: 1.04-3.31, 0.04**
	10%	163	219	1.24: 0.87-1.76, 0.22	1.38: 0.87-2.18, 0.16
	Median (12%)	188	194	1.34: 0.95-1.90, 0.09	1.37: 0.88-2.13, 0.17
	15%	215	167	1.35: 0.96-1.90, 0.09	**1.64: 1.05-2.56, 0.03**
	20%	265	117	1.23: 0.85-1.77, 0.28	**1.71: 1.09-2.68, 0.02**
	75th percentile (23%)	287	95	1.24: 0.84-1.82, 0.29	**1.61: 1.00-2.58, 0.05**
PD-L2 microenvironment	75th percentile (1%)	258	121	1.00: 0.69-1.45, 1.00	0.90: 0.55-1.46, 0.66
	2%	304	75	1.05: 0.67-1.62, 0.84	0.98: 0.56-1.70, 0.93
	5%	338	41	1.00: 0.56-1.77, 0.99	1.15: 0.59-2.25, 0.67
	10%	361	18	0.65: 0.24-1.76, 0.36	1.05: 0.38-2.86, 0.93
	15%	368	11	1.14: 0.42-3.10, 0.80	1.82: 0.66-4.99, 0.28
PD-L1 HRS*	5%	194	188	1.01: 0.71-1.42, 0.98	1.02: 0.66-1.59, 0.92
	10%	207	175	1.03: 0.73-1.46, 0.85	1.04: 0.67-1.61, 0.87
	20%	216	166	0.99: 0.70-1.39, 0.94	1.01: 0.65-1.57, 0.96
	50%	251	131	1.02: 0.71-1.46, 0.91	0.97: 0.61-1.54, 0.90
	75th percentile (60%)	283	99	1.01: 0.68-1.50, 0.96	0.77:0.45-1.30, 0.32
	90%	348	34	1.11: 0.61-2.02, 0.73	0.47: 0.17-1.29, 0.14
PD-L2 HRS*	5%	273	106	0.85: 0.57-1.27, 0.43	0.77: 0.45-1.31, 0.33
	75th percentile (10%)	281	98	0.78: 0.52-1.19, 0.25	0.67: 0.38-1.18, 0.15

	20%	303	76	0.90: 0.58-1.41, 0.65	0.69: 0.37-1.28, 0.24
	40%	333	46	0.70: 0.38-1.26, 0.23	0.55: 0.24-1.27, 0.16
	50%	345	34	0.45: 0.20-1.02, 0.06	0.47: 0.17-1.28, 0.14

EFS=Event-free survival, OS=Overall survival, PD-1=programmed death receptor 1, PD-L1=programmed death-ligand 1, PD-L2=programmed death-ligand 2, HRS=Hodgkin Reed-Sternberg

*Median=0%

Supplementary Table 2. Relative risk of an event (progression, discontinuation of treatment, relapse or death due to any cause) estimated as hazard ratios (HR) with 95% confidence intervals (CI) and p-values among classical Hodgkin lymphoma (cHL) patients by putative prognostic factors

Exposure	No.*	Univariate	Age adjusted	Age<45	Age≥45	Stage I-IIA	Stage IIB- IV
PD-1 ≥10% microenvironment	387	**1.91: 1.26-2.88, 0.002**	**1.65: 1.09-2.50, 0.02**	1.70: 0.91-3.18, 0.10	**1.89: 1.08-3.31, 0.02**	1.86: 0.96-3.61, 0.067	**2.30: 1.35-3.92, 0.002**
PD-L1 ≥5% microenvironment	382	**1.74: 1.14-2.68, 0.01**	**1.64: 1.06-2.52, 0.03**	2.01: 1.08-3.75, 0.03	1.45: 0.80-2.63, 0.22	1.60: 0.79-3.23, 0.19	**1.82: 1.05-3.13, 0.03**
PD-L2 ≥5% microenvironment	379	1.00: 0.56-1.77, 0.99	0.98: 0.55-1.74, 0.94	0.90: 0.39-2.08, 0.80	1.00: 0.45-2.19, 1.00	1.01: 0.36-2.83, 0.99	0.94: 0.47-1.89, 0.87
PD-L1 ≥90% HRS	382	1.11: 0.61-2.02, 0.73	1.23: 0.68-2.23, 0.50	1.02: 0.44-2.36, 0.96	1.39: 0.59-3.24, 0.45	0.89: 0.28-2.90, 0.85	1.15: 0.57-2.29, 0.70
PD-L2 ≥50% HRS	379	0.45: 0.20-1.02, 0.06	0.50: 0.22-1.14, 0.10	0.52: 0.19-1.44, 0.21	0.44: 0.11-1.81, 0.26	0.44: 0.11-1.82, 0.26	0.45: 0.17-1.23, 0.12
Age	387	**1.03: 1.02-1.04, <0.001**	**	1.02: 0.99-1.06, 0.12	**1.06: 1.04-1.09, <0.001**	**1.04: 1.02-1.05, <0.001**	**1.03: 1.02-1.04, <0.001**
Stage IIB-IV	386	**1.85: 1.29-2.65, <0.001**	**2.13: 1.48-3.06, <0.001**	**1.93: 1.14-3.26, 0.01**	**2.14: 1.30-3.52, 0.003**	**	**
Male gender	387	1.14: 0.80-1.60, 0.47	1.07: 0.76-1.51, 0.70	1.05: 0.65-1.69, 0.85	1.10: 0.67-1.82, 0.71	0.62: 0.34-1.11, 0.11	**1.60: 1.03-2.48, 0.04**
Nodular sclerosis	386	0.72: 0.48-1.07, 0.11	0.85: 0.56-1.27, 0.42	0.78: 0.43-1.40, 0.40	0.72: 0.42-1.24, 0.24	0.69: 0.35-1.33, 0.26	0.72: 0.44-1.19, 0.21
EBV positive	385	1.08: 0.75-1.56, 0.67	0.96: 0.66-1.38, 0.82	1.05: 0.61-1.79, 0.87	0.94: 0.57-1.55, 0.80	1.63: 0.90-2.93, 0.10	0.89: 0.55-1.43, 0.62
White blood cell count >15x10^9/L	378	1.46: 0.90-2.38, 0.13	**1.86: 1.13-3.04, 0.01**	1.33: 0.68-2.62, 0.40	**2.34: 1.15-4.77, 0.02**	0.72: 0.22-2.35, 0.59	1.65: 0.96-2.85, 0.07
Hemoglobin <105 g/L	377	**1.93: 1.23-3.03, 0.004**	**1.90: 1.21-2.98, 0.006**	1.85: 0.97-3.54, 0.06	**2.01: 1.07-3.79, 0.03**	**4.21: 1.27-13.94, 0.02**	1.43: 0.87-2.36, 0.16
Albumin <40 g/L	341	**1.60: 1.12-2.30, 0.01**	**1.61: 1.12-2.31, 0.01**	1.35: 0.80-2.28, 0.26	**1.91: 1.15-3.18, 0.01**	1.04: 0.49-221, 0.91	1.49: 0.95-2.33, 0.08
ESR ≥50 mm/h	318	1.22: 0.82-1.81, 0.32	1.33: 0.89-1.96, 0.16	1.01: 0.58-1.75, 0.97	**1.86: 1.05-3.29, 0.03**	1.01: 0.39-2.62, 0.98	0.93: 0.58-1.48, 0.76
Lymphocyte count <0,6x10^9/L	350	0.89: 0.36-2.19, 0.80	1.05: 0.43-2.58, 0.91	0.89: 0.28-2.85, 0.85	1.01: 0.25-4.16, 0.99	1.14: 0.16-8.27, 0.90	0.70: 0.26-1.92, 0.49
Bulky tumor	366	1.34: 0.92-1.95,	**1.56: 1.08-2.30, 0.02**	1.44: 0.87-2.39,	1.45: 0.82-2.54,	0.85: 0.38-1.93,	1.33: 0.86-2.06,

		0.13		0.16	0.20	0.70	0.20
B-symptoms	385	**1.61: 1.14-2.28, 0.007**	**1.70: 1.21-2.41, 0.003**	1.59: 0.98-2.58, 0.06	1.60: 0.98-2.63, 0.06	1.73: 0.83-3.60, 0.14	1.01: 0.61-1.66, 0.99
Extranodal involvement	384	**2.11: 1.14-3.94, 0.02**	**2.15: 1.15-4.00, 0.02**	1.41: 0.51-3.87, 0.51	**2.87: 1.29-6.37, 0.01**	**7.66: 1.81-32.33, 0.006**	1.43: 0.71-2.86, 0.32
Bone marrow involvement	109	1.30: 0.31-5.45, 0.72	0.77: 0.18-3.35, 0.73	***	1.90: 0.41-8.67, 0.41	***	0.96: 0.22-4.09, 0.96

PD-1=programmed death receptor 1, PD-L1=programmed death-ligand 1, PD-L2=programmed death-ligand 2, HRS=Hodgkin Reed-Sternberg, EBV=Epstein-Barr virus, ESR=Erythrocyte sedimentation rate, L=Liter, g=Gram, mm=Millimeter, h=Hour

*Number of cases with information enabling evaluation of event-free survival

**Not applicable

***Too few cases

Supplementary table 3. Relative risk of death due to any cause estimated as hazard ratios (HR) with 95% confidence intervals (CI) and p-values among classical Hodgkin lymphoma (cHL) patients by putative prognostic factors

Exposure	No.*	Univariate	Age adjusted	Age<45	Age≥45	Stage IA-IIA	Stage IIB- IV
PD-1 ≥10% microenvironment	387	1.20: 0.66-2.17, 0.55	1.01: 0.56-1.83, 0.98	0.55: 0.13-2.34, 0.42,	1.28: 0.66-2.50, 0.46	0.80: 0.28-2.33, 0.69	1.69: 0.83-3.47, 0.15
PD-L1 ≥5% microenvironment	382	**1.86: 1.04-3.31, 0.04**	1.58: 0.89-2.83, 0.12	2.32: 0.80-6.75, 0.12	1.51: 0.76-3.01, 0.24	3.29: 0.99-10.96, 0.052	1.44: 0.74-2.79, 0.29
PD-L2 ≥5% microenvironment	379	1.15: 0.59-2.25, 0.67	1.10: 0.57-2.16, 0.76	1.50: 0.51-4.36, 0.46	0.94: 0.40-2.21, 0.89	1.54: 0.53-4.51, 0.43	0.94: 0.40-2.20, 0.89
PD-L1 ≥90% HRS	382	0.47: 0.17-1.29, 0.14	0.47: 0.17-1.30, 0.15	0.37: 0.05-2.71, 0.32	0.47: 0.15-1.53, 0.21	0.37: 0.05-2.71, 0.33	0.50: 0.16-1.62, 0.25
PD-L2 ≥50% HRS	379	0.47: 0.17-1.28, 0.14	0.62: 0.23-1.72, 0.36	0.61: 0.14-2.57, 0.50	0.54: 0.13-2.34, 0.40	0.77: 0.18-3.27, 0.73	0.34: 0.08-1.38, 0.13
Age	387	**1.06: 1.05-1.08, <0.001**	**	**1.07: 1.02-1.13, 0.006**	**1.10: 1.06-1.13, <0.001**	**1.09: 1.06-1.11, <0.001**	**1.06: 1.05-1.08, <0.001**
Stage IIB-IV	386	**1.77: 1.11-2.83, 0.02**	**2.39: 1.48-3.84, <0.001**	2.00: 0.84-4.76, 0.11	**2.31: 1.32-4.06, 0.004**	**	**
Male gender	387	1.48: 0.94-2.35, 0.09	1.40: 0.89-2.20, 0.14	**1.49: 0.68-3.29, 0.32**	1.25: 0.71-2.20, 0.43	1.35: 0.61-2.99, 0.45	1.55: 0.88-2.72, 0.13
Nodular sclerosis	386	0.68: 0.41-1.13, 0.14	0.93: 0.55-1.56, 0.79	1.70: 0.51-5.67, 0.39	**0.54: 0.30-0.96, 0.04**	0.57: 0.25-1.31, 0.19	0.73: 0.38-1.39, 0.34
EBV positive	385	1.36: 0.86-2.16, 0.19	1.08: 0.68-1.72, 0.75	1.31: 0.56-3.03, 0.53	1.09: 0.62-1.90, 0.77	2.13: 0.99-4.60, 0.054	1.12: 0.61-2.03, 0.72
White blood cell count, >15x10^9/L	378	**1.91: 1.07-3.40, 0.03**	**3.31: 1.83-6.00, <0.001**	2.30: 0.92-5.77, 0.08	**2.88: 1.34-6.19, 0.007**	1.45: 0.43-4.83, 0.55	1.87: 0.96-3.65, 0.07
Hemoglobin <105 g/L	377	1.36: 0.72-2.57, 0.35	1.33: 0.70-2.53, 0.38	1.58: 0.54-4.60, 0.40	1.26: 0.57-2.80, 0.57	1.27: 0.17-9.38, 0.82	1.11: 0.56-2.23, 0.76
Albumin <40 g/L	341	**2.05: 1.28-3.29, 0.003**	**2.01: 1.25-3.24, 0.004**	**2.85: 1.19-6.82, 0.02**	1.68: 0.95-2.97, 0.08	1.15: 0.45-2.96, 0.77	**2.16: 1.17-3.98, 0.01**
ESR ≥50 mm/h	318	1.41: 0.85-2.34, 0.18	**1.67, 1.00-2.78, 0.048**	1.64: 0.69-3.85, 0.26	1.50: 0.79-2.83, 0.21	1.34: 0.45-3.96, 0.60	1.22: 0.65-2.30, 0.54
Lymphocyte count <0,6x10^9/L	350	0.83: 0.26-2.64, 0.75	0.94: 0.30-3.00, 0.92	1.75: 0.41-7.47, 0.45	0.39: 0.05-2.85, 0.35	**	0.89: 0.28-2.86, 0.84
Bulky tumor	366	1.36: 0.84-2.21,	**1.93: 1.18-3.15,**	2.04: 0.91-4.55,	1.44: 0.77-2.67,	1.10: 0.41-2.96,	1.27: 0.72-2.24,

		0.21	**0.009**	0.08	0.25	0.85	0.40
B-symptoms	385	**2.25: 1.41-3.58, <0.001**	**2.46: 1.54-3.93, <0.001**	**4.09: 1.64-10.20, 0.002**	1.70: 0.98-2.96, 0.06	**3.55: 1.54-8.19, 0.003**	1.52: 0.74-3.11, 0.26
Extranodal involvement	384	**2.82: 1.40-5.66, 0.004**	**2.06: 1.02-4.13, 0.04**	**5.81: 1.96-17.19, 0.001**	1.32: 0.52-3.32, 0.56	3.14: 0.42-23.47, 0.26	**2.30: 1.08-4.91, 0.03**
Bone marrow involvement	109	1.89: 0.44-8.07, 0.39	0.60: 0.13-2.69, 0.50	***	1.93: 0.43-8.69, 0.39	***	1.79: 0.40-8.01, 0.45

PD-1=programmed death receptor 1, PD-L1=programmed death-ligand 1, PD-L2=programmed death-ligand 2, HRS=Hodgkin Reed-Sternberg, EBV=Epstein-Barr virus, ESR=Erythrocyte sedimentation rate, L=Liter, g=Gram, mm=Millimeter, h=Hour

*Number of cases with information enabling evaluation of overall survival

**Not applicable

***Too few cases

Supplementary table 4. Correlation of PD-1, PD-L1 and PD-L2 to one another and other leukocytes, Spearman correlation coefficient and p-value

	PD-1 microenvironment	PD-L1 microenvironment	PD-L2 microenvironment	PD-L1 HRS
PD-L1 microenvironment	0.094, 0.07	-	-	-
PD-L2 microenvironment	0.07, 0.17	**0.30, <0.001**	-	-
PD-L1 HRS	-0.04, 0.48	**0.48, <0.001**	**0.23, <0.001**	-
PD-L2 HRS	0.06, 0.26	**0.33, <0.001**	**0.44, <0.001**	**0.43, <0.001**

PD-1=programmed death receptor 1, PD-L1=programmed death-ligand 1, PD-L2=programmed death-ligand 2, HRS=Hodgkin Reed-Sternberg
*Analyzed on Swedish cohort only (n=128)

Supplementary Table 5. Relative risk of an event (progression, discontinuation of treatment, relapse or death due to any cause) estimated as hazard ratios (HR) with 95% confidence intervals (CI) and p-values among classical Hodgkin lymphoma (cHL) patients with advanced stage (IIB-IV) by putative prognostic factors

Exposure	No.*	Univariate	Age adjusted	Multivariate**
PD-1 ≥10% microenvironment	208	**2.30: 1.35-3.92, 0.002**	**1.88: 1.10-3.23, 0.02**	**1.80: 1.02-3.17, 0.04**
Age ≥45 years	208	**2.46: 1.62-3.75, <0.001**	***	**2.37: 1.43-3.91, <0.001**
Stage IV	207	1.21: 0.73-2.00, 0.47	1.09: 0.66-1.82, 0.74	1.09: 0.63-1.90, 0.76
Male gender	208	**1.60: 1.03-2.48, 0.04**	1.54: 0.99-2.38, 0.054	1.48: 0.91-2.40, 0.11
White blood cell count >15x10^9/L	203	1.65: 0.96-2.85, 0.07	1.93: 1.11-3.34, 0.02	**1.94: 1.06-3.54, 0.03**
Hemoglobin <105 g/L	203	1.43: 0.87-2.36, 0.16	1.27: 0.76-2.10, 0.36	1.12: 0.63-2.00, 0.68
Albumin <40 g/L	185	1.49: 0.95-2.33, 0.08	1.25: 0.79-1.97, 0.34	1.22: 0.71-2.09, 0.47
Lymphocyte count <0,6x10^9/L	188	0.70: 0.26-1.92, 0.49	0.79: 0.29-2.16, 0.65	1.03: 0.36-2.94, 0.95
Country (Sweden)	208	0.79: 0.50-1.29, 0.30	0.84: 0.53-1.32, 0.45	0.92: 0.54-1.59, 0.77

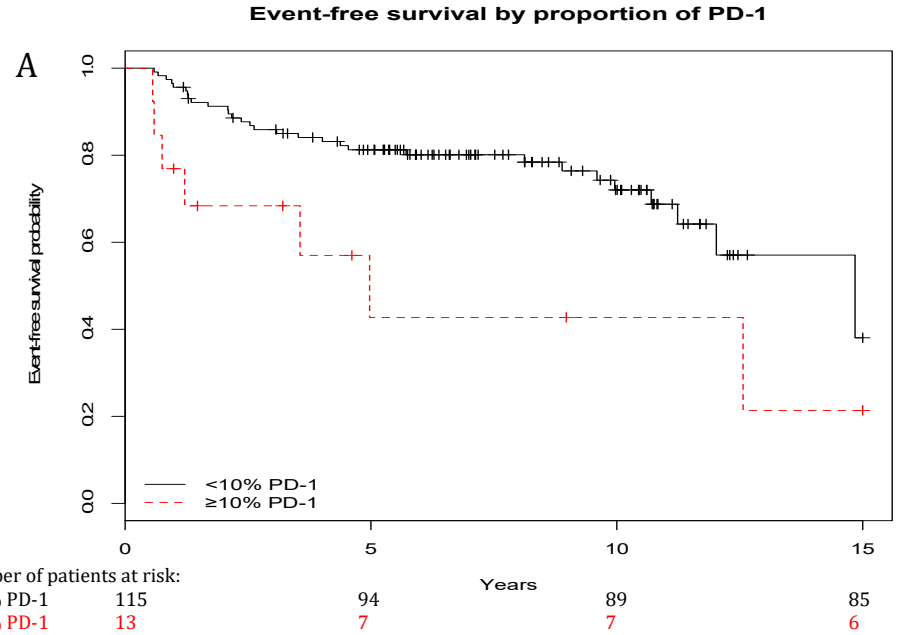
PD-1=Programmed death receptor 1, L=liter, g=gram, mm=millimeter, h=hour
*Number of cases with information enabling evaluation of event-free survival
**For the multivariate model, all factors were included (PD-1, age, stage, male gender, white blood cell count, hemoglobin, albumin, lymphocyte count and country)
***Not applicable

Supplementary Table 6. Relative risk of death due to any cause estimated as hazard ratios (HR) with 95% confidence intervals (CI) and p-values among classical Hodgkin lymphoma (cHL) patients with advanced stage (IIB-IV) by putative prognostic factors

Exposure	**No.***	**Univariate**	**Age adjusted**	**Multivariate****
PD-1 ≥10% microenvironment	208	1.69: 0.83-3.47, 0.15	1.41: 0.68-2.90, 0.35	1.58: 0.74-3.38, 0.24
PD-L1 ≥5% microenvironment	206	1.44: 0.74-2.79, 0.29	1.31: 0.67-2.55, 0.43	1.31: 0.60-2.87, 0.50
Age ≥45 years	208	5.80: 3.29-10.22, <0.001	***	**5.58: 2.81-11.04, <0.001**
Stage IV	207	1.41: 0.75-2.64, 0.28	0.92: 0.48-1.73, 0.79	0.92: 0.46-1.85, 0.81
Male gender	208	1.55: 0.88-2.72, 0.13	1.47: 0.84-2.58, 0.18	1.29: 0.68-2.46, 0.44
White blood cell count >15x10^9/L	203	1.87: 0.96-3.65, 0.07	**2.59: 1.30-5.16, 0.007**	**2.16: 1.01-4.62, 0.048**
Hemoglobin <105 g/L	203	1.11: 0.56-2.23, 0.76	0.81: 0.40-1.63, 0.56	0.75: 0.35-1.59, 0.45
Albumin <40 g/L	185	**2.16: 1.17-3.98, 0.01**	1.42: 0.76-2.66, 0.27	1.65: 0.79-3.42, 0.18
Lymphocyte count <0,6x10^9/L	188	0.89: 0.28-2.86, 0.84	0.79: 0.25-2.55, 0.70	1.33: 0.37-4.72, 0.66
Country (Sweden)	208	0.68: 0.38-1.21, 0.19	0.73: 0.41-1.31, 0.30	0.80: 0.39-1.66, 0.55

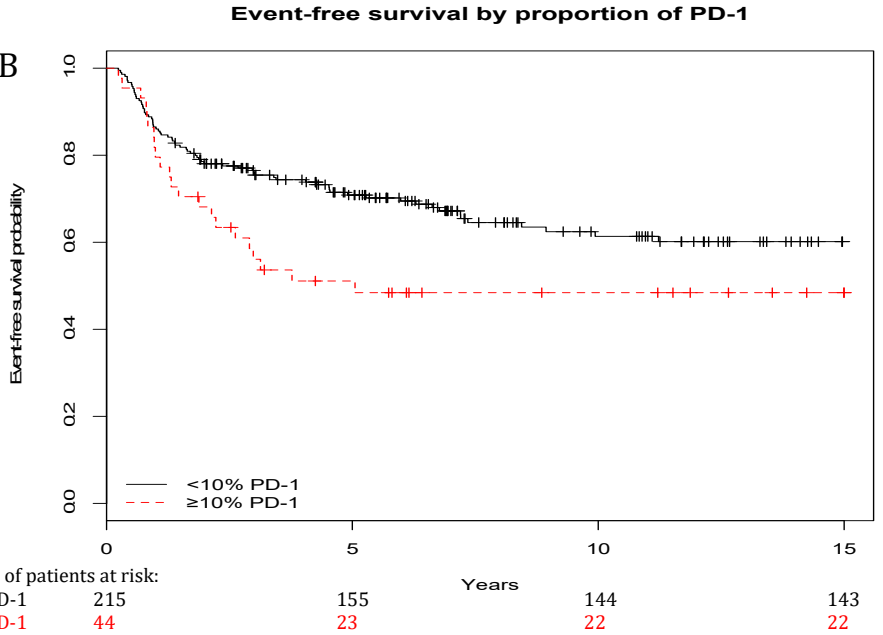
PD-1=Programmed death receptor 1, PD-L1=programmed death-ligand 1, L=liter, g=gram, mm=millimeter, h=hour
*Number of cases with information enabling evaluation of overall survival
**For the multivariate model, all factors were included (PD-1, PD-L1, age, stage, male gender, white blood cell count, hemoglobin, albumin, lymphocyte count and country)
***Not applicable

Supplementary Figure 1. Kaplan-Meier estimates for survival according to ≥10% (red, dashed line) PD-1 and <10% (black, solid line) PD-1 expressing leukocytes for: EFS for Swedish (A) and Danish (B) patients (log-rank p value=0.005 and 0.05 respectively), and OS for Swedish (C) and Danish (D) patients (log-rank p value=0.66 and 0.78 respectively).



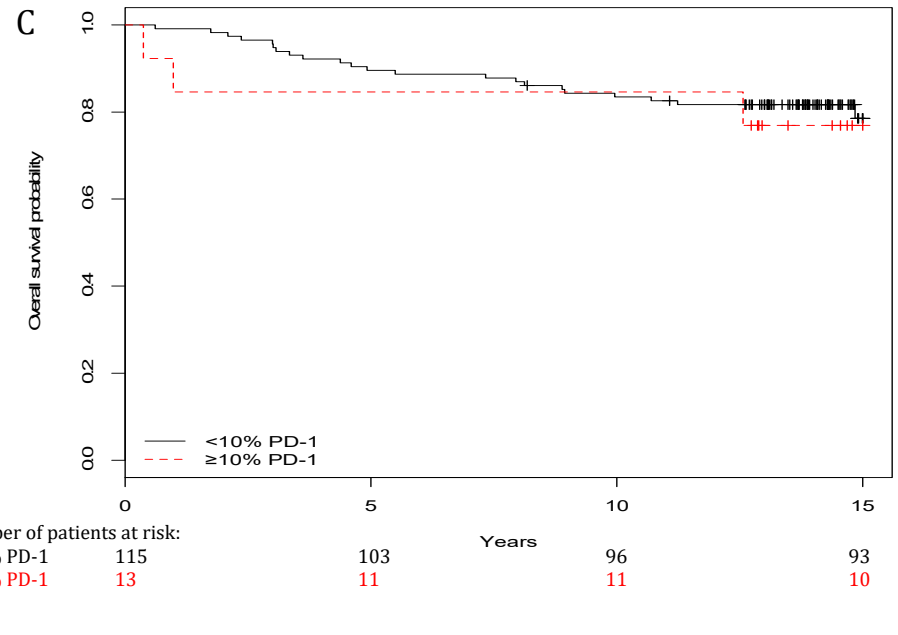
Number of patients at risk:

<10% PD-1	115	94	89	85
≥10% PD-1	13	7	7	6



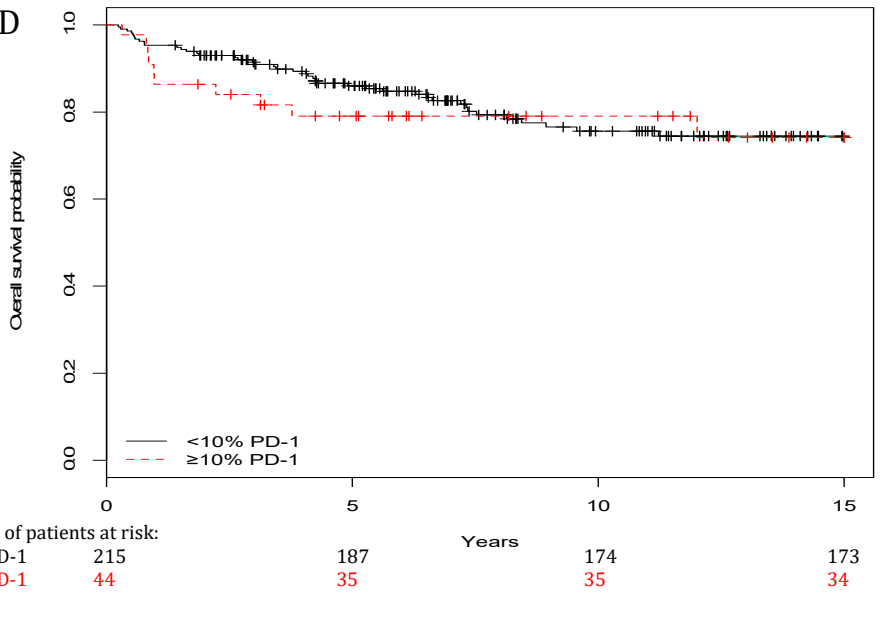
Number of patients at risk:

<10% PD-1	215	155	144	143
≥10% PD-1	44	23	22	22



Number of patients at risk:

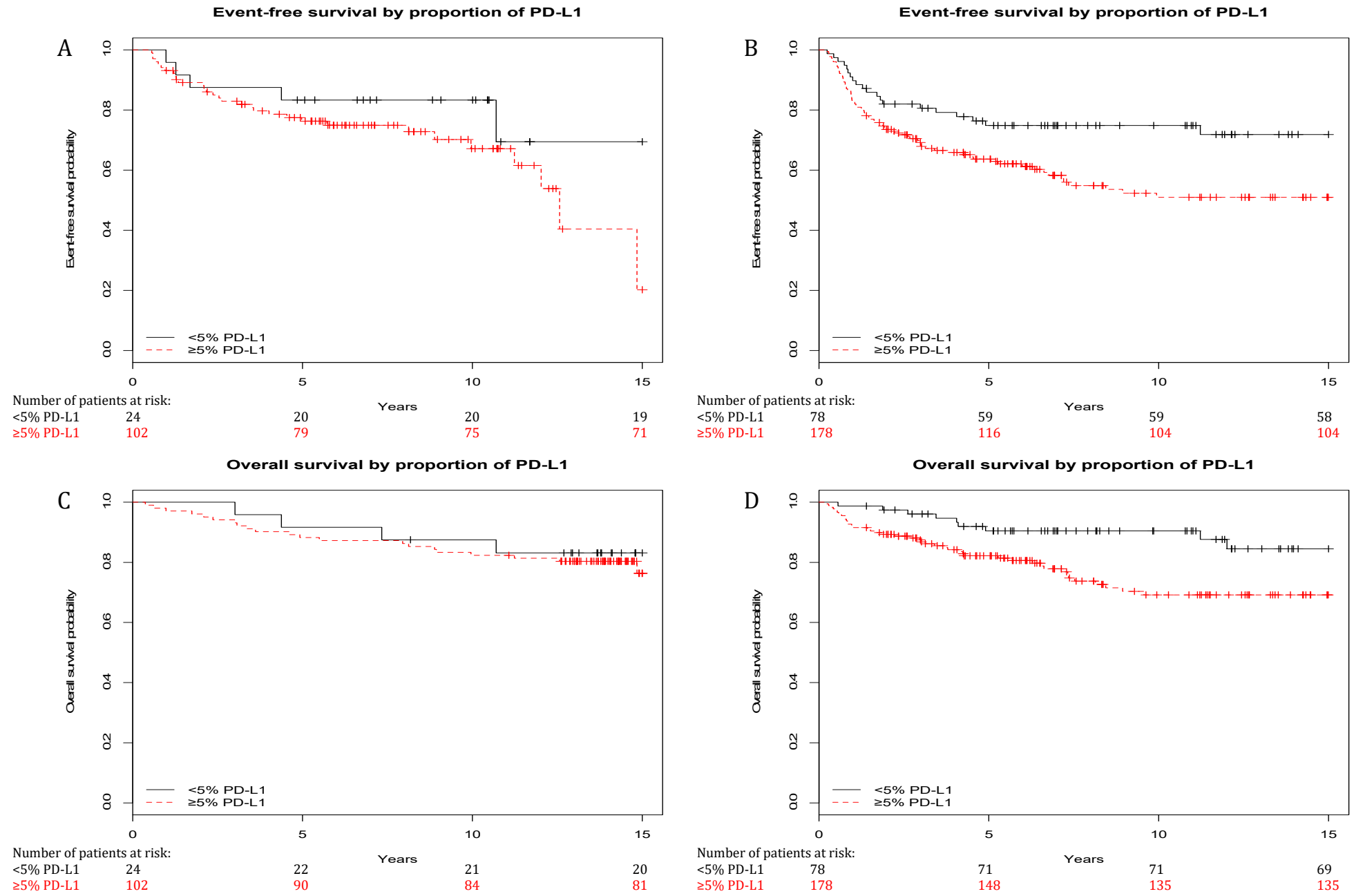
<10% PD-1	115	103	96	93
≥10% PD-1	13	11	11	10



Number of patients at risk:

<10% PD-1	215	187	174	173
≥10% PD-1	44	35	35	34

Supplementary Figure 2. Kaplan-Meier estimates for survival according to ≥5% (red, dashed line) PD-L1 and <5% (black, solid line) PD-L1 expressing leukocytes for: EFS for Swedish (A) and Danish (B) patients (log-rank p value=0.40 and 0.01 respectively), and OS for Swedish (C) and Danish (D) patients (log-rank p value=0.67 and 0.01 respectively).



Supplementary Figure 3. Boxplots of distribution of proportions of PD-1 (A), PD-L1 (B) and PD-L2 (C) positive leukocytes