Supplement Table 1 Description of clinical trials [a]

Group/Study Name	Years accrual	Patients in trial (model)[a]	Stages in trial (model)[c]	Ages in trial (model)[d]	Trial design
GITIL HD0607	2008-2014	782 (736)	IIB, III, IV (IIB, III, IV)	18-60y (18-60y)	ABVD x 2, then PET: • If PET negative, ABVD x 4, randomize RT vs no RT (n=629 of which 148 received RT) • If PET positive, escBEACOPP x 4 + BEACOPP x 4 +/- rituximab (n=149)
UK RATHL	2008 - 2012	1 203 (909)	IIA, IIB, III, IV (IIB, III, IV)	≥18y (18-65y)	ABVD x 2, then PET: • If PET negative, randomize to ABVD x 4 (n=470) vs. AVD x 4 (n=465) • If PET positive, escBEACOPP x 4 or BEACOPP14 x 6 (n=172)
SWOG0816	2009 - 2012	336 (322)	III, IV (III, IV)	18-60y (18-60y)	ABVD x 2, then PET: • If PET negative, ABVD x 4 (n=270) • If PET positive, escBEACOPP x 6 (n=55)

Abbreviations: ABVD, Adriamycin, bleomycin, vinblastine, dacarbazine; BEACOPP, bleomycin, etoposide, Adriamycin, cyclophosphamide, vincristine, procarbazine and prednisone; esc, escalated; PET, positron emission tomography.

[a] Each clinical trial is represented by at least one of the co-authors of this manuscript (GITIL HD0607: AG; SWOG0816: DS, JF; UK RATHL: PMJ).

[b]Number of eligible patients in the original trial cohort and number of patients included in this analytic cohort based on our inclusion/exclusion criteria in parenthesis.

[c]Stages included in the original trial cohort and stages included in this analytic cohort

[d]Ages included in the original trial cohort and stages included in this analytic cohort

Supplement Table 2 Study population and outcomes by clinical trial[a]

	GITIL HD0607, n=736	SWOG0816, n=322	UK RATHL, n=909
Age (years), mean (SD)	33.7 (10.8)	34.8 (11.3)	35.7 (13.2)
Age (years), median (IQR)	31.0 (25.0-41.0)	31.9 (25.5-42.6)	33.0 (24.0-45.0)
Female sex, n (%)	380 (51.6%)	141 (43.8%)	404 (44.4%)
Stage, n (%)			
IIB	266 (36.1%)	0 (0.0%)	282 (31.0%)
III	235 (31.9%)	169 (52.5%)	318 (35.0%)
IV	235 (31.9%)	153 (47.5%)	309 (34.0%)
B symptoms, n (%)	598 (81.3%)	199 (61.8%)	667 (73.4%)
Histology, n (%)			
Lymph Depleted	12 (1.6%)	3 (0.9%)	1 (0.1%)
Lymph Rich	22 (3.0%)	6 (1.9%)	14 (1.5%)
Mixed Cellularity	104 (14.1%)	29 (9.0%)	103 (11.3%)
Nodular Sclerosis	597 (81.1%)	205 (63.7%)	603 (66.3%)
NOS or unknown cHL subtype	1 (0.1%)	79 (24.5%)	188 (20.7%)
Bulky disease [b]	145 (19.7%)	62 (19.3%)	285 (31.6%)
WBC count (10^3/uL), mean (SD)	11.5 (5.1)	10.9 (4.9)	11.0 (5.3)
Lymphocyte count (10^3/uL), mean (SD)	1.5 (0.7)	1.3 (0.7)	1.4 (0.7)
Hemoglobin (g/dL), mean (SD)	12.1 (1.8)	11.7 (2.0)	12.0 (1.8)
Albumin (g/dL), mean (SD)	3.7 (0.6)	3.7 (0.6)	3.8 (0.6)
ESR (mm/hr), mean (SD)	NA (NA)	61.4 (35.2)	56.4 (36.0)
A-HIPI probability of event, mean (SD)	21.9 (5.9)	24.7 (6.4)	23.0 (6.8)
A-HIPI probability of event-free, mean (SD)	78.1 (5.9)	75.3 (6.4)	77.0 (6.8)
Outcomes			
Follow-up in months, median (IQR)[c]	43 (35, 49)	60 (53, 60)	60 (50, 60)
Treatment failure by 5 years, (%)	129 (18%)	67 (21%)	155 (17%)
Deaths by 5 years, (%)	30 (4.1%)	15 (4.7%)	43 (4.7%)

Abbreviations: ESR, erythrocyte sedimentation rate; IQR=interquartile range; NOS, not otherwise specified; SD, standard deviation; WBC, white blood cell.

[a] Number of patients by trial and registry refer to the subset of patients who met the eligibility criteria for the analytic cohort (***Figure S1***).

[b] Bulk disease defined according to each trial (any mass ≥10 cm for GITIL HD0607 and SWOG0816; >1/3 thoracic diameter for mediastinal mass or >10cm for non-mediastinal mass for UK RATHL)

[c] Follow-up truncated at 5 years

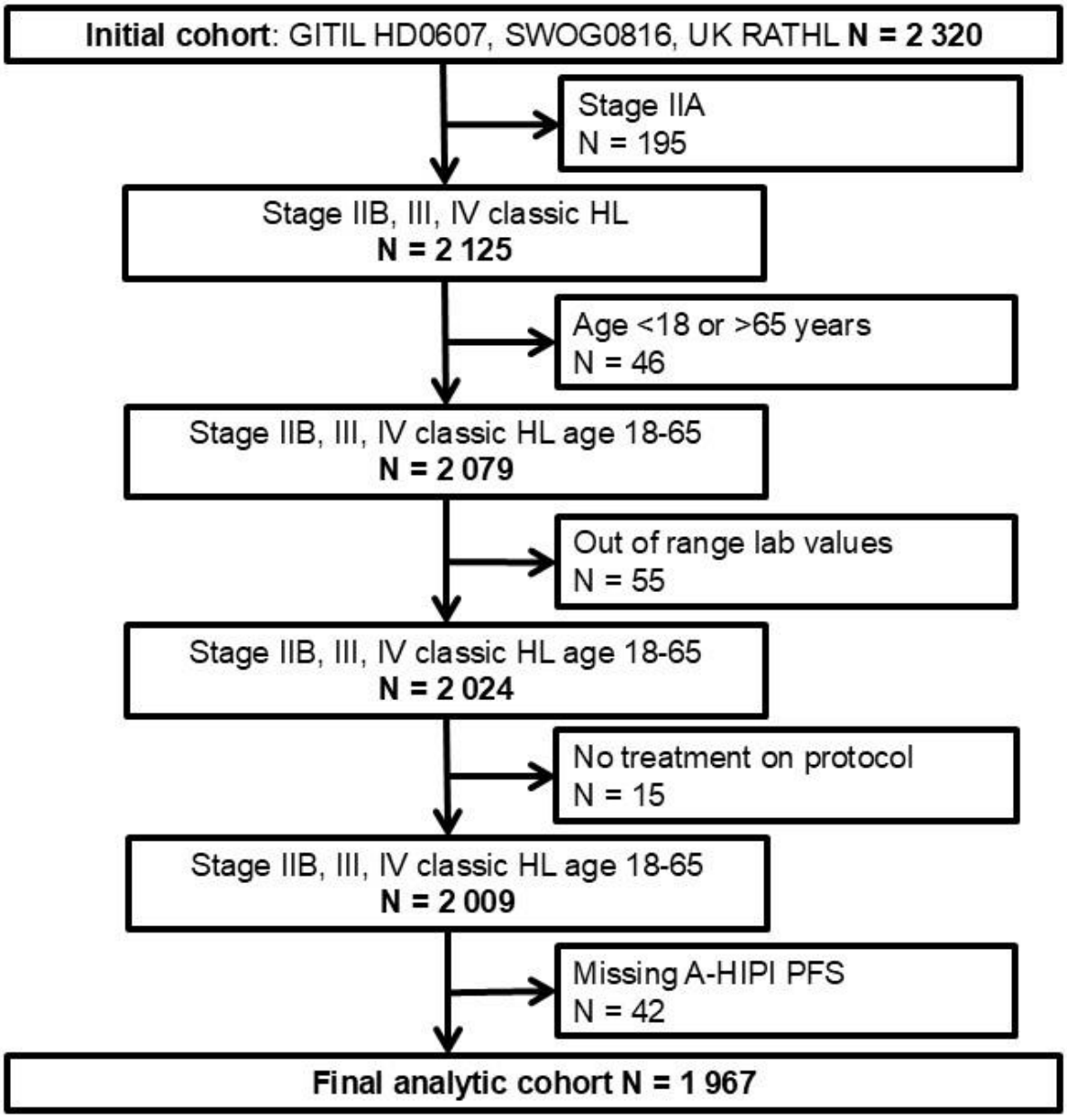
Missingness: 852 missing ESR overall, missingness for rest of variables is <10

Supplement Table 3 Description of censoring across MSM states

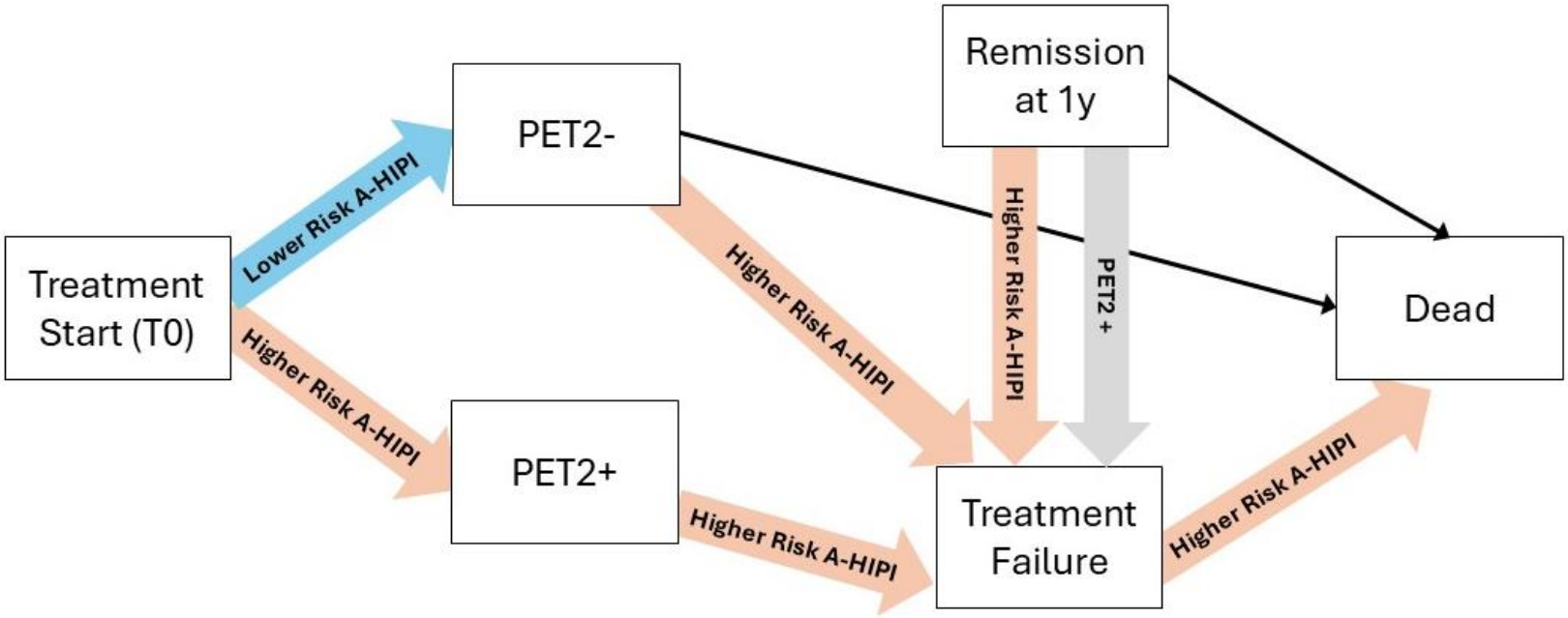
Censoring state	N	Description
Treatment start (T0)	57	• Censoring occurred when patients were lost to follow-up without a PET2 result or an event by 60 days • 46 (80.7%) were censored at 60 days • Among remaining 11 (19.3%) patients, median time to censoring was 43 days (IQR=18-54)
PET2-	34	• Censoring occurred when patients were lost to follow-up without having an event by 1 year or did not achieve remission at 1 year • 0 patients were censored at 365 days • Median time to censoring was 210 days (IQR=133-264)
PET2+	24	• Censoring occurred when patients were lost to follow-up without having an event by 1 year or did not achieve remission at 1 year • 5 (20.8%) were censored at 365 days • Among remaining 19 (79.2%) patients, median time to censoring was 156 days (IQR=89-216)
Remission at 1 year	1 483	• Censoring occurred when patients were lost to follow-up or if no event occurred by 5 years. • Median time to censoring was 1826 days (IQR=1 330-1 826)
Treatment failure	281	• Censoring occurred when patients were lost to follow-up or if they had not died by 5 years. • Median time to censoring was 1 826 days (IQR=1 297-1 826)

IQR=interquartile range

Supplement Figure 1 Flow diagram for analytic cohort



Supplement Figure 2 Prognostic significance of A-HIPI and PET2 throughout disease course based on MSM



Results based on multivariable multistate model (Table 2). Transitions without arrows were not modeled (Figure 1). Colored arrows represent variables that were significantly associated with that transition at $p<0.5$. Orange arrows show patients with higher risk A-HPI scores had a higher rate of making that transition; blue arrows show patients with lower risk A-HPI scores had a higher rate of making that transition; and grey arrows show patients with PET2 positive had a higher rate of making that transition compared to those with PET2 negative.