Supporting Information

Supporting information include the following contents:

1) Supplementary Doc. S1: JCOG1305 Patient Selection Criteria
2) Supplementary Doc. S2: JCOG1305 Details of PET imaging standardization/quality assurance and interim PET central judgment
3) Supplementary Table S1: ABVD therapy (Induction ABVD, Additional ABVD) and Escalated BEACOPP therapy
4) Supplementary Table S2: JCOG1305 Investigators and number of enrolled patients
5) Supplementary Table S3: Summary of SWOG S0816 and JCOG1305
6) Supplementary Fig. S1: Study design of JCOG1305
7) Supplementary Fig. S2: Central PET2 judgement time
8) Supplementary Fig. S3: Progression-free survival stratified by clinical stage
9) Supplementary Fig. S4A and S4B: Progression-free survival stratified by interim-PET Deauville scale score
10) Supplementary Fig. S5A and S5B: Progression-free survival stratified by interim-PET Deauville scale score in patients confirmed by central pathology review
11) Supplementary Figure Legends

Supplementary Doc. S1

JCOG1305

Patient Selection Criteria

Patients satisfying all of the following eligibility criteria and no exclusion criteria shall be considered eligible for study enrollment.

Eligibility criteria (inclusion criteria)

1) Patients whose condition was diagnosed histopathologically via biopsy as classical Hodgkin lymphoma (CHL) (nodular sclerosis CHL, mixed cellularity CHL, lymphocyte-depletion CHL, or lymphocyte-rich CHL: WHO classification (2008)).

2) Patients whose condition falls under one of the following Ann Arbor staging classifications, based on a whole-body contrast CT examination*1 or PET (or PET/CT)*2 within 28 days prior to enrollment

① Stage III or Stage IV.

② Any Stage IIB case in which a bulky mediastinal mass (a bulky mediastinal mass is defined as a mediastinal lesion with a maximum diameter greater than 1/3 of the maximum intrathoracic diameter or 10 cm or more on CT (transverse sectional image)), or continuous infiltration into extralymphatic organs in contact with nodal lesions is observed.

*1 Diagnosis via simple CT is also possible for patients with a history of allergies to contrast agents, bronchial asthma, or renal dysfunction.

*2 In principle PET (or PET/CT) is performed prior to treatment, but if PET (or PET/CT) cannot be performed before treatment administration for medical reasons, this procedure can be omitted. The reason(s) for omission must be described in the accompanying CRF.

3) No central nervous system lesions are observed (pre-enrollment cerebrospinal fluid testing and cerebral contrast MRI are not required).

4) The prospective subject’s age at the time of enrollment is between 20 and 60 years.

5) Performance status (PS) is 0-2 in the ECOG criteria (PS must be recorded in his/her medical charts).

6) Lesions must be measurable.

A measurable lesion is defined as a lesion that satisfies each of the 3 following criteria:

① Lymph nodes diagnosed as containing lymphoma lesions (nodal lesions), or lesions of extralymphatic organs (extranodal lesions), by either diagnostic imaging, biopsy pathological diagnosis, or cytological testing.
② Clearly measurable in two orthogonal directions in CT cross-sectional imaging.
③ Diameter of 1.5 cm or more on CT cross-sectional imaging.
7) Patient has no history of receiving either chemotherapy or radiotherapy, including treatments for other types of cancer. Whether the patient has a history of receiving hormone therapy is not relevant.
8) The most recent test values from within 14 days prior to enrollment (results from up to two weeks prior to the enrollment date are acceptable) satisfy each of the following:
① Number of neutrophils (ANC (Absolute Neutrophil Count (ANC) ≥ 1,000/mm3
② Platelet count ≥ 10 × 104/mm3
③ Total bilirubin ≤ 2.0 mg/dL
④ AST (GOT) ≤ 150 U/L
⑤ ALT (GPT) ≤ 150 U/L
⑥ Serum creatinine ≤ 1.6 mg/dL (men), serum creatinine ≤ 1.2 mg/dL (women)
⑦ Fasting blood glucose ≤ 150 mg/dL (if the blood glucose value is only occasionally lower than 150 mg/dL, the patient achieves eligibility without confirmation of whether the fasting blood glucose value ≤ 150 mg/dL)
⑧ PaO2 ≥ 70 torr (room air)
9) No ischemic changes, atrial fibrillation, or ventricular arrhythmia requiring treatment were observed based on the most recent 12-lead electrocardiogram (ECG) examination, performed within 28 days prior to enrollment (the same day as four weeks before the registration day is acceptable).
10) Left ventricular ejection fraction was ≥ 50%, according to the most recent ECG that was performed within 28 days prior to enrollment (the same day as four weeks before the registration day is acceptable).
11) Patient consent to participation has been submitted in writing.

Exclusion criteria

1) Patients with multiple active cancers (multiple concurrent/multifocal cancers with a disease-free period of five years or less. However, even though

the clinical disease-free period is five years or less, this does not include Stage I prostate cancer or a history(ies) of radically-resected cancers of the following pathological stages:
gastric cancer (adenocarcinoma (general type)): Stage 0-Stage I; colon cancer (adenocarcinoma): Stage 0 – Stage I; rectal cancer (adenocarcinoma): Stage 0 – Stage I; esophageal cancer (squamous cell carcinoma, adenosquamous carcinoma, basal cell carcinoma): stage 0; breast cancer (noninvasive ductal carcinoma, noninvasive lobular carcinoma): Stage 0; breast cancer (invasive ductal carcinoma, invasive lobular carcinoma, Paget's disease): Stage 0-Stage IIA; endometrial cancer (endometrioid adenocarcinoma, mucinous adenocarcinoma): Stage I; prostate cancer (adenocarcinoma): Stage I – Stage II; cervical cancer (squamous cell carcinoma): Stage 0; thyroid cancer (papillary carcinoma, follicular carcinoma): Stage I, Stage II, Stage III; renal cancer (clear cell carcinoma, chromophobe cell carcinoma): Stage I).

2) Have an infection that requires systemic treatment.

3) Women who are pregnant, may become pregnant, are 28 days or less postpartum, or are currently breastfeeding.

4) Patients presenting with psychosis or whose condition is complicated by psychiatric symptoms that result in the determination that study participation will be difficult.

5) Patients receiving continuous systemic administration of steroids or other immunosuppressants (oral or intravenous).

6) Patients who must continue use of insulin for diabetes during treatment or with poorly controlled diabetes.

7) Patients with unstable angina (angina for which onset or episodes have worsened within the previous three weeks), or patients who have a history of myocardial infarction that occurred within the past six months.

8) Patients who are HBs antigen-positive or HCV antibody-positive.

9) Patients who are HIV antibody-positive or who have not been tested.

10) Patients who have a combination of one or more of interstitial pneumonia, pulmonary fibrosis, or advanced emphysema, diagnosed by chest CT.

Supplementary Doc. S2

JCOG1305
Details of PET imaging standardization/quality assurance and interim PET central judgment

1) PET imaging standardization and quality assurance
The PET imaging method used at the participating institutions of this clinical study and its sub-clinical institutions is required to have undergone the procedures of standardization and quality assurance according to “Research on determining the therapeutic effect of cancer treatment based on standardized imaging diagnosis procedures” (Terauchi research group) supported by the National Cancer Center Research and Development Fund (25-A-13)”.

The standardization and quality assurance procedures will target the participating institutions of this clinical study and sub-clinical institutions; the procedures will start at any time after an institution declares that it will be a participating institution in this study and be completed before the first patient’s registration.

These procedures will be conducted by a contractor outsourced by the Terauchi Study Group using the FDG-PET Test Standardization Operation Implementation Plan (attached document).

Based on the FDG-PET Test Standardization Operation Implementation Plan, institution visits will take place only when they are conducting phantom tests. Meanwhile, since it is possible to manage the quality of PET images by checking the submitted images and contacting the institutions by e-mail or telephone, subsequent institution visits will not be conducted.

The PET certification office will issue a PET Imaging Conditions Confirmation Document to the institutions that have completed standardization and quality assurance procedures.

The research coordinator will manage the institution information issued by the PET Imaging Conditions Confirmation Document and will contact the JCOG data center as soon as the abovementioned standardization procedures are completed. Information on institutions that complete the standardization of PET imaging will be open to public on the JCOG website.

Only institutions that complete the standardization and quality assurance for

PET equipment can be registered for this clinical study.

2) Interim PET central judgment

In this clinical study, the interim PET central judgment will be conducted by nuclear medicine specialists who are familiar with PET judgment of malignant lymphomas using an image consultation system. The data transmission procedure is detailed in JCOG1305 Image Diagnosis Procedure Manual. Additionally, in this study, institution judgment results will collected in conjunction with the interim PET central judgment.

1）Central judgment

A judgment will be made within 2 days of receipt of the image. Central judgment will be made by three PET central judgment committee members, and the judgment result of at least two members will be the central judgment result.

2）Transmission of judgment result

The interim PET central judgment result will be communicated from the central judgment office to the study coordinator and study chair. The study coordinator or chair investigator will report the interim PET central judgment result to the principal investigator/sub-investigator by e-mail or fax.

Supplementary Table S1:

ABVD therapy (Induction ABVD, Additional ABVD)

4 weeks, one cycle

Drug	Dosage	Method of administration	Administration days
Doxorubicin	25 mg/m^2	30 minutes intravenous drip infusion	Day 1, 15
Bleomycin	9 mg/m^2	30 minutes intravenous drip infusion (maximum 15 mg/body)	Day 1, 15
Vinblastine	6 mg/m^2	Intravenous injection (up to 10 mg/body)	Day 1, 15
Dacarbazine	375 mg/m^2	30 minutes intravenous drip infusion (in shaded environment)	Day 1, 15

Escalated BEACOPP therapy

3 weeks, one cycle

Drug	Dosage	Method of administration	Administration days
Bleomycin	10 mg/m^2	30-minute intravenous drip infusion (maximum 15 mg/body)	Day 8
Etoposide	200 mg/m^2	4-hour intravenous infusion	Days 1-3
Doxorubicin	35 mg/m^2	30-minute intravenous drip infusion	Day 1
Cyclophosphamide	1,250 mg/m^2	60-minute intravenous drip infusion	Day 1
Vincristine	1.4 mg/m^2	Intravenous injection (maximum 2 mg/body)	Day 8
Procarbazine	100 mg/m^2	Oral	Days 1-7
Prednisolone	40 mg/m^2	Oral	Days 1-14
G-CSF	Approved dosage	Subcutaneous injection	Day 4-

Supplementary Table S2: JCOG1305 Investigators and number of enrolled patients

Institutions	Investigators	Number of enrolled patients
National Cancer Center Hospital	Koji Izutsu, Wataru Munakata、Suguru Fukuhara, Shinichi Makita	15
Nagoya City University Hospital	Shinsuke Iida, Shigeru Kusumoto, Tomotaka Suzuki	8
Kumamoto University Hospital	Kisato Nosaka, Hiro Tatetsu	6
Nagoya Medical Center	Hirokazu Nagai, Yasuhiro Suzuki	4
Toyota Kosei Hospital	Junji Hiraga, Yasuhiko Harada	4
Mie University Hospital	Motoko Yamaguchi, Kana Miyazaki	4
Ehime University Hospital	Katsuto Takenaka, Masaki Maruta	4
Tohoku University Hospital	Hideo Harigae, Noriko Fukuhara	3
Yamagata University Hospital	Kenichi Ishizawa, Tomomi Toubai	3
Saitama Prefectural Cancer Center	Yasuko Kubota	3
Tokai University Hospital	Kiyoshi Ando, Ken Ohmachi	3
Aichi Cancer Center Hospital	Kazuhito Yamamoto, Shigeru Kusumoto, Harumi Kato, Toko Saito	3
Kindai University Hospital	Itaru Matsumura, Takahiro Kumode	3
Hyogo Cancer Center	Toru Murayama, Hiroshi Gomyo, Ishikazu Mizuno	3
Saitama Medical Center	Masahiro Kizaki, Takayuki Tabayashi	2
Chiba Cancer Center	Kyoya Kumagai, Hedeki Tsujimura	2
Kyorin University Hospital	Nobuyki Takayama	2
Shiga General Hospital	Kosuke Asagoe	2
Shikoku Cancer Center	Isao Yoshida	2
Fukuoka University Hospital	Yasushi Takamatsu, Hidenori Sasaki	2
National Cancer Center Hospital East	Yosuke Minami, Hirotaka Nakamura	1
Jikei University Hospital	Shingo Yano, Takashi Shimada	1
NTT Medical Center Tokyo	Kensuke Usuki	1
Hamamatsu University Hospital	Takaaki Ono	1
Nagoya University Hospital	Kazuyuki Shimada, Katsuya Furukawa	1
Kyoto Prefectural University of Medicine Hospital	Junya Kuroda, Takahiro Fujino	1
Hiroshima University Hospital	Tatsuo Ichinohe	1
Kyushu Cancer Center	Yoko Suehiro, Ilseung Choi	1
Nagasaki Medical Center	Shinichiro Yoshida, Yoshitaka Imaizumi	1
Kumamoto Medical Center	Michihiro Hidaka	1
Oita Prefectural Hospital	Eiichi Otsuka, Masuho Saburi	1
Imamura General Hospital	Yoshikiyo Ito	1
University of the Ryukyus Hospital	Satoko Morishima	1
Komagome Hospital	Tatsu Shimoyama	1
Kanazawa Medical University Hospital	Yasufumi Masaki	1

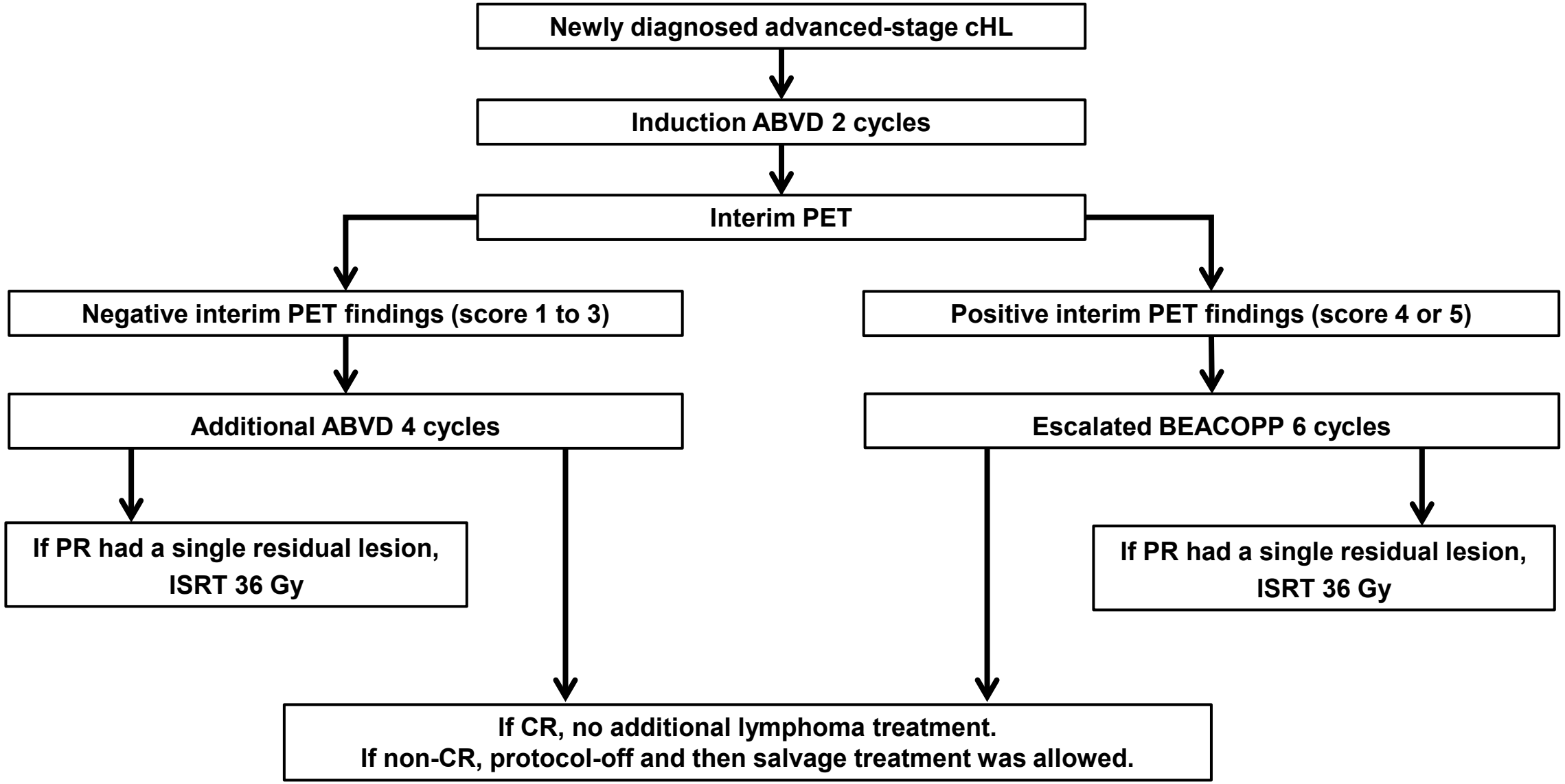
Supplementary Table S3: Summary of SWOG S0816 and JCOG1305

		SWOG S0816[1),2)]	JCOG 1305
Eligible patient number		n = 331	n = 92
Median age (range)		32 (18-60)	35 (20-60)
Clinical stage III/IV		331 (100%)	83 (90%)
PET2-positive patients		61 (18%)	19 (21%)
PET2-positive patients treated with eBEACOPP (at least 1 cycle administered)		49 (80%)	19 (100%)
ARDI	Post-PET2 ABVD	93%	97%
	eBEACOPP	75%	82%
ISRT		Not permitted	3 (3%)
Eligible patients	2-year PFS/ 5-year PFS	79%/74%	85%/NA
	2-year OS/ 5-year OS	98%/94%	99%/NA
PET2-positive patients	2-year PFS/ 5-year PFS	64%/66%	84%/NA
	2-year OS/ 5-year OS	NA/86%	95%/NA
PET2-negative patients	2-year PFS/ 5-year PFS	82%/76%	85%/NA
	2-year OS/ 5-year OS	NA/96%	100%/NA
Secondary malignancies	Post-ABVD	6 (2%)	1 (1%)
	Post-eBEACOPP	7 (14%)	0 (0%)

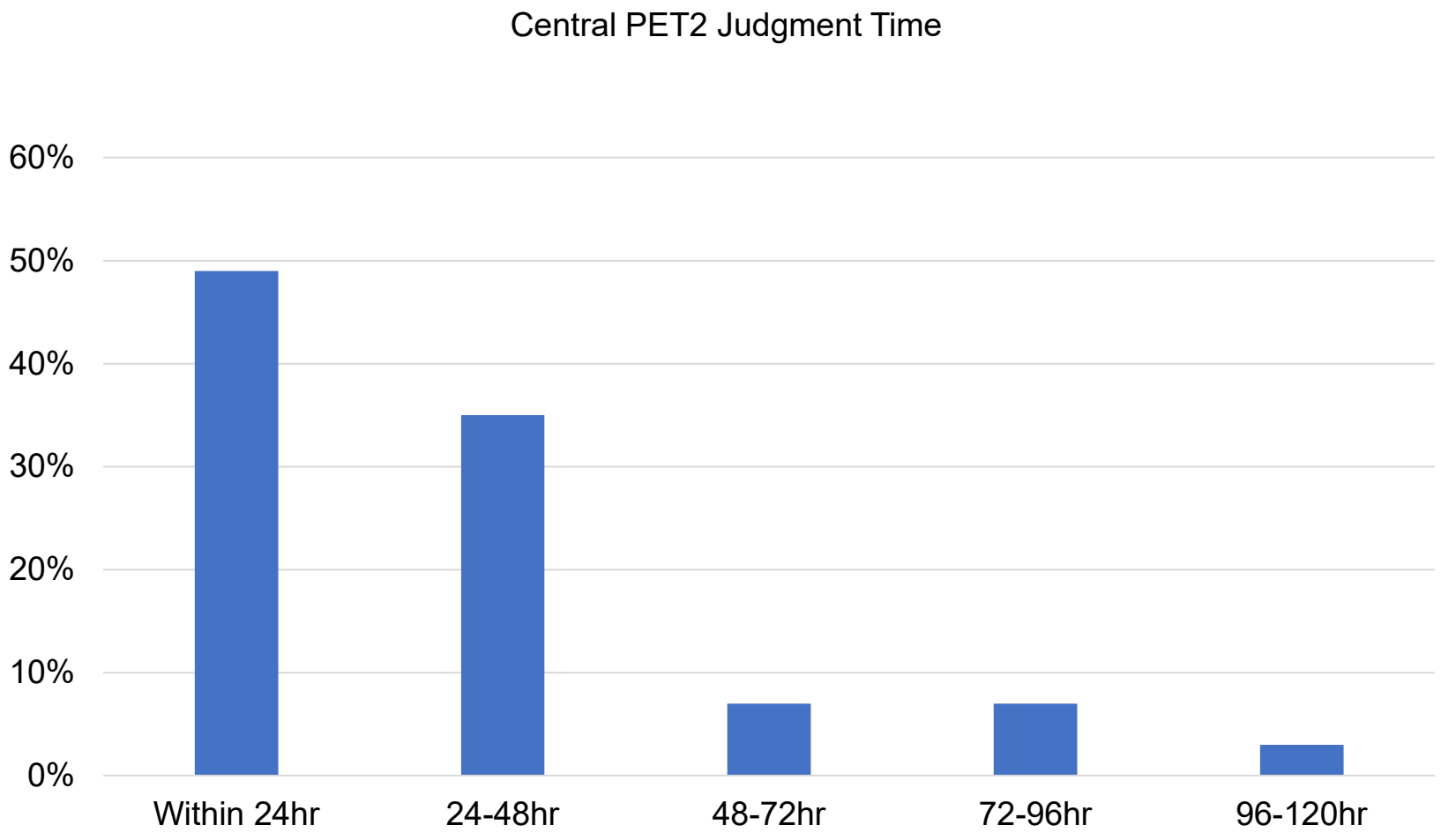
PET2, positron emission tomography after 2 cycles of ABVD (doxorubicin, bleomycin, vinblastine, and dacarbazine); eBEACOPP, escalated BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisolone); ARDI, average relative dose intensity; PFS, progression-free survival; OS, overall survival; NA, not available.

1) Press OW, et al. J Clin Oncol. 2016; 34: 2020-7.
2) Stephens DM, et al. Blood. 2019; 134: 1238-1246.

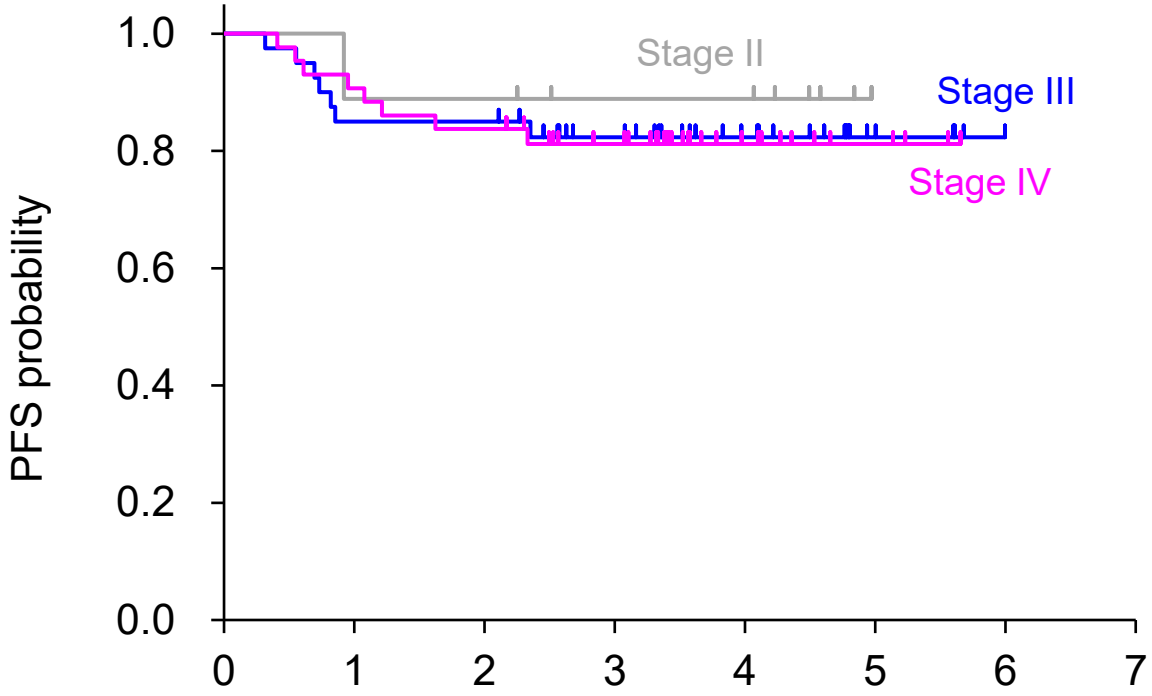
Supplementary Fig. S1: Study design of JCOG1305



Supplementary Fig. S2

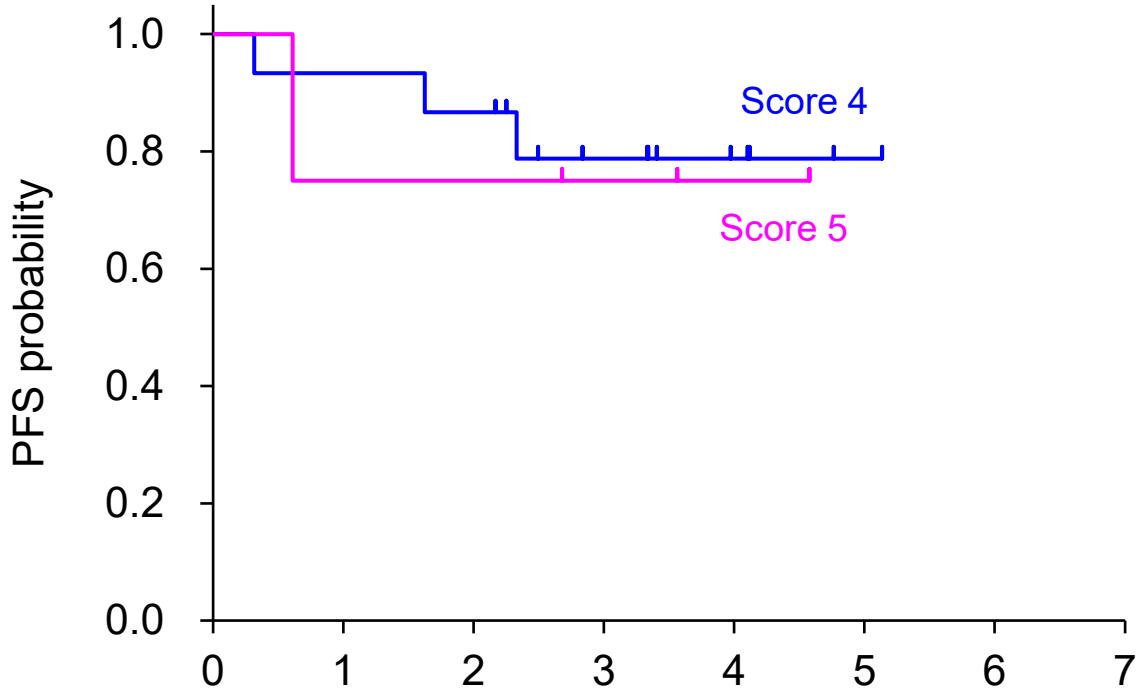


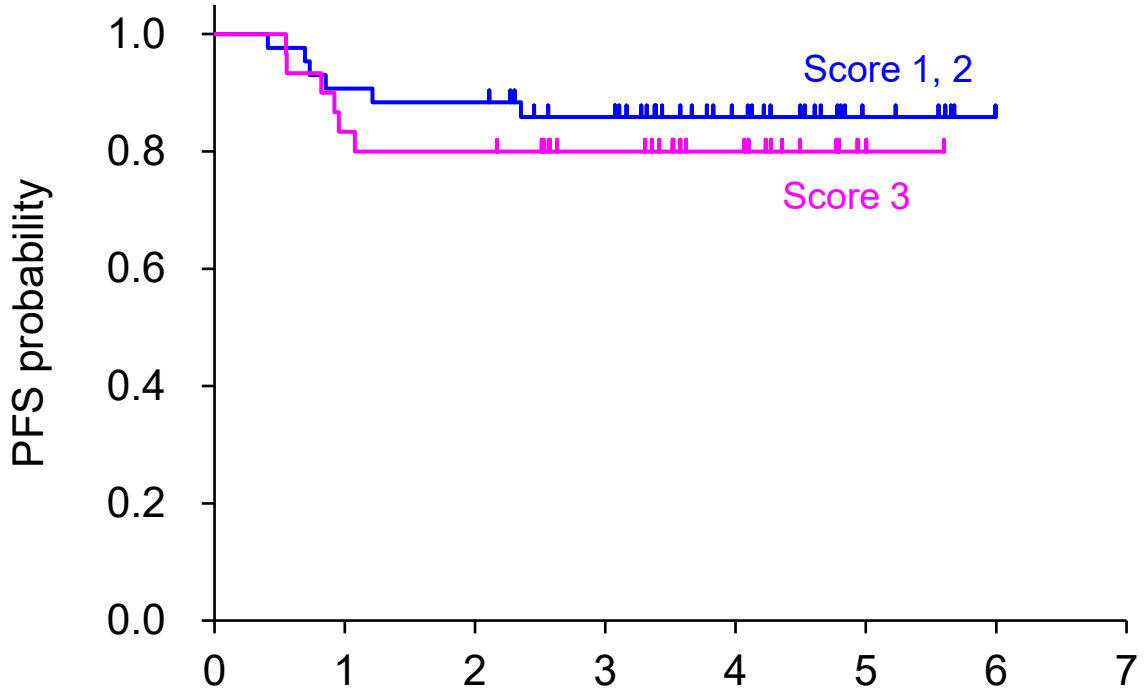
Supplementary Fig. S3



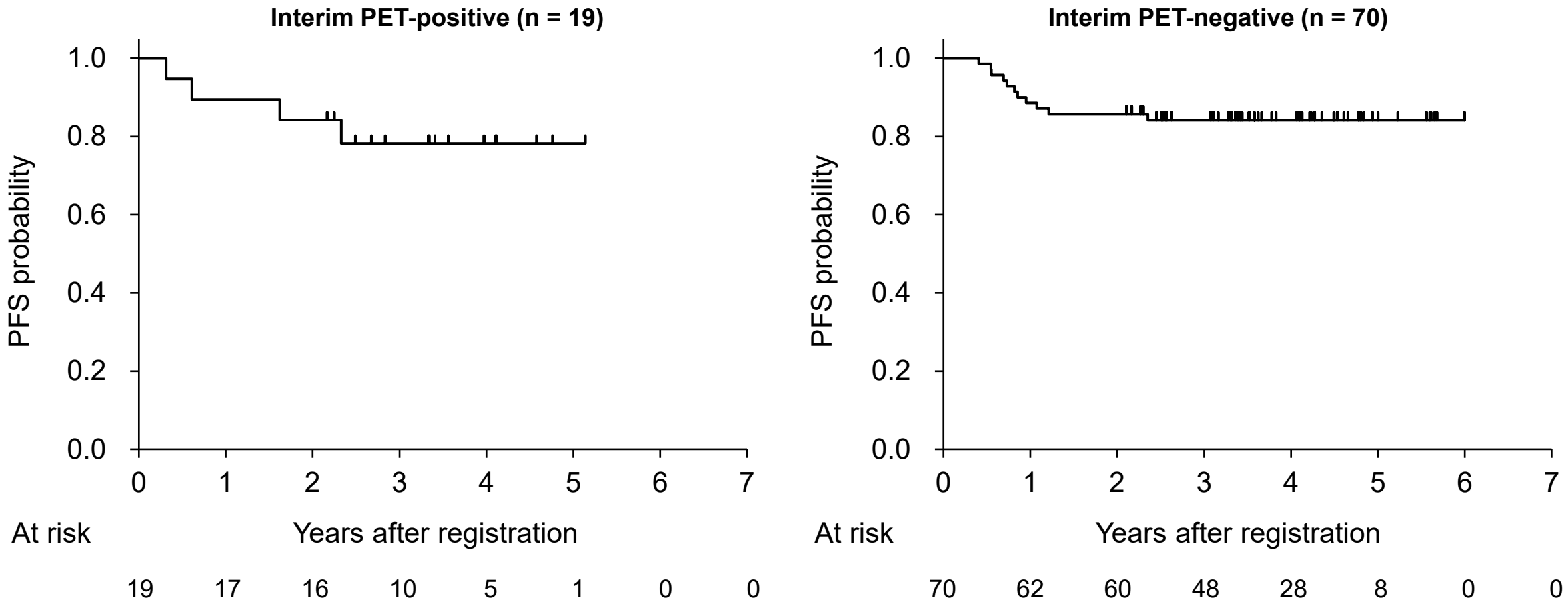
At risk								
Stage II	9	8	8	6	6	0	0	0
Stage III	40	34	34	26	16	5	0	0
Stage IV	43	39	36	28	12	4	0	0

Supplementary Fig. S4A and S4B





Supplementary Fig. S5A and S5B



Supplementary Figure Legends

Supplementary Fig. S1

Study design of JCOG1305. Patients with newly diagnosed advanced-stage classic Hodgkin lymphoma (cHL) received 2 cycles of ABVD as an induction chemotherapy, and then underwent an interim PET scan. Images were centrally reviewed with the use of a 5-point scale for PET findings for further response guided treatments. Patients with negative interim PET findings (defined as score 1 to 3) continued additional 4 cycles of ABVD, whereas those with positive interim PET findings (score 4 or 5) switched to 6 cycles of escalated BEACOPP. Involved site radiation therapy (ISRT) was set as a protocol treatment if patients with partial response (PR) had a single residual lesion after completion of chemotherapy.
ABVD, doxorubicin, bleomycin, vinblastine, and dacarbazine; PET, positron emission tomography; BEACOPP, bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone; CR, complete response.

Supplementary Fig. S2

Central PET2 judgment time was defined as the time from PET2 imaging data receipt to central PET2 judgment transmission for each investigator.

Supplementary Fig. S3

Progression-free survival for all 92 eligible patients stratified by clinical stage (II, III and IV).

Supplementary Fig. S4

(A) Progression-free survival (PFS) for 19 interim PET-positive patients stratified by Deauville scale (DS) score (4 and 5).
(B) PFS for 73 interim PET-negative patients stratified by Deauville scale (DS) score (1-2 and 3).

Supplementary Fig. S5

(A) Progression-free survival (PFS) for 19 interim PET-positive patients confirmed by central pathology review.
(B) PFS for 70 interim PET-negative patients confirmed by central pathology review.