Supplementary material

Manuscript title: Polatuzumab vedotin in previously untreated DLBCL: an Asia subpopulation analysis from the Phase 3 POLARIX trial

Supplemental methods

Testing and management of hepatitis B virus

In patients with a prior history of hepatitis B virus (HBV) infection, HBV DNA levels were obtained monthly for ≥12 months after the last cycle of therapy using a real-time polymerase chain reaction assay. If the HBV DNA assay became positive (ie, above the sensitivity cut-off of ≥10 IU/mL) but was within the World Health Organization (WHO)-recommended range of 10–100 IU/mL,[1] the patient was re-tested within 2 weeks. If the assay remained positive or was positive and above the WHO cut-off of 100 IU/mL, all study treatment was withheld, and the patient was treated with an appropriate nucleoside analog (for ≥1 year after the last dose of rituximab or polatuzumab vedotin) and immediately referred to a gastroenterologist or hepatologist for management. Study treatment was resumed when HBV DNA levels were undetectable. In the event of HBV DNA levels >100 IU/mL while receiving antiviral medication, study treatment was discontinued.

Supplemental Tables

Supplemental Table 1. Baseline demographics and clinical characteristics of patients in the Asia and China subgroups and global population of the POLARIX study (ITT)

	Asia subpopulation		Mainland China and Taiwan cohort*		Global population	
	Pola-R-CHP (n=141)	**R-CHOP (n=140)**	**Pola-R-CHP (n=79)**	**R-CHOP (n=86)**	**Pola-R-CHP (n=440)**	**R-CHOP (n=439)**
Median age (range), years	63 (19–79)	64 (23–78)	62 (19–77)	63 (23–76)	65 (19–80)	66 (19–80)
Age, n (%)						
<65 years	83 (58.9)	73 (52.1)	52 (65.8)	54 (62.8)	209 (47.5)	203 (46.2)
≥65 years	58 (41.1)	67 (47.9)	27 (34.2)	32 (37.2)	231 (52.5)	236 (53.8)

Sex, n (%)						
Female	70 (49.6)	62 (44.3)	39 (49.4)	34 (39.5)	201 (45.7)	205 (46.7)
Male	71 (50.4)	78 (55.7)	40 (50.6)	52 (60.5)	239 (54.3)	234 (53.3)
Ann Arbor Stage, n (%)						
I–II	19 (13.5)	21 (15.0)	8 (10.1)	7 (8.1)	47 (10.7)	52 (11.8)
III–IV	122 (86.5)	119 (85.0)	71 (89.9)	79 (91.9)	393 (89.3)	387 (88.2)
Extranodal sites, n (%)						
0–1	77 (54.6)	82 (58.6)	45 (57.0)	47 (54.7)	227 (51.6)	226 (51.5)
≥2	64 (45.4)	58 (41.4)	34 (43.0)	39 (45.3)	213 (48.4)	213 (48.5)

Bulky disease, n (%)[†]						
<7.5 cm	97 (68.8)	93 (66.4)	56 (70.9)	61 (70.9)	247 (56.1)	247 (56.3)
≥7.5 cm	44 (31.2)	47 (33.6)	23 (29.1)	25 (29.1)	193 (43.9)	192 (43.7)
ECOG PS, n (%)						
0–1	116 (82.3)	121 (86.4)	62 (78.5)	73 (84.9)	374 (85.0)	363 (82.7)
2	25 (17.7)	19 (13.6)	17 (21.5)	13 (15.1)	66 (15.0)	75 (17.1)
Unknown	0	0	0	0	0	1 (0.2)
LDH level, n (%)						
Normal	45 (31.9)	41 (29.3)	28 (35.4)	28 (32.6)	146 (33.2)	154 (35.1)

Elevated	96 (68.1)	99 (70.7)	51 (64.6)	58 (67.4)	291 (66.1)	284 (64.7)
Unknown	0	0	0	0	3 (0.7)	1 (0.2)
IPI score, n (%)[†]						
2	54 (38.3)	53 (37.9)	31 (39.2)	31 (36.0)	167 (38.0)	167 (38.0)
3–5	87 (61.7)	87 (62.1)	48 (60.8)	55 (64.0)	273 (62.0)	272 (62.0)
Median time from initial diagnosis to treatment initiation (IQR), days	17 (10–29)	15 (10–26)	14 (9–26)	15 (10–25)	26 (16–37.5)	27 (19–41)
Cell-of-origin, n (%)[‡]	n=100	n=100	n=54	n=56	n=330	n=338
GCB	30 (30.0)	40 (40.0)	10 (18.5)	21 (37.5)	184 (55.8)	168 (49.7)

ABC	55 (55.0)	46 (46.0)	35 (64.8)	26 (46.4)	102 (30.9)	119 (35.2)
Unclassified	15 (15.0)	14 (14.0)	9 (16.7)	9 (16.1)	44 (13.3)	51 (15.1)
Double expressor lymphoma, n (%)[‡]	n=110	n=113	n=54	n=62	n=362	n=366
DEL	35 (31.8)	41 (36.3)	15 (27.8)	19 (30.6)	139 (38.4)	151 (41.3)
Non-DEL	75 (68.2)	72 (63.7)	39 (72.2)	43 (69.4)	223 (61.6)	215 (58.7)
Double-/triple-hit lymphoma, n (%)[‡]	n=103	n=99	n=51	n=54	n=331	n=334
Yes	3 (2.9)	5 (5.1)	0	1 (1.9)	26 (7.9)	19 (5.7)
No	100 (97.1)	94 (94.9)	51 (100.0)	53 (98.1)	305 (92.1)	315 (94.3)
Prior history of hepatitis B infection[§]	45 (32.1)[§]	59 (42.4)[¶]	–	–	44 (10.0)	50 (11.4)

*Included 150 patients from mainland China and 15 patients from Taiwan.

†According to stratification.

‡Centrally performed tests: cell-of-origin was performed by NanoString Lymph 2Cx, MYC and BCL2 immunohistochemistry were performed for DEL; *MYC* and *BCL2*, and/or *BCL6* rearrangements were performed for double- and triple-hit lymphoma; percentages are calculated from the evaluable population. The remainder of the results were considered unknown and represent test failures.

§Based on laboratory data at screening (hepatitis B core antibody detected).

¶Based on the safety-evaluable population; Pola-R-CHP, n=140; R-CHOP, n=139.

Supplemental Table 2. Primary and key secondary efficacy outcomes for the China extension cohort* (ITT)

Outcome	Pola-R-CHP (n=79)	R-CHOP (n=86)
PFS, number of events (%)†	16 (20.3)	23 (26.7)
HR (95% CI)	0.66 (0.35–1.26)	
2-year rate (95% CI)	58.3 (37.3–79.4)	58.3 (42.1–74.5)
EFS, number of events (%)†	16 (20.3)	24 (27.9)
HR (95% CI)	0.62 (0.33–1.17)	
2-year rate (95% CI)	58.4 (37.4–79.4)	56.4 (39.0–73.2)
ORR at EOT, n (%)‡	73 (92.4)	66 (76.7)
CR, n (%)	66 (83.5)	65 (75.6)
PR, n (%)	7 (8.9)	1 (1.2)

SD, n (%)	2 (2.5)	3 (3.5)
PD, n (%)	0	8 (9.3)
Non-evaluable	0	2 (2.3)
Not included/missing	4 (5.1)	7 (8.1)
OS events, n (%)	4 (5.1)	10 (11.6)
HR (95% CI)	0.41 (0.13–1.32)	
2-year rate (95% CI)	91.1 (81.8–100)	84.0 (73.9–94.2)
DFS events, n (%)[§]	11 (15.5)	14 (20.3)
Unstratified HR (95% CI)	0.69 (0.31–1.53)	

BICR, blinded independent central review; CI, confidence interval; CR, complete response; DFS, disease-free survival; EFS, event-free survival; EOT, end of treatment; HR, hazard ratio; ITT, intent-to-treat; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; Pola-R-CHP, polatuzumab vedotin + rituximab + cyclophosphamide, doxorubicin, and prednisone; PR, partial response; R-CHOP, rituximab + cyclophosphamide, doxorubicin, vincristine, and prednisone; SD, stable disease.

*Included 150 patients from mainland China and 15 patients from Taiwan.

[†]Assessed by investigator.

[‡]Assessed by BICR.

[§]Pola-R-CHP, n=71; R-CHOP, n=69. Patients with an investigator-assessed best response of CR at any time during the study were evaluable for DFS.

Supplemental Table 3. Patients receiving subsequent anti-lymphoma therapy (ITT)

	Pola-R-CHP (n=141)	R-CHOP (n=140)
Total number of subsequent anti-lymphoma treatments (radiotherapy and systemic)*, n	62	82
Total number of patients with ≥1 subsequent anti-lymphoma treatment, n (%)	31 (22.0)	46 (32.9)
Total number of radiotherapy treatments, n	13	11
Total number of patients with ≥1 radiotherapy treatment, n (%)	13 (9.2)	10 (7.1)
Pre-planned	4 (2.8)	1 (0.7)
Unplanned	9 (6.4)	9 (6.4)
Total number of systemic therapy regimens†, n	49	71
Total number of patients who received ≥1 systemic therapy, n (%)	24 (17)	39 (28)
Stem cell transplantation	6 (4.3)	4 (2.9)

CAR-T	3 (2.1)	2 (1.4)

CAR-T, chimeric antigen receptor T-cell therapy; EFS, event-free survival; ITT, intention-to-treat; Pola-R-CHP, polatuzumab vedotin + rituximab + cyclophosphamide, doxorubicin, and prednisone; R-CHOP, rituximab + cyclophosphamide, doxorubicin, vincristine and prednisone.

*Subsequent anti-lymphoma treatment is defined as non-protocol anti-lymphoma therapy, and does not include intrathecal central nervous system disease prophylaxis as part of treatment; preplanned radiotherapy is included within radiotherapy here, though is not included as an event in EFS analyses.

[†]Includes any monotherapy, multi-drug, or cell-based regimen.

Supplemental Table 4. Key safety data for the China extension cohort* (safety evaluable)

AEs, n (%)	Pola-R-CHP (n=79)	R-CHOP (n=85)
Any grade	78 (98.7)	85 (100)
Grade ≥3	58 (73.4)	57 (67.1)
Serious	29 (36.7)	30 (35.3)
Grade 5	1 (1.3)	1 (1.2)
Leading to study discontinuation	1 (1.3)	1 (1.2)
Leading to dose discontinuation		
Any study treatment	4 (5.1)	6 (7.1)
Polatuzumab vedotin/placebo	2 (2.5)	3 (3.5)
Vincristine/placebo	2 (2.5)	3 (3.5)
Leading to dose reduction		
Any study treatment	7 (8.9)	9 (10.6)

Polatuzumab vedotin/placebo	2 (2.5)	4 (4.7)
Vincristine/placebo	2 (2.5)	4 (4.7)
Leading to dose interruption		
Any study treatment	21 (26.6)	23 (27.1)
Polatuzumab vedotin/placebo	12 (15.2)	17 (20.0)
Vincristine/placebo	12 (15.2)	17 (20.0)
Grade 3–5 AEPIs[†]		
Neutropenia[‡]	45 (57.0)	41 (48.2)
Anemia	6 (7.6)	10 (11.8)
Thrombocytopenia	11 (13.9)	12 (14.1)
Infections and infestations	11 (15.2)	17 (20.0)

AE, adverse event; AEPI, adverse events of particular interest; Pola-R-CHP, polatuzumab vedotin + rituximab + cyclophosphamide, doxorubicin, and prednisone; R-CHOP, rituximab + cyclophosphamide, doxorubicin, vincristine and prednisone.

*Included 150 patients from mainland China and 15 patients from Taiwan.

[†]Most common was defined as all-grade AEs occurring in ≥5% of patients in any treatment arm.

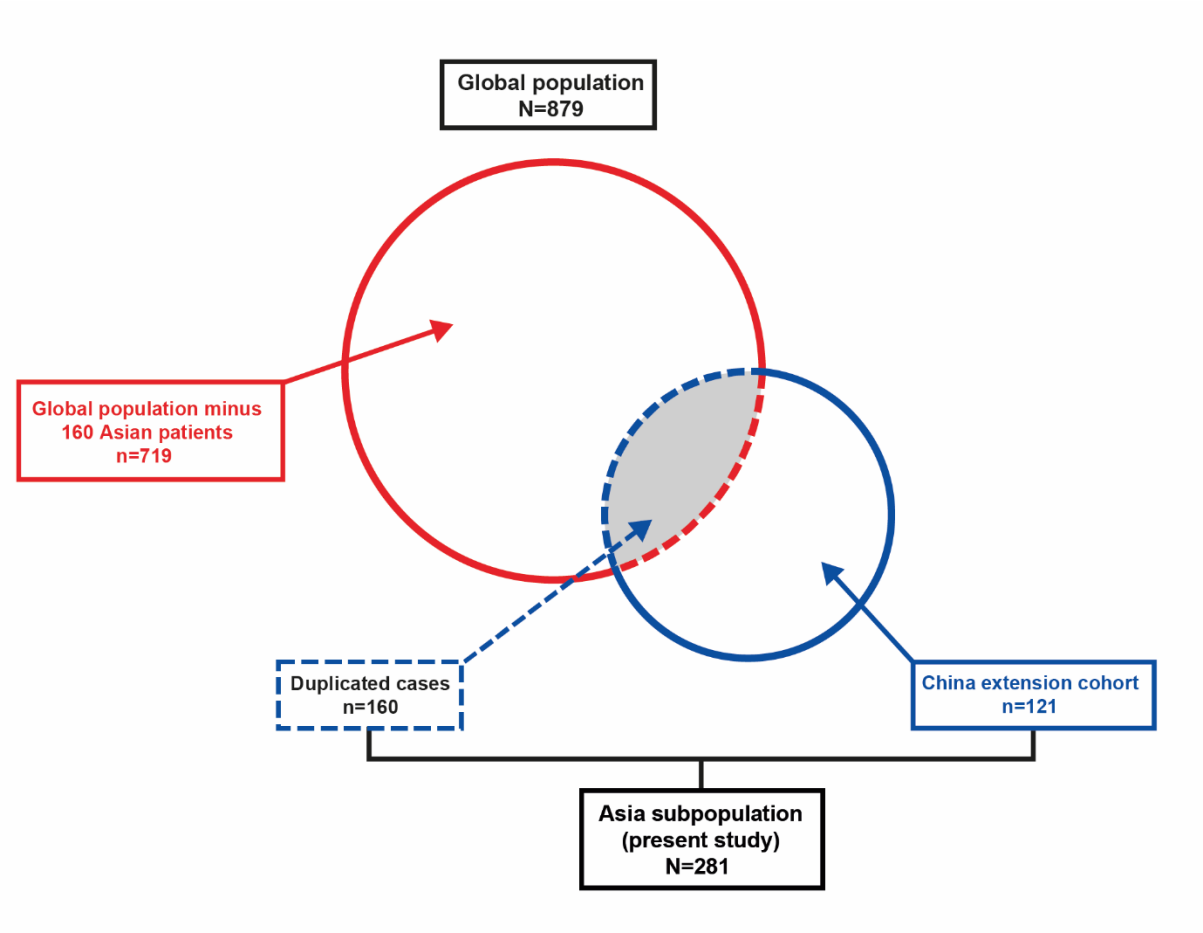
[‡]Includes febrile neutropenia.

Supplemental Table 5. Incidence of hepatitis B reactivation and antiviral prophylaxis among patients with prior hepatitis B infection

n (%)	Pola-R-CHP n=45	R-CHOP n=59
All patients with HBV reactivation	2 (4.4)	11 (18.6)
Received antiviral therapy prophylaxis	21 (46.7)	30 (50.8)
HBV reactivation	1 (4.8)	8 (26.7)
Did not receive antiviral therapy prophylaxis	24 (53.3)	29 (49.2)
HBV reactivation	1 (4.2)	3 (10.3)

HBV, hepatitis B virus; Pola-R-CHP, polatuzumab vedotin + rituximab + cyclophosphamide, doxorubicin, and prednisone; R-CHOP, rituximab + cyclophosphamide, doxorubicin, vincristine and prednisone.

Supplemental Figure 1: Schematic of the patient population analyzed



Treatment regimen administration in practice

Drug names

- Polatuzumab vedotin; POLIVY®
- Rituximab; MabThera®; Rituxan®
- Cyclophosphamide
- Doxorubicin
- Vincristine
- Prednisone

Treatment schedule (dose, cycle length, number of cycles)

- Patients were randomized 1:1 to receive either:
  - *Investigational arm:* Polatuzumab vedotin was administered by intravenous (IV) infusion at 1.8 mg/kg in combination with IV rituximab 375 mg/m^2, cyclophosphamide 750 mg/m^2, doxorubicin 50 mg/m^2, and vincristine placebo on Day 1 and oral prednisone 100 mg once daily on days 1–5 of every 21-Day cycle for 6 cycles. Rituximab 375 mg/m^2 IV was administered as monotherapy in Cycles 7 and 8.
  - *Control arm:* IV rituximab 375 mg/m^2, cyclophosphamide 750 mg/m^2, doxorubicin 50 mg/m^2, vincristine 1.4 mg/m^2 (maximum 2 mg/dose), and polatuzumab vedotin placebo on Day 1, and oral prednisone 100 mg once daily on Days 1–5, for 6 cycles. Rituximab 375 mg/m^2 IV was administered as monotherapy in Cycles 7 and 8.

Polatuzumab vedotin

- Lyophilized polatuzumab vedotin was provided as a 140 mg/vial drug product.
- A single-dose solution containing 20 mg/mL polatuzumab vedotin was yielded after reconstitution with 7.2 mL sterile water for injection and dilution into intravenous (IV) bags containing isotonic sodium chloride solution (0.9% NaCl).
- Polatuzumab vedotin was administered by IV infusion using a dedicated standard administration set with 0.2- or 0.22-µm in-line filters at a final concentration determined by the patient-specific dose (between 0.72–2.7 mg/mL).
- Central venous access was not required.
- The total dose of polatuzumab vedotin for all treatment cycles was determined by the patient's weight obtained during screening (Day −28 to Day −1), or the patient's weight within 96 hours prior to Day 1 of a given treatment cycle if it had changed >10% since the screening.
- The initial dose was administered to patients who were well hydrated over 90 (± 10) minutes.
- Slowing or interruption of the infusion was permitted for patients experiencing infusion-associated symptoms.
- Following the initial dose, patients were observed for 90 minutes for fever, chills, rigors, hypotension, nausea, or other infusion-associated symptoms. If prior infusions were well tolerated, subsequent doses were administered over 30 (± 10) minutes, followed by a 30-minute observation period.
- Polatuzumab vedotin was discontinued in the event of Grade 4 peripheral neuropathy (PN); patients were evaluated regarding the continuation of rituximab, cyclophosphamide, doxorubicin and prednisone (R-CHP) on the basis of their risk/benefit.
- Premedication with 500–1000 mg of oral acetaminophen/paracetamol and 50–100 mg diphenhydramine, as per institutional standard practice, was permitted.

- Administration of corticosteroids was permitted at the discretion of the treating Physician; if infusion-related reactions were observed with the first infusion in the absence of premedication, premedication was required before subsequent doses.

Rituximab

- Rituximab was provided at a concentration of 10 mg/mL in 100 mg (10 mL) and 500 mg (50 mL) single-dose vials and administered by IV infusion at a dose of 375 mg/m^2 on Day 1 of Cycles 1–8.
- Rituximab infusion was initiated at a rate of 50 mg/h and was increased in 50 mg/h increments every 30 minutes, to a maximum of 400 mg/h if no infusion-related or hypersensitivity reactions occurred.
- If the patient experienced an infusion-related or hypersensitivity reaction during infusion, subsequent infusions were initiated at 50 mg/h as per the protocol for the first infusion, or at a rate of 100 mg/h in the absence of Grade 2 reactions during a final infusion rate of ≥100 mg/h. If no reaction occurred, the infusion rate was increased by 100 mg/h every 30 minutes, to a maximum of 400 mg/h.
- If an infusion reaction developed during any infusion, administration was stopped or slowed, and infusion-reaction medications and supportive care was administered; upon resolution of the reaction, infusion was resumed at a 50% reduction in the rate at the time of the reaction.
- No dose modifications of rituximab were allowed.
- Prior to all initial rituximab infusions, patients received oral acetaminophen (650–1000 mg) and an antihistamine such as diphenhydramine hydrochloride (50–100 mg) ≥30 minutes before the start of each infusion (unless contraindicated). For

patients who did not experience infusion-related symptoms with their previous infusion, premedication at subsequent infusions may be omitted at the investigator's discretion.

Vincristine

- Vincristine was provided at a concentration of 1 mg/mL as a sterile, colorless solution for injection and administered by IV infusion at a dose of 1.4 mg/m^2 (maximum dose 2 mg) on Day 1 of cycles 1–6; administration was via minibag over approximately 10–30 minutes through a dedicated line.
- Vincristine dose was reduced (from 1.8 mg/kg to 1.4 mg/kg) in cases of hyperbilirubinemia (1.5–3.0 mg/dL) related to hepatic injury; full doses were administered with subsequent courses of treatment if bilirubin returned to levels of ≤1 mg/dL. For bilirubin levels >3.0 mg/dL, vincristine dose was withheld until improvement to Grade ≤1.
- Vincristine was discontinued in the event of Grade 4 PN; patients were evaluated regarding the continuation of R-CHP on the basis of their risk/benefit.

Cyclophosphamide, Doxorubicin and Prednisone

- Cyclophosphamide, doxorubicin and prednisone chemotherapy was administered to patients randomized in both arms of the study and consisted of cyclophosphamide and doxorubicin administered via IV and oral prednisone. Doxorubicin and cyclophosphamide were administered after both rituximab and polatuzumab vedotin/placebo infusions.
- Dosages were based on the following:
  - Cyclophosphamide 750 mg/m^2 administered IV on Day 1 of Cycles 1–6
  - Doxorubicin 50 mg/m^2 administered IV on Day 1 of Cycles 1–6
  - Oral Prednisone 100 mg/day on Days 1–5 of each Cycle (1–6)

- **Note:** Prednisone could be replaced with prednisolone (100 mg/day) or IV methylprednisolone (80 mg/day); hydrocortisone could not be used as a substitute.

Criteria for treatment discontinuation

- Patients permanently discontinued study treatment (though continued on the study) if they experienced any of the following:
  - Any medical condition that could jeopardize their safety if they continue to receive study treatment, as determined by the investigator
  - Investigator determines it is in the best interest of the patient
  - Pregnancy
  - Use of an anti-cancer therapy not required per protocol
  - Symptomatic deterioration attributed to disease progression
  - Confirmed disease progression per investigator assessment according to the Lugano Response Criteria for Malignant Lymphoma[1]
  - Unacceptable toxicity
  - Patient/investigator decision.

Premedications and concurrent medications

- The administration of granulocyte colony-stimulating factor (G-CSF) was required as a primary prophylaxis in each therapy cycle. The dose, form, and additional use of G-CSF (for the treatment and prophylaxis of neutropenia) was determined by the investigator.
- Patients with high tumor burden and considered by the investigator to be at risk of tumor lysis syndrome received tumor lysis prophylaxis prior to initiation of treatment. Starting

1–2 days before the first dose of study treatment, fluid intake of approximately 3 L/day was maintained, and patients received oral allopurinol at 300 mg/day or a suitable alternative treatment (e.g., rasburicase) starting 48–72 hours prior to Day 1 of Cycle 1. Patients continued to receive allopurinol and adequate hydration, if deemed appropriate by the investigator, prior to each subsequent cycle of treatment.

Patient-monitoring parameters

- Patients were closely monitored for safety and tolerability throughout the study and assessed for toxicity prior to each dose; dosing occurred only if the clinical assessment and local laboratory test values were acceptable. Safety was evaluated by monitoring all adverse events, serious adverse events, and abnormalities identified through physical examinations, vital signs, and laboratory assessments. Laboratory safety assessments included routine monitoring of hematology and blood chemistry, and tests of immunologic parameters. Laboratory, biomarker, and other biological samples were obtained up to 72 hours before start of study treatment administration on Day 1 of each treatment cycle.
- A peripheral blood sample for minimal residual disease analysis was required for all patients at Cycle 1, Day 1; Cycle 2, Day 1; between Cycle 4, Day 15 and Cycle 5, Day 1; and at the treatment completion visit. A peripheral blood sample for minimal residual disease analysis was also required at the following post-treatment follow-up visits: 6 months, 12 months, 18 months, and 24 months.
- Positron emission tomography/computer tomography (PET-CT) and dedicated CT scans were required at screening and 6–8 weeks after completion of study treatment, and an interim assessment after Cycle 4 of study treatment. During follow-up, CT scans (PET-CT also acceptable) were performed every 6 months until the end of Year 2 of follow-up (approximately 2.5 years after the first dose) in accordance with study (clinic) visits and included the neck (if involved at baseline), chest, abdomen, and pelvis. During years 3, 4,

and 5 of follow-up, CT scans (PET-CT acceptable) of sites of prior involvement were obtained every 12 months. If disease in other areas was suspected, additional areas were imaged at all subsequent imaging assessments.

- A full tumor assessment, including anatomic scans, was performed whenever disease progression was suspected.

References

1. World Health Organization (2015). Guidelines for the prevention, care and treatment of persons with chronic hepatitis B infection. Available at: http://apps.who.int/iris/bitstream/handle/10665/154590/9789241549059_eng.pdf. Accessed September 2022.

2. Cheson B, Fisher R, Barrington S, et al. Recommendations for initial evaluation, staging and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. *J Clin Oncol.* 2014;32:1–9.