Fertility in patients with advanced-stage classic Hodgkin lymphoma treated with BrECADD versus eBEACOPP: a secondary analysis of the multicentre, randomised, parallel, open-label, phase 3 HD21 trial

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Summary

Background BrECADD (brentuximab vedotin, etoposide, cyclophosphamide, doxorubicin, dacarbazine, and dexamethasone) has shown higher efficacy and better acute tolerability than eBEACOPP (escalated doses of bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone) in newly diagnosed, advanced-stage classic Hodgkin lymphoma. In this secondary analysis of the HD21 trial, we aimed to compare gonadal function recovery and fertility outcomes between these two regimens.

Methods In the multicentre, parallel, open-label, phase 3 HD21 trial, conducted across 233 trial sites in nine countries, patients aged 18–60 years with newly diagnosed, advanced-stage classic Hodgkin lymphoma and an Eastern Cooperative Oncology Group performance status of 0–2 were randomly assigned (1:1) to receive 4–6 cycles of eBEACOPP or BrECADD, guided by interim response. Patients and investigators were not masked to treatment assignment. Primary outcomes were progression-free survival and treatment-related morbidity (reported elsewhere). Here we report an unplanned analysis of fertility outcomes. Fertility outcomes included gonadal function recovery (via follicle-stimulating hormone [FSH] concentrations), concentrations of anti-Müllerian hormone (AMH; women only) and inhibin B (men only), frequencies of pregnancies, and incidence of parenthood. Gonadal function recovery, AMH, and inhibin B were assessed in the patients of childbearing potential (POCBP) cohort, which included women younger than 40 years and men younger than 50 years without baseline gonadal dysfunction. Pregnancy and parenthood analyses also included patients with baseline gonadal dysfunction. The HD21 trial was registered at ClinicalTrials.gov (NCT02661503) and is ongoing but closed to enrolment.

Findings Between July 22, 2016, and Aug 27, 2020, 1183 POCBP were enrolled (592 in the eBEACOPP group, 591 in the BrECADD group; 692 men, 491 women). FSH measurements were available for 767 patients (420 men and 347 women). Median follow-up was 49·6 months (IQR 39·7–58·4). BrECADD was associated with significantly higher 4-year gonadal function recovery rates compared with eBEACOPP (95·3% [95% CI 92·0–98·8] in the BrECADD group *vs* 73·3% [66·9–80·4] in the eBEACOPP group, HR 1·69 [95% CI 1·34–2·14] in women; 85·6% [80·8–90·8] *vs* 39·7% [33·6–46·9], HR 3·28 [2·51–4·30] in men). AMH and inhibin B concentrations were generally higher in the BrECADD group compared with the eBEACOPP group. A total of 92 pregnancies were reported among female patients, and 36 among partners of male patients. These led to 108 reported childbirths in 99 patients (59 in the BrECADD group and 40 in the eBEACOPP group). After therapy, 5-year incidence of parenthood was significantly higher in men (9·3% [95% CI 6·0–14·5] *vs* 3·3% [1·7–6·5], p=0·014), but not significantly higher in women (19·3% [13·7–27·3] *vs* 17·1% [11·9–24·6], p=0·53) with BrECADD versus eBEACOPP.

Interpretation Compared with eBEACOPP, BrECADD led to significantly better gonadal function recovery, as well as higher parenthood rates (significantly so in men). These findings support BrECADD as preferred first-line therapy, especially for patients wishing to preserve fertility.

Funding Takeda Oncology.

Introduction

Treatment for advanced-stage classic Hodgkin Lymphoma with eBEACOPP (escalated doses of bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone) is highly effective, but can cause gonadal dysfunction with

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Research in context

Evidence before this study

Intensified chemotherapy including alkylating agents for advanced-stage classic Hodgkin lymphoma is highly effective but can result in persisting gonadal dysfunction and infertility. Since this disease often affects young adults with family plans, this specific adverse event has an impact on the risk–benefit ratio of therapy. We therefore searched PubMed for articles published in English between inception and March 23, 2024, using the terms "gonadal function", "Hodgkin lymphoma", "fertility", and "chemotherapy". We found a few reports from prospective studies in this setting indicating adverse effects of eBEACOPP (escalated doses of bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone) on gonadal function and registry data associating eBEACOPP with reduced parenthood rates in men. There were no available data for novel regimens such as BrECADD (brentuximab vedotin, etoposide, cyclophosphamide, doxorubicin, dacarbazine, and dexamethasone).

Added value of this study

We analysed the gonadal function recovery assessed by follicle-stimulating hormone concentrations and childbirth in patients treated in the randomised, phase 3, HD21 trial, which compared eBEACOPP with BrECADD in newly diagnosed patients with advanced-stage classic Hodgkin lymphoma. As compared with eBEACOPP, we found relevant improvements in gonadal function recovery following BrECADD for both women and men. In women, recovery of gonadal function reached 95% at 3 years after treatment. Interestingly, men and patients at more advanced age, who are at higher risk for persisting gonadal dysfunction from treatment with eBEACOPP, had a particular benefit. The endocrine gonadal function recovery was accompanied by higher rates of pregnancies and parenthood after treatment in men and women receiving BrECADD in HD21. Our study provides a first detailed description of gonadal function recovery and fertility in this novel regimen compared with the former standard eBEACOPP.

Implications of all the available evidence

BrECADD caused significantly less gonadal damage compared with eBEACOPP, which is a main concern with this effective regimen. Together with the high primary cure rate associated with BrECADD, this study supports its use for patients with advanced-stage classic Hodgkin lymphoma who desire to have children.

detrimental effects on fertility and quality of life. These effects are particularly pronounced in women with severe menopausal symptoms due to premature ovarian insufficiency. Men and older patients have an even higher risk of persisting gonadal damage than women and younger patients when exposed to alkylating agents.[1–4] In contrast to females, male survivors of Hodgkin lymphoma have a decreased parenthood rate after treatment with eBEACOPP compared with the less gonadotoxic ABVD (doxorubicin, bleomycin, vinblastine, and dacarbazine) regimen.[5] However, while ABVD is associated with lower gonadotoxicity, it has demonstrated inferior disease control in advanced-stage classic Hodgkin lymphoma.[6]

Consequently, there is an unmet need for first-line treatments with high anti-lymphoma efficacy without relevant impact on gonadal function for this young patient cohort. The BrECADD regimen (brentuximab vedotin, etoposide, cyclophosphamide, doxorubicin, dacarbazine, and dexamethasone) was designed to reduce the general acute burden of treatment compared with the eBEACOPP regimen while maintaining its efficacy. To reduce gonadal toxicity, procarbazine was replaced with dacarbazine. The BrECADD regimen was compared with eBEACOPP in the HD21 trial for the first-line treatment of advanced-stage classic Hodgkin lymphoma.[7] Primary endpoints of the HD21 study were met by demonstrating superior efficacy and improved acute tolerability of BrECADD.[8] In this Article, we report an unplanned analysis of the effect of BrECADD on gonadal function recovery and fertility.

Methods

Study design

HD21 was a multicentre, randomised, parallel, open-label, phase 3 trial that recruited patients in 233 study sites in nine countries: Germany, Austria, Switzerland, the Netherlands, Denmark, Sweden, Norway, Australia, and New Zealand. This was an intergroup study including the German Hodgkin Study Group (GHSG), the Swiss Group for Clinical Cancer Research, the Arbeitsgemeinschaft Medikamentöse Tumortherapie, the Nordic Lymphoma Group, and the Australasian Leukaemia & Lymphoma Group. Ethics approval was granted by the Ethics Committee of the Medical Faculty at the University of Cologne (reference number 16-008). All patients provided written informed consent before study entry according to the Good Clinical Practice guidelines of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use. The study was monitored by an independent data monitoring committee. This trial is registered with ClinicalTrials.gov (NCT02661503) and is currently ongoing but closed to enrolment.

Participants

Patients aged 18–60 years with newly diagnosed advanced-stage classic Hodgkin lymphoma were enrolled in the HD21 trial. Definition of advanced stage included Ann Arbor stage III–IV as well as stage II with B symptoms and one or both risk factors of large mediastinal mass (at least a third of the maximal thoracic

diameter) or extranodal lesions. Other inclusion criteria were an Eastern Cooperative Oncology Group performance status of 0–2, HIV negativity, and freedom from concurrent disease that would preclude treatment according to the protocol. Participants' sex and race were assessed by the local investigator using electronic medical records. Enrolment was done at the GHSG central office. Following enrolment, the histopathological diagnosis was reassessed by a panel of lymphoma expert pathologists.

Women younger than 40 years and men younger than 50 years from the intention-to-treat cohort of HD21 were included in the present analysis of pregnancies and parenthood. Recovery of gonadal function (measured by follicle-stimulating hormone [FSH]), as well as anti-Müllerian hormone (AMH) and inhibin B concentrations, were analysed in all female patients younger than 40 years with baseline FSH up to 25 U/L and male patients younger than 50 years with baseline FSH up to 15 U/L included in the intention-to-treat population (patients of childbearing potential [POCBP] cohort).

Randomisation and masking

Detailed randomisation procedures were reported previously.[8] In brief, patients were randomly assigned (1:1) to receive standard treatment with eBEACOPP or experimental treatment with BrECADD. Randomisation was done at the GSHG central trial office using the minimisation method including a random component and stratified according to area of recruitment (Europe *vs* Australia and New Zealand), age (<45 years *vs* ≥45 years), International Prognostic Score (0–2 *vs* 3–7), and sex (male *vs* female). Patients and investigators were not masked to treatment assignment.

Procedures

Detailed treatment procedures were reported previously.[8] In summary, cycles of BEACOPP were escalated doses of etoposide (200 mg/m² intravenously on days 1–3), doxorubicin (35 mg/m² intravenously on day 1), and cyclophosphamide (1250 mg/m² intravenously on day 1), and standard doses of bleomycin (10 mg/m² intravenously on day 8), vincristine (1·4 mg/m² intravenously on day 8), procarbazine (100 mg/m² orally on days 1–7), and prednisone (40 mg/m² orally on days 1–14). Cycles of BrECADD were brentuximab vedotin (1·8 mg/kg up to a maximum of 180 mg absolute dose intravenously on day 0), etoposide (150 mg/m² intravenously on days 1–3), cyclophosphamide (1250 mg/m² intravenously on day 1), doxorubicin (40 mg/m² intravenously on day 1), dacarbazine (250 mg/m² intravenously on days 2–3), and dexamethasone (40 mg orally on days 1–4). BEACOPP and BrECADD cycles were administered in 21-day intervals. PET-based response assessments were done after the second cycle (PET2) and last cycle (end-of-treatment PET) of chemotherapy. A multidisciplinary expert panel centrally reviewed PET2 and end-of-treatment imaging. PET2 and end-of-treatment PET positivity was defined as a Deauville Score of 4 or higher. Radiotherapy was recommended for residual PET-positive disease on the end-of-treatment PET in both groups. On March 13, 2017, following availability of the GHSG HD18 trial results,[9] HD21 was amended for PET2 guidance to either four or six cycles of chemotherapy based on the response after two cycles. Patients with complete response (ie, Deauville Score 1–3) received four cycles of chemotherapy, whereas patients with PET-positive residues received a total of six cycles.

Assessment of gonadal toxicity was strongly recommended but not mandatory as per protocol, and included documentation of FSH (local measurement) in female and male patients before the start of treatment (screening), at the end of chemotherapy (restaging, usually within 3 months), and during follow-up at 12, 24, and 60 months. AMH and inhibin B were measured at the same timepoints as FSH. All hormonal evaluations, including FSH, AMH, and inhibin B were performed locally at each participating centre. Follow-up examinations were scheduled every 3 months in the first year after the end of treatment, every 6 months in years 2–5, and once a year later than 5 years after the end of treatment. Pregnancies and childbirths among patients or their partners had to be reported by the investigators in the entire follow-up period as per protocol, and were recorded on the case report form. German-speaking patients who provided consent to fill out questionnaires were asked about their desire to have children.

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	Women (N=491)		Men (N=692)	
	eBEACOPP (n=243)	BrECADD (n=248)	eBEACOPP (n=349)	BrECADD (n=343)
Age, years	27 (22–32)	26 (22–32)	29 (23–37)	29 (23–35)
Age				
<30 years	158 (65%)	157 (63%)	182 (52%)	181 (53%)
≥30 years	85 (35%)	91 (37%)	167 (48%)	162 (47%)
Number of cycles*				
4 cycles	148/233 (64%)	151/241 (63%)	196/343 (57%)	199/329 (60%)
6 cycles	85/233 (36%)	90/241 (37%)	147/343 (43%)	130/329 (40%)
Hormonal contraception (including GnRH analogues)	149/205 (73%)	151/215 (70%)	NA	NA
Desire to have children	91/155 (59%)	109/161 (68%)	125/207 (60%)	133/208 (64%)
Race				
Asian	4 (2%)	2 (1%)	8 (2%)	8 (3%)
Black	1 (0%)	0 (0%)	1 (0%)	0 (0%)
White	224 (92%)	234 (94%)	309 (89%)	310 (90%)
Other or unknown	14 (6%)	12 (5%)	31 (9%)	25 (7%)

Data are n (%), n/N (%), or median (IQR). BrECADD=brentuximab vedotin, etoposide, cyclophosphamide, doxorubicin, dacarbazine, and dexamethasone. eBEACOPP=escalated doses of bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone. GnRH=gonadotropin-releasing hormone. NA=not applicable. *37 patients (2%) received neither four nor six cycles.

Table: **Baseline and treatment characteristics of the patients of childbearing potential population**

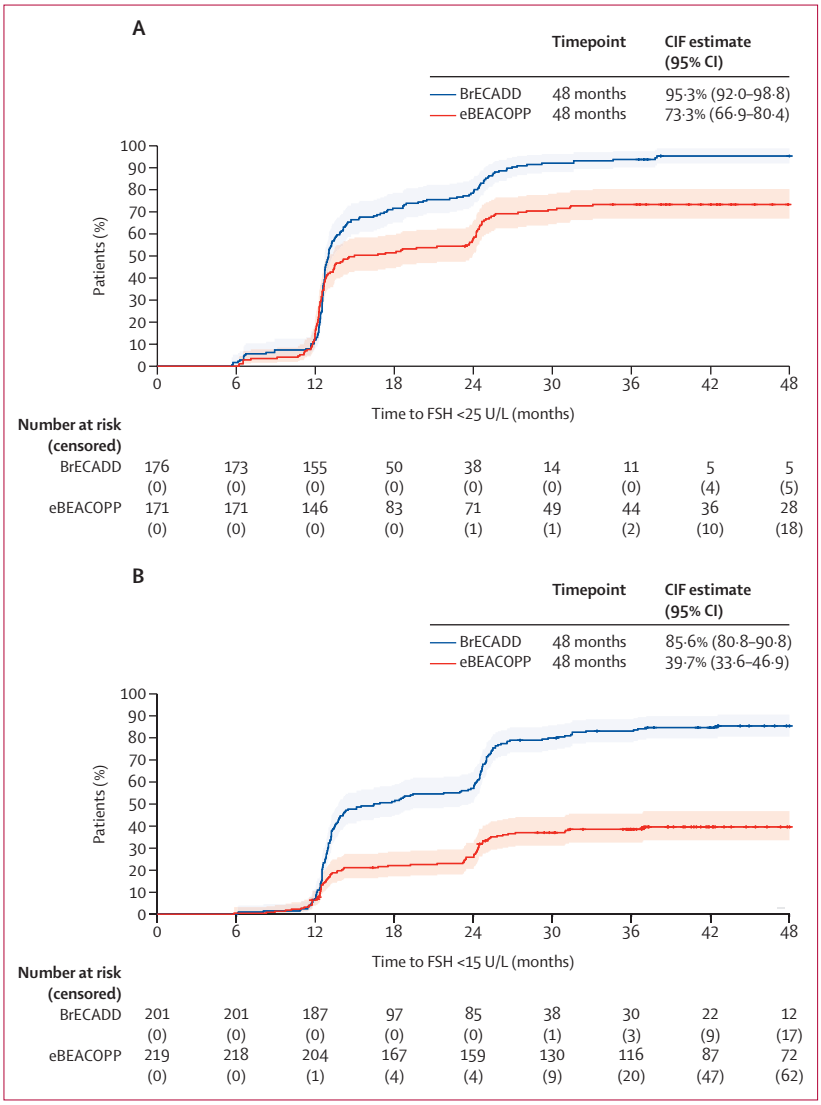

Figure 1: **Gonadal function recovery in female (A) and male (B) patients**
Cumulative incidence of gonadal function recovery, defined as first measurement of FSH concentrations below 25 U/L in female patients and below 15 U/L in male patients. 12 months after treatment, gonadal function was assessed for the first time in most patients. BrECADD=brentuximab vedotin, etoposide, cyclophosphamide, doxorubicin, dacarbazine, and dexamethasone. CIF=cumulative incidence function. eBEACOPP=escalated doses of bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone. FSH=follicle-stimulating hormone.

Outcomes

Primary outcomes of the main trial were progression-free survival and treatment-related morbidity and were reported elsewhere.[8] Secondary outcomes were complete response rate after completion of chemotherapy; overall survival; infertility rate at 1 year (determined by hormone concentrations); second malignancies; number of serious adverse events within 30 days after end of treatment; therapy adherence; quality of life before, during, and after therapy; and event-free survival.

In this unplanned secondary analysis, we report unplanned analyses of the cumulative incidence of gonadal function recovery over time; concentrations of FSH, AMH (women only), and inhibin B (men only) over time; frequencies of pregnancies; and incidence of first parenthood after therapy.

We defined time to gonadal function recovery as time from the end of treatment until the first measurement of FSH concentration below the respective threshold or, if not reached, at last FSH measurement (time of censoring). We defined time to first parenthood after therapy as time from the end of treatment until the first livebirth or, if livebirth did not occur, date of last follow-up or date of death (time of censoring).

See Online for appendix

Statistical analysis

Sample size calculations were based on the primary endpoint and have been reported previously.[8] Recovery of gonadal function was defined as maintaining or retuning to FSH concentrations below the thresholds after therapy (25 U/L for women and 15 U/L for men).[2,10] The rate of FSH recovery was analysed in the POCBP cohort per treatment group according to the Kaplan–Meier method including hazard ratios (HRs) and corresponding 95% CIs. AMH and inhibin B concentrations were analysed in the same cohort. Pregnancy and parenthood analyses also included patients with baseline gonadal dysfunction. Frequencies of pregnancies and livebirths overall and frequency of patients reporting at least one childbirth are reported. The cumulative incidence of first parenthood after therapy was analysed per treatment group and compared by using Gray's test. Non-informative censoring was assumed. Censoring due to salvage treatment or progression was not applied because patients were still able to recover FSH or become pregnant after receiving salvage treatment or having progression. FSH, inhibin B, and AMH concentrations are additionally reported as mean (95% CI) over time. All analyses were done separately for men and women. Additionally, we did subgroup analyses for gonadal function recovery by age group (<30 years *vs* ≥30 years), number of cycles (four *vs* six), and use of contraceptive measures including gonadotropin-releasing hormone (GnRH) analogues for women. We also used multivariable Cox regression models with Efron's method of tie handling to analyse FSH recovery adjusted for the aforementioned subgroups including an interaction between treatment and age group. The proportional hazards assumption was checked using the Schoenfeld residual test. The level of significance was set at a p value of less than 0·05 without correction for multiple testing. SAS (version 9.4) was used for all analyses. The statistical analysis plan is provided in the appendix.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

The HD21 trial enrolled patients between July 22, 2016, and Aug 27, 2020 (appendix pp 15–20). The final POCBP cohort comprised 1183 (80%) of 1482 patients from the intention-to-treat cohort, including 592 in the eBEACOPP group and 591 in the BrECADD group, and 491 women and 692 men (appendix p 1; table). Median follow-up was 49·6 months (IQR 39·7–58·4) and 242 (20%) of 1183 patients were followed up for 60 months or more. 1146 (97%) of 1183 patients received the planned number of treatment cycles as per protocol. Reasons for exclusion from the POCBP cohort were age (women ≥40 years, men ≥50 years; n=282) or gonadal function impairment indicated by high FSH concentrations before treatment initiation (n=17). In general, disease-specific baseline characteristics in the POCBP cohort were well balanced between treatment groups (appendix p 2; table).

Before therapy, 205 (42%) of 491 women underwent cryopreservation procedures, with usage varying by treatment centre type and country (appendix p 3). Additionally, 300 (71%) of 420 female patients received contraceptive measures, including GnRH agonists, during chemotherapy. 395 (57%) of 692 men underwent cryopreservation procedures, with usage varying by treatment centre type and country (appendix p 3).

FSH measurements during follow-up were available for 347 (71%) of 491 women, and characteristics of patients with missing FSH values were similar between treatment groups (appendix p 4). Mean FSH concentrations over time were higher in the eBEACOPP group than in the BrECADD group (appendix pp 4, 8). Additional AMH measurements during follow-up were available in 256 (52%) of 491 women and were generally higher in the BrECADD group compared with the eBEACOPP group (appendix p 9). FSH measurements during follow-up were available for 420 (61%) of 692 men, with higher mean FSH concentrations in the eBEACOPP group than in the BrECADD group (appendix pp 4, 12). Inhibin B serum concentrations were available in 266 (38%) of 692 men during follow-up and were generally higher in the BrECADD group compared with the eBEACOPP group (appendix p 13).

Women assigned to BrECADD had significantly higher 4-year gonadal function recovery rates compared with those receiving eBEACOPP (95·3% [95% CI 92·0–98·8] *vs* 73·3% [66·9–80·4], respectively; HR 1·69 [95% CI 1·34–2·14]; figure 1A). Men assigned to BrECADD also had significantly higher 4-year gonadal function recovery rates compared with those receiving eBEACOPP (85·6% [80·8–90·8] *vs* 39·7% [33·6–46·9]; HR 3·28 [2·51–4·30]; figure 1B).

Regarding the subgroup analyses, in women, the greatest benefit in terms of gonadal function recovery with BrECADD over eBEACOPP was observed in those aged 30 years or older (86·2% [95% CI 77·5–95·9] *vs* 46·4% [35·4–60·8]; HR 2·92 [95% CI 1·84–4·65]) and those receiving six cycles of treatment (92·6% [86·0–99·8] *vs* 63·5% [52·5–76·8]; HR 1·89 [1·25–2·83]; figure 2A, figure 3A). The treatment effect for women was confirmed and higher in the multivariable Cox model (HR 3·58 [2·17–5·92]) accounting for age, number of cycles, and contraceptive use as covariables. We also

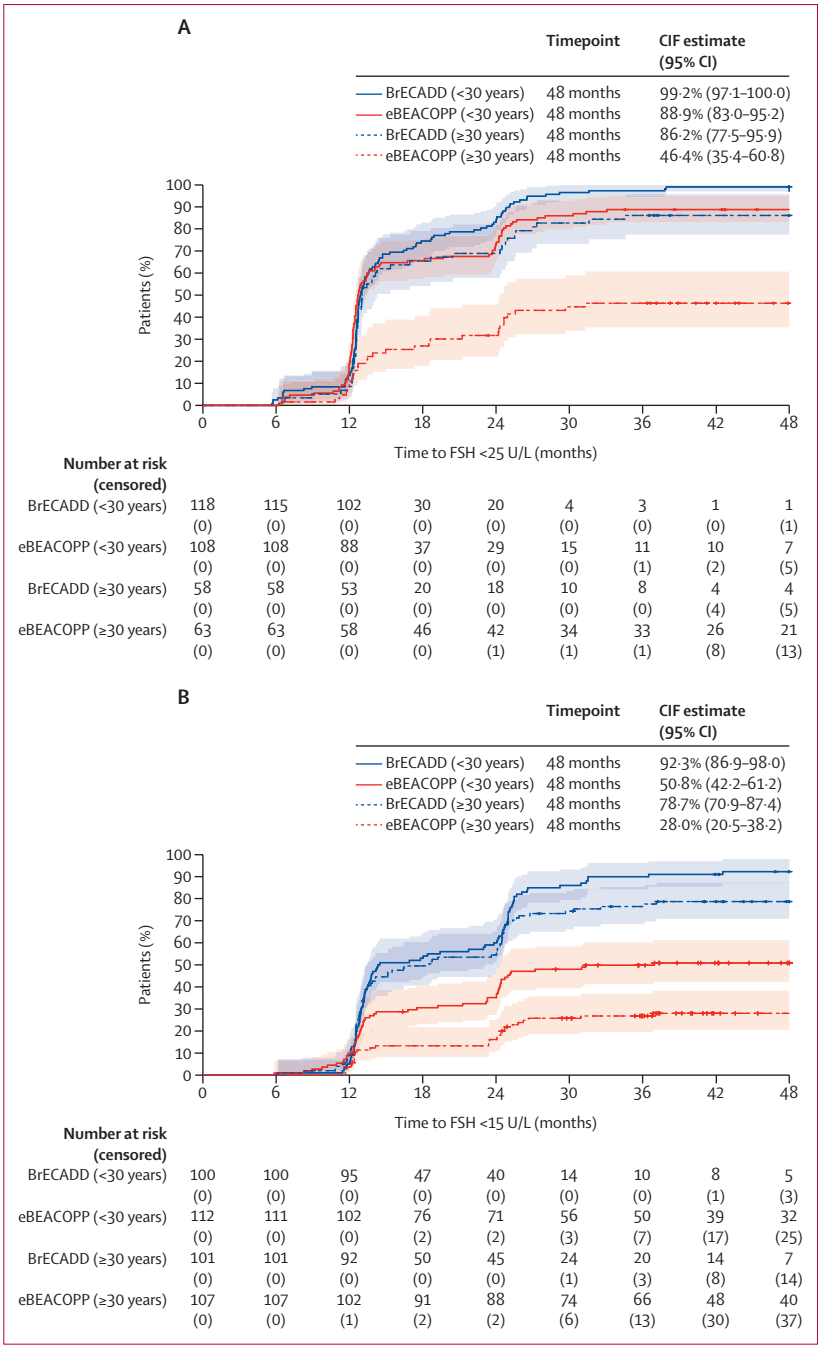

Figure 2: **Gonadal function recovery stratified by age in female (A) and male (B) patients**
Cumulative incidence of gonadal function recovery, defined as first measurement of FSH concentrations below 25 U/L in female patients and below 15 U/L in male patients, stratified by age (<30 years *vs* ≥30 years). BrECADD=brentuximab vedotin, etoposide, cyclophosphamide, doxorubicin, dacarbazine, and dexamethasone. CIF=cumulative incidence function. eBEACOPP=escalated doses of bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone. FSH=follicle-stimulating hormone.

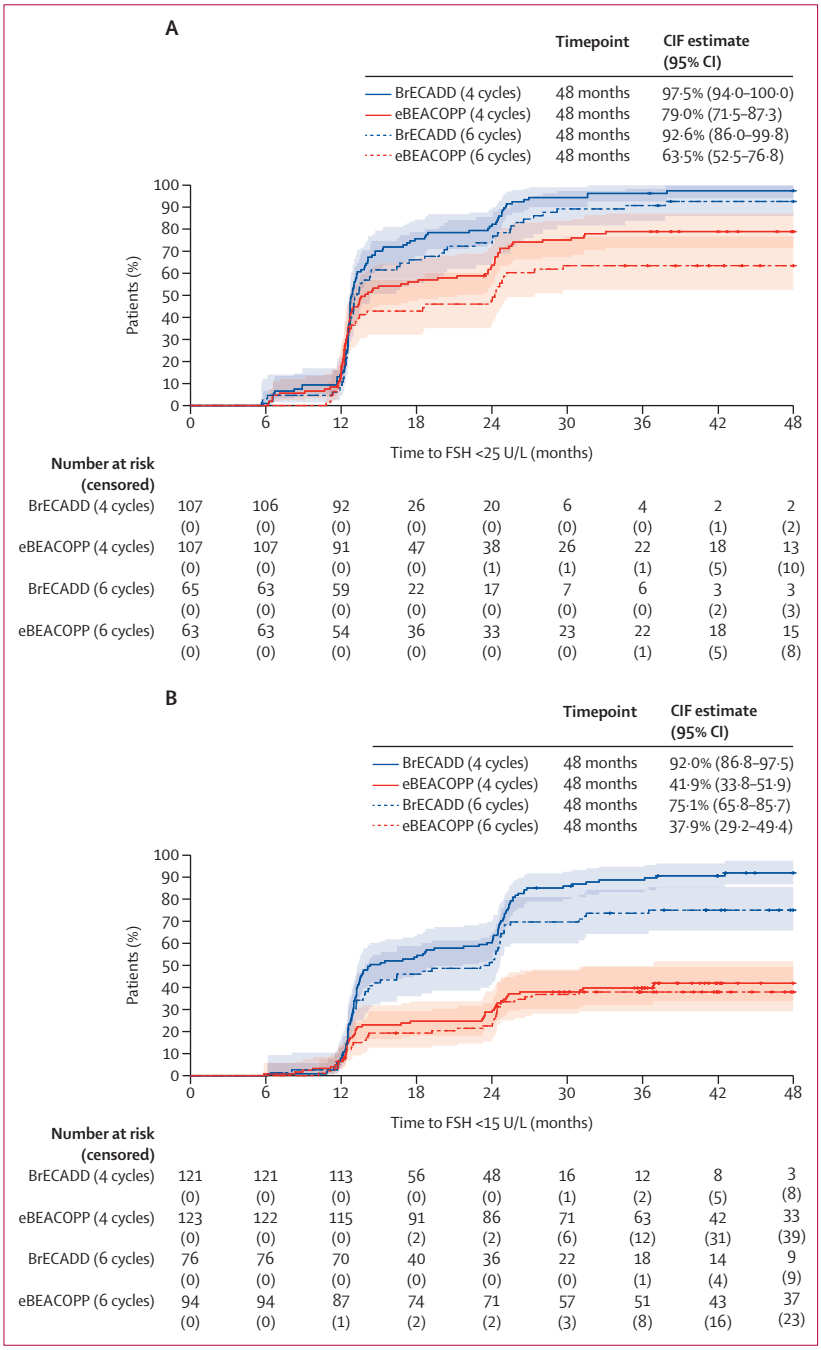

Figure 3: **Gonadal function recovery stratified by number of cycles in female (A) and male (B) patients**
Cumulative incidence of gonadal function recovery, defined as first measurement of FSH concentrations below 25 U/L in female patients and below 15 U/L in male patients, stratified by number of cycles (four *vs* six). BrECADD=brentuximab vedotin, etoposide, cyclophosphamide, doxorubicin, dacarbazine, and dexamethasone. CIF=cumulative incidence function. eBEACOPP=escalated doses of bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone. FSH=follicle-stimulating hormone.

observed significant associations between gonadal function recovery and age group (HR 4·35 [2·74–6·89]) and number of cycles (HR 1·46 [1·13–1·89]) and a significant interaction between treatment effect and age group (HR 0·36 [0·20–0·64]). The proportional hazards assumption was not met for the comparison of the treatment effect. Analysis of FSH recovery stratified by use of GnRH or contraceptives is shown in the appendix (p 10). In men, the greatest benefit was observed in those aged 30 years or older (78·7 [70·9–87·4] *vs* 28·0% [20·5–38·2]; HR 4·56 [2·95–7·05]) and those receiving four cycles of treatment (92·0% [86·8–97·5] *vs* 41·9% [33·8–51·9]; HR 3·60 [2·53–5·12]; figure 2B, figure 3B). The treatment effect for men was confirmed and higher in the multivariable Cox model (HR 4·64 [3·04–7·08]) accounting for age group and number of cycles as covariables and was characterised by a significant interaction between treatment effect and age group (HR 0·53 [0·31–0·91]). We also observed significant associations between gonadal function recovery and age group (HR 2·30 [1·48–3·59]) and cycle number (HR 1·33 [1·03–1·72]). For the comparison of the treatment effect, the assumption of proportional hazards was not met. FSH recovery rates across relevant subgroups for women and men as well as detailed results of multivariate Cox regression models are reported in the appendix (p 5).

Overall in the HD21 study, there were 108 reported childbirths (73 to female patients [one stillbirth], 35 to partners of male patients) in 99 patients (66 female patients, 33 partners of male patients; 59 in the BrECADD group and 40 in the eBEACOPP group). During follow-up, 92 pregnancies were reported among female patients. The median age at first pregnancy was 27 years (IQR 24–30) with BrECADD and 25 years (22–28) with eBEACOPP. 87 (95%) of the 92 pregnancies occurred without using cryopreserved material, and 73 (79%) of the 92 pregnancies resulted in childbirth. Reasons for early pregnancy termination included spontaneous miscarriage in 15 (16%) of 92 cases and induced abortion in four (4%) of 92 cases. Among female patients with a reported desire to have children (n=200), pregnancies occurred in 23 (21%) of 109 patients in the BrECADD group and in 15 (16%) of 91 patients in the eBEACOPP group. Cumulative incidence of first pregnancies among women younger than 40 years is shown in the appendix (p 11). A total of 73 childbirths (including one stillbirth) were reported in 65 (13%) of 496 women younger than 40 years. Among women, the 5-year incidence of first livebirths following BrECADD and eBEACOPP treatment was 19·3% (95% CI 13·7–27·3) and 17·1% (11·9–24·6), respectively (p=0·53, figure 4A). During follow-up, 36 pregnancies were reported among partners of male patients. The median age at first pregnancy was 29 years (IQR 26–33) with BrECADD and 29 years (28–31) with eBEACOPP. Of all pregnancies in partners of male patients, six (17%) of 36 were achieved using cryopreserved material, and 35 (97%) of the 36 pregnancies resulted in childbirth; in one (3%) pregnancy, spontaneous miscarriage occurred. Among male patients with a reported desire to have children (n=258), pregnancies occurred in 16 (13%) of

125 in the BrECADD group and four (3%) of 133 in the eBEACOPP group. Cumulative incidence of first pregnancies among partners of male patients younger than 50 years is shown in the appendix (p 14). A total of 35 childbirths were reported in 33 (5%) of 704 men younger than 50 years. The 5-year incidence of fathering at least one child was significantly higher in the BrECADD group compared with the eBEACOPP group (9·3% [95% CI 6·0–14·5] *vs* 3·3% [1·7–6·5], p=0·014; figure 4B). Expected birth rates per year for the German reference population (females only) and livebirth rates for female and male patients of HD21 are given in the appendix (pp 6–7). Livebirth rates among women in the BrECADD group in years 1 through 4 of follow-up were 0% (0/248), 4% (10/240), 5% (11/232), and 5% (11/207), respectively. According to German population data for females, the expected livebirth rate between years 2 and 4 was approximately 6%.

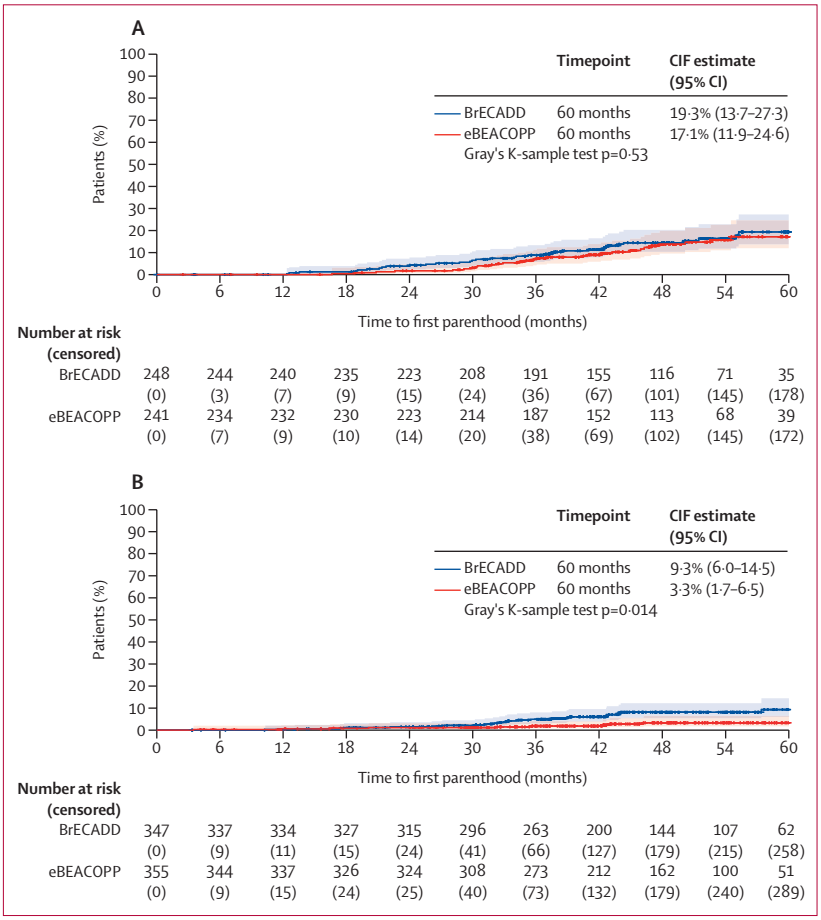

Figure 4: **Incidence of first parenthood in female (A) and male (B) patients**
BrECADD=brentuximab vedotin, etoposide, cyclophosphamide, doxorubicin, dacarbazine, and dexamethasone. CIF=cumulative incidence function. eBEACOPP=escalated doses of bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone. FSH=follicle-stimulating hormone.

Discussion

This analysis of gonadal function recovery and fertility in patients treated with polychemotherapy for newly diagnosed advanced-stage classic Hodgkin lymphoma in the HD21 study provides two key findings. First, the novel BrECADD regimen significantly improved gonadal function recovery compared with eBEACOPP in both male and female patients. This effect was particularly pronounced in women older than 30 years and in men in general—ie, in patients at highest risk for gonadal dysfunction after treatment with eBEACOPP.[1,2,4] Importantly, the 4-year recovery rates after treatment with BrECADD were high (95% for female patients and 86% for male patients). Second, improvements in gonadal function were accompanied by higher incidences of parenthood in the BrECADD group (significantly so in men), indicating a favourable impact on fertility.

The HD21 study was primarily designed to improve the tolerability of eBEACOPP chemotherapy regimen while maintaining its efficacy.[8] Although the primary tolerability endpoint in the HD21 study defined acute and severe treatment-related toxicities as a surrogate for tolerability, the modification in the BrECADD regimen also aimed to diminish gonadal toxicity by replacing procarbazine with dacarbazine. Since alkylators in general are known to induce irreversible gonadal damage in both men and women,[11,12] the large and highly significant benefit of BrECADD compared with eBEACOPP regarding recovery of gonadal function seems to be primarily driven by the omission of procarbazine in the BrECADD regimen.[13,14] Recent evidence supports this favourable long-term toxicity profile of dacarbazine-based regimens. A retrospective genomic study evaluating the effects of eBEACOPP versus eBEACOPDac (ie, eBEACOPP with dacarbazine instead of procarbazine) found that procarbazine-containing chemotherapy led to significantly higher mutation burdens in haematopoietic stem and progenitor cells, with distinct mutational signatures attributed to procarbazine exposure.[15] Moreover, these mutational effects were detectable in sperm DNA and in the germline of offspring conceived after treatment, raising concerns regarding long-term genomic health in survivors of Hodgkin lymphoma. The cumulative doses of the alkylating agent cyclophosphamide in BrECADD (5 g/m² with four cycles, and 7·5 g/m² with six cycles, respectively) would not be expected to have a relevant impact on gonadal function in women.[16,17] By contrast, lower recovery rates relating to increasing cycle numbers indicate cumulative gonadotoxic effects in men.

ABVD is widely recognised as a less gonadotoxic regimen compared with eBEACOPP.[2,18] However, its lower efficacy in advanced-stage Hodgkin lymphoma necessitates salvage therapies, which often include high-dose chemotherapy or autologous stem-cell transplantation with substantial risks.[6] Overall, the gonadotoxic potential of BrECADD seems to be similar to that of the ABVD regimen.[2,18] In the RATHL trial, following treatment with ABVD or AVD (doxorubicin,

vinblastine, and dacarbazine), normalised ovarian function determined by FSH recovery to concentrations of 25 IU/L or below was seen in 96% of low-risk (PET2-negative) female patients.[2] Using the same threshold, but without selection of low-risk patients, we observed a similar FSH recovery rate after treatment with BrECADD. Consistent with this, at a median follow-up of 52 months in RATHL, 16% of female patients reported a pregnancy following an ABVD-based approach, which is similar to the pregnancy rate following BrECADD in HD21 after 4 years. Accordingly, relevant differences between ABVD and BrECADD on ovarian function cannot be assumed. Similarly, a higher number of pregnancies was found in patients treated with BV-AVD (brentuximab vedotin, doxorubicin, vinblastine, and dacarbazine) compared with ABVD.[19] However, comparisons of BrECADD with other contemporary regimens such as BV-AVD[20] or Nivo-AVD (nivolumab, doxorubicin, vinblastine, and dacarbazine)[21] in terms of gonadal function and childbirth are severely limited due to the paucity of reported data. This underlines the importance of the American Society of Clinical Oncology recommendation to include the assessment of gonadal function in clinical trials.[14] In summary, first-line treatment of advanced-stage classic Hodgkin lymphoma with BrECADD appears to preserve gonadal function in most patients of childbearing age.

A key concern with impaired gonadal function is compromised fertility. We observed more children born and more patients becoming parents in those receiving BrECADD versus eBEACOPP; however, adequate determination of fertility might require longer follow-up than the median of 4 years assessed in HD21 and shortened fertile lifespan and risk of premature ovarian insufficiency cannot be excluded. We observed an increasing rate of parenthood per year with longer follow-up in HD21, potentially attributed to both gonadal function recovery over time and possibly deferred family planning after the cancer diagnosis and treatment. Notably, in female patients in the BrECADD group in HD21, the observed birth rate from the third year of follow-up was similar to an age-adjusted rate of motherhood per year of 6% estimated from German populational data. In line with this observation, a recent analysis of registry data from Scandinavia did not find significant differences in terms of reproduction for female patients treated for Hodgkin lymphoma, even with eBEACOPP.[5] Overall, normalised gonadal function in female patients with advanced-stage classic Hodgkin lymphoma following BrECADD treatment seems to be accompanied by normalised birth rates starting about 3 years after the end of treatment.

Compared with women, gonadal toxicity in men is less commonly reported, although their fertility is more severely affected after treatment for advanced-stage classic Hodgkin lymphoma.[1,22] Gonadotoxic effects of identical regimens seem to be more pronounced in males than in females, translating into diminished fatherhood rates, although sperm cryopreservation is more accessible compared with oocyte cryopreservation. Male patients receiving high cumulative doses of alkylators with six to eight cycles of eBEACOPP father children at lower rates than those who have received ABVD.[5] Accordingly, we found low rates of gonadal function recovery in the eBEACOPP group, indicating a large and permanent treatment burden in this cohort. In comparison, we observed much higher rates of gonadal function recovery after BrECADD than eBEACOPP in men, which resulted in a significantly increased incidence of fathering children. However, the large difference in favour of BrECADD is also caused by poor outcomes with eBEACOPP. Our findings indicate that severe gonadal damage with eBEACOPP occurs after four cycles.[1] This matches a previous report of the AHL2011 study, where FSH concentrations and sperm concentration at the end of the follow-up did not return to baseline, even in those who predominantly received just two cycles of eBEACOPP followed by ABVD.[3] In our cohort, mean inhibin B concentrations over time could reflect transitory damage in male POCBP treated with BrECADD, compared with the persistently low concentrations of the peptide in the cohort of male POCBP treated with eBEACOPP, suggesting more profound damage. Even though BrECADD has a high absolute recovery rate of gonadal function at 4 years, we observed a striking difference in the incidence of paternity compared with maternity in the HD21 study. Unlike maternity rates, fatherhood rates per year and age for the German population are not readily available from the German Federal Statistical Office and therefore cannot be adequately used for comparison of our data.

The role of GnRH agonists during chemotherapy for the protection of ovarian function remains controversial, and contraceptives are proven not to be effective in preserving fertility.[23] Nevertheless, contraceptives including GnRH agonists were used with the intention of preserving ovarian function in a majority of female POCBP in HD21. However, the 4-year recovery rate of gonadal function in BrECADD-treated females was more than 95% with or without ovarian protection with contraceptives or GnRH agonists, confirming that gonadal function recovery is highly prevalent even without these measures.

Counselling on fertility preservation methods was recommended per protocol in the HD21 trial, and a substantial proportion of patients made use of cryopreservation methods before treatment. However, only a small fraction of patients in HD21 with reported pregnancy made use of cryopreserved material, with the highest rate seen in males and their partners. This finding suggests that most patients can successfully have children without medically assisted reproduction techniques, at least during the 4 years of reported follow-up in HD21. As premature ovarian insufficiency

can still occur, newly diagnosed female patients should continue to receive individualised counselling regarding potential fertility preservation strategies.

Our analysis comes with limitations. Assessment and tracking of sexual hormones were not mandatory in HD21 but strongly recommended. As a result, there are missing data for several trial patients and assumption of randomness cannot be proven. Still, most patients could be included in the analysis of gonadal function recovery and their baseline characteristics were similar to those of the entire POCBP cohort. Our analysis focuses primarily on FSH serum concentrations as a surrogate for gonadal function. While additional markers such as testosterone and oestrogen could provide further insights and semen analysis remains the gold standard to assess male fertility, they were not consistently reported in HD21. Similarly, menstrual cycle data, including the incidence of amenorrhoea and subsequent recovery of regular cycles, were collected in the electronic case report form, but data completeness was insufficient for a reliable analysis. Consequently, we were unable to establish an association between FSH concentrations and menstrual cycle recovery across treatment groups. However, inhibin B and AMH serum concentrations were available in a larger proportion and support the conclusions drawn from this analysis. Irrespective of measurable gonadal recovery, the issue of fertility cannot be adequately addressed by our analysis, as fertility is also dependent on social, economic, and health-related variables that were not captured in our study. Additionally, there are no available data on the number of premature deliveries and low birthweight infants as this was beyond the scope of this analysis. However, the randomised design of HD21 enables us to draw conclusions on the impact of BrECADD compared with eBEACOPP on reproduction, and provides meaningful information for both patients and caregivers. A salient strength of our analysis is the large number of well-documented patients, which allows firm conclusions to be drawn on gonadal recovery after treatment with either eBEACOPP or BrECADD for advanced-stage classic Hodgkin lymphoma.

In summary, gonadal function in patients treated for advanced-stage classic Hodgkin lymphoma in the HD21 study recovers more frequently after treatment with BrECADD than with eBEACOPP. This results in normalisation of gonadal function and birth rates in most patients. Our study suggests that BrECADD is a valid first-line treatment option in men and women with advanced-stage classic Hodgkin lymphoma who desire to have children.

Contributors

JF, GS, JJ, PB, and KB designed the study and were responsible for data analysis and interpretation. GS and JJ directly accessed and verified the underlying data reported in the manuscript. AM, RG, MHe, VS, AH, FK, JD, MHä, UN, JM, JCH, SM, JMZ, AF, AV, BH, SM, PG, PK, DM, and PB provided study materials or recruited patients. JF, GS, JJ, MF, PB, and KB were responsible for the collection and assembly of data. All authors contributed to manuscript writing, final approval of the manuscript, and are accountable for all aspects of the work. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Declaration of interests

JF reports speaker fees from Takeda and Roche Pharma. AM is an advisor for Janssen, Takeda, and BeiGene. RG reports consulting fees and honoraria from Celgene, Novartis, Roche, BMS, Takeda, AbbVie, AstraZeneca, Janssen, MSD, Amgen, Merck, Gilead, Daiichi Sankyo, and Sanofi; holds stock options from Novo Nordisk, Lilly, and Vertex; and has other financial interests or non-financial interests from Roche, Amgen, Janssen, AstraZeneca, Novartis, MSD, Celgene, Gilead, BMS, AbbVie, and Daiichi Sankyo. MHe reports consulting fees from Roche, Gilead, Takeda, AbbVie, and Menarini; honoraria from Pfizer, Roche, and Takeda; and travel support from Takeda. MHä reports honoraria from Sobi, Novartis, Gilead, Falk Foundation, BMS, and Kite, and is a consultant for Pfizer, Incyte, Sanofi, Roche, Amgen, Sobi, Janssen, Kite, BMS, and BeiGene. JCH has received honoraria from Takeda, travel support from Beigene, and has held advisory roles for PharmaMar and Takeda. AV reports speaker fees and advisory boards from Novartis, Roche, Gilead, BMS, AbbVie, and AstraZeneca, and reports travel grants from Janssen, Sobi, and Gilead. JMZ reports an unrestricted grant from Takeda for minimal residual disease research. AF has received grants from Takeda and Roche; consulting fees from Takeda, Kite Gilead, and Sobi; and honoraria from Johnson & Johnson, BMS, Roche, Eusapharma, Takeda, Kite Gilead, Merck Sharp & Dohme, Kyowa Kirin, and Sobi. PG reports speaker fees from Roche. PK reports travel support from Takeda and Roche as well as other financial interests and non-financial interests from MSD. DM reports speaker fees from Roche. PB reports institutional grants, honoraria, and travel support from Takeda Oncology. KB reports honoraria from Takeda. All other authors declare no competing interests.

Data sharing

Individual patient data from this trial will not be published in the public domain; however, the trial protocol is published elsewhere[8] and will be available online for an indefinite period.

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