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PET-adapted approaches to primary therapy for advanced Hodgkin lymphoma

Noemie Lang and Michael Crump

***Abstract*:** Recent results of randomized phase III studies of FDG-PET-adapted therapy for advanced Hodgkin lymphoma (HL) have clearly demonstrated benefit to alteration of treatment according to interim response, in particular regarding reducing toxicity while maintaining efficacy. However, these studies have differences in design including initial chemotherapy regimen, PET response criteria, patient populations enrolled, and inclusion of radiation, and report different results regarding efficacy and toxicities, which makes cross-trial comparisons difficult. Practitioners are presented with deciding which of these approaches will provide the optimum outcome, balancing toxicity and efficacy, and for which patient with advanced-stage HL. This review summarizes the observations reported from these trials and provides context to help guide physicians and patients in treatment decisions for advanced HL.

Keywords: hodgkin lymphoma, interim, FDG-PET, randomized, toxicity

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Correspondence to:
Michael Crump
Princess Margaret Cancer Centre, University of Toronto, 610 University Avenue, OPG 6-426, Toronto, ON, M5G 2M9, Canada
michael.crump@uhn.ca

Noemie Lang
Princess Margaret Cancer Centre, University of Toronto, Toronto, ON, Canada

Introduction

Improving the risk-benefit balance in advanced-stage Hodgkin lymphoma (HL), maximizing the cure rate while decreasing short- and long-term adverse effects from treatment, has been a challenge addressed by phase III clinical trials over many years. Consistently, polychemotherapy using ABVD (doxorubicin, bleomycin, vinblastine, and dacarbazine) is able to achieve a rate of progression-free survival (PFS) of approximately 75% at 5 years, and has a safety profile that is acceptable to patients and their oncologists.[1–3] The more intensive escalated BEACOPP regimen (escBEACOPP: bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone) developed by the German Hodgkin Study Group (GHSG) has consistently provided a PFS rate of 90%, but with significant added hematologic toxicity and higher rates of febrile neutropenia.[4–12] Although individual comparisons of these two regimens by other cooperative groups have not demonstrated a difference in overall survival (OS), a recent network meta-analysis suggests an meaningful estimated 10% improvement in OS at 5 years favoring escBEACOPP.[13,14] A major limitation of this meta-analysis was its short observation time, limited to 5 years, which does not allow complete identification of late complications such as secondary malignancies, which occur many years after treatment completion, or late cardiac and other long-term side effects that significantly impact quality of life of HL survivors.[15,16]

Functional imaging with fluoro-deoxyglucose (FDG)-positron emission tomography (PET) combined with computed tomography (CT) is recognized as the first-choice imaging technique for staging and response evaluation in HL. The five-point Deauville scale has now been incorporated into study designs as the standard for treatment response interpretation, with a Deauville score of 1–3 (nodal uptake less than or equal to the liver) considered as a complete metabolic response for advanced stage HL.[17] Early interim PET-CT response assessment performed after two cycles of ABVD (PET-2), has been demonstrated to be a powerful predictor of outcome,

although both negative and positive predictive value have varied in cohort studies and retrospective analyses.[18–25] Standardization of response assessment with FDG PET has been important to prospective study design, and our subsequent understanding of results from PET-guided treatment strategies. While the cut-off levels of uptake defining a negative or positive interim scan have varied between trials, these criteria have allowed identification of patients who could be considered for studies aiming to improve outcome of high-risk patients by intensification of their treatment (escalation) and to minimize exposure to toxic drugs without compromising the efficacy of therapy for low-risk patients (de-escalation).[26]

Results of recent frontline therapy trials in advanced-stage HL

Evidence from retrospective analyses, and encouraging results of prospective phase II studies, have suggested an improvement in outcome by escalating chemotherapy to a more intensive regimen for patients with a poor PET-2 response, and a potentially better safety profile with similar efficacy by reduction of treatment intensity for those achieving a complete molecular response (CMR).[27–35] Consequently, three prospective multicentric phase III trials in previously untreated advanced-stage HL have been conducted by international cooperative groups aiming to assess the effectiveness of these individualized approaches.[36–39] At the same time, results of a randomized trial without adaptation based on interim PET scanning evaluating the efficacy of the CD30 chemo-immunoconjugate brentuximab vedotin combined with AVD chemotherapy in advanced HL have also been published.[40] We will briefly describe the design and results of these studies, which are summarized in Tables 1 and 2.

RATHL (Response Adapted Therapy in Advanced Hodgkin Lymphoma) was a non-inferiority study that recruited 1203 patients age 18 years or older with advanced-stage HL, defined as stage II with B symptoms or risk factors (42%), and stage III or IV.[38] Patients first receive two cycles of ABVD chemotherapy followed by a randomization between ABVD (standard arm) or bleomycin omission AVD (de-escalation arm) for those achieving a negative PET-2 scan (Deauville score 1–3); while those with a positive PET-2 scan were assigned to six cycles of BEACOPP-14 or four cycles of escBEACOPP. Consolidative radiotherapy was not recommended for PET-2 negative patients, but was allowed at the treating physician's discretion; radiation was administered to 35/937 patients with negative PET-2 scans and 43/182 patients with a positive PET-2 scan. Primary endpoint was 3-year PFS, with a non-inferiority margin between randomized arms of 5%. After a median follow up of 41.2 months, among the 84% of patients with a CMR on interim PET, 5-year PFS was 80.6% for the AVD arm *versus* 82.7% for the patients receiving ABVD. Therefore, with a minimal estimated risk of treatment failure of 1.6% and no difference in OS, it has been widely accepted that omission of bleomycin allows a reduction in potential toxicity without any significant impairment on clinical outcome. Patients with a positive PET-2 scan reached a 3-year PFS of 67.5% following treatment escalation to BEACOPP-14 or escBEACOPP, which appears better than the previously reported 15–45% rate after six cycles of ABVD.[22]

The GHSG trial HD18 enrolled over 2000 patients aged 18–60 years with stage IIB (14%), III, or IV HL, who were assigned to one of two parallel treatment groups on the basis of their PET-2 findings.[36,37] After administration of two cycles of escBEACOPP, patients with a negative PET-2, (uptake less than the mediastinal blood pool, similar to Deauville score <3), were randomized to receive two additional cycles (de-escalation arm) or four additional cycles of escBEACOPP (standard arm). PET-2 positive patients (uptake greater than the mediastinal blood pool) were randomized to receive four additional cycles escBEACOPP with (escalation arm) or without (standard arm) the addition of the CD20 antibody rituximab. The primary aim of the study was to assess superiority of the escalation arm with a 5-year PFS improvement of at least 15% and non-inferiority of the de-escalated arm with a margin of 6%. In this study, 30 Gy consolidative radiotherapy was administered at the end-of-treatment for all residual masses $\geqslant$2.5 cm that were PET-positive (uptake greater than the mediastinal blood pool). The escalation arm was closed after second interim analysis for futility as it appeared that addition of rituximab does not impact the outcome of PET-2 positive patients.[36] After a median follow up of 66 months, the study met its primary endpoint in the PET-2 negative cohort for

Table 1. Outcome of therapy escalation for patients receiving first-line treatment of HL with a positive interim PET scan.

Trial	Phase	*N* Total (Evaluable)	mFU (mo)	Upfront regimen	Intervention Esc PET-2 + De-esc PET-2 -	Randomi-zation	Consolidative EOT RT (%)	Stage (%)	Age (years)	IPS >3 (%)	Bulk (10 cm or >1/3) (%)	PET-2 + Criteria (Deaville)	PET-2 + (%)	PET-2 + PFS (%)	PET-2 + OS (%)
GITIL/ FIL HD 0607	II	782 (780)	43	ABVD	Esc: 4 eB +4 bB +/- rituximab	Yes RT 30 Gy for PET-2 + (e+bB +/- rituximab)	CR (EOT PET) Randomized if ⩾5 cm	IIB (36) III (32) IV (32)	18–60	12.5	20	4–5	19	60 (3 years)	89 (3 years)
SWOG 0816	II	371 (331)	70.8	ABVD	Esc: 6 eB	None	None	II (0) III (52) IV (48)	18–60	51 (>2)	18	4–5	18	66 (5 years)	86 (5 years)
HD0801	II	519 (512)	25	ABVD	Esc: 4 IGEV + BEAM/ABMT	None	NA	IIB (19) III (35) IV (46)	18–70	44 (>2)	35	4–5	20	74 (2 years)	NA
NCRI RATHL	III	1203 (1119)	41.2	ABVD	Esc: 6bB/4eB	None for PET-2 +	Not recommended	IIAX/IIB (42) III (30) IV (28)	>18	17.5	32	4–5	16	67.5 (3 years)	88 (3 years)
GHSG HD18	III	2102 (1945)	66	eB	Esc: 4eB/6bB + R	Yes PET-2 + (+/- R)	Yes (36)	IIBX/E (14) III (49) IV (36)	18–60	16	29	3–5	48	92.5 (3 years)§ 88 *versus* 90 (5 years)	97 (3 years)§ 94 *versus* 96 (5 years)

ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; ASCT, Autologous Stem Cell Transplantation; AVD, doxorubicin, vinblastine, dacarbazine; BEAM, carmustine, etoposide, cytarabine, melphalan; CR, complete response; de-esc, treatment de-escalation; eB, escalated BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone); Esc, treatment escalation; EOT RT, end of treatment radiation therapy; GHSG, German Hodgkin Study Group; GITIL/FIL, Gruppo Italiano Terapie Innovative nei Linfomi/Fondazione Italiana Linfomi; HL, Hodgkin lymphoma; IGEV, Ifosfamide, gemcitabine, vinorelbine; IPS, international prognostic score; mFu(mo), median follow-up (months); N, number of patients; NA, not available; NCRI, National Cancer Research Institute; OS, overall survival; PET, positron emission tomography ; PET-2, positron emission tomography scan after 2 cycles of chemotherapy; PFS, progression-free survival; RT, radiation therapy; SWOG, Southwest Oncology Group. §, all PET2+ patients.

Table 2. Outcome of therapy de-escalation for patients receiving front-line treatment of HL with a negative interim PET scan.

Trial	Phase	N Total *(Evaluable)*	mFU (mo)	Upfront regimen	Intervention Esc PET-2 + De-esc PET-2 -	Randomization	Stage (%)	Age (years)	IPS > 3 (%)	Bulk > 10 cm or > 1/3 TTD (%)	PET-2 – criteria *	PET-2 – PFS (%)	PET-2 – OS (%)
NCRI RATHL	III	1203 *(1119)*	41.2	ABVD	De-esc: 4 AVD	Yes for PET2 – (ABVD *versus* ABVD/AVD)	IIAX-IIB (42) III (30) IV (28)	>18	17.5	32	D1-3	85	97 (3 years)
GHSG HD18	III	2102 *(1945)*	66	eB	De-esc: 2 eB	Yes for PET2 – (6/8eB *versus* 4eB)	IIBX/E (14) III (49) IV (36)	18–60	16	29	D1,2	93.5 91 *versus* 92 (5 years)	97 (3 years) 95.5 *versus* 97.5 (5 years)
AHL2011	III	823 *(799)*	50.4	eB	De-esc: 4 ABVD	Yes upfront PET-2 (eB *versus* PET-adapted therapy)	IIBX/E (12) III (28) IV (60)	16–60	31	37	D1-3	93.5	97 (3 years)

ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; AVD, doxorubicin, vinblastine, dacarbazine; eB, escalated BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone); Esc, treatment escalation; D, Deauville score; de-esc, treatment de-escalation; GHSG, German Hodgkin Study Group; HL, Hodgkin lymphoma; IPS, international prognostic score; mFu(mo), median follow-up (months); N, number of patients; NCRI, National Cancer Research Institute; OS, overall survival; PET, positron emission tomography ; PET-2, positron emission tomography scan after 2 cycles of chemotherapy; PFS, progression-free survival.

de-escalation, with 5-year PFS and OS of 92% *versus* 91% and 98% *versus* 95% for de-escalated and standard arms, respectively. The 3-year PFS of PET-2 positive patients (88%) was higher than reported in other studies with similar definitions of positive interim scans,[18] and similar to those with a PET-2 CMR, respectively 92.5% *versus* 93.5%. The PFS of patients with a Deauville score on interim scan of 3, representing approximatively 25% of the whole cohort, was similar to those with Deauville 1 or 2 (93.8%). In a *post hoc* analysis of PET-2 Deauville 4 positive patients allocated to six escBEACOPP, PFS and OS were reported slightly inferior to the whole PET-2 positive cohort, at 87.6% and 96.8%, respectively.[41]

The Lymphoma Study Association (LYSA) recently reported the AHL 2011 trial, which is the only RCT to date to compare standard *versus* PET-modified therapy following an interim scan.[39] In this trial, patients were randomized to receive six cycles of escBEACOPP or to a PET-adapted approach, with de-escalation of treatment for patients with a negative PET-2 scan, using a non-inferiority design with a PFS margin of 10%. A total of 823 patients aged 60 or less with stage IIB (12%), III, or IV HL were randomized to either six cycles of escBEACOPP without modification based on PET-2 (standard arm), or a PET-guided arm where patients with a negative interim scan (Deauville score 1–3) received four cycles of ABVD; those with a Deauville score of 4 continued escBEACOPP for four more cycles, and those with a score of 5 were considered for alternative therapies. A second interim PET assessment was performed after 4 cycles for both arms, after which patients were switched to salvage therapy in case of persistent PET-positivity (Deauville 4 or 5). The use of consolidative radiotherapy was left to the investigator's discretion. With a median follow-up of 50.4 months, the 5-year PFS and OS were similar in both groups, at 86% and 95.5%, respectively, demonstrating that PET-2 monitoring of chemotherapy response with reduction of treatment intensity for patients in CMR led to at least equivalent outcomes as six cycles of escBEACOPP.

Recently, Connors and colleagues reported results of ECHELON-1,[40] a multicentric prospective randomized trial evaluating the role of the CD30 chemo-immunoconjugate brentuximab vedotin (Adcetris®) in frontline therapy. Patients over 18 years with stage III and IV previously untreated HL were randomly assigned to receive either brentuximab vedotin in combination with AVD (AAVD, experimental arm) or standard ABVD for six cycles. The primary endpoint of this study was modified PFS, a composite endpoint which includes time to progression, death, and incomplete response, as well as the application of additional anticancer therapies, based on treating physician's discretion following end of treatment PET scanning. In this study, patients had a PET scan after two cycles of therapy, and those with a Deauville score of 5 were considered to have progressive disease and underwent salvage therapy; treatment was otherwise not modified on the basis of PET-2 results. With a median follow-up of 24.9 months, AAVD was shown to be superior to ABVD with 2-year modified PFS of 82% *versus* 77%, respectively. This benefit seems to be maintained at 3 years, but there is no difference in OS between study arms.[42] Of note, patients in either arm with a positive interim PET scan had poor outcomes without treatment escalation: 3-year PFS was 58.2% for patients receiving AAVD and 36.6% for those in the ABVD arm.

Treatment-related toxicities

It has been long recognized that high cure rates of systemic therapy in advanced-stage HL come at the expense of acute and late side effects. Acute toxicities during therapy are well described, and discontinuation of therapy due to toxicity is an important contributor to comparisons of event-free survival.[4] Late effects are potentially underreported in the current literature, as these often occur after several years of follow up, after the primary results of the trials are reported. Acute side effects include myelosuppression resulting in febrile neutropenia and need for transfusion support, infections as well as organ-related toxicity, affecting mainly the gastro-intestinal tract, heart, peripheral nerves, and lungs. Acute adverse events from recent trials are summarized in Table 3. Late complications from treatment include persistent fatigue, psychosocial concerns, fertility impairment, avascular necrosis, cardiovascular diseases, and secondary malignancies.[15,16,43–49] All these long-term side effects have the potential to negatively impact patient quality of life and survival.

Acute side effects

ABVD was shown to be superior in comparison to mechlorethamine-based approaches in terms

Table 3. Acute toxicities of first-line therapies in advanced HL reported in recent phase III trials.

Toxicities	NCRI RATHL			GHSG HD 18			AHL2011		ECHELON–1	
	Esc 4 B/eB	De–esc 4 AVD	4 ABVD	4 eB	6 eB	8 eB	6 eB	De–esc 4 ABVD	6 AAVD	6 ABVD
All Grade 3–5 AE (%)	80–83	65	69	91	95	98	NA	NA	83	66
Hematological grade 3–5 (%)	72–74	60	60	90	94	95	NA	NA	NA	NA
Thrombocytopenia grade 3–5 (%)	19–42	3	1	57	70	74	66	40	NA	NA
Anemia grade 3–5 (%)	NA	NA	NA	39	51	57	69	28	NA	NA
Neutropenia grade 3–5 (%)	63–67	59	59	NA[a,b]	NA[a,b]	NA[a,b]	87[b]	90	54	39
Febrile neutropenia (%)	11–26	5	5	22	23	33	35	23	19	8
Infections (%)	37–42	10	15	8	12	17	22	12	18	10
Gastro–intestinal grade 3–5 (%)	NA	NA	NA	2	7	5	11	11	NA[c]	NA[c]
Cardiac grade 3–5 (%)	0–1	<0.5	1	NA	NA	NA	1	1	2	NA
Vascular grade 3–5 (%)	3–9	3	5	NA	NA	NA	3.4	2.5	NA	NA
Pulmonary grade 3–5 (%)	4–5	1	3	2	2	6	4	4	<1	3
Neurologic grade 3–5 (%)	4–10	3	5	3	7	13	4	2	11	2
Therapy discontinuation due to AE (%)	NA	0.6	1.5	<1	0	4	7	<1	4.2	3.3
Treatment related mortality (%)	2.3	0.9	0	0	1	1	1	<1	1	1

AAVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; AE, adverse event; AVD, doxorubicin, vinblastine, dacarbazine; B/eB, BEACOPP/escalated BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone); Esc, treatment escalation; de-esc, treatment de-escalation; G-CSF, granulocyte colony-stimulating factor; GHSG, German Hodgkin Study Group; HL, Hodgkin lymphoma; NA, not available; NCRI, National Cancer Research Institute.
[a]Leucopenia rate for four escBEACOPP 88%, six escBEACOPP 93%, eight escBEACOPP 93%.
[b]Mandatory G-CSF.
[c]Reported separately: grade 3-4 respectively for AAVD *versus* ABVD is for abdominal pain 3% *versus* <1%, stomatis 2% *versus* <1%, diarrhea 3% *versus* <1%, vomiting 3% *versus* 1%, constipation 2% *versus* <1%.

of PFS,[3] and acute and late effects, and has been the standard chemotherapy regimen in limited stage and advanced HL trials on both sides of the Atlantic. The safety profile of this combination is well understood, and, for the most part, is considered free from effects on fertility and the spectre of hematologic malignancies. Intensification of therapy in order to overcome drug resistance, one of the key principles behind the escBEACOPP regimen, results in significant added hematological toxicity, with rates of leukopenia reaching >95% (*versus* 70% for ABVD) and higher rates of febrile neutropenia, approximately 25%, despite mandatory growth factors support with G-CSF.[7–9] Moreover, grade 3 and 4 thrombocytopenia and anemia are reported in 65% and 60% of patients, depending on number of cycles received, *versus* <10% for ABVD, with transfusion of red blood cells and platelets required in up to 70% and 45% of patients, respectively.

In a combined retrospective analysis of HD9, HD12, and HD15 studies from the GHSG, Wongso and colleagues have reported a rate of

treatment-related mortality (TRM) of 1.9% associated with escBEACOPP, attributed mainly to neutropenic infections, especially in patients above 50 years of age or with a poor performance status.[50] Importantly, however, results of PET-adapted trials show a substantial reduction of grade 3–4 hematologic and nonhematologic adverse events and an extremely low TRM in all de-escalating approaches for PET-2 negative patients (none in HD18 and two patients representing <1% in AHL2011[37,39]). Although cross-trial comparisons have to be made with caution, it seems that hematologic toxicity observed in AHL2011 could be slightly lower than within HD18, with fewer cases of severe anemia (24% *versus* 39%) and thrombocytopenia (36% *versus* 57%). Nevertheless, neutropenic fever still occurs in more than 20% in both trials,[37,39] thus escBEACOPP has to be restricted to young and fit patients and requires close monitoring of blood-counts and anti-infectious prophylaxis. Hematologic toxicities from recent phase III studies featuring treatment escalation and phase III trials are shown in Table 3.

The AAVD regimen reported by Connors and colleagues also caused significant myelosuppression, with a rate of grade 3–4 neutropenia of 54% and of neutropenic infections of 19%.[40] There were seven deaths in the AAVD arm from neutropenic infection, *versus* none in the ABVD arm, leading to a study amendment adding G-CSF primary prophylaxis with this regimen. Moreover, a significant 67% rate of polyneuropathy was observed (*versus* 43% for ABVD), with 11% of grade 3–4 (*versus* 2% for ABVD). Even though roughly two-thirds of incident cases of neuropathy resolved or improved at the time of the last follow-up visit, this might be taking in consideration for treatment decision, in particular when considering this regimen for older patients.

Additional nonhematologic toxicities from the phase III trials reviewed above are summarized in Table 3. Bleomycin exposure is linked to significant morbidity, with a reported mortality rate of 4–5%, particularly in elderly populations.[51–53] The RATHL study demonstrated that omission of bleomycin administration for the last four cycles of treatment in PET2 complete responders was safe and did not compromise disease control; notably, the incidence of grade 3–4 bleomycin lung toxicity was very low in the patients receiving ABVD in that trial (5/468 patients, *versus* 1/457 receiving AVD).[38] Similarly, no excess pulmonary toxicity was reported with two cycles of escBEACOPP plus four cycles of ABVD in AHL 2011 study.[39] Interstitial pneumonitis grade ⩾3 was reported in 5/662 patients (<1%) on AAVD and 21/669 in the ABVD arm (3%) in the ECHELON-1 trial, highlighting the variability of this complication in severity and incidence in recent studies of advanced HL. Acute cardiac toxicity does not appear to differ between trials, with similar doxorubicin exposure reported (Table 3).

Long-term side effects

Approximately 80% of advanced-stage HL presentations occur at the second through fourth decades of life, therefore risk of developing secondary infertility is a major concern in this young population. Unfortunately, only scarce data are available on the subject. End-points of studies vary, and may not accurately reflect the fertility potential of patients enrolled on prospective trials. Alkylating agents, such as procarbazine and cyclophosphamide contained in escBEACOPP and in salvage regimens such as high dose BEAM (carmustine, etoposide, cytarabine and melphalan), increase the risk of gonadal damage and infertility. The risk of amenorrhea rises proportionally to cumulative dose of alkylating agents and with age at treatment, especially in woman age >30 years. ABVD is associated with a low rate of infertility, estimated at <10% in men and <5% in women. Conversely, escBEACOPP uses higher doses of alkylating agents, and, therefore, leads to potential fertility impairment, with up to 90% prolonged azoospermia in men and 5–25% premature ovarian failure in women under the age of 30 years.[43,44,54–57]

Fertility preservation has improved for both men (ejaculated or biopsied-collected sperm cryopreservation) and women (embryo, mature oocyte or ovarian tissue cryopreservation), leading to pregnancy ranging between 3 and 18%.[54] Nevertheless, there are only limited data available regarding fertility with PET-adapted approaches, as median follow up of those trials is still short. AHL 2011 reported a significantly higher rate of pregnancies in the PET-guided group ($N = 45$, 11%) than the standard group ($N = 28$, 7%), but the number that were conceived with assistance was not reported. In ECHELON-1, fertility was

not formally assessed, but a similar number of subsequent pregnancies were reported in both arms; information on male, female, and assisted conception rates was not provided, making interpretation difficult.[40] It has been reported that reduction of the number of cycles of escBEACOPP, and the cumulative dose of alkylating agents, may decrease the risk of gonadal dysfunction with this regimen,[44] and further analysis of the GHSG and AHL2100 trials will be important to verify this in the era of PET-adapted approaches. Patients with advanced-stage HL with a potential parenthood wish started on escBEACOPP should be offered consultation at diagnosis about fertility preservation, and oocyte and sperm collection performed if this will not significantly delay first-line treatment initiation.

Along with cardiovascular disease, secondary malignancies are the major cause of death among HL survivors. In a large-scale retrospective Dutch HL survivors cohort recruited between 1965 and 2000, with a median follow up of 19.1 years, the cumulative incidence of solid malignancies, such as breast, lung, and gastrointestinal cancers, reaches 48.5% at 40 years after treatment completion, representing a 4.6-fold increased risk in comparison to the general population.[46] Published secondary malignancies rates of recent advanced-stage HL trials are summarized in Table 4.

In a dose-dependent manner, alkylating agent chemotherapy as well as topoisomerase-II-inhibitors (doxorubicin, etoposide) substantially increase the risk of treatment-related malignancies. There is a trend after treatment with escBEACOPP toward higher incidence of secondary cancers compared with ABVD, especially secondary acute myeloid leukemia (AML)/myelodysplastic disorders (MDS).[58–60] These long-term complications are rare events, and, therefore, differences may not reach statistical significance between regimen comparisons in phase III trials. Even though secondary AML/MDS are captured mainly by a maximum follow-up time of 10 years, most solid malignancies will occur later and are thus underestimated in published reports.[46]

Data from recent PET-adapted trials are not mature enough, and not likely to be powered, to draw conclusions regarding long-term risk of secondary neoplasia, especially considering solid tumour incidence. Rates of second cancers in the ECHELON1 trial have not been reported, but follow up of patients in that trial is still too short for reliable estimates. In the HD18 study, there were only two AML cases (<1%) among those treated with four cycles, compared with an incidence of 2% among those treated with six or eight cycles of escBEACOPP.[37] In a preplanned analysis of the AHL 2011 trial, 15 second cancers were observed at the time of reporting, 10 (2%) among patients in the standard arm and 5 (1%) among those treated with the PET-guided approach. Of note, only three second cancers (2%) were detected among patients intensified by escBEACOPP in RATHL study after 3.4 years of follow up, similar to the ABVD (2.7%) and AVD arms (2.3%). While the follow-up duration of trials of escBEACOPP varies, there is evidence that risk of second malignancy with this regimen is dose-dependent, with significantly lower MDS/AML occurrences in patients treated with four or fewer cycles (0.5%) compared with more than four cycles (1.5%), and similar to that reported following ABVD (0.3%).[60] Moreover, these results align with the observed decline trend of cumulative incidence of secondary AML among HL survivors treated after 1989 compared with earlier decades, and correlates with reduction in the use of alkylating agents.[46]

Long-term risks of first line choices have to be put context with the risk of treatment failure and need for subsequent therapy, as high dose chemotherapy and autologous stem cell transplantation, considered as the standard salvage treatment for patients able to tolerate it, carries with an even higher rate of long-term side effects.[61]

Discussion

Recent randomized controlled trials of FDG-PET guided therapy for both limited stage and advanced stage HL now provide clinicians and their patients with meaningful data upon which to base individualized treatment approaches. In the advanced stage setting, differences in patient eligibility and study design, as well as length of follow up, make cross-trial comparison or formal meta-analysis difficult. For example, definition of advanced-stage varied across trials, as stage IIB/IIBX might be considered as early unfavorable or advanced stages depending on the trial eligibility and led to enrollment of an heterogenous advance-stage group of patients (stage II 42% in RATHL, 14% in HD18 and 12% in AHL2011).

Table 4. Incidence of secondary malignancies reported in recent advanced HL studies.

Trial	Phase	N Total (evaluable)	Intervention	mFU (years)	AML / MDS *N* patients (%)	NHL *N* patients (%)	Solid cancer *N* patients (%)	All secondary malignancies *N* patients (%)
HD9 GHSG	III	1282 (1196)	8 COPP/ABVD *versus* 8 bB *versus* 8 eB	9.3	8 COPP/ABVD 1 (0.4) 8 bB 7 (1.5) 8 eB 14 (3)	8 COPP/ABVD 7 (2.7) 8 bB 8 (1.7) 8 eB 5 (1)	8 COPP/ABVD 7 (2.7) 8 bB 16(3.4) 8 eB 9 (1.9)	8 COPP/ABVD 15 (5.7) 8 bB 31 (6.6) 8 eB 28 (6)†
HD12 GHSG	III	1670 (1574)	8 eB *versus* 4 eB + 4 bB	6.5	8 eB 12 (1.5) 4 eB + 4 bB 10 (1.3)	8 eB 11 (1.4) 4 eB + 4 bB 5 (0.6)	8 eB 20 (2.5) 4 eB + 4 bB 18 (2.3)	8 eB 43 (5.5) 4 eB + 4 bB 33 (4.2)
HD15 GHSG	III	2182 (2126)	8 eB *versus* 6 eB *versus* 8 B_{14}	4	8 eB 19 (2.7) 6 eB 2 (0.3) 8 B_{14} 8 (1.1)	8 eB 8 (1.1) 6 eB 6 (0.8) 8 B_{14} 5 (0.7)	8 eB 6 (0.9) 6 eB 9 (1.3) 8 B_{14} 9 (1.3)	8 eB 33 (4.7) 6 eB 17 (2.4) 8 B_{14} 22 (3.1)
E2496 ECOG	III	854 (794)	6/8 ABVD *versus* Stanford V	6.4	6/8 ABVD 1 (0.3) Stanford V 3 (0.8)	6/8 ABVD 2 (0.5) Stanford V 3 (0.8)	6/8 ABVD 12 (3) Stanford V 13 (3.3)	6/8 ABVD 15 (3.8) Stanford V 19 (4.8)
EORTC 20012	III	550 (549)	8 ABVD *versus* 4 eB + 4 bB	3.6	8 ABVD 2 (0.7) 4 eB + 4 bB 4 (1.5)	8 ABVD 3 (1.1) 4 eB + 4 bB 2 (0.8)	8 ABVD 3 (1.1) 4 eB + 4 bB 4 (1.5)	8 ABVD 8 (3) 4 eB + 4 bB 10 (3.8)†
HD 2000 FIL	II	307 (305)	6 ABVD 4 eB + 2 bB 6 CEC	10	6 ABVD 0 (0) 4 eB + 2 bB 1 (1.1) 6 CEC 1 (1.1)	6 ABVD 0 (0) 4 eB + 2 bB 1 (1.1) 6 CEC 0	6 ABVD 1 (<1) 4 eB + 2 bB 4 (4.5) 6 CEC 5 (5.4)	6 ABVD 1 (0.9) 4 eB + 2 bB 6 (6.6) 6 CEC 6 (6) §
Viviani[6]	III	331 (322)	6 ABVD *versus* 4 eB + 4 bB	5.1	6 ABVD 1 (1) 4 eB + 4 bB 2 (1)	NA	NA	NA
SWOG 0816	II	371 (331)	Esc: 6x eB	5.9	6 ABVD (0) 2 ABVD + 6 eB 1 (2)	6 ABVD 1 (0.4) 2 ABVD + 6 eB 1 (2)	6 ABVD 5 (1.9) 2 ABVD + 6 eB 5 (10)	6 ABVD 6 (2) 2 ABVD + 6 eB 7 (14)
NCRI RATHL	III	1214 (1119)	Esc: 4eB/4bB De-esc: 4AVD	3.4	NA	NA	NA	Esc: 2 ABVD + 4 bB/4eB 3 (1.7) De-esc: 6 ABVD 13 (2.7) 2 ABVD + 4 AVD 11 (2.3)
GHSG HD18	III	2102 (1945)	Esc: 4–6 e/ bB+R De-esc: 2 eB	5.5	Esc 8 eB 5 (2) 8 eB+R 4 (2) De-esc 8eB/6eB 8 (2) 4 eB 2 (<1)	Esc 8 eB 3 (1) 8 eB+R 2 (1) De-esc 8eB/6eB 5 (1) 4 eB 8 (2)	Esc 8 eB 2 (1) 8 eB+R 8 (4) De-esc 8eB/6eB 5 (1) 4 eB 3 (1)	Esc 8 eB 10 (5) 8 eB+R 8 (4) De-esc 8eB/6eB 18 (4) 4 eB 13 (3)†
AHL2011	III	826 (799)	De-esc: 4 ABVD	4.2	6 eB 4 (1) 2 eB + 4 ABVD 1 (0.2)	6 eB 1 (0.2) 2 eB + 4 ABVD 2 (0.5)	6 eB 5 (1.2) 2 eB + 4 ABVD 2 (0.5)	6 eB 10 (2.4) 2 eB + 4 ABVD 5 (1)

ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; AML/MDS, acute myeloid leukemia/myelodysplasia; AVD, doxorubicin, vinblastine, dacarbazine; B/eB, BEACOPP/escalated BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone) ; CEC, cyclophosphamide lomustine, vindesine melphalan, prednisone, vincristine, procarbazine, vinblastine, bleomycin; COPP, cyclophosphamide, vincristine procarbazine, prednisone; ECOG, Eastern Oncology Cooperative Group; Esc, treatment escalation; de-esc, treatment de-escalation; FIL, Fondazione Italiana Linfomi; GHSG, German Hodgkin Study Group; HL, Hodgkin lymphoma; mFu, median follow-up; N, number of patients; NCRI, National Cancer Research Institute; NHL, non-Hodgkin lymphomas; Stanford V, mechlorethamine, vinblastine, vincristine, bleomycin, etoposide, prednisone + radiation; SWOG, Southwest Oncology Group; NA, not assessed.

Criteria for interpreting FDG-PET scans have evolved during the period of enrolment and follow up of the trials reviewed here, and criteria for inclusion in escalation or de-escalation strategies have varied between studies, creating disparities within PET-2-positive groups. The GHSG HD18 trial considered interim scans with uptake greater than the mediastinum to be positive, and therefore HD18 has a higher PET-2-positive rate (48%) compared with 16% in the RATHL trial and 13% in AHL2011.[37–39] Retrospective analysis of PET-2 results from HD18 demonstrated that patients receiving six cycles of escBEACOPP with a Deauville score of 3 have a favorable outcome similar to those with D1 and D2.[25] The positive predictive value of PET-2 imaging in this trial may have possibly artificially decreased with inclusion of patients with 'false-positive' PET-2 finding into the positive cohort, thus overestimating results obtained among PET-2 positive group.

In addition, the use of consolidative radiotherapy at the-end-of treatment was inconsistent across the trials. In HD18, radiotherapy was systematically applied to patients with ⩾2.5 cm focal FDG-avid residual disease, representing 36% of patients within the PET-2 positive group, and could have influenced the PFS outcome. Based on the results of HD15, it could be reasonably presumed that radiotherapy applied after completion of chemotherapy, may help in early rescue some of incomplete responders, and spare the need of salvage chemotherapy and ASCT.[8] Additional data on the ability to omit involved field radiation from treatment of patients with bulky mediastinal disease enrolled on advanced stage trials are needed.

Taken together, all PET-2 adapted approaches lead to excellent PFS and OS rates for patients achieving CMR, and, even if not proven to be superior to therapy without modification based on interim imaging, these data provide the basis for recommendations that will reduce treatment-related toxicities. For patients age 60 or younger without comorbidities who are able to tolerate aggressive treatment, initial therapy with two cycles escBEACOPP regimen followed by de-escalation to ABVD, or a reduced number of cycles of escBEACOPP, appears to yield a better disease control rate in comparison to escalation after a positive PET-2 scan after two cycles of ABVD (RATHL), or upfront use of AAVD regimen (ECHELON-1). However, given the differences in age and disease extent between the studies evaluated in this review, the possibility of other biases, and the lack of a randomized comparison of these approaches, indirect comparison of results between these trials should be done with caution.

Management of patients with Deauville score 5 on interim PET scan remains problematic. Some of these patients have HL that is truly refractory (those with a FDG uptake above baseline or new lesions considered respectively as Deauville 4 and 5), and additional outcome data and treatment approaches are needed in this small patient population.[62] Integration of PET-response after four cycles and the use of changes in maximum standardized uptake values, as performed within AHL2011, may help to identify this high-risk patient group.

Additional important information regarding patient preferences and treatment approaches favored by clinicians treating patients with advanced HL are provided by a cross-sectional online survey study aiming to elicit preferences for attributes associated with frontline therapies for all stages HL.[63] In this study, patients reported that PFS and OS were the most important parameters in considering therapy, but also valued treatments that were free of pulmonary toxicity and neuropathy. Responses to this survey were influence by patient age and prior experience with chemotherapy, and whether they also had experienced treatment failure. Results from this study aligned with current knowledge suggesting that patients are more likely to accept a higher risk of adverse events in order to avoid relapse.[63]

Young and fit patients (<60 years), especially those with high risk baseline features such as high IPS and advanced stage, may benefit more from an intensive regimen with application of escBEACOPP upfront. Reduction in treatment intensity following a negative interim PET scan will be possible in the majority of patients, with subsequent treatment with either four cycles of ABVD or two cycles of escBEACOPP, and guided by initial toxicity experience as well as preferences with regard to relapse risk, avoidance of certain side effects and preservation of fertility. For those wishing to pursue parenthood and inability to perform fertility preservation, starting with ABVD, might be favored, as it has substantially less gonadal toxicity and a high rate of negative PET-2 scans reported in the trial by Johnson and

colleagues, although at the expense of lower PFS compared with escBEACOPP. The optimum therapy for the approximately 20% of HL patients who are older than 60 years is beyond the scope of this review.[64] Both the RATHL and ECHELON-1 trials included small proportion of patients above age 60 years (10% and 14%, respectively). Outcomes in older patients are not reported separately in the RATHL trial, but while patients over age 60 appeared not to benefit from the substitution of brentuximab vedotin for bleomycin in ECHELON-1, these trials were not powered to evaluate outcomes in patient subsets.[38,40]

In addition, it is evident that treatment strategies for advanced HL do vary significantly with regard to costs. A recent cost-utility analysis using a Markov decision model incorporating published probabilities of relapse, second malignancies, infertility and febrile neutropenia, including studies from this review, concluded that a PET-driven de-escalation strategy as used in AHL2100 provides patients with the highest quality-adjusted life-years and has the lowest direct cost of all regimens.[65] As would be the case in a discussion with patients about benefits and risks of therapy, this model incorporated published disutility values (negative impact) of infertility and development of second malignancies. In this analysis, from the perspective of a publicly funded health-care system, initiating therapy with escBEACOPP and then de-escalating treatment to ABVD following a CMR after two cycles of therapy represented the preferred strategy.

Conclusion

The completion of PET-adapted trials is a first step to a more individualized treatment approach to consistently lead to reduction of toxicity without compromising efficacy in patients achieving CMR at PET-2. The decision of which initial regimen and strategy to choose has to be discussed on an individual basis, depending patient fitness and personal concerns regarding risk of relapse *versus* short- and long-term toxicities. There are no trials completed or ongoing to test a strategy of initial intensive therapy and subsequent de-escalation, compared with treatment initiation with ABVD (or AAVD) and subsequent escalation, based on negative or positive PET2 scan results, respectively.

A significant number of PET-2 negative patients which will experience relapse depending on the regimen administered. Consequently, better identification of high-risk factors at diagnosis is required to improve these results and achieve a better selection of candidates for early salvage treatments. To date, attempts to identify potential molecular biomarkers have been made, but unfortunately none of them were successfully validated.[66,67] Alternative approaches to identifying patients at high risk for treatment failure, such total metabolic tumor volume (TMTV) and genomic analysis of circulating tumor DNA and tumor microenvironment, are currently under investigation.[68,69] In addition, novel and potentially more efficacious regimens incorporating brentuximab vedotin,[70] as well as immune checkpoint inhibitors, are currently being evaluated for frontline therapy for advanced-stage HL (NCT02661503 and NCT03907488).

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ORCID iD

Michael Crump https://orcid.org/0000-0002-2230-8538

References

1. Hoskin PJ, Lowry L, Horwich A, *et al.* Randomized comparison of the stanford V regimen and ABVD in the treatment of advanced Hodgkin's Lymphoma: United Kingdom National Cancer Research Institute Lymphoma Group Study ISRCTN 64141244. *J Clin Oncol* 2009; 27: 5390–5396.
2. Gordon L, Hong F, Fisher RI, *et al.* Randomized phase III trial of ABVD versus Stanford V with or without radiation therapy in locally extensive and advanced-stage Hodgkin lymphoma: an intergroup study coordinated by the Eastern Cooperative Oncology Group (E2496). *J Clin Oncol* 2013; 31: 684–691.
3. Duggan DB, Petroni GR, Johnson JL, *et al.* Randomized comparison of ABVD and MOPP/

ABV hybrid for the treatment of advanced Hodgkin's disease: report of an intergroup trial. *J Clin Oncol* 2003; 21: 607–614.

4. Carde P, Karrasch M, Fortpied C, *et al*. Eight cycles of ABVD versus four cycles of BEACOPPescalated plus four cycles of BEACOPPbaseline in stage III to IV, international prognostic score >/= 3, high-risk hodgkin lymphoma: first results of the phase III EORTC 20012 intergroup trial. *J Clin Oncol* 2016; 34: 2028–2036.
5. Merli F, Luminari S, Gobbi PG, *et al*. Long-term results of the HD2000 trial comparing ABVD versus BEACOPP versus COPP-EBV-CAD in Untreated patients with advanced hodgkin lymphoma: a study by Fondazione Italiana Linfomi. *J Clin Oncol* 2016; 34: 1175–1181.
6. Viviani S, Zinzani PL, Rambaldi A, *et al*. ABVD versus BEACOPP for Hodgkin's lymphoma when high-dose salvage is planned. *N Engl J Med* 2011; 365: 203–212.
7. Engert A, Diehl V, Franklin J, *et al*. Escalated-dose BEACOPP in the treatment of patients with advanced-stage Hodgkin's lymphoma: 10 years of follow-up of the GHSG HD9 study. *J Clin Oncol* 2009; 27: 4548–4554.
8. Engert A, Haverkamp H, Kobe C, *et al*. Reduced-intensity chemotherapy and PET-guided radiotherapy in patients with advanced stage Hodgkin's lymphoma (HD15 trial): a randomised, open-label, phase 3 non-inferiority trial. *Lancet* 2012; 379: 1791–1799.
9. Borchmann P, Haverkamp H, Diehl V, *et al*. Eight cycles of escalated-dose BEACOPP compared with four cycles of escalated-dose BEACOPP followed by four cycles of baseline-dose BEACOPP with or without radiotherapy in patients with advanced-stage Hodgkin's lymphoma: final analysis of the HD12 trial of the German Hodgkin Study Group. *J Clin Oncol* 2011; 29: 4234–4242.
10. Mounier N, Brice P, Bologna S, *et al*. ABVD (8 cycles) versus BEACOPP (4 escalated cycles >4 baseline): final results in stage III-IV low-risk Hodgkin lymphoma (IPS 0-2) of the LYSA H34 randomized trial. *Ann Oncol* 2014; 25: 1622–1628.
11. Federico M, Luminari S, Iannitto E, *et al*. ABVD compared with BEACOPP compared with CEC for the initial treatment of patients with advanced Hodgkin's lymphoma: results from the HD2000 Gruppo Italiano per lo Studio dei Linfomi Trial. *J Clin Oncol* 2009; 27: 805–811.
12. Diehl V, Franklin J, Pfreundschuh M, *et al*. Standard and increased-dose BEACOPP chemotherapy compared with COPP-ABVD for advanced Hodgkin's disease. *N Engl J Med* 2003; 348: 2386–2395.
13. Skoetz N, Trelle S, Rancea M, *et al*. Effect of initial treatment strategy on survival of patients with advanced-stage Hodgkin's lymphoma: a systematic review and network meta-analysis. *Lancet Oncol* 2013; 14: 943–952.
14. Sickinger MT, von Tresckow B, Kobe C, *et al*. Positron emission tomography-adapted therapy for first-line treatment in individuals with Hodgkin lymphoma. *Cochrane Database Syst Rev* 2015; (1): CD010533.
15. van Leeuwen FE and Ng AK. Late sequelae in Hodgkin lymphoma survivors. *Hematol Oncol* 2017; 35(Suppl. 1): 60–66.
16. Behringer K, Goergen H, Müller H, *et al*. Cancer-related fatigue in patients with and Survivors of Hodgkin lymphoma: the impact on treatment outcome and social reintegration. *J Clin Oncol* 2016; 34: 4329–4337.
17. Cheson BD, Fisher RI, Barrington SF, *et al*. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. *J Clin Oncol* 2014; 32: 3059–3068.
18. Gallamini A, Hutchings M, Rigacci L, *et al*. Early interim 2-[18F]fluoro-2-deoxy-D-glucose positron emission tomography is prognostically superior to international prognostic score in advanced-stage Hodgkin's lymphoma: a report from a joint Italian-Danish study. *J Clin Oncol* 2007; 25: 3746–3752.
19. Kobe C, Dietlein M, Franklin J, *et al*. Positron emission tomography has a high negative predictive value for progression or early relapse for patients with residual disease after first-line chemotherapy in advanced-stage Hodgkin lymphoma. *Blood* 2008; 112: 3989–3994.
20. Barrington SF, Mikhaeel NG, Kostakoglu L, *et al*. Role of imaging in the staging and response assessment of lymphoma: consensus of the International Conference on Malignant Lymphomas Imaging Working Group. *J Clin Oncol* 2014; 32: 3048–3058.
21. Adams HJ and Kwee TC. Controversies on the prognostic value of interim FDG-PET in advanced-stage Hodgkin lymphoma. *Eur J Haematol* 2016; 97: 491–498.
22. Adams HJ, Nievelstein RA and Kwee TC. Prognostic value of interim FDG-PET in Hodgkin lymphoma: systematic review and meta-analysis. *Br J Haematol* 2015; 170: 356–366.

23. Zinzani PL, Rigacci L, Stefoni V, *et al*. Early interim 18F-FDG PET in Hodgkin's lymphoma: evaluation on 304 patients. *Eur J Nucl Med Mol Imaging* 2012; 39: 4–12.

24. Terasawa T, Lau J, Bardet S, *et al*. Fluorine-18-fluorodeoxyglucose positron emission tomography for interim response assessment of advanced-stage Hodgkin's lymphoma and diffuse large B-cell lymphoma: a systematic review. *J Clin Oncol* 2009; 27: 1906–1914.

25. Kobe C, Goergen H, Baues C, *et al*. Outcome-based interpretation of early interim PET in advanced-stage Hodgkin lymphoma. *Blood* 2018; 132: 2273–2279.

26. Kostakoglu L and Gallamini A. Interim 18F-FDG PET in Hodgkin lymphoma: would PET-adapted clinical trials lead to a paradigm shift? *J Nucl Med* 2013; 54: 1082–1093.

27. Press OW, Li H, Schöder H, *et al*. US intergroup trial of response-adapted therapy for stage III to IV Hodgkin lymphoma using Early Interim Fluorodeoxyglucose-Positron Emission Tomography Imaging: Southwest Oncology Group S0816. *J Clin Oncol* 2016; 34: 2020–2027.

28. Zinzani PL, Broccoli A, Gioia DM, *et al*. Interim positron emission tomography response-adapted therapy in advanced-stage Hodgkin lymphoma: final results of the phase II part of the HD0801 study. *J Clin Oncol* 2016; 34: 1376–1385.

29. Ganesan P, Rajendranath R, Kannan K, *et al*. Phase II study of interim PET-CT-guided response-adapted therapy in advanced Hodgkin's lymphoma. *Ann Oncol* 2015; 26: 1170–1174.

30. Gallamini A, Patti C, Viviani S, *et al*. Early chemotherapy intensification with BEACOPP in advanced-stage Hodgkin lymphoma patients with a interim-PET positive after two ABVD courses. *Br J Haematol* 2011; 152: 551–560.

31. Carras S, Dubois B, Senecal D, *et al*. Interim PET Response-adapted strategy in untreated advanced stage Hodgkin lymphoma: results of GOELAMS LH 2007 phase 2 multicentric trial. *Clin Lymphoma Myeloma Leuk* 2018; 18: 191–198.

32. Dann EJ, Blumenfeld Z, Bar-Shalom R, *et al*. A 10-year experience with treatment of high and standard risk Hodgkin disease: six cycles of tailored BEACOPP, with interim scintigraphy, are effective and female fertility is preserved. *Am J Hematol* 2012; 87: 32–36.

33. Dann EJ, Bairey O, Bar-Shalom R, *et al*. Modification of initial therapy in early and advanced Hodgkin lymphoma, based on interim PET/CT is beneficial: a prospective multicentre trial of 355 patients. *Br J Haematol* 2017; 178: 709–718.

34. Avigdor A, Bulvik S, Levi I, *et al*. Two cycles of escalated BEACOPP followed by four cycles of ABVD utilizing early-interim PET/CT scan is an effective regimen for advanced high-risk Hodgkin's lymphoma. *Ann Oncol* 2010; 21: 126–132.

35. Stephens DM, Li H, Schöder H, *et al*. Five-year follow-up of SWOG S0816: Limitations and values of a PET-adapted approach for stage III/IV Hodgkin lymphoma. *Blood* 2019; 134: 1238–1246.

36. Borchmann P, Haverkamp H, Lohri A, *et al*. Progression-free survival of early interim PET-positive patients with advanced stage Hodgkin's lymphoma treated with BEACOPP escalated alone or in combination with rituximab (HD18): an open-label, international, randomised phase 3 study by the German Hodgkin Study Group. *Lancet Oncol* 2017; 18: 454–463.

37. Borchmann P, Goergen H, Kobe C, *et al*. PET-guided treatment in patients with advanced-stage Hodgkin's lymphoma (HD18): final results of an open-label, international, randomised phase 3 trial by the German Hodgkin Study Group. *Lancet* 2018; 390: 2790–2802.

38. Johnson P, Federico M, Kirkwood A, *et al*. Adapted treatment guided by interim PET-CT scan in advanced Hodgkin's lymphoma. *N Engl J Med* 2016; 374: 2419–2429.

39. Casasnovas RO, Bouabdallah R, Brice P, *et al*. PET-adapted treatment for newly diagnosed advanced Hodgkin lymphoma (AHL2011): a randomised, multicentre, non-inferiority, phase 3 study. *Lancet Oncol* 2019; 20: 202–215.

40. Connors JM, Jurczak W, Straus DJ, *et al*. Brentuximab vedotin with chemotherapy for stage III or IV Hodgkin's lymphoma. *N Engl J Med* 2018; 378: 331–344.

41. Kobe C, Goergen H, Baues C, *et al*. Outcome-based interpretation of early interim PET in advanced stage Hodgkin lymphoma. *Blood* 2018; 132: 2273–2279.

42. Ramchandren R, Advani RH, Ansell SM, *et al*. Brentuximab vedotin plus chemotherapy in North American subjects with newly diagnosed stage III or IV Hodgkin lymphoma. *Clin Cancer Res* 2019; 25: 1718–1726.

43. Behringer K, Breuer K, Reineke T, *et al*. Secondary amenorrhea after Hodgkin's lymphoma is influenced by age at treatment,

stage of disease, chemotherapy regimen, and the use of oral contraceptives during therapy: a report from the German Hodgkin's Lymphoma Study Group. *J Clin Oncol* 2005; 23: 7555–7564.

44. Behringer K, Mueller H, Goergen H, *et al.* Gonadal function and fertility in survivors after Hodgkin lymphoma treatment within the German Hodgkin Study Group HD13 to HD15 trials. *J Clin Oncol* 2013; 31: 231–239.

45. Kreissl S, Mueller H, Goergen H, *et al.* Cancer-related fatigue in patients with and survivors of Hodgkin's lymphoma: a longitudinal study of the German Hodgkin Study Group. *Lancet Oncol* 2016; 17: 1453–1462.

46. Schaapveld M, Aleman BM, van Eggermond AM, *et al.* Second cancer risk up to 40 years after treatment for Hodgkin's lymphoma. *N Engl J Med* 2015; 373: 2499–2511.

47. van Nimwegen FA, Ntentas G, Darby SC, *et al.* Risk of heart failure in survivors of Hodgkin lymphoma: effects of cardiac exposure to radiation and anthracyclines. *Blood* 2017; 129: 2257–2265.

48. Borchmann S, Muller H, Haverkamp H, *et al.* Symptomatic osteonectrosis as a treatment complication in Hodgkin lymphoma: an analysis of the German Hodgkin Study Group (GHSG). *Leukemia* 2019; 33: 439–446.

49. Aleman BM, van den Belt-Dusebout AW, De Bruin ML, *et al.* Late cardiotoxicity after treatment for Hodgkin lymphoma. *Blood* 2007; 109: 1878–1886.

50. Wongso D, Fuchs M, Plütschow A, *et al.* Treatment-related mortality in patients with advanced-stage hodgkin lymphoma: an analysis of the german hodgkin study group. *J Clin Oncol* 2013; 31: 2819–2824.

51. Martin WG, Ristow KM, Habermann TM, *et al.* Bleomycin pulmonary toxicity has a negative impact on the outcome of patients with Hodgkin's lymphoma. *J Clin Oncol* 2005; 23: 7614–7620.

52. Boll B, Goergen H, Behringer K, *et al.* Bleomycin in older early-stage favorable Hodgkin lymphoma patients: analysis of the German Hodgkin Study Group (GHSG) HD10 and HD13 trials. *Blood* 2016; 127: 2189–2192.

53. Stamatoullas A, Brice P, Bouabdallah R, *et al.* Outcome of patients older than 60 years with classical Hodgkin lymphoma treated with front line ABVD chemotherapy: frequent pulmonary events suggest limiting the use of bleomycin in the elderly. *Br J Haematol* 2015; 170: 179–184.

54. Harel S, Ferme C and Poirot C. Management of fertility in patients treated for Hodgkin's lymphoma. *Haematologica* 2011; 96: 1692–1699.

55. Decanter C, Morschhauser F, Pigny P, *et al.* Anti-Mullerian hormone follow-up in young women treated by chemotherapy for lymphoma: preliminary results. *Reprod Biomed Online* 2010; 20: 280–285.

56. Martins AD, Agarwal A, Baskaran S, *et al.* >Alterations of Spermatozoa proteomic profile in men with Hodgkin's disease prior to cancer therapy. *World J Mens Health*. Epub ahead of print 14 June 2019. DOI: 10.5534/wjmh.190012.

57. Sieniawski M, Reineke T, Nogova L, *et al.* Fertility in male patients with advanced Hodgkin lymphoma treated with BEACOPP: a report of the German Hodgkin Study Group (GHSG). *Blood* 2008; 111: 71–76.

58. Eichenauer DA, Becker I, Monsef I, *et al.* Secondary malignant neoplasms, progression-free survival and overall survival in patients treated for Hodgkin lymphoma: a systematic review and meta-analysis of randomized clinical trials. *Haematologica* 2017; 102: 1748–1757.

59. Eichenauer DA, Thielen I, Haverkamp H, *et al.* Therapy-related acute myeloid leukemia and myelodysplastic syndromes in patients with Hodgkin lymphoma: a report from the German Hodgkin Study Group. *Blood* 2014; 123: 1658–1664.

60. Josting A, Wiedenmann S, Franklin J, *et al.* Secondary myeloid leukemia and myelodysplastic syndromes in patients treated for Hodgkin's disease: a report from the German Hodgkin's Lymphoma Study Group. *J Clin Oncol* 2003; 21: 3440–3446.

61. Bhatia S, Armenian SH and Landier W. How I monitor long-term and late effects after blood or marrow transplantation. *Blood* 2017; 130: 1302–1314.

62. Barrington SF and Kluge R. FDG PET for therapy monitoring in Hodgkin and non-Hodgkin lymphomas. *Eur J Nucl Med Mol Imaging*. 2017; 44(Suppl. 1): 97–110.

63. Brockelmann PJ, McMullen S, Wilson JB, *et al.* Patient and physician preferences for first-line treatment of classical Hodgkin lymphoma in Germany, France and the United Kingdom. *Br J Haematol* 2019; 184: 202–214.

64. Engert A, Ballova V, Haverkamp H, *et al.* Hodgkin's lymphoma in elderly patients: a comprehensive retrospective analysis from the

German Hodgkin's Study Group. *J Clin Oncol* 2005; 23: 5052–5060.

65. Vijenthira A, Chan K, Cheung MC, *et al*. Cost-effectiveness analysis of first-line treatment options for patients with advanced-stage Hodgkin lymphoma: a modeling study. *Lancet Hematol* 2020; 7: e146–e156.
66. Scott DW, Chan FC, Hong F, *et al*. Gene expression-based model using formalin-fixed paraffin-embedded biopsies predicts overall survival in advanced-stage classical Hodgkin lymphoma. *J Clin Oncol* 2013; 31: 692–700.
67. Scott D, Li H, Harvey Y, *et al*. The 23-gene genee Expression-based assay does not predict interim PET scan results after ABVD in advanced stage classical Hodgkin lymphoma in the US Intergroup S0816 Trial. *Hematol Oncol* 2017; 35(S2): 92–93.
68. Zaucha JM, Chauvie S, Zaucha R, *et al*. The role of PET/CT in the modern treatment of Hodgkin lymphoma. *Cancer Treat Rev* 2019; 77: 44–56.
69. Spina V, Bruscaggin A, Cuccaro A, *et al*. Circulating tumor DNA reveals genetics, clonal evolution, and residual disease in classical Hodgkin lymphoma. *Blood* 2018; 131: 2413–2425.
70. Eichenauer DA, Plütschow A, Kreissl S, *et al*. Incorporation of brentuximab vedotin into first-line treatment of advanced classical Hodgkin's lymphoma: final analysis of a phase 2 randomised trial by the German Hodgkin Study Group. *Lancet Oncol* 2017; 18: 1680–1687.