PET-adapted approaches to primary therapy for advanced Hodgkin lymphoma

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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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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 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. 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).

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). 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. 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. 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. 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.

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. 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 ≥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. 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 - | Randomization | Consolidative EOT RT (%) | Stage (%) | Age (years) | IPS > 3 (%) | Bulk (10 cm or > 1/3) (%) | PET-2 + Criteria (Deavelle) (%) | 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]  | 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]   | 18–60       | 51                        | 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 [48]   | 18–70       | 44                        | 35                            | 4–5                        | 20             | 74 [2 years]  | NA           |
| NCRI RATHL             | III   | 1203 [1119]         | 41.2     | ABVD           | Esc: 6 bB /4eB                           | None for PET-2 + | Not recommended | IIA/IIB [42] | III [30]   | >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 + | Yes [36]                    | IIBX/E [14] | III [49]   | 18–60       | 16                        | 29                            | 3–5                        | 48             | 92.5 [3 years] | 97 [3 years] |

ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; ASCT, Autologous Stem Cell Transplantation; AWD, 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.
| 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     | >18         | 17.5        | 32                           | D1-3           | 85            | 97 [3 years] |
| GHS G HD18    | III   | 2102 (1945)         | 66       | eB             | De-esc: 2 eB                          | Yes for PET2 – 1/6/8eB versus 4eB | IIBX/E       | 18–60       | 16          | 29                           | D1,2           | 93.5          | 97 [3 years] |
| AHL2011       | III   | 823 (799)           | 50.4     | eB             | De-esc: 4 ABVD                        | Yes upfront PET-2 leB versus PET-adapted therapy | IIBX/E       | 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 approximately 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 or to 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 under-reported 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
of PFS, 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. 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

| Toxicities | NCRI RATHL | GHSG HD 18 | AH2011 | ECHELON-1 |
|------------|------------|------------|---------|-----------|
|            | Esc 4 B/ eB | De-esc 4 AVD | 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 | NA | NA | 87b | 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 | NA |
| 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.

aLeucopenia rate for four escBEACOPP 88%, six escBEACOPP 93%, eight escBEACOPP 93%.
bMandatory G-CSF.
cReported separately: grade 3–4 respectively for AAVD versus ABVD is for abdominal pain 3% versus <1%, stomatitis 2% versus <1%, diarrhea 3% versus <1%, vomiting 3% versus 1%, constipation 2% versus <1%.
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. 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). 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, 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%. 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. 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). Similarly, no excess pulmonary toxicity was reported with two cycles of escBEACOPP plus four cycles of ABVD in AHL 2011 study. 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.

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%. 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. 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, 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. 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). 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.

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. 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%). 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.

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.

**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 heterogeneous 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 COPP/ABVD 7 (2.7) | 8 COPP/ABVD 16 (3.4)      | 8 COPP/ABVD 15 (5.7)                   |
|             |       |                     |                                     |             | 8 bB 7 (1.5)             | 8 bB 8 (1.7)      | 8 eB 5 (1)                   | 8 bB 31 (6.6)                           |
|             |       |                     |                                     |             | 8 eB 14 (3)              | 8 eB 9 (1.9)      |                               | 8 eB 28 (6)†                           |
| HD12 GHSG   | III   | 1670 (1574)         | 8 eB versus 4 eB + 4 bB            | 6.5         | 8 eB 12 (1.5)            | 8 eB 11 (1.4)     | 8 eB 20 (2.5)                | 8 eB 43 (5.3)                           |
|             |       |                     |                                     |             | 4 eB + 4 bB 10          | 4 eB + 4 bB 5     | 4 eB + 4 bB 18              | 4 eB + 4 bB 33 (4.2)                   |
| HD15 GHSG   | III   | 2182 (2126)         | 8 eB versus 6 eB versus 8 B14      | 4           | 8 eB 19 (2.7)            | 8 eB 8 (1.1)      | 8 eB 6 (0.9)                 | 8 eB 33 (4.7)                           |
|             |       |                     |                                     |             | 6 eB 2 (0.3)             | 6 eB 6 (0.8)      | 6 eB 9 (1.3)                 | 6 eB 17 (2.4)                           |
|             |       |                     |                                     |             | 8 B14 5 (0.7)            | 8 B14 9 (1.3)     |                               | 8 B14 22 (3.1)                          |
| E2496 ECOG  | III   | 854 (794)           | 6/8 ABVD versus Stanford V         | 6.4         | 6/8 ABVD 1 (0.3)         | 6/8 ABVD 2 (0.5)  | 6/8 ABVD 12 (3)              | 6/8 ABVD 15 (3.8)                       |
|             |       |                     |                                     |             | Stanford V 3             | Stanford V 3      | Stanford V 13                | Stanford V 19 (4.8)                     |
| EORTC 20012 | III   | 550 (549)           | 8 ABVD versus 4 eB + 4 bB          | 3.6         | 8 ABVD 2 (0.7)           | 8 ABVD 3 (1.1)    | 8 ABVD 3 (1.1)               | 8 ABVD 8 (3)                            |
|             |       |                     |                                     |             | 4 eB + 4 bB 4 (1.5)      | 4 eB + 4 bB 2     | 4 eB + 4 bB 4               | 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)             | 6 ABVD 0 (0)      | 6 ABVD 1 (<1)                | 6 ABVD 1 (0.9)                          |
|             |       |                     |                                     |             | 4 eB + 2 bB 1            | 4 eB + 2 bB 1 1   | 4 eB + 2 bB 4               | 4 eB + 2 bB 6 (6.6)§                    |
|             |       |                     |                                     |             | 6 CEC 1 (1.1)            | 6 CEC 0           | 6 CEC 5 (5.4)                | 6 CEC 6 (6)§                            |
| Viviani6    | III   | 331 (322)           | 6 ABVD versus 4 eB + 4 bB          | 5.1         | 6 ABVD 1 (1)             | NA               | NA                           | NA                                       |
| SWOG 0816   | II    | 371 (331)           | Esc: 6x eB                         | 5.9         | 6 ABVD [0]               | 6 ABVD 1 (0.4)    | 6 ABVD 5 (1.9)               | 6 ABVD 6 (2)                            |
|             |       |                     |                                     |             | 2 ABVD + 6 eB 1 (2)      | 2 ABVD + 6 eB 1   | 2 ABVD + 6 eB 5 (10)        | 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: 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                      | Esc              | Esc                           | Esc                                      |
|             |       |                     |                                     |             | 8 eB 5 (2)               | 8 eB 3 (1)       | 8 eB 2 (1)                   | 8 eB 10 (5)                             |
|             |       |                     |                                     |             | 8 eB 4 (2)               | 8 eB 3 (1)       | 8 eB 2 (1)                   | 8 eB + R 8 (4)                          |
|             |       |                     |                                     |             | De-esc 8eB/6eB 8 (2)     | De-esc 8eB/6eB 7 (1) | De-esc 8eB/6eB 5 (1)        | De-esc 8eB/6eB 18 (4)                    |
|             |       |                     |                                     |             | 4 eB <1                  | 4 eB 8 (2)       | 4 eB 3 (1)                   | 4 eB 13 (3)†                            |
| AHL2011     | III   | 826 (799)           | De-esc: 4 ABVD                      | 4.2         | 6 eB 4 (1)               | 6 eB 1 (0.2)     | 6 eB 5 (1.2)                 | 6 eB 10 (2.4)                           |
|             |       |                     |                                     |             | 2 eB + 4 ABVD 1 (0.2)    | 2 eB + 4 ABVD 2  (0.5) | 2 eB + 4 ABVD 5 (1)        | 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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