bjh review

Therapeutic recommendations for early stage Hodgkin lymphomas

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Summary

Combined modality treatment has been the standard option for the treatment of early stage Hodgkin lymphoma for several decades. Because of the high success rate and the risk of late toxicities, recent clinical trials have focused on reducing the treatment burden. Field and dose of radiotherapy, and number of cycles of chemotherapy have been successfully reduced, particularly for favourable early stage patients. However, the impact of these treatment reductions on the rate of secondary malignancies remains still unclear. Positron emission tomography-computed tomography (PET-CT) scanning has emerged as a very important tool for disease staging and end of treatment assessment. Interestingly, a PET performed after 2 cycles of ABVD (adriamycin, bleomycin, vinblastine, dacarbazine) has been correlated with final outcome and was recently evaluated in a randomized clinical trial to evaluate individualized therapy based on PET response after 2 or 3 cycles of ABVD. These trials aimed to identify good prognosis (early PET-negative) patients who could be spared radiotherapy, but also patients with a bad prognosis (early PET-positive) who need more intensive treatment. More recently, new drugs, such as brentuximab vedotin and checkpoint inhibitors, have shown efficacy in relapsed/refractory patients and are currently under evaluation in early stage patients.

Keywords: modality treatment, Hodgkin lymphoma, radiotherapy.

The treatment of early stage Hodgkin lymphoma (HL) is one of the great successes in modern oncology with the vast majority of patients cured of their disease. Given the success of initial therapy, the approach towards management has therefore increasingly focused on the quality of long-term survival, where a high rate of treatment-induced mortality and morbidity has been observed (Schaapveld *et al*, 2015). This has led to the observation in long-term follow-up that more patients are dying from the consequences of treatment than from HL (Aleman *et al*, 2003). These late effects most often occur decades after treatment and are mainly well documented in patients who received higher dose extended radiation fields, which have long since been abandoned in the modern era of lower dose involved site radiotherapy (RT) (Maraldo *et al*, 2014). Therefore, the most recent trials have evaluated response-adapted therapies with the goal to reduce the late side effects while maintaining the curative potential of the treatments. More recently, new drugs, such as brentuximab vedotin and checkpoint inhibitors, became available and could potentially also help to reach this goal. This paper reviews the management of classical HL and does not discuss the rare sub-entity of nodular lymphocyte predominant HL.

Prognostic factors

The initial staging of HL is performed by positron emission tomography-computed tomography (PET-CT) scan (PET), as recommended by the Lugano classification (Cheson *et al*, 2014). Interestingly, a bone marrow biopsy (BMB) is no longer required when a PET is performed for initial staging (El-Galaly *et al*, 2012; Eichenauer *et al*, 2018). In the study reported by El-Galaly *et al* (2012), 18% of patients had focal skeletal lesions on PET-CT, but only 6% had positive BMB. None of the patients would have been allocated to another treatment based on BMB results. Patients with early-stage HL rarely show disease involvement in the absence of a suggestive PET finding, confirming that, if a PET-CT is performed, a bone marrow aspirate/biopsy is no longer required for the routine evaluation of patients with HL.

Once a patient is diagnosed with an early stage HL, clinical risk factors are commonly used to separate these patients in two categories: favourable *versus* unfavourable/intermediate. These categories were established decades ago and are based on B symptoms, erythrocyte sedimentation rate (ESR), bulky mediastinum (defined on chest X-ray), number of involved nodal areas, age and extra-nodal areas (Table I). Unfortunately, there are some differences between the

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Table I. Risk factors according to Cooperative treatment group.

	EORTC/LYSA (Ferme *et al*, 2007)	GHSG (Engert *et al*, 2007)	Canada (Meyer *et al*, 2012)
Risk factor	Mediastinal mass	A: Mediastinal mass	
	Age ≥50 years	B: Extranodal site	Age >40 years
	ESR ≥ 50 or ≥30 if B symptoms	C: ESR ≥ 50	ESR > 50
	≥4 nodal areas	D: > ≥3 nodal areas	≥3 sites
Stage			
Favourable	I–II without risk factors	I–II without risk factors	I–II without risk factors
Unfavourable or intermediate	I–II with ≥1 risk factor	I–II with ≥1 risk factor and IIB with C/D without A or B	I–II with ≥1 risk factor

EORTC, European Organization for Research and Treatment of Cancer; ESR, erythrocyte sedimentation rate; GHSG, German Hodgkin Study Group; LYSA, Lymphoma Study Association.

classifications used by cooperative groups, which sometimes makes comparison of different studies very challenging.

Long term side effects

The most severe late effect of therapy for HL is second cancer. In a recent large study (Schaapveld *et al*, 2015), with a median follow-up of 19·1 years, the standardized incidence ratio (SIR) was 4·6 [95% confidence interval (CI), 4·3–4·9] in the study cohort as compared with the general population. The risk was still elevated 35 years or more after treatment (SIR, 3·9; 95% CI, 2·8–5·4), and the cumulative incidence of a second cancer in the study cohort at 40 years was 48·5% (95% CI, 45·4–51·5). Unfortunately, the cumulative incidence of second solid cancers did not differ according to study period (1965–1976, 1977–1988 or 1989–2000) ($P = 0·71$ for heterogeneity), suggesting that the efforts made to reduce the burden of treatment did not translate into a reduction in second cancers. However, the impact of treatment modifications in the last 20 years is currently not well known. Also, as the risk is better known, it might be suggested that well-conducted cancer screening programmes could also reduce the severity of late malignancies. However, a recent study found that many women are not getting the proper dual screening for breast cancer despite their increased risk, with only 36·6% of the study sample receiving dual screening (Baxstrom *et al*, 2018). Proper screening allows for detection of secondary breast cancer at earlier stages, where treatment can be localised therapy, but this study raised the issue of compliance of this population to cancer screening programmes. Finally, cancer screening is not yet possible for thyroid, lung and soft tissue cancers.

Cardio-vascular and valvular diseases are another important late effect that can occur in patients receiving mediastinal RT (Cutter *et al*, 2015; Hahn *et al*, 2017). The decrease in the doses and volume of RT used led to a reduction of these complications. Nevertheless, RT may still result in substantial incidental cardiac exposure if the disease affects the mediastinum.

Non PET-adapted treatment strategies

Extended-field (EF) RT was the first established treatment to cure a large proportion of early-stage HL. However, two large randomized trials performed by the German Hodgkin Study Group (GHSG) and European Organization for Research and Treatment of Cancer/Lymphoma Study Association (EORTC/LYSA) demonstrated a better disease control with the combination of chemotherapy and RT. In the H8 study, EF-RT was compared to 3 cycles of nitrogen mustard, vincristine, procarbazine and prednisone alternating with adriamycin, bleomycin and vinblastine (MOPP-ABV) and involved-field (IF) RT and showed a significantly higher progression-free survival (PFS) (74% vs. 98%, $P = 0·001$) (Ferme *et al*, 2007). Similar results were shown in the HD7 trial of the GHSG (Engert *et al*, 2007), defining combined modality treatment (CMT) as a new standard of care.

Favourable early stage

To further reduce long-term toxicities, a reduction of the dose of RT was evaluated for early favourable HL patients. The HD10 GHSG study is a two by two design trial with the aim to compare both 4 *versus* 2 cycles of adriamycin, bleomycin, vinblastine and dacarbazine (ABVD) and 30 Gy vs. 20 Gy of IF-RT (Engert *et al*, 2010). There was no difference between 2 and 4 cycles of ABVD with respect to freedom from treatment failure ($P = 0·39$) or overall survival (OS) ($P = 0·61$). At 5 years, the rates of freedom from treatment failure were 93·0% (95% CI, 90·5–94·8) with the 4-cycle ABVD regimen and 91·1% (95% CI, 88·3–93·2) with the 2-cycle regimen. When the effects of 20 Gy and 30 Gy doses of RT were compared, there were also no significant differences in freedom from treatment failure ($P = 1·00$) or OS ($P = 0·61$). Adverse events and acute toxic effects of treatment were most common in the patients who received four cycles of ABVD and 30 Gy RT.

The similar efficacy of the 20 Gy regimen was recently confirmed in the EORTC-LYSA H9-F (Thomas *et al*, 2018). All patients received 6 cycles of epirubicin, bleomycin, vinblastine and prednisone (EBVP). Those who obtained a complete response or unconfirmed complete response were randomized to receive either 36 Gy IF-RT, 20 Gy IF-RT or no further RT. Results in the 20 Gy arm [5-year relapse-free survival (RFS), 84·2%] were not inferior to those in the 36 Gy arm (5-year RFS, 88·6%) (Difference: 4·4%; 90% CI, −1·2 to 9·9%).

A reduction in disease control was observed for the no RT arm(Thomas *et al*, 2018). After the inclusion of 130 patients in the no RT arm, this arm was prematurely stopped because of a 20% rate of unacceptable events: toxicity, treatment modification, early relapse or death. The study could not demonstrate noninferiority of the no RT arm, its primary endpoint, (5-year RFS estimate, 69·8%) compared with the 36-Gy arm (86·3%) with a difference of 16·5% (90% CI, 8·0–25·0%) between the 2 arms, because the upper bound of the 90% CI exceeded the prespecified noninferiority margin (10%); the hazard ratio (HR) estimate was 2·55 (95% CI, 1·44–4·53; $P < 0.001$). However, no difference in OS was observed between the 3 different arms.

Similarly, another study evaluated the omission of RT in unselected early favourable patients. Meyer *et al* (2012) randomized 405 patients with previously untreated stage IA or IIA non-bulky HL to ABVD alone or to a treatment with subtotal nodal RT, with or without ABVD. The median length of follow-up was 11·3 years. At 12 years, the rate of OS was 94% among those receiving ABVD alone, as compared with 87% among those receiving RT (HR for death with ABVD alone, 0·50; 95% CI, 0·25–0·99; $P = 0.04$); the rates of freedom from disease progression were 87% and 92% in the two groups, respectively (HR for disease progression, 1·91; 95% CI, 0·99–3·69; $P = 0.05$). This study showed that omission of RT in unselected patients was associated with an inferior disease control. However, survival was better in the no-RT arm; whereas among the 24 deaths in the RT arm, 4 were related to HL or early toxic effects of treatment and 20 were related to another cause. Finally, at the time the study was published (around 20 years after initial recruitment), the RT used (Subtotal nodal RT) had become outdated and replaced by IF-RT as standard practice.

In the HD13 study of the GHSG, reduction of chemotherapy was evaluated by omission of bleomycin and/or dacarbazine because of the toxicity of these drugs (Behringer *et al*, 2015). Both the assignment to the AV and ABV arms were stopped early due to a high event rate (relapse or death). Assignment to ABVD and AVD could continue until the end of the trial. Non-inferiority of AVD compared with ABVD could also not be detected (5-year difference: −3·9%, 95% CI, −7·7 to −0·1; HR 1·50, 95% CI, 1·00 to 2·26). According to this study, the standard of care for patients with early-stage favourable HL should remain ABVD followed by IF-RT.

Unfavourable early stage

The use of large-field RT was abandoned after both the GHSG HD8 (Engert *et al*, 2003) and the EORTC/LYSA H8U (Ferme *et al*, 2007) trials. HD8 demonstrated long-term noninferiority of IF-RT compared with EF-RT. With regard to treatment-associated long-term toxicity, a non-significant trend toward less secondary neoplasia with IF-RT was observed in the recent follow-up analysis (15-year cumulative, 14% vs. 17%; $P = 0.3$) (Sasse *et al*, 2017). This trend is more pronounced when examining only the incidence of acute myeloid leukaemia or myelodysplastic syndromes (2·4% vs. 0·8%; $P = 0.1$), but not in non-Hodgkin lymphoma (2·6% vs. 2·9%; $P = 1.0$). In solid second neoplasia, the trend became more pronounced with longer follow-up but did not reach statistical significance (12% vs. 10·4%; $P = 0.7$). Because of the long latency of solid second neoplasia, prolonged follow-up is crucial to finally assess the risk of secondary neoplasia with more limited RT fields.

Among the 766 patients who had a confirmed or unconfirmed complete remission after RT in H8U, 42 (5%) relapsed: 15 of 253 patients (6%) in the group receiving six cycles of MOPP-ABV plus IF-RT, 14 of 259 patients (5%) in the group receiving four cycles of MOPP-ABV plus IF-RT, and 13 of 254 patients (5%) in the group receiving MOPP-ABV plus subtotal nodal RT (Ferme *et al*, 2007). There were no significant differences in the 5-year event-free survival (EFS) estimates among the three groups.

Therefore, after these two trials, 4 cycles of ABVD and 30 Gy IF-RT was considered as a standard of care.

The GHSG HD11 study was a two by two design study that aimed to compare two different chemotherapy regimens in unfavourable early stage HL: 4 cycles ABVD vs. 4 cycles $BEACOPP_{baseline}$ (bleomycin, etoposide, adriamycin, cyclophosphamide, vincristine, procarbazine, prednisone); and 30 Gy IF-RT vs. 20 Gy (Eich *et al*, 2010). No improvement was demonstrated using 4-cycle $BEACOPP_{baseline}$ *versus* ABVD. Concerning RT, the 20 Gy arm was inferior to 30 Gy when ABVD was used but when BEACOPP was used this difference disappeared and 20 Gy was equivalent to 30 Gy.

Similarly, the EORTC/LYSA H9U study compared 6 cycles ABVD and 30 Gy IF-RT (standard arm) vs. 4 cycles ABVD and 30 Gy IF-RT and 4 cycles $BEACOPP_{baseline}$ and 30 Gy IF-RT (Ferme *et al*, 2017). Results in the 4-cycle ABVD and IF-RT (5-year EFS, 85·9%) and the 4-cycle $BEACOPP_{baseline}$ and IF-RT (5-year EFS, 88·8%) were not inferior to 6 cycles ABVD and IF-RT (5-year EFS, 89·9%): difference of 4·0% (90% CI, −0·7 to 8·8%) and 1·1% (90% CI, −3·5 to 5·6%) respectively. The 5-year OS estimates were 94%, 93% and 93%, respectively. Because 4 cycles of $BEACOPP_{baseline}$ were more toxic but equally efficient to 4 cycles of ABVD, it was not considered as a new standard.

As there is a potential to improve the disease control obtained with 4 cycles of ABVD and RT, the GHSG HD14 trial compared 4 cycles ABVD and 30 Gy IF-RT vs. 2 cycles

of escalated BEACOPP ($BEACOPP_{esc}$) plus 2 cycles ABVD and 30 Gy IF-RT. It resulted in a significant PFS advantage for «2 + 2» compared with 4cycles ABVD, with a 5-year PFS of 6·2% (95·4% vs. 89·1%; HR, 0·45; 95% CI, 0·3–0·69) (von Tresckow *et al*, 2012). This «2 + 2» approach is associated with more acute, predominantly haematological, toxicity, but no difference in long-term toxicity or OS has been documented so far. A longer follow-up is needed to assess potential long-term benefits and risks with upfront intensive therapy in patients with early-stage unfavourable disease.

PET-adapted treatment strategies

Gallamini *et al* (2007) consecutively enrolled 260 newly diagnosed HL to evaluate the prognostic role of an interim 2-[18F] fluoro-2-deoxy-D-glucose positron emission tomography (iPET). Most of the patients were advanced HL and the study showed that iPET overshadows the prognostic value of the International Prognostic Score and emerges as the single most important tool for planning risk-adapted treatment in advanced HL (Gallamini *et al*, 2007). A similar evaluation conducted in 257 stage I to IIA patients treated with chemotherapy plus RT, led to a similar conclusion and showed that iPET was a strong prognostic factor for both PFS and OS (Simontacchi *et al*, 2015).

Consequently, several trials were launched in order to evaluate early treatment adaptation according to iPET results after 2 or 3 cycles of ABVD.

Favourable early stage

In the UK RAPID (Randomised Phase III Trial to Determine the Role of FDG–PET Imaging in Clinical Stages IA/IIA Hodgkin's Disease) trial, 602 patients with newly diagnosed stage IA or stage IIA HL underwent iPET after receiving 3 cycles of ABVD (Radford *et al*, 2015). RAPID included both favourable (2/3) and unfavourable (1/3) early stage HL in the same trial. Patients with negative iPET findings [Deauville score (DS), 1 or 2] were randomly assigned to receive IF-RT or no further treatment; patients with positive iPET findings (DS, 3–5) received a fourth cycle of ABVD and RT. Approximately two-thirds of patients enrolled had a favourable risk profile according to GHSG or EORTC/LYSA risk classification (personal communication, J Radford, Institute of Cancer Sciences, University of Manchester, Manchester, UK). The 3-year PFS rate was 94·6% (95% CI, 91·5–97·7) in the RT group and 90·8% (95% CI, 86·9–94·8) in the group that received no further therapy, with an absolute risk difference of −3·8 percentage points (95% CI, −8·8 to 1·3). As the upper CI limit exceeded the predefined noninferiority margin of 7%, the study did not show noninferiority of the strategy of no further treatment. Nevertheless, patients in this study with early-stage HL and negative PET findings after three cycles of ABVD had a very good prognosis either with or without consolidation RT. The impact on OS and late effects need additional follow-up.

The EORTC/LYSA/Fondazione Italiani di Limfomi (FIL) H10 study also evaluated an early treatment adaptation according to iPET (André *et al*, 2017). In the favourable group (patients without any of the following: age ≥50 years, more than three nodal areas, mediastinal-thoracic ratio ≥0·35, no B symptoms and ESR ≥ 50 or B symptoms and ESR ≥ 30) received 2 cycles ABVD followed by an iPET. In the standard arm iPET-negative patients [according to International Harmonization Project criteria (Juweid *et al*, 2007)] were randomized between 1 additional cycle of ABVD and 30 Gy involved-node (IN) RT *versus* 2 cycles of ABVD. Among the 465 iPET-negative patients, after a median follow-up of 5·0 years, a total of 33 events for PFS occurred: two patients experienced relapse in the ABVD + IN-RT arm *versus* 30 patients who experienced relapse and one patient died from a cause not related to lymphoma in the ABVD-only arm. Intention to treat (ITT) 5-year PFS rates were 99·0% (95% CI, 95·9–99·7) and 87·1% (95% CI, 82·1–90·8) in the ABVD + IN-RT and ABVD only arms, respectively, with HR, 15·8 (95% CI, 3·8–66·1) in favour of ABVD + IN-RT. Noninferiority could not be demonstrated because the upper bound of the 95% CI for the estimated HR (66·07) exceeded the pre-specified noninferiority margin (3·2).

In the Cancer and Leukemia Group B (CALGB) 50 604 phase 2 trial, patients with non-bulky stage I/II disease with a negative iPET (135 of 149 patients, DS, 1–3) after 2 cycles of ABVD were treated with an additional 2 cycles of ABVD without consolidative RT, whereas patients with a positive iPET (14 of 149 patients) received 2 cycles of $BEACOPP_{esc}$ and 30 Gy IF-RT. The estimated 3-year PFS rates were 91% and 66%, respectively, for the iPET-negative and PET-positive cohorts ($P = 0·011$), HR 3·84 (95% CI, 1·50–9·84) (Straus *et al*, 2018). These data support that four cycles of ABVD results in durable remissions for the majority of patients with early stage non-bulky HL and negative iPET.

In summary, in the context of favourable patients, RAPID (Radford *et al*, 2015) and EORTC/LYSA/FIL H10 (André *et al*, 2017), although showing several differences in their respective design (Table II), and on the basis of the preset assumptions, showed that CMT resulted in a better immediate disease control and noninferiority of the no RT arm could not be demonstrated in iPET negative patients.

One additional study (GHSG HD16, NCT 0073632) has also evaluated this strategy in the context of early favorable HL and compares 2 cycles ABVD and IF-RT *versus* 2 cycles ABVD. Recruitment is completed but results are pending.

Unfavorable early stage

About one third of the patients included in RAPID trial (Radford *et al*, 2015) meet the criteria for unfavourable patients. The EORTC/LYSA/FIL H10 trial is the only published study to evaluate an iPET approach in the specific

group of unfavourable HL (André *et al*, 2017). Unfavourable patients were defined as: age ≥50 years, large mediastinal mass [M/T ratio ≥0·35, elevated ESR (with B symptoms, ≥30 mm/h; without B symptoms, ≥50 mm/h), >3 nodal areas]. Patients with a negative iPET were randomized between 4 cycles ABVD and IN-RT ($n = 292$) *versus* 6 cycles ABVD ($n = 302$). After a median follow-up of 5·1 years, a total of 54 events for PFS occurred: 16 patients experienced relapse and six died from causes not related to HL in the ABVD + IN-RT arm, whereas 30 patients experienced relapse and two died from causes not related to HL in the ABVD-only arm. ITT 5-year PFS rates were 92·1% (95% CI, 88·0–94·8) and 89·6% (95% CI, 85·5–92·6) in the ABVD + IN-RT and ABVD only arms, respectively, with HR, 1·45 (95% CI, 0·8–2·5) in favour of ABVD + IN-RT. Noninferiority could not be demonstrated because the upper bound of the 95% CI for the estimated HR (2·50) exceeded the prespecified noninferiority margin (2·10). However, the difference for the 5-years PFS is only 2·5% (95% CI: −6·6 to 0·5%), within the range of the 10% prespecified noninferiority margin. Therefore, in this group of unfavourable patients, the benefit of CMT seems to be less clinically relevant than in the favourable group. Sparing selected unfavourable patients from large/mediastinal RT fields might be appropriate in the context of young age or pre-existing cardiovascular and pulmonary diseases.

The GHSG HD17 study (NCT 01356680), evaluating iPET-adapted treatment in unfavourable patients, has completed recruitment but results are pending. This trial compares 2 cycles $BEACOPP_{esc}$ + 2 cycles ABVD, with or without RT, in iPET-negative patients.

Management of iPET positive patients

In the RAPID (Radford *et al*, 2015), GHSG HD16 and HD17, patients with a positive iPET received the standard arm of treatment. So far, only the data from RAPID have been published (Radford *et al*, 2015). Among the 571 patients enrolled in the study and having an iPET after 3 ABVD, 145 were iPET-positive (DS 3–5) and 127 of the 145 patients (87·6%) in the group with positive PET findings were alive without disease progression. There has been 18 events in this group; 10 events of disease progression (6·9%), 5 deaths with disease progression (3·4%), and 3 deaths without disease progression (2·1%). A total of 8 of the 14 patients (57·1%) in this group who received second-line treatment underwent transplantation.

The EORTC/LYSA/FIL H10 study grouped both favourable and unfavourable iPET-positive patients together, because of their presumed shared poor prognosis, in a randomized trial comparing 3–4 cycles ABVD and RT *versus* 2 cycles ABVD + 2 cycles $BEACOPP_{esc}$ + IN-RT (André *et al* (2017). In the overall iPET-positive group ($n = 361$), after a median follow-up of 4·5 years, a total of 57 events for PFS occurred: 41 (36 relapses and 5 deaths not related to HL) in the ABVD + IN-RT arm and 16 (13 relapses and 3 deaths not related to HL) in the $BEACOPP_{esc}$ + IN-RT arm. ITT 5-year PFS rates were 77·4% (95% CI, 70·4–82·9) and 90·6% (95% CI, 84·7–94·3) in the ABVD + IN-RT and $BEACOPP_{esc}$ + IN-RT arms, respectively, with HR, 0·42 (95% CI, 0·23–0·74; $P = 0·002$) in favour of $BEACOPP_{esc}$ + IN-RT. The 5-year OS rates were 89·3% vs. 96·0% for ABVD + IN-RT and $BEACOPP_{esc}$ + IN-RT, respectively, with HR, 0·45 (95% CI, 0·19–1·07; $P = 0·062$ (Fig 1).

European Society for Medical Oncology (ESMO), National Comprehensive Cancer Network (NCCN) and personal recommendations

The recently published ESMO guidelines (Eichenauer *et al*, 2018) recommend that patients with early stage favourable disease should receive either 2 cycles ABVD and 20 Gy involved site (IS) RT or 2 cycles ABVD and an iPET; if iPET-negative, patients should be treated with 1 cycle ABVD and 20 Gy IS-RT; iPET-positive patients should receive 2 cycles $BEACOPP_{esc}$ and 30 Gy IS-RT. Intermediate/unfavourable stage patients should be treated with 4 cycles

Table II. Comparison of EORTC/LYSA/FIL H10 and RAPID trials.

	EORTC/LYSA/FIL H10 (André *et al*, 2017)	RAPID (Radford *et al*, 2015)
PET baseline	95%	0%
Interim PET	2 cycles ABVD	3 cycles ABVD
PET review	75%	100%
Non-inferiority margin	10%	7%
Stage	I-IIB (bulky)	I-IIA
Radiotherapy	IN-RT 30 Gy	IF-RT 30 Gy
PET interpretation	International Harmonization Project (Juweid *et al*, 2007)	5-point scale

ABVD, adriamycin, bleomycin, vinblastine, dacarbazine; EORTC, European Organization for Research and Treatment of Cancer; FIL, Fondazione Italiani di Limfomi; IF-RT, involved-field radiotherapy; IN-RT, involved-node radiotherapy; LYSA, Lymphoma Study Association; PET, positron emission tomography-computed tomography scan; RAPID, randomised phase III trial to determine the role of FDG–PET imaging in clinical stages IA/IIA Hodgkin's disease.

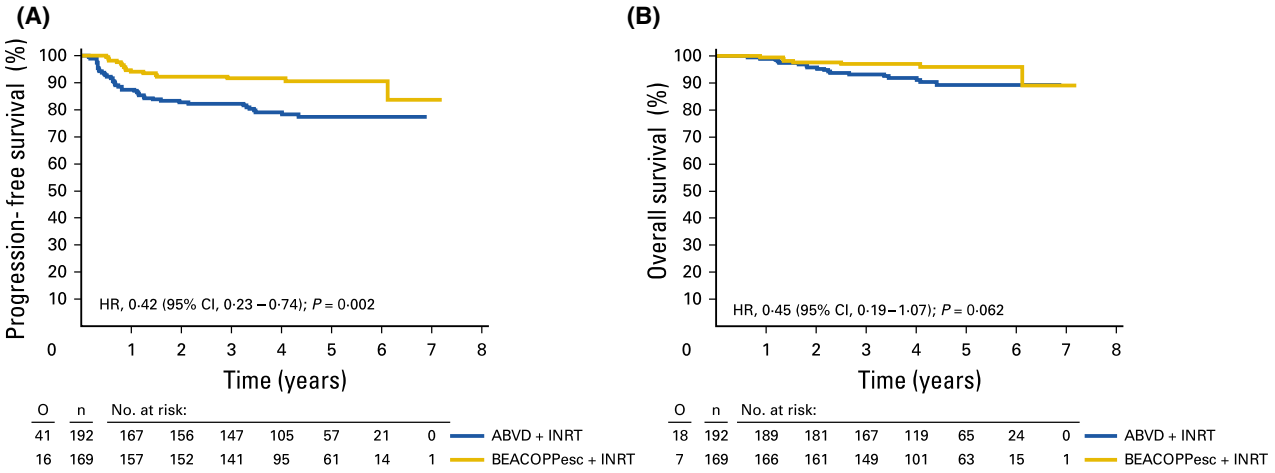

Fig 1. Progression-free survival (A) and overall survival (B) of iPET-positive patients included in the EORTC/LYSA/FIL H10 trial. After 2 cycles ABVD, patients were randomized between 2 cycles ABVD and 30 Gy INRT *versus* 2 cycles BEACOPP$_{esc}$ and 30 Gy INRT. Reprinted with permission from: André, M.P.E., Girinsky, T., Federico, M., Reman, O., Fortpied, C., Gotti, M., Casasnovas, O., Brice, P., van der Maazen, R., Re, A., Edeline, V., Ferme, C., van Imhoff, G., Merli, F., Bouabdallah, R., Sebban, C., Specht, L., Stamatoullas, A., Delarue, R., Fiaccadori, V., Bellei, M., Raveloarivahy, T., Versari, A., Hutchings, M., Meignan, M. & Raemaekers, J. (2017) Early Positron Emission Tomography Response-Adapted Treatment in Stage I and II Hodgkin Lymphoma: Final Results of the Randomized EORTC/LYSA/FIL H10 Trial. *J Clin Oncol*, **35,** 1786–1794. © 2017 American Society of Clinical Oncology. ABVD, adriamycin, bleomycin, vinblastine, dacarbazine; BEACOPP$_{esc}$, escalated bleomycin, etoposide, adriamycin, cyclophosphamide, vincristine, procarbazine, prednisone; CI, confidence interval; HR, hazard ratio; INRT, involved-node radiotherapy; O, observed event.

ABVD or 2 cycles BEACOPP$_{esc}$ + 2 cycles ABVD and 30 Gy IS-RT or 2 cycles ABVD and an iPET; if iPET-negative, treatment should continue with 2 cycles ABVD and 30 Gy IS-RT; if iPET-positive patients should receive 2 cycles BEACOPP$_{esc}$ and 30 Gy IS-RT (Eichenauer *et al*, 2018).

The 2017 NCCN guidelines (Hoppe *et al*, 2017) recommend a PET-guided approach for early stage favourable disease. For stage IA-IIA and no bulky mediastinum, three recommendations are made:

1 3 cycles ABVD and iPET. DS 1–2: observe or 1 cycle ABVD + 30 Gy IS-RT; for DS 3–4: 1 cycle ABVD + 30 Gy IS-RT; for DS 5: biopsy.
2 2 cycles ABVD and iPET. DS 1–2: 1 cycle ABVD and 30 Gy IS-RT; DS 3–4: 2 cycles ABVD + IS-RT 30 Gy or 2 cycles BEACOPP$_{esc}$ + 30 Gy IS-RT; DS 5: biopsy.
3 Stanford V 8 weeks and iPET. DS 1–4: IS-RT 30 Gy; DS 5: biopsy.

For intermediate or unfavourable disease and bulky mediastinum, several options are discussed, including the GHSG HD14 and EORTC/LYSA/FIL H10 approaches but also Stanford V (Hoppe *et al*, 2017).

Although several approaches are possible, we do recommend an iPET-guided strategy. For early stage favourable patients, an iPET is performed after 2 cycles ABVD. For iPET-negative patients (DS 1–3), we propose 1 additional cycle of ABVD and 20 Gy IN-RT. Rare patients with a positive iPET (DS 4 or 5) will receive 2 cycles of BEACOPP$_{esc}$ + 30 Gy IN-RT. For early stage unfavourable patients, an iPET is performed after 2 cycles ABVD. For iPET-negative patients (DS 1–3), we propose 4 additional cycles of ABVD for young patients. If late toxicity of RT is not a concern, 2 cycles ABVD and 30 Gy IN-RT are proposed. Patients with a positive iPET (DS 4 or 5) will receive 2 cycles of BEACOPP$_{esc}$ + 30 Gy IN-RT. This treatment strategy is essentially based on the results of the EORTC/LYSA/FIL H10 study (André *et al*, 2017).

Conclusions and future strategies

The reduction of chemotherapy dose and size of RT, but also more recently, PET-adapted strategies have reduced the burden of treatment in early stage HL. Unfortunately, there is currently no evidence that this could reduce long-term toxicities. Recently, three new drugs (brentuximab vedotin, nivolumab and pembrolizumab) have shown very interesting results in relapsing patients (Younes *et al*, 2012, 2016; Chen *et al*, 2017). These drugs are now also actively evaluated in first-line for early stage HL, either alone (i.e. in elderly patients) or in combination with AVD (NCT 02292979, NCT 02567851). Bleomycin is omitted in this situation because of increased lung toxicity. Phase II data show very promising data, but only randomized phase III trials can change the standard of care in this highly curable group of patients. Finally, circulating cell-free DNA could emerge as a very interesting tool to refine response evaluation and better define cure (Spina *et al*, 2018).

Author contributions

Julien Depaus wrote the paper and approved final version. Anne Delcourt critically revised the paper and approved final version. Marc André wrote the paper, critically revised and approved final version.

References

Aleman, B.M., van den Belt-Dusebout, A.W., Klokman, W.J., Van't Veer, M.B., Bartelink, H. & van Leeuwen, F.E. (2003) Long-term cause-specific mortality of patients treated for Hodgkin's disease. *Journal of Clinical Oncology*, **21**, 3431–3439.

André, M.P.E., Girinsky, T., Federico, M., Reman, O., Fortpied, C., Gotti, M., Casasnovas, O., Brice, P., van der Maazen, R., Re, A., Edeline, V., Ferme, C., van Imhoff, G., Merli, F., Bouabdallah, R., Sebban, C., Specht, L., Stamatoullas, A., Delarue, R., Fiaccadori, V., Bellei, M., Raveloarivahy, T., Versari, A., Hutchings, M., Meignan, M. & Raemaekers, J. (2017) Early positron emission tomography response-adapted treatment in stage I and II Hodgkin lymphoma: final results of the randomized EORTC/LYSA/FIL H10 trial. *Journal of Clinical Oncology*, **35**, 1786–1794.

Baxstrom, K., Peterson, B.A., Lee, C., Vogel, R.I. & Blaes, A.H. (2018) A pilot investigation on impact of participation in a long-term follow-up clinic (LTFU) on breast cancer and cardiovascular screening among women who received chest radiation for Hodgkin lymphoma. *Supportive Care in Cancer*, **26**, 2361–2368.

Behringer, K., Goergen, H., Hitz, F., Zijlstra, J.M., Greil, R., Markova, J., Sasse, S., Fuchs, M., Topp, M.S., Soekler, M., Mathas, S., Meissner, J., Wilhelm, M., Koch, P., Lindemann, H.W., Schalk, E., Semrau, R., Kriz, J., Vieler, T., Bentz, M., Lange, E., Mahlberg, R., Hassler, A., Vogelhuber, M., Hahn, D., Mezger, J., Krause, S.W., Skoetz, N., Boll, B., von Tresckow, B., Diehl, V., Hallek, M., Borchmann, P., Stein, H., Eich, H. & Engert, A. (2015) Omission of dacarbazine or bleomycin, or both, from the ABVD regimen in treatment of early-stage favourable Hodgkin's lymphoma (GHSG HD13): an open-label, randomised, non-inferiority trial. *Lancet*, **385**, 1418–1427.

Chen, R., Zinzani, P.L., Fanale, M.A., Armand, P., Johnson, N.A., Brice, P., Radford, J., Ribrag, V., Molin, D., Vassilakopoulos, T.P., Tomita, A., von Tresckow, B., Shipp, M.A., Zhang, Y., Ricart, A.D., Balakumaran, A. & Moskowitz, C.H. (2017) Phase II study of the efficacy and safety of pembrolizumab for relapsed/refractory classic Hodgkin lymphoma. *Journal of Clinical Oncology*, **35**, 2125–2132.

Cheson, B.D., Fisher, R.I., Barrington, S.F., Cavalli, F., Schwartz, L.H., Zucca, E. & Lister, T.A. (2014) Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. *Journal of Clinical Oncology*, **32**, 3059–3068.

Cutter, D.J., Schaapveld, M., Darby, S.C., Hauptmann, M., van Nimwegen, F.A., Krol, A.D., Janus, C.P., van Leeuwen, F.E. & Aleman, B.M. (2015) Risk of valvular heart disease after treatment for Hodgkin lymphoma. *Journal of the National Cancer Institute*, **107**, 2257–2265.

Eich, H.T., Diehl, V., Gorgen, H., Pabst, T., Markova, J., Debus, J., Ho, A., Dorken, B., Rank, A., Grosu, A.L., Wiegel, T., Karstens, J.H., Greil, R., Willich, N., Schmidberger, H., Dohner, H., Borchmann, P., Muller-Hermelink, H.K., Muller, R.P. & Engert, A. (2010) Intensified chemotherapy and dose-reduced involved-field radiotherapy in patients with early unfavorable Hodgkin's lymphoma: final analysis of the German Hodgkin Study Group HD11 trial. *Journal of Clinical Oncology*, **28**, 4199–4206.

Eichenauer, D.A., Aleman, B.M.P., Andre, M., Federico, M., Hutchings, M., Illidge, T., Engert, A. & Ladetto, M. (2018) Hodgkin lymphoma: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. *Annals of Oncology*, **29**, 19–29. https://doi.org/10.1093/annonc/mdy080

El-Galaly, T.C., d'Amore, F., Mylam, K.J., de Nully Brown, P., Bogsted, M., Bukh, A., Specht, L., Loft, A., Iyer, V., Hjorthaug, K., Nielsen, A.L., Christiansen, I., Madsen, C., Johnsen, H.E. & Hutchings, M. (2012) Routine bone marrow biopsy has little or no therapeutic consequence for positron emission tomography/computed tomography-staged treatment-naive patients with Hodgkin lymphoma. *Journal of Clinical Oncology*, **30**, 4508–4514.

Engert, A., Schiller, P., Josting, A., Herrmann, R., Koch, P., Sieber, M., Boissevain, F., De Wit, M., Mezger, J., Duhmke, E., Willich, N., Muller, R.P., Schmidt, B.F., Renner, H., Muller-Hermelink, H.K., Pfistner, B., Wolf, J., Hasenclever, D., Loffler, M. & Diehl, V. (2003) Involved-field radiotherapy is equally effective and less toxic compared with extended-field radiotherapy after four cycles of chemotherapy in patients with early-stage unfavorable Hodgkin's lymphoma: results of the HD8 trial of the German Hodgkin's Lymphoma Study Group. *Journal of Clinical Oncology*, **21**, 3601–3608.

Engert, A., Franklin, J., Eich, H.T., Brillant, C., Sehlen, S., Cartoni, C., Herrmann, R., Pfreundschuh, M., Sieber, M., Tesch, H., Franke, A., Koch, P., de Wit, M., Paulus, U., Hasenclever, D., Loeffler, M., Muller, R.P., Muller-Hermelink, H.K., Duhmke, E. & Diehl, V. (2007) Two cycles of doxorubicin, bleomycin, vinblastine, and dacarbazine plus extended-field radiotherapy is superior to radiotherapy alone in early favorable Hodgkin's lymphoma: final results of the GHSG HD7 trial. *Journal of Clinical Oncology*, **25**, 3495–3502.

Engert, A., Plutschow, A., Eich, H.T., Lohri, A., Dorken, B., Borchmann, P., Berger, B., Greil, R., Willborn, K.C., Wilhelm, M., Debus, J., Eble, M.J., Sokler, M., Ho, A., Rank, A., Ganser, A., Trumper, L., Bokemeyer, C., Kirchner, H., Schubert, J., Kral, Z., Fuchs, M., Muller-Hermelink, H.K., Muller, R.P. & Diehl, V. (2010) Reduced treatment intensity in patients with early-stage Hodgkin's lymphoma. *New England Journal of Medicine*, **363**, 640–652.

Ferme, C., Eghbali, H., Meerwaldt, J.H., Rieux, C., Bosq, J., Berger, F., Girinsky, T., Brice, P., van't Veer, M.B., Walewski, J.A., Lederlin, P., Tirelli, U., Carde, P., Van den Neste, E., Gyan, E., Monconduit, M., Divine, M., Raemaekers, J.M., Salles, G., Noordijk, E.M., Creemers, G.J., Gabarre, J., Hagenbeek, A., Reman, O., Blanc, M., Thomas, J., Vie, B., Kluin-Nelemans, J.C., Viseu, F., Baars, J.W., Poortmans, P., Lugtenburg, P.J., Carrie, C., Jaubert, J., Henry-Amar, M. & Trial, E.-G.H. (2007) Chemotherapy plus involved-field radiation in early-stage Hodgkin's disease. *New England Journal of Medicine*, **357**, 1916–1927.

Ferme, C., Thomas, J., Brice, P., Casasnovas, O., Vranovsky, A., Bologna, S., Lugtenburg, P.J., Bouabdallah, R., Carde, P., Sebban, C., Eghbali, H., Salles, G., van Imhoff, G.W., Thyss, A., Noordijk, E.M., Reman, O., Lybeert, M.L.M., Janvier, M., Spina, M., Audhuy, B., Raemaekers, J.M.M., Delarue, R., Anglaret, B., de Weerdt, O., Marjanovic, Z., Tersteeg, R., de Jong, D., Briere, J. & Henry-Amar, M. (2017) ABVD or BEACOPPbaseline along with involved-field radiotherapy in early-stage Hodgkin Lymphoma with risk factors: results of the European Organisation for Research and Treatment of Cancer (EORTC)-Groupe d'Etude des Lymphomes de l'Adulte (GELA) H9-U intergroup randomised trial. *European Journal of Cancer*, **81**, 45–55.

Gallamini, A., Hutchings, M., Rigacci, L., Specht, L., Merli, F., Hansen, M., Patti, C., Loft, A., Di Raimondo, F., D'Amore, F., Biggi, A., Vitolo, U., Stelitano, C., Sancetta, R., Trentin, L., Luminari, S., Iannitto, E., Viviani, S., Pierri, I. & Levis, A. (2007) 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. *Journal of Clinical Oncology*, **25**, 3746–3752.

Hahn, E., Jiang, H., Ng, A., Bashir, S., Ahmed, S., Tsang, R., Sun, A., Gospodarowicz, M. & Hodgson, D. (2017) Late cardiac toxicity after mediastinal radiation therapy for Hodgkin lymphoma: contributions of coronary artery and whole heart dose-volume variables to risk prediction. *International Journal of Radiation Oncology Biology Physics*, **98**, 1116–1123.

Hoppe, R.T., Advani, R.H., Ai, W.Z., Ambinder, R.F., Aoun, P., Bello, C.M., Benitez, C.M., Bernat, K., Bierman, P.J., Blum, K.A., Chen, R., Dabaja, B., Forero, A., Gordon, L.I., Hernandez-Ilizaliturri, F.J., Hochberg, E.P., Huang, J., Johnston, P.B., Kaminski, M.S., Kenkre, V.P., Khan, N., Maloney, D.G., Mauch, P.M., Metzger, M., Moore, J.O., Morgan, D., Moskowitz, C.H., Mulroney, C., Poppe, M., Rabinovitch, R., Seropian, S., Smith, M., Winter, J.N., Yahalom, J., Burns, J., Ogba, N. & Sundar, H. (2017) Hodgkin lymphoma version 1.2017, NCCN clinical practice guidelines in oncology. *Journal of the National Comprehensive Cancer Network*, **15**, 608–638.

Juweid, M.E., Stroobants, S., Hoekstra, O.S., Mottaghy, F.M., Dietlein, M., Guermazi, A.,

Wiseman, G.A., Kostakoglu, L., Scheidhauer, K., Buck, A., Naumann, R., Spaepen, K., Hicks, R.J., Weber, W.A., Reske, S.N., Schwaiger, M., Schwartz, L.H., Zijlstra, J.M., Siegel, B.A. & Cheson, B.D. (2007) Use of positron emission tomography for response assessment of lymphoma: consensus of the Imaging Subcommittee of International Harmonization Project in Lymphoma. *Journal of Clinical Oncology*, **25**, 571–578.

Maraldo, M.V., Jorgensen, M., Brodin, N.P., Aznar, M.C., Vogelius, I.R., Petersen, P.M., Berthelsen, A.K., Christensen, C.B., Hjalgrim, L.L. & Specht, L. (2014) The impact of involved node, involved field and mantle field radiotherapy on estimated radiation doses and risk of late effects for pediatric patients with Hodgkin lymphoma. *Pediatric Blood & Cancer*, **61**, 717–722.

Meyer, R.M., Gospodarowicz, M.K., Connors, J.M., Pearcey, R.G., Wells, W.A., Winter, J.N., Horning, S.J., Dar, A.R., Shustik, C., Stewart, D.A., Crump, M., Djurfeldt, M.S., Chen, B.E. & Shepherd, L.E. (2012) ABVD alone versus radiation-based therapy in limited-stage Hodgkin's lymphoma. *New England Journal of Medicine*, **366**, 399–408.

Radford, J., Illidge, T., Counsell, N., Hancock, B., Pettengell, R., Johnson, P., Wimperis, J., Culligan, D., Popova, B., Smith, P., McMillan, A., Brownell, A., Kruger, A., Lister, A., Hoskin, P., O'Doherty, M. & Barrington, S. (2015) Results of a trial of PET-directed therapy for early-stage Hodgkin's lymphoma. *New England Journal of Medicine*, **372**, 1598–1607.

Sasse, S., Brockelmann, P.J., Goergen, H., Plutschow, A., Muller, H., Kreissl, S., Buerkle, C., Borchmann, S., Fuchs, M., Borchmann, P., Diehl, V. & Engert, A. (2017) Long-term follow-up of contemporary treatment in early-stage Hodgkin lymphoma: updated analyses of the German Hodgkin study group HD7, HD8, HD10, and HD11 trials. *Journal of Clinical Oncology*, **35**, 1999–2007.

Schaapveld, M., Aleman, B.M., van Eggermond, A.M., Janus, C.P., Krol, A.D., van der Maazen, R.W., Roesink, J., Raemaekers, J.M., de Boer, J.P., Zijlstra, J.M., van Imhoff, G.W., Petersen, E.J., Poortmans, P.M., Beijert, M., Lybeert, M.L., Mulder, I., Visser, O., Louwman, M.W., Krul, I.M., Lugtenburg, P.J. & van Leeuwen, F.E. (2015) Second cancer risk up to 40 years after treatment for Hodgkin's lymphoma. *New England Journal of Medicine*, **373**, 2499–2511.

Simontacchi, G., Filippi, A.R., Ciammella, P., Buglione, M., Saieva, C., Magrini, S.M., Livi, L., Iotti, C., Botto, B., Vaggelli, L., Re, A., Merli, F. & Ricardi, U. (2015) Interim PET after two ABVD cycles in early-stage Hodgkin lymphoma: outcomes following the continuation of chemotherapy plus radiotherapy. *International Journal of Radiation Oncology Biology Physics*, **92**, 1077–1083.

Spina, V., Bruscaggin, A., Cuccaro, A., Martini, M., Di Trani, M., Forestieri, G., Manzoni, M., Condoluci, A., Arribas, A., Terzi-Di-Bergamo, L., Locatelli, S.L., Cupelli, E., Ceriani, L., Moccia, A.A., Stathis, A., Nassi, L., Deambrogi, C., Diop, F., Guidetti, F., Cocomazzi, A., Annunziata, S., Rufini, V., Giordano, A., Neri, A., Boldorini, R., Gerber, B., Bertoni, F., Ghielmini, M., Stussi, G., Santoro, A., Cavalli, F., Zucca, E., Larocca, L.M., Gaidano, G., Hohaus, S., Carlo-Stella, C. & Rossi, D. (2018) Circulating tumor DNA reveals genetics, clonal evolution, and residual disease in classical Hodgkin lymphoma. *Blood*, **131**, 2413–2425.

Straus, D.J., Jung, S.H., Pitcher, B., Kostakoglu, L., Grecula, J.C., Hsi, E.D., Schoder, H., Popplewell, L.L., Chang, J.E., Moskowitz, C.H., Wagner-Johnston, N., Leonard, J.P., Friedberg, J.W., Kahl, B.S., Cheson, B.D. & Bartlett, N.L. (2018) CALGB 50604: risk-adapted treatment of non-bulky early-stage Hodgkin lymphoma based on interim PET. *Blood*, **132**, 1013–1021.

Thomas, J., Ferme, C., Noordijk, E.M., Morschhauser, F., Girinsky, T., Gaillard, I., Lugtenburg, P.J., Andre, M., Lybeert, M.L.M., Stamatoullas, A., Beijert, M., Helias, P., Eghbali, H., Gabarre, J., van der Maazen, R.W.M., Jaubert, J., Bouabdallah, K., Boulat, O., Roesink, J.M., Christian, B., Ong, F., Bordes-soule, D., Tertian, G., Gonzalez, H., Vranovsky, A., Quittet, P., Tirelli, U., de Jong, D., Audouin, J., Aleman, B.M.P. & Henry-Amar, M. (2018) Comparison of 36 Gy, 20 Gy, or no radiation therapy after 6 cycles of EBVP chemotherapy and complete remission in early-stage Hodgkin lymphoma without risk factors: results of the EORT-GELA H9-F intergroup randomized trial. *International Journal of Radiation Oncology Biology Physics*, **100**, 1133–1145.

von Tresckow, B., Plutschow, A., Fuchs, M., Klimm, B., Markova, J., Lohri, A., Kral, Z., Greil, R., Topp, M.S., Meissner, J., Zijlstra, J.M., Soekler, M., Stein, H., Eich, H.T., Mueller, R.P., Diehl, V., Borchmann, P. & Engert, A. (2012) Dose-intensification in early unfavorable Hodgkin's lymphoma: final analysis of the German Hodgkin Study Group HD14 trial. *Journal of Clinical Oncology*, **30**, 907–913.

Younes, A., Gopal, A.K., Smith, S.E., Ansell, S.M., Rosenblatt, J.D., Savage, K.J., Ramchandren, R., Bartlett, N.L., Cheson, B.D., de Vos, S., Forero-Torres, A., Moskowitz, C.H., Connors, J.M., Engert, A., Larsen, E.K., Kennedy, D.A., Sievers, E.L. & Chen, R. (2012) Results of a pivotal phase II study of brentuximab vedotin for patients with relapsed or refractory Hodgkin's lymphoma. *Journal of Clinical Oncology*, **30**, 2183–2189.

Younes, A., Santoro, A., Shipp, M., Zinzani, P.L., Timmerman, J.M., Ansell, S., Armand, P., Fanale, M., Ratanatharathorn, V., Kuruvilla, J., Cohen, J.B., Collins, G., Savage, K.J., Trneny, M., Kato, K., Farsaci, B., Parker, S.M., Rodig, S., Roemer, M.G., Ligon, A.H. & Engert, A. (2016) Nivolumab for classical Hodgkin's lymphoma after failure of both autologous stem-cell transplantation and brentuximab vedotin: a multicentre, multicohort, single-arm phase 2 trial. *The Lancet Oncology*, **17**, 1283–1294.