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Review

REVIEW

Hodgkin Lymphoma: Current Status and Clinical Trial Recommendations

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Abstract

The National Clinical Trials Network lymphoid malignancies Clinical Trials Planning Meeting (CTPM) occurred in November of 2014. The scope of the CTPM was to prioritize across the lymphoid tumors clinically significant questions and to foster strategies leading to biologically informed and potentially practice changing clinical trials. This review from the Hodgkin lymphoma (HL) subcommittee of the CTPM discusses the ongoing clinical challenges in HL, outlines the current standard of care for HL patients from early to advanced stage, and surveys the current science with respect to biomarkers and the landscape of ongoing clinical trials. Finally, we suggest areas of unmet need in HL and elucidate promising therapeutic strategies to guide future HL clinical trials planning across the NCTN.

Despite the overall favorable outcomes for most patients with Hodgkin lymphoma (HL), the young median age at diagnosis results in unique treatment challenges and consequences. Among patients with early-stage and advanced disease who are cured, serious acute and long-term treatment-related toxicities remain a concern. For HL with relapsed or refractory disease, the loss of young lives and the treatment-related morbidity associated with high-dose therapy increase the societal burden of this disease. In a cost-per-death analysis of malignancies throughout Europe, HL had the second highest "cost per death" or lost productivity cost due to premature cancer-related mortality, after melanoma (1). The top priority in HL remains improvement of cure rates; however, true success will only come with treatments that do not impair the long-term quality of life of HL survivors or result in life-threatening or life-altering acute or late effects.

Background/Disease Progress Summary

Epidemiology and Burden of Disease

Hodgkin Lymphoma is the most common lymphoma affecting the young population, with approximately 9200 estimated new cases of HL in the United States in 2014 (2). The incidence of HL is bimodal, with the highest incidence at age 15 to 34 years and a second peak in those older than age 60 years. Higher HL-specific survival is observed for children and adolescents than for adults

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Table 1. SOC regimens in upfront therapy*

Disease setting	Treatment regimen	Trials
Stage I–IIA favorable (<3 sites of disease, no extranodal disease, nonbulky adenopathy, ESR < 50 and ESR < 30 if B symptoms)	ABVD for 2 cycles followed by 20 Gy of IFRT	HD10 (13) HD13 (73)
	ABVD for 3–6 cycles	HD6 (14,77) RAPID (20) H10 (21)
Stage I–II nonbulky, unfavorable (extranodal disease, high erythrocyte sedimentation rate or ≥ 3 nodal sites, B symptoms)	ABVD for 4 cycles plus 30 Gy IFRT	HD11 (16)
	BEACOPP for 2 cycles+ ABVD for 2 cycles + 30 Gy IFRT	HD14 (24)
	ABVD x 3–6	RAPID (20) H10 (21) HD6 (76) CALGB 50401 (77)
Stage I–II bulky (mediastinal mass ratio > 1/3 or mass > 10 cm)	ABVD for 4–6 cycles plus 30 Gy IFRT	HD11 (16) E2496 (25) H10 (21)
	BEACOPP for 2 cycles+ ABVD for 2 cycles + 30 Gy IFRT	HD 14 (24)
Advanced disease (stage III–IV)	ABVD x 6 cycles	CALGB 8952 (26) LY09 Trial (27) EORTC (28)
	escBEACOPP x 6 cycles	HD12 (29)
	ABVD for 2 cycles followed by escBEACOPP x 6 in PET+	GITIL HD0607 (78)

*ABVD = doxorubicin, bleomycin, vinblastine, dacarbazine; BEACOPP = bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procabazine, prednisone; CALGB = Cancer and Leukemia Group B; EORTC = European Organization for the Research and Treatment of Cancer; ESR = erythrocyte sedimentation rate; GITIL = Gruppo Italiano Terapie Innovative nei Linfomi; IFT = involved field radiotherapy; PET = positron emission tomography; RAPID = Randomized Phase III Trial to Determine the Role of FDG–PET Imaging in Clinical Stages IA/IIA Hodgkin's Disease.

(five-year survival rate = 96%, SE = 0.4%, vs 88%, SE = 0.3%; $P < .001$, calculated by Kaplan-Meier analysis and two-sided log-rank test to compare survival curves) (3). Approximately 25% of patients experience a relapse or are found to have disease refractory to initial therapy. While 90% of early-stage HL patients are cured with conventional treatment, only 70% of advanced-stage patients are cured with standard therapeutic approaches. For HL patients with relapsed disease, only half are cured with standard salvage therapies (4).

Over the past 30 years, data regarding the late effects of therapy, specifically cardiovascular toxicity and risk of second cancers, have led to treatment modifications of radiation dose and field size. This has led to risk reduction of therapy-related causes of death. However, long-term complications of therapy remain a clinically significant concern over the lives of this predominantly young patient population. In addition to second cancers, cardiac and peripheral vascular disease, and pulmonary disease, less serious but potentially life-altering effects of infertility and sexual dysfunction, neurocognitive dysfunction, chronic fatigue, and thyroid disease are associated with current therapeutics used for HL (5–10). Of particular concern are the adolescent and young adult (AYA) patients who commonly present with bulky mediastinal disease, which currently is optimally treated with combined modality therapy (CMT) including radiotherapy (RT). Unfortunately, treatment of the developing breast with RT induces a statistically significant increased risk of secondary breast cancer. In addition to current efforts to develop treatment approaches that minimize late effects, improved surveillance of HL survivors also has the potential to save lives.

Current Standard of Care Disease Management

The management of early-stage, nonbulky favorable HL (<3 sites of disease, no extranodal disease, no bulky adenopathy, ESR < 50 and Erythrocyte Sedimentation Rate (ESR) < 30 if B symptoms) or intermediate HL (large mediastinal mass, extranodal disease, high erythrocyte sedimentation rate or > 3 nodal sites) remains based on the chemotherapy regimen of doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD). This became the standard of care (SOC) in this group of patients more than 30 years ago, when its superiority to mechlorethamine, vincristine, procarbazine, and prednisone (MOPP) chemotherapy was demonstrated (11). Current SOC in early-stage disease has been informed by large European and North American cooperative group trials focusing on how to minimize toxicity while maximizing curability; these trials have attempted to address the optimal number of chemotherapy cycles, the dose of radiotherapy, and the comparison of combined modality therapy (CMT) vs chemotherapy alone (12–15). Current SOC includes either CMT, consisting of short-course ABVD (ie, 2 to 4 cycles) followed by RT (20 to 30 Gy) based in part on the HD10 and HD11 trials (13,16), or ABVD chemotherapy (ie, 4 to 6 cycles) as monotherapy. The latter was based initially on smaller studies that showed equivalent five-year overall survival (OS) rates and was recently confirmed with the long-term follow-up of the large phase III NCI Canada (NCIC) HD6 trial (17,18). In the most recent clinical trials of CMT, the radiation fields were "involved field" (IFRT); however, with accurate PET-CT imaging, radiation fields have been further reduced, to "involved site" irradiation, which has been adopted in the United States as the standard (19). Radiation dose varies from 20–30 Gy, depending on the absence or presence of various unfavorable prognostic factors.

The results of the UK RAPID trial, which compared chemotherapy alone with chemotherapy followed by involved field radiation, suggest a modest improvement in PFS with the addition of IFRT in patients who are 18F-fluorodeoxyglucose positron emission tomography (PET)–negative after three cycles of ABVD (absolute increase = 3.8%, relative reduction in risk of progression = 47%), but per protocol analysis there was there

was no difference in OS (20). The EORTC H10 reported a preplanned interim futility analysis of 1137 early-stage HL patients who were PET negative after two cycles of ABVD, who were randomly assigned between involved node radiotherapy or no RT. On the basis of this analysis, CMT resulted in fewer early progressions in early-stage I/II HL, although outcome was excellent in both arms. In the favorable subgroup, 85.8% had a negative early PET scan (standard arm: 1 event vs experimental arm: 9 events); in the unfavorable subgroup, 74.8% had a negative early PET scan (standard arm: 7 events vs experimental arm: 16 events). The independent data monitoring committee concluded it was unlikely that the trial would show noninferiority in the final results for the experimental arm and advised stopping random assignment for early PET-negative patients (21). These studies suggest that to date early interim PET appears to be prognostic but has not yet proven to be predictive in answering whether the omission of radiation in PET-negative patients can result in an equivalent failure-free survival (FFS). Despite the fact that PET has not been predictive for acute disease control/FFS, longer follow-up is needed to determine whether it will make a difference for late events and late effects. With a goal of minimizing therapy for early-stage HL, the recently published HD13 trial investigated whether the omission of dacarbazine or bleomycin from ABVD-based CMT reduced the efficacy of the regimen and concluded that the SOC for these favorable-risk, early-stage patients should remain short-course ABVD-based CMT because omission of either (or both) drug resulted in increased risk of relapse (22). Data from the de-escalation arms of the response-adapted therapy based on interim FDG-PET scans in an advanced Hodgkin lymphoma study (RATHL) presented at the 13th International Conference on Malignant Lymphoma in 2015 demonstrated that in 984 HL patients stage II–IV who were FDG-PET negative after two cycles of ABVD, outcomes were equivalent in patients who received four subsequent cycles of ABVD or AVD (PFS = 85.4% vs 84.4%, OS = 97% vs 97.5%) (23). These preliminary data suggest that in patients who have a complete response by PET after two cycles of therapy it may be safe to omit the bleomycin from the subsequent four cycles of therapy.

For HL patients with early-stage bulky disease, ABVD-based CMT is SOC in the United States (eg, ABVD x 4–6 cycles followed by RT). In Europe as an alternative, intensified chemotherapy regimens such as bleomycin, etoposide, adriamycin, cyclophosphamide, oncovin, procarbazine, and prednisone (BEACOPP) standard dose or escalated, either alone or combined with ABVD, are based on data that demonstrate superior FFTF for the high-dose regimen, but with a cost of increased toxicity and, to date, no difference in OS. One thousand five hundred twenty-eight patients with early-stage unfavorable HL received ABVD for four cycles or escalated doses of BEACOPP for two cycles plus ABVD for two cycles. All patients received 30 Gy IFRT. The freedom from treatment failure favored the aggressive chemotherapy arm, with a difference of 7.2% at five years, but there was no difference in OS and increased toxicity was seen in the aggressive chemotherapy arm (24). In some centers, end-of-treatment PET/CT, rather than degree of pretreatment bulk, is used to determine the need for RT, which results in fewer patients receiving RT. Large phase III cooperative group clinical trials comparing alternate regimens such as Stanford V (Intergroup trial E2496) and BEACOPP chemotherapy (HD11) failed to consistently demonstrate superiority to ABVD (16,25) for these patients. See Table 1 for SOC regimens for upfront therapy.

For patients with locally extensive and advanced-stage HL, the SOC in the United States was defined as ABVD chemotherapy more than 20 years ago based on phase III US cooperative group studies (26–29). In the German Hodgkin Lymphoma Study Group (GHSG), escalated BEACOPP is the SOC for these patients, based on the HD9 and HD12 studies (30). Preliminary data from the phase II S0816 US intergroup study exploring response-adapted therapy showed that for patients who were PET/CT positive after two cycles of ABVD and were subsequently escalated to BEACOPP the two-year PFS was 64% (95% confidence interval [CI] = 50% to 75%), suggesting a benefit for escalating therapy in the PET/CT-positive group (31). The two-year PFS in the interim PET/CT-negative group was 82% (95% CI = 77% to 86%), suggesting an opportunity for improvement even in early complete responders. The HD0801 study also suggests a potential benefit with escalation of therapy for advanced-stage HL patients who remain PET positive after two cycles of ABVD; 519 advanced-stage HL patients were treated with ABVD, and patients who were PET positive after two cycles received intensified therapy and autologous stem cell transplant. With two years of follow-up, the PFS for the PET-positive group was equivalent to that of the PET-negative patients, suggesting that early intensification may improve the durable complete response rate for interim PET-positive patients (32).

Hodgkin lymphoma patients with relapsed or refractory disease, both in the pretransplant setting and relapsing after autologous stem cell transplant (ASCT), continue to represent a high priority for study and innovation. For patients with progression after primary treatment with multi-agent chemotherapy, the standard treatment approach commonly consists of second-line chemotherapy followed by ASCT, which results in a cure of about 50% of such patients (33). Several studies have shown that achieving a complete response (CR) prior to ASCT is associated with better long-term disease control and cure. Yet the CR rate for both standard chemotherapy regimens such as ifosfamide, carboplatin, and etoposide (ICE), as well as novel therapies such as brentuximab vedotin (BV), is approximately 34% (95% CI = 25.2% to 44.4%), indicating that many patients likely proceed to transplant with suboptimal disease control (34). In a single-institution study, patients in first relapse were treated sequentially with BV with a 27% CR rate (95% CI = 13% to 30%), followed by augmented ICE chemotherapy for the patients who did not achieve a CR, yielding a 76% CR rate (95% CI = 62% to 89%) for the patients treated on the sequential combination (35). This may represent a strategy for patients with chemotherapy-sensitive disease; however, whether this sequential approach results in improved long-term disease control vs ICE induction alone requires validation in larger multicenter studies and more mature outcome data. Additionally, combinations that include novel agents with high activity such as the checkpoint inhibitors nivolumab, now FDA approved for HL relapsed or progressed after ASCT and post-transplantation BV, and pembrolizumab, may obviate the need for such sequential therapies.

The phase III AETHERA trial investigating BV maintenance in the post-ASCT setting demonstrated an increase in PFS compared with patients who received placebo (median of 43 months vs 24 months, respectively; hazard ratio = 0.57, 95% CI = 62% to 89%, $P = .001$, calculated by stratified COX regression models with one-sided alpha level of .025), albeit with a higher incidence of therapy-related toxicities (36). Long-term survival analysis is needed to evaluate whether this may influence the natural history of disease for these patients and how this will inform the design of future studies. Beyond these indications, there is no clear SOC in the relapsed patient population, and to date there have been no large US cooperative group trials

beyond small phase II studies examining new agents and novel combinations.

Chemotherapeutic agents used for the initial treatment of pediatric HL are similar to those used in adults; however, because of the recognition of the elevated risk for long-term effects in the younger population (37), pediatric cooperative group studies have developed different strategies from the adult cooperative groups investigating hybrid regimens using lower cumulative doses of alkylators, doxorubicin, and bleomycin, especially for low-risk (stages I–IIA, no bulk, no B symptoms) and intermediate-risk (all stage I and II patients not classified as early stage, stage IIIA, and variably stage IVA) disease. No single standard of care regimen exists, and trials differ by the use of chemotherapy regimens of varying dose intensity, as well as the criteria for omission of radiotherapy. In general, pediatric radiotherapy approaches utilize lower doses (15–25 Gy) and smaller fields (involved field or node), resulting in lower exposure to heart and lung compared with that administered in adult trials (38). The German Society of Pediatric Oncology, now in conjunction with other European pediatric oncology centers (Euronet consortium), has investigated vincristine, etoposide, prednisone, doxorubicin (OEPA) for low risk and OEPA with cyclophosphamide, vincristine, prednisone, dacarbazine (COPDac) for intermediate- and high-risk groups, with involved field radiotherapy utilized for all except the 30% of low-risk patients achieving a CR to two cycles of chemotherapy (39). In North America, the Children's Oncology Group has primarily evaluated doxorubicin, bleomycin, vincristine, etoposide, prednisone, cyclophosphamide (ABVE-PC) and its derivatives across the risk groups, with radiotherapy omission in more recent trials in early-responding low- and intermediate-risk groups (40–43).

Recent Progress in Biological Understanding of HL

Hodgkin lymphoma has a unique biology whereby the malignant Hodgkin Reed-Sternberg (HRS) cells are few in number (generally less than 1% of the total tumor bulk) and are surrounded by non-neoplastic immune cells in the tumor microenvironment, including T-cells, B-cells, macrophages, mast cells, and eosinophils. Recent advances in biology of HL have elucidated the key role of the cross-talk between the HRS cells and the immune cells of the tumor microenvironment in promoting lymphomagenesis. Tumor-associated macrophages (TAMs) and, specifically, increased TAM expression of CD68 by immunohistochemistry (IHC), have been demonstrated to be associated with an inferior outcome in HL, including outcome after salvage chemotherapy with autologous transplantation (44,45). Patient samples from the phase III cooperative group trial of Stanford V vs ABVD (E2496) were used to validate the initial CD68 results and confirmed a statistically significantly inferior OS in the 38% of patients with high CD68 expression (46). Gene expression profiling of microdissected HRS cells demonstrated that a macrophage-like signature (CSFIR) is statistically significantly associated with treatment failure and, in combination with CD68 IHC, is an independent predictor for inferior progression-free survival in an independent set of 132 patients (47). More recently, using NanoString technology, a 23-gene outcome predictor in advanced-stage HL patients has been developed from 290 patients on the E2496 study that may identify patients at increased risk of death independently of IPS and CD68 when treated with standard-intensity firstline chemotherapy (48).

Other advances in the knowledge of HL biology include the discovery of 9p24.1 amplification and high increased PD-1 ligand expression by HRS cells, the contribution of the Epstein-Barr virus (EBV) to HL pathogenesis, such as in influencing the expression of inhibitory cytokines such as CXCL10, CCL5, and CCL3, and the role of the microenvironment in contributing to deregulation of signaling pathways such as nuclear factor kappa B (NFκB) and Janus kinase signal transducer and activation of transcription signaling (JAK-STAT) (49–51). A prospective correlative study evaluating plasma EBV-DNA at several time points before, during, and after therapy on E2496 showed that the presence of plasma EBV-DNA was associated with a statistically significantly worse failure-free survival (52). Recent data also suggest an association with inhibitory cytokines and chemokines such as thymus and activation-regulated chemokine (TARC) and the pretreatment cytokine profile, with higher levels of inhibitory cytokines such as IL-6 and IL-2R associated with a higher risk of early relapse (53–56) and mutation of the β-2 microglobulin gene (B2M) in primary HRS cells associated with NS subtype, younger age, and favorable survival (57).

These scientific advances in HL biology are exciting and clinically significant, yet they must now be translated into clinical benefit or validated as truly predictive, surrogate end points. Moving forward, the goal of HL-focused research should be to translate these discoveries into improved risk stratification tools and biologically based therapeutic strategies for high-risk disease. Through translational aims embedded within clinical trials, it is also of fundamental importance to use patient-focused research to further elucidate HL disease biology.

Key Clinical Knowledge Gaps and Unmet Clinical Needs

We believe that despite the curability of HL, strong unmet needs remain in the management of HL that should be considered high priorities for research in the cooperative group setting. These include:

1) improved therapeutic strategies that maximize the CR rate for patients treated for first relapse, which is likely to be associated with a higher cure rate for these patients;
2) improving the ability to identify the 10% to 30% of patients whose primary therapy will fail and developing more effective treatments for these high-risk patients;
3) improved therapies that prolong life for multiply relapsed patients who are not cured with ASCT;
4) identifying and eliminating "unnecessary therapy" in low-risk patients in order to minimize long-term consequences of "successful" treatments (eg, increased second cancers and arterial diseases, preservation of quality of life (QOL).

In order to achieve the dual goals of cure and minimization of therapeutic toxicity, it is critical to identify subgroups of patients, for example, the AYA and older populations, who might benefit most from these novel treatment approaches and from whom, if successful, we would be able to extrapolate outcomes to a more generalized setting. Major challenges and unmet needs for the management of high-risk patients include: improved risk stratification, the sequencing of standard therapy with promising new agents, and the role of consolidation strategies for the highest-risk patients.

Current Landscape of Ongoing Clinical Trials

The current landscape of ongoing or completed trials with results pending that may inform the SOC (Table 1) is described in

Table 2. Selected open or recently completed phase III and phase II clinical trials in Hodgkin lymphoma*

Title Frontline	Regimen	Population	NCT number/ sponsor	Estimated enrollment	Start date/completion date	Preliminary data
ECHELON 1	ABVD vs AAVD	Advanced stage (IIb–IV)	01712490 Millennium Pharmaceuticals, Inc.	1240	November 2012–December 2015	Phase 1 AAVD: 3-y FFS = 96%, OS = 100%
HD16	ABVD × 2 +/- 20 Gy IFRT	Early stage without bulk (Ia–IIb)	NCT00736320 University of Cologne	1150	November 2009–May 2020	
HD18	escBEACOPP x 2 + PET+ → escBEACOPP x 6 vs escBEACOPP x 6 + rituximab PET- → esc BEACOPP × 4 vs escBEACOPP × 8	Advanced stage HL (IIB with bulky disease, III, IV)	00515554 University of Cologne	1500	May 2008–July 2014	PET+ 3-y interim analysis: PFS = 91.4% for BEACOPP; 93% for R-BEACOPP; OS = 96.5% vs 94.4% at 3 y
BV and combination chemotherapy	ABVEPC vs ABvVEPC + response-directed ISRT	High-risk/ advanced-stage pediatric classical HL (2–18 y)	0216643 COG	600	March 2015–November 2019	
CALGB: response-based therapy assessed by PET scan	ABVD +/- BEACOPP + radiation	Bulky stage I and stage II cHL	01118026 CALGB	123	September 2010–July 2017	
BV + AVD	BV × 2 → AVD + BV x 4–6	Limited-stage HL	01534078 Mass General Hospital	34	March 2012–April 2015	CR = 88%, PFS = 90%, OS = 97% at 14 mo; grade 3–4 neuropathy = 24%
Sequential BV → AVD	BV-AVD	Elderly HL	NCT01476410 Northwestern	48	November 2011–May 2016	
Sequential BV → AVD	BV + AVD and 30 Gy IFRT	Early-stage unfavorable HL	01868451 Memorial Sloan Kettering Cancer Center	30	May 2013–May 2016	
BV + DTIC or bendamustine	BV + dacarbazine or bendamustine	Elderly (60 y and older)	NCT01716806 Seattle Genetics	70	October 2012–October 2018	Interim analysis 100% ORR for both combinations
Response-adjusted therapy for Hodgkin lymphoma (RATHL)	2 cycles ABVD →PET- ABVD vs AVD × 4 PET + BEACOPP x 6 vs escBEACOPP × 4 +/- IFRT	Advanced stage (IIB with bulky disease, III, IV)	CRUK/07/033	1214		Median FU of 36.3 mo, PFS = 85.4% ABVD vs 84.4% AVD; OS = 97% ABVD vs 97.5% AVD
AEPA	(BV, etoposide, prednisone, doxorubicin) × 2, CAPDac (cyclophosphamide, BV prednisone, dacarbazine) × 4, with low-dose IFRT	Advanced-stage pediatric	01920932 Pediatric HL Consortium (St. Jude, DFCI, Stanford)	77	August 2013–August 2021	

(continued)

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Table 2. (continued)

Title Frontline	Regimen	Population	NCT number/ sponsor	Estimated enrollment	Start date/completion date	Preliminary data
Targeted BEACOPP variants	BrECADD, BrECAPP	Newly diagnosed advanced stage	German Hodgkin Lymphoma Study Group	104	October 2012–May 2014	BrECADD: CRR = 88%, CR/CRu = 88%, and 18 month PFS = 89%; BreCAP: CRR = 86%, CR/CRu = 94%, and 18 month PFS = 93%
Relapsed						
BV first salvage	BV	HL in first relapse	01393717 City of Hope Medical Center	57	October 2011–December 2015	ORR (CR + PR) = 69%, CR = 33%
E4412	BV + ipilimumab and nivolumab	Relapsed HL (first or later)	NCT01896999/ ECOG 4412	70	Jan 2014–December 2017	Preliminary efficacy BV + ipilimumab: ORR = 72%, CR = 50%
BV bendamustine	BV + bendamustine	Relapsed HL pre-ASCT	01874054 Seattle Genetics, Inc. 01657331 Columbia University	55 71	July 2012 June 2013–May 2015 October 2015	CR = 82%, ORR = 94% ; stem cell mobilization and collection was adequate
BV + gemcitabine		Pediatric and AYA HL in first relapse	01780662 COG	63	Phase 1: January 2013; phase 2: February 2015–2018	
CheckMate	Nivolumab	Relapsed HL	0218738 Bristol-Myers Squibb	120	July 2014–May 2016	Interim report on 80 patients: ORR = 66%, (57.5% PR, 8.8% CR); six-mo PFS = 77% (63)
Nivolumab		Pediatric relapsed HL	02304458 COG	204 (multiple tumor types); 20 with HL	February 2015–November 2016	
Pembrolizumab		Relapsed HL post-ASCT	02362997 Dana-Farber Cancer Institute	60	March 2015–March 2022	Phase 1: ORR of 53% in 15 patients, (CR = 20%, PR = 33%)
Keynote	Pembrolizumab	R/R HL	NCT02453594 Merck	180	June 2015–May 2017	60 patients (cohorts 1 and 2); cohort 1: ORR = 70%, CR = 20%, PR = 50%; cohort 2: ORR = 80% CR = 27%, PR = 53% (64)
BV and nivolumab	BV + nivolumab	Frontline elderly HL	NCT02758717	75	May 2016–February 2018	
BV and nivolumab	BV + nivolumab × 4 cycles	First relapse HL	NCT02572167	60	October 2015–May 2020	

*AAVD = brentuximab, adriamcyin vinblastine, dacarbazine; ABVD = doxorubicin, bleomycin, vinblastine, dacarbazine; AEPA = brentuximab, etoposide, prednisone, adriamycin; ASCT = autologous stem cell transplant; BEACOPP = bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procabazine, prednisone; BrECADD = brentuximab vedotin, etoposide, cyclophosphamide, doxorubicin, dacarbazine, and dexamethasone; BreCAP = brentuximab, cyclophosphamide, adriamycin, prednisone; BV = brentuximab vedotin; CALGB = Cancer and Leukemia Group B; CR = complete response; HL = Hodgkin lymphoma; IFRT = involved field radiotherapy; ISRT = involved site radiotherapy; NCT = National Center for Tumor Diseases; ORR = overall response rate; OS = overall survival; PET = positron emission tomography; PFS = progression-free survival; PR = partial response; R/R = relapsed or refractory.

Table 2. Current frontline phase III studies are primarily focused on investigating the benefit of the addition of BV to standard chemotherapy, with the exception of the German study HD18, which examines whether to escalate or de-escalate therapy with BEACOPP based on PET/CT data after two cycles of therapy. In a phase II study of 104 advanced-stage HL patients, the integration of BV into the BEACOPP regimen demonstrated equivalent PFS with decreased toxicity compared with standard BEACOPP, and the regimen of BV, etoposide, cyclophosphamide, doxorubicin, dacarbazine, and dexamethasone (BrECADD) is planned to be compared against BEACOPP in a phase III clinical trial (58). Existing phase II studies are similarly examining the addition of BV to upfront treatment in specialized populations such as older patients and low-risk early-stage patients. For HL patients who have relapsed after ASCT and BC, the checkpoint inhibitor Nivolumab is now approved on the basis of the phase II CheckMate registration study (NCT02181738), and the checkpoint inhibitor pembrolizumab remains under investigation in the phase II registration study Keynote (NCT02453594). Current phase II studies and early-phase studies for relapsed patients include the combination of BV and bendamustine, BV and checkpoint inhibitor therapy, BV and gemcitabine, or BV with sequential chemotherapy for nonresponders, both as pretransplant salvage or for multiply relapsed patients.

The agents most likely to impact the next generation of clinical trials are the antibody-drug conjugate BV and the checkpoint inhibitors nivolumab and pembrolizumab. Clinically, the success of the first antibody drug-conjugate, BV targeting the TNF receptor superfamily member CD30, which is highly and differentially expressed by HRS cells, represents a striking recent advance in the management of HL. Brentuximab vedotin was FDA approved in 2011 for the treatment of HL patients not eligible for ASCT based on the pivotal phase II study who relapsed either after ASCT or after two lines of combination chemotherapy.

Immune modulatory therapy, in particular with checkpoint inhibitors nivolumab and pembrolizumab, appears extremely promising in HL, with extremely high response rates and little toxicity. In a phase I study of patients with relapsed HL treated with nivolumab at a dose of 3 mg/kg every two weeks, the ORR was 87% (CR = 17%, PR = 70%, 95% CI = 66% to 97%); the remaining 13% had SD. Progression-free survival (PFS) at 24 weeks was 86% (95% CI = 62% to 95%) (59). Similar data were reported for PD-1 inhibitor pembrolizumab at the 2014 American Society of Hematology (ASH) Annual Meeting in a similar population of relapsed HL patients, with an ORR of 53% in 15 patients (CR = 20%, PR = 33, 95% CIs were not reported) (60). The data for both agents was updated at ASH 2015 and demonstrates that with longer follow-up (86 weeks and 9.7 months, respectively, durable responses persist in approximately 50% of patients) (61,62). A preliminary report of the phase II studies for both checkpoint inhibitors was reported at the 2016 American Society of Clinical Oncology Annual Meeting. In the CheckMate study, an interim analysis of 80 patients with relapsed HL treated with Nivolumab showed an ORR of 66% (PR = 57.5%, CR = 8.8%), with a six-month PFS of 77% (95% CIs were not reported) (63). The Keynote study presented data on the first two cohorts of the study patients with relapsed or refractory HL after ASCT and subsequent BV therapy (cohort 1), and patients ineligible for ASCT because of chemoresistance and BV therapy failure (cohort 2, 60 patients total). For cohort 1, the ORR was 70% (CR = 20%, PR = 50%); for cohort 2, the ORR was 80% (CR = 27%, PR = 53%, 95% CIs were not reported) (64). If this emerging data is confirmed by larger studies, checkpoint inhibitors have the potential to redefine treatment paradigms in all aspects of HL management.

Recommended Top Clinical Trial Questions

The following populations of patients have been identified as representing the highest immediate priority for further study.

- Patients in first relapse or with primary refractory disease. Such patients still have the potential for cure but are at substantial risk of dying from their disease, with a cure rate of approximately 50% with current therapies. For patients in first relapse, we suggest a multi-arm randomized phase II design with ICE as the comparator arm, PET/CT CR as the primary end point, and one- to two-year PFS, toxicity, and biomarker studies (eg, TARC and gene signature) as secondary end points. Several recently described regimens incorporating new agents would be appropriate to test in a randomized study.
- Optimizing initial therapy for patients with bulky disease is also a priority. Incorporating highly active novel agents into firstline therapy may allow elimination of RT in this population of primarily adolescents and young adults who are at statistically significant risk for second cancers and cardiovascular disease. We suggest a trial that includes both pediatric and adult patients and uses early interim PET/CT or end-of-treatment PET/CT to determine the need for RT. While a phase III study would be preferred, small patient numbers and difficulty accruing patients on previous adult studies in this population may justify the use of a less stringent level of evidence to allow for a smaller randomized comparison employing larger alpha (and potentially bigger treatment effects); in the rare circumstances where nonrandomized data can be shown to be sufficient to produce practice-changing evidence, a single-arm design can be used.
- While optimizing upfront therapy for patients with advanced disease remains an important priority, the large phase III study currently ongoing comparing ABVD with AVD plus brentuximab, and BrECADD with BEACOPP, may define new SOCs for this population. Further studies in advanced-stage disease will need to await results of these studies; however, potential integration of checkpoint inhibitors into frontline therapy is an intriguing option.
- Improving the outcome of special populations such as the elderly and AYA are high priorities, but we agreed that large-scale clinical investigations are challenging for the US NCTN groups, given the modest patient numbers of these populations treated at large academic centers.

End Points for Clinical Trials in HL

For firstline therapy, we recommend that a PFS-based end point be considered the primary end point in HL clinical trials. While not a surrogate for OS, a PFS improvement that is sustained over time would represent a major clinical benefit in HL, avoiding the toxic effects of second-line therapy such as ASCT, the potential need for multiple lines of therapy, and the decreased QOL and increased risk of late complications related to undergoing repeated treatments. In the older patient population with a statistically significantly inferior outcome and limited treatment options, PFS may indeed be a surrogate for OS. Quality-of-life end points should be considered secondary end points in HL clinical trials, especially in the pediatric and AYA populations, as well as in studies for older patients. If possible, in a selected subset of patients, long-term OS should be determined prospectively in order to capture the cumulative long-term toxicity of treatment in this predominantly young patient population.

Table 3. Biomarkers in Hodgkin lymphoma*

Recommendations Histopathology	Standard of care	Integral	Integrated	Exploratory	Validated	Identifies high-/low-risk groups	Identifies therapeutic target
Full diagnostic immunohistochemistry (including CD30, CD15, CD20, others)	Yes	Yes	No	No	Yes	No	Yes
Prognostic IHC-focused on HRS cells: EBV (80–84), BCL2, HLA II (85), BCL-XL (86), p53 (86), T-cell antigens (87)	No	No	No	Yes	No	Yes	Yes
Prognostic IHC focused on microenvironment: tumor-associate macrophages (44–46) CD68 (88), FOXP3 (88), CD20 (88), FGF2 (89), Syndecan-1 (89), CD163 (90)	No	No	No	Yes	No	Yes	Yes
Cytokines/chemokines Serum TARC (90,91), IL10 (92–94), sIL10R (93), IL6 (93), TNF (93), sTNFR (93), sCD30 (93,94), galectin-1 (95,96), CD4/8/25/54 (94)	No	No	No	Yes	No	Yes	No
Molecular Gene expression profile for risk group (26-gene predictor from Nanostring) (48)	No	No	Yes	Yes	No	Yes	No
Global microRNA levels including MIR21, MIR30E, MIR30D, and MIR92B (97,98)	No	No	No	Yes	No	Yes	No
Host germline polymorphisms and mutations IL-10-specific polymorphism 592AA (99)	No	No	No	Yes	No	No	No
IL-6-specific polymorphism 174GG (99)	No	No	No	Yes	No	No	No
Germline *NPAT* mutation (100)	No	No	No	Yes	No	No	No

*IHC = immunohistochemistry.

Interim PET/CT has not been validated as a predictive or surrogate end point for clinical trials at this time and remains investigational. The possibility of end of treatment (EOT) PET/CT serving as a surrogate for PFS remains an open question that requires further investigation. For patients with relapsed HL, PET/CT-negative CR may be considered an end point for phase II trials of pretransplant salvage regimens and regimens for post-transplant failures with PFS and OS as secondary end points.

While we recognize the importance of being conscientious about the cost of integrating novel targeted therapeutics into standard HL regimens, we would not at this time recommend the exclusion of any potential regimen based solely on cost. However, we recommend that prospective clinical trials include cost-effectiveness analyses (CEAs) for all regimens being studied in randomized phase II or III trials, as have been incorporated in the ongoing COG high-risk phase III trial. These analyses should take into consideration the cost of the current therapy as well as balance this with patient outcomes and potential cost savings related to the elimination of future therapy or prolonged therapy. Well-validated CEA measures have been studied and can form a basis for those planned for these trials (65).

Potential Surrogate Biomarkers and the Integration of Biomarkers Into Future Clinical Trials

While there have been many potential biomarker candidates identified in retrospective analyses, there are no prospectively validated integral markers in HL for risk stratification or for use as a surrogate end point. We unanimously agree with the National Cancer Institute that this is a top priority, but integral markers and surrogates are not likely to be identified without a

large prospective trial incorporating these potential markers. For example, multiple phase II studies have not been able to define the utility of the interim PET/CT. We encourage the study of surrogate biomarkers both for risk stratification and prognosis in HL, strongly recommend that translational aims focusing on correlative biomarkers be included in all future prospective clinical trials, and would support this as the primary aim of the study. At the present time, however, the only validated clinical index to assign upfront risk in HL is the International Prognostic Score (IPS), a retrospectively developed clinical model with a primary end point of freedom from progression (FFP) (66); however, recent studies suggest that its predictive range may have narrowed due to improved patient outcomes in the modern era (67,68). Despite advances in knowledge of disease biology, there are insufficient data currently to support the use of any specific biomarker to reliably identify high-risk subsets of patients for treatment decision-making or prognostication during therapy.

There is a myriad of potential markers in HL that are promising and have been described as correlating with patient risk and or clinical outcome. These are listed in Table 3 and can be grouped into the following categories: 1) markers related to Reed-Sternberg immunohistochemistry, 2) assessment of micro-environmental or circulating non-neoplastic cells, cytokines, and membrane-associated antigens, 3) gene expression and miRNA profiling reflecting the tumor microenvironment and host germline polymorphisms and mutations. To date, the largest group of these biomarkers includes those assessed by immunohistochemistry, and in the circulation yet to date none of these markers have been validated in a large-scale prospective randomized trial. Several promising biomarkers including the chemokine TARC and the 23-gene signature, which have correlated with disease outcome but remain to be validated in large-scale prospective clinical trials (48).

Potential integrated biomarker candidates as described in Table 3 include BCL-XL, p53, BCL-2 on HRS cells, tumor-associated macrophages in the tumor microenvironment, serum cytokines, and chemokines such as serum: TARC, galectin-1, IL-10, CD30, and gene expression profiling. Potential biomarkers of late effects include host polymorphisms and should be assembled from large databases (69).

With regards to imaging biomarkers, the committee feels that important questions include improving the reproducibility of PET and optimizing the timing for PET to best guide treatment response, standardizing and optimizing response definition (Deauville criteria may depend on treatment and extent of disease), elucidating the combined role of anatomic and functional volume imaging, and evaluating metabolic volume assessment as a new tool to guide treatment decision-making. Possible areas for imaging biomarker research include investigation of the predictive value of combinatorial approaches of PET and CT scan using both morphologic and metabolic change during therapy, particularly in PET-2-positive HL, and quantitative PET assessment at baseline and change in tumor metabolism during therapy. It is imperative to adopt standardized acquisition, reconstruction, and analysis protocols for the use of quantitative PET metrics. Data suggest that quantitative PET measures, mainly standardized uptake value (SUV), may be used to improve visual analysis for response assessment in DLBCL (70); however, this has yet to be validated in HL.

To further increase the interpretation accuracy and reproducibility of PET results, novel quantitative techniques beyond SUV, which are currently under investigation, may be integrated into therapeutic protocols. These include tumor functional volume parameters (eg, metabolically active tumor volume [MTV] and total lesion glycolysis [TLG]). To date, the bulk of the literature has been published on DLBCL patients (71). In HL, metabolic tumor volumes may be relevant to patient management, particularly in the better definition of tumor bulk at baseline, which is an important prognostic factor. The high reproducibility for volume-derived image indices suggests a potential superior role compared with SUVs (72–74). If these functional volume parameters are validated as independent or complementary prognostic factors, they may facilitate identification of patients at high risk of treatment failure, which may direct early treatment intensification. More research on all of these areas is necessary to make the translation from research into clinical practice feasible.

Given the ongoing evaluation of multiple biomarkers using several different techniques (IHC, gene expression profiling, sequencing, NanoString, imaging), not only in HL but in multiple lymphoma subtypes, we believe the best approach for further study is a post hoc biomarker analysis as opposed to randomization, risk stratification, response assessment, or monitoring based on these biomarkers at this time. We recommend collecting tumor samples (peripheral blood, bone marrow, lymph node) at baseline, at interim response evaluation, at completion of treatment in both PET/CT-negative and PET/CT-positive patients, and if feasible at relapse in those patients who achieve initial PET/CT negativity. While biomarkers should be included in every clinical study, they should not at this time be used to determine clinical outcome, but rather analyzed after completion of the trial with the eventual goal of using them for an adaptive trial design in future clinical trials. We believe that the 23-gene signature and the serum biomarker TARC should be prioritized for prospective investigation.

Promising Novel Agents and Integration Into Current Standard Therapies

The integration of novel agents into treatment paradigms either to replace or augment current treatment strategies should be a primary goal of future research in HL. The emergence of biologically derived targeted therapies and immunotherapies provides new and exciting treatment options for patients.

To date, of these novel agents, only BV has mature data and is FDA approved as a single agent. Combination strategies going forward will be extremely important as many of these agents are well tolerated but have moderate single-agent activity in the relapsed setting.

While the checkpoint inhibitors nivolumab and pembrolizumab are the most exciting novel agents, there are many other new therapies for HL under development. Agents that appear promising in combination strategies include immune modulatory agents such as the checkpoint inhibitors ipilimumab, nivolumab, and pembrolizumab, the novel alkylator bendamustine, and mTOR inhibitors, all of which have demonstrated encouraging single-agent activity in small early-phase studies. Other agents that have shown more limited single-agent activity but may in the future prove promising in combination include epigenetic therapy such as the histone deacetylase inhibitor (HDACI) panobinostat, agents targeting the NFκB or the JAK-STAT pathways, PI3 Kinase inhibitors, and other modulators of the tumor microenvironment, macrophages, and immune milieu such as lenalidomide. Many of these drugs have demonstrated synergistic effects with nonoverlapping toxicity in small early-phase studies, such as the combination of lenalidomide

with either mTOR inhibition or bendamustine. Preliminary safety and efficacy data from the ongoing early-phase clinical trial investigating the combination of brentuximab vedotin with the immune checkpoint inhibitors ipilimumab and nivolumab demonstrated that the combination of BV and ipilimumab was safe and highly active, with an ORR of 72% and a CR of 50% (95% CIs were not reported) (75). Going forward, the challenge will be choosing which of these agents to combine and where in the sequence of treatments (upfront vs first relapse vs relapsed after transplant) they should be integrated.

Immunotherapy and targeted therapies have the potential to change treatment paradigms for HL and potentially for other lymphomas over the next decade. For relapsed patients, integrating these agents into standard therapy and combining them with other novel agents may allow more patients to successfully be transplanted or control disease longer-term in patients who have relapsed post-transplant. For patients with high-risk or advanced-stage disease, integrating these therapies into standard treatment platforms may cure more patients in the upfront setting, avoiding the excessive toxicity of current high-dose regimens. For low-risk patients, substitution of immune and novel therapies for elements of standard therapy may lower treatment-related toxicity and reduce long-term complications. For special populations such as the frail and the elderly, alternative treatment regimens may allow disease control without cytotoxic chemotherapy.

Clinical trials in first relapse should be planned as randomized two- or three-arm studies using standard second-line ifosfamide, carboplatin, and etoposide chemotherapy as a comparator. Based on current data, combination strategies testing chemotherapy-immunotherapy platforms vs ICE with CR as a primary end point and employing a Simon 2 stage design would allow a fast and efficient comparison between the novel and standard arms. Comparing two novel arms against the standard of care would allow the simultaneous evaluation of two promising approaches within one clinical trial.

Final Recommendations and Conclusions

While relapsed HL subsequent to ASCT remains incurable and the management of high-risk and relapsed disease without excessive long-term toxicity remains challenging, there are more treatment options currently available than ever previously. Recent progress in novel therapeutics such as checkpoint inhibitors and advances in biomarker discovery bring us to an exciting point in time. As we move forward, the challenge will be how to thoughtfully and scientifically integrate these novel therapies to modify and reshape current treatment paradigms, potentially altering the landscape for relapsed HL patients by providing long-term disease control and for newly diagnosed patients by providing therapies with equivalent or superior efficacy and less toxicity. Improvements in risk stratification will help to better tailor appropriate therapies and therapeutic intensity in high-risk patients, allowing avoidance of toxic therapies for patients who do not require them, and may guide therapeutic selection for HL patients in relapse. Going forward, both relapsed/refractory patients and bulky/high-risk newly diagnosed patients remain a high priority for clinical investigation. Clinical trials in this space should include novel targeted and immunologic agents and novel design strategies such as an adaptive design, for which the cooperative group setting is ideal.

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References

1. Hanly P, Soerjomataram I, Sharp L. Measuring the societal burden of cancer: The cost of lost productivity due to premature cancer-related mortality in Europe. *Int J Cancer*. 2015;136(4):E136–E145.
2. National Cancer Institute Surveillance, Epidemiology and End Results Program (SEER). http://seer.cancer.gov/statfacts/html/hodg.html.
3. Bazzeh F, Rihani R, Howard S, et al. Comparing adult and pediatric Hodgkin lymphoma in the Surveillance, Epidemiology and End Results Program, 1988–2005: An analysis of 21 734 Cases. *Leuk Lymph*. 2010;51(12):2198–2207.
4. Evens AM, Hutchings M, Diehl V. Treatment of Hodgkin lymphoma: The past, present, and future. *Nat Clin Pract Oncol*. 2008;5(9):543–556.
5. Koontz MZ, Horning SJ, Balise R, et al. Risk of therapy-related secondary leukemia in Hodgkin lymphoma: The Stanford University experience over three generations of clinical trials. *J Clin Oncol*. 2013;31(5):592–598.
6. De Bruin ML, Sparidans J, van't Veer MB, et al. Breast cancer risk in female survivors of Hodgkin's lymphoma: Lower risk after smaller radiation volumes. *J Clin Oncol*. 2009;27(26):4239–4246.
7. De Bruin ML, Burgers JA, Baas P, et al. Malignant mesothelioma after radiation treatment for Hodgkin lymphoma. *Blood*. 2009;113(16):3679–3681.
8. De Bruin ML, Dorresteijn LD, van't Veer MB, et al. Increased risk of stroke and transient ischemic attack in 5-year survivors of Hodgkin lymphoma. *J Natl Cancer Inst*. 2009;101(13):928–937.
9. Aleman BM, van den Belt-Dusebout AW, De Bruin ML, et al. Late cardiotoxicity after treatment for Hodgkin lymphoma. *Blood*. 2007;109(5):1878–1886.
10. Hodgson DC. Late effects in the era of modern therapy for Hodgkin lymphoma. *Hematology Am Soc Hematol Educ Program*. 2011;2011:323–329.
11. Bonadonna G, Zucali R, Monfardini S, et al. Combination chemotherapy of Hodgkin's disease with adriamycin, bleomycin, vinblastine, and imidazole carboxamide versus MOPP. *Cancer*. 1975;36(1):252–259.
12. Bonadonna G, Bonfante V, Viviani S, et al. ABVD plus subtotal nodal versus involved-field radiotherapy in early-stage Hodgkin's disease: Long-term results. *J Clin Oncol*. 2004;22(14):2835–2841.
13. Engert A, Plutschow A, Eich HT, et al. Reduced treatment intensity in patients with early-stage Hodgkin's lymphoma. *N Engl J Med*. 2010;363(7):640–652.
14. Meyer RM, Gospodarowicz MK, Connors JM, et al. ABVD alone versus radiation-based therapy in limited-stage Hodgkin's lymphoma. *N Engl J Med*. 2012;366(5):399–408.
15. Brusamolino E, Lazzarino M, Orlandi E, et al. Early-stage Hodgkin's disease: Long-term results with radiotherapy alone or combined radiotherapy and chemotherapy. *Ann Oncol*. 1994;5(suppl 2):101–106.
16. Eich HT, Diehl V, Gorgen H, et al. 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. *J Clin Oncol*. 2010;28(27):4199–206.
17. Canellos GP, Abramson JS, Fisher DC, et al. Treatment of favorable, limited-stage Hodgkin's lymphoma with chemotherapy without consolidation by radiation therapy. *J Clin Oncol*. 2010;28(9):1611–1615.
18. Meyer RM, Gospodarowicz MK, Connors JM, et al. Randomized comparison of ABVD chemotherapy with a strategy that includes radiation therapy in patients with limited-stage Hodgkin's lymphoma: National Cancer Institute of Canada Clinical Trials Group and the Eastern Cooperative Oncology Group. *J Clin Oncol*. 2005;23(21):4634–4642.
19. Specht L, Yahalom J, Illidge T, et al. Modern radiation therapy for Hodgkin lymphoma: Field and dose guidelines from the international lymphoma radiation oncology group (ILROG). *Int J Radiat Oncol Biol Phys*. 2014;89(4):854–862.
20. Radford J, Illidge T, Counsell N, et al. Results of a trial of PET-directed therapy for early-stage Hodgkin's lymphoma. *N Engl J Med*. 2015;372(17):1598–1607.
21. Raemaekers JM, Andre MP, Federico M, et al. Omitting radiotherapy in early positron emission tomography-negative stage I/II Hodgkin lymphoma is associated with an increased risk of early relapse: Clinical results of the preplanned interim analysis of the randomized EORTC/LYSA/FIL H10 trial. *J Clin Oncol*. 2014;32(12):1188–1194.
22. Behringer K, Goergen H, Hitz F, et al. 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*. 2015 Apr 11;385(9976):1418–1427.
23. Moskowitz CH. Response-adapted therapy based on interim FDG-PET scans in advanced Hodgkin lymphoma: First analysis of the safety of deescalation and efficacy of escalation in the international RATHL study (CRUK/07/033). *Clin Adv Hematol Oncol*. 2015;13(8 suppl 9):6–7.

24. von Tresckow B, Plutschow A, Fuchs M, et al. Dose-intensification in early unfavorable Hodgkin's lymphoma: Final analysis of the German Hodgkin Study Group HD14 trial. *J Clin Oncol*. 2012;30(9):907–913.
25. Gordon LI, 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(6):684–691.
26. 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(4):607–614.
27. Johnson PW, Radford JA, Cullen MH, et al. Comparison of ABVD and alternating or hybrid multidrug regimens for the treatment of advanced Hodgkin's lymphoma: Results of the United Kingdom Lymphoma Group LY09 Trial (ISRCTN97144519). *J Clin Oncol*. 2005;23(36):9208–9218.
28. Aleman BM, Raemaekers JM, Tirelli U, et al. Involved-field radiotherapy for advanced Hodgkin's lymphoma. *N Engl J Med*. 2003;348(24):2396–2406.
29. Canellos GP, Anderson JR, Propert KJ, et al. Chemotherapy of advanced Hodgkin's disease with MOPP, ABVD, or MOPP alternating with ABVD. *N Engl J Med*. 1992;327(21):1478–1484.
30. 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(32):4234–4242.
31. Press OW, Li H, Schoder H, et al. US Intergroup Trial of response-adapted therapy for stage III to IV Hodgkin lymphoma using early interim fluorodeoxyglucose-positron emission tmography imaging: Southwest Oncology Group S0816. *J Clin Oncol*. 2016;34: in press.
32. 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(12): 1376–1385.
33. Schmitz N, Pfistner B, Sextro M, et al. Aggressive conventional chemotherapy compared with high-dose chemotherapy with autologous haemopoietic stem-cell transplantation for relapsed chemosensitive Hodgkin's disease: A randomised trial. *Lancet*. 2002;359(9323):2065–2071.
34. Younes A, Gopal AK, Smith SE, et al. Results of a pivotal phase II study of brentuximab vedotin for patients with relapsed or refractory Hodgkin's lymphoma. *J Clin Oncol*. 2012;30(18):2183–2189.
35. Moskowitz AJ, Schoder H, Yahalom J, et al. PET-adapted sequential salvage therapy with brentuximab vedotin followed by augmented ifosamide, carboplatin, and etoposide for patients with relapsed and refractory Hodgkin's lymphoma: A non-randomised, open-label, single-centre, phase 2 study. *Lancet Oncol*. 2015;16(3):284–292.
36. Moskowitz CH, Nademanee A, Masszi T, et al. Brentuximab vedotin as consolidation therapy after autologous stem-cell transplantation in patients with Hodgkin's lymphoma at risk of relapse or progression (AETHERA): A randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet*. 2015; 385(9980):1853–1862.
37. Castellino SM, Geiger AM, Mertens AC, et al. Morbidity and mortality in long-term survivors of Hodgkin lymphoma: A report from the Childhood Cancer Survivor Study. *Blood*. 2011;117:1806–1816.
38. Pieters RS, Wagner H, Baker S, et al. The impact of protocol assignment for older adolescents with hodgkin lymphoma. *Front Oncol*. 2014;4:317.
39. Mauz-Körholz C, Hasenclever D, Dörffel W, et al. Procarbazine-free OEPA-COPDAC chemotherapy in boys and standard OPPA-COPP in girls have comparable effectiveness in pediatric Hodgkin's lymphoma: The GPOH-HD-2002 study. *J Clin Oncol*. 2010;28:3680–3686.
40. Schwartz CL, Constine LS, Villaluna D, et al. A risk-adapted, response-based approach using ABVE-PC for children and adolescents with intermediate- and high-risk Hodgkin lymphoma: The results of P9425. *Blood*. 2009;114: 2051–2059.
41. Keller FG, Nachman J, Constine L, et al. A phase III study for the treatment of children and adolescents with newly diagnosed low risk Hodgkin lymphoma (HL). *Blood*. 2010;116:21.
42. Tebbi CK, Mendenhall NP, London WB, et al. Response-dependent and reduced treatment in lower risk Hodgkin lymphoma in children and adolescents, results of P9426: A report from the Children's Oncology Group. *Pediatr Blood Cancer*. 2012;59(7):1259–1265.
43. Friedman D, Chen L, Wolden S, et al. Dose-intensive response-based chemotherapy and radiation therapy for children and adolescents with newly diagnosed intermediate-risk hodgkin lymphoma: A report from the Children's Oncology Group Study AHOD0031. *J Clin Oncol*. 2014 32(32):3651–3658.
44. Steidl C, Lee T, Shah SP, et al. Tumor-associated macrophages and survival in classic Hodgkin's lymphoma. *N Engl J Med*. 2010;362(10):875–885.
45. Steidl C, Farinha P, Gascoyne RD. Macrophages predict treatment outcome in Hodgkin's lymphoma. *Haematologica*. 2011;96(2):186–189.
46. Tan KL, Scott DW, Hong F, et al. Tumor-associated macrophages predict inferior outcomes in classic Hodgkin lymphoma: A correlative study from the E2496 Intergroup trial. *Blood*. 2012;120(16):3280–3287.
47. Steidl C, Diepstra A, Lee T, et al. Gene expression profiling of microdissected Hodgkin Reed-Sternberg cells correlates with treatment outcome in classical Hodgkin lymphoma. *Blood*. 2012;120(17):3530–3540.
48. 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(6):692–700.
49. Kuppers R. The biology of Hodgkin's lymphoma. *Nat Rev Cancer*. 2009;9(1): 15–27.
50. Emmerich F, Meiser M, Hummel M, et al. Overexpression of I kappa B alpha without inhibition of NF-kappaB activity and mutations in the I kappa B alpha gene in Reed-Sternberg cells. *Blood*. 1999;94(9):3129–3134.
51. Green MR, Monti S, Rodig SJ, et al. Integrative analysis reveals selective 9p24.1 amplification, increased PD-1 ligand expression, and further induction via JAK2 in nodular sclerosing Hodgkin lymphoma and primary mediastinal large B-cell lymphoma. *Blood*. 2010;116(17):3268–3277.
52. Kanakry JA, Li H, Gellert LL, et al. Plasma Epstein-Barr virus DNA predicts outcome in advanced Hodgkin lymphoma: Correlative analysis from a large North American cooperative group trial. *Blood*. 2013;121(18):3547–3553.
53. van den Berg A, Visser L, Poppema S. High expression of the CC chemokine TARC in Reed-Sternberg cells. A possible explanation for the characteristic T-cell infiltratein Hodgkin's lymphoma. *Am J Pathol*. 1999;154(6):1685–1691.
54. Buglio D, Georgakis GV, Hanabuchi S, et al. Vorinostat inhibits STAT6-mediated TH2 cytokine and TARC production and induces cell death in Hodgkin lymphoma cell lines. *Blood*. 2008;112(4):1424–1433.
55. Weihrauch MR, Manzke O, Beyer M, et al. Elevated serum levels of CC thymus and activation-related chemokine (TARC) in primary Hodgkin's disease: Potential for a prognostic factor. *Cancer Res*. 2005;65(13):5516–5519.
56. Marri P, Hodge LS, Maurer MJ, et al. Prognostic significance of pretreatment serum cytokines in classical Hodgkin lymphoma. *Clin Cancer Res*. 2013;19(24): 6812–6819.
57. Reichel J, Chadburn A, Rubinstein PG, et al. Flow sorting and exome sequencing reveal the oncogenome of primary Hodgkin and Reed-Sternberg cells. *Blood*. 2015;125(7):1061–1072.
58. Borchmann P, Eichenauer DA, Pluetschow A, et al. Targeted Beacopp variants in patients with newly diagnosed advanced stage classical Hodgkin lymphoma: Final analysis of a randomized phase II study. *Blood*. 2015;126(23):580.
59. Ansell SM, Lesokhin AM, Borrello I, et al. PD-1 blockade with nivolumab in relapsed or refractory Hodgkin's lymphoma. *N Engl J Med*. 2015;372(4):311–319.
60. Moskowitz, C et al. PD-1 blockade with the monclonal antibody pembrolizumab in patients with classical Hodgkin lymphoma after brentuximab vedotin failure: Preliminary results from a phase 1b study presented at the 56th meeting of the American Society for Hematology; December 2014; San Franciso, CA.
61. Ansell S, Armand P, Timmerman JM, et al. Nivolumab in patients (Pts) with relapsed or refractory classical Hodgkin lymphoma (R/R cHL): Clinical outcomes from extended follow-up of a phase 1 study (CA209-039). Preliminary results presented at the 57th meeting of the American Society for Hematology; December 2015; Orlando, FL.
62. Armand P, Shipp MA, Ribrag V, et al. PD-1 blockade with pembrolizumab in patients with classical Hodgkin lymphoma after brentuximab vedotin failure: Safety, efficacy, and biomarker assessment. Preliminary results presented at the 57th meeting of the American Society for Hematology; December 2015; Orlando, FL.
63. Checkmate 205: Nivolumab (nivo) in classical Hodgkin lymphoma (cHL) after autologous stem cell transplant (ASCT) and brentuximab vedotin (BV)–A phase 2 study. Preliminary results presented at the meeting of the American Society for Clinical Oncology; June 2016; Chicago, IL.
64. Pembrolizumab for relapsed/refractory classical Hodgkin lymphoma (R/R cHL): phase 2 KEYNOTE-087 study. Preliminary results presented at the meeting of the American Society for Clinical Oncology; June 2016; Chicago, IL.
65. Saret CJ, Winn AN, Shah G, et al. Value of innovation in hematologic malignancies: A systematic review of published cost-effectiveness analyses. *Blood*. 2015;125(12):1866–1869.
66. Hasenclever D, Diehl V. A prognostic score for advanced Hodgkin's disease. International Prognostic Factors Project on Advanced Hodgkin's Disease. *N Engl J Med*. 1998;339(21):1506–1514.
67. Moccia AA, Donaldson J, Chhanabhai M, et al. International Prognostic Score in advanced-stage Hodgkin's lymphoma: Altered utility in the modern era. *J Clin Oncol*. 2012;30(27):3383–3388.
68. Diefenbach CS, Li H, Hong F, et al. Evaluation of the International Prognostic Score (IPS-7) and a Simpler Prognostic Score (IPS-3) for advanced Hodgkin lymphoma in the modern era. *Br J Haematol*. 2015;171(4):530–538.
69. Best T, Li D, Skol AD, et al. Variants at 6q21 implicate PRDM1 in the etiology of therapy-induced second malignancies after Hodgkin's lymphoma. *Nat Med*. 2011;17(8):941–943.
70. Itti E, Meignan M, Berriolo-Riedinger A, et al. An international confirmatory study of the prognostic value of early PET/CT in diffuse large B-cell lymphoma: Comparison between Deauville criteria and DeltaSUVmax. *Eur J Nucl Med Mol Imaging*. 2013;40(9):1312–1320.
71. Adams HJ, de Klerk JM, Fijnheer R, et al. Prognostic superiority of the National Comprehensive Cancer Network International Prognostic Index over pretreatment whole-body volumetric-metabolic FDG-PET/CT metrics in diffuse large B-cell lymphoma. *Eur J Haematol*. 2015;94(6):532–539.
72. Hatt M, Cheze-Le Rest C, Aboagye EO, et al. Reproducibility of 18F-FDG and 3'-deoxy-3'-18F-fluorothymidine PET tumor volume measurements. *J Nucl Med*. 2010;51(9):1368–1376.

73. Hatt M, Cheze-le Rest C, van Baardwijk A, et al. Impact of tumor size and tracer uptake heterogeneity in (18)F-FDG PET and CT non-small cell lung cancer tumor delineation. *J Nucl Med*. 2011;52(11):1690–1697.
74. van Velden FH, Cheebsumon P, Yaqub M, et al. Evaluation of a cumulative SUV-volume histogram method for parameterizing heterogeneous intratumoural FDG uptake in non-small cell lung cancer PET studies. *Eur J Nucl Med Mol Imaging*. 2011;38(9):1636–1647.
75. Diefenbach CS, Hong F, Cohen JB, et al. Preliminary safety and efficacy of the combination of brentuximab vedotin and ipilimumab in relapsed/refractory Hodgkin lymphoma: A trial of the ECOG-ACRIN Cancer Research Group (E4412). *Blood*. 2015;126(23):585.
76. Behringer K, Goergen H, Hitz F, et al. 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*. 2015;385(9976):1418–1427.
77. Hay AE, Klimm B, Chen BE, et al. An individual patient-data comparison of combined modality therapy and ABVD alone for patients with limited-stage Hodgkin lymphoma. *Ann Oncol*. 2013;24(12):3065–3069.
78. 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(5):551–560.
79. Simon R. Optimal two-stage designs for phase II clinical trials. *Controlled Clin Trials*. 1989;10:1–10.
80. Kanakry JA, Ambinder RF. EBV-related lymphomas: new approaches to treatment. *Curr Treat Options Oncol*. 2013;14(2):224–236.
81. Diepstra A, van Imhoff GW, Schaapveld M, et al. Latent Epstein-Barr virus infection of tumor cells in classical Hodgkin's lymphoma predicts adverse outcome in older adult patients. *J Clin Oncol*. 2009;27(23):3815–3821.
82. Keegan TH, Glaser SL, Clarke CA, et al. Epstein-Barr virus as a marker of survival after Hodgkin's lymphoma: a population-based study. *J Clin Oncol*. 2005; 23(30):7604–7613.
83. Jarrett RF, Stark GL, White J, et al. Impact of tumor Epstein-Barr virus status on presenting features and outcome in age-defined subgroups of patients with classic Hodgkin lymphoma: a population-based study. *Blood*. 2005; 106(7):2444–2451.
84. Flavell KJ, Billingham LJ, Biddulph JP, et al. The effect of Epstein-Barr virus status on outcome in age- and sex- defined subgroups of patients with advanced Hodgkin's disease. *Ann Oncol*. 2003;14(2):282–290.
85. Diepstra A, van Imhoff GW, Karim-Kos HE, et al. HLA class II expression by Hodgkin Reed-Sternberg cells is an independent prognostic factor in classical Hodgkin's lymphoma. *J Clin Oncol*. 2007;25(21):3101–3108.
86. Montalban C, Garcia JF, Abraira V, et al. Influence of biologic markers on the outcome of Hodgkin's lymphoma: a study by the Spanish Hodgkin's Lymphoma Study Group. *J Clin Oncol*. 2004;22(9):1664–1673.
87. Venkataraman G, Song JY, Tzankov A, et al. Aberrant T-cell antigen expression in classical Hodgkin lymphoma is associated with decreased event-free survival and overall survival. *Blood*. 2013;121(10):1795–1804.
88. Greaves P, Clear A, Coutinho R, et al. Expression of FOXP3, CD68, and CD20 at Diagnosis in the Microenvironment of Classical Hodgkin Lymphoma Is Predictive of Outcome. *J Clin Oncol*. 2013;31(2):256–262.
89. Gharbaran R, Goy A, Tanaka T, et al. Fibroblast growth factor-2 (FGF2) and syndecan-1 (SDC1) are potential biomarkers for putative circulating CD15+/CD30+ cells in poor outcome Hodgkin lymphoma patients. *J Hematol Oncol*. 2013;6:62.
90. Jones K, Vari F, Keane C, et al. Serum CD163 and TARC as disease response biomarkers in classical Hodgkin lymphoma. *Clin Cancer Res*. 2013;19(3): 731–742.
91. Sauer M, Plutschow A, Jachimowicz RD, et al. Baseline serum TARC levels predict therapy outcome in patients with Hodgkin lymphoma. *Am J Hematol*. 2013;88(2):113–115.
92. Rautert R, Schinkothe T, Franklin J, et al. Elevated pretreatment interleukin-10 serum level is an International Prognostic Score (IPS)-independent risk factor for early treatment failure in advanced stage Hodgkin lymphoma. *Leuk & lymp*. 2008;49(11):2091–2098.
93. Casasnovas RO, Mounier N, Brice P, et al. Plasma cytokine and soluble receptor signature predicts outcome of patients with classical Hodgkin's lymphoma: a study from the Groupe d'Etude des Lymphomes de l'Adulte. *J Clin Oncol*. 2007;25(13):1732–1740.
94. Axdorph U, Sjoberg J, Grimfors G, et al. Biological markers may add to prediction of outcome achieved by the International Prognostic Score in Hodgkin's disease. *Ann Oncol*. 2000;11(11):1405–1411.
95. Ouyang J, Plutschow A, von Strandmann EP, et al. Galectin-1 serum levels reflect tumor burden and adverse clinical features in classical Hodgkin lymphoma. *Blood*. 2013;121(17):3431–3433.
96. Kamper P, Ludvigsen M, Bendix K, et al. Proteomic analysis identifies galectin-1 as a predictive biomarker for relapsed/refractory disease in classical Hodgkin lymphoma. *Blood*. 2011;117(24):6638–6649.
97. Sanchez-Espiridion B, Martin-Moreno AM, Montalban C, et al. MicroRNA signatures and treatment response in patients with advanced classical Hodgkin lymphoma. *British J Haematol*. 2013;162(3):336–347.
98. Navarro A, Gaya A, Martinez A, et al. MicroRNA expression profiling in classic Hodgkin lymphoma. *Blood*. 2008;111(5):2825–2832.
99. Hohaus S, Giachelia M, Di Febo A, et al. Polymorphism in cytokine genes as prognostic markers in Hodgkin's lymphoma. *Ann Oncol*. 2007;18(8): 1376–1381.
100. Saarinen S, Aavikko M, Aittomaki K, et al. Exome sequencing reveals germline NPAT mutation as a candidate risk factor for Hodgkin lymphoma. *Blood*. 2011;118(3):493–498.