Clinical Controversies of Double-Hit Lymphoma

Deborah M. Stephens, DO, and John W. Sweetenham, MD

Abstract

Double-hit lymphoma (DHL) has been identified as a subset of diffuse large B-cell lymphoma with poor clinical outcomes. Because minimal data about this subtype of lymphoma have been published, many controversies in diagnosis and treatment surround DHL. In this article, we review the current definition, proper diagnosis, central nervous system prophylaxis, current treatment regimens, and potential novel therapeutic options for DHL.

Key words: double-hit lymphoma, double-protein expressing lymphoma, diffuse large B-cell lymphoma

Introduction

Double-hit lymphomas (DHLs), as currently defined by the World Health Organization classification, are those lymphomas expressing the co-occurrence of *MYC* and *BCL2* or *BCL6* rearrangement as detected by fluorescence in situ hybridization (FISH) or standard cytogenetics.[1] DHLs are not restricted to any particular histologic subtype of lymphoma, although most of the available data are restricted to diffuse large B-cell lymphoma (DLBCL). The presence of cytogenetic abnormalities in addition to *MYC* rearrangement, such as *BCL2* or *BCL6* rearrangements, generally excludes the diagnosis of Burkitt lymphoma. Aberrant MYC expression is associated with uncontrolled cell growth, division, and metastasis.[2] *BCL2* is an anti-apoptotic gene, which when dysregulated can lead to extended cell survival.[3] *BCL6* normally encodes a transcriptional repressor, and when overexpressed can downregulate several other genes, including the *p53* tumor suppressor gene, which subsequently allows DNA-damaged cells to escape from apoptosis.[4] Theoretically, lymphomas that harbor mutations that lead to both uncontrolled cell growth and anti-apoptotic activity demonstrate enhanced survival of malignant cells.[5]

Clinical data support the predicted aggressive behavior of DHLs. Nineteen patients (4.8%) in the Adult Lymphoma Treatment Study Group with de novo DLBCL with both *MYC* and *BCL2* translocations were identified. The dual translocation was observed more frequently in patients with high lactate dehydrogenase (LDH), B symptoms, bone marrow involvement, and advanced stage. Progression-free survival (PFS; 0%) and overall survival (OS; 23.3%) rates were significantly lower in patients with the dual translocation than in those with other translocation (compared with PFS rates 36.1% to 69.8% and OS rates 65.2% to 83.7%; P =.001 for all comparisons).[6]

A single-center analysis of 53 patients with DLBCL identified 17 cases of DHL by FISH or metaphase karyotyping. Median OS was significantly shorter for DHL compared with non-DHL (8.2 vs 56.8 months; P <.001).[7] Another study identified 54 (4%) of 1260 patients with lymphoma with dual translocation by FISH. This group was more likely to have bone marrow involvement, a high International Prognostic Index (IPI) score, and to have demonstrated a median OS of less than 1 year.[5] MD Anderson reported its experience with 129 cases of DHLs. The 2-year event-free survival (EFS) was much lower than reported outcomes in patients with DLBCL and was reported as 25%, 67%, and 32% in patients who received R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone), R-EPOCH (rituximab, etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin), and R-Hyper-CVAD/MA (rituximab-hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone/methotrexate-cytarabine), respectively.[8]

As a result of the poor clinical outcomes in this subset of DLBCL, much research interest has been directed at DHL in the past few years. Many clinical controversies in diagnosis and treatment surround this subtype of lymphoma, and this article's aim is to review and provide our input regarding these controversies.

Controversy #1: Is the current definition of "double-hit" lymphoma adequate?

We argue that the current definition of "double-hit" lymphoma does not encompass all clinically or pathologically distinct subtypes. MYC, *BCL2*, and *BCL6* rearrangements can be detected by FISH or cytogenetics; however, the genes can also be amplified, mutated, or overexpressed as detected by immunohistochemistry (IHC) or comparative genome hybridization. Many studies have investigated the clinical impact of "double-protein"-expressing lymphoma as detected by IHC, and also found negative clinical implications (**Table**)[9-14] as observed in "double-hit"

lymphoma (as detected by FISH). The use of IHC is an appealing alternative to FISH, as FISH is not always readily available, and is costly and time-consuming. However, traditional IHC techniques and scoring are performed visually by pathologists and have been reported to be quite variable. Additionally, optimal cutoff points between positive and negative IHC stains have not been firmly established.

In published data of the double-protein-expressing DLBCL, most studies have considered the sample to be MYC-positive if the IHC stains demonstrate ≥40% MYC-expressing cells. However, the cutoff point is more discordant for *BCL2* positivity with studies reporting values of ≥30% to ≥70% *BCL2*-positive cells (**Table**).[5,9,10,12-14] We consider ≥40% MYC-positive cells with ≥70% *BCL2*-positive cells to be a double-protein-expressing DLBCL. The **Figure** depicts a representative pathology sample of a double-protein-expressing DLBCL.

Controversy #2: Should all patients with DLBCL be tested to determine whether they have DHLs?

We argue that all DLBCL patient pathology samples should be tested for *MYC*, *BCL2*, and *BCL6* translocations and by IHC because there are adverse clinical implications for these patients that will require alternate or targeted treatment approaches (See "Controversy #4"). We have described the adverse clinical implications for patients with both traditional double-hit DLBCL and double-protein-expressing DLBCL in the Introduction. Emerging evidence shows that although these 2 patient groups have lower PFS and OS, a patient with double-protein-expressing DLBCL may not have DHL. In a combined data set of 290 patients with DLBCL initially treated with RCHOP, 14 cases (5%) of DHL were detected. These patients had worse 5-year PFS and OS rates (18% and 27%, respectively) than the remaining patients who were double-protein-expressing (n = 55; 5-year PFS =

TABLE. Retrospective Studies Detailing Methods of Diagnosis and Outcomes for Patients With Double-Protein-Expressing Lymphoma

Authors	IHC Cutoff MYC+ (%)	IHC Cutoff BCL2+ (%)	N	DE (%)	Regimen	DE Impact on PFS[a]	DE Impact on OS[a]
Green et al[9]	≥40	≥70	193	29	R-CHOP	3-yr PFS 39% vs 75% (*P* <.001)	3-yr OS 43% vs 86% (*P* <.001)
Hu et al[10]	≥40	≥70	466	34	R-CHOP	5-yr PFS 27% vs 73% (*P* <.001)	5-yr OS 30% vs 75% (*P* <.001)
Johnson et al[11]	≥40	≥50	167	21	R-CHOP	5-yr PFS 21% vs 63% (*P* = .020)[b]	5-yr OS 30% vs 70% (*P* = .018)[b]
Molina et al[12]	≥40	≥70	670	21	R-CHOP/ R-miniCHOP or R-ACVBP[c]	Decreased PFS (*P* = .003)	Decreased OS (*P* = .005)
Perry et al[13]	≥50	≥30	106	44	CHOP+/-R	Independent predictor of EFS (*P* = .0017)	Independent predictor of OS (*P* <.001)
Dunleavy et al[14]	≥40	Same or more intense staining as T-cell control	66	20	R-EPOCH	10-yr PFS = 67.5%; 10-yr PFS not inferior to other groups (*P* = .5)	10-yr OS = 75%; 10-yr OS not inferior to other groups (*P* = .8)

DE indicates double protein expressor; EFS, event-free survival; IHC, immunohistochemistry; OS, overall survival; PFS, progression-free survival; R-ACVBP, rituximab, doxorubicin, cyclophosphamide, vindesine, bleomycin, prednisone; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone; R-EPOCH, rituximab, etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin.

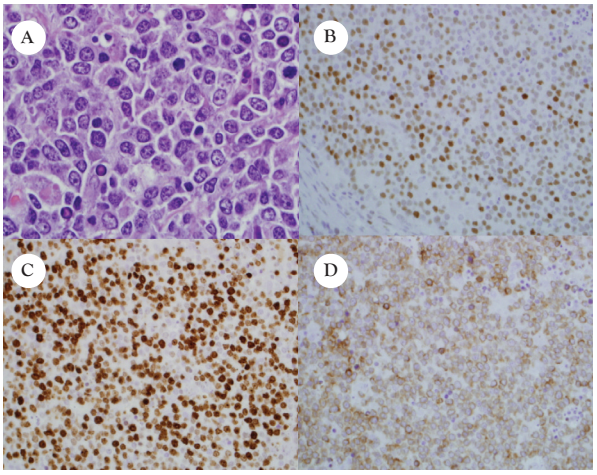
[a]Compared with patients without double protein expression.
[b]Validation cohort.
[c]R-CHOP/R-miniCHOP: n = 433; R-ACVBP: n = 237.

32%; 5-year OS = 36%; *P* <.05). Additionally, both groups had lower 5-year PFS and OS when compared with patients without double-hit or double-protein-expressing disease (n = 236; 5-year PFS = 65%; 5-year OS = 71%; *P* 0.05).[11] These data indicate that there may be a difference in these 2 patient groups that may require different targeted treatment strategies, as described below.

Some proponents of limiting the amount of patients evaluated for DHL have suggested restricting evaluation to pathology samples that have a high Ki67 index (or MiB-1 IHC staining), based on an initial study that demonstrated patients with MYC-aberrant DLBCL were more likely to have a Ki67 index >80%.[15] However, subsequent studies have found that Ki67 index cannot be used as a baseline predictive factor for double-hit status.[7, 11] One study found that only 1 out of 14 confirmed cases of double-hit lymphoma had a Ki67 index >90%.[11] These data suggest that testing for double-hit or double-protein-expressing lymphoma should not be limited to those DLBCL samples with high-proliferation indices.

Another argument has been to limit testing for double-hit or double-protein-expressing DLBCL to those samples that have a germinal center B-cell–like (GCB) cell of origin as initial studies reported that *MYC*-rearranged DLBCL[16,17] and FISH-defined double-hit DLBCL[18] were strongly associated with GCB derivation. However, a large study of 893 patients demonstrated that double-protein-expressing lymphomas were more likely to have activated B-cell (ABC) cell of origin.[10] Therefore, until a clear-cut way to predict which DLBCL sample will be a double-hit or double-protein-expressing lymphoma, we feel that all DLBCL samples should be closely scrutinized for rearrangements and protein expression.

FIGURE. Representative Pathology Sample Depicting Double Protein Expressing Diffuse Large B Cell Lymphoma



A. Hematoxylin and eosin staining
B. MYC immunohistochemical (IHC) staining (~70% positive in this sample)
C. MIB-1 IHC staining (~90% positive in this sample)
D. BCL2 IHC staining (~80% positive in this sample)

Controversy #3: Should all patients receive intrathecal prophylaxis for central nervous system disease?

A clinical dilemma is whether these patients require central nervous system (CNS) prophylaxis. Multiple cases of an increased incidence of CNS involvement have been reported. A small study described 40 patients with DLBCL with leukemic-phase disease, 14 of whom had CNS disease. Eight of these patients had FISH-confirmed double-hit lymphoma. In logistic regression analysis, double-hit status was found to be the one independent factor correlated with CNS involvement.[19] In the MD Anderson experience, the incidence of CNS involvement at diagnosis was 4%, with a cumulative incidence of CNS involvement of 13% at 3 years. In patients who did not have documented CNS disease at the time of diagnosis, the incidence of eventual CNS involvement was lower in those receiving prophylactic intrathecal therapy (5% at 3 years) than in those who did not (15% at 3 years; *P* =.017).[8] At this time, secondary to the paucity of data, we can make no firm recommendations about using CNS prophylaxis in this set of patients, but feel that these data indicating a potential higher risk of CNS disease should be discussed with the patient, along with the risks of intrathecal chemotherapy administration.

Controversy #4: What are the best treatment options for patients with double-hit or double-protein-expressing lymphoma?

As described in the Introduction, prognosis for this patient group when treated with standard DLBCL therapy of R-CHOP is guarded, and novel approaches are needed to improve survival in this group. Strategies previously investigated for this patient group include intensification of induction regimens and/or immediate consolidation with autologous or allogeneic stem cell transplantation (SCT). From the start, this strategy is hampered by the typical demographics of this group, in which elderly patients—the majority with comorbid conditions—are heavily overrepresented.[11] Additionally, published data to guide treatment options for this group is limited to mostly small retrospective studies, the majority with a focus on FISH-defined DHL. Many of these studies have contradictory findings.

Data evaluating the need for a more intensive induction chemotherapy are described by several small retrospective analyses. In a single-center analysis, 33 patients with DHL received therapy with R-CHOP (n = 15), R-EPOCH (n = 12), or R-CODOX-M/IVAC (n = 6; rituximab-cyclophosphamide, vincristine, doxorubicin with methotrexate/ifosfamide, etoposide, and cytarabine). Although this was a small retrospective analysis, the median PFS

and OS for patients who received R-EPOCH were 21 and 34 months, respectively, compared with 6 and 8 months for patients who received RCHOP, and 6 and 7 months for patients who received R-CODOX-M/IVAC. This small study indicated a possible improvement in clinical outcomes for patients with DHL who receive therapy with R-EPOCH.[20] In another small single-center analysis, 31 patients with DHL received therapy with R-CHOP (n = 15), R-EPOCH (n = 8), R-Hyper-CVAD (n = 6), or other (n = 2). This study demonstrated no statistical difference in PFS or OS when comparing R-CHOP with the other regimens. However, this study was small and restricted by the low number of patients.[21]

Additional small retrospective studies have attempted to answer the question of whether consolidation with SCT should be required for patients with DHL. One small study supporting the use of SCT for this population included 36 patients with DHL where 24 patients (66%) were treated with a dose-intense (DI) induction regimen (R-Hyper-CVAD, R-EPOCH, or R-CODOX-M/IVAC) and 12 patients (33%) received a standard-dose (SD) induction regimen (R-CHOP or R-CHOP–like). The group found a statistically significant increase in the PFS of patients treated with a DI (46 months) versus SD regimen (8 months; HR = .26; *P* =.005). Within the DI group, 42% of the patients underwent SCT (73% allogeneic). Of the patients who received DI and SCT, there was additional increase in OS compared with patients who received SD; this was not seen in the patients who received DI and did not receive SCT. However, this study is likely limited by small numbers and generally favorable patient characteristics in those patients selected for intensive induction and SCT.[22]

In contrast, other small studies do not support a survival advantage for the patients who receive SCT as a frontline therapy for DHL. A retrospective study of 52 patients with DHL was reported with 19 patients who received R-CHOP and 30 patients who received aggressive therapy with the R-Hyper-CVAD regimen. Eleven patients went on to autologous SCT. There was no statistically significant difference in PFS or OS between the patients who received R-Hyper-CVAD or other treatments and those who underwent SCT versus no SCT.[18] In a retrospective review of 27 patients with DHL, 20 patients received treatment with an aggressive regimen of R-CODOX-M/IVAC, with the remainder receiving R-CHOP–like regimens. Fourteen patients went on to receive SCT (7 autologous and 7 allogeneic). Overall, the 2-year EFS was 35%. For patients who received R-CODOX-M/IVAC and those who received this regimen followed by SCT, the 2-year EFS was 37% and 43%, respectively.[23] These patients were likely highly selected for good performance status but did not have improved survival despite the aggressive therapy.

In a retrospective study of 54 patients with DHL, 6 patients received high-dose chemotherapy with or without SCT; however, this group had similar poor outcomes compared with those patients (n = 14) treated with palliative care (median survival, 3 months vs 1 month, respectively; *P* >.05).[5]

Two large retrospective studies support the notion that regardless of induction regimen or SCT, achieving a complete response (CR) to induction therapy is a more accurate prognostic factor than the choice of therapy. In MD Anderson Cancer Center's experience of 129 patients with DHL, CR rates in response to frontline R-EPOCH (68%) or R-Hyper-CVAD/M (68%) were higher than those observed among patients who received R-CHOP (40%; *P* ~.01 for both comparisons). Interestingly, despite a higher CR rate after R-Hyper-CVAD/M, the clinical outcomes were similar between these patients and those who received R-CHOP. In contrast, patients receiving R-EPOCH demonstrated a longer EFS (*P* =.004) and OS (*P* =.057) than those patients who received R-CHOP. In patients who achieved a CR with induction therapy (n = 71), the 2-year OS rates were 70% and not statistically different between patients who did (n = 23) or did not (n = 48) receive SCT.[8]

The largest retrospective study of patients with DHL described 311 patients treated at 23 academic centers. Of the patients, 32% (n = 100) received R-CHOP, 21% (n = 64) R-EPOCH, 21% (n = 65) R-Hyper-CVAD, 14% (n = 42) R-CODOX-M/IVAC, 3% (n = 9) RICE (rituximab, ifosfamide, carboplatin, etoposide), and 10% (n = 31) other. After achieving CR, 53 patients (17%) went on to receive SCT (autologous, n = 39). Although PFS was prolonged for patients who received any intensive induction regimen compared with R-CHOP (*P* =.001), OS was not statistically different between the 2 groups (*P* =.564). Among patients who achieved CR to frontline therapy, median OS was similar for those who were observed (103 months) and those who underwent consolidation SCT of any type (OS not reached; *P* =.14). This study concluded that achievement of CR with induction therapy, a measure of chemotherapy sensitivity, was a more important predictive factor of outcome than type of induction therapy or whether or not a patient received SCT.[24] In summary, data gleaned from these retrospective studies indicate that:

- A more-intensive induction regimen than R-CHOP is likely needed to induce CR in patients with DHL
- CR appears to be a more predictive factor of outcome than choice of initial therapy
- Patients with DHL do not necessarily need to proceed directly to consolidation with SCT, especially those who can achieve CR with induction therapy

In limited prospective data, the R-EPOCH regimen has come forth as a promising frontline treatment for patients with double-hit or double-protein-expressing DLBCL. The NIH analyzed 2 prospective studies of 59 patients with DLBCL who received R-EPOCH at their institution (10% with *MYC* rearrangement). They found no difference in 4-year EFS between patients with and without *MYC* rearrangement (83% vs 76%, respectively; *P*

=.46).[25] The same group reviewed 66 patients with DLBCL who received R-EPOCH (20% double-protein-expressing) and found no difference in 10-year OS between double-protein-expressing patients versus all others.[14] The NIH group led a multicenter prospective phase II study including 52 patients with MYC-rearranged DLBCL (*BCL2* was rearranged in 14/31 and overexpressed by IHC in 24/43 cases tested). With a median follow-up of 14 months, this preliminary report described PFS and OS of 79% and 77%, respectively. PFS was 87% and 64%, respectively, in cases that were FISH-positive and IHC-positive for *BCL2*.[26]

With a paucity of data using standard regimens, attention has turned to evaluation of these patient groups in clinical trials. Intuitively, drugs that directly or indirectly interfere with MYC function are attractive therapeutic targets. Preclinical data showed that mammalian target of rapamycin (mTOR) complex 1–dependent evasion of senescence is critical for cellular transformation and tumor maintenance by MYC in B-lymphocytes.[27] In mouse models of MYC-associated lymphoma, mTOR inhibition demonstrated promising activity.[28] In a phase II study, temsirolimus (an mTOR inhibitor) demonstrated single-agent activity in DLBCL.[29] Although preclinical data showed that an aurora A kinase inhibitor in combination with a histone deacetylase inhibitor enhanced lymphoma cell death through repression of C-MYC and C-MYC-responsive microRNAs,[30] in a small clinical trial of this combination, the 3 patients with DHL developed progressive disease.[31] MLN9708, a second-generation proteasome inhibitor, degraded MYC and induced cell death at nanomolar concentrations in preclinical lymphoma models[32]; however, a phase I trial in relapsed/refractory lymphoma showed only modest single-agent activity.[33] Bromodomain and extraterminal proteins have demonstrated selective sensitivity toward MYC inhibition, and small-molecule inhibitors of this pathway may present a future therapeutic option for MYC-associated lymphomas.

Another obvious druggable target is *BCL2*. ABT-199 is a platelet-sparing BCL2 inhibitor that has shown early success in chronic lymphocytic leukemia. As a single agent, a very preliminary report described responses to ABT-199 in 3 of the 8 patients with relapsed/refractory DLBCL treated in the higher-dose cohorts.[34] Recently published preclinical data showed that ABT-199 may enhance the antitumor activity of chemotherapy agents including doxorubicin, cytarabine, and bortezomib in DHL cell lines.[35] These data have prompted clinical investigation of ABT-199 combinations; however, the trials are still in early stages.

Other potentially interesting therapies for double-hit or double-protein-expressing lymphomas under early investigation include small-molecule inhibitors of BCL6[36] and chimeric antigen receptor modified T-cells directed against CD19+ B-cells.[37]

As there are no definitive data to describe the best treatment for these patients, our practice is to enroll these patients in a clinical trial if available. Outside of a clinical trial, dose-adjusted R-EPOCH is our preferred regimen. We do not routinely refer patients for consolidation to SCT, especially those who achieve CR with induction chemotherapy.

Conclusion

In summary, many diagnostic and clinical controversies surround double-hit and double-protein-expressing DLBCL. In our opinion, although both double-hit and double-protein expressing lymphomas appear to have poor prognosis, these groups should be classified separately as they appear to have different clinical outcomes. We feel that all DLBCL should be tested for both dual translocation and dual protein-expressing status as treatment recommendations may differ from other DLBCL. Our practice is to enroll these patients in clinical trials when available; we prefer dose-adjusted R-EPOCH for treatment off-study. We do not routinely refer patients for consolidation to SCT, especially those who achieve CR with induction chemotherapy. Secondary to the increased incidence of CNS involvement of these lymphomas, CNS prophylaxis should at least be discussed with the patient. We strongly support investigation of new agents in this patient population.

Acknowledgment: The authors would like to thank Dr Rodney Miles from the University of Utah Hematopathology Department for preparation of the Figure.

Affiliations: Drs Stephens and Sweetenham are from the Division of Hematology, Department of Internal Medicine, University of Utah, Salt Lake City.

Disclosures: Drs Stephens and Sweetenham report no relevant conflicts of interest to disclose.

Address correspondence to: Deborah M. Stephens, DO, Huntsman Cancer Institute, The University of Utah, 2000 Circle of Hope, Room 4246, Salt Lake City, UT 84112. Phone: 801-587-4354; fax: 801-581-4136; email: deborah.stephens@hci.utah.edu.

REFERENCES

1. Swerdlow SH, Campo E, Harris NL, et al. *World Health Organization Classification of Tumours of Haematopoietic and Lymphoid Tissue*, 4th Edition. Lyon, France: International Agency on Research for Cancer; 2008.

2. Adhikary S, Eilers M. Transcriptional regulation and transformation by Myc proteins. *Nat Rev Mol Cell Biol*. 2005;6:635-645.

3. Korsmeyer SJ. Bcl-2 initiates a new category of oncogenes: regulators of cell death. *Blood*. 1992;80:879-886.

4. Phan RT, Dalla-Favera R. The BCL6 proto-oncogene suppresses p53 expression in germinal-centre B cells. *Nature*. 2004;432:635-639.

5. Johnson NA, Savage KJ, Ludkovski O, et al. Lymphomas with concurrent BCL2 and MYC translocations: the critical factors associated with survival. *Blood*. 2009;114:2273-2279.

6. Niitsu N, Okamoto M, Miura I, Hirano M. Clinical features and prognosis of de novo diffuse large B-cell lymphoma with

t(14;18) and 8q24/c-MYC translocations. *Leukemia*. 2009;23:777-783.
7. Landsburg DJ, Nasta SD, Svoboda J, et al. 'Double-hit' cytogenetic status may not be predicted by baseline clinicopathological characteristics and is highly associated with overall survival in B cell lymphoma patients. *Br J Haematol*. 2014;166:369-374.
8. Oki Y, Noorani M, Lin P, et al. Double hit lymphoma: the MD Anderson Cancer Center clinical experience. *Br J Haematol*. 2014;166:891-901.
9. Green TM, Young KH, Visco C, et al. Immunohistochemical double-hit score is a strong predictor of outcome in patients with diffuse large B-cell lymphoma treated with rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone. *J Clin Oncol*. 2012;30:3460-3467.
10. Hu S, Xu-Monette ZY, Tzankov A, et al. MYC/BCL2 protein coexpression contributes to the inferior survival of activated B-cell subtype of diffuse large B-cell lymphoma and demonstrates high-risk gene expression signatures: a report from The International DLBCL Rituximab-CHOP Consortium Program. *Blood*. 2013;121:4021-4031; quiz 4250.
11. Johnson NA, Slack GW, Savage KJ, et al. Concurrent expression of MYC and BCL2 in diffuse large B-cell lymphoma treated with rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone. *J Clin Oncol*. 2012;30:3452-3459.
12. Molina TJ, Briere J, Copie-Bergman C, et al. Overexpression of MYC, BCL2, MYC/BCL2, IGM, and non-germinal centre B cell-like immunophenotype predicts a worse progression-free survival and overall survival in a series of 670 *de novo* diffuse large B-cell lymphomas: S Lysa Study. *Hematol Oncol Clin North Am*. 2013;31(suppl 1):151-200. Abstract 178.
13. Perry AM, Alvarado-Bernal Y, Laurini JA, et al. MYC and BCL2 protein expression predicts survival in patients with diffuse large B-cell lymphoma treated with rituximab. *Br J Haematol*. 2014;165:382-391.
14. Dunleavy K, Pittaluga S, Shovlin M, et al. Concurrent expression of MYC/BCL2 protein in newly diagnosed DLBCL is not associated with an inferior survival following EPOCH-R therapy. Presented at: the 2013 American Society of Hematology Annual Meeting; December 7-10, 2013; New Orleans, LA. *Blood*. 2013. Abstract 3029.
15. Savage KJ, Johnson NA, Ben-Neriah S, et al. MYC gene rearrangements are associated with a poor prognosis in diffuse large B-cell lymphoma patients treated with R-CHOP chemotherapy. *Blood*. 2009;114:3533-3537.
16. Horn H, Ziepert M, Becher C, et al. MYC status in concert with BCL2 and BCL6 expression predicts outcome in diffuse large B-cell lymphoma. *Blood*. 2013;121:2253-2263.
17. Valera A, Lopez-Guillermo A, Cardesa-Salzmann T, et al. MYC protein expression and genetic alterations have prognostic impact in patients with diffuse large B-cell lymphoma treated with immunochemotherapy. *Haematologica*. 2013;98:1554-1562.
18. Li S, Lin P, Fayad LE, et al. B-cell lymphomas with MYC/8q24 rearrangements and IGH@BCL2/t(14;18)(q32;q21): an aggressive disease with heterogeneous histology, germinal center B-cell immunophenotype and poor outcome. *Mod Pathol*. 2012;25:145-156.
19. Shuhua Y, Zhong S, Zou D et al. BCL2 and MYC rearrangements in leukemic phase of diffuse large B-cell lymphoma predicts central nervous system involvement. Presented at: the 2014 American Society of Hematology Annual Meeting; December 5-8, 2014; San Francisco, CA. *Blood*. 2014. Abstract 2958.
20. Abramson JS, Barnes JA, Feng Y, et al. Double hit lymphomas: evaluation of prognostic factors and impact of therapy. Presented at: the 2012 American Society of Hematology Annual Meeting; December 8-11, 2012; Atlanta, GA. Abstract 1619.
21. Tsai J, Greer JP, Morgan DS, et al. Role of aggressive chemotherapeutic regimens in double hit lymphoma: can alternate aggressive induction regimens overcome the poor prognosis of diffuse large B cell lymphoma? Presented at: the 2013 American Society of Hematology Annual Meeting; December 7-10, 2013; New Orleans, LA. *Blood*. 2013. Abstract 4361.
22. Howlett C, Goy A, Zielonka T, et al. Dose intensive induction followed by allogeneic stem cell transplantation more than doubles progression-free and overall survival in "double-hit' lymphoma. Presented at: the 2013 American Society of Hematology Annual Meeting; December 7-10, 2013; New Orleans, LA. *Blood*. 2013. Abstract 2141.
23. Sun H, Savage KJ, Karsan A, et al. Outcome of patients with double-hit lymphomas treated with CODOX-M/IVAC + R followed by hematopoietic stem cell transplantation in British Columbia. Presented at: the 2013 American Society of Hematology Annual Meeting; December 7-10, 2013; New Orleans, LA. *Blood*. 2013. Abstract 1788.
24. Petrich AM, Cassaday RD, Press OW, et al. Impact of induction regimen and consolidative stem cell transplantation in patients with double hit lymphoma: a large multicenter retrospective analysis. Presented at: the 2013 American Society of Hematology Annual Meeting; December 7-10, 2013; New Orleans, LA. *Blood*. 2013. Abstract 640.
25. Dunleavy K, Pittaluga S, Wayne A. MYC+ aggressive B-cell lymphomas: novel therapy of untreated Burkitt lymphoma and MYC+ diffuse large B-cell lymphoma with DA-REPOCH. *Ann Oncol*. 2011;22(suppl 4):71.
26. Dunleavy K, Fanale M, LaCasce A, et al. Preliminary report of a multicenter prospective phase II study of DA-EPOCH-R in MYC-rearranged aggressive B-cell lymphoma. Presented at: the 2014 American Society of Hematology Annual Meeting; December 5-8, 2014; San Francisco, CA. *Blood*. 2014. Abstract 395.
27. Wall M, Poortinga G, Stanley KL, et al. The mTORC1 inhibitor everolimus prevents and treats Emu-Myc lymphoma by restoring oncogene-induced senescence. *Cancer Discov*. 2013;3:82-95.
28. Pourdehnad M, Truitt ML, Siddiqi IN, et al. Myc and mTOR

converge on a common node in protein synthesis control that confers synthetic lethality in Myc-driven cancers. *Proc Natl Acad Sci U S A*. 2013;110:11988-11993.
29. Smith SM, van Besien K, Karrison T, et al. Temsirolimus has activity in non-mantle cell non-Hodgkin's lymphoma subtypes: The University of Chicago phase II consortium. *J Clin Oncol*. 2010;28:4740-4746.
30. Kretzner L, Scuto A, Dino PM, et al. Combining histone deacetylase inhibitor vorinostat with aurora kinase inhibitors enhances lymphoma cell killing with repression of c-Myc, hTERT, and microRNA levels. *Cancer Res*. 2011;71:3912-3920.
31. Fanale MA, Hagemeister FB, Fayad L, et al. A phase I trial of alisertib plus romidepsin for relapsed/refractory aggressive B- and T-cell lymphomas. Presented at: the 2014 American Society of Hematology Annual Meeting; December 5-8, 2014; San Francisco, CA. *Blood*. 2014. Abstract 1744.
32. Evens AM, Dashnamoorthy R, Kandela I, Mazar A. The novel 2nd generation proteasome inhibitor MLN9708 induces redox- and MAPK-related cell death in T-cell lymphoma and Hodgkin lymphoma cell lines and human lymphoma xenograft models. *Hematol Oncol Clin North Am*. 2013;31(suppl 1):96-150. Abstract 030.
33. Assouline S, Chang JE, Cheson BD, et al. Results of a phase 1 dose-escalation study of once-weekly MLN9708, an investigational proteasome inhibitor, in patients with relapsed/refractory lymphoma. Presented at: the 2012 American Society of Hematology Annual Meeting; December 8-11, 2012; Atlanta, GA. Abstract 3646.
34. Davids MS, Seymour JF, Gerecitano JF, et al. Phase I study of ABT-199 (GDC-0199) in patients with relapsed/refractory (R/R) non-Hodgkin lymphoma (NHL): responses observed in diffuse large B-cell (DLBCL) and follicular lymphoma (FL) at higher cohort doses. *J Clin Oncol*. 2014;32(15 suppl; abstr 8522).
35. Johnson-Farley N, Veliz J, Bhagavathi S, Bertino JR. ABT-199, a BH3 mimetic that specifically targets Bcl-2, enhances the antitumor activity of chemotherapy, bortezomib, and JQ1 in "double hit " lymphoma cells. *Leuk Lymphoma*. 2014:1-12.
36. Cerchietti LC, Ghetu AF, Zhu X, et al. A small-molecule inhibitor of BCL6 kills DLBCL cells in vitro and in vivo. *Cancer Cell*. 2010;17:400-411.
37. Sauter CS, Riviere I, Bernal YJ, et al. Interim safety analysis: a phase I trial of high dose therapy and autologous stem cell transplantation followed by infusion of chimeric antigen receptor modified T-cells (19-28z CAR-T) directed against CD19+ B-cells for relapsed and refractory aggressive B-cell non-Hodgkin lymphoma. Presented at: the 2014 American Society of Hematology Annual Meeting; December 5-8, 2014; San Francisco, CA. *Blood*. 2014. Abstract 677.