Abstract

Double-hit lymphoma (DHL) is a rare type of aggressive B-cell lymphoma defined as a high-grade B-cell lymphoma (HGBCL) with the presence of MYC, BCL2 and/or BCL6 rearrangements. Patients usually present with rapidly progressive and advanced stage of disease and, commonly, with extranodal involvement. Typically, patients become refractory to standard R-CHOP, and more aggressive regimens such as DA-EPOCH-R, R-hyperCVAD or CODOX-R regimens are typically needed. MYC is considered an “undruggable” mutation. Recent evidence suggests that pathogenic mechanisms associated with MYC could be potential targets. In this review, we also discuss the role of hematopoietic stem cell transplantation (HCT) and chimeric antigen receptor (CAR) T-cell therapy in DHL. We also discuss the role of potential novel agents such as BCL2 inhibitors, checkpoint inhibitors, bromodomain and extraterminal (BET) family inhibitors, PI3K inhibitors, and others.

Keywords: double-hit lymphoma, MYC, targeted therapy.

Citation

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Introduction

Diffuse large B-cell lymphoma (DLBCL) encompasses a spectrum of pathologic and molecular subtypes with different biologic behaviors, responses in treatment, and outcomes. Now categorized as high-grade B-cell lymphoma (HGBL), the 2016 World Health Organization (WHO) classification defines double-hit lymphoma (DHL) as HGBL harboring MYC rearrangement occurring with either a B-cell CLL/lymphoma 2 (BCL2) and/or B-cell CLL/lymphoma (BCL6) rearrangement.1 These are referred to as triple-hit lymphoma (THL) if all three gene rearrangements are present, and double expressor lymphoma (DEL) is DLBCL that exhibits co-expression of the respective proteins in the absence of gene rearrangement. The MYC proto-oncogene on chromosome 8q24 functions in cell proliferation, differentiation, and apoptosis, and BCL2 on chromosome 18q21 and BCL6 on chromosome 3q27 also regulate apoptosis. MYC also regulates posttranscriptional events such as the modulation of non-coding RNAs such as microRNAs (specially the miR 17-92 cluster) and RNA processing (such as splicing and capping of mRNA).2 MYC translocation or rearranged LBCL may have poorer survival outcomes with standard chemoimmunotherapy, and the synergistic effect of dysregulation of both MYC with BCL2 and/or BCL6 rearrangements promotes lymphomagenesis and increases resistance to chemotherapy.3-5 DHL with MYC and BCL6 rearrangements occur primarily in germinal center B-cell-like (GCB) DLBCL, but can also be found in activated B-cell-like (ABC) subtype; however, combined MYC and BCL2 rearranged DHL occurs predominantly in GCB subtype.6 In a study by Scott and colleagues, more than 1,200 newly diagnosed DLBCL were analyzed by cell of origin (COO) and fluorescence in situ hybridization (FISH) to detect c-MYC, BCL2, and BCL6 rearrangements, and of the 7.9% DLBCL cases assigned to DHL/HGBL; these comprised 13% GCB signature versus 1.7% within ABC category.6 DEL are defined by overexpression on immunohistochemistry (IHC) of both c-MYC and BCL2 (>40% and >50%, respectively), are usually from the ABC subtype.7

Although gene expression profiling (GEP) serves as the reference standard for identification of cell of origin, it is not widely available, and IHC-based algorithms (i.e., Hans algorithm) continue to be routinely utilized.8 Thus, biologic heterogeneity with distinct molecular subgroups within GCB and ABC still needs further characterization to subsequently translate into clinical applications.9 The NanoString gene expression system utilizes sequence-specific probes for direct measurement of mRNA without amplification. Compared with IHC, NanoString...
has the ability to perform multiplex analyses of hundreds of distinct targets while only needing a small amount of input from formalin-fixed, paraffin-embedded diagnostic tissue.10

Characterizing gene expression signatures within DLBCL facilitates identification of molecular subtypes based on co-occurrence of genetic alterations that may determine clinical behavior, prognostication, and future targets for treatment.11,12 Using exome and transcriptome sequencing, array-based DNA copy-number analysis, and targeted amplicon resequencing, Schmitz and colleagues identified four prominent genetic subtypes in DLBCL: MCD with co-occurrence of MYD88 and CD79B mutations, BN2 with BCL6 fusions and NOTCH2 mutations, N1 based on NOTCH1 mutations, and EZB with EZH2 mutations and BCL2 translocations.12 Each subtype differs in clinical phenotype and outcomes with chemoimmunotherapy, with more favorable responses and survival in the BN2 and EZB subtypes while MCD and N1 had inferior outcomes.

Ennishi and colleagues also developed a double-hit signature (DHITsig) that identified a distinct subgroup within DLBCL with inferior outcomes irrespective of DHL/THL or HGBL status.13 Further utilizing DHITsig, Hilton and colleagues evaluated 20 DHITsig-positive GCB-DLBCL cases with whole genome sequencing and identified DHITsig-positive DLBCL not rearranged and cryptic to break-apart FISH, adding to the importance of refining molecular characterization.14 Rosenwald and colleagues analyzed the role of MYC rearrangements in a large cohort of patients with the goal of evaluating the role of the non-immunoglobulin (IG) partner in the outcomes of DLBCL. Overall, DLBCL patients with single-hit MYC rearrangement with an IG or non-IG partner had the same prognostic effect as DHL/THL with a non-IG partner (as opposed to DHL/THL with IG partner as translocations that had a very poor prognosis in this cohort). This effect was exclusively seen within the first 2 years after diagnosis.9

Although DHL only represents around 10% of newly diagnosed HGBL,1,2 these patients more commonly present with advanced stage III or IV disease with high-risk international prognostic index (IPI) score, and they are more likely to have extranodal and/or central nervous system (CNS) involvement.15,16 DHL/THL has a worse prognosis with inferior outcomes when treated with R-CHOP without high-dose chemotherapy consolidation, especially when patients do not achieve a complete response (CR). The utilization of intensive chemotherapy regimens has helped improve responses, but robust data on improvement in overall survival (OS) are lacking.17-20 Ongoing research strives to optimize frontline treatment of DHL as well as evaluate new treatment strategies in the relapsed/refractory (R/R) setting, and the growth of gene expression profiling with associated targeted therapies provides new potential therapeutic strategies.12

Herein, we review the current standard of care for management of DHL with chemoimmunotherapy and the role of hematopoietic stem cell transplant (HSCT). We also review the potential role of chimeric antigen receptor T-cell (CART) therapy as well as evidence for other evolving treatments that may play a future role in the treatment of DHL. Investigational therapies include agents targeting bromodomain containing 4 (BRD4), cyclin-dependent kinase (CDK), histone deacetylase (HDAC), phosphoinositide-3-kinase (PI3K), aurora kinase, EZH2, BCL2 family, and checkpoint inhibition.

### Chemoimmunotherapy

R-CHOP (rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone) remains the standard of care for DLBCL. However, DHL, DEL, and MYC rearranged DLBCL/HGBL have inferior progression-free survival (PFS) and OS when treated with R-CHOP with 5-year PFS and OS approximately 20–30%.19,21-23 Based on these historical outcomes, currently many centers consider higher-intensity chemotherapy regimens in DHL, such as dose-adjusted EPOCH-R (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, and rituximab), R-HyperCVAD/MA (rituximab, cyclophosphamide, vincristine, doxorubicin, and dexamethasone/ methotrexate, cytarabine), and R-CODOX-M/IVAC (rituximab, cyclophosphamide, vincristine, doxorubicin, methotrexate, ifosfamide, etoposide, and cytarabine).

A prospective, single-arm phase II study of 53 patients with untreated aggressive B-cell lymphoma with MYC rearrangement received six cycles of DA-EPOCH-R with CNS prophylaxis with a total of eight doses of intrathecal methotrexate.24 Twenty-four of 53 (45%) patients had confirmed DHL/THL, and the 48-month event-free survival (EFS) and OS values were 73.4% and 82%, respectively, indicating improved outcomes over R-CHOP based on historical controls. Dose adjustments were carried out based on count nadir with grade 4 toxicities primarily related to neutropenia and thrombocytopenia, and three treatment-related deaths were related to infections.24

Retrospective data also showed improved response rates and PFS with R-HyperCVAD/MA and R-CODOX-M/IVAC as well as DA-EPOCH-R compared to R-CHOP. The highest rates of CR were seen with DA-EPOCH-R in the 50–60% range, compared to CR rates of 32–36% achieved with R-HyperCVAD/MA and R-CODOX-M/IVAC.25-27 The largest retrospective, multi-institutional cohort of 311 treatment-naïve DHL patients showed a median PFS of 7.8 months when treated with R-CHOP compared with 21.6 months for those treated with more intensive chemotherapies.25 CR was associated with improved outcomes by multivariant modeling, and deeper responses were achieved with intense therapies. However, significant improvement in OS has not been observed across all retrospective data sets.25-27

The recent large phase III Intergroup Trial Alliance/CALGB 50303 prospective study of 491 eligible patients with newly diagnosed DLBCL compared frontline DA-EPOCH-R with R-CHOP.28 Among all patients, there was no significant difference in survival with 2-year PFS 78.9% for DA-EPOCH-R and 75.5% for R-CHOP, and 2-year OS was 86.5% for DA-EPOCH-R and 85.7% for R-CHOP. There were 270/491 (55.0%) patients in the trial who were assessed for double expressor status, and 42 patients were classified as
DEL. MYC rearrangement data were available for 249/491 (50.7%) patients, and 13 patients were found to be MYC rearranged with 3 of the 13 patients being further classified as DHL. There was no significant difference in PFS or OS between the two regimens for the 42 DEL patients, but the preplanned subgroup analysis based on FISH classification has not yet been reported.28

Due to the lack of appropriate prospective data, and based on several retrospective series including a systematic review and meta-analysis by Howlett and colleagues, DA-EPOCH-R is currently often preferred in clinical practice due to better risk–benefit profile.29 R-HyperCVAD/MA and R-CODOX-M/IVAC typically have greater toxicity and are poorly tolerated in older patients30 (Table 1).

### Table 1. Chemoimmunotherapy studies with DHL.

| Authors and study type | Number of patients included | Treatment(s) analyzed | Progression-/relapse-/ event-free survival (months) | Overall survival (months) |
|------------------------|-----------------------------|-----------------------|---------------------------------------------------|---------------------------|
| Savage KJ et al. Blood 2009 | 12 MYC+ (8 BCL2+ on IHC) 123 MYC− | R-CHOP in MYC+ vs. MYC− DLBCL | 5-year PFS: 66% MYC− vs. 31% MYC+ (p=0.006) | 5-year OS: 72% MYC− vs. 33% MYC+ (p=0.016) |
| Johnson NA et al. JCO 2012 | 14 DHL 55 DEL 236 other DLBCL | R-CHOP in de novo DLBCL | 5-year PFS: DHL: 18% DEL: 32% Non-DHL/DEL DLBCL: 65% | 5-year OS: DHL: 27% (p<0.001) DEL: 36% (p=0.014) Non-DHL/DEL DLBCL: 71% |
| Akyurek N et al. Cancer 2012 | 7 DHL/THL 232 other DLBCL | R-CHOP in de novo DLBCL | Median survival DHL/THL: 9 months (p=0.003) | DHL/THL: 2-year OS 14% (p<0.001) |
| Horn H et al. Blood 2013 | 29 DHL/THL 321 other DLBCL with measurable BCL2/BCL6/MYC | CHOP-14 +/− rituximab in de novo DLBCL on RICOVER study | 3-year EFS R-CHOP DHL group: 38.1% for MYC+/BCL2+ (CI: 0.0–77.1) 50.0% for MYC+/BCL6+ (CI: 1.0–99.0) | 3-year OS R-CHOP DHL group: 35.7% for MYC+/BCL2+ (CI: 0.0–74.5) 75.0% for MYC+/BCL6+ (CI: 32.5–100.0) |
| Petrich AM et al. Blood 2014 | 311 total patients 286 DHL 25 THL | R-Hyper-CVAD: 65 patients DA-EPOCH-R: 64 patients R-CODOX-M/IVAC: 42 patients R-CHOP: 100 patients R-ICE: 9 patients Other regimens: 31 patients | Median PFS: Intensive regimen: 21.6 months R-CHOP: 7.8 months (p=0.001) All patients: 10.9 months 2-year PFS all patients: 40% | Median OS all patients: 21.9 months Median OS NR if CR to frontline therapy; no difference with consolidation auto/allo SCT 2-year OS all patients: 49% |
| Oki Y et al. BJH 2014 | 129 DHL | R-CHOP: 57 patients R-EPOCH: 28 patients R-HyperCVAD/MA: 34 patients Other regimen: 10 patients | 2-year & 3-year EFS: R-CHOP: 25% & 20% R-EPOCH: 67% & 67% R-HyperCVAD/MA: 32% & 32% Other: < 10% & < 10% All: 33% & 29% | 2-year & 3-year OS: R-CHOP: 41% & 35% R-EPOCH: 76% & 76% R-HyperCVAD/MA: 44% & 40% Other: <12% & <12% All: 44% & 38% |

(Continued)
particularly poor, and inferior outcomes have been observed in patients who did not receive CNS-directed prophylaxis.\textsuperscript{25,26}

With R/R DHL, there is currently no standard of care for optimal salvage second-line chemotherapy treatments and beyond. Traditional DLBCL management with salvage regimens such as R-ICE (rituximab, ifosfamide, carboplatin, and etoposide) or R-DHAP (rituximab, dexamethasone, high-dose cytarabine, and cisplatin) followed by autologous stem cell transplantation (autoSCT) result in inferior PFS and OS for DHL compared with DLBCL without MYC rearrangements.\textsuperscript{33,34} This emphasizes the need for further research into novel treatments to expand options available as standard care.

**HSCT**

With intensive chemoimmunotherapy regimens such as DA-EPOCH-R becoming the standard of care for DHL, there have been attempts to further intensify treatment with...
consolidative autoSCT. If a patient does not receive intensive chemoimmunotherapy frontline, autoSCT as consolidation after R-CHOP may help improve relapse-free survival (RFS) and OS compared with R-CHOP alone. \( ^{35} \) Patients receiving R-CHOP without autoSCT in the first CR (CR1) had 3-year RFS of 51% and OS of 75%, but patients who received R-CHOP frontline with autoSCT in CR1 had 3-year RFS 75% with OS 83%, indicating improved outcomes. However, in patients who received a frontline intensive regimen (such as DA-EPOCH or R-HyperCVAD) with subsequent CR1, consolidative autoSCT was not associated with improved survival outcomes.\(^{25,26,35,36} \)

High-dose chemotherapy with autoSCT remains a standard of care for R/R DLBCL achieving CR after salvage chemotherapy. However, in the setting of DEL/DHL the outcomes are particularly poor. For R/R DEL and DHL, retrospective data of 117 patients with chemotherapy-sensitive R/R DLBCL reported inferior PFS and OS with autoSCT within the DEL/DHL patients.\(^{37} \) For 47 DEL patients, there was a 4-year PFS of 48% and 4-year OS of 56%, and the non-DEL patients had 4-year PFS and OS of 59% and 67%, respectively. The 12 DHL patients had a 4-year PFS of 28% and 4-year OS of 25%, whereas the non-DHL patients had 4-year PFS and OS of 57% and 61%, respectively.\(^{37} \) Newer treatment modalities for R/R DEL/DHL may supplant the role of autologous HSCT.

Limited data on outcomes of allogeneic stem cell transplantation (alloSCT) in DHL and efficacy of graft-versus-lymphoma for R/R DHL/DEL are available.\(^{38} \) Herrera and colleagues retrospectively studied outcomes after alloSCT in 78 patients with R/R aggressive B-cell non-Hodgkin lymphoma, and 37/78 (47%) had DEL, whereas 10/78 (13%) had DHL.\(^{39} \) There was no significant difference in PFS or OS after alloSCT irrespective of DEL and DHL status, indicating its potential role for producing durable remissions. Although alloSCT may potentially provide durable remissions for those with poor prognosis in R/R DEL/DHL, this must be carefully weighed with the risks of transplant-related mortality and long-term complications.\(^{40,41} \) (Table 2).

**CART therapy**

CART cell therapy has revolutionized the treatment of R/R DLBCL, and this has significantly changed the previously very poor prognosis in the chemoresistant or post-HDT-autoSCT relapse setting. Chimeric antigen receptors (CARs) consist of fusion proteins with antigen-recognition and T-cell signaling domains, and patients’ T-cells with engineered anti-CD19 CARs recognize lymphoma B-cells expressing CD19 for destruction with enhanced responses utilizing costimulatory domains.\(^{42} \) CART has produced dramatic response rates and durable remissions for R/R DLBCL.\(^{43,44} \)

Axicabtagene ciloleucel (Yescarta\textregistered) developed by Kite Pharma consists of a CD3z-CD28 CART construct, and tisagenlecleucel (Kymriah\textregistered) produced by Novartis is an anti-CD19 CART that uses 4-1BB as a costimulatory domain.\(^{45,46} \) The phase I–II ZUMA-1 trial with axicabtagene ciloleucel found an objective response rate of 83% with 58% of patients achieving CR, 25% with partial

### Table 2. Studies of stem cell transplant in DHL.

| Authors and study type | Patients included | Progression-/relapse-/event-free survival (months) | Overall survival (months) |
|------------------------|-------------------|-------------------------------------------------|--------------------------|
| Peniket AJ et al. BMT 2003 Retrospective | 255 alloSCT for high-grade NHL | Median PFS: 7.1 months 4-year PFS: 39.3% | Median OS: 1 year 4-year OS: 41.2% 4-year procedure-related mortality: 33.0% |
| Petrich AM et al. Blood 2014 Retrospective | 311 total patients: 286 DHL, 25 THL | Not reported for transplant patients: 83 total SCT patients including 39 autoSCT and 14 alloSCT in CR1 | Median OS: Observation with CR1: 103 months Consolidation SCT (any type): not reached \( (p=0.14) \) Auto- or allo-SCT in CR1: not reached \( (p=0.302) \) |
| Oki Y et al. BJH 2014 Retrospective | 129 DHL: 71 achieved CR1 23 SCT in CR1 | EFS all stages achieving CR, frontline SCT: HR 0.53 (95% CI: 0.21–1.31, \( p=0.170) \) EFS advanced stage achieving CR, frontline SCT: HR 0.42 (95% CI: 0.17–1.05, \( p=0.065) \) | All stages achieving CR, frontline SCT: HR 0.74 (95% CI: 0.27–2.04, \( p=0.566) \) Advanced stage achieving CR, frontline SCT: HR 0.58 (95% CI: 0.21–1.60, \( p=0.292) \) |

(Continued)
response, and 10% with stable disease.\textsuperscript{47} With a median follow-up of 27.1 months, the median duration of response (mDOR) on ZUMA-1 was 11.1 months for all patients (95% confidence interval [CI] 4.2–not estimable) and not reached for patients in CR (95% CI 12.9–not estimable). Median OS was not reached (95% CI 3.3–15.0 months), and 39% of patients had an ongoing response. By investigator assessment, 33 patients had DE/HGBL with seven patients with confirmed DHL/THL or HGBL that achieved 90% objective responses and 33% ongoing CRs at last follow up.\textsuperscript{47}

The JULIET trial with tisagenlecleucel observed a best overall response rate of 52% (95% CI: 41–62) with 40% achieving CR whereas 12% had partial responses (PR), and 12-month RFS was 65%.\textsuperscript{46} Of the 19 patients with confirmed DHL/THL on the JULIET trial, there was a response rate of 50% and CR rate of 25%. The TRANSCEND-NHL-001 study is currently testing lisocabtagene maraleucel (JCAR017 or liso-cel) construct with 4-1BB costimulatory molecule with a predefined 1:1 CD4:CD8 ratio, and initial phase I data report a best overall response rate of 75–84% in all DLBCL patients and 81% among the 16 patients

| Authors and study type | Patients included | Progression-/relapse-/event-free survival (months) | Overall survival (months) |
|------------------------|-------------------|--------------------------------------------------|--------------------------|
| **Landshurg DJ et al.** | 159 DHL: 62 AutoSCT in CR1 27 R-CHOP/Non-AutoSCT 8 R-CHOP/AutoSCT 70 Intensive/Non-AutoSCT 54 Intensive/AutoSCT | 3-year RFS: All patients: 80% AutoSCT in CR1: 75% Non-AutoSCT: 89% R-CHOP/Non-AutoSCT: 51% R-CHOP/AutoSCT in CR1: 75% Intensive Regimen/Non-AutoSCT CR1: 86% (p=0.002, compared with R-CHOP) Intensive Regimen/AutoSCT CR1: 91% | 3-year OS: All patients: 87% AutoSCT in CR1: 85% Non-AutoSCT: 91% R-CHOP/non-autoSCT: 75% R-CHOP/autoSCT in CR1: 83% Intensive regimen/non-autoSCT CR1: 89% Intensive regimen/autoSCT CR1: 92% |
| **Herrera AF et al.** | 117 DLBCL s/p autoSCT: 52 DEL 12 DHL | 4-year PFS: Non-DEL/DHL: 60% (95% CI: 46–72) DEL: 48% (95% CI: 34–61) DHL: 28% (95% CI: 6–57, p=0.013) | 4-year OS: Non-DEL/DHL: 70% (95% CI: 55–80) DEL: 56% (95% CI: 40–69) DHL: 25% (95% CI: 5–54, p<0.001) |
| **Chen AI et al.** | 36 DHL treated with DA-EPOCH-R 17 received autoSCT | 2-year PFS: 69% (95% CI: 54–84) 2-year PFS autoSCT: 94% (95% CI: 83–100) 2-year PFS observation: 79% (95% CI: 52–100, p=0.59) | 2-year OS: 71% (95% CI: 56–86) 2-year OS autoSCT: 94% (95% CI: 83–100) 2-year PFS observation: 79% (95% CI: 52–100) (p=0.59) |
| **Herrera AF et al.** | 78 total HGBL: 31 DEL 10 DHL | 4-year PFS: DHL: 40% (p=0.62) Non-DHL: 34% DEL: 30% (p=0.24) Non-DEL: 39% | 4-year OS: DHL: 50% (p=0.46) Non-DHL: 38% DEL: 31% (p=0.46) Non-DEL: 49% |
| **Salhotra A et al.** | 22 patients with lymphoma s/p alloSCT: 10 DLBCL | 2-year EFS: 58.3% (95% CI: 35–75.8) 2-year cumulative incidence of relapse: 31.8% (95% CI: 13.6–51.8) | 2-year OS: 45.5% (95% CI: 24.4–64.3) 2-year non-relapse mortality: 27.7% (95% CI: 8.0–42.0) |

**Table 2.** (Continued)
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Table 3. CART studies that included DHL.

| Authors and study type | Patient population | Clinical efficacy | Response durations |
|------------------------|--------------------|-------------------|--------------------|
| Abramson JS et al. JCO 2018 phase 1 TRANSCEND NHL 001 trial | 91 patients received lisocabtagene maraleucel (JCAR017) (81 evaluable for efficacy) | ORR: 74% in FULL dataset, 80% in CORE dataset; CR: 52% in FULL, 55% in CORE dataset, dose-level 2: ORR 50%, CR 50% CORE dataset, dose-level 1: ORR 40%, CR 30% | Not reported |
| Locke FL et al. Lancet Oncol 2019 Single-arm, phase I/II ZUMA-1 trial | 101 assessable patients received axicabtagene ciloleucel: 30 DEL 7 HGBL (1 THL, 4 DHL, 2 HGBL NOS) | All patients: Objective Response: 83% CR: 58% PR: 25% SD: 10% PD: 5% DEL/HGBL patients: Objective Response: 91% CR: 70% | All patients: Median time to response: 1 month Median duration of response: 11.1 months Median duration of response if CR: Not Reached Median PFS: 5.9 months (95% CI: 3.3–15.0) 24-month PFS: 72.0% if CR at 3 months, 75.0% if PR at 3 months, 22.2% if SD at 3 months |
| Schuster SJ et al. NEJM 2019 Single-group phase II JULIET trial | 93 patients with relapsed/refractory DLBCL received tisagenlecleucel | ORR: 52% (95% CI: 41–62) CR: 40% PR: 12% | 12-month RFS: 65% (79% among patients with CR) |

CI, confidence interval; CR, complete response; DHL, double hit lymphoma; DLBCL, diffuse large B-cell lymphoma; HGBL NOS, high-grade B-cell lymphoma not otherwise specified; ORR, overall response rate; PD, progressive disease; PFS, progression-free survival; PR, partial response; RFS, relapse-free survival; SD, stable disease; THL, triple hit lymphoma.

with DHL/THL.48,49 The DHL/THL patients also had a 3-month CR rate of 60%, also within the range of all DLBCL patients under study (Table 3).

The efficacy of CART therapy in refractory DLBCL was also evaluated outside clinical trials in an effort of the US CART Consortium that included nearly 300 patients treated with axi-cel after its FDA approval in October 2017.50 The objective responses and CR rates were 81% and 57%, respectively, and similar to the ZUMA-1 findings. This data set included 62 patients with DHL/THL, and although the report did not include overall efficacy rates, the multivariate analysis showed that DHL/THL status was not predictive of the lack of response.

Although CART therapy has changed the landscape of DLBCL treatment, relapses do occur. Some of the strategies include targeting the tumor microenvironment (TME). The checkpoint molecules PD-1 and PD-L1 are present and upregulated in CART cells and TME, especially after infusion. A clinical trial evaluated the efficacy of pembrolizumab 200 mg every 3 weeks until disease progression in R/R DLBCL post-tisagenlecleucel infusion. The study included 12 patients and showed an ORR of 27% (one patient achieved CR). Re-expansion of CART cells were noted after the first infusion of pembrolizumab. The ZUMA-6 study examined the efficacy of axicabtagene ciloleucel in combination with atezolizumab (PD-L1 inhibitor) at doses of 1200 mg every 3 weeks at different starting points (cohorts). The phase 1 portion was completed and showed an ORR and CR rates of 90% and 60%, respectively. CART cell expansion was twice higher than that in ZUMA-1-treated patients. Of interest, grade 3 NT was higher (50%) than that reported in the ZUMA-1 trial.

Further enhancement of CART involves optimizing the expansion and persistence of CART. Preclinical models have shown potential synergistic immunomodulatory effects and increased activity of CART targeting CD19 with combining agents such as lenalidomide, Bcl-2 family apoptosis inhibitors, and ibrutinib.52–54 Potential mechanisms for enhancing antitumor function of CART include stronger signaling via CAR, increased interferon gamma production, increasing tumor cell apoptosis, and other possible immune-mediated mechanisms of deepening or augmenting the response of CART.

Potential novel targets

Despite being one of the most characterized oncogenes, c-MYC has been considered the “undruggable” target, and efforts to
successfully target MYC have been disappointing. Thus, many of the efforts carried out in MYC-related lymphomas have focused on targeting post-transcriptional or translational mechanism that regulates MYC expression and function.

**Bromodomain-containing 4 (BRD4) inhibitors**

BRD4 is a key component of the bromodomain and extra-terminal (BET) family and it also a key regulator of the transcriptional process of MYC. BRD4 specifically binds acetylated histones among those the transcription elongation factor b (P-TEFb) that enhances transcriptional functions. BET inhibitors compete with BRD4 binding sites and displace promoters/enhancers of the MYC oncogene. Preclinical data showed that the BET inhibitor, birabresib (OTX015), showed antitumor activity especially in ABC subtype DLBCL cell lines as single agent and in combination with other agents such as rituximab, ibrutinib, everolimus, and vorinostat. A phase I clinical trial included 33 patients with lymphoma. Objective responses were seen in 40% ABC-DLBCL (10), 17% GCB-DLBCL (17), and 20% of MYC+ DLBCL (5). There are ongoing clinical trials specifically in MYC-altered DLBCL in combination with venetoclax that are currently enrolling (NCT03255096).

**CDK7 and CDK9**

MYC deregulation and enhanced transcription are related to super-enhancers (SEs) that include transcription factors and chromatin regulators such as CDK7 and CDK9. As opposed to other CDKs (that regulates cell cycle transition), CDK7 and CDK9 are tightly related to transcription initiation and elongation. Current ongoing trials are not only focused in lymphomas but in myeloid malignancies and solid tumors. Recent evidence shows that voruciclib (a CDK9 inhibitor) seems to synergize with BCL2 inhibitors through MCL-1 inhibition (which is a known resistance mechanism for BCL-2 inhibitors in lymphomas). There is currently a clinical trial with voruciclib that includes patients with DLBCL (NCT03547115).

**Dual histone deacetylases (HDAC) and PI3K**

HDACs are critical in maintaining acetylation of histones that are key in gene expression and DNA transcription. Their role in cancer and specifically in lymphomas is very well established. The PI3Ks are also a very well-known B-cell lymphoma pathway. HDAC has been shown to affect MYC expression and BCL2 regulation. PI3K is known to decrease MYC stability by dysregulating the post-transcription phase of MYC-dependent proteins. In DLBCL cell lines and mouse models, HDACs and PI3K inhibition have been shown to have a synergistic antitumor effect through MYC-dependent transcriptional pathways. There are currently several HDAC and PI3K inhibitors that have been approved by the FDA for the treatment of lymphomas and chronic lymphocytic leukemia. A phase I trial studied the safety and tolerability of fimepinostat, a dual HDAC/PI3K inhibitor (formerly CUDC-907), and included 40 patients with lymphoma and four patients with multiple myeloma. Among lymphoma patients there were 12 DLBCL patients. Remarkably, five of nine evaluable DLBCL patients (five with transformed follicular lymphoma) had an objective response (PR + CR). The expanded Phase I trial with this agent included 14 patients with relapsed MYC-altered DLBCL with an objective response of 64% and mDOR of 13.6 months. A pooled analysis of the phase I and II portions included 60 patients with MYC-altered DLBCL and showed an objective response in 14 patients (23%) with an mDOR of 13.6 months. Fimepinostat is being currently tested in a phase I clinical trial in combination with venetoclax (NCT01742988).

**Aurora kinase Inhibitors**

The Aurora kinase family are key regulators of mitosis and have several subcomponents. Aurora kinase A (AURKA) is associated with tumor development mediated by interactions between TP53 and MYC. Overexpression of AURKA has been associated with increased malignant transformation of normal cells. Alisertib (MLN8237) is an oral Aurora kinase A inhibitor that was tested in a Phase 1 clinical trial in combination with rituximab (MR) and rituximab plus vincristine (MRV) for refractory aggressive B-cell lymphomas and included 45 patients (37 evaluable patients). The objective response was 38% (MR 25% and MRV 44%) with a mDOR of 10.6 months. Of the 10 responding patients with available tissue for correlative studies, none had MYC overexpression.

**EZH2 inhibitors**

EZH2 mutations occur in approximately 20% of DLBCL- GCB subtype, and subsequent aberrations in histone methylation can silence tumor suppressor genes and promote lymphomagenesis. Tazemetostat is a first-in-class selective inhibitor of EZH2, and phase I data from 21 patients with B-cell non-Hodgkin lymphomas yielded objective responses in 8 of them (38%). An interim update of the phase II study with tazemetostat 800 mg twice daily found overall response rates of 17% in those with and without EZH2 mutations and 9% when in combination with prednisolone. A phase Ib LYSAs study of tazemetostat in combination with R-CHOP also found a recommended phase II dose of 800 mg twice daily, and a phase II trial is ongoing.

**BCL2 inhibitors**

BCL2 plays a role in regulating the apoptotic pathway with overexpression leading to resistance to cell death, and BCL2 translocations are present in 15 to 30% of DLBCL, whereas BCL2 amplification occurs in 8 to 30% of patients. Venetoclax is a highly selective BCL2 inhibitor commonly used in other disease types including chronic lymphocytic leukemia and
acute myeloid leukemia that may also offer potential activity in DLBCL. The phase Ib CAVALLI trial evaluated venetoclax in dose escalation in combination with R-CHOP or obinutuzumab with CHOP (G-CHOP). A recommended phase II dose of venetoclax 800 mg days 4 to 10 of cycle 1 and days 1 to 10 of cycles 2 through 8 was determined. Overall response rates seen were 87.5% in R/G-CHOP with venetoclax, and CR was achieved in 79.2% who received R-CHOP and 78.1% with G-CHOP in combination with venetoclax.

**Checkpoint inhibitors**

Immune checkpoint blockade targeting programmed cell death-1 receptor (PD-1) or its ligand (PD-L1) as well as cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) dramatically improves outcomes and survival in different diseases such as malignant melanoma and lung cancers. Pembrolizumab is currently FDA approved for R/R primary mediastinal large B-cell lymphoma (PMBCL) based on KEYNOTE-170/-013, but PMBCL typically has higher expression of PD-L1 compared with DLBCL. The clinical efficacy of PD-1 inhibition in DLBCL as a single agent is very low (ORR and CR rates at 10 and 3%, respectively), likely due to low PD-L1 expression (especially in DHL/THL) and/or low frequency of 9p24.1 genetic alterations.

**Conclusions**

DHL remains an unmet need and is still considered a difficult-to-treat lymphoma. While significant progress has been made in understanding the best frontline regimens, DHL is still considered a poor prognosis disease. There is promising activity with CART cell therapy, but the proper timing and post-remission approach is yet to be determined. Targeted approaches focusing on MYC-related pathways (BRD4, CKD6 and 9, HDAC, etc.) are needed.

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**References**

1. Swerdlow SH, Campo E, Pileri SA, et al. The 2016 revision of the World Health Organization classification of lymphoid neoplasms. *Blood*. 2016;127(20):2375–2390. [http://dx.doi.org/10.1182/blood-2016-01-643569](http://dx.doi.org/10.1182/blood-2016-01-643569)

2. Hamard PJ, Santiago GE, Liu F, et al. PRMT5 regulates DNA repair by controlling the alternative splicing of histone-modifying enzymes. *Cell Rep*. 2018;24(10):2643–2657. [http://dx.doi.org/10.1016/j.celrep.2018.08.002](http://dx.doi.org/10.1016/j.celrep.2018.08.002)

3. Riedell PA, Smith SM. Double hit and double expressors in lymphoma: definition and treatment. *Cancer*. 2018;124(24):4622–4632. [http://dx.doi.org/10.1002/cncr.31646](http://dx.doi.org/10.1002/cncr.31646)
4. Rosenwald A, Bens S, Advani R, et al. Prognostic significance of MYC rearrangement and translocation partner in diffuse large B-cell lymphoma: a study by the Lunenburg Lymphoma Biomarker Consortium. J Clin Oncol. 2019;Jco1900743. http://dx.doi.org/10.1200/jco.19.00743.

5. Davies A. Double-hit lymphoma: so what? Hematol Oncol. 2019;37(Suppl 1):19–23. http://dx.doi.org/10.1002/hon.2581

6. Scott DW, King RL, Staiger AM, et al. High-grade B-cell lymphoma with MYC and BCL2 and/or BCL6 rearrangements with diffuse large B-cell lymphoma morphology. Blood. 2018;131(18):2060–2064. http://dx.doi.org/10.1182/blood-2017-12-820605

7. Miura K, Takahashi N, Nakagawa M, et al. Clinical significance of co-expression of MYC and BCL2 protein in aggressive B-cell lymphomas treated with a second line immunochemotherapy. Leuk Lymphoma. 2016;57(6):1335–1341. http://dx.doi.org/10.3109/10428194.2015.1096352

8. Hans CP, Weisenburger DD, Greiner TC, et al. Confirmation of the molecular classification of diffuse large B-cell lymphoma by immunohistochemistry using a tissue microarray. Blood. 2004;103(1):275–282. http://dx.doi.org/10.1182/blood-2003-05-1545

9. Cabanillas F, Shah B. Advances in diagnosis and management of diffuse large B-cell lymphoma. Clin Lymphoma Myeloma Leuk. 2017;17(12):783–796. http://dx.doi.org/10.1016/j.clml.2017.10.007

10. Veldman-Jones MH, Lai Z, Wappett M, et al. Reproducible, quantitative, and flexible molecular subtyping of clinical DLBCL samples using the nanostring ncounter system. Clin Cancer Res. 2015;21(10):2367–2378. http://dx.doi.org/10.1158/1078-0432.Ccr-14-0357

11. Abramson JS. Hitting back at lymphoma: how do modern diagnostics identify high-risk diffuse large B-cell lymphoma subsets and alter treatment? Cancer. 2019;125(18):3111–3120. http://dx.doi.org/10.1002/cnr.32145

12. Schmitz R, Wright GW, Huang DW, et al. Genetics and pathogenesis of diffuse large B-cell lymphoma. N Engl J Med. 2018;378(15):1396–1407. http://dx.doi.org/10.1056/NEJMoai1801445

13. Ennishi D, Jiang A, Boyle M, et al. Double-hit gene expression signature defines a distinct subgroup of germinal center B-cell-like diffuse large B-cell lymphoma. J Clin Oncol. 2019;37(3):190–201. http://dx.doi.org/10.1200/jco.18.01583

14. Hilton LK, Tang J, Ben-Neriah S, et al. The double hit signature identifies double-hit diffuse large B-cell lymphoma with genetic events cryptic to FISH. Blood. 2019;134(18):1528–1532. http://dx.doi.org/10.1182/blood.2019002600

15. Zeng D, Desai A, Yan F, et al. Challenges and opportunities for high-grade B-cell lymphoma with MYC and BCL2 and/or BCL6 rearrangement (double-hit lymphoma). Am J Clin Oncol. 2019;42(3):304–316. http://dx.doi.org/10.1097/co.0000000000004027

16. Reagan PM, Davies A. Current treatment of double hit and double expressor lymphoma. Hematology Am Soc Hematol Educ Program. 2017;2017(1):295–297. http://dx.doi.org/10.1182/asheducation-2017.1.295

17. Johnson NA, Savage KJ, Ludkovski O, et al. Genetics and pathogenesis of diffuse large B-cell lymphoma: a study by the Lunenburg Lymphoma Biomarker Consortium. Blood. 2014;126(16):2600–2608. http://dx.doi.org/10.1182/blood-2014-05-578963

18. Merron B, Davies A. Double hit lymphoma: how do we define it and how do we treat it? Best Pract Res Clin Haematol. 2013;31(3):233–240. http://dx.doi.org/10.1016/j.beha.2018.07.012

19. 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(28):3452–3459. http://dx.doi.org/10.1200/jco.2011.41.0985

20. Akyurek N, Uner A, Benekli M, et al. Prognostic significance of MYC, BCL2, and BCL6 rearrangements in patients with diffuse large B-cell lymphoma treated with cyclophosphamide, doxorubicin, vincristine, and prednisone plus rituximab. Cancer. 2012;118(17):4173–4183. http://dx.doi.org/10.1002/cncr.27396

21. 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(12):2253–2263. http://dx.doi.org/10.1182/blood-2012-06-435842

22. Dunleavy K, Fanale MA, Abramson JS, et al. Dose-adjusted EPOCH-R (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, and rituximab) in untreated aggressive diffuse large B-cell lymphoma with MYC rearrangement: a prospective, multicentre, single-arm phase 2 study. Lancet Haematol. 2018;5(12):e609–e617. http://dx.doi.org/10.1016/s2352-3026(18)30177-7

23. Petrich AM, Gandhi M, Jovanovic B, et al. Impact of induction regimen and stem cell transplantation on outcomes in double-hit lymphoma: a multicenter retrospective analysis. Blood. 2014;124(15):2354–2361. http://dx.doi.org/10.1182/blood-2014-05-578963

24. Oki Y, Noorani M, Lin P, et al. Double hit lymphoma: the MD Anderson cancer center clinical experience. Br J Haematol. 2014;166(6):891–901. http://dx.doi.org/10.1111/bjh.12982
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27. Sun H, Savage KJ, Karsan A, et al. Outcome of patients with non-Hodgkin lymphomas with concurrent MYC and BCL2 rearrangements treated with CODOX-M/IVAC with rituximab followed by hematopoietic stem cell transplantation. *Clin Leuk Myeloma Leuk*. 2015;16(6):341–348. http://dx.doi.org/10.1016/j.cllm.2014.12.015

28. Bartlett NL, Wilson WH, Jung S-H, et al. Dose-adjusted EPOCH-R compared with R-CHOP as frontline therapy for diffuse large B-cell lymphoma: clinical outcomes of the phase III intergroup trial alliance/calgb 50303. *J Clin Oncol*. 37(21):1790–1799. http://dx.doi.org/10.1200/jco.2018.01994

29. Howlett C, Snedecor SJ, Landsburg DJ, et al. Front-line, dose-escalated immunochemotherapy is associated with a significant progression-free survival advantage in patients with double-hit lymphomas: a systematic review and meta-analysis. *Br J Haematol*. 2015;170(4):504–514. http://dx.doi.org/10.1111/bjh.13463

30. Friedberg JW. How I treat double-hit lymphoma. *Blood*. 2017;130(5):590–596. http://dx.doi.org/10.1182/blood-2017-04-737320

31. Schmitz N, Zeynalova S, Nickelsen M, et al. CNS international prognostic index: a risk model for CNS relapse in patients with diffuse large B-cell lymphoma treated with R-CHOP. *J Clin Oncol*. 2016;34(26):3150–3156. http://dx.doi.org/10.1200/jco.2015.65.6520

32. Savage KJ. Secondary CNS relapse in diffuse large B-cell lymphoma: defining high-risk patients and optimization of prophylaxis strategies. *Hematology Am Soc Hematol Educ Program*. 2017;2017(1):578–586. http://dx.doi.org/10.1182/ashemeducation-2017.1.578

33. Thieblemont C, Briere J, Mounier N, et al. The germinal center/activated B-cell subclassification has a prognostic impact for response to salvage therapy in relapsed/refractory diffuse large B-cell lymphoma: a bio-CORAL study. *J Clin Oncol*. 2011;29(31):4079–4087. http://dx.doi.org/10.1001/jco.2011.35.4423

34. Cuccuini W, Briere J, Mounier N, et al. MYC+ diffuse large B-cell lymphoma is not salvaged by classical R-ICE or R-DHAP followed by beam plus autologous stem cell transplantation. *Blood*. 2012;119(20):4619–4624. http://dx.doi.org/10.1182/blood-2012-01-406033

35. Landsburg DJ, Falkiewicz MK, Maly J, et al. Outcomes of patients with double-hit lymphoma who achieve first complete remission. *J Clin Oncol*. 2017;35(20):2260–2267. http://dx.doi.org/10.1200/jco.2017.72.2157

36. Chen AI, Leonard JT, Okada CY, et al. Outcomes of DA-EPOCH-R induction plus autologous transplant consolidation for double hit lymphoma. *Leuk Lymphoma*. 2018;59(8):1884–1889. http://dx.doi.org/10.1080/10428194.2017.1406085

37. Herrera AF, Mei M, Low L, et al. Relapsed or refractory double-expressor and double-hit lymphomas have inferior progression-free survival after autologous stem-cell transplantation. *J Clin Oncol*. 2017;35(1):24–31. http://dx.doi.org/10.1200/jco.2016.68.2740

38. van Besien KW, de Lima M, Giralt SA, et al. Management of lymphoma recurrence after allogeneic transplantation: the relevance of graft-versus-lymphoma effect. *Bone Marrow Transplant*. 1997;19(10):977–982. http://dx.doi.org/10.1038/sj.bmt.1700781

39. Herrera AF, Rodig SJ, Joy JY, et al. Outcomes after autologous stem cell transplantation in patients with double-hit and double-expressor lymphoma. *Biol Blood Marrow Transplant*. 2018;24(3):514–520. http://dx.doi.org/10.1016/j.bbmt.2017.11.023

40. Peniket AJ, Ruiz de Elvira MC, Taghipour G, et al. An EBMT registry matched study of allogeneic stem cell transplants for lymphoma: allogeneic transplantation is associated with a lower relapse rate but a higher procedure-related mortality rate than autologous transplantation. *Bone Marrow Transplant*. 2003;31(8):667–678. http://dx.doi.org/10.1038/sj.bmt.1703891

41. Salhotra A, Mei M, Stiller T, et al. Outcomes of patients with recurrent and refractory lymphoma undergoing allogeneic hematopoietic cell transplantation with beam conditioning and sirolimus- and tacrolimus-based GVHD prophylaxis. *Biol Blood Marrow Transplant*. 2019;25(2):287–292. http://dx.doi.org/10.1016/j.bbmt.2018.09.009

42. Chavez JC, Locke FL. CAR T cell therapy for b-cell lymphomas. *Best Pract Res Clin Haematol*. 2018;31(2):135–146. http://dx.doi.org/10.1016/j.beha.2018.04.001

43. Kochenderfer JN, Dudley ME, Kassim SH, et al. Chemotherapy-refractory diffuse large B-cell lymphoma and indolent B-cell malignancies can be effectively treated with autologous T cells expressing an anti-CD19 chimeric antigen receptor. *J Clin Oncol*. 2015;33(6):540–549. http://dx.doi.org/10.1200/jco.2014.56.2025

44. Kochenderfer JN, Somerville RPT, Lu T, et al. Long-duration complete remissions of diffuse large B-cell lymphoma: allogeneic transplantation is associated with a lower relapse rate but a higher procedure-related mortality rate than autologous transplantation. *Bone Marrow Transplant*. 2003;31(8):667–678. http://dx.doi.org/10.1038/sj.bmt.1703891

45. Remberger MK, Kastritis E, Hazleman BL, et al. Autologous stem cell transplantation for double-hit lymphoma: clinical outcomes of the phase III intergroup trial alliance/calgb 50303. *J Clin Oncol*. 2015;33(26):3150–3156. http://dx.doi.org/10.1200/jco.2015.65.6520

46. Lefebvre EM, Vey N, Soubeyran P, et al. Autologous stem cell transplantation for diffuse large B-cell lymphoma: allogeneic transplantation is associated with a lower relapse rate but a higher procedure-related mortality rate than autologous transplantation. *Bone Marrow Transplant*. 2003;31(8):667–678. http://dx.doi.org/10.1038/sj.bmt.1703891

47. Schuster SJ, Bishop MR, Tam CS, et al. Tisagenlecleucel in adult relapsed or refractory diffuse large B-cell lymphoma. *N Engl J Medicine*. 2019;380(1):45–56. http://dx.doi.org/10.1056/NEJMoa1804980

48. Abramson JS, Siddiqi T, Palomba ML, et al. High durable CR rates and preliminary safety profile for JCAR017 in R/R aggressive B-NHL (TRANSCEND NHL 001 study): a defined composition CD19-directed CAR T-cell product with potential for outpatient administration. *J Clin Oncol*. 2018;36(S Suppl):120. http://dx.doi.org/10.1200/JCO.2018.36.5_suppl.120
49. Sommermeyer D, Hudecek M, Kosasih PL, et al. Chimeric antigen receptor-modified T cells derived from defined CD8+ and CD4+ subsets confer superior antitumor reactivity in vivo. *Leukemia*. 2016;30(2):492–500. http://dx.doi.org/10.1038/leu.2015.247

50. Nastoupil LJ, Jain MD, Spiegel JY, et al. Axicabtagene ciloleucel (Axi-cell) CD19 chimeric antigen receptor (CAR) T-cell therapy for relapsed/refractory large B-cell lymphoma: real world experience. *Blood*. 2018;132(Suppl 1):91. http://dx.doi.org/10.1182/blood-2018-99-114152

51. Cherkassky L, Morello A, Villena-Vargas J, et al. Human CAR T cells with cell-intrinsic PD-1 checkpoint blockade resist tumor-mediated inhibition. *J Clin Invest*. 2016;126(8):3130–3144. http://dx.doi.org/10.1172/JCI83092

52. Karlsson H, Lindqvist AC, Fransson M, et al. Combining CAR T cells and the BCL-2 family apoptosis inhibitor ABT-737 for treating B-cell malignancy. *Cancer Gene Ther*. 2013;20(7):386–393. http://dx.doi.org/10.1038/cgt.2013.35

53. Otahal P, Prukova D, Kral V, et al. Lenalidomide enhances antitumor functions of chimeric antigen receptor modified T cells. *Oncotarget*. 2016;5(4):e111540. http://dx.doi.org/10.1080/2162402x.2015.1115940

54. Ruella M, Kenderian SS, Shrestova O, et al. The addition of the BTK inhibitor ibrutinib to anti-CD19 chimeric antigen receptor T cells (CART19) improves responses against mantle cell lymphoma. *Clin Cancer Res*. 2016;22(11):2684–2696. http://dx.doi.org/10.1158/1078-0432.Ccr-15-1527

55. Boi M, Gaudio E, Bonetti P, et al. The BET bromodomain inhibitor OTX015 affects pathogenetic pathways in preclinical B-cell tumor models and synergizes with targeted drugs. *Clin Cancer Res*. 2015;21(7):1628-1638. http://dx.doi.org/10.1158/1078-0432.CCR-14-1561

56. Gaudio E, Tarantelli C, Ponzoni M, et al. Bromodomain inhibitor OTX015 (MK-8628) combined with targeted agents shows strong in vivo antitumor activity in lymphoma. *Oncotarget*. 2016;7(36):58142–58147. http://dx.doi.org/10.18632/oncotarget.10983

57. Amorim S, Stathis A, Gleeson M, et al. Bromodomain inhibitor OTX015 in patients with lymphoma or multiple myeloma: a dose-escalation, open-label, pharmacokinetic, phase 1 study. *Lancet Haematol*. 2016;3(4):e196–e204. http://dx.doi.org/10.1016/S2352-3026(16)00021-1

58. Hashiguchi T, Bruss N, Best S, et al. Cyclin-dependent kinase-9 is a therapeutic target in MYC-expressing diffuse large B-cell lymphoma. *Mol Cancer Ther*. 2019. http://dx.doi.org/10.1158/1535-7163.MCT-18-1023

59. Dey J, Deckwerth TL, Kerwin WS, et al. Voruciclib, a clinical stage oral CDK9 inhibitor, represses MCL-1 and sensitizes high-risk diffuse large B-cell lymphoma to BCL2 inhibition. *Sci Rep*. 2017;7(1):18007. http://dx.doi.org/10.1038/s41598-017-18368-w

60. Zhang X, Zhao X, Fiskus W, et al. Coordinated silencing of MYC-mediated MIR-29 by HDAC3 and EZH2 as a therapeutic approach to MYC-expressing diffuse large B-cell lymphoma. *Mol Cancer Ther*. 2016;15(10):2589–2600. http://dx.doi.org/10.1158/1078-0432.CCR-15-1527

61. Kumar A, Marques M, Carrera AC. Phosphoinositide 3-kinase activation in late G1 is required for C-MYC stabilization and S phase entry. *Mol Cell Biol*. 2006;26(23):9116–9125. http://dx.doi.org/10.1128/MCB.00783-06

62. Rahmani M, Aust MM, Benson EC, et al. PI3K/MTOR inhibition markedly potentiates HDAC inhibitor activity in NHL cells through BIM- and MCL-1-dependent mechanisms in vitro and in vivo. *Clin Cancer Res*. 2014;20(18):4849–4860. http://dx.doi.org/10.1158/1078-0432.CCR-14-0034

63. Younes A, Berdeja JG, Patel MR, et al. Safety, tolerability, and preliminary activity of CUDC-907, a first-in-class, oral, dual inhibitor of HDAC and PI3K, in patients with relapsed or refractory lymphoma or multiple myeloma: an open-label, dose-escalation, phase 1 trial. *Lancet Oncol*. 2016;17(5):622–631. http://dx.doi.org/10.1016/S1470-2045(15)00584-7

64. Oki Y, Kelly KR, Flinn I, et al. CUDC-907 in relapsed/refractory diffuse large B-cell lymphoma, including patients with MYC-alterations: results from an expanded phase I trial. *Haematologica*. 2017;102(11):1923–1930. http://dx.doi.org/10.3324/haematol.2017.172882

65. Landsburg DJ, Ramchandren R, Lugtenburg PJ, et al. A pooled analysis of relapsed/refractory diffuse large B-cell lymphoma patients treated with the dual PI3K and HDAC inhibitor fimepinostat (CUDC-907), including patients with MYC-altered disease. *Blood*. 2018;132(Suppl 1):4184–4184. http://dx.doi.org/10.1182/blood-2018-99-112527

66. Nikonova AS, Astsaturov I, Serebriiskii IG, et al. Aurora A kinase (AURKA) in normal and pathological cell division. *Cell Mol Life Sci*. 2013;70(4):661–687. http://dx.doi.org/10.1007/s00018-012-1073-7

67. Kelly KR, Friedberg JW, Park SI, et al. Phase I study of the investigational aurora A kinase inhibitor alisertib plus rituximab or rituximab/vincristine in relapsed/refractory aggressive B-cell lymphoma. *Clin Cancer Res*. 2018;24(24):6150–6159. http://dx.doi.org/10.1158/1078-0432.CCR-18-0286

68. Italiano A, Soria JC, Toulmonde M, et al. Tazemetostat, an EZH2 inhibitor, in relapsed or refractory B-cell non-Hodgkin lymphoma and advanced solid tumours: a first-in-human, open-label, phase 1 study. *Lancet Oncol*. 2018;19(5):649–659. http://dx.doi.org/10.1016/S1470-2045(18)30145-1

69. Ribrag V, Morschhauser F, McKay P, et al. Interim results from an ongoing phase 2 multicenter study of tazemetostat, an EZH2 inhibitor, in patients with relapsed or refractory (R/R) diffuse large B-cell lymphoma (DLBCL). *Blood*. 2018;132(Suppl 1):4196–4196. http://dx.doi.org/10.1182/blood-2018-99-113411
70. Sarkozy C, Morschhauser F, Michot J-M, et al. Results from a phase IB evaluation of tazemetostat (EPZ-6438) in combination with R-CHOP in poor prognosis newly diagnosed diffuse large B-cell lymphoma (DLBCL): a LYSA study. *Blood.* 2018;132(Suppl 1):4191–4191. [http://dx.doi.org/10.1182/blood-2018-99-113193](http://dx.doi.org/10.1182/blood-2018-99-113193)

71. Zelenetz AD, Salles G, Mason KD, et al. Venetoclax plus R- or G-CHOP in non-Hodgkin lymphoma: results from the CAVALLI phase 1b trial. *Blood.* 2019;133(18):1964–1976. [http://dx.doi.org/10.1182/blood-2018-11-880526](http://dx.doi.org/10.1182/blood-2018-11-880526)

72. Uchida A, Isobe Y, Asano J, et al. Targeting BCL2 with venetoclax is a promising therapeutic strategy for “double-proteinexpression” lymphoma with MYC and BCL2 rearrangements. *Haematologica.* 2019;104(7):1417–1421. [http://dx.doi.org/10.3324/haematol.2018.204958](http://dx.doi.org/10.3324/haematol.2018.204958)

73. Xu-Monette ZY, Zhou J, Young KH. PD-1 expression and clinical PD-1 blockade in B-cell lymphomas. *Blood.* 2018;131(1):68–83. [http://dx.doi.org/10.1182/blood-2017-07-740993](http://dx.doi.org/10.1182/blood-2017-07-740993)

74. Zinzani PL, Ribrag V, Moskowitz CH, et al. Safety and tolerability of pembrolizumab in patients with relapsed/refractory primary mediastinal large B-cell lymphoma. *Blood.* 2017;130(3):267–270. [http://dx.doi.org/10.1182/blood-2016-12-758383](http://dx.doi.org/10.1182/blood-2016-12-758383)

75. Elbaek MV, Pedersen MO, Breinholt MF, et al. PD-L1 expression is low in large B-cell lymphoma with MYC or double-hit translocation. *Hematol Oncol.* 2019. [http://dx.doi.org/10.1002/hon.2664](http://dx.doi.org/10.1002/hon.2664)

76. Ansell SM, Minnema MC, Johnson P, et al. Nivolumab for relapsed/refractory diffuse large B-cell lymphoma in patients ineligible for or having failed autologous transplantation: a single-arm, phase II study. *J Clin Oncol.* 2019;37(6):481–489. [http://dx.doi.org/10.1200/JCO.18.00766](http://dx.doi.org/10.1200/JCO.18.00766)