

eTable. Selected Clinical Trials of DA-R-EPOCH in DLBCL

Clinical Trial	Study Design	Patient Population	Outcomes	Conclusions
High-Grade B-Cell Lymphoma With Double-Hit Lymphoma/Triple-Hit Lymphoma				
Dunleavy, 2018 ⁵³	Phase 2 single-arm study of DA-R-EPOCH in DLBCL with <i>MYC</i> rearrangement	53 patients aged >18 y with untreated DLBCL and <i>MYC</i> rearrangement by FISH	In the entire cohort, the 4-y OS rate was 77%. In the 45% of patients with DHL, the 4-y OS rate was 82%, and the 4-y OS rate was 72% in the patients who had DHL with a high IPI of 3-5.	DA-R-EPOCH was effective, achieving durable remissions in patients with <i>MYC</i> -rearranged DLBCL, including those with DHL and a high-risk IPI score.
Primary Mediastinal B-Cell Lymphoma				
Dunleavy, 2013 ⁵⁴	Phase 2 single-arm study of DA-R-EPOCH without radiation in PMBL	51 patients with untreated PMBL	5-y EFS was 93%, and 5-y OS was 97%.	DA-R-EPOCH was efficacious in PMBL, without any need for consolidative radiation.
HIV-Associated DLBCL				
Sparano, 2010 ⁵⁵	Phase 2 randomized trial of EPOCH with either concurrent or sequential rituximab in HIV-associated lymphomas	106 patients aged >18 y with untreated HIV-associated lymphomas, including DLBCL	2-y OS rates were 70% with concurrent DA-R-EPOCH and 67% with sequential EPOCH and rituximab; 70%-75% of surviving patients in the entire cohort were without evidence of progressive lymphoma at 2 y.	DA-R-EPOCH was effective for HIV-associated lymphoma; patients who had a baseline CD4 cell count of less than 50/ μ L had a high infectious death rate in the concurrent DA-R-EPOCH arm.
Gray Zone Lymphoma				
Wilson, 2014 ⁵⁶	Single-arm study of DA-R-EPOCH in GZL	24 patients with untreated mediastinal GZL	3-y EFS rate was 62%, and 3-y OS rate was 74%.	DA-R-EPOCH has efficacy in mediastinal GZL without the use of mediastinal radiation.
High-Risk International Prognostic Index Scores				
Wilson, 2002 ²⁶	Single-arm study of DA-R-EPOCH in all comers with DLBCL	38 patients with untreated or relapsed/refractory DLBCL	Untreated patients had an ORR of 85% and a 1-y OS of 79%.	Rituximab in addition to EPOCH was efficacious in patients with untreated DLBCL in a study with a significant number of high-risk patients; 61% of untreated patients had at least high-intermediate IPI scores.
Wilson, 2008 ⁵⁷	Phase 2 single-arm study of influence of biomarkers and GCB vs non-GCB cell of origin subtype on outcomes with DA-R-EPOCH	72 patients aged >18 y with untreated stage II-IV DLBCL	5-y PFS was 79%, 5-y OS was 80%. Survival was significantly worse in high-risk IPI.	DA-R-EPOCH had efficacy in low- and intermediate-IPI DLBCL.
Purroy, 2015 ⁵⁸	Phase 2, single-arm study of DA-R-EPOCH in poor-prognosis DLBCL	81 patients aged 18-75 y with untreated DLBCL and IPI >2, age-adjusted IPI >1, or any IPI if bulky disease	10-y EFS was 48% and 10-y OS was 64%, with no significant difference in survival based on IPI or GCB vs ABC subtype. 46% of patients had neutropenic fever, and 91% completed all planned cycles of DA-R-EPOCH.	DA-R-EPOCH demonstrated good long-term outcomes in high-risk DLBCL, with 86% of patients in the study having a high-risk IPI of 3-5.

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eTable. (Continued) Selected Clinical Trials of DA-R-EPOCH in DLBCL

Clinical Trial	Study Design	Patient Population	Outcomes	Conclusions
High-Risk International Prognostic Index Scores (continued)				
Bartlett, 2019 ⁵⁹	Phase 3 randomized controlled trial of DA-R-EPOCH vs R-CHOP	491 patients aged >18 y with untreated stage II-IV DLBCL; fresh frozen tumor biopsy required before registration for assessment of double-hit and double-expressor status	Response rates and survival did not differ significantly between the R-CHOP and DA-R-EPOCH cohorts, with 5-y OS rates of 79% for R-CHOP and 78% for DA-R-EPOCH.	Negative: DA-R-EPOCH was more toxic and did not improve PFS or OS compared with R-CHOP. Post hoc subgroup analyses revealed a significantly longer PFS in the DA-R-EPOCH group for IPI 3-5, although no significant difference in OS.
Activated B-Cell Subtype				
Wilson, 2008 ⁵⁷	Phase 2 single-arm study of influence of biomarkers and GCB vs non-GCB cell of origin subtype on outcomes with DA-R-EPOCH	72 patients aged >18 y with untreated stage II-IV DLBCL	5-y PFS was 79% and 5-y OS was 80%, and PFS was better in GCB compared with non-GCB subtype.	DA-R-EPOCH possibly has better activity in the GCB subtype of DLBCL.
Wilson, 2012 ⁶⁰	Phase 2 single-arm study of influence of GCB vs non-GCB cell of origin subtype with DA-R-EPOCH	69 patients aged >18 y with untreated stage II-IV DLBCL	51% of patients had non-GCB/ABC subtype, and TTP, EFS, and OS were all significantly worse in non-GCB vs GCB.	DA-R-EPOCH had better activity in GCB than in non-GCB DLBCL.
Double-Expressor Lymphoma				
Bartlett, 2019 ⁵⁹	Phase 3 randomized controlled trial of DA-R-EPOCH vs R-CHOP	491 patients aged >18 y with untreated stage II-IV DLBCL; fresh frozen tumor biopsy required before registration for assessment of double-hit and double-expressor status	Response rates and survival did not differ significantly between the R-CHOP or DA-R-EPOCH cohorts.	Negative: No subgroup survival differences were found between R-CHOP and DA-R-EPOCH, including no difference in patients with DEL. More favorable results for R-CHOP vs historical controls, as well as the small percentage (only 16%) of patients with DEL and the small number (only 3) of patients with DHL, suggest selection bias and lack of generalizability.

ABC, activated B-cell; DA-R-EPOCH, dose-adjusted rituximab, etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin; DEL, double-expressor lymphoma; DHL, double-hit lymphoma; DLBCL, diffuse large B-cell lymphoma; EFS, event-free survival; FISH, fluorescence in situ hybridization; GCB, germinal center B-cell; GZL, gray zone lymphoma; IPI, International Prognostic Index; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PMBL, primary mediastinal B-cell lymphoma; R-CHOP, rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone; THL, triple-hit lymphoma; TTP, time to progression; y, year(s).