

B-Cell Lymphomas: Diffuse Large B-Cell Lymphoma

Clinical Trials: The NCCN recommends cancer patient participation in clinical trials as the gold standard for treatment.

Cancer therapy selection, dosing, administration, and the management of related adverse events can be a complex process that should be handled by an experienced healthcare team. Clinicians must choose and verify treatment options based on the individual patient; drug dose modifications and supportive care interventions should be administered accordingly. The cancer treatment regimens below may include both U.S. Food and Drug Administration-approved and unapproved indications/regimens. These regimens are only provided to supplement the latest treatment strategies.

These Guidelines are a work in progress that may be refined as often as new significant data becomes available. The National Comprehensive Cancer Network Guidelines® are a consensus statement of its authors regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult any NCCN Guidelines® is expected to use independent medical judgment in the context of individual clinical circumstances to determine any patient's care or treatment. The NCCN makes no warranties of any kind whatsoever regarding their content, use, or application and disclaims any responsibility for their application or use in any way.

Note: All recommendations are category 2A unless otherwise indicated.

► Primary Mediastinal Large B-Cell Lymphoma (PMBL)¹

REGIMEN	DOSING
First-Line Therapy	
Dose-adjusted EPOCH-R (Etoposide + Prednisone + Vincristine + Cyclophosphamide + Doxorubicin) + Rituximab ^{2-7,a,g,u,gg}	<p>Days 1-4 (Cycle 1): Etoposide 50mg/m² IV continuous infusion over 24 hours daily, followed by:</p> <p>Days 1-4 (Cycle 2 and beyond): Etoposide IV continuous infusion over 24 hours daily^a, with:</p> <p>Days 1-4 (Cycle 1): Vincristine 0.4mg/m² IV continuous infusion over 24 hours daily, with:</p> <p>Days 1-4 (Cycle 1): Doxorubicin 10mg/m² IV continuous infusion over 24 hours daily^a, followed by:</p> <p>Days 1-4 (Cycle 2 and beyond): Doxorubicin IV continuous infusion over 24 hours daily</p> <p>Day 5 (Cycle 1): Cyclophosphamide 750mg/m² IV over 30 minutes, followed by:</p> <p>Day 5 (Cycle 2 and beyond): Cyclophosphamide IV over 30 minutes^a</p> <p>Day 1: Rituximab 375mg/m² IV</p> <p>Days 1-5: Prednisone 60mg/m² orally twice daily.</p> <p>Repeat cycle every 3 weeks for 6 cycles.</p>
RCHOP (Rituximab + Cyclophosphamide + Doxorubicin + Vincristine + Prednisone) +/- ISRT (Category 1) ^{5-8,b,d,g,h,i,u,gg}	<p>Day 1: Cyclophosphamide 750 mg/m² IV over 30 minutes</p> <p>Day 1: Doxorubicin 50mg/m² IV push</p> <p>Day 1: Vincristine 1.4mg/m² (maximum 2 mg) IV over 5-10 minutes</p> <p>Day 1-5: Prednisone 100mg orally once daily</p> <p>Day 1: Rituximab 375mg/m² IV.</p> <p>Repeat cycle every 3 weeks for 6 cycles (followed by radiation).</p>
RCHOP (Cyclophosphamide + Doxorubicin + Vincristine + Prednisone) + Rituximab followed by ICE (Ifosfamide + Carboplatin + Etoposide) ^{5-7,9,b-g,j,u,gg}	<p>Day 1: Cyclophosphamide 1,000mg/m² IV over 30 minutes</p> <p>Day 1: Doxorubicin 50mg/m² IV push</p> <p>Day 1: Vincristine 1.4mg/m² (uncapped) IV over 5-10 minutes</p> <p>Days 1-5: Prednisone 100mg orally once daily</p> <p>Day 1: Rituximab 375mg/m² IV.</p> <p>Repeat cycle every 2 weeks for 4 cycles, followed by:</p> <p>Day 2: Ifosfamide 5,000mg/m² IV continuous infusion over 24 hours, with:</p> <p>Day 2: Mesna 5,000mg/m² IV continuous infusion over 24 hours</p> <p>Day 2: Carboplatin AUC 5 IV over 30 minutes</p> <p>Days 1-3: Etoposide 100mg/m² IV over 60 minutes daily.</p> <p>Repeat cycle every 2 week for 3 cycles</p>
RCHOP (Cyclophosphamide + Doxorubicin + Vincristine + Prednisone) + Rituximab followed by ICE (Ifosfamide + Carboplatin + Etoposide) + Rituximab ^{5-7,9,b-g,j,u,gg}	<p>Day 1: Cyclophosphamide 1,000mg/m² IV over 30 minutes</p> <p>Day 1: Doxorubicin 50mg/m² IV push</p> <p>Day 1: Vincristine 1.4mg/m² (uncapped) IV over 5-10 minutes</p> <p>Days 1-5: Prednisone 100mg orally daily</p> <p>Day 1: Rituximab 375mg/m² IV.</p> <p>Repeat cycle every 2 weeks for 4 cycles, followed by:</p> <p>Day 2: Ifosfamide 5,000mg/m² IV continuous infusion over 24 hours, with:</p> <p>Day 2: Mesna 5,000mg/m² IV continuous infusion over 24 hours</p> <p>Day 2: Carboplatin AUC 5 IV over 30 minutes</p> <p>Days 1-3: Etoposide 100mg/m² IV over 60 minutes daily</p> <p>Day 1: Rituximab 375mg/m² IV.</p> <p>Repeat cycle every 2 weeks for 3 cycles.</p>
Relapsed/Refractory Therapy	
Pembrolizumab ¹⁰⁻¹²	<p>Day 1: Pembrolizumab 200mg IV over 30 minutes.</p> <p>Repeat cycle every 3 weeks up to 2 years of therapy.</p> <p>OR</p> <p>Day 1: Pembrolizumab 400mg IV over 30 minutes.</p> <p>Repeat cycle every 6 weeks up to 2 years of therapy.</p>
Nivolumab (Category 2B) ¹³⁻¹⁵	<p>Day 1: Nivolumab 240mg IV over 30 minutes.</p> <p>Repeat cycle every 3 weeks.</p>

continued

B-Cell Lymphomas: Diffuse Large B-Cell Lymphoma

► Primary Mediastinal Large B-Cell Lymphoma (PMBL)¹ (continued)

REGIMEN	DOSING
Relapsed/Refractory Therapy (continued)	
Nivolumab + Brentuximab Vedotin (CD30-positive disease) (Category 2B) ^{13,14,16,k,u}	<p>Day 1: Brentuximab Vedotin 1.8mg/kg (maximum dosing weight is 100 kg) IV over 30 minutes, followed by:</p> <p>Day 8 (Cycle 1): Nivolumab 240mg IV over 30 minutes, followed by:</p> <p>Day 1 (Cycle 2 and beyond): Nivolumab 240mg IV over 30 minutes.</p> <p>Repeat cycle every 3 weeks.</p>

► Diffuse Large B-Cell Lymphoma¹

First-Line Therapy	
Preferred Regimens	
RCHOP (Cyclophosphamide + Doxorubicin + Vincristine + Prednisone) + Rituximab (Category 1) ^{5-8,17,b,d,i,u,gg}	<p>Day 1: Cyclophosphamide 750mg/m² IV over 30 minutes</p> <p>Day 1: Doxorubicin 50mg/m² IV push</p> <p>Day 1: Vincristine 1.4mg/m² (maximum 2mg) IV over 5-10 minutes</p> <p>Day 1-5: Prednisone 100mg orally daily</p> <p>Day 1: Rituximab 375mg/m² IV.</p> <p>Repeat cycle every 3 weeks for 3 cycles (stage I,II) nonbulky disease (<7.5 cm) followed by radiation or 6 cycles (stage I,II) nonbulky disease (<7.5 cm) or bulky disease (≥7.5 cm) with or without subsequent radiation or 6 cycles (stage III-IV) with interim restaging after 2-4 cycles.</p>
Other Recommended Regimens	
Dose-adjusted EPOCH (Etoposide + Prednisone + Vincristine + Cyclophosphamide + Doxorubicin) + Rituximab ^{2,3,5-7,18,a-g,u,gg}	<p>Days 1-4 (Cycle 1): Etoposide 50mg/m² IV continuous infusion over 24 hours daily, followed by:</p> <p>Days 1-4 (Cycle 2 and beyond): Etoposide IV continuous infusion over 24 hours daily^a, with:</p> <p>Days 1-4: Vincristine 0.4mg/m² IV continuous infusion over 24 hours daily, with:</p> <p>Days 1-4 (Cycle 1): Doxorubicin 10mg/m² IV continuous infusion over 24 hours daily, followed by:</p> <p>Days 1-4 (Cycle 2 and beyond): Doxorubicin IV continuous infusion over 24 hours daily^a</p> <p>Day 5 (Cycle 1): Cyclophosphamide 750mg/m² IV over 30 minutes, followed by:</p> <p>Day 5 (Cycle 2 and beyond): Cyclophosphamide IV over 30 minutes^a</p> <p>Days 1-5: Prednisone 60mg/m² orally twice daily</p> <p>Day 1: Rituximab 375mg/m² IV.</p> <p>Repeat cycle every 3 weeks for 6 cycles.</p>
First-Line Therapy for Patients with Poor Left Ventricular Function^{1,n}	
Other Recommended Regimens (No Preferred Regimens)	
Dose-adjusted EPOCH (Etoposide + Prednisone + Vincristine + Cyclophosphamide + Doxorubicin) + Rituximab ^{2,3,5-7,18,a-g,u,gg}	<p>Days 1-4 (Cycle 1): Etoposide 50mg/m² IV continuous infusion over 24 hours daily, followed by:</p> <p>Days 1-4 (Cycle 2 and beyond): Etoposide IV continuous infusion over 24 hours daily^a, with:</p> <p>Days 1-4: Vincristine 0.4mg/m² IV continuous infusion over 24 hours daily, with:</p> <p>Days 1-4 (Cycle 1): Doxorubicin 10mg/m² IV continuous infusion over 24 hours daily, followed by:</p> <p>Days 1-4 (Cycle 2 and beyond): Doxorubicin IV continuous infusion over 24 hours daily^a</p> <p>Day 5 (Cycle 1): Cyclophosphamide 750mg/m² IV over 30 minutes, followed by:</p> <p>Day 5 (Cycle 2 and beyond): Cyclophosphamide IV over 30 minutes^a</p> <p>Days 1-5: Prednisone 60mg/m² orally twice daily</p> <p>Day 1: Rituximab 375 mg/m² IV.</p> <p>Repeat cycle every 3 weeks for 6 cycles.</p>
RCDOP (Rituximab + Cyclophosphamide + Liposomal Doxorubicin + Vincristine + Prednisone) ^{5-7,19,20,b-g,i,u,gg}	<p>Day 1: Cyclophosphamide 750mg/m² IV over 30 minutes</p> <p>Day 1: Liposomal Doxorubicin 30mg/m² IV over 60 minutes</p> <p>Day 1: Vincristine 1.4mg/m² (maximum 2 mg) IV over 5-10 minutes</p> <p>Days 1-5: Prednisone 100mg orally once daily</p> <p>Day 1: Rituximab 375 mg/m² IV.</p> <p>Repeat cycle every 3 weeks for 6 cycles.</p>
RCEOP (Rituximab + Cyclophosphamide + Etoposide + Vincristine + Prednisone) ^{5-7,21,b,d-g,u,gg}	<p>Day 1: Cyclophosphamide 750 mg/m² IV over 30 minutes</p> <p>Day 1: Etoposide 50mg/m² IV over 60 minutes, followed by:</p> <p>Days 2-3: Etoposide 50mg/m² IV over 60 minutes daily, OR Day 1: Etoposide 50mg/m² IV over 60 minutes, followed by:</p> <p>Days 2-3: Etoposide 100mg/m² orally once daily.</p> <p>Day 1: Vincristine 1.4mg/m² (maximum 2 mg) IV over 5-10 minutes</p> <p>Days 1-5: Prednisone 100mg orally daily</p> <p>Day 1: Rituximab 375 mg/m² IV.</p> <p>Repeat cycle every 3 weeks for 6 cycles.</p>

continued

B-Cell Lymphomas: Diffuse Large B-Cell Lymphoma

► Diffuse Large B-Cell Lymphoma¹ (continued)

REGIMEN	DOSING
First-Line Therapy for Patients with Poor Left Ventricular Function^m (continued)	
Other Recommended Regimens (No Preferred Regimens) (continued)	
RCEPP (Rituximab + Cyclophosphamide + Etoposide + Prednisone + Procarbazine) ^{5-7,22,b,d-g,gg}	Days 1,8: Cyclophosphamide 600mg/m ² IV over 30 minutes Days 1-3: Etoposide 70mg/m ² IV over 60 minutes daily Days 1-10: Procarbazine 60mg/m ² orally once daily Days 1-10: Prednisone 60mg/m ² orally once daily Day 1: Rituximab 375 mg/m ² IV. Repeat cycle every 4 weeks for 6 cycles.
RGCVP (Rituximab + Gemcitabine + Cyclophosphamide + Vincristine + Prednisone) ^{5-7,23,b-g,u,gg}	Days 1,8 (Cycle 1): Gemcitabine 750mg/m ² IV over 30 minutes, if tolerated, followed by: Days 1,8 (Cycle 2): Gemcitabine 875mg/m ² IV over 30 minutes, if tolerated, followed by: Days 1,8 (Cycles 3-6): Gemcitabine 1,000mg/m ² IV over 30 minutes Day 1: Cyclophosphamide 750mg/m ² IV over 30 minutes Day 1: Vincristine 1.4mg/m ² (maximum 2 mg) IV over 5-10 minutes Days 1-5: Prednisone 10mg orally daily Day 1: Rituximab 375mg/m ² IV. Repeat cycle every 3 weeks for 6 cycles.
First-Line Therapy For Very Frail Patients and Patients >80 Years Of Age With Comorbidities^{m,n}	
Other Recommended Regimens	
RCDOP (Rituximab + Cyclophosphamide + Liposomal Doxorubicin + Vincristine + Prednisone) ^{5-7,19,20,b,d-i,u,gg}	Day 1: Cyclophosphamide 750mg/m ² IV over 30 minutes Day 1: Liposomal Doxorubicin 30mg/m ² IV over 60 minutes Day 1: Vincristine 1.4mg/m ² (maximum 2 mg) IV over 5-10 minutes Days 1-5: Prednisone 100mg orally daily Day 1: Rituximab 375mg/m ² IV. Repeat cycle every 3 weeks for 6 cycles.
RCEPP (Rituximab + Cyclophosphamide + Etoposide + Prednisone + Procarbazine) ^{5-7,22,b,d-g,gg}	Days 1,8: Cyclophosphamide 600mg/m ² IV over 30 minutes Days 1-3: Etoposide 70mg/m ² IV over 60 minutes daily Days 1-10: Procarbazine 60mg/m ² orally daily Days 1-10: Prednisone 60mg/m ² orally daily Day 1: Rituximab 375mg/m ² IV. Repeat cycle every 4 weeks for 6 cycles.
R-mini-CHOP (Rituximab + Cyclophosphamide + Doxorubicin + Vincristine + Prednisone) ^{5-7,24,b,d-i,u,gg}	Day 1: Cyclophosphamide 400mg/m ² IV over 30 minutes Day 1: Doxorubicin 25mg/m ² IV push Day 1: Vincristine 1mg IV over 5-10 minutes Days 1-5: Prednisone 40mg/m ² orally daily Day 1: Rituximab 375 mg/m ² IV. Repeat cycle every 3 weeks for 6 cycles.
RGCVP (Rituximab + Gemcitabine + Cyclophosphamide + Vincristine + Prednisone) ^{5-7,23,b-g,u,gg}	Days 1,8 (Cycle 1): Gemcitabine 750mg/m ² IV over 30 minutes, if tolerated followed by: Days 1,8 (Cycle 2): Gemcitabine 875mg/m ² IV over 30 minutes if tolerated, followed by: Days 1,8 (Cycles 3-6): Gemcitabine 1,000mg/m ² IV over 30 minutes Day 1: Cyclophosphamide 750mg/m ² IV over 30 minutes Day 1: Vincristine 1.4mg/m ² (maximum 2 mg) IV over 5-10 minutes Days 1-5: Prednisone 10mg orally daily Day 1: Rituximab 375mg/m ² IV. Repeat cycle every 3 weeks for 6 cycles.
First-Line Consolidation (Optional)	
Lenalidomide Maintenance (Category 2B) (for patients 60–80 years of age) ^{25,26}	Days 1-21: Lenalidomide 25mg orally daily. Repeat cycle every 4 weeks for 2 years.
Concurrent Presentation With CNS Disease	
Parenchymal Disease	
High-Dose Methotrexate on Day 15 of 3-week RCHOP cycle ^{27c,p,q}	Day 15 of each 3-week R-CHOP cycle: Methotrexate 3,000-3,500mg/m ² IV over 4 hours Day 16: Leucovorin 25 mg IV over 15 minutes OR orally starting 24 hours from initiation of Methotrexate infusion and continuing every 6 hours (until methotrexate serum concentration is <0.05 micromol/L).
Leptomeningeal Disease	
IT Methotrexate + Cytarabine (CNS Prophylaxis) ^{28,29}	Day 1: Cytarabine 50-100mg intrathecal, with: Day 1: Methotrexate 12-15mg intrathecal, with: Day 1: Hydrocortisone 50-100mg (preservative-free) intrathecal. Frequency and duration are dependent on risk of patient and CNS status.

continued

B-Cell Lymphomas: Diffuse Large B-Cell Lymphoma

► Diffuse Large B-Cell Lymphoma¹ (continued)

REGIMEN	DOSING
Concurrent Presentation With CNS Disease (continued)	
Leptomeningeal Disease (continued)	
High-Dose Methotrexate in combination with RCHOP or as consolidation after RCHOP + IT Methotrexate + Cytarabine ^{27b,g,p,q}	<p>Dependent on chemotherapy regimen given and count recovery for 1-8 cycles.</p> <p>Day 1 on alternate cycles of chemotherapy regimen: Methotrexate 3,000-3,500mg/m² IV over 4 hours.</p> <p>Day 2 starting 24 hours from initiation of Methotrexate infusion and continuing every 6 hours (until methotrexate serum concentration is <0.05 micromol/L): Leucovorin 25mg IV over 25 minutes or orally.</p>
Second-Line And Subsequent Therapy (Intention to Proceed To Transplant) ^{1,r,s}	
Preferred Regimens	
DHAP (Dexamethasone + Cisplatin + Cytarabine) ^{30,c,t,u}	<p>Days 1-4: Dexamethasone 40mg orally OR IV daily</p> <p>Day 1: Cisplatin 100mg/m² IV continuous infusion over 24 hours</p> <p>Day 2: Cytarabine 2,000mg/m² (age ≤70 years) IV over 3 hours every 12 hours for 2 doses, OR:</p> <p>Day 2: Cytarabine 1,000mg/m² (age >70 years) IV over 3 hours every 12 hours for 2 doses.</p> <p>Repeat cycle every 3 or 4 weeks for 6-10 cycles.</p>
DHAP (Dexamethasone + Cisplatin + Cytarabine) + Rituximab ^{5,7,30,31,c,g,t,u}	<p>Day 1: Rituximab 375mg/m² IV</p> <p>Days 1-4: Dexamethasone 40mg orally OR IV daily</p> <p>Day 1: Cisplatin 100mg/m² IV continuous infusion over 24 hours</p> <p>Day 2: Cytarabine 2,000mg/m² (age ≤70 years) IV over 3 hours every 12 hours for 2 doses, OR:</p> <p>Day 2: Cytarabine 1,000mg/m² (age >70 years) IV over 3 hours every 12 hours for 2 doses.</p> <p>Repeat cycle every 3 or 4 weeks for 6-10 cycles.</p>
DHAX (Dexamethasone + Cytarabine + Oxaliplatin) ^{32,33,c,t,u}	<p>Days 1-4: Dexamethasone 40mg IV OR orally</p> <p>Day 2: Cytarabine 2,000mg/m² (age ≤70 years) IV over 3 hours every 12 hours for 2 doses, OR:</p> <p>Day 2: Cytarabine 1,000mg/m² (age >70 years) IV over 3 hours every 12 hours for 2 doses</p> <p>Day 1: Oxaliplatin 130mg/m² IV over 2 hours.</p> <p>Repeat cycle every 3 weeks for 2-6 cycles.</p>
DHAX (Dexamethasone + Cytarabine + Oxaliplatin) + Rituximab ^{33,34,c,g,t,u}	<p>Days 1-4: Dexamethasone 40mg IV OR orally</p> <p>Day 2: Cytarabine 2,000mg/m² (age ≤70 years) IV over 3 hours every 12 hours for 2 doses, OR:</p> <p>Day 2: Cytarabine 1,000mg/m² (age >70 years) IV over 3 hours every 12 hours for 2 doses</p> <p>Day 1: Oxaliplatin 130mg/m² IV over 2 hours</p> <p>Day 1: Rituximab 375mg/m² IV.</p> <p>Repeat cycle every 3 weeks for 2-6 cycles.</p>
Gemcitabine + Dexamethasone + Carboplatin ^{35,h,i,u}	<p>Days 1,8: Gemcitabine 1,000mg/m² IV over 30 minutes</p> <p>Days 1-4: Dexamethasone 40mg orally OR IV</p> <p>Day 1: Carboplatin AUC 5 IV over 30 minutes.</p> <p>Repeat cycle every 3 weeks for 4 cycles.</p>
Gemcitabine + Dexamethasone + Carboplatin + Rituximab ^{5,7,35,d,i,u}	<p>Days 1,8: Gemcitabine 1,000mg/m² IV over 30 minutes</p> <p>Days 1-4: Dexamethasone 40mg orally OR IV</p> <p>Day 1: Carboplatin AUC 5 IV over 30 minutes.</p> <p>Day 1: Rituximab 375mg/m² IV.</p> <p>Repeat cycle every 3 weeks for 4 cycles.</p>
GDP (Gemcitabine + Dexamethasone + Cisplatin) ^{36,h,i,t,u}	<p>Days 1,8: Gemcitabine 1,000mg/m² IV over 30 minutes</p> <p>Days 1-4: Dexamethasone 40mg orally OR IV</p> <p>Day 1: Cisplatin 75mg/m² IV over 60 minutes.</p> <p>Repeat cycle every 3 weeks for 6 cycles.</p>
GDP (Gemcitabine + Dexamethasone + Cisplatin) + Rituximab ^{5,7,36,37,d-i,t,u}	<p>Days 1,8: Gemcitabine 1,000mg/m² IV over 30 minutes</p> <p>Days 1-4: Dexamethasone 40mg orally OR IV</p> <p>Day 1: Cisplatin 75mg/m² IV over 60 minutes.</p> <p>Day 1: Rituximab 375mg/m² IV.</p> <p>Repeat cycle every 3 weeks for 6 cycles.</p>
ICE (Ifosfamide + Carboplatin + Etoposide) ^{38,c,j,u}	<p>Day 2: Ifosfamide 5,000mg/m² IV continuous infusion over 24 hours</p> <p>Day 2: Mesna 5,000mg/m² IV continuous infusion over 24 hours</p> <p>Day 2: Carboplatin AUC 5 IV over 30 minutes</p> <p>Days 1-3: Etoposide 100mg/m² IV over 60 minutes daily.</p> <p>Repeat cycle every 2 weeks for 3 cycles.</p>

continued

B-Cell Lymphomas: Diffuse Large B-Cell Lymphoma

► Diffuse Large B-Cell Lymphoma¹ (continued)

REGIMEN	DOSING
Second-Line And Subsequent Therapy (Intention to Proceed To Transplant)^{1,r,s} (continued)	
Preferred Regimens (continued)	
ICE (Ifosfamide + Carboplatin + Etoposide) + Rituximab ^{5-7,39,c,g,j,u}	Days 1-3: Etoposide 100mg/m ² IV over 60 minutes Day 2: Ifosfamide 5,000mg/m ² IV continuous infusion over 24 hours Day 2: Mesna 5,000mg/m ² IV continuous infusion over 24 hours Day 2: Carboplatin AUC 5 IV over 30 minutes Day 1: Rituximab 375mg/m ² IV. Repeat cycle every 2 weeks for 3 cycles.
Other Recommended Regimens	
ESHAP (Etoposide + Methylprednisolone + Cytarabine + Cisplatin) ^{40,c,t,u}	Days 1-4: Etoposide 40mg/m ² IV over 60 minutes daily Days 1-5: Methylprednisolone 50 mg IV over 15 minutes daily Day 5: Cytarabine 2,000mg/m ² IV over 3 hours Days 1-4: Cisplatin 25mg/m ² IV continuous infusion over 24 hours daily Repeat cycle every 3 or 4 weeks for 6-8 cycles.
ESHAP (Etoposide + Methylprednisolone + Cytarabine + Cisplatin) + Rituximab ^{5-7,40,41,c,g,t,u}	Days 1-4: Etoposide 40mg/m ² IV over 60 minutes daily Days 1-5: Methylprednisolone 500mg IV over 15 minutes daily Day 5: Cytarabine 2,000mg/m ² IV over 3 hours Days 1-4: Cisplatin 25mg/m ² IV continuous infusion over 24 hours daily Day 1: Rituximab 375mg/m ² IV. Repeat cycle every 3 or 4 weeks for 6-8 cycles.
GemOX (Gemcitabine + Oxaliplatin) ^{42-44,u}	Day 1: Gemcitabine 1,000mg/m ² IV over 30 minutes Day 1: Oxaliplatin 100mg/m ² IV over 2 hours. Repeat cycle every 2 weeks (preferred) for 6 cycles or every 3 weeks for 6 cycles.
GemOX (Gemcitabine + Oxaliplatin) + Rituximab ^{5-7,d-g,u}	Day 1: Gemcitabine 1,000mg/m ² IV over 30 minutes Day 1: Oxaliplatin 100mg/m ² IV over 2 hours Day 1: Rituximab 375mg/m ² IV. Repeat cycle every 2 weeks (preferred) for 6 cycles or every 3 weeks for 6 cycles.
MINE (Mesna + Ifosfamide + Mitoxantrone + Etoposide) ^{45,c,j,u}	Days 1-3: Mesna 400mg/m ² IV over 15 minutes three times daily (before Ifosfamide, then at 4 and 8 hours from the start of each Ifosfamide dose) Days 1-3: Ifosfamide 2,000mg/m ² over 3 hours daily Day 1: Mitoxantrone 8mg/m ² IV over 30 minutes. Days 1-3: Etoposide 100mg/m ² IV over 60 minutes. Repeat cycle every 3 weeks for 3 cycles.
MINE (Mesna + Ifosfamide + Mitoxantrone + Etoposide) + Rituximab ^{5-7,45,c-g,j,u}	Days 1-3: Mesna 400mg/m ² IV over 15 minutes three times daily (before Ifosfamide, then at 4 and 8 hours from the start of each Ifosfamide dose) Days 1-3: Ifosfamide 2,000mg/m ² over 3 hours daily Day 1: Mitoxantrone 8mg/m ² IV over 30 minutes Days 1-3: Etoposide 100mg/m ² IV over 60 minutes Day 1 (Cycles 1-3): Rituximab 375mg/m ² IV, followed by: Day 7 (Cycle 3): Rituximab 375mg/m ² IV. Repeat cycle every 3 weeks for 3 cycles.
Second-Line and Subsequent Therapy (non-candidates for transplant)^{1,r,s}	
Preferred Regimens	
GemOX (Gemcitabine + Oxaliplatin) ^{42-44,u}	Day 1: Gemcitabine 1,000mg/m ² IV over 30 minutes Day 1: Oxaliplatin 100mg/m ² IV over 2 hours. Repeat cycle every 2 weeks (preferred) for 6 cycles or every 3 weeks for 6 cycles.
GemOX (Gemcitabine + Oxaliplatin) + Rituximab ^{5-7,42-44,d-g,u}	Day 1: Gemcitabine 1,000mg/m ² IV over 30 minutes Day 1: Oxaliplatin 100mg/m ² IV over 2 hours Day 1: Rituximab 375mg/m ² IV. Repeat cycle every 2 weeks (preferred) for 6 cycles or every 3 weeks for 6 cycles.
Polatuzumab Vedotin-piiq ^{46-49,i,u,v}	Day 1: Polatuzumab Vedotin-piiq 1.8mg/kg IV over 90 minutes Repeat cycle every 3 weeks for 6 cycles.
Polatuzumab Vedotin-piiq + Bendamustine + Rituximab ^{5-7,48-51,d-g,i,u,v,w,x}	Days 1-2: Bendamustine 90mg/m ² IV over 10-60 minutes daily Day 1: Polatuzumab Vedotin-piiq 1.8mg/kg IV over 90 minutes Day 1: Rituximab 375mg/m ² IV. Repeat cycle every 3 weeks for 6 cycles.

continued

B-Cell Lymphomas: Diffuse Large B-Cell Lymphoma

► Diffuse Large B-Cell Lymphoma¹ (continued)

REGIMEN	DOSING
Second-Line and Subsequent Therapy (non-candidates for transplant)^{1,r,s} (continued)	
Preferred Regimens (continued)	
Polatuzumab Vedotin-piiq + Rituximab ^{5-7,46,48,50,d-g,i,u,v,w,u}	Day 1: Polatuzumab Vedotin-piiq 1.8mg/kg IV over 90 minutes Day 1: Rituximab 375mg/m ² IV. Repeat cycle every 3 weeks for 6 cycles.
Other Recommended Regimens	
CEPP (Cyclophosphamide + Etoposide + Prednisone + Procarbazine) ^{22,b,u}	Days 1,8: Cyclophosphamide 600mg/m ² IV over 30 minutes Days 1-3: Etoposide 70mg/m ² IV over 60 minutes daily Days 1-10: Procarbazine 60mg/m ² orally daily Days 1-10: Prednisone 60mg/m ² orally daily. Repeat cycle every 4 weeks for 6 cycles.
RCEPP (Rituximab + Cyclophosphamide + Etoposide + Prednisone + Procarbazine) ^{5-7,22,b,d-g,u,gg}	Days 1,8: Cyclophosphamide 600mg/m ² IV over 30 minutes Days 1-3: Etoposide 70mg/m ² IV over 60 minutes daily Days 1-10: Procarbazine 60mg/m ² orally once daily Days 1-10: Prednisone 60mg/m ² orally once daily Day 1: Rituximab 375 mg/m ² IV. Repeat cycle every 4 weeks for 6 cycles.
CEOP (Cyclophosphamide + Etoposide + Vincristine + Prednisone) ^{21,b,u}	Day 1: Cyclophosphamide 750 mg/m ² IV over 30 minutes Day 1: Etoposide 50mg/m ² IV over 60 minutes, followed by: Days 2-3: Etoposide 50mg/m ² IV over 60 minutes daily, OR Day 1: Etoposide 50mg/m ² IV over 60 minutes, followed by: Days 2-3: Etoposide 100mg/m ² orally once daily. Day 1: Vincristine 1.4mg/m ² (maximum 2 mg) IV over 5-10 minutes Days 1-5: Prednisone 100mg orally daily. Repeat cycle every 3 weeks for 6 cycles.
RCEOP (Rituximab + Cyclophosphamide + Etoposide + Vincristine + Prednisone) ^{5-7,21,b,d-g,u,gg}	Day 1: Cyclophosphamide 750 mg/m ² IV over 30 minutes Day 1: Etoposide 50mg/m ² IV over 60 minutes, followed by: Days 2-3: Etoposide 50mg/m ² IV over 60 minutes daily, OR Day 1: Etoposide 50mg/m ² IV over 60 minutes, followed by: Days 2-3: Etoposide 100mg/m ² orally once daily. Day 1: Vincristine 1.4mg/m ² (maximum 2 mg) IV over 5-10 minutes Days 1-5: Prednisone 100mg orally daily Day 1: Rituximab 375 mg/m ² IV. Repeat cycle every 3 weeks for 6 cycles.
Dose-adjusted EPOCH (Etoposide + Prednisone + Vincristine + Cyclophosphamide + Doxorubicin) ^{3,18,19,a-g,u}	Days 1-4 (Cycle 1): Etoposide 50mg/m ² IV continuous infusion over 24 hours daily, followed by: Days 1-4 (Cycle 2 and beyond): Etoposide IV continuous infusion over 24 hours daily ^a , with: Days 1-4 (Cycle 1): Vincristine 0.4mg/m ² IV continuous infusion over 24 hours daily, with: Days 1-4 (Cycle 1): Doxorubicin 10mg/m ² continuous infusion over 24 hours daily ^a , followed by: Days 1-4 (Cycle 2 and beyond): Doxorubicin IV continuous infusion over 24 hours daily Day 5 (Cycle 1): Cyclophosphamide 750mg/m ² IV over 30 minutes, followed by: Day 5 (Cycle 2 and beyond): Cyclophosphamide IV over 30 minutes ^a Days 1-5: Prednisone 60mg/m ² orally twice daily. Repeat cycle every 3 weeks for 6 cycles.
Dose-adjusted EPOCH (Etoposide + Prednisone + Vincristine + Cyclophosphamide + Doxorubicin) + Rituximab ^{2,3,5-7,18,a-g,u,gg}	Days 1-4 (Cycle 1): Etoposide 50mg/m ² IV continuous infusion over 24 hours daily, followed by: Days 1-4 (Cycle 2 and beyond): Etoposide IV continuous infusion over 24 hours daily ^a , with: Days 1-4: Vincristine 0.4mg/m ² IV continuous infusion over 24 hours daily, with: Days 1-4: (Cycle 1) Doxorubicin 10mg/m ² continuous infusion over 24 hours daily, followed by: Days 1-4 (Cycle 2 and beyond): Doxorubicin IV continuous infusion over 24 hours daily ^a Day 5 (Cycle 1): Cyclophosphamide 750mg/m ² IV over 30 minutes, followed by: Day 5 (Cycle 2 and beyond): Cyclophosphamide IV over 30 minutes ^a Days 1-5: Prednisone 60mg/m ² orally twice daily Day 1: Rituximab 375 mg/m ² IV. Repeat cycle every 3 weeks for 6 cycles.
Gemcitabine + Dexamethasone + Carboplatin ^{35,h,i,u}	Days 1,8: Gemcitabine 1,000mg/m ² IV over 30 minutes Days 1-4: Dexamethasone 40mg orally OR IV Day 1: Carboplatin AUC 5 IV over 30 minutes. Repeat cycle every 3 weeks for 4 cycles.

continued

B-Cell Lymphomas: Diffuse Large B-Cell Lymphoma

► Diffuse Large B-Cell Lymphoma¹ (continued)

REGIMEN	DOSING
Second-Line and Subsequent Therapy (non-candidates for transplant)^{1,rs} (continued)	
Other Recommended Regimens (continued)	
Gemcitabine + Dexamethasone + Carboplatin + Rituximab ^{5-7,35,d-i,u}	Days 1,8: Gemcitabine 1,000mg/m ² IV over 30 minutes Days 1-4: Dexamethasone 40mg orally OR IV Day 1: Carboplatin AUC 5 IV over 30 minutes. Day 1: Rituximab 375mg/m ² IV. Repeat cycle every 3 weeks for 4 cycles.
GDP (Gemcitabine + Dexamethasone + Cisplatin) ^{36,h,i,u,t}	Days 1,8: Gemcitabine 1,000mg/m ² IV over 30 minutes Days 1-4: Dexamethasone 40mg orally OR IV Day 1: Cisplatin 75mg/m ² IV over 60 minutes. Repeat cycle every 3 weeks for 6 cycles.
GDP (Gemcitabine + Dexamethasone + Cisplatin) + Rituximab ^{5-7,36,37,d-i,u,t}	Days 1,8: Gemcitabine 1,000mg/m ² IV over 30 minutes Days 1-4: Dexamethasone 40mg orally OR IV Day 1: Cisplatin 75mg/m ² IV over 60 minutes. Day 1: Rituximab 375mg/m ² IV. Repeat cycle every 3 weeks for 6 cycles.
Gemcitabine + Vinorelbine (Category 3) ^{52,h,i,u}	Days 1,8: Gemcitabine 1,000mg/m ² IV over 30 minutes Days 1,8: Vinorelbine 30mg/m ² IV over 5-10 minutes. Repeat cycle every 3 weeks for a maximum of 6 cycles.
Gemcitabine + Vinorelbine + Rituximab (Category 3) ^{5-7,52,53,d-i,u}	Days 1,8: Gemcitabine 1,000mg/m ² IV over 30 minutes Days 1,8: Vinorelbine 30mg/m ² IV over 5-10 minutes Day 1: Rituximab 375mg/m ² IV. Repeat cycle every 3 weeks for a maximum of 6 cycles.
Rituximab ^{5-7,54,d-g,u}	Day 1: Rituximab 375mg/m ² IV. Repeat cycle every week for 8 weeks.
Tafasitamab-cxix + Lenalidomide ^{26,55,56,i,y,z}	Days 1,4,8,15,22 (Cycle 1): Tafasitamab-cxix 12mg/kg IV, followed by: Days 1,8,15,22 (Cycles 2-3): Tafasitamab-cxix 12mg/kg IV, followed by: Days 1,15 (Cycle 4 and beyond): Tafasitamab-cxix 12mg/kg IV, with: Days 1-21 (Cycles 1-12): Lenalidomide 25mg orally daily. Repeat cycle every 4 weeks for 12 cycles, followed by: Days 1,15: Tafasitamab-cxix 12mg/kg IV. Repeat cycle every 4 weeks.
Useful In Certain Circumstances	
Brentuximab vedotin (for CD30-positive disease) ^{16,57,k,u}	Day 1: Brentuximab vedotin 1.8mg/kg (maximum 180 mg) IV over 30 minutes. Repeat cycle every 3 weeks.
Bendamustine (Category 2B) ^{49,58,u}	Days 1-2: Bendamustine 120mg/m ² IV over 10-60 minutes. Repeat cycle every 3 weeks for 6 cycles.
Bendamustine + Rituximab (Category 2B) ^{5-7,49,59,60,d,g,u}	Days 1-2: Bendamustine 120mg/m ² IV over 10-60 minutes Day 1: Rituximab 375mg/m ² IV. Repeat cycle every 3 weeks for 6 cycles.
Ibrutinib (non-GCB-like DLBCL) ^{61,62,h,aa}	Days 1-28: Ibrutinib 560mg orally daily. Repeat cycle every 4 weeks.
Lenalidomide (non-GCB-like DLBCL) ^{26,63,64,h,u}	Days 1-21: Lenalidomide 25mg orally daily. Repeat cycle every 4 weeks.
Lenalidomide + Rituximab (non-GCB-like DLBCL) ^{5-7,26,65,d-h,u}	Days 1-21: Lenalidomide 20mg orally daily Days 1,8,15,22: Rituximab 375mg/m ² IV. Administer for one 4-week cycle, followed by: Days 1-21: Lenalidomide 20mg orally daily. Repeat cycle every 4 weeks.
Consolidation After Alternate Second-Line Therapy	
Allogeneic hematopoietic cell transplant (Nonmyeloablative or Myeloablative) for CR/PR following alternative second-line therapy. ^h	
Third-Line And Subsequent Therapy (only after ≥2 lines of systemic therapy)	
Anti-CD19 CAR T-cell therapy (only after ≥2 prior chemoimmunotherapy regimens) ^{h,x}	
<ul style="list-style-type: none"> • Axicabtagene ciloleucel • Lisocabtagene maraleucel • Tisagenlecleucel^{bb} 	

continued

B-Cell Lymphomas: Diffuse Large B-Cell Lymphoma

► Diffuse Large B-Cell Lymphoma¹ (continued)

REGIMEN	DOSING
Third-Line And Subsequent Therapy (only after ≥2 lines of systemic therapy) (continued)	
Loncastuximab Tesirine ^{66,67,u,z,cc}	<p>Day 1: Loncastuximab Tesirine-Ipyl 0.15 mg/kg IV over 30 minutes. Repeat cycle every 3 weeks for 2 cycles. followed by:</p> <p>Day 1: Loncastuximab tesirine-Ipyl 0.075 mg/kg IV over 30 minutes. Repeat cycle every 3 weeks.</p>
Selinexor (only after ≥2 lines of systemic therapy, including patients with disease progression after transplant or CAR-T therapy) ^{68,69,dd}	<p>Days 1,3,8,10,15,17,22,24: Selinexor 60mg orally. Repeat cycle for 4 weeks.</p>

► High-Grade B-Cell Lymphomas with Translocations of *MYC* and *BCL2* and/or *BCL6* (Double-/Triple-Hit Lymphoma)^z

Dose-adjusted EPOCH-R (Etoposide + Prednisone + Vincristine + Cyclophosphamide + Doxorubicin) + Rituximab ^{2-7,a-g,u,gg}	<p>Days 1-4 (Cycle 1): Etoposide 50mg/m² IV continuous infusion over 24 hours daily, followed by:</p> <p>Days 1-4 (Cycle 2 and beyond): Etoposide IV continuous infusion over 24 hours daily^a, with:</p> <p>Days 1-4 (Cycle 1): Vincristine 0.4mg/m² IV continuous infusion over 24 hours daily, with:</p> <p>Days 1-4 (Cycle 1): Doxorubicin 10mg/m² IV continuous infusion over 24 hours daily^a, followed by:</p> <p>Days 1-4 (Cycle 2 and beyond): Doxorubicin IV continuous infusion over 24 hours daily</p> <p>Day 5 (Cycle 1): Cyclophosphamide 750mg/m² IV over 30 minutes, followed by:</p> <p>Day 5 (Cycle 2 and beyond): Cyclophosphamide IV over 30 minutes^a</p> <p>Day 1: Rituximab 375mg/m² IV</p> <p>Days 1-5: Prednisone 60mg/m² orally twice daily. Repeat cycle every 3 weeks for 6 cycles.</p>
R-HyperCVAD (Rituximab + Cyclophosphamide + Vincristine + Doxorubicin, + Dexamethasone) alternating with High-dose Methotrexate and Cytarabine ^{5-7,70,71,b-g,p,u}	<p>Cycle A</p> <p>Days 1-3: Cyclophosphamide 300mg/m² IV over 3 hours every 12 hours for 6 doses</p> <p>Days 1-3: Mesna 600mg/m² IV continuous infusion over 24 hours starting 1 hour before the first dose of Cyclophosphamide and completing 12 hours after the last dose of Cyclophosphamide</p> <p>Days 4,11: Vincristine 1.4mg/m² (maximum 2mg) IV over 5-10 minutes</p> <p>Day 4: Doxorubicin 50mg/m² IV push</p> <p>Days 1-4,11-14: Dexamethasone 40mg IV OR orally</p> <p>Day 1: Rituximab 375mg/m² IV.</p> <p>Repeat cycle every 3 weeks for 4 cycles (A1, A2, A3 and A4), alternating with Cycle B course.</p> <p>Cycle B</p> <p>Day 1: Methotrexate 200mg/m² IV over 2 hours, followed by:</p> <p>Day 1: Methotrexate 800mg/m² IV over 22 hours</p> <p>12 hours after completion of Methotrexate Infusion: Leucovorin 50mg IV over 15 minutes OR orally, followed by:</p> <p>Every 6 hours for at least 8 doses (until Methotrexate serum concentration is <0.5micromol/L): Leucovorin 15mg IV over 15 minutes OR orally</p> <p>Days 2-3: Cytarabine (age ≤60 years) 3,000mg/m² IV over 3 hours every 12 hours for 4 doses OR</p> <p>Days 2-3: Cytarabine (age >60 years) 1,000mg/m² IV over 3 hours every 12 hours for 4 doses</p> <p>Day 1: Rituximab 375mg/m² IV.</p> <p>Repeat cycle every 3 weeks for 4 cycles (B1, B2, B3, B4), alternating with Cycle A course for a total of 8 cycles (A1, B1, A2, B2, A3, B3, A4, B4).</p>
R-CODOX-M/R-IVAC (Rituximab-Cyclophosphamide + Vincristine + Doxorubicin with Methotrexate/ Ifosfamide + Etoposide + Cytarabine) ^{5-7,72-74,b-g,i,u}	<p>Cycle A</p> <p>Days 1-2: Cyclophosphamide 800mg/m² IV over 30 minutes daily</p> <p>Days 1,15: Vincristine 1.4mg/m² (maximum 2mg) IV over 5-10 minutes.</p> <p>Day 1: Doxorubicin 50mg/m² IV push</p> <p>Day 15: Methotrexate 3,000mg/m² IV over 4 hours.</p> <p>Day 11: Leucovorin 200mg/m² IV over 15 minutes starting 24 hours from the initiation of Methotrexate infusion, followed by:</p> <p>Leucovorin 15mg/m² IV over 15 minutes OR orally every 6 hours (until Methotrexate serum concentration is <0.05micromol/L)</p> <p>Day 1: Rituximab 375mg/m² IV</p> <p>Days 1,3: Cytarabine 50mg intrathecal.</p> <p>Day 1: Methotrexate 12mg intrathecal</p> <p>Repeat cycle every 4 weeks (or when post-nadir ANC is ≥1000 cells/mm³) for 2 cycles (A1, A2) alternating with Cycle B.</p>

continued

B-Cell Lymphomas: Diffuse Large B-Cell Lymphoma

► High-Grade B-Cell Lymphomas with Translocations of *MYC* and *BCL2* and/or *BCL6* (Double-/Triple-Hit Lymphoma)^z (continued)

REGIMEN	DOSING
R-CODOX-M/R-IVAC (Rituximab-Cyclophosphamide + Vincristine + Doxorubicin with Methotrexate/ Ifosfamide + Etoposide + Cytarabine) ^{5-7,72-74,b,g,j,u} (continued)	<p>Cycle B Days 1-5: Ifosfamide 1,500mg/m² IV over 3 hours daily, with: Days 1-5: Mesna 500mg/m² IV over 15 minutes three times daily (before Ifosfamide, then at 4 and 8 hours from start of each Ifosfamide dose) Days 1-5: Etoposide 60mg/m² IV over 60 minutes daily Days 1-2: Cytarabine 2,000mg/m² IV over 3 hours every 12 hours for 4 doses Day 1: Rituximab 375mg/m² IV Day 5: Methotrexate 12 mg intrathecal. Repeat cycle every 4 weeks (or when post-nadir ANC is ≥1000 cells/mm³) for 2 cycles (B1, B2) alternating with Cycle A for a total of 4 cycles (A1, B1, A2, B2).</p>

► High-Grade B-Cell Lymphomas, NOS^{ee}

RCHOP (Rituximab + Cyclophosphamide + Doxorubicin + Vincristine + Prednisone) ^{5-8,b,d,g}	<p>Day 1: Cyclophosphamide 750 mg/m² IV over 30 minutes Day 1: Doxorubicin 50mg/m² IV push Day 1: Vincristine 1.4mg/m² (maximum 2 mg) IV over 5-10 minutes Day 1-5: Prednisone 100mg orally once daily Day 1: Rituximab 375mg/m² IV. Repeat cycle every 3 weeks for 6 cycles.</p>
Dose-adjusted EPOCH-R (Etoposide + Prednisone + Vincristine + Cyclophosphamide + Doxorubicin) + Rituximab ^{2-7,a,b,d,g}	<p>Days 1-4 (Cycle 1): Etoposide 50mg/m² IV continuous infusion over 24 hours daily, followed by: Days 1-4 (Cycle 2 and beyond): Etoposide IV continuous infusion over 24 hours daily^a, with: Days 1-4 (Cycle 1): Vincristine 0.4mg/m² IV continuous infusion over 24 hours daily, with: Days 1-4 (Cycle 1): Doxorubicin 10mg/m² IV continuous infusion over 24 hours daily^a, followed by: Days 1-4 (Cycle 2 and beyond): Doxorubicin IV continuous infusion over 24 hours daily Day 5 (Cycle 1): Cyclophosphamide 750mg/m² IV over 30 minutes, followed by: Day 5 (Cycle 2 and beyond): Cyclophosphamide IV over 30 minutes^a Day 1: Rituximab 375mg/m² IV Days 1-5: Prednisone 60mg/m² orally twice daily. Repeat cycle every 3 weeks for 6 cycles.</p>
R-HyperCVAD (Rituximab + Cyclophosphamide + Vincristine + Doxorubicin, + Dexamethasone) alternating with High-dose Methotrexate and Cytarabine ^{5-7,70,71,b,g,p,ff}	<p>Cycle A Days 1-3: Cyclophosphamide 300mg/m² IV over 3 hours every 12 hours for 6 doses Days 1-3: Mesna 600mg/m² IV continuous infusion over 24 hours starting 1 hour before the first dose of Cyclophosphamide and completing 12 hours after the last dose of Cyclophosphamide Days 4,11: Vincristine 1.4mg/m² (maximum 2mg) IV over 5-10 minutes Day 4: Doxorubicin 50mg/m² IV push Days 1-4,11-14: Dexamethasone 40mg IV OR orally Day 1: Rituximab 375mg/m² IV. Repeat cycle every 3 weeks for 4 cycles (A1, A2, A3 and A4), alternating with Cycle B course. Cycle B Day 1: Methotrexate 200mg/m² IV over 2 hours, followed by: Day 1: Methotrexate 800mg/m² IV over 22 hours 12 hours after completion of Methotrexate Infusion: Leucovorin 50mg IV over 15 minutes OR orally, followed by: Every 6 hours for at least 8 doses (until Methotrexate serum concentration is <0.5micromol/L): Leucovorin 15mg IV over 15 minutes OR orally Days 2-3: Cytarabine (age ≤60 years) 3,000mg/m² IV over 3 hours every 12 hours for 4 doses OR Days 2-3: Cytarabine (age >60 years) 1,000mg/m² IV over 3 hours every 12 hours for 4 doses Day 1: Rituximab 375mg/m² IV. Repeat cycle every 3 weeks for 4 cycles (B1, B2, B3, B4), alternating with Cycle A course for a total of 8 cycles (A1, B1, A2, B2, A3, B3, A4, B4).</p>
R-CODOX-M/R-IVAC (Rituximab-Cyclophosphamide + Vincristine + Doxorubicin with Methotrexate/ Ifosfamide + Etoposide + Cytarabine) ^{5-7,72-74,b,g,j,ff}	<p>Cycle A Days 1-2: Cyclophosphamide 800mg/m² IV over 30 minutes daily Days 1,15: Vincristine 1.4mg/m² (maximum 2mg) IV over 5-10 minutes. Day 1: Doxorubicin 50mg/m² IV push Day 15: Methotrexate 3,000mg/m² IV over 4 hours. Day 11: Leucovorin 200mg/m² IV over 15 minutes starting 24 hours from the initiation of Methotrexate infusion, followed by: Leucovorin 15mg/m² IV over 15 minutes OR orally every 6 hours (until Methotrexate serum concentration is <0.05micromol/L) Day 1: Rituximab 375mg/m² IV Days 1,3: Cytarabine 50mg intrathecal. Day 1: Methotrexate 12mg intrathecal Repeat cycle every 4 weeks (or when post-nadir ANC is ≥1000 cells/mm³) for 2 cycles (A1, A2) alternating with Cycle B.</p>

continued

B-Cell Lymphomas: Diffuse Large B-Cell Lymphoma

► High-Grade B-Cell Lymphomas, NOS^{ee} (continued)

REGIMEN	DOSING
R-CODOX-M/R-IVAC (Rituximab-Cyclophosphamide + Vincristine + Doxorubicin with Methotrexate/ Ifosfamide + Etoposide + Cytarabine) ^{5-7,72-74,b-g,i,ff} (continued)	Cycle B Days 1-5: Ifosfamide 1,500mg/m ² IV over 3 hours daily, with: Days 1-5: Mesna 500mg/m ² IV over 15 minutes three times daily (before Ifosfamide, then at 4 and 8 hours from start of each Ifosfamide dose) Days 1-5: Etoposide 60mg/m ² IV over 60 minutes daily Days 1-2: Cytarabine 2,000mg/m ² IV over 3 hours every 12 hours for 4 doses Day 1: Rituximab 375mg/m ² IV Day 5: Methotrexate 12 mg intrathecal. Repeat cycle every 4 weeks (or when post-nadir ANC is ≥1000 cells/mm ³) for 2 cycles (B1, B2) alternating with Cycle A for a total of 4 cycles (A1, B1, A2, B2).

- ^a Dosing for cycle 2 and beyond based on absolute neutrophil count and platelet nadir measurements during the previous cycle.
- ^b Oral hydration is strongly encouraged with Cyclophosphamide; poorly hydrated patients may need supplemental IV hydration. Patients should attain combined oral and IV hydration of 2,000-3,000 mL/day on day of chemotherapy.
- ^c Supportive care includes myeloid growth factor support with filgrastim or pegfilgrastim.
- ^d Rituximab and hyaluronidase human for subcutaneous injection may be substituted for Rituximab in patients who have received one full dose of a Rituximab product by intravenous route without experiencing severe adverse reactions. Dose: Rituximab and hyaluronidase human 1,400 mg subcutaneous.⁷
- ^e Initiate treatment with Rituximab and hyaluronidase human only after a patient has received at least one full dose of a Rituximab product by intravenous infusion.
- ^f An FDA-approved biosimilar is an appropriate substitute for Rituximab.
- ^g For Rituximab, premedication for infusion reactions is required. The recommended dosing is: diphenhydramine 12.5-50mg IV OR oral 30-40 minutes pre-Rituximab AND acetaminophen 650mg orally 30-40 minutes pre-Rituximab.
- ^h CAR, chimeric antigen receptor; CNS, central nervous system; CR, complete response; CSFs, colony-stimulating factors; DLBCL, diffuse large b-cell lymphoma; FDA, U.S. Food and Drug Administration; GCB, Germinal Center B-cell; HGBL, high-grade B-cell lymphoma; ISRT, involved site radiation therapy; IT, intrathecal; NOS, not otherwise specified; PR, partial response.
- ⁱ CSFs may be considered for primary prophylaxis based on the febrile neutropenia risk of the chemotherapy regimen.
- ^j Hydration is required pre- and post-administration of Ifosfamide.
- ^k For Brentuximab Vedotin: Consider premedication for hypersensitivity. Acetaminophen 650-1000mg orally 30-40 minutes pre-Brentuximab Vedotin AND diphenhydramine 12.5-50mg IV or orally 30-60 minutes pre-Brentuximab Vedotin with or without corticosteroid per institutional protocol 30-40 minutes pre-Brentuximab Vedotin (consider for subsequent infusions if prior reaction).
- ^l Inclusion of any anthracycline or anthracenedione in patients with impaired cardiac functioning should have more frequent monitoring.
- ^m There are limited published data regarding use of these regimens; however, they are used at NCCN Member institutions for the first-line treatment of DLBCL for patients with poor left ventricular function, very frail patients, and patients >80 years of age with comorbidities.
- ⁿ There are limited data for treatment of early-stage disease with these regimens; however, short-course chemotherapy + RT for stage I-II disease is practiced at NCCN Member Institutions.
- ^o If upward dose adjustment is necessary, Doxorubicin should be maintained at base dose and not increased.
- ^p Alkaline hydration is required pre- and post-administration of high-dose Methotrexate.
- ^q Concurrent high-dose Methotrexate with dose adjusted EPOCH can result in unacceptable toxicities.
- ^r If additional anthracycline is administered after a full course of therapy, careful monitoring is essential. Dexrazoxane may be added as a cardioprotectant.
- ^s Rituximab should be included as second-line therapy if there is a relapse after a reasonable remission (>6 months); however, Rituximab should often be omitted in patients with primary refractory disease.
- ^t Hydration with supplemental electrolytes is required pre- and post-administration of Cisplatin.
- ^u This regimen may be associated with a risk of tumor lysis syndrome with the first cycle. Tumor lysis prophylaxis and/or treatment may be indicated.
- ^v For Polatuzumab Vedotin-piiq: Premedication for infusion reactions is required. The recommended dosing is: diphenhydramine 12.5-50mg IV OR orally 30-40 minutes pre-Polatuzumab Vedotin-piiq AND acetaminophen 650mg orally 30-40 minutes pre-Polatuzumab Vedotin-piiq.
- ^w Premedication for Polatuzumab Vedotin-piiq may be omitted if already premedicated for Rituximab within the chemotherapy regimen.
- ^x Bendamustine, Rituximab, and Polatuzumab Vedotin-piiq is indicated for the treatment of adult patients with relapsed or refractory DLBCL or HGBL, with translocations of *MYC* and *BCL2* and/or *BCL6*.
- ^y For Tafasitamab-cxix: Premedication for infusion reaction is required. The recommended dosing is: Famotidine 20mg IV or orally (or equivalent H2 blocker) 30 minutes pre-Tafasitamab-cxix AND H1 antagonist (diphenhydramine 25-50mg IV or orally 30 minutes pre-Tafasitamab-cxix AND acetaminophen 650-1,000mg orally 30 minutes pre-Tafasitamab-cxix AND/OR glucocorticoids may be considered 30 minutes pre-tafasitamab-cxix. For patients not experiencing infusion-related reactions during the first 3 infusions, premedication is option for subsequent infusions.
- ^z It is unclear whether Tafasitamab or Loncastuximab Tesirine or if any other CD-19 directed therapy would have a negative impact on the efficacy of subsequent anti-CD19 CAR T-cell therapy.
- ^{aa} This agent has multiple drug-drug interactions.
- ^{bb} Tisagenlecleucel is not FDA-approved for relapsed/refractory primary mediastinal large B-cell lymphoma.
- ^{cc} For Loncastuximab Tesirine-lpyl: premedication with dexamethasone for fluid retention is required. Dexamethasone 4mg orally or IV twice daily for 3 days beginning the day before administration. If dexamethasone administration does not begin the day before, dexamethasone should begin at least 2 hours prior to administration.
- ^{dd} Selinexor is FDA approved only for DLBCL and transformed DLBCL arising from follicular lymphoma.
- ^{ee} While the standard of care has not been established, the following induction regimens have been used at NCCN Member Institutions.
- ^{ff} Potentially toxic regimen; performance status and comorbidities should be considered.
- ^{gg} There may be an increased risk of CNS events in selected cases (4-6 factors according to prognostic model to assess risk of CNS disease, HIV-associated lymphoma, testicular lymphoma, high-grade B-cell lymphomas (HGBLs) with translocations of *MYC* and *BCL2* and/or *BCL6* (Double/Triple Hit Lymphoma), HGBLs not otherwise specified, Primary cutaneous DLBCL, leg type, stage IE DLBCL of the breast, or kidney or adrenal involvement). CNS prophylaxis can be considered (4- 8 doses of intrathecal methotrexate and/or cytarabine, or high-dose systemic methotrexate) during or after the course of treatment.

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B-Cell Lymphomas: Diffuse Large B-Cell Lymphoma

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