Central Nervous System Cancers

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.

▶Adult Glioma: WHO Grade 1[1]

REGIMEN	DOSING
Adjuvant Treatment	
Useful in Certain Circumstances (No Preferred or Other Recommended Regimens)	
Dabrafenib/Trametinib (for PA, PXA, ganglioglioma if *BRAF* V600E mutation positive)[2-5,a]	**DAYS 1-28:** Dabrafenib 150mg orally twice daily. **DAYS 1-28:** Trametinib 2mg orally once daily. Repeat cycle every 4 weeks.
Everolimus (for SEGA)[6-9,a]	**DAYS 1-28:** Everolimus 4.5mg/m^2 orally once daily (titrated to achieve blood trough concentration 5-15ng/mL). Repeat cycle every 4 weeks.
Vemurafenib/Cobimetinib (for PA, PXA, ganglioglioma if *BRAF* V600E mutation positive)[10-14,a]	**DAYS 1-21:** Cobimetinib 60mg orally once daily **DAYS 1-28:** Vemurafenib 960mg orally twice daily. Repeat cycle every 4 weeks.
Recurrent or Progressive Disease[d]	
Other Recommended Regimens (No Preferred Regimens)	
Carmustine[15-18,b]	**DAYS 1-3**: Carmustine 80mg/m^2 IV over 2 hours daily. Repeat cycle every 8 weeks or until reaching a lifetime cumulative carmustine dose for a maximum of 6 cycles. **OR** **DAY 1**: Carmustine 150-200mg/m^2 IV over 2 hours daily. Repeat cycle every 8 weeks or until reaching a lifetime cumulative carmustine dose.
Lomustine[19-21,b]	**DAY 1:** Lomustine 100-130mg/m^2 orally once daily. Repeat cycle every 6 weeks or until reaching a lifetime cumulative lomustine dose.
PCV (Procarbazine/Lomustine/ Vincristine) [19,22-27,a-c]	**DAY 1:** Lomustine 110-130mg/m^2 orally once daily **DAYS 8-21**: Procarbazine 60-75mg/m^2 orally once daily **DAYS 8,29**: Vincristine 1.4mg/m^2 (maximum 2mg) IV over 5-10 minutes. Repeat cycle every 6-8 weeks until disease progression or reaching a lifetime cumulative dose of Lomustine.
RT + adjuvant PCV (Procarbazine/Lomustine/ Vincristine) [19,22,23,28-32,a-c]	**DAY 1:** Lomustine 110mg/m^2 orally once daily **DAYS 8-21**: Procarbazine 60mg/m^2 orally once daily **DAYS 8,29**: Vincristine 1.4mg/m^2 (maximum 2mg) IV over 5-10 minutes. Repeat cycle every 6-8 weeks until disease progression or reaching a lifetime dose of Lomustine.
RT + adjuvant TMZ[33-36,a]	**DAYS 1-5**: Temozolomide 150-200mg/m^2 (increase as tolerated) orally once daily. Repeat cycle every 4 weeks for 6-12 cycles.
RT + concurrent and adjuvant TMZ[33,34,36,37,a]	**DAYS 1-42:** Temozolomide 75mg/m^2 orally once daily. Repeat cycle every 6 weeks with RT, **followed by:** **DAYS 1-5:** Temozolomide 150-200mg/m^2 (increase as tolerated) once orally daily. Repeat cycle every 4 weeks for 6-12 cycles starting 4 weeks after the completion of concurrent Temozolomide and RT.
TMZ[33,38-43,a,e]	**DAYS 1-5:** Temozolomide 150-200mg/m^2 orally once daily. Repeat cycle every 4 weeks for 12 cycles. **OR** **DAYS 1-28:** Temozolomide 50mg/m^2 orally. Repeat cycle every 4 weeks for a maximum of 12 cycles.

continued

▶Adult Glioma: WHO Grade 1[1] (continued)

REGIMEN	DOSING
Recurrent or Progressive Disease[d] (continued)	
Useful in Certain Circumstances	
Carboplatin (for pilocytic astrocytoma)[44-46]	**Day 1:** Carboplatin AUC 4-6 IV over 30 minutes. Repeat cycle every 4 weeks. **OR** **Day 1:** Carboplatin 560mg/m^2 IV over 1 hour. Repeat cycle every 4 weeks.
Carboplatin/Vincristine (for pilocytic astrocytoma) (Category 2B)[1]	See NCCN Central Nervous System Guidelines[1]
Cisplatin/Etoposide (for pilocytic astrocytoma)[47-49,f]	**Days 1-3:** Cisplatin 25mg/m^2 IV over 1 hour daily. **Days 1-3:** Etoposide 100mg/m^2 IV over 1 hour daily. Repeat cycle every 4 weeks for a maximum of 10 cycles.
Dabrafenib/Trametinib (if *BRAF* V600E mutation positive)[6-9]	**Days 1-28:** Dabrafenib 150mg orally twice daily. **Days 1-28:** Trametinib 2 mg orally once daily. Repeat cycle every 4 weeks.
Entrectinib (if *NTRK* gene fusion positive)[50-52]	**Days 1-28:** Entrectinib 600mg orally once daily. Repeat cycle every 4 weeks.
Larotrectinib (for *NTRK* gene fusion tumors)[53-56]	**Days 1-28:** Larotrectinib 100 mg orally twice daily. Repeat cycle every 4 weeks.
Selumetinib (for PA with *BRAF* fusion or *BRAF* V600E activation mutation)[57,58]	**Days 1-28:** Selumetinib 25mg/m^2 orally twice daily. Repeat cycle every 4 weeks.
Thioguanine + PCV (for pilocytic astrocytoma) (Category 2B)[1,a,c]	See NCCN Central Nervous System Guidelines[1]
Vemurafenib/Cobimetinib (if *BRAF* V600E mutation positive)[10-14]	**Days 1-21:** Cobimetinib 60mg orally daily **Days 1-28:** Vemurafenib 960mg orally twice daily. Repeat cycle every 4 weeks.

▶Adult Gliomas: Oligodendroglioma (IDH-Mutant, 1p19q Codeleted)[1]

Adjuvant Treatment WHO Grade 2 (KPS ≥60)[a]	
Preferred Regimens	
RT with adjuvant PCV (Procarbazine/Lomustine/ Vincristine) (Category 1)[19,22,23,28-32,a,c]	**Day 1:** Lomustine 110mg/m^2 orally once daily **Days 8-21**: Procarbazine 60mg/m^2 orally once daily **Days 8,29**: Vincristine 1.4mg/m^2 (maximum 2mg) IV over 5-10 minutes. Repeat cycle every 6-8 weeks for 6 cycles.
RT + adjuvant TMZ[33-36,a]	**Days 1-5**: Temozolomide 150-200mg/m^2 (increase as tolerated) orally once daily. Repeat cycle every 4 weeks for 6-12 cycles.
RT + concurrent and adjuvant TMZ[33,34,36,37,a]	**Days 1-42:** Temozolomide 75mg/m^2 orally once daily. Repeat cycle every 6 weeks with RT, **followed by:** **Days 1-5:** Temozolomide 150-200mg/m^2 (increase as tolerated) once orally daily. Repeat cycle every 4 weeks for 6-12 cycles starting 4 weeks after the completion of concurrent Temozolomide and RT.
Other Recommended Regimens	
PCV[19,22-27,a,c]	**Day 1:** Lomustine 110-130mg/m^2 orally **Days 8-21:** Procarbazine 60-75mg/m^2 orally daily **Days 8,29:** Vincristine 1.4mg/m^2 (maximum 2mg) IV over 5-10 minutes. Repeat cycle every 6-8 weeks for 6 cycles.
TMZ[33,59-61,a]	**Days 1-21:** Temozolomide 75mg/m^2 orally daily Repeat cycle every 4 weeks for a maximum of 12 cycles.

continued

▶Adult Gliomas: Oligodendroglioma (IDH-Mutant, 1p19q Codeleted)[1] (continued)

REGIMEN	DOSING
Adjuvant Treatment WHO Grade 3, KPS ≥60[a]	
Preferred Regimens	
RT + adjuvant PCV (Category 1)[19,22,23,28-32,a,c,g]	**Day 1:** Lomustine 110mg/m^2 orally once daily **Days 8-21:** Procarbazine 60mg/m^2 orally once daily **Days 8,29**: Vincristine 1.4mg/m^2 (maximum 2mg) IV over 5-10 minutes. Repeat cycle every 6-8 weeks for 6 cycles.
RT + neoadjuvant PCV (Category 1)[19,22,23,28-32,a,c,g]	**Day 1:** Lomustine 110mg/m^2 orally once daily **Days 8-21:** Procarbazine 60mg/m^2 orally once daily **Days 8,29**: Vincristine 1.4mg/m^2 (maximum 2mg) IV over 5-10 minutes. Repeat cycle every 6-8 weeks for 6 cycles.
Other Recommended Regimens	
RT + adjuvant TMZ[33-36,a]	**Days 1-5**: Temozolomide 150-200mg/m^2 (increase as tolerated) orally once daily. Repeat cycle every 4 weeks for 6-12 cycles.
RT + concurrent and adjuvant TMZ[33,34,36,37,a]	**Days 1-42:** Temozolomide 75mg/m^2 orally once daily. Repeat cycle every 6 weeks with RT, **followed by:** **Days 1-5:** Temozolomide 150-200mg/m^2 (increase as tolerated) once orally daily. Repeat cycle every 4 weeks for 6-12 cycles starting 4 weeks after the completion of concurrent Temozolomide and RT.
Adjuvant Treatment, KPS <60[a]	
Other Recommended Regimens (No Preferred Regimens)	
RT + concurrent and adjuvant TMZ[33,34,36,37,a]	**Days 1-42:** Temozolomide 75mg/m^2 orally once daily. Repeat cycle every 6 weeks with RT, **followed by:** **Days 1-5:** Temozolomide 150-200mg/m^2 (increase as tolerated) once orally daily. Repeat cycle every 4 weeks for 6-12 cycles starting 4 weeks after the completion of concurrent Temozolomide and RT.
TMZ (Category 2B)[33,59-61,a,h]	**Days 1-21:** Temozolomide 75mg/m^2 orally daily Repeat cycle every 4 weeks for a maximum of 12 cycles.
Recurrent or Progressive Disease WHO Grade 2, KPS ≥60[d]	
Other Recommended Regimens (No Preferred Regimens)	
Carmustine[15-18,b]	**Days 1-3**: Carmustine 80mg/m^2 IV over 2 hours daily. Repeat cycle every 8 weeks or until reaching a lifetime cumulative carmustine dose for a maximum of 6 cycles. **OR** **Day 1**: Carmustine 150-200mg/m^2 IV over 2 hours daily. Repeat cycle every 8 weeks or until reaching a lifetime cumulative carmustine dose.
Lomustine[19-21,b]	**Day 1:** Lomustine 100-130mg/m^2 orally once daily. Repeat cycle every 6 weeks or until reaching a lifetime cumulative lomustine dose.
PCV[19,22-27,a,c]	**Day 1:** Lomustine 110-130mg/m^2 orally **Days 8-21:** Procarbazine 60-75mg/m^2 orally daily **Days 8,29:** Vincristine 1.4mg/m^2 (maximum 2mg) IV over 5-10 minutes. Repeat cycle every 6-8 weeks until disease progression or reaching a lifetime cumulative lomustine dose.
RT + adjuvant PCV[19,22,23,28-32,a,c]	**Day 1:** Lomustine 110mg/m^2 orally once daily **Days 8-21:** Procarbazine 60mg/m^2 orally once daily **Days 8,29**: Vincristine 1.4mg/m^2 (maximum 2mg) IV over 5-10 minutes. Repeat cycle every 6-8 weeks until disease progression or reaching a lifetime dose of Lomustine.
RT + adjuvant TMZ[33-36,a]	**Days 1-5**: Temozolomide 150-200mg/m^2 (increase as tolerated) orally once daily. Repeat cycle every 4 weeks for 6-12 cycles.
RT + concurrent and adjuvant TMZ[33,34,36,37,a]	**Days 1-42:** Temozolomide 75mg/m^2 orally once daily. Repeat cycle every 6 weeks with RT, **followed by:** **Days 1-5:** Temozolomide 150-200mg/m^2 (increase as tolerated) once orally daily. Repeat cycle every 4 weeks for 6-12 cycles starting 4 weeks after the completion of concurrent Temozolomide and RT.
TMZ[33,38-43,a,e]	**Days 1-5:** Temozolomide 150-200mg/m^2 orally once daily. Repeat cycle every 4 weeks for a maximum of 12 cycles. **OR** **Days 1-28:** Temozolomide 50mg/m^2 orally. Repeat cycle every 4 weeks for a maximum of 12 cycles.

continued

▶Adult Gliomas: Oligodendroglioma (IDH-Mutant, 1p19q Codeleted)[1] (continued)

REGIMEN	DOSING
Recurrent or Progressive Disease WHO Grade 2, KPS ≥60[d] (continued)	
Useful in Certain Circumstances	
Dabrafenib/Trametinib (for PA, PXA, ganglioglioma if *BRAF* V600E mutation positive)[2-5,a]	**Days 1-28:** Dabrafenib 150mg orally twice daily **Days 1-28:** Trametinib 2mg orally once daily. Repeat cycle every 4 weeks.
Entrectinib (if *NTRK* gene fusion positive)[50-52]	**Days 1-28:** Entrectinib 600mg orally once daily. Repeat cycle every 4 weeks.
Larotrectinib (for *NTRK* gene fusion tumors)[53-56]	**Days 1-28:** Larotrectinib 100 mg orally twice daily. Repeat cycle every 4 weeks.
Vemurafenib/Cobimetinib (for PA, PXA, ganglioglioma if *BRAF* V600E mutation positive)[10-14,a]	**Days 1-21:** Cobimetinib 60mg orally once daily **Days 1-28:** Vemurafenib 960mg orally twice daily. Repeat cycle every 4 weeks.
Recurrent Disease WHO Grade 3, KPS ≥60[a,i]	
Preferred Regimens	
Bevacizumab[62-68,j,k]	**Day 1:** Bevacizumab 10mg/kg IV. Repeat cycle every 2 weeks. **OR** **Day 1:** Bevacizumab 5-15mg/kg IV. Repeat cycle every 3 weeks.
Carmustine[15-18,b]	**Days 1-3**: Carmustine 80mg/m^2 IV over 2 hours daily. Repeat cycle every 8 weeks or until reaching a lifetime cumulative carmustine dose for a maximum of 6 cycles. **OR** **Day 1**: Carmustine 150-200mg/m^2 IV over 2 hours daily. Repeat cycle every 8 weeks or until reaching a lifetime cumulative carmustine dose.
Lomustine[19-21,b]	**Day 1:** Lomustine 100-130mg/m^2 orally once daily. Repeat cycle every 6 weeks or until reaching a lifetime cumulative lomustine dose.
PCV[19,22,27,a,c]	**Day 1:** Lomustine 110-130mg/m^2 orally **Days 8-21:** Procarbazine 60-75mg/m^2 orally daily **Days 8,29:** Vincristine 1.4mg/m^2 (maximum 2mg) IV over 5-10 minutes. Repeat cycle every 6-8 weeks until disease progression or reaching a lifetime cumulative dose of Lomustine.
TMZ[33,38-43,a]	**Days 1-5:** Temozolomide 150-200mg/m^2 orally once daily. Repeat cycle every 4 weeks for a maximum of 12 cycles. **OR** **Days 1-28:** Temozolomide 50mg/m^2 orally. Repeat cycle every 4 weeks for a maximum of 12 cycles.
Other Recommended Regimens	
Carmustine + Bevacizumab[15,17,62,63,69,b,j-l]	**Days 1-3:** Carmustine 80mg/m^2 IV over 2 hours daily **Days 1,15,29,43:** Bevacizumab 5-10mg/kg IV. Repeat cycle every 6-8 weeks or until reaching a lifetime cumulative Carmustine dose. **OR** **Days 1:** Carmustine 150-200mg/m^2 IV over 2 hours daily **Days 1,15,29,43:** Bevacizumab 5-10mg/kg IV. Repeat cycle every 6-8 weeks or until reaching a lifetime cumulative Carmustine dose.
Lomustine + Bevacizumab[19,20,62,70,b,j-l]	**Day 1:** Lomustine 90-110mg/m^2 orally **Days 1,15,29:** Bevacizumab 5-10mg/kg IV. Repeat cycle every 6 weeks or until reaching a lifetime cumulative Lomustine dose.
TMZ + Bevacizumab[33,62,71,72,a,j-l]	**Days 1,15:** Bevacizumab 5-10mg/kg IV **Days 1-28:** Temozolomide 50mg/m^2 orally daily. Repeat cycle every 4 weeks.

continued

▶Adult Gliomas: Oligodendroglioma (IDH-Mutant, 1p19q Codeleted)[1] (continued)

REGIMEN	DOSING
Recurrent Disease WHO Grade 3, KPS ≥60[a,i] (continued)	
Useful in Certain Circumstances	
Carboplatin (if failure or intolerance to the preferred or other recommended regimens) (Category 3)[44-46]	**Day 1:** Carboplatin AUC 4-6 IV over 30 minutes. Repeat cycle every 4 weeks. **OR** **Day 1:** Carboplatin 560mg/m^2 IV over 1 hour. Repeat cycle every 4 weeks.
Cisplatin (if failure or intolerance to the preferred or other recommended regimens) (Category 3)[47,73,74,210,211,f]	**Day 1:** Cisplatin 60mg/m^2 IV over 1 hour daily. Repeat cycle every 3 or 4 weeks.
Dabrafenib + Trametinib (if *BRAF* V600E mutation positive)[2-5]	**Days 1-28:** Dabrafenib 150mg orally twice daily. **Days 1-28:** Trametinib 2mg orally once daily. Repeat cycle every 4 weeks.
Entrectinib (for *NTRK* gene fusion tumors)[50-52]	**Days 1-28:** Entrectinib 600mg orally once daily. Repeat cycle every 4 weeks
Etoposide (if failure or intolerance to the preferred or other recommended regimens) (Category 2B)[49,75-79]	**Days 1-21:** Etoposide 50mg/m^2 orally daily. Repeat cycle every 4-5 weeks.
Larotrectinib (for *NTRK* gene fusion tumors)[53-56]	**Days 1-28:** Larotrectinib 100mg orally twice daily. Repeat cycle every 4 weeks.
Vemurafenib + Cobimetinib (if *BRAF* V600E mutation positive)[10-14]	**Days 1-21:** Cobimetinib 60mg orally once daily **Days 1-28:** Vemurafenib 960mg orally twice daily. Repeat cycle every 4 weeks.

▶Adult Glioma: *IDH*-Mutant Astrocytoma

Adjuvant Treatment WHO Grade 2, KPS >60[a]	
Preferred Regimens	
RT with adjuvant PCV (Procarbazine/Lomustine/Vincristine) (Category 1)[19,22,23,28-32,a,c]	**Day 1:** Lomustine 110mg/m^2 orally once daily **Days 8-21:** Procarbazine 60mg/m^2 orally once daily **Days 8,29**: Vincristine 1.4mg/m^2 (maximum 2mg) IV over 5-10 minutes. Repeat cycle every 6-8 weeks for 6 cycles.
RT +adjuvant TMZ[33-36,a]	**Days 1-5**: Temozolomide 150-200mg/m^2 (increase as tolerated) orally once daily. Repeat cycle every 4 weeks for 6-12 cycles.
RT + concurrent and adjuvant TMZ[33,34,36,37,a]	**Days 1-42:** Temozolomide 75mg/m^2 orally once daily. Repeat cycle every 6 weeks with RT, **followed by:** **Days 1-5:** Temozolomide 150-200mg/m^2 (increase as tolerated) once orally daily. Repeat cycle every 4 weeks for 6-12 cycles starting 4 weeks after the completion of concurrent Temozolomide and RT.
Other Recommended Regimens	
PCV[19,22-27,a,c]	**Day 1:** Lomustine 110-130mg/m^2 orally **Days 8-21:** Procarbazine 60-75mg/m^2 orally daily **Days 8,29:** Vincristine 1.4mg/m^2 (maximum 2mg) IV over 5-10 minutes. Repeat cycle every 6-8 weeks for 6 cycles.
TMZ[33,59-61,a]	**Days 1-21:** Temozolomide 75mg/m^2 orally daily Repeat cycle every 4 weeks for a maximum of 12 cycles.
Adjuvant Treatment WHO Grade 3 or 4, KPS ≥60[a]	
Preferred Regimens	
RT + adjuvant TMZ (12 cycles)[33-36,a]	**Days 1-5**: Temozolomide 150-200mg/m^2 (increase as tolerated) orally once daily. Repeat cycle every 4 weeks for 12 cycles.
RT + concurrent and adjuvant TMZ[33,34,36,37,a]	**Days 1-42:** Temozolomide 75mg/m^2 orally once daily. Repeat cycle every 6 weeks with RT, **followed by:** **Days 1-5:** Temozolomide 150-200mg/m^2 (increase as tolerated) once orally daily. Repeat cycle every 4 weeks for 6-12 cycles starting 4 weeks after the completion of concurrent Temozolomide and RT.

continued

▶Adult Glioma: IDH-Mutant Astrocytoma (continued)

REGIMEN	DOSING
Adjuvant Treatment, KPS <60[a]	
Other Recommended Regimens (No Preferred Regimens)	
RT + adjuvant TMZ[33-36,a]	**Days 1-5**: Temozolomide 150-200mg/m^2 (increase as tolerated) orally once daily. Repeat cycle every 4 weeks for 6-12 cycles.
RT + concurrent and adjuvant TMZ[33,34,36,37,a]	**Days 1-42:** Temozolomide 75mg/m^2 orally once daily. Repeat cycle every 6 weeks with RT, **followed by:** **Days 1-5:** Temozolomide 150-200mg/m^2 (increase as tolerated) once orally daily. Repeat cycle every 4 weeks for 6-12 cycles starting 4 weeks after the completion of concurrent Temozolomide and RT.
Recurrent or Progressive Disease WHO Grade 2, KPS ≥60[a,d]	
Other Recommended Regimens (No Preferred Regimens)	
Carmustine[15-18,b]	**Days 1-3**: Carmustine 80mg/m^2 IV over 2 hours daily. Repeat cycle every 8 weeks or until reaching a lifetime cumulative Carmustine dose for a maximum of 6 cycles. **OR** **Day 1**: Carmustine 150-200mg/m^2 IV over 2 hours daily. Repeat cycle every 8 weeks or until reaching a lifetime cumulative Carmustine dose.
Lomustine[19-21,b]	**Day 1:** Lomustine 100-130mg/m^2 orally once daily. Repeat cycle every 6 weeks or until reaching a lifetime cumulative Lomustine dose.
PCV[19,22-27,a,c]	**Day 1:** Lomustine 110-130mg/m^2 orally **Days 8-21:** Procarbazine 60-75mg/m^2 orally daily **Days 8,29:** Vincristine 1.4mg/m^2 (maximum 2mg) IV over 5-10 minutes. Repeat cycle every 6-8 weeks until disease progression or reaching a lifetime cumulative Lomustine dose.
RT + adjuvant PCV[19,22,23,28-32,a,c]	**Day 1:** Lomustine 110mg/m^2 orally once daily **Days 8-21:** Procarbazine 60mg/m^2 orally once daily **Days 8,29**: Vincristine 1.4mg/m^2 (maximum 2mg) IV over 5-10 minutes. Repeat cycle every 6-8 weeks until disease progression or reaching a lifetime dose of Lomustine.
RT + adjuvant TMZ[33-36,a]	**Days 1-5**: Temozolomide 150-200mg/m^2 (increase as tolerated) orally once daily. Repeat cycle every 4 weeks for 6-12 cycles.
RT + concurrent and adjuvant TMZ[33,34,36,37,a]	**Days 1-42:** Temozolomide 75mg/m^2 orally once daily. Repeat cycle every 6 weeks with RT, **followed by:** **Days 1-5:** Temozolomide 150-200mg/m^2 (increase as tolerated) once orally daily. Repeat cycle every 4 weeks for 6-12 cycles starting 4 weeks after the completion of concurrent Temozolomide and RT.
TMZ[33,38-43,a,e]	**Days 1-5:** Temozolomide 150-200mg/m^2 orally once daily. Repeat cycle every 4 weeks for a maximum of 12 cycles. **OR** **Days 1-28:** Temozolomide 50mg/m^2 orally. Repeat cycle every 4 weeks for a maximum of 12 cycles.
Useful in Certain Circumstances	
Dabrafenib/Trametinib (if *BRAF* V600E mutation positive)[2-5]	**Days 1-28:** Dabrafenib 150 mg orally twice daily **Days 1-28:** Trametinib 2mg orally once daily. Repeat cycle every 4 weeks.
Entrectinib (if *NTRK* gene fusion positive)[50-52]	**Days 1-28:** Entrectinib 600mg orally once daily. Repeat cycle every 4 weeks.
Larotrectinib (for *NTRK* gene fusion tumors)[53-56]	**Days 1-28:** Larotrectinib 100mg orally twice daily. Repeat cycle every 4 weeks.
Vemurafenib/Cobimetinib (if *BRAF* V600E mutation positive)[10-14]	**Days 1-21:** Cobimetinib 60mg orally once daily **Days 1-28:** Vemurafenib 960mg orally twice daily. Repeat cycle every 4 weeks.
Recurrent or Progressive Disease, WHO Grade 3 or 4, KPS ≥60[a,d,i]	
Preferred Regimens	
Bevacizumab[62-68,j,k]	**Day 1:** Bevacizumab 10mg/kg IV. Repeat cycle every 2 weeks. **OR** **Day 1:** Bevacizumab 5-15mg/kg IV. Repeat cycle every 3 weeks.

continued

▶Adult Glioma: IDH-Mutant Astrocytoma (continued)

REGIMEN	DOSING
Recurrent or Progressive Disease, WHO Grade 3 or 4, KPS ≥60[a,d,i] (continued)	
Preferred Regimens (continued)	
Carmustine[15-18,b]	**Days 1-3**: Carmustine 80mg/m^2 IV over 2 hours daily. Repeat cycle every 8 weeks or until reaching a lifetime cumulative carmustine dose for a maximum of 6 cycles. **OR** **Day 1**: Carmustine 150-200mg/m^2 IV over 2 hours daily. Repeat cycle every 8 weeks or until reaching a lifetime cumulative carmustine dose.
Lomustine[19-21,b]	**Day 1:** Lomustine 100-130mg/m^2 orally once daily. Repeat cycle every 6 weeks or until reaching a lifetime cumulative lomustine dose.
PCV[19,22-27,a,c]	**Day 1:** Lomustine 110-130mg/m^2 orally **Days 8-21:** Procarbazine 60-75mg/m^2 orally daily **Days 8,29:** Vincristine 1.4mg/m^2 (maximum 2mg) IV over 5-10 minutes. Repeat cycle every 6-8 weeks until disease progression or reaching a lifetime cumulative Lomustine dose.
TMZ[33,38-43,a]	**Days 1-5:** Temozolomide 150-200mg/m^2 orally once daily. Repeat cycle every 4 weeks for a maximum of 12 cycles. **OR** **Days 1-28:** Temozolomide 50mg/m^2 orally. Repeat cycle every 4 weeks for a maximum of 12 cycles.
Other Recommended Regimens	
Carmustine + Bevacizumab[15,17,62,63,69,b,j-l]	**Days 1-3:** Carmustine 80mg/m^2 IV over 2 hours daily **Days 1,15,29,43:** Bevacizumab 5-10mg/kg IV. Repeat cycle every 6-8 weeks or until reaching a lifetime cumulative Carmustine dose. **OR** **Days 1:** Carmustine 150-200mg/m^2 IV over 2 hours daily **Days 1,15,29,43:** Bevacizumab 5-10mg/kg IV. Repeat cycle every 6-8 weeks or until reaching a lifetime cumulative Carmustine dose.
Lomustine + Bevacizumab[19,20,62,70,b,j-l]	**Day 1:** Lomustine 90-110mg/m^2 orally **Days 1,15,29:** Bevacizumab 5-10mg/kg IV. Repeat cycle every 6 weeks or until reaching a lifetime cumulative lomustine dose.
TMZ + Bevacizumab[33,62,71,72,b,j-l]	**Days 1,15:** Bevacizumab 5-10 mg/kg IV **Days 1-28:** Temozolomide 50mg/m^2 orally daily. Repeat cycle every 4 weeks.
Useful in Certain Circumstances	
Carboplatin (if failure or intolerance to the preferred or other recommended regimens) (Category 3)[44-46]	**Day 1:** Carboplatin AUC 4-6 IV over 30 minutes. Repeat cycle every 4 weeks. **OR** **Day 1:** Carboplatin 560mg/m^2 IV over 1 hour. Repeat cycle every 4 weeks.
Cisplatin (if failure or intolerance to the preferred or other recommended regimens) (Category 3)[47,73,74,210,211,f]	**Day 1:** Cisplatin 60mg/m^2 IV over 1 hour daily. Repeat cycle every 3 or 4 weeks.
Dabrafenib + Trametinib (if *BRAF* V600E mutation positive)[2-5]	**Days 1-28:** Dabrafenib 150mg orally twice daily. **Days 1-28:** Trametinib 2mg orally once daily. Repeat cycle every 4 weeks.
Entrectinib (for *NTRK* gene fusion tumors)[50-52]	**Days 1-28:** Entrectinib 600mg orally once daily. Repeat cycle every 4 weeks
Etoposide (if failure or intolerance to the preferred or other recommended regimens) (Category 2B)[49,75-79]	**Days 1-21:** Etoposide 50mg/m^2 orally daily. Repeat cycle every 4-5 weeks.
Larotrectinib (for *NTRK* gene fusion tumors)[53-56]	**Days 1-28:** Larotrectinib 100mg orally twice daily. Repeat cycle every 4 weeks.
Vemurafenib + Cobimetinib (if *BRAF* V600E mutation positive)[10-14]	**Days 1-21:** Cobimetinib 60mg orally once daily **Days 1-28:** Vemurafenib 960mg orally twice daily. Repeat cycle every 4 weeks.

continued

▶Adult Glioma: Glioblastoma[1]

REGIMEN	DOSING
Adjuvant Treatment, KPS ≥60[a]	
Preferred Regimens	
RT with concurrent and adjuvant TMZ + TTF[33,34,36,37,a]	**Days 1-42:** Temozolomide 75mg/m^2 orally daily. Repeat cycle every 6 weeks with RT, **followed by:** **Days 1-5:** Temozolomide 150-200mg/m^2 (increase as tolerated) orally daily. Repeat cycle every 4 weeks for 6-12 cycles starting 4 weeks after the completion of concurrent temozolomide and RT).
Useful in Certain Circumstances	
RT + concurrent and adjuvant Lomustine and TMZ (for patients with *MGMT* promoter-methylated tumors and age ≤70 years) (Category 2B)[19,33,80,a,b,m]	**Day 1:** Lomustine 100mg/m^2 orally once daily **Days 2-6:** Temozolomide 100mg/m^2 orally once daily. Administer for one 6-week cycle with concurrent RT, **followed by:** **Day 1:** Lomustine 100mg/m^2 orally once daily **Days 2-6:** Temozolomide 100-200mg/m^2 orally once daily. Repeat cycle for 6 weeks for 5 cycles.
TMZ (for patients with *MGMT* promoter-methylated tumors and age >70 years)[33-36,a]	**Days 1-5:** Temozolomide 150-200mg/m^2 (increase as tolerated) orally once daily. Repeat cycle every 4 weeks for 6-12 cycles.
Adjuvant Treatment, KPS <60[a]	
Useful in Certain Circumstances (No Preferred or Other Recommended Regimens)	
RT + concurrent and adjuvant TMZ (for patients age 70 or younger)[33,34,36,37,a]	**Days 1-42:** Temozolomide 75mg/m^2 orally once daily. Repeat cycle every 6 weeks with RT, **followed by:** **Days 1-5:** Temozolomide 150-200mg/m^2 (increase as tolerated) once orally daily. Repeat cycle every 4 weeks for 6-12 cycles starting 4 weeks after the completion of concurrent Temozolomide and RT.
TMZ (for patients with *MGMT* promoter-methylated tumors)[33-36,a]	**Days 1-5:** Temozolomide 150-200mg/m^2 (increase as tolerated) orally once daily. Repeat cycle every 4 weeks for 6-12 cycles.
Recurrence Therapy[l,n]	
Preferred Regimens	
Bevacizumab[62-68,j,k]	**Day 1:** Bevacizumab 10mg/kg IV. Repeat cycle every 2 weeks. **OR** **Day 1:** Bevacizumab 5-15mg/kg IV. Repeat cycle every 3 weeks.
Carmustine[15-18,b]	**Days 1-3**: Carmustine 80mg/m^2 IV over 2 hours daily. Repeat cycle every 8 weeks or until reaching a lifetime cumulative Carmustine dose for a maximum of 6 cycles. **OR** **Day 1**: Carmustine 150-200mg/m^2 IV over 2 hours daily. Repeat cycle every 8 weeks or until reaching a lifetime cumulative Carmustine dose.
Lomustine[19-21,b]	**Day 1:** Lomustine 100-130mg/m^2 orally once daily. Repeat cycle every 6 weeks or until reaching a lifetime cumulative Lomustine dose.
PCV (Procarbazine/Lomustine/Vincristine) [19,22-27,a-c]	**Day 1:** Lomustine 110-130mg/m^2 orally once daily **Days 8-21**: Procarbazine 60-75mg/m^2 orally once daily **Days 8 and 29**: Vincristine 1.4mg/m^2 (maximum 2mg) IV over 5-10 minutes. Repeat cycle every 6-8 weeks until reaching a lifetime cumulative dose of Lomustine.
Regorafenib[81,82]	**Days 1-21:** Regorafenib 160mg orally once daily. Repeat cycle every 4 weeks.
TMZ[33,38-43,59-61,a]	**Days 1-21:** Temozolomide 75mg/m^2 orally once daily. Repeat cycle every 4 weeks for 12 cycles. **OR** **Days 1-5:** Temozolomide 150-200mg/m^2 orally daily. Repeat cycle every 4 weeks for a maximum of 12 cycles. **OR** **Days 1-28:** Temozolomide 50mg/m^2 orally daily. Repeat cycle every 4 weeks for a maximum of 12 cycles.

continued

▶Adult Glioma: Glioblastoma[1] (continued)

REGIMEN	DOSING
Recurrence Therapy[l,n] (continued)	
Other Recommended Regimens	
Carmustine + Bevacizumab[15,17,62,63,69,b,j-l]	**Days 1-3:** Carmustine 80mg/m^2 IV over 2 hours daily **Days 1,15,29,43:** Bevacizumab 5-10mg/kg IV. Repeat cycle every 6-8 weeks or until reaching a lifetime cumulative Carmustine dose. **OR** **Days 1:** Carmustine 150-200mg/m^2 IV over 2 hours daily **Days 1,15,29,43:** Bevacizumab 5-10mg/kg IV. Repeat cycle every 6-8 weeks or until reaching a lifetime cumulative Carmustine dose.
Lomustine + Bevacizumab[19,20,62,70,b,j-l]	**Day 1:** Lomustine 90-110mg/m^2 orally **Days 1,15,29:** Bevacizumab 5-10mg/kg IV. Repeat cycle every 6 weeks or until reaching a lifetime cumulative Lomustine dose.
TMZ + Bevacizumab[33,62,71,72,a,j-l]	**Days 1,15:** Bevacizumab 5-10mg/kg IV **Days 1-28:** Temozolomide 50mg/m^2 orally daily. Repeat cycle every 4 weeks.
Useful in Certain Circumstances	
Carboplatin/Etoposide (if failure or intolerance to the preferred or other recommended regimens) (Category 3)[44,48,49,88,211]	**Days 1-3:** Carboplatin 100mg/m^2 IV over 30 minutes daily. **Days 1-3:** Etoposide 120mg/m^2 over 1 hour daily. Repeat cycle every 4 weeks for a maximum of 12 cycles. **OR** **Day 1:** Carboplatin AUC 4-6 IV. **Days 1-3:** Etoposide 100-120mg/m^2 over 1 hour daily. Repeat cycle every 4 weeks for a maximum of 12 cycles.
Cisplatin/Etoposide (if failure or intolerance to the preferred or other recommended regimens) (Category 3)[47-49,f]	**Days 1-3:** Cisplatin 25mg/m^2 IV over 1 hour daily. **Days 1-3:** Etoposide 100mg/m^2 IV over 1 hour daily. Repeat cycle every 4 weeks for a maximum of 10 cycles.
Dabrafenib/Trametinib (if *BRAF* V600E mutation positive)[2-5]	**Days 1-28:** Dabrafenib 150 mg orally twice daily. **Days 1-28:** Trametinib 2 mg orally once daily. Repeat cycle every 4 weeks.
Entrectinib (if *NTRK* gene fusion positive)[50-52]	**Days 1-28:** Entrectinib 600mg orally once daily. Repeat cycle every 4 weeks.
Etoposide (if failure or intolerance to the preferred or other recommended regimens) (Category 2B)[49,75-79]	**Days 1-21:** Etoposide 50mg/m^2 orally daily. Repeat cycle every 4-5 weeks.
Larotrectinib (for *NTRK* gene fusion tumors)[52-56]	**Days 1-28:** Larotrectinib 100mg orally twice daily. Repeat cycle every 4 weeks.
Vemurafenib/Cobimetinib (if *BRAF* V600E mutation positive)[10-14]	**Days 1-21:** Cobimetinib 60mg orally once daily **Days 1-28:** Vemurafenib 960mg orally twice daily. Repeat cycle every 4 weeks.

▶Adult Intracranial and Spinal Ependymoma (Excluding Subependymoma)[1]

Recurrence Therapy	
Other Recommended Regimens (No Preferred Regimens)	
Bevacizumab[62-68,j,k]	**Day 1:** Bevacizumab 10mg/kg IV. Repeat cycle every 2 weeks. **OR** **Day 1:** Bevacizumab 5-15mg/kg IV. Repeat cycle every 3 weeks.

continued

▶Adult Intracranial and Spinal Ependymoma (Excluding Subependymoma)[1] (continued)

REGIMEN	DOSING
Recurrence Therapy (continued)	
Other Recommended Regimens (No Preferred Regimens) (continued)	
Carboplatin (if failure or intolerance to the preferred or other recommended regimens)[44-46]	**Day 1:** Carboplatin AUC 4-6 IV over 30 minutes. Repeat cycle every 4 weeks. **OR** **Day 1:** Carboplatin 560mg/m^2 IV over 1 hour. Repeat cycle every 4 weeks.
Carboplatin/Etoposide (if failure or intolerance to the preferred or other recommended regimens)[44,48,49,88,210]	**Days 1-3:** Carboplatin 100mg/m^2 IV over 30 minutes daily **Days 1-3:** Etoposide 120mg/m^2 over 1 hour daily. Repeat cycle every 4 weeks for a maximum of 12 cycles. **OR** **Day 1:** Carboplatin AUC 4-6 IV **Days 1-3:** Etoposide 100-120mg/m^2 over 1 hour daily. Repeat cycle every 4 weeks for a maximum of 12 cycles.
Carmustine[15-18,b]	**Days 1-3**: Carmustine 80mg/m^2 IV over 2 hours daily. Repeat cycle every 8 weeks or until reaching a lifetime cumulative Carmustine dose for a maximum of 6 cycles. **OR** **Day 1**: Carmustine 150-200mg/m^2 IV over 2 hours daily. Repeat cycle every 8 weeks or until reaching a lifetime cumulative Carmustine dose.
Cisplatin (if failure or intolerance to the preferred or other recommended regimens) (Category 3)[47,73,74,210,211,f]	**Day 1:** Cisplatin 60mg/m^2 IV over 1 hour daily. Repeat cycle every 3 or 4 weeks.
Cisplatin/Etoposide (if failure or intolerance to the preferred or other recommended regimens) (Category 3)[47-49,f]	**Days 1-3:** Cisplatin 25mg/m^2 IV over 1 hour daily **Days 1-3:** Etoposide 100mg/m^2 IV over 1 hour daily. Repeat cycle every 4 weeks for a maximum of 10 cycles.
Etoposide (if failure or intolerance to the preferred or other recommended regimens)[49,75-79]	**Days 1-21:** Etoposide 50mg/m2 orally daily. Repeat cycle every 4-5 weeks
Lapatinib + TMZ (Category 2B)[33,83,84,a]	**Days 1-28:** Lapatinib 1,250mg orally once daily **Days 1-7,15-21:** Temozolomide 125-150mg/m2 orally once daily. Administer for one 4-week cycle for a maximum of 24 cycles.
Lomustine[19-21,b]	**Day 1:** Lomustine 100-130mg/m2 orally once daily. Repeat cycle every 6 weeks or until reaching a lifetime cumulative lomustine dose.
TMZ[33,49-53,a]	**Days 1-5:** Temozolomide 150-200mg/m2 orally once daily. Repeat cycle every 4 weeks for a maximum of 12 cycles.

▶Adult Medulloblastoma[1]

Regimens Following Weekly Vincristine During Craniospinal RT[a,o]	
Preferred Regimens	
Cisplatin, Cyclophosphamide, and Vincristine[23,47,85,86,f,o,p]	**Day 1:** Vincristine 1.5mg/m^2 (maximum 2mg) IV over 5-10 minutes. Repeat cycle weekly for 8 weeks with concurrent craniospinal RT, **followed by:** **Day 1:** Cisplatin 75mg/m^2 IV over 2 hours **Days 2,8,15:** Vincristine 1.5mg/m^2 (maximum 2mg) IV over 5-10 minutes (maximum 8 doses) **Days 22-23:** Cyclophosphamide 1,000mg/m^2 IV over 30 minutes. Repeat cycle every 6 weeks for 8 cycles beginning 6 weeks after craniospinal RT.
Cisplatin, Lomustine, and Vincristine[19,23,47,86,b,f,o]	**Day 1:** Vincristine 1.5mg/m^2 (maximum 2mg) IV over 5-10 minutes. Repeat cycle weekly for 8 weeks with concurrent craniospinal RT, **followed by:** **Day 1:** Lomustine 75mg/m^2 orally once daily **Day 2:** Cisplatin 75mg/m^2 IV over 2 hours **Days 2,8,15:** Vincristine 1.5mg/m^2 (maximum 2mg) IV over 5-10 minutes (maximum 8 doses). Repeat cycle every 6 weeks for 8 cycles beginning 6 weeks after craniospinal RT.

continued

▶Adult Medulloblastoma[1] (continued)

REGIMEN	DOSING
Recurrence Therapy	
Other Recommended Regimens (No Preferred Regimens)	
Carboplatin/Etoposide/ Cyclophosphamide (no prior systemic chemotherapy)[44,45,85,87,88,p]	**Days 1-3:** Carboplatin 100mg/m^2 IV over 30 minutes **Days 1-4:** Etoposide 40mg/m^2 IV over 1 hour **Day 4:** Cyclophosphamide 1,000mg/m^2 IV over 30 minutes. Repeat cycle every 4 weeks.
Cisplatin/Etoposide/ Cyclophosphamide (no prior systemic chemotherapy)[47,49,85,87,f,p]	**Days 1-4:** Cisplatin 25mg/m^2 IV over 1 hour **Days 1-4:** Etoposide 40mg/m^2 IV over 1 hour **Day 4:** Cyclophosphamide 1,000mg/m^2 IV over 30 minutes. Repeat cycle every 4 weeks.
High-dose Cyclophosphamide (no prior systemic chemotherapy)[1,p]	See NCCN Central Nervous System Guidelines.[1]
High-dose Cyclophosphamide + Etoposide (no prior systemic chemotherapy)[1,p]	See NCCN Central Nervous System Guidelines.[1]
High-dose Cyclophosphamide (prior systemic chemotherapy)[1,p]	See NCCN Central Nervous System Guidelines.[1]
High-dose Cyclophosphamide + Etoposide (prior systemic chemotherapy)[1,p]	See NCCN Central Nervous System Guidelines.[1]
Oral Etoposide (prior systemic chemotherapy)[49,75-79]	**Days 1-21:** Etoposide 50mg/m^2 orally once daily. Repeat cycle every 4 or 5 weeks.
TMZ (prior systemic chemotherapy)[33,38-42,a]	**Days 1-5:** Temozolomide 150-200mg/m^2 orally once daily. Repeat cycle every 4 weeks for a maximum of 12 cycles.
Useful in Certain Circumstances	
Vismodegib (for mutations in sonic hedgehog pathway and if prior systemic chemotherapy)[89,90]	**Days 1-28:** Vismodegib 150 mg orally once daily. Repeat cycle every 4 weeks.
Consider high-dose chemotherapy with autologous stem cell reinfusion in patients who achieve a CR with conventional doses of chemotherapy or have no residual disease after re-resection.[a]	

▶Primary CNS Lymphoma[1]

Induction Therapy	
Preferred Regimens	
High-dose Methotrexate/ Procarbazine/Vincristine + Rituximab (R-MPV) and consider WBRT[22,23,91-96,a,q-v] *Rituximab requires premedication.*	**Day 1:** Rituximab 500mg/m^2 IV **Day 2:** Methotrexate 3,500 mg/m^2 IV over 2 hours **Day 2:** 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 <0.05micromol/L)[u] **DAY 2:** Vincristine 1.4mg/m^2 (maximum 2mg) IV over 5-10 minutes **Days 2-8:** Procarbazine 100mg/m^2 orally once daily of Cycles 1, 3, 5, and 7 **Days 5-12:** Methotrexate (if CSF cytology positive) 12mg intrathecal **OR** intraventricular once. Repeat cycle every 2 weeks for 5-7 cycles, **conditionally followed by:** **Day 1:** Rituximab 500mg/m^2 IV **Day 2:** Methotrexate 3,500 mg/m^2 IV over 2 hours **Day 2:** Leucovorin 25mg IV over 15 minutes **OR** orally starting 24 hours from initiation of Methotrexate infusion and continuing every 6 hours (until Methotrexate serum concentration is <0.05micromol/L)[u] **Day 2:** Vincristine 1.4mg/m^2 IV over 5-10 minutes **Days 2-8:** Procarbazine 100mg/m^2 orally once daily of odd cycles. Repeat cycle for 4 weeks for a maximum of 1 year.

continued

▶Primary CNS Lymphoma[1] (continued)

REGIMEN	DOSING
Induction Therapy (continued)	
Preferred Regimens (continued)	
High-dose Methotrexate + Rituximab [91-93,97-99,q-u] *Rituximab requires premedication.*	**Day 1:** Methotrexate 8,000mg/m^2 IV over 4 hours (if CrCl >60mL/min) **OR** Methotrexate 4,000mg/m^2 IV over 4 hours (if CrCl <60mL/min), **followed by** **Day 2:** 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 <0.05micromol/L)[u] **Day 3 or 8:** Rituximab 375mg/m^2 IV once daily. Repeat cycle for 2 weeks for 4-6 cycles (induction), **followed by:** **Day 1:** Methotrexate 8,000mg/m^2 IV over 4 hours (if CrCl >60mL/min) **OR** Methotrexate 4,000mg/m^2 IV over 4 hours (if CrCl <60mL/min), **followed by** **Day 2:** Leucovorin 25mg IV over 15 minutes **OR** orally starting 24 hours from initiation of Methotrexate infusion and continuing every 6 hours (until Methotrexate serum concentration is <0.05micromol/L).[u] Repeat cycle every 4 weeks for a maximum of 1 year.
High-Dose Methotrexate/ TMZ + Rituximab[33,91-93,100,a,q-u] *Rituximab requires premedication.*	**Day 1:** Methotrexate 8,000mg/m^2 IV over 4 hours **Day 2:** Leucovorin 100mg IV over 15 minutes **OR** orally starting 24 hours from initiation of Methotrexate infusion and continuing every 6 hours (until Methotrexate serum concentration is <0.05micromol/L)[u] **Day 3 (Cycles 1-6):** Rituximab 375mg/m^2 IV of **Days 7-11 (Cycles 1, 3, 5, and 7):** Temozolomide 150mg/m^2 orally once daily of. Repeat every 2 weeks for 8-11 cycles, **conditionally followed by consolidation therapy with:** **Day 1:** Methotrexate 8,000mg/m^2 IV over 4 hours **Day 2:** Leucovorin 100mg IV over 15 minutes starting 24 hours from initiation of Methotrexate infusion and continuing every 6 hours (until Methotrexate serum concentration is <0.05micromol/L)[u] **Days 7-11 (Odd Cycles):** Temozolomide 150mg/m^2 orally once daily. Repeat cycle every 4 weeks for a maximum of 1 year.
High-Dose Methotrexate/ TMZ + Rituximab followed by Postirradiation TMZ and consider WBRT[33,91,92,101,a,q-v] *Rituximab requires premedication.*	**Day 1:** Rituximab 375mg/m^2 IV **Day 4:** Methotrexate 3,500mg/m^2 IV over 4 hours **Day 5:** Leucovorin 25mg IV over 15 minutes **OR** orally starting 24 hours from initiation of Methotrexate infusion and continuing every 6 hours (until Methotrexate serum concentration is <0.05micromol/L).[u] Administer for one 2-week cycle, **followed by:** **Day 1:** Methotrexate 3,500 mg/m^2 IV over 4 hours **Day 2:** Leucovorin 25mg IV over 15 minutes **OR** orally starting 24 hours from initiation of Methotrexate infusion and continuing every 6 hours (until Methotrexate serum concentration is <0.05micromol/L)[u] **Days 8-12:** Temozolomide 100mg/m^2 orally once daily. Repeat cycle every 2 weeks for 4 cycles, **followed by post-irradiation:** **Days 1-5:** Temozolomide 150-200mg/m^2 orally once daily. Repeat cycle for 4 weeks for a maximum of 10 cycles.
Other Recommended Regimens	
High-dose Methotrexate/ Cytarabine/ Thiotepa/Rituximab (MATRix)[91-93,102-104,q-u,w-y] *Rituximab requires premedication.*	**Days -5,0 of Cycles 1-4:** Rituximab 375mg/m^2 IV. **Day 1:** Methotrexate 500mg/m^2 IV over 15 minutes, **followed by:** Methotrexate 3,000mg/m^2 IV over 3 hours Leucovorin 15mg/m^2 IV over 15 minutes **or** orally every 6 hours for 12 doses (beginning 24 hours after the start of Methotrexate)[u] **Days 2-3:** Cytarabine 2,000mg/m^2 IV over 1 hour every 12 hours **Day 4:** Thiotepa 30mg/m^2 IV over 30 minutes. Repeat cycle every 3 weeks for 4 cycles.
Useful in Certain Circumstances	
Cytarabine (intra-CSF therapy if CSF positive or spinal MRI positive)[103-105,a]	**Days 1,4:** Cytarabine 50mg intrathecal or intraventricular. Repeat cycle weekly for 4 cycles (induction), **followed by:** **Day 1:** Cytarabine 50mg intrathecal or intraventricular. Repeat cycle weekly for 8 cycles if CSF cytology negative (consolidation), **followed by:** **Day 1:** Cytarabine 50mg intrathecal or intraventricular. Repeat cycle every 2 weeks for 2 cycles (consolidation), **followed by:** **Day 1:** Cytarabine 50mg intrathecal or intraventricular. Repeat cycle every 4 weeks for 4 cycles (maintenance).

continued

▶Primary CNS Lymphoma[1] (continued)

REGIMEN	DOSING
Induction Therapy (continued)	
Useful in Certain Circumstances (continued)	
Methotrexate (intra-CSF therapy if CSF positive or spinal MRI positive)[92,105,106,a]	**Days 1,4:** Methotrexate 10-15mg intrathecal or intraventricular. Repeat cycle weekly for 4 cycles (induction), **followed by:** **Day 1:** Methotrexate 10-15mg intrathecal or intraventricular. Repeat cycle weekly for 4 cycles if CSF cytology negative (consolidation), **followed by:** **Day 1:** Methotrexate 10-15mg intrathecal or intraventricular. Repeat cycle every 2 weeks for 4 cycles (consolidation), **followed by:** **Day 1:** Methotrexate 10-15mg intrathecal or intraventricular. Repeat cycle every 4 weeks (maintenance).
Rituximab (intra-CSF therapy if CSF positive or spinal MRI positive)[91,107,108,a,r,s] *Rituximab requires premedication.*	**Days 1,4:** Rituximab 25mg intrathecal or intraventricular Repeat cycle weekly for 4 cycles (induction), **followed by:** **Days 1,4:** Rituximab 25mg intrathecal or intraventricular Repeat cycle every 4 weeks if CSF cytology negative (maintenance).
If patient is unsuitable for or intolerant to high-dose Methotrexate, see "Other Recommended Regimens" for Relapsed or Refractory Disease.	
Consolidation Therapy	
Preferred Regimens	
High-dose Cytarabine[103,109,110]	**Days 1-2:** Cytarabine 3,000mg/m^2 IV over 3 hours. Repeat cycle every 4 weeks for 2 cycles (this course is preceded by 5-7 cycles of High-dose Methotrexate/ Vincristine/Procarbazine + Rituximab and then whole brain RT).
Cytarabine + Thiotepa followed by Carmustine + Thiotepa (for high-dose chemotherapy stem cell rescue)[1,a-c]	See NCCN Central Nervous System Guidelines[1]
High-dose Cytarabine + Etoposide (EA)[49,100,103]	**Days 1-4:** Etoposide 10mg/kg IV continuous infusion over 24 hours daily **Days 1-4:** Cytarabine 2,000mg/m^2 IV over 2 hours every 12 hours. Administer for one 4-week cycle (this course is preceded by 8-11 cycles of High-dose Methotrexate/Temozolomide + Rituximab course).
Thiotepa, Busulfan, and Cyclophosphamide (TBC) (for high-dose chemotherapy stem cell rescue)[85,102,111,112,p]	**Days 1-3**: Thiotepa 250mg/m^2 IV over 3 hours **Days 4-6**: Busulfan 0.67-0.8mg/kg IV over 2 hours every 3 hours **Days 7-8**: Cyclophosphamide 60mg/kg IV over 30 minutes. Mesna 12mg/kg IV over 15 minutes three times daily (one dose before Cyclophosphamide, then at 4 and 8 hours from the start of each Cyclophosphamide dose). Administer for one cycle prior to HSCT.
Relapsed or Refractory Disease	
Other Recommended Regimens (No Preferred Regimens)	
High-dose Cytarabine[103,109,110]	**Days 1-2:** Cytarabine 3,000mg/m^2 IV over 3 hours. Repeat cycle every 3 weeks.
Ibrutinib[113,114,z]	**Days 1-28:** Ibrutinib 560mg orally once daily. Repeat cycle every 4 weeks. **OR** **Days 1-28:** Ibrutinib 840mg orally once daily. Repeat cycle every 4 weeks.
Lenalidomide[115,116]	**Days 1-21:** Lenalidomide 15mg orally once daily Repeat cycle every 4 weeks.
Lenalidomide + Rituximab[91,108,115,116,r,s] *Rituximab requires premedication.*	**Days 1-21:** Lenalidomide 15mg orally once daily **Days 1,8,15,22:** Rituximab 375mg/m^2 IV, **followed by:** **Days 1,8,15,22:** Rituximab 25mg intrathecal or intraventricular administered 1 hour after initiation of rituximab. Administer for one 4-week cycle, **followed by** **Days 1-21:** Lenalidomide 15mg orally once daily **Days 1,15:** Rituximab 25mg intrathecal or intraventricular. Repeat cycle every 4 weeks.

continued

▶Primary CNS Lymphoma[1] (continued)

REGIMEN	DOSING
Relapsed or Refractory Disease (continued)	
Other Recommended Regimens (No Preferred Regimens) (continued)	
Pemetrexed[117,118,aa] ***Pemetrexed requires premedication.***	**Day 1:** Pemetrexed 900mg/m^2 IV over 10 minutes. Repeat cycle every 3 weeks.
Pomalidomide[119,120]	**Days 1-21:** Pomalidomide 5mg orally once daily **Days 1,8,15,22:** Dexamethasone 40mg orally once daily. Repeat cycle every 4 weeks for 2 cycles, **followed by** **Days 1-21:** Pomalidomide 5 mg orally once daily. Repeat cycle every 4 weeks.
Retreat with High-dose Methotrexate[92,93,121-123,q,t,u]	**Day 1:** Methotrexate 3,500-8,000mg/m^2 IV over 4 hours **Day 2:** Leucovorin 25mg IV over 15 minutes or orally once starting 24 hours from initiation of Methotrexate infusion and continuing every 6 hours (until methotrexate serum concentration is <0.05micromol/L).[u] Repeat cycle every 2 weeks for a maximum of 8 cycles, **followed by:** **Day 1:** Methotrexate 3,500-8,000mg/m^2 IV over 4 hours **Day 2:** Leucovorin 25mg IV over 15 minutes or orally once starting 24 hours from initiation of Methotrexate infusion and continuing every 6 hours (until methotrexate serum concentration is <0.05micromol/L).[u] Repeat cycle every 2 weeks for 2 cycles, **followed by:** **Day 1:** Methotrexate 3,500-8,000mg/m^2 IV over 4 hours **Day 2:** Leucovorin 25mg IV over 15 minutes or orally once starting 24 hours from initiation of Methotrexate infusion and continuing every 6 hours (until Methotrexate serum concentration is <0.05micromol/L).[u] Repeat cycle every 4 weeks.
Retreat with High-dose Methotrexate with Rituximab[91-93,97-99,q-u] ***Rituximab requires premedication.***	**Day 1:** Methotrexate 8,000mg/m^2 IV over 4 hours (if CrCl >60mL/min) **OR** Methotrexate 4,000mg/m^2 IV over 4 hours (if CrCl <60mL/min), **followed by:** **Day 2:** 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 <0.05micromol/L)[u] **Day 3 or 8:** Rituximab 375mg/m^2 IV once. Repeat cycle for 2 weeks for 4-6 cycles (induction), **followed by:** **Day 1:** Methotrexate 8,000mg/m^2 IV over 4 hours (if CrCl >60mL/min) **OR** Methotrexate 4,000mg/m^2 IV over 4 hours (if CrCl <60mL/min), **followed by:** **Day 2:** 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 <0.05micromol/L).[u] Repeat cycle every 4 weeks.
Retreat with High-dose Methotrexate with Rituximab and Ibrutinib[91-93,113,124,q-u,z] ***Rituximab requires premedication.***	**Days 1,15,29 of Cycle 1:** Rituximab 500mg/m^2 IV, **followed by:** **Days 15,29 of Cycle 2-3:** Rituximab 500mg/m^2 IV, **followed by:** **Days 15 of Cycle 4:** Rituximab 500mg/m^2 IV **Days 2,16:** Methotrexate 3,500mg/m^2 IV over 4 hours every 2 weeks **Days 3,17:** Leucovorin 25mg IV over 15 minutes or orally once daily starting 24 hours from initiation of Methotrexate infusion and continuing every 6 hours (until Methotrexate serum concentration is <0.05micromol/L)[u] **Days 6-15,20-29:** Ibrutinib 560mg orally once daily (dependent on Methotrexate clearance) **OR** Ibrutinib 840mg orally once daily (dependent on Methotrexate clearance). Repeat cycle every 29 days for 4 cycles, **followed by maintenance therapy with:** **Days 1-28:** Ibrutinib 560mg orally once daily **OR** Ibrutinib 840mg orally once daily. Repeat cycle every 4 weeks.
Rituximab[91,125,r,s] ***Rituximab requires premedication.***	**Day 1:** Rituximab 375mg/m^2 IV. Repeat cycle weekly for 8 cycles.
Rituximab + TMZ[33,91,126,127,a,r,s] ***Rituximab requires premedication.***	**Day 1,8,15,22:** Rituximab 750mg/m^2. **Day 1-7,15-21:** Temozolomide 100-200mg/m^2 orally once daily. Repeat cycle every 4 weeks for 1-2 cycles (induction), **followed by:** **Day 1-5:** Temozolomide 150-200mg/m^2 orally once daily. Repeat cycle every 4 weeks for 6 cycles or until disease progression or unacceptable toxicity (consolidation), **followed by:** **Day 1:** Methylprednisolone 1,000mg IV over 90 minutes. Repeat every 4 weeks (optional maintenance).
TMZ[33,38-42,a]	**Days 1-5:** Temozolomide 150-200mg/m^2 orally once daily. Repeat cycle every 4 weeks for a maximum of 12 cycles.

continued

▶Primary CNS Lymphoma[1] (continued)

REGIMEN	DOSING
Relapsed or Refractory Disease (continued)	
Useful in Certain Circumstances	
Consider high-dose chemotherapy with autologous stem cell reinfusion with eligible patients	
High-dose Cytarabine/Etoposide followed by Thiotepa/Bisulfan/ Cyclophosphamide[49,102,103,111,11,p]	**Days 1-4:** Etoposide 10mg/kg IV continuous infusion over 24 hours daily **Days 1-4:** Cytarabine 2,000mg/m^2 IV over 2 hours every 12 hours Administer for one 4-week cycle**, followed by:** **Days 1-3:** Thiotepa 250mg/m^2 IV over 3 hours **Days 4-6:** Bisulfan 0.67-0.8mg/kg IV over 2 hours every 6 hours **Days 7-8:** Cyclophosphamide 60mg/kg IV over 30 minutes Mesna 12mg/kg IV over 15 minutes three times daily (one dose before Cyclophosphamide, then at 4 and 8 hours from the start of each Cyclophosphamide dose) Administer for one cycle prior to HSCT.
High-dose Cytarabine + Rituximab + Thiotepa followed by Rituximab + Carmustine[15,91,102,103,212,b,r,s]	See NCCN Central Nervous System Guidelines[1]
High-dose Methotrexate followed by Cytarabine + Thiotepa followed by Carmustine + Thiotepa[15,92,102,103,112,b,t]	See NCCN Central Nervous System Guidelines[1]
For intra-CSF therapy, see induction therapy above.[a]	

▶Meningiomas[1]

Recurrent or Progressive	
(No Preferred Regimens)	
Other Recommended Regimens	
Bevacizumab[62-68,j,k]	**Day 1:** Bevacizumab 10mg/kg IV. Repeat cycle every 2 weeks. **OR** **Day 1:** Bevacizumab 5-15mg/kg IV. Repeat cycle every 3 weeks.
Bevacizumab + Everolimus (Category 2B)[6,62,128,j,k]	**Days 1,15:** Bevacizumab 10mg/kg IV **Days 1-28:** Everolimus 10mg orally once daily. Repeat cycle every 4 weeks.
Sunitinib (Category 2B)[129,130]	**Days 1-28:** Sunitinib 50mg orally once daily. Repeat cycle every 6 weeks.
Useful in Certain Circumstances	
Octreotide Acetate LAR (Category 2B)[131-133]	**Day 1 of Cycles 1-2:** Octreotide Acetate (LAR) 30mg IM. Repeat cycle every 4 weeks for 2 cycles, **followed by:** **Day 1 (Beginning with Cycle 3):** Octreotide Acetate (LAR) 40mg IM. Repeat cycle every 4 weeks.
Octreotide Acetate (short-acting) (Category 2B)[134,135]	**Day 1:** Octreotide acetate 150mcg subcutaneous twice daily, **followed by:** **Day 2:** Octreotide acetate 250mcg subcutaneous twice daily, **followed by:** **Day 3-28:** Octreotide acetate 500mcg subcutaneous three times daily. Administer for one 4-week cycle, **followed by:** **Day 1-28:** Octreotide acetate 500mcg subcutaneous three times daily. Repeat cycle every 4 weeks (for at least 6 months if stable disease).

continued

Central Nervous System Cancers

▶Miscellaneous CNS Tumors[1]

REGIMEN	DOSING
Useful in Certain Circumstances (No Preferred or Other Recommended Regimens)	
Belzutifan (VHL-associated CNS hemagioblastoma not requiring immediate surgery)[136,137]	**Days 1-28:** Belzutifan 120mg orally once daily. Repeat cycle every 4 weeks.

▶Brain Metastases[1]

Tumor Agnostic (See appropriate NCCN treatment guidelines for systemic therapy recommendations for newly diagnosed brain metastases for any cancers not listed here)[1]	
Preferred Regimens	
Entrectinib (if *NTRK* gene fusion positive)[50-52]	**Days 1-28:** Entrectinib 600mg orally once daily. Repeat cycle every 4 weeks.
Larotrectinib (for *NTRK* gene fusion tumors)[53-56]	**Days 1-28:** Larotrectinib 100mg orally twice daily. Repeat cycle every 4 weeks.
TMZ 5/28 Schedule[33-36,a]	**Days 1-5:** Temozolomide 150-200mg/m^2 orally once daily. Repeat cycle every 4 weeks for a maximum of 12 cycles.
Breast Cancer (Use active agents against primary tumor)	
HER2 Positive Regimens[a]	
Ado-Trastuzumab Emtansine (T-DM1)[138,139]	**Day 1 (Cycle 1):** Ado-trastuzumab emtansine 3.6mg/kg IV over 90 minutes, **followed by:** **Day 1 (Beginning with Cycle 2):** Ado-trastuzumab emtansine 3.6mg/kg IV over 30 minutes. Repeat cycle every 3 weeks.
Capecitabine + Lapatinib[140-143]	**Days 1-14:** Capecitabine 1,000mg/m^2 orally twice daily **Days 1-21:** Lapatinib 1,250mg orally once daily. Repeat cycle every 3 weeks.
Capecitabine + Neratinib[140,144,145,cc]	**Days 1-14:** Capecitabine 750mg/m^2 orally twice daily **Days 1-21:** Neratinib 240mg orally once daily. Repeat cycle every 3 weeks.
Fam-Trastuzumab Deruxtecan-nxki[146-148]	**Day 1:** Fam-Trastuzumab 5.4 mg/kg IV. Repeat cycle every 3 weeks.
Paclitaxel + Neratinib (Category 2B)[144,149,150,cc,dd] *Paclitaxel requires premedication.*	**Days 1-21:** Neratinib 240mg orally once daily **Days 1,8,15:** Paclitaxel 80mg/m^2 IV over 1 hour. Repeat cycle every 4 weeks.
Pertuzumab + High-dose Trastuzumab[151-153,bb]	**Day 1 (Cycle 1):** Pertuzumab 840mg IV **followed by**: **Day 1 (Beginning with Cycle 2):** Pertuzumab 420mg IV Repeat cycle every 3 weeks, **with:** **Day 1:** Trastuzumab 6mg/kg IV. Repeat cycle weekly.
Tucatinib + Trastuzumab + Capecitabine (Category 1) (if previously treated with 1 or more anti-HER2-based regimens)[140,151,154,155,a,bb]	**Days 1-14:** Capecitabine 1,000mg/m^2 orally twice daily **Days 1-21:** Tucatinib 300mg orally once twice daily **Day 1 (Cycle 1):** Trastuzumab 8mg/kg IV over 90 minutes, **followed by:** **Day 2 (Beginning with Cycle 2):** Trastuzumab 6mg/kg IV over 30 minutes. Repeat cycle every 3 weeks.
HER2 Non-Specific Regimens[a]	
Capecitabine[140,156,157]	**Days 1-14:** Capecitabine 1,000mg/m^2 orally twice daily Repeat cycle every 3 weeks.
Cisplatin (Category 2B)[47,73,74,210,211]	**Day 1:** Cisplatin 100mg/m^2 IV over 2 hours. Repeat cycle every 3 weeks.

continued

▶Brain Metastases[1] (continued)

REGIMEN	DOSING
Breast Cancer (Use active agents against primary tumor) (continued)	
HER2 Non-Specific Regimens[a] (continued)	
Cisplatin + Etoposide (Category 2B)[47,49,158,211,f]	**Day 1:** Cisplatin 100mg/m^2 IV over 2 hours **Days 1,3,5:** Etoposide 100mg/m^2 IV over 1 hour daily. Repeat cycle every 3 weeks. **OR** **Day 1-3:** Cisplatin 40mg/m^2 IV over 1 hours **Days 1-3:** Etoposide 150mg/m^2 IV over 1 hour daily. Repeat cycle every 3 weeks.
Etoposide (Category 2B)[49,159,211]	**Days 1,3,5:** Etoposide 100mg/m^2 IV over 1 hour daily. Repeat cycle every 3 weeks.
High-dose Methotrexate (Category 2B)[92,93,121-123,q,t,u]	**Day 1:** Methotrexate 3,500mg/m^2 IV over 4 hours Leucovorin 25mg IV over 15 minutes or orally once starting 24 hours from initiation of Methotrexate infusion and continuing every 6 hours (until Methotrexate serum concentration is <0.05micromol/L).[u] Repeat cycle every 2 weeks.
Melanoma	
***BRAF* V600E Positive Regimens**	
Dabrafenib/Trametinib if *BRAF* V600E mutation positive[2-5]	**Days 1-28:** Dabrafenib 150mg orally twice daily. **Days 1-28:** Trametinib 2mg orally once daily. Repeat cycle every 4 weeks.
Vemurafenib/Cobimetinib if *BRAF* V600E mutation positive (Category 2B)[10-14]	**Days 1-21:** Cobimetinib 60mg orally once daily **Days 1-28:** Vemurafenib 960mg orally twice daily. Repeat cycle every 4 weeks.
***BRAF* Non-Specific Regimens**	
Ipilimumab[160,161,ee]	**Day 1:** Ipilimumab 10mg/kg IV over 90 minutes. Repeat cycle every 3 weeks for 4 cycles, **conditionally followed by:** **Day 1 (Beginning with Week 24):** Ipilimumab 10mg/kg IV over 90 minutes. Repeat cycle every 12 weeks beginning week 24.
Ipilimumab + Nivolumab (preferred)[160,162-164,ee]	**Day 1:** Nivolumab 1mg/kg IV over 30 minutes, **followed by:** **Day 1:** Ipilimumab 3mg/kg IV over 90 minutes. Repeat cycle every 3 weeks for 4 cycles, **followed by:** **Day 1:** Nivolumab 240mg IV over 30 minutes. Repeat cycle every 2 weeks. **OR** **Day 1:** Nivolumab 1mg/kg IV over 30 minutes, **followed by:** **Day 1:** Ipilimumab 3mg/kg IV over 90 minutes. Repeat cycle every 3 weeks for 4 cycles, **followed by:** **Day 1:** Nivolumab 480mg IV over 30 minutes. Repeat cycle every 4 weeks.
Nivolumab[162,163,164,166,ee]	**Day 1:** Nivolumab 240mg IV over 30 minutes. Repeat cycle every 2 weeks. **OR** **Day 1:** Nivolumab 480mg IV over 30 minutes. Repeat cycle every 4 weeks.
Pembrolizumab[167-169,ee]	**Day 1:** Pembrolizumab 10mg/kg IV over 30 minutes. Repeat cycle every 2 weeks. **OR** **Day 1:** Pembrolizumab 200mg IV over 30 minutes. Repeat cycle every 2 weeks.
Non-Small Cell Lung Cancer (Use active agents against primary tumor)	
***EGFR*-Sensitizing Mutation Positive Regimens**[a]	
Afatinib (Category 2B)[170-172]	**Days 1-28:** Afatinib 40mg orally once daily. Repeat cycle every 4 weeks.

continued

▶Brain Metastases[1] (continued)

REGIMEN	DOSING
Non-Small Cell Lung Cancer (Use active agents against primary tumor) (continued)	
***EGFR*-Sensitizing Mutation Positive Regimens**[a] (continued)	
Gefitnib (Category 2B)[173-175]	**Days 1-28:** Gefitnib 250mg orally once daily. Repeat cycle every 4 weeks.
Osimertinib[176-179]	**Days 1-28:** Osimertinib 80mg orally once daily. Repeat cycle every 4 weeks.
Pulsatile Erlotinib[180-183]	**Days 1,8,15,22:** Erlotinib 1,500mg orally once daily. Repeat cycle every 4 weeks. **OR** **Days 1-28:** Erlotinib 150mg orally once daily. Repeat cycle every 4 weeks. **OR** **Days 1-2,8-9,15-16:** Erlotinib 1,200mg orally once daily, **followed by:** **Days 3-7,10-14,17-21:** Erlotinib 50mg orally once daily. Repeat cycle every 3 weeks.
***MET* Exon 14 Skipping Mutated Regimens**[a]	
Capmatinib[184,185]	**Days 1-28:** Capmatinib 400mg orally twice daily. Repeat cycle every 4 weeks.
***RET* Fusion-Positive Regimens**	
Selpercatinib[186,187]	**Days 1-28:** Selpercatinib 120mg orally twice daily (<50mg); 160mg orally twice daily (≥50kg). Repeat cycle every 4 weeks.
***ALK* Rearrangement Positive Regimens**[a]	
Alectinib[188-190]	**Days 1-28:** Alectinib 600mg orally twice daily. Repeat cycle every 4 weeks.
Brigatinib[191-193]	**Days 1-7:** Brigatinib 90mg orally once daily, **followed by:** **Days 8-28:** Brigatinib 180mg orally once daily. Administer for one 4-week cycle, **followed by:** **Days 1-28:** Brigatinib 180mg orally once daily. Repeat cycle every 4 weeks.
Ceritinib[194-196]	**Days 1-28:** Ceritinib 450mg orally once daily. Repeat cycle every 4 weeks.
Lorlatinib[197,198]	**Days 1-28:** Lorlatinib 100mg orally once daily. Repeat cycle every 4 weeks.
***ALK* Rearrangement Positive or *ROS1* Rearrangement Positive Regimens**[a]	
Crizotinib (Category 2B)[199,200]	**Days 1-28:** Crizotinib 250mg orally twice daily. Repeat cycle every 4 weeks.
PD-L1 Positive Regimens[a]	
Nivolumab[162,163,165,166,ee]	**Day 1:** Nivolumab 240mg IV over 30 minutes. Repeat cycle every 2 weeks. **OR** **Day 1:** Nivolumab 480mg IV over 30 minutes. Repeat cycle every 4 weeks.
Pembrolizumab[167-169,ee]	**Day 1:** Pembrolizumab 10mg/kg IV over 30 minutes. Repeat cycle every 2 weeks. **OR** **Day 1:** Pembrolizumab 200mg IV over 30 minutes. Repeat cycle every 2 weeks.
Small Cell Lung Cancer (Use active agents against primary tumor)	
Preferred Regimen	
Topotecan (Category 2B)[201,202]	**Days 1-5:** Topotecan 1.5mg/m^2 IV over 30 minutes. Repeat cycle every 3 weeks.

continued

▶Brain Metastases[1] (continued)

REGIMEN	DOSING
Lymphoma (Use active agents against primary tumor)	
Preferred Regimen	
High-dose Methotrexate (Category 2B)[92,93,121-123,t,u]	**Day 1:** Methotrexate 3,500mg/m^2 IV over 4 hours **Day 2:** Leucovorin 25mg IV over 15 minutes or orally once starting 24 hours from initiation of Methotrexate infusion and continuing every 6 hours (until Methotrexate serum concentration is <0.05micromol/L).[u] Repeat cycle every week for a maximum of 12 cycles.

▶Leptomeningeal and Spine Metastases[1]

Non-Small Cell Lung Cancer (Use active agents against primary tumor)	
Systemic therapy specific to primary cancer type; emphasizing drugs with good CNS penetration.	
Intra-CSF Systemic Chemotherapy	
Cytarabine[103,203]	**Days 1,4:** Cytarabine 50mg intrathecal or intraventricular. Repeat cycle weekly for 4 cycles (induction), **followed by:** **Day 1:** Cytarabine 50mg intrathecal or intraventricular. Repeat cycle for weekly for 8 cycles if CSF cytology negative (consolidation), **followed by:** **Day 1:** Cytarabine 50mg intrathecal or intraventricular. Repeat cycle every 2 weeks for 2 cycles (consolidation), **followed by:** **Day 1:** Cytarabine 50mg intrathecal or intraventricular. Repeat cycle every 4 weeks for 4 cycles (maintenance).
Etoposide[49,204]	**Days 1-5:** Etoposide 0.5mg intrathecal or intraventricular. Repeat cycle for 2 weeks for 4 cycles, **followed by:** **Days 1-5:** Etoposide 0.5mg intrathecal or intraventricular. Repeat cycle every 4 weeks (maintenance if CSF cytology negative).
Methotrexate[92,111,203]	**Days 1,4:** Methotrexate 10-15mg intrathecal or intraventricular. Repeat cycle for 1 week for 4 cycles (induction), **followed by:** **Day 1:** Methotrexate 10-15mg intrathecal or intraventricular. Repeat cycle for 1 week for 4 cycles if CSF cytology negative (consolidation), **followed by:** **Day 1:** Methotrexate 10-15mg intrathecal or intraventricular. Repeat cycle every 2 weeks for 4 cycles (consolidation), **followed by:** **Day 1:** Methotrexate 10-15mg intrathecal or intraventricular. Repeat cycle every 4 weeks (maintenance).
Thiotepa[102,205,206]	**Day 1,4:** Thiotepa 10mg intrathecal or intraventricular. Repeat cycle weekly for 8 cycles (induction), **followed by:** **Day 1:** Thiotepa 10mg intrathecal or intraventricular. Repeat cycle weekly for 4 cycles if CSF cytology negative (consolidation), **followed by:** **Day 1:** Thiotepa 10mg intrathecal or intraventricular. Repeat cycle every 4 weeks for 4 cycles (maintenance).
Topotecan[201,207]	**Day 1,4,8,11:** Topotecan 0.4mg intrathecal or intraventricular. Repeat cycle every 2 weeks for 3 cycles (induction), **followed by:** **Day 1,8:** Topotecan 0.4mg intrathecal or intraventricular. Repeat cycle every 2 weeks for 3 cycles (consolidation), **followed by:** **Day 1:** Topotecan 0.4mg intrathecal or intraventricular. Repeat cycle every 2 weeks for 8 cycles (maintenance 1), **followed by:** **Day 1:** Topotecan 0.4mg intrathecal or intraventricular. Repeat cycle every 4 weeks (maintenance 2).
Lymphoma	
High-dose Methotrexate[92,93,121-123,q,t,u]	**Day 1:** Methotrexate 3,500mg/m^2 IV over 4 hours **Day 2:** Leucovorin 25mg IV over 15 minutes or orally once starting 24 hours from initiation of Methotrexate infusion and continuing every 6 hours (until Methotrexate serum concentration is <0.05micromol/L).[u] Repeat cycle weekly for a maximum of 12 cycles.
Rituximab (Intra-CSF systemic chemotherapy)[91,107,108,a,r] *Rituximab requires premedication.*	**Days 1,4:** Rituximab 25mg intrathecal or intraventricular Repeat cycle for weekly for 4 cycles (induction), **followed by:** **Days 1,4:** Rituximab 25mg intrathecal or intraventricular Repeat cycle every 4 weeks if CSF cytology negative (maintenance).

continued

▶Leptomeningeal and Spine Metastases[1] (continued)

REGIMEN	DOSING
Breast Cancer	
High-dose Methotrexate[92,93,121-123,q,t,u]	**Day 1:** Methotrexate 3,500mg/m^2 IV over 4 hours **Day 2:** Leucovorin 25mg IV over 15 minutes or orally once starting 24 hours from initiation of Methotrexate infusion and continuing every 6 hours (until Methotrexate serum concentration is <0.05micromol/L).[u] Repeat cycle every 2 weeks.
Methotrexate (Intra-CSF systemic chemotherapy)[92,111,204,a]	**Days 1,4:** Methotrexate 10-15mg intrathecal or intraventricular. Repeat cycle weekly for 4 cycles (induction), **followed by:** **Day 1:** Methotrexate 10-15mg intrathecal or intraventricular. Repeat cycle weekly for 4 cycles if CSF cytology negative (consolidation), **followed by:** **Day 1:** Methotrexate 10-15mg intrathecal or intraventricular. Repeat cycle every 2 weeks for 4 cycles (consolidation), **followed by:** **Day 1:** Methotrexate 10-15mg intrathecal or intraventricular. Repeat cycle every 4 weeks (maintenance).
Trastuzumab (HER2 positive) (Intra-CSF systemic chemotherapy)[152,208,209,a,bb]	**Days 1:** Trastuzumab 25-150mg intrathecal or intraventricular. Repeat cycle for 1-3 weeks.
Non-Small Cell Lung Cancer	
Weekly Pulse Erlotinib (for *EGFR* exon 19 deletion or exon 21 L858R mutation) (Category 2B)[180-183,a]	**Days 1,8,15,22:** Erlotinib 1,500mg orally once daily. Repeat cycle every 4 weeks. **OR** **Days 1-28:** Erlotinib 150mg orally once daily. Repeat cycle every 4 weeks. **OR** **Days 1-2,8-9,15-16:** Erlotinib 1,200mg orally once daily, **followed by:** **Days 3-7,10-14,17-21:** Erlotinib 50mg orally once daily. Repeat cycle every 3 weeks.
Osimertinib (for *EGFR* mutation positive)[176-179]	**Days 1-28:** Osimertinib 80mg orally once daily. Repeat cycle every 4 weeks.
Metastatic Spine Tumors	
Use regimen for disease-specific site.	

[a] ALK = anaplastic lymphoma kinase; CR = complete response; CrCl = creatinine clearance; CSF = cerebral spinal fluid or colony-stimulating factor; EGFR = epidermal growth factor receptor; HER2 = human epidermal growth factor receptor 2; HSCT = hematopoietic stem cell transplantation; KPS = Karnovsky performance scale; transition; RT = radiation therapy; PA = pilocytic astrocytoma; PCV = Procarbazine/Lomustine/Vincristine; PD-L1 = programmed death-ligand 1; PXA = pleomorphic xanthoastrocytoma; RT = radiotherapy; SEGA = subependymal giant cell astrocytoma; TMZ = temozolomide; TTF = tumor treating fields; WBRT = whole brain radiotherapy

[b] Cumulative Lomustine and Carmustine dosages should be monitored.

[c] When PCV is recommended, Carmustine may be substituted for Lomustine.

[d] There are multiple reasonable options, but there is no uniform standard of care at this time for recurrent disease.

[e] For patients not previously treated.

[f] Hydration is required with supplemental electrolytes pre- and post-administration of cisplatin.

[g] The NCCN panel recommends that PCV be administered right after RT (as per EORTC 26951) since the intensive PCV regimen given prior to RT (RTOG 9402) was not tolerated as well.

[h] Consider TMZ if tumor is *MGMT* promoter methylated.

[i] Strongly suggest consideration of clinical trials prior to treating recurrent disease with standard chemotherapy, as additional therapies may eliminate the majority of clinical trial options.

[j] Patients who have evidence of radiographic progression may benefit from continuation of Bevacizumab to prevent rapid neurologic deterioration.

[k] An FDA-approved biosimilar is an appropriate substitute for bevacizumab.

[l] Bevacizumab + chemotherapy can be considered if Bevacizumab monotherapy fails and it is desirable to continue the steroid-sparing effects of bevacizumab.

[m] Moderate to significant myelosuppression was observed, but the toxicity profile for this regimen is not fully defined.

[n] There are no identified targeted agents with demonstrated efficacy in glioblastoma. However, the panel encourages molecular testing of tumor because if a driver mutation is detected, it may be reasonable to treat with a targeted therapy on a compassionate use basis and/or the patient may have more treatment options in the context of a clinical trial. Molecular testing also has a valuable role in improving diagnostic accuracy and prognostic stratification that may inform treatment selection.

[o] Omission of Vincristine during radiotherapy phase of therapy or dose modification may be required for adults because they do not tolerate this regimen as well. Data supporting Vincristine's use have been found in pediatric trials only. Patients should be monitored closely for neurologic toxicity with periodic exams.

[p] Oral hydration is strongly encouraged with Cyclophosphamide; poorly hydrated patients may need supplemental IV hydration (combined oral and IV hydration of 2,000-3,000mL/day on day of chemotherapy).

[q] Consider glucarpidase (carboxypeptidase G2) for prolonged Methotrexate clearance due to Methotrexate-induced renal toxicity.

[r] An FDA-approved biosimilar agent may be substituted for Rituximab. Premedication for infusion reactions is required. The recommended dosing is diphenhydramine 12.5mg-50mg IV/orally 30-60 minutes pre-Rituximab AND acetaminophen 650 mg orally 30-60 minutes pre-Rituximab.

continued

[s] Hepatitis B testing is indicated because of the risk of reactivation with immunotherapy + chemotherapy.

[t] Alkaline hydration is required pre- and post-administration of high-dose Methotrexate. Preservative-free formulation must be used for high-dose Methotrexate to prevent benzyl alcohol toxicity.

[u] Leucovorin dose should be titrated for delayed Methotrexate clearance or increases in serum creatinine (<10-fold decrement in serum Methotrexate levels per day).

[v] Other combinations with Methotrexate may be used.

[w] There are concerns about WBRT being used in the trials that evaluated these regimens, especially for patients older than 65 years of age.

[x] This regimen is associated with significant myeloid toxicity

[y] CSF's may be considered for primary prophylaxis based on the febrile neutropenia risk of the chemotherapy regimen.

[z] Ibrutinib is associated with risk of aspergillus infection.

[aa] For Pemetrexed: premedication and supplemental medications to reduce the incidence and severity of hematologic, gastrointestinal, and cutaneous toxicities are required. The recommended dosing is: Vitamin 12 1,000mcg intramuscularly during the week preceding the first cycle and every 3 cycles thereafter AND folic acid 100-1,000mcg orally once daily starting 7 days before the first cycle and continuing for 21 days after the last dose of Pemetrexed AND dexamethasone 4 mg orally twice daily starting the day prior to Pemetrexed.

[bb] An FDA-approved biosimilar is an appropriate substitute for Trastuzumab.

[cc] For Neratinib: initiate antidiarrheal prophylaxis with loperamide with the first dose of Neratinib, and continue during the first 8 weeks of treatment. Additional antidiarrheal agents may be required to manage diarrhea in patients with loperamide-refractory diarrhea.

[dd] Premedication for hypersensitivity is required for Paclitaxel: famotidine 20mg IV or orally (or equivalent H2 blocker) 30-60 minutes pre-paclitaxel AND diphenhydramine 12.5-50mg IV or orally 30-60 minutes pre-Paclitaxel AND dexamethasone 10mg IV 30 minutes pre-Paclitaxel. In the absence of infusion reactions for Doses 1-3, may consider dexamethasone 4mg IV 30 minutes pre-Paclitaxel starting with Dose 4.

[ee] Early- and late-onset immune-related adverse events affecting multiple organ systems can occur in patients receiving immune checkpoint inhibitors. Patients with neurologic or life-threatening autoimmune disorders as well as those receiving high levels of immunosuppression for their underlying disease should be approached with caution when considering immunotherapy. All patients will require extensive resources including ongoing intensive monitoring and supportive care.

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