BRAIN CANCER TREATMENT REGIMENS (Part 1 of 9)

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 NCCN 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 National Comprehensive Cancer Network 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.

Systemic Therapy for Adult Low-Grade Infiltrative Supratentorial Astrocytoma/Oligodendroglioma¹

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

Adjuwant Treatment

Adjuvant Treatment	
REGIMEN	DOSING
Temozolomide ²⁻⁴	Days 1-49: Temozolomide 75mg/m ² orally. Repeat cycle every 11 weeks (7 weeks on/4 weeks off) for 6 cycles. OR For children/adolescents: Temozolomide monthly 5-day courses at doses of 200mg/m ² /day (patients with no prior craniospinal irradiation [CSI]) or
	OR Days 1-21: Temozolomide 75mg/m ² /day.
	Repeat cycle every 28 days.
Recurrence or Progressive	, Low Grade Disease
Temozolomide ^{2,5} *	Days 1-49: Temozolomide 75mg/m ² orally. Repeat cycle every 11 weeks (7 weeks on/4 weeks off) for 6 cycles. OR Days 1-5: Temozolomide 150mg/m ² to 200mg/m ² ; when patients progress
	during conventional temozolomide treatment, change temozolomide to a 50mg/m ² daily regimen. Repeat cycle every 28 days.
Combination PCV regimens (lomustine + procarbazine + vincristine) ⁶	Day 1: Lomustine 110mg/m ² orally Days 8–21: Procarbazine 60mg/m ² orally once daily Days 8 and 29: Vincristine 1.4mg/m ² (maximum 2mg) IV. Repeat every 6 weeks.
Platinum-based regimen: Carboplatin ⁷	Day 1: Carboplatin 350mg/m ² Days 1–3: Teniposide 50mg/m ² . Repeat cycle every 4 weeks.
Platinum-based regimen: Carboplatin ⁸	Carboplatin 560mg/m ² IV at 4-week intervals; continued until disease progression, unacceptable toxicity, or for 12 additional courses after achieving maximal response.
Platinum-based regimen: Cisplatin ⁹	Days 1–3: Cisplatin 25mg/m ² /day IV + etoposide 100mg/m ² /day IV. Repeat cycle every 4 weeks for first 3 cycles, then repeat every 5 weeks for next 3 cycles, then repeat every 6 weeks for the last 3 cycles; total 10 cycles over approximately 10–11 months (total dose 750mg/m ² cisplatin and 3,000mg/m ² etoposide).
Systemic Therapy for Anap	lastic Gliomas ¹
Adjuvant Treatment	
Temozolomide ^{10,11}	Days 1–5: Temozolomide 200mg/m ² /day orally. Repeat cycle every 4 weeks until disease progression or for up to 24 cycles.
PCV with deferred RT ¹⁰	Day 1: Lomustine 110mg/m ² orally Days 8–21: Procarbazine 60mg/m ² orally once daily Days 8 and 29: Vincristine 1.4mg/m ² (maximum 2mg) IV. Repeat every 6 weeks.
Concurrent temozolomide (with RT) ¹²	2 Gy given 5 days/week for 6 weeks plus continuous daily oral temozolomide (75mg/m²/day, 7 days per week from the first to the last day of radiotherapy), followed by 6 cycles of adjuvant temozolomide 150–200mg/m²/day for 5 days. Repeat cycle every 28 days.
	continuea

BRAIN CANCER TREATMENT REGIMENS (Part 2 of 9)

Systemic Therapy for Anaplastic Gliomas¹ (continued) **Recurrence/Salvage Therapy** REGIMEN DOSING Temozolomide^{3,5,13} Temozolomide 50mg/m² daily for up to 1 year or until disease progression. For children/adolescents: Temozolomide monthly 5-day courses at doses of 200mg/m²/day (patients with no prior CSI) or 180mg/m²/day (prior CSI). OR Days 1-5: Temozolomide 150mg/m² to 200mg/m² 5 days of each 28-day cycle; when patients progress during conventional temozolomide treatment, change temozolomide to a 50mg/m² daily regimen. ٨D Days 1-5: Temozolomide 150mg/m² to 200mg/m². Repeat cycle every 28 days. Lomustine or carmustine¹⁴ Day 1: Lomustine 100-130mg/m²/day orally. Repeat cycle every 6 weeks. **Combination PCV regimens** Day 1: Lomustine 110mg/m² orally Days 8-21: Procarbazine 60mg/m² orally once daily (lomustine + procarbazine + vincristine)6 Days 8 and 29: Vincristine 1.4mg/m² (maximum 2mg) IV. Repeat every 6 weeks. Bevacizumab15-17† Day 1: Bevacizumab 10mg/kg IV. Repeat cycle every 14 days. Bevacizumab + irinotecan18,19‡ Day 1: Bevacizumab 10mg/kg IV plus irinotecan 125mg/m². Repeat cycle every 2 weeks. OR Bevacizumab 10mg/mg² IV plus irinotecan 340mg/m² IV in patients receiving enzyme-inducing antiepileptic drugs (EIAED). Repeat cycle every 14 days. Bevacizumab + nitrosurea²⁰ Days 1 and 15: Bevacizumab 10mg/kg IV Davs 1 and 8: Fotemustine 75mg/m² IV Followed after a 3-week interval by a maintenance phase of bevacizumab 10mg/kg IV plus fotemustine 75mg/m² IV. Repeat cycle every 3 weeks. Bevacizumab + carboplatin^{21,22} **Day 1:** Bevacizumab 10mg/kg IV plus carboplatin AUC 4-6mg·min/mL. depending on the patient's prior treatment history and bone marrow reserves; cycle 2 doses of carboplatin (every 28 days) and 3 doses of bevacizumab (every 14 days) and lasted 6 weeks. Irinotecan^{23,24} Day 1: Irinotecan 350mg/m² IV to patients on non-enzyme-inducing antiepileptic drugs (NEIAED) or 600mg/m² to patients on EIAED. Repeat cycle every 21 days. **OR** Day 1: Irinotecan 350mg/m² IV. Repeat cycle every 21 days. Platinum-based regimen: Day 1: Carboplatin 350mg/m² Carboplatin⁷ Days 1-3: Teniposide 50mg/m². Repeat cycle every 4 weeks. Carboplatin 560mg/m² IV at 4-week intervals: continued until disease progression. Platinum-based regimen: Carboplatin⁸ unacceptable toxicity, or for 12 additional courses after achieving maximal response. Platinum-based regimen: Days 1-3: Cisplatin 25mg/m²/day IV + etoposide 100mg/m²/day IV. Cisplatin⁹ Repeat cycle every 4 weeks for first 3 cycles, then repeat every 5 weeks for next 3 cycles, then repeat every 6 weeks for the last 3 cycles; total 10 cycles over approximately 10-11 months (total dose 750mg/m² cisplatin and 3.000mg/m² etoposide). Cyclophosphamide^{25,26} Days 1-2: Cyclophosphamide 750mg/m² IV. Repeat cycle every 28 days. Etoposide27 Etoposide 50mg/day given until the neutrophil count dropped to < 1.0 x 109/L or the platelets fell to $< 75 \times 109/L$ and resumed when the counts rose to normal levels.

BRAIN CANCER TREATMENT REGIMENS (Part 3 of 9)

BRAIN CANCER TREATMENT REGIMENS (Part 3 of 9)		
Systemic Therapy for Anaplastic Oligoastrocytoma ¹		
Adjuvant Treatment		
REGIMEN	DOSING	
Radiotherapy + PCV for 1p19q co-deleted (category 1) ²⁸	59.6 4 Gy of RT, followed by 6 cycles of standard PCV: Day 1: Lomustine 110mg/m ² orally Days 8-21: Procarbazine 60mg/m ² orally once daily Days 8 and 29: Vincristine 1.4mg/m ² (maximum 2mg) IV. Repeat every 6 weeks.	
Systemic Therapy for Gliobla	stoma ¹	
Adjuvant Treatment		
Concurrent temozolomide (with RT) ¹²	2 Gy given 5 days/week for 6 weeks plus continuous daily oral temozolomide (75mg/m²/day, 7 days per week from the first to the last day of radiotherapy), followed by 6 cycles of adjuvant temozolomide 150–200mg/m²/day for 5 days. Repeat cycle every 28 days.	
Post-RT or non-post temozolomide ²⁹	Days 1–5: Temozolomide 150–200mg/m ² /day orally for 5 days. Repeat cycle every 28 days.	
Temozolomide + standard RT ³⁰	Days 1–5: Temozolomide 200mg/m ² , orally plus: Standard RT: 60.0 Gy administered in 2.0 Gy fractions over 6 weeks.	
Recurrence/Salvage Therapy	<u>/</u>	
Bevacizumab ^{31-33†}	Day 1: Bevacizumab 10mg/kg IV. Repeat cycle every 14 days.	
Bevacizumab + irinotecan ^{19,31-33‡}	Day 1: Bevacizumab 10mg/kg IV. Repeat cycle every 14 days. After tumor progression, immediately treat with bevacizumab 10mg/kg IV plus irinotecan 340mg/m ² or 125mg/m ² IV every 14 days, depending on use of EIAEDs.	
Bevacizumab + nitrosurea ^{20‡}	Days 1 and 15: Bevacizumab 10mg/kg IV Days 1 and 8: Fotemustine 75mg/m ² IV Followed after a 3-week interval by a maintenance phase of bevacizumab 10mg/kg IV plus fotemustine 75mg/m ² IV. Repeat cycle every 3 weeks.	
Bevacizumab + carboplatin ^{21,22‡}	Day 1: Bevacizumab 10mg/kg IV plus carboplatin AUC 4–6mg • min/mL, depending on the patient's prior treatment history and bone marrow reserves; cycle 2 doses of carboplatin (every 28 days) and 3 doses of bevacizumab (every 14 days) for 6 weeks.	
Temozolomide ^{5,29,34}	 Days 1-5: Temozolomide 150mg/m² to 200mg/m²; when patients progress during conventional temozolomide treatment, change temozolomide to a 50mg/m² daily regimen. Repeat cycle every 28 days. OR 2 Gy given 5 days/ week for 6 weeks plus continuous daily oral temozolomide (75mg/m²/day, 7 days per week from the first to the last day of radiotherapy), followed by 6 cycles of adjuvant temozolomide 150-200mg/m²/day for 5 days. OR OR OR 2 Gy every 28 days. OR 2 Gy given 5 days/ week from the first to the last day of radiotherapy), followed by 6 cycles of adjuvant temozolomide 150-200mg/m²/day for 5 days. OR OR 	
	Chemotherapy-naive patients: Days 1-5: Temozolomide 200mg/m ² /day. Chemotherapy-experienced patients: Days 1-5: Temozolomide 150mg/m ² /day, increasing to 200mg/m ² /day in the absence of grade 3/4 toxicity. Repeat cycle every 28 days.	
Lomustine or carmustine ¹⁴	Day 1: Lomustine 100–130mg/m ² /day orally. Repeat cycle every 6 weeks.	
Combination PCV regimens (lomustine + procarbazine + vincristine) ⁶	Day 1: Lomustine 110mg/m ² orally Days 8–21: Procarbazine 60mg/m ² orally once daily Days 8 and 29: Vincristine 1.4mg/m ² (maximum 2mg) IV. Repeat every 6 weeks.	
Cyclophosphamide (category 2B) ²⁵	Days 1-2: Cyclophosphamide 750mg/m ² IV. Repeat cycle every 28 days.	
	continued	

BRAIN CANCER TREATMENT REGIMENS (Part 4 of 9)

DRAIN CANCER TREATMENT REGIMENS (Part 4 01 9)		
Systemic Therapy for Glioblastoma ¹ (continued)		
Recurrence/Salvage Thera	ipy (continued)	
REGIMEN	DOSING	
Platinum-based regimen: Carboplatin ⁷	Day 1: Carboplatin 350mg/m ² Days 1–3: Teniposide 50mg/m ² . Repeat cycle every 4 weeks.	
Platinum-based regimen: Carboplatin ⁸	Carboplatin 560mg/m ² IV at 4-week intervals; continued until disease progression, unacceptable toxicity, or for 12 additional courses after achieving maximal response.	
Platinum-based regimen: Cisplatin ⁹	Days 1–3: Cisplatin 25mg/m ² /day IV + etoposide 100mg/m ² /day IV. Repeat cycle every 4 weeks for first 3 cycles, then repeat every 5 weeks for next 3 cycles, then repeat every 6 weeks for the last 3 cycles; total 10 cycles over approximately 10–11 months (total dose 750mg/m ² cisplatin and 3,000mg/m ² etoposide).	
Systemic Therapy for Intra	cranial and Spinal Ependymoma (excluding supependymoma) ¹	
Recurrence Therapy		
Etoposide ²⁷	Etoposide 50mg/day given until the neutrophil count dropped to $<1.0 \times 109/L$ or the platelets fell to $<75 \times 109/L$ and resumed when the counts rose to normal levels.	
Bevacizumab ^{31-33†}	Day 1: Bevacizumab 10mg/kg IV. Repeat cycle every 14 days.	
Temozolomide ²⁻⁴	Days 1-49: Temozolomide 75mg/m ² orally. Repeat cycle every 11 weeks (7 weeks on/4 weeks off) for 6 cycles. OR Days 1-21: Temozolomide 75mg/m ² /day. Repeat cycle every 28 days.	
Systemic Therapy for Adult N	/Iedulloblastoma and Supratentorial Primitive Neuroectodermal Tumor (PNET)	
Adjuvant Treatment		
omission of vincristine during rebecause they do not tolerate the	ospinal radiation therapy followed by either of the following regimens. Note that adiation therapy phase of therapy or dose modification may be required for adults his regimen as well. Data supporting the use of vincristine has been found in pediatric closely monitored for neurologic toxicity with periodic exams.	
Vincristine + cisplatin + lomustine ³⁵	During craniospinal radiotherapy (RT) Day 1: Lomustine 75mg/m ² orally Day 2: Cisplatin 75mg/m ² IV Days 2, 8 and 15: Vincristine 1.5mg/m ² IV bolus, max 2mg bolus; up to max 8 doses	
Vincristine + cisplatin + cyclophosphamide ³⁶	Day 1: Cisplatin 75mg/m ² IV Days 2, 8 and 15: Vincristine 1.5mg/m ² IV bolus, max 2mg bolus Days 22, 23: Cyclophosphamide 1,000mg/m ² IV.	
Recurrence/Salvage Thera	ру	
	ler high-dose chemotherapy with autologous stem cell reinfusion in patients who with conventional doses of salvage chemotherapy or have no residual disease after	
Carboplatin + thiotepa + etoposide ³⁶	Days –8 to –6: Carboplatin AUC 7mg•min/mL IV, maximum 500mg/m²/day) Days –5 to –3: Thiotepa 300mg/m²/day IV plus etoposide 250mg/m²/day I Day 0: Autologous stem cell rescue (ASCR).	
	nigh-dose chemotherapy with autologous stem cell reinfusion in patients who achieve ventional doses of salvage chemotherapy or have no residual disease after	
Temozolomide ³	For children/adolescents: Temozolomide monthly 5-day courses at doses of 200mg/m ² /day (patients with no prior CSI) or 180mg/m ² /day (prior CSI).	
Oral etoposide ^{37,38}	Days 1–21: Etoposide 50mg daily. Repeat cycle every 4 weeks.	

BRAIN CANCER TREATMENT REGIMENS (Part 5 of 9)

Primary Treatment	
REGIMEN	DOSING
High dose methotrexate + chemotherapy ³⁹⁻⁴¹	High dose methotrexate combined with the following plus radiation therapy: Weeks 1, 3, 5, 7, and 9: MTX 2.5g/m ² + vincristine 1.4mg/m ² with a cap of 2.8mg (2m Weeks 1, 5, and 9: Procarbazine 100mg/m ² /day orally for 7 days Weeks, 2, 4, 6, 8, and 10: Methotrexate 12mg intraventicularly Weeks 1, 3, 5, 7, and 9: Leucovorin 20mg every 6 hours orally for 12 doses Weeks, 2, 4, 6, 8, and 10: Leucovorin 10mg orally twice daily for 8 doses Weeks 11-15: Whole-brain RT in 1.80-Gy fractions for a total dose of 45 Gy Weeks 16 and 19: Cytarabine 3mg/m ² /day IV for 2 days. Repeat for 5 cycles. OR
	Day 1: MTX 3.5g/m ² Days 2-3: Cytarabine 2g/m ² IV twice a day. OR Day 1: MTX 4gm/m ² IV, followed by leucovorin 20-25mg IV every 6 hours starting 24 hours after MTX for 72 hours or until serum MTX level <1 x 10-8mg/dL. Increase leucovorin to 40mg every 4 hours if MTX level <1 x 10-8mg/dL at 48 hours or >1 x 10-8mg/dL at 72 hours. Days 3-5: Ifosfamide 1.5gm/m ² IV + mesna 400mg IV before ifosfamide, then 4 hours and 8 hours after.
High dose methotrexate (MTX 2.5-4.0mg/m²) + chemotherapy ± monoclonal antibody ⁴²	Day 1: Rituximab 500mg/m ² IV Day 2: MTX 3.5mg/m ² IV plus vincristine 1.4mg/m ² Procarbazine 100mg/m ² /day was administered for 7 days with odd-numbered cycle
	High dose methotrexate combined with the following plus radiation therapy deferred radiation therapy: Induction therapy MTX 8g/m ² IV administered every 2 weeks until complete response achieved or max of 8 cycles reached. Consolidation MTX 8g/m ² IV administered every 2 weeks for 2 cycles. Maintenance therapy MTX 8g/m ² IV administered every 4 weeks for 11 cycles. Plus Day 1: Rituximab 375mg/m ² IV. Repeat cycle every 4 weeks for 4 cycles. OR Induction therapy Days 1-5: Temozolomide 150-200mg/m ² orally daily, after rituximab infusion. Repeat cycle every 4 weeks for 4 cycles. Maintenance therapy Days 1-5: Temozolomide 150-200mg/m ² orally daily. Repeat cycle every 4 weeks for 8 cycles.
Consider urgent glucarpidase (carboypeptidase G2) for prolonged MTX clearance due to MTX-induced renal toxicity ⁴⁶	Glucarpidase, one 50U/kg dose IV, 2 doses 24 hours apart, or 3 doses every 4 hours; thymidine 8 g/m ² /day IV administered as continuous IV infusion for \geq 48 hours after the last dose of glucarpidase; leucovorin 1g/m ² IV every 6 hours before administration of glucarpidase and at a dose of 250mg/m ² IV every 6 hours for 48 hours after administration of the last dose of glucarpidase.
Recurrent or Progressive Dise	ease
	with autologous stem cell reinfusion in patients who achieve a complete of salvage chemotherapy or have no residual disease after re-resection. ³⁵
Re-treat with high-dose methotrexate ⁴³	Induction therapy MTX 8g/m ² IV administered every 2 weeks until complete response achieved or max of 8 cycles reached. Consolidation MTX 8g/m ² IV administered every 2 weeks for 2 cycles.

BRAIN CANCER TREATMENT REGIMENS (Part 6 of 9)

	ANCER TREATMENT REGIMENS (Part 6 01 9)	
Primary CNS Lymphoma ¹ (continued) Recurrent or Progressive Disease (continued)		
Rituximab + temozolomide47	Induction therapy Day 1: Rituximab 375mg/m² IV, plus Days 1-5: Temozolomide 150-200mg/m² orally daily, administered after rituximab infusión. Repeat cycle every 4 weeks for 4 cycles. Maintenance therapy Days 1-5: Temozolomide 150-200mg/m² orally daily, administered after rituximab infusion. Repeat cycle every 4 weeks for 8 cycles.	
Pemetrexed ⁴⁸	Pemetrexed 900mg/m ² IV every 21 days for 6 weeks.	
Meningioma ¹		
Interferon-alfa ⁴⁹	$\alpha\text{-IFN}$ 106 units/m² SC every other day for 4 weeks. Repeat cycle every 4 weeks.	
Somatostatin analog ⁵⁰	Sandostatin LAR Depot 10–30mg IM every 4 weeks.	
	(1-3) Metastatic or Multiple (>3) Metastatic Lesions ¹	
	per the regimens of the primary tumor (‡ Bevacizumab + chemotherapy can be failed monotherapy with bevacizumab)	
Carmustine wafer ⁵¹	8 wafers (7.7mg) for a total of 61.6mg implanted intracranially.	
High-dose methotrexate (MTX; breast and lymphoma) ^{52,53}	Breast: MTX 3.5g/m ² IV. Lymphoma: Treatment based on weekly high-dose MTX 3.5g/m ² and weekly intra-CSF cytarabine; oral procarbazine 100mg/m ² days 2–15 was added to patients whose bone marrow reserve could tolerate this drug.	
Capecitabine ± lapatinib, cisplatin, etoposide ⁵⁴⁻⁶²	Days 1-14: lapatinib 1,250mg orally plus capecitabine 1,000mg/m² orally twice per day. Repeat cycle every 21 days. OR Days 1-14: Capecitabine 2,000mg/m²/day in 2 divided doses for 14 days, followed by a 7-day rest and lapatinib 1,250mg once daily continuously. OR Days 1-14: Capecitabine 2,000mg/m²/day in 2 divided doses for 14 days, followed by a 7-day rest and lapatinib 1,250mg once daily continuously. OR Days 1. Cisplatin 100mg/m² IV Days 4, 6, and 8: Etoposide 100mg/m². Repeat cycle every 21 days. OR Days 1, 3, and 5 OR Days 4, 6, and 8: Etoposide 100mg/m² IV. Repeat cycle every 21 days. OR (breast) Capecitabine orally starting at a dose of 1,800mg/m²/day (up to 2,000mg/m²/day) in 2 divided doses, and temozolomide given orally once daily at a starting dose of 75mg/m²/day. Concomitant daily doses given on days 1–5 and days 8–12, with cycles repeated every 21 days until disease progression. OR (breast) Days 1-14: Capecitabine 2,000mg/m²/day orally once daily. Repeat cycle every 21 days. OR (breast) Days 1-21: Capecitabine 2,400mg/m²/day orally once daily. Repeat cycle every 21 days. OR (breast) Days 1-21: Capecitabine 2,400mg/m²/day orally once daily. Repeat cycle every 28 days.	
lpilimumab (melanoma) ⁶³	Day 1: Ipilimumab 10mg/kg IV. Repeat cycle every 21 days for a maximum 4 cycles. Individuals who were clinically stable at week 24 were eligible to receive ipilimumab 10mg/kg every 12 weeks.	
BRAF inhibitors (melanoma): Dabrafenib ⁶⁴	Dabrafenib 150mg orally twice daily.	
BRAF inhibitors (melanoma): Vemurafenib ⁶⁵	Vemurafenib 960mg orally twice daily.	

BRAIN CANCER TREATMENT REGIMENS (Part 7 of 9)

Systemic Therapy for Leptomeningeal Metastases¹

Organ-specific Systemic Chemotherapy; Emphasizing Drugs with Good CNS Penetration	
REGIMEN	DOSING
Intra-CSF chemotherapy: Liposomal (slow-release) cytarabine (lymphoma/ leukemias) ^{66,67}	Induction Liposomal cytarabine 50mg intrathecally once every 14 days for 2 doses. Maintenance Liposomal cytarabine 50mg every 14 days for 2 doses, followed by 50mg every 28 days for 2 doses.
	OR Induction Liposomal cytarabine 50mg intraventricularly every 14 days for 3 doses plus rituximab 25mg intraventricularly twice per week for 8 doses. Maintenance Liposomal cytarabine 50mg intraventricularly once weekly plus rituximab 25mg intraventricularly twice weekly for 4 weeks.
Intra-CSF chemotherapy: topotecan ⁶⁸	Repeat cycle every 4 weeks until disease progression Topotecan 400 µg intraventrically twice weekly for 6 weeks.
Intra-CSF chemotherapy: etoposide ⁶⁹	Induction Days 1-5: Etoposide 0.5mg/day intra-CSF every other week for 8 weeks. <u>Maintenance</u> Days 1-5: Etoposide 0.5mg/day every 4 weeks.
Intra-CSF chemotherapy: trastuzumab ⁷⁰	Cumulative dose of intrathecal trastuzumab given in clinical studies was 1,040mg (SD 697.9, median 1,215, range 55–1,675)
Intra-CSF chemotherapy: Interferon-alfa (category 2B) ⁷¹	$\mbox{\rm IFN-}\alpha$ 1 x 106 IU subcutaneously every other day 3 times per week for 4 weeks by induction.
High-dose methotrexate for lymphoma and breast ⁵²	Breast: MTX 3.5g/m ² IV.
Erlotinib (Category 2B) ⁷²	Weekly pulse erlotinib for EGFR exon 19 or exon 21 L858R mutation non-small cell lung cancer; trial demonstrates that a new schedule of erlotnib administration may overcome acquired resistance to erlotinib. Pulsatile high-dose erlotinib was found to be effective against brain metastases in patients who had progressed while on treatment with standard-dose erlotinib. Pulsatile high-dose erlotinib 1,500mg (median dose with range of 900–1,500mg) once weekly.

Systemic Therapy for Metastatic Spine Tumors

Use regimen for disease specific site

- * For patients not previously treated
- † Patients who have good performance status but evidence of radiographic progression may benefit from continuation of bevacizumab to prevent rapid neurologic deterioration
- # Bevacizumab + chemotherapy can be considered for patients who have failed monotherapy with bevacizumab

References

- NCCN Clinical Practice Guidelines in Oncology[™]. Central Nervous System Cancers. v 1.2014. Available at http://www. nccn.org/professionals/physician_gls/pdf/cns.pdf. Accessed August 18, 2014.
- Kesari S, Schiff D, Drappatz J, et al. Phase II study of protracted daily temozolomide for low-grade gliomas in adults. *Clin Cancer Res.* 2009;15:330–337.
- Nicholson HS, Kretschmar CS, Krailo M, et al. Phase 2 study of temozolomide in children and adolescents with recurrent central nervous system tumors: a report from the Children's Oncology Group. Cancer. 2007;110:1542–1550.
- Pouratian N, Gasco J, Sherman JH, Shaffrey ME, Schiff D. Toxicity and efficacy of protracted low dose temozolomide for the treatment of low grade gliomas. J Neurooncol. 2007;82:281–288.
- Perry JR, Rizek P, Cashman R, Morrison M, Morrison T. Temozolomide rechallenge in recurrent malignant glioma by using a continuous temozolomide schedule: the "rescue" approach. *Cancer*. 2008;113:2152–2157.

- Triebels VH, Taphoorn MJ, Brandes AA, et al. Salvage PCV chemotherapy for temozolomide-resistant oligodendrogliomas. *Neurology*. 2004;63:904–906.
- Brandes AA, Basso U, Vastola F, et al. Carboplatin and teniposide as third-line chemotherapy in patients with recurrent oligodendroglioma or oligoastrocytoma: a phase II study. *Ann Oncol.* 2003;14:1727–1731.
- Moghrabi A, Friedman HS, Ashley DM, et al. Phase II study of carboplatin (CBDCA) in progressive low-grade gliomas. *Neurosurg Focus*. 1998;4:e3.
- Massimino M, Spreafico F, Riva D, et al. A lower-dose, lowertoxicity cisplatin-etoposide regimen for childhood progressive low-grade glioma. J Neurooncol. 2010;100:65–71.
- Wick W, Hartmann C, Engel C, et al. NOA-04 randomized phased III trials of sequential radiochemotherapy of ana plastic glioma with procarbazine, lomustine, and vincristine or temozolamide. J Clin Oncol. 2009;27:5874–5880.

BRAIN CANCER TREATMENT REGIMENS (Part 8 of 9)

References (continued)

- Taliansky-Aronov A, Bokstein F, Lavon I, Siegal T. Temozolomide treatment for newly diagnosed anaplastic oligodendrogliomas: a clinical efficacy trial. J Neurooncol. 2006;79:153–157.
- Stupp R, Mason WP, van den Bent MJ, et al. European Organisation for Research and Treatment of Cancer Brain Tumor and Radiotherapy Groups; National Cancer Institute of Canada Clinical Trials Group. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. N Engl J Med. 2005;352:987-996.
- Perry JR, Bélanger K, Mason WP, et al. Phase II trial of continuous dose-intense temozolomide in recurrent malignant glioma: RESCUE study. J Clin Oncol. 2010;28:2051–2057.
- Wick W, Puduvalli VK, Chamberlain MC, et al. Phase III study of enzastaurin compared with lomustine in the treatment of recurrent intracranial glioblastoma. J Clin Oncol. 2010;28:1168–1174.
- Chamberlain MC, Johnston S. Bevacizumab for recurrent alkylator-refractory anaplastic oligodendroglioma. *Cancer*. 2009;115:1734-1743.
- Chamberlain MC, Johnston S. Salvage chemotherapy with bevacizumab for recurrent alkylator-refractory anaplastic astrocytoma. J Neurooncol. 2009;91:359–367.
- Norden AD, Young GS, Setayesh K, et al. Bevacizumab for recurrent malignant gliomas: efficacy, toxicity, and patterns of recurrence. *Neurology*. 2008;70:779–787.
- Taillibert S, Vincent LA, Granger B, et al. Bevacizumab and irinotecan for recurrent oligodendroglial tumors. *Neurology*. 2009;72:1601–1606.
- Vredenburgh JJ, Desjardins A, Herndon JE 2nd, et al. Phase II trial of bevacizumab and irinotecan in recurrent malignant glioma. *Clin Cancer Res*. 2007;13:1253–1259.
- Soffietti R, Rudà R, Trevisan E, et al. Phase II study of bevacizumab and nitrosourea in patients with recurrent malignant glioma: a multicenter Italian study [abstract 2012] J Clin Oncol. 2009;27(Suppl 15):90s.
- Mrugala MM, Crew LK, Fink JR, Spence AM. Carboplatin and bevacizumab for recurrent malignant glioma. Oncol Lett. 2012;4:1082–1086.
- Thompson EM, Dosa E, Kraemer DF, Neuwelt EA. Treatment with bevacizumab plus carboplatin for recurrent malignant glioma. *Neurosurgery*. 2010;67:87–93.
- Chamberlain MC, Wei-Tsao DD, Blumenthal DT, Glantz MJ. Salvage chemotherapy with CPT-11 for recurrenttemozolomide-refractory anaplastic astrocytoma. *Cancer*. 2008;112:2038–2045.
- Chamberlain MC. Salvage chemotherapy with CPT-11 for recurrent oligodendrogliomas. J Neurooncol. 2002;59:157–163.
- Chamberlain MC, Tsao-Wei DD. Salvage chemotherapy with cyclophosphamide for recurrent, temozolomide-refractory glioblastoma multiforme. *Cancer*. 2004;100:1213–1220.
- Chamberlain MC, Tsao-Wei DD, Groshen S. Salvage chemotherapy with cyclophosphamide for recurrent temozolomiderefractory anaplastic astrocytoma. *Cancer.* 2006;106:172–179.
- Fulton D, Urtasun R, Forsyth P. Phase II study of prolonged oral therapy with etoposide (VP16) for patients with recurrent malignant glioma. J Neurooncol. 1996;27:149–155.
- van den Bent MJ, Brandes AA, Taphoorn MJ, et al. Adjuvant procarbazine, lomustine, and vincristine chemotherapy in newly diagnosed anaplastic oligodendroglioma: long-term follow-up of EORTC brain tumor group study 26951. J Clin Oncol. 2013;31:344–350.
- 29. Malmström A, Grønberg BH, Marosi C, et al ; Nordic Clinical Brain Turnour Study Group (NCBTSG). Temozolomide versus standard 6-week radiotherapy versus hypofractionated radiotherapy in patients older than 60 years with glioblastoma: the Nordic randomised, phase 3 trial. *Lancet Oncol.* 2012; 13:916–926.

- Cloughesy TF, Prados MD, Wen PY. A phase II randomized noncomparative clinical trial of the effect of bevacizumab alone or in combination with irinotecan on 6 month progression free survival (PFS6) in recurrent treatment-refractory glioblastoma (GBM) [abstract]. J Clin Oncol. 2008;26(suppl 15):2010b.
- Friedman HS, Prados MD, Wen PY, et al. Bevacizumab alone and in combination with irinotecan in recurrent glioblastoma. *J Clin Oncol.* 2009;27:4733–4740.
- Kreisl TN, Kim L, Moore K, et al. Phase II trial of single-agent bevacizumab followed by bevacizumab plus irinotecan at tumor progression in recurrent glioblastoma. J Clin Oncol. 2009;27:740–745.
- 33. Yung WK, Prados MD, Yaya-Tur R, et al. Multicenter phase II trial of temozolomide in patients with anaplastic astrocytoma or anaplastic oligoastrocytoma at first relapse. Temodal Brain Tumor Group. J Clin Oncol. 1999;17:2762–2771.
- Packer RJ, Gajjar A, Vezina G, et al. Phase III study of craniospinal radiation therapy followed by adjuvant chemotherapy for newly diagnosed average-risk medulloblastoma. *J Clin Oncol.* 2006;24:4202–4208.
- 35. Dunkel JJ, Gardner SL, Garvin JH Jr, Goldman S, Shi W, Finlay JL. High-dose carboplatin, thiotepa, and etoposide with autologous stem cell rescue for patients with previously irradiated recurrent medulloblastoma. *Neuro Oncol.* 2010;12:297–303.
- Ashley DM, Meier L, Kerby T, et al. Response of recurrent medulloblastoma to low-dose oral etoposide. J Clin Oncol. 1996;14:1922-1927.
- Chamberlain MC, Kormanik PA. Chronic oral VP-16 for recurrent medulloblastoma. *Pediatr Neurol.* 1997;17:230–234.
- DeAngelis LM, Seiferheld W, Schold SC, Fisher B, Schultz CJ; Radiation Therapy Oncology Group Study 93-10. Combination chemotherapy and radiotherapy for primary central nervous system lymphoma: Radiation Therapy Oncology Group Study 93-10. J Clin Oncol. 2002;20:4643-4648.
- 39. Ferreri AJ, Reni M, Foppoli M, et al; International Extranodal Lymphoma Study Group (IELSG). High-dose cytarabine plus high-dose methotrexate versus high-dose methotrexate alone in patients with primary CNS lymphoma: a randomised phase 2 trial. *Lancet*. 2009;374:1512–1520.
- Thiel E, Korfel A, Martus P et al. High-dose methotrexate with or without whole brain radiotherapy for primary CNS lymphoma (G-PCNSL-SG-1): a phase 3, randomised, non-inferiority trial. *Lancet Oncol.* 2010;11:1036–1047.
- Shah GD, Yahalom J, Correa DD, et al. Combined immunochemotherapy with reduced whole-brain radiotherapy for newly diagnosed primary CNS lymphoma. J Clin Oncol. 2007;25:4730–4735.
- Batchelor T, Carson K, O'Neill A, Grossman SA, Alavi J, New P, Hochberg F, Priet R. Treatment of primary CNS lymphoma with methotrexate and deferred radiotherapy: a report of NABTT 96–07. J Clin Oncol. 2003;21:1044–1049.
- Chamberlain MC, Johnson SK. High-dose methotrexate and rituximab with deferred radiotherapy for newly diagnosed primary B-cell CNS lymphoma. *Neuro Oncol.* 2010;12:736–744.
- 44. Wieduwilt MJ, Valles F, Issa S, et al. Immunotherapy with intensive consolidation for primary central nervous system lymphoma: a pilot study and prognostic assessment by diffusion-weighted MRI. *Clin Cancer Res.* 2012 Jan 6. [Epub ahead of print]
- 45. Widemann BC, Balis FM, Kim A, et al. Glucarpidase, leucovorin, and thymidine for high-dose methotrexate-induced renal dysfunction: clinical and pharmacologic factors affecting outcome. J Clin Oncol. 2010;28:3979–3986.
- Enting RH, Demopoulos A, DeAngelis LM, Abrey LE. Salvage therapy for primary CNS lymphoma with a combination of rituximab and temozolomide. *Neurology*. 2004;63:901–903.

BRAIN CANCER TREATMENT REGIMENS (Part 9 of 9)

References (continued)

- 47. Raizer JJ, Rademaker A, Evens AM, et al. Pemetrexed in the treatment of relapsed/refractory primary central nervous system lymphoma. *Cancer.* 2012;118:3743–3748.
- Chamberlain MC, Glantz MJ. Interferon-alpha for recurrent World Health Organization grade 1 intracranial meningiomas. *Cancer*. 2008;113:2146–2151.
- Chamberlain MC, Glantz MJ, Fadul CE. Recurrent meningioma: salvage therapy with long-acting somatostatin analogue. *Neurology*. 2007;69:969–973.
- Ewend MG, Brem S, Gilbert M, et al. Treatment of single brain metastasis with resection, intracavity carmustine polymer wafers, and radiation therapy is safe and provides excellent local control. *Clin Cancer Res.* 2007;13:3637–3641.
- Lassman AB, Abrey LE, Shah GD, et al. Systemic high-dose intravenous methotrexate for central nervous system metastases. J Neurooncol. 2006;78:255–260.
- Bokstein F, Lossos A, Lossos IS, et al. Central nervous system relapse of systemic non-Hodgkin's lymphoma: Results of treatment based on high-dose methotrexate combination chemotherapy. *Leuk Lymphoma*. 2002;43:587–593.
- Metro G, Foglietta J, Russillo M, et al. Clinical outcome of patients with brain metastases from HER2-positive breast cancer treated with lapatinib and capecitabine. *Ann Oncol.* 2011;22:625–630.
- Sutherland S, Ashley S, Miles D, et al. Treatment of HER2-positive metastatic breast cancer with lapatinib and capecitabine in the lapatinib expanded access programme, including efficacy in brain metastases--the UK experience. Br J Cancer. 2010; 102:995–1002.
- 55. Cocconi G, Lottici R, Gisagni G et al, Combination therapy with platinum and etoposide in brain metastases from breast carcinoma. *Cancer Invest.* 1990;8:327–334.
- Franciosi V, Cocconi G, Michiara M, et al. Front-line chemotherapy with cisplatin and etoposide for patients with brain metastases from breast carcinoma, nonsmall cell lung carcinoma, or malignant melanoma. *Cancer.* 1999;85: 1599–1605.
- Rivera E, Meyers C, Groves M, et al. Phase I study of capecitabine in combination with temozolomide in the treatment of patients with brain metastases from breast carcinoma. *Cancer.* 2006;107:1348–1354.
- Fabi A, Vidiri A, Ferretti G, et al. Dramatic regression of multiple brain metastases from breast cancer with Capecitabine: another arrow at the bow? *Cancer Invest.* 2006;24:466-8.

- Siegelmann-Danieli N, Stein M, Bar-Ziv J. Complete response of brain metastases originating in breast cancer to capecitabine therapy. Isr Med Assoc J. 2003;5:833–834.
- Wang MLH, Yung AWK, Royce ME, et al. Capecitabine for 5-fluorouracil-resistant brain metastases from breast cancer. *Am J Clin Oncol.* 2001;24:421–424.
- Hikino H, Yamada T, Johbara K, et al. Potential role of chemoradiation with oral capecitabine in a breast cancer patient with central nervous system relapse. *Breast*. 2006;15:97–99.
- Margolin K, Ernstoff MS, Hamid O, et al. Ipilimumab in patients with melanoma and brain metastases: an open-label, phase 2 trial. *Lancet Oncol.* 2012;13:459–465.
- 63. Long GV, Trefzer U, Davies MA, et al. Dabrafenib in patients with Val600Glu or Val600Lys BRAF-mutant melanoma metastatic to the brain (BREAK-MB): a multicentre, open-label, phase 2 trial. *Lancet Oncol.* 2012;13:1087–1095.
- 64. Dummer R, Goldinger SM, Turtschi CP, et al. Vemurafenib in patients with BRAF(V600) mutation-positive melanoma with symptomatic brain metastases: final results of an open-label pilot study. *Eur J Cancer.* 2014;50:611–621.
- Jaeckle KA, Phuphanich S, Bent MJ, et al Intrathecal treatment of neoplastic meningitis due to breast cancer with a slow-release formulation of cytarabine. Br J Cancer. 2001; 84:157–163.
- Chamberlain MC, Johnston S, Van Horn A, Glantz MJ. Recurrent lymphomatous meningitis treated with intra-CSF rituximab and liposomal ara-C. J Neurooncol. 2009;91:271–277.
- Groves MD, Glantz MJ, Chamberlain MC, et al. A multicenter phase II trial of intrathecal topotecan in patients with meningeal malignancies. *Neuro Oncol.* 2008;10:208-215.
- Chamberlain MC, Tsao-Wei DD, Groshen S. Phase II trial of intracerebrospinal fluid etoposide in the treatment of neoplastic meningitis. *Cancer.* 2006;106:2021–2027.
- 69. Zagouri F, Sergentanis TN, Bartsch R, et al. Intrathecal administration of trastuzumab for the treatment of meningeal carcinomatosis in HER2-positive metastatic breast cancer: a systematic review and pooled analysis. *Breast Cancer Res Treat*. 2013;139:13–22.
- Chamberlain MC. A phase II trial of intra-cerebrospinal fluid alpha interferon in the treatment of neoplastic meningitis. *Cancer.* 2002; 94:2675–2680.
- Grommes C, Oxnard GR, Kris MG et al. 'Pulsatile' high-dose weekly erlotinib for CNS metastases from EGFR mutant nonsmall cell lung cancer. *Neuro Oncol.* 2011;13,1364–1369.

(Revised 9/2014) © 2014 by Haymarket Media, Inc.