BONE CANCER TREATMENT REGIMENS (Part 1 of 5)

Clinical Trials: The National Comprehensive Cancer Network 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 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.

General Treatment Notes[1]

- Chemotherapy for Ewing's Sarcoma, Mesenchymal Chondrosarcoma, Osteosarcoma, and Undifferentiated Pleomorphic Sarcoma (UPS) should include growth factor support (see NCCN Guidelines for Myeloid Growth Factors).
- Conventional chondrosarcoma (Grades 1–3) has no known standard chemotherapy options.
- Mesenchymal chondrosarcoma: follow Ewing's sarcoma regimens (category 2B).
- Dedifferentiated chondrosarcoma: follow osteosarcoma regimens (category 2B).
- High-Grade Undifferentiated Pleomorphic Sarcoma (UPS): follow osteosarcoma regimens (category 2B)

Chordoma[1]

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

REGIMEN	DOSING
Imatinib[2,3,4]	**Days 1-28:** Imatinib 800mg orally once daily **OR** **Days 1-28:** Imatinib 400mg orally twice daily Repeat cycle every 28 days until disease progression or unacceptable toxicity.
Imatinib + cisplatin[5]	**Days 1-7:** Imatinib 400mg orally once daily **Day 1:** Cisplatin 25mg/m^2 IV over 60 minutes Repeat cycle weekly until disease progression or unacceptable toxicity.
Imatinib + sirolimus[6]	**Days 1-28:** Imatinib 400mg orally once daily **Days 1-28:** Sirolimus 2mg orally once daily Repeat cycle every 28 days until disease progression or unacceptable toxicity
Erlotinib[7]	**Days 1-28:** Erlotinib 150mg orally once daily Repeat cycle every 28 days until disease progression or unacceptable toxicity
Sunitinib[8]	**Days 1-28:** Sunitinib 37.5mg orally once daily Repeat cycle every 28 days until disease progression or unacceptable toxicity
Lapatinib for epidermal growth factor receptor (EGFR)-positive chordomas (Category 2B)[9]	**Days 1-28:** Lapatinib 1500mg orally once daily Repeat cycle every 28 days until disease progression or unacceptable toxicity.
Sorafenib[10,11]	**Days 1-28:** Sorafenib 400mg orally twice daily Repeat cycle until disease progression or unacceptable toxicity

Ewing's Sarcoma and Mesenchymal Chondrosarcoma[1]

First-line Therapy (Primary/Neoadjuvant/Adjuvant)†

VAC/IE (vincristine + doxorubicin + cyclophosphamide alternating with ifosfamide + etoposide)[12,13,††]	**Alternating VAC and IE cycles** *VAC cycles* **Day 1:** Vincristine 2mg/m^2 (max 2mg) IV over 5-10 minutes **Day 1:** Doxorubicin 75mg/m^2 IVP or Dactinomycin 1250mcg/m^2 IVP (Substitute for doxorubicin when cumulative lifetime doxorubicin dose of 375mg/m^2 has been met) **Day 1:** Cyclophosphamide 1200mg/m^2 IV over 60 minutes + Mesna *IE cycles* **Days 1-5:** Ifosfamide 1800 mg/m^2 IV over 3 days + Mesna **Days 1-5:** Etoposide 100mg/m^2 IV over 60 minutes Repeat each cycle every 3 weeks for 17 cycles
VAIA (vincristine + dactinomycin [actinomycin D] + ifosfamide + doxorubicin)[14,15]	**Day 1:** Vincristine 1.5mg/m^2 IV **Days 1-3:** Ifosfamide 2,000mg/m^2 IV + mesna **Days 1, 3, and 5:** Dactinomycin 0.5mg/m^2 IV **Days 2 and 4:** Doxorubicin 30mg/m^2 IV. Repeat cycle every 21 days for 4 cycles, then proceed to local therapy. After local therapy, high-risk patients should receive 10 additional cycles of VAIA; standard-risk patients should receive 10 additional cycles of VAIA or 10 cycles of VACA: **Day 1:** Vincristine 1.5mg/m^2 IV + cyclophosphamide 1,200mg/m^2 IV + mesna **Days 1, 3, and 5:** Dactinomycin 0.5mg/m^2 IV **Days 2 and 4:** Doxorubicin 30mg/m^2 IV. Repeat cycle every 21 days for 10 cycles. **OR** **Days 1, 8, 15, and 22:** Vincristine 1.5mg/m^2 IV **Days 1, 2, 22, 23, 43, and 44 :** Ifosfamide 3,000mg/m^2 IV + mesna **Days 1, 2, 43, and 44 :** Doxorubicin 30mg/m^2 IV **Days 22, 23, and 24:** Dactinomycin 0.5mg/m^2 IV After completion of one 9-week cycle, proceed to local therapy. High-risk patients should then receive 3 additional cycles.

continued

BONE CANCER TREATMENT REGIMENS (Part 2 of 5)

Ewing's Sarcoma and Mesenchymal Chondrosarcoma[1] (continued)

First-line Therapy (Primary/Neoadjuvant/Adjuvant)† (continued)

REGIMEN	DOSING
VIDE (vincristine + ifosfamide + doxorubicin + etoposide)[16]	**Day 1:** Vincristine 1.5 mg/m² (max 2mg) IV push over 5-10 minutes **Days 1-3:** Ifosfamide 3g/mg² IV continuous infusion over 1-3 hours + Mesna (give concurrently with ifosfamide) **Days 1-3:** Doxorubicin 20mg/m² IV continuous infusion over 4 hours or Dactinomycin 500mcg/m² IV (Substitute for doxorubicin when cumulative lifetime doxorubicin dose of 375mg/m² has been met) **Days 1-3:** Etoposide 150mg/m² IV over 1 hour Repeat cycle every 3 weeks for up to 6 cycles

Primary Therapy for Metastatic Disease at Initial Presentation†

VAC/IE (vincristine + doxorubicin + cyclophosphamide alternating with ifosfamide + etoposide)[12]	**Alternating VAC and IE cycles** *VAC cycles* **Day 1:** Vincristine 2mg/m² (max 2mg) IV over 5-10 minutes **Day 1:** Doxorubicin 75mg/m² IVP or Dactinomycin 1250mcg/m² IVP (Substitute for doxorubicin when cumulative lifetime doxorubicin dose of 375mg/m² has been met) **Day 1:** Cyclophosphamide 1200mg/m² IV over 60 minutes + Mesna *IE cycles* **Days 1-5:** Ifosfamide 1800 mg/m² IV over 3 days + Mesna **Days 1-5:** Etoposide 100mg/m² IV over 60 minutes Repeat each cycle every 3 weeks for 17 cycles
VAIA (vincristine + dactinomycin [actinomycin D] + ifosfamide + doxorubicin)[14,15]	**Day 1:** Vincristine 1.5mg/m² IV **Days 1-3:** Ifosfamide 2,000mg/m² IV + mesna **Days 1, 3, and 5:** Dactinomycin 0.5mg/m² IV **Days 2 and 4:** Doxorubicin 30mg/m² IV. Repeat cycle every 21 days for 4 cycles, then proceed to local therapy. After local therapy, high-risk patients should receive 10 additional cycles of VAIA; standard-risk patients should receive 10 additional cycles of VAIA of 10 cycles of VACA: **Day 1:** Vincristine 1.5mg/m² IV + cyclophosphamide 1,200mg/m2 IV + mesna **Days 1, 3, and 5:** Dactinomycin 0.5mg/m² IV **Days 2 and 4:** Doxorubicin 30mg/m² IV. Repeat cycle every 21 days for 10 cycles. **OR** **Days 1, 8, 15, and 22:** Vincristine 1.5mg/m² IV **Days 1, 2, 22, 23, 43, and 44 :** Ifosfamide 3,000mg/m² IV + mesna **Days 1, 2, 43, and 44 :** Doxorubicin 30mg/m² IV **Days 22, 23, and 24:** Dactinomycin 0.5mg/m² IV. After completion of one 9-week cycle, proceed to local therapy. High-risk patients should then receive 3 additional cycles.
VIDE (vincristine + ifosfamide + doxorubicin + etoposide)[16]	**Day 1:** Vincristine 1.5 mg/m² (max 2mg) IV push over 5-10 minutes **Days 1-3:** Ifosfamide 3g/mg² IV continuous infusion over 1-3 hours + Mesna (give concurrently with ifosfamide) **Days 1-3:** Doxorubicin 20mg/m² IV continuous infusion over 4 hours or Dactinomycin 500mcg/m² IV (Substitute for doxorubicin when cumulative lifetime doxorubicin dose of 375mg/m² has been met) **Days 1-3:** Etoposide 150mg/m² IV over 1 hour Repeat cycle every 3 weeks for up to 6 cycles
VAdriaC (vincristine + doxorubicin + cyclophosphamide + dactinomycin)[17]	**Day 1:** Cyclophosphamide 1200mg/m² IV **Day 1:** Vincristine 2mg/m² (max 2mg) IV **Day 1:** Doxorubicin 75mg/m² IV (for the first 5 cycles) or Dactinomycin 1250mcg/m² IV (for subsequent cycles) Repeat cycle every 3 weeks for 17 cycles

Second-line Therapy (Relapsed/Refractory Disease or Metastatic Disease)†††

Cyclophosphamide + topotecan[18–21]	**Days 1–5:** Cyclophosphamide 250mg/m² IV over 30 minutes **Days 1–5:** Topotecan 0.75mg/m2 IV over 30 minutes Repeat cycle every 3 weeks for 12-14 cycles
Irinotecan ± temozolomide[22–28]	**Days 1–5:** Temozolomide 100mg/m²/day orally, **plus** **Days 1–5 and 8–12:** Irinotecan 10–20mg/m²/day IV at least 1 hour after temozolomide. Repeat cycle every 3 or 4 weeks.
Ifosfamide (high dose) ± etoposide[29,30]	**Days 1–5:** Ifosfamide 1,800mg/m²/day IV + mesna **Days 1–5:** Etoposide 100mg/m²/day IV. Repeat every 3 weeks for 12 cycles.
Ifosfamide + carboplatin + etoposide[31]	**Days 1 and 2:** Carboplatin 400mg/m²/day IV, **plus** **Days 1–5:** Ifosfamide 1,800mg/m²/day IV + mesna + etoposide 100mg/m²/day IV. Repeat cycle every 3 weeks for up to 12 cycles (median 1 cycle).

continued

BONE CANCER TREATMENT REGIMENS (Part 3 of 5)

Ewing's Sarcoma and Mesenchymal Chondrosarcoma[1] (continued)

Second-line Therapy (Relapsed/Refractory Disease or Metastatic Disease)††† (continued)

REGIMEN	DOSING
Ifosfamide + carboplatin + etoposide[31]	**Days 1 and 2:** Carboplatin 400mg/m²/day IV, **plus** **Days 1–5:** Ifosfamide 1,800mg/m²/day IV + mesna + etoposide 100mg/m²/day IV. Repeat cycle every 3 weeks for up to 12 cycles (median 1 cycle).
Docetaxel + gemcitabine[32]	**Days 1 and 8:** Gemcitabine 675mg/m² IV, **plus** **Day 8:** Docetaxel 75–100mg/m² IV. Repeat cycle every 3 weeks for up to 13 cycles (median 4 cycles).
Vincristine + irinotecan	References and specific dosing guidance from the NCCN's Guideline Panel will be included in the next Guideline update.

Giant Cell Tumor of Bone[1]

Denosumab[33–35]	**Days 1, 8, and 15:** Denosumab 120mg subcutaneously for first cycle only **Followed by** **Day 1:** Denosumab 120mg subcutaneously Repeat cycle every 4 weeks until disease progression or unacceptable toxicity
Interferon alfa-2b[35–37]	Interferon alfa-2b (3,000,000 units/m²) 48 to 72 hours postoperatively **OR** increasing dosage from 4 x 10^6 units 3 times a week to 9 × 10^6 units 3 times a week.

Osteosarcoma and Dedifferentiated Chrondrosarcoma[1]

First-line Therapy (Primary/Neoadjuvant/Adjuvant Therapy or Metastatic Disease)

Cisplatin + doxorubicin[38–40]	**Days 1–3:** Doxorubicin 25mg/m²/day IV, **plus** **Day 1:** Cisplatin 100mg/m² IV continuous infusion. Repeat cycle every 3 weeks for 6 cycles.
MAP (high-dose methotrexate + cisplatin + doxorubicin)[40–43]	**Preoperative Chemotherapy** **Days 1 and 28:** Methotrexate 8g/m² IV followed by citrovorum factor rescue **Days 7-9 and 34-36:** Cisplatin 120mg/m² by intra-arterial infusion for 72 hours **Days 9 and 36:** Doxorubicin 60mg/m² IV starting 8 hours after the beginning of cisplatin. **Postoperative Chemotherapy (Necrosis ≥90%)** **Days 1, 48, 96, and 144:** Doxorubicin 45mg/m²/day for 2 consecutive days in a 4-hour IV infusion **Days 21, 69, and 117:** Methotrexate 8g/m² IV followed by citrovorum factor rescue **Days 27, 75, and 123:** Cisplatin 120mg/m² by intra-arterial infusion for 72 hours. **Postoperative Chemotherapy (Necrosis <90%)** **Days 1, 69, 138, and 207:** Doxorubicin 45mg/m²/day for 2 consecutive days in a 4-hour IV infusion **Days 21, 90, and 159:** Ifosfamide 2g/m²/day IV for 5 consecutive days in 90 minutes + mesna **Days 42, 111, and 180:** Methotrexate 8g/m² IV followed by citrovorum factor rescue **Days 48, 117, and 186:** Etoposide 120mg/m²/day in a 1-hour infusion for 3 days.
Doxorubicin + cisplatin + ifosfamide + high-dose methotrexate[44]	**Days 0, 6, 18, 27, and 36:** Methotrexate 12g/m² as a 4-hour infusion, increased by 2g/m² if the hour-4 level of serum methotrexate in the previous course was <1000 µmol/L **Days 1, 7, 19, 28, and 37:** Cisplatin 60mg/m²/day as a 48-hour continuous IV infusion (total dose 120mg/m²) **Days 1 and 7:** Doxorubicin (preoperative): 75mg/m² as a 24-hour continuous IV infusion **Day 12:** Surgery **Days 13, 22, and 31:** Doxorubicin (postoperative): 90mg/m² as a 24-hour continuous IV infusion **Days 4, 10, 16, 25, and 34:** Ifosfamide: 3 g/m²/day as a 120-hour (5-day) continuous IV infusion (total dose 15g/m²).
Ifosfamide + cisplatin + epirubicin[45]	**Day 1:** Cisplatin 100mg/m² IV **Day 1:** Epirubicin 90 mg/m² IV **Days 2-4:** Ifosfamide 2000 mg/m² IV over 3 hours + Equivalent dose of Mesna Repeat every 3 weeks for 6 cycles (3 cycles preoperatively and 3 cycles postoperatively)

Second-line Therapy (Relapsed/Refractory or Metastatic Disease)

Carboplatin + ifosfamide + etoposide[31]	**Days 1 and 2:** Carboplatin 400mg/m²/day IV, **plus** **Days 1–5:** Ifosfamide 1,800mg/m²/day IV + mesna + etoposide 100mg/m²/day IV. Repeat cycle every 3 weeks for up to 12 cycles (median 1 cycles).
Gemcitabine + docetaxel[32]	**Days 1 and 8:** Gemcitabine 675mg/m² IV, **plus** **Day 8:** Docetaxel 75–100mg/m² IV. Repeat cycle every 3 weeks for up to 13 cycles (median 4 cycles).
Cyclophosphamide + topotecan[21]	**Days 1–5:** Cyclophosphamide 250mg/m2 IV over 30 minutes **Days 1–5:** Topotecan 0.75mg/m2 IV over 30 minutes Repeat cycle every 3 weeks for 12–14 cycles.

continued

BONE CANCER TREATMENT REGIMENS (Part 4 of 5)

Osteosarcoma and Dedifferentiated Chrondrosarcoma[1] (continued)

Second-line Therapy (Relapsed/Refractory Disease or Metastatic Disease) (continued)

REGIMEN	DOSING
Sorafenib[54]	**Days 1-28:** Sorafenib 400mg twice daily Repeat cycle every 4 weeks until disease progression or unacceptable toxicity
Ifosfamide (high dose) ± etoposide[29,48]	**Days 1–5:** Ifosfamide 1,800mg/m^2/day IV + mesna, **plus** **Days 1–5:** Etoposide 100mg/m^2/day IV. Repeat every 3 weeks for 12 cycles.
Cyclophosphamide + etoposide[46]	**Day 1:** Cyclophosphamide 4,000mg/m^2 3-hour IV infusion; all patients received mesna 1,400mg/m^2 before and after 4 hours and 8 hours from cyclophosphamide start **Days 2–4:** Etoposide 100mg/m^2 over 1 hour twice daily for 3 days on Days 2, 3, and 4 (total dose 600mg/m^2). Repeat in 21-28 days for total of two cycles.
Gemcitabine[47]	**Days 1 and 8:** Gemcitabine 1,200mg/m^2 IV Repeat cycle every 3 weeks until disease progression or unacceptable toxicity
High-dose methotrexate + etoposide + ifosfamide[49]	**Weeks 1, 2, 3, 7, 8, 12, and 13:** High-dose methotrexate IV **Weeks 4 and 9:** Etoposide 75mg/m^2/day IV + ifosfamide 3g/m^2/day + mesna 3.6mg/m^2/day continuous IV infusion for 4 days.
Sorafenib + everolimus[55]	Sorafenib 800mg orally + everolimus 5mg orally once daily until disease progression or unacceptable toxicity.
^{153}Sm-EDTMP (for relapsed or refractory disease beyond second-line therapy)[50]	Samarium-153 ethylene diamine tetramethylene phosphonate (^{153}Sm-EDTMP) 1.0, 3.0, 4.5, 6.0, 12.0, 19.0, or 30.0mCi/kg can be considered; however, the 30mCi/kg dosage requires peripheral-blood progenitor cell grafts with more than x 10^6 CD34(+)/kg to overcome the myeloa47 vfects of skeletal irradiation.
^{223}RA[51-53]	Three 75kBq/kg ^{223}RA infusion given in 4-week intervals (total administered dose of 14.44MBq or 0.390mCi); ^{223}RA doses of 50kBq/kg and 100Bq/kg are being investigated.

For MSI-H/dMMR tumors

Pembrolizumab[56]	**Day 1:** Pembrolizumab 10mg/kg IV once daily Repeat cycle every 14 days until disease progression or unacceptable toxicity.

* Indicated for high-grade chondrosarcoma for systemic recurrence.

† Dactinomycin can be substituted for doxorubicin because of concerns regarding cardiotoxicity.

†† In patients younger than 18 years, evidence supports 2-week compressed treatment

††† Vincristine could be added to any of the regimens

†††† Pembrolizumab is a systemic treatment option for adult and pediatric patients with unresectable or metastatic, microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options. Not for Giant Cell Tumor of Bone or Chordoma.

References

1. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology™. Breast Cancer. v1.2018. Available at: http://www.nccn.org/ professionals/physician_gls/pdf/bone.pdf. Accessed December 19, 2017.
2. Geoerger B, Morland B, Ndiaye A, et al. Berger M, Grignani G, Ferrari S, et al. Target-driven exploratory study of imatinib mesylate in children with solid malignancies by the innovative therapies for children with cancer (ITCC) european consortium. *Eur J Cancer* 2009;45:2342-2351.
3. Casali PG, Messina A, Stacchiotti S, et al. Imatinib mesylate in chordoma. *Cancer.* 2004;101(9):2086–2097.
4. Stacchiotti S, Longhi A, Ferraresi V, et al. Phase II study of imatinib in advanced chordoma. *J Clin Oncol.* 2012;30(9):914–920.
5. Casali PG, Stacchiotti S, Sangalli C, et al. Chordoma. *Current Opin Oncol.* 2007;19(4):367–370.
6. Stacchiotti S, Marrari A, Tamborini E, et al. Response to imatinib plus sirolimus in advanced chordoma. *Ann Oncol.* 2009; 20(11):1886–1894.
7. Singhal N, Kotasek D, Parnis FX. Response to erlotinib in a patient with treatment refractory chordoma. *Anti Cancer Drugs.* 2009;20(10):953–955
8. George S, Merriam P, Maki RG, et al. Multicenter phase II trial of sunitinib in the treatment of nongastrointestinal stromal tumor sarcomas. *J Clin Oncol.* 2009;27(19):3154–3160.
9. Stacchiotti S, Tamborini E, LoVullo S, et al. A phase II study on lapatinib in advanced EGFR-positive chordoma. *Ann Oncol.* 2013;24(7):1931–1936.
10. Amela E, Bompas E, Le Cesne A, et al. A phase II trial of sorafenib (SO) in advanced chordoma patients (pt.). *J Clin Oncol.* 2015; 33(15):Supplement 10520.
11. Bompas E, Le Cesne A, Tresch-Bruneel E, et al. Sorafenib in pateints with locally advanced and metastatic chordomas: a phase II trial of the French Sarcoma Group (GSF/GETO). *Ann Oncol.* 2015;10:2168-2173.
12. Grier HE, Krailo MD, Tarbell NJ, et al. Addition of ifosfamide and etoposide to standard chemotherapy for Ewing's sarcoma and primitive neuroectodermal tumor of bone. *N Engl J Med.* 2003;348(8):694–701.
13. Womer RB, West DC, Krailo MD, et al. Randomized controlled trial of interval-compressed chemotherapy for the treatment of localized Ewing sarcoma: a report from the Children's Oncology Group. *J Clin Oncol.* 2012 Nov 20;30(33):4148-54.
14. Paulussen M, Craft AW, Lewis I, et al; European Intergroup Cooperative Ewing's Sarcoma Study-92. Results of the EICESS-92 Study: two randomized trials of Ewing's sarcoma treatment—cyclophosphamide compared with ifosfamide in standard-risk patients and assessment of benefit of etoposide added to standard treatment in high-risk patients. *J Clin Oncol.* 2008;26(27):4385–4393.
15. Paulussen M, Ahrens S, Dunst J, et al. Localized Ewing tumor of bone: final results of the cooperative Ewing's Sarcoma Study CESS 86. *J Clin Oncol.* 2001;19:1818–1829.
16. Juergens C, Weston C, Lewis I, et al. Safety assessment of intensive induction with vincristine, ifosfamide, doxorubicin, and etoposide (VIDE) in the treatment of Ewing tumors in the EURO-E.W.I.N.G. 99 clinical trial. *Pediatr Blood Cancer.* 2006;47(1):22–29.
17. Miser JS, Krailo MD, Tarbell NJ, et al. Treatment of metastatic Ewing's sarcoma or primitive neuroectodermal tumor of bone: evaluation of combination ifosfamide and etoposide—a Children's Cancer Group and Pediatric Oncology Group study. *J Clin Oncol.* 2004;22(14):2873–2876.

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References

18. Bernstein ML, Devidas M, Lafreniere D, et al. Intensive therapy with growth factor support for patients with Ewing tumor metastatic at diagnosis: Pediatric Oncology Group/Children's Cancer Group Phase II Study 9457—a report from the Children's Oncology Group. *J Clin Oncol*. 2006;24(1):152–159.
19. Hunold A, Weddeling N, Paulussen M, Ranft A, Liebscher C, Jürgens H. Topotecan and cyclophosphamide in patients with refractory or relapsed Ewing tumors. *Pediatr Blood Cancer.* 2006;47(6):795–800.
20. Kushner BH, Kramer K, Meyers PA, et al. Pilot study of topotecan and high-dose cyclophosphamide for resistant pediatric solid tumors. *Med Pediatr Oncol*. 2000;35(5): 468–474.
21. Saylors RL 3rd, Stine KC, Sullivan J, et al; Pediatric Oncology Group. Cyclophosphamide plus topotecan in children with recurrent or refractory solid tumors: a Pediatric Oncology Group phase II study. *J Clin Oncol*. 2001;19(15):3463–3469.
22. Casey DA, Wexler LH, Merchant MS, et al. Irinotecan and temozolomide for Ewing sarcoma: the Memorial Sloan-Kettering Experience. *Pediatr Blood Cancer.* 2009;53(6):1029–1034.
23. Wagner LM, Crews KR, Iacono LC, et al. Phase I trial of temozolomide and protracted irinotecan in pediatric patients with refractory solid tumors. *Clin Cancer Res*. 2004;10(3): 840–848.
24. Wagner LM, McAllister N, Goldsby RE, Rausen AR, McNall-Knapp RY, McCarville MB, Albritton K. Temozolomide and intravenous irinotecan for treatment of advanced Ewing sarcoma. *Pediatr Blood Cancer.* 2007;48(2):132–139.
25. McNall-Knapp RY, Williams CN, Reeves EN, et al. Extended phase I evaluation of vincristine, irinotecan, temozolomide, and antibiotic in children with refractory solid tumors. *Pediatr Blood Cancer.* 2010;54(7):909–915.
26. Blaney S, Berg SL, Pratt C, et al. A phase I study of irinotecan in pediatric patients: a pediatric oncology group study. *Clin Cancer Res*. 2001;7(1):32–37.
27. Furman WL, Stewart CF, Poquette CA, et al. Direct translation of a protracted irinotecan schedule from a xenograft model to a phase I trial in children. *J Clin Oncol.* 1999;17(6):1815–1824.
28. McGregor LM, Stewart CF, Crews KR, et al. Dose escalation of intravenous irinotecan using oral cefpodoxime: a phase I study in pediatric patients with refractory solid tumors. *Pediatr Blood Cancer.* 2012;58(3):372–379.
29. Miser JS, Kinsella TJ, Triche TJ, et al. Ifosfamide with mesna uroprotection and etoposide: an effective regimen in the treatment of recurrent sarcomas and other tumors of children and young adults. *J Clin Oncol.* 1987;5(8):1191–1198.
30. Magnan H, Goodbody CM, Riedel E, Pratilas CA, Wexler LH, Chou AJ. Ifosfamide dose-intensification for patients with metastatic Ewing sarcoma. *Pediatr Blood Cancer*. 2015;62(4):594–597.
31. Van Winkle P, Angiolillo A, Krailo M, et al. Ifosfamide, carboplatin, and etoposide (ICE) reinduction chemotherapy in a large cohort of children and adolescents with recurrent/refractory sarcoma: the Children's Cancer Group (CCG) experience. *Pediatr Blood Cancer.* 2005;44(4):338–347.
32. Navid F, Willert JR, McCarville MB, Furman W, Watkins A, Roberts W, Daw NC. Combination of gemcitabine and docetaxel in the treatment of children and young adults with refractory bone sarcoma. *Cancer*. 2008;113(2):419–425.
33. Branstetter DG, Nelson SD, Manivel JC, et al. Denosumab induces tumor reduction and bone formation in patients with giant-cell tumor of bone. *Clin Cancer Res*. 2012;18(16):4415–4424.
34. Thomas D, Henshaw R, Skubitz K, et al. Denosumab in patients with giant-cell tumour of bone: an open-label, phase 2 study. *Lancet Oncol*. 2010;11(3):275–280.
35. Kaiser U, Neumann K, Havemann K. Generalised giant-cell tumour of bone: successful treatment of pulmonary metastases with interferon alpha, a case report. *J Cancer Res Clin Oncol*. 1993;119(5):301–303.
36. Kaban LB, Troulis MJ, Ebb DJ, et al. Antiangiogenic therapy with interferon alpha for giant cell lesions of the jaws. *Oral Maxillofac Surg*. 2002;60(10):1103–1113.
37. Yasko AW. Interferon therapy for giant cell tumor of bone. *Curr Opin Orthop*. 2006;17(6):568–572.
38. Bramwell VH, Burgers M, Sneath R, et al. A comparison of two short intensive adjuvant chemotherapy regimens in operable osteosarcoma of limbs in children and young adults: the first study of the European Osteosarcoma Intergroup. *J Clin Oncol*. 1992;10(10):1579–1591.
39. Lewis IJ, Nooij MA, Whelan J, et al; MRC BO06 and EORTC 80931 collaborators; European Osteosarcoma Intergroup. Improvement in histologic response but not survival in osteosarcoma patients treated with intensified chemotherapy: a randomized phase III trial of the European Osteosarcoma Intergroup. *J Natl Cancer Inst.* 2007;99(2):112–128.
40. Souhami RL, Craft AW, Van der Eijken JW, et al. Randomised trial of two regimens of chemotherapy in operable osteosarcoma: a study of the European Osteosarcoma Intergroup. *Lancet.* 1997;350(9082):911–917.
41. Bacci G, Ferrari S, Bertoni F, et al. Long-term outcome for patients with nonmetastatic osteosarcoma of the extremity treated at the istituto ortopedico rizzoli according to the istituto ortopedico rizzoli/osteosarcoma-2 protocol: an updated report. *J Clin Oncol*. 2000;18(24):4016–4027.
42. Winkler K, Beron G, Delling G. Neoadjuvant chemotherapy of osteosarcoma: results of a randomized cooperative trial (COSS-82) with salvage chemotherapy based on histological tumor response. *J Clin Oncol*. 1988;6(2):329–337.
43. Marina NM, Smeland S, Bielack SS, et al. Comparison of MAPIE versus MAP in patients with a poor response to preoperative chemotherapy for newly diagnosed high-grade osteosarcoma (EUARMOS-1): an open-label, international, randomized controlled trial. *Lancet Oncol*. 2016;17:1396-408.
44. Bacci G, Briccoli A, Rocca M, et al. Neoadjuvant chemotherapy for osteosarcoma of the extremities with metastases at presentation: recent experience at the Rizzoli Institute in 57 patients treated with cisplatin, doxorubicin, and a high dose of methotrexate and ifosfamide. *Ann Oncol.* 2003;14(7):1126–1134.
45. Basaran M, Bavbek ES, Saglam S, et al. A phase II study of cisplatin, ifosfamide and epirubicin combination chemotherapy in adults with nonmetastatic and extremity osteosarcomas. *Oncology.* 2007;72(3–4):255–260.
46. Berger M, Grignani G, Ferrari S, et al. Phase 2 trial of two courses of cyclophosphamide and etoposide for relapsed high-risk osteosarcoma patients. *Cancer.* 2009;115(13):2980–2987.
47. Maki RG, Wathen JK, Patel SR, et al. Randomized phase II study of gemcitabine and docetaxel compared with gemcitabine alone in patients with metastatic soft tissue sarcomas: results of sarcoma alliance for research through collaboration study 002. *J Clin Oncol.* 2007;25(19):2755–2763.
48. Goodrin AM, Harris MB, Bernstein M, et al. Phase II/III trial of etoposide and high-dose ifosfamide in newly diagnosed metastatic osteosarcoma: a pediatric oncology group trial. *J Clin Oncol*. 2002; 20(2):426-33. http://www.ncbi.nlm.nih.gov/pubmed/11786570.
49. Le Deley MC, Guinebretiere JM, Gentet JC, et al. SFOP OS93: a randomised trial comparing preoperative high-dose methotrexate plus doxorubicin to high-dose methotrexate plus etoposide and ifosfamide in osteosarcoma patients. *Eur J Cancer.* 2007;43(4);752–761.
50. Anderson PM, Wiseman GA, Dispenzieri A, et al. High-dose samarium-153 ethylene diamine tetramethylene phosphonate: low toxicity of skeletal irradiation in patients with osteosarcoma and bone metastases. *J Clin Oncol*. 2002;20(1):189–196.
51. Subbiah V, Anderson P, Rohren E. Alpha emitter radium 223 in high-risk osteosarcoma: first clinical evidence of response and blood-brain barrier penetration. *JAMA Oncol*. 2015;1(2):253–255.
52. Anderson PM, Subbiah V, Rohren E. Bone-seeking radiopharmaceuticals as targeted agents of osteosarcoma: samarium-153-EDTMP and radium-223. *Adv Exp Med Biol*. 2014;804:291–304.
53. Subbiah V, Rohren E, Huh W, Kappadath C, Anderson PM. Phase 1 dose escalation trial of intravenous radium 223 dichloride alpha-particle therapy in osteosarcoma. *J Clin Oncol*. 2014;32(5s): Abstract TPS10600.
54. Grignani G, Palmerini E, Dileo P, et al. A phase II trial of sorafenib in relapsed and unresectable high-grade osteosarcoma after failure of standard multimodal therapy: an Italian Sarcoma Group study. *Ann Oncol.* 2012;23(2):508–516.
55. Grignani G, Palmerini E, Ferraresi V, et al. Italian Sarcoma Group. Sorafenib and everolimus for patients with unresectable high-grade osteosarcoma progressing after standard treatment: a non-randomised phase 2 clinical trial. *Lancet Oncol*. 2015;16(1):98-107.
56. Dung LT, Durham JN, Smith KN, et al. Mismatch-repair deficiency predicts response of solid tumors to PD-1 blockade. *Science*. 2017;10.1126/science.aan6733

(Revised 6/2018)