**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**
- 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)

**Chordomas**

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

<table>
<thead>
<tr>
<th>REGIMEN</th>
<th>DOISING</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Imatinib</strong>&lt;sup&gt;2,3,4&lt;/sup&gt;</td>
<td>Days 1-28: Imatinib 800mg orally once daily <strong>OR</strong> Days 1-28: Imatinib 400mg orally twice daily Repeat cycle every 28 days until disease progression or unacceptable toxicity.</td>
</tr>
<tr>
<td><strong>Imatinib + cisplatin</strong>&lt;sup&gt;5&lt;/sup&gt;</td>
<td>Days 1-7: Imatinib 400mg orally once daily Day 1: Cisplatin 25mg/m&lt;sup&gt;2&lt;/sup&gt; IV over 60 minutes Repeat cycle weekly until disease progression or unacceptable toxicity.</td>
</tr>
<tr>
<td><strong>Imatinib + sirolimus</strong>&lt;sup&gt;6&lt;/sup&gt;</td>
<td>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</td>
</tr>
<tr>
<td><strong>Erlotinib</strong>&lt;sup&gt;7&lt;/sup&gt;</td>
<td>Days 1-28: Erlotinib 150mg orally once daily Repeat cycle every 28 days until disease progression or unacceptable toxicity</td>
</tr>
<tr>
<td><strong>Sunitinib</strong>&lt;sup&gt;8&lt;/sup&gt;</td>
<td>Days 1-28: Sunitinib 37.5mg orally once daily Repeat cycle every 28 days until disease progression or unacceptable toxicity</td>
</tr>
<tr>
<td><strong>Lapatinib for epidermal growth factor receptor (EGFR)-positive chordomas (Category 2B)</strong>&lt;sup&gt;9&lt;/sup&gt;</td>
<td>Days 1-28: Lapatinib 1500mg orally once daily Repeat cycle every 28 days until disease progression or unacceptable toxicity</td>
</tr>
<tr>
<td><strong>Sorafenib</strong>&lt;sup&gt;10,11&lt;/sup&gt;</td>
<td>Days 1-28: Sorafenib 400mg orally twice daily Repeat cycle until disease progression or unacceptable toxicity</td>
</tr>
</tbody>
</table>

**Ewing’s Sarcoma and Mesenchymal Chondrosarcoma**

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

<table>
<thead>
<tr>
<th>VAC/IE (vincristine + doxorubicin + cyclophosphamide alternating with ifosfamide + etoposide)</th>
<th>Alternating VAC and IE cycles</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>VAC cycles</strong></td>
<td><strong>IE cycles</strong></td>
</tr>
<tr>
<td>Day 1: Vincristine 2mg/m&lt;sup&gt;2&lt;/sup&gt; (max 2mg) IV over 5-10 minutes Day 1: Doxorubicin 75mg/m&lt;sup&gt;2&lt;/sup&gt; IV + Cyclophosphamide 1250mg/m&lt;sup&gt;2&lt;/sup&gt; IV (Substitute for doxorubicin when cumulative lifetime doxorubicin dose of 375mg/m&lt;sup&gt;2&lt;/sup&gt; has been met)</td>
<td>Day 1: Cyclophosphamide 1200mg/m&lt;sup&gt;2&lt;/sup&gt; IV over 60 minutes + Mesna Days 1-5: Ifosfamide 1800mg/m&lt;sup&gt;2&lt;/sup&gt; IV over 3 days + Mesna Days 1-5: Etoposide 100mg/m&lt;sup&gt;2&lt;/sup&gt; IV over 60 minutes Repeat each cycle every 3 weeks for 17 cycles</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>VAIA (vincristine + dactinomycin [actinomycin D] + ifosfamide + doxorubicin)</strong></th>
<th><strong>Day 1: Vincristine 1.5mg/m&lt;sup&gt;2&lt;/sup&gt; IV</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Days 1-3: Ifosfamide 2,000mg/m&lt;sup&gt;2&lt;/sup&gt; IV + mesna Days 1, 3, and 5: Dactinomycin 0.5mg/m&lt;sup&gt;2&lt;/sup&gt; IV Days 2 and 4: Doxorubicin 30mg/m&lt;sup&gt;2&lt;/sup&gt; 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&lt;sup&gt;2&lt;/sup&gt; IV + cyclophosphamide 1,200mg/m&lt;sup&gt;2&lt;/sup&gt; IV + mesna Days 1, 3, and 5: Dactinomycin 0.5mg/m&lt;sup&gt;2&lt;/sup&gt; IV Days 2 and 4: Doxorubicin 30mg/m&lt;sup&gt;2&lt;/sup&gt; IV. Repeat cycle every 21 days for 10 cycles. OR Day 1, 8, 15, and 22: Vincristine 1.5mg/m&lt;sup&gt;2&lt;/sup&gt; IV Days 1, 2, 22, 23, 43, and 44: Ifosfamide 3,000mg/m&lt;sup&gt;2&lt;/sup&gt; IV + mesna Days 1, 2, 43, and 44: Doxorubicin 30mg/m&lt;sup&gt;2&lt;/sup&gt; IV Days 22, 23, and 24: Dactinomycin 0.5mg/m&lt;sup&gt;2&lt;/sup&gt; IV After completion of one 9-week cycle, proceed to local therapy. High-risk patients should then receive 3 additional cycles.</td>
<td></td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>REGIMEN</th>
<th>DOSSING</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>VIDE (vincristine + ifosfamide + doxorubicin + etoposide)</strong>[18,29,30]</td>
<td><strong>Day 1:</strong> Vincristine 1.5 mg/m² (max 2mg) IV push over 5-10 minutes&lt;br&gt;<strong>Days 1-3:</strong> Ifosfamide 3g/mg² IV continuous infusion over 1-3 hours + Mesna (give concurrently with ifosfamide)&lt;br&gt;<strong>Days 1-3:</strong> 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)&lt;br&gt;<strong>Days 1-3:</strong> Etoposide 150mg/m² IV over 1 hour Repeat cycle every 3 weeks for up to 6 cycles</td>
</tr>
<tr>
<td><strong>Primary Therapy for Metastatic Disease at Initial Presentation</strong>[1]</td>
<td><strong>Alternating VAC and IE cycles</strong>&lt;br&gt;<strong>Day 1:</strong> Vincristine 2mg/m² (max 2mg) IV over 5-10 minutes&lt;br&gt;<strong>Day 1:</strong> Doxorubicin 75mg/m² IV or Dactinomycin 1250mcg/m² IV (Substitute for doxorubicin when cumulative lifetime doxorubicin dose of 375mg/m² has been met)&lt;br&gt;<strong>Day 1:</strong> Cyclophosphamide 1200mg/m² IV over 60 minutes + Mesna&lt;br&gt;<strong>IE cycles</strong>&lt;br&gt;<strong>Days 1-5:</strong> Ifosfamide 1800 mg/m² IV over 3 days + Mesna&lt;br&gt;<strong>Days 1-5:</strong> Etoposide 100mg/m² IV over 60 minutes Repeat each cycle every 3 weeks for 17 cycles</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>REGIMEN</th>
<th>DOSSING</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>VAIA (vincristine + dactinomycin [actinomycin D] + ifosfamide + doxorubicin)</strong>[14,15]</td>
<td><strong>Day 1:</strong> Vincristine 1.5mg/m² IV&lt;br&gt;<strong>Days 1, 3, and 5:</strong> Dactinomycin 0.5mg/m² IV&lt;br&gt;<strong>Days 2 and 4:</strong> 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:&lt;br&gt;<strong>Day 1:</strong> Vincristine 1.5mg/m² IV + cyclophosphamide 1,200mg/m² IV + mesna&lt;br&gt;<strong>Days 1, 3, and 5:</strong> Dactinomycin 0.5mg/m² IV&lt;br&gt;<strong>Days 2 and 4:</strong> Doxorubicin 30mg/m² IV. Repeat cycle every 21 days for 10 cycles. OR&lt;br&gt;<strong>Days 1, 8, 15, and 22:</strong> Vincristine 1.5mg/m² IV&lt;br&gt;<strong>Days 1, 2, 22, 23, 43, and 44:</strong> Ifosfamide 3,000mg/m² IV + mesna&lt;br&gt;<strong>Days 1, 2, 43, and 44:</strong> Doxorubicin 30mg/m² IV&lt;br&gt;<strong>Days 22, 23, and 24:</strong> 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.</td>
</tr>
<tr>
<td><strong>VIDE (vincristine + ifosfamide + doxorubicin + etoposide)</strong>[16]</td>
<td><strong>Day 1:</strong> Vincristine 1.5 mg/m² (max 2mg) IV push over 5-10 minutes&lt;br&gt;<strong>Days 1-3:</strong> Ifosfamide 3g/mg² IV continuous infusion over 1-3 hours + Mesna (give concurrently with ifosfamide)&lt;br&gt;<strong>Days 1-3:</strong> 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)&lt;br&gt;<strong>Days 1-3:</strong> Etoposide 150mg/m² IV over 1 hour Repeat cycle every 3 weeks for up to 6 cycles</td>
</tr>
<tr>
<td><strong>VAdriaC (vincristine + doxorubicin + cyclophosphamide + dactinomycin)</strong>[17]</td>
<td><strong>Day 1:</strong> Cyclophosphamide 1200mg/m² IV&lt;br&gt;<strong>Day 1:</strong> Vincristine 2mg/m² (max 2mg) IV&lt;br&gt;<strong>Day 1:</strong> 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</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>REGIMEN</th>
<th>DOSSING</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cyclophosphamide + topotecan</strong>[18-21]</td>
<td><strong>Days 1-5:</strong> Cyclophosphamide 250mg/m² IV over 30 minutes&lt;br&gt;<strong>Days 1-5:</strong> Topotecan 0.75mg/m² IV over 30 minutes Repeat cycle every 3 weeks for 12-14 cycles</td>
</tr>
<tr>
<td><strong>Irinotecan ± temozolomide</strong>[22-28]</td>
<td><strong>Days 1-5:</strong> Temozolomide 100mg/m²/day orally, plus&lt;br&gt;<strong>Days 1-5 and 8-12:</strong> Irinotecan 10-20mg/m²/day for at least 1 hour after temozolomide. Repeat cycle every 3 or 4 weeks.</td>
</tr>
<tr>
<td><strong>Ifosfamide (high dose) ± etoposide</strong>[29,30]</td>
<td><strong>Days 1-5:</strong> Ifosfamide 1,800mg/m²/day IV + mesna&lt;br&gt;<strong>Days 1-5:</strong> Etoposide 100mg/m²/day IV. Repeat every 3 weeks for 12 cycles.</td>
</tr>
<tr>
<td><strong>Ifosfamide + carboplatin + etoposide</strong>[21]</td>
<td><strong>Days 1 and 2:</strong> Carboplatin 400mg/m²/day IV, plus&lt;br&gt;<strong>Days 1-5:</strong> 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).</td>
</tr>
</tbody>
</table>

**continued**
# Bone Cancer Treatment Regimens (Part 3 of 5)

## Ewing's Sarcoma and Mesenchymal Chondrosarcoma

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

<table>
<thead>
<tr>
<th>REGIMEN</th>
<th>DOSING</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ifofamide + carboplatin + etoposide&lt;sup&gt;31&lt;/sup&gt;</td>
<td>Days 1 and 2: Carboplatin 400mg/m²/day IV, plus Days 1–5: Ifofamide 1,800mg/m²/day IV + mesna + etoposide 100mg/m²/day IV. Repeat cycle every 3 weeks for up to 12 cycles (median 1 cycle).</td>
</tr>
<tr>
<td>Docetaxel + gemcitabine&lt;sup&gt;32&lt;/sup&gt;</td>
<td>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).</td>
</tr>
<tr>
<td>Vincristine + irinotecan</td>
<td>References and specific dosing guidance from the NCCN's Guideline Panel will be included in the next Guideline update.</td>
</tr>
</tbody>
</table>

## Giant Cell Tumor of Bone

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

- Denosumab<sup>33–35</sup>
  - 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<sup>36–37</sup>
  - Interferon alfa-2b (3,000,000 units/m²) 48 to 72 hours postoperatively OR increasing dosages from 4 x 10⁶ units 3 times a week to 9 x 10⁶ units 3 times a week.

## Osteosarcoma and Dedifferentiated Chondrosarcoma

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

- Cisplatin + doxorubicin<sup>38–40</sup>
  - 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)<sup>40–43</sup>
  - 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 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: Ifofamide 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.

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

- Carboplatin + ifosfamide + etoposide<sup>31</sup>
  - Days 1 and 2: Carboplatin 400mg/m²/day IV, plus Days 1–5: Ifofamide 1,800mg/m²/day IV + mesna + etoposide 100mg/m²/day IV. Repeat cycle every 3 weeks for up to 12 cycles (median 1 cycle).

- Gemcitabine + docetaxel<sup>32</sup>
  - 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<sup>32</sup>
  - 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.

---

**References and specific dosing guidance from the NCCN's Guideline Panel will be included in the next Guideline update.**
Osteosarcoma and Dedifferentiated Chondrosarcoma (continued)

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

**REGIMEN**

**Sorafenib**

**DOsing**

**Days 1-28:** Sorafenib 400mg twice daily

Repeat cycle every 4 weeks until disease progression or unacceptable toxicity

**Ivodrubicin (high dose)** + etoposide

**Days 1 and 8:** Ivodrubicin 1,800mg/m²/day IV + mesna, **plus**

**Days 1-5:** Etoposide 100mg/m²/day IV. Repeat every 3 weeks for 12 cycles.

**Cyclophosphamide + etoposide**

**Day 1:** Cyclophosphamide 4,000mg/m² 3-hour IV infusion; all patients received mesna 1,400mg/m² before and after 4 hours and 8 hours from cyclophosphamide start

**Days 2-4:** Etoposide 100mg/m² over 1 hour twice daily for 3 days on Days 2, 3, and 4 (total dose 600mg/m²). Repeat in 21-28 days for total of two cycles.

**Gemcitabine**

**Days 1 and 8:** Gemcitabine 1,200mg/m² IV Repeat cycle every 3 weeks until disease progression or unacceptable toxicity

**High-dose methotrexate + etoposide + ifosfamide**

**Weeks 1, 2, 3, 7, 8, 12, and 13:** High-dose methotrexate IV

**Weeks 4 and 9:** Etoposide 75mg/m²/day IV + ifosfamide 3g/m²/day + mesna 3.6mg/m³/day continuous IV infusion for 4 days.

**Sorafenib + everolimus**

Sorafenib 800mg orally + everolimus 5mg orally once daily until disease progression or unacceptable toxicity.

**153Sm-EDTMP (for relapsed or refractory disease beyond second-line therapy)**

Samarium-153 ethylene diamine tetramethylene phosphonate (153Sm-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 1x10⁹ CD34⁺/kg to overcome the myelotoxic effects of skeletal irradiation.

**223Ra-RA**

Three 75kBq/kg 223Ra infusion given in 4-week intervals (total administered dose of 14.44MBq or 0.390mCi); 223Ra doses of 50kBq/kg and 100kBq/kg are being investigated.

**For MSI-H/dMMR tumors**

**Pembrolizumab**

**Day 1:** Pembrolizumab 10mg/kg IV once daily

Repeat cycle every 14 days until disease progression or unacceptable toxicity.

**References**


