

## LEUKEMIA TREATMENT REGIMENS: Acute Lymphoblastic Leukemia (ALL) (Part 1 of 12)

**Note:** The National Comprehensive Cancer Network (NCCN) Guidelines® for Acute Lymphoblastic Leukemia (ALL) should be consulted for the management of patients with lymphoblastic lymphoma.

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

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

The NCCN Guidelines are a work in progress that may be refined as often as new significant data becomes available. They 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.

### Ph(+) AYA (Age 15–39 years) <sup>1,a,b,c</sup>

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

#### PROTOCOL

**Children's Oncology Group (COG) AALL-0031<sup>2</sup>**

#### REGIMEN AND DOSING

##### **Induction**

4 weeks of standard induction chemotherapy

##### **Consolidation**

##### **Block 1 (3 weeks)**

**Day 1:** Methotrexate (MTX) intrathecally (IT), etoposide 100mg/m<sup>2</sup>/day intravenously (IV), ifosfamide 3.4g/m<sup>2</sup>/day IV

**Days 1–21:** Imatinib 340mg/m<sup>2</sup>/day orally

**Days 6–15:** Filgrastim 5g/kg/day subcutaneously (SC) ± imatinib

**Days 8 and 15:** CNS leukemia only: MTX IT, hydrocortisone IT, cytarabine IT.

##### **Block 2 (3 weeks)**

**Day 1:** Age adjusted: MTX IT, hydrocortisone IT, cytarabine IT + MTX 5g/m<sup>2</sup> IV over 24 hours

**Days 1–21:** Imatinib 340mg/m<sup>2</sup>/day orally (hold imatinib if patient does not achieve count recovery within 2 weeks of last dose of previous course)

**Days 2–3:** Leucovorin 75mg/m<sup>2</sup> 36 hours after MTX, followed by 15mg/m<sup>2</sup> IV or orally every 6 hours for 6 doses + cytarabine 3g/m<sup>2</sup>/dose IV every 12 hours for 4 doses

**Days 4–13:** Filgrastim 5g/kg/day SC ± imatinib.

##### **Reinduction**

**Day 1:** Vincristine 1.5mg/m<sup>2</sup> IV + age adjusted: MTX IT, hydrocortisone IT, cytarabine IT

**Days 1–2:** Daunorubicin 45mg/m<sup>2</sup>/day IV bolus

**Days 1–21:** Dexamethasone 6mg/m<sup>2</sup>/day orally ± imatinib 340mg/m<sup>2</sup>/day orally (hold imatinib if patient does not achieve count recovery within 2 weeks of last dose of previous course)

**Days 3–4:** Cyclophosphamide 250mg/m<sup>2</sup>/dose IV every 12 hours for 4 doses + mesna 125mg/m<sup>2</sup>/dose IV every 12 hours for 4 doses

**Days 4, 6, 8, 10, 12, 15, 17, 19, and 21:** L-asparaginase 6,000 IU/m<sup>2</sup> intramuscularly (IM)

**Days 5–14:** Filgrastim 5g/kg/day SC

**Days 8 and 15:** Vincristine 1.5mg/m<sup>2</sup> IV

**Day 15:** Age adjusted: MTX IT, hydrocortisone IT, cytarabine IT.

##### **Intensification**

**Day 1:** Age adjusted: MTX IT, hydrocortisone IT, cytarabine IT + MTX 5g/m<sup>2</sup> IV over 24 hours

**Days 1–63:** Imatinib 340mg/m<sup>2</sup>/day orally (hold imatinib if patient does not achieve count recovery within 2 weeks of last dose of previous course)

**Days 2–3:** Leucovorin 75mg/m<sup>2</sup> 36 hours after MTX, followed by 15mg/m<sup>2</sup> IV or orally every 6 hours for 6 doses

**Day 8:** MTX 5g/m<sup>2</sup> IV over 24 hours

**Days 9–10:** Leucovorin 75mg/m<sup>2</sup> 36 hours after MTX, followed by 15mg/m<sup>2</sup> IV or orally every 6 hours for 6 doses

**Day 15:** Age adjusted: MTX IT, hydrocortisone IT, cytarabine IT

**Days 15–19:** Etoposide 100mg/m<sup>2</sup>/day IV + cyclophosphamide 300mg/m<sup>2</sup>/day IV + mesna 150mg/m<sup>2</sup>/day IV

**Days 20–29:** Filgrastim 5mcg/kg/day SC

**Days 36–37:** Cytarabine 3g/m<sup>2</sup> IV

**Day 37:** L-asparaginase 6,000 IU/m<sup>2</sup> IM ± imatinib (hold imatinib if patient does not achieve count recovery within 2 weeks of last dose of previous course)

**Days 43–44:** Cytarabine 3g/m<sup>2</sup> IV

**Day 44:** L-asparaginase 6,000 IU/m<sup>2</sup> IM ± imatinib (hold imatinib if patient does not achieve count recovery within 2 weeks of last dose of previous course).

Repeat reinduction block 2 (3 weeks) and intensification block 2 (9 weeks) sequentially.

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# LEUKEMIA TREATMENT REGIMENS: Acute Lymphoblastic Leukemia (ALL) (Part 2 of 12)

**Ph(+)** AYA (Age 15–39 years)<sup>1,a,b,c</sup> (continued)

PROTOCOL	REGIMEN AND DOSING
<b>COG AALL-0031</b> <sup>2</sup> (continued)	<p><b>Maintenance</b></p> <p><b>Cycles 1–4 (8 weeks)</b></p> <p><b>Day 1:</b> Age adjusted: MTX IT, hydrocortisone IT, cytarabine IT + vincristine 1.5mg/m<sup>2</sup> IV + MTX 5g/m<sup>2</sup> IV over 24 hours</p> <p><b>Days 1–5:</b> Dexamethasone 6mg/m<sup>2</sup>/day orally</p> <p><b>Days 1–56:</b> Imatinib 340mg/m<sup>2</sup>/day orally (hold imatinib if patient does not achieve count recovery within 2 weeks of last dose of previous course)</p> <p><b>Days 2–3:</b> Leucovorin 75mg/m<sup>2</sup> 36 hours after MTX, followed by 15mg/m<sup>2</sup> IV or orally every 6 hours for 6 doses</p> <p><b>Days 8, 15, and 22:</b> MTX 20mg/m<sup>2</sup>/week orally</p> <p><b>Days 8–28:</b> 6-mercaptopurine (MP) 75mg/m<sup>2</sup>/day</p> <p><b>Day 29:</b> Age adjusted: MTX IT, hydrocortisone IT, cytarabine IT + vincristine 1.5mg/m<sup>2</sup> IV</p> <p><b>Days 29–33:</b> Dexamethasone 6mg/m<sup>2</sup>/day orally</p> <p><b>Days 29–40:</b> Imatinib 340mg/m<sup>2</sup>/day orally (hold imatinib if patient does not achieve count recovery within 2 weeks of last dose of previous course)</p> <p><b>Days 36–40:</b> Etoposide 100mg/m<sup>2</sup> IV + cyclophosphamide 300mg/m<sup>2</sup> IV</p> <p><b>Days 41–50:</b> Filgrastim 5g/kg/day SC.</p> <p><b>Cycles 5–12 (8 weeks)</b></p> <p><b>Cycle 5 only:</b> Cranial irradiation 12 Gy</p> <p><b>Day 1:</b> Vincristine 1.5mg/m<sup>2</sup> IV</p> <p><b>Days 1–5:</b> Dexamethasone 6mg/m<sup>2</sup>/day orally</p> <p><b>Days 1–14:</b> Imatinib 340mg/m<sup>2</sup>/day orally (hold imatinib if patient does not achieve count recovery within 2 weeks of last dose of previous course)</p> <p><b>Days 8, 15, and 22:</b> MTX 20mg/m<sup>2</sup>/week orally</p> <p><b>Days 8–28:</b> 6-MP 75mg/m<sup>2</sup>/day</p> <p><b>Day 29:</b> Vincristine 1.5mg/m<sup>2</sup> IV</p> <p><b>Days 29–33:</b> Dexamethasone 6mg/m<sup>2</sup>/day orally</p> <p><b>Days 29–42:</b> Imatinib 340mg/m<sup>2</sup>/day orally (hold imatinib if patient does not achieve count recovery within 2 weeks of last dose of previous course)</p> <p><b>Day 36:</b> MTX 20mg/m<sup>2</sup>/week orally</p> <p><b>Days 36–56:</b> 6-MP 75mg/m<sup>2</sup>/day</p> <p><b>Days 43 and 50:</b> MTX 20mg/m<sup>2</sup>/week orally.</p>
<b>EsPhALL regimen (imatinib + backbone of Berlin-Frankford-Munster regimen)</b> <sup>3</sup>	<p><b>Induction</b></p> <p>Standard induction protocols per national guidelines.</p> <p><b>Post-Induction Block 1</b></p> <p><b>Days 1–28:</b> 6-MP 60mg/m<sup>2</sup> orally + imatinib 300mg/m<sup>2</sup></p> <p><b>Days 1 and 28:</b> Cyclophosphamide 1000mg/m<sup>2</sup> IV</p> <p><b>Days 3–6, 10–13, 17–20, and 24–27:</b> Cytosine arabinoside (ARA-C) 75mg/m<sup>2</sup> SC</p> <p><b>Days 3 and 7:</b> Age adjusted: MTX IT (dosages: ≥1 year &lt;2 years = 8mg; ≥2 years &lt;3 years = 10mg; ≥3 years = 12mg).</p> <p><b>Post-Induction Block 2</b></p> <p><b>Day 1:</b> MTX 5,000mg/m<sup>2</sup> IV + Age adjusted: MTX IT + ARA-C IT + prednisone (PRED) IT (dosages: ≥1 year &lt;2 years = MTX 8mg, ARA-C 20mg, PRED 6mg; ≥2 years &lt;3 years = MTX 10mg, ARA-C 26mg, PRED 8mg; ≥3 years = MTX 12mg, ARA-C 30mg, PRED 10mg)</p> <p><b>Days 1–5:</b> Dexamethasone 20mg/m<sup>2</sup> orally or IV</p> <p><b>Days 1 and 6:</b> Vincristine 1.5mg/m<sup>2</sup> IV</p> <p><b>Days 2–4:</b> Cyclophosphamide 200mg/m<sup>2</sup> IV</p> <p><b>Day 5:</b> ARA-C 2,000mg/m<sup>2</sup> IV</p> <p><b>Day 6:</b> L-Asparaginase 25,000IU/m<sup>2</sup> intramuscular (IM)</p> <p><b>Days 6–20:</b> Imatinib 300mg/m<sup>2</sup> orally.</p> <p><b>Post-Induction Block 3</b></p> <p><b>Day 1:</b> MTX 5,000mg/m<sup>2</sup> IV + Age adjusted: MTX IT + ARA-C IT + PRED IT (dosages: ≥1 year &lt;2 years = MTX 8mg, ARA-C 20mg, PRED 6mg; ≥2 years &lt;3 years = MTX 10mg, ARA-C 26mg, PRED 8mg; ≥3 years = MTX 12mg, ARA-C 30mg, PRED 10mg)</p> <p><b>Days 1–5:</b> Dexamethasone 20mg/m<sup>2</sup> orally or IV</p> <p><b>Days 1 and 6:</b> Vindesine 3mg/m<sup>2</sup> IV</p> <p><b>Days 2–4:</b> Ifosfamide 800mg/m<sup>2</sup> IV</p> <p><b>Day 5:</b> Daunorubicin 30mg/m<sup>2</sup> IV</p> <p><b>Day 6:</b> L-Asparaginase 25,000IU/m<sup>2</sup> IM</p> <p><b>Days 6–20:</b> Imatinib 300mg/m<sup>2</sup> orally.</p> <p><b>Post-Induction Block 4</b></p> <p><b>Days 1–2:</b> ARA-C 2,000mg/m<sup>2</sup> IV</p> <p><b>Days 1–5:</b> Dexamethasone 20mg/m<sup>2</sup> orally or IV</p> <p><b>Day 1:</b> Age adjusted: MTX IT + ARA-C IT + PRED IT (dosages: ≥1 year &lt;2 years = MTX 8mg, ARA-C 20mg, PRED 6mg; ≥2 years &lt;3 years = MTX 10mg, ARA-C 26mg, PRED 8mg; ≥3 years = MTX 12mg, ARA-C 30mg, PRED 10mg)</p> <p><b>Days 3–5:</b> Vepeside 100mg/m<sup>2</sup> IV</p> <p><b>Day 6:</b> L-Asparaginase 25,000IU/m<sup>2</sup> IM</p> <p><b>Days 6–20:</b> Imatinib 300mg/m<sup>2</sup> orally.</p>

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**LEUKEMIA TREATMENT REGIMENS:  
Acute Lymphoblastic Leukemia (ALL) (Part 3 of 12)**

**Ph(+)** AYA (Age 15–39 years)<sup>1,a,b,c</sup> (continued)

PROTOCOL	REGIMEN AND DOSING
<p><b>EsPhALL regimen (imatinib + backbone of Berlin-Frankford-Munster regimen)<sup>3</sup></b> (continued)</p>	<p><b>Reinduction</b>  <b>Days 1–21 + tapering:</b> Dexamethasone 10mg/m<sup>2</sup> orally  <b>Days 8, 15, 22, and 29:</b> Vincristine 1.5mg/m<sup>2</sup> IV + doxorubicin 25mg/m<sup>2</sup> IV  <b>Days 8, 11, 15, and 18:</b> L-Asparaginase 10,000IU/m<sup>2</sup> IM  <b>Day 36:</b> Cyclophosphamide 1000mg/m<sup>2</sup> IV  <b>Days 36–49:</b> 6-Thioguanine 60mg/m<sup>2</sup> orally  <b>Days 38–41 and 45–48:</b> ARA-C 75mg/m<sup>2</sup> SC  <b>Days 38–45:</b> Age adjusted: MTX IT (dosages: ≥1 year &lt;2 years = 8mg; ≥2 years &lt;3 years = 10mg; ≥3 years = 12mg)  <b>Days 36–63:</b> Imatinib 300mg/m<sup>2</sup> orally.                      Administer reinduction twice, once before and once after interim maintenance. Omit IT therapy from second administration due to previous cranial irradiation.</p> <p><b>Interim Maintenance</b>  <b>Days 1–29:</b> 6-MP 50mg/m<sup>2</sup> orally  <b>Days 8, 15, 22, and 29:</b> MTX 20mg/m<sup>2</sup> orally                      Cranial irradiation 1.4–1.7Gy (total dose per phase: standard = 18Gy; if &lt;2 years = 12Gy; if CNS invasive = 24Gy).</p> <p><b>Continuation Therapy (Maintenance)</b>                      6-MP 50mg/m<sup>2</sup> orally daily until day +728 from diagnosis                      MTX 20mg/m<sup>2</sup> orally weekly till day +728 from diagnosis.</p>
<p><b>Hyper-CVAD (cyclophosphamide, vincristine, doxorubicin, and dexamethasone) + Tyrosine Kinase Inhibitors (TKIs)<sup>4,7</sup></b></p>	<p><b>Induction</b>                      4 cycles Hyper-CVAD alternating with 4 cycles of high dose cytarabine and MTX.  <b>Days 1–14 of each cycle:</b> Dasatinib 50mg orally twice daily (or 100mg daily) <b>OR</b> imatinib 400mg orally daily.  <b>OR</b>  <b>Day 1:</b> Cyclophosphamide 1,200mg/m<sup>2</sup> IV over 3 hours  <b>Days 1–3:</b> Daunorubicin 60mg/m<sup>2</sup> IV over 1 hour  <b>Days 1–21:</b> Prednisolone 60mg/m<sup>2</sup> orally  <b>Days 1, 8, 15, and 22:</b> Vincristine 1.3mg/m<sup>2</sup> IV bolus  <b>Days 8–63:</b> Imatinib 600mg orally  <b>Day 29:</b> MTX 15mg IT, cytarabine 40mg IT, dexamethasone 4mg IT.  <b>OR</b>  <b>Pretreatment for 7 days:</b> Prednisone at increasing doses from 10–40mg/m<sup>2</sup>/day.  <b>Days 1–45:</b> Imatinib 800mg orally daily + prednisone 40mg/m<sup>2</sup> daily (patients &gt;60 years).  <b>OR</b>  <b>Pretreatment for 7 days:</b> Prednisone at increasing doses from 10–60mg/m<sup>2</sup>/day  <b>Days 1–48:</b> Dasatinib 70mg orally twice daily  <b>Days 1–24:</b> Prednisone 60mg/m<sup>2</sup> daily (max 120mg daily)  <b>Days 22 and 43:</b> MTX IT  <b>Days 25–32:</b> Prednisone taper.</p> <p><b>Consolidation</b>                      Allogeneic hematopoietic cell transplant (HCT), if a donor is available and consider post-HCT TKI.  <b>OR</b>                      Continue multiagent chemotherapy + TKI.</p> <p><b>Maintenance</b>                      MTX weekly + 6-MP daily + vincristine pulse monthly + prednisone pulse monthly for 2 to 3 years.</p>
<p><b>Multiagent Chemotherapy + TKIs<sup>8,9</sup></b></p>	<p><b>Induction</b>  <b>Day 1:</b> Cyclophosphamide 1,200mg/m<sup>2</sup> IV over 3 hours  <b>Days 1–3:</b> Daunorubicin 60mg/m<sup>2</sup> IV over 1 hour  <b>Days 1, 8, 15, and 22:</b> Vincristine 1.3mg/m<sup>2</sup> IV bolus  <b>Days 1–21:</b> Prednisolone 60mg/m<sup>2</sup> orally daily  <b>Days 8–63:</b> Imatinib 600mg orally daily  <b>Day 29:</b> MTX 15mg IT + cytarabine 40mg IT + dexamethasone 4mg IT.</p> <p><b>Consolidation 1</b>  <b>Day 1:</b> MTX 1g/m<sup>2</sup> IV over 24 hours + MTX 15mg IT + cytarabine 40mg IT + dexamethasone 4mg IT  <b>Days 1–3:</b> Methylprednisolone 50mg IV over 1 hour × 2 doses  <b>Days 2 and 3:</b> Cytarabine 2g/m<sup>2</sup> IV over 3 hours.                      Repeat for 4 cycles.</p> <p><b>Consolidation 2</b>  <b>Day 1:</b> MTX 15mg IT + cytarabine 40mg IT + dexamethasone 4mg IT.                      Repeat for 4 cycles.  <b>Day 1–28:</b> Imatinib 600mg orally daily.</p> <p><b>Maintenance</b>  <b>Day 1:</b> Vincristine 1.3mg/m<sup>2</sup> IV bolus  <b>Days 1–5:</b> Prednisolone 60mg/m<sup>2</sup> orally daily  <b>Day 1–28:</b> Imatinib 600mg orally daily                      Repeat every 4 weeks up to 2 years from the date of complete remission.</p>

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## LEUKEMIA TREATMENT REGIMENS: Acute Lymphoblastic Leukemia (ALL) (Part 4 of 12)

**Ph(+)** Adult (Age ≥40 years)<sup>1,a,b,c</sup>

PROTOCOL	REGIMEN AND DOSING
<b>Hyper-CVAD + TKIs<sup>4-7</sup></b>	<p><b>Induction</b> 4 cycles Hyper-CVAD alternating with 4 cycles of high dose cytarabine and MTX. <b>Days 1-14 of each cycle:</b> Dasatinib 50mg orally twice daily (or 100mg daily)<sup>3</sup> <b>OR</b> imatinib 400mg orally daily.</p> <p style="text-align: center;"><b>OR</b></p> <p><b>Day 1:</b> Cyclophosphamide 1,200mg/m<sup>2</sup> IV over 3 hours <b>Days 1-3:</b> Daunorubicin 60mg/m<sup>2</sup> IV over 1 hour <b>Days 1-21:</b> Prednisolone 60mg/m<sup>2</sup> orally <b>Days 1, 8, 15, and 22:</b> Vincristine 1.3mg/m<sup>2</sup> IV bolus <b>Days 8-63:</b> Imatinib 600mg orally <b>Day 29:</b> MTX 15mg IT, cytarabine 40mg IT, dexamethasone 4mg IT.</p> <p style="text-align: center;"><b>OR</b></p> <p><b>Pretreatment for 7 days:</b> Prednisone at increasing doses from 10-40mg/m<sup>2</sup>/day <b>Days 1-45:</b> Imatinib 800mg orally daily + prednisone 40mg/m<sup>2</sup> daily (patients &gt;60 years).</p> <p style="text-align: center;"><b>OR</b></p> <p><b>Pretreatment for 7 days:</b> Prednisone at increasing doses from 10-60mg/m<sup>2</sup>/day <b>Days 1-24:</b> Prednisone 60mg/m<sup>2</sup> daily (max 120mg daily) <b>Days 1-48:</b> Dasatinib 70mg orally twice daily <b>Days 22 and 43:</b> MTX IT <b>Days 25-32:</b> Prednisone taper.</p> <p><b>Consolidation</b> Allogeneic hematopoietic cell transplant (HCT), if a donor is available and consider post-HSCT TKI.</p> <p style="text-align: center;"><b>OR</b></p> <p>Continue multiagent chemotherapy + TKI.</p> <p><b>Maintenance</b> MTX weekly + 6-MP daily + vincristine pulse monthly + prednisone pulse monthly for 2 to 3 years.</p>
<b>Multiagent Chemotherapy + TKIs<sup>8,9</sup></b>	<p><b>Induction</b> <b>Day 1:</b> Cyclophosphamide 1,200mg/m<sup>2</sup> IV over 3 hours <b>Days 1-3:</b> Daunorubicin 60mg/m<sup>2</sup> IV over 1 hour <b>Days 1, 8, 15, and 22:</b> Vincristine 1.3mg/m<sup>2</sup> IV bolus <b>Days 1-21:</b> Prednisolone 60mg/m<sup>2</sup> orally daily <b>Days 8-63:</b> Imatinib 600mg orally daily <b>Day 29:</b> MTX 15mg IT + cytarabine 40mg IT + dexamethasone 4mg IT.</p> <p><b>Consolidation 1</b> <b>Day 1:</b> MTX 1g/m<sup>2</sup> IV over 24 hours + MTX 15mg IT + cytarabine 40mg IT + dexamethasone 4mg IT <b>Days 1-3:</b> Methylprednisolone 50mg IV over 1 hour × 2 <b>Days 2 and 3:</b> Cytarabine 2g/m<sup>2</sup> IV over 3 hours. Repeat for 4 cycles.</p> <p><b>Consolidation 2</b> <b>Day 1:</b> MTX 15mg IT + cytarabine 40mg IT + dexamethasone 4mg IT. Repeat for 4 cycles. <b>Days 1-28:</b> Imatinib 600mg orally daily</p> <p><b>Maintenance</b> <b>Day 1:</b> Vincristine 1.3mg/m<sup>2</sup> IV bolus <b>Days 1-5:</b> Prednisolone 60mg/m<sup>2</sup> orally daily <b>Day 1-28:</b> Imatinib 600mg orally daily. Repeat every 4 weeks up to 2 years from the date of complete remission.</p>
<b>Corticosteroids + TKIs<sup>10-12</sup></b>	<p><b>Pretreatment</b> <b>Days 1-7:</b> Prednisone at increasing doses from 10-40mg/m<sup>2</sup> orally daily.</p> <p><b>Induction</b> <b>Days 1-45:</b> Imatinib 800mg orally daily + prednisone 40mg/m<sup>2</sup> orally daily.</p> <p style="text-align: center;"><b>OR</b></p> <p><b>Pretreatment</b> <b>Days 1-7:</b> Prednisone at increasing doses from 10-60mg/m<sup>2</sup> orally daily.</p> <p><b>Induction</b> <b>Days 1-84:</b> Dasatinib 70mg orally twice daily <b>Days 1-32:</b> Prednisone 60mg/m<sup>2</sup> orally daily (maximum 120mg daily) until day 24, then tapered and stopped at day 32 <b>Days 22 and 43:</b> MTX 15mg IT.</p>

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## LEUKEMIA TREATMENT REGIMENS: Acute Lymphoblastic Leukemia (ALL) (Part 5 of 12)

**Ph(+) Adult (Age ≥40 years)** <sup>1,a,b,c</sup> (continued)

PROTOCOL	REGIMEN AND DOSING
<b>Vincristine + Dexamethasone + TKIs</b> <sup>13,14</sup>	<p><b>Pretreatment</b>  <b>Days 1-7:</b> Prednisone at increasing doses from 10-40mg/m<sup>2</sup> orally daily.</p> <p><b>Induction</b>  <b>Cycle 1:</b>  <b>Days 1-28:</b> Imatinib 800mg orally daily  <b>Days 1, 8, 15, and 22:</b> Vincristine 2mg IV  <b>Days 1-2, 8-9, 15-16, and 22-23:</b> Dexamethasone 40mg orally daily.</p> <p><b>Cycle 2:</b>  <b>Day 1:</b> MTX 1g/m<sup>2</sup> IV  <b>Days 2 and 3:</b> Cytarabine 3g/m<sup>2</sup> IV every 12 hours  <b>Days 1-14:</b> Imatinib 800mg orally daily.</p> <p style="text-align: center;"><b>OR</b></p> <p><b>Pretreatment</b>  <b>Days 1-7:</b> Prednisone at increasing doses from 10-40mg/m<sup>2</sup> orally daily.</p> <p><b>Induction</b>  <b>Cycle 1:</b>  <b>Days 1-28:</b> Dasatinib 140mg orally once daily (100mg if patient &gt;70 years)  <b>Days 1, 8, 15, and 22:</b> Vincristine 1mg IV  <b>Days 1-2, 8-9, 15-16, and 22-23:</b> Dexamethasone 40mg orally daily (20mg if patient &gt;70 years).</p> <p><b>Consolidation</b>  <b>Cycles 1, 3, and 5:</b>  <b>Days 1-28:</b> Dasatinib 100mg orally daily  <b>Day 1:</b> MTX 1g/m<sup>2</sup> IV (500mg/m<sup>2</sup> if patient &gt;70 years)  <b>Day 2:</b> Asparaginase 10,000IU/m<sup>2</sup> IM (5,000IU/m<sup>2</sup> if patient &gt;70 years)</p> <p><b>Cycles 2, 4, and 6:</b>  <b>Days 1-28:</b> Dasatinib 100mg orally daily  <b>Day 1, 3, and 5:</b> Cytarabine 1,000mg/m<sup>2</sup> every 12 hours IV (500mg/m<sup>2</sup> if patient &gt;70 years).</p> <p><b>Maintenance</b>  Dasatinib sequentially with 6-MP and MTX orally one every other month, <b>plus</b> dexamethasone and vincristine every 2 months up to 24 months, <b>followed by</b> dasatinib alone until relapse or death.</p>

**Ph(-) AYA (Age 15-39 years)** <sup>1,a,b,c</sup>

<b>GRAALL-2003</b> <sup>15</sup>	<p><b>Corticosteroid Pre-Phase</b>  <b>1-7 days before induction therapy:</b> Prednisone 60mg/m<sup>2</sup>/day  <b>4-7 days before induction therapy:</b> MTX 15mg IT.</p> <p><b>Induction</b>  <b>Day 1:</b> Cyclophosphamide 750mg/m<sup>2</sup>/day + vincristine 2mg IV  <b>Days 1-3:</b> Daunorubicin 50mg/m<sup>2</sup>/day  <b>Days 1-14:</b> Prednisone 60mg/m<sup>2</sup>/day  <b>Day 8:</b> Vincristine 2mg IV + L-asparaginase 6,000IU/m<sup>2</sup>/day  <b>Days 10 and 12:</b> L-asparaginase 6,000IU/m<sup>2</sup>/day  <b>Day 15:</b> Vincristine 2mg IV  <b>Day 15:</b> For Good Early Responders: Cyclophosphamide 750mg/m<sup>2</sup>/day.</p> <p style="text-align: center;"><b>OR</b></p> <p><b>Days 15 and 16:</b> For Poor Early Responders: Cyclophosphamide 500mg/m<sup>2</sup>/12 hours  <b>Days 15 and 16:</b> Daunorubicin 30mg/m<sup>2</sup>/day  <b>Day 17:</b> Lenograstim 150mcg/m<sup>2</sup>/day to myeloid recovery  <b>Days 20 and 22:</b> L-asparaginase 6,000IU/m<sup>2</sup>/day  <b>Day 22:</b> Vincristine 2mg IV  <b>Days 24, 26, and 28:</b> L-asparaginase 6,000IU/m<sup>2</sup>/day.</p> <p><b>Salvage</b>  <b>Days 1-3:</b> Idarubicin 12mg/m<sup>2</sup>/day  <b>Days 1-4:</b> Cytarabine 2g/m<sup>2</sup>/12 hours  <b>Day 9:</b> Filgrastim to myeloid recovery.</p> <p><b>Consolidation</b>  <b>Blocks 1, 4, and 7:</b>  <b>Days 1 and 2:</b> Cytarabine 2g/m<sup>2</sup>/12 hours + dexamethasone 10mg/12 hours  <b>Day 3:</b> L-asparaginase 10,000IU/m<sup>2</sup>/day  <b>Days 7-13:</b> Filgrastim to myeloid recovery.</p> <p><b>Blocks 2, 5, and 8:</b>  <b>Day 15:</b> MTX 3g/m<sup>2</sup> continuous infusion + vincristine 2mg IV + 6-MP 60mg/m<sup>2</sup>/day  <b>Day 16:</b> L-asparaginase 10,000IU/m<sup>2</sup>/day  <b>Days 16-21:</b> 6-MP 60mg/m<sup>2</sup>/day  <b>Days 22-27:</b> Filgrastim to myeloid recovery.</p> <p><b>Blocks 3, 6, and 9:</b>  <b>Day 29:</b> MTX 25mg/m<sup>2</sup>/day  <b>Days 29 and 30:</b> Cyclophosphamide 500mg/m<sup>2</sup>/day + etoposide 75mg/m<sup>2</sup>/day  <b>Day 31:</b> Filgrastim to myeloid recovery.</p>
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## LEUKEMIA TREATMENT REGIMENS: Acute Lymphoblastic Leukemia (ALL) (Part 6 of 12)

Ph(-) AYA (Age 15–39 years)<sup>1,a,b,c</sup>

PROTOCOL	REGIMEN AND DOSING
GRAALL-2003 <sup>15</sup> (continued)	<p><b>Late intensification between consolidation blocks 6 and 7 (for patients in complete remission [CR] after the first induction course)</b>  <b>Day 1:</b> Vincristine 2mg IV  <b>Days 1–3:</b> Daunorubicin 30mg/m<sup>2</sup>/day  <b>Days 1–14:</b> Prednisone 60mg/m<sup>2</sup>/day  <b>Day 8:</b> Vincristine 2mg IV  <b>Days 8, 10, and 12:</b> L-asparaginase 6,000IU/m<sup>2</sup>/day  <b>Day 15:</b> Vincristine 2mg IV + cyclophosphamide 500mg/m<sup>2</sup>/12 hours  <b>Days 18, 20, and 22:</b> L-asparaginase 6,000IU/m<sup>2</sup>/day.</p> <p><b>Late intensification between consolidation blocks 6 and 7 (for patients in CR after salvage course)</b>  <b>Days 1–3:</b> Idarubicin 9mg/m<sup>2</sup>/day  <b>Days 1–4:</b> Cytarabine 2g/m<sup>2</sup>/12 hours  <b>Day 9:</b> Filgrastim to myeloid recovery.</p> <p><b>Maintenance</b>  <b>Months 1–12</b>  <b>Day 1:</b> Vincristine 2mg IV  <b>Days 1–7:</b> Prednisone 40mg/m<sup>2</sup>/day.  <b>Months 1–24</b>  <b>Daily:</b> 6-MP 60mg/m<sup>2</sup>/day  <b>Weekly:</b> MTX 25mg/m<sup>2</sup>/week.</p> <p><b>CNS Therapy—Prophylaxis</b>  <b>Triple IT Injection</b>            1 IT injection at <b>Days 1 and 8</b> of induction; 1 IT injection at <b>Day 29</b> of each series of consolidation blocks; 1 IT injection at <b>Day 1</b> of late intensification.</p> <p><b>Cranial Irradiation</b>            18Gy before maintenance therapy initiation. 6-MP 60mg/m<sup>2</sup>/day during irradiation.</p> <p><b>CNS Therapy—Treatment of patients with initial CNS involvement:</b>  <b>Triple IT Injection</b>            8 IT injections starting from 7 days before induction to <b>Day 21</b> of induction;            4 IT injections during the first 2 consolidation blocks; 1 IT injection at <b>Day 29</b> of consolidation blocks 3 and 6.</p> <p><b>Cranial Irradiation</b>            15Gy before HCT or 24Gy before maintenance therapy initiation            6-MP 60mg/m<sup>2</sup>/day during irradiation.</p>
COG AALL-0434 <sup>16</sup>	<p><b>Induction (4 weeks)</b>  <b>Day 1:</b> Cytarabine IT  <b>Days 1, 8, 15, and 22:</b> Vincristine IV + daunorubicin IV  <b>Days 1–28:</b> Prednisone IV or orally twice daily  <b>Day 4, 5, or 6:</b> Pegaspargase IM or IV over 1–2 hours  <b>Days 8 and 29:</b> MTX IT.</p> <p><b>Consolidation</b>  <b>Days 1–5 and 43–47:</b> Nelarabine IV over 60 minutes  <b>Days 15, 22, 57, and 64:</b> MTX IT  <b>Days 8 and 50:</b> Cyclophosphamide IV over 30 minutes  <b>Days 8–11, 15–18, 50–53, and 57–60:</b> Cytarabine IV over 15–30 minutes or SC  <b>Days 8–21 and 50–63:</b> Mercaptopurine orally  <b>Days 22, 29, 64, and 71:</b> Vincristine sulfate IV  <b>Days 22 and 64:</b> Pegaspargase IM or IV over 1–2 hours.</p>
COG AALL0232 <sup>17,18</sup>	<p><b>Induction</b>  <b>Days 1–28:</b> Prednisone oral or IV twice daily  <b>Day 1:</b> Cytarabine IT  <b>Days 1, 8, 15, and 22:</b> Vincristine IV + daunorubicin IV  <b>Days 4, 5, or 6:</b> Pegaspargase IM  <b>Days 8 and 29:</b> MTX IT  <b>Days 15 and 22:</b> Only patients with CNS3 disease: MTX IT.</p> <p><b>Extended Induction</b>  <i>Only for patients with M2 disease of M1 disease with &gt;1% MRD</i>  <b>Days 1–14:</b> Prednisone oral or IV twice daily  <b>Days 1 and 8:</b> Vincristine IV  <b>Day 1:</b> Daunorubicin IV  <b>Days 4, 5, or 6:</b> Pegaspargase IM.</p> <p><b>Consolidation (7–8 weeks)</b>  <b>Days 1 and 29:</b> Cyclophosphamide IV over 30 min  <b>Days 2–5, 9–12, 30–33, and 37–40:</b> Cytarabine IV or SC  <b>Days 1–14 and 29–42:</b> Mercaptopurine orally  <b>Days 15, 22, 43, and 50:</b> Vincristine IV  <b>Days 15 and 43:</b> Pegaspargase IM  <b>Days 1, 8, 15, and 22:</b> MTX IT (patients with CNS3 disease receive MTX on Days 1 and 8 only).</p>

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## LEUKEMIA TREATMENT REGIMENS: Acute Lymphoblastic Leukemia (ALL) (Part 7 of 12)

Ph(-) AYA (Age 15–39 years)<sup>1,a,b,c</sup> (continued)

PROTOCOL	REGIMEN AND DOSING
<p><b>COG AALL0232</b><sup>17,18</sup> (continued)</p>	<p><b>Interim Maintenance I</b>  <b>Days 1, 11, 21, 31, and 41:</b> Vincristine IV + escalating dose MTX IV  <b>Days 1 and 21:</b> MTX IT  <b>Days 2 and 22:</b> Pegaspargase IM.  <b>OR</b>  <b>Days 1, 15, 29, and 43:</b> Vincristine IV and high-dose MTX IV over 24 hours  <b>Days 1–56:</b> Mercaptopurine orally  <b>Days 1 and 29:</b> MTX IT.  <b>Delayed Intensification I</b>  <b>Days 1, 8, 15, 43, and 50:</b> Vincristine IV  <b>Days 1–21:</b> Only patients aged 1–12: Dexamethasone orally or IV twice daily  <b>Days 1–7 and 15–21:</b> Only patients aged ≥13 years: Dexamethasone orally or IV twice daily  <b>Days 1, 8, and 15:</b> Doxorubicin IV  <b>Days 4, 5, or 6 and day 43:</b> Pegaspargase IM  <b>Day 29:</b> Cyclophosphamide IV  <b>Days 30–33 and 37–40:</b> Cytarabine IV or SC  <b>Days 29–42:</b> Oral thioguanine  <b>Days 1, 29, and 36:</b> MTX IT.  <b>Interim Maintenance II</b>  <b>Days 1, 11, 21, 31, and 41:</b> Vincristine IV + MTX IV  <b>Days 2 and 22:</b> Pegaspargase IM  <b>Days 1 and 21:</b> MTX IT.  <b>Delayed Intensification II</b>  <i>Same regimen as delayed intensification I</i>  <b>Day 29:</b> CNS3 patients only: Start radiotherapy for 3–10 days; All other slow early response patients: Start prophylactic cranial radiotherapy for 8 days.  <b>Maintenance Therapy</b>  <b>Day 1:</b> MTX IT  <b>Days 1, 29, and 57:</b> Vincristine IV  <b>Days 1–5, 29–33, and 57–61:</b> Dexamethasone orally twice daily  <b>Days 1–84:</b> Mercaptopurine orally  <b>Days 1, 8, 15, 22, 29, 36, 43, 50, 57, 64, 71, and 78:</b> MTX orally.</p>
<p><b>DFCI ALL Regimen per DFCI Protocol 00-01</b><sup>19,20</sup></p>	<p><b>Induction (4 weeks)</b>  <b>Days 0, 7, 14, and 21:</b> Vincristine 1.5mg/m<sup>2</sup> weekly (maximum, 2mg)  <b>Days 0–28:</b> Prednisone 40mg/m<sup>2</sup>/day  <b>Days 0 and 1:</b> Doxorubicin 30mg/m<sup>2</sup>/dose (high-risk patients: with dexrazoxane 300mg/m<sup>2</sup>/dose) + MTX 4g/m<sup>2</sup> (8–24 hours after doxorubicin) with leucovorin rescue  <b>1 dose:</b> L-asparaginase 25,000IU/m<sup>2</sup> IM  <b>Day 0:</b> Cytarabine IT  <b>Day 14 (1 dose):</b> MTX IT + cytarabine IT + hydrocortisone IT  <b>CNS Therapy (3 weeks)</b>  <b>Day 1:</b> Vincristine 2mg/m<sup>2</sup>  <b>14 days:</b> 6-Mercaptopurine (6-MP) 50mg/m<sup>2</sup>/day orally at bedtime  <b>Standard-risk patients:</b> MTX IT + cytarabine IT + hydrocortisone IT twice weekly × 4 doses  <b>High-risk patients:</b> MTX IT + cytarabine IT twice weekly × 4 doses + doxorubicin 30mg/m<sup>2</sup> + dexrazoxane 300mg/m<sup>2</sup> + cranial radiation  <b>Intensification (30 weeks)</b>  <i>Cycle every 3 weeks</i>  <b>Day 1:</b> Vincristine 2mg/m<sup>2</sup>  <b>14 doses:</b> 6-MP 50mg/m<sup>2</sup>/day orally at bedtime  <b>Once Weekly:</b> MTX 30mg/m<sup>2</sup> (1mg/kg if &lt;0.6 m<sup>2</sup>) IV or IM  <b>Days 1–5:</b> Prednisone 40mg/m<sup>2</sup>/day orally + twice daily (20mg/m<sup>2</sup> per dose)  <b>Weekly:</b> L-asparaginase 25,000IU/m<sup>2</sup> IM, weekly × 30 weeks OR 12,500IU/m<sup>2</sup> IM (starting dose) weekly, with dose adjusted every 3 weeks to maintain nadir serum asparaginase activity between 0.1–0.14IU/mL  <b>Start of a cycle every 9 weeks:</b> MTX IT + cytarabine IT + hydrocortisone IT × 6 doses, then every 18 weeks through completion of therapy (at start of a cycle).  <b>High-risk patients:</b> Same as above, except higher corticosteroid dose  <b>Days 1–5:</b> Prednisone 120mg/m<sup>2</sup>/day  <b>Day 1 of each cycle:</b> Doxorubicin 30mg/m<sup>2</sup> (cumulative dose 300mg/m<sup>2</sup>) + dexrazoxane 300mg/m<sup>2</sup>/dose [NOTE: No weekly MTX IV/IM until doxorubicin completed, and IT therapy of MTX/cytarabine every 18 weeks]  <b>Continuation (74 weeks)</b>  <i>Cycle every 3 weeks</i>  <b>Standard-risk patients:</b> Same as intensification, except no L-asparaginase  <b>High-risk patients:</b> Same as SR patients, including lower corticosteroid dose of dexamethasone 6mg/m<sup>2</sup> per day and prednisone 40mg/m<sup>2</sup> per day on days 1 to 5.</p>

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## LEUKEMIA TREATMENT REGIMENS: Acute Lymphoblastic Leukemia (ALL) (Part 8 of 12)

Ph(-) AYA (Age 15–39 years)<sup>1,a,b,c</sup> (continued)

PROTOCOL	REGIMEN AND DOSING
<p><b>USC ALL Regimen per CCG-1882<sup>21</sup></b></p>	<p><b>Induction Phase I</b>  <b>Days 1–3:</b> Daunorubicin 60mg/m<sup>2</sup> IV  <b>Days 1, 8, 15, and 22:</b> Vincristine 1.4mg/m<sup>2</sup> IV (maximum, 2mg)  <b>Day 15:</b> Pegaspargase 2,000IU/m<sup>2</sup> IV  <b>Days 1–28:</b> Prednisone 60mg/m<sup>2</sup> orally  <b>Days 8 and 15:</b> MTX 12mg IT.</p> <p><b>Induction Phase II</b>  <b>Days 1 and 29:</b> Cyclophosphamide 1g/m<sup>2</sup> IV  <b>Days 1–4, 8–11, 29–32, and 36–39:</b> Cytarabine 75mg/m<sup>2</sup> IV  <b>Days 15, 22, 43, and 50:</b> Vincristine 1.4mg/m<sup>2</sup> IV (maximum, 2mg)  <b>Day 15:</b> Pegaspargase 2,000IU/m<sup>2</sup> IV  <b>Days 15–29:</b> Prednisone 20mg/m<sup>2</sup> orally  <b>Days 1–14 and 29–43:</b> Mercaptopurine 60mg/m<sup>2</sup> orally  <b>Days 1, 8, 15, and 22:</b> MTX 12mg IT.</p> <p><b>Intensification</b>  <b>Days 1 and 15:</b> MTX 1g/m<sup>2</sup> IV (T-cell ALL, 2.5g/m<sup>2</sup> IV) + leucovorin 15mg every 6 hours IV starting 36 hours from start of MTX  <b>Day 16:</b> Pegaspargase 2,000IU/m<sup>2</sup> IV  <b>Days 16–30:</b> Prednisone 20mg/m<sup>2</sup> orally</p> <p><b>Consolidation</b>  <b>Days 1–5:</b> Cytarabine 75mg/m<sup>2</sup> IV + teniposide 60mg/m<sup>2</sup> IV.</p> <p><b>Delayed Reinduction</b>  <b>Days 1, 8, and 15:</b> Daunorubicin 25mg/m<sup>2</sup> IV  <b>Days 1, 8, 15, 43, and 50:</b> Vincristine 1.4mg/m<sup>2</sup> IV (maximum, 2mg)  <b>Days 15–22 and 43–50:</b> Dexamethasone 10mg/m<sup>2</sup> orally  <b>Day 15:</b> Pegaspargase 2,000IU/m<sup>2</sup> IV  <b>Day 29:</b> Cyclophosphamide 1g/m<sup>2</sup>  <b>Days 29–32 and 36–39:</b> Cytarabine 75mg/m<sup>2</sup> IV  <b>Days 26–42:</b> Thioguanine 60mg/m<sup>2</sup> orally  <b>Days 1, 29, and 36:</b> MTX 12mg IT.</p> <p><b>Maintenance</b>  <i>Monthly for 24 months from end of all consolidations</i>  <b>Days 1–5:</b> Prednisone 60mg/m<sup>2</sup> orally (year 1, monthly; year 2, every 2 months)  <b>Day 1:</b> Vincristine 1.4mg/m<sup>2</sup> (maximum, 2mg) IV (year 1, monthly; year 2, every 2 months)  <b>Days 1–28:</b> Mercaptopurine 60mg/m<sup>2</sup> orally  <b>Days 1, 8, 15, and 22:</b> MTX 20mg/m<sup>2</sup> orally + MTX 12mg IT (year 1, once every 3 months).                      Imatinib 600mg once daily from induction until end of standard maintenance regimen added for Philadelphia chromosome–positive patients.</p>
<p><b>PETHEMA ALL-96<sup>22</sup></b></p>	<p><b>Induction</b>  <b>Days 1, 8, 15, and 22:</b> Vincristine 2mg IV + daunorubicin 30mg/m<sup>2</sup> IV  <b>Days 1–27:</b> Prednisone 60mg/m<sup>2</sup> IV or orally  <b>Days 1 and 29:</b> MTX 15mg IT + cytarabine 30mg IT + hydrocortisone 20mg IT  <b>Days 10–12, 17–19, and 24–26:</b> Asparaginase 10,000U/m<sup>2</sup>  <b>Days 28–35:</b> Prednisone 30mg/m<sup>2</sup> IV or orally  <b>Day 36:</b> Cyclophosphamide 1,000mg/m<sup>2</sup> IV.</p> <p><b>Consolidation</b>  <b>Days 1–7:</b> Mercaptopurine 50mg/m<sup>2</sup> orally  <b>Days 1, 28, and 56:</b> MTX 3g/m<sup>2</sup> IV over 24 hours  <b>Days 14 and 42:</b> Teniposide 150mg/m<sup>2</sup> IV every 12 hours  <b>Days 14, 15, 42, and 43:</b> Cytarabine 500mg/m<sup>2</sup> IV every 12 hours  <b>Days 1, 28, and 56:</b> MTX 15mg IT + cytarabine 30mg IT + hydrocortisone 20mg IT.</p> <p><b>Consolidation-2/Reinduction</b>  <b>Days 1–14:</b> Dexamethasone 10mg/m<sup>2</sup> orally or IV daily  <b>Days 1, 2, 8, and 9:</b> Daunorubicin 30mg/m<sup>2</sup> IV  <b>Days 1–3 and 15–17:</b> Asparaginase 10,000U/m<sup>2</sup> IM or IV  <b>Days 1, 8, and 15:</b> Vincristine 1.5mg/m<sup>2</sup> IV  <b>Days 1 and 15:</b> Cyclophosphamide 600mg/m<sup>2</sup> IV + MTX 15mg IT + cytarabine 30mg IT + hydrocortisone 20mg IT  <b>Days 15–21:</b> Dexamethasone 5mg/m<sup>2</sup> orally or IV daily.</p> <p><b>Maintenance-1</b>                      MTX 20mg/m<sup>2</sup> IM weekly until week 52                      Mercaptopurine 50mg/m<sup>2</sup> orally daily until week 52.</p>

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## LEUKEMIA TREATMENT REGIMENS: Acute Lymphoblastic Leukemia (ALL) (Part 9 of 12)

Ph(-) AYA (Age 15–39 years)<sup>1,a,b,c</sup> (continued)

PROTOCOL	REGIMEN AND DOSING
<b>CALGB 10403</b> <sup>23</sup>	<p><b>Induction</b>  <b>Day 1:</b> Cytarabine IT  <b>Days 8 and 29:</b> MTX IT  <b>Days 1, 8, 15, and 22:</b> Daunorubicin IV + Vincristine IV  <b>Day 4:</b> PEG-asparaginase.</p> <p><b>Consolidation</b>  <b>Days 1, 8, 15, and 22:</b> MTX IT  <b>Days 1 and 29:</b> Cyclophosphamide IV  <b>Days 1–4, 8–11, 29–32, and 36–39:</b> Cytarabine  <b>Days 1–14 and 29–42:</b> 6-Mercaptopurine orally  <b>Days 15, 22, 43, and 50:</b> Vincristine IV  <b>Day 15 and 43:</b> PEG-asparaginase.</p> <p><b>Interim Maintenance</b>  <b>Days 1 and 31:</b> MTX IT  <b>Days 1, 11, 21, 31, and 41:</b> Vincristine IV + MTX  <b>Days 2 and 22:</b> PEG-asparaginase.</p> <p><b>Delayed Intensification</b>  <b>Days 1, 29, and 36:</b> MTX IT  <b>Days 1–7 and 15–21:</b> Dexamethasone orally  <b>Days 1, 8, and 15:</b> Doxorubicin IV  <b>Days 4 and 43:</b> PEG-asparaginase  <b>Day 29:</b> Cyclophosphamide IV  <b>Days 29–32 and 36–39:</b> Cytarabine IV  <b>Days 29–42:</b> 6-Thioguanine orally.</p> <p><b>Maintenance</b>  <b>Days 15 and 29:</b> MTX IT of first 4 courses of maintenance  <b>Days 1, 29, and 57:</b> Vincristine IV  <i>For Females:</i> <b>Days 1–5, 29–33, and 57–61:</b> Dexamethasone orally for 2 years from interim maintenance  <i>For Males:</i> <b>Days 1–84:</b> 6-Mercaptopurine orally for 3 years from interim maintenance  <b>Days 8, 15, 22, 29, 36, 43, 50, 57, 64, 71, and 78:</b> MTX; held on Day 29 of first 4 courses of maintenance when methotrexate IT is given.</p>
<b>CALGB 8811 (Larson Regimen)</b> <sup>24</sup>	<p><b>Induction</b>  <b>Day 1:</b> Cyclophosphamide 1, 200mg/m<sup>2</sup> IV  <b>Days 1–3:</b> Daunorubicin 45mg/m<sup>2</sup> IV  <b>Days 1, 8, 15, and 22:</b> Vincristine 2mg IV  <b>Days 1–21:</b> Prednisone 60mg/m<sup>2</sup>/day orally  <b>Days 5, 8, 11, 15, 18, and 22:</b> L-asparaginase 6,000IU/m<sup>2</sup> SC.</p> <p><b>Consolidation</b>  <b>Day 1:</b> MTX 15mg IT + cyclophosphamide 1,000mg/m<sup>2</sup> IV  <b>Days 1–14:</b> 6-Mercaptopurine 60mg/m<sup>2</sup>/day orally  <b>Days 1–4 and 8–11:</b> Cytarabine 75mg/m<sup>2</sup>/day SC  <b>Days 15 and 22:</b> Vincristine 2mg IV  <b>Days 15, 18, 22, and 25:</b> L-asparaginase 6,000IU/m<sup>2</sup> SC.  Repeat cycle every 4 weeks for 2 cycles, <b>followed by:</b>  <b>Days 1–12:</b> Cranial irradiation 2,400cGy  <b>Days 1, 8, 15, 22, and 29:</b> MTX 15mg IT  <b>Days 1–70:</b> 6-Mercaptopurine 60mg/m<sup>2</sup>/day orally  <b>Days 36, 43, 50, 57, and 64:</b> MTX 20mg/m<sup>2</sup> orally, <b>followed by:</b>  <b>Days 1, 8, and 15:</b> Doxorubicin 30mg/m<sup>2</sup> IV  <b>Days 1, 8, and 15:</b> Vincristine 2mg IV  <b>Days 1–14:</b> Dexamethasone 10mg/m<sup>2</sup>/day orally  <b>Day 29:</b> Cyclophosphamide 1,000mg/m<sup>2</sup> IV  <b>Days 29–42:</b> 6-Thioguanine 60mg/m<sup>2</sup>/day orally  <b>Days 29–32 and 36–39:</b> Cytarabine 75mg/m<sup>2</sup>/day SC, <b>followed by:</b>  <b>Day 1:</b> Vincristine 2mg IV  <b>Days 1–5:</b> Prednisone 60mg/m<sup>2</sup>/day orally  <b>Days 1, 8, 15, and 22:</b> MTX 20mg/m<sup>2</sup> orally  <b>Days 1–28:</b> 6-Mercaptopurine 60mg/m<sup>2</sup>/day orally.  Repeat cycle every 4 weeks until 24 months from diagnosis.</p>
<b>Linker 4-Drug Regimen</b> <sup>25</sup>	<p><b>Induction</b>  <b>Days 1–3:</b> Daunorubicin 50mg/m<sup>2</sup>/day IV  <b>Days 1, 8, 15, and 22:</b> Vincristine 2mg IV  <b>Days 1–28:</b> Prednisone 60mg/m<sup>2</sup>/day orally  <b>Days 17–28:</b> L-asparaginase 6,000IU/m<sup>2</sup>/day IM.  <b>If bone marrow on Day 14 has residual leukemia:</b>  <b>Day 15:</b> Daunorubicin 50mg/m<sup>2</sup> IV.  <b>If bone marrow on Day 28 has residual leukemia:</b>  <b>Day 29 and 30:</b> Daunorubicin 50mg/m<sup>2</sup> IV  <b>Days 29–35:</b> L-asparaginase 6,000IU/m<sup>2</sup>/day IM.  <b>Days 29–42:</b> Prednisone 60mg/m<sup>2</sup>/day orally.</p>

continued

## LEUKEMIA TREATMENT REGIMENS: Acute Lymphoblastic Leukemia (ALL) (Part 10 of 12)

**Ph(-) Adult (Age ≥40 years)** <sup>1,a,b,c</sup> (continued)

PROTOCOL	REGIMEN AND DOSING
<b>Linker 4-Drug Regimen</b> <sup>25</sup> (continued)	<b>Consolidation</b> <b>Cycles 1, 3, 5, and 7:</b> <b>Days 1 and 2:</b> Daunorubicin 50mg/m <sup>2</sup> /day IV <b>Days 1 and 8:</b> Vincristine 2mg IV <b>Days 1-14:</b> Prednisone 60mg/m <sup>2</sup> /day orally <b>Days 4, 7, 9, 11, and 14:</b> L-asparaginase 12,000IU/m <sup>2</sup> /day IM. <b>Cycles 2, 4, 6, and 8:</b> <b>Days 1, 4, 8, and 11:</b> Teniposide 165mg/m <sup>2</sup> IV + cytarabine 300mg/m <sup>2</sup> IV. <b>Cycle 9:</b> MTX 690mg/m <sup>2</sup> IV over 42 hours, followed by leucovorin 15mg/m <sup>2</sup> IV every 6 hours x 12 doses, <b>followed by:</b> MTX 20mg/m <sup>2</sup> orally weekly + 6-Mercaptopurine 75mg/m <sup>2</sup> orally daily for 30 months.
<b>Hyper-CVAD ± Rituximab</b> <sup>26,27</sup>	<b>Cycles 1, 3, 5, and 7</b> <b>Days 1-3:</b> Cyclophosphamide 300mg/m <sup>2</sup> IV every 12 hours + mesna 600mg/m <sup>2</sup> /day continuous IV infusion starting 1 hour before cyclophosphamide until 12 hours after completion of cyclophosphamide <b>Days 1-4 and 11-14:</b> Dexamethasone 40mg orally daily, ± <b>Days 1 and 8:</b> Rituximab 375mg/m <sup>2</sup> IV <b>Day 4:</b> Doxorubicin 50mg/m <sup>2</sup> IV over 24 hours <b>Days 4 and 11:</b> Vincristine 2mg IV. <b>Cycles 2, 4, 6, and 8</b> <b>Day 1:</b> MTX 200mg/m <sup>2</sup> IV over 2 hours followed by 800mg/m <sup>2</sup> continuous IV infusion over 22 hours followed by leucovorin 50mg IV every 6 hours starting 12 hours after completion of MTX until MTX level <0.05uM <b>Days 2-3:</b> Cytarabine 3g/m <sup>2</sup> (1g/m <sup>2</sup> for patients >60 years old) IV over 2 hours every 12 hours, ± <b>Days 1 and 8:</b> Rituximab 375mg/m <sup>2</sup> IV. <b>CNS Prophylaxis</b> <b>Day 2:</b> MTX 12mg IT <b>Day 8:</b> Cytarabine 100mg IT.
<b>MRC UKALLXII/ECOG2993</b> <sup>28</sup>	<b>Induction</b> <b>Phase 1 (Weeks 1-4):</b> <b>Days 1, 8, 15, and 22:</b> Daunorubicin 60mg/m <sup>2</sup> IV + vincristine 1.4mg/m <sup>2</sup> IV <b>Days 1-28:</b> Prednisone 60mg/m <sup>2</sup> orally daily <b>Day 15:</b> MTX 12.5mg IT <b>Days 17-28:</b> L-asparaginase 10,000IU IV or IM. <b>Phase 2 (Weeks 5-8):</b> <b>Days 1, 15, and 29:</b> Cyclophosphamide 650mg/m <sup>2</sup> IV <b>Days 1-4, 8-11, 15-18, and 22-25:</b> Cytarabine 75mg/m <sup>2</sup> IV <b>Days 1-28:</b> 6-Mercaptopurine 6mg/m <sup>2</sup> orally daily <b>Days 1, 8, 15, and 22:</b> MTX 12.5mg IT. <b>Intensification</b> <b>Days 1, 8, and 22:</b> MTX 3g/m <sup>2</sup> IV <b>Days 2, 9, and 23:</b> L-asparaginase 10,000IU IM or IV + standard leucovorin rescue. <b>Consolidation</b> <b>Cycle 1:</b> <b>Days 1-5:</b> Etoposide 100mg/m <sup>2</sup> IV + cytarabine 75mg/m <sup>2</sup> IV <b>Days 1, 8, 15, and 22:</b> Vincristine 1.4mg/m <sup>2</sup> IV <b>Days 1-28:</b> Dexamethasone 10mg/m <sup>2</sup> orally daily. <b>Cycle 2 (4 Weeks After Cycle 1):</b> <b>Days 1-5:</b> Cytarabine 75mg/m <sup>2</sup> IV + etoposide 100mg/m <sup>2</sup> IV. <b>Cycle 3 (4 Weeks After Cycle 2):</b> <b>Days 1, 8, 15, and 22:</b> Daunorubicin 25mg/m <sup>2</sup> IV <b>Day 29:</b> Cyclophosphamide 650mg/m <sup>2</sup> IV <b>Days 31-34 and 38-41:</b> Cytarabine 75mg/m <sup>2</sup> IV <b>Days 29-42:</b> Thioguanine 60mg/m <sup>2</sup> orally daily. <b>Maintenance:</b> Vincristine 1.4mg/m <sup>2</sup> IV every 3 months Prednisone 60mg/m <sup>2</sup> orally for 5 days every 3 months 6-Mercaptopurine 75mg/m <sup>2</sup> orally daily MTX 20mg/m <sup>2</sup> orally or IV once weekly. Continue for 2.5 years from start of intensification therapy.

### Relapsed or Refractory ALL<sup>1a</sup>

**Ph(+)** ALL

<b>Dasatinib (preferred)</b> <sup>29,30,d</sup>	Dasatinib 140mg orally daily. Continue until disease progression or unacceptable toxicity.
<b>Nilotinib</b> <sup>31,e</sup>	Nilotinib 400mg orally twice daily. Continue until disease progression or unacceptable toxicity.

*continued*

## LEUKEMIA TREATMENT REGIMENS: Acute Lymphoblastic Leukemia (ALL) (Part 11 of 12)

### Relapsed or Refractory ALL<sup>1a</sup> (continued)

#### Ph(+) ALL (continued)

PROTOCOL	REGIMEN AND DOSING
<b>Imatinib (preferred)</b> <sup>32</sup>	Imatinib 600mg orally daily. Continue until disease progression or unacceptable toxicity.
<b>Ponatinib (preferred)</b> <sup>33, f</sup>	Ponatinib 45mg orally daily. Continue until disease progression or unacceptable toxicity.

#### Ph(-) ALL

<b>Clofarabine-Containing Regimens (for B-ALL)</b> <sup>34,35</sup>	<b>Induction</b> <b>Days 1-5:</b> Clofarabine 40mg/m <sup>2</sup> IV over 2 hours + etoposide 100mg/m <sup>2</sup> IV over 2 hours + cyclophosphamide 440mg/m <sup>2</sup> IV over 1 hours. <b>Consolidation</b> <b>Days 1-4:</b> Clofarabine 40mg/m <sup>2</sup> IV over 2 hours + etoposide 100mg/m <sup>2</sup> IV over 2 hours + cyclophosphamide 440mg/m <sup>2</sup> IV over 1 hours.
<b>Cytarabine-Containing Regimens</b> <sup>36</sup>	<b>Days 1-5:</b> Cytarabine 3g/m <sup>2</sup> IV over 3 hours <b>Day 3:</b> Idarubicin 40mg/m <sup>2</sup> .
<b>Alkylator-Containing Regimens</b> <sup>37</sup>	<b>Days 1-3:</b> Mitoxantrone 8mg/m <sup>2</sup> IV daily <b>Days 1-5:</b> Etoposide 100mg/m <sup>2</sup> IV daily + ifosfamide 1.5g/m <sup>2</sup> IV daily.
<b>Nelarabine (for T-ALL)</b> <sup>38</sup>	<b>Days 1, 3, and 5:</b> Nelarabine 1.5g/m <sup>2</sup> /day IV over 2 hours. Repeat cycle every 21 days.
<b>Augmented Hyper-CVAD</b> <sup>39</sup>	<b>Cycles 1, 3, 5, and 7</b> <b>Day 1:</b> Pegaspargase 2,500units/m <sup>2</sup> IV <b>Days 1-3:</b> Cyclophosphamide 300mg/m <sup>2</sup> IV every 12 hours for 6 doses + MESNA 600mg/m <sup>2</sup> continuous IV infusion over 24 hours daily <b>Day 4:</b> Doxorubicin 50mg/m <sup>2</sup> IV over 24 hours <b>Days 1, 8, and 15:</b> Vincristine 2mg IV <b>Days 1-4 and 15-18:</b> Dexamethasone 80mg IV or orally. <b>Cycles 2, 4, 6, and 8</b> <b>Day 1:</b> MTX 1g/m <sup>2</sup> IV over 24 hours with leucovorin 50mg IV given 12 hours after completion of MTX, followed by leucovorin 15mg IV every 6 hours for 8 doses <b>Days 2-3:</b> Cytarabine 3g/m <sup>2</sup> IV every 12 hours for 4 doses <b>Day 5:</b> Pegaspargase 2,500units/m <sup>2</sup> IV. <b>Maintenance</b> Mercaptopurine 50mg orally 3 times daily + MTX 20mg/m <sup>2</sup> orally weekly + vincristine 2mg IV every 28-35 days + prednisone 200mg orally daily on days 1-5.
<b>Vincristine Sulfate Liposome Injection</b> <sup>40,41</sup>	Liposomal vincristine sulfate 2.25mg/m <sup>2</sup> IV over 1 hour once weekly until response, progression, toxicity, or pursuit of HCT.
<b>Blinatumomab (for B-ALL; preferred)</b> <sup>42-44, g</sup>	<b>Cycle 1</b> <b>Days 1-7:</b> Blinatumomab 9mcg/day continuous IV infusion <b>Days 8-28:</b> Blinatumomab 28mcg/day continuous IV infusion. <b>Subsequent Cycles</b> <b>Days 1-28:</b> Blinatumomab 28mcg/day continuous IV infusion. Repeat cycle every 42 days.

<sup>a</sup> All regimens include CNS prophylaxis with systemic therapy (eg, methotrexate, cytarabine, 6-MP) and/or IT therapy (eg, IT methotrexate, IT cytarabine; triple IT therapy with methotrexate, cytarabine, corticosteroid).

<sup>b</sup> For patients receiving 6-MP, consider testing for *TPMT* gene polymorphisms, particularly in patients who develop severe neutropenia after starting 6-MP.

<sup>c</sup> Dose modifications for antimetabolites in maintenance should be consistent with the chosen treatment regimen. It may be necessary to reduce dose/eliminate antimetabolite in the setting of myelosuppression and/or hepatotoxicity.

<sup>d</sup> For patients with mutations Y253H, E255K/V or F359V/C/I.

<sup>e</sup> For patients with mutations F317L/V/I/C, T315A or V299L.

<sup>f</sup> Ponatinib has activity against T315I mutations and is effective in treating patients with resistant or progressive disease on multiple TKIs, but is associated with a high frequency of serious vascular events. The FDA indications are for the treatment of adult patients with T315I-positive PH+ ALL and for the treatment of adult patients with PH+ ALL for whom no other TKI therapy is indicated.

<sup>g</sup> Blinatumomab may cause severe, life-threatening, or fatal adverse events, including cytokine release syndrome and neurologic toxicities. Understanding the REMS programs and/or experience in the use of the drug as well as resources to monitor the patient closely are essential. It is important that the instruction for blinatumomab product preparation (including admixing) and administration are strictly followed to minimize medication errors, including underdose and overdose.

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