

LEUKEMIA TREATMENT REGIMENS: Acute Lymphoblastic Leukemia (ALL) (Part 1 of 11)

Note: The 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.

These Guidelines are a work in progress that may be refined as often as new significant data becomes available. The NCCN Guidelines® are a consensus statement of its authors regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult any NCCN Guidelines® is expected to use independent medical judgment in the context of individual clinical circumstances to determine any patient's care or treatment. The National Comprehensive Cancer Network makes no warranties of any kind whatsoever regarding their content, use, or application and disclaims any responsibility for their application or use in any way.

Ph(+) AYA (Age 15–39 years)^{1*††}

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

REGIMEN	DOSING
COG AALL-0031²	<p><u>Induction</u> Four weeks of standard induction chemotherapy</p> <p><u>Consolidation</u> Block 1 (3 weeks) Day 1: Methotrexate (MTX) intrathecally (IT), etoposide 100mg/m²/day IV, ifosfamide 3.3g/m²/day IV Days 1–21: Imatinib 340mg/m²/day orally Days 6–15: Filgrastim 5mcg/kg/day SC Days 8 and 15: CNS leukemia only: MTX IT, hydrocortisone IT, cytarabine IT.</p> <p>Block 2 (3 weeks) Day 1: Age adjusted: MTX IT, hydrocortisone IT, cytarabine IT + MTX 5g/m² IV over 24 hours Days 1–21: Imatinib 340mg/m²/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/m² 36 hours after MTX followed by 15mg/m² IV or orally every 6 hours for 6 doses + cytarabine 3g/m²/dose IV every 12 hours for 4 doses Days 4–13: Filgrastim 5mcg/kg/day SC.</p> <p><u>Reinduction</u> Day 1: Vincristine 1.5mg/m² IV + age adjusted: MTX IT, hydrocortisone IT, cytarabine IT Days 1–2: Daunorubicin 45mg/m²/day IV bolus Days 1–21: Dexamethasone 6mg/m²/day orally + imatinib 340mg/m²/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/m²/dose IV every 12 hours for 4 doses, plus mesna 125mg/m²/dose IV every 12 hours for 4 doses Days 4, 6, 8, 10, 12, 15, 17, 19, and 21: L-asparaginase 6,000 units/m² IM Days 5–14: Filgrastim 5mcg/kg/day SC Days 8 and 15: Vincristine 1.5mg/m² IV Day 15: Age adjusted: MTX IT, hydrocortisone IT, cytarabine IT.</p> <p><u>Intensification</u> Day 1: Age adjusted: MTX IT, hydrocortisone IT, cytarabine IT Day 1: MTX 5g/m² IV over 24 hours Days 1–63: Imatinib 340mg/m²/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/m² 36 hours after MTX, followed by 15mg/m² IV or orally every 6 hours for 6 doses Day 8: MTX 5g/m² IV over 24 hours Days 9–10: Leucovorin 75mg/m² 36 hours after MTX, followed by 15mg/m² IV or orally every 6 hours for 6 doses Day 15: Age adjusted: MTX IT, hydrocortisone IT, cytarabine IT Days 15–19: Etoposide 100mg/m²/day IV + cyclophosphamide 300mg/m²/day IV + mesna 150mg/m²/day IV Days 20–29: Filgrastim 5mcg/kg/day SC Days 36–37: Cytarabine 3g/m² IV Day 37: L-asparaginase 6,000 units/m² IM Days 43–44: Cytarabine 3g/m² IV Day 44: L-asparaginase 6,000 units/m² IM.</p>

continued

LEUKEMIA TREATMENT REGIMENS: Acute Lymphoblastic Leukemia (ALL) (Part 2 of 11)

Ph(+) AYA (Age 15–39 years)^{1,††} (continued)

REGIMEN	DOSING
COG AALL-0031 ² (continued)	<p>Maintenance Cycles 1–4 (8 weeks) Day 1: Age adjusted: MTX IT, hydrocortisone IT, cytarabine IT Day 1: Vincristine 1.5mg/m² IV Day 1: MTX 5g/m² IV over 24 hours Days 1–5: Dexamethasone 6mg/m²/day orally Days 1–56: Imatinib 340mg/m²/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/m² 36 hours after MTX, followed by 15mg/m² IV or orally every 6 hours for 6 doses Days 8–28: 6-mercaptopurine (MP) 75mg/m²/day Day 8: MTX 20mg/m²/week orally Day 15: MTX 20mg/m²/week orally Day 22: MTX 20mg/m²/week orally Day 29: Age adjusted: MTX IT, hydrocortisone IT, cytarabine IT Day 29: Vincristine 1.5mg/m² IV Days 29–33: Dexamethasone 6mg/m²/day orally Days 36–40: Etoposide 100mg/m² IV Days 36–40: Cyclophosphamide 300mg/m² IV Days 41–50: Filgrastim 5mcg/kg/day SC.</p> <p>Cycles 5–12 (8 weeks) Cycle 5 only: Cranial irradiation 12 Gy Day 1: Vincristine 1.5mg/m² IV Days 1–5: Dexamethasone 6mg/m²/day orally Days 1–14: Imatinib 340mg/m²/day orally (hold imatinib if patient does not achieve count recovery within 2 weeks of last dose of previous course) Days 8, 15, and 22: MTX 20mg/m²/week orally Days 8–28: 6-MP 75mg/m²/day Days 29–42: Imatinib 340mg/m²/day orally (hold imatinib if patient does not achieve count recovery within 2 weeks of last dose of previous course) Days 29–33: Dexamethasone 6mg/m²/day orally Day 29: Vincristine 1.5mg/m² IV Day 36: MTX 20mg/m²/week orally Days 36–56: 6-MP 75mg/m²/day Day 43: MTX 20mg/m²/week orally Day 50: MTX 20mg/m²/week orally.</p>
Hyper-CVAD + Tyrosine Kinase Inhibitors (TKIs) ^{3,6}	<p>Induction 4 cycles Hyper-CVAD alternating with 4 cycles of high dose cytarabine and MTX. Days 1–14 of each cycle: Dasatinib 50mg orally twice daily (or 100mg daily)³ OR imatinib 400mg orally daily. OR Day 1: Cyclophosphamide 1,200mg/m² IV over 3 hours Days 1–3: Daunorubicin 60mg/m² IV over 1 hour Days 1–21: Prednisolone 60mg/m² orally Days 1, 8, 15, and 22: Vincristine 1.3mg/m² IV bolus Days 8–63: Imatinib 600mg orally Day 29: MTX 15mg IT, cytarabine 40mg IT, dexamethasone 4mg IT. OR Pretreatment for 7 days: Prednisone at increasing doses from 10–40mg/m²/day. Days 1–45: Imatinib 800mg orally daily Days 1–45: Prednisone 40mg/m² daily (patients >60 years). OR Pretreatment for 7 days: Prednisone at increasing doses from 10–60mg/m²/day Days 1–48: Dasatinib 70mg orally twice daily Days 1–24: Prednisone 60mg/m² daily (max 120mg daily) Days 22 and 43: MTX IT Days 25–32: Prednisone taper.</p> <p>Consolidation Allogeneic hematopoietic stem cell transplant (HSCT), if a donor is available and consider post-HSCT TKI. OR Continue multi-agent chemotherapy + TKI.</p> <p>Maintenance MTX weekly + 6-MP daily + vincristine pulse monthly + prednisone pulse monthly for 2–3 years.</p>

continued

LEUKEMIA TREATMENT REGIMENS: Acute Lymphoblastic Leukemia (ALL) (Part 3 of 11)

Ph(+) AYA (Age 15–39 years)^{1,††} (continued)

REGIMEN	DOSING
Multiagent Chemotherapy + TKIs^{7,8}	<p>Induction Day 1: Cyclophosphamide 1,200mg/m² IV over 3 hours Days 1–3: Daunorubicin 60mg/m² IV over 1 hour Days 1, 8, 15, and 22: Vincristine 1.3mg/m² IV bolus Days 1–21: Prednisolone 60mg/m² PO daily Days 8–63: Imatinib 600mg PO daily Day 29: MTX 15mg IT + cytarabine 40mg IT + dexamethasone 4mg IT.</p> <p>Consolidation 1 Day 1: MTX 1g/m² IV over 24 hours Days 2–3: Cytarabine 2g/m² IV over 3 hours Days 1–3: Methylprednisolone 50mg IV over 1 hour Day 1: MTX 15mg IT + cytarabine 40mg IT + dexamethasone 4mg IT. Repeat for four cycles.</p> <p>Consolidation 2 Day 1–28: Imatinib 600mg PO daily Day 1: MTX 15mg IT + cytarabine 40mg IT + dexamethasone 4mg IT. Repeat for four cycles.</p> <p>Maintenance Day 1: Vincristine 1.3mg/m² IV bolus Days 1–5: Prednisolone 60mg/m² PO daily Day 1–28: Imatinib 600mg PO daily Repeat every four weeks up to 2 years from the date of complete remission.</p>

Ph(+) Adult (Age ≥40 years)^{1,*††}

Hyper-CVAD + TKIs^{3,6}	<p>Induction 4 cycles Hyper-CVAD alternating with 4 cycles of high dose cytarabine and MTX. Days 1–14 of each cycle: Dasatinib 50mg orally twice daily (or 100mg daily)³ OR imatinib 400mg orally daily.</p> <p style="text-align: center;">OR</p> <p>Day 1: Cyclophosphamide 1,200mg/m² IV over 3 hours Days 1–3: Daunorubicin 60mg/m² IV over 1 hour Days 1–21: Prednisolone 60mg/m² orally Days 1, 8, 15, and 22: Vincristine 1.3mg/m² IV bolus Days 8–63: Imatinib 600mg orally Day 29: MTX 15mg IT, cytarabine 40mg IT, dexamethasone 4mg IT.</p> <p style="text-align: center;">OR</p> <p>Pretreatment for 7 days: Prednisone at increasing doses from 10–40mg/m²/day Days 1–45: Imatinib 800mg orally daily Days 1–45: Prednisone 40mg/m² daily (patients >60 years).</p> <p style="text-align: center;">OR</p> <p>Pretreatment for 7 days: Prednisone at increasing doses from 10–60mg/m²/day Days 1–48: Dasatinib 70mg orally twice daily Days 1–24: Prednisone 60mg/m² daily (max 120mg daily) Days 22 and 43: MTX IT Days 25–32: Prednisone taper.</p> <p>Consolidation Allogeneic hematopoietic stem cell transplant (HSCT), if a donor is available and consider post-HSCT TKI.</p> <p style="text-align: center;">OR</p> <p>Continue multi-agent chemotherapy + TKI.</p> <p>Maintenance MTX weekly + 6-MP daily + vincristine pulse monthly + prednisone pulse monthly for 2–3 years.</p>
Multiagent Chemotherapy + TKIs^{7,8}	<p>Induction Day 1: Cyclophosphamide 1,200mg/m² IV over 3 hours Days 1–3: Daunorubicin 60mg/m² IV over 1 hour Days 1, 8, 15, and 22: Vincristine 1.3mg/m² IV bolus Days 1–21: Prednisolone 60mg/m² PO daily Days 8–63: Imatinib 600mg PO daily Day 29: MTX 15mg IT + cytarabine 40mg IT + dexamethasone 4mg IT.</p>

continued

LEUKEMIA TREATMENT REGIMENS: Acute Lymphoblastic Leukemia (ALL) (Part 4 of 11)

Ph(+) Adult (Age ≥40 years)^{1,*††} (continued)

REGIMEN	DOSING
Multiagent Chemotherapy + TKIs^{7,8} (continued)	<p>Consolidation 1 Day 1: MTX 1g/m² IV over 24 hours Days 2-3: Cytarabine 2g/m² IV over 3 hours Days 1-3: Methylprednisolone 50mg IV over 1 hour Day 1: MTX 15mg IT + cytarabine 40mg IT + dexamethasone 4mg IT. Repeat for four cycles.</p> <p>Consolidation 2 Days 1-28: Imatinib 600mg PO daily Day 1: MTX 15mg IT + cytarabine 40mg IT + dexamethasone 4mg IT. Repeat for four cycles.</p> <p>Maintenance Day 1: Vincristine 1.3mg/m² IV bolus Days 1-5: Prednisolone 60mg/m² PO daily Day 1-28: Imatinib 600mg PO daily. Repeat every four weeks up to 2 years from the date of complete remission.</p>
Corticosteroids + TKIs⁹⁻¹¹	<p>Pretreatment Days 1-7: Prednisone at increasing doses from 10-40mg/m² PO daily.</p> <p>Induction Days 1-45: Imatinib 800mg PO daily + prednisone 40mg/m² PO daily. OR Pretreatment Days 1-7: Prednisone at increasing doses from 10-60mg/m² PO daily.</p> <p>Induction Days 1-84: Dasatinib 70mg PO twice daily Days 1-32: Prednisone 60mg/m² PO daily (maximum 120mg daily) until day 24, then tapered and stopped at day 32 Days 22 and 43: MTX 15mg IT.</p>
Vincristine + Dexamethasone + TKIs^{12,13}	<p>Pretreatment Days 1-7: Prednisone at increasing doses from 10-40mg/m² PO daily</p> <p>Induction Cycle 1: Days 1-28: Imatinib 800mg PO daily Days 1, 8, 15, and 22: Vincristine 2mg IV Days 1-2, 8-9, 15-16, and 22-23: Dexamethasone 40mg PO daily.</p> <p>Cycle 2: Day 1: MTX 1g/m² IV Days 2 and 3: Cytarabine 3g/m² IV every 12 hours Days 1-14: Imatinib 800mg PO daily. OR Pretreatment Days 1-7: Prednisone at increasing doses from 10-40mg/m² PO daily</p> <p>Induction Cycle 1: Days 1-28: Dasatinib 140mg PO daily Days 1, 8, 15, and 22: Vincristine 1mg IV Days 1-2, 8-9, 15-16, and 22-23: Dexamethasone 40mg PO daily.</p> <p>Consolidation Cycles 1, 3, and 5: Days 1-28: Dasatinib 100mg PO daily Day 1: MTX 1g/m² IV Day 2: Asparaginase 10,000IU/m² IM</p> <p>Cycles 2, 4, and 6: Days 1-28: Dasatinib 100mg PO daily Day 1, 3, and 5: Cytarabine 1,000mg/m² every 12 hours IV.</p> <p>Maintenance Dasatinib sequentially with 6-MP and MTX orally one every other month, plus dexamethasone and vincristine every 2 months up to 24 months, followed by dasatinib alone until relapse or death.</p>

continued

LEUKEMIA TREATMENT REGIMENS: Acute Lymphoblastic Leukemia (ALL) (Part 5 of 11)

Ph(-) AYA (Age 15-39 years)^{1*††}

REGIMEN	DOSING
GRAALL-2003¹⁴	<p>Corticosteroid Pre-Phase: 1-7 days before induction therapy: Prednisone 60mg/m²/day 4-7 days before induction therapy: MTX 15mg IT.</p> <p>Induction: Day 1: Cyclophosphamide 750mg/m²/day + vincristine 2mg IV Days 1-3: Daunorubicin 50mg/m²/day Days 1-14: Prednisone 60mg/m²/day Day 8: Vincristine 2mg IV + L-asparaginase 6,000 units/m²/day Days 10 and 12: L-asparaginase 6,000 units/m²/day Day 15: For Good Early Responders: Cyclophosphamide 750mg/m²/day. OR Days 15-16: For Poor Early Responders: Cyclophosphamide 500mg/m²/12 hours Day 15: Vincristine 2mg IV Days 15-16: Daunorubicin 30mg/m²/day Day 17: Lenograstim 150mcg/m²/day to myeloid recovery Days 20 and 22: L-asparaginase 6,000 units/m²/day Day 22: Vincristine 2mg IV Days 24, 26, and 28: L-asparaginase 6,000 units/m²/day.</p> <p>Salvage: Days 1-3: Idarubicin 12mg/m²/day Days 1-4: Cytarabine 2g/m²/12 hours Day 9: Filgrastim to myeloid recovery.</p> <p>Consolidation: Blocks 1, 4, and 7: Days 1-2: Cytarabine 2g/m²/12 hours Days 1-2: Dexamethasone 10mg/12 hours Day 3: L-asparaginase 10,000 units/m²/day Days 7-13: Filgrastim to myeloid recovery. Blocks 2, 5, and 8: Day 15: MTX 3g/m² continuous infusion + vincristine 2mg IV + 6-MP 60mg/m²/day Day 16: L-asparaginase 10,000 units/m²/day Days 16-21: 6-MP 60mg/m²/day Days 22-27: Filgrastim to myeloid recovery. Blocks 3, 6, and 9: Day 29: MTX 25mg/m²/day Days 29-30: Cyclophosphamide 500mg/m²/day Days 29-30: Etoposide 75mg/m²/day Day 31: Filgrastim to myeloid recovery.</p> <p>Late intensification between consolidation blocks 6 and 7 (for patients in CR after the first induction course): Days 1-3: Daunorubicin 30mg/m²/day Day 1: Vincristine 2mg IV Days 1-14: Prednisone 60mg/m²/day Day 8: Vincristine 2mg IV Days 8, 10, and 12: L-asparaginase 6,000 units/m²/day Day 15: Vincristine 2mg IV + cyclophosphamide 500mg/m²/12 hours Days 18, 20, and 22: L-asparaginase 6,000 units/m²/day.</p> <p>Late intensification between consolidation blocks 6 and 7 (for patients in CR after salvage course): Days 1-3: Idarubicin 9mg/m²/day Days 1-4: Cytarabine 2g/m²/12 hours Day 9: Filgrastim to myeloid recovery.</p> <p>Maintenance: Months 1-12 Day 1: Vincristine 2mg IV Days 1-7: Prednisone 40mg/m²/day. Months 1-24 Daily: 6-MP 60mg/m²/day Weekly: MTX 25mg/m²/week.</p>

continued

LEUKEMIA TREATMENT REGIMENS: Acute Lymphoblastic Leukemia (ALL) (Part 6 of 11)

Ph(-) AYA (Age 15–39 years)^{1*†‡} (continued)

REGIMEN	DOSING
GRAALL-2003 ¹⁴ (continued)	<p>CNS Therapy—Prophylaxis: Triple IT Injection 1 IT injection at Days 1 and 8 of induction; 1 IT injection at Day 29 of each series of consolidation blocks; 1 IT injection at Day 1 of late intensification.</p> <p>Cranial Irradiation 18Gy before maintenance therapy initiation. 6-MP 60mg/m²/day during irradiation.</p> <p>CNS Therapy—Treatment of patients with initial CNS involvement: Triple IT Injection 8 IT injections starting from 7 days before induction to Day 21 of induction; 4 IT injections during the first 2 consolidation blocks; 1 IT injection at Day 29 of consolidation blocks 3 and 6.</p> <p>Cranial Irradiation 15Gy before HSCT or 24Gy before maintenance therapy initiation 6-MP 60mg/m²/day during irradiation.</p>
COG AALL-0434 ¹⁵	<p>Induction: Day 1: Cytarabine intrathecally Days 1, 8, 15, and 22: Vincristine IV + daunorubicin IV Days 1–28: Prednisone IV or PO twice daily Day 4, 5, or 6: Pegasparginase IM or IV over 1–2 hours Days 8 and 29: Methotrexate intrathecally.</p> <p>Consolidation: Days 1–5 and 43–47: Nelarabine IV over 60 minutes Days 15, 22, 57, and 64: Methotrexate intrathecally Days 8 and 50: Cyclophosphamide IV over 30 minutes Days 8–11, 15–18, 50–53, and 57–60: Cytarabine IV over 15–30 minutes or SC Days 8–21 and 50–63: Mercaptopurine orally Days 22, 29, 64, and 71: Vincristine sulfate IV Days 22 and 64: Pegasparginase IM or IV over 1–2 hours.</p>
CCG-1961 ^{16,17}	<p>Induction: Day 0: Cytarabine IT Days 0 and 7: Vincristine IV + daunorubicin IV over 15 minutes to 2 hours Days 0–7: Prednisone PO daily Days 3, 5, and 7: Asparaginase or pegasparginase IM.</p>
PETHEMA ALL-96 ¹⁸	<p>Induction: Days 1, 8, 15, and 22: Vincristine 2mg IV + daunorubicin 30mg/m² IV Days 1–27: Prednisone 60mg/m² IV or PO Days 28–35: Prednisone 30mg/m² IV or PO Days 10–12, 17–19, 24–26: Asparaginase 10,000U/m² Day 36: Cyclophosphamide 1,000mg/m² IV Days 1 and 29: Methotrexate 15mg IT + cytarabine 30mg IT + hydrocortisone 20mg IT.</p> <p>Consolidation: Days 1–7: Mercaptopurine 50mg/m² PO Days 1, 28, and 56: Methotrexate 3g/m² IV over 24 hours Days 14 and 42: Teniposide 150mg/m² IV every 12 hours Days 14–15 and 42–43: Cytarabine 500mg/m² IV every 12 hours Days 1, 28, and 56: Methotrexate 15mg IT + cytarabine 30mg IT + hydrocortisone 20mg IT.</p> <p>Consolidation-2/Reinduction: Days 1–14: Dexamethasone 10mg/m² PO or IV daily Days 15–21: Dexamethasone 5mg/m² PO or IV daily Days 1, 8, and 15: Vincristine 1.5mg/m² IV Days 1, 2, 8, and 9: Daunorubicin 30mg/m² IV Days 1 and 15: Cyclophosphamide 600mg/m² IV Days 1–3 and 15–17: Asparaginase 10,000U/m² IM or IV Days 1 and 15: Methotrexate 15mg IT + cytarabine 30mg IT + hydrocortisone 20mg IT.</p> <p>Maintenance-1 + Reinductions Methotrexate 20mg/m² IM weekly until week 52 Mercaptopurine 50mg/m² PO daily until week 52.</p>

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LEUKEMIA TREATMENT REGIMENS: Acute Lymphoblastic Leukemia (ALL) (Part 7 of 11)

Ph(-) AYA (Age 15-39 years)^{1*†‡} (continued)

REGIMEN	DOSING
CALGB 10403¹⁹	<p>Induction: Day 1: Cytarabine IT Days 8 and 29: Methotrexate IT Days 1, 8, 15, and 22: Daunorubicin IV + Vincristine IV Day 4: Peg-asparaginase.</p> <p>Consolidation: Days 1, 8, 15, and 22: Methotrexate IT Days 1 and 29: Cyclophosphamide IV Days 1-4, 8-11, 29-32, and 36-39: Cytarabine Days 1-14 and 29-42: 6-Mercaptopurine PO Days 15, 22, 43, and 50: Vincristine IV Day 15 and 43: Peg-asparaginase.</p> <p>Interim Maintenance: Days 1 and 31: Methotrexate IT Days 1, 11, 21, 31, and 41: Vincristine IV + methotrexate Days 2 and 22: Peg-asparaginase</p> <p>Delayed Intensification: Days 1, 29, and 36: Methotrexate IT Days 1-7 and 15-21: Dexamethasone PO Days 1, 8, and 15: Doxorubicin IV Days 4 and 43: Peg-asparaginase Day 29: Cyclophosphamide IV Days 29-32 and 36-39: Cytarabine IV Days 29-42: 6-Thioguanine PO</p> <p>Maintenance: Days 15 and 29: Methotrexate IT of first four courses of maintenance Days 1, 29, and 57: Vincristine IV For Females: Days 1-5, 29-33, and 57-61: Dexamethasone PO for 2 years from interim maintenance For Males: Days 1-84: 6-Mercaptopurine PO for 3 years from interim maintenance Days 8, 15, 22, 29, 36, 43, 50, 57, 64, 71, and 78: Methotrexate; held on day 29 of first four courses of maintenance when methotrexate IT is given.</p>

Ph(-) Adult (Age ≥40 years)^{1*†‡}

CALGB 8811 Larson²⁰	<p>Induction: Day 1: Cyclophosphamide 1,200mg/m² IV Days 1-3: Daunorubicin 45mg/m² IV Days 1, 8, 15, and 22: Vincristine 2mg IV Days 1-21: Prednisone 60mg/m²/day PO Days 5, 8, 11, 15, 18, and 22: L-asparaginase 6,000units/m² SC.</p> <p>Consolidation: Day 1: Methotrexate 15mg IT + cyclophosphamide 1,000mg/m² IV Days 1-14: 6-Mercaptopurine 60mg/m²/day PO Days 1-4 and 8-11: Cytarabine 75mg/m²/day SC Days 15 and 22: Vincristine 2mg IV Days 15, 18, 22, and 25: L-asparaginase 6,000units/m² SC. Repeat cycle every 4 weeks for 2 cycles, followed by: Days 1-12: Cranial radiation 2,400cGy Days 1, 8, 15, 22, and 29: Methotrexate 15mg IT Days 1-70: 6-Mercaptopurine 60mg/m²/day PO Days 36, 43, 50, 57, and 64: Methotrexate 20mg/m² PO, followed by: Days 1, 8, and 15: Daunorubicin 30mg/m² IV Days 1, 8, and 15: Vincristine 2mg IV Days 1-14: Dexamethasone 10mg/m²/day PO Day 29: Cyclophosphamide 1,000mg/m² IV Days 29-42: 6-Thioguanine 60mg/m²/day PO Days 29-32 and 36-39: Cytarabine 75mg/m²/day SC, followed by: Day 1: Vincristine 2mg IV Days 1-5: Prednisone 60mg/m²/day PO Days 1, 8, 15, and 22: Methotrexate 20mg/m² PO Days 1-28: 6-Mercaptopurine 80mg/m²/day PO. Repeat cycle every 4 weeks until 24 months from diagnosis.</p>
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LEUKEMIA TREATMENT REGIMENS: Acute Lymphoblastic Leukemia (ALL) (Part 8 of 11)

Ph(-) Adult (Age ≥40 years)^{1*††} (continued)

REGIMEN	DOSING
Linker 4-Drug Regimen ²¹	<p>Induction: Days 1-3: Daunorubicin 50mg/m²/day IV Days 1, 8, 15, and 22: Vincristine 2mg IV Days 1-28: Prednisone 60mg/m²/day PO Days 17-28: L-asparaginase 6,000 units/m²/day IM. If bone marrow on day 14 has residual leukemia: Day 15: Daunorubicin 50mg/m² IV. If bone marrow on day 28 has residual leukemia: Day 29 and 30: Daunorubicin 50mg/m² IV Days 29-42: Prednisone 60mg/m²/day PO Days 29-35: L-asparaginase 6,000 units/m²/day IM.</p> <p>Consolidation: Cycles 1, 3, 5, and 7: Days 1-2: Daunorubicin 50mg/m²/day IV Days 1 and 8: Vincristine 2mg IV Days 1-14: Prednisone 60mg/m²/day PO Days 4, 7, 9, 11, and 14: L-asparaginase 12,000 units/m²/day IM. Cycles 2, 4, 6, & 8: Days 1, 4, 8, and 11: Teniposide 165mg/m² IV + cytarabine 300mg/m² IV. Cycle 9: Methotrexate 690mg/m² IV over 42 hours, followed by leucovorin 15mg/m² IV every 6 hours x 12 doses, followed by: Methotrexate 20mg/m² PO weekly + 6-Mercaptopurine 75mg/m² PO daily for 30 months.</p>
Hyper-CVAD ± Rituximab ^{22,23}	<p>Cycles 1, 3, 5, and 7: Days 1-3: Cyclophosphamide 300mg/m² IV every 12 hours + mesna 600mg/m²/day continuous IV infusion starting 1 hour before cyclophosphamide until 12 hours after completion of cyclophosphamide Days 4 and 11: Vincristine 2mg IV Day 4: Doxorubicin 50mg/m² IV over 24 hours Days 1-4 and 11-14: Dexamethasone 40mg orally daily, ± Days 1 and 8: Rituximab 375mg/m² IV.</p> <p>Cycles 2, 4, 6, and 8: Day 1: Methotrexate 200mg/m² IV over 2 hours followed by 800mg/m² continuous IV infusion over 22 hours following by leucovorin 50mg IV every 6 hours starting 12 hours after completion of MTX until MTX level <0.05uM Days 2-3: Cytarabine 3g/m² (1g/m² for patients >60 years old) IV over 2 hours every 12 hours, ± Days 1 and 8: Rituximab 375mg/m² IV.</p> <p>CNS Prophylaxis: Day 2: Methotrexate 12mg intrathecally Day 8: Cytarabine 100mg intrathecally.</p>
MRC UKALLXII/ECOG2993 ²⁴	<p>Induction: Phase 1 (Weeks 1-4): Days 1, 8, 15, and 22: Daunorubicin 60mg/m² IV + vincristine 1.4mg/m² IV Days 17-28: L-asparaginase 10,000 units IV or IM Days 1-28: Prednisone 60mg/m² PO daily Day 15: Methotrexate 12.5mg IT.</p> <p>Phase 2 (Weeks 5-8): Days 1, 15, and 29: Cyclophosphamide 650mg/m² IV Days 1-4, 8-11, 15-18, and 22-25: Cytarabine 75mg/m² IV Days 1-28: 6-Mercaptopurine 6mg/m² PO daily Days 1, 8, 15, and 22: Methotrexate 12.5mg IT.</p> <p>Intensification: Days 1, 8, and 22: Methotrexate 3g/m² IV Days 2, 9, and 23: L-asparaginase 10,000 units IM or IV + standard leucovorin rescue.</p>

continued

LEUKEMIA TREATMENT REGIMENS: Acute Lymphoblastic Leukemia (ALL) (Part 9 of 11)

Ph(-) Adult (Age ≥40 years)^{1*††} (continued)

REGIMEN	DOSING
MRC UKALLXII/ECOG2993²⁴ (continued)	Consolidation: Cycle 1: Days 1-5: Etoposide 100mg/m ² IV Days 1, 8, 15, and 22: Vincristine 1.4mg/m ² IV Days 1-28: Dexamethasone 10mg/m ² PO daily. Cycle 2 (Four Weeks After Cycle 1): Days 1-5: Cytarabine 75mg/m ² IV + etoposide 100mg/m ² IV. Cycle 3 (Four Weeks After Cycle 2): Days 1, 8, 15, and 22: Daunorubicin 25mg/m ² IV Day 29: Cyclophosphamide 650mg/m ² IV Days 31-34 and 38-41: Cytarabine 75mg/m ² IV Days 29-42: Thioguanine 60mg/m ² PO daily. Maintenance: Vincristine 1.4mg/m ² IV every 3 months Prednisone 60mg/m ² PO for 5 days every 3 months 6-Mercaptopurine 75mg/m ² PO daily Methotrexate 20mg/m ² PO or IV once weekly.

Relapsed or Refractory ALL^{1*}

Ph(+) ALL

Dasatinib^{25,26§}	Dasatinib 140mg PO daily Continue until disease progression or unacceptable toxicity.
Nilotinib^{27¶}	Nilotinib 400mg PO twice daily Continue until disease progression or unacceptable toxicity.
Bosutinib²⁸	Bosutinib 500mg PO daily Continue until disease progression or unacceptable toxicity.
Ponatinib^{29**}	Ponatinib 45mg PO daily Continue until disease progression or unacceptable toxicity.

Ph(-) ALL

Clofarabine-Containing Regimens^{30,31}	Induction Days 1-5: Clofarabine 40mg/m ² IV over 2 hours + etoposide 100mg/m ² IV over 2 hours + cyclophosphamide 440mg/m ² IV over 1 hours. Consolidation Days 1-4: Clofarabine 40mg/m ² IV over 2 hours + etoposide 100mg/m ² IV over 2 hours + cyclophosphamide 440mg/m ² IV over 1 hours.
Cytarabine-Containing Regimens³²	Days 1-5: Cytarabine 3g/m ² IV over 3 hours Day 3: Idarubicin 40mg/m ² .
Alkylator-Containing Regimens³³	Days 1-3: Mitoxantrone 8mg/m ² IV daily Days 1-5: Etoposide 100mg/m ² IV daily + ifosfamide 1.5g/m ² IV daily.
Nelarabine (for T-ALL)³⁴	Days 1, 3, and 5: Nelarabine 1.5g/m ² /day IV over 2 hours Repeat cycle every 21 days.
Augmented Hyper-CVAD³⁵	Cycles 1, 3, 5, and 7: Day 1: Pegasparginase 2,500units/m ² IV Days 1-3: Cyclophosphamide 300mg/m ² IV every 12 hours for 6 doses + MESNA 600mg/m ² continuous IV infusion over 24 hours daily Day 4: Doxorubicin 50mg/m ² IV over 24 hours Days 1, 8, and 15: Vincristine 2mg IV Days 1-4 and 15-18: Dexamethasone 80mg IV or PO. Cycles 2, 4, 6, and 8: Day 1: MTX 1g/m ² 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 Days 2-3: Cytarabine 3g/m ² IV every 12 hours for 4 doses Day 5: Pegasparginase 2,500units/m ² IV. Maintenance Mercaptopurine 50mg PO three times daily + MTX 20mg/m ² PO weekly + vincristine 2mg IV every 28-35 days + prednisone 200mg PO daily on days 1-5.
Vincristine Sulfate Liposome Injection^{36,37}	Day 1: Liposomal vincristine sulfate 2.25mg/m ² IV over 1 hour every 7 days.

continued

LEUKEMIA TREATMENT REGIMENS: Acute Lymphoblastic Leukemia (ALL) (Part 10 of 11)

Relapsed or Refractory ALL^{1*} (continued)

Ph(-) ALL (continued)

REGIMEN	DOSING
Blinatumomab ^{38-40***}	<p>Cycle 1: Days 1-7: Blinatumomab 9mcg/day continuous IV infusion Days 8-28: Blinatumomab 28mcg/day continuous IV infusion.</p> <p>Subsequent Cycles: Days 1-28: Blinatumomab 28mcg/day continuous IV infusion. Repeat cycle every 42 days.</p>

* All regimens include CNS prophylaxis with systemic therapy (eg, methotrexate, cytarabine, 6-mercaptopurine) and/or IT therapy (eg, IT methotrexate, IT cytarabine; triple IT therapy with methotrexate, cytarabine, corticosteroid).

† For patients receiving 6-MP, consider testing for TPMT gene polymorphisms, particularly in patients that develop severe neutropenia after starting 6-MP.

‡ 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.

§ For patients with mutations Y253H, E255K/V or F359V/C/I.

¶ For patients with mutations F317L/V/I/C, T315A or V299L.

|| For patients with mutations E255K/V, F317L/V/I/C, T315A or Y253H.

** 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.

*** 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.

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

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