

Acute Lymphoblastic Leukemia (ALL) Treatment Regimens

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 National Comprehensive Cancer Network 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.

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

► CNS Prophylaxis^{1,a}

PROTOCOL ^{1,b}	REGIMEN and DOSING
Intrathecal (IT) Cytarabine ^{2,4}	Day 1: Cytarabine 50-100mg intrathecal with or without 50mg Hydrocortisone (preservative free). Note: Frequency and duration are dependent on CNS disease status and risk of CNS relapse.
IT Cytarabine/Methotrexate/Hydrocortisone ^{2,4}	Day 1: Cytarabine 50-100mg intrathecal, with: Day 1: Methotrexate 12-15mg intrathecal, with: Day 1: Hydrocortisone 50-100mg (preservative-free) intrathecal. Note: Frequency and duration are dependent on CNS disease status and risk of CNS relapse.
IT Methotrexate ^{2,4}	Day 1: Methotrexate 12-15mg intrathecal with or without 50mg Hydrocortisone (preservative-free). Note: Frequency and duration are dependent on CNS disease status and risk of CNS relapse.

► Newly-diagnosed ALL^{1,a}

Adolescents and Young Adults (AYA) (15-39 years) ^c	
Philadelphia Chromosome-Positive [Ph (+)] Disease ^d	
Other Recommended Regimens	
CALGB 10701 ^{5,e}	<p>Course I (First Induction): Days 1-7: Dasatinib 140 mg orally daily Days 1-7: Dexamethasone 10mg/m² orally or IV. Course II (If ≤20% lymphoblasts in marrow at Day 15): Days 1-7: Dasatinib 140 mg orally daily Days 1-7: Dexamethasone 10mg/m² orally or IV. Course II (If >20% lymphoblasts in marrow at Day 15): Days 1-7: Dasatinib 140 mg orally daily Days 1-7: Dexamethasone 10mg/m² orally or IV. Vincristine and Daunorubicin also administered. Course III (Second Induction for patients not in complete remission (CR) or CR with incomplete hematologic recovery (CRi): Patients received Dasatinib, Cyclophosphamide, Vincristine, Daunorubicin, Dexamethasone. Course IV (CNS Prophylaxis): Patients received Dasatinib, IV Vincristine, and IV, oral, and intrathecal Methotrexate. Course V : Patients treated with stem cell transplantation or chemotherapy. Course VI (Maintenance): Dasatinib Starting on Day 30 of Course V and continued for 12 months and until 2 consecutive negative <i>BCR-ABL1</i> RT-PCR assays 3 months apart or relapse.</p>
Corticosteroids + TKI ^{6,7,e}	<p>• Dasatinib + Prednisone PrePhase: Days (-7-[-1]): Prednisone 10-60mg/m² in increasing doses. Induction Therapy: Dasatinib 70mg twice daily for 84 days Prednisone 60mg/m² daily (capped at 120mg daily) administered until Day 24 and then tapered and stopped at Day 32. Days 22,43: Methotrexate intrathecal.</p> <p>• Imatinib + Prednisone PrePhase: Days (-7-[-1]): Prednisone 10-40mg/m² in increasing doses. Induction Therapy: Days 1-45: Imatinib 800mg orally Days 1-45: Prednisone 40mg/m² Note: Induction Therapy with Corticosteroid + Nilotinib is also a recommended regimen. Note: These regimens are used for induction therapy and additional therapy is needed.</p>

continued

Acute Lymphoblastic Leukemia (ALL) Treatment Regimens

► Newly-diagnosed ALL^{1,a} (continued)

PROTOCOL ^{1,b}	REGIMEN and DOSING
Adolescents and Young Adults (AYA) (15-39 years) ^c (continued)	
Philadelphia Chromosome-Positive [Ph (+)] Disease ^d (continued)	
Other Recommended Regimens (continued)	
EsPhALL Regimen: TKI and a backbone of the Berlin-Frankfurt-Munster regimen ^{8,9,e}	<p>• Imatinib-Based Therapy</p> <p>Protocol IB: Day 1,28: Cyclophosphamide 1000mg/m² IV Days 1-28: 6-Mercaptopurine 60mg/m² orally Days 3-6, 10-13, 17-20, 24-27: Cytarabine 75mg/m² subcutaneous Days 3,7: Methotrexate 12mg intrathecal Days 1-28: Imatinib 300mg/m² orally.</p> <p>Consolidation Block HR1: Days 1-5: Dexamethasone 20mg/m² oral or IV Days 1,6: Vincristine 1.5mg/m² IV Day 1: Methotrexate 5000mg/m² IV Day 5: Cytarabine 2000mg/m² IV Day 6: L-Asparaginase 25,000 IU/m² IM Day 2-4: Cyclophosphamide 200mg/m² IV Day 1: Methotrexate 12mg intrathecal Day 1: Cytarabine 30mg intrathecal Day 1: Prednisone 10mg intrathecal Days 6-20: Imatinib 300mg/m² orally.</p> <p>Consolidation Block HR2: Day 1-5: Dexamethasone 20mg/m² oral or IV Days 1,6: Vindesine 3mg/m² IV Day 1: Methotrexate 5,000mg/m² IV Days 2-4: Ifosfamide 800mg/m² IV Days 6: L-Asparaginase 25,000 IU/m² IM Day 5: Daunorubicin 30mg/m² IV Day 1: Methotrexate 12mg intrathecal Day 1: Cytarabine 30mg intrathecal Day 1: Prednisone 10mg intrathecal Days 6-20: Imatinib 300mg/m² orally.</p> <p>Consolidation Block HR3: Days 1-5: Dexamethasone 20mg/m² oral or IV Days 1-2: Cytarabine 2,000mg/m² IV Days 3-5: Vepeside 100mg/m² IV Day 6: L-Asparaginase 25,000 IU/m² IM Day 1: Methotrexate 12mg intrathecal Day 1: Cytarabine 30mg intrathecal Day 1: Prednisone 10mg intrathecal Days 6-20: Imatinib 300mg/m² orally.</p> <p>Reinduction Protocol II: Days 1-21 + tapering: Dexamethasone 10mg/m² orally Days 8,15,22,29: Vincristine 1.5mg/m² IV Days 8,15,22,29: Doxorubicin 25mg/m² IV Days 8,11,15,18: L-Asparaginase 10,000 IU/m² IM Day 36: Cyclophosphamide 1,000 mg/m² IV Days 36-49: 6-Thioguanine 60mg/m² orally Days 38-41, 45-48: Cytarabine 75mg/m² subcutaneous Days 38,45: Methotrexate 12mg intrathecal Days 36-63: Imatinib 300mg/m² orally.</p> <p>Interim Maintenance: Days 1-29: 6-Mercaptopurine 50mg/m² orally Days 8,15,22,29: Methotrexate 20mg/m² orally With cranial irradiation.</p>

continued

Acute Lymphoblastic Leukemia (ALL) Treatment Regimens

► Newly-diagnosed ALL^{1,a} (continued)

PROTOCOL ^{1,b}	REGIMEN and DOSING
Adolescents and Young Adults (AYA) (15-39 years) ^c (continued)	
Philadelphia Chromosome-Positive [Ph (+)] Disease ^d (continued)	
Other Recommended Regimens (continued)	
EsPhALL Regimen: TKI and a backbone of the Berlin-Frankfurt-Munster regimen ^{8,9,e} (continued)	<p>• Imatinib-Based Therapy (continued)</p> <p>Reinduction Protocol II: Days 1-21 + tapering: Dexamethasone 10mg/m² orally Days 8,15,22,29: Vincristine 1.5mg/m² IV Days 8,15,22,29: Doxorubicin 25mg/m² IV Days 8,11,15,18: L-Asparaginase 10,000 IU/m² IM Day 36: Cyclophosphamide 1,000 mg/m² IV Days 36-49: 6-Thioguanine 60mg/m² orally Days 38-41, 45-48: Cytarabine 75mg/m² subcutaneous Days 36-63: Imatinib 300mg/m² orally.</p> <p>Continuation Therapy Maintenance: 6-Mercaptopurine 50mg/m² orally daily until Day +728 from diagnosis Methotrexate 20mg/m² orally weekly until day +728 from diagnosis. Note: This regimen has also been studied in combination with Dasatinib.</p>
Hyper CVAD with TKI and High-Dose Methotrexate, Cytarabine ^{10-13,e}	<p>• Dasatinib-based Therapy</p> <p>Cycle A: Days 1-3: Cyclophosphamide 300mg/m² over 3 hours every 12 hours for 6 doses^f Days 1-3: Mesna 600mg/m² IV continuous infusion over 24 hours daily starting 15 minutes before the first dose of Cyclophosphamide and completing 12 hours after the last dose of Cyclophosphamide is started. Day 4: Doxorubicin 50mg/m² IV push OR IV continuous infusion over 24 hours Days 4, 11: Vincristine 2mg IV over 5-10 minutes Days 1-4, 11-14: Dexamethasone 40mg IV OR orally daily Day 2: Methotrexate 12mg intrathecal Day 7: Cytarabine 100mg intrathecal. Days 1-14: Dasatinib 100mg orally daily. Repeat cycle every 3 weeks for 4 cycles alternating with Cycle B.</p> <p>Cycle B: Day 1: Methotrexate 200mg/m² IV over 2 hours, then 800mg/m² IV continuous infusion over 22 hours. (Alkaline hydration is required pre- and post-administration of high-dose Methotrexate.) Day 2: Leucovorin 50mg IV over 15 minutes administered 12 hours after completion of 22-hour Methotrexate infusion, then 15mg IV over 15 minutes OR orally every 6 hours for at least 8 doses (until Methotrexate serum concentration is <0.05 micromol/L) Days 2-3: Cytarabine (age <60 years) 3,000mg/m² IV over 3 hours every 12 hours for 4 doses OR Cytarabine (age ≥60 years) 1,000 mg/m² IV over 3 hours every 12 hours for 4 doses Day 2: Methotrexate 12mg intrathecal Day 7: Cytarabine 100mg intrathecal Days 1-14: Dastinib 100mg orally daily. Repeat cycle every 3 weeks for 4 cycles alternating with Cycle A.</p> <p>• Imatinib-Based Therapy</p> <p>Cycle A: Days 1-3: Cyclophosphamide 300mg/m² over 3 hours every 12 hours for 6 doses^f Days 1-3: Mesna 600mg/m² IV continuous infusion over 24 hours daily starting 15 minutes before the first dose of Cyclophosphamide and completing 12 hours after the last dose of Cyclophosphamide is started. Day 4: Doxorubicin 50mg/m² IV push OR IV continuous infusion over 24 hours Days 4, 11: Vincristine 2mg IV over 5-10 minutes Days 1-4, 11-14: Dexamethasone 40mg IV OR orally daily Day 2: Methotrexate 12mg intrathecal Day 7: Cytarabine 100mg intrathecal. Days 1-14: Imatinib 400mg orally daily. Repeat cycle every 3 weeks for 4 cycles alternating with Cycle B.</p>

continued

Acute Lymphoblastic Leukemia (ALL) Treatment Regimens

► Newly-diagnosed ALL^{1,a} (continued)

PROTOCOL ^{1,b}	REGIMEN and DOSING
Adolescents and Young Adults (AYA) (15-39 years) ^c (continued)	
Philadelphia Chromosome-Positive [Ph (+)] Disease ^d (continued)	
Other Recommended Regimens (continued)	
Hyper CVAD with TKI and High-Dose Methotrexate, Cytarabine ^{10-13e} (continued)	<p>• Imatinib-Based Therapy (continued)</p> <p>Cycle B: Day 1: Methotrexate 200mg/m² IV over 2 hours, then 800mg/m² IV continuous infusion over 22 hours. (Alkaline hydration is required pre- and post-administration of high-dose Methotrexate.) Day 2: Leucovorin 50mg IV over 15 minutes administered 12 hours after completion of 22-hour Methotrexate infusion, then 15mg IV over 15 minutes OR orally every 6 hours for at least 8 doses (until Methotrexate serum concentration is <0.05 micromol/L) Days 2-3: Cytarabine (age <60 years) 3,000mg/m² IV over 3 hours every 12 hours for 4 doses OR Cytarabine (age ≥60 years) 1,000 mg/m² IV over 3 hours every 12 hours for 4 doses Day 2: Methotrexate 12mg intrathecal Day 7: Cytarabine 100mg intrathecal Days 1-14: Imatinib 400mg orally daily. Repeat cycle every 3 weeks for 4 cycles alternating with Cycle A.</p> <p>• Ponatinib-Based Therapy</p> <p>Cycle A: Days 1-3: Cyclophosphamide 300mg/m² over 3 hours every 12 hours for 6 doses^f Days 1-3: Mesna 600mg/m² IV continuous infusion over 24 hours daily starting 15 minutes before the first dose of Cyclophosphamide and completing 12 hours after the last dose of Cyclophosphamide is started. Day 4: Doxorubicin 50mg/m² IV push OR IV continuous infusion over 24 hours Days 4 and 11: Vincristine 2mg IV over 5-10 minutes Days 1-4, 11-14: Dexamethasone 40mg IV OR orally daily Day 2: Methotrexate 12mg intrathecal Day 7: Cytarabine 100mg intrathecal. Days 1-14: Ponatinib 45mg orally daily (cycle 1), followed by: Days 1-21: Ponatinib 30mg orally daily (cycles 2-4). Repeat cycle every 3 weeks for 4 weeks alternating with Cycle B.</p> <p>Cycle B: Day 1: Methotrexate 200mg/m² IV over 2 hours, then 800mg/m² IV continuous infusion over 22 hours. (Alkaline hydration is required pre- and post-administration of high-dose Methotrexate.) Day 2: Leucovorin 50mg IV over 15 minutes administered 12 hours after completion of 22-hour Methotrexate infusion, then 15mg IV over 15 minutes OR orally every 6 hours for at least 8 doses (until Methotrexate serum concentration is <0.05 micromol/L) Days 2-3: Cytarabine (age <60 years) 3,000mg/m² IV over 3 hours every 12 hours for 4 doses OR Cytarabine (age ≥60 years) 1,000 mg/m² IV over 3 hours every 12 hours for 4 doses Day 2: Methotrexate 12mg intrathecal Day 7: Cytarabine 100mg intrathecal Days 1-21: Ponatinib 30mg orally. Repeat cycle every 3 weeks for 4 cycles alternating with Cycle A.</p>
Multiagent Chemotherapy (Daunorubicin, Vincristine, Prednisone, Dexamethasone) + TKI ^{14-16e}	<p>Representative Regimens</p> <p>• Dasatinib-Based Therapy</p> <p>Induction Therapy: Weeks 1-2: All patient received the first 2 weeks of Induction Therapy on a frontline COG or DCFI ALL trial Weeks 3-4: Days 1,8 of AALL0622 regimen or Days 15,22 of induction regimen: Vincristine 1.5mg/m² IV/dose (maximum dose: 2mg) Days 1,8 of AALL0622 regimen or Days 15,22 of induction regimen: Daunorubicin 25mg/m² IV/dose Days 15 of AALL0622 regimen or Day 29 of induction therapy: Triple intrathecal therapy Note: Patients who were CNS3^g also received triple intrathecal therapy on Days 1,8 of AALL0622 regimen or Days 15 and 22 of induction regimen Days 1-14 or 1-21: Dasatinib 60mg/m² orally twice daily.</p> <p>Consolidation Therapy - Block I (weeks 6-8) Days 1-5: Etoposide 100mg/m² IV Days 1-5: Ifosfamide 1800mg/m² with Mesna Day 1: Triple intrathecal therapy Note: Prior to study amendment, all patients received dose of triple intrathecal therapy on Day 1, which is Day 36 of protocol therapy. After study amendment, patients did not receive triple intrathecal therapy on Day 1 of consolidation. Patients who were classified as CNS 2a, 2b, or 2c^g and those with traumatic taps who did not receive 2 triple intrathecal doses in induction also received doses on Days 8,15.</p>

continued

Acute Lymphoblastic Leukemia (ALL) Treatment Regimens

► Newly-diagnosed ALL^{1,a} (continued)

PROTOCOL ^{1,b}	REGIMEN and DOSING
Adolescents and Young Adults (AYA) (15-39 years) ^c (continued)	
Philadelphia Chromosome-Positive [Ph (+)] Disease ^d (continued)	
Other Recommended Regimens (continued)	
Multiagent Chemotherapy (Daunorubicin, Vincristine, Prednisone, Dexamethasone) + TKI ^{14-16,e} (continued)	<p>Representative Regimens (continued)</p> <ul style="list-style-type: none"> • Dasatinib-Based Therapy (continued) <p>Consolidation Therapy - Block II</p> <p>Day 1: High-dose Methotrexate 500mg/m² over 30 minutes, then 4,500mg/m² over remainder of 24 hours</p> <p>Day 1: Triple intrathecal therapy (see note above)</p> <p>Days 2,3: Cytarabine 3,000mg/m²/dose IV over 3 hours every 12 hours x 4 doses</p> <p>Beginning on Day 4: Filgrastim (G-CSF) 5mcg/kg/dose subcutaneous/IV continued until ANC >1,500/uL.</p> <p>Days 1-14 or 1-21: Dasatinib 60mg/m² orally twice daily.</p> <p>Re-Induction Therapy – Block I (weeks 12-14; patients not proceeding to HSCT):</p> <p>Days 1,8,15: Vincristine 1.5mg/m² IV (maximum dose: 2mg)</p> <p>Days 1,2: Daunorubicin 45mg/m² IV</p> <p>Days 3,4: Cyclophosphamide 250mg/m² IV every 12 hours^f</p> <p>Day 4: PEG-Asparaginase 2,500 IU/m² IM or IV</p> <p>Day 1,15: Triple intrathecal therapy</p> <p>Days 1-7, 15-21: Dexamethasone 6mg/m² orally divided twice daily</p> <p>Day 5: Filgrastim (G-CSF): 5mcg/kg subcutaneous or IV and continued until ANC >1,500/uL</p> <p>Days 1-14 or 1-21: Dasatinib 60mg/m² orally twice daily.</p> <p>Intensification Therapy – Block I (weeks 15-23; patients not proceeding to HSCT):</p> <p>Days 1,15: High-dose Methotrexate 500mg/m² IV over 30 minutes, then 4,500mg/m² over remainder of 24 hours</p> <p>Day 1,22: Triple intrathecal therapy</p> <p>Days 22-26: Etoposide 100mg/m² over 1 hour</p> <p>Days 22-26: Cyclophosphamide 300mg/m² IV over 1 hour^g with Mesna</p> <p>Day 27: Filgrastim (G-CSF) 5mcg/kg subcutaneous or IV and continued until ANC >1500/uL</p> <p>Days 43,44: Cytarabine 3,000 mg/m² IV every 12 hours x 4 doses</p> <p>Day 44: L-Asparaginase 6,000 IU/m² administered 6 hours after completion of Cytarabine</p> <p>Days 1-14, 22-35, 43-56 or Days 1-63: Dasatinib 60mg/m² orally twice daily.</p> <p>Re-Induction Therapy – Block II (weeks 24-26; patients not proceeding to HSCT):</p> <p>Days 1,8,15: Vincristine 1.5mg/m² IV (maximum dose: 2mg)</p> <p>Days 1,2: Daunorubicin 45mg/m² IV</p> <p>Days 3,4: Cyclophosphamide 250mg/m² IV every 12 hours x 4 doses^f</p> <p>Day 4: PEG-Asparaginase 2,500 IU/m² IM after last dose of Cyclophosphamide</p> <p>Days 1,15: Triple intrathecal therapy</p> <p>Days 1-7, 15-21: Dexamethasone 6mg/m² orally divided twice daily</p> <p>Beginning on Day 5: Filgrastim (G-CSF) 5mcg/kg subcutaneous or IV</p> <p>Days 1-14 or 1-21: Dasatinib 60mg/m² orally twice daily.</p> <p>Intensification Therapy – Block II (weeks 27-35; patients not proceeding to HSCT):</p> <p>Days 1,15: High-dose Methotrexate 500mg/m² IV over 30 minutes, then 4,500mg/m² over remainder of 24 hours</p> <p>Day 1,22: Triple intrathecal therapy</p> <p>Days 22-26: Etoposide 100mg/m² IV over 1 hour</p> <p>Days 22-26: Cyclophosphamide 300mg/m² IV over 1 hour^g with Mesna</p> <p>Beginning Day 27: Filgrastim (G-CSF) 5mcg/kg subcutaneous or IV</p> <p>Days 43,44: Cytarabine 3,000mg/m² IV every 12 hours x 4 doses</p> <p>Day 44: L-Asparaginase 6,000 IU/m² IM given 6 hours after completion of Cytarabine</p> <p>Days 1-14, 22-35, 43-56 or Days 1-63: Dasatinib 60mg/m² orally twice daily.</p> <p>Maintenance Therapy – Cycles 1-4 (weeks 36-67; patients not proceeding to HSCT):</p> <p>Day 1: High-Dose Methotrexate 500mg/m² IV over 30 minutes, then 4,500mg/m² IV over remainder of 24 hours</p> <p>Day 1,29: Triple intrathecal therapy</p> <p>Days 1,29: Vincristine 1.5mg/m² IV (maximum dose: 2mg)</p> <p>Days 1-5, 29-33: Dexamethasone 6mg/m² orally divided twice daily</p> <p>Days 8-28: Mercaptopurine 75mg/m² orally</p> <p>Days 8,15,22: Methotrexate 20mg/m² orally on an empty stomach</p> <p>Days 29-33: Etoposide 100mg/m² IV over 1 hour</p> <p>Days 29-33: Cyclophosphamide 300mg/m² IV given immediately following Etoposide with Mesna^f</p> <p>Beginning on Day 34: Filgrastim (G-CSF) 5mcg/m² and continued until ANC >1,500/uL</p> <p>Days 1-14, 29-42 or Days 1-49: Dasatinib 60mg/m² orally twice daily.</p>

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Acute Lymphoblastic Leukemia (ALL) Treatment Regimens

► Newly-diagnosed ALL^{1,a} (continued)

PROTOCOL ^{1,b}	REGIMEN and DOSING
Adolescents and Young Adults (AYA) (15-39 years) ^c (continued)	
Philadelphia Chromosome-Positive [Ph (+)] Disease ^d (continued)	
Other Recommended Regimens (continued)	
Multiagent Chemotherapy (Daunorubicin, Vincristine, Prednisone, Dexamethasone) + TKI ^{14-16, e} (continued)	<p>Representative Regimens (continued)</p> <ul style="list-style-type: none"> • Dasatinib-Based Therapy (continued) <p>Maintenance Therapy – Cycle 5 (weeks 68-75; patients not proceeding to HSCT): Beginning on Day 1: Cranial irradiation Days 1,29: Vincristine 1.5mg/m² IV (maximum dose: 2mg) Days 1-5, 29-33: Dexamethasone 6mg/m² orally divided twice daily First Day after Cranial Irradiation Completion: Mercaptopurine 75mg/m² orally daily Day 8,15,22,29,36,43,50: Methotrexate 20mg/m² orally Days 1-14, 29-42 or Days 1-49: Dasatinib 60mg/m² orally twice daily.</p> Maintenance Therapy – Cycles 6-12 (weeks 76-131; patients not proceeding to HSCT) Days 1,29: Vincristine 1.5mg/m² IV (maximum dose: 2mg) Days 1-5, 29-33: Dexamethasone 6mg/m² orally divided twice daily Days 1-56: Mercaptopurine 75mg/m² orally given on an empty stomach Days 1,8,15,22,29,36,43,50: Methotrexate 20mg/m² orally Days 1-14, 29-42 or Days 1-49 or 1-21: Dasatinib 60mg/m² orally twice daily. • Imatinib-Based Therapy <p>Induction Therapy: Day 1: Cyclophosphamide 1,200mg/m² IV over 3 hours^f Days 1-3: Daunorubicin 60mg/m² IV over 1 hour Days 1,8,15,22: Vincristine 1.3mg/m² IV bolus Days 1-21: Prednisolone 60mg/m² orally Days 8-63: Imatinib 600mg orally Day 29: Methotrexate 15mg intrathecal Day 29: Cytarabine 40mg intrathecal Day 29: Dexamethasone 4mg intrathecal.</p> Consolidation Therapy – Cycle I: Day 1: Methotrexate 1,000mg/m² IV over 24 hours Days 2,3: Cytarabine 2,000/m² over 3 hours × 2 Days 1-3: Methylprednisolone 50mg IV over 1 hour × 2 Day 1: Methotrexate 15mg intrathecal Day 1: Cytarabine 40mg intrathecal Day 1: Dexamethasone 4mg intrathecal. Administer for 4 cycles alternating with Cycle II. Consolidation Therapy – Cycle II: Days 1-28: Imatinib 600mg orally Day 1: Methotrexate 15mg intrathecal Day 1: Cytarabine 40mg intrathecal Day 1: Dexamethasone 4mg intrathecal. Administer for 4 cycles alternating with Cycle I. Maintenance Therapy: Day 1: Vincristine 1.3mg/m² IV (bolus) (2mg maximum) Days 1-5: Prednisolone 60mg/m² orally Days 1-28: Imatinib 600mg orally. Maintenance therapy administered every 4 weeks up to 2 years from the date of CR. • Nilotinib-Based Therapy <p>Induction Therapy: Days 1-3: Daunorubicin 90mg/m² IV continuous 24 hour infusion Days 1,8: Vincristine 2mg IV push Days 1-14: Prednisolone 60mg/m² orally or 48mg/m² IV Day 8 to start of conditioning for allo-HCT or until the end of 2 years of maintenance therapy: Nilotinib 400mg orally twice daily.</p> Consolidation – Cycle A: Days 1,2: Daunorubicin 45mg/m² IV continuous 24-hour infusion Days 1-8: Vincristine 2mg IV push Day 1-14: Prednisolone 60mg/m² orally Nilotinib 400mg orally twice daily. Administer for 1 cycle.

continued

Acute Lymphoblastic Leukemia (ALL) Treatment Regimens

► Newly-diagnosed ALL^{1,a} (continued)

PROTOCOL ^{1,b}	REGIMEN and DOSING
Adolescents and Young Adults (AYA) (15-39 years) ^c (continued)	
Philadelphia Chromosome-Positive [Ph (+)] Disease ^d (continued)	
Other Recommended Regimens (continued)	
Multiagent Chemotherapy (Daunorubicin, Vincristine, Prednisone, Dexamethasone) + TKI ^{14-16, e} (continued)	<p>Representative Regimens (continued)</p> <p>• Nilotinib-Based Therapy (continued)</p> <p>Consolidation – Cycle B: Days 1-4: Cytarabine 2000mg/m² IV over 2 hours Days 1-4: Etoposide 150mg/m² IV over 3 hours Nilotinib 400mg orally twice daily. Administer for 2 cycles alternating with Cycle C.</p> <p>Consolidation – Cycle C: Days 1-2, 15-16: Methotrexate 220mg/m² IV bolus, then 60mg/m² per hour for 36 hours Leucovorin, followed immediately by 50mg/m² IV every 6 hours for 3 doses; then Leucovorin orally until serum Methotrexate <0.05 micromol/L Nilotinib 400mg orally twice daily. Administer for 2 cycles alternating with Cycle B.</p> <p>Maintenance Therapy: Nilotinib 400mg orally twice daily for 2 years.</p> <p>CNS Prophylaxis: Up to 10 doses of Methotrexate 15mg intrathecal, with: Hydrocortisone 50mg during or after Induction Therapy.</p>
Vincristine + Dexamethasone + TKI ¹⁷	<p>PrePhase Therapy: Days (-7)-(-1): Prednisone 60mg/m² orally Between Days (-7)-(-1): Methotrexate 15mg intrathecal</p> <p>• Imatinib-Based Regimen</p> <p>Induction Therapy: Days 1,8,15,22: Vincristine 2mg IV Days 1-2, 8-9, 15-16, 22-23: Dexamethasone 40mg orally Days 1-28: Imatinib 400mg orally twice daily</p> <p>Note: Induction Therapy with Vincristine + Dexamethasone + Dasatinib and Vincristine + Dexamethasone + Nilotinib are also recommended regimens.</p> <p>Note: These regimens are used for induction therapy and additional therapy is needed.</p>
Ph (-) Disease ^h	
Preferred Regimens	
CALGB 10403 (for patients <40 years) ^{18,i}	<p>Induction Therapy: Allopurinol 300mg daily (unless allergic) should be administered until peripheral blasts and extramedullary disease are reduced. Day 1: Cytarabine 70mg intrathecal Days 1-28: Prednisone 60mg/m² daily orally or IV in 2 divided doses Days 1,8,15,22: Vincristine 1.5mg/m² IV (maximum dose 2mg) Days 1,8,15,22: Daunorubicin 25mg/m² IV Day 4: Pegylated Asparaginase 2,500 IU/m² IM or IV Days 8,29 (also administered on Days 15, 22 for patients with CNS3^e): Methotrexate 15mg intrathecal.</p> <p>Extended Remission Induction Therapy (if required): Days 1-14: Prednisone 60mg/m² daily orally or IV in 2 divided doses Day 1: Daunorubicin 25mg/m² IV Days 1,8: Vincristine 1.5mg/m² (maximum dose 2mg) IV Day 4: Pegylated Asparaginase 2,500 IU/m² IM or IV.</p> <p>Remission Consolidation Therapy: Days 1,29: Cyclophosphamide 1000mg/m² IV^f Days 1-4,8-11,29-32,36-39: Cytarabine 75mg/m² IV or SC Days 1-14,29-42: 6-Mercaptopurine 60mg/m² orally Days 15,22,43,50: Vincristine 1.5mg/m² (maximum 2mg) IV Days 15,43: Pegylated Asparaginase 2,500 IU/m² IM or IV Days 1,8,15,22 (omit doses on Days 15 and 22 for patients with CNS3^e): Methotrexate 15 mg intrathecal.</p>

continued

Acute Lymphoblastic Leukemia (ALL) Treatment Regimens

► Newly-diagnosed ALL^{1,a} (continued)

PROTOCOL ^{1,b}	REGIMEN and DOSING
Adolescents and Young Adults (AYA) (15-39 years) ^c (continued)	
Ph (-) Disease ^h (continued)	
Preferred Regimens (continued)	
CALGB 10403 (for patients <40 years) ^{18,i} (continued)	<p>Interim Maintenance Therapy: Days 1,11,21,31,41: Methotrexate at a starting dose of 100mg/m² IV escalated by 50mg/m²/dose Days 1,11,21,31,41: Vincristine 1.5mg/m² IV (maximum dose 2mg) Days 2,22: Pegylated Asparaginase 2,500 IU/m² IM or IV Days 1,31: Methotrexate 15mg intrathecal.</p> <p>Delayed Intensification Therapy: Days 1,8,15,43,50: Vincristine 1.5mg/m² (maximum dose 2mg) Days 1-7,15-21: Dexamethasone 10mg/m² orally or IV administered in 2 divided doses Days 1,,8,15: Doxorubicin 25mg/m² IV Days 4 (or Day 5 or Day 6), 43: Pegylated Asparaginase 2,500 IU/m² IM or IV Day 29: Cytarabine 1,000mg/m² IV Days 29-32, 36-39: Cytarabine 75mg/m² IV or SC Days 29-42: 6-Thioguanine 60mg/m² orally daily Days 1,29,36: Methotrexate 15mg intrathecal.</p> <p>Maintenance Therapy: Days 1,29,57: Vincristine 1.5mg/m² (maximum dose 2mg) IV Days 1-5,29-33,57-61: Dexamethasone 6mg/m² orally daily in 2 divided doses Days 1-84: 6-Mercaptopurine 75mg/m² orally daily Day 1 (and on Day 29 for first course of maintenance): Methotrexate 15mg intrathecal Days 8,15,22,29,36,43,50,57,64,71,78 (held on Day 29 of the first 4 courses of maintenance with intrathecal Methotrexate is given): Methotrexate 20mg/m² orally weekly.</p>
COG AALL0232 (for patients ≤21 years) ^{19,20,i}	<p>Induction Therapy (for 4 weeks): Day 0: Cytarabine 15mg intrathecal Days 1,8,15,22: Vincristine 1.5mg/m² IV (2mg maximum) Day 1,8,15,22: Daunorubicin 25mg/m² IV Days 1-28: Prednisone 30mg/m² orally or IV twice daily Days 4,5, or 6: Pegaspargase 2,500mg/m² IMⁱ Note: Patients with CNS3^g disease also receive Methotrexate intrathecal on Days 15 and 22.</p> <p>Extended Induction Therapy (only for patients with M2 disease or M1 disease with >1% minimal residual disease): Days 8,29 (CNS3^g +15,22): Methotrexate 15mg intrathecal Days 1-14: Prednisone 30mg/m² orally or IV twice daily Days 1,8: Vincristine 1.5mg/m² (2mg maximum) IV Day 1: Daunorubicin 25mg/m² IV Days 4,5, or 6: 2,500 U/m² Pegaspargase IMⁱ</p> <p>Consolidation Therapy (for about 7-8 weeks): Days 1,29: Cyclophosphamide 1,000mg/m² IV over 30 minutes^f Days 1-4, 8-11, 29-32, 36-39: Cytarabine 75mg/m² Days 1-14, 29-42: Mercaptopurine 60mg/m² orally Days 15,22,43,50: Vincristine 1.5mg IV (2mg maximum) Days 15,43: Pegaspargase 2,500 U/m² IM Days 1,8,15,22: Methotrexate 15mg intrathecal.</p> <p>Interim Maintenance I: Days 1,15,29,43: Vincristine 1.5mg/m² IV (2mg maximum) IV over 24 hours Days 1,15,29,43: Methotrexate 5,000mg/m² IV over 24 hours, Days 1-56: Mercaptopurine 25mg/m² orally Days 1,29: Methotrexate 15mg intrathecal</p> <p>Delayed Intensification I: Days 1,8,15,43,50: Vincristine 1.5mg/m² IV (2mg maximum) Days 4 or 5 or 6, and 43: Pegaspargase 2,500 U/m² IMⁱ Days 1-7, 15-21: Dexamethasone 10mg/m² Days 1,8,15: Doxorubicin 25mg/m² IV Days 29-32, 36-39: Cytarabine 75mg/m² Day 29: Cyclophosphamide 1,000mg/m² IV^f Days 29-42: Thioguanine 60mg/m² orally Days 1,29,36: Methotrexate 15mg intrathecal.</p>

continued

Acute Lymphoblastic Leukemia (ALL) Treatment Regimens

► Newly-diagnosed ALL^{1,a} (continued)

PROTOCOL ^{1,b}	REGIMEN and DOSING
Adolescents and Young Adults (AYA) (15-39 years) ^c (continued)	
Ph (-) Disease ^h (continued)	
Preferred Regimens (continued)	
COG AALL0232 (for patients ≤21 years) ^{19,20,i} (continued)	<p>Interim Maintenance II: Days 1,11,21,31,41: Vincristine 1.5mg/m² IV Days 1,11,21,31,41: Methotrexate 100mg/m² IV Days 2,22: Pegaspargase 2,500mg/m² IMⁱ Days 1,31: Methotrexate 15mg intrathecal.</p> <p>Delayed Intensification II: Same regimen as Delayed Intensification I.</p> <p>Maintenance Therapy: Days 1,29,57: Vincristine 1.5mg/m² (2mg maximum) IV Days 1-5, 29-33, 57-61: Prednisone 20mg/m² twice daily Daily: Mercaptopurine 75mg/m² orally Weekly: Methotrexate 20mg/m² orally Days 1 (and 29 first 4 cycles): Methotrexate 15mg intrathecal.</p>
COG AALL0434 (with Nelarabine added to Consolidation Regimen) ^{21,22,i} (for patients with T-ALL)	<p>Induction Therapy: At diagnostic lumbar puncture or Day 1: Cytarabine 15mg intrathecal Days 1,8,15,22: Vincristine 1.5mg/m² IV (2 mg maximum) Days 1-28: Prednisone 30mg/m² IV twice daily Days 1,8,16,22: Daunorubicin 25mg/m² IV Days 4,5, or 6: Pegaspargase 2,500 U/m² IMⁱ Days 8,29 (CNS3^e + Days 15,22): Methotrexate 15mg intrathecal.</p> <p>Consolidation Therapy With Nelarabine: Days 8,50: Cyclophosphamide 1,000mg/m² IV^f Days 8-11, 15-18, 50-53, 57-60: Cytarabine 75mg/m² Days 8-21, 50-63: Mercaptopurine 60mg/m² Days 22,29,64,71: Vincristine 1.5mg/m² IV (2mg maximum) Days 22,64: Pegaspargase 2,500 U/m² IMⁱ Days 15,22,57,64 (omit Day 22 for CNS3^e): Methotrexate 15mg intrathecal Days 1-5, 43-47: Nelarabine 650mg/m² IV, with: Cranial radiation therapy and testicular radiation therapy.</p> <p>Interim Maintenance: Days 1,11,21,31,41 (every 10 days x 5 doses): Vincristine 1.5mg/m² IV (2 mg maximum) Days 1,11,21,31,41 (every 10 days x 5 doses): Methotrexate 100mg/m² IV Days 2,22: Pegaspargase 2,500 U/m² IMⁱ Days 1,31: Methotrexate 15mg intrathecal.</p> <p>Delayed Intensification without Nelarabine: Days 1,8,15,43,50: Vincristine 1.5mg/m² IV (2mg maximum) Days 4 or 5 or 6, 43: Pegaspargase 2,500 U/m² IMⁱ Days 1-7,15-21: Dexamethasone 5mg/m² twice daily Days 1,8,15: Doxorubicin 25mg/m² IV Days 29-32, 36-39: Cytarabine 75mg/m² Day 29: 1,000mg Cyclophosphamide 1,000mg/m² IV^f Days 29-42 (omit for patients receiving cranial irradiation therapy): Thioguanine 60mg/m² Days 1,29,36: Methotrexate 15mg intrathecal.</p> <p>Delayed Intensification with Nelarabine: Days 1,8,15,50: Vincristine 1.5mg/m² IV (2mg maximum) Days 4 or 5 or 6 and 50: Pegaspargase 2,500 U/m² IMⁱ Days 1-7, 15-21: Dexamethasone 5mg/m² twice daily Days 1,8,15: Doxorubicin 25mg/m² IV Days 36-39, 43-46: Cytarabine 75mg/m² IV Day 36: Cyclophosphamide 1,000 mg/m² IV^f Days 36-49 (omit for patients receiving cranial irradiation therapy): Thioguanine 60mg/m² IV Days 1,36,43: Methotrexate 15mg intrathecal (Days 29-33: Nelarabine 650 mg/m² IV), with: Cranial irradiation therapy.</p>

continued

Acute Lymphoblastic Leukemia (ALL) Treatment Regimens

► Newly-diagnosed ALL^{1,a} (continued)

PROTOCOL ^{1,b}	REGIMEN and DOSING
Adolescents and Young Adults (AYA) (15-39 years) ^c (continued)	
Ph (-) Disease ^h (continued)	
Preferred Regimens (continued)	
COG AALL0434 (with Nelarabine added to Consolidation Regimen) ^{21,22,i} (for patients with T-ALL) (continued)	<p>Maintenance Therapy without Nelarabine (12-week cycles): Days 1,29,57: Vincristine 1.5mg/m² IV (2mg maximum) Days 1-5, 29-33, 57-61: Prednisone 20mg/m² twice daily Days 1-84: Mercaptopurine 75mg/m² orally daily Days 8,15,22,36,43,50,52,64,71: Methotrexate 20mg/m² orally Day 1 (and Day 29 first 4 cycles; low-risk only): Methotrexate 15mg intrathecal.</p> <p>Maintenance Therapy with Nelarabine (12-week cycles): Days 1,57: Vincristine 1.5mg/m² IV (2mg maximum) Days 1-5, 29-33, 57-61: Prednisone 20mg/m² twice daily Days 1-28, 36-84: Mercaptopurine 75mg/m² orally daily Day 1: Methotrexate 15mg intrathecal Days 29-33 (first 3 cycles): Nelarabine 650mg/m² IV</p>
DFCI ALL (study performed in patients <50 years) ^{23,i}	<p>Induction Therapy (4 weeks): Days 1,8,15,22: Vincristine 2mg IV Days 1-28: Prednisone 40mg/m² Days 1,2: Doxorubicin 30mg/m² IV Day 3: Methotrexate 4g/m² (8-24 hours after Doxorubicin) with Leucovorin rescue Day 5: <i>E. coli</i> L-Asparaginase 25,000 IU/m² IM Day 0: Cytarabine 50mg intrathecal (prior to initiation of systemic therapy) Days 15,29: Methotrexate 12mg intrathecal Days 15,29: Cytarabine 40mg intrathecal Days 15,29: Hydrocortisone 50mg intrathecal.</p> <p>CNS Therapy (3 Weeks): Vincristine 2mg IV x 1 dose 6-Mercaptopurine 50mg/m² orally x 14 consecutive days Doxorubicin 30mg/m² IV x 1 dose Methotrexate 12mg intrathecal twice weekly x 4 doses Cytarabine 40mg intrathecal twice weekly x 4 doses, with: Cranial irradiation.</p> <p>Intensification (30 weeks; every 3-week cycles): Day 1: Vincristine 2mg IV Days 1-5: Dexamethasone 18mg/m²/day orally twice daily Day 1 of each cycle to a cumulative dose of 300mg/m² Day 1: Doxorubicin 30mg/m² IV 6-Mercaptopurine 50mg/m²/day orally x 14 consecutive days <i>E. coli</i> Asparaginase: Individualized dosing: 12,500 IU/m²/dose (starting dose) Methotrexate 30mg/m² IV or IM weekly, 1 day after asparaginase (no weekly Methotrexate until Doxorubicin completed) At start of cycle: Methotrexate 12mg intrathecal; Cytarabine 40mg intrathecal; Hydrocortisone 50mg intrathecal every 18 weeks. Note: Intrathecal therapy of Methotrexate/Cytarabine at start of cycle every 18 weeks.</p> <p>Continuation Therapy (74 weeks; every 3-week cycles): Same as intensification except no Asparaginase and Dexamethasone dose reduced to 6mg/m²/day.</p>
GRAALL-2005 (for patients <60 years, with Rituximab for CD20-positive disease) ^{24,i}	<p>Rituximab (375mg/m² IV): Days 1,7: First induction course Days 1,7: Salvage Reinduction (if needed) Days 1,29: Consolidation Phase I, II, III Days 1,7: Late Intensification Day 1 of Months 1,3,5,7,9,11 of Maintenance Therapy</p> <p>Prephase Treatment: Days (-7)-(-1): Prednisone 60mg/m² orally Between Days (-7) and (-4): Methotrexate 15mg intrathecal.</p>

continued

Acute Lymphoblastic Leukemia (ALL) Treatment Regimens

► Newly-diagnosed ALL^{1,a} (continued)

PROTOCOL ^{1,b}	REGIMEN and DOSING
Adolescents and Young Adults (AYA) (15-39 years) ^c (continued)	
Ph (-) Disease ^h (continued)	
Other Recommended Regimens (continued)	
GRAALL-2005 (for patients <60 years, with Rituximab for CD20-positive disease) ^{24,i} (continued)	<p>Induction Therapy: Days 1-14: Prednisone 60mg/m² orally Days 1,8,15,22: Vincristine 2 mg IV Days 1-3: Daunorubicin 50mg/m² IV Days 15,16: Daunorubicin 30mg/m² IV Days 8,10,12: L-Asparaginase 6,000 IU/m² daily IV over 1 hour (not done if CNS involvement), then Days 20,22,24,26,28: L-Asparaginase 6,000 IU/m² daily IV over 1 hour Day 1: Cyclophosphamide 750mg/m² IV over 3 hours^f Day 15: Cyclophosphamide 750mg/m² IV over 3 hours (1 infusion) OR Days 15-17: Cyclophosphamide 300mg/m² over 3 hours every 12 hours (6 infusions)^f Day 18 to neutrophil recovery: Lenograstim 263 mcg/day subcutaneous or IV. Salvage Reintroduction Therapy: Days 1-3: Idarubicin 12mg/m² IV over 1 hour Days 1-4 (8 infusions): Cytarabine 2,000mg/m² IV over 2 hours every 12 hours Day 9 to neutrophil recovery: Lenograstim 263 mcg subcutaneous or IV daily. Interphase-1 Therapy: Day 1: Vincristine 2mg IV Day 1: Dexamethasone 40mg orally daily. Consolidation Therapy I – Block 1: Days 1,2 (4 infusions): Cytarabine 2,000mg/m² IV over 2 hours every 12 hours Days 1,2: Dexamethasone 10mg orally every 12 hours Day 3: L-Asparaginase (<i>E coli</i>): 10,000 IU/m² IV over 1 hour Days 9-13: Lenograstim 263 mcg orally or IV Consolidation Therapy I – Block 2: Day 15: Vincristine 2mg IV Day 15: Methotrexate 3,000 mg/m² continuous IV over 24 hours Day 16: L-Asparaginase 10,000 IU/m² IV over 1 hour Day 15-21: 6-Methotrexate 60mg/m² orally Days 23-27: Lenograstim 263 mcg SC or IV daily Consolidation Therapy I – Block 3: Day 29: Methotrexate 25mg/m² IV Days 29,30: Cyclophosphamide 500mg/m² IV daily over 3 hours^f Days 28,30: Etoposide 75mg/m² IV over 1 hour. Day 31 to neutrophil recovery: Lenograstim 263mcg SC or IV daily. Consolidation Therapy II: Block 4 – identical to Block 1 Block 5 – identical to Block 2 Block 6 – identical to Block 3 Late Intensification Therapy (if CR after 1st course): Day 1-14: Prednisone 60mg/m² orally Day 1,8,15,22: Vincristine 2mg IV Day 1-3, 15,16: Daunorubicin 30mg/m² IV Day 8,10,12,20,22,24,26,28: L-Asparaginase 6,000 IU/m² IV over 1 hour Day 1: Cyclophosphamide 750mg/m² IV over 3 hours, then, Day 15 (1 infusion): Cyclophosphamide 750mg/m² over 3 hours OR Days 15-17 (6 infusions): 300mg/m² over 3 hours every 12 hours^g Day 18 to neutrophil recovery: Lenograstim 263mcg subcutaneous or IV daily. Late Intensification Therapy (if late CR): Days 1-3: Idarubicin 9mg/m² IV over 1 hour daily Days 1-4 (8 infusions): Cytarabine 2,000mg/m² IV over 2 hours every 12 hours Day 9 to neutrophil recovery: Lenograstim 263mcg SC or IV daily. Consolidation Therapy III: Repeat Consolidation Therapy I Blocks 1-3. Maintenance Therapy Day 1 (month 1-12): Vincristine 2mg IV Days 1-7 (month 1-12): Prednisone 40mg/m² orally daily Months 1-24: 6-Mercaptopurine 60mg/m² orally daily Months 1-24: Methotrexate 25mg/m² orally weekly.</p>

continued

Acute Lymphoblastic Leukemia (ALL) Treatment Regimens

► Newly-diagnosed ALL^{1,a} (continued)

PROTOCOL ^{1,b}	REGIMEN and DOSING
Adolescents and Young Adults (AYA) (15-39 years) ^e (continued)	
Ph (-) Disease ^h (continued)	
Other Recommended Regimens (continued)	
Hyper CVAD high-dose Methotrexate/Cytarabine ^{10,11}	<p>Cycle A: Days 1-3: Cyclophosphamide 300mg/m² over 3 hours every 12 hours for 6 doses^f Days 1-3: Mesna 600mg/m² IV continuous infusion over 24 hours daily starting 15 minutes before the first dose of Cyclophosphamide and completing 12 hours after the last dose of Cyclophosphamide is started Day 4: Doxorubicin 50mg/m² IV push OR IV continuous infusion over 24 hours Days 4 and 11: Vincristine 2mg IV over 5-10 minutes Days 1-4, 11-14: Dexamethasone 40mg IV OR orally daily Day 2: Methotrexate 12mg intrathecal Day 7: Cytarabine 100mg intrathecal</p> <p>Cycle B: Day 1: Methotrexate 200mg/m² IV over 2 hours, then 800mg/m² IV continuous infusion over 22 hours. (Alkaline hydration is required pre- and post-administration of high-dose Methotrexate.) Day 2: Leucovorin 50mg IV over 15 minutes administered 12 hours after completion of 22-hour Methotrexate infusion, then 15mg IV over 15 minutes OR orally every 6 hours for at least 8 doses (until Methotrexate serum concentration is <0.05micromol/L) Days 2-3: Cytarabine (age <60 years) 3,000mg/m² IV over 3 hours every 12 hours for 4 doses OR Cytarabine (age ≥60 years) 1,000 mg/m² IV over 3 hours every 12 hours for 4 doses Day 2: Methotrexate 12mg intrathecal Day 7: Cytarabine 100mg intrathecal Repeat every 3 weeks for 4 cycles alternating with Cycle A.</p>
Hyper CVAD + Rituximab – high dose Methotrexate/Cytarabine (for patients with CD20-positive disease) ^{10,11}	<p>Cycle A: Day 1: Rituximab 375mg/m² IV Days 1-3: Cyclophosphamide 300mg/m² over 3 hours every 12 hours for 6 doses^f Days 1-3: Mesna 600mg/m² IV continuous infusion over 24 hours daily starting 15 minutes before the first dose of Cyclophosphamide and completing 12 hours after the last dose of Cyclophosphamide is started. Day 4: Doxorubicin 50mg/m² IV push OR IV continuous infusion over 24 hours Days 4, 11: Vincristine 2mg IV over 5-10 minutes Days 1-4, 11-14: Dexamethasone 40mg IV OR orally daily Day 2: Methotrexate 12mg intrathecal Day 7: Cytarabine 100mg intrathecal. Repeat every 3 weeks for 4 cycles alternating with Cycle B.</p> <p>Cycle B: Day 1: Rituximab 375mg/m² IV Day 1: Methotrexate 200mg/m² IV over 2 hours, then 800mg/m² IV continuous infusion over 22 hours. (Alkaline hydration is required pre- and post-administration of high-dose Methotrexate.) Day 2: Leucovorin 50mg IV over 15 minutes administered 12 hours after completion of 22-hour Methotrexate infusion, then 15mg IV over 15 minutes OR orally every 6 hours for at least 8 doses (until Methotrexate serum concentration is <0.05micromol/L) Days 2-3: Cytarabine (age <60 years) 3,000mg/m² IV over 3 hours every 12 hours for 4 doses OR Cytarabine (age ≥60 years) 1,000 mg/m² IV over 3 hours every 12 hours for 4 doses Day 2: Methotrexate 12mg intrathecal Day 7: Cytarabine 100mg intrathecal Repeat every 3 weeks for 4 cycles alternating with Cycle A.</p>
Linker Regimen ^{26,27}	<p>Induction Therapy (1A): Days 1-3: Daunorubicin 60mg/m² IV push, followed by: Day 15: Daunorubicin 60mg/m² IV push (only if Day 14 bone marrow has residual leukemia) Days 1,8,15,22: Vincristine 1.4mg/m² IV (maximum 2mg if age >40 years) over 5-10 minutes Days 1-28: Prednisone 60mg/m² orally Days 1-4,15-18: Dexamethasone 9mg/m² orally twice daily Day 15: Pegaspargase 2,000 international units/m² (maximum 3,750 international units, rounded to vial size) IV over 1 hour Day 1: Methotrexate 12mg intrathecal. Administer for one 4-week cycle, followed by:</p> <p>Consolidation Therapy (1B): Days 1-4: Cytarabine 2,000 mg/m² IV over 2 hours Days 1-4: Etoposide 500mg/m² IV over 3 hours Days 1,8,15: Methotrexate 12mg intrathecal. Administer for one 4-week cycle, followed by:</p>

continued

Acute Lymphoblastic Leukemia (ALL) Treatment Regimens

► Newly-diagnosed ALL^{1,a} (continued)

PROTOCOL ^{1,b}	REGIMEN and DOSING
Adolescents and Young Adults (AYA) (15-39 years) ^c (continued)	
Ph (-) Disease ^h (continued)	
Other Recommended Regimens (continued)	
Linker Regimen ^{26,27} (continued)	<p>Consolidation Therapy (1C): Days 1,15: Methotrexate 220mg/m² IV over 15 minutes, then immediately followed by 60mg/m²/hour IV continuous infusion over 36 hours (Alkaline hydration required for high-dose Methotrexate.) Days 2, 16: Leucovorin 50mg/m² IV over 15 minutes every 6 hours for 3 doses starting immediately after completion of 36-hour Methotrexate infusion on days 2 and 16, then, Leucovorin 25mg IV over 15 minutes or orally every 6 hours (until Methotrexate serum concentration is <0.05micromol.) Days 1-28: Mercaptopurine 75mg/m² orally daily Days 1, 8: Methotrexate 12mg intrathecal (after adequate clearance of serum Methotrexate). Administer for one 4-week cycle, followed by:</p> <p>Consolidation Therapy (2A): Days 1-3: Daunorubicin 60mg/m² IV push Days 1,8,15: Vincristine 1.4mg/m² (maximum 2mg if age >40 years) IV over 5-10 minutes Days 1-21: Prednisone 60mg/m² orally daily OR Days 1-4,15-18: Dexamethasone 9mg/m² orally twice daily Day 4: Pegaspargase 2,000 international units/m², followed by:</p> <p>Consolidation Therapy (2B): Days 1-4: Cytarabine 2,000 mg/m² IV over 2 hours Days 1-4: Etoposide 500mg/m² IV over 3 hours Days 1,8,15: Methotrexate 12mg intrathecal. Administer for one 4-week cycle, followed by:</p> <p>Consolidation Therapy (2C): Days 1,15: Methotrexate 220mg/m² IV over 15 minutes, then immediately followed by 60mg/m²/hour IV continuous infusion over 36 hours (Alkaline hydration required for high-dose Methotrexate.) Days 2, 16: Leucovorin 50mg/m² IV over 15 minutes every 6 hours for 3 doses starting immediately after completion of 36-hour Methotrexate infusion on days 2 and 16, then, Leucovorin 25mg IV over 15 minutes or orally every 6 hours (until Methotrexate serum concentration is <0.05micromol.) Days 1-28: Mercaptopurine 75mg/m² orally daily. Administer for one 4-week cycle, followed by:</p> <p>Consolidation Therapy (3C): Days 1,15: Methotrexate 220mg/m² IV over 15 minutes, then immediately followed by 60mg/m²/hour IV continuous infusion over 36 hours (Alkaline hydration required for high-dose Methotrexate.) Days 2, 16: Leucovorin 50mg/m² IV over 15 minutes every 6 hours for 3 doses starting immediately after completion of 36-hour Methotrexate infusion on days 2 and 16, then, Leucovorin 25mg IV over 15 minutes or orally every 6 hours (until Methotrexate serum concentration is <0.05micromol.) Days 1-28: Mercaptopurine 75mg/m² orally daily Administer for one 4-week cycle, followed by:</p> <p>Maintenance Therapy: Days 1-28: Mercaptopurine 75mg/m² orally Days 1,8,15,22: Methotrexate 20mg/m² orally. Repeat cycle every 4 weeks until patient is in complete remission for 30 months.</p>
PETHEMA ALL-96 (patients aged <30 years) ^{28,i}	<p>Remission Induction Therapy: Days 1,8,15,22: Vincristine 2mg IV Days 1,8,15,22: Daunorubicin 30mg/m² IV Days 1-27: Prednisone 60mg/m² IV or orally daily Days 28-35: Prednisone 30mg/m² IV or orally daily Days 10-12, 17-19, 24-26: Asparaginase 10,000 U/m² IV Day 36: Cyclophosphamide 1,000mg/m² IV^f Days 1,29: Methotrexate 15mg intrathecal Days 1,29: Cytarabine 30mg intrathecal Days 1,29: Hydrocortisone 20mg intrathecal</p> <p>Consolidation Therapy I: Days 1-7: Mercaptopurine 50mg/m² orally Days 1,28,56: Methotrexate 3,000mg/m² (with folinic acid rescue, beginning 12 hours after the end of Methotrexate infusion) IV over 24 hours Days 14,42: Teniposide 150mg/m² IV every 12 hours Days 14-15,42-43: Cytarabine 500mg/m² every 12 hours Days 1,28,56: Methotrexate 15mg intrathecal Days 1,28,56: Cytarabine 30mg intrathecal Days 1,28,56: Hydrocortisone 20mg intrathecal</p>

continued

Acute Lymphoblastic Leukemia (ALL) Treatment Regimens

► Newly-diagnosed ALL^{1,a} (continued)

PROTOCOL ^{1,b}	REGIMEN and DOSING
Adolescents and Young Adults (AYA) (15-39 years) ^c (continued)	
Ph (-) Disease ^h (continued)	
Other Recommended Regimens (continued)	
PETHEMA ALL-96 (patients aged <30 years) ^{28,i} (continued)	<p>Consolidation Therapy II/Reinduction: Days 1-14: Dexamethasone 10mg/m² orally or IV daily Days 15-21: Dexamethasone 5mg/m² orally or IV daily Days 1,8,15: Vincristine 1.5mg/m² IV (maximum 2mg) Days 1,2,8,9: Daunorubicin 30mg/m² IV Days 1,15: Cyclophosphamide 600mg/m² IV daily^f Days 1-3, 15-17: Asparaginase 10,000 U/m² IM or IV Days 1,15: Methotrexate 15mg intrathecal Days 1,15: Cytarabine 30mg intrathecal Days 1,15: Hydrocortisone 20mg intrathecal</p> <p>Maintenance Therapy I (+ Reinductions until week 52): Methotrexate 20mg/m² IM weekly Mercaptopurine 50mg/m² orally daily.</p> <p>Reinductions (every 4 weeks): Day 1: Vincristine 1.5 mg/m² IV (maximum 2mg) Days 1-7: Prednisone 60mg/m² IV or orally daily Day 1: Asparaginase 20,000 U/m² IV Day 1: Methotrexate 15mg intrathecal Day 1: Cytarabine 30mg intrathecal Day 1: Hydrocortisone 20mg intrathecal</p> <p>Maintenance Therapy II (weeks 53-104): Methotrexate 20mg/m² IM weekly Mercaptopurine 50mg/m² orally daily.</p>
USC ALL Based on CCG-1882 (for patients aged 18-57 years) ²⁷	<p>Induction Therapy I: Days 1-3: Daunorubicin 60mg/m² IV Days 1,8,15,22: Vincristine 1.4mg/m² IV (maximum, 2mg) Day 15: Pegaspargase 2,000 IU/m² IV Days 1-28: Prednisone 60mg/m² orally Days 8,15: Methotrexate 12mg intrathecal.</p> <p>Induction Therapy II: Days 1,29: Cyclophosphamide 1,000mg/m² IV^f Days 1-4, 8-11, 29-32, 36-39: Cytarabine 75mg/m² IV Days 15,22,43,50: Vincristine 1.4mg/m² IV (maximum, 2mg) Day 15: Pegaspargase 2,000 IU/m² IV Days 15-29: Prednisone 20mg/m² orally Days 1-14, 29-43: Mercaptopurine 60mg/m² orally Days 1,8,15,22: Methotrexate 12mg intrathecal.</p> <p>Intensification Therapy: Days 1, 15: Methotrexate 1,000mg/m² IV (T-cell ALL, 2,500mg/m² IV), with Leucovorin 15mg every 6 hours IV starting 36 hours from start of Methotrexate Day 16: Pegaspargase 2,000 IU/m² IV Days 16-30: Prednisone 20mg/m² orally.</p> <p>Consolidation Therapy: Days 1-5: Cytarabine 75mg/m² IV Days 1-5: Teniposide 60mg/m² IV.</p> <p>Delayed Reinduction Therapy: Days 1,8,15: Daunorubicin 25mg/m² IV Days 1,8,15,43,50: Vincristine 1.4mg/m² IV (maximum, 2mg) Days 15-22, 43-50: Dexamethasone 10mg/m² orally Day 15: Pegaspargase 2,000 IU/m² IV Day 29: Cyclophosphamide 1,000mg/m² IV^f Days 29-32, 36-39: Cytarabine 75mg/m² IV Days 26-42: Thioguanine 60mg/m² orally Days 1,29,36: Methotrexate 12mg intrathecal.</p>

continued

Acute Lymphoblastic Leukemia (ALL) Treatment Regimens

► Newly-diagnosed ALL^{1,a} (continued)

PROTOCOL ^{1,b}	REGIMEN and DOSING
Adolescents and Young Adults (AYA) (15-39 years) ^c (continued)	
Ph (-) Disease ^h (continued)	
Other Recommended Regimens (continued)	
USC ALL Based on CCG-1882 (for patients aged 18-57 years) ²⁷ (continued)	<p>Maintenance Therapy Days 1-5 (year 1, monthly; year 2, every 2 months): Prednisone 60mg/m² IV orally Day 1 (year 1, monthly; year 2, every 2 months): Vincristine 1.4mg/m² IV (maximum, 2mg) Days 1-28: Mercaptopurine 60mg/m² orally Days 1,8,15,22: Methotrexate 20mg/m² orally Once every 3 months (year 1): Methotrexate 12mg intrathecal.</p>
Adults (age 40-64 years, unless otherwise specified) ^d	
Ph (+) Disease ^d	
Other Recommended Regimens	
CALGB 10701 ^{5,e}	<p>Course I (First Induction): Days 1-7: Dasatinib 140mg orally daily Days 1-7: Dexamethasone 10mg/m² orally or IV Course II (If ≤20% lymphoblasts in marrow at Day 15): Days 1-7: Dasatinib 140mg orally daily Days 1-7: Dexamethasone 10mg/m² orally or IV. Course II (If >20% lymphoblasts in marrow at Day 15): Days 1-7: Dasatinib 140 mg orally daily Days 1-7: Dexamethasone 10mg/m² orally or IV. Vincristine and Daunorubicin also administered. Course III (Second Induction for patients not in CR/CRi): Patients received Dasatinib, Cyclophosphamide, Vincristine, Daunorubicin, Dexamethasone. Course IV (CNS Prophylaxis): Patients received Dasatinib, IV Vincristine, and IV, oral, and intrathecal Methotrexate. Course V: Patients treated with stem cell transplantation or chemotherapy. Course VI (Maintenance): Dasatinib Starting on Day 30 of Course V and continued for 12 months and until 2 consecutive negative <i>BCR-ABL1</i> RT-PCR assays 3 months apart or relapse.</p>
Corticosteroids + TKI ^{6,7,d}	<p>• Dasatinib + Prednisone PrePhase: Days (-7-[-1]): Prednisone 10-60mg/m² in increasing doses. Induction Therapy: Dasatinib 70mg twice daily for 84 days Prednisone 60mg/m² daily (capped at 120mg daily) administered until Day 24 and then tapered and stopped at Day 32. Days 22,43: Methotrexate intrathecal.</p> <p>• Imatinib + Prednisone PrePhase: Days (-7-[-1]): Prednisone 10-40mg/m² in increasing doses from 10-40mg/m². Induction Therapy: Days 1-45: Imatinib 800mg orally Days 1-45: Prednisone 40mg/m² Note: Induction Therapy with Corticosteroid + Nilotinib is also a recommended regimen. Note: These regimens are used for induction therapy and additional therapy is needed.</p>
Hyper CVAD with TKI and High-Dose Methotrexate/ Cytarabine ^{10,13,d}	<p>• Dasatinib-based Therapy Cycle A: Days 1-3: Cyclophosphamide 300mg/m² over 3 hours every 12 hours for 6 doses^f Days 1-3: Mesna 600mg/m² IV continuous infusion over 24 hours daily starting 15 minutes before the first dose of Cyclophosphamide and completing 12 hours after the last dose of Cyclophosphamide is started Day 4: Doxorubicin 50mg/m² IV push OR IV continuous infusion over 24 hours Days 4 and 11: Vincristine 2mg IV over 5-10 minutes Days 1-4, 11-14: Dexamethasone 40mg IV OR orally daily Day 2: Methotrexate 12mg intrathecal Day 7: Cytarabine 100mg intrathecal. Days 1-14: Dasatinib 100mg orally daily. Repeat cycle every 3 weeks for 4 cycles alternating with Cycle B.</p>

continued

Acute Lymphoblastic Leukemia (ALL) Treatment Regimens

► Newly-diagnosed ALL^{1,a} (continued)

PROTOCOL ^{1,b}	REGIMEN and DOSING
Adults (age 40-64 years, unless otherwise specified) ^d	
Ph (+) Disease ^d	
Other Recommended Regimens	
Hyper CVAD with TKI and High-Dose Methotrexate/ Cytarabine ^{10,13,d} (continued)	<p>• Dasatinib-based Therapy (continued)</p> <p>Cycle B: Day 1: Methotrexate 200mg/m² IV over 2 hours, then 800mg/m² IV continuous infusion over 22 hours. (Alkaline hydration is required pre- and post-administration of high-dose Methotrexate.) Day 2: Leucovorin 50mg IV over 15 minutes administered 12 hours after completion of 22-hour Methotrexate infusion, then 15mg IV over 15 minutes OR orally every 6 hours for at least 8 doses (until Methotrexate serum concentration is <0.05micromol/L) Days 2-3: Cytarabine (age <60 years) 3,000mg/m² IV over 3 hours every 12 hours for 4 doses OR Cytarabine (age ≥60 years) 1,000 mg/m² IV over 3 hours every 12 hours for 4 doses Day 2: Methotrexate 12mg intrathecal Day 7: Cytarabine 100mg intrathecal Days 1-14: Dastinib 100mg orally daily. Repeat cycle every 3 weeks for 4 cycles alternating with Cycle A.</p> <p>• Imatinib-Based Therapy</p> <p>Cycle A: Days 1-3: Cyclophosphamide 300mg/m² over 3 hours every 12 hours for 6 doses^f Days 1-3: Mesna 600mg/m² IV continuous infusion over 24 hours daily starting 15 minutes before the first dose of Cyclophosphamide and completing 12 hours after the last dose of Cyclophosphamide is started. Day 4: Doxorubicin 50mg/m² IV push OR IV continuous infusion over 24 hours Days 4 and 11: Vincristine 2mg IV over 5-10 minutes Days 1-4, 11-14: Dexamethasone 40mg IV OR orally daily Day 2: Methotrexate 12mg intrathecal Day 7: Cytarabine 100mg intrathecal Days 1-14: Imatinib 400mg orally daily. Repeat cycle every 3 weeks for 4 cycles alternating with Cycle B.</p> <p>Cycle B: Day 1: Methotrexate 200mg/m² IV over 2 hours, then 800mg/m² IV continuous infusion over 22 hours. (Alkaline hydration is required pre- and post-administration of high-dose Methotrexate.) Day 2: Leucovorin 50mg IV over 15 minutes administered 12 hours after completion of 22-hour Methotrexate infusion, then 15mg IV over 15 minutes OR orally every 6 hours for at least 8 doses (until Methotrexate serum concentration is <0.05 micromol/L) Days 2-3: Cytarabine (age <60 years) 3,000mg/m² IV over 3 hours every 12 hours for 4 doses OR Cytarabine (age ≥60 years) 1,000 mg/m² IV over 3 hours every 12 hours for 4 doses Day 2: Methotrexate 12mg intrathecal Day 7: Cytarabine 100mg intrathecal Days 1-14: Imatinib 400mg orally daily. Repeat cycle every 3 weeks for 4 cycles alternating with Cycle A.</p> <p>• Ponatinib-Based Therapy</p> <p>Cycle A: Days 1-3: Cyclophosphamide 300mg/m² over 3 hours every 12 hours for 6 doses^f Days 1-3: Mesna 600mg/m² IV continuous infusion over 24 hours daily starting 15 minutes before the first dose of Cyclophosphamide and completing 12 hours after the last dose of Cyclophosphamide is started. Day 4: Doxorubicin 50mg/m² IV push OR IV continuous infusion over 24 hours Days 4 and 11: Vincristine 2mg IV over 5-10 minutes Days 1-4, 11-14: Dexamethasone 40mg IV OR orally daily Day 2: Methotrexate 12mg intrathecal Day 7: Cytarabine 100mg intrathecal. Days 1-14: Ponatinib 45mg orally daily (cycle 1), followed by: Days 1-21: Ponatinib 30mg orally daily (cycles 2-4). Repeat cycle every 3 weeks for 4 weeks alternating with Cycle B.</p>

continued

Acute Lymphoblastic Leukemia (ALL) Treatment Regimens

► Newly-diagnosed ALL^{1,a} (continued)

PROTOCOL ^{1,b}	REGIMEN and DOSING
Adults (age 40-64 years, unless otherwise specified) ^d (continued)	
Ph (+) Disease ^d (continued)	
Other Recommended Regimens (continued)	
Hyper CVAD with TKI and High-Dose Methotrexate/Cytarabine ^{10-13,d} (continued)	<p>• Ponatinib-Based Therapy (continued)</p> <p>Cycle B: Day 1: Methotrexate 200mg/m² IV over 2 hours, then 800mg/m² IV continuous infusion over 22 hours (Alkaline hydration is required pre- and post-administration of high-dose Methotrexate.) Day 2: Leucovorin 50mg IV over 15 minutes administered 12 hours after completion of 22-hour Methotrexate infusion, then 15mg IV over 15 minutes OR orally every 6 hours for at least 8 doses (until Methotrexate serum concentration is <0.05 micromol/L) Days 2-3: Cytarabine (age <60 years) 3,000mg/m² IV over 3 hours every 12 hours for 4 doses OR Cytarabine (age ≥60 years) 1,000 mg/m² IV over 3 hours every 12 hours for 4 doses Day 2: Methotrexate 12mg intrathecal Day 7: Cytarabine 100mg intrathecal Days 1-21: Ponatinib 30mg orally. Repeat cycle every 3 weeks for 4 cycles alternating with Cycle A.</p>
Multiagent Chemotherapy (Daunorubicin, Vincristine, Prednisone, Dexamethasone) + TKI ^{14-16,d}	<p>Representative Regimens</p> <p>• Dasatinib-Based Therapy</p> <p>Induction Therapy: Weeks 1-2: All patient received the first 2 weeks of Induction Therapy on a frontline COG or DCFI ALL trial Weeks 3-4: Days 1,8 of AALL0622 regimen OR Days 15,22 of induction regimen: Vincristine 1.5mg/m² IV/dose (maximum dose: 2mg) Days 1,8 of AALL0622 regimen OR Days 15,22 of induction regimen: Daunorubicin 25mg/m² IV/dose Days 15 of AALL0622 regimen OR Day 29 of induction therapy: Triple intrathecal therapy Note: Patients who were CNS3^e also received triple intrathecal therapy on Days 1,8 of AALL0622 regimen or Days 15 and 22 of induction regimen Days 1-14 or 1-21: Dasatinib 60mg/m² orally twice daily. Consolidation Therapy - Block I (weeks 6-8) Days 1-5: Etoposide 100mg/m² IV Days 1-5: Ifosfamide 1800mg/m² with Mesna Day 1: Triple intrathecal therapy Note: Prior to study amendment, all patients received dose of triple intrathecal therapy on Day 1, which is Day 36 of protocol therapy. After study amendment, patients did not receive triple intrathecal therapy on Day 1 of consolidation. Patients who were classified as CNS 2a, 2b, or 2c^e and those with traumatic taps who did not receive 2 triple intrathecal doses in induction also received doses on Days 8,15. Consolidation Therapy - Block II Day 1: High-dose Methotrexate 500mg/m² over 30 minutes, then 4,500mg/m² over remainder of 24 hours Day 1: Triple intrathecal therapy (see note above) Days 2,3: Cytarabine 3,000mg/m²/dose IV over 3 hours every 12 hours × 4 doses Beginning on Day 4: Filgrastim (G-CSF) 5mcg/kg/dose subcutaneous/IV continued until ANC >1,500/uL. Days 1-14 or 1-21: Dasatinib 60mg/m² orally twice daily. Re-Induction Therapy – Block I (weeks 12-14; patients not proceeding to HSCT): Days 1,8,15: Vincristine 1.5mg/m² IV (maximum dose: 2mg) Days 1,2: Daunorubicin 45mg/m² IV Days 3,4: Cyclophosphamide 250mg/m² IV every 12 hours^f Day 4: PEG-Asparaginase 2,500 IU/m² IM or IV Day 1,15: Triple intrathecal therapy Days 1-7, 15-21: Dexamethasone 6mg/m² orally divided twice daily Day 5: Filgrastim (G-CSF): 5mcg/kg subcutaneous or IV and continued until ANC >1,500/uL Days 1-14 or 1-21: Dasatinib 60mg/m² orally twice daily. Intensification Therapy – Block I (weeks 15-23; patients not proceeding to HSCT): Days 1,15: High-dose Methotrexate 500mg/m² IV over 30 minutes, then 4,500mg/m² over remainder of 24 hours Day 1,22: Triple intrathecal therapy Days 22-26: Etoposide 100mg/m² over 1 hour Days 22-26: Cyclophosphamide 300mg/m² IV over 1 hour with Mesna^f Day 27: Filgrastim (G-CSF) 5mcg/kg subcutaneous or IV and continued until ANC >1500/uL Days 43,44: Cytarabine 3,000 mg/m² IV every 12 hours × 4 doses Day 44: L-Asparaginase 6,000 IU/m² administered 6 hours after completion of Cytarabine Days 1-14, 22-35, 43-56 or Days 1-63: Dasatinib 60mg/m² orally twice daily.</p>

continued

Acute Lymphoblastic Leukemia (ALL) Treatment Regimens

► Newly-diagnosed ALL^{1,a} (continued)

PROTOCOL ^{1,b}	REGIMEN and DOSING
Adults (age 40-64 years, unless otherwise specified) ^d (continued)	
Ph (+) Disease ^d (continued)	
Other Recommended Regimens (continued)	
Multiagent Chemotherapy (Daunorubicin, Vincristine, Prednisone, Dexamethasone) + TKI ^{14-16,d} (continued)	<p>Representative Regimens (continued)</p> <p>• Dasatinib-Based Therapy (continued)</p> <p>Re-Induction Therapy – Block II (weeks 24-26; patients not proceeding to HSCT): Days 1,8,15: Vincristine 1.5mg/m² IV (maximum dose: 2mg) Days 1,2: Daunorubicin 45mg/m² IV Days 3,4: Cyclophosphamide 250mg/m² IV every 12 hours × 4 doses Day 4: PEG-Asparaginase 2,500 IU/m² IM after last dose of Cyclophosphamide^f Days 1,15: Triple intrathecal therapy Days 1-7, 15-21: Dexamethasone 6mg/m² orally divided twice daily Beginning on Day 5: Filgrastim (G-CSF) 5mcg/kg subcutaneous or IV Days 1-14 or 1-21: Dasatinib 60mg/m² orally twice daily.</p> <p>Intensification Therapy – Block II (weeks 27-35; patients not proceeding to HSCT): Days 1,15: High-dose Methotrexate 500mg/m² IV over 30 minutes, then 4,500mg/m² over remainder of 24 hours Day 1,22: Triple intrathecal therapy Days 22-26: Etoposide 100mg/m² IV over 1 hour Days 22-26: Cyclophosphamide 300mg/m² IV over 1 hour with Mesna^f Beginning Day 27: Filgrastim (G-CSF) 5mcg/kg subcutaneous or IV Days 43,44: Cytarabine 3,000mg/m² IV every 12 hours × 4 doses Day 44: L-Asparaginase 6,000 IU/m² IM given 6 hours after completion of Cytarabine Days 1-14, 22-35, 43-56 or Days 1-63: Dasatinib 60mg/m² orally twice daily.</p> <p>Maintenance Therapy – Cycles 1-4 (weeks 36-67; patients not proceeding to HSCT): Day 1: High-Dose Methotrexate 500mg/m² IV over 30 minutes, then 4,500mg/m² IV over remainder of 24 hours Day 1,29: Triple intrathecal therapy Days 1,29: Vincristine 1.5mg/m² IV (maximum dose: 2mg) Days 1-5, 29-33: Dexamethasone 6mg/m² orally divided twice daily Days 8-28: Mercaptopurine 75mg/m² orally Days 8,15,22: Methotrexate 20mg/m² orally on an empty stomach Days 29-33: Etoposide 100mg/m² IV over 1 hour Days 29-33: Cyclophosphamide 300mg/m² IV given immediately following Etoposide with Mesna^f Beginning on Day 34: Filgrastim (G-CSF) 5mcg/m² and continued until ANC >1,500/uL Days 1-14, 29-42 or Days 1-49: Dasatinib 60mg/m² orally twice daily.</p> <p>Maintenance Therapy – Cycle 5 (weeks 68-75; patients not proceeding to HSCT): Beginning on Day 1: Cranial irradiation Days 1,29: Vincristine 1.5mg/m² IV (maximum dose: 2mg) Days 1-5, 29-33: Dexamethasone 6mg/m² orally divided twice daily First Day after Cranial Irradiation Completion: Mercaptopurine 75mg/m² orally daily Day 8,15,22,29,36,43,50: Methotrexate 20mg/m² orally Days 1-14, 29-42 or Days 1-49: Dasatinib 60mg/m² orally twice daily.</p> <p>Maintenance Therapy – Cycles 6-12 (weeks 76-131; patients not proceeding to HSCT) Days 1,29: Vincristine 1.5mg/m² IV (maximum dose: 2mg) Days 1-5, 29-33: Dexamethasone 6mg/m² orally divided twice daily Days 1-56: Mercaptopurine 75mg/m² orally given on an empty stomach Days 1,8,15,22,29,36,43,50: Methotrexate 20mg/m² orally Days 1-14, 29-42 or Days 1-49 or 1-21: Dasatinib 60mg/m² orally twice daily.</p> <p>• Imatinib-Based Therapy</p> <p>Induction Therapy: Day 1: Cyclophosphamide 1,200mg/m² IV over 3 hours^f Days 1-3: Daunorubicin 60mg/m² IV over 1 hour Days 1,8,15,22: Vincristine 1.3mg/m² IV bolus Days 1-21: Prednisolone 60mg/m² orally Days 8-63: Imatinib 600mg orally Day 29: Methotrexate 15mg intrathecal Day 29: Cytarabine 40mg intrathecal Day 29: Dexamethasone 4mg intrathecal.</p>

continued

Acute Lymphoblastic Leukemia (ALL) Treatment Regimens

► Newly-diagnosed ALL^{1,a} (continued)

PROTOCOL ^{1,b}	REGIMEN and DOSING
Adults (age 40-64 years, unless otherwise specified) ^d (continued)	
Ph (+) Disease ^d (continued)	
Other Recommended Regimens (continued)	
Multiagent Chemotherapy (Daunorubicin, Vincristine, Prednisone, Dexamethasone) + TKI ^{14-16,d} (continued)	<p>Representative Regimens (continued)</p> <ul style="list-style-type: none"> • Imatinib-Based Therapy (continued) <p>Consolidation Therapy – Cycle I: Day 1: Methotrexate 1,000mg/m² IV over 24 hours Days 2,3: Cytarabine 2,000/m² over 3 hours × 2 Days 1-3: Methylprednisolone 50mg IV over 1 hour × 2 Day 1: Methotrexate 15mg intrathecal Day 1: Cytarabine 40mg intrathecal Day 1: Dexamethasone 4mg intrathecal. Administer for 4 cycles alternating with Cycle II.</p> <p>Consolidation Therapy – Cycle II: Days 1-28: Imatinib 600mg orally Day 1: Methotrexate 15mg intrathecal Day 1: Cytarabine 40mg intrathecal Day 1: Dexamethasone 4mg intrathecal. Administer for 4 cycles alternating with Cycle I.</p> <p>Maintenance Therapy: Day 1: Vincristine 1.3mg/m² IV (bolus) (2mg maximum) Days 1-5: Prednisolone 60mg/m² orally Days 1-28: Imatinib 600mg orally. Maintenance therapy administered every 4 weeks up to 2 years from the date of CR.</p> • Nilotinib-Based Therapy <p>Induction Therapy: Days 1-3: Daunorubicin 90mg/m² IV continuous 24 hour infusion Days 1,8: Vincristine 2mg IV push Days 1-14: Prednisolone 60mg/m² orally or 48mg/m² IV Day 8 to start of conditioning for allo-HCT or until the end of 2 years of maintenance therapy: Nilotinib 400mg orally twice daily.</p> <p>Consolidation – Cycle A: Days 1,2: Daunorubicin 45mg/m² IV continuous 24-hour infusion Days 1-8: Vincristine 2mg IV push Days 1-14: Prednisolone 60mg/m² orally Nilotinib 400mg orally twice daily. Administer for 1 cycle.</p> <p>Consolidation – Cycle B: Days 1-4: Cytarabine 2000mg/m² IV over 2 hours Days 1-4: Etoposide 150mg/m² IV over 3 hours Nilotinib 400mg orally twice daily. Administer for 2 cycles alternating with Cycle C.</p> <p>Consolidation – Cycle C: Days 1-2, 15-16: Methotrexate 220mg/m² IV bolus, then 60mg/m² per hour for 36 hours Leucovorin, followed immediately by 50mg/m² IV every 6 hours for 3 doses; then Leucovorin orally until serum Methotrexate <0.05micromol/L Nilotinib 400mg orally twice daily. Administer for 2 cycles alternating with Cycle B.</p> <p>Maintenance Therapy: Nilotinib 400mg orally twice daily for 2 years.</p> <p>CNS Prophylaxis: Up to 10 doses of Methotrexate 15mg intrathecal, with: Hydrocortisone 50mg during or after Induction Therapy.</p>

continued

Acute Lymphoblastic Leukemia (ALL) Treatment Regimens

► Newly-diagnosed ALL^{1,a} (continued)

PROTOCOL ^{1,b}	REGIMEN and DOSING
Adults (age 40-64 years, unless otherwise specified) ^d (continued)	
Ph (+) Disease ^d (continued)	
Other Recommended Regimens (continued)	
Vincristine + Dexamethasone + TKI ^{17,d}	<p>PrePhase Therapy: Days (-7)-(-1): Prednisone 60mg/m² orally Between Days (-7)-(-1): Methotrexate 15mg intrathecal</p> <p>• Imatinib-Based Regimen Induction Therapy: Days 1,8,15,22: Vincristine 2mg IV Days 1-2, 8-9, 15-16, 22-23: Dexamethasone 40mg orally Days 1-28: Imatinib 400mg orally twice daily</p> <p>Note: Induction Therapy with Vincristine + Dexamethasone + Dasatinib and Vincristine + Dexamethasone + Nilotinib are also recommended regimens.</p> <p>Note: These regimens are used for induction therapy and additional therapy is needed.</p>
Ph (-) Disease ^h	
Other Recommended Regimens	
CALGB 8811 Larson Regimen ^{27,29}	<p>Induction Therapy (patients age <60 years): Day 1: Cyclophosphamide 1,200mg/m² IV over 30 minutes^f Days 1-3: Daunorubicin 45mg/m² IV push Days 1,8,15,22: Vincristine 2mg IV over 5-10 minutes Days 1-21: Prednisone 60mg/m² orally daily Day 5: Pegaspargase 2,000 international units/m² (maximum 3,750 international units, rounded to vial size) IV over 1 hour. Administer for one 4-week cycle.</p> <p>OR</p> <p>Induction Therapy (patients ≥60 years): Day 1: Cyclophosphamide 800mg/m² IV over 30 minutes^f Days 1-3: Daunorubicin 30mg/m² IV push Days 1,8,15,22: Vincristine 2mg IV over 5-10 minutes Days 1-7: Prednisone 60mg/m² orally daily Day 5: Pegaspargase 2,000 international units/m² (maximum 3,750 international units, rounded to vial size) IV over 1 hour. Administer for one 4-week cycle, followed by:</p> <p>Early Intensification: Day 1: Cyclophosphamide 1,000mg/m² IV over 30 minutes^f Days 1-14: Mercaptopurine 60mg/m² orally daily Days 1-4, 8-11: Cytarabine 75mg/m² subcutaneous Day 1: Methotrexate 15mg intrathecal Days 15,22: Vincristine 2mg IV over 5-10 minutes Day 5: Pegaspargase 2,000 international units/m² (maximum 3,750 international units, rounded to vial size) IV over 1 hour. Repeat every 4 weeks for 2 cycles, followed by:</p> <p>CNS Prophylaxis and Interim Maintenance: Days 1,8,15,22,29: Methotrexate 15mg intrathecal Days 1-70: Mercaptopurine 60mg/m² orally daily Days 36,43,50,57,64: Methotrexate 20mg/m² orally daily Administer for one 84-day cycle with cranial irradiation on days 1-12, followed by:</p> <p>Late Intensification: Days 1,8,15: Doxorubicin 30mg/m² IV push Days 1,8,15: Vincristine 2mg IV over 5-10 minutes Days 1-14: Dexamethasone 10mg/m² orally daily Day 29: Cyclophosphamide 1,000mg/m² IV over 30 minutes^f Days 29-42: Thioguanine 60mg/m² orally daily Days 29-32, 36-39: Cytarabine 75 mg/m² subcutaneous daily. Administer for one 56-day cycle, followed by:</p> <p>Prolonged Maintenance: Day 1: Vincristine 2mg IV over 5-10 minutes Days 1-5: Prednisone 60mg/m² orally daily Days 1,8,15,22: Methotrexate 20mg/m² orally daily Days 1-28: Mercaptopurine 60mg/m² orally daily. Repeat cycle every 4 weeks until 24 months from diagnosis.</p> <p>Note: For Patients aged 60 years or older, reduced doses of Cyclophosphamide, Daunorubicin, and Prednisone.</p>

continued

Acute Lymphoblastic Leukemia (ALL) Treatment Regimens

► Newly-diagnosed ALL^{1,a} (continued)

PROTOCOL ^{1,b}	REGIMEN and DOSING
Adults (age 40-64 years, unless otherwise specified) ^d (continued)	
Ph (-) Disease ^h (continued)	
Other Recommended Regimens (continued)	
GRAALL-2005 (with Rituximab for CD20-Positive Disease) – for patients aged <60 years ²⁴	<p>Rituximab (375mg/m² IV): Days 1,7: First induction course Days 1,7: Salvage Reinduction (if needed) Days 1,29: Consolidation Phase I, II, III Days 1,7: Late Intensification Day 1 of Months 1,3,5,7,9,11 of Maintenance Therapy</p> <p>Prephase Treatment: Days (-7)-(-1): Prednisone 60mg/m² orally Between Days (-7) and (-4): Methotrexate 15mg intrathecal.</p> <p>Induction Therapy: Days 1-14: Prednisone 60mg/m² orally Days 1,8,15,22: Vincristine 2 mg IV Days 1-3: Daunorubicin 50mg/m² IV Days 15,16: Daunorubicin 30mg/m² IV Days 8,10,12: L-Asparaginase 6,000 IU/m² daily IV over 1 hour (not done if CNS involvement), then, Days 20,22,24,26,28: L-Asparaginase 6,000 IU/m² daily IV over 1 hour Day 1: Cyclophosphamide 750mg/m² IV over 3 hours^f Day 15: Cyclophosphamide 750mg/m² IV over 3 hours (1 infusion) OR Days 15-17: Cyclophosphamide 300mg/m² over 3 hours every 12 hours (6 infusions)^f Day 18 to neutrophil recovery: Lenograstim 263 mcg/day subcutaneous or IV.</p> <p>Salvage Reintroduction Therapy: Days 1-3: Idarubicin 12mg/m² IV over 1 hour Days 1-4 (8 infusions): Cytarabine 2,000mg/m² IV over 2 hours every 12 hours Day 9 to neurotrophil recovery: Lenograstim 263 mcg subcutaneous or IV daily.</p> <p>Interphase-1 Therapy: Day 1: Vincristine 2mg IV Day 1: Dexamethasone 40mg orally daily.</p> <p>Consolidation Therapy I – Block 1: Days 1,2 (4 infusions): Cytarabine 2,000mg/m² IV over 2 hours every 12 hours Days 1,2: Dexamethasone 10mg orally every 12 hours Day 3: L-Asparaginase (<i>E. coli</i>): 10,000 IU/m² IV over 1 hour Days 9-13: Lenograstim 263 mcg orally or IV</p> <p>Consolidation Therapy I – Block 2: Day 15: Vincristine 2mg IV Day 15: Methotrexate 3,000 mg/m² continuous IV over 24 hours Day 16: L-Asparaginase 10,000 IU/m² IV over 1 hour Day 15-21: 6-Methotrexate 60mg/m² orally Days 23-27: Lenograstim 263 mcg SC or IV daily</p> <p>Consolidation Therapy I – Block 3: Day 29: Methotrexate 25mg/m² IV Days 29,30: Cyclophosphamide 500mg/m² IV daily over 3 hours^f Days 28,30: Etoposide 75mg/m² IV over 1 hour. Day 31 to neutrophil recovery: Lenograstim 263 mcg SC or IV daily.</p> <p>Consolidation Therapy II: Block 4 – identical to Block 1 Block 5 – identical to Block 2 Block 6 – identical to Block 3</p> <p>Late Intensification Therapy (if CR after 1st course): Day 1-14: Prednisone 60mg/m² orally Day 1,8,15,22: Vincristine 2mg IV Day 1-3, 15,16: Daunorubicin 30mg/m² IV Day 8,10,12,20,22,24,26,28: L-Asparaginase 6,000 IU/m² IV over 1 hour Day 1: Cyclophosphamide 750mg/m² IV over 3 hours, then, Day 15 (1 infusion): Cyclophosphamide 750mg/m² over 3 hours OR Days 15-17 (6 infusions): 300mg/m² over 3 hours every 12 hours^f Day 18 to neutrophil recovery: Lenograstim 263mcg subcutaneous or IV daily.</p>

continued

Acute Lymphoblastic Leukemia (ALL) Treatment Regimens

► Newly-diagnosed ALL^{1,a} (continued)

PROTOCOL ^{1,b}	REGIMEN and DOSING
Adults (age 40-64 years, unless otherwise specified) ^d (continued)	
Ph (-) Disease ^h (continued)	
Other Recommended Regimens (continued)	
GRAALL-2005 (with Rituximab for CD20-Positive Disease) – for patients aged <60 years ²⁴ (continued)	<p>Late Intensification Therapy (if late CR): Days 1-3: Idarubicin 9mg/m² IV over 1 hour daily Days 1-4 (8 infusions): Cytarabine 2,000mg/m² IV over 2 hours every 12 hours Day 9 to neutrophil recovery: Lenograstim 263mcg SC or IV daily.</p> <p>Consolidation Therapy III: Repeat Consolidation Therapy I Blocks 1-3.</p> <p>Maintenance Therapy Day 1 (month 1-12): Vincristine 2mg IV Days 1-7 (month 1-12): Prednisone 40mg/m² orally daily Months 1-24: 6-Mercaptopurine 60mg/m² orally daily Months 1-24: Methotrexate 25mg/m² orally weekly.</p>
Hyper CVAD high-dose Methotrexate/Cytarabine ^{10,11}	<p>Cycle A: Days 1-3: Cyclophosphamide 300mg/m² over 3 hours every 12 hours for 6 doses^f Days 1-3: Mesna 600mg/m² IV continuous infusion over 24 hours daily starting 15 minutes before the first dose of Cyclophosphamide and completing 12 hours after the last dose of Cyclophosphamide is started. Day 4: Doxorubicin 50mg/m² IV push OR IV continuous infusion over 24 hours Days 4 and 11: Vincristine 2mg IV over 5-10 minutes Days 1-4, 11-14: Dexamethasone 40mg IV OR orally daily Day 2: Methotrexate 12mg intrathecal Day 7: Cytarabine 100mg intrathecal. Repeat every 3 weeks for 4 cycles alternating with Cycle B.</p> <p>Cycle B: Day 1: Methotrexate 200mg/m² IV over 2 hours, then 800mg/m² IV continuous infusion over 22 hours. (Alkaline hydration is required pre- and post-administration of high-dose Methotrexate.) Day 2: Leucovorin 50mg IV over 15 minutes administered 12 hours after completion of 22-hour Methotrexate infusion, then 15mg IV over 13 minutes OR orally every 6 hours for at least 8 doses (until Methotrexate serum concentration is <0.05micromol/L) Days 2-3: Cytarabine (age <60 years) 3,000mg/m² IV over 3 hours every 12 hours for 4 doses OR Cytarabine (age ≥60 years) 1,000mg/m² IV over 3 hours every 12 hours for 4 doses Day 2: Methotrexate 12mg intrathecal Day 7: Cytarabine 100mg intrathecal Repeat every 3 weeks for 4 cycles alternating with Cycle A.</p>
Hyper CVAD + Rituximab – high dose Methotrexate/Cytarabine [for patients with CD20-positive disease] ^{10,11}	<p>Cycle A: Day 1: Rituximab 375mg/m² IV Days 1-3: Cyclophosphamide 300mg/m² over 3 hours every 12 hours for 6 doses^f Days 1-3: Mesna 600mg/m² IV continuous infusion over 24 hours daily starting 15 minutes before the first dose of Cyclophosphamide and completing 12 hours after the last dose of Cyclophosphamide is started. Day 4: Doxorubicin 50mg/m² IV push OR IV continuous infusion over 24 hours Days 4 and 11: Vincristine 2mg IV over 5-10 minutes Days 1-4, 11-14: Dexamethasone 40mg IV OR orally daily Day 2: Methotrexate 12mg intrathecal Day 7: Cytarabine 100mg intrathecal. Repeat every 3 weeks for 4 cycles alternating with Cycle B.</p> <p>Cycle B: Day 1: Rituximab 375mg/m² IV Day 1: Methotrexate 200mg/m² IV over 2 hours, then 800mg/m² IV continuous infusion over 22 hours. (Alkaline hydration is required pre- and post-administration of high-dose Methotrexate.) Day 2: Leucovorin 50mg IV over 15 minutes administered 12 hours after completion of 22-hour Methotrexate infusion, then 15mg IV over 15 minutes OR orally every 6 hours for at least 8 doses (until Methotrexate serum concentration is <0.05 micromol/L) Days 2-3: Cytarabine (age <60 years) 3,000mg/m² IV over 3 hours every 12 hours for 4 doses OR Cytarabine (age ≥60 years) 1,000 mg/m² IV over 3 hours every 12 hours for 4 doses Day 2: Methotrexate 12mg intrathecal Day 7: Cytarabine 100mg intrathecal Repeat every 3 weeks for 4 cycles alternating with Cycle A.</p>

continued

Acute Lymphoblastic Leukemia (ALL) Treatment Regimens

▶ Newly-diagnosed ALL^{1,a} (continued)

PROTOCOL ^{1,b}	REGIMEN and DOSING
Adults (age 40-64 years, unless otherwise specified) ^d (continued)	
Ph (-) Disease ^h (continued)	
Other Recommended Regimens (continued)	
Linker Regimen (for patients aged <60 years) ^{26,27}	<p>Induction Therapy (1A): Days 1-3: Daunorubicin 60mg/m² IV push, followed by: Day 15: Daunorubicin 60mg/m² IV push (only if Day 14 bone marrow has residual leukemia) Days 1,8,15,22: Vincristine 1.4mg/m² IV (maximum 2mg if age >40 years) over 5-10 minutes Days 1-28: Prednisone 60mg/m² orally Days 1-4,15-18: Dexamethasone 9mg/m² orally twice daily Day 15: Pegaspargase 2,000 international units/m² (maximum 3,750 international units, rounded to vial size) IV over 1 hour Day 1: Methotrexate 12mg intrathecal. Administer for one 4-week cycle, followed by:</p> <p>Consolidation Therapy (1B): Days 1-4: Cytarabine 2,000 mg/m² IV over 2 hours Days 1-4: Etoposide 500mg/m² IV over 3 hours Days 1,8,15: Methotrexate 12mg intrathecal. Administer for one 4-week cycle, followed by:</p> <p>Consolidation Therapy (1C): Days 1,15: Methotrexate 220mg/m² IV over 15 minutes, then immediately followed by 60mg/m²/hour IV continuous infusion over 36 hours (Alkaline hydration required for high-dose Methotrexate.) Days 2,16: Leucovorin 50mg/m² IV over 15 minutes every 6 hours for 3 doses starting immediately after completion of 36-hour Methotrexate infusion on days 2 and 16, then, Leucovorin 25mg IV over 15 minutes or orally every 6 hours (until Methotrexate serum concentration is <0.05 micromol.) Days 1-28: Mercaptopurine 75mg/m² orally daily Days 1 8: Methotrexate 12mg intrathecal (after adequate clearance of serum Methotrexate). Administer for one 4-week cycle, followed by:</p> <p>Consolidation Therapy (2A): Days 1-3: Daunorubicin 60mg/m² IV push Days 1,8,15: Vincristine 1.4mg/m² (maximum 2mg if age >40 years) IV over 5-10 minutes Days 1-21: Prednisone 60mg/m² orally daily OR Days 1-4,15-18: Dexamethasone 9mg/m² orally twice daily Day 4: Pegaspargase 2,000 international units/m², followed by:</p> <p>Consolidation Therapy (2B): Days 1-4: Cytarabine 2,000 mg/m² IV over 2 hours Days 1-4: Etoposide 500mg/m² IV over 3 hours Days 1,8,15: Methotrexate 12mg intrathecal. Administer for one 4-week cycle, followed by:</p> <p>Consolidation Therapy (2C): Days 1,15: Methotrexate 220mg/m² IV over 15 minutes, then immediately followed by 60mg/m²/hour IV continuous infusion over 36 hours (Alkaline hydration required for high-dose Methotrexate.) Days 2, 16: Leucovorin 50mg/m² IV over 15 minutes every 6 hours for 3 doses starting immediately after completion of 36-hour Methotrexate infusion on days 2 and 16, then, Leucovorin 25mg IV over 15 minutes or orally every 6 hours (until Methotrexate serum concentration is <0.05 micromol.) Days 1-28: Mercaptopurine 75mg/m² orally daily. Administer for one 4-week cycle, followed by:</p> <p>Consolidation Therapy (3C): Days 1,15: Methotrexate 220mg/m² IV over 15 minutes, then immediately followed by 60mg/m²/hour IV continuous infusion over 36 hours (Alkaline hydration required for high-dose Methotrexate.) Days 2, 16: Leucovorin 50mg/m² IV over 15 minutes every 6 hours for 3 doses starting immediately after completion of 36-hour Methotrexate infusion on days 2 and 16, then, Leucovorin 25mg IV over 15 minutes or orally every 6 hours (until Methotrexate serum concentration is <0.05 micromol.) Days 1-28: Mercaptopurine 75mg/m² orally daily. Administer for one 4-week cycle, followed by:</p> <p>Maintenance Therapy: Days 1-28: Mercaptopurine 75mg/m² orally Days 1,8,15,22: Methotrexate 20mg/m² orally. Repeat cycle every 4 weeks until patient is in complete remission for 30 months.</p> <p>Note: Rituximab can be administered with this regimen for patients with CD20-positive disease. Refer to GRAALL-2005 regimen for timing and frequency of administration.</p>

continued

Acute Lymphoblastic Leukemia (ALL) Treatment Regimens

► Newly-diagnosed ALL^{1,a} (continued)

PROTOCOL ^{1,b}	REGIMEN and DOSING
Adults (age 40-64 years, unless otherwise specified)^d (continued)	
Ph (-) Disease^h (continued)	
Other Recommended Regimens (continued)	
MRC UKALLXII/ECOG2993 ³⁰	<p>Induction Therapy:</p> <p><i>Phase 1, weeks 1-4:</i> Days 1,8,15,22: Daunorubicin 60mg/m² IV Days 1,8,15,22: Vincristine 1.4mg/m² IV Days 17-28: L-Asparaginase 10,000 U IV or IM Days 1-28: Prednisone 60mg/m² orally daily Day 15: Methotrexate 12.5mg intrathecal.</p> <p><i>Phase 2, weeks 5-8:</i> Days 1,15,29: Cyclophosphamide 650mg/m² IV^f Days 1-4,8-11,15-18,22-25: Cytarabine 75mg/m² IV Days 1-28: 6-Mercaptopurine 6mg/m² orally Days 1,8,15,22: Methotrexate 12.5mg intrathecal.</p>
Older Adults (age ≥65 years, unless otherwise specified)^{i,o}	
Ph (+) Disease	
Low-Intensity	
Corticosteroids + TKI ^{6,7,e}	<p>• Dasatinib + Prednisone</p> <p>PrePhase: Days (-7-[-1]): Prednisone 10-60mg/m² in increasing doses.</p> <p>Induction Therapy: Dasatinib 70mg twice daily for 84 days Prednisone 60mg/m² daily (capped at 120mg daily) administered until Day 24 and then tapered and stopped at Day 32. Days 22,43: Methotrexate intrathecal.</p> <p>• Imatinib + Prednisone</p> <p>PrePhase: Days (-7-[-1]): Prednisone in increasing doses from 10-40mg/m².</p> <p>Induction Therapy: Days 1-45: Imatinib 800mg orally Days 1-45: Prednisone 40mg/m² Note: Induction Therapy with Corticosteroid + Nilotinib is also a recommended regimen. Note: These regimens are used for induction therapy and additional therapy is needed.</p>
Vincristine + Dexamethasone + TKI ^{17,e}	<p>PrePhase Therapy: Days (-7)-(-1): Prednisone 60mg/m² orally Between Days (-7)-(-1): Methotrexate 15mg intrathecal</p> <p>• Imatinib-Based Regimen</p> <p>Induction Therapy: Days 1,8,15,22: Vincristine 2mg IV Days 1-2, 8-9, 15-16, 22-23: Dexamethasone 40mg orally Days 1-28: Imatinib 400mg orally twice daily Note: Induction Therapy with Vincristine + Dexamethasone + Dasatinib and Vincristine + Dexamethasone + Nilotinib are also recommended regimens. Note: These regimens are used for induction therapy and additional therapy is needed.</p>
Moderate Intensity	
CALGB 10701 ^{5,e}	<p>Course I (First Induction): Days 1-7: Dasatinib 140 mg orally daily Days 1-7: Dexamethasone 10mg/m² orally or IV</p> <p>Course II (If ≤20% lymphoblasts in marrow at Day 15): Days 1-7: Dasatinib 140 mg orally daily Days 1-7: Dexamethasone 10mg/m² orally or IV.</p> <p>Course II (If >20% lymphoblasts in marrow at Day 15): Days 1-7: Dasatinib 140 mg orally daily Days 1-7: Dexamethasone 10mg/m² orally or IV. Vincristine and Daunorubicin also administered.</p>

continued

Acute Lymphoblastic Leukemia (ALL) Treatment Regimens

► Newly-diagnosed ALL^{1,a} (continued)

PROTOCOL ^{1,b}	REGIMEN and DOSING
Older Adults (age ≥65 years, unless otherwise specified) ^{1,c} (continued)	
Ph (+) Disease (continued)	
Moderate Intensity (continued)	
CALGB 10701 ^{5,e} (continued)	<p>Course III (Second Induction for patients not in CR/CRi : Patients received Dasatinib, Cyclophosphamide, Vincristine, Daunorubicin, Dexamethasone.</p> <p>Course IV (CNS Prophylaxis): Patients received Dasatinib, IV Vincristine, and IV, oral, and intrathecal Methotrexate.</p> <p>Course V : Patients treated with stem cell transplantation or chemotherapy.</p> <p>Course VI (Maintenance): Dasatinib Starting on Day 30 of Course V and continued for 12 months and until 2 consecutive negative <i>BCR-ABL1</i> RT-PCR assays 3 months apart or relapse.</p>
EWALL ^{31-33,e}	<p>• EWALL + Dasatinib (EWALL-Ph-001)</p> <p>Prephase Period Days (-7)-(-3): Dexamethasone 10mg daily Methotrexate 15mg intrathecal administered once.</p> <p>Induction Therapy: Days 1-7: TKI (Dasatinib 140mg orally once daily [100mg for patients >70 years]). Administer for 4 weeks, with: Day 1: Vincristine 2mg IV (1mg for patients >70 years) with: Days 1-2: Dexamethasone 40mg (20mg for patients >70 years).</p> <p>Consolidation Therapy – Cycle A: Day 1: TKI (Dasatinib 100mg orally once daily), followed by: Day 1: Methotrexate 1000mg/m² IV (500mg/m² for patients >70 years) Day 2: Asparaginase 10,000 IU/m² IM (5,000 IU/m² IM for patients >70 years). Repeat every 4 weeks for 3 cycles alternating with Consolidation Therapy Cycle B.</p> <p>Consolidation Therapy – Cycle B: Days 1,3,5: Cytarabine 1000mg/m² IV (500mg/m² IV for patients >70 years) every 12 hours. Repeat every 4 weeks for 3 cycles alternating with Consolidation Therapy Cycle A.</p> <p>Maintenance Therapy – Cycle A: Days 1-28: TKI (Dasatinib 100mg orally once daily). Repeat cycle every 4 weeks alternating with Maintenance Therapy – Cycle B until 24 months from diagnosis.</p> <p>Maintenance Therapy – Cycle B: Days 1-28: 6-Mercaptopurine 60mg/m² Days 1: Methotrexate 35mg/m² orally weekly. Repeat cycle every 4 weeks alternating with Maintenance Therapy – Cycle A until 24 months from diagnosis.</p> <p>Maintenance Therapy – Cycle C: Day 1: Vincristine 2mg IV (1mg for patients >70 years) Days 1-2: Dexamethasone 40mg (20mg for patients >70 years). Administer every 3 months during Maintenance Therapy until 24 months from diagnosis.</p> <p>• EWALL + Nilotinib (EWALL-Ph-002) Nilotinib administered at 400mg twice daily during induction and then continuously through consolidation and maintenance therapy.</p>
High Intensity	
Hyper CVAD with TKI alternating with High-Dose Methotrexate/ Cytarabine (with dose-reduced Cytarabine to 1000mg/m ²) ^{12,13,e}	<p>• Dasatinib-based Therapy</p> <p>Cycle A: Days 1-3: Cyclophosphamide 300mg/m² over 3 hours every 12 hours for 6 doses^f Days 1-3: Mesna 600mg/m² IV continuous infusion over 24 hours daily starting 15 minutes before the first dose of Cyclophosphamide and completing 12 hours after the last dose of Cyclophosphamide is started. Day 4: Doxorubicin 50mg/m² IV push OR IV continuous infusion over 24 hours Days 4 and 11: Vincristine 2mg IV over 5-10 minutes Days 1-4, 11-14: Dexamethasone 40mg IV OR orally daily Day 2: Methotrexate 12mg intrathecal Day 7: Cytarabine 100mg intrathecal. Days 1-14: Dasatinib 100mg orally daily. Repeat cycle every 3 weeks for 4 cycles alternating with Cycle B.</p>

continued

Acute Lymphoblastic Leukemia (ALL) Treatment Regimens

► Newly-diagnosed ALL^{1,a} (continued)

PROTOCOL ^{1,b}	REGIMEN and DOSING
Older Adults (age ≥65 years, unless otherwise specified)^{f,o} (continued)	
Ph (+) Disease (continued)	
High Intensity (continued)	
Hyper CVAD with TKI alternating with High-Dose Methotrexate/ Cytarabine (with dose-reduced Cytarabine to 1000mg/m ²) ^{12,13,e} (continued)	<p>• Dasatinib-based Therapy (continued)</p> <p>Cycle B: Day 1: Methotrexate 200mg/m² IV over 2 hours, then 800mg/m² IV continuous infusion over 22 hours. (Alkaline hydration is required pre- and post-administration of high-dose Methotrexate.) Day 2: Leucovorin 50mg IV over 15 minutes administered 12 hours after completion of 22-hour Methotrexate infusion, then 15mg IV over 15 minutes OR orally every 6 hours for at least 8 doses (until Methotrexate serum concentration is <0.05 micromol/L) Days 2-3: Cytarabine 1,000mg/m² IV over 3 hours every 12 hours for 4 doses Day 2: Methotrexate 12mg intrathecal Day 7: Cytarabine 100mg intrathecal Days 1-14: Dastinib 100mg orally daily. Repeat cycle every 3 weeks for 4 cycles alternating with Cycle A.</p> <p>• Ponatinib-Based Therapy</p> <p>Cycle A: Days 1-3: Cyclophosphamide 300mg/m² over 3 hours every 12 hours for 6 doses^f Days 1-3: Mensa 600mg/m² IV continuous infusion over 24 hours daily starting 15 minutes before the first dose of Cyclophosphamide and completing 12 hours after the last dose of Cyclophosphamide is started. Day 4: Doxorubicin 50mg/m² IV push OR IV continuous infusion over 24 hours Days 4 and 11: Vincristine 2mg IV over 5-10 minutes Days 1-4, 11-14: Dexamethasone 40mg IV OR orally daily Day 2: Methotrexate 12mg intrathecal Day 7: Cytarabine 100mg intrathecal. Days 1-14: Ponatinib 45mg orally daily (cycle 1), followed by: Days 1-21: Ponatinib 30mg orally daily (cycles 2-4). Repeat cycle every 3 weeks for 4 weeks alternating with Cycle B.</p> <p>Cycle B: Day 1: Methotrexate 200mg/m² IV over 2 hours, then 800mg/m² IV continuous infusion over 22 hours. (Alkaline hydration is required pre- and post-administration of high-dose Methotrexate.) Day 2: Leucovorin 50mg IV over 15 minutes administered 12 hours after completion of 22-hour Methotrexate infusion, then 15mg IV over 15 minutes OR orally every 6 hours for at least 8 doses (until Methotrexate serum concentration is <0.05 micromol/L) Days 2-3: Cytarabine 1,000mg/m² IV over 3 hours every 12 hours for 4 doses Day 2: Methotrexate 12mg intrathecal Day 7: Cytarabine 100mg intrathecal Days 1-21: Ponatinib 30mg orally. Repeat cycle every 3 weeks for 4 cycles alternating with Cycle A.</p>
Ph (-) Disease	
Low Intensity	
Vincristine + Prednisone ³⁴	Prednisone 60mg/m ² in divided doses for 2-4 weeks and then tapered off over about another 10-14 days Vincristine 1-3.3mg/m ² IV (typically within range of 1.5-2.0mg/m ²) weekly in 2-4 doses.
POMP ^{10,35}	Days 1-5: Prednisone 200mg orally Days 1: Vincristine 2mg IV (maximum dose: 2mg) Days 1-5: 6-Mercaptopurine 1,000/m ² IV over 1 hour Days 1-5: Methotrexate 10mg/m ² IV over 1 hour. Repeat cycle every 4 weeks.
Moderate Intensity	
GMALL ³²	See Reference and NCCN Acute Lymphoblastic Leukemia Guidelines.
GRAALL ²⁴	Prephase Treatment: Days (-7)-(-1): Prednisone 60mg/m ² orally Between Days (-7) and (-4): Methotrexate 15mg intrathecal.

continued

Acute Lymphoblastic Leukemia (ALL) Treatment Regimens

► Newly-diagnosed ALL^{1,a} (continued)

PROTOCOL ^{1,b}	REGIMEN and DOSING
Older Adults (age ≥65 years, unless otherwise specified) ^{1,c} (continued)	
Ph (-) Disease (continued)	
Moderate Intensity (continued)	
GRAALL ²⁴ (continued)	<p>Induction Therapy: Days 1-14: Prednisone 60mg/m² orally Days 1,8,15,22: Vincristine 2mg IV Days 1-3: Daunorubicin 50mg/m² IV Days 15,16: Daunorubicin 30mg/m² IV Days 8,10,12: L-Asparaginase 6,000 IU/m² daily IV over 1 hour (not done if CNS involvement), then, Days 20,22,24,26,28: L-Asparaginase 6,000 IU/m² daily IV over 1 hour Day 1: Cyclophosphamide 750mg/m² IV over 3 hours Day 15: Cyclophosphamide 750mg/m² IV over 3 hours (1 infusion) OR Days 15-17: Cyclophosphamide 300mg/m² over 3 hours every 12 hours (6 infusions)^f Day 18 to neutrophil recovery: Lenograstim 263 mcg/day subcutaneous or IV. Salvage Reintroduction Therapy: Days 1-3: Idarubicin 12mg/m² IV over 1 hour Days 1-4 (8 infusions): Cytarabine 2,000mg/m² IV over 2 hours every 12 hours Day 9 to neurotrophil recovery: Lenograstim 263 mcg subcutaneous or IV daily. Interphase-1 Therapy: Day 1: Vincristine 2mg IV Day 1: Dexamethasone 40mg orally daily. Consolidation Therapy I – Block 1: Days 1,2 (4 infusions): Cytarabine 2,000mg/m² IV over 2 hours every 12 hours Days 1,2: Dexamethasone 10mg orally every 12 hours Day 3: L-Asparaginase (<i>E coli</i>): 10,000 IU/m² IV over 1 hour Days 9-13: Lenograstim 263 mcg orally or IV Consolidation Therapy I – Block 2: Day 15: Vincristine 2mg IV Day 15: Methotrexate 3,000 mg/m² continuous IV over 24 hours Day 16: L-Asparaginase 10,000 IU/m² IV over 1 hour Day 15-21: 6-Methotrexate 60mg/m² orally Days 23-27: Lenograstim 263 mcg SC or IV daily Consolidation Therapy I – Block 3: Day 29: Methotrexate 25mg/m² IV Days 29,30: Cyclophosphamide 500mg/m² IV daily over 3 hours^f Days 28,30: Etoposide 75mg/m² IV over 1 hour. Day 31 to neutrophil recovery: Lenograstim 263 mcg SC or IV daily. Consolidation Therapy II: Block 4 – identical to Block 1 Block 5 – identical to Block 2 Block 6 – identical to Block 3 Late Intensification Therapy (if CR after 1st course): Days 1-14: Prednisone 60mg/m² orally Day 1,8,15,22: Vincristine 2mg IV Day 1-3,15,16: Daunorubicin 30mg/m² IV Day 8,10,12,20,22,24,26,28: L-Asparaginase 6,000 IU/m² IV over 1 hour Day 1: Cyclophosphamide 750mg/m² IV over 3 hours, then,^f Day 15 (1 infusion): Cyclophosphamide 750mg/m² over 3 hours OR Days 15-17 (6 infusions): 300mg/m² over 3 hours every 12 hours Day 18 to neutrophil recovery: Lenograstim 263mcg subcutaneous or IV daily. Late Intensification Therapy (if late CR): Days 1-3: Idarubicin 9mg/m² IV over 1 hour daily Day 1-4 (8 infusions): Cytarabine 2,000mg/m² IV over 2 hours every 12 hours Day 9 to neutrophil recovery: Lenograstim 263 mcg SC or IV daily. Consolidation Therapy III: Repeat Consolidation Therapy I Blocks 1-3. Maintenance Therapy Day 1 (month 1-12): Vincristine 2mg IV Day 1-7 (month 1-12): Prednisone 40mg/m² orally daily Months 1-24: 6-Mercaptopurine 60mg/m² orally daily Months 1-24: Methotrexate 25mg/m² orally weekly.</p>

continued

Acute Lymphoblastic Leukemia (ALL) Treatment Regimens

► Newly-diagnosed ALL^{1,a} (continued)

PROTOCOL ^{1,b}	REGIMEN and DOSING
Older Adults (age ≥65 years, unless otherwise specified) ^{1,c} (continued)	
Ph (-) Disease (continued)	
Moderate Intensity (continued)	
Inotuzumab Ozogamicin + Mini-Hyper CVD (for B-ALL) ³⁶	<p>Cycle A (Cycles 1,3,5,7): Days 1-3: Cyclophosphamide 150mg/m² every 12 hours^f Days 1-4, 11-14: Dexamethasone 20mg Days 1-8: Vincristine IV (2mg, flat dose) Repeat cycle every 4 weeks for 4 cycles alternating with Cycle B.</p> <p>Cycle B (Cycles 2,3,6,8): Day 1: Methotrexate 250mg/m² Days 2,3: Cytarabine 580mg/m² every 12 hours Repeat cycle every 4 weeks for 4 cycles alternating with Cycle A.</p> <p>Note: Day 3 (Cycle 1): Inotuzumab Ozogamicin 1.3mg/m² Day 3 (Cycles 2-4): Inotuzumab Ozogamicin 1.0mg/m² Note: Rituximab administered during first 4 cycles for patients with CD-20 positive disease.</p>
Modified DFCI 91-01 ³⁷	<p>Induction Therapy (4 weeks): Days 1-4, 9-12: Dexamethasone 40mg orally Days 1,2: Doxorubicin 30mg/m² IV Days 1,8,15: Vincristine 2mg IV Day 3: Methotrexate 40mg/m² IV Day 1: Cytarabine 70mg intrathecal Day 15: Cytarabine 40mg/Methotrexate 12mg/Hydrocortisone 15mg intrathecal Day 4: Asparaginase 12,000 IU/m² IM.</p> <p>Central Nervous System Therapy (3 weeks): Day 1: Vincristine 2mg IV Day 1: Doxorubicin 30mg/m² IV Days 1-14: 6-Mercaptopurine 50mg/m² orally Days 1,4,8,11: Cytarabine 40mg/Methotrexate 12mg/Hydrocortisone 15mg intrathecal.</p> <p>Intensification Therapy (21 weeks; 7 x 3 week cycles): Days 1-5: Dexamethasone 6mg orally twice daily Day 1: Vincristine 2mg IV Day 1: Doxorubicin 30mg/m² IV Days 1-14: 6-Mercaptopurine 50mg/m² orally Every 18 weeks: Cytarabine 40mg/Methotrexate 12mg/Hydrocortisone 15mg intrathecal Days 1,8,15: Asparaginase 6,000 IU/m² IM</p> <p>Maintenance Therapy (72 weeks: 24 x 3 week cycles): Days 1-5: Dexamethasone 6mg orally twice daily Day 1: Vincristine 2mg IV Days 1-14: 6-Mercaptopurine 50mg/m² orally Days 1,8,15: Methotrexate 30mg/m² orally Every 18 weeks: Cytarabine 40mg/Methotrexate 12mg/Hydrocortisone 15mg intrathecal.</p>
PETHEMA – Based Regimen: ALLLOD07 ³⁸	<p>Pre-Phase Regimen: Days (-5)-(-1): Dexamethasone 10mg/m² IV</p> <p>Induction Therapy 1: Days 1,8: Vincristine 1mg IV Days 1,2,8,9: Idarubicin 10mg IV Days 1,2,8-11: Dexamethasone 10mg/m² IV.</p> <p>Induction Therapy 2: Days 15-17: Cyclophosphamide 300mg/m² IV^e Days 16-19, 23,26: Cytarabine 60mg/m² IV. Administer Induction Therapy 1 and 2 over a 4-week period.</p> <p>Consolidation Therapy – Cycle A: Day 1: Methotrexate 1,000mg/m² IV continuous 24 hour infusion followed by folinic acid rescue Day 2: Asparaginase (<i>E. coli</i>) 10,000 IU/m² IV.</p> <p>Consolidation Therapy – Cycle B: Days 1,3,5: Cytarabine 1,000mg/m² IV. Note: Consolidation therapy consists of 6 alternating cycles of Cycle A (cycles 1,3, and 5) and Cycle B (cycles 2,4, and 6).</p>

continued

Acute Lymphoblastic Leukemia (ALL) Treatment Regimens

► Newly-diagnosed ALL^{1,a} (continued)

PROTOCOL ^{1,b}	REGIMEN and DOSING
Older Adults (age ≥65 years, unless otherwise specified) ^{1,c} (continued)	
Ph (-) Disease (continued)	
Moderate Intensity (continued)	
PETHEMA – Based Regimen: ALLLOD07 ³⁸ (continued)	<p>Maintenance Therapy: 6-Mercaptopurine 60mg/m² orally daily Methotrexate 25mg/m² IM weekly.</p> <p>Reinduction Cycles: Days 1,2: Dexamethasone 40mg orally or IV Day 1: Vincristine 1mg IV. Administer every 3 months in the first year, and every 3 months in the second year. Note: Administer maintenance therapy with reinduction pulses for a total treatment duration of 2 years.</p>
High Intensity	
CALGB 9111 ³⁹	<p>Induction Therapy (4 weeks): Day 1: Cyclophosphamide 800mg/m² IV[†] Days 1-3: Daunorubicin 30mg/m² IV Days 1-21: Prednisone 60mg/m² orally or IV once daily Days 5,8,11,15,18,22: L-Asparaginase (<i>E. coli</i>): 6,000 IU/m² subcutaneous or IM.</p> <p>Early Intensification (4 weeks; repeat once): Day 1: Methotrexate 15mg intrathecal Day 1: Cyclophosphamide 1000mg/m² IV[†] Days 1-14: 6-Mercaptopurine 60mg/m² orally Days 1-4,8-11: Cytarabine 75mg/m² subcutaneous Days 15,22: Vincristine 2mg IV Days 15,18,22,25: L-Asparaginase (<i>E. coli</i>): 6,000 IU/m² subcutaneous or IM.</p> <p>CNS Prophylaxis and Interim Maintenance (12 weeks): Days 1-12: Cranial irradiation Days 1,8,15,22,29: Methotrexate 15 mg intrathecal Days 1-70: 6-Mercaptopurine 60mg/m² orally Days 36,43,50,57,64: Methotrexate 20mg/m² orally.</p> <p>Late Intensification (8 weeks): Days 1,8,15: Doxorubicin 30mg/m² IV Days 1,8,15: Vincristine 2mg IV Days 1-14: Dexamethasone 10mg/m² orally Day 29: Cyclophosphamide 1,000mg/m² IV[†] Days 29-42: 6-Thioguanine 60mg/m² orally Days 29-32, 36-39: Cytarabine 75mg/m² subcutaneous daily.</p> <p>Prolonged Maintenance (every 4 weeks until 2 years from diagnosis): Day 1: Vincristine 2mg IV Days 1-5: Prednisone 60mg/m² orally Days 1-28: 6-Mercaptopurine 60mg/m² orally Days 1,8,15,22: Methotrexate 20mg/m² orally.</p>
Hyper CVAD high-dose Methotrexate/Cytarabine (with Cytarabine dose reduced to 1,000mg/m ²) ^{10,11,40}	<p>Cycle A: Days 1-3: Cyclophosphamide 300mg/m² IV over 3 hours every 12 hours for 6 doses[†] Days 1-3: Mesna 600mg/m² IV continuous infusion over 24 hours daily starting 15 minutes before the first dose of Cyclophosphamide and completing 12 hours after the last dose of Cyclophosphamide is started. Day 4: Doxorubicin 50mg/m² IV push OR IV continuous infusion over 24 hours Days 4 and 11: Vincristine 2mg IV over 5-10 minutes Days 1-4, 11-14: Dexamethasone 40mg IV OR orally daily Day 2: Methotrexate 12mg intrathecal Day 7: Cytarabine 100mg intrathecal. Repeat every 3 weeks for 4 cycles alternating with Cycle B.</p> <p>Cycle B: Day 1: Methotrexate 200mg/m² IV over 2 hours, then 800mg/m² IV continuous infusion over 22 hours. (Alkaline hydration is required pre- and post-administration of high-dose Methotrexate.) Day 2: Leucovorin 50mg IV over 15 minutes administered 12 hours after completion of 22-hour Methotrexate infusion, then 15mg IV over 15 minutes OR orally every 6 hours for at least 8 doses (until Methotrexate serum concentration is <0.05 micromol/L) Days 2-3: Cytarabine (age ≥60 years) 1,000 mg/m² IV over 3 hours every 12 hours for 4 doses Day 2: Methotrexate 12mg intrathecal Day 7: Cytarabine 100mg intrathecal Repeat every 3 weeks for 4 cycles alternating with Cycle A.</p>

continued

Acute Lymphoblastic Leukemia (ALL) Treatment Regimens

► Relapsed/Refractory ALL^{1,a,p}

PROTOCOL ^{1,b}	REGIMEN and DOSING
Ph (+) Disease^{p-t}	
Other Recommended Regimens	
Blinatumomab (for B-ALL; TKI intolerant/refractory) (Category 1) ^{41,42}	<p>Prephase Therapy: Before start of treatment until Cycle 1, induction, Day 1: Dexamethasone 10mg/m² orally or IV daily (maximum 24mg/day), followed by: Cycle 1 Induction Therapy: Days 1-7: Blinatumomab 9mcg IV continuous infusion over 24 hours daily Days 8-28: Blinatumomab 28mcg IV continuous infusion over 24 hours daily Administer for one 6-week cycle (4 weeks on followed by 2 weeks off treatment), followed by: Cycle 2 Induction Therapy: Days 1-28: Blinatumomab 28mcg IV continuous infusion over 24 hours daily. Administer for one 6-week cycle (4 weeks on followed by 2 weeks off treatment). Consolidation Therapy: Days 1-28: Blinatumomab 28mcg IV continuous infusion over 24 hours daily. Repeat cycle every 6 weeks (4 weeks on followed by 2 weeks off treatment) for 3 cycles. Continued Therapy: Days 1-28: Blinatumomab 28mcg IV continuous infusion over 24 hours daily. Repeat 12-week cycle (4 weeks on followed by 8 weeks off treatment) for 4 cycles. Note: For patients <45kg, BSA-based dosing should be used. Blinatumomab may be given up to a total of 9 cycles (2 cycles of induction followed by 3 cycles of consolidation followed by 4 cycles of continued therapy).</p>
Bosutinib ^{43,q,r}	Bosutinib 400mg twice daily or 600mg twice daily.
Dasatinib ^{44,q}	Dasatinib 140mg orally once daily or 70mg orally twice daily.
Imatinib ^{45,q}	Imatinib 400mg or 600mg once daily.
Inotuzumab Ozogamicin (for B-ALL; TKI intolerant/refractory) ⁴⁶	<p>Day 1: Inotuzumab Ozogamicin 0.8mg/m² IV Days 8,15: Inotuzumab Ozogamicin 0.5mg/m² IV Administer for one 21-day cycle, then repeat subsequent cycles every 4 weeks for up to 6 cycles. Once CR or CRi achieved, dose of Inotuzumab Ozogamicin reduced to 0.5mg/m² IV.</p>
MOPAD + TKI with and without Rituximab (Category 2B) ⁴⁷	<p>Days 1,15: Methotrexate 200mg/m² IV (reduced by 50% for creatinine clearance) Days 1,8,15: Vincristine 1.4mg/m² IV (reduced dose to 1mg for pre-existing neuropathy and/or bilirubin 2-3mg/dL, hold for bilirubin >3mg/dL; maximum dose 2mg) Days 2,16: Pegylated-L-Asparaginase 2,500 IU/m² IV (no capping of dose; decrease by 50% if direct bilirubin between 2 and 3mg/dL; hold for bilirubin ≥3mg/dL, especially serous pancreatitis, thrombosis not controlled with anticoagulation, or disseminated intravascular coagulation) Days 1-4, 15-18: Dexamethasone 40mg IV or orally Dasatinib 70-100mg orally daily, Imatinib 400-800mg orally daily, or Nilotinib 200-400 mg orally once daily in combination with chemotherapy. <i>For patients with CD20-positive leukemia:</i> Days 1,15: Rituximab 375mg/m² IV during the first 4 cycles.</p>
Nilotinib ^{48,q,r}	Nilotinib 200-400mg orally once daily.
Ponatinib ^{49,q,s,t}	Ponatinib 45 mg orally once daily.
Tisagenlecleucel (for patients <26 years with refractory disease or ≥2 relapses and failure of 2 TKIs) ⁵⁰	See NCCN Acute Lymphoblastic Leukemia Guidelines ¹
Ph (-) Disease^{u,v}	
Preferred Regimens	
B-ALL	
Blinatumomab (Category 1) ^{41,42}	<p>Prephase Therapy: Before start of treatment until Cycle 1, induction, Day 1: Dexamethasone 10mg/m² orally or IV daily (maximum 24mg/day), followed by: Cycle 1 Induction Therapy: Days 1-7: Blinatumomab 9mcg IV continuous infusion over 24 hours daily Days 8-28: Blinatumomab 28mcg IV continuous infusion over 24 hours daily Administer for one 6-week cycle (4 weeks on followed by 2 weeks off treatment), followed by: Cycle 2 Induction Therapy: Days 1-28: Blinatumomab 28mcg IV continuous infusion over 24 hours daily. Administer for one 6-week cycle (4 weeks on followed by 2 weeks off treatment).</p>

continued

Acute Lymphoblastic Leukemia (ALL) Treatment Regimens

► Relapsed/Refractory ALL^{1,a,p} (continued)

PROTOCOL ^{1,b}	REGIMEN and DOSING
Ph (-) Disease ^{u,v} (continued)	
Preferred Regimens (continued)	
B-ALL (continued)	
Blinatumomab (Category 1) ^{41,42} (continued)	<p>Consolidation Therapy: Days 1-28: Blinatumomab 28mcg IV continuous infusion over 24 hours daily. Repeat cycle every 6 weeks (4 weeks on followed by 2 weeks off treatment) for 3 cycles.</p> <p>Continued Therapy: Days 1-28: Blinatumomab 28mcg IV continuous infusion over 24 hours daily. Repeat 12-week cycle (4 weeks on followed by 8 weeks off treatment) for 4 cycles.</p> <p>Note: For patients <45kg, BSA-based dosing should be used. Blinatumomab may be given up to a total of 9 cycles (2 cycles of induction followed by 3 cycles of consolidation followed by 4 cycles of continued therapy).</p>
Inotuzumab Ozogamicin (Category 1) ⁴⁶	<p>Day 1: Inotuzumab Ozogamicin 0.8mg/m² IV Days 8,15: Inotuzumab Ozogamicin 0.5mg/m² IV Administer for one 21-day cycle, then repeat subsequent cycles every 4 weeks for up to 6 cycles. Once CR or CRi achieved, dose of Inotuzumab Ozogamicin reduced to 0.5mg/m² IV.</p>
Tisagenlecleucel (patients <26 years with refractory disease or ≥2 relapses) ⁵⁰	See NCCN Acute Lymphoblastic Leukemia Guidelines ¹
T-ALL	
Other Recommended Regimens	
Nelarabine (for T-ALL) ^{51,52}	<p>Days 1,3,5: Nelarabine (age >16 years) 1,500mg/m² IV over 2 hours. Repeat cycle every 3 weeks.</p> <p>OR</p> <p>Day 1-5: Nelarabine (age ≤21 years) 650mg/m² IV over 60 minutes. Repeat cycle every 3 weeks.</p>
Nelarabine, Etoposide, Cyclophosphamide (for T-ALL) ^{53,54}	<p>Days 1-5: Etoposide 100mg/m² IV Days 1-5: Cyclophosphamide 440mg/m² IV^f Days 7(8)-11(12): Nelarabine 650mg/m² IV Intrathecal Methotrexate or triplet intrathecal therapy (Methotrexate, Cytarabine, Hydrocortisone) typically preceding a nelarabine dose by 6 hours or following Nelarabine by 2 days.</p>
B-ALL or T-ALL	
Other Recommended Regimens	
Alkylator Combination Regimen ⁵⁵	<p>Days 1-5: Etoposide 100mg/m² IV over 1.5 hours Days 1-3: Mitoxantrone 8mg/m² IV over 1 hour Days 1-5: Ifosfamide 1/5mg/m² IV over 30 minutes All patients received Mesna 120mg/m² IV immediately prior to first dose of Ifosfamide and thereafter received a continuous infusion of Mesna 1,000mg/m² daily for 6 days.</p>
Augmented Hyper CVAD ⁵⁶	<p>Cycle A (every 21-35 days) Days 1-3: Cyclophosphamide 300mg/m² IV every 12 hours^f, with: Days 1-3: Mesna 600mg/m² IV continuous infusion over 24 hours daily Day 4: Doxorubicin 50mg/m² IV over 24 hours Days 1,8,15: Vincristine 2mg IV Days 1-4, 15-18: Dexamethasone 80mg IV or orally Day 1: Pegaspargase 2,500 units/m² IV. Repeat every 21-35 days for 4 cycles alternating with Cycle B.</p> <p>Cycle B (every 21-35 days): Day 1: Methotrexate 1,000mg/m² over 24 hours Days 2,3: Cytarabine 3,000m/m² IV every 12 hours once serum Methotrexate levels at the end of infusion reached ≤20 umole/L. IV alkalization used to promote excretion of Methotrexate in all course. Calcium Leucovorin 50mg IV given 12 hours after completion of Methotrexate, then 15mg given every 6 hours for 8 doses or until Methotrexate levels were <0.1 umol/L. Oral Acetazolamide given for urine pH <7.0.</p>

continued

Acute Lymphoblastic Leukemia (ALL) Treatment Regimens

► Relapsed/Refractory ALL^{1,a,p} (continued)

PROTOCOL ^{1,b}	REGIMEN and DOSING
Ph (-) Disease ^{u,v} (continued)	
Other Recommended Regimens (continued)	
B-ALL or T-ALL (continued)	
Augmented Hyper CVAD ⁵⁶ (continued)	<p>Cycle B (every 21-35 days): (continued) Day 4: Doxorubicin 50mg/m² IV over 24 hours Days 1,8,15: Vincristine 2mg IV Days 1-4, 15-18: Dexamethasone 80mg IV or orally Day 5: Pegaspargase 2,500 units/m² IV. Repeat every 21-35 days for 4 cycles alternating with Cycle A. Filgrastim 10mcg/kg subcutaneous daily started 24 hours after chemotherapy completion and continued until the postnadir ANC reached $\geq 1 \times 10^9$/L. CNS Prophylaxis (first 2 courses; 4 treatments total): Day 2: Alternating Methotrexate 12mg intrathecal Day 7: Cytarabine 100mg intrathecal. Maintenance Therapy (following Induction and Intensified Consolidation) (up to 12 months): Mercaptopurine 50mg orally three times daily Methotrexate 20mg/m² orally weekly Vincristine 2mg IV every 28-55 days Days 1-5 starting with Vincristine: Prednisone 200mg orally daily.</p>
Clofarabine ⁵⁷	Clofarabine 52mg/m ² IV over 2 hours daily for 5 consecutive days every 2-6 weeks for up to 12 cycles.
Clofarabine-containing regimens ⁵⁸	<p>• Clofarabine/Cyclophosphamide/Etoposide Regimen Induction Therapy: Clofarabine 40mg/m² IV over 2 hours daily, followed by: Etoposide 100mg/m² IV over 2 hours daily, with: Cyclophosphamide 440mg/m² IV over 1 hour.^f Administered for 5 consecutive days as 1 or 2 induction cycles. Consolidation Therapy: 1-3 cycles (4 days of chemotherapy). Maximum of 4 cycles (induction + consolidation). A daily dose of Prednisone 0.5mg/kg was administered.</p>
Cytarabine-containing regimens ⁵⁹	<p>Days 1-5: Cytarabine 3,000mg/m² IV over 3 hours Day 3: Idarubicin 40mg/m² IV rapid infusion Starting on Day 7: Filgrastim (G-CSF) 5mcg/kg subcutaneous twice daily (every 12 hours) and continued until ANC >5,000/uL Days 2,4: Methotrexate 6mg/m² intrathecal.</p>
FLAG-IDA ⁶⁰	<p>Days 1-5: Fludarabine 30mg/m² IV over 30 minutes Days 1-5: Cytarabine 2,000mg/m² IV over 4 hours Days 1-3: Idarubicin 10mg/m² IV G-CSF 5mcg/kg subcutaneous commenced 24 hours after completion of chemotherapy and continued until neutrophils >1.5 x 10⁹/L.</p>
FLAM ⁶¹	<p>Days 1,2,8,9: Fludarabine 15mg/m² over 30 minutes every 12 hours, followed by: Days 1,2,8,9: Cytarabine 100mg/m² IV over 45 minutes Days 3,10: Mitoxantrone 10mg/m² over 20 minutes.</p>
Inotuzumab Ozogamicin + Mini-HyperCVD (for B-ALL) ³⁶	<p>Cycle A (Cycles 1,3,5,7): Days 1-3: Cyclophosphamide 150mg/m² every 12 hours^f Days 1-4, 11-14: Dexamethasone 20mg Days 1-8: Vincristine IV (2mg, flat dose) Repeat cycle every 4 weeks for 4 cycles alternating with Cycle B. Cycle B (Cycles 2,3,6,8): Day 1: Methotrexate 250mg/m² Days 2,3: Cytarabine 580mg/m² every 12 hours Repeat cycle every 4 weeks for 4 cycles alternating with Cycle A. Note: Day 3 (Cycle 1): Inotuzumab Ozogamicin 1.3mg/m² Day 3 (Cycles 2-4): Inotuzumab Ozogamicin 1.0mg/m² Note: Rituximab administered during first 4 cycles for patients with CD-20 positive disease.</p>

continued

Acute Lymphoblastic Leukemia (ALL) Treatment Regimens

► Relapsed/Refractory ALL^{1,a,p} (continued)

PROTOCOL ^{1,b}	REGIMEN and DOSING
Ph (-) Disease ^{u,v} (continued)	
Other Recommended Regimens (continued)	
B-ALL or T-ALL (continued)	
MOpAD Regimen ⁴⁷	<p>Days 1,15: Methotrexate 200mg/m² IV (reduced by 50% for creatinine clearance)</p> <p>Days 1,8,15: Vincristine 1.4mg/m² IV (reduced dose to 1mg for pre-existing neuropathy and/or bilirubin 2-3mg/dL, hold for bilirubin >3mg/dL maximum dose 2mg)</p> <p>Days 2,16: Pegylated-L-Asparaginase 2,500 IU/m² IV (no capping of dose; decrease by 50% if direct bilirubin between 2 and 3mg/dL; hold for bilirubin ≥3mg/dL, especially serous pancreatitis, thrombosis not controlled with anticoagulation, or disseminated intravascular coagulation)</p> <p>Days 1-4, 15-18: Dexamethasone 40mg IV or orally</p> <p><i>For patients with CD20-positive ALL:</i></p> <p>Days 1,15: Rituximab 375mg/m² IV during the first 4 cycles.</p>
Vincristine Sulfate Liposome Injection ⁶²	<p>Days 1,8,15,22: Vincristine Sulfate Liposome Injection 2.25mg/m² IV over 60 minutes.</p> <p>Repeat cycle every 4 weeks.</p>

- While these guidelines pertain primarily to patients with leukemia, patients with lymphoblastic lymphoma (LL) (B- or T-cell) also benefit from ALL-like regimens versus traditional lymphoma therapy. Such patients should be treated in a center that has experience with LL.
- All regimens include CNS prophylaxis with systemic therapy (eg, methotrexate, cytarabine) and/or Intrathecal (IT) therapy (eg, IT methotrexate, IT cytarabine, triple IT therapy with methotrexate, cytarabine, corticosteroid).
- The ALL Panel considers AYA to be within the age range of 15-39 years. However, this age is not a firm reference point because some of the recommended regimens have not been comprehensively tested across all ages.
- Add tyrosine kinase inhibitors (TKIs) to maintenance regimen; optimal duration is unknown. Monthly vincristine/prednisone pulses (for 2-3 years). May include weekly methotrexate + daily 6-Mercaptopurine as tolerated. For patients receiving 6-Mercaptopurine, consider testing for *TPMT* gene polymorphisms, particularly in patients who develop severe neutropenia 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.
- TKI options include (in alphabetical order): Bosutinib, Dasatinib, Imatinib, Nilotinib, or Ponatinib. Dasatinib and Imatinib are the preferred TKIs for induction therapy; Ponatinib is also preferred for the hyper-CVAD regimen. Not all TKIs have been directly studied within the context of each specific regimen and the panel notes that there are limited data for Bosutinib in Ph+ ALL. Use of a specific TKI should account for the anticipated/prior TKI intolerance and disease-related features.
- Oral hydration is strongly encouraged with cyclophosphamide; poorly hydrated patients may need supplemental IV hydration. Patients should attain combined oral and IV hydration of 2000-3000 mL/day on day of chemotherapy.
- CNS1=patients with white blood cell (WBC) count in CSF <5 and having no blasts in the CSF, CNS2=patients with WBC count in CSF <5 and having blasts in the CSF, CNS3=patients with WBC count in CSF ≥5 and having blasts in the CSF.
- Maintenance regimen: Weekly methotrexate + daily 6-Mercaptopurine + monthly vincristine/prednisone pulses (duration based on regimen). For patients receiving 6-Mercaptopurine, consider testing for *TPMT* gene polymorphisms, particularly in patients who 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.
- Pegasparagase may be substituted with calaspargase pegol-mknl, an asparagine-specific enzyme, in patients ≤21 years for more sustained asparaginase activity. Silverman LB, et al. *Blood*. 2016;128:175; Angiolillo AL, et al. *J Clin Oncol*. 2014;32:3874-3882.^{63,64}
- Older adults (defined as those aged 65 years and older) benefit from therapy, in spite of higher treatment-related morbidity and mortality.
- Careful assessment of comorbid conditions, performance status, and ability to attend to activities of daily living (ADLs) and instrumental ADLs (IADLs) is important when deciding treatment intensity.
- Dose reduction of pegylated asparaginase (1000 IU/m²), anthracycline (50% dose), and/or other myelosuppressive agents may be warranted.
- The categorization of regimens as low, moderate, or high intensity is based on 2 factors: 1) the presence of absence of myelosuppressive cytotoxic agents, and 2) the relative dose intensity of the included agents.
- All regimens should include CNS prophylaxis, antimicrobial prophylaxis, and growth factor support.
- For appropriate fit individuals achieving remission, consideration of autologous or reduced-intensity allogeneic SCT may be appropriate.
- The safety of relapsed/refractory regimens in older adults (≥65 years) has not been established.
- Bosutinib is contraindicated in patients with disease characterized by *BCR-ABL1* mutations T315I, V299L, G250E, F317L; Dasatinib is contraindicated in patients with disease characterized by *BCR-ABL1* mutations T315L/A, F317L/V/I/C, V299L; Nilotinib is contraindicated in patients with disease characterized by *BCR-ABL1* mutations IT315I, Y253H, E255K/V; F359V/C/I, G250E.
- Bosutinib has minimal activity against F317L mutation. Nilotinib may be preferred over bosutinib in patients with F317L mutation.
- Ponatinib is a treatment option for patients with a T315I mutation and/or for patients for whom no other TKI is indicated.
- Ponatinib has activity against T315I mutations and is effective in treating patients with resistant or progressive disease on multiple TKIs. However, it is associated with a high frequency of serious vascular events (eg, strokes, heart attacks, tissue ischemia). The FDA indications are for the treatment of adult patients with T315I-positive, Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ ALL) and for the treatment of patients with Ph+ ALL for whom no other TKI therapy is indicated.
- The regimens for relapsed/refractory, Philadelphia-negative ALL may be considered for Philadelphia-positive ALL refractory to TKIs.
- For patients in late relapse (>3 years from initial diagnosis), consider treatment with the same induction regimen.

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Acute Lymphoblastic Leukemia (ALL) Treatment Regimens

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