Clinical Advances in
HEMATOLOGY & ONCOLOGY™
A Peer-Reviewed Journal

June 2014 Volume 12, Issue 6, Supplement 12

New Developments in Acute Lymphoblastic Leukemia

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December 7-10, 2013 • New Orleans, Louisiana

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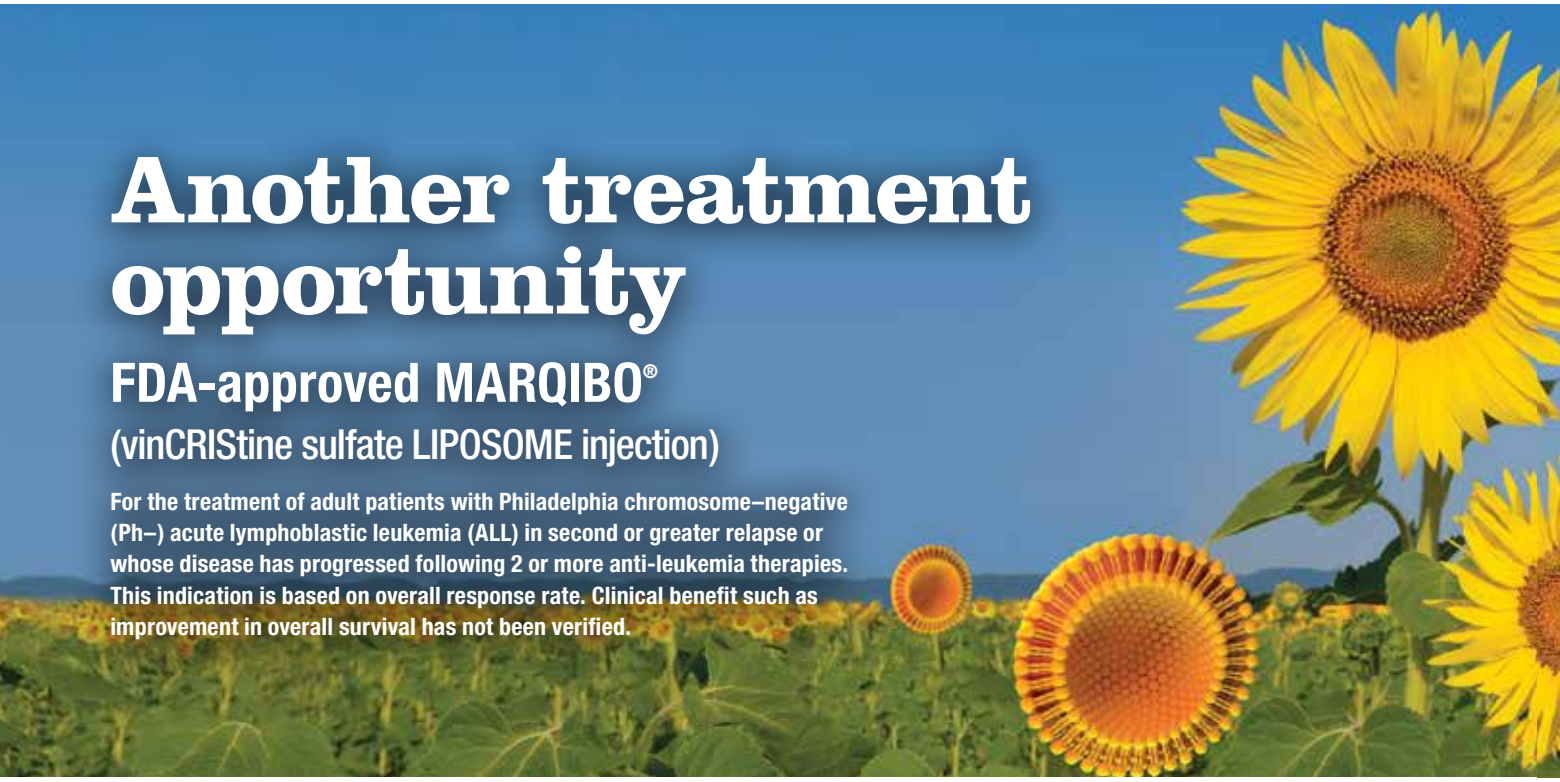
(PubMed/MEDLINE), PubMed Central (PMC), and EMBASE



Another treatment opportunity

FDA-approved MARQIBO®

(vinCRIStine sulfate LIPOSOME injection)

For the treatment of adult patients with Philadelphia chromosome–negative (Ph–) acute lymphoblastic leukemia (ALL) in second or greater relapse or whose disease has progressed following 2 or more anti-leukemia therapies. This indication is based on overall response rate. Clinical benefit such as improvement in overall survival has not been verified.

- **15.4% (10/65) overall response rate in patients who received multiple prior therapies (4.6% CR + 10.8% CRi) (95% CI 7.6–26.5)[1]**
  - 100% had previously received non-liposomal (standard) vincristine
  - 48% had undergone prior hematopoietic stem cell transplant (HSCT)
  - 51% had received 3 or more prior therapies
  - 45% were refractory to their immediate prior therapy
  - 85% had precursor B-cell ALL and 15% had precursor T-cell ALL
  - 100% were ineligible for immediate HSCT at enrollment
  - 34% had not received asparaginase products
- **Median duration of CR or CRi[1]**
  - 28 days (95% CI 7, 36) based on the first date of CR or CRi to the date of the last available histologic assessment of the same response (n=8)
  - 56 days (95% CI 9, 65) based on the first date of CR or CRi to the date of documented relapse, death, or subsequent chemotherapies, including HSCT (n=10)
- **MARQIBO is sphingomyelin/cholesterol-based liposome–encapsulated vincristine[1]**
  - Plasma clearance of MARQIBO is slow, 345 mL/h, at a dose of 2.25 mg/m^2. This is in comparison to the rapid clearance of non-liposomal vincristine sulfate at 189 mL/min/m^2 (11,340 mL/h)
  - Slow clearance of MARQIBO contributes to a much higher area under the curve (AUC) for MARQIBO relative to non-liposomal vincristine sulfate
- **The recommended dose of MARQIBO is 2.25 mg/m^2 intravenously over 1 hour every 7 days.[1] A dose of MARQIBO is calculated based on the patient's actual body surface area**

Important Safety Information

WARNING

- **For Intravenous Use Only—Fatal if Given by Other Routes**
- **Death has occurred with intrathecal administration**
- **MARQIBO (vinCRIStine sulfate LIPOSOME injection) has different dosage recommendations than vincristine sulfate injection. Verify drug name and dose prior to preparation and administration to avoid overdosage**

Contraindications

- MARQIBO is contraindicated in patients with demyelinating conditions, including Charcot-Marie-Tooth syndrome; in patients with hypersensitivity to vincristine sulfate or any of the other components of MARQIBO; and for intrathecal administration

SPECTRUM™ PHARMACEUTICALS
and its wholly-owned subsidiary TALON® THERAPEUTICS

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Warnings and Precautions

- MARQIBO is for intravenous use only—fatal if given by other routes. Intrathecal use is fatal
- Extravasation causes tissue injury. If extravasation is suspected, discontinue infusion immediately and consider local treatment measures
- Sensory and motor neuropathy are common and cumulative. Monitor patients for peripheral motor and sensory, central and autonomic neuropathy and reduce, interrupt, or discontinue dosing. Patients with preexisting severe neuropathy should be treated with MARQIBO only after careful risk-benefit assessment
- Neutropenia, thrombocytopenia, or anemia may occur. Monitor blood counts prior to each dose. Consider dose modification or reduction as well as supportive care measures if Grade 3 or 4 myelosuppression develops
- Anticipate, monitor for, and manage tumor lysis syndrome
- A prophylactic bowel regimen should be instituted with MARQIBO to prevent constipation, bowel obstruction, and/or paralytic ileus
- Severe fatigue can occur requiring dose delay, reduction, or discontinuation of MARQIBO
- Fatal liver toxicity and elevated levels of aspartate aminotransferase have occurred. Monitor liver function and modify or interrupt dosing for hepatic toxicity
- MARQIBO can cause fetal harm. Advise women of potential risk to fetus

Adverse Events

- The most commonly reported adverse reactions (incidence >30%) in clinical studies include constipation (57%), nausea (52%), pyrexia (43%), fatigue (41%), peripheral neuropathy (39%), febrile neutropenia (38%), diarrhea (37%), anemia (34%), decreased appetite (33%), and insomnia (32%)
- A total of 75.9% of patients experienced serious adverse events (SAEs) during the studies. The most commonly reported SAEs included febrile neutropenia (20.5%), pyrexia (13.3%), hypotension (7.2%), respiratory distress (6.0%), and cardiac arrest (6.0%)
- Twenty-eight percent of patients experienced adverse reactions leading to treatment discontinuation. The most common adverse reactions that caused treatment discontinuation were peripheral neuropathy (10%), leukemia-related (7%), and tumor lysis syndrome (2%)
- Deaths occurred in 23% of patients in study 1. The nonleukemia-related causes of death were brain infarct (1), intracerebral hemorrhage (2), liver failure (1), multisystem organ failure (2), pneumonia and septic shock (3), respiratory failure (4), pulmonary hemorrhage (1), and sudden cardiac death (1)

Drug Interactions

- MARQIBO is expected to interact with drugs known to interact with non-liposomal vincristine sulfate, therefore the concomitant use of strong CYP3A inhibitors or the use of potent P-glycoprotein inhibitors or inducers should be avoided

Use in Specific Populations

- The safety and effectiveness of MARQIBO in pediatric patients have not been established
- It is not known whether MARQIBO is excreted in human milk

Please see Brief Summary of Prescribing Information, including the BOXED WARNINGS, for MARQIBO on adjacent pages. Please see Prescribing Information at MARQIBO.com.

1. MARQIBO [prescribing information]. October 2012.

Marqibo®

(vinCRIStine sulfate LIPOSOME injection)

for intravenous infusion

Consider the Opportunity

Marqibo® (vinCRIStine sulfate LIPOSOME injection) BRIEF SUMMARY
Please see the Marqibo package insert for full Prescribing Information.

WARNING

- **For Intravenous Use Only—Fatal if Given by Other Routes.**
- **Death has occurred with intrathecal administration.**
- **Marqibo (vinCRIStine sulfate LIPOSOME injection) has different dosage recommendations than vinCRIStine sulfate injection. Verify drug name and dose prior to preparation and administration to avoid overdosage.**

INDICATIONS AND USAGE

Adult ALL in Second or Greater Relapse

Marqibo® is indicated for the treatment of adult patients with Philadelphia chromosome-negative (Ph-) acute lymphoblastic leukemia (ALL) in second or greater relapse or whose disease has progressed following two or more anti-leukemia therapies. This indication is based on overall response rate. Clinical benefit such as improvement in overall survival has not been verified.

DOSAGE AND ADMINISTRATION

For Intravenous Use Only—Fatal if Given by Other Routes.

Marqibo (vinCRIStine sulfate LIPOSOME injection) has different dosage recommendations than vincristine sulfate injection. Verify drug name and dose prior to preparation and administration to avoid overdosage.

Recommended Dosage

The recommended dose of Marqibo is 2.25 mg/m^2 intravenously over 1 hour once every 7 days. Marqibo is liposome-encapsulated vincristine.

Dose Modifications: Peripheral Neuropathy

Marqibo is contraindicated in patients with demyelinating conditions including Charcot-Marie-Tooth syndrome [*see Contraindications*]. Patients with preexisting severe neuropathy should be treated with Marqibo only after careful risk-benefit assessment [*see Warnings and Precautions*]. For dose or schedule modifications guidelines for patients who experience peripheral neuropathy, see Table 1.

Table 1. Recommended Dose Modifications for Marqibo-related Peripheral Neuropathy

Severity of Peripheral Neuropathy Signs and Symptoms[a]	Modification of Dose and Regimen
If the patient develops Grade 3 (severe symptoms; limiting self-care activities of daily living [ADL][b]) or persistent Grade 2 (moderate symptoms; limiting instrumental ADL[c]) peripheral neuropathy:	Interrupt Marqibo. If the peripheral neuropathy remains at Grade 3 or 4, discontinue Marqibo. If the peripheral neuropathy recovers to Grade 1 or 2, reduce the Marqibo dose to 2 mg/m^2.
If the patient has persistent Grade 2 peripheral neuropathy after the first dose reduction to 2 mg/m^2:	Interrupt Marqibo for up to 7 days. If the peripheral neuropathy increases to Grade 3 or 4, discontinue Marqibo. If the peripheral neuropathy recovers to Grade 1, reduce the Marqibo dose to 1.825 mg/m^2.
If the patient has persistent Grade 2 peripheral neuropathy after the second dose reduction to 1.825 mg/m^2:	Interrupt Marqibo for up to 7 days. If the peripheral neuropathy increases to Grade 3 or 4, discontinue Marqibo. If the toxicity recovers to Grade 1, reduce the Marqibo dose to 1.5 mg/m^2.

[a] Grading based on the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v3.0.
[b] Self-care ADL: refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.
[c] Instrumental ADL: refers to preparing meals, shopping for groceries and clothes, using telephone, managing money, etc.

Preparation and Handling

Items Required by the Pharmacy to Prepare Marqibo

- Marqibo Kit
- Water bath[a]
- Calibrated thermometer[a] (0°C to 100°C)
- Calibrated electronic timer[a]
- Sterile venting needle or other suitable device equipped with a sterile 0.2 micron filter
- 1 mL or 3 mL sterile syringe with needle, and
- 5 mL sterile syringe with needle.

[a] The manufacturer will provide the water bath, calibrated thermometer, and calibrated electronic timer to the medical facility at the initial order of Marqibo and will replace them every 2 years.

Preparation Instructions for Marqibo (vinCRIStine sulfate LIPOSOME injection), 5 mg/31 mL (0.16 mg/mL)

Procedures for handling and disposal of anticancer drugs should be followed [*see References*]. Call [1 888 292 9617] if you have questions about the preparation of Marqibo. Marqibo takes approximately 60 to 90 minutes to prepare. The preparer should have dedicated uninterrupted time to prepare Marqibo due to the extensive monitoring of temperature and time required for the preparation.

Aseptic technique must be strictly observed since no preservative or bacteriostatic agent is present in Marqibo. The preparation steps of Marqibo that involve mixing the Sodium Phosphate Injection, Sphingomyelin/Cholesterol Liposome Injection, and VinCRIStine Sulfate Injection must be done in a biological safety cabinet or by established pharmacy safety procedures for the preparation of sterile injectable formulations and hazardous drugs. However, the preparation steps that involve placement of the vial in the water bath must be done outside of the sterile area.

Do not use with in-line filters. Do not mix with other drugs.

1. Fill a water bath with water to a level of at least 8 cm (3.2 inches) measured from the bottom and maintain this minimum water level throughout the procedure. The water bath must remain outside of the sterile area.
2. Place a calibrated thermometer in the water bath to monitor water temperature and leave it in the water bath until the procedure has been completed.
3. Preheat water bath to 63°C to 67°C. Maintain this water temperature until completion of the procedure using the calibrated thermometer.
4. Visually inspect each vial in the Marqibo Kit for particulate matter and discoloration prior to preparation, whenever solution and container permit. Do not use if a precipitate or foreign matter is present.
5. Remove all the caps on the vials and swab the vials with sterile alcohol pads.
6. Vent the Sodium Phosphate Injection vial with a sterile venting needle equipped with a sterile 0.2 micron filter or other suitable venting device in the biological safety cabinet. Always position venting needle point well above liquid level before adding Sphingomyelin/Cholesterol Liposome Injection and VinCRIStine Sulfate Injection.
7. Withdraw 1 mL of Sphingomyelin/Cholesterol Liposome Injection.
8. Inject 1 mL of Sphingomyelin/Cholesterol Liposome Injection into the Sodium Phosphate Injection vial.
9. Withdraw 5 mL of VinCRIStine Sulfate Injection.
10. Inject 5 mL of VinCRIStine Sulfate Injection into the Sodium Phosphate Injection vial.
11. Remove the venting needle and gently invert the Sodium Phosphate Injection vial 5 times to mix. DO NOT SHAKE.
12. Fit Flotation Ring around the neck of the Sodium Phosphate Injection vial.
13. Confirm that the water bath temperature is at 63°C to 67°C using the calibrated thermometer. Remove the Sodium Phosphate Injection vial containing VinCRIStine Sulfate Injection, Sphingomyelin/Cholesterol Liposome Injection, and Sodium Phosphate Injection from the biological safety cabinet and place into the water bath for 10 minutes using the calibrated electronic timer. Monitor the temperature to ensure the temperature is maintained at 63°C to 67°C.
14. IMMEDIATELY after placing the Sodium Phosphate Injection vial into the water bath, record the constitution start time and water temperature on the Marqibo Overlabel.
15. At the end of the 10 minutes, confirm that the water temperature is 63°C to 67°C using the calibrated thermometer. Remove the vial from the water bath (use tongs to prevent burns) and remove the Flotation Ring.
16. Record the final constitution time and the water temperature on the Marqibo Overlabel.
17. Dry the exterior of the Sodium Phosphate Injection vial with a clean paper towel, affix Marqibo (vinCRIStine sulfate LIPOSOME injection) Overlabel, and gently invert 5 times to mix. DO NOT SHAKE.
18. Permit the constituted vial contents to equilibrate for at least 30 minutes to controlled room temperature (15°C to 30°C, 59°F to 86°F).
19. Marqibo (vinCRIStine sulfate LIPOSOME injection) contains 5 mg/31 mL (0.16 mg/mL) vincristine sulfate. ONCE PREPARED, STORE AT CONTROLLED ROOM TEMPERATURE (15°C to 30°C, 59°F to 86°F) FOR NO MORE THAN 12 HOURS.
20. Swab the top of the vial now containing Marqibo with a sterile alcohol pad and return the vial back into the biological safety cabinet.
21. Calculate the patient's Marqibo dose based on the patient's actual body surface area (BSA) and remove the volume corresponding to the patient's Marqibo dose from an infusion bag containing 100 mL of 5% Dextrose Injection or 0.9% Sodium Chloride Injection.
22. Inject the dose of Marqibo into the infusion bag to result in a final volume of 100 mL.
23. Complete the information required on the Infusion Bag Label and apply to the infusion bag.
24. Finish administration of the diluted product within 12 hours of the initiation of Marqibo preparation.
25. Empty, clean, and dry the water bath after each use.
26. Deviations in temperature, time, and preparation procedures may fail to ensure proper encapsulation of vincristine sulfate into the liposomes. In the event that the preparation deviates from the instructions in the above steps, the components of the kit should be discarded and a new kit should be used to prepare the dose.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Do not use if a precipitate or foreign matter is present.

CONTRAINDICATIONS

Marqibo is contraindicated in patients with demyelinating conditions including Charcot-Marie-Tooth syndrome.

Marqibo is contraindicated in patients with hypersensitivity to vincristine sulfate or any of the other components of Marqibo (vinCRIStine sulfate LIPOSOME injection).

Marqibo is contraindicated for intrathecal administration.

WARNINGS AND PRECAUTIONS

For Intravenous Use Only

Fatal if Given by Other Routes. Death has occurred with intrathecal use.

Extravasation Tissue Injury

Only administer through a secure and free-flowing venous access line. If extravasation is suspected, discontinue infusion immediately and consider local treatment measures.

Neurologic Toxicity

Sensory and motor neuropathies are common and are cumulative. Monitor patients for symptoms of neuropathy, such as hypoesthesia, hyperesthesia, paresthesia, hyporeflexia, areflexia, neuralgia, jaw pain, decreased vibratory sense, cranial neuropathy, ileus, burning sensation, arthralgia, myalgia, muscle spasm, or weakness, both before and during treatment. Orthostatic hypotension may occur. The risk of neurologic toxicity is greater if Marqibo is administered to patients with preexisting neuromuscular disorders or when other drugs with risk of neurologic toxicity are being given. In the studies of relapsed and/or refractory adult ALL patients, Grade ≥3 neuropathy events occurred in 32.5% of patients. Worsening neuropathy requires dose delay, reduction, or discontinuation of Marqibo [*see Dosage and Administration*].

Myelosuppression

Monitor complete blood counts prior to each dose of Marqibo. If Grade 3 or 4 neutropenia, thrombocytopenia, or anemia develops, consider Marqibo dose modification or reduction as well as supportive care measures.

Tumor Lysis Syndrome

Tumor lysis syndrome (TLS) may occur in patients with ALL receiving Marqibo.

Anticipate, monitor for, and manage.

Constipation and Bowel Obstruction

Ileus, bowel obstruction, and colonic pseudo-obstruction have occurred. Marqibo can cause constipation [*see Adverse Reactions*]. Institute a prophylactic bowel regimen to mitigate potential constipation, bowel obstruction, and/or paralytic ileus, considering adequate dietary fiber intake, hydration, and routine use of stool softeners, such as docusate. Additional treatments, such as senna, bisacodyl, milk of magnesia, magnesium citrate, and lactulose may be considered.

Fatigue

Marqibo can cause severe fatigue. Marqibo dose delay, reduction, or discontinuation may be necessary.

Hepatic Toxicity

Fatal liver toxicity and elevated levels of aspartate aminotransferase have occurred. Elevated levels of aspartate aminotransferase of Grade ≥3 occurred in 6-11% of patients in clinical trials. Monitor hepatic function tests. Reduce or interrupt Marqibo for hepatic toxicity.

Embryofetal Toxicity

Marqibo can cause fetal harm when administered to a pregnant woman. Vincristine sulfate liposome injection was teratogenic or caused embryo-fetal death in animals.

Women of childbearing potential should avoid becoming pregnant while being treated with Marqibo. There are no adequate and well-controlled studies of Marqibo in pregnant women and there were no reports of pregnancy in any of the clinical studies in the Marqibo clinical development program. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus [*see Use in Specific Populations*].

ADVERSE REACTIONS

The following adverse reactions are also discussed in other sections of the labeling:

- For intravenous use only [*see Warnings and Precautions*]
- Extravasation tissue injury [*see Warnings and Precautions*]
- Peripheral Neuropathy [*see Warnings and Precautions*]
- Myelosuppression [*see Warnings and Precautions*]
- Tumor lysis syndrome [*see Warnings and Precautions*]
- Constipation and bowel obstruction [*see Warnings and Precautions*]
- Fatigue [*see Warnings and Precautions*]
- Hepatic toxicity [*see Warnings and Precautions*]

Clinical Trials Safety Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

Integrated Summary of Safety in Relapsed and/or Refractory Ph- Adult Acute Lymphoblastic Leukemia

Marqibo, at a dose of 2.25 mg/m^2 weekly, was studied in a total of 83 patients in two trials: study 1 and study 2. Adverse reactions were observed in 100% of patients. The most common adverse reactions (>30%) were constipation (57%), nausea (52%), pyrexia (43%), fatigue (41%), peripheral neuropathy (39%), febrile neutropenia (38%), diarrhea (37%), anemia (34%), decreased appetite (33%), and insomnia (32%)

Adverse reactions of Grade 3 or greater were reported in 96% of patients.

Adverse reactions of Grade 3 or greater and occurring in ≥5% of patients are summarized in Table 2.

Table 2. Most Commonly Reported (>5%) Grade[a] 3 or Greater Adverse Reactions among 83 Patients Receiving the Clinical Dosing Regimen

Adverse Reactions ≥3	Study 1 and 2 (N=83) n (%)
Blood and Lymphatic System Disorders	*47 (56.6)*
Febrile Neutropenia	26 (31.3)
Neutropenia	15 (18.1)
Anemia	14 (16.9)
Thrombocytopenia	14 (16.9)
Infections	*33 (39.8)*
Pneumonia	7 (8.4)
Septic Shock	5 (6.0)
Staphylococcal Bacteremia	5 (6.0)
Neuropathy[b]	*27 (32.5)*
Peripheral Sensory and Motor Neuropathy	14 (16.7)
Constipation	4 (4.8)
Ileus, Colonic Pseudo-Obstruction	5 (6.0)
Asthenia	4 (4.8)
Muscular Weakness	1 (1.2)
Respiratory Thoracic and Mediastinal Disorders	*17 (20.5)*
Respiratory Distress	5 (6.0)
Respiratory Failure	4 (4.8)
General Disorders and Administration Site Condition	*31 (37.3)*
Pyrexia	12 (14.5)
Fatigue	10 (12.0)
Pain	7 (8.4)
Gastrointestinal Disorders	*21 (25.3)*
Abdominal Pain	7 (8.4)
Investigations	*20 (24.1)*
Aspartate Aminotransferase Increased	6 (7.2)
Vascular Disorders	*8 (9.6)*
Hypotension	5 (6.0)
Psychiatric Disorders	*9 (10.8)*
Mental Status Changes	3 (3.6)
Cardiac Disorders	*9 (10.8)*
Cardiac Arrest	5 (6.0)
Renal and Urinary Disorders	*6 (7.2)*
Musculoskeletal and Connective Tissue Disorders	*7 (8.4)*

[a] National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v3.0.
[b] Including neuropathy-associated adverse reactions.

A total of 75.9% of patients experienced serious adverse events (SAEs) during the studies. The most commonly reported SAEs included febrile neutropenia (20.5%), pyrexia (13.3%), hypotension (7.2%), respiratory distress (6.0%), and cardiac arrest (6.0%).

Dose reduction, delay, or omission occurred in 53% of patients during the treatment.

Twenty-eight percent of patients experienced adverse reactions leading to treatment discontinuation. The most common adverse reactions that caused treatment discontinuation were peripheral neuropathy (10%), leukemia-related (7%), and tumor lysis syndrome (2%).

Adverse reactions related to neuropathy and leading to treatment discontinuation were decreased vibratory sense, facial palsy, hyporeflexia, constipation, asthenia, fatigue, and musculoskeletal pain, each reported in at least 1 patient.

Deaths occurred in 23% of patients in study 1. The nonleukemia-related causes of deaths were brain infarct (1), intracerebral hemorrhage (2), liver failure (1), multi system organ failure (2), pneumonia and septic shock (3), respiratory failure (4), pulmonary hemorrhage (1), and sudden cardiac death (1).

DRUG INTERACTIONS

No formal drug interaction studies have been conducted with Marqibo. Marqibo is expected to interact with drugs known to interact with non-liposomal vincristine sulfate.

Simultaneous oral or intravenous administration of phenytoin and antineoplastic chemotherapy combinations that included non-liposomal vincristine sulfate have been reported to reduce blood levels of phenytoin and to increase seizure activity.

CYP3A Interactions

Vincristine sulfate, the active agent in Marqibo, is a substrate for cytochrome P450 3A isozymes (CYP3A); therefore, the concomitant use of strong CYP3A inhibitors should be avoided (e.g., ketoconazole, itraconazole, voriconazole, posaconazole, clarithromycin, atazanavir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin). Similarly, the concomitant use of strong CYP3A inducers should be avoided (e.g., dexamethasone, phenytoin, carbamazepine, rifampin, rifabutin, rifapentine, phenobarbital, St. John's Wort).

P-glycoprotein Interactions

Vincristine sulfate, the active agent in Marqibo, is also a substrate for P-glycoprotein (P-gp). The effect of concomitant use of potent P-gp inhibitors or inducers has not been investigated; it is likely that these agents will alter the pharmacokinetics or pharmacodynamics of Marqibo. Therefore the concomitant use of potent P-gp inhibitors or inducers should be avoided.

USE IN SPECIFIC POPULATIONS

Pregnancy

Pregnancy Category D [*see Warnings and Precautions*]

Based on its mechanism of action and findings from animal studies, Marqibo can cause fetal harm when administered to pregnant women.

If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus. In an embryofetal developmental study, pregnant rats were administered vincristine sulfate liposome injection intravenously during the period of organogenesis at vincristine sulfate doses of 0.022 to 0.09 mg/kg/day. Drug-related adverse effects included fetal malformations (skeletal and visceral), decreases in fetal weights, increased numbers of early resorptions and post-implantation losses, and decreased maternal body weights. Malformations were observed at doses ≥0.044 mg/kg/day in animals at systemic exposures approximately 20-40% of those reported in patients at the recommended dose.

Nursing Mothers

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants, a decision should be made whether to discontinue nursing or discontinue the drug taking into account the importance of the drug to the mother.

Pediatric Use

The safety and effectiveness of Marqibo in pediatric patients have not been established.

Geriatric Use

Safety and effectiveness in elderly individuals have not been established. In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

Renal Impairment

The influence of renal impairment on the safety, efficacy, and pharmacokinetics of Marqibo has not been evaluated.

Hepatic Impairment

Non-liposomal vincristine sulfate is excreted primarily by the liver. The influence of severe hepatic impairment on the safety and efficacy of Marqibo has not been evaluated.

The pharmacokinetics of Marqibo was evaluated in patients with moderate hepatic dysfunction (Child-Pugh B) secondary to melanoma liver metastases. The dose-adjusted maximum plasma concentration (C_{max}) and area under the concentration-time curve (AUC) of Marqibo in patients with moderate hepatic impairment was comparable to the C_{max} and AUC of patients with ALL who had otherwise normal hepatic function.

OVERDOSAGE

When Marqibo (vinCRIStine sulfate LIPOSOME injection) was administered at a dose of 2.4 mg/m^2, severe toxicities including motor neuropathy of Grade 3, grand mal seizure of Grade 4, and elevated aspartate aminotransferase and hyperbilirubinemia of Grade 4 were reported in 1 patient each. There is no known antidote for overdosage.

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility

No carcinogenicity studies have been conducted with Marqibo or non-liposomal vincristine sulfate. Based on the mechanism of action and genotoxicity findings in nonclinical studies conducted with non-liposomal vincristine sulfate, Marqibo may be carcinogenic.

No genotoxicity studies have been conducted with Marqibo. Non-liposomal vincristine was genotoxic in some *in vitro* and *in vivo* studies.

The single- and repeat-dose animal toxicology study results indicate that Marqibo can impair male fertility, consistent with the literature on non-liposomal vincristine sulfate. Administration of vincristine liposome injection causes testicular degeneration and atrophy, and epididymal aspermia in rats.

Gonadal dysfunction has been reported in both male and female post-pubertal patients who received multi-agent chemotherapy including non-liposomal vincristine sulfate.

The degree to which testicular or ovarian functions are affected is age-, dose-, and agent-dependent. Recovery may occur in some but not all patients.

Animal Toxicology and/or Pharmacology

In a repeat-dose comparative toxicology study in rats, vincristine sulfate liposome injection or non-liposomal vincristine sulfate was administered to animals intravenously once per week for 6 weeks. Clinical signs of toxicity consistent with neurotoxicity were greater with vincristine sulfate liposome injection than with non-liposomal vincristine sulfate at equal vincristine sulfate doses of 2 mg/m^2/week and included uncoordinated movements, weakness, reduced muscle tone, and limited usage of the limbs. Neurological testing indicated drug-induced peripheral neurotoxicity with both drugs. Based on the histopathology examination after 6 weekly doses, vincristine sulfate liposome injection induced greater peripheral neurotoxicity (nerve fiber degeneration) and secondary skeletal muscle atrophy than the equal dose of non-liposomal vincristine sulfate. In a separate tissue distribution study in rats, administration of 2 mg/m^2 of intravenous liposomal or non-liposomal vincristine sulfate showed greater accumulation of vincristine sulfate in sciatic and tibial nerves (as well as the lymph nodes, spleen, and bone marrow) of the animals following vincristine sulfate liposome injection.

PATIENT COUNSELING INFORMATION

Physicians are advised to discuss the following with patients prior to treatment with Marqibo:

Extravasation Tissue Injury: Advise patients to report immediately any burning or local irritation during or after the infusion [*see Warnings and Precautions*].

Ability to Drive or Operate Machinery or Impairment of Mental Ability: Marqibo may cause fatigue and symptoms of peripheral neuropathy. Advise patients not to drive or operate machinery if they experience any of these symptoms [*see Warnings and Precautions*].

Gastrointestinal/Constipation: Patients receiving Marqibo may experience constipation. Advise patients how to avoid constipation by a diet high in bulk fiber, fruits and vegetables, and adequate fluid intake as well as use of a stool softener, such as docusate. Instruct patients to seek medical advice if they experience symptoms of constipation such bowel movement infrequency, abdominal pain, bloating, diarrhea, nausea, or vomiting [*see Warnings and Precautions*].

Pregnancy/Nursing: Advise patients to use effective contraceptive measures to prevent pregnancy during treatment with Marqibo [*see Warnings and Precautions*]. Instruct patients to report pregnancy to their physicians immediately. Advise patients that they should not receive Marqibo while pregnant or breastfeeding. If a patient wishes to re-start breastfeeding after treatment, she should be advised to discuss the appropriate timing with her physician [*see Use in Specific Populations*].

Concomitant Medications: Advise patients to speak with their physicians about any other medication they are currently taking [*see Drug Interactions*].

Peripheral Neuropathy: Advise patients to contact their physicians if they experience new or worsening symptoms of peripheral neuropathy such as tingling, numbness, pain, a burning feeling in the feet or hands, or weakness in the feet or hands [*see Warnings and Precautions*].

Other: Instruct patients to notify their physicians if they experience fever, productive cough, or decreased appetite [*see Warnings and Precautions*].

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Distributed by:

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0125-080401

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Highlights in Acute Lymphoblastic Leukemia From the 2013 American Society of Hematology Annual Meeting and Exposition

3903 Frontline-Treatment of Acute Lymphoblastic Leukemia (ALL) in Older Adolescents and Young Adults (AYA) Using a Pediatric Regimen Is Feasible: Toxicity Results of the Prospective US Intergroup Trial C10403 (Alliance)[1]

Advani AS, Sanford B, Luger S, Devidas M, Larsen EC, Liedtke M, Voorhees PM, Foster MC, Claxton DF, Geyer S, Parker E, Coffan K, Carroll WL, Winick NJ, Coutre SE, Tallman MS, Appelbaum FR, Erba H, Stone RM, Hunger SP, Larson RA, Stock W

Adolescents and young adults with acute lymphoblastic leukemia (ALL) may achieve superior outcomes when treated with modified pediatric therapeutic regimens.[2] The single-arm C10403 trial is the largest prospective study to evaluate the feasibility of using a pediatric regimen in ALL patients ages 16 to 39 years under the care of hematologists/oncologists who treat adults.[3] To aid modification of the regimen for this patient group, toxicities of grade 3 to 5 that could limit treatment were identified by age cohorts and compared with data from the Children's Oncology Group (COG) AALL0232/COG0232 trial, which enrolled patients ages 1 year to 30 years undergoing the same treatment.[1,4] All patients received treatment with prednisone plus escalating doses of methotrexate as described for the interim maintenance arm from the COG0232 trial. Among the 318 patients in C10403, 61% were male. During induction, the rates of grade 3/4 hyperglycemia, hyperbilirubinemia, pancreatitis, thrombosis, and febrile neutropenia in trial C10403 were higher than for the comparison group treated in COG0232 (Table 1). Induction mortality rates for both trials were 2%. During interim maintenance, 5.6% of patients in C10403 developed grade 3/4 mucositis. A C10403 protocol amendment to require premedication led to a decline in grade 3/4 hypersensitivity reactions to polyethylene glycol (PEG) asparaginase of 12.9% to 7.9%. Analysis of grade 3 to 5 adverse events (AEs) by age cohort among C10403 patients revealed significant differences in the incidences of neuropathy, osteonecrosis, and mucositis in patients ages 20 years or older. The comparison group from COG0232 had higher rates of hypersensitivity (without premedication) and motor neuropathy and lower rates of thrombosis than the C10403 patients. Hepatotoxicity, pancreatitis, and osteonecrosis occurred at similar rates between the 2 studies. The overall treatment-related mortality rate in C10403 was 3%.

Table 1. Grade 3-5 Adverse Events During Induction Treatment in Older Patients (C10403) and Younger Patients (COG0232) With ALL

	C10403[3] (%)	COG0232[4] (%)
Hyperglycemia	29.3	22.0
Hyperbilirubinemia	15.9	6.7
Allergic reaction	0.7	0.8
Pancreatitis	1.1	0.5
Thrombosis	2.9	1.5
Febrile neutropenia (induction)	19.2	7.0

ALL, acute lymphoblastic leukemia.

Data from Advani AS et al. ASH abstract 3903. *Blood*. 2013;122(21).[1]

69 Safe and Effective Re-Induction of Complete Remissions in Adults With Relapsed B-ALL Using 19-28z CAR CD19-Targeted T Cell Therapy[5]

Davila ML, Riviere I, Wang X, Bartido S, Stefanski J, He Q, Borquez-Ojeda O, Taylor C, Wasielewska T, Qu J, Bouhassira D, Bernal YJ, Yoo S, Purdon T, Halton E, Quintanilla H, Park JH, Curran KJ, Sadelain M, Brentjens RJ

The need to improve treatment options for patients with relapsed B-cell ALL has led to the development of a novel T-cell–based therapy. T cells are isolated from patients with relapsed or refractory B-cell ALL and are genetically modified with a chimeric antigen receptor (CAR) construct, 19-28z, which consists of a CD19-binding domain fused to the signaling domains of the CD28 costimulatory receptor and the ζ-chain of the CD3 complex. Expression of this CAR construct by T cells enables them to bind to the CD19 antigen on B cells, resulting in cytotoxicity, cytokine release, and proliferation. To test the efficacy and safety of the construct, a phase 1 clinical trial of 13 adults with relapsed or refractory B-cell ALL was initiated.[5] Enrolled patients were treated with leukapheresis followed by salvage induction chemotherapy and infusion of 3×10^6 19-28z CAR T cells/kg. The patients' median age was 42 years (range, 23-74 years), and 3 patients had Philadelphia-positive disease, signifying high risk. The required T-cell dose was achieved in all but 1 patient. At the time of the 19-28z CAR T-cell infusion, 7 patients had gross residual disease, and 6 patients had minimal residual disease (MRD). Toxicities developed in 6 patients and included high-grade fevers (>40ºC), hypotension, hypoxia, mental status changes, and seizures; however, all AEs were completely reversible. Toxicities were observed in patients with gross residual disease, defined as more than 5% blasts in the bone marrow, whereas patients with MRD had no evidence of toxicities. Ten patients with detectable disease prior to T-cell infusion were MRD-negative after treatment, including the 3 patients with Philadelphia-positive disease and 5 patients with gross residual disease at baseline. Patients showed rapid responses to treatment, with MRD-negative results obtained as early as 7 to 14 days after the CAR T-cell infusion.

70 A Phase 1/2 Study of Blinatumomab in Pediatric Patients With Relapsed/Refractory B-Cell Precursor Acute Lymphoblastic Leukemia[6]

von Stackelberg A, Zugmaier G, Handgretinger R, Locatelli F, Rizzari C, Trippett TM, Borkhardt A, Rheingold SR, Bader P, Bhojwani D, Cooper TM, DuBois SG, O'Brien MM, Zwaan CM, Holland C, Mergen N, Fischer A, Zhu M, Hijazi Y, Whitlock J, Gore L

Blinatumomab, a bispecific T-cell engager antibody, induced long-term remissions in a phase 2 study of adult patients with relapsed acute B-lineage ALL.[7] A multicenter phase 1/2 study was conducted in pediatric patients with relapsed or refractory precursor B-cell ALL; the optimal dose was assessed in the phase 1 portion.[6] The study included 23 patients younger than 18 years who received up to 5 cycles of blinatumomab administered by continuous intravenous infusion throughout 28 days, followed by 14 days without treatment. The study used a rolling 6 design and originally included 4 dose levels ranging from 5 μg/m²/day to 30 μg/m²/day. The maximum tolerated dose, defined as the highest dose level at which no more than 1 patient experienced a dose-limiting toxicity within the first treatment cycle, was established at 15 μg/m²/day. Cytokine-release syndrome was observed in 7 patients (30%); in 2 of the 5 patients treated at a dosage of 30 μg/m²/day, the syndrome was grade 4 or 5. In order to reduce the risk of cytokine-release syndrome, an escalating dose of 5 μg/m²/day for 7 days followed by 15 μg/m²/day for the remainder of the first cycle and all subsequent cycles was evaluated as the recommended dose. Among the 11 patients treated with the escalating dose, there were no reports of cytokine-release syndrome or grade 3 AEs related to the central nervous system. Across all dose levels, the most common AEs of any grade, regardless of causality, were pyrexia (62%), headache (35%), anemia (29%), and hypertension (29%). Across all dose levels, the overall response rate was 41%; 11 patients (32%) had a complete response (CR), 1 patient (3%) had hypocellular blast-free bone marrow, and 2 patients (6%) had a partial response within the first 2 treatment cycles. Two patients experienced hematologic relapse: 1 at 15 μg/m²/day and the other at 30 μg/m²/day. Pharmacokinetic analysis at the recommended escalating dose of 5 μg/m²/day to 15 μg/m²/day is ongoing.

839 Significant Improvement of Outcome in Adolescents and Young Adults (AYAs) Aged 15-35 Years With Acute Lymphoblastic Leukemia (ALL) With a Pediatric Derived Adult ALL Protocol; Results of 1529 AYAs in 2 Consecutive Trials of the German Multicenter Study Group for Adult ALL (GMALL)[8]

Gökbuget NM, Beck J, Brandt K, Brüggemann M, Burmeister T, Diedrich H, Faul C, Hüttmann A, Kondakci M, Kraemer DM, Ottmann OG, Schwartz S, Serve H, Starck M, Stelljes M, Stuhlmann R, Viardot A, Waesch RM, Wendelin K, Beelen D, Arnold R, Hoelzer D

Studies from the German Multicenter Study Group for Adult ALL are investigating the use of modified pediatric regimens in adults. Dr Nicola M. Gökbuget and colleagues examined outcomes in adolescents and young adults from 2 clinical trials, 05/93 and 07/03.[8-10] The treatment regimen in study 07/03 incorporated the following changes: intensified and shortened induction with dexamethasone instead of pred-

Table 2. Outcome in GMALL Studies 05/93 and 07/03 in ALL

	GMALL Study 05/93[9]				GMALL Study 07/03[10]			
	Total	15-17 Years	18-25 Years	26-35 Years	Total	15-17 Years	18-25 Years	26-35 Years
Evaluable	642	106	252	384	887	53	458	376
Complete response	88%	91%	88%	86%	91%	94%	91%	90%
Early death	3%	1%	3%	3%	4%	0%	3%	6%
Failure	9%	8%	8%	11%	5%	6%	5%	4%
Remission duration at 5 years	49%	52%	50%	46%	61%	60%	62%	59%
Overall survival at 5 years	46%	57%	45%	42%	65%	73%	69%	60%

ALL, acute lymphoblastic leukemia; GMALL, German Multicenter Study Group for Adult AA.

Data from Gökbuget NM et al. ASH abstract 839. *Blood*. 2013;122(21).[8]

nisone, use of PEG-asparaginase in place of native asparaginase, intensified first consolidation, 6 courses of high-dose methotrexate/asparaginase during consolidation, matched unrelated stem cell transplantation (SCT) for patients at high risk or very high risk who lacked a sibling donor, and SCT indication in patients with persistent MRD. The protocol was amended to allow some patients to receive intensified PEG-asparaginase, rituximab in CD20-positive ALL, and imatinib in Philadelphia-positive ALL. Patients at high risk or very high risk were candidates for SCT during their first CR. Among the 3060 patients recruited into both trials, 1529 were ages 15 to 35 years. Reported outcomes, such as CR rate, overall survival (OS), and remission duration at 5 years, were better in study 07/03 than study 05/93. The CR rate increased from 88% in study 05/93 to 91% in study 07/03 (P=.001), with the greatest increase seen in patients ages 26 to 35 years (86% vs 90%; P=.001; Table 2). OS increased from 46% to 65% (P<.0001) and was significant in all age groups. Remission duration at 5 years increased from 49% to 61% (P=.0001), most prominently in patients ages 26 to 35 years, who experienced an increase of 46% to 59% (P=.005). OS improved in patients with B-cell lineage (45% to 66%; P<.0001) and T-cell lineage ALL (47% to 63%; P=.0007), as well as in patients at standard risk (58% to 74%; P<.0001), high risk (24% to 58%; P<.0001), and very high risk (36% to 55%; P=.0003). The percentage of patients undergoing SCT increased from 15% in study 05/93 to 43% in study 07/03. The proportion of SCT increased from 22% to 68% (P<.0001) in high-risk patients and from 62% to 73% (P<.0001) in patients at very high risk. Concomitantly, OS after SCT improved from 36% to 68% (P<.0001). In the 274 patients ages 15 to 35 years treated according to the final amended protocol, OS was 71%.

55 Nilotinib Combined With Multi-Agent Chemotherapy for Adult Patients With Newly Diagnosed Philadelphia Chromosome-Positive Acute Lymphoblastic Leukemia: Final Results of Prospective Multicenter Phase 2 Study[11]

Kim D-Y, Joo YD, Kim S-D, Lee J-H, Lee J-H, Kim D-H, Kim K, Jung CW, Kim I, Yoon S-S, Park S, Ahn J-S, Yang D-H, Lee J-J, Kim YS, Mun Y-C, Kim H, Moon JH, Sohn SK, Lee WS, Won J-H, Hyun MS, Park J, Lee JH, Shin H-J, Eom HS, Lee GW, Lim S-N, Kim YJ, Cho Y-U, Chi H-S, Lee K-H

Dr Dae-Young Kim and colleagues presented final results of a multicenter, prospective phase 2 trial of nilotinib plus combination chemotherapy as frontline treatment for adults with ALL.[11] All patients received induction treatment consisting of vincristine, daunorubicin, prednisolone, and nilotinib. Patients who demonstrated a CR received 5 courses of consolidation therapy followed by 2 years of maintenance therapy with nilotinib, or they underwent allogeneic hematopoietic SCT. Selection of treatment was based on donor availability, patient tolerability, and patient preference. Nilotinib (400 mg twice daily) was administered from day 8 of induction until the initiation of conditioning for allogeneic SCT or the end of maintenance therapy. Monitoring for MRD was performed at a central laboratory at the time of diagnosis, at hematologic CR, and every 3 months thereafter. CR was defined as a BCR-ABL/glucose-6-phosphate dehydrogenase mRNA ratio of less than 1×10^{-6}. The study enrolled 91 subjects (45 male); their median age was 47 years (range, 18-71 years). The median BCR-ABL/glucose-6-phosphate dehydrogenase ratios were 6.09 for bone marrow and 3.28 for peripheral blood at diagnosis. Nonhematologic AEs of grade 4 or higher included elevated alanine aminotransferase (18%), jaundice (17%), lipase elevation (13%), and pancreatitis (2%). The rate of hematologic CR was 90%, with a median time to hematologic CR of 27 days (range, 13-72 days). Eight patients died of aplasia during induction. The molecular CR rate was 55% at hematologic CR. The cumulative molecular CR rate was 84%, with a median time to molecular CR of 1.1 months (range, 0.6-15.8 months). Study withdrawal was most often caused by treatment-related death that occurred during induction/consolidation (n=12) or after allogeneic SCT (n=10). At a median follow-up of 20.7 months for surviving subjects, the

estimated 2-year hematologic relapse-free survival and OS were 74% and 70%, respectively.

1432 Inotuzumab Ozogamicin in Combination With Low-Intensity Chemotherapy (Mini-Hyper-CVD) as Frontline Therapy for Older Patients (≥60 years) With Acute Lymphoblastic Leukemia (ALL)[12]

Jain N, O'Brien S, Thomas DA, Jabbour E, Faderl S, Ravandi F, Borthakur G, York S, Garris R, Cortes JE, Kantarjian HM

Inotuzumab ozogamicin is a CD22 monoclonal antibody bound to calicheamicin, a DNA-targeting agent. It has shown single-agent activity in relapsed or refractory ALL.[13] Because elderly patients show a reduced tolerance to intensive chemotherapy, a clinical trial was conducted to assess the safety and efficacy of the immunoconjugate combined with reduced intensity chemotherapy in this population.[12] The trial enrolled patients ages 60 years or older with newly diagnosed B-cell ALL. Standard hyper-CVAD (Course 1: cyclophosphamide [300 mg/m^2 on days 1-3], vincristine [2 mg on days 4 and 11], doxorubicin [50 mg/m^2 on day 4], dexamethasone [40 mg on days 1-4 and 11-14], cytarabine [70 mg on day 7], mesna [given with cyclophosphamide], and methotrexate [given with chemotherapy]; Course 2: methotrexate [1000 mg/m^2 on day 1], leucovorin [25 mg/m^2 24 hours after methotrexate], sodium bicarbonate [600 mg 3 times daily 1 day before and 3 days after methotrexate], and cytarabine [3000 mg/m^2 every 12 hours for 4 doses on days 2 and 3) was modified to deliver a reduced intensity chemotherapy regimen consisting of cyclophosphamide and dexamethasone at 50% dose reductions, methotrexate at a 75% dose reduction, no anthracycline, and 4 doses of cytarabine at 0.5 g/m^2. Rituximab (375 mg/m^2 on days 1 and 11) and intrathecal chemotherapy were given during the first 4 courses. The first 6 patients received inotuzumab ozogamicin on day 3 of each of the first 4 courses dosed at 1.3 mg/m^2 during cycle 1 followed by 0.8 mg/m^2 for all other cycles. All subsequent patients received the immunoconjugate at 1.8 mg/m^2 for cycle 1 followed by 1.3 mg/m^2 for the remaining cycles. The 15 treated patients (10 male) had a median age of 69 years (range, 60-79 years). After a median follow-up of 10.8 months, grade 3/4 nonhematologic toxicity was observed in 2 patients with grade 3 liver function test elevation. Eleven patients experienced at least 1 infection, and 6 patients developed thrombocytopenia necessitating an early switch to maintenance therapy. No dose-limiting toxicities were observed. Among the 14 patients evaluable for response, 13 patients (93%) achieved a CR (12 patients) or a CR with incomplete blood count recovery (CRi; 1 patient). All patients who achieved a CR also achieved MRD-negative status by flow cytometry, and all but 1 were continuing on study treatment. One-year disease-free survival and OS were 83% and 93%, respectively.

650 Ponatinib in Patients (pts) With Chronic Myeloid Leukemia (CML) and Philadelphia Chromosome-Positive Acute Lymphoblastic Leukemia (Ph+ ALL) Resistant or Intolerant to Dasatinib or Nilotinib or With the T315I BCR-ABL Mutation: 2-Year Follow-Up of the PACE Trial[14]

Cortes JE, Kim D-W, Pinilla-Ibarz J, Coutre PD, Paquette R, Chuah C, Nicolini FE, Apperley JF, Khoury HJ, Talpaz M, DiPersio JF, DeAngelo DJ, Abruzzese E, Rea D, Baccarani M, Müller MC, Gambacorti-Passerini C, Lustgarten S, Rivera VM, Clackson T, Turner CD, Haluska FG, Guilhot F, Deininger MW, Hochhaus A, Hughes TP, Goldman JM, Shah NP

Ponatinib is a potent, oral tyrosine kinase inhibitor (TKI) with activity against wild-type and mutant forms of BCR-ABL, including the TKI-resistant T315I mutant. The efficacy and safety of ponatinib were evaluated in the international, open-label, phase 2 PACE (Ponatinib Ph ALL and CML Evaluation) trial in patients with drug-resistant or drug-intolerant chronic myelogenous leukemia (CML) or Philadelphia-positive ALL.[15] The 449 enrolled patients had drug resistance, unacceptable side effects to dasatinib or nilotinib, or the T315I mutation. Patients received ponatinib at a dosage of 45 mg/day. The median age was 59 years (range, 18-94 years), and 53% of the patients were male. The patients were heavily pretreated; 58% had received at least 3 prior TKIs. No BCR-ABL mutations were detected at baseline in 44% of patients. After 2 years of follow-up, among the 267 patients with chronic-phase CML, 156 (58%) had a major cytogenetic response, 138 (52%) had a complete cytogenetic response, and 95 (36%) had a major molecular response.[14] All of the response rates were greater by 13% to 17% in patients with the T315I mutation compared with the patients who were drug-resistant or drug-intolerant. Responses were durable and were observed in patients with any of the baseline BCR-ABL kinase mutations. Overall responses for patient subsets based on disease are presented

Table 3. Responses at 2 Years in the PACE Trial

Disease	Type of Response, n (%)		
	Major Hematologic Response	Major Cytogenetic Response	Complete Cytogenetic Response
AP-CML (n=83)	51 (61)	32 (39)	20 (24)
BP-CML (n=62)	19 (31)	14 (23)	11 (18)
Philadelphia-positive ALL (n=32)	13 (41)	15 (47)	12 (38)

ALL, acute lymphoblastic leukemia; AP-CML, acute-phase chronic myelogenous leukemia; BP-CML, blast-phase chronic myelogenous leukemia; PACE, Ponatinib Ph ALL and CML Evaluation.

Data from Cortes JE et al. ASH abstract 650. *Blood*. 2013;122(21).[14]

in Table 3. Progression-free survival (PFS) at 27 months was estimated to be 80%, and OS at 12 months was estimated to be 94%. The most common treatment-related AEs of any grade included thrombocytopenias (37%), rash (34%), and dry skin (32%). Serious arterial thrombotic events considered related to treatment were observed in 3% of patients, and 12% of patients discontinued treatment owing to an AE.

2664 Phase II Study of the Hyper-CVAD Regimen in Combination With Ofatumumab as Frontline Therapy for Adults With CD-20 Positive Acute Lymphoblastic Leukemia (ALL)[16]

Jabbour E, Kantarjian H, Thomas D, Garcia-Manero G, Hoehn D, Garris R, Faderl SH, Cortes JE, Kadia TM, Ravandi F, Verstovsek S, O'Brien S

The addition of rituximab to hyper-CVAD has been shown to improve outcomes in patients with CD20-positive ALL. Ofatumumab targets a different epitope on the CD20 molecule, and in vitro data suggest that ofatumumab may possess greater cytotoxic capability than rituximab. Based on these findings, patients with newly diagnosed ALL and those who had received 1 prior course of chemotherapy were enrolled in a phase 2 clinical trial evaluating ofatumumab plus hyper-CVAD.[16] Patients received 4 cycles of hyper-CVAD (on courses 1, 3, 5, 7), with ofatumumab given on courses 1 and 3, alternating with 4 courses of methotrexate/cytarabine (on courses 2, 4, 6, 8), with ofatumumab given on courses 2 and 4. Maintenance treatment consisted of 6-mercaptopurine, methotrexate, vincristine, and prednisone for approximately 30 months, plus intervention with the induction treatment at weeks 6, 7, 18, and 19. Seventeen patients with newly diagnosed ALL and 2 patients in CR received a median of 5 cycles of therapy (range, 1-8 cycles). Median age was 50 years (range, 39-71 years). CD20 expression levels greater than 20% were detected in 11 patients (58%). Eighteen patients achieved a CR after 1 cycle of treatment. One patient died of septic shock and multiple organ failure on day 21 of cycle 1. The remaining 18 patients achieved MRD negativity based on flow cytometry, including 12 (67%) who achieved MRD negativity after induction. Toxicities of grade 3 or higher included elevated results on liver function tests (37%), increased bilirubin (26%), thrombotic events (5%), and neuropathy (5%). Febrile neutropenia occurred in 76% of patients during induction and 65% of patients during consolidation. At a median follow-up of 8 months (range, 1-23 months), 18 patients were alive and in CR, including 1 patient who underwent allogeneic SCT after cycle 3. The 1-year CR duration and OS rates were 100% and 95%, respectively.

3916 A Phase I/II Study of Hyper-CVAD Plus Everolimus in Patients With Relapsed/Refractory Acute Lymphoblastic Leukemia[17]

Daver N, Kantarjian HM, Thomas DA, Rytting ME, Ravandi F, Jain N, Cortes JE, Garris R, Richie MA, Konopleva M, Hu H, Kawedia J, Culotta K, O'Brien S, Basnett J, Xiao L, Haung X, Bendall LJ

Everolimus is an oral mammalian target of rapamycin (mTOR) inhibitor approved for the treatment of breast cancer, renal cell carcinoma, and other malignancies. A phase 1/2 study was conducted to determine the safety and efficacy of everolimus plus hyper-CVAD in patients with relapsed or refractory ALL and lymphoblastic lymphoma.[17] Patients were ages 10 years and older. They received everolimus (5 mg/day or 10 mg/day continuously) concurrently with 8 cycles of standard hyper-CVAD. After 2 cycles, the maximum tolerated dose of everolimus was established as 5 mg/day. Of the 20 patients enrolled at the time of the presentation, 9 (45%) were in first salvage, 2 (10%) were in second salvage, and 9 (45%) were in third or later salvage. Patients received a median 2 treatment cycles (range, 1-5 cycles), and median follow-up was 19 months (range, 1-35 months). The overall response rate was 35% and included 6 patients (30%) in CR (all of whom were in first salvage), 1 patient (5%) in CRi, and 2 patients (10%) with a partial response. Four patients in CR proceeded to SCT. Among patients in first salvage, the median event-free survival (EFS) was 6 months, and the median OS was 7 months. For patients in second salvage or later, median EFS and median OS were 2 months and 4 months, respectively. One-year OS was 47% for patients in first salvage and 9% for patients in second salvage and beyond. The dose-limiting toxicity was grade 3 mucositis; other grade 3/4 toxicities included infections (90%), transaminitis (30%), diarrhea (10%), headache (10%), and increased bilirubin (10%). Analysis by reverse-phase protein arrays showed inhibition of mTOR signaling in 7 tested patients (70%), and inhibition of protein S6 was observed with both the 5-mg and 10-mg doses. Gene set enrichment analysis showed enrichment of the *ABC* transporter gene set in patients who failed to respond. Patients who achieved a CR showed a significantly higher area under the curve and lower clearance of everolimus at steady state compared with patients who had a partial response or no response.

3914 Final Report of Single-Center Study of Chemotherapy Plus Dasatinib for the Initial Treatment of Patients With Philadelphia-Chromosome Positive Acute Lymphoblastic Leukemia[18]

Ravandi F, O'Brien S, Garris R, Faderl SH, Thomas DA, Burger JA, Ferrajoli A, Jabbour E, Cortes JE, Kantarjian HM

Dasatinib has shown significant clinical activity in patients with imatinib-resistant lymphoid blast-phase CML and Philadelphia-positive ALL. Dasatinib plus hyper-CVAD was investigated in a phase 2 trial to assess the long-term

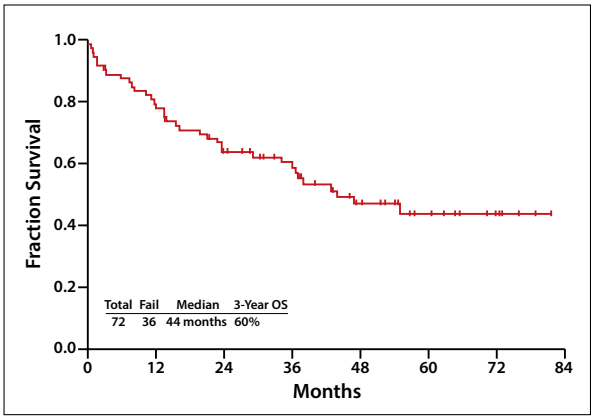

Figure 1. Overall survival in a single-center study of chemotherapy plus dasatinib for the initial treatment of patients with Philadelphia-chromosome positive acute lymphoblastic leukemia. OS, overall survival.

Adapted from Ravandi F et al. ASH abstract 3914. *Blood*. 2013;122(21).[18]

efficacy of the combination when used as induction plus consolidation.[18] Patients with newly diagnosed Philadelphia-positive ALL received 8 cycles of hyper-CVAD alternating with high-dose cytarabine and methotrexate, plus dasatinib for the first 14 days of each cycle. The initial 42 patients received 50 mg of dasatinib twice daily. The protocol was then amended to give 100 mg/day of dasatinib during the first 14 days of cycle 1, followed by 70 mg/day of dasatinib continuously for subsequent cycles. Patients in CR continued to receive maintenance dasatinib at either 50 mg twice daily or 100 mg once daily indefinitely, as well as vincristine and prednisone monthly for 2 years. The trial enrolled 63 treatment-naive patients and 9 patients who had received up to 2 prior cycles of chemotherapy. Patients had a median age of 55 years (range, 21-80 years) and received a median 6 cycles (range, 1-8 cycles) of induction/consolidation therapy. Sixty-nine patients (96%) achieved CR after the first treatment cycle or were in CR at the trial's start. Three patients died of infections before response assessment. Of the 69 evaluable patients, 57 (83%) achieved a cytogenetic CR after 1 cycle, and 5 had a major cytogenetic response. Forty-five patients (65%) achieved complete molecular remission and another 19 (28%) achieved a major molecular response at a median of 4 weeks (range, 2-38 weeks) from initiation of treatment. MRD-negative status by flow cytometry was observed in 65 patients (94%) at a median of 3 weeks (range, 2-37 weeks). Grade 3/4 AEs included bleeding, pleural and pericardial effusions, deep vein thromboses, and pulmonary emboli. After a median follow-up of 48 months in surviving patients, 36 patients (50%) were alive, and 31 patients (43%) were in CR. Twelve patients underwent allogeneic SCT, and 36 patients died. Median disease-free survival was 31 months (range, 0.3-81 months), and median OS was 44 months (range, 0.2-82 months; Figure 1).

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New Developments in Acute Lymphoblastic Leukemia

Abstract Acute lymphoblastic leukemia (ALL) occurs in both children and adults. Significant improvements in survival outcomes have been realized over the last decade for all age groups with de novo ALL. Frontline treatment incorporates a tailored approach, based on factors such as the patient's age and the disease subtype. Children, adolescents, and young adults are likely to receive intensifying or deintensifying chemotherapy regimens using standard chemotherapeutics (eg, anthracyclines, vincristine, asparaginase) based on risk stratification. Older adults appear to benefit from reduced-intensity chemotherapy regimens, which incorporate targeted therapy (eg, monoclonal antibodies). New data suggest that a more intensive pediatric protocol might be feasible in adult patients. More than half of ALL patients relapse, and their limited survival has led to the development of novel approaches. Recently approved chemotherapeutic agents include clofarabine, nelarabine, asparaginase *Erwinia chrysanthemi*, and vincristine sulfate liposome injection, a novel formulation that permits administration of a higher dosage of vincristine than that used in standard regimens. Approaches under investigation include cell therapy using autologous T-cell technologies, antibody-drug conjugates, and agents targeting common gene mutations. Many novel agents are undergoing evaluation in both the frontline and relapsed settings.

Current Treatment Approaches in Acute Lymphoblastic Leukemia

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Acute lymphoblastic leukemia (ALL) occurs in both children and adults, but the peak incidence is seen between the ages of 2 to 5 years.[1] An estimated 6000 new cases (with a male:female prevalence of roughly 1.3:1) are diagnosed yearly in the United States.[2] Approximately 60% of the cases occur in patients younger than 20 years. Although survival rates for childhood ALL exceed 90%, they are significantly inferior in infants (who generally have mixed leukemia lineage [MLL] leukemias) and adults (who are more likely to have the Philadelphia [Ph] chromosome).

ALL likely arises from interactions between exogenous or endogenous exposures, genetic susceptibility, and other variables.[3] The association between ALL and exposure to exogenous or endogenous factors, such as electromagnetic fields, has not been widely supported owing to lack of reproducibility and definitive data. Ionizing radiation, although no longer a relevant concern, has been associated with development of childhood ALL after in utero exposure. An association between ALL and infection, particularly when virally mediated, has been supported by epidemiologic data, and infection appears to be an indirect inducer of leukemia via an abnormal or dysregulated immune response in susceptible individuals.

Diagnosis

Morphologic identification of lymphoblasts by microscopy and immunophenotypic assessments of lineage and development stage by flow cytometry are paramount for the diagnosis of ALL. Despite advances in fluorescent in situ hybridization (FISH) and the reverse transcriptase polymerase chain reaction (PCR) techniques used to detect relevant gene rearrangements, chromosomal analysis remains important in the diagnostic work-up. Additional advances in genome-wide analysis may allow this technique to replace several of the other assays. Table 1 lists a few of the relevant diagnostic assessments generally considered to have both prognostic and therapeutic implications.

Prognosis

Infants with constitutive trisomy 21 or Down syndrome have a substantially increased risk of developing ALL

Table 1. Prognostic Factors in Acute Lymphoblastic Leukemia

Test	Findings	Prognosis (Risk)	Potential Therapy
Immunophenotyping	Early T-cell precursor immunophenotype	High	AML-directed therapy, JAK inhibitor
	CRLF2 overexpression	High	JAK inhibitor
Cytogenetics/ reverse transcriptase polymerase chain reaction	Hyperdiploidy	Standard	
	t(12;21)(p13;q22)/*ETV6-RUNX1* (*TEL-AML1*)	Standard	
	Hypodiploidy (<44 chromosomes)	High	
	t(9;22)(q34;q11)/*BCR-ABL1*	High	ABL1 kinase inhibitor
	11q23/*MLL* gene rearrangement	High	Epigenetic therapy, histone deacetylase inhibitor, FLT-3 inhibitor
	iAMP21	High	
Molecular	*IKZF1* alterations	High	ABL1 kinase, PDGFRB, or JAK inhibitor
	CRLF2 rearrangement	High	JAK inhibitor
	JAK1 or *JAK2* mutation	High	JAK inhibitor
	BCR-ABL–like phenotype	High	ABL1 kinase, PDGFRB, or JAK inhibitor
	NUP214-ABL1	High	ABL1 kinase inhibitor
	BCR-JAK2	High	JAK inhibitor
	IL7R mutation	High	JAK inhibitor
	CREBBP mutation	High	Histone deacetylase inhibitor
	TP53 mutation	High	

Table 2. Pediatric-Inspired Chemotherapy Regimens for Adolescents and Adults With Acute Lymphoblastic Leukemia

Country	Regimen	Age Range (years) [Median P, A]	Patients (n)	CR (%)	EFS (%) (years)
Retrospective					
United States[30]	CCG (P)	16-20 [16, 19]	197	90	63 (7)
	CALGB (A)		124	90	34 (7)
France[31]	FRALLE93 (P)	15-20 [16, 18]	77	94	67 (5)
	LALA94 (A)		100	83	41 (5)
Italy[32]	AIEOP (P)	14-18 [15, 16]	150	94	80 (2)
	GIMEMA (A)		95	89	71 (2)
United Kingdom[33]	ALL97 (P)	15-17 [NR, NR]	61	98	65 (5)
	UKALLXII/E2993 (A)		67	94	49 (5)
United States[34]	Hyper-CVAD (A) (includes modified ± rituximab)	13-21 [19]	83	98	62 (4) 70 (4)*
Prospective					
United States[35,36]	DFCI 91-01, 9501	15-18	51	94	78 (5)
	DFCI	18-50	74	82	73 (2)
Spain[37]	PETHEMA ALL-96	15-18	35	94	60 (6)
		19-30	46	100	63 (6)
France[11]	GRAALL-2003	15-45	172	95	58 (3.5)
Canada[38]	Modified DFCI	18-60	85	89	63 (5)*
United States[39]	Augmented BFM	12-40	85	93	74 (3)*

A, adult; AIEOP, Associazione Italiana di Ematologia e Oncologia Pediatrica; ALL, acute lymphoblastic leukemia; BFM, Berlin-Frankfurt-Munster; CALGB, Cancer and Leukemia Group B; CCG, Children's Cancer Group; CR, complete remission; DCOG, Dutch Childhood Oncology Group; DFCI, Dana-Farber Cancer Institute; EFS, event-free survival; FRALLE, French Acute Lymphoblastic Leukaemia Group; GIMEMA, Gruppo Italiano Malattie e Matologiche dell'Adulto; GRAALL, Group for Research on Adult Acute Lymphoblastic Leukemia; LALA, Lymphoblastic Acute Leukemia in Adults; NOPHO, Nordic Society for Pediatric Hematology and Oncology; NR, not reported; P, pediatric; PETHEMA, Programa para el Estudio de la Terapéutica en Hemopatía Maligna. *Denotes overall survival. Adapted from Thomas DA. *Clin Adv Hematol Oncol*. 2010;8(3);168-171.[40]

(with a 40-fold increased risk between the ages of 0-4 years).[4] Genome-wide association studies of childhood ALL compare the whole genome via DNA analysis of blood during remission. They focus on the single nucleotide polymorphisms in DNA sequences that are associated with childhood ALL, such as *IKZF1*, *ARID5B*, *CEBPE*, and *CDKN2A-*, genes that help regulate blood cell development, proliferation, and differentiation. The extent and nature of inherited variant alleles could lead to as much as a 10-fold increased risk of developing ALL.

The association of gross chromosomal alterations with prognosis in B-lymphoblastic leukemia has been well established.[5,6] Examples include recurring translocations such as t(12;21)(p13;q22) encoding *ETV6-RUNX1*, t(1;19)(q23;p13) encoding *TCF3-PBX1,* t(9;22)(q34;q11) encoding *BCR-ABL1*; MLL rearrangements at 11q23 with a variety of partner genes; and high hyperdiploidy with nonrandom gain of at least 5 chromosomes (including X, 4, 6, 10, 14, 17, 18, and 21) or hypodiploidy with fewer than 44 chromosomes. *ETV6-RUNX1* and high hyperdiploidy have been associated with favorable prognosis, whereas MLL-rearranged ALL is associated with an extremely poor prognosis. T-lymphoblastic leukemia is often associated with dysregulation of the TAL1, TLX1, TXL3, and LYL1 loci and activating mutations in *NOTCH1*. Early T-cell precursor ALL is an aggressive high-risk subtype characterized by an immature immunophenotype with aberrant expression of myeloid and stem cell antigens and a distinct genetic expression profile mimicking acute myelogenous leukemia.

In both childhood and adult ALL, alterations in *IKZF1* (encodes IKAROS, required for lymphoid lineage development) are associated with significantly worse outcomes. High-risk subtypes such as *BCR-ABL1*–positive ALL or *BCR-ABL1*–like ALL frequently harbor *IKZF1* alterations. Other novel subtypes of childhood ALL include those that harbor rearrangements of *CRLF2*, which encodes the receptor for thymic stromal lymphopoietin. Approximately 50% of these cases also harbor activating mutations in *JAK1* or *JAK2*. In cases of non-Down's syndrome ALL, *CRLF2* and *JAK* alterations are associated with deleterious *IKZF1* alterations and poor prognosis. Approximately 50% of *BCR-ABL1*-like ALL cases harbor *CRLF2* rearrangements and *JAK* mutations.

Relapse often arises from the emergence of a minor subclone that often has genetic alterations distinct from the predominant clone present at diagnosis. An example is the acquisition of *TP53*, which is present in only a minority of cases at diagnosis.

Therapy

Frontline treatment for de novo ALL has evolved from a "one size fits all" approach to tailored approaches with chemotherapy regimens designed to be subtype-oriented. The significant improvement in survival outcomes observed in childhood ALL has been derived from intensifying or deintensifying chemotherapy regimens using standard chemotherapeutics (eg, anthracyclines, vincristine, and asparaginase) based on risk stratification. A similar approach has been applied to adolescents and young adults with respect to the use of pediatric-inspired chemotherapy regimens (Table 2). However, older adults appear to benefit from reduced intensity chemotherapy regimens that incorporate targeted therapy (eg, monoclonal antibodies).

Therefore, the traditional factors that influence the selection of frontline therapy are age, disease lineage, and karyotype. Age is particularly relevant with respect to prognosis and tolerance of chemotherapy. Disease features such as lineage help direct therapy; for example, nelarabine or NOTCH inhibitors are specifically used in the T-cell subtype. In B-cell lineage ALL, expression of surface molecules allows treatment with monoclonal antibodies directed against specific antigens (such as blinatumomab for CD19; rituximab or ofatumumab for CD20; and epratuzumab, inotuzumab, or moxetumomab for CD22). The therapeutic implications of the karyotype relate to recurrent translocations resulting in fusion genes, including *BCR-ABL,* which have led to the incorporation of ABL tyrosine kinase inhibitors (TKIs).

Therapy by Age

Childhood

The success of pediatric regimens has generally been achieved by risk stratification based on presenting disease features and response to induction chemotherapy, with intensification of anthracyclines, vincristine, corticosteroids, and asparaginase in patients with high-risk features.[5] Incorporation of TKIs such as imatinib or dasatinib has also improved outcomes for childhood Ph-positive ALL to the extent that allogeneic stem cell transplant (SCT) in first complete remission (CR) can be deferred in the setting of optimal response to therapy.[7,8] In contrast to the current frontline regimens used in adults, the use of monoclonal antibody therapy has not been extensively employed in regimens for de novo childhood ALL with the exception of rituximab for Burkitt leukemia/lymphoma.[9]

Adolescents and Young Adults

Treatment of adolescents and young adults (AYA; ages 15-39 years) with de novo ALL has been impacted significantly by several retrospective analyses that consistently show superior outcomes for the pediatric regimens compared with the adult ALL regimens (Table 2). These reports were further confirmed in a meta-analysis conducted by Ram and colleagues of 11 trials including 2489 patients.[10] AYA patients treated with pediatric-inspired regimens had a statistically significant lower all-cause mortality rate at 3 years (relative risk [RR], 0.58; 95% CI, 0.51-0.67).[10] The rates of CR after induction

Table 3. Frontline Treatment in Acute Lymphoblastic Leukemia

Feature	Age (years)	Regimen
T-lymphoblastic	<30 >30	Augmented BFM Modified hyper-CVAD + nelarabine
B-lymphoblastic, Ph-negative	<30 >30 ≥18 ≥60 ≥60	Augmented BFM Modified hyper-CVAD ± ofatumumab Hyper-CMAD ± rituximab Mini–hyper-CVD + inotuzumab ± rituximab Modified Larson (liposomal vincristine vs standard vincristine)
B-lymphoblastic, Ph-positive	All	Hyper-CVAD + ponatinib ± rituximab Hyper-CMAD ± dasatinib or imatinib ± rituximab
Burkitt leukemia/lymphoma (mature B-cell)	All	Hyper-CVAD + ofatumumab

BFM, Berlin-Frankfurt-Munster; CMAD, cyclophosphamide, liposomal vincristine, doxorubicin, dexamethasone; CVAD, cyclophosphamide, vincristine, doxorubicin, dexamethasone; CVD, cyclophosphamide, vincristine, dexamethasone; Ph, Philadelphia chromosome.

chemotherapy and event-free survival were superior with the pediatric-inspired regimens (RR, 1.05; 95% CI, 1.01-1.10 and RR, 1.66; 95% CI, 1.39-1.99, respectively). The relapse rate was also lower (RR, 0.51; 95% CI, 0.39-0.66), with comparable nonrelapse mortality between the 2 groups (RR, 0.53; 95% CI, 0.19-1.48). Improved outcomes with the pediatric regimens have been attributed in part to the higher dose intensity of the nonmyelosuppressive components of therapy, including vincristine, corticosteroids, and asparaginase.

Prospective clinical trials have demonstrated similar benefits of pediatric-inspired chemotherapy regimens, although the optimal age range that distinguishes the "younger" adult benefiting from this approach vs an "older" adult intolerant of intensive therapy appears to be 40 to 45 years. In older patients, higher treatment-related mortality negates the benefits of intensification.[11]

Adults

Older adults are typically treated with one of a variety of accepted standard induction-consolidation regimens followed by maintenance chemotherapy.[12] Long-term overall survival rates continue to range from 35% to 40%, with improvements in outcomes observed in subsets of patients treated with a combination of chemotherapy and targeted agent approaches, such as the addition of rituximab to hyper-CVAD (fractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone) or German multicenter ALL (GMALL) regimens for younger patients with Ph-negative ALL.[13,14]

Adults older than 50 years with de novo ALL have a higher incidence of harboring the Ph chromosome. Frontline chemotherapy regimens for patients with Ph-positive or *BCR-ABL*–positive ALL should include a TKI (imatinib, nilotinib, dasatinib, or ponatinib).[15] The addition of imatinib or dasatinib to hyper-CVAD has been shown to improve outcomes for Ph-positive ALL.[16-19]

There are limited data using nilotinib in the frontline setting.[20] Regimens incorporating ponatinib should be conducted under the auspices of a clinical trial.[21]

Newer lineage-specific frontline therapy approaches for adults include the incorporation of novel chemotherapeutics, such as nelarabine for T-lymphoblastic leukemia/lymphoma (hyper-CVAD and nelarabine)[22,23] or vincristine sulfate liposomal injection (VSLI) in lieu of standard vincristine (hyper-CMAD).[24] In addition, the incorporation of the second-generation anti-CD20 monoclonal antibody ofatumumab in lieu of rituximab has been implemented for Burkitt leukemia/lymphoma or CD20-positive B-lymphoblastic leukemia/lymphoma subtypes owing to the improvements in clinical outcomes observed with hyper-CVAD and rituximab.[25]

Inotuzumab is an anti-CD22 monoclonal antibody bound to calicheamicin, a cytotoxic natural product of *Micromonospora echinospora*.[26] In a phase 2 trial of single-agent inotuzumab in children and adults with relapsed/refractory B-lymphoblastic leukemia, the overall response rate was 57% (18% CR, 29% CR with incomplete platelet count recovery [CRp], 10% CRi).[27] In another study of elderly patients with Ph-negative B-lymphoblastic leukemia, inotuzumab was incorporated into a regimen of mini–hyper-CVD (with omission of doxorubicin) that included use of dose-attenuated chemotherapeutics with or without rituximab. The CR/CRp rate in 15 patients was 93%, with encouraging 1-year disease-free and overall survival rates of 83% and 93%, respectively.[28] A summary of the frontline subtype-oriented regimens as applied to adolescents and adults at the MD Anderson Cancer Center is depicted in Table 3.

Allogeneic Stem Cell Transplantation

High-risk subtypes of ALL such as those with early T-cell precursor immunophenotype and MLL gene rearrangements warrant consideration for allogeneic SCT in first CR owing to a lack of effective targeted therapy approaches. Persistence of minimal residual disease (MRD) either by PCR or multiparameter flow cytometry after approximately 16 weeks of appropriate induction/consolidation

chemotherapy has been shown to predict for high risk of disease recurrence in both Ph-negative and Ph-positive ALL. Although the anti-CD19 bispecific, T-cell engaging (BiTE) monoclonal antibody blinatumomab has been shown to effectively eradicate MRD and induce durable complete remissions,[29] this agent is not yet available for use outside of a clinical trial, and cannot yet supplant allogeneic SCT. The role of allogeneic SCT in first CR still remains in flux in the context of the pediatric-based regimens applied to younger adults older than 35 years, and in the setting of Ph-positive ALL with optimal response to frontline chemotherapy incorporating second- or third-generation TKIs.

Conclusions

Significant improvements in survival outcomes have been realized over the last decade for all age groups with de novo ALL. Further advances will likely be derived from a deeper understanding of the pathobiology of the disease, including identification of *BCR-ABL*–like phenotypes in adults, use of and development of novel agents modulating relevant molecular pathways and targeting surface antigens, and risk stratification approaches that identify subsets of ALL amenable to these therapeutic strategies.

Q&A

H&O What are some unmet needs in ALL?

Deborah A. Thomas Truly challenging subtypes of ALL that remain elusive are the extremely poor-risk immunophenotypes of T-lymphoblastic leukemia and MLL-rearranged ALL. Unlike in B-lineage ALL, there are few monoclonal antibodies that specifically target T-lineage antigens. Although novel agents targeting the product of MLL rearrangements are under development (eg, DOT1L modulators), significant progress is needed in order to attain success similar to that achieved by targeting *BCR-ABL* rearrangements.

H&O How will novel therapies impact management?

Deborah A. Thomas The novel agents under development include monoclonal antibodies such as inotuzumab and blinatumomab, which have unprecedented efficacy in the relapsed/refractory setting and allow patients to proceed to allogeneic SCT with curative intent. These agents also have the potential to eradicate MRD in the frontline setting and can potentially not only avert relapse but perhaps eventually obviate the need for SCT.

Acknowledgment

Dr Thomas is on the advisory boards of Amgen, Pfizer, and Spectrum Pharmaceuticals. She has received honoraria from Amgen and Spectrum Pharmaceuticals.

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Novel Treatment Approaches in Acute Lymphoblastic Leukemia

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Several approaches are now in use for the treatment of adult ALL and are successful in achieving a CR in almost all patients. However, more than half of patients still relapse, and the survival rate in relapsed disease is dismal.[1] Therefore, novel agents are clearly needed. This review will summarize several novel agents, some already in clinical use and others in development.

Considerations in the Development of Novel Agents

Although novel therapies are usually developed for use as single agents, some will eventually be evaluated in combination with chemotherapy. In the absence of a standard regimen in ALL, it is challenging to select an optimal chemotherapy "backbone." Another consideration is the disease burden. ALL patients can have overt, active disease, which requires immediate treatment, or MRD that is detectable only by very sensitive tests. Patients with minimal disease are usually healthier before they develop overt clinical disease.

The disease setting is another aspect to consider. Most new agents are being developed for patients with relapsed disease, a population that is rarely cured and that represents a strong unmet need. An agent that is active in the relapsed setting is likely to be evaluated in newly diagnosed patients, with or without chemotherapy. Another consideration is how to coordinate the new agents with bone marrow transplant; they can be used as a "bridge" to transplant or after the procedure to reduce the risk of relapse.

Chemotherapy

Four new chemotherapy drugs have been recently approved by the US Food and Drug Administration (FDA) for ALL. Clofarabine has been approved for relapsed ALL in children and young adults aged 21 years or younger. The CR rate is approximately 20% to 30%.[2,3] Nelarabine has been approved for T-cell ALL in adults and children; the single-agent CR rate is approximately 30%.[4] Both clofarabine and nelarabine are undergoing evaluation in frontline treatment together with other chemotherapy regimens; clofarabine is being studied in pediatric patients,[5] and nelarabine is being studied in adults with T-cell ALL.[6]

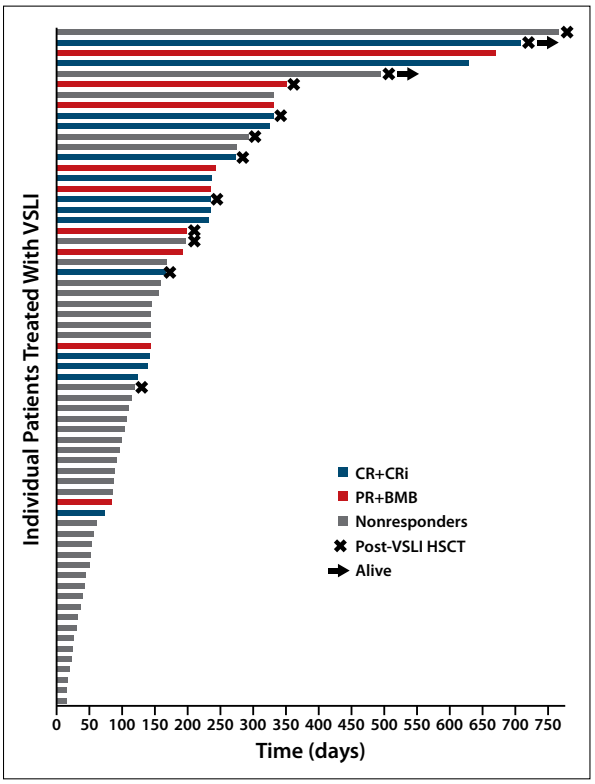

Figure 1. Overall survival and HSCT among patients treated with VSLI in a phase 2 trial.

CR, complete response; CRi, complete response with incomplete hematologic recovery; HSCT, hematopoietic cell transplant; PR, partial remission; BMB, bone marrow blast response; VSLI, vincristine sulfate liposome injection. Adapted from O'Brien S et al. *J Clin Oncol*. 2013;31(6):676-683.[16]

The third recently approved chemotherapeutic agent is VSLI, which is indicated for adult patients with Ph-negative ALL who experience a second or subsequent relapse or whose disease has progressed after at least 2 antileukemia therapies. Vincristine is a standard component of every ALL chemotherapy regimen. The dose is 1.4 mg/m^2, but the drug is almost always capped at 2 mg because of neurotoxicity concerns. Therefore, patients with a body surface area at or above 1.42 m^2 (which includes most adults) are potentially underdosed based on this measurement. This universal dosage cap has limited evidence to support it; the few available studies report conflicting results.[7-14] VSLI is a sphingomyelin/cholesterol-based liposome-encapsulated vincristine formulation that is delivered in a 1-hour infusion, once weekly.[15] Vincristine is slowly released from the liposome and delivered into the tissues more efficiently than with the standard preparation. The dose of VSLI is 2.25 mg/m^2, without a cap. Therefore, a dose higher than 2 mg is delivered to all patients, per their body surface area. A phase 2 trial of 65 patients examined the dosage of 2.25 mg/m^2 without the cap.[16] All patients had received previous treatment with standard vincristine, and half had undergone transplant. Among the 65 patients, 23 (35%) had a response, with 13 patients (20%) having a CR or CR with incomplete hematologic recovery (CRi). The response rates were the same regardless of whether VSLI was given in the third-line, fourth-line, or fifth-line setting. The median overall survival of all patients was 4.6 months; among those who achieved a CR or CRi, the median survival was 7.7 months (Figure 1). Some of these patients were able to bridge to transplant. The most common all-grade toxicities were constipation, which occurred in 34% of patients, and peripheral neuropathy, which occurred in 29%. These rates are similar to those seen with standard vincristine, despite the higher dose of vincristine used in the study.

The response rate of VSLI, although modest, is impressive for a single agent. In ALL, standard vincristine is never used as a single agent, but always as part of a multidrug regimen in the frontline setting. The ability for the first time to deliver a higher dose of vincristine has led to ongoing randomized studies comparing chemotherapy with standard vincristine vs chemotherapy with VSLI in frontline lymphoma and frontline ALL.[17,18]

The fourth recently approved drug in ALL is asparaginase *Erwinia chrysanthemi*. This agent is indicated for patients who develop hypersensitivity to *Escherichia coli*–derived asparaginase, such as the long-acting pegaspargase, which is standard in all frontline pediatric regimens and most adult regimens. Prolonged asparaginase activity, an important component in ALL treatments,[19] is made possible with asparaginase *Erwinia chrysanthemi*. The agent has a very short half-life[20] and is given 3 times a week for 2 weeks, replacing each planned dose of pegaspargase.[21]

Immunotherapy

Two immunotherapy modalities are under development in ALL: cell therapy and antibodies.

Cell Therapy

Cell therapy involves use of the patient's own normal T cells (autologous T cells) that are activated and targeted against the cancer cells. Autologous T cells are not able to fight against a patient's own cancer cells unless modified to gain such activity. Two types of cell therapy approaches using autologous T-cell manipulation technologies are being investigated. The first is called *chimeric antigen receptor* (CAR) *T-cell technology*, and the second utilizes a "smart antibody," blinatumomab. Both approaches are limited in ALL to patients with the pre–B-cell subtype.

The CAR T-cell technology involves a genetic engineering of autologous T cells, which are removed from the patient by leukapheresis and transduced with a novel single gene that is constructed so that its product targets CD19 (an antigen present on B-cell ALL cells) and at the same time activates the T cells. These genetically engineered T cells are transfused back into the patient, where they target the CD19 antigen–positive ALL cells. They proliferate and become active, and then are able to kill the leukemia cells. The Memorial Sloan Kettering Cancer Center reported on the use of CAR T cells

in 16 relapsed or refractory ALL patients[22]; 14 of the 16 patients (88%) achieved a complete remission. Among the 9 patients with overt disease, 7 responded (78%). In fact, 7 of the 14 responders proceeded to allogeneic transplant. All of the patients, except 1, are still alive. The time to CR was approximately 30 days. Two other groups presented their CAR therapy study results at the 2013 meeting of the American Society of Hematology (ASH) and showed similar outcomes.[23,24] An interesting observation from one of the studies is that a patient who relapsed after CAR treatment lost expression of the CD19 antigen.[24]

A similar approach involves the novel agent blinatumomab, which is a BiTE antibody that consists of a component that binds to CD19 on the leukemic B cell linked to another component that binds to the patient's own normal T cells. Blinatumomab is infused into the patient and then engages the normal T cells and redirects them to the tumor cells. As with the CAR T-cell approach, autologous T cells fight against the leukemia cells. With the CAR T-cell technology, the autologous T cells are manipulated outside of the body—ex vivo—by genetic modification, whereas with blinatumomab, the process is in vivo; an antibody is injected into the body and only then binds to the autologous T cells. Therefore, CAR T cells can stay in the body for months and remain continuously active, whereas blinatumomab is active only for as long as the antibody is administered, resulting in a very short duration of activity and necessitating a continuous intravenous infusion. This requirement adds some logistic challenges, as infusion bags with the drug must be changed every 48 hours.

Preliminary data evaluating blinatumomab in relapsed pre–B-cell ALL patients are promising. Among 21 ALL patients with molecular disease (ie, who were MRD-positive), 80% became MRD-negative after treatment with blinatumomab.[25] Among 18 patients with overt disease, the CR rate was 67%; all 12 patients became MRD-negative, with a median remission duration of 8 months. Results from a larger confirmatory study of blinatumomab were presented at the 2014 meeting of the American Society of Clinical Oncology. The trial enrolled 189 patients with relapsed/refractory pre–B-cell ALL; 47 patients were in first relapse and 53 were in second or greater relapse or had primary refractory disease.[26] Blinatumomab was administered by continuous intravenous infusion with a portable minipump system for 4 weeks on followed by 2 weeks off for up to 5 cycles. In the primary analysis, 43% of patients achieved a CR or CR with partial hematologic recovery. In a secondary analysis, the CR rate was 34%, with a median overall survival of 6.1 months. In 74% of patients, the CR was molecular, with MRD negativity. Although the CR rate was lower than in the preliminary study, these results are very impressive for a single agent in a difficult-to-treat patient population using a nonchemotherapy novel immunotherapy approach that engages autologous T-cells. A randomized trial from the Eastern Cooperative Oncology Group is evaluating blinatumomab in combination with chemotherapy in frontline ALL.[27] Newly diagnosed patients will receive the same standard ALL chemotherapy alone or with blinatumomab.

CAR and blinatumomab have similar complications. The interaction of the autologous T cells with the leukemic cells can lead to the release of a variety of cytokines, a condition known as the *cytokine-release syndrome* (CRS). Clinically, CRS manifests with fever, hypotension, and hypoxia; it resembles shock and may be severe. Patients must be monitored and often require treatment in an intensive care unit.[28,29] There are also reports of neurologic side effects, such as seizures. CRS is more common in patients with a larger disease burden, and therefore treatment with CAR or blinatumomab should be preceded by debulking (although patients need not achieve a CR). When blinatumomab is stopped, the associated toxicity will decrease. In contrast, the adverse events associated with CAR T cells are more likely to persist after treatment because the cells remain in the body. The use of steroids can stop the adverse events by blocking the T cells, but it will also eradicate the lymphotoxicity benefits. So far, both approaches are not considered as cures, but the high CR rate, especially with CAR T cells, allows more patients to undergo allogeneic SCT with less disease burden. Overall, both approaches provide a proof of principal that host autologous T cells can be manipulated, in vivo or ex vivo, to act against the host's leukemia cells.

Antibodies

Antibodies target different antigens on the cell. Rituximab is the most commonly used antibody in B-cell lymphoma.[30] Rituximab targets CD20, which is present in approximately half of patients with pre–B-cell lymphoma ALL.[31] As a single agent, rituximab has minimal activity in ALL. Preliminary observations suggest that the addition of rituximab to standard chemotherapy improves outcome.[32,33] Rituximab has not been studied in the relapsed setting.

Another targeted antigen is CD22, which is present on 90% of pre–B-cell ALL cells.[34] Anti-CD22 can be conjugated with a toxin; the resulting agent then targets and kills the leukemia cells. Epratuzumab is a naked unconjugated antibody targeting CD22 that had very limited single-agent activity in pediatric studies.[35] Inotuzumab ozogamicin consists of an anti-CD22 antibody conjugated to the powerful toxin calicheamicin. The antibody directs calicheamicin to the leukemia cells, which are then killed. At the 2013 ASH meeting, DeAngelo and colleagues presented results from a phase 1/2 trial of inotuzumab ozogamicin in adult patients with relapsed or refractory CD22-positive ALL.[36] The remission rate was 79% for patients in a dose-escalation cohort and 46% for patients in a dose-expansion cohort. Data from MD Anderson also showed that inotuzumab ozogamicin has activity as a single agent, without chemotherapy, in relapsed patients.[37] An ongoing phase 3 study is comparing single-agent inotuzumab ozogamicin to chemotherapy in relapsed ALL patients.[38] There are plans to evaluate inotuzumab ozogamicin as part of a chemotherapy regimen in the frontline setting. There were concerns that inotuzumab ozogamicin

might be associated with liver toxicity and veno-occlusive disease, which has been seen with gemtuzumab ozogamicin.[39] These events have not been reported in preliminary observations, but they remain under consideration.

Another antibody-drug conjugate in development is SGN-CD19A, which targets CD19. Phase 1 studies are under way in adult and pediatric patients with relapsed or refractory B-lineage ALL, Burkitt lymphoma or leukemia, and B-lineage lymphoblastic lymphoma[40] and in patients with relapsed or refractory B-lineage non-Hodgkin lymphoma.[41]

Small Molecules

An ongoing effort is under way to define common mutations in ALL. Work began in children and young adults and is now being done in older adults. Researchers have identified several different mutated genes, and their products, that can be targeted. The classic examples are the TKIs, such as imatinib, dasatinib, and nilotinib, used in Ph-positive ALL, which target the disease-specific *BCR/ABL1* gene rearrangement protein product.[42]

This principle is being studied with other mutations and novel agents. The *NOTCH1* gene is mutated in approximately half of ALL patients[43] and drives the cells to proliferate. Several drugs are in development to block this mutation and prevent the leukemic cells from dividing. Another target is the product of the *MLL* gene, which is involved in methylation.[44] Other small molecules in development target the Janus kinase/STAT, mammalian target of rapamycin, and phosphatidylinositol-3-kinase pathways.

Summary

The field of novel agents for ALL is expanding. There are opportunities to develop new therapies; one example is vincristine sulfate liposome injection. Novel agents might be used by themselves or in combination with chemotherapy. Cell therapies and selective molecules, such as the TKIs in Ph-positive ALL, have good activity as single agents. Conjugated antibodies, such as inotuzumab, have modest activity. Naked antibodies and many of the small molecules have minimal activity as single agents. Further studies will be needed to resolve questions about novel therapies, such as whether treatments with minimal activity as single agents will improve the activity of chemotherapy, which types of chemotherapy should be used, and whether treatment should be limited to patients with overt disease or include those with MRD.

Q&A

H&O Are there particular types of patients who are most likely to benefit from novel agents?

Dan Douer, MD In general, novel agents are more likely to be effective in patients with less disease, and most studies are focusing on these patients. With a cellular therapy agent such as blinatumomab, the toxicity is less in patients with a lower disease burden. The cytokine-release syndrome is more likely to occur in patients with more leukemic cells. With targeted treatments, theoretically, patients with the mutation are more likely to benefit. Clinical trials for NOTCH inhibitors are not selecting patients who are NOTCH-mutated; all patients are eligible. Retrospective data will determine whether the NOTCH inhibitors are acting through the expected mechanism. There are several examples in which a drug targeted to a certain mutation showed benefit in patients who lacked that mutation.[45] Further research is needed to identify those patients who are most likely to respond to certain novel therapies.

H&O Is there any experience in using novel agents in the frontline setting?

Dan Douer, MD We are hoping to be able to use novel agents earlier in the course of therapy; it is always preferable to use the best treatment at the beginning. Vincristine sulfate liposome injection is being studied in the frontline setting instead of standard vincristine.[17,18] Blinatumomab plus chemotherapy is being compared with chemotherapy alone in the frontline setting of B-cell ALL.[26] Nelarabine is being introduced into T-cell ALL in the frontline setting. The TKIs are used in the frontline setting in Ph-positive ALL.[6]

H&O What are some common questions you receive from community physicians about how to treat their ALL patients?

Dan Douer, MD We often receive questions about the best frontline treatment because there is no standard approach. Guidelines from the National Comprehensive Cancer Network recommend a clinical trial; when one is not available, they provide a list of regimens with the same activity.[46] The most commonly used regimen is hyper-CVAD, owing to its simple structure, but this approach has no advantage over any other regimen. New data suggest that using a pediatric or "pediatric-inspired" protocol with higher cumulative doses of asparaginase improves the survival of adults, at least those younger than 40 years (or potentially up to ages 55 to 60 years, according to some studies).[47] We now recommend such approaches in young adults.

Another question concerns which patients should undergo transplant. The data are controversial, and the studies are difficult to interpret because all are biased in some way. It is our hope that transplant can be avoided by using the new chemotherapy regimens based on those employed in pediatric patients. Physicians also ask how to treat relapsed disease. There is no standard treatment, and clinical trials are recommended for these patients.

Acknowledgment

Dr Douer is on the advisory boards of Amgen, Pfizer, and Spectrum

Pharmaceuticals. He has received a research grant from Amgen.

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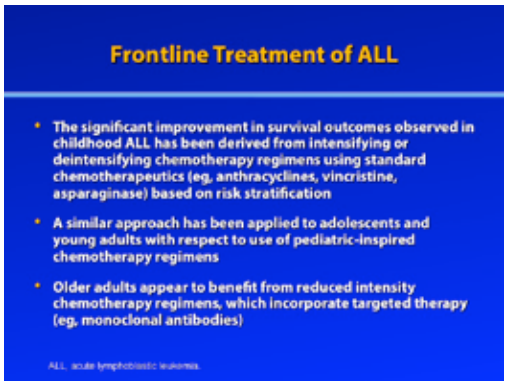

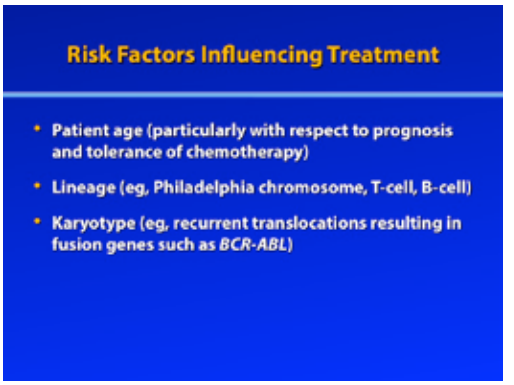

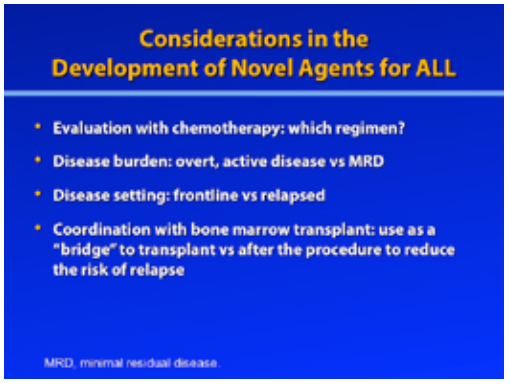

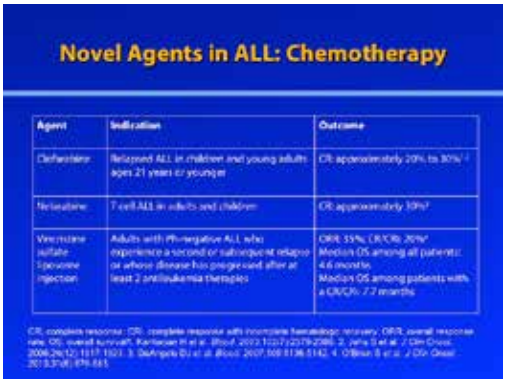

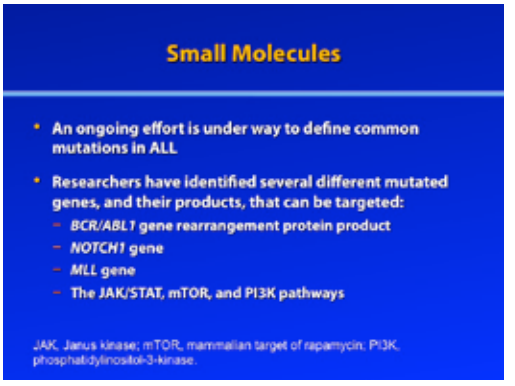

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