

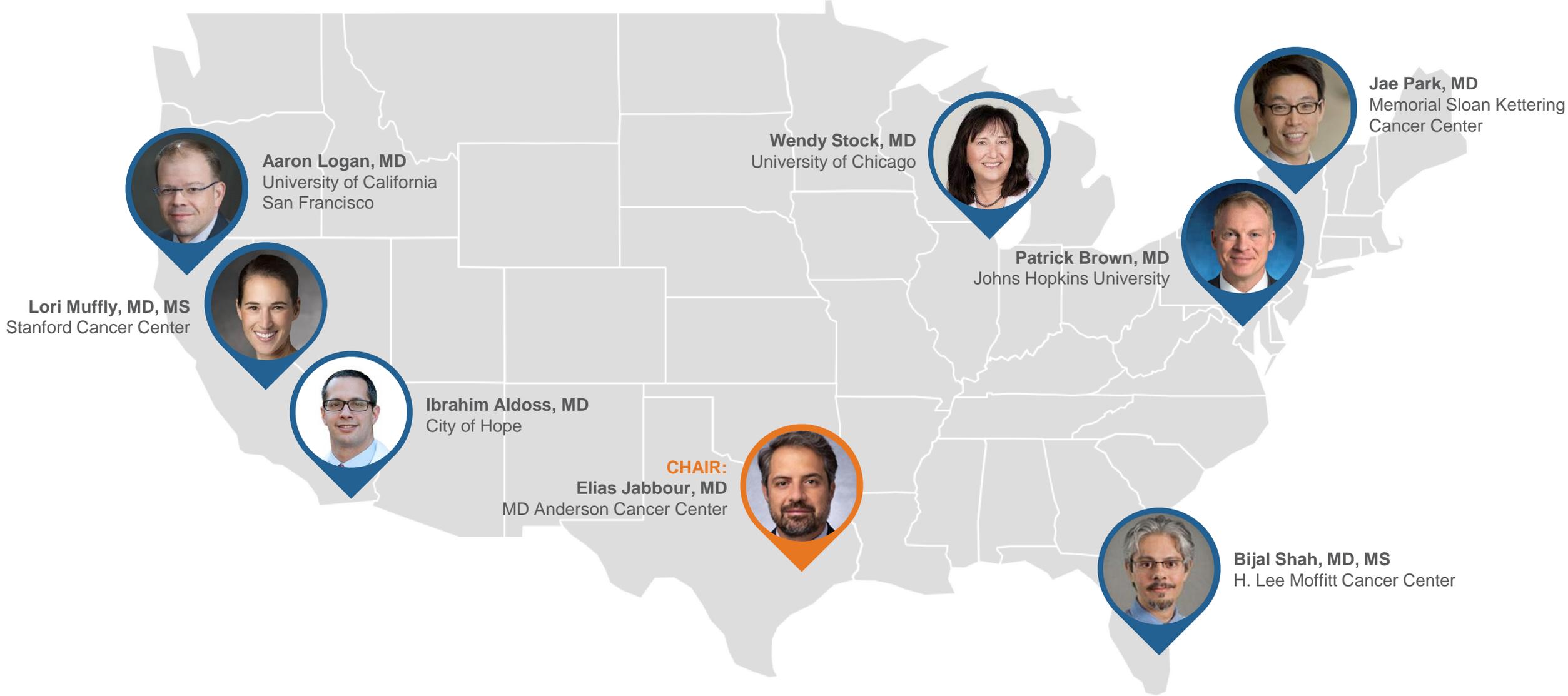
 EPICS A decorative graphic on the left side of the slide consists of several thick, curved lines in various colors (cyan, green, orange, grey, blue) arranged in a circular pattern, resembling a stylized sunburst or a cluster of abstract shapes.

EPICS: Consensus in Acute Lymphoblastic Leukemia (ALL)

August 23, 2021

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Panel Consisting of 8 US ALL Experts



Meeting Agenda

Time (CT)	Topic	Speaker/Moderator
5.00 PM – 5.10 PM	Welcome, Introductions, and Meeting Overview	Elias Jabbour, MD
5.10 PM – 5.30 PM	MRD in ALL	Aaron Logan, MD
5.30 PM – 5.50 PM	Bispecific Approaches in ALL	Ibrahim Aldoss, MD; Patrick Brown, MD
5.50 PM – 6.10 PM	Anti-CD19 CAR Ts in ALL	Bijal Shah, MD, MS; Jae Park, MD
6.10 PM – 7.10 PM	Case-Based Discussion on Therapy Decisions in ALL	All
7.10 PM – 7.20 PM	BREAK	
7.20 PM – 7.40 PM	Generation of an Algorithm	All
7.40 PM – 8.00 PM	Conclusions and Next Steps	Elias Jabbour, MD

- > The objective of this meeting was to generate expert consensus discussion around bispecifics and CAR T on their respective roles in the treatment of ALL, leading to a potential treatment algorithm
- > The meeting consisted of 2 parts

Part 1:

1. Expert overview and update of actual available scientific data: MRD, bispecifics, and CAR T in ALL
2. Case-based discussions to assess clinical areas where specific therapies may be warranted

Part 2:

Determination of drivers for therapeutic choice and development of a treatment algorithm that is based on expert overview and clinical cases

- > Advisors discussed parameters that would impact their decision of therapy choice in ALL
 - Identified main parameters were: MRD positivity, disease burden, whether there is a plan for ASCT, history of extramedullary disease, prior therapies, mutational status, number of relapses, and whether the patient has relapsed after a previous ASCT
- > Ultimately, the experts agreed that many parameters factor into the decision between bispecifics and CAR T. Both clinical aspects and external factors (eg, cost) may dictate one choice over the other
- > On the basis of the expert output, schematics were developed that may serve as a basis for future discussion

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Key Insights: Main Drivers of Therapy Choice in ALL

Parameters for Choice of Therapy in ALL (1/3)

MRD+ Disease

Plan for ASCT

With MRD positivity in first remission (within 2 cycles of

For patients who have a clear transplant plan, either CAR T or

Parameters for Choice of Therapy in ALL (2/3)

Extramedullary Disease

Prior Therapy

For patients with a history of EMD, including CNS disease,

Patients who have received prior treatment with blinatumomab

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Which Relapse?

Blinatumomab is preferred for first relapse, while advisors



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Main Drivers of Therapy Choice

> The following main drivers were discussed/determined during this discussion

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Schematics





Plan for ASCT



Extramedullary Disease



Prior Therapies



Relapsed Disease





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Key Insights: Expert Presentations

MRD

Bispecifics

Anti-CD19 CAR T

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MRD in ALL

Aaron Logan, MD

Main Slides and Conclusions

MRD Is an Essential Component of Patient Evaluation Over the Course of Sequential Therapy

Minimal Residual Disease (MRD) is a critical component of patient evaluation over the course of sequential therapy. It is defined as the presence of residual disease in the blood or bone marrow after treatment. MRD is a key prognostic factor in many hematologic malignancies, including acute leukemia, multiple myeloma, and non-Hodgkin lymphoma. The detection of MRD is typically achieved through sensitive techniques such as flow cytometry, immunophenotyping, and next-generation sequencing (NGS). MRD status is used to guide treatment decisions, including the timing of subsequent therapy and the use of targeted agents. The presence of MRD is associated with a higher risk of relapse and a shorter overall survival. Therefore, regular monitoring for MRD is essential for optimizing patient outcomes and tailoring therapy to individual patients.



Limited Utilization of MRD Testing in Community Settings

Further education is needed

Participants (N = 180) were practicing oncologists or hematologists, with 2–35 years experience, who actively monitored or treated ≥ 5 BCP-ALL patients during the study, working in either academic or community practice*



*Of the community treaters, most were affiliated with non-teaching hospitals (n = 55, 55%) and worked in a group practice of 0–20 physicians (n = 50, 50%).

BCP-ALL, B-cell precursor acute lymphoblastic leukemia; MRD, measurable/minimal residual disease.

Kim C, et al. *Hematology*. 2019;24:70-78.

MRD Summary

- MRD quantification is an essential component in the management of ALL

- MRD is strongly prognostic for ALL and MRD

- The first serial volume (20-100 mL) post of bone marrow aspirate should be used for MRD quantification

- Flow based and NGS based MRD quantification have high correlation for 2×10^{-4} detection limit

- Patients may choose which methodology works best in their practice environment
 - Emerging evidence supports use of NGS with lower sensitivity

- On the basis of current evidence, serial monitoring of MRD is recommended

- Additional studies are needed to corroborate MRD for different protocols and to determine optimal, and cost-effective, testing frequency

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Bispecific Approaches in ALL

Ibrahim Aldoss, MD

Patrick Brown, MD

Main Slides and Conclusions

Favorable response

- > MRD/low disease burden

Limited response

- High disease burden

- The first overall response (OR) in ALL, a part of some minimal response criteria, should be used for MRD quantification.
- Flow-based and MRD-based MRD quantification have high correlation for 200-1000 leukocytes burden.
 - However, flow-based methods may not be as precise as MRD-based methods.
 - Emerging evidence supports use of MRD with disease severity.
- On the basis of current evidence, serial monitoring of MRD is recommended.
- Additional studies are needed to corroborate MRD for different genotypes and to determine optimal, and cost-effective, testing frequency.

➤ Low disease burden

- EPIC is strongly recommended for CR1 and CR2

- The first small volume (20-40 mL) part of bone marrow aspirate should be used for MRD quantification

- Flow based and MRD based MRD quantification have high correlation for CR1-2
low disease burden

- Proven to be disease free relapse-free survival in first practice assessment

- Emerging evidence supports use of MRD with disease severity

- On the basis of current evidence, serial monitoring of MRD is recommended

- Additional studies are needed to corroborate MRD for different genotypes and to determine optimal, and cost-effective, testing frequency

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Anti-CD19 CAR Ts in ALL

Bijal Shah, MD, MS

Jae Park, MD

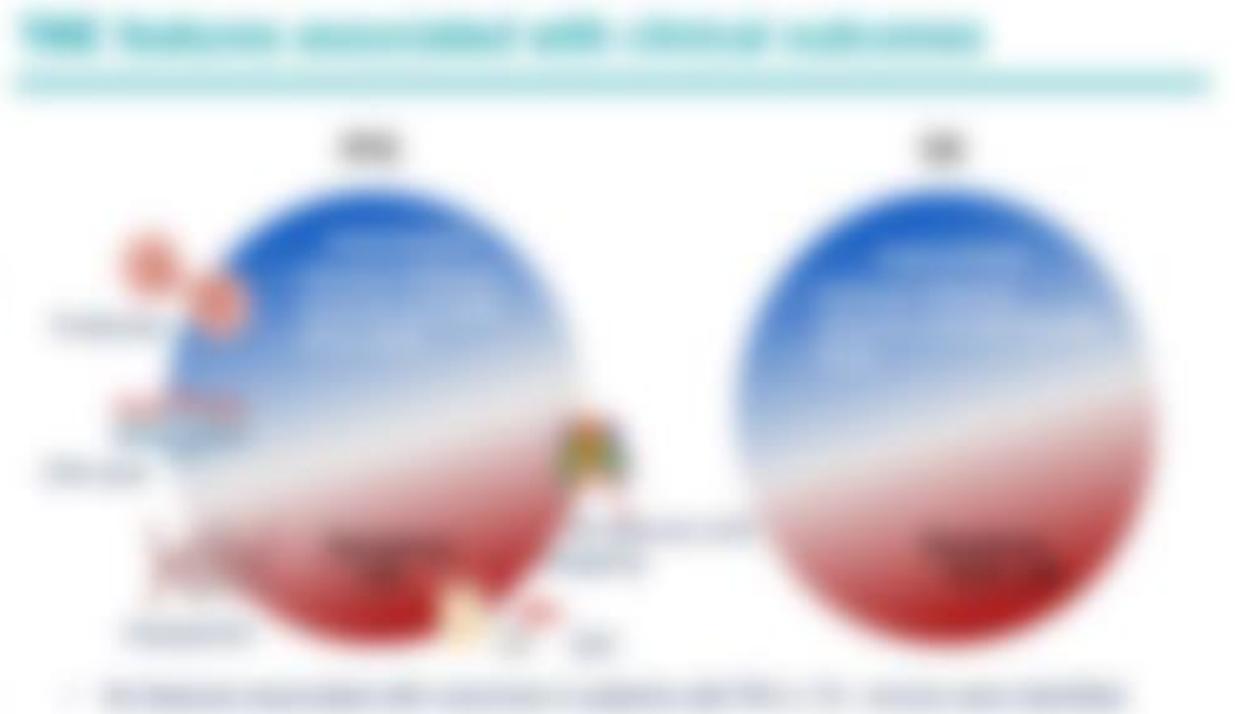
Main Slides and Conclusions

CAR T-Cell Efficacy

Introduction: CAR T-cell therapy is a form of immunotherapy that uses a patient's own T cells, which are genetically engineered to express a chimeric antigen receptor (CAR) that recognizes and kills cancer cells.

How it works: The process involves several steps: 1. T cells are collected from the patient. 2. They are genetically modified in a laboratory to express a CAR that targets a specific antigen on the surface of cancer cells. 3. The modified T cells are expanded and then reimplanted into the patient. 4. The CAR T cells seek out and kill cancer cells by recognizing the target antigen.

Advantages: CAR T-cell therapy has shown promising results in the treatment of certain types of cancer, such as acute leukemia and multiple myeloma. It is a personalized treatment that uses the patient's own immune system to fight the disease.



Challenges: CAR T-cell therapy is still in the early stages of development, and there are several challenges that need to be addressed. These include: 1. Limited availability of CAR T-cell therapy, as it is a personalized treatment that requires specialized facilities. 2. Potential side effects, such as cytokine release syndrome (CRS) and neurotoxicity. 3. The need for further research to optimize the design and use of CAR T cells.

Future Outlook: Despite the challenges, CAR T-cell therapy has the potential to revolutionize the treatment of cancer. Continued research and clinical trials are needed to improve the efficacy and safety of this innovative treatment.

Perspective: Adult ALL

Background

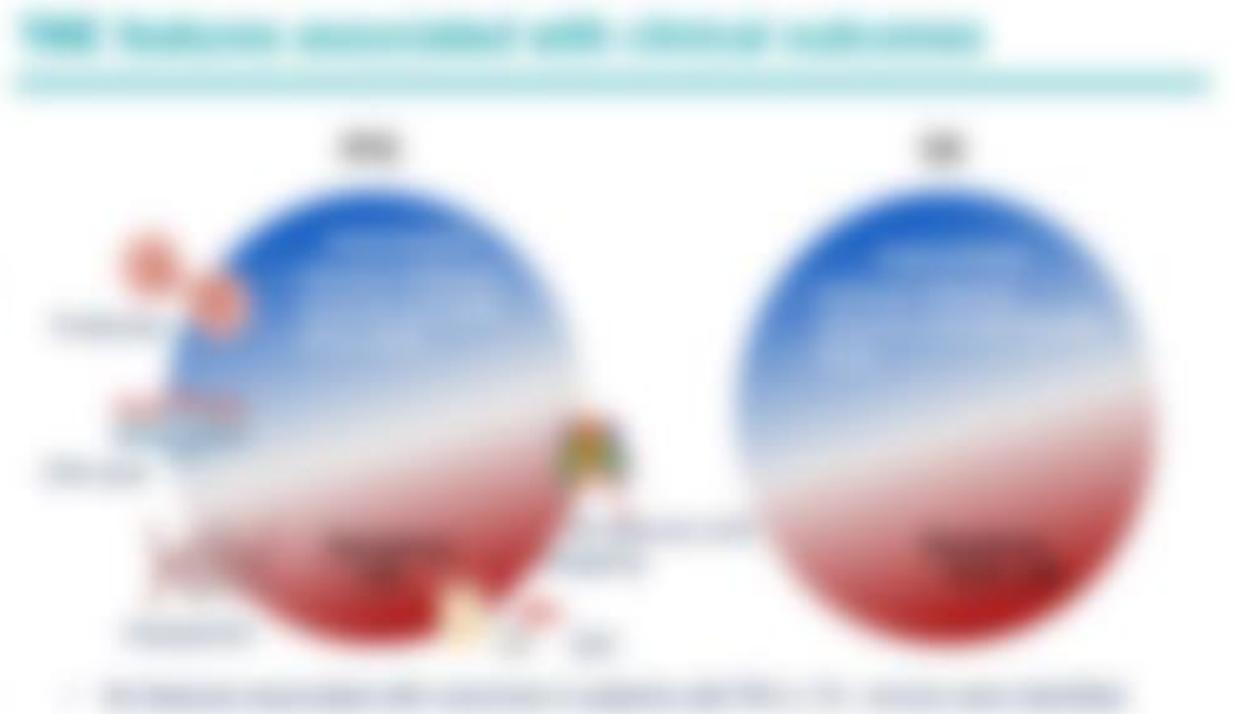
Acute lymphoblastic leukemia (ALL) is a cancer of the white blood cells, which are part of the immune system. It is most common in children, but can also occur in adults. In adults, ALL is often more aggressive and has a poorer prognosis than in children.

Diagnosis

ALL is diagnosed through a combination of blood tests, bone marrow biopsy, and genetic testing. The bone marrow biopsy is the most definitive test, as it allows for the identification of the specific type of leukemia cells and any genetic abnormalities.

Treatment

The standard treatment for adult ALL is chemotherapy, which typically involves a combination of drugs such as prednisone, vincristine, and asparaginase. In some cases, targeted therapy or stem cell transplantation may be used, particularly in relapsed or refractory cases.



Prognosis

The prognosis for adult ALL is generally poorer than for children. The overall survival rate is around 40-50% for first remission, and around 20-30% for long-term survival. Factors such as age, performance, and genetic abnormalities can influence the prognosis.

Research

Research is ongoing to improve the treatment of adult ALL. New drugs, such as tyrosine kinase inhibitors and monoclonal antibodies, are being tested in clinical trials. Additionally, stem cell transplantation and gene therapy are being explored as potential treatment options.

Summary

- CD19 CAR T cells induce 80% CR in R/R B-ALL regardless of BM blast %

- CD19 CAR T cells induce 80% CR in R/R B-ALL regardless of BM blast %

- The first small volume (20-50 mL) part of bone marrow aspirate should be used for MRD quantification

- Flow based and NGS based MRD quantification have high correlation for 2×10^{-4} detection limit

- Flow based may detect other leukocytosis which lead to false positive assessment
- Emerging evidence supports use of NGS with deeper sensitivity

- On the basis of current evidence, serial monitoring of MRD is recommended

- Additional studies are needed to corroborate MRD for different genotypes and to determine optimal, and cost effective, testing frequency

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Key Insights: Case-Based Discussion on Therapy Decisions in ALL

> Advisors were presented with 5 fictitious case studies and were asked to discuss

→ How they would approach therapy decisions for ALL and MRD

→ The first case study involves ALL with a high burden of MRD. Advisors should be asked for MRD quantification

→ Case-based and MRD-based MRD quantification have high correlation for ALL. However, burden

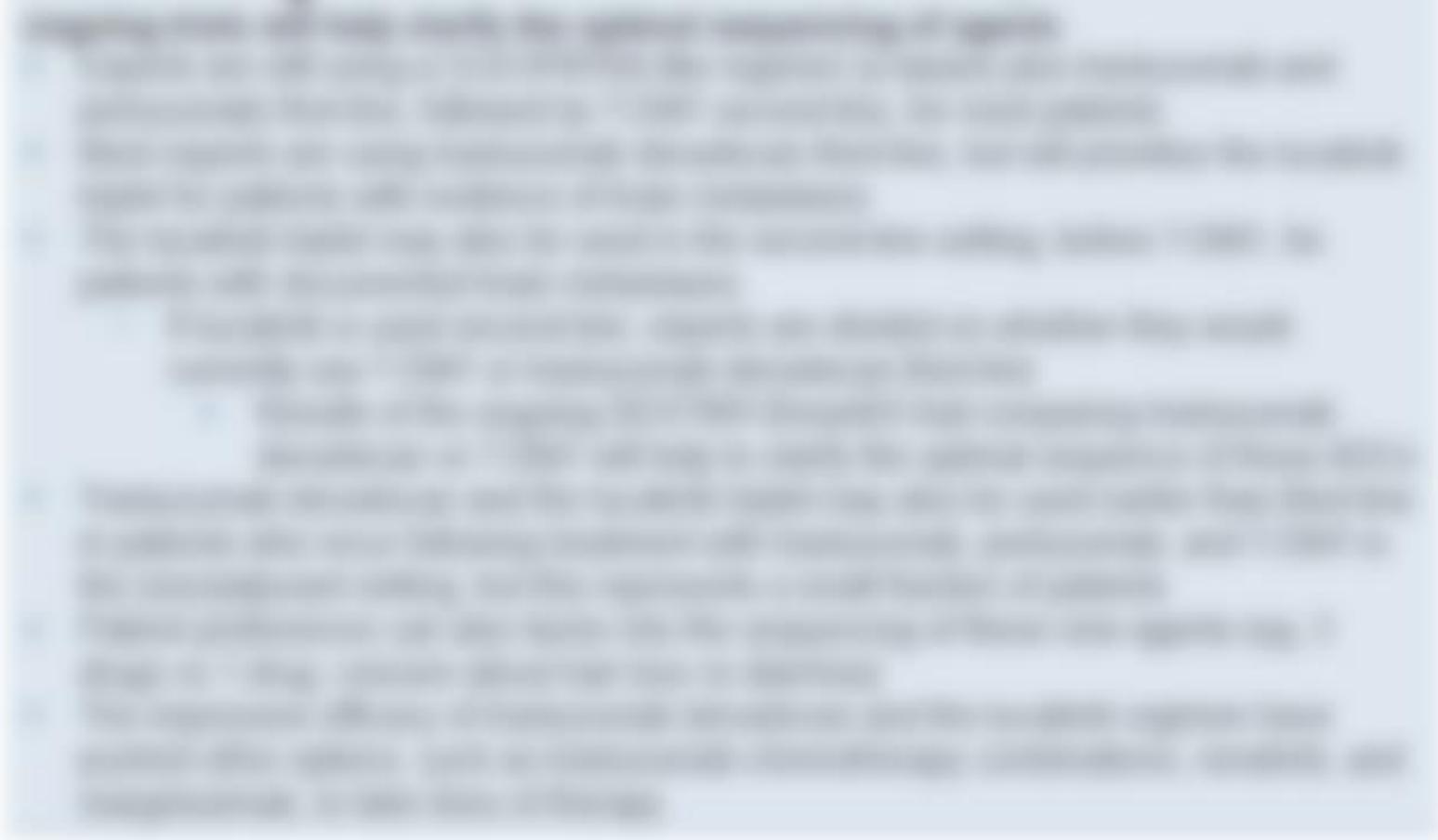
- Evidence may change which methodology works best in their practice environment
- Emerging evidence supports use of MRD with disease severity

→ On the basis of current evidence, serial monitoring of MRD is recommended

→ Additional studies are needed to investigate MRD for different genotypes and to determine optimal, and cost-effective, testing frequency

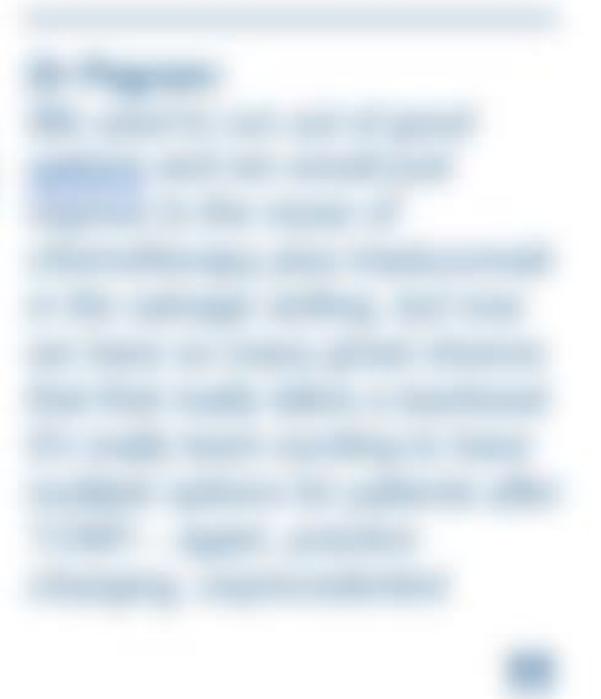
Case 1

- 38-year-old female presents with fatigue and increased bruising



Treatment of Frontline Ph-Like ALL

For frontline treatment of a young *CRLF2+* patient. advisors



Case 2

Treatment of MRD+ Ph-Like ALL

Identification	Presentation at Time of Diagnosis
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Advisors would typically wait until after consolidation to decide

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Case 3

- Mr K is a 24-year-old gentleman who presents with a 2-week history of

[Blurred text area containing the main case description]

Treatment of First Relapse

Advisors were divided on treatment of first relapse in this



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Case 4: ALL With Extramedullary Relapse Post-ASCT

Case 4

Treatment of Extramedullary Relapse Post-ASCT

- 24-year-old Hispanic female diagnosed with Ph-like ALL was induced with

Advisors agreed they would treat this patient with CAR T

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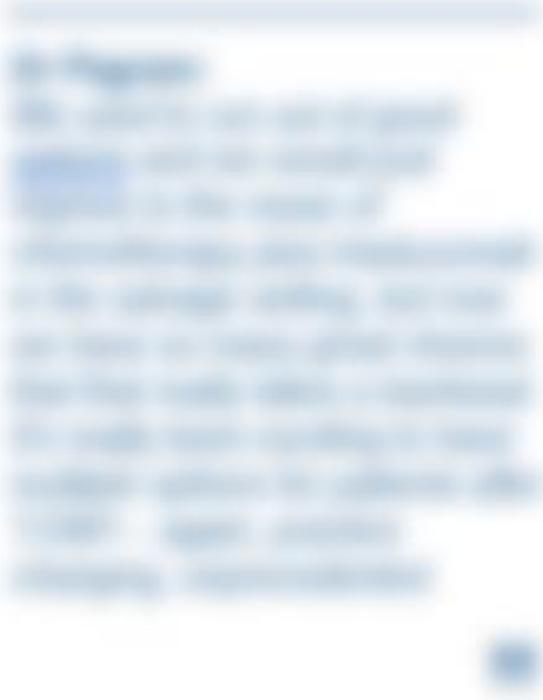


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Case 4 (continued)

- Patient received inotuzumab x 2 cycles with very good response but

Treatment of MRD+ Disease Post-relapse



Case 5

Treatment of Ph+ ALL

- 48-year-old female complaining of 1-week fever, fatigue, and nosebleed;

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[Blurred text area containing treatment information]