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EPICS: Consensus in Acute Lymphoblastic Leukemia (ALL)

August 23, 2021

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Panel Consisting of 8 US ALL Experts

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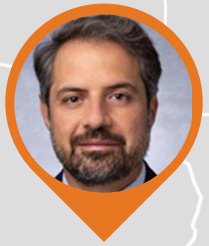
Aaron Logan, MD
University of California
San Francisco

Lori Muffly, MD, MS
Stanford Cancer Center

Ibrahim Aldoss, MD
City of Hope

Wendy Stock, MD
University of Chicago



CHAIR:
Elias Jabbour, MD
MD Anderson Cancer Center

Jae Park, MD
Memorial Sloan Kettering
Cancer Center

Patrick Brown, MD
Johns Hopkins University

Bijal Shah, MD, MS
H. Lee Moffitt Cancer Center

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Meeting Agenda

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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

Objectives and Methodology

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- 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

Generation of an Algorithm

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- 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)

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MRD+ Disease

With MRD positivity in first remission (within 2 cycles of

Plan for ASCT

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

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

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Extramedullary Disease

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

Prior Therapy

Patients who have received prior treatment with blinatumomab

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

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Which Relapse?

Blinatumomab is preferred for first relapse, while advisors

“

Main Drivers of Therapy Choice

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

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Schematics

MRD+ Disease

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Disease Burden

Plan for ASCT

Extramedullary Disease

Prior Therapies

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Relapsed Disease

Ph-Like ALL

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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

Akabane and Logan. *Clin Adv Hematol Oncol*. 2020; 18(7):413-422.

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 = 99, 55%) and worked in a group practice of 6–20 physicians (n = 96, 53%).

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

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Bispecific Approaches in ALL

Ibrahim Aldoss, MD

Patrick Brown, MD

Main Slides and Conclusions

Blinatumomab Therapy in Adult ALL

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Favorable response

- MRD/low disease burden

Limited response

- High disease burden

Optimal Use for Blinatumomab in R/R B-Cell ALL in Adults

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- Low disease burden
  - It is a strong prognostic factor for OS and EFS

- The first small volume (≤3 mL) pull of bone marrow aspirate should be used for MRD quantification

- Flow-based and NGS-based MRD quantification have high correlation for ≥10⁻⁴ leukemia burden
  - Providers may choose which methodology works best in their practice environment
  - 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 contextualize MRD for different genotypes and to determine optimal, and cost-effective, testing frequency

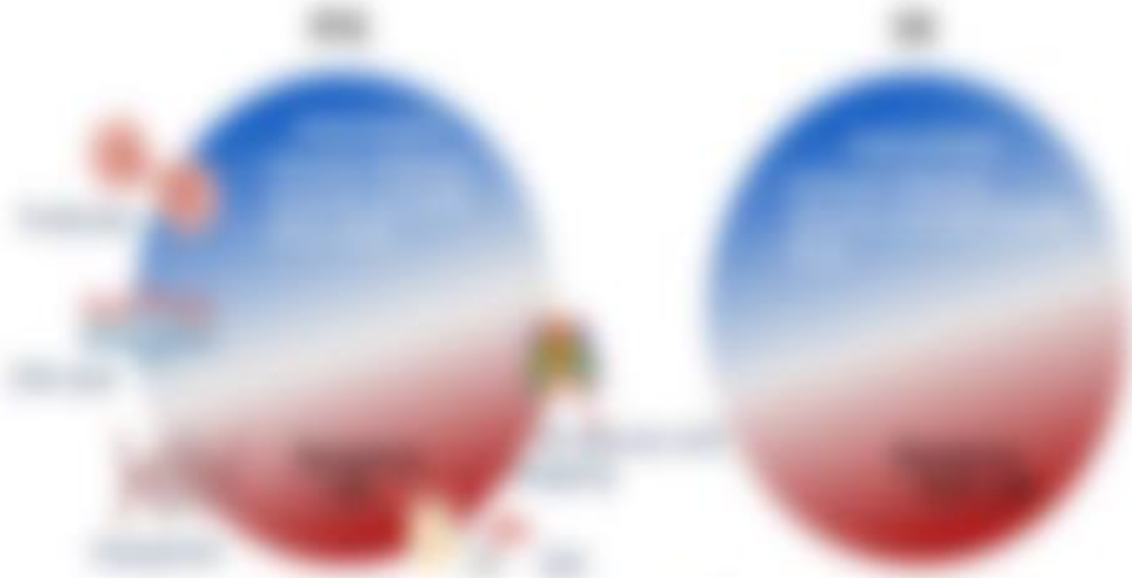
Exploratory analysis

1. Characterization of TME in patients treated with rate-positive vs. decitabine vs. flipped vs. PD-1

Results

1. Improved PFS with decitabine plus rate-positive vs. positive plus rate-positive was seen in PD-L1 immune cell (IC) > influenced and excluded tumors
2. Improved OS was limited to PD-L1 IC+ influenced tumors
3. PD-L1 IC+ basal-like immune activation and immune suppressed subgroups showed PFS benefit
4. OS benefit was limited to PD-L1 IC+ basal-like immune activated subgroup

TME features associated with clinical outcomes



A) Features associated with outcomes in patients with PD-L1 IC+ immune cell subsets

Dr. O' Shaughnessy's conclusions

1. PFS and OS improvements were only observed in the PD-L1 IC+ population. The immunotherapy were numerically predictive in the PD-L1 IC+ population and none of the biomarkers found any benefit from decitabine in the PD-L1 IC+ population.
2. The PD-L1 IC+ population demonstrated immune inflammation, higher proliferation, more TME basal, inflammatory, angiogenesis, and higher IFN response. More benefits were observed in patients with basal-like immune activated subgroup.
3. PD-L1 IC+ patients with basal-like immune activated subsets would benefit more from the CPI. There are hypothesis generating findings.

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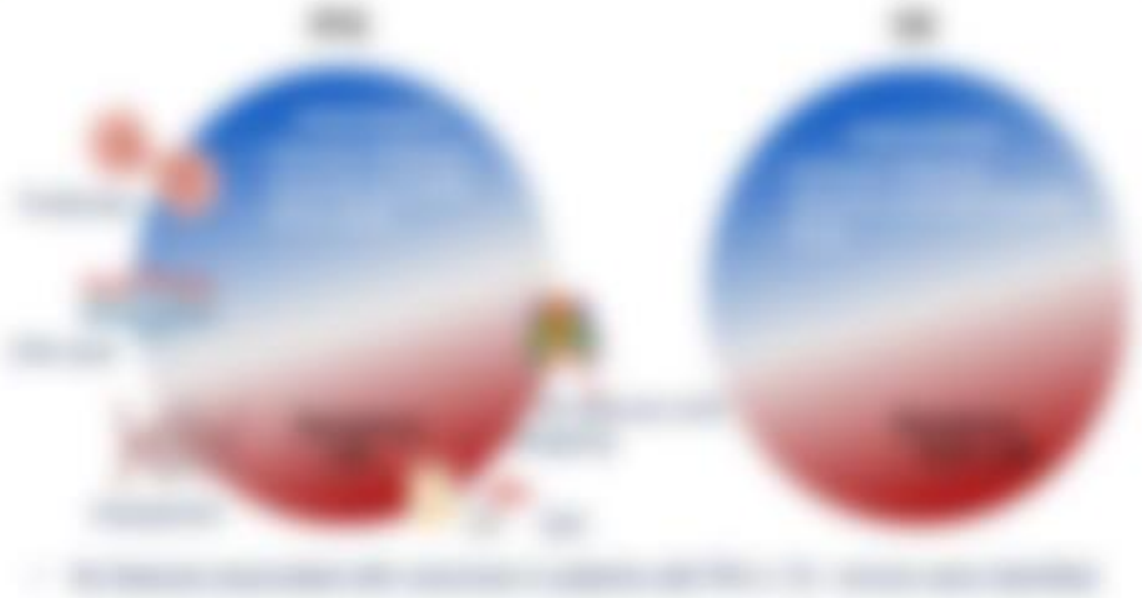
Anti-CD19 CAR Ts in ALL

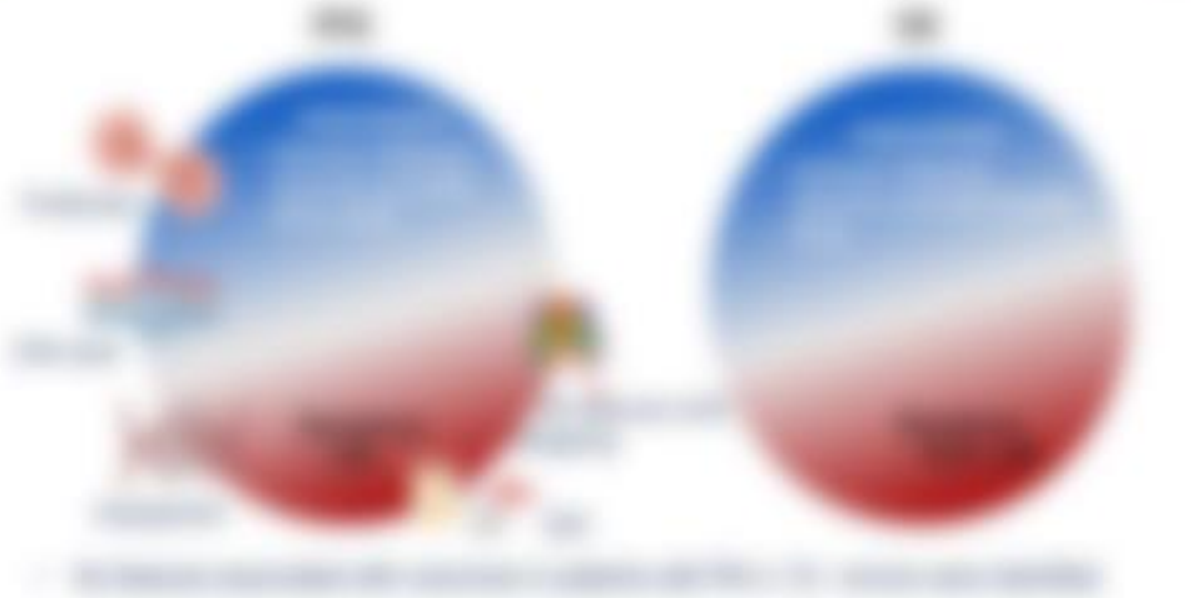
Bijal Shah, MD, MS
Jae Park, MD

Main Slides and Conclusions

CAR T-Cell Efficacy



Perspective: Adult ALL



Summary

- CD19 CAR T cells induce 80% CR in R/R B-ALL regardless of BM blast %
  - It is a strong prognostic factor for OS and EFS

- The first small volume (≤3 mL) pull of bone marrow aspirate should be used for MRD quantification

- Flow-based and NGS-based MRD quantification have high correlation for ≥10^{-4} leukemia burden
  - Providers may choose which methodology works best in their practice environment
  - Emerging evidence supports use of NGS with deeper sensitivity

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

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

Case-Based Discussion on Therapy Decisions in ALL

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

Case 1: Frontline Ph-Like ALL

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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: MRD+ Ph-Like ALL

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Case 2

Identification	Presentation at Time of Diagnosis

Treatment of MRD+ Ph-Like ALL

Advisors would typically wait until after consolidation to decide

Case 3: Relapsed ALL

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Case 3

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

Treatment of First Relapse

Advisors were divided on treatment of first relapse in this

Case 4: ALL With Extramedullary Relapse Post-ASCT

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Case 4

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

Treatment of Extramedullary Relapse Post-ASCT

Advisors agreed they would treat this patient with CAR T

Case 4 (cont.): MRD+ Disease Post-relapse

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Case 4 (continued)

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

Treatment of MRD+ Disease Post-relapse

Case 5: Ph+ ALL

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Case 5

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

Treatment of Ph+ ALL