



EPICS

ASH 2019 – FOCUS ON ACUTE LEUKEMIA

Time	Topic	Speaker/Moderator
6.00 PM – 6.05 PM (5 min)	Welcome and Introductions	Elias Jabbour, MD
6.05 PM – 6.15 PM (10 min)	Advances in AML: Newly Diagnosed	Amir Fathi, MD
6.15 PM – 6.35 PM (20 min)	Discussion	All
6.35 PM – 6.45 PM (10 min)	Advances in AML: Relapsed/Refractory	Naval Daver, MD
6.45 PM – 7.05 PM (20 min)	Discussion	All
7.05 PM – 7.15 PM (10 min)	Advances in ALL: Newly Diagnosed	Eunice Wang, MD
7.15 PM – 7.30 PM (15 min)	Discussion	All
7.30 PM – 7.40 PM (10 min)	Advances in ALL: Relapsed/Refractory	Bijal Shah, MD
7.40 PM – 7.55 PM (15 min)	Discussion	All
7.55 PM – 8.00 PM (5 min)	Summary and Closing Remarks	Elias Jabbour, MD

PARTICIPANT LIST

CHAIR

Elias Jabbour, MD

MD Anderson Cancer Center
Houston, TX

ATTENDEES

Naval Daver, MD

MD Anderson Cancer Center
Houston, TX

Amir Fathi, MD

Massachusetts General Hospital
Boston, MA

Guillermo Garcia-Manero, MD

MD Anderson Cancer Center
Houston, TX

Farhad Ravandi-Kashani, MD

MD Anderson Cancer Center
Houston, TX

Bijal Shah, MD

Moffitt Cancer Center
Tampa, FL

Eunice Wang, MD

Roswell Park Comprehensive Cancer Center
Buffalo, NY

- > 643 Enasidenib Plus Azacitidine Significantly Improves Complete Remission and Overall Response Compared with Azacitidine Alone in Patients with Newly Diagnosed Acute Myeloid Leukemia (AML) with Isocitrate Dehydrogenase 2 (*IDH2*) Mutations: Interim Phase II Results from an Ongoing, Randomized Study. DiNardo et al
 - Phase II portion of a phase Ib/II trial (N = 101)
 - Outcomes (enasidenib + azacitidine vs azacitidine)
 - Objective response rate (ORR): 71% vs 42% ($P = .0064$)
 - Complete remission (CR): 53% vs 12% ($P = .0001$)
 - Overall survival (OS) similar between the 2 groups (22.0 months vs 22.3 months)
- > 176 A Phase Ib/II Study of the BCL-2 Inhibitor Venetoclax in Combination with Standard Intensive AML Induction/Consolidation Therapy with FLAG-IDA in Patients with Newly Diagnosed or Relapsed/Refractory AML. Aboudalle et al
 - N = 14 patients in the newly diagnosed cohort
 - No clinical tumor lysis syndrome (TLS) occurred
 - ORR: 93%; CR + CR with incomplete hematologic recovery (CRi): 85%
 - At 5.5 months of follow-up, OS and recurrence-free survival (RFS) are 100%

- > LBA-3 The QUAZAR AML-001 Maintenance Trial: Results of a Phase III International, Randomized, Double-Blind, Placebo-Controlled Study of CC-486 (Oral Formulation of Azacitidine) in Patients with Acute Myeloid Leukemia (AML) in First Remission. Wei et al
 - Maintenance therapy with CC-486 vs placebo in patients with CR or CRi following induction
 - N = 469
 - Safety
 - Main adverse events (AEs) were gastrointestinal, primarily grade 1/2
 - Neutropenia most common AE requiring dose interruption/reduction
 - Treatment discontinuation: 13% vs 4%
 - Outcomes (CC-486 vs placebo)
 - OS: 24.7 months vs 14.8 months (hazard ratio [HR] 0.69; $P = .0009$)
 - RFS: 10.2 months vs 4.8 months (HR 0.65; $P = .0001$)

- > 115 Maintenance Decitabine (DAC) Improves Disease-Free (DFS) and Overall Survival (OS) after Intensive Therapy for Acute Myeloid Leukemia (AML) in Older Adults, Particularly in FLT3-ITD-Negative Patients: ECOG-ACRIN (E-A) E2906 Randomized Study. Foran et al
 - Maintenance decitabine vs observation in patients with CR/CRi following consolidation (n = 120)
 - Outcomes (decitabine vs observation)
 - DFS: 0.77 (protocol-specified 1-sided $P = .12$)
 - OS: 0.69 ($P = .06$)
- > 829 Efficacy and Safety of Azacitidine (AZA) in Combination with the Anti-PD-L1 Durvalumab (durva) for the Front-Line Treatment of Older Patients (pts) with Acute Myeloid Leukemia (AML) Who Are Unfit for Intensive Chemotherapy (IC) and Pts with Higher-Risk Myelodysplastic Syndromes (HR-MDS): Results from a Large, International, Randomized Phase 2 Study. Zeidan et al
 - AZA ± durvalumab in patients unfit for induction chemotherapy; N = 129 in AML cohort
 - Outcomes (AZA + durvalumab vs AZA)
 - ORR: 31.3% vs 35.4%
 - Median duration of response: 24.6 weeks vs 51.7 weeks
 - No meaningful differences in progression-free survival or OS

DISCUSSION: NEWLY DIAGNOSED AML

- > Results from the QUAZAR study strongly support the role for maintenance therapy in some newly diagnosed patients with AML, but the experts are not certain this is an appropriate approach for all patients
- > The majority of experts are now using hypomethylating agent (HMA) + venetoclax as their standard first-line treatment for transplant-ineligible patients, regardless of mutation status

- > 229 Updated Results from the Venetoclax (Ven) in Combination with Idasanutlin (Idasa) Arm of a Phase 1b Trial in Elderly Patients (Pts) with Relapsed or Refractory (R/R) AML Ineligible for Cytotoxic Chemotherapy. Daver et al
 - N = 49
 - Manageable safety profile
 - Diarrhea, nausea, and vomiting most common AEs of any grade
 - Febrile neutropenia of grade 3 or higher in 47%
 - Doses selected for expansion: Ven 600 mg/Idasa 150 mg and Ven 600 mg/Idasa 200 mg
 - cCR* 38% (600-mg/150-mg group) and 33% (600-mg/200-mg group)
- > 3910 Venetoclax in Combination with Gilteritinib in Patients with Relapsed/Refractory Acute Myeloid Leukemia: A Phase 1b Study. Perl et al
 - N = 23; 18 with *FLT3* mutations
 - ORR: 88% in *FLT3*-mutated population

- > 832 Multi-Center Phase 2 Study of Pembroluzumab (Pembro) and Azacitidine (AZA) in Patients with Relapsed/Refractory Acute Myeloid Leukemia (AML) and in Newly Diagnosed (≥ 65 Years) AML Patients. Gojo et al
 - 37 patients in R/R cohort
 - CR/CRi: 14%
 - Median OS: 10.8 months
- > 830 Azacitidine (AZA) with Nivolumab (Nivo), and AZA with Nivo + Ipilimumab (Ipi) in Relapsed/Refractory Acute Myeloid Leukemia: A Non-Randomized, Prospective, Phase 2 Study. Daver et al
 - N = 70
 - Outcomes (AZA-Nivo vs control)
 - ORR: 33% vs 20%
 - ORR in prior HMA naive: 52% vs 19% ($P < .001$)
 - ORR in prior HMA exposed: 22% vs 23%

- > 569 The First-in-Class Anti-CD47 Antibody Magrolimab (5F9) in Combination with Azacitidine Is Effective in MDS and AML Patients: Ongoing Phase 1b Results. Sallman et al
 - Macrophage checkpoint
 - N = 62; primarily a high-risk population
 - Outcomes in AML
 - ORR: 64%
 - Complete cytogenetic response: 60%
 - MRD negativity: 57%

- > Results seen with venetoclax in the R/R population have been extremely promising, although the best combination partner(s) for venetoclax in the R/R setting are not yet clear
- > Currently, the role for immunotherapy in AML is extremely limited, as the experts feel the response rates in studies thus far have not been impressive, particularly compared with other agents available in this setting,

- > 739 First Analysis of the UKALL14 Phase 3 Randomised Trial to Determine If the Addition of Rituximab to Standard Induction Chemotherapy Improves EFS in Adults with Precursor B-ALL (CRUK/09/006). Fielding et al
 - N = 577
 - Failed to meet primary endpoint (event-free survival [EFS] in standard of care [SOC] + rituximab vs SOC)
 - Median EFS: 34.5 months vs 22.3 months (HR 0.88; $P = .25$)
 - No difference in OS (HR 0.90; $P = .39$)
- > 823 Updated Results of a Phase II Study of Reduced-Intensity Chemotherapy with Mini-Hyper-CVD in Combination with Inotuzumab Ozogamicin, with or without Blinatumomab, in Older Adults with Newly Diagnosed Philadelphia Chromosome-Negative Acute Lymphoblastic Leukemia. Short et al
 - N = 59 evaluable
 - Veno-occlusive disease (VOD) in 9%, with 3 related deaths
 - Patients subsequently received ursodiol 300 mg three times daily for VOD prophylaxis and reduced inotuzumab ozogamicin dose
 - ORR: 98%
 - MRD negativity in 95%
 - 3-year OS: 55% in total patient population, 44% in patients over 70 years of age

- > 740 Dasatinib-Blinatumomab Combination for the Front-Line Treatment of Adult Ph+ ALL Patients. Updated Results of the Gimema LAL2116 D-Alba Trial. Chiaretti et al
 - “Chemo-free” frontline therapy
 - N = 63 patients, median age 54 years
 - Complete molecular remission (CMR) by cycle 2 in 60.4% (primary endpoint)
 - OS (median follow-up 14.3 months): 95.2%; DFS: 89.7%
 - 24 patients proceeded to allogeneic stem cell transplantation (SCT)
 - 6 patients relapsed
- > 743 Dasatinib-Based Two-Step Induction Prior to Allogeneic Hematopoietic Cell Transplantation for Newly Diagnosed Philadelphia Chromosome-Positive Acute Lymphoblastic Leukemia: Results of the JALSG Ph+ALL213 Study. Sugiura et al
 - N = 81; 70 evaluable
 - 3-year EFS: 66.2%
 - CR/CRI: 100% at day 42
 - 3-year OS: 80.5% in all patients; 84.5% in patients who went on to hematopoietic SCT (HSCT)

- > 283 Long-Term Safety and Efficacy of Hyper-CVAD Plus Ponatinib As Frontline Therapy for Adults with Philadelphia Chromosome-Positive Acute Lymphoblastic Leukemia. Short et al
 - N = 86
 - Initial results show high rates of cardiovascular AEs, leading to modification of ponatinib dose from 45 mg daily to 30 mg or 15 mg daily
 - Safety
 - Venous thromboembolism in 13% of patients prior to dose reduction
 - Arterial cardiovascular events in 7%, including 2 fatal myocardial infarctions (45-mg ponatinib dose)
 - Efficacy
 - CMR: 86%; CR: 100%
 - 5-year OS: 74% in total population
 - 5-year EFS: 68%
 - Better survival in patients who did not go on to receive SCT

- > Treatment of Ph-positive acute lymphoblastic leukemia (ALL) is very straightforward, as tyrosine kinase inhibitors are highly effective in this setting
- > Some experts are intrigued by the idea of replacing dasatinib with ponatinib in frontline, due to its superior efficacy in this setting
- > Treatment of Ph-negative ALL remains a major challenge, and there is no clear consensus on the best treatment option in these patients

- > 285 Safety and Efficacy of Venetoclax in Combination with Navitoclax in Adult and Pediatric Relapsed/Refractory Acute Lymphoblastic Leukemia and Lymphoblastic Lymphoma. Lacayo et al
 - N = 45; median 4 lines of prior therapy
 - Safety
 - Grade 3/4 AEs: venetoclax related, 58%; navitoclax related, 42%
 - Febrile neutropenia was the most common grade 3/4 AE
 - 1 occurrence of laboratory TLS
 - Efficacy
 - CR/CRi/CR with incomplete platelet recovery: 49%
 - MRD negative: CR 29%
 - Median OS: 9.7 months

- > 741 A Phase 2 Trial of Inotuzumab Ozogamicin (InO) in Children and Young Adults with Relapsed or Refractory (R/R) CD22+ B-Acute Lymphoblastic Leukemia (B-ALL): Results from Children's Oncology Group Protocol AALL1621. O'Brien et al
 - Inotuzumab in combination with intrathecal chemotherapy
 - N = 48 heavily pretreated patients
 - Toxicity
 - Febrile neutropenia grade 3 or higher in 27.1%
 - Hepatic toxicity: four grade 3 alanine aminotransferase elevation and one grade 3 bilirubin
 - VOD in 5 patients (10.4%)
 - Efficacy
 - 12-month EFS: 35.7%
 - 12-month OS: 39.6%

- > LBA-1 A Randomized Phase 3 Trial of Blinatumomab Vs. Chemotherapy As Post-Reinduction Therapy in High and Intermediate Risk (HR/IR) First Relapse of B-Acute Lymphoblastic Leukemia (B-ALL) in Children and Adolescents/Young Adults (AYAs) Demonstrates Superior Efficacy and Tolerability of Blinatumomab: A Report from Children's Oncology Group Study AALL1331. Brown et al
 - N = 208 patients with intermediate- or high-risk disease
 - AEs
 - Chemotherapy was associated with higher rates of AEs than blinatumomab
 - Blinatumomab-associated AEs included grade 3/4 cytokine release syndrome (CRS) in 1%, and grade 3/4 neurotoxicity in 3%
 - MRD clearance (chemo vs blinatumomab)
 - Cycle 1: 29% vs 76%
 - Cycle 2: 33% vs 66%
 - 2-year OS (chemo vs blinatumomab): 59.2% vs 79.4%
 - Less benefit for blinatumomab in patients with extramedullary disease

- > 224 Analysis of Factors Predicting Treatment Response of 254 Patients Who Received CD19-Targeted CAR-T Cell Therapy for Relapsed/Refractory (R/R) B-Cell Acute Lymphoblastic Leukemia (B-ALL). Zhang et al
 - Evaluated a variety of CAR T constructs
 - N = 254
 - CR rate 94.27% in males and 84.54% in females
 - Prior blinatumomab associated with lower rate of response
 - Factors predicting for nonresponse included female gender, bone marrow >20%, *TP53* mutation, and CD28 costimulatory domain
 - 2-year OS 67.37% in patients who received allo-HSCT post-CAR T
- > 284 Anti-CD19/CD22 Dual CAR-T Therapy for Refractory and Relapsed B-Cell Acute Lymphoblastic Leukemia. Lu et al
 - N = 20
 - Low toxicity; 70% grade 1 CRS, but no severe CRS or neurotoxicity
 - 93.8% of patients in medium- and high-dose groups achieved CR/CRi by day 28

- > The experts are enthusiastic about the potential role for allogeneic CAR T cells in the future, as these are much more convenient than autologous CAR T cells and can potentially be combined with other treatments, such as blinatumomab or inotuzumab
- > In general, the experts feel there are many potentially interesting treatment options on the horizon for R/R ALL, but these are in their infancy and it is too early to tell which will be the most effective or play a key role in this setting