New Paradigms in the Treatment of Acute Lymphoblastic Leukemia, Chronic Lymphocytic Leukemia, Acute Myeloid Leukemia and Chronic Myeloid Leukemia

Saturday, April 27, 2019
7:00 AM - 3:30 PM

Educational Grants:
Novartis Pharmaceuticals Corporation
Takeda Oncology

To view full slide handouts, visit www.cancernetus.com/leukemia2019

For online registration and more information visit: www.cancernetus.com

Houston Marriott at the Texas Medical Center
6580 Fannin Street
Houston, TX 77030
Phone: (713) 796-0080

Jointly provided by:
Baylor Scott & White Health
AMEDCO
Cancernet
Statement of Need/Program Overview

This symposium is intended to improve care of patients with acute lymphoblastic leukemia (ALL), chronic lymphocytic Leukemia (CLL), acute myeloid leukemia (AML) and chronic myelogenous leukemia (CML) by accelerating adoption of new guidelines and evidence-based practice change. The format will include didactic lectures from known opinion leaders, question and answer sessions, and ample opportunity for participant interaction with faculty.

Target Audience

This symposium is directed primarily to hematologists/oncologists, physician assistants, nurse practitioners, registered nurses, pharmacists and fellows in training interested in new development in ALL, CLL, AML and CML. No specific skill or knowledge other than a basic training in hematology/oncology is required for successful participation in this activity.

Learning Objectives

After completing this activity, the participant should be better able to:

- Describe the alterations in cytogenetic, molecular abnormalities, NOTCH1, CRLF2 mutations, epigenetic markers in the diagnosis and treatment of patients with acute lymphoblastic leukemia (ALL)
- Identify the novel therapeutic options for adolescents and young adults (AYA) relapsed/refractory Philadelphia-positive and Philadelphia-negative patients with ALL
- Assess the prognostic markers, risk stratification and their impact on clinical practice of patients with chronic lymphocytic lymphoma (CLL)
- Identify and apply individualized treatment strategies based on current and emerging novel therapies for CLL
- Describe the alterations in driver mutations revealing molecular subgroups leading to disease classification and prognostic stratification in acute myeloid leukemia (AML)
- Recognize how compound genotypes are related to clinical outcomes in AML patients treated with novel agents
- Evaluate the first line therapy options for chronic myeloid leukemia (CML) in chronic phase
- Identify response assessment and management of tyrosine kinase inhibitors resistance in the treatment of CML
- Recognize the time-based response milestones and monitoring in patients with CML
# Agenda

<table>
<thead>
<tr>
<th>Time</th>
<th>Event</th>
<th>Speaker(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>7:00 AM</td>
<td>Onsite Registration and Buffet Breakfast</td>
<td></td>
</tr>
<tr>
<td>7:55 AM</td>
<td>Opening Remarks</td>
<td>William G. Wierda, MD, PhD</td>
</tr>
<tr>
<td>8:00 AM</td>
<td>Pretest – Case Vignettes</td>
<td>Nitin Jain, MD/Elias Jabbour, MD</td>
</tr>
<tr>
<td>8:15 AM</td>
<td>Overview of Diagnosis Based on Cytogenetic and Molecular Abnormalities</td>
<td>Nitin Jain, MD</td>
</tr>
<tr>
<td>8:45 AM</td>
<td>Novel Therapies for adolescents and young adults (AYA), Philadelphia-positive and Philadelphia-negative Relapsed/Refractory Patients with ALL</td>
<td>Elias Jabbour, MD</td>
</tr>
<tr>
<td>9:15 AM</td>
<td>Posttest – Case Vignettes</td>
<td>Nitin Jain, MD / Elias Jabbour, MD</td>
</tr>
<tr>
<td>9:30 AM</td>
<td>BREAK</td>
<td></td>
</tr>
<tr>
<td>9:45 AM</td>
<td>Pretest – Case Vignettes</td>
<td>Courtney DiNardo, MD</td>
</tr>
<tr>
<td>10:00 AM</td>
<td>Overview of Disease Classification and Prognostic Stratification in Patients with AML</td>
<td>Courtney DiNardo, MD</td>
</tr>
<tr>
<td>10:30 AM</td>
<td>Treatment Options with Novel IDH1/2, FLT3 and CD33 Targeted Agents in Genomic Subgroups of AML</td>
<td>Courtney DiNardo, MD</td>
</tr>
<tr>
<td>11:00 AM</td>
<td>Posttest – Case Vignettes</td>
<td>Courtney DiNardo, MD</td>
</tr>
<tr>
<td>11:15 AM</td>
<td>Pretest – Case Vignettes</td>
<td>Ghayas C. Issa, MD / Guillermo Garcia-Manero, MD</td>
</tr>
<tr>
<td>11:30 AM</td>
<td>Response Assessment and Management of TKIs Resistance in the Management of CML</td>
<td>Ghayas C. Issa, MD</td>
</tr>
<tr>
<td>12:00 PM</td>
<td>LUNCH</td>
<td></td>
</tr>
<tr>
<td>1:00 PM</td>
<td>Understanding of Time-based Response Milestones and Monitoring in Patients with CML</td>
<td>G. Garcia-Manero, MD</td>
</tr>
<tr>
<td>1:30 PM</td>
<td>Posttest – Case Vignettes</td>
<td>Ghayas C. Issa, MD / G. Garcia-Manero, MD</td>
</tr>
<tr>
<td>1:45 PM</td>
<td>Pretest – Case Vignettes</td>
<td>Jan A. Burger, MD, PhD / William G. Wierda, MD</td>
</tr>
<tr>
<td>2:00 PM</td>
<td>Emerging Prognostic Markers and Risk Stratification in Treatment Decision Making for Patients with CLL</td>
<td>Jan A. Burger, MD, PhD</td>
</tr>
<tr>
<td>2:30 PM</td>
<td>BREAK</td>
<td></td>
</tr>
<tr>
<td>2:45 PM</td>
<td>Changing the Treatment Paradigm for CLL: Chemo-immunotherapy versus Targeted Therapy</td>
<td>William G. Wierda, MD, PhD</td>
</tr>
<tr>
<td>3:15 PM</td>
<td>Posttest – Case Vignettes</td>
<td>Jan A. Burger, MD, PhD / William G. Wierda, MD</td>
</tr>
<tr>
<td>3:30 PM</td>
<td>Closing Remarks and Adjourn</td>
<td>William G. Wierda, MD, PhD</td>
</tr>
</tbody>
</table>
Faculty

Jan A. Burger, MD, PhD
Associate Professor, Department of Leukemia, The University of Texas MD Anderson Cancer Center, Houston, TX

Courtney DiNardo, MD
Assistant Professor, Department of Leukemia, The University of Texas MD Anderson Cancer Center, Houston, TX

Guillermo Garcia-Manero, MD
Professor, Department of Leukemia, The University of Texas MD Anderson Cancer Center, Houston, TX

Ghayas C. Issa, MD
Assistant Professor, Department of Leukemia, The University of Texas MD Anderson Cancer Center, Houston, TX

Elias Jabbour, MD
Associate Professor, Department of Leukemia, The University of Texas MD Anderson Cancer Center, Houston, TX

Nitin Jain, MD
Associate Professor, Department of Leukemia, The University of Texas MD Anderson Cancer Center, Houston, TX

William G. Wierda, MD, PhD
Professor, Department of Leukemia, The University of Texas MD Anderson Cancer Center, Houston, TX
Disclosure of Relevant Financial Relationships

A. Webb Roberts Center for Continuing Medical Education of Baylor Scott & White Health and Amedco, assess conflicts of interest with its instructors, planners, managers and other individuals who are in a position to control the content of CME/CE activities. All relevant financial relationships are identified and conflicts of interest are resolved prior to the activity to ensure fair balance, scientific objectivity of studies utilized in this activity, and validity of patient care recommendations. Amedco is committed to providing its learners with high quality CME/CE activities and related materials that promote improvements or quality in healthcare and not a specific proprietary business interest of a commercial interest.

The faculty reported the following financial relationships or relationships to products or devices they or their spouse/life partner have with commercial interests related to the content of this CME/CE activity:

<table>
<thead>
<tr>
<th>Name</th>
<th>Conflict of Interest Disclosures</th>
</tr>
</thead>
</table>
| Jan A. Burger, MD, PhD                    | **Speakers’ Bureau:** Janssen  
**Research Support:** Pharmacyclics, Gilead                                                   |
| Courtney DiNardo, MD                      | **Consultant:** AbbVie, Agios, Celgene  
**Advisory Board:** Karyopharm Therapeutics, Syros Pharmaceuticals, Jazz Pharmaceuticals, MedImmune |
| Guillermo Garcia-Manero, MD               | **Grant and Research Support:** Amphivena, Helsinn, Novartis, AbbVie, Celgene, Astex, Onconova, Merck  
**Consultant:** Celgene, Astex, Amphivena                                                     |
| Ghayas C. Issa, MD                        | No relevant financial relationships                                                                |
| Elias Jabbour, MD                         | **Research Support:** BMS, AbbVie, Pfizer, Amgen, Takeda, Adaptive Biotechnologies                   |
| Nitin Jain, MD                            | **Research Support and Advisory Board:** AbbVie, Pharmacyclics, AstraZeneca, Genentech, Verastem, Pfizer, Servier, ADC Therapeutics, Precision Biosciences, Adaptive Biotechnologies  
**Research Support:** Cellectis, Incyte, Seattle Genetics, Celgene, BMS  
**Advisory Board:** Janssen  
**Grant:** Andrew Sabin Family Foundation                                                        |
| William G. Wierda, MD, PhD                | **Advisory Board:** Genzyme  
**Research Support:** GSK/Novartis, Abbvie, Genentech, Karyopharm, Pharmacyclics LLC, Acerta Pharma, Gilead Sciences, Juno Therapeutics, KITE Pharma, Sunesis, Miragen, Oncternal Therapeutics, Inc., Cyclacel, Loxo Oncology, Inc., Janssen, Xencor |
| Kamatham A. Naidu, PhD                    | No relevant financial relationships                                                                |

All other individuals in a position to control content have no relevant financial relationships to disclose.
Overview of Diagnosis Based on Cytogenetic and Molecular Abnormalities in Patients with ALL

Nitin Jain, MD
Overview of Diagnosis Based on Cytogenetic and Molecular Abnormalities in Patients with ALL

Nitin Jain, MD
Department of Leukemia
MD Anderson Cancer Center
Houston, TX

Conflict of Interest Disclosure

Research Funding
Pharmacyclics, AbbVie, Genentech, BMS, Pfizer, ADC Therapeutics, Seattle Genetics, Inoeye, Celgene, AstraZeneca, Servier, Cellectis, Verastem, Adaptive Biotechnologies, Precision Biosciences

Advisory Board / Honoraria
Pharmacyclics, AbbVie, Genentech, AstraZeneca, Verastem, Pfizer, Servier, Adaptive Biotechnologies, Janssen, Precision Biosciences

Acute Lymphoblastic Leukemia

Kantarjian et al. Cancer 2008

Hunger. NEJM. 2015; 373(16):1541-1552


Reasons Why Pediatric ALL Does Better Than Adult ALL

<table>
<thead>
<tr>
<th>Entity</th>
<th>Prognosis</th>
<th>% Pediatric</th>
<th>% Adult</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperdiploid</td>
<td>Favorable</td>
<td>25-30</td>
<td>5</td>
</tr>
<tr>
<td>t(12;21), ETV6-RUNX1</td>
<td>Favorable</td>
<td>20-25</td>
<td>2</td>
</tr>
<tr>
<td>Ph+ALL</td>
<td>Unfavorable</td>
<td>5</td>
<td>25</td>
</tr>
<tr>
<td>Ph-like ALL</td>
<td>Unfavorable</td>
<td>10</td>
<td>25</td>
</tr>
</tbody>
</table>

Current Genomic Classification of B-ALL

Philadelphia-like (Ph-like) ALL

For Philadelphia Chromosome
Den Boer et al. Lancet Oncology 2008
**Ph-like ALL - Characteristics**

- Gene expression profile = Similar to Ph+ ALL
- No Ph chromosome or BCR-ABL1
- Negative for most recurrent genetic abnormalities (MLL-rearrangement, ETV6-RUNX1, E2A-rearrangement, hyperdiploidy)
- IKZF1 alterations – IKAROS for lymphoid lineage development


---

**2016 WHO Classification**

- B-lymphoblastic leukemia/lymphoma
- B-lymphoblastic leukemia/lymphoma, MDS
- B-lymphoblastic leukemia/lymphoma with recurrent genetic abnormalities
- B-lymphoblastic leukemia/lymphoma with t(9;22)(q34.1;q11.2), BCR-ABL1
- B-lymphoblastic leukemia/lymphoma with t(11q23.3)/MLL-rearrangement
- B-lymphoblastic leukemia/lymphoma with t(12;21)(p13.2;q22.1), ETV6-RUNX1
- B-lymphoblastic leukemia/lymphoma with hyperdiploidy
- B-lymphoblastic leukemia/lymphoma with hypodiploidy
- B-lymphoblastic leukemia/lymphoma with t(1;19)(q23.1;p13.3):TCF3-PBX1

Provisional entity:  B-lymphoblastic leukemia/lymphoma, BCR-ABL1-like
Provisional entity:  B-lymphoblastic leukemia/lymphoma with JAK2V617F
T-lymphoblastic leukemia/lymphoma
Provisional entity:  Early T-cell precursor lymphoblastic leukemia


---

**Ph-like ALL Occurs in 25-30% of Young Adults with B-cell ALL**

---

**Ph-like ALL Molecular Lesions**

- CRLF2 Overexpression (Flow-cytometry)
- JAK2 (JAK2R683) or JAK1 Mutations
- Fusions - ABL1, ABL2, JAK2, EPOR, PDGFRB
- Mutations – IL7R, FLT3, Ras

Roberts et al. NEJM Sept. 2014

---

**Ph-like ALL: CRLF2**

1. Rearrangement of CRLF2:
   - translocation to the immunoglobulin heavy chain enhancer region at 14q32.33 (IGH-CRLF2)
   - a focal deletion proximal to CRLF2 resulting in the expression of a P2RY8-CRLF2 fusion
   - Both alterations result in overexpression of CRLF2 (detectable by flow-cytometry)
   - Half of CRLF2-rearranged cases harbor concomitant activating mutations of JAK2 and JAK1, most commonly at JAK2R683G
   - Potentially amenable to therapy with ruxolitinib

---

**JAK2 Mutations in Ph-like ALL**

Roberts et al. NEJM Sept. 2014
Ph-like ALL: non-CRLF2

II. Alterations activating cytokine receptor and tyrosine signaling

- Genes deregulating tyrosine kinases/receptors
  - NUP214-ABL1, ETV6-ABL1, RANBP2-ABL1, RCSD1-ABL1
  - BCR-JAK2, PAX5-JAK2, STRN3-JAK2
  - EBF1-PDGFRB
  - IGH-EPOR

- Activate signaling pathways
  - ABL1, PDGFRB fusions: Dasatinib
  - JAK2 fusions: Ruxolitinib

CRLF2: Cytokine Receptor–Like Factor

Recurring Kinase Alterations in Ph-like ALL


Ph-like ALL: Incidence (N=148)

Ph-like ALL. Higher MRD+ Rate

<table>
<thead>
<tr>
<th>B-ALL Categories (N=155)</th>
<th>Ph-Like</th>
<th>Ph+</th>
<th>B-other</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>56</td>
<td>46</td>
<td>53</td>
<td></td>
</tr>
<tr>
<td>CR/CRp</td>
<td>50 (89)</td>
<td>43 (93)</td>
<td>50 (94)</td>
<td>0.57</td>
</tr>
<tr>
<td>MRD at CR* (n=98)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MRD Pos</td>
<td>23 (70)</td>
<td>15 (44)</td>
<td>4 (13)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>MRD Neg</td>
<td>10 (30)</td>
<td>19 (56)</td>
<td>27 (57)</td>
<td></td>
</tr>
</tbody>
</table>

MRD assessed by flow-cytometry, sensitivity 0.01%


Ph-like ALL: Poor Prognosis

Ph-like ALL Testing Algorithm MDACC

CRLF2 by Flow

- Patient Eligible for the Trial (RUXO arm)
- CRLF2 FISH (Cyto Lab)
- Non-CRLF2 cases
  - Need to know if a fusion is present
    - Send-out to Child Lab for the fusion assay
      - FISH Cyto lab (ABL2, CSF1R, JAK2, EPOR, PDGFRB)
  - JAK2 (JAK2R683) or JAK1 Mutations
    - 28-gene panel (MDL lab)
      - Send-out to Child Lab
  - If a fusion is detected, patient eligible for the RUXO or DASATINIB arm (depending on the fusion)
Ongoing/Planned Studies: CRLF2-R, JAK2 or EPOR fusion, SH2B3-deleted, IL7R-mutant

- MDACC Study (Jain et al. ASH 2017)
  - RR study, age 10+ years
  - Ruxolitinib dose 25 mg PO BID, alone and with hyperCVAD
- CHOP/UCSF Study (Tasian et al. ASH 2018)
  - Frontline study
  - MRD+ after induction eligible
  - 4-drug induction regimen on or as per AALL1131
  - Ruxo dose 40 mg/m² BID, 2 weeks on, 2 weeks off
- Univ. of Chicago Study
  - Frontline study
  - Standard induction with CALGB 10403
  - Ruxolitinib (Ruxo) added from cycle 2
  - Ruxo dose 40 mg BID, 2 weeks on, 2 weeks off

A Phase 2 Study of Ruxolitinib With Chemotherapy in Children with Philadelphia Chromosome-Like ALL (INCB18424-269/AALL1521): Dose-Finding Results from the Part 1 Safety Phase

- Part 1 findings demonstrate safety and tolerability of ruxolitinib with intensive multi-agent chemotherapy in children and AYAs with newly-diagnosed high-risk Ph-like ALL.
- The RP2D of ruxolitinib is 50 mg/m² BID x 14-days-on/14-days-off (dose level 2).
- Part 2 is actively accruing for efficacy assessment.

Early T Cell Precursor ALL (ETP ALL)

- T-cell Development

Early T-cell Precursor (ETP) Flow-cytometry Definition

- CD1a negative (<5%)
- CD8 negative (<5%)
- Absent or weak CD5 (<75%)
- Presence of 1 or more of myeloid/stem cell marker (>25%)
  - CD117, CD34, HLA-DR, CD13, CD33, CD11b, CD65

WHO Classification T-cell ALL

<table>
<thead>
<tr>
<th>CD1a</th>
<th>CD2</th>
<th>sCD3</th>
<th>CD3</th>
<th>CD4</th>
<th>CD8</th>
<th>CD34</th>
</tr>
</thead>
<tbody>
<tr>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+/–</td>
</tr>
<tr>
<td>Early</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+/–</td>
</tr>
</tbody>
</table>

Cortical T (Thymic T)

<table>
<thead>
<tr>
<th>Pre-T</th>
<th>Pro-T</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Medullary T (Mature T)

<table>
<thead>
<tr>
<th>Cortical T (Thymic T)</th>
<th>Medullary T (Mature T)</th>
</tr>
</thead>
<tbody>
<tr>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

ETP ALL (12% Childhood T ALL) Poor Outcomes

- Overall Survival
- Event-free Survival
- Relapse Rate
**MDACC ETP ALL Project**
- Newly-diagnosed T cell ALL or lymphoblastic lymphoma
- Year 2000 – 2014
- 127 patients identified
  - 16 excluded (insufficient immunophenotype data)
- 111 patients analyzed
  - WHO Classification
  - ETP vs. non-ETP
- 17% of T ALL were ETP ALL
- CR/CRp rate 73% vs. 91% for non-ETP-ALL (p=0.03)

**Overall Survival in T-ALL by Subtype**
CD1a(-), CD8(-), CD5(-/dim), and positivity for one or more stem cell or myeloid antigens

**Survival by WHO Groups and ETP Status**

**Mutations in ETP ALL**
- 142/1241 (11.4%) of adult T-cell ALL is ETP (GMALL)
- FLT3 (ITD and D835V) 35%
- DNMT3A 14%
- NOTCH1 Only 14% (compared to 72% in non-ETP T-cell ALL)
- EZH2 6%

Other:
- Loss-of-function or DN translocations, deletions and sequence mutations in regulators of haematopoietic and lymphoid development (RUNX1, IKZF1, ETV6, GATA3 and EP300)
- Mutations activating Ras and cytokine receptor signaling pathways (NRAS, IL7R, KRAS, JAK1, JAK3, NF1, PTPN11 and SH2B3)
- Loss-of-function mutations targeting chromatin-modifying genes encoding the polycomb repressor complex 2 (PRC2) and SET domain containing 2 (SETD2).

**Treatment Strategy for ETP ALL (2)**
- ETP cells are preferentially sensitive to venetoclax

**Summary**
- Outcomes of adult ALL remain suboptimal
- Inferior outcomes in adult compared to pediatric ALL are associated with increased frequency of high-risk genomic lesions
- Ph-like ALL is a poor risk category ALL driven by activation of kinase signaling, and may be responsive to selective TKIs
- The role of allo SCT and monoclonal antibodies in Ph-like ALL is under investigation
- In ETP ALL, therapy intensification with myeloid regimens, nelarabine, asparaginase and venetoclax is warranted
Thank you

Nitin Jain, MD
Department of Leukemia
MD Anderson Cancer Center
Houston, TX
Novel Therapies for adolescents and young adults (AYA), Philadelphia-positive and Philadelphia-negative Relapsed/Refractory Patients with ALL

Elias Jabbour, MD
Novel Therapies for Patients with Relapsed/Refractory Acute Lymphocytic Leukemia

Elias Jabbour MD
Department of Leukemia
The University of Texas MD Anderson Cancer Center, Houston, TX

April, 2019

Survival of 39,697 Children With ALL Treated on Sequential CCG/COG Clinical Trials

Survival of 972 Adults with Ph-negative ALL

Reasons Why Pediatric ALL Does Better Than Adult ALL

<table>
<thead>
<tr>
<th>Entity</th>
<th>Prognosis</th>
<th>% Pediatric</th>
<th>% Adult</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperdiploid</td>
<td>Favorable</td>
<td>25-30</td>
<td>5</td>
</tr>
<tr>
<td>t(12;21), ETV6-RUNX1</td>
<td>Favorable</td>
<td>20-25</td>
<td>2</td>
</tr>
<tr>
<td>Ph+ALL</td>
<td>Unfavorable</td>
<td>5</td>
<td>25</td>
</tr>
<tr>
<td>Ph-like ALL</td>
<td>Unfavorable</td>
<td>10</td>
<td>25</td>
</tr>
</tbody>
</table>

Ph-like ALL - Characteristics

- Gene expression profile similar to Ph+ ALL
- No Ph chromosome or BCR-ABL1
- Negative for most recurrent genetic abnormalities (MLL-rearrangement, ETV6-RUNX1, E2A-rearrangement, hyperdiploidy)
- IKZF1 alterations—IKAROS for lymphoid lineage development
**Ph-like ALL Molecular Lesions**

- Ph-like 25-30% of ALL; poor prognosis

**Ph-like ALL**

- 80% CRLF2 Overexpression
- 20% Non-CRLF2 cases
- 50% JAK2 (JAK2R683) Mutations
- 50% JAK1 Mutations
- Fusions – ABL1, ABL2, JAK2, EPOR, POSH, Mutations – IL7R, FLT3, RAB

**Non-CRLF2 cases**

- 50%

**Fusions – ABL1, ABL2, JAK2, EPOR, POSH, Mutations – IL7R, FLT3, RAB**

- Add MoAb/BCL-2 inhibitor
- Add TKI if ABL fusions
- MoAb/BCL-2 inhibitor

**Ph-like ALL: Summary and Future Directions**

- Ph-like 25-30% of ALL; poor prognosis
- 50-80% have CRLF2 rearrangement, of which 50% have JAK mutations
- ABL and JAK fusions in CRLF2 non-rearranged cases
- FISH and RT-PCR identifies fusions
- Plans: add TKI if ABL fusions, and antibodies/venetoclax if CRLF2+, to frontline and salvage ALL

**Reasons for Recent Success in Adult ALL Rx**

- Addition of TKIs to chemoRx in Ph-positive ALL
- Addition of rituximab to chemoRx in Burkitt and pre-B ALL
- Potential benefit of addition of CD19 bispecific antibody construct blinatumomab, and of CD22 monoclonal antibody inotuzumab to chemoRx in salvage and frontline ALL Rx
- CAR-T

**The Present... ALL Therapy or “Personalized Therapy”**

<table>
<thead>
<tr>
<th>Entity</th>
<th>Management</th>
<th>% Cure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Burkitt</td>
<td>HCVAD-R x 8; ITx16; R/O-EPOCH</td>
<td>80-90</td>
</tr>
<tr>
<td>Ph-positive ALL</td>
<td>HCVAD + TKI; TKI maintenance; allo SCT in CR1</td>
<td>50+</td>
</tr>
<tr>
<td>T-ALL (except ETP-ALL)</td>
<td>Lots of HD CTX, HD ara-C, Asp; nelarabine?</td>
<td>60</td>
</tr>
<tr>
<td>CD20 – positive ALL</td>
<td>ALL chemo Rx+ rituximab/ Ofatumumab</td>
<td>50</td>
</tr>
<tr>
<td>Ph-like ALL</td>
<td>HCVAD + TKI/MoAbs</td>
<td>77</td>
</tr>
<tr>
<td>AYA</td>
<td>Augmented BFM; HCVAD-R/O</td>
<td>65+</td>
</tr>
<tr>
<td>MRD by FCM</td>
<td>Prognosis; need for allo SCT in CR1</td>
<td>--</td>
</tr>
</tbody>
</table>
**SCT for Ph+ ALL. Pre-TKI**

- Donor (n=60) - 3-year OS: 37%
- No donor (n=43) – 3-year OS: 12%

Dombret H et al Blood 2002

---

**TKI for Ph+ ALL**

- Imatinib; 5-yr OS=43%
- Dasatinib; 5-yr OS=46%
- Ponatinib; 5-yr OS=71%

Daver, Haematologica 2015; Ravandi, Cancer 2015; Jabbour, Lancet Onc 2015; Jabbour, Lancet Hematology 2018

---

**Low-intensity chemo Rx + Dasatinib in Ph+ ALL ≥ 55 yrs**

- 71 pts (2007-2010); median age 69 yrs (58-83)
- Dasatinib 100-140 mg/D, VCR 1mg Q wk, Dex 20-40 mg/D x 2, QwK
- Consolidations: dasatinib 100 mg/D; MTX-Asp C1,3,5; ara-C C2,4,6. Maintenance: dasatinib + POMP
- CR 96%; MMR 65%; CMR 24%
- 5-yr survival 36%; EFS 25%
- T315I at Dx 23% by NGS
- 36 relapses; T315I in 75%


---

**Hyper-CVAD + Ponatinib: Design**

- Intensive phase
- Maintenance phase
- 12 intrathecal CNS prophylaxis
- After the emergence of vascular toxicity, protocol was amended: Beyond induction, ponatinib 30 mg daily, then 15 mg daily once in CMR


---

**Hyper-CVAD + Ponatinib in Ph-Positive ALL: Overall Results**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR*</td>
<td>65/65 (100)</td>
</tr>
<tr>
<td>CCyR**</td>
<td>55/55 (100)</td>
</tr>
<tr>
<td>MMR***</td>
<td>74/76 (97)</td>
</tr>
<tr>
<td>CMR***</td>
<td>64/76 (84)</td>
</tr>
<tr>
<td>Flow negativity***</td>
<td>74/75 (99)</td>
</tr>
<tr>
<td>Early death</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

* 11 pts in CR at start
** 21 pts diploid by CG at start or insufficient metaphases
*** 1 pts no sample

Jabbour. Lancet Hematology 2018

---

**Hyper-CVAD + Ponatinib in Ph-Positive ALL: Survival**

- Median follow up of 36 months (<1-77)

Jabbour. Lancet Hematology 2018
Hyper-CVAD + Ponatinib in Ph+ ALL: Landmark Analysis at 6 Months by SCT

Propensity Score Analysis: HCVAD + Ponatinib vs HCVAD + Dasatinib in Ph-Positive ALL.

CMR in Ph-Positive ALL: OS for CMR vs. Others

Blinatumomab and Inotuzumab in R-R Ph-positive ALL

Questions in Ph-positive ALL

Blinatumomab-ponatinib in Ph-Positive ALL
Hyper-CVD + Ponatinib + Blinatumomab in Ph-positive ALL

Intensive phase
- 1, 2, 3, 4
- 1, 2, 3, 4

Maintenance phase
- Risk-adapted intrathecal CNS prophylaxis (N=12)
- Mini-Hyper-CVD
- Ponatinib 30 mg →15 mg
- Mini-MTX-cytarabine
- Vincristine + prednisone
- Blinatumomab

16 months
5 years

Therapy of Burkitt Leukemia

<table>
<thead>
<tr>
<th>% Survival</th>
<th>MDACC</th>
<th>Germany</th>
<th>CALGB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Therapy</td>
<td>4-year</td>
<td>3-year</td>
<td>4-year</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>50</td>
<td>50</td>
<td>52</td>
</tr>
<tr>
<td>Chemotherapy + Rituximab</td>
<td>77</td>
<td>79</td>
<td>78</td>
</tr>
</tbody>
</table>

Results of the Randomized Intergroup (GRAALL-Lysa) LMBA02 Study

Event Free Survival

Overall Survival

Hyper-CVAD + Rituximab in Precursor B-ALL

- N=97 pts; CR=95%
- <60 yrs: CRD/OS 70% and 75%
- ≥60 yrs: CRD/OS 45% and 28%

Chemo Rx +/- Rituximab: Results of the Randomized GRAALL-R 2005 in Pre B-ALL

- Median follow-up 30 months

Hyper-CVAD + Ofatumumab. Design
Hyper-CVAD + Ofatumumab: Overall Results

<table>
<thead>
<tr>
<th>Parameter</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR/CRp*</td>
<td>65/66 (98)</td>
</tr>
<tr>
<td>CR after induction</td>
<td>63/66 (95)</td>
</tr>
<tr>
<td>MRD negativity at CR</td>
<td>40/63 (63)</td>
</tr>
<tr>
<td>MRD overall</td>
<td>63/68 (93)</td>
</tr>
<tr>
<td>Early death</td>
<td>1/69 (1)</td>
</tr>
</tbody>
</table>

* Median time to negative MRD 0.7 mos

Hyper-CVAD + Ofatumumab: Overall Survival and Complete Remission Duration

- Median follow up of 36 months (4-80)

Hyper-CVAD + Ofatumumab: Overall Survival by CD20 Expression

Pediatric vs Adult ALL Regimens in AYA

- Ages 16-20
  - Pediatric
  - Adult

Pediatric Adult


Augmented BFM and Hyper-CVAD

<table>
<thead>
<tr>
<th>Response</th>
<th>No. (Percent)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABFM (n=106)</td>
<td></td>
</tr>
<tr>
<td>Hyper-CVAD (n=102)</td>
<td></td>
</tr>
<tr>
<td>Complete response</td>
<td>99 (93)</td>
</tr>
<tr>
<td>Induction mortality</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Resistant disease</td>
<td>6 (6)</td>
</tr>
</tbody>
</table>

Under review, 2018
Hyper-CVAD vs. ABFM: Overall Survival

ABFM vs HyperCVAD: Severe Toxicities

<table>
<thead>
<tr>
<th>% Toxicity</th>
<th>ABFM (n=106)</th>
<th>Hyper-CVAD (n=102)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asparaginase allergy</td>
<td>19 N/A</td>
<td>14</td>
<td>NS</td>
</tr>
<tr>
<td>Hypofibrinogenemia</td>
<td>35 11</td>
<td>14 3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Pancreatitis</td>
<td>11 3</td>
<td>3 0.02</td>
<td></td>
</tr>
<tr>
<td>↑ LFTs</td>
<td>41 18</td>
<td>44 18</td>
<td>0.60</td>
</tr>
<tr>
<td>↑ Bili</td>
<td>36 8</td>
<td>18 9</td>
<td>0.001</td>
</tr>
<tr>
<td>Osteonecrosis</td>
<td>9 8</td>
<td>8 9</td>
<td>0.64</td>
</tr>
<tr>
<td>Thrombosis</td>
<td>19 12</td>
<td>12 16</td>
<td>0.16</td>
</tr>
<tr>
<td>Stroke</td>
<td>3 0</td>
<td>0 0.09</td>
<td></td>
</tr>
<tr>
<td>Induction infections</td>
<td>22 45</td>
<td>45 45</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Induction bleeding</td>
<td>1 5</td>
<td>5 0.09</td>
<td></td>
</tr>
<tr>
<td>Infections in CR first 60 days</td>
<td>30 65</td>
<td>65 &lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Bleeding in CR first 60 days</td>
<td>1 5</td>
<td>5 0.09</td>
<td></td>
</tr>
<tr>
<td>Deaths in CR</td>
<td>8 7</td>
<td>7 8</td>
<td>.85</td>
</tr>
</tbody>
</table>

Hyper-CVAD + Blinatumomab in FL B-ALL

Response assessment N (%)

- CR after induction: 14/15 (93)
- CR at any time: 19/19 (100)
- MRD negativity after induction: 17/19 (89)
- MRD negativity at any time: 18/19 (95)
- Early death: 0/15 (0)

Median time to MRD negativity: 17 days

Hyper-CVAD + Blinatumomab in FL B-ALL Outcome

RFS

OS
**Overall Survival in T-ALL by Subtype**

- CD1a(−), CD8(−), CD5(dim), and positivity for one or more stem cell or myeloid antigens

* Low frequency of NOTCH1 mutations, harbors at least one lesion in DNMT3A, IDH1, IDH2, ETV6; hyperactivation of JAK-STAT pathway

**Overall Survival in T-ALL by Subtype: GRAALL Experience**

- 213 ALL (47 ETP; 22%)
  - MRD positivity post induction 20% vs 70% (non ETP)
  - ASCT in CR1 in 49% of ETP-ALL
  - 5-yr OS rates 60% (ETP) vs 66% (non-ETP)

**Venetoclax in ETP-ALL**

- ETP cells are preferentially sensitive to ABT-199
  - ABT-199 + mini-hyper-CVD

**MRD in ALL**

Blinatumomab in ALL MRD-positive

- 116 pts (median age 45 yr; 18-76) with ALL in CR but MRD ≥ 0.1% post ≥ 3 intensive courses; 35% in ≥ CRD2
- 88 pts (78%) MRD-negative post Course 1
- 96 (78%) received allo-SCT

<table>
<thead>
<tr>
<th></th>
<th>Median (mos)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>Overall</td>
<td>MRD negative</td>
</tr>
<tr>
<td>OS</td>
<td>36</td>
<td>39</td>
</tr>
<tr>
<td>RFS</td>
<td>19</td>
<td>35</td>
</tr>
<tr>
<td>DOR</td>
<td>NR</td>
<td>NR</td>
</tr>
</tbody>
</table>

* No difference in OS (HR=1.39; p=0.37) and RFS (HR=0.89; p=0.73) between allo-SCT vs no allo-SCT
Blinatumomab in ALL MRD-positive


- 113 pts Rx. Post blina MRD-negative 88/113=78%
- 110 evaluated (blasts <5%, MRD+). 74 received alloSCT. Median FU 53 mos
- Median OS 36.5 mos; 4-yr OS 45%; 4-yr OS if MRD-negative 52%
- Continuous CR 30/74 post alloSCT (40%); 12/36 without SCT (33%)

ALL Salvage Standards of Care in 2019

- Refer for investigational therapies— MoAb + ChemoRx; CAR-T
- Ph-positive ALL-- TKIs+ chemoRx; blinatumomab
- Pre-B ALL--
  - Blinatumomab (FDA approval 12.2014)
  - Inotuzumab (FDA approval 8.2017)
- T ALL: nelarabine
- ChemoRx: FLAG IDA, Hyper CVAD, augmented HCVAD, MOAD

Historical Results in R/R ALL

- Poor prognosis in R-R ALL Rx with standard of care (SOC) chemotherapy

<table>
<thead>
<tr>
<th>Rate (95% CI)</th>
<th>No prior salvage (S1)</th>
<th>One prior salvage (S2)</th>
<th>22 prior salvages (S3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rate of CR, %</td>
<td>40</td>
<td>21</td>
<td>11</td>
</tr>
<tr>
<td>Median OS, months</td>
<td>5.8</td>
<td>3.4</td>
<td>2.9</td>
</tr>
</tbody>
</table>

ALL -- Historical Survival Rates after 1st Relapse

MRC UKALL2/ ECOG2993 Study (n=609)
- Outcome of patients after 1st relapse
  - 2-yr OS: 11% & 5-yr OS: 8%

LALA-94 Study (n=421)
- Outcome of patients after 1st relapse
  - 5-yr OS: 7%

Blinatumomab vs ChemoRx in R-R ALL (Phase 3 TOWER)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Blinatumomab</th>
<th>Chemo Rx</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>% CR</td>
<td>34</td>
<td>16</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>% marrow CR</td>
<td>44</td>
<td>25</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>% MRD negative in CR</td>
<td>76</td>
<td>48</td>
<td>--</td>
</tr>
<tr>
<td>Median OS (mos)</td>
<td>7.7</td>
<td>4.0</td>
<td>.01</td>
</tr>
<tr>
<td>Safety Profile</td>
<td>CRSNE+++</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- 113 pts Rx. Post blina MRD-negative 88/113=78%
- 110 evaluated (blasts <5%, MRD+). 74 received alloSCT. Median FU 53 mos
- Median OS 36.5 mos; 4-yr OS 45%; 4-yr OS if MRD-negative 52%
- Continuous CR 30/74 post alloSCT (40%); 12/36 without SCT (33%)
**Phase 3 TOWER Study: Survival by Salvage**

- **K-M Median (95% CI), months**
  - S1: Blinatumomab: 5.5 (3.7, 9.0)
  - S2+: Blinatumomab: 3.0 (2.1, 4.0)

- **K-M Median (95% CI), months**
  - S1: SOC chemotherapy: 11.1 (8.2, NR)
  - S2+: SOC chemotherapy: 5.1 (3.2, 7.1)

- **NR** = not reached

- **Stratified log-rank P =**
  - S1: Blinatumomab
  - S2+: Blinatumomab

- **S1: Stratified log-rank P = 0.016**
- **S2+: Stratified log-rank P = 0.055**

**Inotuzumab vs ChemoRx in R-R ALL**

**Parameter** | **INO** | **Chemo Rx** | **p value**
---|---|---|---
% CR/CRi | 81 | 29 | <.0001
% MRD negative in CR | 78 | 28 | <0.0001
Median OS (mos) | 7.7 | 6.2 | .01
**Safety Profile**

**VOD +++**

**Impact of MRD in R-R ALL Rx with INO**

**VOD/SOS Among InO-Treated Pts**
- VOD incidence: InO, 13% (n=22) vs SOC, 1% (n=1)
- 5 (3%) pts had VOD during study Rx (2 with pre-study SCT)
- 77/164 (47%) on InO had post-study SCT vs 33/162 (20%) in the SOC arm
- 17/77 (22%) on InO had VOD post-SCT (5/17 also had pre-study SCT)
- Median (range) time to VOD after SCT: 15 (3–57) days

**Overall Survival: 2-yr F/U**

**MVA Analysis of Factors Associated With Post-SCT VOD**

<table>
<thead>
<tr>
<th>Factor</th>
<th><strong>CR (95% CI)</strong></th>
<th><strong>P value</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Alkylator conditioning (dual vs single)</td>
<td>7.8 (1.7–33.8)</td>
<td>.008</td>
</tr>
<tr>
<td>Age (≥55 vs &lt;55 y)</td>
<td>4.8 (1.5–22.0)</td>
<td>.043</td>
</tr>
</tbody>
</table>
MiniHCVD-INO-Blina in ALL: Design

- Dose reduced HyperCVD for 4-8 courses
  - Cyclophosphamide (150 mg/m² x 6) 50% dose reduction
  - Dexamethasone (20 mg) 50% dose reduction
  - No anthracycline
  - Methotrexate (250 mg/m²) 75% dose reduction
  - Cytarabine (0.5 g/m² x 4) 83% dose reduction
- Inotuzumab on D3 (first 4 courses)
  - Modified to 0.9 mg/m² C1 (0.6 and 0.3 on D1&8) and 0.6 mg/m² C2-4 (0.3 and 0.3 on D1&8)
- Rituximab D2 and D8 (first 4 courses) for CD20+
- IT chemotherapy days 2 and 8 (first 4 courses)
- Blinatumomab 4 courses and 3 courses during maintenance
- POMP maintenance for 3 years, reduced to 1 year

Historical Comparison

INO + mini-HCVD +/- Blinatumomab in S1: Overall Survival/Progression-free Survival

Response by Salvage (N=89)

<table>
<thead>
<tr>
<th>Response</th>
<th>N</th>
<th>(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Salvage 1</td>
<td>51/56</td>
<td>91</td>
</tr>
<tr>
<td>S1, Primary refractory</td>
<td>5/5</td>
<td>100</td>
</tr>
<tr>
<td>S1, CRD1 &lt; 12 mos</td>
<td>19/23</td>
<td>83</td>
</tr>
<tr>
<td>S1, CRD1 ≥ 12 mos</td>
<td>27/28</td>
<td>96</td>
</tr>
<tr>
<td>Salvage 2</td>
<td>9/16</td>
<td>56</td>
</tr>
<tr>
<td>≥ Salvage 3</td>
<td>9/15</td>
<td>60</td>
</tr>
<tr>
<td>Overall</td>
<td>69/87</td>
<td>79</td>
</tr>
<tr>
<td>MRD negativity</td>
<td>55/67</td>
<td>82</td>
</tr>
<tr>
<td>Salvage 1</td>
<td>42/48</td>
<td>86</td>
</tr>
<tr>
<td>≥ Salvage 2</td>
<td>13/18</td>
<td>72</td>
</tr>
<tr>
<td>Early death</td>
<td>7/87</td>
<td>8</td>
</tr>
</tbody>
</table>

Mini-HCVD + INO ± Blinatumomab in R/R ALL CR Duration and OS (Median F/U 31 months)

Optimizing Outcome

- Earlier Administration
  - S1 or MRD vs later
- Combination
  - Better efficacy
  - Lower dose
  - Financial benefit (OS 7 vs 14 months)
- Combination and better safety profile
  - Less CRS
  - Less VOD
- Using NGS
  - Compare outcome by NGS
  - NGS vs FCM

Tisagenlecleucel (CD19-CART) in R-R ALL

- 113 pts screened; 97 enrolled; 79 infused
  - Median age 11 yrs (3-24)
  - CR-CRi 65/97=66%; MRD-negative in 64
  - CRS grade 3-4 48%; CNS grade 3 13%
  - 18-mo OS 70%; RFS 66%
  - Ongoing responses 29 pts

Salvage Therapies in ALL

- Very effective salvage therapy in R/R ALL
  - High MRD negativity rate
  - Best outcome in Salvage 1
- Combination with low dose chemotherapy
  - Safe and effective
  - Median survival 14 months
  - Salvage-1 24 months (2-year OS rate >50%)
  - AE better controlled
  - CRS: debulk with sequential chemotherapy
  - VOD lower doses explored
- Sequential combination chemotherapy and inotuzumab with blinatumomab in frontline ongoing
  - Salvage-1 24 months (2-year OS rate >50%)
  - High efficacy in newly diagnosed elderly ALL (3-year survival rate of 56%)
  - VOD: Lower dose into schedules being explored
**Elderly ALL: Historical Results**

<table>
<thead>
<tr>
<th></th>
<th>MDACC</th>
<th>GMALL</th>
<th>SEER</th>
<th>Medicare</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>122</td>
<td>268</td>
<td>1675</td>
<td>727</td>
</tr>
<tr>
<td>Median Survival (mos)</td>
<td>15</td>
<td>NA</td>
<td>4</td>
<td>10</td>
</tr>
<tr>
<td>OS (%)</td>
<td>20 (3-yr)</td>
<td>23 (5-yr)</td>
<td>13 (3-yr)</td>
<td>NA</td>
</tr>
</tbody>
</table>

**Mini-HCVD + INO ± Blinatumab in R/R ALL Modified Design**

**Intensive phase**
- Mini-HCVD
- Mini-MTX-cytarabine
- Blinatumomab
- IT MTX, Ara-C
- POMP

**Consolidation phase**
- INO
- Total dose (mg/m²)
- Dose per day (mg/m²)
  - C1
  - 0.9
  - 0.5 DL, 0.3 DB
  - C2-4
  - 0.6
  - 0.5 DL and DB
- Total INO dose = 2.7 mg/m²

**Maintenance phase**
- 18 months

**Mini-HCVD + INO ± Blinatumab in Older ALL: Response Rates**

<table>
<thead>
<tr>
<th>Response</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR</td>
<td>55 (96)</td>
</tr>
<tr>
<td>CR</td>
<td>49 (88)</td>
</tr>
<tr>
<td>CRp</td>
<td>5 (9)</td>
</tr>
<tr>
<td>CRi</td>
<td>1 (2)</td>
</tr>
<tr>
<td>No response</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Early death</td>
<td>0</td>
</tr>
<tr>
<td>Flow MRD response</td>
<td>N (%)</td>
</tr>
<tr>
<td>D21</td>
<td>45/58 (78)</td>
</tr>
<tr>
<td>Overall</td>
<td>56/59 (95)</td>
</tr>
</tbody>
</table>

* 4 pts were enrolled in CR

**Mini-HCVD + INO ± Blinatumab in Older ALL: CRD and OS (Entire Cohort)**

**Mini-HCVD + INO ± Blinatumab vs. HCVAD in Elderly ALL: Response and Outcome**

<table>
<thead>
<tr>
<th></th>
<th>Pre-matched Cohort</th>
<th>Matched Cohort</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>mini-HCVD +INO ±Blna</td>
<td>HCVAD P</td>
</tr>
<tr>
<td>(N=55)</td>
<td>(N=77)</td>
<td>(N=38)</td>
</tr>
<tr>
<td>Response (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CR/CRi/CRp</td>
<td>53/54 (98)</td>
<td>68/77 (88)</td>
</tr>
<tr>
<td>Early death</td>
<td>0</td>
<td>6 (8)</td>
</tr>
<tr>
<td>Death in CR w/ 3 months</td>
<td>3 (5)</td>
<td>13 (17)</td>
</tr>
</tbody>
</table>

* VOD: 5 pt (9%) in prematched, 1 pt (3%) in matched

**Mini-HCVD + INO ± Blinatumab vs. HCVAD in Elderly ALL: Overall Survival**
How Should targeted Rx's be used in Acute Leukemia?

- Very expensive as single agents, with limited/modest response rates and survival prolongation
- FDA approval for many is as single agents, and in R-R disease
- FDA approval may also use historical, perhaps suboptimal dose-schedules – eg midostaurin 2 wks x 2 courses; inotuzumab 1.8mg/m²
- Thus, FDA approved regimens may not offer good “Rx value”; may deliver suboptimal efficacy and excess toxicity
- Studies ongoing to define better dose schedules, combinations with ChemoRx and with cocktails of targeted Rx's
- How should they be used today, in standard of care, until more data?
- I propose use as per peer-reviewed publications, when new data significantly better and safer

How Might Future Optimal ALL Regimens Look Like?

- Intensive Phase
- Consolidative Phase I
- Consolidative phase II
- CAR-T
  - Total Rx 10-11 mo; Chemo Rx minimal = 4 mo
  - Possible better CD19, CD22, CD123 MoAb or bispecific Ab constructs

Survival of 972 Adults with Ph-negative ALL

- 972 pts Rx 1980-2016; median F/U 10.4 years

HyperCVAD in ALL- Dynamic Bayesian Strategy to Answer Multiple Questions

- Ph-positive ALL: HCVAD+ponatinib vs miniCVD+ponatinib vs ponatinib+blinatumomab
- Dose of inotuzumab: 1.8 vs 0.9 mg/m² (0.6/0.3); number of courses (not to exceed 5.4mg/m² total)
- Courses of blinatumomab: 4 vs 7-8
- Schedules combining chemoRx with inotuzumab and blinatumomab
- Duration and intensity of chemoRx: 3 vs 1 year; HCVAD vs miniCVD
- Role of allo SCT; CAR-T to replace SCT as consolidation in CR1
- IT prophylaxis: 3 vs more
- Venetoclax in T and pre-B ALL

Survival of 972 Adults with Ph-negative ALL

- 972 pts Rx 1980-2016; median F/U 10.4 years
Survival of 972 Adults with Ph-negative ALL
• 972 pts Rx 1980-2016; median F/U 10.4 years

15%
79%
44%
8%
70%

New Entities
MoAb
CAR T-cell Therapy
BCL-2 Inhibitors
Less intensive Rx

The Future of ALL Therapy...

It is plausible that incorporating active monoclonal antibodies/CAR T-cells Rx into frontline adult ALL therapy, in a concomitant or sequential fashion, may induce higher rates of MRD negativity and increase the cure rates to levels achieved in pediatric ALL, and may reduce the need for allo-SCT and intensive and prolonged chemotherapy schedules.

Sasaki. Blood 2025; 128:3975
Jabbour E. Blood 125: 4010; 2015

Thank You

Elias Jabbour MD
Department of Leukemia
The University of Texas MD Anderson Cancer Center
Houston, TX
Overview of Disease Classification and Prognostic Stratification in Patients with AML

Coutney DiNardo, MD
Disease Classification and Prognostic Stratification in Acute Myeloid Leukemia

Courtney DiNardo, MD MSCE
Department of Leukemia
MD Anderson Cancer Center
Houston, TX

Conflict of Interest Disclosure

• Research Support (to institution):
  • Abbvie, Agios, Bayer, Calithera, Celgene, Daiichi-Sankyo, Novartis

• Consultant/Advisory Board:
  • Abbvie, Agios, Bayer, Celgene, Jazz, Karyopharm, MedImmune, Syros

Principles of AML Therapy

- Consider age, performance status, comorbidities, cytogenetics/molecular genetics, patient with
  - Young, fit patients
  - Older, less fit patients
- Induction or front-line treatment: intensive or lower intensity
- Consolidation therapy
- Allogeneic HCT in patients with approximately 10% risk of relapse

CR rate: ~75% in young pts
40-50% in > 60 yr olds

CR rate: ~25% with HMA
<20% with LDAC

Age, Survival, and Treatment Era in AML


5-Year Survival in Patients With AML

Age at Diagnosis, y

58.4 41.0 29.8 12.5 2.6

5-Year Survival Among US Patients With AML, Stratified by Age at Diagnosis (2007-2013)

Health Care Utilization for Older Patients with AML

Health related services received within last 10 years of life
Genomics in AML: Prognostic and Therapeutic Implications

Cytogenetics in AML

Historical Prognostication in AML:
- Age
- Performance Status
- Cytogenetics


www.nccn.org

Cytogenetic and Mutational Landscape of AML

2017 ELN Risk Stratification by Genetics

Risk Category | Genetic lesions
--- | ---
Favorable | ETV6-RUNX1, NPM1 mutation, KIT mutation, 5q deletion
Intermediate | Mutations in FLT3, NPM1, and RUNX1
Advances | Mutations in ASXL1, TP53, IDH1, IDH2, SF3B1

Risk Category | Genetic lesions
--- | ---
Favorable | ETV6-RUNX1, NPM1 mutation, KIT mutation, 5q deletion
Intermediate | Mutations in FLT3, NPM1, and RUNX1
Advances | Mutations in ASXL1, TP53, IDH1, IDH2, SF3B1

Molecular Classes and Concurrent Mutations

Updated AML Genomic Classifications


Haferlach C et al, ASH 2016
NPM1 Mutations in AML

- Occur in 1/3 of AML, 1/2 of CN-AML
- Distinct expression profile, stable throughout disease course
- NPM1 mutated AML, without FLT3-ITD or DNMT3A, shows chemosensitivity and overall favorable outcomes

CEBPα Mutations in AML

- Mutations in ~10% of CN-AML
- Key transcription factor involved in lineage-specific myeloid differentiation
- Biallelic (i.e. double mutant or dm) CEBPα mutated patients show favorable prognosis

Individualizing Therapy: AraC-based

Better selection of patients for intensive cytarabine-based chemotherapy
- CBF leukemia
- Diploid, FLT3-ITD neg AML with NPM1, dmCEBPα, tIDH2-R172

Individualizing Therapy: HMA-based Treatment

Adult MDS/AML pts treated with decitabine
- n=116 patients
- n=108 10-day DAC
- Median age 74 yrs (29-88)
- n=43 unfavorable karyotype
- n=21 TP53-mutated (20 CR-AML)
Initial Therapy for Adult AML Patients
Fit for Intensive, Potentially Curative Chemotherapy

Patients with AML sensitive to conventional chemotherapeutic agents:
- CBF leukemia
- Diploid AML with NPM1 or CEBPα mutation
- Younger patients; esp without AHD/tAML

Current Paradigm for the Initial Treatment of AML

Complete response?

Induction therapy → Consolidation chemotherapy → Risk Stratify

Initial Diagnosis of AML → Complete response?

Primary refractory → Allogeneic Hematopoietic Stem Cell Transplant

Recurrence? → Salvage therapy

Complete response?

Cumulative Incidence of Relapse

MRC 15: FLAG-Ida vs. ADE

OS p=NS

Cumulative incidence of Relapse

p=0.001

Death in CR

p=0.02

Initial Therapy for Older AML Patients
Fit for Intensive, Potentially Curative Chemotherapy

CPX-351 (Vyxeos): Liposomal Formulation of Cytarabine and Daunorubicin Encapsulated at a 5:1 Molar Ratio

- Fixed molar ratio maintained in human plasma for at least 24 hours after final dose
- Selective uptake by leukemic vs normal cells in bone marrow of leukemia-bearing mice

CPX-351 Study Design
Randomized, open-label, parallel-arm, 1:1 randomization

Key Eligibility
- Previously untreated
- Ages 60–75
- Able to tolerate intensive therapy
- EGOG PS 0–2

Stratifications:
- Therapy-related AML
- AML with history of MDS with and without prior HMA therapy
- AML with history of CMMML
- De novo AML with NCCN cytogenetic
  - 60–69 years
  - 70–75 years

Follow-up:
- Death or CR
- 5 years

Lancet J et al, JCO 2018
<table>
<thead>
<tr>
<th></th>
<th>CYF-351 m=151</th>
<th>723 m=156</th>
<th>Hazard Ratio</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Event-Free Survival</td>
<td>2.53 (2.07, 4.99)</td>
<td>1.31 (1.38, 1.64)</td>
<td>1.76</td>
<td>0.021</td>
</tr>
<tr>
<td>Remission Duration</td>
<td>6.93 (4.60, 9.23)</td>
<td>6.11 (4.15, 8.71)</td>
<td>0.77</td>
<td>0.291</td>
</tr>
<tr>
<td>Deaths ≤ 60 Days*</td>
<td>13.8%</td>
<td>21.8%</td>
<td>Odds Ratio</td>
<td>P value</td>
</tr>
<tr>
<td>CR</td>
<td>37.3%</td>
<td>25.6%</td>
<td>1.67 (1.02, 2.74)</td>
<td>0.040</td>
</tr>
<tr>
<td>CRi/CRI</td>
<td>47.7%</td>
<td>33.3%</td>
<td>1.77 (1.11, 2.81)</td>
<td>0.016</td>
</tr>
<tr>
<td>Stem Cell Transplant</td>
<td>34.0%</td>
<td>25.0%</td>
<td>1.54 (0.92, 2.56)</td>
<td>0.098</td>
</tr>
</tbody>
</table>

**Exploratory Analysis by Age: Overall Survival**

- Age 60–69 years, hazard ratio of 0.68 (95% CI: 0.49, 0.95)
- Age 70–75 years, hazard ratio of 0.55 (95% CI: 0.36, 0.84)

**Initial Therapy for Adult AML Patients**

UNFIT for Intensive Cytotoxic Chemotherapy

Patients with AML resistant to conventional chemotx

- Adverse cytogenetics and/or TP53 mutations
- Patients with AHD/tAML
- Older patients and/or significant comorbidities

**Survival of Older AML Patients: Population Based**

SEER-Medicare 2000-2007

38.6% received therapy

Median age: 78 years

Median OS: 3 mo

OS treated: 6 mo

OS untreated: 2 mo

Allo HSCT: 0.8%

Oran and Weisdorf, Haematologica 2012

**AZA or DAC + Venetoclax for Newly dx Unfit AML**

Venetoclax with HMAs induces rapid, deep, and durable responses in older patients with AML | ASH 2018
**Molecular Determinants of Outcome with Venetoclax Combos**

<table>
<thead>
<tr>
<th>CR/CRi</th>
<th>HMA + VEN</th>
<th>LDAC + VEN</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=243, median age 73</td>
<td>N=84, median age 75</td>
<td></td>
</tr>
<tr>
<td>Median OS: 10.4m</td>
<td>Median OS: 16.9m</td>
<td></td>
</tr>
<tr>
<td>1 year OS: 46.5%</td>
<td>1 year OS: 57%</td>
<td></td>
</tr>
<tr>
<td>CR/CRi 28%</td>
<td>CR/CRi 71%</td>
<td></td>
</tr>
<tr>
<td>AZA</td>
<td>AZA + VEN</td>
<td></td>
</tr>
<tr>
<td>Early death 7.5%</td>
<td>Early death 2%</td>
<td></td>
</tr>
</tbody>
</table>

**Evaluation (and Targeting) of MRD in AML**

- Quantification of MRD increasingly important in patients achieving CR to better assess risk of relapse

<table>
<thead>
<tr>
<th>METHOD</th>
<th>TARGET</th>
<th>SENSITIVITY</th>
<th>PROS/CONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytogenetics</td>
<td>Chromosomal abnormalities</td>
<td>1 in 20 (5%)</td>
<td>Cheap, readily available; Applicable for ~50% AML</td>
</tr>
<tr>
<td>Flow Cytometry</td>
<td>Leukemia-associated aberrant immunophenotype (LAMP)</td>
<td>1 in 10,000 (0.01%)</td>
<td>Applicable to most AML; Relatively cheap; Not easily standardized</td>
</tr>
<tr>
<td>RT-PCR</td>
<td>Fusion transcripts (CBF1), gene mutations (NPM1)</td>
<td>Up to 1 in 1,000,000 (0.0001%)</td>
<td>Highly sensitive; Very standardized; Applicable for ~30-40% AML</td>
</tr>
</tbody>
</table>

**Minimal/Measurable Residual Disease (MRD)**

**PCR Based MRD for AML in CR1 with NPM1 Mutation**

Most prognostic time-point was after 2nd cycle of HIDAC consolidation.
Importance of MRD Prior to AlloSCT

- 358 consecutive patients undergoing alloHCT in 1st or 2nd morphologic CR/CRi or with active disease

Conclusions

• Improved understanding of the genomic landscape of AML has contributed to a refined disease classification, better prognostication, and is informing the development of targeted agents

• Integrated evaluation of baseline and on treatment factors and assessment of MRD will improve risk assessment, and inform post-remission therapy

• Expanded treatment options are now available, and are leading to improved AML clinical outcomes

THANK YOU!

Questions: cdinardo@mdanderson.org
Treatment Options with Novel IDH1/2, FLT3 and CD33 Targeted Agents in Genomic Subgroups of AML

Courtnery DiNardo, MD
Targeted Therapeutics in Acute Myeloid Leukemia

April 27, 2019

Courtney DiNardo, MD
Department of Leukemia
UT MD Anderson Cancer Center
Houston, TX

Conflict Interest Disclosure

• Research Support (to institution):
  – Abbvie, Agios, Bayer, Calithera, Celgene, Daiichi-Sankyo, Novartis

• Consultant/Advisory Board:
  – Abbvie, Agios, Bayer, Celgene, Jazz, Karyopharm, MedImmune, Syros

Chemotherapy first introduced for AML in 1960s
Cytarabine + anthracycline regimens (3+7) become standard of care for AML in 1970s
Allogeneic stem-cell transplantation shows OS advantage in younger AML pts

2012: Decitabine approved for older AML in EU, but not in US
2015: Azacitidine approved for older AML >30% blasts in EU

Midostaurin plus induction/consolidation chemo for untreated FLT3-mut AML
Gilteritinib for mFLT3 R/R AML
Enasidenib for mIDH2 R/R AML
Ivosidenib for mIDH1 R/R AML
CPX-351 for untreated t-AML or AML-MRC
Gemtuzumab +/- induction for CD33+ AML
HMA or LDAC + Venetoclax in untreated elderly unfit AML
LDAC + glasdegib in untreated elderly unfit AML

2017-2018

2000: Gemtuzumab approved in US in R/R but withdrawn in 2010 due to toxicities

Targeting FLT3 Mutations

• FLT3-ITD in ~25% and FLT3-TKD in ~10% AML
• More frequent in younger pts, de novo AML and diploid cytogenetics
• Leads to constitutive activation of FLT-3 receptor
• FLT3-ITD independent predictor of poor prognosis

Characteristics of FLT3 Mutations in AML

Clinical settings for FLT3 TKI in FLT3mut AML

Relapsed/refractory AML
  - Monotherapy (giltertinib, quizartinib)
  - Combination with salvage chemotherapy (crenoalanib)

De novo AML
  - TKIs plus 7+3 induction and consolidation (fit) (mido, cren, gilt, quiz)
  - TKIs plus low dose chemotherapy (i.e. AZA + gilt, mido, quiz, cren)

Maintenance of AML
  - Post allogeneic stem cell transplantation (mido, sorafenib, giltertinib)

*Italics indicates not (yet) approved for this indication
Phase 3 RATIFY Study: Chemotherapy ± Midostaurin in Newly Diagnosed AML

CALGB 10603

FLT3-ITD or FLT3-TKD

Age ≤ 60 y

Treatment-naïve patients with AML with activating FLT3 mutations (N = 717)

Cytarabine (200 mg/m²/d, d 1-7) + Daunorubicin (60 mg/m²/d, d 1-3) + Midostaurin (50 mg twice daily, d 8-21)

Cytarabine (200 mg/m²/d, d 1-7) + Daunorubicin (60 mg/m²/d, d 1-3) + Placebo (twice daily, d 8-21)

High-dose cytarabine (3 g/m²/d twice daily, d 1, 3, 5) + Midostaurin (50 mg twice daily, d 8-21)

High-dose cytarabine (3 g/m²/d twice daily, d 1, 3, 5) + Placebo (twice daily, d 8-21)

Midostaurin (50 mg twice daily, d 1-28)

Placebo (twice daily, d 1-28)

**CR** by day 60

Rate

327 patients screened - 906 mFLT3 patients identified - 717 randomized

*Identification: mFLT with allelic ratio <0.7 vs ≥0.7

In RATIFY, OS Showed Improvement Across All FLT3 Subgroups

<table>
<thead>
<tr>
<th>N</th>
<th>HR (95% CI)</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall (intentional)</td>
<td>717</td>
<td>0.78 (0.68-0.90)</td>
</tr>
<tr>
<td>FLT3-ITD high</td>
<td>214</td>
<td>0.80 (0.57-1.12)</td>
</tr>
<tr>
<td>FLT3-ITD low</td>
<td>341</td>
<td>0.61 (0.40-1.11)</td>
</tr>
<tr>
<td>FLT3-TKD</td>
<td>162</td>
<td>0.65 (0.39-1.09)</td>
</tr>
</tbody>
</table>

Individualizing Therapy: FLT3 Inhibitors

- Selective vs multikinase FLT3i preferable?
- Off target effects (i.e. KIT)
- Resistance mutations (D835, others)
- Best schedule and combination?
- Will combinations with more selective FLT3 inhibitors be transformative?

**Selective, Potent FLT3 Inhibitors in AML**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Half-Life (Dosing)</th>
<th>3D3 Activity</th>
<th>Single Agent</th>
<th>Dose (months) (Grade 1-2)</th>
<th>Post-HCT Maintenance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quizartinib (AC220)</td>
<td>Long; once daily</td>
<td>No</td>
<td>Phase 3 completed</td>
<td>Myelosuppression, Diaphanositis, QT prolongation</td>
<td>Pilot study completed, included in phase 3</td>
</tr>
<tr>
<td>Crenolanib</td>
<td>Short; twice daily</td>
<td>Yes</td>
<td>Phase 2 completed</td>
<td>Fluid retention, LFT elevation, NV</td>
<td>Phase 2 ongoing</td>
</tr>
<tr>
<td>Gilteritinib (ASP2215)</td>
<td>Long; once daily</td>
<td>Yes</td>
<td>Phase 3 completed</td>
<td>Myelosuppression, LFT elevation, Diaphanositis</td>
<td>Pilot study completed, phase 3 ongoing</td>
</tr>
</tbody>
</table>

**QuANTUM-R Study Design**

Primary endpoint: overall survival

Secondary endpoints: event-free survival

Select eligibility: AML with FLT3-ITD or FLT3-TKD

Entry criteria: May 2014 to September 2017

Data cutoff: February 2018

Quizartinib (n = 245)

30 mg × 15 days × 48 days ± 450 mg or 600 mg on day 49 or day 56

Savage chemotherapy

Leuco (n = 24)

M2C (n = 48) or SKSD-A (n = 50)

HSCT

Optional treatment

**QuANTUM-R Best Response**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Quizartinib</th>
<th>Salvage Chemotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Best response</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CR</td>
<td>48 (42-55)</td>
<td>27 (19-36)</td>
</tr>
<tr>
<td>CRp</td>
<td>4 (2-7)</td>
<td>3 (0-5)</td>
</tr>
<tr>
<td>CRi</td>
<td>40 (34-47)</td>
<td>26 (19-35)</td>
</tr>
<tr>
<td>CRc</td>
<td>21 (16-27)</td>
<td>3 (1-8)</td>
</tr>
<tr>
<td>ORR (CRc + PR)</td>
<td>69 (63-75)</td>
<td>30 (22-39)</td>
</tr>
<tr>
<td>No response</td>
<td>25 (20-31)</td>
<td>37 (28-46)</td>
</tr>
<tr>
<td>Non-evaluable</td>
<td>5 (3-9)</td>
<td>33 (25-42)</td>
</tr>
</tbody>
</table>

Duration of CRc: quizartinib 12 weeks; salvage chemo 5 weeks
HSCT rate: quizartinib 32%; salvage chemo 12%

**QuANTUM-R Overall Survival**

HR, 0.76 (95% CI, 0.58-0.98)

**Gilteritinib: ADMIRAL Phase III Trial in RR FLT3mut AML**

<table>
<thead>
<tr>
<th>Parameter*</th>
<th>Gilteritinib (n=247)</th>
<th>Salvage Chemotherapy (n=124)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR, n (%)</td>
<td>52 (21)</td>
<td>13 (11)</td>
</tr>
<tr>
<td>CRh, n (%)</td>
<td>32 (13)</td>
<td>6 (5)</td>
</tr>
<tr>
<td>CRi, n (%)</td>
<td>63 (26)</td>
<td>14 (11)</td>
</tr>
<tr>
<td>CRp, n (%)</td>
<td>19 (8)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>CRc, n (%)</td>
<td>134 (54)</td>
<td>27 (22)</td>
</tr>
<tr>
<td>CR/CRh, n (%)</td>
<td>84 (34)</td>
<td>13 (11)</td>
</tr>
<tr>
<td>PR, n (%)</td>
<td>33 (13)</td>
<td>5 (4)</td>
</tr>
<tr>
<td>ORR, n (%)</td>
<td>167 (68)</td>
<td>32 (24)</td>
</tr>
<tr>
<td>NR, n (%)</td>
<td>66 (27)</td>
<td>43 (35)</td>
</tr>
</tbody>
</table>

Median duration of drug exposure (range), months
4.1 (0.1–29.1) 0.9 (0.2–7.1)

Median time to achieve CRc (95% CI), months
1.8 (0.9, 2.9) 1.8 (0.9, 2.9)

Median DoR† (95% CI), months
11.0 (4.6, NE) 1.8 (NE, NE)

Allogeneic HSCT, n (%) 63 (26) 19 (15)

*Response was not evaluable in 14 patients (6%) in the gilteritinib arm and in 49 patients (40%) in the salvage chemotherapy arm.
†Duration of remission was defined as the duration of CR/CRh post alloSCT

**ADMIRAL Trial: Overall Survival (n=371)**

**ADMIRAL trial: Post-HSCT Survival in the Gilteritinib Arm**

**Response Outcomes (ITT Population: N=371)**

**ADMIRAL Trial: Overall Survival**

HR, 0.76 (95% CI, 0.58-0.98)

**ADMIRAL Trial: Post-HSCT Survival in the Gilteritinib Arm**

**Effect of Maintenance Therapy (Landmark Analysis Day 60 Post-HSCT, n=51)**

**Response Outcomes (ITT Population: N=371)**

Response was not evaluable in 12 patients (3%) in the gilteritinib arm and in 28 patients (7%) in the salvage chemotherapy arm.

Duration of remission was defined as the duration of CR/CRh post alloSCT

**ADMIRAL Trial: Overall Survival**

HR, 0.76 (95% CI, 0.58-0.98)

**ADMIRAL Trial: Post-HSCT Survival in the Gilteritinib Arm**

Effect of Maintenance Therapy (Landmark Analysis Day 60 Post-HSCT, n=51)
**De novo younger fit FLT3\textsuperscript{mut} AML patients**

<table>
<thead>
<tr>
<th>FLT3 TKI</th>
<th>No. pts</th>
<th>CR/CRi/CRh</th>
<th>2 yr OS</th>
<th>Ongoing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Midostaurin + 7+3</td>
<td>N=717 (ph 3)</td>
<td>59%</td>
<td>60%</td>
<td>AraC/DNR vs. AraC/Ida</td>
</tr>
<tr>
<td>Quizartinib + 7+3</td>
<td>n=16 (ph 1)</td>
<td>84%</td>
<td>Ph 3 ongoing</td>
<td>Phase 3 (7+3) ongoing</td>
</tr>
<tr>
<td>Crenolanib + 7+3</td>
<td>N=38 (ph 2)</td>
<td>88%</td>
<td>79%</td>
<td>Phase 3 (mido) ongoing</td>
</tr>
<tr>
<td>Gilteritinib + 7+3</td>
<td>n=30 (ph 1)</td>
<td>93%</td>
<td>Not known Ph 3</td>
<td>Phase 3 (mido) planned</td>
</tr>
</tbody>
</table>


**Targeted Therapy: FLT3 Inhibitors**

- FLT3-inhibitors are safe and effective targeted therapeutics
- Well tolerated
- Improved outcomes
- Responses short-lived as single agents
- Resistance is common with single agents and depends on the unique FLT3i
- FLT3 inhibitors improve outcomes in newly diagnosed and R/R patients, rational combinations to prevent resistance will further improve upon FLT3 outcomes

**Characteristics of mIDH AML**

- IDH mutations occur in ~ 20% of AML
- Most (~85%) occur in de novo diploid or +8 AML
- IDH1 in ~8% AML, IDH2 in ~12% AML
- 1 prevalence with 1 patient age
- Hot-Spot mutations in enzymatic active site
  - IDH1-R132, IDH2-R140 or IDH2-R172
- Often early mutational events
  - Ancestral in 20% IDH1 and 39% IDH2 cases
  - Can be acquired at progression
    - ~10-15% of AML from MDS
    - ~20-25% of AML from MPN

**Pathophysiology of IDH Mutations**

- mIDH results in accumulation of the oncometabolite 2-HG which competitively inhibits aKG-dependent reactions
- 2HG leads to DNA and histone hypermethylation, and a resultant block in differentiation

**Targeted mIDH Inhibitor Therapy in the Clinic**

The new class of “...sidenibs”

- mIDH2 Inhibitor:
  - AG-221 (enasidenib or IDHIFA)
- mIDH1 Inhibitor:
  - AG-120 (ivosidenib or TIBSOVO)
  - FT-2103
  - BAY19036
- Pan mIDH1/IDH2 Inhibitor:
  - AG-881

*Targeted mutant IDH1/2 inhibitors evaluated in the clinic for hematologic malignancies*
Effective Inhibition of Oncometabolite 2HG

- Plasma 2-HG levels reduced to the normal range of healthy volunteers (up to 99.7% inhibition) in most patients at all doses
- Favorable PK profile following oral administration, with high plasma exposure and long half-life and trough levels above the predicted efficacious exposure

Example of effective plasma D-2-hydroxyglutarate (2HG) inhibition in patients with IDH1 mutations treated with AG120 (ivosidenib)


IDH-inhibitor monotherapy in R/R AML

- CR rate ~ 20%
- CR/Cr rate ~ 30%
- ORR ~ 40%
- Median OS ~ 18.8 mo
- Non-CR/CRh responders = 9 mo
- Non-responders = 5 mo

Evolution of Response with Enasidenib

Identification and Treatment of Clinical IDH-DS

- Impact of IDH1 Mutation-Clearance Status with AG120
- Patients with “deep IDH mutational clearance” had improved DOR and OS vs those in CR/CRh with persistent IDH1 mutation detected.
- Defined as a reduction in mIDH1 VAF to below the limit of detection by digital PCR (0.02-0.04%)

Impact of Co-occurring Mutations at Start of Enasidenib
IDH Inhibitors in Combinations

IVO or ENA with azacitidine for unfit newly diagnosed AML

### Key Eligibility Criteria

- Newly diagnosed AML
- Age ≥18
- Ineligible for intensive chemotherapy
- Patients with antecedent hematologic disorders allowed but prior HMA excluded

#### Dose-finding phase

- Ivosidenib 500 mg QD + AZA (n=7)
- Enasidenib 100 mg QD + AZA (n=3)
- Enasidenib 200 mg QD + AZA (n=3)

#### Randomized Phase 2 (N≈99)

- Ivosidenib 500 mg QD + AZA (n=16)
- Enasidenib 100 mg QD + AZA (n≈66)
- AZA Monotherapy (n≈33)

#### Follow-up

- Phase 1b: Dose-finding (3+3) and Expansion (N=29)

### Primary Endpoints:

- Recommended combination dose
- Safety

### Key Secondary and Exploratory Endpoints:

- ORR
- CR rate
- Mutant-IDH VAF

### SC AZA 75mg/m²/day x 7 days / 28-day cycle (all study phases)

#### Induction + Enasidenib/Ivosidenib

- Ivosidenib 500mg + ARA-C (200mg/m²/d x 7d) + DNR (60mg/m²/d x 3d)
- Enasidenib 100mg + ARA-C (200mg/m²/d x 7d) + DNR (60mg/m²/d x 3d)
- Enasidenib 100mg + ARA-C (200mg/m²/d x 7d) + IDR (12mg/m²/d x 3d)

#### Consolidation

- Ivosidenib 500mg + ARA-C (up to 4 cycles)
- Enasidenib 100mg + ARA-C (up to 4 cycles)

#### Maintenance

- Ivosidenib or enasidenib daily for up to 2 years from Induction Day 1

### Induction + Enasidenib/Ivosidenib

<table>
<thead>
<tr>
<th>Induction + Enasidenib/Ivosidenib</th>
<th>Ivosidenib-treated patients</th>
<th>Enasidenib-treated patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>71%</td>
<td>62%</td>
</tr>
<tr>
<td>CR/CRi/CRp</td>
<td>83%</td>
<td>72%</td>
</tr>
<tr>
<td>DMR</td>
<td>86%</td>
<td>85%</td>
</tr>
<tr>
<td>SD     OS (%)</td>
<td>7%</td>
<td>7%</td>
</tr>
<tr>
<td>Median OS, max</td>
<td>Not estimable</td>
<td>Not estimable</td>
</tr>
</tbody>
</table>

### IDH Inhibitor Therapy Take Aways

- Ivosidenib and enasidenib are safe and effective oral targeted therapies for patients with IDH1 or IDH2 mutant AML
- Well tolerated oral therapies
- Durable responses
- Improved outcomes

- Ivosidenib and enasidenib in combination therapies will further enhance responses
  - In combination with standard agents; i.e. 7+3 and azacitidine
  - With other small molecule & targeted therapies (FLT3i, MEKi, VEN, others)
CD33 Targeted Therapy: Gemtuzumab Ozogamicin

Gemtuzumab Ozogamicin: CD33 Targeted Antibody Drug Conjugate

Early studies demonstrated a substantial survival benefit for patients treated with gemtuzumab ozogamicin:

Addition of Gemtuzumab to Standard Therapy According to Cytogenetic Risk (n=3325 pts)

- (A) OS of 246 pts with favorable risk AML
- (B) OS of 1827 pts with intermediate risk AML
- (C) OS of 583 pts with adverse risk AML

Individual Patient Data Meta-Analysis: N=3325, median age 58 years

<table>
<thead>
<tr>
<th>Protocol</th>
<th>Patient Population</th>
<th>GO Dosing</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALFA-0701</td>
<td>50-70 years</td>
<td>3 mg/m² x 3</td>
<td>278</td>
</tr>
<tr>
<td>SWOG 50106</td>
<td>18-60 years</td>
<td>6 mg/m² x 1</td>
<td>595</td>
</tr>
<tr>
<td>MRC AML15</td>
<td>15-71 years</td>
<td>3 mg/m² x 1</td>
<td>1099</td>
</tr>
<tr>
<td>NCRI AML16</td>
<td>51-84 years</td>
<td>3 mg/m² x 1</td>
<td>1115</td>
</tr>
<tr>
<td>GOELAMS AML2006IR</td>
<td>18-60 years</td>
<td>6 mg/m² x 1</td>
<td>238</td>
</tr>
</tbody>
</table>


CD33 expression and impact on outcome according to treatment arm of ALFA-0701 (newly diagnosed AML, age 18-70, daunorubicin + ara-C + GO)

- In low/intermediate CD33+ (~70%), 2-yr EFS was 25% vs 26% in GO vs control. P=0.66
- In high CD33+ (~70% expression), 2-yr EFS was 49% vs 17% in GO vs control, p = 0.005
- In low/intermediate CD33+ patients (~70%), 2-yr RFS was estimated at 25% vs 38% at 2 years in GO vs control (p=0.87)
- In high-CD33+ patients (~70% expression), 2-yr RFS was 62% vs 22% in GO vs control p=0.0016

Kleppe M & Levine RL, Nat Med 2014

Grimwade D et al, Blood 2016

Individualizing Therapy: At Relapse

Leukemia is not a static condition!
Repeat genomic analysis at relapse is necessary
Conclusions

Targeted Therapy and Precision Medicine: Transitioning from Population-based → Individual "genotype-phenotype" based treatment

- Understanding the genomic landscape has contributed to a refined disease classification, better prognostication, and is informing the development of targeted agents.

- Can now be used to guide and inform clinical practice:
  - Optimal treatment strategies (at diagnosis and relapse)
  - Addition of target-specific drugs
  - Improved treatment options for poor risk patients still needed

- NGS-panel testing for prognostic and therapeutically informative mutations should be performed at diagnosis and relapse time-points to optimize informed decision-making.

THANK YOU!

Questions: cdinardo@mdanderson.org
Response Assessment and Management of TKIs Resistance in the Management of CML

Ghayas C. Issa, MD
Response Assessment and Management of TKI Resistance in CML

Ghayas C. Issa, MD
Department of Leukemia
The University of Texas MD Anderson Cancer Center
Houston, Texas

New Paradigms in the Treatment of ALL, CLL, AML and CML
Houston, TX – April 27, 2019

Outline

• Introduction
• Initial workup
• Response assessment
• Available treatments
• Management for failure following first line therapy

Introduction

CML is Driven by BCR-ABL1

Management of Resistance in CML

Epidemiology

Increasing CML prevalence

- Estimated New Cases in 2019: 8,990
- % of all New Cancer Cases: 0.5%
- % of all Leukemia Cases (Adults): 12%
- Estimated Deaths in 2019: 1,140
- % of All Cancer Deaths: 0.2%

Conflict of Interest Disclosure

* No relevant financial relationships

Outcomes with TKI

- Survival Probability

TKI vs. Chemotherapy vs. Interferon

Graphs showing survival rates over time with different treatments.
Initial Workup

- Performance status, splenomegaly, extramedullary disease
- CBC, CMP
- BM Asp, CG
- FISH, Quantitative RT-PCR (possibility of Ph-neg CML)

CCA/Ph+ on CG

Clonal evolution = CCA/Ph+ during Tx
46XX, t(9;22) (q34;q11.2), +8 [20]

CCA/Ph- = NOT clonal evolution
46XX, t(9;22) (q34;q11.2) [3]; 46XX, +8 [5]; 46X [12]

Variant Ph
46XX, t(9;22) (q34;q11.2) [20]

CML Phases

- Chronic
  - Past: 3-5 years
  - Present: 25+ years
- Accelerated
  - 12-18 months
- Blastic
  - 4-6 years
  - 6-12 months

* Asymptomatic (if treated)
* None of criteria for accelerated or blast blast phase

Criteria for AP CML

<table>
<thead>
<tr>
<th>MDACC</th>
<th>IBMTR</th>
<th>WHO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blasts</td>
<td>1%</td>
<td>20%</td>
</tr>
<tr>
<td>Blasts+Pro's</td>
<td>≥50%</td>
<td>≥20%</td>
</tr>
<tr>
<td>Basophils</td>
<td>≥20%</td>
<td>≥20%*</td>
</tr>
<tr>
<td>Platelets</td>
<td>&lt;100</td>
<td>Unresponsive</td>
</tr>
<tr>
<td>WBC</td>
<td>NA</td>
<td>Difficult to control, or doubling &lt;5d</td>
</tr>
<tr>
<td>Anemia</td>
<td>NA</td>
<td>Unresponsive</td>
</tr>
<tr>
<td>Splenomegaly</td>
<td>NA</td>
<td>Increasing</td>
</tr>
<tr>
<td>Other</td>
<td>NA</td>
<td>Chloromas, myelofibrosis</td>
</tr>
</tbody>
</table>

* Basophils + eosinophils
** Blast phase ≥20% blasts (≥30% for MDACC and IBMTR)

Prognostic Scores

- Sokal: age, spleen, platelets, blasts
- Hasford: age, spleen, platelets, blasts, eosinophils, basophils
- EUTOS: spleen, basophils

Evaluating Response in CML

- BCR-ABL: Molecular response (PCR)
  - CCyG 0/20 Ph+ metaphases
  - MMR ≤ 0.1% (IS)
  - MR4.0 ≤ 0.01% (IS)
  - MR4.5 ≤ 0.0032% (IS)
- Hematologic response
  - CR
  - CC (β2m)

** Preferably use the same lab**
Available Treatments for CP CML

<table>
<thead>
<tr>
<th>First Line</th>
<th>Second Line</th>
</tr>
</thead>
<tbody>
<tr>
<td>Imatinib</td>
<td>Dasatinib</td>
</tr>
<tr>
<td>Dasatinib</td>
<td>Nilotinib</td>
</tr>
<tr>
<td>Nilotinib</td>
<td>Bosutinib</td>
</tr>
<tr>
<td>Bosutinib</td>
<td>Ponatinib (T315I or if no other TKI indicated)</td>
</tr>
<tr>
<td></td>
<td>Omacetaxine (2 2 TKI)</td>
</tr>
<tr>
<td></td>
<td>HSCT</td>
</tr>
</tbody>
</table>

Clinical trial Clinical trial

Monitoring Recommendations ELN 2013

<table>
<thead>
<tr>
<th>When</th>
<th>What</th>
</tr>
</thead>
</table>
| At diagnosis | +CG (BM aspiration)  
|            | +FISH (in case of Ph-)  
|            | +Qualitative PCR |
| During treatment | +PCR every 3 months until MMR then every 3-6 months  
|            | +CG at 3, 6 and 12 months (until CCyR) – Not needed if adequate PCR |
| Failure, progression | +PCR, mutation analysis, cytogenetics  
|            | +Immunophenotype for BP |
| Warning | +PCR and CG more frequently |

Adherence Is Critical for Achieving Molecular Responses

- CP CML (N=87) with CCyR monitored for 3 mo. with a microelectronic monitoring device

Criteria for Failure and Suboptimal Response to Imatinib – ELN 2013

<table>
<thead>
<tr>
<th>Time (mo)</th>
<th>Failure</th>
<th>Response</th>
<th>Warning</th>
<th>Optimal</th>
</tr>
</thead>
</table>
| 3         | No CHR  
|          | and/or Ph+ >=95%  
|          | and/or Ph+ 36-95%  
|          | and/or Ph+ <35%  
| 6         | BCR-ABL >10%  
|          | and/or Ph+ >=95%  
|          | and/or Ph+ 36-95%  
|          | and/or Ph+ <35%  
| 12        | BCR-ABL >1%  
|          | and/or Ph+ >=95%  
|          | and/or Ph+ 36-95%  
|          | and/or Ph+ <35%  
| Any       | Loss of CHR  
|          | Loss of CCyR  
|          | Confirmed loss of MMR  
|          | Mutations  
|          | Clonal evolution  
|          | CCA/Ph- (-7, or 7q-)  
|          | BCR-ABL <0.1%  

Evaluate for resistance mutations

IRIS 8-year Update

- At least 37% Unacceptable Outcome
  - No CCyR
  - Lost CCyR
  - CoR Other
  - Safety
  - Lost-regained CoR
  - Sustained CoR on study

When to Look For Mutations?

- Mutation analysis in 1301 pts on imatinib or 2nd generation TKI (GIMEMA)

Clinical condition | % Positive
|-------------------|--------|
| Failure  
| No CHR @ 3 mo  
| No CCyR @ 3 mo  
| No PCyR @ 12 mo  
| Loss CCyR  
| Loss CHR  
|                | 22%    |
| Suboptimal  
| No CHR @ 3 mo  
| No PCyR @ 6 mo  
| No CCyR @ 12 mo  
| No MMR @ 18 mo  
| Loss MMR  
|                | 3%     |

Soverini et al. ASH 2011; Abstract #112

Mutations in ABL

<table>
<thead>
<tr>
<th>Mutation</th>
<th>Imatinib</th>
<th>Bosutinib</th>
<th>Dasatinib</th>
<th>Nilotinib</th>
</tr>
</thead>
<tbody>
<tr>
<td>WT</td>
<td>1.11</td>
<td>1.11</td>
<td>1.11</td>
<td>1.11</td>
</tr>
<tr>
<td>L248V</td>
<td>3.54</td>
<td>2.97</td>
<td>5.11</td>
<td>2.80</td>
</tr>
<tr>
<td>G250E</td>
<td>6.86</td>
<td>4.31</td>
<td>4.45</td>
<td>4.56</td>
</tr>
<tr>
<td>Q252H</td>
<td>1.39</td>
<td>0.31</td>
<td>3.05</td>
<td>2.64</td>
</tr>
<tr>
<td>Y253F</td>
<td>3.58</td>
<td>0.96</td>
<td>1.58</td>
<td>3.23</td>
</tr>
<tr>
<td>E255K</td>
<td>6.02</td>
<td>9.47</td>
<td>5.61</td>
<td>6.69</td>
</tr>
<tr>
<td>E255V</td>
<td>16.99</td>
<td>5.53</td>
<td>3.44</td>
<td>10.31</td>
</tr>
<tr>
<td>D276G</td>
<td>2.18</td>
<td>0.60</td>
<td>1.44</td>
<td>2.00</td>
</tr>
<tr>
<td>E279K</td>
<td>3.55</td>
<td>0.95</td>
<td>1.64</td>
<td>2.05</td>
</tr>
<tr>
<td>V299L</td>
<td>1.54</td>
<td>26.10</td>
<td>8.65</td>
<td>1.34</td>
</tr>
<tr>
<td>T315I</td>
<td>17.50</td>
<td>45.42</td>
<td>75.03</td>
<td>39.41</td>
</tr>
<tr>
<td>F317L</td>
<td>2.60</td>
<td>2.42</td>
<td>4.46</td>
<td>2.22</td>
</tr>
<tr>
<td>M351T</td>
<td>1.76</td>
<td>0.70</td>
<td>0.88</td>
<td>0.44</td>
</tr>
<tr>
<td>F359V</td>
<td>2.86</td>
<td>0.93</td>
<td>1.49</td>
<td>5.16</td>
</tr>
<tr>
<td>L384M</td>
<td>1.28</td>
<td>0.47</td>
<td>2.21</td>
<td>2.33</td>
</tr>
<tr>
<td>H396P</td>
<td>2.43</td>
<td>0.43</td>
<td>1.07</td>
<td>2.41</td>
</tr>
<tr>
<td>H396R</td>
<td>3.91</td>
<td>0.81</td>
<td>1.63</td>
<td>3.10</td>
</tr>
<tr>
<td>G398R</td>
<td>0.35</td>
<td>1.16</td>
<td>0.69</td>
<td>0.49</td>
</tr>
<tr>
<td>F486S</td>
<td>8.10</td>
<td>2.31</td>
<td>3.04</td>
<td>1.85</td>
</tr>
</tbody>
</table>

Impact of CCA/Ph+

- MCyR / CCyR (within 2 yr) | 63 / 50 (%)
- IM Resistant | 59 / 44 (%)
- IM Intolerant | 77 / 67 (%)
- MMR | 37 (%)
- 6-yr OS | 71 (%)
- 6-yr PFS | 49 (%)
- 6-YR TFS | 76 (%)
- Discontinued treatment | 69 (%)

**Dasatinib in CP CML After Imatinib Failure**

- 670 pts randomized to 4 schedules (6-year follow-up)
- Outcome (100 mg/d) Percent
  - MCyR / CCyR (within 2 yr) | 63 / 50 (%)
  - IM Resistant | 59 / 44 (%)
  - IM Intolerant | 77 / 67 (%)
  - MMR | 37 (%)
  - 6-yr OS | 71 (%)
  - 6-yr PFS | 49 (%)
  - 6-YR TFS | 76 (%)
  - Discontinued treatment | 69 (%)

**Nilotinib in CP CML After Imatinib Failure**

- 321 pts with imatinib resistance (71%) or intolerance (29%)
- Minimum 48 mo follow-up
- Nilotinib 400 mg PO SID
  - Outcome Percent
    - CHR | 85 (%)
    - MCyR / CCyR | 59 / 45 (%)
    - Resistant* | 56 / 41 (%)
    - Intolerant* | 66 / 51 (%)
    - 48-month OS | 78 (%)
    - 48-month PFS | 57 (%)
    - Discontinued treatment | 70 (%)

*Median dose intensity 709 mg/d
*Includes pts on additional MCyR who achieved CCyR after 24 mo.

**Workup If Resistance Suspected**

- Assess compliance
- Same as initial workup
- Include BM Asp, CG: need to know if AP/BP!
- ABL mutational analysis

**Impact of CCA/Ph+**

- MCyR / CCyR (within 2 yr) | 63 / 50 (%)
- IM Resistant | 59 / 44 (%)
- IM Intolerant | 77 / 67 (%)
- MMR | 37 (%)
- 6-yr OS | 71 (%)
- 6-yr PFS | 49 (%)
- 6-YR TFS | 76 (%)
- Discontinued treatment | 69 (%)

**Dasatinib in CP CML After Imatinib Failure**

- 670 pts randomized to 4 schedules (6-year follow-up)
- Outcome (100 mg/d) Percent
  - MCyR / CCyR (within 2 yr) | 63 / 50 (%)
  - IM Resistant | 59 / 44 (%)
  - IM Intolerant | 77 / 67 (%)
  - MMR | 37 (%)
  - 6-yr OS | 71 (%)
  - 6-yr PFS | 49 (%)
  - 6-YR TFS | 76 (%)
  - Discontinued treatment | 69 (%)

**Nilotinib in CP CML After Imatinib Failure**

- 321 pts with imatinib resistance (71%) or intolerance (29%)
- Minimum 48 mo follow-up
- Nilotinib 400 mg PO SID
  - Outcome Percent
    - CHR | 85 (%)
    - MCyR / CCyR | 59 / 45 (%)
    - Resistant* | 56 / 41 (%)
    - Intolerant* | 66 / 51 (%)
    - 48-month OS | 78 (%)
    - 48-month PFS | 57 (%)
    - Discontinued treatment | 70 (%)

*Median dose intensity 709 mg/d
*Includes pts on additional MCyR who achieved CCyR after 24 mo.
**Bosutinib in CP CML**

After Imatinib Resistance/Intolerance

- 288 pt CML CP wit imatinib resistance (n=200) or intolerance (n=88)
- Bosutinib 500 mg orally daily. Median follow-up 47 months

<table>
<thead>
<tr>
<th>Response</th>
<th>IM Resistant</th>
<th>IM Intolerant</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHR</td>
<td>86</td>
<td>84</td>
</tr>
<tr>
<td>MCyR</td>
<td>59</td>
<td>61</td>
</tr>
<tr>
<td>CCyR</td>
<td>43</td>
<td>52</td>
</tr>
<tr>
<td>MMR</td>
<td>64</td>
<td>65</td>
</tr>
<tr>
<td>CMR</td>
<td>49</td>
<td>61</td>
</tr>
<tr>
<td>2-yr PFS**</td>
<td>73</td>
<td>95</td>
</tr>
</tbody>
</table>

Discontinued therapy

- Median dose intensity: IM-resistant 485 mg/d, IM-intolerant : 394 mg/d

*Data from 2-yr follow-up among pts in CCyR; overall (all patients, 2-y) MMR 41%, CMR 34%

** 4-yr cumulative incidence of on-treatment progression or death 22% for resistant, 10% for intolerant

Brummendorf et al. ASH 2013; Abstract 2723; Cortes et al. Blood 2011; 118: 4567-76

---

**Ponatinib**

- Oral pan-BCR-ABL TKI. Has a unique triple-bond structure evades the T315I gatekeeper mutation
- Approved for CML or Ph+ ALL with T315I mutation or in whom no other TKI is indicated
- Black box warning for fatal arterial or venous thromboembolic events
- Also associated with hepatotoxicity and pancreatitis

---

**Omacetaxine**

- Protein synthesis inhibitor, independent of Bcr-Abl binding (SC injection)
- Indicated for CP or AP CML with resistance/intolerance ≥ 2 TKI
- CML 202 study (N = 62, resistant to prior TKI or T315I):
  - MCyR, CCyR and MMR in 23%, 16% and 17%
  - T315I declined to below detection limits in 61% of pts
- Most common grade 3/4 AEs: Thrombocytopenia, neutropenia and anemia

---

**2nd-Generation TKI Toxicities**

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Dasatinib</th>
<th>Nilotinib</th>
<th>Bosutinib</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pleural effusion</td>
<td>++</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Liver</td>
<td>*</td>
<td>+</td>
<td>*</td>
</tr>
<tr>
<td>Transaminases</td>
<td>-</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>Bilirubin</td>
<td>-</td>
<td>++</td>
<td>-</td>
</tr>
<tr>
<td>Rash</td>
<td>*</td>
<td>+</td>
<td>*</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>-</td>
<td>-</td>
<td>++</td>
</tr>
<tr>
<td>Lipase</td>
<td>- (+)</td>
<td>++</td>
<td>-</td>
</tr>
<tr>
<td>Glucose</td>
<td>-</td>
<td>++</td>
<td>-</td>
</tr>
<tr>
<td>Hypophosphatemia</td>
<td>++</td>
<td>++</td>
<td>*</td>
</tr>
<tr>
<td>Bleeding</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>QTc</td>
<td>++</td>
<td>++</td>
<td>-</td>
</tr>
</tbody>
</table>

Arterio-thrombotic events: Ponatinib > nilotinib > dasatinib > bosutinib

---

**AP/BP CML**

- BP CML is still a therapeutic challenge
- De novo BP has relatively better prognosis
- Combination of adapted chemotherapy (myeloid vs lymphoid) + TKI followed by HSCT

---

**Allogeneic HSCT is Curative (For Some)**

- Indications: BP at diagnosis, progression to AP/BP, resistance to TKIs, and rarely if intolerant to all TKIs
- Best if CP prior to HSCT
- Prior TKI does not affect outcomes post-HSCT
- Other prognostic factors: donor type, comorbidity index
Survival and Relapse after Allogeneic HSCT for CP CML

- 2444 pts with CML alive and in remission for at least 5 years after SCT
- Cumulative incidence relapse at 15 yrs: 8% sibling donor, 2% MUD

Goldman et al. JCO 2010; 28: 1888-95

Management Algorithm

Response Failure After 1st Line Tx

Evaluate Compliance
- BMA, CG, FISH
- ABL Mutation

- ABL Mutation?
  - No
  - TKI Based on Predicted Sensitivity
  - Yes
  - TKI Based on Toxicity Profile

Inadequate Response
- T315I
- Ponatinib > Omacetaxine

SCT Consult

Questions?

Ghayas C. Issa, MD
Department of Leukemia
The University of Texas MD Anderson Cancer Center
Houston, Texas
Understanding of Time-based Response Milestones and Monitoring in Patients with CML

Guillermo Garcia-Manero, MD
Understanding of Time-based Response Milestones and Monitoring in Patients with CML

Guillermo Garcia-Manero, MD
Department of Leukemia
The University of Texas MD Anderson Cancer Center
Houston, TX
April 2019

Chronic Myeloid Leukemia

• Clonal myeloproliferative disorder of pluripotent stem cells
• ↑ proliferation, ↓ apoptosis
• Hallmarks: Cytogenetic: Ph-chromosome Molecular: BCR/ABL
• 7% to 15% of adult leukemias
• Incidence 1.5/10^5; prevalence 5/10^5 annually until 2040; prevalence = 35x incidence = 50/10^5
• 2010 statistics: 4,870 new patients, 440 deaths
• Etiology: irradiation in <5%
unknown in 95%

CML: The Past and Today

Parameter Before 2000 Today
• Course Fatal Indolent
• Prognosis Poor Excellent
• 10-yr survival 10% 84 - 90%
• Frontline Rx Allo SCT; IFN-α Imatinib; dasatinib;
nilotinib; bosutinib
• Second line Rx ? Bosutinib, ponatinib; allo SCT

CML: Survival at MDACC 1975 - 2019

Relative Survival with TKI by Response to Therapy

• 483 pts with CML treated with imatinib 400mg (n=71), imatinib 800 mg (n=201), dasatinib (n=111)
or nilotinib (n=101)
• 5-yr relative survival 94.8% [92.1 - 97.4%

Conflict of Interest Disclosure

Grant and Research Support: Amphivena, Helsinn, Novartis, AbbVie, Celgene, Astex, Onconova, Merck

Consultant: Celgene, Astex, Amphivena
Population-Based CML Outcome in Sweden

- 3173 pts Dx in 1973-2008; median age 62 yrs

Bjorkholm, JCO 29: 2514; 2011

21%
23%
37%
54%
80%

Patients at risk

Final Results CML-IV: Molecular Response with Imatinib

- 1538 pts newly diagnosed CML-CP randomized to imatinib 400, imatinib 800, imatinib + IFN, imatinib + ara-C, or imatinib after IFN


CML - Increasing Prevalence Over Time

- Incidence 4700 per year
- Age-matched mortality ratio vs normal population = 1.50
- Accounts for increased US population to 410 million in 2050


CML Transformation: Survival by Era

- High-risk CML—blasts ≥ 10%; basophils ≥ 15-20%; CE with iso17/17p-, 3q26.2 rearrangement; p190 CML
- Accelerated phase CML—blasts ≥ 15%; basophils ≥ 20%; CE with iso17/17p-; 3q26.2 rearrangement


CML Accelerated Phase Criteria

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Old Criteria</th>
<th>New Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>% Blasts</td>
<td>≥ 15%</td>
<td>≥ 20%</td>
</tr>
<tr>
<td>% Blasts + Pros</td>
<td>≥ 30%</td>
<td>??</td>
</tr>
<tr>
<td>% Basophils</td>
<td>≥ 20%</td>
<td>?</td>
</tr>
<tr>
<td>CG Clonal evolution</td>
<td>Any</td>
<td>Iso 17, 17p</td>
</tr>
<tr>
<td>Platelets</td>
<td>&lt; 100x10^9/L</td>
<td>--</td>
</tr>
<tr>
<td>BCR-ABL1 p 190</td>
<td>--</td>
<td>yes</td>
</tr>
</tbody>
</table>
Clinical Relevance of Alternative BCR-ABL Transcripts

- At diagnosis: Ph+ by CG t (9;22), or FISH positive, but PCR negative → consider e13a3, e14a3 (p210), e6a2-3 (p195), or e19a2-3 (p230)
- Therefore, must do PCR at Dx. Otherwise later PCRs falsely negative = false CMR

BCR-ABL Transcripts and Messages

- BCR breakpoints: e13 (b2), e14 (b3), e1, e6, e19
- ABL breakpoints: a2, a3
- Total 10 possible transcripts/messages

<table>
<thead>
<tr>
<th>Transcripts</th>
<th>Oncoprotein</th>
<th>Incidence</th>
<th>Detected by Routine PCR</th>
<th>Needs Alternative Assay/ not Quantitative</th>
</tr>
</thead>
<tbody>
<tr>
<td>e13 a2 (b2 a2)</td>
<td>p210</td>
<td>55%</td>
<td>Yes</td>
<td>--</td>
</tr>
<tr>
<td>e14 a2 (b3 a2)</td>
<td>p210</td>
<td>40%</td>
<td>Yes</td>
<td>--</td>
</tr>
<tr>
<td>e13 a3 (b2 a3)</td>
<td>p210</td>
<td>1%</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>e14 a3 (b3 a3)</td>
<td>p210</td>
<td>1%</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>e1 a2a3</td>
<td>p190</td>
<td>1%</td>
<td>Yes</td>
<td>No (but not IS)</td>
</tr>
<tr>
<td>e6 a2a3</td>
<td>p195</td>
<td>&lt; 1%</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>e19 a2a3</td>
<td>p230</td>
<td>&lt; 1%</td>
<td>No</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Therapy of CML in 2019

- Frontline
  - imatinib 400 mg daily
  - dasatinib 100 mg daily
  - nilotinib 300 mg BID
  - bosutinib 400 mg daily
- Second / third line
  - nilotinib, dasatinib, bosutinib, ponatinib, omacetaxine
  - allogeneic SCT
- Other
  - decitabine, peg IFN
  - hydrea, cytarabine, combos of TKIs and with TKIs

Sequence of Frontline and Salvage Strategies in CML

<table>
<thead>
<tr>
<th>Choice of TKI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frontline Rx</td>
</tr>
<tr>
<td>Salvage for Resistance</td>
</tr>
<tr>
<td>- Ponatinib 30 mg/D if no guiding mutations - if V299L, T315A, F317L/V/I/C then nilotinib 300-400 mg BID</td>
</tr>
<tr>
<td>- Dasatinib 50 - 100 mg/D or bosutinib 300-500 mg/D</td>
</tr>
<tr>
<td>- If failure then ponatinib</td>
</tr>
<tr>
<td>Salvage for toxicities</td>
</tr>
<tr>
<td>- Bosutinib 300-500 mg/D</td>
</tr>
<tr>
<td>- Dasatinib or bosutinib</td>
</tr>
</tbody>
</table>

- I do not use nilotinib frontline because of 10-yr CV problems 10-12%
- Always adjust TKI dose if side-effects before considering change of TKI

CML Questions

- Best frontline TKI therapy
- Generic imatinib vs Gleevec and second generation TKIs
- Endpoint of Rx: CGCR vs CMR
- Aim of Rx: survival vs Rx-free remission
- Long-term side effects; costs
- Role and timing of allo SCT
- TKIs vs allo SCT— cost considerations
- Optimal monitoring of CML
- TKI Rx discontinuation

Survival with Imatinib vs IFN + ara-C in Newly Dx CML (IRIS; 10 yr)

- 553 pts randomized to imatinib
- 10 yr survival 83.3%
- Cumulative CGCR rate 83%
- 10-Yr CGCR rate 22%
- 10-Yr MMR rate 93%
- 10-Yr MR 4.5 rate 23%
- 10 yr survival by Sokal: low 90%; intermediate 80%; high 69%
- Annual rate of transformation: 1.5%, 2.8%, 1.8%, 0.9%, 0.5%, 0%, 0%, & 0.4%
CML Frontline Therapy

- Up to 16, and 8 main studies compared new generation TKIs to imatinib frontline: ENEST-nd (nilotinib), DASISION (dasatinib), BELA (bosutinib), EPIC (ponatinib), others

- All showed higher rates of favorable early surrogate endpoints: CG CR, MMR, MR4.5, ↓ AP/BP

- Increased uncommon toxicities with newer TKIs: PAOD-Mi-TIA, pancreatitis, pleural effusions; HT and pulmonary HT, ↑BS, vasospastic reactions, ↑non-CML deaths

DASISION – The Final Report

- 519 pts randomized to dasatinib (n=259) or imatinib (n=260)
- Minimum follow-up 5 yrs

<table>
<thead>
<tr>
<th>Outcome (%)</th>
<th>Dasatinib</th>
<th>Imatinib</th>
<th>P value or HR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Discontinued</td>
<td>39</td>
<td>37</td>
<td></td>
</tr>
<tr>
<td>12m cCCyR</td>
<td>77</td>
<td>66</td>
<td>P=0.007</td>
</tr>
<tr>
<td>5y MMR</td>
<td>76</td>
<td>64</td>
<td>P=0.0022</td>
</tr>
<tr>
<td>5y MR4.5</td>
<td>42</td>
<td>33</td>
<td>P=0.025</td>
</tr>
<tr>
<td>3m &lt;10%</td>
<td>84</td>
<td>64</td>
<td></td>
</tr>
<tr>
<td>5y AP/BP</td>
<td>4.6</td>
<td>7.3</td>
<td></td>
</tr>
<tr>
<td>5y OS</td>
<td>91</td>
<td>90</td>
<td>HR 1.01</td>
</tr>
<tr>
<td>5y PFS</td>
<td>85</td>
<td>86</td>
<td>HR 1.06</td>
</tr>
</tbody>
</table>

GIMEMA – ATE with Frontline Nilotinib Rx for CML-CP

- 33/472 (7%) developed ATE (2 fatal) 
  - CV 16 (3%), peripheral 9 (2%), other 8 (2%) 
  - 19.7/1000 patient-years

<table>
<thead>
<tr>
<th>Outcome (%)</th>
<th>Nilotinib 600 (n=282)</th>
<th>Nilotinib 800 (n=281)</th>
<th>Imatinib (n=283)</th>
<th>P value or HR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Discontinued</td>
<td>50</td>
<td>50</td>
<td>50</td>
<td></td>
</tr>
<tr>
<td>5y MMR</td>
<td>60</td>
<td>60</td>
<td>60</td>
<td>P&lt;0.0001</td>
</tr>
<tr>
<td>5y MR4.5</td>
<td>33</td>
<td>33</td>
<td>33</td>
<td>P&lt;0.0001</td>
</tr>
<tr>
<td>3m &lt;10%</td>
<td>67</td>
<td>67</td>
<td>67</td>
<td></td>
</tr>
<tr>
<td>6y AP/BP</td>
<td>7.4</td>
<td>7.4</td>
<td>7.4</td>
<td>P=0.06/0.003</td>
</tr>
<tr>
<td>6y OS</td>
<td>92</td>
<td>96</td>
<td>92</td>
<td>HR 0.9/0.46</td>
</tr>
</tbody>
</table>

ENSSTnd – The 6-Year Update

- 846 pts: nilotinib 600 (n=282), nilotinib 800 (n=281) or imatinib (n=283)
- Minimum follow-up 6 yrs

<table>
<thead>
<tr>
<th>Outcome (%)</th>
<th>Nilotinib 600</th>
<th>Nilotinib 800</th>
<th>Imatinib</th>
<th>P value or HR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Discontinued</td>
<td>40</td>
<td>38</td>
<td>50</td>
<td></td>
</tr>
<tr>
<td>5y MMR</td>
<td>77</td>
<td>77</td>
<td>60</td>
<td>P&lt;0.0001</td>
</tr>
<tr>
<td>6y MR4.5</td>
<td>56</td>
<td>55</td>
<td>33</td>
<td>P&lt;0.0001</td>
</tr>
<tr>
<td>3m &lt;10%</td>
<td>91</td>
<td>89</td>
<td>67</td>
<td></td>
</tr>
<tr>
<td>6y AP/BP</td>
<td>3.9</td>
<td>2.1</td>
<td>7.4</td>
<td>P=0.06/0.003</td>
</tr>
<tr>
<td>6y OS</td>
<td>92</td>
<td>96</td>
<td>92</td>
<td>HR 0.9/0.46</td>
</tr>
</tbody>
</table>
CML: What Happens in 2019?

Parameter | Imatinib | 2nd TKIs
--- | --- | ---
Efficacy | excellent | even better
Tolerance | excellent | even better
Cost ($/yr) | 2-10,000 | > 120,000
\%5 – 10 yr survival | 80 – 90 | ? > 90
EFS | 50-60 | ???

→ difference at 5-10 yrs in EFS and OS determines frontline Rx
→ new long-term side-effects of 2nd TKIs; Rx value

CML Therapy in 2019

- Imatinib for low-risk Sokal and older pts (≥ 65-70 yrs)
- Second TKIs for higher-risk Sokal
  - until CGCR, then back to imatinib
  - second TKI indefinitely
- Second TKIs for younger pts (< 50 yrs) in whom Rx DC important

Rx Endpoints When Comparing Second TKIs to Imatinib in Frontline Rx

- Lower incidence of early transformation to AP-BP
- Survival
- Molecular cure
- Long-term safety
- Cost; cost-effectiveness = “Rx value”

Cost-Benefit of TKIs. “Treatment Value” with Survival as Rx Endpoint

- Using frontline second TKIs vs imatinib generic (at 1/3 of patent price) results in cost of $800,000/QALY
- Simply stated, cost per additional year lived in $800,000, 16x more than accepted threshold of $50,000/QALY
- Therefore, we need strong justification to use second TKIs as frontline CML Rx (vs generic imatinib), or lower prices of second TKIs

Generic Imatinib in India-- Survival of the Cheapest

- 1367 pts newly diagnosed CML: 1193 “innovator”, 174 generic
- CP 90% & 83%; AP 7% & 10%; BP 4% & 7%

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Innovator</th>
<th>Generic</th>
</tr>
</thead>
<tbody>
<tr>
<td>CCyR</td>
<td>67</td>
<td>64</td>
</tr>
<tr>
<td>MMR</td>
<td>22</td>
<td>14</td>
</tr>
<tr>
<td>MR4</td>
<td>17</td>
<td>24</td>
</tr>
<tr>
<td>AP/BP</td>
<td>8</td>
<td>7</td>
</tr>
</tbody>
</table>

AEs
- Edema, any grade | 12 | 6 |
- Myalgia, any grade | 15 | 10 |
- Rash, grade 3 | <1 | 3 |
- Thrombocytopenia, any grade | 6 | 9 |
- Neutropenia, any grade | 5 | 3 |
- Anemia, any grade | 9 | 6 |


Larson et al. Blood. 2014; Abstract #4541; Cortes et al. JCO 2016; 34: 2333-40

ENESTnd DASISION

Madhav et al. ASH 2016; abstract #630

TKIs Rx DC and Rx-Free Remissions in CML

- 758 pts Rx with TKIs for >3 yrs and in Deep MR for >1 yr Relapse=loss of MMR; BCR-ABL transcripts [IS] >0.1%
- 2-yr molecular RFS 61%

Saussele. Lancet Oncology 19: 747-757, 2018

TKIs Rx DC in Clinical Practice--Requirements

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sokal risk</td>
<td>low-intermediate</td>
<td>high</td>
</tr>
<tr>
<td>BCR-ABL transcripts</td>
<td>quantifiable-B2A2, B3A2 (e13a2 or e14a2)</td>
<td>not quantifiable</td>
</tr>
<tr>
<td>CML past Hx</td>
<td>chronic</td>
<td>AP-BP</td>
</tr>
<tr>
<td>Response to first TKI</td>
<td>optimal</td>
<td>failure</td>
</tr>
<tr>
<td>Duration of all TKIs Rx</td>
<td>&gt; 8 yrs</td>
<td>≤ 3 yrs</td>
</tr>
<tr>
<td>Depth of molecular response</td>
<td>CMR (MR 4.5)</td>
<td>less than MR 4.0</td>
</tr>
<tr>
<td>Duration of molecular response</td>
<td>&gt; 2-3 yrs</td>
<td>&lt; 2 yrs</td>
</tr>
<tr>
<td>Monitoring availability/center-pt</td>
<td>ideal (q2 mo in yrs 1-2)</td>
<td>poor, non-compliant</td>
</tr>
</tbody>
</table>

Therapy of CML- General Principles

- Patient with CML should be on daily TKIs everyday, whether in CG CR or even if 100% Ph-positive, in the course of CML-CP or in transformation (AP-BP= TKIs combinations)
- Exceptions: lower-risk CML post allo SCT; “molecular cure”; severe cytopenias

Monitoring CML Course

- Cytogenetics
- Fluorescent in situ hybridization (FISH)
- Quantitative PCR (QPCR): real time, competitive
- Abl mutations
- Must do FISH and PCR pre-Rx for FU

The Simple Guide to Molecular Monitoring

- If it is going down, it is good
- If it is stable, it is OK
- If it is going up, monitor more frequently
  - Not a failure by itself
- If continues to go up (> 1 log w/o MMR)
  - Check CG
  - If CG relapse check mutation analysis

% Survival/TFS by Early Molecular Response

<table>
<thead>
<tr>
<th>Study</th>
<th>QPCR &lt; 10%</th>
<th>QPCR &gt; 10%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marin (8-yr)</td>
<td>93</td>
<td>54</td>
</tr>
<tr>
<td>MD Anderson (10-yr)</td>
<td>98</td>
<td>94</td>
</tr>
<tr>
<td>ENEST-nd</td>
<td>97</td>
<td>87</td>
</tr>
<tr>
<td>DASISION</td>
<td>97</td>
<td>86</td>
</tr>
<tr>
<td>BELA</td>
<td>98</td>
<td>88</td>
</tr>
</tbody>
</table>

BCR-ABL Transcripts < 10% at 6 mos
Associated with Better Outcome

<table>
<thead>
<tr>
<th>Response</th>
<th>3 Mo</th>
<th>6 Mo</th>
<th>No.</th>
<th>% Survival</th>
<th>% PFS</th>
<th>% FFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 10</td>
<td>≤ 1</td>
<td>342</td>
<td></td>
<td>97</td>
<td>97</td>
<td>87</td>
</tr>
<tr>
<td>≤ 10</td>
<td>1-10</td>
<td>42</td>
<td></td>
<td>100</td>
<td>97</td>
<td>79</td>
</tr>
<tr>
<td>≤ 10</td>
<td>&gt; 10</td>
<td>10</td>
<td></td>
<td>89</td>
<td>90</td>
<td>51</td>
</tr>
<tr>
<td>&gt; 10</td>
<td>≤ 1</td>
<td>18</td>
<td></td>
<td>100</td>
<td>100</td>
<td>76</td>
</tr>
<tr>
<td>&gt; 10</td>
<td>1-10</td>
<td>36</td>
<td></td>
<td>100</td>
<td>94</td>
<td>79</td>
</tr>
<tr>
<td>&gt; 10</td>
<td>&gt; 10</td>
<td>10</td>
<td></td>
<td>74</td>
<td>69</td>
<td>11</td>
</tr>
</tbody>
</table>

Brandford. Blood 122: abst 254; 213
CML. Criteria for Failure and Suboptimal Response to Imatinib – ELN 2013

<table>
<thead>
<tr>
<th>Time (mo)</th>
<th>Failure</th>
<th>Warning</th>
<th>Optimal</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>No CHR, Ph+ &gt;95%</td>
<td>BCR-ABL &gt;10%, Ph+ ≤25%</td>
<td>BCR-ABL ≤10%, Ph+ ≤25%</td>
</tr>
<tr>
<td>6</td>
<td>BCR-ABL &gt;10%, Ph+ &gt;25%</td>
<td>BCR-ABL 1-10%, Ph+ 1-35%</td>
<td>BCR-ABL &lt;1%, Ph+ &lt;35%</td>
</tr>
<tr>
<td>12 and beyond</td>
<td>BCR-ABL &gt;1%, Ph+ &gt;0%</td>
<td>BCR-ABL &gt;0.1-1%</td>
<td>BCR-ABL &lt;0.1%</td>
</tr>
</tbody>
</table>

Any Loss of CHR
Loss of CCyR
Confirmed loss of MMR
Mutations
CCA/Ph− (-7, or 7q−)

BCR-ABL ≤ 10% at 6 mos; CCyR later
Significantly improved survival

MMR
Modest improvement in EFS; possible longer duration CCyR; no survival benefit

CMR
Possibility of Rx discontinuation

Important Response Categories in CML

- **BCR-ABL ≤ 10% at 6 mos; CCyR later**: Significantly improved survival
- **MMR**: Modest improvement in EFS; possible longer duration CCyR; no survival benefit
- **CMR**: Possibility of Rx discontinuation

Therapy of CML Post Frontline Failure

- **Dasatinib 100 mg/D**
- **Nilotinib 400 mg BID**
- **Bosutinib 500 mg/D**
- **Ponatinib 45 mg/D approved dose (T315I; failure≥2 TKIs)**
- **Omacetaxine, hydrea, HMA, LD ara-C can be added to TKI**

When to Look for Mutations?

- Mutation analysis in 1301 pts receiving imatinib or 2nd generation TKI (GIMEMA)

<table>
<thead>
<tr>
<th>Clinical condition</th>
<th>% Positive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Failure</td>
<td></td>
</tr>
<tr>
<td>No CHR at 3 mo</td>
<td>27</td>
</tr>
<tr>
<td>No CyR at 6 mo</td>
<td>19</td>
</tr>
<tr>
<td>No PCyR at 12 mo</td>
<td>11</td>
</tr>
<tr>
<td>No CCyR at 16 mo</td>
<td>17</td>
</tr>
<tr>
<td>Loss OCR</td>
<td>31</td>
</tr>
</tbody>
</table>

- **Loss CHR**: 50

- **Suboptimal**: 0
  - No CHR at 3 mo
  - No CyR at 6 mo
  - No PCyR at 12 mo
  - No CCyR at 16 mo
  - No MMR at 18 mo
  - Loss MMR

Analysis of Mutations in CML

- If CG or hematologic relapse, mutations studies help
- No role for mutation studies pre-Rx or in imatinib responding patients
- T315I: ponatinib; allo SCT; others (DAC/AZA, ara-C, omacetaxine)
- Y253H, E255K/V, F359V/C/I: dasatinib
- V299L, T315A, F317L/V/I/C: nilotinib
How Do You Choose The Second Generation TKIs?

- Disease characteristics
  - AP/BP: favor Dasatinib/ponatinib and combinations
  - chronic: see below
- Mutations
  - T315I → ponatinib
  - nilotinib IC50 > 150nM → avoid
  - dasatinib IC50 > 3nM → avoid
- Patient Hx
  - Hypertension, CHF, lung problems, COPD → avoid dasatinib
  - Severe diabetes, pancreatitis Hx, atherosclerosis → avoid nilotinib
  - QTc problems/CV Risk factors → Bosutinib

CML: Role and Timing of allo SCT

<table>
<thead>
<tr>
<th>Status</th>
<th>TKIs</th>
<th>Allo SCT</th>
</tr>
</thead>
<tbody>
<tr>
<td>AP-BP</td>
<td>Interim Rx to MRD</td>
<td>ASAP</td>
</tr>
<tr>
<td>IM failure in CP, T315I</td>
<td>Ponatinib</td>
<td>If no/loss response to ponatinib</td>
</tr>
<tr>
<td>IM failure in CP – no CE, no mutations, good initial response</td>
<td>Long-term second line TKIs</td>
<td>Third line post second TKI failure</td>
</tr>
<tr>
<td>IM failure in CP – CE, bad mutations, no CG response</td>
<td>Interim Rx to MRD</td>
<td>Second line</td>
</tr>
<tr>
<td>Older ≥75 – 70 post IM failure</td>
<td>Long-term</td>
<td>May forgo allo SCT for many yrs of QOL</td>
</tr>
</tbody>
</table>

Predictors of Outcome to 2nd Line TKI in CML

- 123 pts treated with dasatinib (n=78) or nilotinib (n=45) after imatinib failure
- Median follow-up 76 months (range, 25-109)
- MCyR 63%, CCyR 59%, 3-yr EFS 55%, 3-yr OS 84%
- 3-mo CCyR 33%

- MVA: 3-mo CCyR only factor independently associated with EFS (p<0.001) and OS (p=0.03)
Failure-free Survival in Chronic Phase Patients Treated With Nilotinib Or Dasatinib After Imatinib Resistance

- No resistant mutations
- Resistant mutations – sequencing
- Sub-clonal resistant mutations – mass spectrometry

Parker et al. JCO 2011;29:2450

Ponatinib in CML—CP (PACE)
- 449 pts Rx; 270 in CP
- CG major 60%, MMR 40%, 5-yr OS 73%

Ponatinib or SCT for T315I CML
- Pts ≥18 yrs with CML T315I in any stage enrolled in PACE (n=449) or EBMT (1999-2010; n=222)

3rd Line TKI in CML
- 185 pts Rx with 3rd TKI: nilotinib 36%, dasatinib 35%, ponatinib 12%, imatinib 10%, bosutinib 7%
- Median time from Dx: 55 mo (3 – 199 mo)
- 1st TKI: intolerance 44%, resistance 67%; 2nd TKI: intolerance 60%, resistance 49%

Response %

<table>
<thead>
<tr>
<th>Disease group</th>
<th>Median survival (mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CP</td>
<td>103</td>
</tr>
<tr>
<td>AP</td>
<td>56</td>
</tr>
<tr>
<td>BP</td>
<td>11</td>
</tr>
<tr>
<td>Ph+ ALL</td>
<td>32</td>
</tr>
</tbody>
</table>


Therapy of CML Transformation
- Accelerated--TKI alone or combo with low intensity Rx (DAC, AZA, LD ara C, HU, etc)
- Lymphoid BP--TKI + ALL Rx (e.g. HCVAD)
- Non-lymphoid BP--TKI + AML Rx or DAC/AZA

Survival in Advanced Phase CML

CML-BP. MDACC Experience (1997-2016)

- 477 pts Rx: lymphoid BP 28%; TKI alone 35%, TKI + ChemoRx 48%; allo SCT 22%
- MHR 50%; CGCR 21%; MHR with TKI alone 43%; TKI + chemo 64%
- Median OS 12 mos
- MVA for OS: TKI combo, allo SCT, lymphoid BP favorable

Frontline CML Therapy in 2018+

- Dasatinib 50mg daily produces similar efficacy and significantly less toxicity than 100mg daily
- Current frontline: dasatinib 50 mg daily + venetoclax 400 mg daily. Aim to achieve high rates of durable CMRs and Rx discontinuation= molecular cures

Low-dose Dasatinib in CML-CP: Response

<table>
<thead>
<tr>
<th>No. Response / Total</th>
<th>3 mos</th>
<th>6 mos</th>
<th>12 mos</th>
<th>18 mos</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCR &lt;10%</td>
<td>78/83 (94%)</td>
<td>78/83 (94%)</td>
<td>71/76 (93%)</td>
<td>48/55 (89%)</td>
</tr>
<tr>
<td>PCR &lt; 1%</td>
<td>62/83 (75%)</td>
<td>73/83 (88%)</td>
<td>69/76 (91%)</td>
<td>48/55 (89%)</td>
</tr>
<tr>
<td>CCyR</td>
<td>41/83 (49%)</td>
<td>72/83 (87%)</td>
<td>69/76 (91%)</td>
<td>47/55 (87%)</td>
</tr>
<tr>
<td>MMR</td>
<td>27/83 (33%)</td>
<td>54/83 (65%)</td>
<td>61/76 (80%)</td>
<td>43/55 (78%)</td>
</tr>
<tr>
<td>MR 4.0</td>
<td>5/83 (6%)</td>
<td>29/83 (35%)</td>
<td>46/76 (61%)</td>
<td>35/55 (64%)</td>
</tr>
<tr>
<td>MR 4.5*</td>
<td>2/83 (2%)</td>
<td>18/83 (22%)</td>
<td>34/76 (45%)</td>
<td>28/55 (51%)</td>
</tr>
</tbody>
</table>

* MR 4.5 = <0.0035% or complete molecular remission

CML Summary – 2019

- Excellent therapy for CML: imatinib, dasatinib, nilotinib, bosutinib, ponatinib, omacetaxine
- CGCR is endpoint of Rx = improves survival
- Early response (3-6 mos) predictive—Do not change at 3 mos, monitor at 6 mos and decide
- Aim for PCR<10% by 6 mos, and for CG CR by 12+mos—these are only indications to change Rx
- Deeper molecular responses (MMR) improve EFS; no impact on transformation or survival
- No clear benefit for CMR (except DC Rx?)
- Patients comorbidities be optimized

Thank you

Guillermo Garcia-Manero, MD
Department of Leukemia
The University of Texas MD Anderson Cancer Center
Houston, TX
April, 2019
Emerging Prognostic Markers and Risk Stratification in Treatment Decision Making for Patients with CLL

Jan A. Burger, MD, PhD
Emerging Prognostic Markers and Risk Stratification in Treatment Decision Making for Patients with CLL

Jan A. Burger, MD
Department of Leukemia
MD Anderson Cancer Center
Houston, Texas
jaburger@mdanderson.org

Conflict of Interest Disclosure
Speaker's Bureau: Janssen
Research Support: Pharmacyclics, Gilead

Chronic Lymphocytic Leukemia
- Most common leukemia in Western world
- Accounts for 30% of adult leukemias
- Median age at diagnosis 70 years
- Median survival ~9 years (before novel agents)
- Advanced disease has increased morbidity and mortality, often from infection

The Rai System for Clinical Staging of CLL

<table>
<thead>
<tr>
<th>Stage</th>
<th>System</th>
<th>Features</th>
<th>Median Survival (y)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Low risk</td>
<td>Lymphocytosis</td>
<td>&gt;10</td>
</tr>
<tr>
<td>I</td>
<td>Intermediate risk</td>
<td>Lymphadenopathy</td>
<td>7</td>
</tr>
<tr>
<td>II</td>
<td>Splenomegaly ± hepatomegaly</td>
<td></td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>High risk</td>
<td>Anemia</td>
<td>2-5</td>
</tr>
<tr>
<td>IV</td>
<td>Thrombocytopenia</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


Prognostic Factors Associated with Inferior Survival
- Advanced stage at diagnosis
- Short lymphocyte doubling time
- Diffuse pattern of marrow infiltration
- Advanced age/males
- High serum levels of \( \beta_2 \)-microglobulin
- CLL–PLL

Genomic Aberrations In CLL
Interphase FISH Results 82% Abnormal

<table>
<thead>
<tr>
<th>Abnormality</th>
<th>No. Patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>13q deletion</td>
<td>178 (55)</td>
</tr>
<tr>
<td>11q deletion</td>
<td>58 (18)</td>
</tr>
<tr>
<td>trisomy 12</td>
<td>53 (16)</td>
</tr>
<tr>
<td>17p deletion</td>
<td>23 (7)</td>
</tr>
<tr>
<td>6q deletion</td>
<td>21 (6)</td>
</tr>
</tbody>
</table>

Dohner et al. NEJM 343:1910, 2000
**Summary of Key Points**

### B-Cell Diversity: $V_H$ Rearrangement and Mutation

- **$V_H$ in B-cell chronic lymphocytic leukemia**
- Somatic mutations (<98% homology)

### Prognostic Factors in CLL

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Bad</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\beta_2$ microglobulin increased</td>
<td></td>
</tr>
<tr>
<td>FISH Del 11q, del 17p</td>
<td></td>
</tr>
<tr>
<td>IGHV Mutation Status unmutated</td>
<td></td>
</tr>
<tr>
<td>CD38 positive</td>
<td></td>
</tr>
<tr>
<td>ZAP70 positive</td>
<td></td>
</tr>
<tr>
<td>Complex karyotype +/- TP53 disruption</td>
<td>predicts for relapse after ibrutinib and venetoclax</td>
</tr>
<tr>
<td>New genomic predictors</td>
<td>NOTCH1, SF3B1, RPS15, and PAX5, telomere length</td>
</tr>
</tbody>
</table>

### FCR300: PFS by IGHV Mutation Status

- *p < 0.0001*

### Probability of Survival


### Comparison of CLL Patients with Mutated and Unmutated $V_H$ Genes

- **Hamblin et al. Blood. 1999;94:1848-1854.**

### Prognostic Factors in CLL


### Additional Key Points

- **Somatic mutations**
  - VH in B-cell chronic lymphocytic leukemia
  - Somatic mutations (<98% homology)

- **Comparison of CLL Patients with Mutated and Unmutated $V_H$ Genes**

- **Prognostic Factors in CLL**

- **FCR300: PFS by IGHV Mutation Status**
PFS of FCR-based According to FISH Hierarchy

Available New Agents in CLL

AGENT
- Ibrutinib
- Idelalisib
- Obinutuzumab
- Venetoclax

TARGET
- BTK
- PI3K-DELTA
- CD20
- BCL2

Novel Agents in CLL: Targeting Disease Biology

Breakthrough in CLL Therapy: Targeting BCR Signaling

Ibrutinib Randomized Trials: Improved PFS in 1st line and RR CLL

Do risk factors matter with novel agents? Yes and No
ASH 2014, PCYC-1117, O'Brien S et al.

RESONATE-2: Ibrutinib Significantly Improved PFS in Patients Regardless of IGHV Status >65 years

- Ibrutinib led to 83% and 92% reduction in the risk of progression or death in patients with mutated and unmutated IGHV, respectively, compared to chemotherapy (n=40) (n=58) (n=42) (n=60)

Barr et al. ASH 2016, Abstract 234

ASH 2014, PCYC-1117, O'Brien S et al.

7-Year Experience with Ibrutinib Monotherapy Survival Outcomes (PCYC 1102/1103)

Progression-Free Survival: TN vs RR

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Median PFS</th>
<th>7-year PFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Del17p (n=34)</td>
<td>26 mo</td>
<td>22%</td>
</tr>
<tr>
<td>Del 11q (n=28)</td>
<td>51 mo</td>
<td>23%</td>
</tr>
<tr>
<td>Trisomy 12 (n=5)</td>
<td>NR</td>
<td>53%</td>
</tr>
<tr>
<td>Del 13q (n=13)</td>
<td>NR</td>
<td>73%</td>
</tr>
<tr>
<td>No abnormality</td>
<td>NR</td>
<td>66%</td>
</tr>
</tbody>
</table>

Byrd et al. 2019, Blood

Resonate Trial: Ibrutinib in RR CLL

Ven+R vs. BR: PFS and OS

PB-MRD negative

Seymour J, et al. NEJM. 2018;378:1107-20

Pairwise Comparisons

- I vs BR: Hazard Ratio 0.39, 95% CI: 0.26-0.58 (1-sided P-value <0.001)
- IR vs BR: Hazard Ratio 0.38, 95% CI: 0.25-0.59 (1-sided P-value <0.001)
- IR vs I: Hazard Ratio 1.00, 95% CI: 0.62-1.62 (1-sided P-value 0.49)

Arm N 24 Month Estimate

- BR 176 74% (95% CI: 66-80%)
- I 178 87% (95% CI: 81-92%)
- IR 170 88% (95% CI: 81-92%)

MURANO Study Design

Adapted from the Intramurine presentation at Annual December, 2017

Venetoclax 400 mg orally once daily to PD, resistant for 7 years to or max. 3 years from Cycle 1 Day 1

Rituximab

200 mg/m^2 IV 10, Cycle 1-3, Days 1 and 8, Cycles 1-6

Bendamustine

70 mg/m^2 Day 1 and 2, Cycles 1-6

Rituximab

Primary Endpoint

- IGHV- mutated PFS

Major Secondary Endpoints

- PC, CR = PFS, ORR, OS (time from randomization to progression, death or last follow-up)

Key Safety Endpoints

- Overall safety profile, focusing on serious adverse events and Grade >3 adverse events

Sample Size

- Approximately 540 Phases I/II M2 patients will be randomized (75% of total enrollment): 190 patients in the rituximab + venetoclax combination arm, 190 in the venetoclax arm, and 160 in the placebo arm.

Videoclip - Hybrid-Regimen versus Chemotherapy in Older Patients with Unmutated CLL
Ibrutinib + Obinutuzumab Versus Chlorambucil + Obinutuzumab as First-Line Treatment in Patients With Chronic Lymphocytic Leukemia or Small Lymphocytic Lymphoma (CLL/SLL): Results From Phase 3 ILLUMINATE

PFS Benefit with Ibrutinib-Obinutuzumab Consistent Across Subgroups

Overall Survival

Superior Progression-Free Survival with Ibrutinib-Obinutuzumab

Study Design
**Conclusions**

- Ibrutinib and rituximab provides superior PFS and OS compared to FCR for patients with previously untreated CLL.
- Ibrutinib and rituximab was well tolerated in patients <70.
- The need for indefinite therapy should be evaluated in future clinical trials testing novel agent combination therapy.
  - EA9161 (NCT03701282; pts <70) & A041702 (NCT03737981; pts ≥70).

**Algorithm for Management of Patients with CLL**

- Risk factors established in the chemotherapy era.
- Therefore, risk factors reflect sensitivity to chemotherapy-based regimen (i.e. chemo-immunotherapy like FCR).
- High-risk patients have shorter PFS and OS survival with chemo-immunotherapy.
- Low-risk patients (i.e. IGHV mutated) have durable remissions with FCR.
- High-risk patients, especially del17p/TP53 mutated should not receive chemotherapy-based regimen in any line of therapy.
- Low-risk patients (i.e. IGHV mutated) can be offered CIT, but randomized trials with novel agents indicate that survival outcomes are better with the novel agents.
Thank you!

Collaborators:
- Würzburg University: A Rosenwald, E Hartmann
- CLLGRC: F Caligaris-Cappio, N Chiorazzi, Z Estrov, N Kay
- UCSF: T Kipps, L Rassenti
- UC Irvine: D Wodarz, N Komarova
- DFCI, Broad I: C Wu, DA Landau

My laboratory: Marilea Sivina, Julia Hoellenriegel, Stefan Koehrer, Ekaterina Kim, Elisa ten Hacken, Shubchintan Randhawa

Funding: CPRIT, MD Anderson Moonshot, Leukemia & Lymphoma Society

Dept. of Leukemia, MDACC
Changing the Treatment Paradigm for CLL: Chemo-immunotherapy versus Targeted Therapy

William G. Wierda, MD, PhD
Changing the Treatment Paradigm for CLL: Chemo-immunotherapy versus Targeted Therapy

William G. Wierda, MD, PhD
Department of Leukemia
Division of Cancer Medicine
U.T. M.D. Anderson Cancer Center
Houston, TX USA

Treatment Goals for CLL

- Potentially curative treatments: FCR for m-IgHV and allo-SCT
- Majority requiring treatment are older (>70yo) with comorbidities and more treatment-associated toxicities
- Goals for first-line –
  - Best opportunity for most effective treatment, most eventually relapse and need retreatment:
    - Deeper remission and treatment-free interval, later retreat
    - Maintain disease control on continuous (IBR) treatment
- Goal for relapsed and refractory:
  - Durable disease control, keep options open

iLLUMINATE (PCYC-1130) Study Design

Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Chlorambucil-obluzimab N=116</th>
<th>Ibrutinib-obluzimab N=113</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (range), years</td>
<td>70 (60–80)</td>
<td>72 (60–80)</td>
</tr>
<tr>
<td>Age ≥65 years, n (%)</td>
<td>56 (48)</td>
<td>62 (53)</td>
</tr>
<tr>
<td>ECOG performance status, n (%)</td>
<td>52 (46)</td>
<td>54 (46)</td>
</tr>
<tr>
<td>Del(17p) and/or mutTP53, n (%)</td>
<td>73 (65)</td>
<td>70 (60)</td>
</tr>
<tr>
<td>High-risk population: unmutated BCR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bulky disease ≥5 cm, n (%)</td>
<td>22 (19)</td>
<td>22 (19)</td>
</tr>
<tr>
<td>Advanced stage disease (Rai III or IV), n (%)</td>
<td>57 (50)</td>
<td>57 (50)</td>
</tr>
<tr>
<td>CrCl &lt;60 mL/min, n (%)</td>
<td>26 (23)</td>
<td>38 (33)</td>
</tr>
<tr>
<td>CIRS ≥6, n (%)</td>
<td>37 (33)</td>
<td>36 (31)</td>
</tr>
</tbody>
</table>

Conflict of Interest Disclosure

<table>
<thead>
<tr>
<th>Commercial Interest</th>
<th>Nature of Relevant Financial Relationship</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genentech/ Roche</td>
<td>Consultant</td>
</tr>
<tr>
<td>PharmacyEcs</td>
<td>Aventuzumab access</td>
</tr>
<tr>
<td>AbbVie</td>
<td></td>
</tr>
<tr>
<td>Acerta/AZ</td>
<td></td>
</tr>
<tr>
<td>Octumal</td>
<td></td>
</tr>
<tr>
<td>JUNO</td>
<td>Research Grant</td>
</tr>
<tr>
<td>Immnzon/ Ziofarm</td>
<td>Clinical trial agreement</td>
</tr>
<tr>
<td>KITE</td>
<td></td>
</tr>
<tr>
<td>Miragen</td>
<td></td>
</tr>
<tr>
<td>Sunesis</td>
<td></td>
</tr>
<tr>
<td>LOBO</td>
<td></td>
</tr>
<tr>
<td>Cyclacel</td>
<td></td>
</tr>
</tbody>
</table>

First-line Phase III Randomized Trials

- iLLUMINATE (PCYC-1130) (>65yo or ≤65yo with comorb.)
  - IRB + OBI vs.
  - CHLOR + OBI
- Alliance (A041202) (>65yo)
  - IRB vs.
  - IRB + RIT vs.
- BR
  - ECOG E1912 [<70yo; non-del(17p)]
  - IRB + RIT vs.
  - FCR

<table>
<thead>
<tr>
<th>Patients (N=220)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Previously untreated CLL/SLL</td>
</tr>
<tr>
<td>Requiring treatment per IWCLL criteria</td>
</tr>
<tr>
<td>Age &gt;65 years or &lt;65 years, n (%) with ≥1 comorbid condition</td>
</tr>
<tr>
<td>CrCl &lt;60 mL/min, n (%)</td>
</tr>
<tr>
<td>CIRS score &gt;6, n (%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Secondary and tobluzimab characteristic</th>
<th>Median age (range), years</th>
<th>No of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment arms</td>
<td>70 (60–80)</td>
<td>56 (48)</td>
</tr>
<tr>
<td>Chlorambucil-obluzimab</td>
<td>57 (50)</td>
<td>57 (50)</td>
</tr>
<tr>
<td>Ibrutinib-obluzimab</td>
<td>52 (46)</td>
<td>54 (46)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Randomized 1:1</th>
</tr>
</thead>
<tbody>
<tr>
<td>ECOG E1912 [&lt;70yo; non-del(17p)]</td>
</tr>
<tr>
<td>Alliance (A041202) (&gt;65yo)</td>
</tr>
<tr>
<td>iLLUMINATE (PCYC-1130) (&gt;65yo or ≤65yo with comorb.)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Secondary End Points</th>
<th>Ibrutinib-obluzimab vs. Chlorambucil-obluzimab</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rate of undetectable MRD</td>
<td>70 (50) vs. 67 (53)</td>
</tr>
<tr>
<td>PFS by IRC in high-risk population</td>
<td>69 (50) vs. 67 (53)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study Design</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyclacel</td>
</tr>
<tr>
<td>KITE</td>
</tr>
<tr>
<td>Miragen</td>
</tr>
<tr>
<td>LOBO</td>
</tr>
<tr>
<td>Sunesis</td>
</tr>
<tr>
<td>JUNO</td>
</tr>
<tr>
<td>Immnzon/ Ziofarm</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Conflict of Interest Disclosure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Commercial Interest</td>
</tr>
<tr>
<td>---------------------</td>
</tr>
<tr>
<td>Genentech/ Roche</td>
</tr>
<tr>
<td>PharmacyEcs</td>
</tr>
<tr>
<td>AbbVie</td>
</tr>
<tr>
<td>Acerta/AZ</td>
</tr>
<tr>
<td>Octumal</td>
</tr>
<tr>
<td>JUNO</td>
</tr>
<tr>
<td>Immnzon/ Ziofarm</td>
</tr>
<tr>
<td>KITE</td>
</tr>
<tr>
<td>Miragen</td>
</tr>
<tr>
<td>Sunesis</td>
</tr>
<tr>
<td>LOBO</td>
</tr>
<tr>
<td>Cyclacel</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Patients (N=116)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Previously untreated CLL/SLL</td>
</tr>
<tr>
<td>Requiring treatment per IWCLL criteria</td>
</tr>
<tr>
<td>Age &gt;65 years or &lt;65 years, n (%) with ≥1 comorbid condition</td>
</tr>
<tr>
<td>CrCl &lt;60 mL/min, n (%)</td>
</tr>
<tr>
<td>CIRS score &gt;6, n (%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Secondary and tobluzimab characteristic</th>
<th>Median age (range), years</th>
<th>No of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment arms</td>
<td>70 (60–80)</td>
<td>56 (48)</td>
</tr>
<tr>
<td>Chlorambucil-obluzimab</td>
<td>57 (50)</td>
<td>57 (50)</td>
</tr>
<tr>
<td>Ibrutinib-obluzimab</td>
<td>52 (46)</td>
<td>54 (46)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Randomized 1:1</th>
</tr>
</thead>
<tbody>
<tr>
<td>ECOG E1912 [&lt;70yo; non-del(17p)]</td>
</tr>
<tr>
<td>Alliance (A041202) (&gt;65yo)</td>
</tr>
<tr>
<td>iLLUMINATE (PCYC-1130) (&gt;65yo or ≤65yo with comorb.)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Secondary End Points</th>
<th>Ibrutinib-obluzimab vs. Chlorambucil-obluzimab</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rate of undetectable MRD</td>
<td>70 (50) vs. 67 (53)</td>
</tr>
<tr>
<td>PFS by IRC in high-risk population</td>
<td>69 (50) vs. 67 (53)</td>
</tr>
</tbody>
</table>
Even after excluding patients with del(17p): 74% reduction in risk of progression or death with ibrutinib-obinutuzumab

- Median follow-up, 31.3 months (range, 0.2–36.9)
- Progression-free survival (%)
  - 100%
  - 70%
  - 50%
  - 30%
  - 20%
  - 10%
  - 5%

- Improved ORR and CR rates with Ibrutinib-Obinutuzumab by IRC
  - IRC-assessed ORR rates were 90% vs. 68% with ibrutinib-obinutuzumab vs. chlorambucil-obinutuzumab

- Fewer grade ≥3 or serious IRRs with ibrutinib-obinutuzumab: 3% vs. 9% with chlorambucil-obinutuzumab
- Similar rates of any grade ≥3 AEs between study arms with ~6 times longer exposure on ibrutinib-obinutuzumab

- Median PFS by high-risk features with ibrutinib-obinutuzumab vs. chlorambucil-obinutuzumab:
  - Not reached vs. 11.3 mo
  - Del(17p): not reached vs. 11.3 mo
  - Del(11q): not reached vs. 15.2 mo
  - Unmutated IGHV: not reached vs. 14.6 mo
  - Del(13q): not reached vs. 15.2 mo

- 46 of 116 patients (40%) randomized to chlorambucil-obinutuzumab crossed over to receive single-agent ibrutinib

- Alliance (A041202) Schema
  - Bendamustine 90mg/m² days 1 & 2 of each 28 day cycle
  - Rituximab 375 mg/m² day 0 cycle 1, then 500 mg/m² day 1 cycles 2-6
  - Untreated patients age ≥65 who meet IWCLL criteria for CLL treatment

- Stratification
  - High risk vs intermediate risk for Stage
  - Presence vs absence of del(11q22.3) or del(13q14.3) on FISH performed locally
  - < 20% vs ≥20% 2p-15 methylation of Cqg 3 performed centrally
### Patient Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total</th>
<th>BR N=183</th>
<th>Ibrutinib N=182</th>
<th>IR N=182</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years median (range)</td>
<td>69 (21-88)</td>
<td>68 (21-88)</td>
<td>69 (21-88)</td>
<td>69 (21-88)</td>
</tr>
<tr>
<td>Sex, %</td>
<td>Male</td>
<td>67</td>
<td>69</td>
<td>68</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>33</td>
<td>31</td>
<td>32</td>
</tr>
<tr>
<td>ECOG 0-1, %</td>
<td>97</td>
<td>95</td>
<td>97</td>
<td>98</td>
</tr>
<tr>
<td>White blood cell count, median (range)</td>
<td>8·10^3</td>
<td>8·10^3</td>
<td>8·10^3</td>
<td>8·10^3</td>
</tr>
<tr>
<td>FISH Characteristics, %</td>
<td>Del(14q)</td>
<td>19</td>
<td>18</td>
<td>24</td>
</tr>
<tr>
<td></td>
<td>Del(15q)</td>
<td>64</td>
<td>8</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>TP53 mutation, %</td>
<td>10</td>
<td>9</td>
<td>12</td>
</tr>
<tr>
<td>Complex karyotype, %</td>
<td>20</td>
<td>27</td>
<td>24</td>
<td>26</td>
</tr>
<tr>
<td>ZAP70 unmutated, %</td>
<td>53</td>
<td>52</td>
<td>53</td>
<td>52</td>
</tr>
<tr>
<td>IgH unmutated*, %</td>
<td>64</td>
<td>58</td>
<td>63</td>
<td>61</td>
</tr>
</tbody>
</table>

* N= 360 total

---

### Response Rates and Minimal Residual Disease

**Intention-to-Treat Patient Population**

- **Overall Response Rates**
  - BR: 81% (95% CI: 75 - 87%)
  - Ibrutinib: 93% (95% CI: 88 - 96%)
  - IR: 94% (95% CI: 89 - 97%)

- **Complete Response Rates**
  - BR: 26% (95% CI: 20 - 33%)
  - Ibrutinib: 7% (95% CI: 4 - 12%)
  - IR: 12% (95% CI: 8 - 18%)

- **Minimal Residual Disease negative in marrow at 9 months**
  - BR: 8% (95% CI: 5 - 13%)
  - Ibrutinib: 1% (95% CI: <1 - 3%)
  - IR: 4% (95% CI: 2 - 8%)

---

### Grade 3, 4, or 5 Adverse Events

During treatment or follow-up (excluding crossover)

- **All grade**
  - GI 22 (15%) 5 (3%) 0 (0%)
  - Hematologic 9 (6%) 0 (0%) 0 (0%)
  - Non-hematologic 23 (16%) 14 (8%) 8 (4%)
  - Infection 2 (1%) 5 (3%) 1 (0%)
  - Hypertension 3 (2%) 3 (2%) 1 (0%)
  - Neutropenia 0 (0%) 0 (0%) 0 (0%)
  - Anemia 0 (0%) 0 (0%) 0 (0%)

* Deaths during active treatment + 30 days: 15 (11%), 13 (7%), 13 (7%)

---

### Primary Endpoint: Progression Free Survival

**Eligible Patient Population**

- **Overall Survival**
  - BR 183 95% (95% CI: 91-98%)
  - Ibrutinib 182 94% (95% CI: 89-97%)
  - IR 183 90% (95% CI: 85-94%)

- **Progression-Free Survival**
  - BR 183 87% (95% CI: 81-92%)
  - Ibrutinib 182 88% (95% CI: 84-97%)
  - IR 182 88% (95% CI: 84-97%)

- **Pairwise Comparisons**
  - IR vs BR: Hazard Ratio 0.38 (95% CI: 0.25-0.59) (1-sided P-value <0.001)
  - IR vs I: Hazard Ratio 1.00 (95% CI: 0.62-1.62) (1-sided P-value 0.49)

---

### Ibrutinib ± Rituximab: Outcomes

**PFS**

- Ibrutinib (n=102) 25.2 (95% CI: 23.7 - 26.9)
- Ibrutinib ± R (n=104) 22.7 (95% CI: 20.8 - 24.7)

No difference in PFS and OS for patients receiving ibrutinib versus ibrutinib plus rituximab
**Patient Characteristics**

<table>
<thead>
<tr>
<th>Baseline characteristics</th>
<th>IR n=354</th>
<th>FCR n=175</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age [y]</td>
<td>58</td>
<td>57</td>
<td>58</td>
</tr>
<tr>
<td>Age &gt; 60</td>
<td>41.0%</td>
<td>40.0%</td>
<td>40.6%</td>
</tr>
<tr>
<td>Female</td>
<td>33.3%</td>
<td>31.4%</td>
<td>32.7%</td>
</tr>
<tr>
<td>ECOG = 0</td>
<td>63.8%</td>
<td>62.3%</td>
<td>63.3%</td>
</tr>
<tr>
<td>Rai stage 0</td>
<td>3.1%</td>
<td>5.1%</td>
<td>3.8%</td>
</tr>
<tr>
<td>Rai stage I-II</td>
<td>52.8%</td>
<td>53.7%</td>
<td>53.1%</td>
</tr>
<tr>
<td>Rai stage III-IV</td>
<td>44.1%</td>
<td>43.1%</td>
<td>43.5%</td>
</tr>
<tr>
<td>FISH 11q deletion</td>
<td>22.0%</td>
<td>22.3%</td>
<td>22.2%</td>
</tr>
<tr>
<td>Trisomy 12</td>
<td>19.8%</td>
<td>15.4%</td>
<td>18.1%</td>
</tr>
<tr>
<td>13q deletion</td>
<td>34.2%</td>
<td>33.1%</td>
<td>33.6%</td>
</tr>
<tr>
<td>IGHV Unmutated</td>
<td>75.0%</td>
<td>61.7%</td>
<td>71.1%</td>
</tr>
</tbody>
</table>

**PFS Sub-Group Analysis**

**Causes of Death**

<table>
<thead>
<tr>
<th>Cause of Death</th>
<th>IR n=354</th>
<th>FCR n=175</th>
</tr>
</thead>
<tbody>
<tr>
<td>CLL</td>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td>Unexplained/unwitnessed</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Other: acute/chronic respiratory failure; fx lung adenocarcinoma</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Acute respiratory failure</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Metastatic colon Cancer</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Drug overdose</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td><strong>4</strong></td>
<td><strong>10</strong></td>
</tr>
</tbody>
</table>

*Death during active treatment +30 days, RR=0.56, FCR vs IR*
Grade 3-5 Treatment Related Adverse Events Throughout Observation

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>IR (%)</th>
<th>FCR (%)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia</td>
<td>22.7%</td>
<td>43.7%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Anemia</td>
<td>2.6%</td>
<td>12.0%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>2.9%</td>
<td>13.9%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Any Infection</td>
<td>7.1%</td>
<td>19.0%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Infection</td>
<td>5.4%</td>
<td>8.2%</td>
<td>0.24</td>
</tr>
<tr>
<td>Neutropenic fever</td>
<td>2.3%</td>
<td>15.8%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>2.9%</td>
<td>0.0%</td>
<td>0.04</td>
</tr>
<tr>
<td>Bleeding</td>
<td>1.1%</td>
<td>0.0%</td>
<td>0.32</td>
</tr>
<tr>
<td>Hypertension</td>
<td>7.4%</td>
<td>1.9%</td>
<td>0.01</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>2.6%</td>
<td>0.0%</td>
<td>0.19</td>
</tr>
<tr>
<td>Any Grade 3 or higher AE</td>
<td>58.5%</td>
<td>72.1%</td>
<td>P=0.004</td>
</tr>
</tbody>
</table>

Shanafelt et al; ASH2018, Abstract LL4-4

FCR300: PFS by IGHV Mutation Status


CLL10 Study: FCR vs BR in Front-line

Progression-free survival by IGHV-MS

Eichhorst et al., Lancet Oncology 17:928, 2016

First-line Treatment for CLL

TP53 Status

<table>
<thead>
<tr>
<th>TP53 Status</th>
<th>Age / Fitness</th>
<th>IGHV-MS</th>
<th>1st Line Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intact</td>
<td>Young / Fit</td>
<td>Mutated</td>
<td>FCR</td>
</tr>
<tr>
<td>BTK/PLCG2</td>
<td>Unmutated</td>
<td>BTK-inhibitor</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>BCL2i + CD20 mAb ?</td>
<td></td>
</tr>
<tr>
<td>Deletion</td>
<td>Older / Unfit</td>
<td>Irrelevant</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>BTK-inhibitor</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>BCL2i + CD20 mAb ?</td>
<td></td>
</tr>
</tbody>
</table>

CLL14

Risk Prognostication of CLL Patients Treated with Ibrutinib

<table>
<thead>
<tr>
<th>Variable</th>
<th>Adverse Factor</th>
<th>Standard Model</th>
<th>Alt. Model</th>
</tr>
</thead>
<tbody>
<tr>
<td>TP53 (17p)</td>
<td>mutated and/or deleted</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Prior treatment</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>B2M</td>
<td>&gt; 4.0 mg/L</td>
<td>Yes</td>
<td>-</td>
</tr>
<tr>
<td>K Rai</td>
<td>R/IW</td>
<td>Yes</td>
<td>-</td>
</tr>
</tbody>
</table>

Ahn et al; ASH2018, Abstract 695

Differentiated Kinase Inhibition Profile

<table>
<thead>
<tr>
<th>BTK/PLCG2 mutations</th>
<th>TEC family Kinases</th>
<th>Inhibition of Other Kinases</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>IC50 (nM) BTK</td>
<td>ITK</td>
</tr>
<tr>
<td>Ibrutinib</td>
<td>0.5</td>
<td>30.7</td>
</tr>
<tr>
<td>Acalabrutinib</td>
<td>5.1</td>
<td>&gt;1000</td>
</tr>
<tr>
<td>Zanubrutinib</td>
<td>0.22</td>
<td>30</td>
</tr>
<tr>
<td>Vecabrutinib</td>
<td>3.15</td>
<td>&gt;10000</td>
</tr>
<tr>
<td>Loxo-3056</td>
<td>4.23</td>
<td>&gt;10000</td>
</tr>
<tr>
<td>CG-8056 (Apoptosis)</td>
<td>3.15</td>
<td>&gt;10000</td>
</tr>
</tbody>
</table>

* Three-factor models can risk stratify CLL in the context of ibrutinib therapy.
  * BTK/PLCG2 mutations were more frequently detected in the high- and intermediate-risk groups than the low-risk group.

Byrd et al., NEJM 2016
Tam et al., ASH 2016
Eathiraj et al., Pan Pacific Lymphoma Conference 2016
Brandhuber et al., SOHO 2018
Zhang et al, EHA 2018
Combinations with BTK-i + BCL2-i-based Tx

- IBR + VEN (MDACC)
- IBR + VEN (CLARITY – UK)
- IBR + VEN + OBIN (OSU)

Ibrutinib + Venetoclax

- Investigator-initiated phase II trial
- Ibrutinib monotherapy - 3 mo
- Ibrutinib+venetoclax – 24 mo
- Option to continue IBR if <CR or MRD*

Tx-naive with at least 1 high-risk feature:
- Del(17p) or mutated TP53
- Del(11q)
- Unmutated IGHV
- Age ≥65 yrs

Baseline Characteristics (N=80)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>n (%) or median [range]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>≥65 43 (54) 65 [26-83]</td>
</tr>
<tr>
<td>Gender, M</td>
<td>57 (71) 136 (17) 57 (71)</td>
</tr>
<tr>
<td>BCL2, %</td>
<td>32 (41) 32 (41) 32 (41)</td>
</tr>
<tr>
<td>MCL, %</td>
<td>72 (91) 72 (91) 72 (91)</td>
</tr>
<tr>
<td>FISH Del(17p)</td>
<td>14 (18) 14 (18) 14 (18)</td>
</tr>
<tr>
<td>FISH Trisomy 12</td>
<td>17 (21) 17 (21) 17 (21)</td>
</tr>
<tr>
<td>FISH Negative</td>
<td>18 (23) 18 (23) 18 (23)</td>
</tr>
<tr>
<td>FISH Del(13q)</td>
<td>14 (18) 14 (18) 14 (18)</td>
</tr>
<tr>
<td>FISH Trisomy 12</td>
<td>15 (19) 15 (19) 15 (19)</td>
</tr>
<tr>
<td>FISH Complex</td>
<td>12 (15) 12 (15) 12 (15)</td>
</tr>
<tr>
<td>FISH Complex</td>
<td>12 (15) 12 (15) 12 (15)</td>
</tr>
<tr>
<td>FISH Del(17p)</td>
<td>14 (18) 14 (18) 14 (18)</td>
</tr>
<tr>
<td>FISH Trisomy 12</td>
<td>17 (21) 17 (21) 17 (21)</td>
</tr>
<tr>
<td>FISH Negative</td>
<td>18 (23) 18 (23) 18 (23)</td>
</tr>
<tr>
<td>FISH Del(13q)</td>
<td>14 (18) 14 (18) 14 (18)</td>
</tr>
<tr>
<td>FISH Trisomy 12</td>
<td>15 (19) 15 (19) 15 (19)</td>
</tr>
<tr>
<td>FISH Complex</td>
<td>12 (15) 12 (15) 12 (15)</td>
</tr>
<tr>
<td>FISH Complex</td>
<td>12 (15) 12 (15) 12 (15)</td>
</tr>
<tr>
<td>FISH Del(17p)</td>
<td>14 (18) 14 (18) 14 (18)</td>
</tr>
<tr>
<td>FISH Trisomy 12</td>
<td>17 (21) 17 (21) 17 (21)</td>
</tr>
<tr>
<td>FISH Negative</td>
<td>18 (23) 18 (23) 18 (23)</td>
</tr>
<tr>
<td>FISH Del(13q)</td>
<td>14 (18) 14 (18) 14 (18)</td>
</tr>
<tr>
<td>FISH Trisomy 12</td>
<td>15 (19) 15 (19) 15 (19)</td>
</tr>
<tr>
<td>FISH Complex</td>
<td>12 (15) 12 (15) 12 (15)</td>
</tr>
<tr>
<td>FISH Complex</td>
<td>12 (15) 12 (15) 12 (15)</td>
</tr>
<tr>
<td>FISH Del(17p)</td>
<td>14 (18) 14 (18) 14 (18)</td>
</tr>
<tr>
<td>FISH Trisomy 12</td>
<td>17 (21) 17 (21) 17 (21)</td>
</tr>
<tr>
<td>FISH Negative</td>
<td>18 (23) 18 (23) 18 (23)</td>
</tr>
<tr>
<td>FISH Del(13q)</td>
<td>14 (18) 14 (18) 14 (18)</td>
</tr>
<tr>
<td>FISH Trisomy 12</td>
<td>15 (19) 15 (19) 15 (19)</td>
</tr>
<tr>
<td>FISH Complex</td>
<td>12 (15) 12 (15) 12 (15)</td>
</tr>
<tr>
<td>FISH Complex</td>
<td>12 (15) 12 (15) 12 (15)</td>
</tr>
<tr>
<td>FISH Del(17p)</td>
<td>14 (18) 14 (18) 14 (18)</td>
</tr>
<tr>
<td>FISH Trisomy 12</td>
<td>17 (21) 17 (21) 17 (21)</td>
</tr>
<tr>
<td>FISH Negative</td>
<td>18 (23) 18 (23) 18 (23)</td>
</tr>
<tr>
<td>FISH Del(13q)</td>
<td>14 (18) 14 (18) 14 (18)</td>
</tr>
<tr>
<td>FISH Trisomy 12</td>
<td>15 (19) 15 (19) 15 (19)</td>
</tr>
<tr>
<td>FISH Complex</td>
<td>12 (15) 12 (15) 12 (15)</td>
</tr>
<tr>
<td>FISH Complex</td>
<td>12 (15) 12 (15) 12 (15)</td>
</tr>
<tr>
<td>FISH Del(17p)</td>
<td>14 (18) 14 (18) 14 (18)</td>
</tr>
<tr>
<td>FISH Trisomy 12</td>
<td>17 (21) 17 (21) 17 (21)</td>
</tr>
<tr>
<td>FISH Negative</td>
<td>18 (23) 18 (23) 18 (23)</td>
</tr>
<tr>
<td>FISH Del(13q)</td>
<td>14 (18) 14 (18) 14 (18)</td>
</tr>
<tr>
<td>FISH Trisomy 12</td>
<td>15 (19) 15 (19) 15 (19)</td>
</tr>
<tr>
<td>FISH Complex</td>
<td>12 (15) 12 (15) 12 (15)</td>
</tr>
<tr>
<td>FISH Complex</td>
<td>12 (15) 12 (15) 12 (15)</td>
</tr>
</tbody>
</table>

Responses Improve with Ongoing Therapy

- PR% 96
- CR/CRi % 43
- BM U-MRD4 % 27
- 6 mo VEN+IBR 83
- 9 mo VEN+IBR 88
- 12 mo VEN+IBR 96
- 18 mo VEN+IBR 69

MRD Response by Pretreatment Characteristics

<table>
<thead>
<tr>
<th>Pretreatment Characteristics</th>
<th>12 mo, BM U-MRD4, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Patients</td>
<td>33 20 (61)</td>
</tr>
<tr>
<td>Age, years &lt;65</td>
<td>16 7 (44)</td>
</tr>
<tr>
<td>Age, years ≥65</td>
<td>17 13 (76)</td>
</tr>
<tr>
<td>FISH Del(17p)</td>
<td>6 5 (83)</td>
</tr>
<tr>
<td>FISH Del(11q)</td>
<td>9 8 (89)</td>
</tr>
<tr>
<td>FISH Trisomy 12</td>
<td>5 2 (40)</td>
</tr>
<tr>
<td>FISH Negative</td>
<td>4 2 (50)</td>
</tr>
<tr>
<td>FISH Del(13q)</td>
<td>9 4 (44)</td>
</tr>
<tr>
<td>FISH Complex</td>
<td>5 4 (80)</td>
</tr>
<tr>
<td>FISH Del(17p)</td>
<td>6 5 (83)</td>
</tr>
<tr>
<td>FISH Del(11q)</td>
<td>9 8 (89)</td>
</tr>
<tr>
<td>FISH Trisomy 12</td>
<td>5 2 (40)</td>
</tr>
<tr>
<td>FISH Negative</td>
<td>4 2 (50)</td>
</tr>
<tr>
<td>FISH Del(13q)</td>
<td>9 4 (44)</td>
</tr>
<tr>
<td>FISH Complex</td>
<td>5 4 (80)</td>
</tr>
</tbody>
</table>

Patient Disposition (N=80)

- 11 pts have come off study

Ibrutinib monotherapy (n=5)
- Skin rash (n=1)
- Hypertension (n=1)
- Use of prohibited medication (n=1)
- Unrelated infection (cryptococcus) (n=1)
- Withdrew consent to receive treatment with a local physician (n=1)

Combination (n=6)
- Recurrent neutropenia (n=2)
- DLBCL transformation (n=1)
- Hemolytic anemia* (n=1)
- Allogeneic SCT (n=1)
- Fallopian tube cancer (n=1)

* Pt later developed MDS
No pt had CLL progression
One pt with Richter transformation
One early death due to disseminated Cryptococcus

G3-4 Heme Toxicities (N=80)
- G3-4 neutropenia: 38 (48%) pts
  - 19 (24%) pts during IBR monotherapy
  - 29 (39%) pts during combination
- 10 pts had G3-4 neutropenia both during IBR monotherapy and combination
- G3-4 neutropenia rate was similar among <65 yrs (49%) vs. ≥65 yrs (47%)
- 24% required G-CSF
- G3 thrombocytopenia: 2 (2%) pts
  - Both in combination phase
  - No G4 thrombocytopenia

Non-Heme Toxicities (N=80)

<table>
<thead>
<tr>
<th>Event</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Easy Fatigue</td>
<td>46 (60)</td>
<td>0</td>
<td>0</td>
<td>46</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>38 (48)</td>
<td>1 (1)</td>
<td>0</td>
<td>39</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>33 (41)</td>
<td>0</td>
<td>0</td>
<td>33</td>
</tr>
<tr>
<td>Nausea/vomiting</td>
<td>29 (36)</td>
<td>0</td>
<td>0</td>
<td>29</td>
</tr>
<tr>
<td>Myelitis</td>
<td>22 (28)</td>
<td>1 (1)</td>
<td>0</td>
<td>23</td>
</tr>
<tr>
<td>Skin rash</td>
<td>17 (21)</td>
<td>0</td>
<td>0</td>
<td>17</td>
</tr>
<tr>
<td>Atrial Fibrillation/flutter</td>
<td>12 (15)</td>
<td>0</td>
<td>0</td>
<td>12</td>
</tr>
<tr>
<td>Nail changes</td>
<td>12 (15)</td>
<td>0</td>
<td>0</td>
<td>12</td>
</tr>
<tr>
<td>Hyperuricemia</td>
<td>11 (14)</td>
<td>0</td>
<td>0</td>
<td>11</td>
</tr>
<tr>
<td>Oral mucositis</td>
<td>11 (14)</td>
<td>0</td>
<td>0</td>
<td>11</td>
</tr>
<tr>
<td>Fatigue</td>
<td>10 (13)</td>
<td>1 (1)</td>
<td>0</td>
<td>11</td>
</tr>
<tr>
<td>Dry skin</td>
<td>9 (11)</td>
<td>0</td>
<td>0</td>
<td>9</td>
</tr>
<tr>
<td>Gastroesophageal reflux disease</td>
<td>6 (8)</td>
<td>0</td>
<td>0</td>
<td>6</td>
</tr>
<tr>
<td>Headache</td>
<td>6 (8)</td>
<td>0</td>
<td>0</td>
<td>6</td>
</tr>
<tr>
<td>Epistaxis</td>
<td>5 (6)</td>
<td>0</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>Infections (G2)</td>
<td>3 (4)</td>
<td>0</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Infections (G3)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Infections (G4)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

49/50 patients have reached at least Month 14 and have had a bone marrow
MRD PB or BM <0.01% CLL cells (10^-4) by flow cytometry

Using statistical significance (alpha) of 2.5% and statistical power of 95.5%, the A'Hern design requires at least
10 of 50 patients to achieve MRD eradication in the marrow to approve the combined treatment.
Assumptions: Ibr+Ven 30% MRD eradication; Ibr monotherapy <10% MRD eradication

All patients* 49/50 (98%) 22 (44%) 5 (10%) 20 (40%) 47 (94%)
FCR/BR relapsed <36 months1 20 8 (40%) 2 (10%) 9 (45%) 19 (95%)
Prior idelalisib2 9 3 (33%) 1 (11%) 4 (44%) 8 (89%)

Hillmen et al. ASH 2018; Abst 182

Primary end-point: undetectable MRD4
(0.01%) in BM after 12 months I+V

All at Month 14

<table>
<thead>
<tr>
<th>% CR</th>
<th>% CRi</th>
<th>% PR</th>
<th>% ORR</th>
</tr>
</thead>
<tbody>
<tr>
<td>22</td>
<td>5</td>
<td>20</td>
<td>47</td>
</tr>
</tbody>
</table>
FCR/BR relapsed <36 months1 | 8 | 2 | 9 | 19 |
Prior idelalisib2 | 9 | 3 | 1 | 4 |

IWCLL Responses
Month 14 (12 months I+V)
Minimal Residual Disease

Response to Treatment

Treatment Related Non-Hematologic Adverse Events

Baseline Patient Characteristics

Study Diagram
Primary endpoint: investigator-assessed PFS; secondary endpoints include rate of undetectable MRD (uMRD).

- Clinical response and MRD in PB/BM during Ven single-agent and at follow-up visits were assessed.

- Primary analysis was pre-planned at 140 PFS events; this follow-up analysis was conducted 1 yr later.

- Clinical response and MRD in PB/BM during Ven single-agent and at follow-up visits were assessed.

- Median follow-up: 36.0 months (range 0.0–48.6). Median per arm: VenR 36.1 months, BR 35.9 months.

- Treatment Pts with relapsed / refractory CLL - Durable disease control

- Superior PFS with VenR vs BR maintained with 1 additional year of follow-up: update

- Richter’s transformations occurred in similar numbers of patients in each arm

- Standard Treatments for Rel/Ref CLL by Disease Characteristics

- Relapsed / Refractory CLL - Durable disease control
  - Del(17p) / m-TP53
  - Age / comorbidities
  - Prior CIT
  - Fludarabine-refractory (CIT)
  - Ibrutinib-refractory
  - Idelalisib-refractory
  - Venetoclax-refractory

- Treatment Options:
  - BTK-inhibitor
  - Bcl-2-inhibitor ± rituximab
  - PI3K-inhibitor + rituximab
  - Lenalidomide ± CD20 mAb
  - CIT
  - Allo-SCT
Modest progression in the first 12 months after completion of Ven monotherapy

Most patients did not progress after cessation of Ven monotherapy at EOT

Predictors of disease progression after Ven cessation at EOT

BCL2 coding mutation detected in four patients with CLL-type progression on venetoclax

Background: CART cells for CLL

Patient characteristics of infused patients (n=19)
### Efficacy: iwCLL, Blood and MB Response

<table>
<thead>
<tr>
<th></th>
<th>Concurrent Ibrutinib</th>
<th>No Ibrutinib</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any grade CRS</td>
<td>14/19 (74%)</td>
<td>22/24 (92%)</td>
<td>0.21</td>
</tr>
<tr>
<td>Grade ≥ 3 CRS</td>
<td>0/19 (0%)</td>
<td>6/24 (25%)</td>
<td>0.03</td>
</tr>
<tr>
<td>Any grade neurotoxicity</td>
<td>6/19 (32%)</td>
<td>10/24 (42%)</td>
<td>0.54</td>
</tr>
<tr>
<td>Grade 3 neurotoxicity</td>
<td>5/19 (26%)</td>
<td>7/24 (29%)</td>
<td>1</td>
</tr>
</tbody>
</table>

### Dose Level

<table>
<thead>
<tr>
<th>Dose Treated (N=16)</th>
<th>DL1</th>
<th>DL2</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.5 × 10^7 CAR+ T cells</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>15 × 10^7 CAR+ T cells</td>
<td>6</td>
<td>6</td>
</tr>
</tbody>
</table>

### Minimal Residual Disease

- All Grade 1–4 CRS and neurotoxicity events were reversible
- CRS grading according to Lee DW et al Blood 2014. Neurotoxicity grading per CTCAE 4.03.
- All Grade 1–4 CRS and neurotoxicity events were reversible
- Grade 5 (fatal) events

### High responses rates at four weeks after CAR-T cell infusion

<table>
<thead>
<tr>
<th></th>
<th>Concurrent Ibrutinib</th>
<th>No Ibrutinib</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>MCLL 2018 (CR/CRi/PR)</td>
<td>15/18 (83%)</td>
<td>15/23 (65%)</td>
<td>0.08</td>
</tr>
<tr>
<td>Marrow CR by flow cytometry</td>
<td>13/18 (72%)</td>
<td>17/23 (74%)</td>
<td>1</td>
</tr>
<tr>
<td>Marrow CR by iGH seqt</td>
<td>11/13 (85%)</td>
<td>7/14 (50%)</td>
<td>0.10</td>
</tr>
<tr>
<td>Nodal (CR/PR per iwCLL 2018 CT)^</td>
<td>10/14 (71%)</td>
<td>14/22 (64%)</td>
<td>0.73</td>
</tr>
</tbody>
</table>

### Transcend CLL 004 Phase 1 study design (NCT03331198)

**Key Eligibility**
- Relapsed/refractory CLL/SLL
- Failed or ineligible for BTKi
- High-risk disease: failed ≥2 prior therapies
- ECOG PS 0–1
- Standard-risk disease: failed ≥3 prior therapies
- ECOG PS 0–1
- High-risk diseaseb: failed ≥2 prior therapies
- Failed or ineligible for BTKia
- Failure defined as SD or PD as best response, or PD after previous response, or discontinuation due to intolerance (unmanageable toxicity).
- Ineligibility defined as requirement for full-dose anticoagulation or history of arrhythmia.
- Complex cytogenetics abnormalities, del(17p), TP53 mutation, or unmutated IGHV.
- Data on file 21 September 2018.

**Primary Objective**
- Determine recommended dose

**Safety**
- Exploratory Objectives
- Antitumor activity
- Pharmacokinetic profile

**Dose-escalation: mTPI-2 Design†**
- 28-day DLT period
- Primary Objective
- Key Eligibility
- Exploratory Objectives
- Pharmacokinetic profile

**Response Rates**

- Bone marrow, NGS
  - CR, complete response; CRi, complete response with incomplete blood count recovery; DL, dose level; mTPI, modified toxicity probability interval; PD, progressive disease; SD, stable disease; SLL, small lymphocytic lymphoma.

**Minimal Residual Disease**

- uMRD4 at any time point, n (%)
  - Blood, flow
    - CR, complete response
    - N=18
    - N=23
    - 0.05

- Bone marrow, NGS
  - CR, complete response
  - N=18
  - N=23
  - 0.05

*Among those with available PET scans and nodal disease per Lugano 2014

†Among those with available PET scans and nodal disease per Lugano 2014

‡Among those with available PET scans and nodal disease per Lugano 2014

≠Among those with available PET scans and nodal disease per Lugano 2014

@Among those with available PET scans and nodal disease per Lugano 2014

• ECOG PS 0–1
• Standard-risk disease: failed ≥3 prior therapies
• 5 patients have post-dose follow-up at Month 6
• 11 of 15 (73.3%) patients had uMRD4 in blood by flow at Day 30
  - All continue to remain undetectable at latest follow-up
• 5 patients have post-dose follow-up at Month 6
  - All continue to maintain uMRD4 response (CR, n=4 and PR, n=1 by iwCLL criteria)

<table>
<thead>
<tr>
<th></th>
<th>Concurrent Ibrutinib</th>
<th>No Ibrutinib</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evaluable for response</td>
<td>N = 18</td>
<td>N = 23</td>
<td>0.05</td>
</tr>
<tr>
<td>MCLL 2018 (CR/CRi/PR)</td>
<td>15/18 (83%)</td>
<td>15/23 (65%)</td>
<td>0.08</td>
</tr>
<tr>
<td>Marrow CR by flow cytometry</td>
<td>13/18 (72%)</td>
<td>17/23 (74%)</td>
<td>1</td>
</tr>
<tr>
<td>Marrow CR by iGH seqt</td>
<td>11/13 (85%)</td>
<td>7/14 (50%)</td>
<td>0.10</td>
</tr>
<tr>
<td>Nodal (CR/PR per iwCLL 2018 CT)^</td>
<td>10/14 (71%)</td>
<td>14/22 (64%)</td>
<td>0.73</td>
</tr>
</tbody>
</table>

**Transcend CLL 004 Phase 1 study design (NCT03331198)**

**Efficacy: iwCLL, Blood and MB Response**

**Response Rates**

- Bone marrow, NGS
  - CR, complete response
  - N=18
  - N=23
  - 0.05

- Bone marrow, NGS
  - CR, complete response
  - N=18
  - N=23
  - 0.05
Relapsed/Refractory CLL - Issues

- **Mechanism(s) of resistance**
  - BTK-i (irreversible BTK-i) (BTK/PLCG2-M)
  - BCL2-i (venetoclax) (BCL2-M)
  - CD19-CAR-T/NK
    - Product vs. host factors
- **Salvage strategies**
  - Reversible BTK-i (SNS-062 / LOXO-305)
  - Other BCL-2-i (APG-2575)
  - MCL1-i (CYC-065, AmGen)
  - Combinations
  - Microenvironment targeted – trabectedin
- **Novel immune-based**
  - CD23xCD20 bispecific
  - Checkpoint inhibitors (PDL-1, CTLA4)
- **Cell-based strategies**

### AEs of Special Interest

<table>
<thead>
<tr>
<th>Total</th>
<th>DL1</th>
<th>DL2</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Grade 4/5 AEs of special interest occurred</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>AE of Special Interest</th>
<th>Total</th>
<th>DL1</th>
<th>DL2</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRS – any grade, n (%)</td>
<td>12 (75.0)</td>
<td>6 (100.0)</td>
<td>6 (60.0)</td>
</tr>
<tr>
<td>Median time to first onset, d (range)</td>
<td>6.5 (1–10)</td>
<td>6.5 (1–9)</td>
<td>5.0 (1–10)</td>
</tr>
<tr>
<td>Median duration, d (range)</td>
<td>5.5 (2–30)</td>
<td>5.5 (2–30)</td>
<td>5.5 (2–10)</td>
</tr>
<tr>
<td>Grade 3, n (%)</td>
<td>3 (18.8)</td>
<td>0</td>
<td>1 (10.0)</td>
</tr>
</tbody>
</table>

| Neurologic events (NE) – any grade, n (%) | 6 (37.5) | 2 (33.3) | 4 (40.0) |
| Median time to first onset, d (range) | 10.0 (4–21) | 16.0 (11–21) | 8.0 (3–13) |
| Median duration, d (range) | 6.5 (2–20) | 4.0 (2–6) | 8.0 (3–20) |
| Grade 3, n (%) | 3 (18.8) | 2 (33.3) | 1 (10.0) |

| Grade 3 or NE | 3 (18.8) | 2 (33.3) | 1 (10.0) |

<table>
<thead>
<tr>
<th>Any, n (%)</th>
<th>CRS or NE^+</th>
<th>CRS and NE^+</th>
<th>Tocilizumab and/or dexamethasone use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 3 or NE &gt;= 2</td>
<td>12 (75.0)</td>
<td>6 (100.0)</td>
<td>7 (70.0)</td>
</tr>
<tr>
<td>Median time to first onset, d (range)</td>
<td>6.5 (2–30)</td>
<td>6.5 (2–30)</td>
<td>5.5 (2–10)</td>
</tr>
<tr>
<td>Median duration, d (range)</td>
<td>5.5 (2–30)</td>
<td>5.5 (2–30)</td>
<td>5.5 (2–10)</td>
</tr>
</tbody>
</table>

| Tumor lysis syndrome – any grade, n (%) | 2 (12.5) | 1 (16.7) | 1 (10.0) |
| Grade 3, n (%) | 2 (12.5) | 1 (16.7) | 1 (10.0) |

No Grade 4/5 AEs of special interest occurred

Siddiqi et al; ASH2018, Abstract 300

### Relapsed/Refractory CLL - Issues

- **Mechanism(s) of resistance**
  - BTK-i (irreversible BTK-i) (BTK/PLCG2-M)
  - BCL2-i (venetoclax) (BCL2-M)
  - CD19-CAR-T/NK
    - Product vs. host factors
- **Salvage strategies**
  - Reversible BTK-i (SNS-062 / LOXO-305)
  - Other BCL-2-i (APG-2575)
  - MCL1-i (CYC-065, AmGen)
  - Combinations
  - Microenvironment targeted – trabectedin
- **Novel immune-based**
  - CD23xCD20 bispecific
  - Checkpoint inhibitors (PDL-1, CTLA4)
- **Cell-based strategies**

THANK YOU!

wwierda@mdanderson.org

Twitter: @wwierda

Siddiqi et al; ASH2018, Abstract 300
New Paradigms in the Treatment of Acute Lymphoblastic Leukemia, Chronic Lymphocytic Leukemia, Acute Myeloid Leukemia and Chronic Myeloid Leukemia

Physician Continuing Education
Accreditation Statement:
This activity has been planned and implemented in accordance with the accreditation requirements and the policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint providership of A. Webb Roberts Center for Continuing Medical Education of Baylor Scott & White Health and CancerNet, LLC. The A. Webb Roberts Center for Continuing Medical Education of Baylor Scott & White Health is accredited by the ACCME to provide continuing medical education for physicians.

Credit Designation:
The A. Webb Roberts Center for Continuing Medical Education of Baylor Scott & White Health designates this educational activity for a maximum of 60 AMA PRA Category 1 Credit(s)™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

Nursing and Pharmacist Continuing Education
In support of improving patient care, this activity has been planned and implemented by Amedco LLC and CancerNet LLC. Amedco LLC is jointly accredited by the Accreditation Council for Continuing Medical Education (ACCME), the Accreditation Council for Pharmacy Education (ACPE), and the American Nurses Credentialing Center (ANCC), to provide continuing education for the healthcare team.

Credit Designation Statement: Amedco LLC designates this live activity for a maximum of 600 contact hours for nurses and 600 knowledge-based contact hours for pharmacists. Learners should claim only the credit commensurate with the extent of their participation in the activity. Event UAN: JA4008163-9999-19-015-L04-P

REGISTRATION

First Name ____________________________________ Middle Initial _______ Last Name ___________________________

Physician □ Pa-C □ NP □ PhD □ Pharmacist □ Industry □ Nurse □ Other

Mailing Address ____________________________________________________________

City ___________________ State _________ Zip Code ____________

Phone ___________________ Fax __________________

E-Mail ____________________

Speciality ____________________

Pharmacists only:

NABP e-profile # ____________________ Birth Date (MMDD): ____________________

Registration Fee

Registration fee partially covers breakfast buffet, lunch and syllabus book.

Early Registration Fee (Up to 4/15/19) $100.00
Discounted Registration Fee (4/16/19 - 4/22/19) $130.00
Regular Registration Fee (4/23/19 - 4/27/19) $160.00

- Physicians
- Registered Nurses, Nurse Practitioners, Physician Assistants $75.00
- Pharmacists, Fellow $75.00
- Industry $350.00

$105.00
$95.00
$115.00
$450.00

† Person(s) employed by for-profit organizations such as pharmaceutical and biotech companies, and financial institutions

No Refund. Substitution is allowed

Payment may be made: □ MC □ Visa □ Discover □ Check

Credit Card Number ___________________________________________ Expiration Date ________

Name and address (as given on the monthly credit card statement)

Signature

Register online at www.cancernetus.com

Fax registration to: 443-267-0016

Mail registration to: 860 Hebron Pkwy, Suite 1104 Lewisville, TX 75057

To reserve your place for the meeting, please complete the registration form and fax it to 443-267-0016. For questions, please call Brian Waggoner at 972-459-5222 or E-mail: brianw@cancernetus.com