DISCLOSURES

- Consulting fees – Amgen
- Research support – Amgen
- Off-label/Investigative Use
  - Blinatumomab
  - Inotuzumab ozogamicin
  - Chimeric Antigen Receptor-Modified T Cells
  - Dasatinib
  - Midostaurin
  - Ibrutinib
Question

- Which of the following is a bispecific T cell engaging antibody that has shown efficacy in the treatment of acute lymphoblastic leukemia?
  1. Inotuzumab
  2. Blinatumomab
  3. Rituxumab
  4. Alemtuzumab
Presentation Objectives

• Assess the role of treatment with pediatric-intensive regimens, BMT, monoclonal antibodies tyrosine kinase inhibitors in acute lymphoblastic leukemia

• Review the role of FLT3 inhibitors and other new agents in the treatment of acute myeloid leukemia

• Discuss the role of chemoimmunotherapy and new agents in the therapy of chronic lymphocytic leukemia

• No data presented on chronic myeloid leukemia because I don’t have time!!
Acute Lymphoblastic Leukemia
USA CCG-CALGB Comparison

Overall Survival

Estimated EFS probability

Years

0 2 4 6 8 10 12 14

7-year EFS
67% (CI 58-75%)
46% (CI 36-56%)

RHR
1.9 (CI 1.32-2.7)

P=0.0002

At risk

<table>
<thead>
<tr>
<th>Years</th>
<th>CCG</th>
<th>CALGB</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>197</td>
<td>124</td>
</tr>
<tr>
<td>1</td>
<td>151</td>
<td>94</td>
</tr>
<tr>
<td>2</td>
<td>131</td>
<td>63</td>
</tr>
<tr>
<td>3</td>
<td>98</td>
<td>48</td>
</tr>
<tr>
<td>4</td>
<td>57</td>
<td>37</td>
</tr>
<tr>
<td>5</td>
<td>19</td>
<td>30</td>
</tr>
<tr>
<td>6</td>
<td>2</td>
<td>8</td>
</tr>
</tbody>
</table>

## Specified Cumulative Postremission Doses

<table>
<thead>
<tr>
<th></th>
<th>CCG (2 trials)</th>
<th>CALGB</th>
</tr>
</thead>
<tbody>
<tr>
<td>VCR (mg/m²)</td>
<td>22/45</td>
<td>14</td>
</tr>
<tr>
<td>Cytarabine (mg/m²)</td>
<td>1,800/2,400</td>
<td>1,200</td>
</tr>
<tr>
<td>DXM (mg/m²)</td>
<td>210/420</td>
<td>140</td>
</tr>
<tr>
<td>ASP (U/m²)</td>
<td>90,000/318,000</td>
<td>48,000</td>
</tr>
<tr>
<td>Doxorubicin (mg/m²)</td>
<td>75/150</td>
<td>90</td>
</tr>
<tr>
<td>CPM (mg/m²)</td>
<td>3000/4,000</td>
<td>3,000</td>
</tr>
<tr>
<td>MTX (IV or oral) (mg/m²)</td>
<td>90/1,000</td>
<td>100</td>
</tr>
<tr>
<td>Intrathecal MTX/cranial RT</td>
<td>132</td>
<td>105</td>
</tr>
<tr>
<td></td>
<td>mg/1,800 cGy</td>
<td>mg/2, 400 cGy</td>
</tr>
</tbody>
</table>

Favorable Outcomes for Older Adolescents and Young Adults (AYA) with Acute Lymphoblastic Leukemia: Early Results of US Intergroup Trial C10403
Abstract #796, ASH 2014


On Behalf of the Alliance for Clinical Trials, the Eastern Cooperative Oncology Group and the Southwest Oncology Group
C10403: US Intergroup study for AYA—Identical to 1 Arm of a 4-Arm COG Study (AALL0232)

<table>
<thead>
<tr>
<th>I</th>
<th>C</th>
<th>IM</th>
<th>DI</th>
<th>M</th>
</tr>
</thead>
<tbody>
<tr>
<td>DNR</td>
<td>Cyclo</td>
<td>MTX</td>
<td>DOX</td>
<td>DEX</td>
</tr>
<tr>
<td>VCR</td>
<td>VCR</td>
<td>VCR</td>
<td>Cyclo</td>
<td>VCR</td>
</tr>
<tr>
<td>Dex</td>
<td>Dex</td>
<td>Peg-ASP</td>
<td>Dex</td>
<td>6MP</td>
</tr>
<tr>
<td>Peg-Asp</td>
<td>Peg-Asp</td>
<td>IT-MTX</td>
<td>Peg-Asp</td>
<td>MTX</td>
</tr>
<tr>
<td>IT-MTX</td>
<td>Ara-C</td>
<td>(R-CD20+)</td>
<td>Ara-C</td>
<td>6-TG</td>
</tr>
<tr>
<td>IT-AraC</td>
<td>6MP</td>
<td>IT-MTX</td>
<td>6-TG</td>
<td>IT-MTX</td>
</tr>
</tbody>
</table>

Maintenance therapy continues for 2 (F) – 3 (M) years

CD22 positive B-cell ALL (Stock et al ASH 2014)
Toxicity Comparison: Induction Only

- 2% induction mortality rate (identical to COG AALL0232)
- Grade 3-5 toxicities only

<table>
<thead>
<tr>
<th></th>
<th>C10403</th>
<th>COG 0232 16-29 yrs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperglycemia</td>
<td>29.2%</td>
<td>22.0%</td>
</tr>
<tr>
<td>Bilirubin</td>
<td>16.4%</td>
<td>6.7%</td>
</tr>
<tr>
<td>AST/ALT</td>
<td>26.6%</td>
<td>N/A</td>
</tr>
<tr>
<td>Pancreatitis</td>
<td>1.1%</td>
<td>0.5%</td>
</tr>
<tr>
<td>Thrombosis/ CNS hemorrhage</td>
<td>3.0%</td>
<td>1.5%</td>
</tr>
</tbody>
</table>
Overall Survival

Outcomes similar between ages 16-20, 21-29, 30-39

n=296, events=71
Median OS: Not reached
2 year OS rate: 79% (95% CI: 74%, 84%)
Absence of MRD using Q-PCR after Induction: Associated with Excellent DFS

- Undetectable: n=18; events = 2
- Detectable: n=25; events = 11; P=0.01

P=0.01
Mechanisms of action of monoclonal antibody conjugates

A. Naked (unconjugated) antibodies
B. Bi-specific T-cell-engaging antibody
C. Antibodies linked to toxins
D. Antibodies linked to drugs
E. Chimeric antigen receptor T cells

Inotuzumab Ozogamicin (INO)

AcBut Linker:
4-(4’-acetylphenoxy) butanoic acid dimethyl hydrazide

MOA retains activity against tumor cells with slow cycling times

Humanized IgG4 anti-CD22

Intact ADC

N-Acetyl γ Calicheamicin
Average loading of calicheamicin derivative on mAb is
5–6 moles of calicheamicin/mole of mAb (range, 3–9) for InO;
~100% of mAbs conjugated
New AYA ALL Trial - Alliance 041501
-A Phase III Trial of INO in Young Adults with Pre B-Cell ALL

Stratification:
Age, CD20 status
LDA-card (Ph-like signature)

Primary Endpoint:
3-yr EFS

Eligibility
Previously untreated B-cell ALL
Patients ages 18-39.9 years
Presence of surface CD22 positive lymphoblasts
Philadelphia negative cytogenetics
US Intergroup study for AYA: Proposal for Randomized Phase III trial (CD22+; Ph-neg)

Maintenance therapy continues for 2 (F) – 3 (M) years
CD22 positive B-cell ALL (Stock et al ASH 2014)
Pediatric Chemotherapy vs AlloHCT for Ph neg Adult ALL in CR1

- 422 RD (42%) or URD (68%) HCT recipients age 18-50 reported to CIBMTR
  - Myeloablative conditioning, most TBI
- 107 rec’d DFCI ALL Consortium pediatric regimen
- HCT cohort slightly older, higher WBC
- t(4;11) 8% HCT vs 10% Chemo

Seftel M et al: ASH ‘14 abstract #319
AJH 91:322, March 2016
HR 6.88 (3.02-15.70); P<0.0001

HR 3.12 (1.99-4.90); P<0.0001

HR 1.77 (1.07-2.94); P=0.027

HR 3.10 (2.04-4.70); P<0.0001

Kaplan Meier Estimate of Overall Survival

Kaplan Meier Estimate of Disease Free Survival

CIF of Treatment Related Mortality

CIF of Relapse

Left-truncated at time of HT for HCT patients
Chemo vs BMT
Recommendations for Ph neg ALL

- Ph neg ALL
  - Up to age 35-45, enroll on peds intensity regimen, if high risk consider BMT
  - 45-55 years – consider BMT, possibly reduced intensity conditioning (RIC)
  - >55 years, chemotherapy, but consider RIC if fit

“Could ALL be a setting where more older than younger patients are treated with BMT?”

Tony Goldstone
Mode of Action of BiTE® Antibody Blinatumomab

Blinatumomab is a bispecific T-cell engager (BiTE®) antibody designed to direct cytotoxic T cells to CD19-expressing cancer cells.

Study Design-Randomized, Open Label Phase 3 Trial of Blinatumomab in Rel/Ref Ph-neg B-ALL

A phase 3 study: 405 patients randomized (TOWER ; NCT02013167)

- Relapsed/refractory Philadelphia neg B precursor ALL
- Refractory
- Relapsed
  - CR1<12 months
  - Untreated 2nd relapse
  - Post alloHSCT

2:1 Randomization (N=405)

Blinatumomab
- Starting dose 9 mcg/day for one week
- Then 28 mcg/day for 3 weeks
- 2 weeks off and repeat for 2 induction cycles

Standard of Care (SOC)
- FLAG +/-anthracycline or
- HD MTX-based regimens or
- HIDAC-based regimens or
- Clofarabine-based regimens

Stratifications:
- Prior Salvage
- Therapy
- Aged ≥35 y vs <35 y
- Prior alloHSCT

Patients in remission after 2 induction cycles were eligible to continue therapy until relapse

Topp et al. EHA 2016, abstract S149
Randomized, Open Label Phase 3 Trial of Blinatumomab in Rel/Ref Ph-neg B-ALL

- 405 pts randomized
  - Blinatumomab 271 (2% rec’d no Rx)
  - SOC chemoRx 134 (19% rec’d no Rx)

- Baseline characteristics balanced

- CR/CRh/CRi rates: Blina 46%, CRx 28%; P=0.001

- Median OS
  - Blinatumomab 7.8 mos (95% CI 5.7-10)
  - ChemoRx 4.0 mos (95% CI 2.9-5.4), p=0.011

- Safety data similar

Topp, et al. EHA abstract S149, June, ‘16
E1910: Randomized Ph III Adult Frontline ALL

Study Design
- U.S. Intergroup study
- $n=127/360$ patients
- U.S., Canada, Israel
- 1:1 Randomization
Chimeric Antigen Receptor-Modified T Cells

- CARs consist of:
  - scFv
  - Hinge region
  - Transmembrane & signaling domain – usually CD3ζ or FcεRIγ, also CD28 and CD137 (41BB)

Chimeric Antigen Receptor-Modified T Cells

- T cells are collected from a patient
- Retrovirally transduced with CAR genes
- Expanded ex vivo
- Infused back to the patient

CD19-Targeted CAR T Cell Therapy for rel/ref B-ALL: Role of CAR Design?

<table>
<thead>
<tr>
<th>CAR Design</th>
<th>CR (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MSKCC 19-28z</td>
<td>88</td>
</tr>
<tr>
<td>NCI FMC63-28z</td>
<td>71</td>
</tr>
<tr>
<td>UPenn CD19-BB-z</td>
<td>89</td>
</tr>
</tbody>
</table>
Impact of Disease Burden on Long-Term Outcome of CD19-Targeted 19-28z CAR Modified Autologous T Cells in Adult Patients with Relapsed or Refractory B-ALL

Jae H. Park, Isabelle Riviere, Xiuyan Wang, Terrence Purdon, Michel Sadelain, and Renier J. Brentjens

Memorial Sloan Kettering Cancer Center
Study Design

R/R CD19+ALL +/- prior HSCT, age ≥18 years, no active CNS disease, no cardiac disease, no GVHD Rx
## Baseline Disease Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Number of Patients, N=51 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Prior Lines of Therapy</strong></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>20 (39)</td>
</tr>
<tr>
<td>3</td>
<td>13 (25)</td>
</tr>
<tr>
<td>≥4</td>
<td>18 (35)</td>
</tr>
<tr>
<td><strong>Prior allogeneic HSCT</strong></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>18 (39)</td>
</tr>
<tr>
<td>No</td>
<td>33 (61)</td>
</tr>
<tr>
<td><strong>Philadelphia chromosome (Ph)+</strong></td>
<td></td>
</tr>
<tr>
<td>T315I mutation</td>
<td>15 (30)</td>
</tr>
<tr>
<td><strong>Disease burden immediately prior to T cells</strong></td>
<td></td>
</tr>
<tr>
<td>Morphologic disease (10-100%, median 63%)</td>
<td>31 (61)</td>
</tr>
<tr>
<td>Minimal disease (&lt;5%)</td>
<td>20 (39)</td>
</tr>
</tbody>
</table>
Overall Survival by Baseline Disease Burden

All Patients

Med gan OS follow-up = 13.0 mo

Median OS
Minimal disease
median OS = not reached

Morphologic
median OS = 9.0 mos

CR rate 90%, MRD neg 78%
P=0.25

CR rate 77%, MRD neg 90%
Overall Survival by Baseline Disease Burden
MRD-CR Patients by Post CAR-T HSCT

Time since CAR T cell infusion (months)

% overall survival

- Minimal Dz, No HSCT (n=8)
- Minimal Dz, with HSCT (n=6)
- Morphologic Dz, No HSCT (=12)
- Morphologic Dz, with HSCT (=7)
Philadelphia Chromosome
t(9;22)(q34;q11)
Multi-Center US Intergroup Study (SWOG S0805) of Intensive Chemotherapy with HyperCVAD plus Dasatinib Followed by Allogeneic Stem Cell Transplant in Patients with Philadelphia Chromosome Positive Acute Lymphoblastic Leukemia Younger Than 60

Farhad Ravandi, Megan Othus, Susan M. O’Brien, Stephen J. Forman, Chul S. Ha, Jeffrey Y.C. Wong, Martin Tallman, Elisabeth Paietta, Janis Racevskis, Geoffrey L. Uy, Uma Borate, Partow Kebriaei, Laura Kingsbury, Hagop M. Kantarjian, Jerald P. Radich, Harry P. Erba, Frederick R. Appelbaum
## SWOG S0805 – Induction Response

<table>
<thead>
<tr>
<th>Response</th>
<th>Number (%) n=94</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>81 (86)</td>
</tr>
<tr>
<td>CRi</td>
<td>2 (2)</td>
</tr>
<tr>
<td>No CR/CRi</td>
<td>10 (11)</td>
</tr>
<tr>
<td>Missing data</td>
<td>1 (1)</td>
</tr>
</tbody>
</table>
SWOG S0805 – Overall Survival (Whole Cohort)

n=94, deaths = 26
3-year OS: 71%
SWOG S0805 - Landmark Analysis; No ASCT vs ASCT

Landmark Overall Survival, 175 Days after CR/CRi

- No protocol transplant, n=40, deaths = 11
- Protocol transplant, n=37, deaths = 5

P=0.088

Months since study registration
Multicenter Total Therapy Gimema LAL 1509 Protocol for De Novo Adult Ph+ Acute Lymphoblastic Leukemia (ALL) Patients. Updated Results and Refined Genetic-Based Prognostic Stratification

**GIMEMA LAL 1509: Study Design**

- **Steroid pre-treatment**
  - **Dasatinib + steroids**
  - **Response evaluation (d +85)**

**CHR+ CMR**
- **Dasatinib 6-month maintenance**

**CHR but NO CMR**
- **AlloSCT eligibility**
  - **Yes**
    - **If >40 days from CHR, Clopha + CTX**
      - **Allo SCT**
        - **MRD positive**
          - **Dasatinib maintenance until relapse or progression**
        - **MRD negative**
          - **Dasatinib 6-month maintenance**
  - **No**
    - **Clopha + CTX**
      - **MRD evaluation**
        - **MRD increase**
          - **HAM**
            - **Positive response**
              - **Dasatinib maintenance until relapse or progression**
            - **Negative response**
              - **Off-treatment**
        - **Stable MRD**
          - **Dasatinib maintenance until relapse or progression**

* BCR-ABL1/ABL1=0
### Response to Induction Treatment

<table>
<thead>
<tr>
<th>Steroids pre-treatment response (n=60)</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>%</td>
</tr>
<tr>
<td>&lt;75%</td>
<td>22</td>
<td>36.7</td>
</tr>
<tr>
<td>&gt;75%</td>
<td>38</td>
<td>63.3</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Complete molecular remission at day +85* (n=58)</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>%</td>
</tr>
<tr>
<td>Yes</td>
<td>11</td>
<td>19</td>
</tr>
<tr>
<td>No</td>
<td>47</td>
<td>81</td>
</tr>
</tbody>
</table>

*Defined as Q-PCR=0 at day +85; confirmatory BM after 15 days

<table>
<thead>
<tr>
<th>Hematologic response at day +57 (n=60)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>%</td>
</tr>
<tr>
<td>CHR</td>
<td>60</td>
<td>100</td>
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</table>

<table>
<thead>
<tr>
<th>Hematologic response at day +85 (n=60)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>%</td>
</tr>
<tr>
<td>CHR</td>
<td>58</td>
<td>97</td>
</tr>
<tr>
<td>No CHR</td>
<td>2*</td>
<td>3</td>
</tr>
</tbody>
</table>

*Both carried the p210 fusion protein

**NO deaths in induction**
OS and DFS

OS: 58.3% (CI 95%: 44.4-76.6) at 36 months

DFS: 49% (CI 95%: 36.8-64.9) at 30 months
Long-term follow-up of imatinib in pediatric Philadelphia chromosome-positive acute lymphoblastic leukemia: Children’s Oncology Group Study AALL0031


Survival probability

Years

Chemo only, n=28
URD BMT, n=13
MRD BMT, n=21  P=0.60
Chemo only, n=24
URD BMT, n=6
MRD BMT, n=13  P=0.89
Schema Overview-Proposed US Intergroup Trial

Ph+ ALL

Induction
TKI + Steroids + blinatumomab

MRD eradication
MRD neg

Randomization
TKI + Steroids + chemotherapy

Randomization
Allo-SCT?

TKI maintenance

Allo-SCT Followed by TKI maintenance
Acute Myeloid Leukemia
Activating \textit{FLT3} Mutations in AML

- **ITD**: 25-30%
  - High relapse, poor prognosis
- **TKD**: 5-10%

Litzow MR: Blood 106:3331, 2005
## FLT3 Inhibitors

<table>
<thead>
<tr>
<th>Inhibitor</th>
<th>IC50 (medium)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>IC50 (plasma)&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lestaurtinib</td>
<td>2 nM</td>
<td>700 nM</td>
</tr>
<tr>
<td>Midostaurin</td>
<td>6 nM</td>
<td>~1000 nM</td>
</tr>
<tr>
<td>Sorafenib</td>
<td>3 nM</td>
<td>~265 nM</td>
</tr>
<tr>
<td>Quizartinib</td>
<td>1 nM</td>
<td>18 nM</td>
</tr>
</tbody>
</table>

<sup>a</sup> – Molm-14 cells incubated in RPMI/10% FBS  
<sup>b</sup> – Molm-14 cells incubated in plasma

Human kinome image generated using TREEspot™ software tool and reprinted with permission from KINOMEscan™, a division of DiscoveRx Co.
A Phase III Randomized Double-blinded Study of Chemotherapy +/- Midostaurin (PKC412) in Newly Diagnosed Adults aged 18-60 With FLT3 Mutated Acute Myeloid Leukemia (AML)


Participants: ALLIANCE/CALGB, AMLSG, CETLAM, ECOG, EORTC, GIMEMA, NCIC, OSHO, PETHEMA, SAL, SWOG CTEP sponsored, Novartis provided drug and sponsored outside North America, and Alliance (formerly CALGB) chaired study, collected data and performed analysis
Schema

Pre-Register

Stratify* FLT3 ITD or TKD

Randomize

DNR ARA-C Midostaurin → CR → HidAC Midostaurin → Midostaurin Maintenance 12 months

DNR ARA-C Placebo → CR → HidAC Placebo → Placebo Maintenance 12 months

FLT3 WILD TYPE not eligible for enrollment

Ages 18-60

Stratification: TKD; ITD with allelic ratio <0.7 ‘vs’ ≥0.7
Overall Survival (Primary Endpoint)

23% Reduced Risk of Death in the Mido Arm

Arm | 4-year Survival
---|------------------
MIDO | 51.4% (95%CI: 46, 57)
PBO  | 44.2% (95%CI: 39, 50)

Hazard Ratio*: 0.77
1-sided log-rank P*: 0.0074

- Median OS: Mido 74.7 (31.7-NE); PBO 25.6 (18.6-42.9) months

* 'Controlled for FLT3 subtype (TKD, ITD-Low, ITD-High)
Overall Survival Post-transplant

Treatment with Mido increases OS after SCT in CR1

* 'Controlled for FLT3 subtype (TKD, ITD-Low, ITD-High)

SCT in CR1
HR 0.61

SCT outside CR1
HR 0.98

Alive (%)

Midostaurin
Placebo

0 20 40 60 80 100

0 12 24 36 48 60 72

Months
North American Leukemia, Intergroup Phase III Randomized Trial of Single Agent Clofarabine as Induction & Post-Remission Therapy, and Decitabine as Maintenance Therapy, in Newly-Diagnosed Acute Myeloid Leukemia in Older Adults (Age ≥60 Years): ECOG-ACRIN Cancer Research Group (E2906)


*Mayo Clinic Cancer Center
Jacksonville, FL
Step 1: Induction

Arm A: Induction
- Daunorubicin 60 mg/m², IV days 1-3 x 1-2 cycles
- Cytarabine 100 mg/m², IV days 1-7 x 1-2 cycles

Arm B: Induction
- Cytarabine 1500 mg/m², IV once daily, days 1-6 x 2 cycles
- Clofarabine 20 mg/m², IV days 1-5 x 2 cycles

Stratification:
- Age 60-69 vs ≥70 yr
- Cytogenetics unfavorable vs ‘other’
- Therapy-related AML
- Antecedent Hematologic Disorder (AHD)

Step 2: Consolidation

Arm C: Consolidation
- Age 60-69 at initial randomization
- Cytarabine 1500 mg/m², IV once daily, days 1-6 x 2 cycles

Arm D: Consolidation
- Clofarabine 20 mg/m², IV days 1-5 x 2 cycles

Step 3: Maintenance

Arm E: Maintenance
- Observation
- Decitabine 20 mg/m², IV days 1-3
  Repeat Q4 weeks for 12 months

Arm F: Maintenance
- Observation
- Decitabine 20 mg/m², IV days 1-3
  Repeat Q4 weeks for

* Re-induction: Clofarabine 20 mg/m² days 1-5
1. See Section 3.6.5
2. For patients with an HLA matched donor who will proceed to transplant-see instruction for consolidation treatment in schema ii
3. Consolidation treatment is determined by induction

n=363
n=364
n=156
n=154
n=61
n=120
n=59
n=72
E2906
Overall Survival – Weighted Analysis

HR 1.41 [95% CI: 1.12-1.77]
380 patients died (177 standard; 203 clofarabine)

Arm A: 13.8 mo, 95% CI 11.7-16.5
Arm B: 9.99 mo, 95% CI 8.35-12.0
Weight Cox Regression P=0.003

Median follow-up surviving patients: 8.2 months
Data censored at Feb 23, 2015
Abstract #327

A Phase 1b Study of Venetoclax (Selective BCL-2 Inhibitor) (ABT-199) in Combination with Decitabine or Azacitidine in Treatment-Naive Patients with Acute Myelogenous Leukemia Who Are ≥65 Years and Not Eligible for Standard Induction Therapy

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*Both authors contributed equally to this work.
Venetoclax: Mechanism of Action

1. An Increase in BCL-2 Expression Allows the Cancer Cell to Survive
   - Proapoptotic proteins (BAX, BAK)
   - Antiapoptotic proteins (BCL-2)

2. Venetoclax Binds to and Inhibits Overexpressed BCL-2
   - BH3-only
   - Venetoclax

3. Apoptosis is Initiated
   - Apoptosome
   - APAF-1
   - Cytochrome C
   - Active caspase
   - Procaspase

Kumar S, et al. ASCO 2015. Abstract 8576
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Methods: Phase 1, Open-Label, Nonrandomized, 2-Arm, 2-Stage Study

Eligibility
- Adult patients ≥65 years of age with untreated AML who are not eligible for standard induction therapy due to comorbidity or other factors
- Adverse or intermediate-risk cytogenetic

Endpoints
- Safety – maximum tolerated dose, DLTs, RP2D, tolerability (# cycles), early deaths, AEs (assessed throughout the study), PK
- Efficacy – overall response rate (CR+CRi+PR) per IWG criteria for AML, duration of response, TTP, PFS, OS, minimal residual disease (time of disease assessment – end of Cycle 1 & 4 and every 12 weeks thereafter)
- Exploratory – molecular markers, characterization of BCL-2 family and mutational profiling, or ex vivo testing of patient samples

Phase 1b Safety
PK & Dose Finding

VEN + DEC (ARM A)
20 mg/m² D1–5, IV 28-D cycles
n=~24

VEN + AZA (ARM B)
75 mg/m² D1–7, IV/SC 28-D cycles
n=~24

One HMA combo at RP2D

VEN + HMA
n=40

Expansion stage for confirmation of safety and efficacy
## Best Responses in All Evaluable Patients in All Cohorts

<table>
<thead>
<tr>
<th>Best response, no. (%)</th>
<th>VEN + DEC 400 mg n=6</th>
<th>VEN + DEC 800 mg n=12</th>
<th>VEN + AZA 400 mg n=4</th>
<th>VEN + AZA 800 mg n=12</th>
<th>ITT responses n=34</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>2 (33)</td>
<td>2 (17)</td>
<td>3 (75)</td>
<td>5 (42)</td>
<td>12 (35)</td>
</tr>
<tr>
<td>CRi</td>
<td>1 (17)</td>
<td>6 (50)</td>
<td>1 (25)</td>
<td>4 (33)</td>
<td>12 (35)</td>
</tr>
<tr>
<td>PR</td>
<td>0</td>
<td>2 (17)</td>
<td>0</td>
<td>0</td>
<td>2 (6)</td>
</tr>
<tr>
<td>MLFS</td>
<td>0</td>
<td>1 (8)</td>
<td>0</td>
<td>0</td>
<td>1 (3)</td>
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<tr>
<td>RD</td>
<td>1 (17)</td>
<td>1 (8)</td>
<td>0</td>
<td>2 (17)</td>
<td>4 (12)</td>
</tr>
<tr>
<td>Not evaluable&lt;sup&gt;a&lt;/sup&gt;</td>
<td>2 (33)</td>
<td>0</td>
<td>0</td>
<td>1 (8)</td>
<td>3 (9)</td>
</tr>
<tr>
<td>ORR (CR/CRi/PR)</td>
<td>3 (50)</td>
<td>10 (83)</td>
<td>4 (100)</td>
<td>9 (75)</td>
<td>26 (76)</td>
</tr>
<tr>
<td>CR+CRi</td>
<td>3 (50)</td>
<td>8 (67)</td>
<td>4 (100)</td>
<td>9 (75)</td>
<td>24 (71)</td>
</tr>
</tbody>
</table>

Median time on study: 106.5 days (range: 6–305)

<sup>a</sup>Three of the 34 patients discontinued prior to the first disease assessment.
Final Results of a Phase III Randomized Trial of VYXEOS™ (CPX-351) Versus 7+3 in Older Patients With Newly Diagnosed High-Risk (Secondary) AML


June 4, 2016
Final results of a phase III randomized trial of CPX-351 versus 7+3 in older patients with newly diagnosed high risk (secondary) AML

- Randomized, Company-sponsored, open-label trial
- First-line Liposomal Ara-C/Daunorubicin (5:1) vs 7+3
  - Older (60-75 yrs)
  - High-risk sAML
- Phase 2 (2014): ORR, EFS, OS benefit in Secondary AML

Cpx-351 Uses a Nano-Scale Delivery Complex

- 100 nm bilamellar liposomes
- 5:1 molar ratio of cytarabine to daunorubicin
- 1 unit = 1.0 mg cytarabine plus 0.44 mg daunorubicin
Phase 3 study of CPX-351 vs Standard Induction in Older Patients with Newly Diagnosed High-Risk AML

Key eligibility
• Previously untreated
• Age 60-75 years
• Able to tolerate intensive therapy
• PS0-2

Stratifications
• Therapy-related AML
• AML with history of MDS with and without prior HMA therapy
• AML with history of CMML
• *de novo* AML with MDS karyotype
• 60-69 years
• 70-75 years

CPX-351
n=153

Follow-up
• Death OR
• 5 years

Induction (1-2 cycles)

Patients in CR or Cri
Consolidation (1-2 cycles)

7 + 3
n=156

*Primary endpoint: Overall survival*
Overall Survival Was Greater in the CPX-351 Arm Compared to the 7+3 Arm

Kaplan-Meier curve for overall survival
ITT analysis population

<table>
<thead>
<tr>
<th>Events/no.</th>
<th>Median surv (95% CI)</th>
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<tbody>
<tr>
<td>CPX-351</td>
<td>104/153</td>
</tr>
<tr>
<td>7+3</td>
<td>132/156</td>
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</table>

HR = 0.69
P=0.005

Survival (%)

Months from randomization

<table>
<thead>
<tr>
<th>Months from randomization</th>
<th>Events</th>
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<tbody>
<tr>
<td></td>
<td>CPX-351</td>
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<tr>
<td>0</td>
<td>153</td>
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<td>6</td>
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<td>21</td>
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<td>24</td>
<td>16</td>
</tr>
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<td>27</td>
<td>11</td>
</tr>
<tr>
<td>30</td>
<td>5</td>
</tr>
<tr>
<td>33</td>
<td>1</td>
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</table>
Chronic Lymphocytic Leukemia
Chemoimmunotherapy (CIT) 2015

• Now over a decade of testing CIT in various forms
  • FCR (Fludarabine)
  • FR
  • PCR (Pentostatin)
  • BR (Bendamustine)

• Current Data suggest that high OR with approximately 45-50% CRs in upfront setting but
  • High RISK FISH and IGVH unmutated do not do well
  • Can see significant cytopenias
  • A subset of patient can have very durable
Long-term Remissions After FCR

CLL 8 Design

Patients with untreated active CLL & good physical fitness*

Randomization

Fludarabine Cyclophosphamide

Fludarabine Cyclophosphamide Rituximab

Six courses of therapy

Follow-up phase

* CIRS ≤ 6, Creatinine Clearance ≥ 70 ml/min
Long Term Remissions After FCR

- FCR: 69.4% alive, Median not reached
- FC: 62.3% alive, Median 86 months

Median observation time: 5.9 years

HR 0.68, 95% CI 0.535-0.858, P=0.001

Fischer K et al. iwCLL 2013
Long Term Remissions After FCR

Median observation time 5.9 years

Cumulative survival

Time to event [OS] (months)

FCR IGHV\textsuperscript{mutated} Not reached
FC IGHV\textsuperscript{mutated} Not reached
FCR IGHV\textsuperscript{unmutated} 86 months
FC IGHV\textsuperscript{unmutated} 75 months

FC vs FCR
HR 1.63, 95% CI 0.908 - 2.916

Fischer K et al. iwCLL 2013
Summary

- Modern Standard Therapy (CIT) has been tested extensively in phase 3 trials and can induce very long term CRs in IGVH mutated CLL.
- Therefore even for elderly patients it may be the treatment of choice in these patients and should not be withheld because of age.
Critical Signaling Pathways and New Targeted Agents in B-Cell Malignancies

- BCR signaling is required for tumor expansion and proliferation
- BCR signaling up-regulated in CLL
- New inhibitors are targeting multiple components of BCR signaling including PI3K delta, BTK, and Syk
# Selected “New” and Emerging Therapies

<table>
<thead>
<tr>
<th>Agent</th>
<th>MOA</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alemtuzumab</td>
<td>Anti-CD52 MoAb</td>
<td>Approved 2007*</td>
</tr>
<tr>
<td>Bendamustine</td>
<td>Alkylating agent</td>
<td>Approved 2008</td>
</tr>
<tr>
<td>Ofatumumab</td>
<td>Anti-CD20 MoAb</td>
<td>Approved 2009, 2014</td>
</tr>
<tr>
<td>Obinutuzumab**</td>
<td>Anti-CD20 MoAb</td>
<td>Approved 2014</td>
</tr>
<tr>
<td>Ibrutinib</td>
<td>BTK inhibitor</td>
<td>Approved 2014</td>
</tr>
<tr>
<td>Idelalisib***</td>
<td>PI3K inhibitor</td>
<td>Approval Q4 2014</td>
</tr>
<tr>
<td>Venetoclax****</td>
<td>BCL-2 inhibitor</td>
<td>Phase 3</td>
</tr>
<tr>
<td>CAR</td>
<td>Chimeric Antigen Receptor therapy</td>
<td>Phase 2</td>
</tr>
</tbody>
</table>

*Withdrawn from commercial sale in 2012; only available by special program

** Also known as Gazyva

*** Also known as Zydelig

**** Also known as GDC-0199
# Response Levels for Novel Agents (Relapsed/Refractory/Naïve)

<table>
<thead>
<tr>
<th>Agent</th>
<th>ORR</th>
<th>CR</th>
<th>PR</th>
<th>PFS (median)</th>
<th>OS</th>
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<tbody>
<tr>
<td><strong>Ibrutinib:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>R/R¹</td>
<td>71%</td>
<td>2/51</td>
<td>34/51</td>
<td>75 %**</td>
<td>83% **</td>
</tr>
<tr>
<td><strong>Ibrutinib:</strong></td>
<td></td>
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</tr>
<tr>
<td>Naïve²</td>
<td>87%</td>
<td>13%</td>
<td>65%</td>
<td>96.3%***</td>
<td>96.6%***</td>
</tr>
<tr>
<td><strong>Idelalisib</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>R/R³</td>
<td>72%</td>
<td></td>
<td>39%*</td>
<td>15.8 mos</td>
<td>NR</td>
</tr>
</tbody>
</table>


* Note that 81.5% achieved a nodal response
** Estimated at 26 months
*** Estimated at 30 months
Therapy Options for CLL (Upfront Therapy)

Oral signal inhibitors\(^1\)\(^-\)\(^4\)

- PI3Kinase (Idelalisib)
  - FDA approved for relapsed/refractory CLL
  - Seems to be well tolerated

- BTK inhibitors (Ibrutinib)
  - Extremely durable remissions\(^5\)
  - FDA approved for relapsed/refractory CLL
  - FDA approved for 17p- CLL who need upfront therapy

High risk FISH (i.e. 17p-) have higher rates of relapse

5. Byrd Blood. 2015 Apr 16;125(16):2497-506
At What Price New Agents?

Two considerations

• New toxicity profiles
• Cost of these agents

Average Whole Sale cost\(^1\) (current pricing)

• Chlorambucil-~$3,500 for 6 cycles of treatment
• CIT- ~$60,000 for standard treatment course
• Ofatumumab-$120,000/treatment

1. Shanafelt et al, Cancer 2015
Concept

• Employ strategy of debulking, induction, & consolidation to sequence administration of novel agents¹

• Use sequential doublet therapy (as opposed to all agents simultaneously) to
  • Take advantage of synergy
  • Minimize overlapping toxicity
  • Decrease risk of TLS
  • Eliminate the need for indefinite ibrutinib therapy

¹Hallek ASH Program Book 2013; page 138
Phase 3 Concept

Primary endpoint
• PFS

Secondary endpoint
• MRD neg rates
• Time off therapy
• Clonal evolution
• Ibrutinib resist
• Richter's transformation
• Cost
• QOL

ARM A
• LL
• Need Trt
• Fit

Cycle Length = 4 weeks
(19 cycles = 18 months)

Cycle 1
Debulking
Ibrutinib
Cycles 2-7
Obinutuzumab
Induction
Cycles 8-13
Venetoclax
Consolidation
Cycles 14-19
Observation
Observation

ARM B
Ibrutinib
Obinutuzumab
Disease progression

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THANK YOU

ANY