<table>
<thead>
<tr>
<th>Disease</th>
<th>Discovery</th>
<th>% 5-10 yr survival</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Historical</strong></td>
<td>Modern</td>
<td></td>
</tr>
<tr>
<td>HCL</td>
<td>DCF, CDA, rituximab</td>
<td>50</td>
</tr>
<tr>
<td>APL</td>
<td>ATRA, As2O3, GO</td>
<td>30-40</td>
</tr>
<tr>
<td>CBF-AML</td>
<td>FLAG-IDA, GO</td>
<td>30</td>
</tr>
<tr>
<td>AML</td>
<td>multiple</td>
<td>10</td>
</tr>
<tr>
<td>CML</td>
<td>imatinib, new TKIs</td>
<td>20</td>
</tr>
<tr>
<td>ALL</td>
<td>Multiple; MoAbs</td>
<td>&lt; 20</td>
</tr>
<tr>
<td>CLL</td>
<td>FCR, BCR inhibitors; ABT199</td>
<td>40-50</td>
</tr>
<tr>
<td>MDS</td>
<td>epigenetic Rx, lenalidomide</td>
<td>30</td>
</tr>
</tbody>
</table>
AML-2016

- APL-ATRA + arsenic trioxide ± GO
- CBFAML-FLAG IDA ± GO
- “3 + 7” poor standard of care--IA; FLAG IDA
- Ida better than DNR 60-90mg/m2
- High-dose araC for induction & consolidation
- IDA + HD araC + “something”: fludarabine, CDA, clofarabine
- GO important; new MoAbs
- FLT3 inhibitors +++ (35% of AML)
- IDH 1-2 inhibitors +++ (20% of AML)
- Hypomethylating agents (older AML): azacitidine, decitabine, SGI-110
- ABT199; checkpoint inhibitors
**AML. General Approach**

<table>
<thead>
<tr>
<th>Entity</th>
<th>Management</th>
<th>% Cure</th>
</tr>
</thead>
<tbody>
<tr>
<td>CG, molecular (FLT3, NPM1, ckit CBF)</td>
<td>Prognosis; need for allo SCT in CR1</td>
<td>--</td>
</tr>
<tr>
<td>MRD by FCM</td>
<td>Prognosis; need for allo SCT in CR1</td>
<td>--</td>
</tr>
<tr>
<td>APL</td>
<td>AIDA; ATRA + ATO</td>
<td>80</td>
</tr>
<tr>
<td>CBF</td>
<td>FLAG-IDA; GO</td>
<td>60+</td>
</tr>
<tr>
<td>Younger AML</td>
<td>3 + 7; DNR60 ara-C; IDA HDara-C; FLAG IDA</td>
<td>40-50</td>
</tr>
<tr>
<td>Older AML; not fit for IC</td>
<td>Low-intensity chemo Rx</td>
<td>10-20</td>
</tr>
<tr>
<td>Marker</td>
<td>%</td>
<td>Prognosis</td>
</tr>
<tr>
<td>--------------------------------</td>
<td>------</td>
<td>------------------------------------------</td>
</tr>
<tr>
<td>FLT3  ITD/mutation</td>
<td>30</td>
<td>Worse</td>
</tr>
<tr>
<td>NPM1 mutation</td>
<td>50</td>
<td>Better</td>
</tr>
<tr>
<td>IDH1-2 mutations</td>
<td>20-30</td>
<td>Worse or neutral</td>
</tr>
<tr>
<td>C-kit mutation- CBF</td>
<td>15</td>
<td>Worse</td>
</tr>
<tr>
<td>↑ BCL2</td>
<td>10-20</td>
<td>Worse</td>
</tr>
<tr>
<td>MLL PTD</td>
<td>7</td>
<td>Worse</td>
</tr>
<tr>
<td>DNMT3A mutation</td>
<td>22</td>
<td>Worse</td>
</tr>
<tr>
<td>ASXL1;TET2</td>
<td>10</td>
<td>Worse; epigenetic modulation</td>
</tr>
<tr>
<td>P53 mutation</td>
<td>5-20</td>
<td>Very poor</td>
</tr>
<tr>
<td>↑ EVI1 expression</td>
<td>10</td>
<td>Very poor</td>
</tr>
</tbody>
</table>
Value of Molecular Studies in AML

• Molecular abnormalities most useful in prognosis/prediction in pts with normal karyotype (e.g. FLT3-ITD, NPM-1, DNMT3A; multiple mutations)

• Significance in pts with adverse CG superseded by adverse CG prognosis

• Significance in pts with favorable CG also minimal (? value of C-KIT in CBF AML)

• Targeted therapies---FLT3, IDH1/2, EZH2, ASXL1
AML MRD Measurements

• PCR-molecular in APL and CBF-AML; also ? NMP1
• FCM-MRD for other AMLs
• Pre-Rx adverse factors (e.g. complex CG, EVI1) precede FCM-MRD in Rx decisions
MRD Assessment - *NPM1* Mutations

A

![Graph A](Image)

Cumulative Incidence of Relapse (%)

Time (months)

B

![Graph B](Image)

Overall Survival (%)

Time (months)

C

![Graph C](Image)

Cumulative Incidence of Relapse (%)

Time (months)

D

![Graph D](Image)

Overall Survival (%)

Time (months)

Krönke J et al. JCO 2011;29:2709-2716
Agents to Eradicate MRD

- Monoclonal antibodies
  - SGN-CD33A, AMG-330, SL-140
- Demethylating agents
  - Oral azacytidine
- Check-point inhibitors
  - Nivolumab
- Small molecule inhibitors
  - FLT3 Kinase inhibitors, IDH inhibitors, ABT-199
- Vaccines
- CAR-T cells
Molecular Targets in AML

- APL-ATRA+arsenic
- CBF AML-FLAG IDA
- FLT3 inhibitors
- IDH1/2 inhibitors
- Monoclonal antibodies targeting CD33 and CD123
- CAR-T cells targeting CD33 and CD123
- ABT199
- Targeting leukemia microenvironment—checkpoint inhibitors
ATRA + As$_2$O$_3$ without Chemotherapy in APL. MD Anderson Experience

- **Induction**
  - ATRA 45 mg/m$^2$/D until CR
  - As$_2$O$_3$ 0.15 mg/kg/D until CR
  - Gemtuzumab (GO) 9 mg/m$^2$x1 if WBC $> 10 \times 10^9$/L

- **Maintenance**
  - ATRA 45 mg/m$^2$/D x 2 wks Q mo x 6
  - As$_2$O$_3$ 0.15/kg/D x 4 wks Q2 mo x 3
  - GO in PCR+

Ravandi. JCO 27:504, 2009
APL. CRD with ATRA + Arsenic

Total=157; Fail=4
5-Year: 97%
Acute Promyelocytic Leukemia as a Model

**Induction**
- ATO
- ATRA
- Until CR

**Consolidation**
- ATO
- 4 weeks on / 4 weeks off
- ATO
- 2 weeks on / 2 weeks off

**Maintenance**
- MTX + 6MP
- 2 years

**Induction**
- IDA
- ATRA
- Until CR

**Consolidation**
- IDA
- MTZ
- IDA
- 3 monthly cycles

**Maintenance**
- ATRA
- 2 years

*Estey et al., Blood 2006*
*Ravandi et al, JCO 2009*
*Lo-Coco et al., Blood 2010*
APL. Outcome with AIDA vs ATRA + As2O3

MDACC - FLAG-GO in CBF AML

- **Induction:** Fludarabine (FL) 30 mg/m$^2$ Days 1-5; Cytarabine (A) 2 g/m$^2$ IV Days 1 to 5; Gemtuzumab Ozogamicin (GO) 3 mg/m$^2$ Day 1; G-CSF (G) 5 mcg/kg Day -1 till neutrophils recovery (can use neulasta 6 mgx1 Day 4)
- **Consolidation:** FL and A for 4 (amended to 3) days, GO (in cycle 2/3 and 5/6) and G as in induction for 6 cycles
- **Peg-GCSF instead of G-CSF allowed beyond day 5 (induction) or day 4 (consolidation)**

Replaced GO by low dose Idarubicin 6mg/m$^2$ days 3 and 4 after patient 50
CBF AML. OS and RFS: Historical Data at MDACC
Patients < 60 years

Relapse-Free Survival Probability

<table>
<thead>
<tr>
<th>Era</th>
<th>Total Fail</th>
<th>Median</th>
</tr>
</thead>
<tbody>
<tr>
<td>1980-89</td>
<td>54</td>
<td>33</td>
</tr>
<tr>
<td>1990-00</td>
<td>66</td>
<td>33</td>
</tr>
<tr>
<td>2000-06</td>
<td>73</td>
<td>NR</td>
</tr>
<tr>
<td>2007-15</td>
<td>95</td>
<td>NR</td>
</tr>
</tbody>
</table>

Survival Probability

<table>
<thead>
<tr>
<th>Era</th>
<th>Total Died</th>
<th>Median</th>
</tr>
</thead>
<tbody>
<tr>
<td>1980-89</td>
<td>59</td>
<td>44</td>
</tr>
<tr>
<td>1990-00</td>
<td>73</td>
<td>42</td>
</tr>
<tr>
<td>2000-06</td>
<td>77</td>
<td>NR</td>
</tr>
<tr>
<td>2007-15</td>
<td>97</td>
<td>NR</td>
</tr>
</tbody>
</table>

p < 0.001
3+7...50 year Anniversary

Cytosine Arabinoside (NSC-63878) and Daunorubicin (NSC-83142) Therapy in Acute Nonlymphocytic Leukemia 1,2,3

Jerome W. Yates, H. James Wallace, Jr., Rose Ruth Ellison, and James F. Holland 4

Early destruction of leukemic infiltration in the induction phase of treatment may reduce the duration of time most hazardous for infection as well as the total period of necessary hospitalization. Daunorubicin produces rapid bone marrow depression, and when adminis-

tensify the effects of cytosine arabinoside and daunorubicin thereby producing rapid destruction of leukemic cells. Such an effect might attain more remissions and earlier discharges from the hospital.
Progress in AML

- “3+7” poor standard of care
- High-dose ara-C in consolidation + induction
- Idarubicin better
- Addition of nucleoside analogs
- Role of gemtuzumab ozogamicin
- Targeted Rx: epigenetic (guadecitabine; SGI110), FLT3 inhibitors, IDH inhibitors, ABT 199
- Checkpoint inhibitors ?; CTL Rx
AML-Survival in Younger Patients (< 60 yrs) – 1970-2015 MDACC

<table>
<thead>
<tr>
<th>Era</th>
<th>Total</th>
<th>Died</th>
<th>5-Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>1970-79</td>
<td>388</td>
<td>357</td>
<td>13%</td>
</tr>
<tr>
<td>1980-89</td>
<td>416</td>
<td>358</td>
<td>21%</td>
</tr>
<tr>
<td>1990-99</td>
<td>640</td>
<td>472</td>
<td>32%</td>
</tr>
<tr>
<td>2000-09</td>
<td>769</td>
<td>434</td>
<td>46%</td>
</tr>
<tr>
<td>2010-15</td>
<td>454</td>
<td>155</td>
<td>49%</td>
</tr>
</tbody>
</table>

p < 0.001
High-dose Ara-C in AML: Meta-Analysis

- 3 trials with 1691 patients randomized to HDAC or SDAC
- CR HDAC = SDAC (RR 1.0)
- 4-year RFS WMD 10.98 (p=0.03) HDAC
- 4-year OS WMD 6.21 (p=0.0005) HDAC
- 5-year EFS WMD 6.00 (p<0.0001) HDAC

HD araC vs. SD araC Induction in AML (EORTC- GIMEMA)

Willemze. JCO 32: 219; 2014
AML. Survival by IDA vs DNR

Overall Survival (probability)

Time Since Random Assignment (months)

P = .19

23%

32-34%

Pautas. JCO January 2010 (epub)
DNR 90 vs 60mg/m² in AML (AML 17)

- 1206 pts randomized to 3 + 7 with DNR 90mg/m² vs 60mg/m² D1, 3, 5. Median age 53 yrs (16-72)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>DNR 90</th>
<th>DNR 60</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>% CR</td>
<td>81</td>
<td>84</td>
<td></td>
</tr>
<tr>
<td>% 30/60 D mortality</td>
<td>6/10</td>
<td>4/5</td>
<td>.09/.001</td>
</tr>
<tr>
<td>% Relapse</td>
<td>37</td>
<td>41</td>
<td>.9</td>
</tr>
<tr>
<td>% 2-yr OS</td>
<td>59</td>
<td>60</td>
<td>.14</td>
</tr>
</tbody>
</table>

- No benefit in subsets (FLT3, fav CG, age)

Burnett. Blood 125: 3878; 2015
DNR 90 vs 60 mg/m² in AML. Survival

Burnett. Blood 125: 3878; 2015
AML. Role of Nucleoside Analogues

- Pilot MDACC studies – FLAG-IDA
- 3 + 7 + CDA (Poland)
- MRC---FLAG IDA x 2 + HD ara-C x 2 = 5 yr survival 63%
MRC-AML 15 - Rx in Younger Patients

Patients with AML (N = 1983)
- DA* (n = 994)
- ADE (n = 989)
- FLAG-Ida* (n = 635)
- ADE (n = 633)

Induction (2 cycles)
- MACE* (Cycle 1) (n = 723)
  - HD Ara-C* (1.5g/m2; n = 329)
  - HD Ara-C* (3g/m2; n = 328)

Rerandomization
- Consolidation (2 cycles)
  - HD Ara-C (n = 112)
  - No Rx (n = 115)

*With or without gemtuzumab ozogamicin in cycles 1 and 3

Burnett. JCO 29:369; 2011
MRC AML 15. ADE/DA vs FLAG-IDA-4 Courses

![Graph showing survival rates over time for ADE/DA and FLAG-IDA-4 courses.](image_url)

- **ADE/DA (4 crs)**: 979 patients, 451 events
- **FLAG-IDA (4 crs)**: 230 patients, 75 events

2P < .001

Burnett. JCO, 2013 (e-Pub)
CDA+DNR+ara-C Improves Survival in Younger AML (Poland)

Holowiecki. JCO 30: 2441; 2012
Gemtuzumab Ozogamicin (GO) Meta-Analysis of 5 AML Randomized Trials

- 5 randomized trials analyzed: SWOG, ALFA, UK-MRC AML15 and 16, GOELAMS
- Addition of GO:
  - no ↑ CR rate: OR 0.91; p=.3
  - increased mortality: HR 1.28; p=.08
  - improved survival: HR .89; p=.01
  - reduced relapse: HR .80; p=<.001
  - improved survival post CR: HR .84; p=.001
- Highly significant survival benefit for favorable risk (HR .50; p=.001) and Int risk (HR .85; p=.007)

Vadastuximab Talirine (SGN-CD33A; 33A) Proposed Mechanism of Action

- **Anti-CD33 antibody**, engineered cysteines to enable uniform site-specific conjugation
- **Cleavable dipeptide linker**, highly stable in circulation
- **Pyrrolobenzodiazepine (PBD) dimer**, binds DNA with high intrinsic affinity

Binds to CD33 antigen

Complex is internalized and traffics to lysosome

PBD is released

DNA repair failed

PBD dimer crosslinks DNA

Apoptotic cell death

Vadastuximab talirine (SGN-CD33A; 33A) is an investigational agent, and its safety and efficacy have not yet been established. ©2015 Seattle Genetics, Inc. All rights reserved.
AMG-330

T-Cell Recruitment → Target Cell Death

CD3 Ab → Bispecific Ab → CD3 Antigen → CD3+ T-cell

CD3+ T-cell → Cytotoxic Granules

Lytic Synapse → Nuclear Condensation → Membrane Blebbing

Perforins

CD33 Ab → CD33+ AML Target Cell
# FLT3 Inhibitors Under Development

<table>
<thead>
<tr>
<th>Preclinical</th>
<th>Phase I</th>
<th>Phase II</th>
<th>Phase III</th>
</tr>
</thead>
<tbody>
<tr>
<td>VX-322</td>
<td>IMC-EB10</td>
<td>Sorafenib</td>
<td>Midostaurin</td>
</tr>
<tr>
<td>VX-398</td>
<td>KW-2449</td>
<td>MLN-518</td>
<td>CEP-701</td>
</tr>
<tr>
<td>MC-2002</td>
<td>AP-24534</td>
<td>Quizartinib</td>
<td></td>
</tr>
<tr>
<td>MC-2006</td>
<td>CHIR-258</td>
<td>Crenolananib</td>
<td></td>
</tr>
<tr>
<td>PLX3397</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
**Quizartinib: A Potent and Selective FLT3 Inhibitor**

<table>
<thead>
<tr>
<th></th>
<th>IC$_{50}$ (medium)$^a$</th>
<th>IC$_{50}$ (plasma)$^b$</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>

---

Phase III Study of Chemotherapy +/- Midostaurin in Newly Diagnosed AML

Study Design

Midostaurin group

Cytarabine (200 mg/m²/day, Days 1 to 7) + Daunorubicin (60 mg/m²/day, days 1-3) + Midostaurin (50 mg, BID, days 8-21)

CR

Consolidation (4 cycles)

High-dose cytarabine (3 g/m²/day BID, Days 1, 3, and 5) + Midostaurin (50 mg, BID, days 8-21)

Control group

Cytarabine (200 mg/m²/day, Days 1 to 7) + Daunorubicin (60 mg/m²/day, days 1-3) + Placebo (BID, days 8-21)

CR

Continuation (12 cycles)

Midostaurin (50 mg, BID, days 1-28)

Treatment-naïve AML patients with activating FLT-3 mutations (N = 514)
<table>
<thead>
<tr>
<th></th>
<th>MIDO (N=360)</th>
<th>PBO (N=357)</th>
<th>pvalue</th>
</tr>
</thead>
<tbody>
<tr>
<td>% CR Day 60</td>
<td>59%</td>
<td>53%</td>
<td>0.15</td>
</tr>
<tr>
<td>Time to CR, median (range)</td>
<td>35 days (20-60)</td>
<td>35 days (20-60)</td>
<td></td>
</tr>
<tr>
<td>% CR post induction/consolidation</td>
<td>66</td>
<td>59</td>
<td>0.045</td>
</tr>
<tr>
<td>Time to CR, median (range)</td>
<td>37 days (20-99)</td>
<td>36 days (20-112)</td>
<td></td>
</tr>
</tbody>
</table>
RATIFY. Survival (Primary Endpoint)

23% reduced risk of death in the Mido arm

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

Hazard Ratio*: 0.77
1-sided log-rank p-value*: 0.0074

RATIFY. Survival by *FLT3* status

<table>
<thead>
<tr>
<th>Status</th>
<th>Favors Treatment</th>
<th>Favors Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall (strat)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>p</em>=0.008</td>
<td>717 0.77 0.63 0.95</td>
<td></td>
</tr>
<tr>
<td>FLT3-ITD-High</td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>p</em>=0.09</td>
<td>214 0.8 0.57 1.12</td>
<td></td>
</tr>
<tr>
<td>FLT3-ITD-Low</td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>p</em>=0.08</td>
<td>341 0.8 0.59 1.1</td>
<td></td>
</tr>
<tr>
<td>FLT3-TKD</td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>p</em>=0.05</td>
<td>162 0.65 0.39 1.08</td>
<td></td>
</tr>
</tbody>
</table>

**IDH Mutations Represent Important Cancer Metabolism Targets**

- **IDHwt**: catalyzes oxidative decarboxylation of isocitrate to produce CO₂ and α-KG

- 3 isoforms exist: IDH1, IDH2, IDH3
  - IDH1: cytoplasm
  - IDH2: mitochondria

- **IDH mutations have neomorphic activity:**
  - Produce high levels of “oncometabolite” 2-HG (gain of function)
  - 2HG leads to differentiation block via epigenetic alterations

AG-221 (IDH2 Inhibitor) in AML

- 198 pts; R140Q (70%); R172k (25%)
- AG-221 starting dose 50mg/D or 30mg BID; highest 600mg/D
- RR AML 138 (70%), unRx 17%, other 6%

<table>
<thead>
<tr>
<th>No Response (%)</th>
<th>Total (n=181)</th>
<th>RR (n=128)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>30 (17)</td>
<td>23 (18)</td>
</tr>
<tr>
<td>CRp/CRi</td>
<td>3 + 1 (3)</td>
<td>1 + 1 (2)</td>
</tr>
<tr>
<td>Marrow CR</td>
<td>15 (8)</td>
<td>8 (6)</td>
</tr>
<tr>
<td>PR</td>
<td>25 (14)</td>
<td>19 (15)</td>
</tr>
<tr>
<td>Overall</td>
<td>74 (41)</td>
<td>52 (41)</td>
</tr>
</tbody>
</table>

- Median response duration 6.9 mos

Stein E. Blood 126: abst 323; 2015
AG-221 (IDH2 Inhibitor) in AML
AG-120 (IDH1 inhibitor) in AML

- 87 ps with IDH1-mutated AML
- AG120 100mg BID-1200 mg/D
- Responses: 12 CR (15%), 7 CRi (9%), 1 PR, 7 marrow CR
- 27 / 78 responses= ORR 35%
- IDH1 associated with DNMT3A (67%), NPM1 (24%)
- Phase 2 dose 500mg/D in R-R AML (n=125), unRx AML (n=25), other IDH1+ (n=25)

AG-120 in AML. Response Durations (N=27)

Study Design: A multi-center, open-label, phase I study to estimate the MTD(s) and/or RDE(s) for IDH305 in patients with advanced malignancies that harbor IDH1^{R132} mutations

- Allows determination of separate MTD and/or RDE for three broad disease areas (glioma, AML/MDS & cholangiocarcinoma/other solid tumors)

Purpose & Rationale: Evaluate the safety, pharmacokinetics, and pharmacodynamics of IDH305

*Classification as oligodendroglioma will be determined by 1p19q loss. Mixed oligoastrocytomas or oligodendrogliomas without 1p19q will be classified as astrocytomas*
An Increase in BCL-2 Expression Allows the Cancer Cell to Survive

Venetoclax Binds to and Inhibits Overexpressed BCL-2

Apoptosis is Initiated

The large # of pro-apoptotic molecules bound and sequestered by BCL2 has cancer cells “primed” for cell death; apoptosis initiated after displacement by ABT199

Konopleva et al, ASH 2014
Venetoxclax (ABT-199)+DAC/AZA in AML

- 22 pts with new Dx AML, median age 74 (65-85)
- VEN 400-800 mg/D + DAC/AZA

<table>
<thead>
<tr>
<th>Therapy</th>
<th>No</th>
<th>Responses</th>
</tr>
</thead>
<tbody>
<tr>
<td>VEN + DAC</td>
<td>12</td>
<td>7CR, 1CRi, 1PR = 75%</td>
</tr>
<tr>
<td>NEN + AZA</td>
<td>10</td>
<td>3 CR, 3 CRi, 1 PR = 70%</td>
</tr>
<tr>
<td>TOTAL</td>
<td>22</td>
<td>10 CR + 4 CRi</td>
</tr>
</tbody>
</table>

- Overall response 16/22 = 73%
VEN + HMAs. Responses

- 28 of the 30 pts (93%) had > 50% blast reduction
- Median time to CR/CRi 29.5 days (24–112 days)
Leukemia Research—Promising Strategies

• FLT3 inhibitors
• IDH 1/2 inhibitors
• CD33, CD123, and CD37 MoAbs: conjugated; bispecific
• Checkpoint inhibitors
• ABT 199
• CAR-T cells (CD33, CD123, CD37)
• EZH2 and DNMT 1/3 targets
Leukemia Research. Immuno-oncology Rx

- MK-3475 (PD1 MoAb)
- MEDI 4736 (PD1 MoAb)
- BMS: nivolumab (PD1 MoAb); urelumab (CD137 MoAb); lirilumab (anti-kir); ipilimumab (CXCR4 MoAb)
- Others?
Ipilimumab for AML Salvage post Allo SCT Relapse

• 28 pts Rx with Ipi 3-10mg/kg Q 3 wks x 4

• 22 Rx with Ipi 10mg/kg: 5 CR (23%), 2 PR (9%), 6 with ↓ tumor (27%)—OR 7/22=32%

• 4 durable responses > 1 yr

• Immune events in 6 pts (21%); 1 death

Davids. NEJM 375: 143; 2016
Ipilimumab Post-SCT

- Relapsed post SCT (n=28)
  - Off IS for >3 mos
  - No h/o G3-4 aGVHD
- Median time from SCT to IPI = 675 days
- Median time from relapse to IPI = 97 days
- 12 AML; 5 CR
  - 8 AML = 1 CR
  - 4 EMD (3 leukemia cutis, 1 myeloid sarcoma) = 4 CR
  - All responders had >99% donor chimerism
- Response by IPI dose (all pts)
  - 3 mg/kg = 0/6
  - 10 mg/kg = 5/22

Davids. NEJM. 2016;375:143.
Azacitidine+Nivolumab for Relapsed AML

• 35 pts; median age 69 yrs

• AZA 50-75mg/m2/Dx7; nivolumab 3mg/kg D1&15

• CR+CRi 6(18%); ↓blasts+HI 5; OR 11/35=32%

• Median survival 9.3 mos; 1-yr survival 38%

Daver. EHA. 2017
CPX-351

- 100 nm bilamellar liposomes
- 5:1 molar ratio of cytarabine to daunorubicin
- Maximally synergistic ratio in cell lines
- Accumulates in BM with preferential uptake by leukemia cells
- MTD: 101 units/m² on days 1, 3, 5

Feldman E, et al. JCO, 2011
### CPX-351 vs 3+7 in Older AML (60-75 yrs)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>CPX-351</th>
<th>3+7</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>% CR</td>
<td>37</td>
<td>26</td>
<td>.04</td>
</tr>
<tr>
<td>% CR + CRi</td>
<td>48</td>
<td>33</td>
<td>.016</td>
</tr>
<tr>
<td>% 60-Day Mortality</td>
<td>14</td>
<td>21</td>
<td>NS</td>
</tr>
</tbody>
</table>

- Survival HR 0.69; p=.005
AML Research at MDACC 2016

- FLT3 inhibitors in frontline AML—FLT3 + vs all
- IDH1/2 combinations (decitabine, IA, FAI) in frontline
- New CD33 and CD123 monoclonals—conjugated, bi-specific, CART
- ABT199 combinations in frontline
- Checkpoint inhibitors in combos, in frontline, and for MRD
- Others: guadecitabine, vosaroxin, CPX351, others
- Extensive genomic profiling of AML clonal evolution, remission and resistance
Developmental Therapeutics in ALL

- Hyper CVAD regimen¹
- CNS prophylaxis with IT chemo Rx (no XRT)¹
- Hyper CVAD+rituximab in Burkitt ALL²
- Hyper CVAD+imatinib/dasatinib in Ph-positive ALL³,⁴
- Hyper CVAD+rituximab in pre-B ALL⁵
- Clofarabine in pediatric ALL salvage (FDA approval 2004)⁶
- Liposomal vincristine (FDA approval 2012)⁷
- Activity of monoclonal antibodies (blinatumomab; inotuzumab) in adult ALL⁸,⁹

# 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</td>
<td>Lots of HD CTX, HD ara-C, Asp; nelarabine?</td>
<td>50-60</td>
</tr>
<tr>
<td>CD20 – positive ALL</td>
<td>ALL chemo Rx+ rituximab/ofatumomab</td>
<td>40-50</td>
</tr>
<tr>
<td>AYA</td>
<td>Augmented BFM; HCVAD-R/O</td>
<td>60+</td>
</tr>
<tr>
<td>MRD by FCM</td>
<td>Prognosis; need for allo SCT in CR1</td>
<td>--</td>
</tr>
</tbody>
</table>
Survival in Ph-ALL by Regimen (Excluding Primary Refractory)

Hyper-CVAD + imatinib

Hyper-CVAD

No. Fail

48  21

50  45

p<0.001

Median follow-up 77 mos (range, 27 to 101+ mos)

Thomas, ASCO 2010, abstract 6506
HyperCVAD + Dasatinib in Ph+ALL - Regimen

Intensive phase

100

1 2 3 4 5 6 7 8

Maintenance phase

100

24 months

Risk-adapted intrathecal CNS prophylaxis

Hyper-CVAD

MTX-cytarabine

Dasatinib 50 mg po bid/ 100 mg daily

Vincristine + prednisone

Ravandi. Blood 126: abst 796; 2015
HyperCVAD+Dasatinib in Ph+ALL. Response

<table>
<thead>
<tr>
<th>Response</th>
<th>N</th>
<th>(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>81</td>
<td>(86)</td>
</tr>
<tr>
<td>CRi</td>
<td>2</td>
<td>(2)</td>
</tr>
<tr>
<td>No CR/CRi</td>
<td>10</td>
<td>(11)</td>
</tr>
<tr>
<td>Missing data</td>
<td>1</td>
<td>(1)</td>
</tr>
</tbody>
</table>

Ravandi. Blood 126: abst 796; 2015
HyperCVAD+Dasatinib in Ph+ALL.

3-year EFS: 54%
3-year OS: 71%

N = 94, events = 40
N = 94, deaths = 26

Ravandi. Blood 126: abst 796; 2015
HyperCVAD+Dasatinib in Ph+ALL. Landmark Analysis; No ASCT vs. ASCT

Landmark overall survival, 175 days after CR/CRi

No protocol transplant, N = 40, deaths = 11
Protocol transplant, N = 38, deaths = 5

Log–rank p–value = 0.088

Ravandi. Blood 126: abst 796; 2015
Hyper-CVAD + Ponatinib. Design

**Intensive phase**
- 1
- 2
- 3
- 4
- 5
- 6
- 7
- 8

**Maintenance phase**
- 1
- 2
- 3
- 4
- 5
- 6
- 7
- 8

24 months

Risk-adapted intrathecal CNS prophylaxis:
- Hyper-CVAD
- MTX-cytarabine
- Ponatinib 45 mg po daily
- Vincristine + prednisone

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>51/51 (100)</td>
</tr>
<tr>
<td>CCyR**</td>
<td>47/47 (100)</td>
</tr>
<tr>
<td>MMR</td>
<td>51/53 (96)</td>
</tr>
<tr>
<td>CMR</td>
<td>42/53 (79)</td>
</tr>
<tr>
<td>Flow</td>
<td>51/52 (98)</td>
</tr>
<tr>
<td>negativity***</td>
<td></td>
</tr>
<tr>
<td>Early death</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

- * 2 pts in CR at start
- ** 6 pts diploid by CG at start
- *** 1 pt had no sample sent for flow

Hyper-CVAD + Ponatinib in Ph-Positive ALL. Survival

Two Evolving Strategies to Treat Ph-positive ALL

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Hyper-CVAD+Ponatinib</th>
<th>TKIs with minimal ChemoRx</th>
</tr>
</thead>
<tbody>
<tr>
<td>% CR</td>
<td>90-100</td>
<td>90-100</td>
</tr>
<tr>
<td>% CMR</td>
<td>80</td>
<td>20</td>
</tr>
<tr>
<td>Allo-SCT required</td>
<td>Only if no CMR</td>
<td>In all</td>
</tr>
<tr>
<td>Outcome p190 vs p210</td>
<td>Same</td>
<td>P190 better</td>
</tr>
<tr>
<td>%3-yr survival/DFS</td>
<td>70-80</td>
<td>40-50</td>
</tr>
</tbody>
</table>

Ph-Positive ALL. General Guidelines

- Combinations of chemo Rx + TKIs
- Early and daily continuous and indefinite TKIs better than later intermittent or limited-duration TKIs
- Newer TKIs better than imatinib
- ? ponatinib best but toxic
- Today – allo SCT in CR1
  Future – allo SCT in CR1 if PCR > 0.1%
Blinatumomab in Ph-positive ALL (ALCANTARA)

- Single agent blinatumomab

- R/R Ph+ ALL to 2+ generation TKI (N=45)
  - T315I (n=10)
  - ≥ 2 TKI (n=27)
  - Prior ponatinib (n=23)

- Primary endpoint (CR/CRh during first 2 cycles)
  - CR/CRh: 16 (36%)
  - T315I: 4 (40%)
  - ≥ 2 TKI: 11 (41%)
  - Prior ponatinib: 8 (35%)

- Secondary endpoints
  - Complete MRD response: 14 (88%)
  - Proceed to alloHSCT: 7 (44%)
  - Median RFS: 6.7 mo (median f/u, 9 mo.)
  - Median OS: 7.1 mo. (median f/u. 8.8 mo)

Martinelli. Blood 2015;126; 679a
## Therapy of Burkitt Leukemia

<table>
<thead>
<tr>
<th>Therapy</th>
<th>MDACC 4-year</th>
<th>Germany 3-year</th>
<th>CALGB 4-year</th>
</tr>
</thead>
<tbody>
<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>

Chemo Rx +/- Rituximab in Burkitt (LMBA-02)-Study Design

Randomization within 72h00 (COP day 1)
Stratification group B-C

Rituximab on D1 and D6
of the 2 COPADM cycles (4 injections)

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

Event Free Survival

Overall Survival

Treatment arm Patients at risk
No Rituximab 129 83 61 43
Rituximab 128 95 74 50

Treatment arm Patients at risk
No Rituximab 119 87 60 44
Rituximab 120 95 73 50

Ribrag. Lancet, in press. 2015
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%

Thomas. JCO 2010; 28:3880-9
ChemoRx +/- Rituximab in Pre-B ALL (French GRAALL-R 2005). EFS

### Augmented BFM and Hyper-CVAD

<table>
<thead>
<tr>
<th>Response</th>
<th>No. (Percent)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ABFM (n=106)</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>

Rytting. Cancer 120: 3660-8; 2014 [Updated 3.2016]
Hyper-CVAD vs. ABFM. Overall Survival

Rytting. Cancer 120: 3660-8; 2014 [Updated 3.2016]
## 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</td>
<td>N/A</td>
<td>NS</td>
</tr>
<tr>
<td>Hypofibrinogenemia</td>
<td>35</td>
<td>14</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Pancreatitis</td>
<td>11</td>
<td>3</td>
<td>0.02</td>
</tr>
<tr>
<td>↑LFTs</td>
<td>41</td>
<td>44</td>
<td>0.60</td>
</tr>
<tr>
<td>↑Bili</td>
<td>38</td>
<td>18</td>
<td>0.001</td>
</tr>
<tr>
<td>Osteonecrosis</td>
<td>9</td>
<td>8</td>
<td>0.68</td>
</tr>
<tr>
<td>Thrombosis</td>
<td>19</td>
<td>12</td>
<td>0.16</td>
</tr>
<tr>
<td>Stroke</td>
<td>3</td>
<td>0</td>
<td>0.09</td>
</tr>
<tr>
<td>Induction infections</td>
<td>22</td>
<td>45</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Induction bleeding</td>
<td>1</td>
<td>5</td>
<td>0.09</td>
</tr>
<tr>
<td>Infections in CR first 60 days</td>
<td>30</td>
<td>60</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Bleeding in CR first 60 days</td>
<td>1</td>
<td>5</td>
<td>0.09</td>
</tr>
<tr>
<td>Deaths in CR</td>
<td>8</td>
<td>7</td>
<td>.85</td>
</tr>
</tbody>
</table>
Why R/O-Hyper-CVAD Better Than Pediatric Regimens?

- Pediatric regimens with asparaginase not compatible with novel/future regimens:
  1. ASP+ponatinib=bad liver toxicities and pancreatitis
  2. ASP+inotuzumab=bad LFTs and VOD

- Future regimens with hyper-CVAD x 3-4, followed by inotuzumab/blinatumomab x 3-4 = 8 to 9 mos total Rx, minimal chemotoxicity, and ↑ cure rates

- ASP effective but highly toxic, particularly with age>40yrs

- Inotuzumab/blinatumomab superior to intensive chemoRx, therefore can replace asparaginase and increase cure rate while reducing toxicity
Outcome of Adult ALL by MRD Status in CR (Week 16)

MolCR: 80% (N=384)
MolFail: 42% (N=120)

ALL, acute lymphoblastic leukaemia; CR, complete remission; MRD, minimal residual disease
Goekbuget. Blood 2012;120:1868
Blinatumomab in ALL MRD-positive

- Median follow-up 29 mos, Median OS 36 mos
- 90 (78%) received allo-SCT

<table>
<thead>
<tr>
<th>Median (mos)</th>
<th>Overall</th>
<th>MRD negative</th>
<th>MRD positive</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>OS</td>
<td>36</td>
<td>40</td>
<td>12</td>
<td>0.001</td>
</tr>
<tr>
<td>RFS</td>
<td>19</td>
<td>35</td>
<td>7</td>
<td>0.002</td>
</tr>
<tr>
<td>DOR</td>
<td>NR</td>
<td>NR</td>
<td>15</td>
<td>0.015</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

Gokbuget. Blood. 2015; 126: Abst # 680
Immuno Oncology in ALL

- Monoclonals + cytotoxic agents—
inotuzumab
- Biallelic monoclonal (CD3 + CD19)—
  blinatumomab
- Modified expanded Tcells—
  CART cells
Immuno-oncology in ALL

- Antibodies, ADCs, immunotoxins, BiTEs, DARTs, CAR-T cells

ADC, antibody–drug conjugate; ALL, acute lymphoblastic leukaemia; BiTE, bi-specific T-cell engagers; CAR, chimeric antigen receptor; DART, dual affinity retargeting molecules; HSV-TK, Herpes Simplex virus thymidine kinase

Inotuzumab ozogamicin

Humanized IgG4 anti-CD22
G544

4-(4-acetylenophenoxy)
butanoic acid linker

N-acetyl gamma calicheamicin
dimethyl hydrazide

Advani et al. JCO 2010
# Inotuzumab Experience

<table>
<thead>
<tr>
<th>Reference</th>
<th>Rx</th>
<th>Ino dose-schedule</th>
<th>ALL Status</th>
<th>Comment</th>
<th>CR/CRp/CRi (%)</th>
<th>Overall Response (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MDACC</td>
<td>49</td>
<td>1.8mg/m² D1</td>
<td>Relapsed, refractory</td>
<td>*Rituximab 375mg/m²</td>
<td>18/ 29/ 10</td>
<td>57</td>
</tr>
<tr>
<td>MDACC</td>
<td>41</td>
<td>0.8mg/m² D1 0.5mg/m² D8, 15</td>
<td>Relapse, refractory</td>
<td>Monotherapy</td>
<td>20/ 32/ 7</td>
<td>59</td>
</tr>
<tr>
<td>Advani</td>
<td>35</td>
<td>0.8mg/m² D1 0.5mg/m² D8, 15</td>
<td>Relapsed, refractor (Salvage 2 or greater)</td>
<td>Monotherapy</td>
<td>31.4/ NR/ 12</td>
<td>65.7</td>
</tr>
<tr>
<td>DeAngelo</td>
<td>218 total 109 Ino</td>
<td>0.8mg/m² D1 0.5mg/m² D8, 15</td>
<td>Relapsed, refractory (Salvage 1 or 2 only)</td>
<td>Monotherapy (COMPARED to SOC)</td>
<td>36/ NR/ 45</td>
<td>81</td>
</tr>
<tr>
<td>MDACC</td>
<td>24</td>
<td>1.8mg/m² C1D3 1.3mg/m² D3 during Cycles 2 - 4</td>
<td>Relapsed, refractory</td>
<td>Mini-hyperCVD-R</td>
<td>46/ 25/ 4</td>
<td>75</td>
</tr>
<tr>
<td>MDACC</td>
<td>33</td>
<td>1.8mg/m² C1D3 1.3mg/m² D3 during Cycles 2 - 4</td>
<td>New Dx</td>
<td>Mini-hyperCVD-R</td>
<td>80/ 17/ NR</td>
<td>97</td>
</tr>
</tbody>
</table>

2. Advani I abstract 2255. (ASH 2014)
**Study Design**

- Open-label, phase 3 study; 326 pts randomized at 117 sites in 19 countries

**INO-VATE: InO vs SOC in R/R ALL**

- **R/R CD22+ ALL**
- **Salvage 1 or 2**
- **Ph− or Ph+**

1:1 Randomization (N=326)

**Stratifications:**
- Duration of 1st CR ≥12 vs <12 mo
- Salvage 2 vs 1
- Aged ≥55 y vs <55 y

**InO**
- Starting dose 1.8 mg/m²/cycle
- 0.8 mg/m² Day 1;
- 0.5 mg/m² Days 8 and 15 of a 21–28 Day cycle (≤6 cycles)

**Standard of Care (SOC)**
- FLAG or
- Ara-C plus mitoxantrone or
- HIDAC
- ≤4 cycles

\(^a\text{InO dose reduced to 1.5 mg/m²/cycle once patient achieved CR/CRi.}
Kantarjian. NEJM. 375: 740; 2016
## CR/CRi Results in ITT218

<table>
<thead>
<tr>
<th>Response, a n (%) [95% CI]</th>
<th>InO (n=109)</th>
<th>SOC (n=109)</th>
<th>1-sided P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR/CRi</td>
<td>88 (80.7)</td>
<td>32 (29.4)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td>[72–88]</td>
<td>[21–39]</td>
<td></td>
</tr>
<tr>
<td>MRD neg b</td>
<td>69/88 (78.4)</td>
<td>9/32 (28.1)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td>[68–87]</td>
<td>[14–47]</td>
<td></td>
</tr>
</tbody>
</table>

- Among the first 218 pts randomized, over 4X more achieved CR/CRi and proceeded directly to SCT after CR/CRi with InO vs SOC (n=41/109 vs n=10/109; \( P<0.0001 \))

Kantarjian. NEJM. 375: 740; 2016
Primary objective to demonstrate significantly improved OS with InO at the prespecified boundary of $P=0.0104$ not met

Kantarjian. NEJM. 375: 740; 2016
## Subgroup Analysis of OS

<table>
<thead>
<tr>
<th></th>
<th>n (No. of Events)</th>
<th>Median OS, mo</th>
<th>In favor of InO</th>
<th>HR (97.5% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>InO</td>
<td>SOC</td>
<td>InO</td>
<td>SOC</td>
</tr>
<tr>
<td>All patients</td>
<td>164 (122)</td>
<td>162 (130)</td>
<td>7.7</td>
<td>6.7</td>
</tr>
<tr>
<td>Duration of 1st CR</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;12 Months</td>
<td>109 (89)</td>
<td>107 (89)</td>
<td>6.6</td>
<td>5.3</td>
</tr>
<tr>
<td>≥12 months</td>
<td>55 (33)</td>
<td>55 (41)</td>
<td>11.1</td>
<td>9.4</td>
</tr>
<tr>
<td>Salvage status</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>108 (75)</td>
<td>107 (87)</td>
<td>8.6</td>
<td>7.1</td>
</tr>
<tr>
<td>2</td>
<td>56 (47)</td>
<td>55 (43)</td>
<td>6.2</td>
<td>5.2</td>
</tr>
<tr>
<td>Age at randomization, y</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;55</td>
<td>104 (70)</td>
<td>103 (79)</td>
<td>8.6</td>
<td>8.0</td>
</tr>
<tr>
<td>≥55</td>
<td>60 (52)</td>
<td>59 (51)</td>
<td>5.6</td>
<td>5.3</td>
</tr>
<tr>
<td>Cytogenetics</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ph+</td>
<td>22 (18)</td>
<td>28 (22)</td>
<td>8.7</td>
<td>7.7</td>
</tr>
<tr>
<td>Ph−</td>
<td>142 (104)</td>
<td>134 (108)</td>
<td>7.4</td>
<td>5.9</td>
</tr>
<tr>
<td>Complex</td>
<td>27 (22)</td>
<td>22 (18)</td>
<td>7.2</td>
<td>3.9</td>
</tr>
<tr>
<td>Normal w/ ≥20 metaphases</td>
<td>35 (24)</td>
<td>34 (28)</td>
<td>8.6</td>
<td>8.9</td>
</tr>
<tr>
<td>Pre-study transplant</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>28 (23)</td>
<td>29 (20)</td>
<td>8.5</td>
<td>13.1</td>
</tr>
<tr>
<td>No</td>
<td>136 (99)</td>
<td>133 (110)</td>
<td>7.1</td>
<td>5.5</td>
</tr>
<tr>
<td>BM blasts</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;50%</td>
<td>53 (37)</td>
<td>48 (42)</td>
<td>7.4</td>
<td>9.1</td>
</tr>
<tr>
<td>≥50%</td>
<td>109 (84)</td>
<td>113 (87)</td>
<td>7.7</td>
<td>5.5</td>
</tr>
</tbody>
</table>

Kantarjian. NEJM. 375: 740; 2016
**MiniHCVD-INO in ALL. Design**

**Intensive phase**

1. **D3**
2. **D3**
3. **D3**
4. **D3**

**Maintenance phase**

- MiniHCVD
- Mini-MTX-cytarabine
- POMP Maintenance

Inotuzumab

<table>
<thead>
<tr>
<th>Inotuzumab</th>
<th>First 6 pts</th>
<th>7 to 34</th>
<th>35 and beyond</th>
</tr>
</thead>
<tbody>
<tr>
<td>First cycle (mg/m²)</td>
<td>1.3</td>
<td>1.8</td>
<td>1.3</td>
</tr>
<tr>
<td>C2-4 (mg/m²)</td>
<td>0.8</td>
<td>1.3</td>
<td>1.0</td>
</tr>
</tbody>
</table>
Inotuzumab + Hyper-CVD in Elderly ALL

<table>
<thead>
<tr>
<th>Parameter</th>
<th>N (%) / Median [Range]</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of pts</td>
<td>33</td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>69 [60-79]</td>
</tr>
<tr>
<td>CD22</td>
<td>98 [72-100]</td>
</tr>
<tr>
<td>CD20 (≥20%)</td>
<td>23/33 (70%) *</td>
</tr>
<tr>
<td>CR</td>
<td>24 (80)</td>
</tr>
<tr>
<td>CRp</td>
<td>5 (17)</td>
</tr>
<tr>
<td>Death in CR</td>
<td>2</td>
</tr>
<tr>
<td>2-year PFS %</td>
<td>85</td>
</tr>
<tr>
<td>2-year OS %</td>
<td>70</td>
</tr>
</tbody>
</table>

Figure 1. Survival with mini-HCVD-INO vs HCVAD +/- Rituximab in frontline ALL

Jabbour . EHA 2015, Abstract #S114
Blinatumomab. A “Serial Killer”

- Pre B-Lymphoblast
- CD19
- Blinatumomab
- CD3
- Lysis
- T Cell
## Blinatumomab-Summary Phase 2 Trials

<table>
<thead>
<tr>
<th>Study, (year)</th>
<th>Study</th>
<th>Rx</th>
<th>CR/CRh (%)</th>
<th>MRD Response (%)</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Topp (2011)</td>
<td>MRD+ ALL</td>
<td>21</td>
<td>--</td>
<td>80</td>
<td>78% RFS at 40 mo.</td>
</tr>
<tr>
<td>Gokbuget; BLAST (2015)</td>
<td>MRD+ ALL</td>
<td>116</td>
<td>--</td>
<td>76</td>
<td>MRD- vs MRD+ RFS: 35.2 vs 7.1mo OS: 40.4 vs 12 mo</td>
</tr>
<tr>
<td>Topp (2014)</td>
<td>R/R ALL</td>
<td>36</td>
<td>69</td>
<td>88</td>
<td>RFS: 7.6 mo. OS: 9.8 mo.</td>
</tr>
<tr>
<td></td>
<td>HSCT</td>
<td>64</td>
<td>45</td>
<td>76</td>
<td>RFS: 6.1 mo. OS: 8.4 mo.</td>
</tr>
</tbody>
</table>

Blinatumomab in Refractory-Relapse ALL

• 189 pts Rx with blina 28mcg CI/D x 4 wks Q 6 wks

<table>
<thead>
<tr>
<th>Response</th>
<th>No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>-CR</td>
<td>63(33)</td>
</tr>
<tr>
<td>-CRh</td>
<td>18(10)</td>
</tr>
<tr>
<td>-CR+CRh</td>
<td>81(43)</td>
</tr>
<tr>
<td>-No marrow blasts</td>
<td>17(9)</td>
</tr>
</tbody>
</table>

• Median OS 5.9 mo; Median RFS 6.1 mo

• Toxicities: CNS

Topps. Lancet Oncology 2015; 1:57
Blinatumomab vs ChemoRx in R-R ALL. Phase 3 TOWER Study

- 405 pts randomized 2:1 to Blinatumomab (n=271) vs SOC chemoRx (n=134)
- Primary endpoint of survival met statistical significance (EHA-2016 plenary session)
**Analysis Sets**

Randomized (Efficacy)

- Never received study Rx
  - 4 (1%)
  - 25 (19%)
- ...Patient request
  - 1 (<1%)
  - 22 (16%)
- ...Adverse event before Rx
  - 0 (0%)
  - 2 (1%)
- ...Death before Rx
  - 2 (1%)
  - 1 (1%)
- ...Clinical deterioration before Rx
  - 1 (<1%)
  - 0 (0%)

Treated (Safety)

- Blinatumomab (N = 271)
  - 267 (99%)
- SOC (N = 134)
  - 109 (81%)

**SOC, n (%):**
- 49 (45%) FLAG ± anthracycline
- 19 (17%) HiDAC-based
- 22 (20%) HD methotrexate-based
- 19 (17%) clofarabine-based

Topp. EHA 2016
TOWER: Blinatumomab in R/R Ph\(^-\) Pre-B ALL

Overall Survival (Intent-to-Treat)

- Median OS (95% CI):
  - Blinatumomab, 7.7 months (5.6, 9.6)
  - SOC, 4.0 months (2.9, 5.3)

- Stratified log-rank p = 0.012
- Hazard ratio: 0.71 (0.55, 0.93)

- At 76% of events, the stratified log-rank test surpassed the O’Brien-Fleming boundary (p < 0.0194) to stop the study for benefit

Topp. EHA 2016
TOWER: Blinatumomab in R/R Ph⁻ Pre-B ALL

Haematologic Response in Induction

Overall response (CR/CRh/CRi)

- Blinatumomab (N = 271): 44%
- SOC (N = 134): 25%

Complete remission (CR)

- Blinatumomab (N = 271): 34%
- SOC (N = 134): 16%

CRh

- Blinatumomab (N = 271): 9%
- SOC (N = 134): 4%

CRI

- Blinatumomab (N = 271): 1%
- SOC (N = 134): 4%

Overall response (as treated)

- Blinatumomab (N = 267): 45%
- SOC (N = 109): 30%

Hazard ratio for EFS 0.55 (0.43, 0.71); p < 0.001

Topp. EHA 2016
2nd generation CD19 CAR T cells in clinic

MSKCC/Fred Hutch  NCI  U Penn  MDACC

Retrovirus  Retrovirus  Lentivirus  Sleeping beauty

Gene transfer

CD19 Ab  CD28/4-1BB  CD3ζ

Retrovirus  Kite Pharma  Lentivirus  Sleeping beauty

Juno Therapeutics  Kite Pharma  Novartis  Ziopharm
# CAR-T Cells in ALL

<table>
<thead>
<tr>
<th>Parameter</th>
<th>U-Penn</th>
<th>MSKCC</th>
<th>NIH</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. Rx</td>
<td>30</td>
<td>16</td>
<td>21</td>
</tr>
<tr>
<td>Median age in yrs (range)</td>
<td>14 (5-60)</td>
<td>50 (18-60+)</td>
<td>13(5-27)</td>
</tr>
<tr>
<td>% CR</td>
<td>90</td>
<td>88</td>
<td>70</td>
</tr>
<tr>
<td>% Estimated 12-mo survival</td>
<td>72</td>
<td>?</td>
<td>50</td>
</tr>
<tr>
<td>% severe CRS</td>
<td>27</td>
<td>43</td>
<td>33</td>
</tr>
</tbody>
</table>

Adult ALL. Summary

- Burkitt – short intensive chemoRx + rituximab + lots of IT
- Ph-positive ALL – hyper CVAD + TKI; TKI maintenance; allo SCT based on PCR
- CD20-positive ALL – ALL chemoRx + rituximab
- AYA – augmented BFM; Hyper CVAD±R
- New promising monoclonal antibodies against CD19 and CD22, and CAR T-cell strategies
Leukemia Questions?

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Email- hkkantarjian@mdanderson.org