Advances in the Management of Acute Leukemia

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THE UNIVERSITY OF KANSAS CANCER CENTER

Conflict of Interest

I have no conflicts to disclose
Outline

ALL
• Newly diagnosed
• SCT in CR1
• Options in the R/R setting

AML
• Optimal management of AML
• SCT in Older AML
• FLT3 inhibitors
• Novel agents

Clinical trials at KUMC
ALL

Newly diagnosed patients

- Age <40 – pediatric inspired induction
- Age 30-70 - ECOG 1910 study
- Older patients (70+) - modified induction, maintenance once in CR
- Ph+ ALL - chemotherapy + TKI
- SCT in CR1

ALL – Myth of second remission

Probability of survival from first relapse.

Stephen J. Forman, and Jacob M. Rowe Blood
2013;121:1077-1082

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ALL – E1910 Protocol

• Patients ages 30-70
• Pediatric-inspired induction, intensification
• Randomized to Blinatumomab/none
• SCT in CR1 if MSD or MUD versus consolidation/maintenance

Ph+ ALL

• 24 hour turn-around for Ph+ status
• Chemotherapy plus TKI
• SCT in CR1 followed by TKI maintenance
Ph+ ALL – S0805 Results

- Ages 18-60 with Ph+ ALL
- hyperCVAD + dasatinib
- Pts with MSD or MUD went to SCT in CR1

- 94 evaluable patients, median f/u 26 months
- Significant RFS advantage to SCT
- Compared to historical controls, addition of TKI improved OS

Farhad Ravandi et al. Blood 2015;126:796
ALL – Management of Relapse

- Ifosfamide-based salvage
- Velcade-based salvage
- Re-treatment with original chemotherapy (length of initial CR)
- FLAG
- Liposomal VCR
- CAR-T cell therapy
- Blinatumomab
- Inotuzumab (targets CD22, compassionate use for now)
ALL – Management of Relapse

Treatment with Anti-CD19 BiTE® Blinatumomab in Adult Patients with Relapsed/Refractory B-Precursor Acute Lymphoblastic Leukemia (r/r ALL) Post-Allogeneic Hematopoietic Stem Cell Transplantation

Anthony Selwyn Stein, MD, Max S. Topp, MD, Hagop M Kantarjian, MD, Nicola Goekbuget, MD, Ralf C Bargou, MD, Mark R Utzow, MD, Alessandro Rambaldi, MD, Josep Ribera, MD PhD, Alicia Zhang, PhD, Zachary Zimmerman, MD PhD, and Stephen J. Forman, MD

- Ages 18+
- primary refractory
- first relapse within 12 months of first remission
- relapse within 12 months of alloHSCT
- second or greater salvage
- 34% had prior SCT

Anthony Selwyn Stein et al. Blood 2015;126:861

Table 1. Summary of efficacy (N=64)

| Patients achieving CR/CRh within first 2 cycles of blinatumomab treatment, n (%) | 29 (45%) |
| CR | 18 (28%) |
| CRh | 11 (17%) |
| MRD response*, n (%) | 22 (70%) |
| MRD complete response* | 19 (66%) |
| Median RFS*, months (95% CI) | 6.1 (5.0 to 7.7) |
| Median OS, months (95% CI) | 8.4 (4.2 to 9.4) |

*In patients achieving CR/CRh

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ALL – Management of Relapse

Outcomes of Hematopoietic Stem Cell Transplantation (HSCT) Among Adults with Relapsed/Refractory Acute Lymphoblastic Leukemia (ALL) Achieving Remission with Blinatumomab

Stein AS, et al.

- Ages 18+
- primary refractory
- first relapse within 12 months of first remission
- relapse within 12 months of alloHSCT
- second or greater salvage

Anthony Selwyn Stein et al. ASBMT 2016 #22

- 83/189 achieved CR (44%)
- Overall HSCT realization rate 41% (34/83)
  - 50% for SCT-naïve, 24% for those with prior SCT
- 80% had MRD response prior to SCT
- OS at 12 mos post-SCT was 73%

Anthony Selwyn Stein et al. ASBMT 2016 #22
Management of Relapse – Ph+ ALL

# 679 Complete Molecular and Hematologic Response in Adult Patients with Relapsed/Refractory (R/R) Philadelphia Chromosome-Positive B-Precursor Acute Lymphoblastic Leukemia (ALL) Following Treatment with Blinatumomab: Results from a Phase 2 Single-Arm, Multicenter Study (ALCANTARA)

Giovanni Martinelli, MD, Hervé Dombret, Patrice Chevallier, MD, PhD, Oliver G. Ottmann, MD, Nicola Goekbuget, MD, Max S. Topp, MD, Adele K. Fielding, MB BS, PhD, Lulu Ren Sterling, PhD, Jonathan Benjamin, MD and Anthony Selwyn Stein, MD

- Ages 18+
- Ph+ ALL refractory to at least one 2nd gen TKI or intolerant to imatinib and 2nd gen TKI

<table>
<thead>
<tr>
<th>Primary endpoint</th>
<th>All Patients (N = 45)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR/Cr + Rh, n (%)</td>
<td>16 (36)</td>
</tr>
<tr>
<td>95% CI: 22%, 51%</td>
<td></td>
</tr>
<tr>
<td>T315I mutation (N = 10)</td>
<td>4 (40)</td>
</tr>
<tr>
<td>≥ 3 prior 2+ generation TKI (N = 27)</td>
<td>11 (41)</td>
</tr>
<tr>
<td>Prior ponsatinib treatment (N = 23)</td>
<td>6 (30)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Secondary endpoints</th>
<th>Responders (n = 16)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Best response, n (%)</td>
<td></td>
</tr>
<tr>
<td>CR</td>
<td>14 (88)</td>
</tr>
<tr>
<td>CRh</td>
<td>2 (4)</td>
</tr>
<tr>
<td>CRI (not including CRh)</td>
<td>2 (4)</td>
</tr>
</tbody>
</table>

Complete MRD response, n (%)         | 14 (88)
Proceeded to allo-HSCT               | 7 (44)

*During the first two cycles. CRI, complete response with incomplete hematologic recovery.
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• Options in the R/R setting

AML

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• FLT3 inhibitors
• Novel agents

Clinical trials at KUMC

Impact of hospital volume on outcomes of patients undergoing chemotherapy for acute myeloid leukemia: a matched cohort study

Smith Giri, Ranjan Pathak, Madan Raj Aryal, Paras Karmacharya, Vijaya Raj Bhatt, and Mike G. Martin

- 3640 hospitalizations
- Hospitals divided high/low volume at 75th percentile
- Can’t distinguish induction vs consolidation vs reinduction

Table 1. In-hospital outcomes of high-volume vs low-volume centers in a matched cohort of patients with acute myeloid leukemia admitted for chemotherapy

<table>
<thead>
<tr>
<th></th>
<th>High volume center</th>
<th>Low volume center</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality</td>
<td>1.59%</td>
<td>4.07%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mean length of stay</td>
<td>14.22</td>
<td>14.59</td>
<td>.88</td>
</tr>
<tr>
<td>Costs of hospitalization</td>
<td>102653</td>
<td>101945</td>
<td>.96</td>
</tr>
</tbody>
</table>

May 21, 2015; Blood: 125 (21)
insert links to clinical trials.gov for each study listed

Tara Lin, 4/12/2016
#533 Overall Survival (OS) of Acute Myeloid Leukemia (AML) Treated at Academic Center (AC) Versus Non-Academic Center (NAC)

Smith Giri, MBBS*, Valerie Shostrom, MS, Krishna Gundabolu, MD, KM Monirul Islam, MD/PhD*, Ranjan Pathak, MD, Lori J. Maness, MD and Vijaya R. Bhatt, MD

- 7823 cases of AML from 1998-2011
- National Cancer Database Participant User File (NCDPPUF)
- Only patients with complete data to at least 30 days were included

- Median OS 12.6 (AC) vs 7 mos (NAC) (p<0.001)
- 1 yr OS 51% AC vs 39% NAC (p<0.001)
- 30 day mortality was significantly worse in NAC vs AC (odds ratio, OR 1.52; 95% confidence interval, CI 1.33-1.74; p <0.001)
7 insert links to clinical trials.gov for each study listed

Tara Lin, 4/12/2016
Relapsed/Refractory AML

**Age 18+**

- A Phase 3 Open-label Randomized Study of Quizartinib (AC220) Monotherapy Versus Salvage Chemotherapy in Subjects with FLT3-ITD Positive Acute Myeloid Leukemia (AML) Refractory to or Relapsed After First-line Treatment

**Age 60+**

- A Phase 1/2 Study of Vadastuximab Talirine Administered in Sequence with Allogenic Hematopoietic Stem Cell Transplant in Patients with Relapsed or Refractory Acute Myeloid Leukemia
- A Phase 1B Dose Escalation Study of OXi4503 as a Single Agent and in Combination with Cytarabine with Subsequent Phase 2 Cohorts for Subjects with Relapsed/Refractory Acute AML and MDS
- Randomized, Open Label, Phase 2 Study of Selective Inhibitor of Nuclear Export (SINE) Selinexor (KPT-330) vs Specified Physician’s Choice in Patients > 60 Years Old with Relapsed/Refractory Acute Myeloid Leukemia (AML) Ineligible for Intensive Chemotherapy/Transplantation

Stem Cell Transplantation in AML and Socioeconomic Factors: National Cancer Database (NCDB) Analysis

Samip Master, Srinivas Devarakonda, Glenn Mills, Runhua Shi.

- Data from 37,820 men and women, between ages 18-64 years diagnosed with AML, registered in the NCDB between 1998 and 2012 was analyzed.

- Patients treated at academic facility were three times more likely to get SCT compared to those in community setting.
insert links to clinical trials.gov for each study listed

Tara Lin, 4/12/2016
AML – newly diagnosed

Clinical trial preferred

• ASP2215 plus 7+3 in age 18+
• CPX-351 EAP for secondary AML ages 60-75
• Venetoclax plus LDAC in ages 65+
• SGI-110 vs standard HMA in ages 65+
  • 7+3
  • HMA
  • LDAC

• **SCT in CR1** for all except “favorable risk” (CBF, NPM1+ in age <60, CEBPA double mutated)

Older pts with AML – SCT in CR1

ASH 2014 #280 Higher Leukemia Free Survival after Post-Induction Hematopoietic Cell Transplantation Compared to Consolidation Therapy in Patients >60 Years with Acute Myelogenous Leukemia (AML): Report from the AML 2004 East German Study Group (OSHO)

• Newly dx AML ages 60+
• Pts in CR1 with MSD or MUD went to SCT
• Analysis of 315 pts ages 60-75
• LFS at 8y 32% SCT vs 13% chemotherapy (p<0.0005)
• Relapse incidence 40% SCT vs 79% chemotherapy (p<0.001)
• OS 35% SCT vs 24% chemotherapy (p=0.18)
Older pts with AML – SCT in CR1

- 114 pts ages 60-74 AML CR1
- At 2 yrs DFS 42%, OS 48%

- NRM 15%
- Grades 2-4 acute GVHD 10%
- Chronic GVHD 28%
- CIR 44%

Steven M. Devine et al. JCO doi:10.1200/JCO.2015.62.7273
4/18/2016

FLT3 inhibitors in AML – ready for prime time?

The Multi-Kinase Inhibitor Midostaurin (M) Prolongs Survival Compared with Placebo (P) in Combination with Daunorubicin (D)/Cytarabine (C) Induction (ind), High-Dose C Consolidation (consol), and As Maintenance (maint) Therapy in Newly Diagnosed Acute Myeloid Leukemia (AML) Patients (pts) Age 18-60 with FLT3 Mutations (muts): An International Prospective Randomized (rand) P-Controlled Double-Blind Trial (CALGB 10603/RATIFY [Alliance])


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
Key Eligibility Criteria

- Age 18-60, normal end-organ function
- Documented AML (non-APL)
- FLT3 mutation centrally determined prior to enrollment
  - Assessed at one of 9 academic labs around the world
  - Results within 48h
- Up to 5 days of hydroxyurea allowed prior to start of treatment while awaiting results of mutation analysis

Protocol Therapy

<table>
<thead>
<tr>
<th>Induction</th>
<th>daunorubicin</th>
<th>60 mg/m² IVP days 1-3</th>
</tr>
</thead>
<tbody>
<tr>
<td>(2nd cycle given based on d21 marrow)</td>
<td>cytarabine</td>
<td>200 mg/m²/d d 1-7 via IVCI</td>
</tr>
<tr>
<td></td>
<td>midostaurin</td>
<td>50 mg po bid days 8-21</td>
</tr>
<tr>
<td></td>
<td>or placebo</td>
<td></td>
</tr>
<tr>
<td>Consolidation</td>
<td>cytarabine</td>
<td>3 gm/m² over 3h q 12h</td>
</tr>
<tr>
<td>(up to 4 cycles)</td>
<td>midostaurin</td>
<td>days 1, 3, and 5</td>
</tr>
<tr>
<td></td>
<td>or placebo</td>
<td>50 mg po bid days 8-21</td>
</tr>
<tr>
<td>Maintenance</td>
<td>midostaurin</td>
<td>50 mg po bid days 1-28 x 12 cycles</td>
</tr>
<tr>
<td></td>
<td>or placebo</td>
<td></td>
</tr>
</tbody>
</table>

- Transplant not specifically mandated
Overall 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

NE: not estimable

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

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-value*: 0.0074

+ Censor

Allogeneic Transplants by Arm

• 408 (57%) patients received a transplant

<table>
<thead>
<tr>
<th>By Arm</th>
<th>MIDO N=360</th>
<th>PBO N=357</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR1 Only, n</td>
<td>100</td>
<td>79</td>
<td>0.08</td>
</tr>
<tr>
<td>%: 95% CI</td>
<td>(28%: 23, 33)</td>
<td>(22%: 18, 26)</td>
<td></td>
</tr>
<tr>
<td>Type: Matched family</td>
<td>47 (47%)</td>
<td>30 (38%)</td>
<td></td>
</tr>
<tr>
<td>Type: Matched unrelated</td>
<td>43 (43%)</td>
<td>42 (53%)</td>
<td></td>
</tr>
<tr>
<td>Type: Other</td>
<td>10 (10%)</td>
<td>7 (9%)</td>
<td></td>
</tr>
<tr>
<td>Transplant at any time, n</td>
<td>212</td>
<td>196</td>
<td>0.28</td>
</tr>
<tr>
<td>%: 95% CI</td>
<td>(59%: 54, 64)</td>
<td>(55%: 50, 60)</td>
<td></td>
</tr>
<tr>
<td>Type: Matched family</td>
<td>95 (45%)</td>
<td>69 (35%)</td>
<td></td>
</tr>
<tr>
<td>Type: Matched unrelated</td>
<td>89 (42%)</td>
<td>108 (56%)</td>
<td></td>
</tr>
<tr>
<td>Type: Other</td>
<td>28 (13%)</td>
<td>18 (9%)</td>
<td></td>
</tr>
</tbody>
</table>
Conclusions

- Midostaurin, a multi-targeted kinase inhibitor, improves OS when added to standard chemo with one year maintenance in newly diagnosed pts aged 18-60 with ITD and TKD FLT3 mutant AML and represents a new standard of care
- OS and EFS benefit was consistent in uncensored as well as censored analyses, despite high SCT rate
- Safety profile similar in each arm
- An international academic-industry collaborative AML study based on genotype at dx is feasible

FLT3 inhibitors in AML – ready for prime time?

Alliance C11001 Phase II Trial Of Sorafenib Plus Standard Induction In Older Adults With Mutant FLT3 Acute Myeloid Leukemia (AML)

- Age 60+
- Untreated AML
- FLT3+ (ITD or TKD)

- Single arm study: Sorafenib added to induction with 7+3, consolidation with IDAC x 2, followed by 12 months sorafenib maintenance
- SCT allowed
Alliance C11001 Results

- CR rate 74%
- 9% induction mortality (all in pts ≥70 yo)

Median f/u 27 months
- Median OS 15 months
- 1 yr OS 63% (vs historical controls 30%)
- 2 yr OS 27%

- OS by age 18.8 months <70 vs 9.7 months ≥70
  (p<0.01)
- Benefit to addition of sorafenib in ages 60-69

FLT3 inhibitors in AML – ready for prime time?

# 321 Antileukemic Activity and Tolerability of ASP2215 80mg and Greater in FLT3 Mutation-Positive Subjects with Relapsed or Refractory Acute Myeloid Leukemia: Results from a Phase 1/2, Open-Label, Dose-Escalation/Dose-Response Study

# 2557 Quizartinib Significantly Improves Overall Survival in FLT3-ITD Positive AML Patients Relapsed after Stem Cell Transplantation or after Failure of Salvage Chemotherapy: A Comparison with Historical AML Database (UK NCRI data)

# 4359 Full Doses of Crenolanib, a Type I FLT3 Inhibitor, Can be Safely Administered in AML Patients Post Allogeneic Stem Cell Transplant
Novel Agents in AML

# 327 A Phase 1b Study of Venetoclax (ABT-199/GDC-0199) in Combination with Decitabine or Azacitidine in Treatment-Naive Patients with Acute Myelogenous Leukemia Who Are ≥ to 65 Years and Not Eligible for Standard Induction Therapy

- CR rates 75% and 70%
- No reported relapses
- Dose escalation ongoing
- AEs febrile neutropenia, cytopenias
- No TLS reported

Novel Agents in AML

# 324 A Phase 1 Trial of SGN-CD33A As Monotherapy in Patients with CD33-Positive Acute Myeloid Leukemia (AML)

- CR+CRi 33% at 40mcg dose (60% in previously untreated)
- 8 patients went on to SCT
- MTD reached
- Studies in upfront AML induction, peri-SCT, relapsed setting, older/unfit
Novel Agents in AML

# 454 SGN-CD33A Plus Hypomethylating Agents: A Novel, Well-Tolerated Regimen with High Remission Rate in Frontline Unfit AML

- 24 pts treated
- One dose of 33a per cycle of HMA
- CR+Cri 65%
- No DLTs
- No treatment related deaths

Novel Agents in AML

# 458 Comparison of Efficacy and Safety Results in 103 Treatment-Naïve Acute Myeloid Leukemia (TN-AML) Patients Not Candidates for Intensive Chemotherapy Using 5-Day and 10-Day Regimens of Guadecitabine (SGI-110), a Novel Hypomethylating Agent (HMA)

- CR rates 57% (5d) and 48% (10d)
- OS 10.5 months (5d) and 8.7 months (10d)
- AEs: febrile neutropenia, cytopenias, infections
- 5 day course moving forward in Phase III trials
Novel Agents in AML

# 323 Safety and Efficacy of AG-221, a Potent Inhibitor of Mutant IDH2 That Promotes Differentiation of Myeloid Cells in Patients with Advanced Hematologic Malignancies: Results of a Phase 1/2 Trial

- Response rate of 41% (CR 17%, SD 45%)
- AEs: indirect hyperbilirubinemia, nausea, cytopenias
- 83/198 pts remain on therapy
- 8 pts achieved response sufficient for SCT
- Phase 3 trials have started

Novel Agents in AML

# 2510 CPX-351 ((Cytarabine:Daunorubicin) Liposome Injection, (Vyxeos)) Does Not Prolong QTcf Intervals, Requires No Dose Adjustment for Impaired Renal Function and Induces High Rates of Complete Remission in Acute Myeloid Leukemia

# 4507 CPX-351 Enables Administration of Consolidation Treatment in the Outpatient Setting and Increases the Time Spent out of the Hospital after Completion of AML Treatment Compared with 7+3
Outline

ALL
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- Blinatumomab

AML
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- SCT in Older AML
- FLT3 inhibitors
- Novel agents

Clinical trials at KUMC

Open Clinical Trials at KUCC
Newly Diagnosed ALL

Combination Chemotherapy With or Without Blinatumomab in Treating Patients With Newly Diagnosed BCR-ABL-Negative B Lineage Acute Lymphoblastic Leukemia
https://clinicaltrials.gov/ct2/show/NCT02003222
insert links to clinical trials.gov for each study listed

Tara Lin, 4/12/2016
## Open Clinical Trials at KUCC

### Newly Diagnosed AML

A Study of ASP2215 in Combination With Induction and Consolidation Chemotherapy in Patients With Newly Diagnosed Acute Myeloid Leukemia (age 18+)

[https://clinicaltrials.gov/ct2/show/NCT02236013](https://clinicaltrials.gov/ct2/show/NCT02236013)

A Study Evaluating ABT-199 in Combination With Low-Dose Cytarabine in Treatment-Naïve Subjects With Acute Myelogenous Leukemia (AML) (age 65+)

[https://clinicaltrials.gov/ct2/show/NCT02287233](https://clinicaltrials.gov/ct2/show/NCT02287233)

SGI-110 in Adults With Untreated Acute Myeloid Leukemia (AML), Not Considered Candidates for Intensive Remission Induction

[https://clinicaltrials.gov/ct2/show/NCT02348489](https://clinicaltrials.gov/ct2/show/NCT02348489)

EAP of CPX-351 for Patients 60-75 Years of Age With Secondary AML

[https://clinicaltrials.gov/ct2/show/NCT02533115](https://clinicaltrials.gov/ct2/show/NCT02533115)

### Relapsed/Refractory AML

Selinexor (KPT-330) in Older Patients With Relapsed AML (SOPRA)

[https://clinicaltrials.gov/ct2/show/NCT02088541](https://clinicaltrials.gov/ct2/show/NCT02088541)

(QuANTUM-R): An Open-label Study of Quizartinib Monotherapy vs. Salvage Chemotherapy in Acute Myeloid Leukemia (AML) Subjects Who Are FLT3-ITD Positive

[https://clinicaltrials.gov/ct2/show/NCT02039726](https://clinicaltrials.gov/ct2/show/NCT02039726)

A Study of Vadastuximab Talirine Given Prior to or After Allogeneic Hematopoietic Stem Cell Transplant in AML Patients

[https://clinicaltrials.gov/ct2/show/NCT02614560](https://clinicaltrials.gov/ct2/show/NCT02614560)
insert links to clinical trials.gov for each study listed

Tara Lin, 4/12/2016
Open Clinical Trials at KUCC
Relapsed/Refractory AML

Dose Escalation of OXi4503 as Single Agent and Combination With Cytarabine w/Subsequent Ph 2 Cohorts for AML and MDS (AML)
https://clinicaltrials.gov/ct2/show/NCT02576301

Expanded Access /Compassionate Use Protocol For Relapsed Or Refractory CD33 Positive AML Patients In The USA Without Access To Comparable Or Alternative Therapy (AML) – gemtuzumab
https://clinicaltrials.gov/ct2/show/NCT02312037

Referral Information

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Tara Lin, 4/12/2016