Acute Myeloid Leukemia: Targets and Curability, so Close But a Journey So Far

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## Disclosure

<table>
<thead>
<tr>
<th>Principal investigator role</th>
<th>Cellerant, ADC Therapeutics, Orsenix, Arog, Bioline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Employee</td>
<td>None</td>
</tr>
<tr>
<td>Consultant</td>
<td>None</td>
</tr>
<tr>
<td>Major Stockholder</td>
<td>None</td>
</tr>
<tr>
<td>Speakers’ Bureau</td>
<td>None</td>
</tr>
<tr>
<td>Scientific Advisory Board</td>
<td>Daiichi Sankyo</td>
</tr>
<tr>
<td>Research Funding</td>
<td>Cellerant, ADC Therapeutics, Orsenix, Arog, Bioline</td>
</tr>
</tbody>
</table>

Presentation includes the following off-label drug use:
Gilteritinib, Quizartinib, Crenolanib, Venetoclax, Selinexor, Tamobarotene, Entospletinib, Palbociclib, Cobimetinib, Pevonedistat, H3B-8800
Practice Changing Treatments in AML

1970
Allogeneic Transplant
7+3
1980
1990
Ara-C Consol
2000
Dauno Intensification
2010

Thomas et al. NEJM, 1979; Mayer et al. NEJM, 1994; Fernandez et al. NEJM, 2009; Stone et al. NEJM, 2017
Practice Changing Treatments in AML

Allogeneic Transplant → 7+3 → Ara-C Consolidation → Dauno Intensification

Midostaurin
Enasidenib
Gemtuzumab
Vyxeous

Practice changing or just commonly used??

Thomas et al. NEJM, 1979; Mayer et al. NEJM, 1994; Fernandez et al. NEJM, 2009; Stone et al. NEJM, 2017
Acute Myeloid Leukemia
State-of-the-Art 2018

- Defined by cytogenetic and molecular interactions
- Intensified induction/less intensive consolidation
- Increased importance of minimal residual disease
- Expanded availability of allogeneic transplantation
- Paradigm shift in older patients
- Incorporation of novel agents
Molecular Classes of AML and Recurrent Gene Mutations

- **RUNX1** (~40%)
- **MLL-PTD** (~25%)
- **ASXL1** (~20%)
- **DNMT3A** (~20%)
- **SRSF2** (~20%)
- **STAG2** (~15%)
- **NRAS** (~15%)
- **FLT3-ITD** (~15%)
- **TET2** (~15%)
- **BCOR** (~10%)
- **U2AF1** (~10%)
- **PHF6** (~10%)
- **ZRSR2** (~5%)
- **SF3B1** (~10%)
- **EZH2** (~5%)

- **Chromatin-spliceosome** (13%)
- **TP53 mutant - chromosomal aneuploidy** (10%)
- **biCEBPA mutant** (4%)
- **GATA2** (~30%)
- **NRAS** (~30%)
- **WT1** (~20%)
- **CSF3R** (~20%)

- **DNMT3A** (~50%)
- **IDH1** (~15%)
- **IDH2** (~15%)
- **PTPN11** (~15%)
- **TET2** (~15%)

- **NPM1 mutant** (30%)

- **t(15;17)(q22;q21); PML-RARA** (13%)
- **t(8;21)(q22;q22); RUNX1-RUNX1T1** (7%)
- **inv(16)(p13.1q22); CBFB-MYH11** (5%)
- **t(v;11q23.3); X-KMT2A** (4%)
- **t(9;22)(q34.1;q11.2); BCR-ABL1** (1%)
- **t(6;9)(p23;q34.1); DEK-NUP214** (1%)
- **t(5;11)(q35.2;p15.4); NUP98-NSD1** (1%)
- **inv(3)(q21.3q26.2); GATA2,MECOM** (1%)

- **Other rare fusions** (1%)
  - **t(3;5)(q25.1;q35.1); NPM1-MLF1**
  - **t(8;16)(p11.2;p13.3); KAT6A-CREBBP**
  - **t(16;21)(p11.2;q22.2); FUS-ERG**
  - **t(10;11)(p12.3;q14.2); PICALM-MLLT10**
  - **t(7;11)(p15.4;p15.2); NUP98-HOXA9**
  - **t(3;21)(q26.2;q22); RUNX1-MECOM**

- **KIT** (~25%)
- **NRAS** (~20%)
- **Cohesin** (~20%)
- **ASXL2** (~20%)
- **ZBTB7A** (~20%)
- **ASXL1** (~10%)
- **EZH2** (~5%)
- **KDM6A** (~5%)
- **MGA** (~5%)
- **DUX15** (~5%)

- **NRAS** (~40%)
- **KIT** (~35%)
- **FLT3-TKD** (~20%)
- **KRAS** (~15%)

- **FLT3-ITD** (~70%)
- **KRAS** (~20%)

- **FLT3-ITD** (~85%)

Other frequent mutations include:
- **KRAS** (~20%)
- **NRAS** (~20%)
- **FLT3-TKD** (~20%)
- **KIT** (~35%)
- **Cohesin** (~20%)
- **ASXL2** (~20%)
- **ZBTB7A** (~20%)
- **ASXL1** (~10%)
- **EZH2** (~5%)
- **KDM6A** (~5%)
- **MGA** (~5%)
- **DUX15** (~5%)

Döhner et al. Blood, 2017
Risk-Stratification and Prognostication of AML Informed by Mutational Profile

Patel et al. NEJM, 2012

Welch et al. NEJM, 2016
Mutation Patterns in Older Adults Predict Response to Chemotherapy

**Good Risk**
- CR 81%: *NPM1* plus
  - Chromatin mutations
  - Cohesin mutations
  - *FLT3-TKD*
  - Spliceosome mutations
  - *RAS* pathway mutations
  - *FLT3-ITD*<sup>wt</sup>
- DFS 46%: *NPM1* plus
  - *ASXL1*
  - *SF1*
  - *SMC1A*
  - *SRSF2*
- OS 45%: *NPM1* plus
  - Chromatin mutations
  - *IDH2* mutation
  - *SF1*
  - *SRSF2*

**Poor Risk**
- CR 32%
  - U2AF1
  - WT1
  - Complex karyotype
- DFS 2%
  - *FLT3*
  - *RUNX1*
  - *TP53, U2AF1*
- OS 4%
  - *BCOR*
  - *FLT3-ITD*
  - *U2AF1, WT1*
  - t(9;11), complex karyotype

Eisfeld et al. ASH abstr 103, 2017
# Gene Mutations Important in Everyday Practice

“Clinically Actionable”

<table>
<thead>
<tr>
<th>Gene</th>
<th>Incidence</th>
<th>Associations</th>
<th>Impact</th>
</tr>
</thead>
<tbody>
<tr>
<td>FLT3-ITD/(TKD)</td>
<td>25%</td>
<td>NPM1</td>
<td>Unfavorable</td>
</tr>
<tr>
<td>NPM1</td>
<td>33%</td>
<td>FLT3</td>
<td>Favorable</td>
</tr>
<tr>
<td>dCEBPα</td>
<td>8%</td>
<td>FLT3</td>
<td>Favorable</td>
</tr>
<tr>
<td>C-KIT</td>
<td>15%</td>
<td>CBF</td>
<td>Unfavorable [in t(8;21), but less clear in inv(16)]; ¹D816 worse than others</td>
</tr>
<tr>
<td>IDH1 and 2</td>
<td>22%</td>
<td>NPM1</td>
<td>Favorable</td>
</tr>
<tr>
<td>P53</td>
<td>7%</td>
<td>t-AML, Complex karyotype (60%)</td>
<td>Unfavorable</td>
</tr>
</tbody>
</table>

¹Yui et al. ASH abstr 2785, 2016
RATIFY (C10603) Trial Schema

Stratification: TKD; ITD with allelic ratio <0.7 ‘vs’ ≥0.7

Stratify* FLT3 ITD or TKD

PRE-REGISTER

P

R

L

T

3

ESA

RN

Z

ME

T

12 months

Midostaurin

MAINTENANCE

12 months

Placebo

MAINTENANCE

12 months

DNR ARA-C Midostaurin

CR

HiDAC Midostaurin

X 4

DNR ARA-C Placebo

CR

HiDAC Placebo

X 4

Stone et al. NEJM, 2017
Overall Survival
23% reduced risk of death in the Mido arm

<table>
<thead>
<tr>
<th>Arm</th>
<th>4-year Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>MIDO</td>
<td>51.4% (95%CI: 46, 57)</td>
</tr>
<tr>
<td>PBO</td>
<td>44.2% (95%CI: 39, 50)</td>
</tr>
</tbody>
</table>

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

Stone et al. NEJM, 2017
Midostaurin in AML

- First agent with (sustained) regulatory approval in 40 years

- BUT, will it be practice changing? Will it have a true (clinically meaningful) impact?
  - OS increase only 7%
  - Benefit more in FLT3-TKD than ITD
  - Which phase of treatment important?
  - Among least potent FLT3 inhibitors
  - Role in maintenance unclear\(^1\)
  - Beneficial effect of Midostaurin most pronounced in \(NPM1^{wt}/FLT3^{high}\) group\(^2\)

\(^1\)Larson et al. ASH abstr 145, 2017;
\(^2\)Dohner et al. ASH abstr 467, 2017
Antileukemic Activity of Gilteritinib

Response in FLT3mut+ and FLT3WT Patients (N=249)

- FLT3WT (N=58)
  - ORR=12%
  - CRc=9%

- FLT3mut+ (N=191)
  - ORR=49%
  - CRc=37%

Gilteritinib ≥80 mg/day:
- CRc (CR+CRp+CRi)=41%
- ORR=52%

- ORR=67%
- CRc=42%

- ORR=55%
- CRc=37%

- ORR=60%
- CRc=30%

- ORR=50%
- CRc=0

Perl et al. Lancet Oncol, 2017
Second Generation *FLT3* Inhibitors

- **Gilteritinib**: inhibits *FLT3-ITD* and *D835*
  - rando trial vs Midostaurin + induction chemo
  - vs placebo as maint posttransplant (MORPHO)
  - vs chemo in rel/refr (registration)
  - with 7+3 and HiDAC, CRc 90% in *FLT3* pos\(^1\)

- **Quizartinib**: most potent *FLT3* inhibitor
  - rando trial vs placebo + induction chemo (QuANTUM-First)
  - vs salvage chemo in R/R (QuANTUM-R)
  - with AZA or LoDAC in R/R, high ORR\(^2\)

- **Crenolanib**: inhibits *FLT3-ITD, D835, PDGFA* and *b*
  - with induction chemo CR 83%, 72% with 1 cycle\(^3\)

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\(^1\)Pratz et al. ASH, 2017 (abstr 722); \(^2\)Swaminathan et al. ASH, 2017 (abstr 723); \(^3\)Wang et al. ASH, 2017 (abstr 566)
**FLT3 Mutations in AML**

- Frequent in normal cytogenetic AML
- Associated with high WBC, packed marrow
- ITD associated with high relapse rate, poor OS; TKD less so
- Most common in APL, but appears not prognostic
- Resistance mechanisms include point mutations, high levels of *FLT3* ligand
Minimal Residual Disease

- Detected by increasingly sensitive techniques (immunophenotyping, PCR, sequencing)
- Most studied in patients with *NPM1* mutation and CBF AMLs\(^1,2\)
- Persistence of somatic mutations with VAF>1% in CR assoc. with increased risk of death and relapse\(^3\)
- Complex due to genetic heterogeneity and multiple subclones
- Has prognostic implications following chemotherapy and before allogeneic transplantation
- Will rapidly become incorporated in routine clinical practice

\(^1\)Ivey et al. NEJM, 2016; \(^2\)Kapp-Schwoerer.et al. ASH abstr 183, 2017; \(^3\)Morita et al. ASH abstr 2667, 2017
Equivalent Post-Transplant Outcomes for Pre-transplant AML MRD (by FC) and Active AML

Flow Cytometry and NGS in AML Assessment Pre-allogeneic Transplant

Overall Survival %

Flow- / NGS-
Flow- / NGS+
Flow+ / NGS+

n=24
n=20
n=18

p=.072

Getta et al. BBMT, 2017
Limitations of MRD Detection in AML

- Methodologies not standardized
- Thresholds for defining MRD vary
- Heterogeneity of the disease
- Clonal hematopoiesis
- Variable distribution of leukemia cells after treatment
- Lack of effective agents to target MRD
- Randomized trials needed to show benefit of intervention
# Agents With Regulatory Approval (or Breakthrough Designation)

<table>
<thead>
<tr>
<th>Agent</th>
<th>Target</th>
<th>Population</th>
<th>Setting</th>
</tr>
</thead>
<tbody>
<tr>
<td>Midostaurin</td>
<td>FLT3</td>
<td>FLT3-ITD or TKD</td>
<td>Treatment naïve w chemo in induc and consol</td>
</tr>
<tr>
<td>Gemtuzumab ozogamicin</td>
<td>CD33</td>
<td>CBF and possibly intermed-risk</td>
<td>Treatment naïve CD33+ adults w chemo or single agent or Rel/refr adults and peds</td>
</tr>
<tr>
<td>CPX-351</td>
<td>Cytotoxic</td>
<td>t-AML or AML with MRC</td>
<td>Treatment naïve with t-AML or AML with MRC</td>
</tr>
<tr>
<td>Enasidenib</td>
<td>IDH2</td>
<td>IDH mutated</td>
<td>Rel/refr AML w mIDH2</td>
</tr>
<tr>
<td>Venetoxlax</td>
<td>BCL-2</td>
<td>Elderly adults</td>
<td>Treatment naïve (with LoDAC)</td>
</tr>
</tbody>
</table>
Gemtuzumab Ozogamicin (Fractionated) in Newly Diagnosed AML Ages 50-70

Kaplan-Meier Plot of Event-Free Survival (mITT Population) ALFA-0701 Trial

Survival Probability

Survival Time (months)

G0 + Daumorubicin + Cytarabine

Daumorubicin + Cytarabine

P=0.003

Gemtuzumab Ozogamicin: Reapproved

- First ab-drug conjugate approved for human use-2000
- Withdrawn, lack of OS benefit and toxicity-2010
- Reapproved for adults with new AML and pts > age 2 with R/R disease-2017
- CD33 single nucleotide polymorphism rs121459419 C→T may be biomarker for response
- OS benefit in fav-risk and trend in intermed-risk
- Risk of SOS/VOD 8% in 146 pts (69 with prophylaxis: heparin or ursodiol or defibrotide) after allograft
- Expression of CD33 blast expression impacts outcome

Lamba et al. JCO, 2017; Burnett et al. JCO, 2011; Battipaglia et al. BBMT, 2017; Olombel et al. Blood, 2016; Lambda et al. ASH abstr 3826, 2017
Venetoclax: Promotes Apoptosis Through Selective Inhibition of BCL-2

BCL-2 overexpression allows cancer cells to evade apoptosis by sequestering pro-apoptotic proteins.¹⁻³

Venetoclax binds selectively to BCL-2, freeing pro-apoptotic proteins that initiate programmed cell death (apoptosis).⁴⁻⁶

CR/CRi Rates
LoDAC + Venetoclax

Median time to response: 1 month (<1–9 months)

<table>
<thead>
<tr>
<th>62%*</th>
<th>76%*</th>
<th>47%*</th>
<th>70%</th>
<th>66%</th>
<th>53%</th>
<th>52%</th>
</tr>
</thead>
</table>

CR + CRi

Wei et al. EHA, 2017 and ASH abstr 890, 2017
DOR, Survival, and Survival by Response

VEN 600 mg

ORR (CR + CRi) is highly correlated with OS

Wei et al. ASH abstr 890, 2017
Outcomes According to Molecular Drivers of AML

### Cytogenetics

<table>
<thead>
<tr>
<th>Risk Level</th>
<th>ORR (CR + CRi)</th>
<th>Median OS, mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intermediate risk</td>
<td>28 (76%)</td>
<td>15.7</td>
</tr>
<tr>
<td>Adverse risk</td>
<td>9 (47%)</td>
<td>5.7</td>
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</table>

### Molecular Subgroups

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>ORR</th>
<th>Median OS, mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>NPM1 (+) n = 7*</td>
<td>7 (100%)</td>
<td>NR</td>
</tr>
<tr>
<td>CEBPA biallelic n = 3</td>
<td>3 (100%)</td>
<td>NR</td>
</tr>
<tr>
<td>Chromatin-spliceosome n = 22</td>
<td>15 (68%)</td>
<td>11.4</td>
</tr>
<tr>
<td>TP53-aneuploidy n = 20</td>
<td>10 (50%)</td>
<td>6.5</td>
</tr>
</tbody>
</table>

*Wei et al. ASH abstr 890, 2017*
Venetoclax and Azacitididine Results in Rapid Eradication of Blasts and LSCs

<table>
<thead>
<tr>
<th>Peripheral Blood Blasts (%)</th>
<th>Pre- Treatment</th>
<th>24 Hours Post-Treatment</th>
<th>72 Hours Post-Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pt 1</td>
<td>71%</td>
<td>50%</td>
<td>16%</td>
</tr>
<tr>
<td>Pt 2</td>
<td>81%</td>
<td>72%</td>
<td>34%</td>
</tr>
</tbody>
</table>

LSCs defined as Lin-/CD34+/CD123+/HLA-DR+/CD117+/CD33

Pollyea et al. ASH abstr 181, 2017
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

US FDA Approved August 2017 for t-AML and AML with MRC
Patients Treated With CPX-351 Exhibited Statistically Significant Improvements in Response Rate

- CR: CPX-351 (n=153) vs. 7+3 (n=156)
  - Patients (%): 37.3 vs. 25.6
  - Odds Ratio: 1.69 (1.03, 2.78)
  - p = 0.040

- CR + CRi:
  - Patients (%): 47.7 vs. 33.3
  - Odds Ratio: 1.77 (1.11, 2.81)
  - p = 0.016

Lancet et al. ASCO abstr 7000, 2016
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></th>
<th>Events/N</th>
<th>Median Surv. (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPX-351</td>
<td>104/153</td>
<td>9.56 (6.60, 11.86)</td>
</tr>
<tr>
<td>7+3</td>
<td>132/156</td>
<td>5.95 (4.99, 7.75)</td>
</tr>
</tbody>
</table>

Hazard Ratio = 0.69  
p-value = 0.005

Lancet et al. ASCO abstr 7000, 2016
Role of *IDH* in Malignancy

- IDH is critical metabolic enzyme in the citric acid cycle
- IDH1 in cytoplasm and IDH2 in mitochondria
- Cancer-associated IDHm produces 2-hydroxyglutarate (2-HG) and blocks normal cellular differentiation
Key Endpoints:

- Safety, tolerability, MTD, DLTs
  - MTD not reached at doses up to 650 mg/day
- Responses assessed by local investigator per IWG criteria¹
- Assessment of clinical activity, with focus on 100-mg daily dose in patients with R/R AML
## Response in R/R AML

<table>
<thead>
<tr>
<th></th>
<th>Relapsed/Refractory AML</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Enasidenib 100 mg/day (n=214)</td>
</tr>
<tr>
<td><strong>Overall response rate, % [n/N]</strong> [95% CI]</td>
<td>37% (79/214) [30.4, 43.8]</td>
</tr>
<tr>
<td><strong>Best response</strong></td>
<td></td>
</tr>
<tr>
<td>CR, n (%) [95% CI]</td>
<td>43 (20.1) [14.9, 26.1]</td>
</tr>
<tr>
<td>CRi or CRp, n (%)</td>
<td>17 (7.9)</td>
</tr>
<tr>
<td>PR, n (%)</td>
<td>8 (3.7)</td>
</tr>
<tr>
<td>MLFS, n (%)</td>
<td>11 (5.1)</td>
</tr>
<tr>
<td>SD, n (%)</td>
<td>110 (51.4)</td>
</tr>
<tr>
<td>PD, n (%)</td>
<td>11 (5.1)</td>
</tr>
<tr>
<td>NE, n (%)</td>
<td>2 (0.9)</td>
</tr>
<tr>
<td><strong>Time to first response (mos), median (range)</strong></td>
<td>1.9 (0.5–11.1)</td>
</tr>
<tr>
<td><strong>Duration of response (mos), median [95%CI]</strong></td>
<td>5.6 [4.6, 7.4]</td>
</tr>
<tr>
<td><strong>Time to CR (mos), median (range)</strong></td>
<td>3.7 (0.7–11.2)</td>
</tr>
<tr>
<td><strong>Duration of response in pts with CR (mos), median [95%CI]</strong></td>
<td>8.8 [5.6, NR]</td>
</tr>
</tbody>
</table>

*Stein et al. ASCO, 2017 and Blood, 2017*
Overall Survival by Best Response

Median response duration: 6.9 months (95%CI 4.9, 9.7)
Responders: n=59
Median Tx duration: 6.8 months (range: 1.8 - 18.0)

Survival Probability

- CR: 19.7 months (11.6, NE)
- Non-CR response: 13.8 months (8.3, 17.0)
- No response: 7.0 months (5.0, 8.3)

Stein et al. ASCO abstr 7004, 2017 and Blood, 2017
Morphological evidence of myeloid differentiation

**Patient 1**

- **Screening**
  - 37% blasts
- **Cycle 1 Day 15**
  - Evidence of cellular differentiation
- **Cycle 3 Day 1**
  - 4% blasts

**FISH evidence of myeloid differentiation**

**Patient 2**

- **C2D1, trisomy 8**
  - Blasts
  - Promyelocytes
  - Mature Granulocyte
  - Lymphocytes

Patient 2

- C2D1, trisomy 8
Molecular Evidence of Differentiation

Screening – PBMC

Cycle 3 day 1 – Remission - Granulocytes

Alan Shih and Ross Levine, MSKCC
Differentiation Syndrome

- 21 days of AG - 221 at 100 mg daily
- Fever, oxygen requirement
- Normal BAL

- Dexaemethasone 10 mg BID for 15 days
- Resolution of clinical symptoms
- Patient achieves a complete remission

Courtesy Dr. Stephane De Botton
Ivosidenib or Enasidenib Plus Chemotherapy Phase I Trial

**INDUCTION** (1-2 cycles)
- ivosidenib 500mg + ARA-C (200mg/m²/d x 7d) + DNR (60mg/m²/d x 3d)
- ivosidenib 500mg + ARA-C (200mg/m²/d x 7d) + IDR (12mg/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**
- CR
- CRi
- CRp
- ivosidenib 500mg + ARA-C (up to 4 cycles)
- enasidenib 100mg + ARA-C (up to 4 cycles)

**MAINTENANCE**
- CR
- CRi
- CRp
- Single agent ivosidenib or enasidenib daily for up to 2 years from Induction Day 1

Stein et al. ASH abstr 726, 2017

Patients who discontinue to go to transplant may not re-start study treatment.
# Best Overall Response Summary

<table>
<thead>
<tr>
<th>Response, n (%)</th>
<th>Ivosidenib (AG-120) + CT</th>
<th>Enasidenib (AG-221) + CT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All (n=30)</td>
<td>De novo (n=21)</td>
</tr>
<tr>
<td>CR+CRi/CRp</td>
<td>77</td>
<td>91</td>
</tr>
<tr>
<td>CR</td>
<td>63</td>
<td>71</td>
</tr>
<tr>
<td>CRi/CRp</td>
<td>13</td>
<td>19</td>
</tr>
<tr>
<td>MLFS</td>
<td>3</td>
<td>-</td>
</tr>
<tr>
<td>PR</td>
<td>7</td>
<td>5</td>
</tr>
<tr>
<td>Persistent disease</td>
<td>7</td>
<td>5</td>
</tr>
<tr>
<td>NE</td>
<td>7</td>
<td>-</td>
</tr>
</tbody>
</table>

*Stein et al. ASH abstr 726, 2017*
## Novel Agents in AML

<table>
<thead>
<tr>
<th>Agent</th>
<th>Target</th>
</tr>
</thead>
<tbody>
<tr>
<td>Selinexor</td>
<td>XPO1</td>
</tr>
<tr>
<td>Tamibarotene</td>
<td>RAR-alpha</td>
</tr>
<tr>
<td>Entospletinib</td>
<td>SYK</td>
</tr>
<tr>
<td>Palbociclib</td>
<td>CDK6</td>
</tr>
<tr>
<td>Cobimetinib</td>
<td>MAPK</td>
</tr>
<tr>
<td>Pevonedistat</td>
<td>NEDD8-activating enzyme</td>
</tr>
<tr>
<td>H3B-8800/E7070, E7820</td>
<td>SF3B1/RBM39</td>
</tr>
<tr>
<td>(Spliceosome inhibitors)</td>
<td></td>
</tr>
</tbody>
</table>

*Daver et al. ASH abstr 1344, 2017; Drusbosky et al. ASH abstr 3909, 2017; Daver et al. ASH abstr 813, 2017; Guo et al. ASH abstr 3820, 2017; Yoshimi et al. ASH abstr 473, 2017*
Questions Generated From New Drug Approvals

- Should Gemtuzumab be given to all CBF AMLs and older adults with fav- and intermed-risk?
- How should transplant strategies be affected by Gemtuzumab in induction?
- Must Gemtuzumab be given as in ALFA trial with specific induction and chemotherapy regimens (dauno in consol)? For Midostaurin?
- When a pt has AML with MRC and an IDH2 mutation, should pt be treated with CPX-351 or on trial with chemotherapy and Enasidenib? If AML-MRC and FLT3 pos: CPX-351 or Mido?
# AML Treatment Strategies in 2018

<table>
<thead>
<tr>
<th>AML subgroup</th>
<th>Candidate for intensive chemo</th>
<th>Not a candidate for intensive chemo</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>Clinical trial preferred</td>
<td>Clinical trial preferred</td>
</tr>
<tr>
<td>CBF</td>
<td>GO + chemo</td>
<td>HMA/LoDAC + Venetoclax*</td>
</tr>
<tr>
<td>CD33 pos</td>
<td>GO + chemo, ? If pretransplant</td>
<td>GO or HMA/LoDAC + Venetoclax</td>
</tr>
<tr>
<td>t-AML or AML w/MRC (incl complex cyto)</td>
<td>CPX-351 ind/consol, transplant</td>
<td>HMA/LoDAC + Venetoclax*</td>
</tr>
<tr>
<td>TP53 mutant</td>
<td>Chemo vs decitabine x 10d</td>
<td>Decitabine x5d or x10d</td>
</tr>
<tr>
<td>FLT3+</td>
<td>Mido + chemo ind/consol/maint, transplant</td>
<td>?AZA + sorafenib or HMA alone</td>
</tr>
<tr>
<td>IDH1/2+</td>
<td>Chemo</td>
<td>HMA/LoDAC + Venetoclax*</td>
</tr>
<tr>
<td>Marker -</td>
<td>Chemo</td>
<td>HMA/LoDAC + Venetoclax*</td>
</tr>
</tbody>
</table>

*HMA/LoDAC + Venetoclax awaiting phase III data
# AML Treatment Strategies in 2018: R/R

<table>
<thead>
<tr>
<th>AML subgroup</th>
<th>Candidate for intensive chemo</th>
<th>Not a candidate for intensive chemo</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>Clinical trial preferred</td>
<td>Clinical trial preferred</td>
</tr>
<tr>
<td>R/R <em>IDH2</em>+</td>
<td>Enasidenib</td>
<td>Enasidenib</td>
</tr>
<tr>
<td>R/R <em>IDH1</em>+</td>
<td>Clinical trial with ivosidenib preferred</td>
<td>Clinical trial with ivosidenib preferred</td>
</tr>
<tr>
<td>R/R <em>FLT3</em>+</td>
<td>Strongly favor clinical trial</td>
<td>Strongly favor clinical trial</td>
</tr>
<tr>
<td>R/R <em>TP53</em> mutant</td>
<td>Chemo vs decitabine x 10d</td>
<td>Decitabine x5d or x10d</td>
</tr>
<tr>
<td>R/R <em>CD33</em>+</td>
<td>Chemo or GO</td>
<td>HMA/LoDAC + Venetoclax* or GO</td>
</tr>
<tr>
<td>R/R post-allo transplant w extramedullary AML</td>
<td>Chemo vs HMA vs ipilimumab</td>
<td>HMA vs ipilimumab</td>
</tr>
<tr>
<td>R/R marker -</td>
<td>Chemo vs HMA vs HMA/LoDAC + Venetoclax*</td>
<td>HMA vs HMA/LoDAC + Venetoclax*</td>
</tr>
</tbody>
</table>

*Lower RR for HMA/LoDAC + Venetoclax in R/R setting ([Dinardo et al. Am J Hematol 2018; Goldberg et al. ASH 2017, abstr 1353](#))
The Circuitous Road To A Clinically Meaningful Impact Of A New Drug

- Promising Results
- Statistical Significance
- Regulatory Approval
- Commonly Used Practice
- Changing Clinically Meaningful Impact
Summary and Conclusions

• AML is a heterogeneous disease of diverse somatic genetic mutations
• Molecular genetics inform classification, prognosis, therapy and depth of remission
• Era of precision medicine is here
• Many novel agents with unique mechanisms of action available
• MRD has emerged an important prognostic factor
• Therapeutic paradigms are shifting
Acknowledgments

Leukemia Service
Memorial Sloan Kettering Cancer Center

ECOG Leukemia Committee