UNDERSTANDING YOUR DIAGNOSIS: ACUTE MYELOID LEUKEMIA (AML)

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DISCLOSURES
Understanding Your Diagnosis: Acute Myeloid Leukemia (AML)

Eunice S. Wang, MD, has affiliations with AbbVie, Agios, Amgen, Astellas, Daiichi, Gilead, Jazz, Macrogenics, Pfizer, Stemline (Consultant); Astellas, Jazz, Novartis, Pfizer, Stemline (Speakers Bureau).
Understanding Acute Myeloid Leukemia

Understanding AML: 2020

• Diagnosis and Time to treatment
• Improving Venetoclax therapy
• Combination approaches
• New agents on the horizon
Acute Myeloid Leukemia: Biology

Disease of older adults (median 67-70 years)
Biologically diverse (karyotype, mutations, antigens)
Clinically aggressive disease with survival in weeks-months

How to diagnose AML

Morphology  Flow Cytometry  FISH  Cytogenetics

Mutation Profiling

- Risk stratification
- Drug targeting
- Disease monitoring
AML is characterized by many mutations

<table>
<thead>
<tr>
<th>Gene</th>
<th>Overall Frequency, %</th>
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<tbody>
<tr>
<td>FLT3 (ITD, TKD)</td>
<td>37 (30,7)</td>
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<td>NPM1</td>
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<td>DNMT3A</td>
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<td>NRAS</td>
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<td>CEBPA</td>
<td>9</td>
</tr>
<tr>
<td>TET2</td>
<td>8</td>
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<tr>
<td>WT1</td>
<td>8</td>
</tr>
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<td>IDH2</td>
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<td>IDH1</td>
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<tr>
<td>KIT</td>
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<th>Gene</th>
<th>Overall Frequency, %</th>
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<td>MLL-PTD</td>
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<td>ASXL1</td>
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<td>PHF6</td>
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<td>KRAS</td>
<td>2</td>
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<td>HRAS</td>
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<tr>
<td>EZH2</td>
<td>0</td>
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</table>

History of AML Therapy

Cytosine Arabinoside (NSC-63878) and Daunorubicin (NSC-39142) Therapy in Acute Nonlymphocytic Leukemia

- Jerome W. Yates, H. James Wallace, Jr., Rose Ruth Ellison, and James F. Holland
- Roswell Park Memorial Institute, Buffalo, NY

1973 to 2017 (44 years!)

US FDA approvals

1. First FLT3 inhibitor midostaurin US FDA approved
2. First IDH2 inhibitor enasidenib US FDA approved
3. Liposomal cytarabine/daunorubicin US FDA approved
4. Gemtuzumab Ozogamicin re-US FDA approved

7+3 = 1973 to 2017 (44 years!)
AML Therapy: Many new drugs

Attributed to John Ozell’s translation of a French play (1738); Translated in 1725 as *The Plague of Riches*

Definition: Generally used to describe an abundance of something, (typically positive) with the idea that there are so many of these good things that it’s difficult to pick just one.

8 Drugs approved for AML in last 2 years
- Midostaurin, Enasidenib, CPX-351, Gemtuzumab
- Ivosidenib, Gilteritinib, Glasdegib, Venetoclax

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Therapy for AML patients based on mutations

Newly diagnosed AML and not fit for intensive chemotherapy and/or age $\geq 60$ years

- No actionable mutations
  - Venetoclax + decitabine
  - Venetoclax + azacitidine
  - Venetoclax + LDAC
  - Aza or decitabine (HMA)
  - Glasdegib + LDAC
  - LDAC alone
  - GO (CD33+)
  - Best supportive care

- Actionable mutation
  - Ivosidenib (IDH1 mutant)
  - Enasidenib (IDH2 mutant)
  - Sorafenib + HMA (FLT3 mutant)
  - Aza or decitabine
  - Venetoclax + HMA/LDAC
Safe to wait for genetic information to start AML therapy

2263 patients with newly dx AML from 46 centers across Germany
Time from diagnosis to intensive induction did NOT affect outcome or survival

Survival probability

0.25
0.50
0.75
1.00

0 12 24 36 48 60

p = 0.21
p = 0.47
p = 0.88

All ages ≤60 yrs >60 yrs

Novel combinations to improve outcomes

Backbone Chemo Novel agents Combinations tailored to individual patients
Venetoclax: BCL-2 inhibitor

Cancer cells evade cell death through overexpression of BCL-2 which sequesters pro-apoptotic proteins.

Venetoclax is a potent small molecule BCL-2 inhibitor which binds to BCL-2, "freeing" pro-apoptotic proteins which then initiate cell death.

Venetoclax + Chemo for Older Patients

**Indicated for:**
- Newly Dx AML
- Age ≥ 75 yrs OR ECOG 2-3
- Cardiac, lung, liver or renal disease
Venetoclax + Chemo: High response rate

- Venetoclax with HMAs induces rapid, deep, and durable responses in older patients with AML.

 Venetoclax-based therapy followed by transplant

- 31 of 304 patients (10%) treated with venetoclax + chemo underwent transplant.
- Over two thirds (68%, 21 of 31) patients were alive 12 months after transplant.
- 55% (17/31) of all patients undergoing transplant have remission of ≥12 months after transplant.
- 71% (12/17) of those patients remained in remission for ≥ 2 years.
Adding Venetoclax to intensive AML chemotherapy

- Single-center, phase Ib/II trial with FLAG-IDA plus venetoclax

Phase Ib: Dose escalation
Filgrastim 5 mcg/kg D1-7* + Fludarabine 30 mg/m² IV D2-6 + Idarubicin 6 mg/m² D4-6 + Cytarabine + Venetoclax† (N = 16 R/R AML)

Phase II: Dose expansion
Filgrastim 5 mcg/kg D1-7* + Fludarabine 30 mg/m² IV D2-6 + Idarubicin 6 mg/m² D4-6 + Cytarabine 1.5 g/m² IV D2-6 + Venetoclax 400 mg D1-14 (N = 14 ND, 26 R/R‡ AML)

Consolidation
Filgrastim 5 mcg/kg D1-7* + Fludarabine 30 mg/m² IV D2-6 + Cytarabine 1.5 g/m² IV D2-6 + Venetoclax 400 mg D1-14

Maintenance (if no ASCT)
Venetoclax 400 mg D1-14 up to 1 year

Adult, fit patients with AML; ECOG PS ≤ 2; AML or high-risk MDS (≥ 10% blasts); satisfactory organ function

*Or peg-filgrastim 6 mg x 1 after D5
†3-level dosing of cytarabine + venetoclax:
1) CYT 2 g/m² D2-6 /VEN 200 mg D1-21; 2) CYT 1.5 g/m² D2-6 /VEN 200 mg D1-14; 3) CYT 1.5 g/m² D2-6 /VEN 400 mg D1-14
‡Including the 16 R/R AML patients from phase I

IDH mutations in AML

- **Isocitrate dehydrogenase (IDH)** is a critical enzyme regulating tumor metabolism
- IDH mutations promote AML development
- **IDH** mutations infrequent in AML
  - IDH1 mut found in 6-9% of AML
  - IDH2 mut found in 8-12% of AML
IDH1 and IDH2 inhibitors in AML

Ivosidenib (IDH1 inhibitor) 500 mg daily

Enasidenib (IDH2 inhibitor) 100 mg daily

Differentiation Syndrome
New onset or worsening of fever, rapid weight gain or swelling in legs, respiratory symptoms, fluid in lungs or surrounding the heart, low blood pressure, kidney problems

Enasidenib + Azacitidine for newly dx IDH2 mutant AML

- Randomized phase I/II study
  - Phase I portion consisted of 3 + 3 dose-finding for enasidenib + azacitidine

Randomized 2:1

Adult patients with mutant IDH2 ND AML, ineligible for intensive CT and no history of treatment with hypomethylating agents (N = 101)

Enasidenib 100 mg QD + Azacitidine 75 mg/m²/day SQ x 7 days/28-day cycle (n = 68)

Azacitidine Monotherapy 75 mg/m²/day SQ x 7 days/28-day cycle (n = 33)

- Results: Higher response rates with combination therapy
- Safety: Combination therapy was tolerated well by patients
Enasidenib + Azacytidine for newly dx IDH2 mutant AML

- Enasidenib + azacitidine showed significantly greater reduction in maximal mutant IDH2 VAF suppression from baseline vs azacitidine alone: median reductions -83.4% vs -17.7%, respectively ($P = .0008$)

**Mutant IDH2 VAF below the limit of detection (0.02% to 0.04%)**

Data cutoff: August 19, 2019.

Mutant IDH2 VAF in bone marrow mononuclear cells were assessed by digital PCR.

### Maximum Mutant IDH2 VAF Reductions From Baseline

<table>
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<tr>
<th>Treatment</th>
<th>Patients (%</th>
<th>CR</th>
<th>R</th>
<th>NR</th>
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</thead>
<tbody>
<tr>
<td>Enasidenib + Azacitidine</td>
<td>92</td>
<td>8</td>
<td>8</td>
<td>1</td>
</tr>
<tr>
<td>Azacitidine Only</td>
<td>22</td>
<td>0</td>
<td>1</td>
<td>21</td>
</tr>
</tbody>
</table>

### Ena + AzA: Mutant IDH2 VAF Clearance

- Not Detected*
- < 0.5%
- ≥ 0.5%

* Patients with molecular remission.

**Maintenance therapy for AML**

- **Induction**: 7+3
- **Consolidation**: HIDAC x 2-4
- **Observation only vs. Maintenance therapy**

BMBx CR

Allogeneic Stem cell Transplant

vs. Observation only
Oral azacitidine: First drug for AML maintenance?

**PRE-RANDOMIZATION**

**Screening**
- Key eligibility criteria:
  - First CR / CRi with IC ± consolidation
  - Age ≥55 years
  - de novo or secondary AML
  - ECOG PS score 0-3
  - Intermediate- or poor-risk cytogenetics
  - Ineligible for HSCT
  - Adequate bone marrow recovery (ANC ≥0.5 × 10⁹/L, platelet count ≥20 × 10⁹/L)

**RANDOMIZATION**

**Randomization (1:1):**
- Within 4 months (±7 days) of CR/CRi
- Stratified by:
  - Age: 55–64 / ≥ 65
  - Prior MDS/CMML: Y / N
  - Cytogenetic risk: Intermediate / Poor
  - Consolidation: Y / N

**TREATMENT PHASE**

- CC-486 300 mg QD × 14 days
  - 28-day cycles
  - Placebo QD × 14 days

**Response Assessment**
- Every 3 Cycles
  - > 15% BM Blasts
  - 5%–15% BM Blasts

**FOLLOW-UP**
- Continue Treatment
- Stop Treatment
- End of Study

Patients randomized to CC-486 had improved survival
Low dose Decitabine can also be used as maintenance

Stratified by: age ≥ 70 yrs, unfavorable cytogenetics, induction therapy

AML patients ≥ 60 yrs of age with BM biopsy-confirmed CR/CRi after consolidation therapy* (N = 120)

Decitabine 20 mg/m² on Days 1-3 Q4W for 1 yr (n = 59)

Observation (n = 61)

Follow-up:
- CBC Q1M for 1 yr, then Q3M
- BM biopsy Q3M for 2 yrs after randomization

*Cytrabine after 7+3 induction, or clofarabine after clofarabine induction.

- Primary endpoint: disease-free survival (relapse or death from any cause)
- Trend to improved survival in FLT3 negative AML patients receiving decitabine

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FLT3 mutations in AML

- FLT3-ITD occurs in ~25-37% of AML
- FLT3-TKD occurs in ~10% of AML
- More frequent in younger patients, de novo AML and diploid cytogenetics
- Associated with resistance to 7+3
- Increased risk of relapse
- Many FLT3 inhibitors developed

**Activated proliferation and pro-survival pathways**
FLT3 inhibitors for AML

**OLD vs NEW Generation FLT3 inhibitors**

<table>
<thead>
<tr>
<th>Lestaurnib</th>
<th>Targets</th>
<th>FLT3 inhibitory dose</th>
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<tbody>
<tr>
<td>Midostaurin*</td>
<td>FLT3, JAK2, TrkA</td>
<td>700 nM</td>
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<tr>
<td>Sorafenib*</td>
<td>FLT3, KIT, PKC, PDGFR, VEGFR</td>
<td>1000 nM</td>
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<tr>
<td>Sorafenib*</td>
<td>FLT3, KIT, PDGFR, RAF, VEGFR</td>
<td>265 nM</td>
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<tr>
<td>Quizartinib</td>
<td>FLT3, KIT, PDGFR, RET</td>
<td>18 nM</td>
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<tr>
<td>Crenolanib</td>
<td>FLT3, PDGFR</td>
<td>48 nM</td>
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<tr>
<td>Gilteritinib*</td>
<td>FLT3, AXL</td>
<td>43 nM</td>
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*FDA approved drugs

**Best FLT3 inhibitor is context dependent**

<table>
<thead>
<tr>
<th>Clinical setting</th>
<th>Standard of care</th>
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<tr>
<td>Newly diagnosed FLT3(^{\text{mut}})</td>
<td>Midostaurin plus 7+3</td>
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<tr>
<td>Older newly diagnosed FLT3(^{\text{mut}})</td>
<td>Sorafenib plus Azacitidine</td>
</tr>
<tr>
<td>FLT3(^{\text{mut}}) after transplant</td>
<td>Sorafenib</td>
</tr>
<tr>
<td>Relapsed FLT3(^{\text{mut}})</td>
<td>Gilteritinib</td>
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APR-246: New drug for p53 mutant AML

- APR-246 binds covalently to p53...
- ...restores wt p53 conformation & activity...
- ...and triggers cell cycle arrest and apoptosis

治疗持续时间（个月）

<table>
<thead>
<tr>
<th>Treatment Duration (months)</th>
<th>Overall</th>
<th>MDS</th>
<th>AML</th>
<th>MDS-MPN + CMML</th>
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<td>0</td>
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<td>33</td>
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<td>1</td>
<td>39 (87)</td>
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<td>18</td>
<td>24 (53)</td>
<td>20</td>
<td>4</td>
<td>0 (0)</td>
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 Evaluable patients, n
 Overall response rate, n (%) CR rate, n (%)
 Duration of CR, months (median) [95% CI]
 Discontinued for transplant, n (%)
Anti-CD47: Telling immune cells to “eat” AML cells

Magrolimab is a an anti-CD47 antibody
- Targets CD47 on AML cells
- Induces macrophage cells to “eat” AML cells
- Eliminates leukemic stem cells in AML models
- Azacitidine induces CD47 expression on AML blasts and increases efficacy of magrolimab

First line AML: 14 of 22 (64%)
CR 41%, CRi 14%
Understanding AML: 2020

- Diagnosis and Time to treatment
- Improving Venetoclax therapy
- Combination approaches
- New agents on the horizon
Example of pediatric ALL

Current survival rate for childhood ALL = >90%

To cure AML, we need to:
- Introduce new drugs
- Design combo Rx
- Conduct clinical trials

Outcomes of pediatric B-ALL

- 2012: 90%
- 1968: 90%

Hunger et al, J Clin Oncol, 2012
Q&A SESSION
Understanding Your Diagnosis: Acute Myeloid Leukemia (AML)

• **Ask a question by phone:**
  – Press star (*) then the number 1 on your keypad.

• **Ask a question by web:**
  – Click “Ask a question”
  – Type your question
  – Click “Submit”

Due to time constraints, we can only take one question per person. Once you’ve asked your question, the operator will transfer you back into the audience line.

LLS EDUCATION & SUPPORT RESOURCES

• **Information Specialists**
  Master’s level oncology professionals, available to help cancer survivors navigate the best route from diagnosis through treatment, clinical trials and survivorship.
  – **EMAIL:** infocenter@LLS.org
  – **TOLL-FREE PHONE:** 1-800-955-4572

• **Free Education Booklets:**
  – www.LLS.org/booklets

• **Free Telephone/Web Programs:**
  – www.LLS.org/programs

• **Live, weekly Online Chats:**
  – www.LLS.org/chat
LLS EDUCATION & SUPPORT RESOURCES

- **LLS Podcast, The Bloodline with LLS**
  Listen in as experts and patients guide listeners in understanding diagnosis, treatment, and resources available to blood cancer patients: [www.thebloodline.org](http://www.thebloodline.org)

- **Education Videos**
  Free education videos about survivorship, treatment, disease updates and other topics: [www.LLS.org/educationvideos](http://www.LLS.org/educationvideos)

- **Patti Robinson Kaufmann First Connection Program**
  Peer-to-peer program that matches newly diagnosed patients and their families: [www.LLS.org/firstconnection](http://www.LLS.org/firstconnection)

- **Free Nutrition Consults**
  Telephone and email consultations with a Registered Dietitian: [www.LLS.org/nutrition](http://www.LLS.org/nutrition)

- **What to Ask**
  Questions to ask your treatment team: [www.LLS.org/whattoask](http://www.LLS.org/whattoask)

- **Other Support Resources**
  LLS Community, discussion boards, blogs, support groups, financial assistance and more: [www.LLS.org/support](http://www.LLS.org/support)

THANK YOU

We have one goal: A world without blood cancers