**AML:**
Understanding your diagnosis and current and emerging treatments

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**AML: numbers**

- New cases each year: ~21,000
- Deaths each year: ~10,500
- Median age: ~67

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**Challenges in MDS/AML diagnosis**

- Does the patient have a neoplasm?
- Should the patient be treated for MDS or should another diagnosis be sought?
- Risk-adapted therapy according to prognosis
- Should the patient receive induction or other intensive chemotherapy with a goal of remission?

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**Genetics 101**

1. 2. 3. 4. 5.
6. 7. 8. 9. 10. 11. 12.
19. 20. 21. 22. y. x.
**AML with recurrent genetic abnormalities**

- t(8;21) RUNX1-RUNX1T1
- inv(16) or t(16;16) CBFB-MYH11
- t(15;17) PML-RARA

**What is a mutation?**

- TTGAGTCG....
- TTGAGTAG....

**Common mutations in AML**

![Image of common mutations in AML]

**ELN Molecular Risk Groups**

![Image of ELN Molecular Risk Groups]

**Conventional chemotherapy for AML**

- Conventional chemotherapies for AML
- Various regimens (IA, 7+3, AcDVP16, etc)
- Cytarabine (continuous infusion or bolus)
- Anthracycline
  - Typically daunorubicin or idarubicin
- Day 14 marrow (e.g. 7+3 chemotherapy)...
  - If aplasia (marrow < 5% cellularity), wait for recovery
  - If residual leukemia, re-treat.
- CR rate 75% (includes those needing 2 courses)
Consolidation

- Most common: High dose cytarabine (HiDAC)
  - Mayer: 3g/m² IV BID Days 1,3,5 for 3-4 cycles
  - Several alternates (e.g., 1.5 g IV q12 x 6 days)
- Allogeneic stem cell transplant

Recent developments

- Liposomal chemotherapy
- Antibody-drug conjugates
- FLT3 inhibitors
- IDH1/IDH2 inhibitors

CPX-351 ("Vyxeos")

- 100 nm bilamellar liposomes
- 5:1 molar ratio of cytarabine to daunorubicin
- 1 unit = 1.0 mg cytarabine plus 0.44 mg daunorubicin

Gemtuzumab ("Mylotarg")

- Anti-CD33 antibody conjugated to calicheamicin
- Calicheamicin hydrolyzed in lysosome after internalization
- Initially approved 2000 in R/R AML
- Hepatotoxicity/VOD issues
Gemtuzumab results

Favorable Intermediate Unfavorable

Approved 9/1/17 for the treatment of adults with newly-diagnosed or R/R CD33+ AML

Ratify Trial

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)


Ratify: Schema

FLT3 inhibitors

<table>
<thead>
<tr>
<th>Drug</th>
<th>IC50 (medium) 1</th>
<th>IC50 (plasma) 2</th>
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<tbody>
<tr>
<td>Lestaurinib</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>~205 nM</td>
</tr>
<tr>
<td>Quiratinib</td>
<td>1 nM</td>
<td>18 nM</td>
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</table>

Approved 4/28/17 for the treatment of adults with newly diagnosed FLT3m AML
IDH as a therapeutic target

- IDH mutations occur in a spectrum of solid and hematologic tumors
  - IDH2m: ~3% of MDS
  - IDH2: 3~6% of MDS


IDH inhibitor trials

- 14-035 (NCT02074839): "Phase I multicenter study of AG-120 in patients with IDH1 mutant advanced hematologic malignancies"
- 13-371 (NCT01915498): "Phase I multicenter study of AG-221 in patients with IDH2 mutant advanced hematologic malignancies"

IDH2 inhibitor trial design

Ongoing, first-in-human, dose escalation study:
- AG-221: First-in-class, oral, potent, reversible, selective inhibitor of mutated IDH2
- IDH2 mutation-positive hematologic malignancies, including relapsed or refractory AML, MDS, or untransformed AML
- AG-221 in continuous oral dosing QD or BID daily 28-day cycles

Key outcome measures:
- Safety and tolerability, DLT
- MTD and recommended phase 2 dose

IDH2i preliminary results

<table>
<thead>
<tr>
<th>Overall Response</th>
<th>CR (CRi) (n = 14)</th>
<th>PR (n = 24)</th>
<th>NC (n = 24)</th>
<th>PD (n = 200)</th>
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<tbody>
<tr>
<td>Overall Response</td>
<td>10 (71%)</td>
<td>2 (13%)</td>
<td>7 (50%)</td>
<td>70 (35%)</td>
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<tr>
<td>CR</td>
<td>2 (14%)</td>
<td>4 (17%)</td>
<td>3 (13%)</td>
<td>27 (14%)</td>
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<tr>
<td>PR</td>
<td>8 (57%)</td>
<td>12 (50%)</td>
<td>1 (4%)</td>
<td>63 (31%)</td>
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<tr>
<td>NC</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>77 (39%)</td>
</tr>
<tr>
<td>PD</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>1 (4%)</td>
<td>23 (11%)</td>
</tr>
</tbody>
</table>

Approved 8/1/17 for the treatment of adults with R/R IDH2m AML

Benefit does not require CR
MDS Experts at Mass General

<table>
<thead>
<tr>
<th>Leukemia Center</th>
<th>BMT Center</th>
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<tbody>
<tr>
<td>Amir Fathi</td>
<td>Yibin Chen</td>
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<tr>
<td>Phil Amrein</td>
<td>Steve McAfee</td>
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<td>Gaby Hobbs</td>
<td>Tom Spitzen</td>
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<td>Eyal Attar</td>
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<td>Tim Graubert</td>
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<td>Hanno Hock</td>
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<td>Zack DeFilipp</td>
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Thanks!

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