Myeloid Malignancies: Current and Emerging Treatment Approaches in First and Later Line Settings

Daniel J. DeAngelo, MD, PhD
Adult Leukemia Program
Dana-Farber Cancer Institute
Brigham and Women’s Hospital
Associate Professor of Medicine
Harvard Medical School
Boston, MA
Presenter Disclosure Information

The following relationships exist related to this presentation:

• Dr. Daniel DeAngelo has served as a consultant for Amgen, Ariad, Celgene, Immunogen, Incyte, Novartis, Pfizer and Shire Pharmaceuticals

Off-Label/Investigational Discussion

In accordance with CME policy, faculty have been asked to disclose discussion of unlabeled or unapproved use(s) of drugs or devices during the course of their presentations. Azacitidine and decitabine for AML
Update on Myeloid Malignancies: Outline

- **AML**: RISK-ADJUSTED TREATMENT
- **MDS**: PROGNOSIS and TREATMENT
- **APL**: CURATIVE TREATMENT OPTIONS
- **CML**: THERAPY in the ERA OF MULTIPLE TYROSINE KINASE INHIBITORS
AML: Risk-Adjusted Treatment
Key Points from *de novo* AML Genome Atlas

9 key categories:
- transcription-factor fusions (18%)
- nucleophosmin (*NPM1*) (27%)
- tumor-suppressor genes (16%)
- DNA-methylation–related genes (44%)
- signaling genes (59%)
- chromatin-modifying genes (30%)
- myeloid transcription-factor genes (22%)
- cohesin-complex genes (13%)
- spliceosome-complex genes (14%)

The Cancer Genome Atlas Research Network
*NEJM* 2013; 368:2059-2074.

Döhner H et al, *NEJM* 2015; 373:1136-1152
Molecular Classes of AML and Concurrent Gene Mutations in Adults < 65 years

# Current Risk Assessment in AML

## Key Prognostic Data in AML in 2017

| **Patient age** (FH, bleeding hx; ?Therapy related; ?Prior MDS) |
| Cytogenetics / fusion mRNA (screen for APL, MLL, Ph+, CBF) |
| Multiparameter flow |
| Molecular studies: |

- **FLT3 ITD** (internal tandem duplication) mutation | Unfavorable |
- **NPM1** mutation | Favorable |
- **CEBPA biallelic** mutation | Favorable |
- **RUNX1, TP53, ASXL1** (KIT in CBF) | Unfavorable |

*Of Future Importance:* mutation status of **IDH1/2, DNMT3A, TET2**, etc.
Relapse-Free and Overall Survival in AML Depend On Combined NPM1 and FLT3-ITD Mutation Status


Disease-Free Survival

Overall Survival

NPM1+/FLT3-ITD-
NPM1+/FLT3-ITD+
NPM1-/FLT3-ITD-
NPM1-/FLT3-ITD+

P = .0010

Disease-Free Survival (%)

Overall Survival (%)

Time (months)

Time (months)
Genomic Classification and Prognosis in AML

Papaemmanuil E et al. NEJM. 2016;374:2209-2221.
TP53 Mutations and Prognosis

Papaemmanuil E et al. NEJM. 2016;374:2209-2221.
### New European Leukemia Net (ELN) 2017: Genetic-Cytogenetic Prognostic Subgroups

<table>
<thead>
<tr>
<th>Genetic Risk Group</th>
<th>Frequency</th>
<th>Survival</th>
<th>Subset</th>
</tr>
</thead>
</table>
| **Favorable**       | 15%       | 65%      | • t(8;21)(q22;q22); *RUNX1-RUNX1T1*  
                  |           |          | • inv(16)(p13.1q22) or t(16;16)(p13.1;q22); *CBFB-MYH11*  
                  |           |          | • Mutated *NPM1* without *FLT3-ITD* or *FLT3-ITD low*  
                  |           |          | • Biallelic Mutated *CEBPA* |
| **Intermediate**    | 55%       | 50%      | • Mutated *NPM1* and *FLT3-ITD high*  
                  |           |          | • Wild-type *NPM1* without *FLT3-ITD* or *FLT3-ITD low* (without adverse-risk genetic lesions)  
                  |           |          | • Wild-type *NPM1* and *FLT3-ITD* (normal karyotype)  
                  |           |          | • t(9;11)(p22;q23); *MLLT3-MLL*  
                  |           |          | • Any cytogenetics not classified as favorable or adverse |
| **Adverse**         | 30%       | 20%      | • t(6;9)(p23;q34); *DEK-NUP214*  
                  |           |          | • t(v;11)(v;q23); *MLL (KMT2A) rearranged*  
                  |           |          | • Inv(3)(q21q26.2) or t(3;3)(q21;q26.2); *RPN1-EVI1* (GATA2, MECOM (EVI1))  
                  |           |          | • t(9;22)(q34.1;q11.2) *BCR-ABL1*  
                  |           |          | • Monosomy 5 or del(5q); monosomy 7; monosomy 17; abnormal 17p  
                  |           |          | • Complex karyotype(≥ 3 abnormalities) or monosomial karyotype  
                  |           |          | • Wild-type *NPM1* and *FLT3-ITD high*  
                  |           |          | • Mutated *RUNX1*  
                  |           |          | • Mutated *ASXL1*  
                  |           |          | • Mutated *TP53*  

AML: General Treatment Principles

• **Goal 1:** Induction therapy to reduce gross leukemia to undetectable levels (2-3 log cell kill)

• **Goal 2:** Reduce $10^9 - 10^{10}$ cells, undetectable by standard means, present at CR, to a level low enough to achieve prolonged disease-free survival (‘cure’)

AML Therapy for Patients Age <60 Years: Guidelines

• Standard induction chemo: “3+7”
  • Daunorubicin 60-90 mg/m²/d x 3
  • (or idarubicin 12 mg/m²/d x 3)
  • Cytarabine 100-200 mg/m²/d x 7 continuous infusion
  • Ida plus high-dose ara-C (IA) inferior to standard 3+7 (SWOG 1203 study)

• Post-remission (consolidation) therapy
  • If poor cytogenetics or CR2: allo SCT
    • Maybe even DUCB or haploidentical SCT
  • If favorable (CBF) cytogenetics, or normal cytogenetics with biallelic CEBPa, or NPM1 mutation and FLT3 wild-type: 4 cycles HiDAC
  • If intermediate cytogenetics, but not favorable: allo SCT if sibling or MUD, otherwise HiDAC

CBF = core-binding factor; DUCB = double umbilical cord blood; HiDAC = high-dose cytarabine.
**Intensified Induction in AML: ECOG E1900 - Overall Survival**


**Comparison:**

- Daunorubicin 90 mg/m²/d x 3 vs Daunorubicin 45 mg/m²/d x 3

- **All patients**
  - Probability OS
  - High dose vs Standard dose
  - *P* = 0.003

- **Unfavorable cytogenetics**
  - Probability OS
  - High dose vs Standard dose
  - *P* = 0.45

- **Favorable cytogenetics**
  - Probability OS
  - High dose vs Standard dose
  - *P* = 0.004

AML17: 90 mg/m² vs 60 mg/m²: Overall Survival

MRD Based on PCR for Mutant NPM1 in Peripheral Blood After the Second Cycle of Chemotherapy Independently Predicts Clinical Outcomes

MRD = minimal residual disease; PCR = polymerase chain reaction.
Consolidation: DFS Benefit Only in Patients Age <60 Years Receiving High-Dose Ara-C

Patients in Remission (%)

Age <60 y

- 3 g/m² = 156
- 400 mg/m² = 156
- 100 mg/m² = 155

P = 0.002

Age >60 y

- 3 g/m² = 31
- 400 mg/m² = 50
- 100 mg/m² = 48

P = 0.19

Patients with CBF cytogenetics or RAS mutations benefited most from HiDAC

DFS = disease-free survival.
What Is the Role of Allogeneic Stem Cell Transplantation in First Remission (CR1) in AML?

• Prospective trials assigning patients with matched sibling donors to allogeneic SCT and others randomized to chemotherapy vs autologous SCT
  • Autologous SCT = chemotherapy alone
  • Allogeneic SCT (low relapse rate) versus autologous SCT/chemo (low TRM) equivocal
    • Depends on timing, intensity of chemo, allo SCT TRM
  • Meta-analyses suggest slight benefit for sibling allo SCT
    • Except favorable cytogenetics¹
    • Matched-pair analysis² suggests benefit for allo SCT, especially in high-risk AML

• Recent studies suggest:
  • MUD allo SCT = sibling donor allo SCT
  • Young donor MUD better than older donor sibling
  • Ablative better than reduced intensity for patients age <65 years³

CR = complete remission; MUD = matched unrelated donor; SCT = stem cell transplantation; TRM = treatment-related mortality.
Is There a Role for Chemotherapy in CR1 in AML Patients With Normal Cytogenetics?

Mutant NPM1, No FLT3-ITD

No benefit from allo SCT in patients with: mutated NPM1 and wild-type FLT3

Other Genotypes

In all other cases: allo SCT may be superior

Why Do Older Patients With AML Experience Inferior Outcomes?

- Decreased host tolerance of intensive therapy
  - Impaired hematopoietic stem cell reserve
  - Presence of comorbid diseases
  - Decreased chemotherapy clearance

- Increased resistance of disease to therapy
  - Ratio of favorable (eg, t[8;21]) to unfavorable (eg, -7) cytogenetics is lower than for younger patients
  - Higher expression of drug resistance proteins (eg, PGP)
  - Higher incidence of antecedent hematologic disorders

PGP = p-glycoprotein.
What Is the Optimal Induction Approach in Older Patients With AML?

- Standard induction: 3+7 (if patient likely to tolerate)\(^1,2\)
  - Daunorubicin 45-90 mg/m\(^2\)/d x 3 d
  - Cytarabine 100-200 mg/m\(^2\)/d x 7 d by continuous infusion
  - Idarubicin or mitoxantrone are not better than daunorubicin\(^3\)
  - Adding etoposide or increasing daunorubicin dosage is possible, but not clearly better\(^4,5\)

- Recent trials\(^6-8\) have assessed whether “tolerable” single-agent therapy (eg, clofarabine, decitabine, laromustine) might replace 3+7 in those destined to do very poorly with 3+7:
  - Age >70 years
  - Performance status ≥2 +/- comorbid disease
  - Adverse cytogenetics
  - Antecedent hematological disorder (eg, myelodysplastic syndrome, myeloproliferative neoplasms)

In Elderly de novo AML, Secondary-Type Mutations Are Associated With Adverse Outcomes

De novo AML, Age $\geq$ 60 y

Genetic Subtype

- Red: De novo/pan-AML
- Blue: Secondary-type
- Green: TP53 mutated

Is the Patient a Candidate for Transplantation?

- Multiple phase II studies of reduced-intensity allogeneic transplantation of older AML patients
  - Fludarabine + low-dose TBI\(^1\)
    - If CR1, 2-year OS of 44% to 63%; low TRM of 6.7%
- If you can get patients to transplant, OS and DFS longer in older patients when they undergo mini-allogeneic transplant rather than chemotherapy in CR1\(^2\)
  - Small retrospective study, but it did account for age, cytogenetics, AHD status, lead-time bias
- Mini-allogeneic appears to be better (OS, DFS) than autologous transplants for AML patients age >50 years, at least beyond CR1\(^3\)

AHD = antecedent hematologic disorder; TBI = total body irradiation; TRM = transplantation-related mortality.
Phase III Trial of Azacitidine vs Conventional Care in Older AML Patients With >30% BM Blasts

<table>
<thead>
<tr>
<th></th>
<th>Azacitidine</th>
<th>Conventional Care</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR/Cri (%)</td>
<td>28%</td>
<td>25%</td>
</tr>
<tr>
<td>Median OS (months)</td>
<td>10.4</td>
<td>6.5</td>
</tr>
<tr>
<td>Median EFS (months)</td>
<td>6.7</td>
<td>4.8</td>
</tr>
<tr>
<td>Median RFS (months)</td>
<td>9.3</td>
<td>10.5</td>
</tr>
<tr>
<td>1-year OS (%)</td>
<td>46.5%</td>
<td>34.5%</td>
</tr>
</tbody>
</table>

BM = bone marrow; CRi = complete remission with incomplete blood count recovery; EFS = event-free survival; LDAC = low-dose Ara-C; RFS = relapse-free survival. Dombret H et al. Blood. 2015;126:291-299.
TP53 and Decitabine in AML

Overall Survival

Survival (%) vs Days

CR/CRI [p=0.02] p=0.002
PR/SD
PD/NA

Survival According to TP53 Mutation

Survival (%) vs Days

P=0.79
Wild-type TP53
TP53 mutation

NA = not applicable; PD = progressive disease; PR = partial remission; SD = stable disease.

Novel Therapy in AML: A Partial List

• Approval in 2017
  • Midostaurin (with chemotherapy in FLT3 mutated)
  • New ‘delivery system’; CPX 351 (older secondary AML)
  • IDH2 inhibition: enasidenib (relapsed refractory IDH2 mutant)
  • New chemo: vosaroxin (with ara-C in older relapsed-Europe only)

• Special Consideration
  • Antibody targeted (gemtuzumab; SGN 33A)
  • venetoclax

• Others
  • Check point inhibitors
  • Bromodomain inhibitors
  • MDM2 inhibitors
  • Nuclear export inhibitors
  • Hedgehog pathway inhibitors
  • Spliceosome inhibitors
  • IDH1 inhibitors
  • Specific FLT3 inhibitors
Activating FLT3 Mutations in AML

ITD:
25-30%
High relapse, poor prognosis

TKD:
5-10%

C10603/RATIFY Schema

PRE-REGISTER
FLT3 SCREEN\textsuperscript{a, b}

\textbf{FLT3 WILD-TYPE}
not eligible for enrollment

\textbf{R}
\textbf{FLT3+}

\textbf{DNR Ara-C Midostaurin} \rightarrow \textbf{CR} \rightarrow \textbf{HiDAC Midostaurin} \rightarrow \textbf{X 4} \rightarrow \textbf{Midostaurin MAINTENANCE 12 months}

\textbf{DNR Ara-C Placebo} \rightarrow \textbf{CR} \rightarrow \textbf{HiDAC Placebo} \rightarrow \textbf{X 4} \rightarrow \textbf{Placebo MAINTENANCE 12 months}

\textsuperscript{a}Stratification: FLT3 ITD or TKD.
\textsuperscript{b}Stratification: TKD; ITD with allelic ratio <0.7 vs \geq 0.7.
R = randomize.

Overall Survival (Primary Endpoint)
23% reduced risk of death in the midostaurin arm

Median OS (months): Midostaurin 74.7 (31.7-NE); Placebo 25.6 (18.6-42.9)

Hazard Ratio\textsuperscript{a}: 0.77
1-sided log-rank $P$ value\textsuperscript{*}: 0.0074

\textsuperscript{a}Controlled for FLT3 subtype (TKD, ITD-low, ITD-high).
NE = not estimable.

Overall Survival - Posttransplant

Treatment with Midostaurin Increases OS after SCT in CR1

## Selective, Potent FLT3 Inhibitors

<table>
<thead>
<tr>
<th>Drug</th>
<th>Half-life (Dosing)</th>
<th>D835 Activity</th>
<th>Single Agent</th>
<th>Frontline CT Combinations</th>
<th>Post-HSCT Maintenance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quizartinib (AC220)</td>
<td>Long; once daily</td>
<td>No</td>
<td>Phase 3 open</td>
<td>Phase 3 ongoing</td>
<td>Pilot study completed, included in phase 3</td>
</tr>
<tr>
<td>Crenolanib</td>
<td>Short; TID</td>
<td>Yes</td>
<td>Phase 2 completed</td>
<td>Phase 2 ongoing</td>
<td>Phase 2 ongoing</td>
</tr>
<tr>
<td>Gilteritinib (ASP2215)</td>
<td>Long; once daily</td>
<td>Yes</td>
<td>Phase 3 open</td>
<td>Phase 1/2 ongoing</td>
<td>Pilot study completed, phase 3 planned</td>
</tr>
</tbody>
</table>

CT = chemotherapy; TID = three times a day.
CPX-351

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

Randomized Phase 3 Trial of CPX-351 vs 7+3 in Older Patients With Secondary AML


Lancet JE et al. J Clin Oncol. 2016;34:(suppl; abstr 7000);

Lancet JE et al. ASH. 2016
IDH is an enzyme of the citric acid cycle

Mutant IDH2 produces 2-hydroxyglutarate (2-HG), which alters DNA methylation and leads to a block in cellular differentiation

Enasidenib (AG-221CC-90007) is a selective, oral, potent inhibitor of the mutant IDH2 (mIDH2) enzyme

AG-120 is a selective, oral, potent inhibitor of the mutant IDH1 (mIDH1) enzyme

Phase 1/2 Study of the IDH2 Inhibitor Enasidenib (AG-221): Response - AML

<table>
<thead>
<tr>
<th>Overall Response (CR, CRp, CRi, mCR, PR)</th>
<th>RR-AML (n = 159)</th>
<th>Untreated AML (n = 24)</th>
<th>MDS (n = 14)</th>
<th>All (N = 209)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall Response</td>
<td>59 (37%)</td>
<td>10 (42%)</td>
<td>7 (50%)</td>
<td>79 (38%)</td>
</tr>
<tr>
<td>CR</td>
<td>29 (18%)</td>
<td>4 (17%)</td>
<td>3 (21%)</td>
<td>37 (18%)</td>
</tr>
<tr>
<td>CRp</td>
<td>1 (1%)</td>
<td>1 (4%)</td>
<td>1 (7%)</td>
<td>3 (1%)</td>
</tr>
<tr>
<td>CRi</td>
<td>3 (2%)</td>
<td>0</td>
<td>0</td>
<td>3 (1%)</td>
</tr>
<tr>
<td>mCR</td>
<td>9 (6%)</td>
<td>1 (4%)</td>
<td>3 (21%)</td>
<td>14 (7%)</td>
</tr>
<tr>
<td>PR</td>
<td>17 (11%)</td>
<td>4 (17%)</td>
<td>0</td>
<td>22 (11%)</td>
</tr>
<tr>
<td>SD</td>
<td>72 (45%)</td>
<td>9 (38%)</td>
<td>6 (43%)</td>
<td>96 (46%)</td>
</tr>
<tr>
<td>PD</td>
<td>10 (6%)</td>
<td>1 (4%)</td>
<td>0</td>
<td>11 (5%)</td>
</tr>
<tr>
<td>Not evaluable</td>
<td>18 (11%)</td>
<td>4 (17%)</td>
<td>1 (7%)</td>
<td>23 (11%)</td>
</tr>
</tbody>
</table>

• Overall response by IDH mutation type: R140Q 36% / R172K 42%

Similar results with the IDH1 Inhibitor AG-120 (Dinardo CD et al. *Blood*. 2016;128:1070).

Vadastuximab (SGN33a) + Hypomethylating Agent in Frontline Older AML

Efficacy Evaluable | All N=49 | Secondary AMLd N=22 | FLT3/ITD+ N=5 | Age ≥75 years N=26
--- | --- | --- | --- | ---
Remission Rate (CR + CRi) | 73% | 77% | 100% | 65%
CR | 47% | 50% | 80% | 38%
CRi (p)a | 20% | 18% | 20% | 19%
CRi (n)b | 6% | 9% | 0 | 8%
mLFSc | 2% | 5% | 0 | 4%
ORR (CR + CRi + mLFS) | 76% | 82% | 100% | 69%

LFS = leukemia-free state.
Phase 1/2 Trial of Venetoclax + LDAC in Treatment-Naïve Patients Age ≥ 65 With AML

Acute Myeloid Leukemia: Conclusions

- **Acute Myeloid Leukemia:**
  - Mutations matter!
  - Favorable chromosome AML
    - CBF cytogenetics with KIT wild type
    - Normal chromosome AML with NPM1 mutation and FLT3 wild type
  - AML in adults age 18-60
    - Understanding molecular heterogeneity
    - More frequent use of allo SCT
  - AML in older adults
    - Essentially incurable; therefore, new insights needed
    - Increasing role of reduced intensity conditioning allo-SCT
    - What to do with TP53 mutations? 10-day decitabine
  - FLT3 inhibitors finally here (Midostaurin, others)
  - New agents on the horizon
    - CPX-351
    - IDH1 and IDH2 inhibitors
    - CD33 antibody-drug conjugates (SGN-33)
    - BCL2 inhibitors
  - Emerging role of MRD assessment in prognosis and possible treatment assignment
APL: Pathways to Cure
Management of APL

Suspect APL based on:
1. Presence of DIC
2. Atypical promyelocytes
3. Flow Negative for HLA-DR

Start ATRA while waiting for cytogenetic and/or molecular confirmation

No t(15;17) or No PML-RARa
Stop ATRA
Treat AML

APL confirmed

Low/Int Risk APL
No QTc prolongation
ATRA plus ATO
Prednisone for prophylaxis
Hydrea if WBC rises > 10K

High Risk APL (Options)
ATRA/ATO + GO (if available)
ATRA/ATO + ida
Follow CALGB 9710
Acute Promyelocytic Leukemia
Low/intermediate risk patients
(WBC ≤10 x 10^9/L, AGE 16-70)

ATRA plus Arsenic Trioxide
APL 0406 Study

LoCoco et al NEJM, 2013
Induction
- ATO
- ATRA
- IDA
- MTZ
- Chemo
- ATRA
- IDA
- MTZ
- IDA
- MTX + 6MP

Consolidation
- ATO
- ATO
- ATO
- ATO
- 2 weeks on / 2 weeks off
- 3 monthly cycles

Maintenance
- ATRA
- ATRA
- ATRA
- ATRA
- 2 years

Induction
- ATO
- ATO
- ATO
- ATO
- ATO
- ATO
- ATO

R

Lo Coco et al, Blood 2010
Estey et al, Blood 2006
Lo Coco et al, NEJM 2013

Hydroxyurea 500 mg qid if WBC ≤50K
and 1 g qid if >50K
Event-free and Overall Survival

Event-free survival probability

- ATRA+ATO: 97.1%
- ATRA+Chemo: 85.6%

Overall survival probability

- ATRA+ATO: 98.7%
- ATRA+Chemo: 91.1%

p = 0.02

LoCoco et al. NEJM 2013
MDS: Prognosis and Therapy
### Key Information for MDS Risk Assessment in 2017

#### Host Factors
- Age
- **Comorbid** conditions
- Performance status

#### Disease Factors
- Proportion of marrow **blasts**
- Number and degree of peripheral blood **cytopenias**
- **Cytogenetics** / karyotype
- **Transfusion** burden
- Other marrow features: presence of heavy marrow **fibrosis**, ring sideroblasts (if low risk/only anemic – to distinguish RA from RARS)

*While not yet routinely part of risk assessment, molecular features will become critical soon.*
### IPSS (1997) Risk Stratification

<table>
<thead>
<tr>
<th>Prognostic Variable</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
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<tr>
<td>Marrow blasts (%)</td>
<td>&lt; 5%</td>
</tr>
<tr>
<td>Karyotype class*</td>
<td>Good</td>
</tr>
<tr>
<td># of cytopenias**</td>
<td>0 or 1</td>
</tr>
</tbody>
</table>

* Karyotype class: **Good** = normal, -Y, del(5q) alone, del(20q) alone; **Poor** = chromosome 7 abnormalities or complex; **Intermediate** = other karyotypes; **Cytopenias**: Hb < 10 g/dL, ANC < 1800/μL, platelets < 100,000/μL

<table>
<thead>
<tr>
<th>Risk Groups</th>
<th>Low</th>
<th>Int-1</th>
<th>Int-2</th>
<th>High</th>
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<tbody>
<tr>
<td>IPSS</td>
<td>0</td>
<td>0.5-1.0</td>
<td>1.5-2.0</td>
<td>2.5-3.5</td>
</tr>
</tbody>
</table>

## MDS IPSS-R Components

(Greenberg P et al., *Blood* 2012)

### Parameter Categories and Associated Scores

#### Cytogenetic risk group

<table>
<thead>
<tr>
<th>Category</th>
<th>Very good</th>
<th>Good</th>
<th>Intermediate</th>
<th>Poor</th>
<th>Very Poor</th>
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<tbody>
<tr>
<td>Score</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
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#### Marrow blast proportion

<table>
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<tr>
<th>Proportion</th>
<th>0</th>
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<th>3</th>
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<tbody>
<tr>
<td>≤ 2%</td>
<td></td>
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<tr>
<td>&gt; 2% - &lt; 5%</td>
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<td></td>
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<tr>
<td>5% - 10%</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 10%</td>
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</table>

#### Hemoglobin (g/dL)

<table>
<thead>
<tr>
<th>Value</th>
<th>0</th>
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<th>1.5</th>
<th>2</th>
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<tbody>
<tr>
<td>≥ 10</td>
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<td></td>
</tr>
<tr>
<td>8 - &lt; 10</td>
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<tr>
<td>&lt; 8</td>
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</tbody>
</table>

#### Platelet count (x 10^9/L)

<table>
<thead>
<tr>
<th>Value</th>
<th>0</th>
<th>0.5</th>
<th>1</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 100</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>50 - &lt; 100</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 50</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

#### Abs. neutrophil count (x 10^9/L)

<table>
<thead>
<tr>
<th>Value</th>
<th>0</th>
<th>0.5</th>
<th>1</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 0.8</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 0.8</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Cytogenetic Risk group

#### Included karyotypes

<table>
<thead>
<tr>
<th>Risk group</th>
<th>Included karyotypes</th>
<th>Median survival, mo</th>
<th>% Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very good</td>
<td>del(11q), -Y</td>
<td>60.8</td>
<td>2.9%</td>
</tr>
<tr>
<td>Good</td>
<td>Normal, del(20q), del(5q) alone or with 1 other anomaly, del(12p)</td>
<td>48.6</td>
<td>65.7%</td>
</tr>
<tr>
<td>Intermediate</td>
<td>+8, del(7q), i(17q), +19, +21, any single or double abnormality not listed, two or more independent clones</td>
<td>26.1</td>
<td>19.2%</td>
</tr>
<tr>
<td>Poor</td>
<td>der(3q), -7, double with del(7q), complex with 3 abnormalities</td>
<td>15.8</td>
<td>5.4%</td>
</tr>
<tr>
<td>Very poor</td>
<td>Complex with &gt; 3 abnormalities</td>
<td>5.9</td>
<td>6.8%</td>
</tr>
</tbody>
</table>
Clonal Evolution from Birth to Death

Embryogenesis

Premalignant lesion

Cancer

Age

Courtesy of B. Ebert
Frequency of Mutations by Age

No. with mutation

<table>
<thead>
<tr>
<th>Age</th>
<th>0</th>
<th>1</th>
<th>50</th>
<th>138</th>
<th>282</th>
<th>219</th>
<th>37</th>
<th>14</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>240</td>
<td>885</td>
<td>2894</td>
<td>5441</td>
<td>5002</td>
<td>2300</td>
<td>317</td>
<td>86</td>
<td>17</td>
</tr>
</tbody>
</table>

Mutation Distribution

Recurrent Genetic Mutations in MDS

~90% of patients have a mutation by NGS

Clonal Hematopoiesis of Indeterminate Potential (CHIP)

**Traditional ICUS**

<table>
<thead>
<tr>
<th>‘Non-clonal’ ICUS</th>
<th>CHIP</th>
<th>CCUS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clonality</td>
<td>−</td>
<td>+</td>
</tr>
<tr>
<td>Dysplasia</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td>Cytopenias</td>
<td>+</td>
<td>−</td>
</tr>
<tr>
<td>BM Blast %</td>
<td>&lt; 5%</td>
<td>−</td>
</tr>
<tr>
<td>Overall Risk</td>
<td>Very Low</td>
<td>Very Low</td>
</tr>
<tr>
<td>Treatments</td>
<td>Obs/BSC</td>
<td>Observation</td>
</tr>
</tbody>
</table>

**MDS by WHO 2008**

<table>
<thead>
<tr>
<th>Lower Risk MDS</th>
<th>Higher Risk MDS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clonal Cytopenias</td>
<td>Clonal Cytopenias</td>
</tr>
<tr>
<td>−</td>
<td>+</td>
</tr>
<tr>
<td>−</td>
<td>+</td>
</tr>
<tr>
<td>+</td>
<td>−</td>
</tr>
<tr>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

**Clonal Cytopenias**

*Courtesy of D. Steensma*
Impact of Mutations by IPSS Group

**TP53 mutated MDS**

*Poor prognosis due to early relapse*

- **TP53 mutation**
  - Median OS = 8 months

- **No TP53 mutation**

### Survival

![Survival graph](image)

- **TP53 mutation**
  - Survival curve
- **No TP53 mutation**
  - Survival curve

- *p < 0.0001*

### Relapse

![Relapse graph](image)

- **TP53 mutation**
  - Relapse curve
- **No TP53 mutation**
  - Relapse curve

- *p < 0.0001*

---

Allogeneic Stem Cell Transplant: The only known curative modality, but practical only in a small subset (<10%) of patients.

Non-Curative Goals: Decreased transfusion needs, decreased infection, delay of disease progression, prolonged survival, increased quality of life
Current MDS Therapeutic Algorithm

MDS initial diagnosis (using WHO 2008 diagnostic criteria, supplemented by novel genomics approaches)

- Is there a need for treatment now?
  - Yes: Clinical monitoring
  - No: Development of a need for therapy

Individualized risk assessment, using IPSS-R or other tools

- Lower-risk
  - Is anemia isolated, or the major problem?
    - Yes: Lenalidomide; if sEPO <500 U/L, ESA trial before or after
    - No, other important cytopenias are also present
      - Serum EPO <500 U/L?
        - Yes: ESA ± G-CSF
          - Failure: Optimal therapy unclear, consider HMA, IST, androgens, lenalidomide (if not already used), or clinical trial
        - No: Optimal approach is unclear, consider G-CSF or TPO agonist, HMA, IST, clinical trial

- Higher-risk
  - Is the patient a transplant candidate?
    - Yes: AlloSCT, perhaps with HMA or chemotherapy as bridging therapy
    - No: Azacitidine or decitabine (i.e. HMA) until disease progression, relapse, or drug intolerance

Enrollment in a clinical trial, or supportive/palliative care

AZA-plus studies

Rigosertib, PDL1 antagonists, many others

Luspatercept (ACE-536)

<table>
<thead>
<tr>
<th></th>
<th>Immediate Transplant</th>
<th>Transplant in 2 Years</th>
<th>Transplant at Progression</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>6.51</td>
<td>6.86</td>
<td><strong>7.21</strong></td>
</tr>
<tr>
<td>Int-1</td>
<td>4.61</td>
<td>4.74</td>
<td><strong>5.16</strong></td>
</tr>
<tr>
<td>Int-2</td>
<td><strong>4.93</strong></td>
<td>3.21</td>
<td>2.84</td>
</tr>
<tr>
<td>High</td>
<td><strong>3.20</strong></td>
<td>2.75</td>
<td>2.75</td>
</tr>
</tbody>
</table>

*This is for fully HLA matched T cell replete myeloablative SCT*

*Update: Koreth J et al JCO 2013: Same applies in era of RIC allo SCT among patients 60-70 years old*

Eligibility:
>2 U pRBCs/8 weeks
Platelet >50 x 10^9/L
ANC >500/uL

**MDS-001**
N = 43, Phase I/II initiated Feb 2002
List A et al *NEJM* 2005

**MDS-002**
N = 214, Phase II initiated July 2003
Raza A et al *Blood* 2008

**MDS-003**
N = 148, Phase II initiated July 2003
List A et al *NEJM* 2006

67% transfusion independence
Median duration of response >2 years
45% complete cytogenetic remission

**MDS-004**
N = 205, Phase III initiated July 2005
Fenaux et al *Blood* 2011

No difference in dose reductions w/ 5 vs 10 mg. ↑cytogenetic CR with 10 mg 21/28 d vs 5 mg/d

**MDS-005**
N = 239, Phase III initiated Nov. 2009

27% v 3% TI, 31 wk resp duration
No diff in QOL overall, but resp assoc w imp QOL
MDS: Newer Approaches for Lower Risk

• Len + EPO better than Len alone in non del 5q-

• Activin trap: luspatercept for low-risk RBC transfusion dependent

• Short course hypomethylating agents
Combined Treatment with Lenalidomide (LEN) and Epoetin Alfa (EA) is Superior to LEN Alone in Patients with Erythropoietin (Epo)-Refractory, Lower Risk (LR) Non-Del(5q) MDS

Randomize \[ n=226 \]

Lenalidomide
10 mg/d x 21d q 28d

Lenalidomide + Epoetin α

Lenalidomide

IWG MER
Continue

NR
Cross-over
LEN Arm only

Week: 0 16

Eligibility: Low/Int-1 IPSS, ESA failure or low response profile, Hgb <9.5 g/dL
Stratification: serum EPO (> vs. <500mU/ml), prior ESA (EA vs. DA vs. None)
Epoetin alfa 60,000 units SC weekly
Primary Endpoint (EP): MER
Secondary EP: Time to MER, MER duration, LEN cross-over MER response, candidate response biomarkers (CD45 isoform profile)

List et al., ASH 2016, abstract 223
### Fifth Interim ITT Response Analysis

<table>
<thead>
<tr>
<th>Response &amp; Cohort</th>
<th>Arm A (%) LEN</th>
<th>Arm B (%) LEN+Epo</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ITT Analysis [n=163]</strong></td>
<td>N=81</td>
<td>N=82</td>
<td></td>
</tr>
<tr>
<td>Major ER</td>
<td>9 (11.1)</td>
<td>21 (25.6)</td>
<td>P=0.025</td>
</tr>
<tr>
<td>Minor ER</td>
<td>15 (18.5)</td>
<td>13 (15.9)</td>
<td>P=0.68</td>
</tr>
<tr>
<td>Overall ER</td>
<td>24 (29.6)</td>
<td>34 (41.5)</td>
<td>P=0.14</td>
</tr>
<tr>
<td>Arm A Crossover MER</td>
<td>N=34</td>
<td>7 (21%)</td>
<td></td>
</tr>
</tbody>
</table>

List et al., ASH 2016, abstract 223
Luspatercept (ACE-536) Activity in MDS

- Luspatercept, a modified activin receptor type IIB (ActRIIB) fusion protein, acts as a ligand trap for GDF11 and other TGF-β family ligands to suppress Smad2/3 activation; increased Hb in healthy volunteers\(^1\)
- In a murine model of MDS, murine analog RAP-536 corrected ineffective erythropoiesis, reduced erythroid hyperplasia and increased Hb\(^2\)

**Luspatercept**

Modified Extracellular Domain of ActRIIB receptor

Fc domain of human IgG\(_1\) antibody

---

GDF: growth and differentiating factor; TGF: transforming growth factor
Hb: hemoglobin

1. Attie, K et al. Am J Hematol 2014;89:766
2. Suragani R et al., Nat Med 2014;20:408
Increase in Mean Hemoglobin in LTB Patients with > 3 Months of Treatment (Extension Study)

- 16/22 (73%) HI-E responders; median time to response: 2.2 months

LTB: Low transfusion burden patients (< 4 units/8 wk, Hb <10 g/dL)

Platzbecker et al., ASH 2016, abstract 3169
Reduction in Transfusion Burden in Patients with > 3 Months of Treatment (Extension Study, N=28)

- 16/20 (80%) HTB patients were HI-E responders (≥ 4 unit decrease /8 wk)

LTB: Low transfusion burden patients (< 4 units/8 wk, Hb <10 g/dL)
HTB: High transfusion burden patients (≥ 4 units/8 wk)

Platzbecker et al., ASH 2016, abstract 3169
Azacitidine Survival Study

AZA-001 Survival Study Design

Azacitidine SC 75 mg/m^2 × 7 days,
Repeated every 28 days

Higher-risk MDS (FAB)
1:1 Randomization

N=358

Standard of Care Options:
1. Best supportive care
2. Low-dose cytarabine
3. 3&7 chemotherapy

AZA-001 MDS Study Results

• **Median survival improved with azacitidine**
  • 24.4 mos for azacitidine vs. 15 mos for conventional care regimens (CCR) (stratified log-rank $P$-value = 0.0001)
  • 9.4 months median survival benefit for patients on azacitidine compared with CCR
  • CR not needed to note survival benefit

• **Two-year survival rate:**
  • 50.8% for azacitidine vs 26.2% for CCR ($P < 0.0001$)

• Note: alternative dosing/scheduling strategies and IV formulation may be equivalent to 7 day SC

Outcomes After Azacitidine Failure Are Poor

- Data available on 350 pts (median survival 3.6 months for those without known treatment)

<table>
<thead>
<tr>
<th>Subsequent therapy</th>
<th>Number of patients (%)</th>
<th>Median survival (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allogeneic transplant</td>
<td>50 (14%)</td>
<td>18.3 months (3-55+)</td>
</tr>
<tr>
<td>Investigational therapy (e.g. IMiD, HDACi, other)</td>
<td>56 (16%)</td>
<td>13.2 months (1-36+)</td>
</tr>
<tr>
<td>Conventional cytotoxic therapy (e.g., 3&amp;7, LDAC, 6-MP etc)</td>
<td>84 (24%)</td>
<td>7.6 months</td>
</tr>
<tr>
<td>Palliative care</td>
<td>160 (46%)</td>
<td>3.3 months</td>
</tr>
</tbody>
</table>

Even in LR MDS, HMA failure=15 mon med OS, Jabbour ASH 2013

Prebet T et al, JCO 2011; 29:3322
Myelodysplastic Syndrome: Conclusions

- **Myelodysplastic Syndrome:**
  - Mutations matter!
  - Clonal hematopoietic disorder vs MDS
  - Waiting for the revised R-IPSS
    - Beware of TP53 mutations
  - Lower risk MDS:
    - ESA, lenalidomide, immune suppression (IST)
    - Luspatercept
    - TPO-mimetic agents
  - Higher risk MDS:
    - HMA (azacitidine, decitabine)
    - Addition of second agent has not proven beneficial
    - Allo-SCT
CML: Management in the Era of Multiple Tyrosine Kinase Inhibitors
CML Current Status: 2017

- **Imatinib**
- **Nilotinib**
- **Dasatinib**

  - Refractory response
  - Suboptimal response
  - Relapse
  - Intolerance

  **Nilotinib**
  - **Dasatinib**
  - **Bosutinib**

  - Refractory response
  - Suboptimal response
  - Relapse
  - Intolerance

  **Ponatinib**

  - Refractory response
  - Suboptimal response
  - Relapse
  - Intolerance
  - T315I

  **SCT**

  **Other:** Omacetaxine
<table>
<thead>
<tr>
<th>Response Type</th>
<th>Response Definition</th>
<th>When It Should be Achieved</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete hematologic response (CHR)</td>
<td>Normalization of blood counts; resolution of disease signs and symptoms</td>
<td>&lt;1-3 months</td>
</tr>
<tr>
<td>Initial Molecular response</td>
<td>Reduction in $BCR-ABL$ transcript levels in peripheral blood by $\geq 1 \text{ log}$, or $BCR-ABL/ABL$ ratio reduced to $\leq 10% \text{ IS}$</td>
<td>&lt;3 months</td>
</tr>
<tr>
<td>Major cytogenetic response (MCyR)</td>
<td>$\leq 35% \text{ Ph+ cells}$</td>
<td>&lt;6 months</td>
</tr>
<tr>
<td>Complete cytogenetic response (CCyR)</td>
<td>$0% \text{ Ph+ cells}$</td>
<td>&lt;12 months</td>
</tr>
<tr>
<td>Major molecular response (MMR)</td>
<td>Reduction in $BCR-ABL$ transcript levels in peripheral blood by $\geq 3 \text{ log}$, or $BCR-ABL/ABL$ ratio reduced to $\leq 0.1% \text{ IS}$</td>
<td>&lt;12 - 18 months</td>
</tr>
<tr>
<td>Complete molecular response (CMR)</td>
<td>Reduction in $BCR-ABL$ transcript levels in peripheral blood by $\geq 4.5 \text{ log}$, or undetectable $BCR-ABL/ABL$ transcript</td>
<td>??</td>
</tr>
</tbody>
</table>
ENESTnd: Nilotinib vs Imatinib in Newly Diagnosed Chronic Phase CML

- **Primary endpoint**: MMR at 12 mos, defined as ≤ 0.1% BCR-ABL(/ABL ratio) on International Scale
- **Secondary endpoint**: CCyR by 12 mos
- **Other endpoints**: time/duration of MMR and CCyR; EFS, PFS, time to AP/BP, OS
- **Stratification**: by Sokal risk

Newly Diagnosed CML-CP (N = 846)
- 217 centers;
- 35 countries

Randomize

<table>
<thead>
<tr>
<th>Treatment</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nilotinib 300 BID</td>
<td>282</td>
</tr>
<tr>
<td>Nilotinib 400 BID</td>
<td>281</td>
</tr>
<tr>
<td>Imatinib 400 QD</td>
<td>283</td>
</tr>
</tbody>
</table>

ENESTnd: Cumulative Incidence of MMR

Values are nominal.

For each arm, the curve stops at the latest time point at which a patient first achieved MMR.

Since the 5-year data cutoff, 1 new progression to AP/BC on study was reported in the nilotinib 300 mg BID arm; this patient had a low Sokal risk score at baseline, achieved BCR-ABL IS ≤ 10% at 3 months, and discontinued core treatment due to neutropenia ≈ 5 years before progression to AP/BC was reported.

Dasatinib vs Imatinib in Treatment-naive CML: DASISION

- **Primary endpoint:** Confirmed CCyR by 12 months
- **Secondary/other endpoints:** Rates of CCyR and MMR; times to confirmed CCyR, CCyR and MMR; time in confirmed CCyR and CCyR; PFS; overall survival

N = 519
108 centers
26 countries

Dasatinib 100 mg QD (n = 259)

Imatinib 400 mg QD (n = 260)

*Stratified by Hasford risk score

Follow-up 5 years

DASISION: Cumulative MMR Rates Over Time

- Dasatinib 100 mg QD
- Imatinib 400 mg QD

% With MMR:
- By 1 year: 28%
- By 2 years: 46%
- By 3 years: 64%
- By 4 years: 67%
- By 5 years: 76%

Cortes et al. J Clinic Oncol 2016: 2333-2340

N =
- Dasatinib: 259
- Imatinib: 260

p = 0.0022
**DASISION: Overall Survival and Progression-Free Survival**

<table>
<thead>
<tr>
<th></th>
<th>Dasatinib 100 mg QD (n=259)</th>
<th>Imatinib 400 mg QD (n=260)</th>
<th>Hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number of deaths, n</td>
<td>26</td>
<td>26</td>
<td>–</td>
</tr>
<tr>
<td>Estimated 5-year OS, % (95% CI)</td>
<td>91 (87–94)</td>
<td>90 (85–93)</td>
<td>1.01 (0.58–1.73)</td>
</tr>
<tr>
<td>Estimated 5-year PFS, % (95% CI)</td>
<td>85 (80–89)</td>
<td>86 (80–89)</td>
<td>1.06 (0.68–1.66)</td>
</tr>
</tbody>
</table>

- Causes of death were cardiovascular disease (2 dasatinib, 1 imatinib); disease progression (9 dasatinib, 17 imatinib); infection (11 dasatinib, 1 imatinib); other malignancy, septic shock and cardiac failure, multi-organ failure, and whole body swelling (1 each dasatinib); stem cell transplantation complications and unknown (2 each imatinib); severe chest pain, clinical deterioration and decrease in performance status, and fatal bleeding (1 each imatinib)

On-study treatment and in follow-up after discontinuation of randomized treatment.
CI, confidence interval; OS, overall survival; PFS, progression-free survival.

## Treatment Options Based on ABL Kinase Domain Mutation Status

<table>
<thead>
<tr>
<th>Mutation</th>
<th>Treatment recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>T315I</td>
<td><strong>Ponatinib, omacetaxine, clinical trial or stem cell transplant</strong></td>
</tr>
<tr>
<td>V299L</td>
<td>Consider <strong>ponatinib</strong> or <strong>nilotinib</strong></td>
</tr>
<tr>
<td>T315A</td>
<td>Consider <strong>ponatinib</strong> or <strong>nilotinib</strong> or <strong>bosutinib</strong> or <strong>imatinib</strong></td>
</tr>
<tr>
<td>F317L/V/I/C</td>
<td>Consider <strong>ponatinib</strong>, <strong>nilotinib</strong> or <strong>bosutinib</strong></td>
</tr>
<tr>
<td>Y253H, E255K/V, F359V/C/I</td>
<td>Consider <strong>ponatinib</strong>, <strong>dasatinib</strong> or <strong>bosutinib</strong></td>
</tr>
<tr>
<td><strong>Any other mutation</strong></td>
<td>Consider <strong>ponatinib</strong> or <strong>nilotinib</strong> or <strong>dasatinib</strong> or <strong>bosutinib</strong> or high-dose <strong>imatinib</strong></td>
</tr>
</tbody>
</table>

Note: Bosutinib approved as second/third line drug based (n=546) on 26 week MCyR rates: imatinib failures-34%; imatinib f/b nilotinib or dasatinib failures-27%

Based on NCCN and ELN guidelines (Soverini S et al *Blood* 2011); Cortes et al *Blood* 118:4567-4576, 2011
### Ponatinib after failure of second generation TKI

<table>
<thead>
<tr>
<th></th>
<th>CML-CP (n=267)</th>
<th>(n=83) CML-AP</th>
<th>CML-BP</th>
<th>Ph+ ALL</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MCyR</td>
<td>CCyR</td>
<td>MMR</td>
<td>MaHR*</td>
</tr>
<tr>
<td>R/I to dasatinib or nilotinib</td>
<td>56%</td>
<td>48%</td>
<td>31%</td>
<td>62%</td>
</tr>
<tr>
<td>T315I mutation</td>
<td>72%</td>
<td>70%</td>
<td>58%</td>
<td>61%</td>
</tr>
<tr>
<td>Total†</td>
<td>60%</td>
<td>54%</td>
<td>38%</td>
<td>61%</td>
</tr>
</tbody>
</table>

CCyR = complete cytogenetic response; MMR = major molecular response

* 14 patients with CML-AP with baseline MaHR and 1 patient with CML-AP with no baseline MaHR assessment were counted as nonresponders
† Total comprises all eligible patients who received ponatinib. It excludes 5 patients (3 CML-CP, 2 CML-AP) who were not cohort assigned (postimatinib, non-T315I) but received treatment; all 5 achieved MCyR.

Cortes JE et al. NEJM 2013.
## Incidence of Vascular Occlusive Events Over Time

Cortes JE et al. ASH 2013;Abstract 650.

* Combined incidence of cardiovascular, cerebrovascular, peripheral vascular, venous thromboembolism events; † EMA press release Nov 22, 2013; ‡ FDA drug safety communication, Oct 31, 2013

USPI = US package insert; SAE = AE reported as serious by the investigator, per standard criteria

<table>
<thead>
<tr>
<th>Category</th>
<th>N = 449</th>
<th>23 July 2012 (USPI)</th>
<th>03 Sep 2013</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N (%)</td>
<td>12 months (340 patient years)</td>
<td>24 months (578 patient years)</td>
</tr>
<tr>
<td><strong>Data as of</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reference 1</td>
<td>Method 1†</td>
<td>41 (9)</td>
<td>62 (14)</td>
</tr>
<tr>
<td>Reference 2‡</td>
<td>Method 2‡</td>
<td>47 (10)</td>
<td>81 (18)</td>
</tr>
<tr>
<td>Medically attended death</td>
<td></td>
<td></td>
<td></td>
</tr>
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<td>N = 313</td>
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<td>72 (9)</td>
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<td>7 (2)</td>
<td>17 (4)</td>
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<tr>
<td><strong>Method 1†</strong></td>
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<td><strong>Method 2‡</strong></td>
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<tr>
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<tr>
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<tr>
<td>N = 184</td>
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<tr>
<td><strong>Total arterial thrombosis</strong></td>
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<td></td>
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</tr>
<tr>
<td>N = 313</td>
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<td></td>
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<tr>
<td><strong>Venous thromboembolism</strong></td>
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</tr>
<tr>
<td>N = 449</td>
<td></td>
<td></td>
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<tr>
<td><strong>Vascular occlusion</strong></td>
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<td>29 (6)</td>
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<td>41 (9)</td>
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<td>13 (3)</td>
<td>18 (4)</td>
<td>25 (6)</td>
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<td>17 (4)</td>
<td>16 (4)</td>
<td>28 (6)</td>
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<td>Total arterial thrombosis</td>
<td>34 (8)</td>
<td>51 (11)</td>
<td>53 (12)</td>
<td>77 (17)</td>
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<td>10 (2)</td>
<td>15 (3)</td>
<td>13 (3)</td>
<td>23 (5)</td>
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</tbody>
</table>

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* Combined incidence of cardiovascular, cerebrovascular, peripheral vascular, venous thromboembolism events; † EMA press release Nov 22, 2013; ‡ FDA drug safety communication, Oct 31, 2013

USPI = US package insert; SAE = AE reported as serious by the investigator, per standard criteria.
ABCDE Steps to Reduce CV Risk in Patients with CML

• A
  • Awareness of CV risks and signs
  • Aspirin in appropriate patients
  • Ankle-brachial Index (ABI) at baseline and f/u

• B
  • Blood pressure control

• C
  • Cigarette/tobacco cessation
  • Cholesterol monitoring and treatment

• D
  • Diabetes mellitus monitoring and treatment (Hgb A1c; fasting glucose)
  • Diet and weight control

• E
  • Exercise

Moslehi and Deininger, J Clin. Oncol. 2015 33: 4210-8
ABL001 is a potent, selective inhibitor of ABL1

- **Biochemistry**
  - Caliper ABL1 assay IC$_{50}$ – 0.4nM

- **Biophysics**
  - ITC ABL1 assay IC$_{50}$ – 0.7nM

- **Selectivity**
  - Kinase selectivity restricted to ABL1 and ABL2

- **Cardio-safety profile**
  - hERG assay >30uM
  - No evidence of QT prolongation in dog jacketed telemetry up to 600mg/kg

Wylie et al., ASH 2014, Abstract #398
Responses in Patients With CML Treated With Single-Agent BID ABL001 With ≥ 3 Months Exposure on Study

**Cytogenetic Response**
- Within 6 mo: CHR: 88% (14/16), CCyR: 75% (9/12)

**Molecular Response**
- Within 6 mo:
  - MMR: 20% (10/50), ≥ 1-log reduction: 30% (10/33)
- Within 12 mo:
  - MMR: 42% (16/38), ≥ 1-log reduction: 48% (12/25)

**Hematologic Response**
- CHR relapse: 88% (14/16)

**Cytogenetic Disease**
- (> 35% Ph+): 75% (9/12)

**Molecular Disease**
- (≤ 0.1% IS): 20% (10/50)
- (≤ 10% IS): ≥ 1-log reduction: 30% (10/33)

**Disease Status at Baseline**

Hughes T et al., ASH 2016, abstract 625

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CCyR, complete cytogenetic response; CHR, complete hematologic response; IS, International Scale; MMR, major molecular response.

* Patients had ≥ 6 months of treatment exposure or achieved response within 6 months.

* BCR-ABL1 reduction achieved.

* Patients had ≥ 12 months of treatment exposure or achieved response within 12 months.
Duration of Therapy: Is TKI Therapy Forever?

• Stop imatinib Trial (STIM)
  • RFS after discontinuation of imatinib, N=100
    • 6-mo: 45%, 12 mo: 43%, 24 mo: 41%

Chronic Myeloid Leukemia: Conclusions

• **Chronic Myeloid Leukemia**
  • Generic imatinib finally here
  • First line imatinib vs nilotinib vs dasatinib?
    • How to choose? Imatinib reasonable for low-risk Sokal CP-CML
    • Late side effects important (CV for nilotinib; pleural effusions for dasatinib)
    • Compliance still most important

• **Ponatinib**
  • T315I
  • Minimize CV risk factors
  • Third line therapy (US)

• **New Agents and ideas**
  • ABL001 in R/R CML
    • ABL001 Combination therapy
Questions & Answers