Myelodysplastic Syndromes

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1/2018

Objectives

- Basic concepts in MDS
- Molecular alterations
- Concept of clonal hematopoiesis
- Innate immune alterations in MDS
- Prognostic models
- Basic concepts therapy of MDS
- Investigational therapies
- Concept of HMA failure

Diagnosis of MDS is based on morphology

Cytogenetic alterations are common in MDS

Haase et al. Blood 2007;110:4385-95

Cause of death in MDS

Dayani et al. Cause of death in lower risk MDS. Cancer 2010;116:2174-9

Blasts versus Cytogenetics in the Prognosis of MDS

Figure 1 A-D. Overall survival and cumulative risk of AML transformation in IPSS cytogenetic and FAB bone marrow blast count subgroups (elatinate analysis, pts. treated with supportive care exclusively)

<table>
<thead>
<tr>
<th>Category</th>
<th>OS (months)</th>
<th>OS (in)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poor (IPSS)</td>
<td>7.5</td>
<td>1.2</td>
</tr>
<tr>
<td>Complex (non 5/7)</td>
<td>7.4</td>
<td>1.2</td>
</tr>
<tr>
<td>Complex (5/7)</td>
<td>6.6</td>
<td>1.4</td>
</tr>
<tr>
<td>Blast (21-30%)</td>
<td>7.4</td>
<td>1.3</td>
</tr>
</tbody>
</table>

(Schanz et al., JCO, 2011)
Cytogenetic Scoring System in MDS

Identification of RPS14 as the del5q gene

- RNA interference (RNAi) to interrogate 41 genes in the 5q-deleted region
- Introduction of 3-5 unique lentivirally expressed short hairpin RNAs targeting each of the 41 genes into normal CD34+ human progenitor cells
- Knockdown of RPS14 → block of erythroid differentiation
- Forced expression of RPS14 cDNA in BM cells of patients with 5q-syndrome → phenotype rescue
- Haploinsufficiency of RPS14 → block in processing of preribosomal RNA and formation of 40S ribosome units; analogous to Diamond-Blackfan Anemia

Point Mutations in MDS

Assocations With Clinical Features

Independent Predictors of Overall Survival

Mutational Frequency

Somatic mutations in 18 genes were identified.

51% of samples had at least one mutation ... 

... including 52% of cases with a normal karyotype.
**Somatic Mutations in MDS Are Associated with Clinical Features and Predict Prognosis Independent of the IPSS-R**

**Bejar et al. ASH 2015 abstract 907**

Analysis of Combined Datasets from the International Working Group for MDS-Molecular Prognosis Committee

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**Mutation Frequency and Distribution**

**Genomics of MDS**

Beird Boidol & Bennett Caughey

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**Overall Survival by Mutation Number**

17 genes sequenced in 1996 patients with OS data

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**Mutated Genes and Clinical Phenotypes**

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**Year Overall Survival (% )**

0 2 4 6 8 10 12 14

0

10

20

30

40

50

60

70

80

90

100

5

10

15

20

25

30

35

40

45

50

55

60

65

70

75

80

85

90

95

100

**Number of Mutated Genes**

---

**Gene**

- ASXL1
- CBL
- DNMT3A
- ETV6
- EZH2
- IDH1
- IDH2
- JAK2
- KRAF
- NPM1
- NRAS
- RUNX1
- SF3B1
- TET2
- TP53
- U2AF1
- ZRSR2

**Overall Survival (%)**

---

**Gene**

- CBL
- SF3B1

---

**Gene**

- ASXL1
- CBL
- DNMT3A
- ETV6
- EZH2
- IDH1
- IDH2
- JAK2
- KRAF
- NPM1
- NRAS
- RUNX1
- SF3B1
- TET2
- TP53
- U2AF1
- ZRSR2

---

**Gene**

- CBL
- SF3B1

---

**Gene**

- CBL
- SF3B1

---

**Gene**

- CBL
- SF3B1

---

**Gene**

- CBL
- SF3B1

---

**Gene**

- CBL
- SF3B1

---

**Gene**

- CBL
- SF3B1

---

**Gene**

- CBL
- SF3B1

---

**Gene**

- CBL
- SF3B1

---

**Gene**

- CBL
- SF3B1

---

**Gene**

- CBL
- SF3B1

---

**Gene**

- CBL
- SF3B1

---

**Gene**

- CBL
- SF3B1

---

**Gene**

- CBL
- SF3B1
**Flt3 alterations in MDS**

Daver et al. AJH 2013

**Effect of acquisition of Flt3 or Ras mutations in MDS**

Koichi Takahashi

**Cytogenetic acquisition in MDS**

Jabbour. ASH 2011 abstract 3802

**Effect of cytogenetic acquisition in MDS**

Jabbour. ASH 2011 abstract 3802

**Hypothesis #5: identification of drivers of transformation**

**Somatic Mutations in “Normal” Individuals**

Clonal Hematopoiesis and Atherosclerosis

Can we predict development of therapy related MDS?


Clonal hematopoiesis increases the risk of therapy-related myeloid neoplasms

Koichi Takahashi1,2, Feng Wang2, Hagop Kantarjian1, Donella Doss1, Kanhai Khanna2, Erika Thompson3, Kayor Patel2, Sattava Nekyla2, Curtis Gumbs2, Carlos Bueno-Ramos2, Courtney B. Dillardo1, Simone Caffa3, Farhad Raswandi1, Song Xingzhi2, Jinfeng Wu2, Felipe Samaniego2, Guillermo García-Manero4, and P. Andrew Futreal2

Department of 1Leukemia, 2Genomic Medicine, 3Genetics, 4Hematopathology, 5Lymphoma and Myeloma, and 6Epidemiology, MD Anderson Cancer Center, Houston, TX

Abstract #38

Takahashi et al. Lancet Oncology 2016
Padron et al. Lancet Oncology 2016

Clonal hematopoiesis increases risk of t-MNs

CI of t-MN at 10 years: 29% (95% CI: 8-53%) vs. 0% (95% CI: 0-0%)

Practical use of NGS in MDS

<table>
<thead>
<tr>
<th>Gene</th>
<th>Implication</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHIP/CCUS (DNMT3A, TET2,ASXL1, JAK2, SF3B1, P53, PPMID1)</td>
<td>Observation Increased risk of T-MN</td>
</tr>
<tr>
<td>PS3</td>
<td>Favor HMA</td>
</tr>
<tr>
<td>Poor outcome alloSCT</td>
<td></td>
</tr>
<tr>
<td>FLT3</td>
<td>At HMA failure</td>
</tr>
<tr>
<td>IDH-2</td>
<td>Consider IDH2 inhibitor</td>
</tr>
<tr>
<td>IDH-1</td>
<td>Consider clinical trial</td>
</tr>
<tr>
<td>NPM1</td>
<td>Consider ARA-C based therapy</td>
</tr>
<tr>
<td>RAS</td>
<td>At HMA failure</td>
</tr>
<tr>
<td>Consider clinical trial</td>
<td></td>
</tr>
<tr>
<td>≥3 mutations</td>
<td>Poor prognosis</td>
</tr>
</tbody>
</table>

14 t-MN cases

14 t-MNs patients with paired samples

Primary cancer (e.g. Lung cancer)

Chemotherapy/XRT

"x" years

32 gene molecular barcode seq (Haloplex HS, Agilent)

Detectable in PB?

295 gene capture seq

Driver mutations
Overexpression of Other Innate Immunity Like Signaling Components in MDS BM CD34+ (non-CHIP-Seq identified)

Genes examined in MDS BM CD34+ cells
TLR1, 2, 4, 6, 7, 8, MYD88, IL-8

expression level in primary MDS BM CD34+ cells

Genes showing potential prognostic value
TLR1 and MYD88 expression levels negatively associate with overall survival (OS) in MDS patients

TLR2 Stimulation Activates Histone Demethylase JMJD3

De Santa F et al Cell 2007

JMJD3 is Overexpressed in MDS CD34+ Cells

Innate Immunity Genes & Patient Response to Epigenetic Targeting Drugs

SAHA/ AZA

Yang H et al

TLR6

CSAR1

FPR1

FPR2

TYROBP

Immune Dysregulation in MDS

Tumor Immune Evasion Mechanisms:
1. Inhibitory B7 expression by tumor, APC and stroma cells.
2. APC
3. Treg.

Prognostic models

• IPSS
• WPSS
• Global MDACC model
• MDACC lower risk model
• Impact of comorbidities
• New “revised IPSS”
1999-2003: Survival by # Blasts

Revised IPSS

<table>
<thead>
<tr>
<th>Prognostic variable</th>
<th>0</th>
<th>0.5</th>
<th>1</th>
<th>1.5</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytogenetics</td>
<td>Very good</td>
<td>Good</td>
<td>Intermediate</td>
<td>Poor</td>
<td>Very poor</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BM blast, %</td>
<td>≤ 2</td>
<td>&gt; 2% - 5%</td>
<td>5%-10%</td>
<td>&gt; 10%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>≥ 10</td>
<td>8% - &lt; 10</td>
<td>&lt; 8</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Platelets</td>
<td>&gt; 50</td>
<td>50 - 100</td>
<td>&lt; 50</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ANC</td>
<td>≥ 0.8</td>
<td>&lt; 0.8</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Greenberg et al. Blood 2012;120:2454-65

Proposed treatment algorithm for patients with MDS

MDS-004: randomized phase III of lenalidomide in lower risk del5q MDS

Efficacy

<table>
<thead>
<tr>
<th>Efficacy</th>
<th>PBO</th>
<th>LEN 5</th>
<th>LEN 10</th>
</tr>
</thead>
<tbody>
<tr>
<td>RBC-Ti ≥ 26 weeks (N, %)</td>
<td>3 (6)</td>
<td>19 (41)</td>
<td>23 (56)</td>
</tr>
<tr>
<td>IWG-Ti (N, %)</td>
<td>4 (8)</td>
<td>23 (50)</td>
<td>25 (61)</td>
</tr>
<tr>
<td>Median t to response (weeks)</td>
<td>0.3 (0.3-2.4)</td>
<td>3.3 (0.3-12.3)</td>
<td>4.3 (0.3-14.7)</td>
</tr>
<tr>
<td>Median Hgb</td>
<td>2.3</td>
<td>5.1</td>
<td>6.3</td>
</tr>
<tr>
<td>CGCR+PCGR</td>
<td>0</td>
<td>8 (17)</td>
<td>17 (41)</td>
</tr>
</tbody>
</table>

Results: AML-Free Survival by CyR in Patients With Isolated del(5q) and del(5q) + 1 Additional Abnormality

For the risk of AML transformation or death, CyR was associated with a 91% reduction (95% CI 0.17-0.66; P < 0.001) in patients with isolated del(5q) and a 59% reduction (95% CI 0.17-0.83; P = 0.0259) in patients with del(5q) + 1 additional abnormality, compared with no CyR.


### 5-azacitidine: alternative dosing

Phase II, prospective, multicenter, randomized, open-label, 3-arm trial

**Screening**

<table>
<thead>
<tr>
<th>Cycle 1-6</th>
</tr>
</thead>
<tbody>
<tr>
<td>AZA 5-2-2 75 mg/m² SC</td>
</tr>
<tr>
<td>AZA 5-2-5 50 mg/m² SC</td>
</tr>
<tr>
<td>AZA 5 75 mg/m² SC q 28 or 42 days</td>
</tr>
</tbody>
</table>

**Day -21 to -1**

<table>
<thead>
<tr>
<th>Initial Randomization</th>
<th>Repeat cycle every 28 days</th>
</tr>
</thead>
<tbody>
<tr>
<td>AZA 5</td>
<td>Maintenance Randomization</td>
</tr>
</tbody>
</table>

Lyons R. JCO 2009;11:223-32

### Hematologic Improvement

- Erythroid Major
- Platelet Major
- Neutrophil Major
- Any HI*

*Pts counted only once for best response in an improvement category
†Minor improvement at top of HI columns

### A Randomized Phase II Study of Low-Dose Decitabine versus Azacitidine in Patients with Low- or Intermediate-1-Risk Myelodysplastic Syndromes: A Report on Behalf of the MDS Clinical Research Consortium

Jabbour E1, Short N1, Huang X1, Matti A1, Kadia T1, Daver N1, Borthakur G1, DiNardo C1, Pemmaraju N1, Sasaki K1, Estrov Z1, Verstovsek S1, Ravanandi F1, Alvarado Y1, Sekeres MA1, Komrokji RR1, Steensma D1, DeZern A1, Roboz G1, Kadia T1, Borthakur G1, DiNardo C1, Miller D1, Dong X1, Kantarjian H1, Garcia-Manero G1

(Blood 2017)

1The University of Texas MD Anderson Cancer Center, Houston, TX; 2Cleveland Clinic, Cleveland, OH; 3Moffitt Cancer Center, Tampa, FL; 4Dana-Farber Cancer Institute, Boston, MA; 5Johns Hopkins University, Baltimore, MD; 6Cornell Medical College, New York, NY

### DAC vs. AZA in LR-MDS. Treatment

- Bayesian adaptive randomization: DAC vs. AZA
- Regimens:
  - DAC 20 mg/m² IV D1-3 every 4 weeks
  - AZA 75 mg/m² IV/SC D1-3 every 4 weeks
- Response assessment by modified IWG 2006
- Between 11/2012 and 2/2016, 113 pts with LR-MDS treated:
  - DAC, n=73
  - AZA, n=40
- Median duration of follow-up = 20 months (range: 2-43 months)

### DAC vs. AZA in LR-MDS. Response (IWG)

<table>
<thead>
<tr>
<th>Response</th>
<th>DAC (N=70) n (%)</th>
<th>AZA (N=39) n (%)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>26 (37)</td>
<td>14 (36)</td>
<td>0.90</td>
</tr>
<tr>
<td>mCR</td>
<td>6 (9)</td>
<td>2 (5)</td>
<td></td>
</tr>
<tr>
<td>HI</td>
<td>17 (24)</td>
<td>3 (8)</td>
<td></td>
</tr>
<tr>
<td>ORR</td>
<td>49 (70)</td>
<td>19 (49)</td>
<td>0.03</td>
</tr>
<tr>
<td>SD</td>
<td>18 (26)</td>
<td>17 (44)</td>
<td></td>
</tr>
<tr>
<td>PD</td>
<td>3 (4)</td>
<td>3 (8)</td>
<td></td>
</tr>
</tbody>
</table>

Median number of cycles: 9 (range: 1-41)

### DAC vs. AZA in LR-MDS. OS

- OS
- Median (OS)
- 1-year (OS)

DAC vs. AZA in LR-MDS.

- DAC 73 not reached
- AZA 40 not reached
- OS 87%
- OS 83%
- OS 87%
**LR MDS post HMA Failure. Outcome**

- Median follow-up: 16 (1-80) months
- Median TFS and OS: 15 and 17 months

Jabbour et al; abstract #388

**Monte Carlo – Low/int-1 IPSS Survival Estimates**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>HMA</th>
<th>Intensive Chemo Rx</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>-% CR + CRp</td>
<td>42</td>
<td>60</td>
<td>.01</td>
</tr>
<tr>
<td>-Median Rem. dur. (mos)</td>
<td>14.7</td>
<td>14.7</td>
<td></td>
</tr>
<tr>
<td>-%8-wk mortality</td>
<td>10</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>-median OS (mos)</td>
<td>18.8</td>
<td>14.6</td>
<td>.32</td>
</tr>
</tbody>
</table>

**Hypomethylators vs Intensive Chemo Rx in MDS with 10-30% Blasts**

- 330 pts: 93 (28%) Rx with HMA and 237 (72%) with chemo Rx
- MVA: worse survival with chemo Rx


**Decitabine vs. Intensive Chemotherapy—Survival**

- Trial Fall

- Decitabine: Trial 13 Fall 13
- Intensive Chemo: Trial 114 Fall 20

- p < .0001

**Proposed treatment algorithm for patients with MDS**

- **Low-risk** (IPSS low, INT-1) (BM blasts < 10%)
  - Age < 60
    - Intensive chemotherapy
    - MTI (5-AZA/decitabine)
    - Clinical trial
  - Age ≥ 60
    - MTI (5-AZA/decitabine)
    - Clinical trial
    - Intensive chemotherapy
- **High-risk** (IPSS INT-2, High) (BM blasts > 10%)
  - Consider younger patients with diploid cytogenetics
  - Consider earlier in younger patients

Atallah. Cancer Inv. 2008:26:208-16

**A Decision Analysis of RIC Allogeneic HSCT for Older Patients with De-Novo MDS: Early Transplantation Offers Survival Benefit in Higher-Risk MDS**

CIBMTR Study #LK08-02

COI Disclosures per ASH
Overall Survival: Azacitidine vs CCR
ITT Population
Log-Rank p=0.0001
HR = 0.58 [95% CI: 0.43, 0.77]
Deaths: AZA = 82, CCR = 113
Difference: 9.4 months

Hazard Ratio and 95% CI for Overall Survival

ITT Subgroups

Total-Event N
RAEB & RAEB-T: AGE = 55
AZA = 150, CCR = 249
p = 0.001

RAEB
AZA = 180, CCR = 258
p = 0.006

RAEB-T
AZA = 150, CCR = 251
p = 0.05

Fenaux et al. Lancet Oncology 2010

Times to First Response with 5-azacitidine

Cumulative Probability
Time (cycles)

Silverman et al. ASH abstr 2020, 2005

CCyR in MDS. OS by CyR

* Median OS for patients with and without CCyR: 20 and 12 months (p=0.01)
Jabbour et al; abstract #2801

TP53 mutation effect on HMA therapy in MDS

Takahashi et al. ASH abstract #1663; Takahashi et al: Oncotarget, in press

Outcome in MDS post hypomethylating failure

Disease status after decitabine Total: Dead
MDS 62 50
AML 23 15
Total 85 65

p = 0.29

Takahashi et al. ASH abstract #1663; Takahashi et al: Oncotarget, in press
Successful Emulation of IV Decitabine Pharmacokinetics with an Oral Fixed-Dose Combination of the Oral Cytidine Deaminase Inhibitor (CDAI) E7727 with Oral Decitabine, in Subjects with Myelodysplastic Syndromes (MDS): Final Data of Phase 1 Study

On Behalf of the ASTX727 Investigative Team

Guillermo Garcia-Manero1, Ohatayoshi Odente2, Philip Amrhein3, David P Steensma4, Amy DeZern1, Laura C Michaelis2, Stefan Faderl1, Haqoo Kantarjian1, James N Lowder2, Pietro Taverna2, Aram Oganesian2, Xiaoping Zhang2, Mohammad Azab2, and Michael R Savona2.

MD Anderson Cancer Center1, University of Chicago1, Massachusetts General Hospital5, Dana-Farber Cancer Institute1, Johns Hopkins University Hospital1, Medical College of Wisconsin/Froedtert3, Hackenack University Medical Center1, Astex Pharmaceuticals2, Vanderbill Ingram Cancer Center, Vanderbilt University Medical Center2.

4/23/2018

ASTX727 Phase 1 Results
5 Days total DAC AUC: Oral/IV

<table>
<thead>
<tr>
<th>Cohort</th>
<th>DAC (mg)</th>
<th>E7727</th>
<th>N</th>
<th>Oral AUC-IV</th>
<th>Oral AUC</th>
<th>Oral (IV)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>20</td>
<td>40</td>
<td>5</td>
<td>260</td>
<td>753</td>
<td>35%</td>
</tr>
<tr>
<td>2</td>
<td>20</td>
<td>60</td>
<td>6</td>
<td>346</td>
<td>899</td>
<td>39%</td>
</tr>
<tr>
<td>3</td>
<td>20</td>
<td>100</td>
<td>6</td>
<td>482</td>
<td>992</td>
<td>49%</td>
</tr>
<tr>
<td>4</td>
<td>40</td>
<td>100</td>
<td>6</td>
<td>1120</td>
<td>775</td>
<td>144%</td>
</tr>
<tr>
<td>5</td>
<td>30</td>
<td>100</td>
<td>19</td>
<td>701</td>
<td>852</td>
<td>85%</td>
</tr>
</tbody>
</table>

1 DAC oral dose not adjusted by Weight or BSA
2 One significant outlier excluded from the PK analysis

• Cohort 4 Oral DAC (at 40 mg) exposure achieved primary objective and exceeded that of IV DAC at 20 mg/m² (Oral/IV 144%)
• Cohort 5 Oral DAC (at 30 mg) exposure was 85% of IV DAC at 20 mg/m²
• Oral DAC dose of 35 mg in ASTX727 (Ongoing Phase 2) should achieve AUC of ~85-140% of IV DAC

Early intervention in LR MDS
(US North American MDS Consortium)

Transfusion dependent

AZA x 3 days
Dac X 3 days
AZAX 5 days

Transfusion independent

Observation

NCT02269280. Funded Edward P Evans Foundation
Cleveland Clinic: M. Sekeres; Dana Farber Cancer Center: D. Steensma; Johns Hopkins: A. DeZern; MDAnderson: Garcia-Manero; Moffitt Cancer Center: R. Komrokji; Weill-Cornell: G Roboz

Ongoing trials of immune checkpoint blockade in acute myeloid leukemia.

<table>
<thead>
<tr>
<th>Type</th>
<th>Therapy</th>
<th>Phase</th>
<th>Primary Disease</th>
<th>Exclusion</th>
<th>ID</th>
<th>NCT Number</th>
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</thead>
<tbody>
<tr>
<td>Phase I</td>
<td>gemcitabine</td>
<td>1</td>
<td>MDS, AML</td>
<td>No prior chemotherapy, prior ARA-MD</td>
<td>1</td>
<td>02215313</td>
</tr>
<tr>
<td>Phase I</td>
<td>gemcitabine + nivolumab</td>
<td>1</td>
<td>MDS, AML</td>
<td>No prior chemotherapy, prior ARA-MD</td>
<td>1</td>
<td>02215313</td>
</tr>
<tr>
<td>Phase I</td>
<td>nivolumab + ruxolitinib</td>
<td>1</td>
<td>MDS, AML</td>
<td>No prior chemotherapy, prior ARA-MD</td>
<td>1</td>
<td>02215313</td>
</tr>
<tr>
<td>Phase I</td>
<td>azacitidine + lenalidomide</td>
<td>1</td>
<td>MDS, AML</td>
<td>No prior chemotherapy, prior ARA-MD</td>
<td>1</td>
<td>02215313</td>
</tr>
<tr>
<td>Phase I</td>
<td>l-ascorbic acid + temsirolimus</td>
<td>1</td>
<td>MDS, AML</td>
<td>No prior chemotherapy, prior ARA-MD</td>
<td>1</td>
<td>02215313</td>
</tr>
<tr>
<td>Phase I</td>
<td>lenalidomide + ruxolitinib</td>
<td>1</td>
<td>MDS, AML</td>
<td>No prior chemotherapy, prior ARA-MD</td>
<td>1</td>
<td>02215313</td>
</tr>
<tr>
<td>Phase I</td>
<td>ruxolitinib + lenalidomide</td>
<td>1</td>
<td>MDS, AML</td>
<td>No prior chemotherapy, prior ARA-MD</td>
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<td>02215313</td>
</tr>
<tr>
<td>Phase I</td>
<td>lenalidomide + rasburicase</td>
<td>1</td>
<td>MDS, AML</td>
<td>No prior chemotherapy, prior ARA-MD</td>
<td>1</td>
<td>02215313</td>
</tr>
<tr>
<td>Phase I</td>
<td>aurothioglucose + lenalidomide</td>
<td>1</td>
<td>MDS, AML</td>
<td>No prior chemotherapy, prior ARA-MD</td>
<td>1</td>
<td>02215313</td>
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</table>

11

FLT3 Inhibitors Under Development

<table>
<thead>
<tr>
<th>Preclinical Phase I</th>
<th>Phase II</th>
<th>Phase III</th>
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<tbody>
<tr>
<td>VX-322</td>
<td>IMC-EB10</td>
<td>Sorafenib</td>
</tr>
<tr>
<td>VX-398</td>
<td>KW-2449</td>
<td>MLN-518</td>
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<tr>
<td>MC-2002</td>
<td>AP-24534</td>
<td>Quizartinib</td>
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<td>MC-2006</td>
<td>CHIR-258</td>
<td>Crenolanib</td>
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<tr>
<td>PLX3397</td>
<td>FLX925</td>
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</table>

Al-Atrash, Daver et al. Pharm Reviews, 2010
Enasidenib (AG-221), a Potent Oral Inhibitor of Mutant Isocitrate Dehydrogenase 2 (IDH2) Enzyme, Induces Hematologic Responses in Patients with Myelodysplastic Syndromes (MDS)

Eytan M. Stein, Amir T. Fathi, Courtney D. DiNardo, Daniel A. Pollyea, Ronan T. Swords, Gail J. Roboz, Robert Collins, Mikkael A. Sekeres, Richard M. Stone, Eyal Attar, Alessandra Tosolini, Qiang Xu, Michael Amatangelo, Ira Gupta, Robert D. Knight, Stéphane De Botton, Marin S. Talman, and Hagop M. Kantarjian

Venetoxclax (ABT-199)+DAC/AZA in AML

- 22 pts with new Dx AML, median age 74 (65-85)
- VEN 400-800 mg/D + DAC/AZA

<table>
<thead>
<tr>
<th>Therapy</th>
<th>No</th>
<th>Responses</th>
</tr>
</thead>
<tbody>
<tr>
<td>VEN + DAC</td>
<td>12</td>
<td>7CR, 1CRi, 1PR =75%</td>
</tr>
<tr>
<td>VEN + AZA</td>
<td>10</td>
<td>3 CR, 3 CRi, 1 PR = 70%</td>
</tr>
<tr>
<td>TOTAL</td>
<td>22</td>
<td>10 CR + 4 CRi</td>
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</tbody>
</table>

Overall response 16/22 =73%

SF3B1 mutations in MDS


Conclusion and needs

- Increased role of genomic annotation in MDS
- New targets: CD33, CD123, Bcl-2, TGF-b, TLR, SF3B1,IDH, Flt-3, NPM1
- Lower dose HMAs for lower risk MDS
- Potent oral forms of HMAs: CC-486, ASTX727
- Second generation HMAs: SGI-110
- Combinations: + PD1/PDL1 inhibitors
- 3 ongoing Phase III trials: CC-486, Rigosertib, ACE-536
- Need: p53, RAS, transplant integration

Thank you very much

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