Genetic changes in MDS
Spectrum of MDS

Asymptomatic, IPSS low
- BM function
- Differentiation
- Apoptosis

Symptomatic, IPSS Int-2/High Risk
- Transfusion
- Proliferation and Blasts

Proliferation and Blasts

IPSS

Gross genomic changes are detected by cytogenetics
MDS cytogenetic studies

MDS

- Normal (1727) 45%
- Complex + -5/-7 (627) 17%
- +8 (203) 5%
- Isolated -7/7q (222) 5%
- 5q- + 1 Abn (173) 6%
- Other complex (195) 5%
- Isolated 20q- (69) 2%
- Other not complex (475) 17%

n = 3860

Haase D. et al 2007
Mutations alter proteins

Small genetic changes can only be detected at the molecular level.

Met Lys Leu His His Trp Lys Phe Asp *
ATG AAG TTA CAT CAT TGG AAA TTT GAT TGA

ATG AAG TTA CAT GAT TGA AAA TTT GAT TGA
Met Lys Leu His Asp * Lys Phe Asp *
Point Mutations in MDS

Tyrosine Kinase Pathway
- JAK2
- KRAS
- NRAS
- BRAF
- RTK’s
- PTPN11
- CBL

Transcription Factors
- RUNX1
- ETV6
- GATA2
- WT1
- PHF6
- EP300

Others
- TP53
- NPM1
- NPM1
- GNAT/GNB1
- BCOR
- RNA helicases
- Cohesins

Epigenetic Dysregulation
- IDH 1 & 2
- DNMT3A
- EZH2
- TET2
- UTX
- ASXL1
- ATRX
- ATRX

Splicing Factors
- SF3B1
- U2AF1
- ZRSF2
- SF1
- SF1
- SF1
- PRPF8
- PRPF40B
- PRPF40B
- SF3A1
- SF3A1
Many mutations are very rare

Only 5 genes are mutated in >10% of patients

Target present on the KCH panel
# KCH: Myeloid Gene Panel (MGP)

## 24 genes mutations panel:

<table>
<thead>
<tr>
<th>Transcripton factors and cell cycle regulators</th>
<th>Spliceosome component</th>
<th>Epigenetic modification s</th>
<th>Signaling</th>
<th>Cohesin complex</th>
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<tbody>
<tr>
<td>RUNX1</td>
<td>SF3B1</td>
<td>TET2</td>
<td>NRAS</td>
<td>STAG2</td>
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<tr>
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<td>U2AF1</td>
<td>IDH1</td>
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<td>NPM1</td>
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<td>ASXL1</td>
<td>KIT</td>
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</table>

Research use only: clinical importance is yet to be determined
• Integrating genomic analysis into diagnostic, prognostic and therapeutic systems for patients.
Lenalidomide (Revlimid)

$TP53^{\text{mut}}$ do not achieve complete cytogenetic response in del5q MDS \textit{(Jadersten JCO, Austin Kulasekararaj BJH)}

5’Azacytidine (Vidaza)

- $TET2^{\text{mut}}$ may respond better
- $TET2^{\text{mut}}$ and $DNMT3A^{\text{mut}}$ may respond better
- $ASXL1$ and $SF3B1$ status also modulate response
Finally

• Genetic testing is more widely available:
  – Cheaper, simpler, faster
• Mutations help in the certainty of diagnosis.
• Incorporation into prognostic models such as IPSS
• The era of biomarker-based therapy may not be too distant
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