Precision Medicine and Molecular Testing.

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Disclosures

• Research funding for Celgene
• Speaker’s Bureau for Celgene
Learning Objectives

• To understand the major molecular testing assays which are utilized in precision oncology

• To explore the utility of molecular testing, predominantly NGS, in myeloid malignancies with regards to prognosis and treatment selection.
Molecular Assays

- Cytogenetics (routinely performed on bone marrow biopsies in patient’s with heme malignancy, moderate turn around time; requires dividing cells)
- FISH (most commonly utilized to evaluate for fusion genes; e.g. BCR-ABL1 in CML, rapid turn around, does not require dividing cells)
- PCR (specific mutation testing, great for hotspot/recurring mutations)
- NGS (mutation testing for large panels of genes; slow turn around (although improving))
Molecular Assays - Sensitivities

• Cytogenetics - ~ 10% (e.g. 2/20 cells)
• FISH – around 5% (can have false positives below this range)
• PCR (can be as low as .00001%, frequent 0.1%-1%)
• NGS – variant allele frequency (clinical labs usual cutoff is 5%, can be as low as 2-3%; high sensitivity NGS assays can get to 0.1%)

PCR and NGS assays being increasingly incorporated for serial NGS to evaluate depth of remission and resistance mechanisms
Cytogenetics
FISH (fluorescent in situ hybridization)
FISH (evaluation of fusion)
Break Apart FISH (e.g ALK in lung ca)

Murakami et al., Frontiers, 2012
PCR testing (e.g. BRAF)

- The activating V600E mutation in exon 15 of the v-raf murine sarcoma viral oncogene homolog B1 gene (BRAF) on human chromosome 7q34 is present in approximately
  - 40% to 60% of advanced melanomas
  - 40% to 80% of papillary thyroid cancers
  - 50% of CRCs exhibiting Mut L homologue-1 (MLH1)-associated microsatellite instability.
ddPCR vs qPCR
PCR Testing (e.g. BRAF for melanoma)

Bidshahri, R et al., 2016; The journal of molecular diagnostics
Ability to test mutations for solid cancer by peripheral blood (via identifying circulating tumor DNA)

- Example of T790M which is gatekeeper mutation leading to EGFR resistance (indication for osimertinib in lung cancer)
- Ideal for rare variants (can identify .01% allele frequency, likely lower)
- Droplet digital PCR (ddPCR) is more sensitive than standard qPCR
Digital droplet PCR in lung cancer

dPCR(tumor testing, new diagnosis)
• EGFR p.L858R (43% of EGFR mutations in lung cancer)
• EGFR exon 19 deletion (48% of EGFR mutations)
dPCR(liquid biopsy, progression or new diagnosis)
• EGFR p.L858R/EGFR exon 19 deletion (to determine if ctDNA is present)
• EGFR p.T790M (to assess for secondary resistance)
Many other mutations with potential future clinical value given they can be targeted (e.g. MET, FGFR1, ERBB2, RET)
Critical Testing (not all inclusive)

- Melanoma
  - BRAF V600
- GIST
  - KIT, PDGFRA
- Colon Cancer
  - KRAS, NRAS, BRAF, MSI
- Acute myeloid leukemia
  - NPM1, FLT3 ITD/TKD, CEBPA, IDH 1/2
- Lung Cancer (any adenocarcinoma, < 50, non-smoker)
  - testing for HER-2, ALK, ROS and EGFR mutations

http://cancergeneticslab.ca/
Compendium diagnostics are frequently PCR based assays

- BRAF (as above for vemurafenib/dabrafenib)
- EGFR (multiple agents)
  - Exception ALK and ROS1 (multiple agents; FISH gold standard although there are PCR based assays)
- IDH2 mutation (for enasidenib)
- FLT3 ITD (for midostaurin)
- BCR-ABL (FISH or PCR; multiple agents)
More than one way to test for each mutation

Murakami et al., Frontiers, 2012
Next generation sequencing (NGS)

- Next Generation Sequencing (NGS) or Massively Parallel Sequencing encompasses class of new sequencing technologies that offers inexpensive sequencing of large regions.
- NGS can be used in ‘cancer panels’ to identify clinically important genes mutated in common cancer types.
- NGS may also be used to detect chromosomal rearrangements, gains, and losses (i.e. may replace testing such as cytogenetics in the future).
Next-generation Sequencing

A

Genomic DNA for sequencing
Fragmented DNA
Fragmented DNA with sequencing adaptors
DNA is attached to a bead, or immobilised directly on sequencing slide
Clonal amplification of DNA on beads or sequencing slide
Beads immobilised on slide
Sequencing

B

DNA synthesis incorporates fluorescently labeled nucleotides
Fluorophore cleaved
Cyclical synthesis, with imaging of each fluorophore in turn
Many molecules sequenced in parallel by imaging cyclical synthesis on a sequencing slide

C

Each sequence fragment is bioinformatically aligned to the genome, and potential sequence variants identified. Here we see a possible heterozygous A>T single nucleotide polymorphism
Deeper NGS (molecular barcoding)

A 1. Digest and denature sample DNA
Target Region

2. Hybridize probe library to DNA targets

3. Ligate and capture uniquely barcoded targets

4. Amplify enriched fragments by PCR

B 1. I2
Molecular barcode, 10 nt

R1
Vector sequence, 1 nt

I1

R2
Sample barcode, 8 nt

Illumina

Ion PGM

Molecular barcode, 10 nt

IonXpress barcode

Vector sequence, 15 nt
Cost of Sequencing

Sequencing Cost per MegaBase

Currently $1,000 to sequence genome
Price will be $250 within 12 months

Source: genome.gov/sequencingcosts
Whole Genome
3x10^9 bp

Exome
5x10^7 bp

Clinical Cancer Panel
5x10^5 bp

* Not to scale

accc-cancer.org/resources
Oncopanel

• 98% sensitivity and 100% specificity for the detection of single-nucleotide variants.

• 84% sensitivity and 100% specificity for the detection of insertions and deletions compared with single-gene assays and mass spectrometry-based genotyping.

• Copy number detection achieved 86% sensitivity and 98% specificity compared with array comparative genomic hybridization.

• The sensitivity of structural variant detection was 74% compared with karyotype, fluorescence in situ hybridization, and polymerase chain reaction.

Garcia et al., Arch Pathol Lab Med. 2017
Guiding Future Clinical Trials

- 22% of patients with actionable mutation
- 8% were enrolled with matched drug (similar to ongoing NCI-MATCH trial; SAFIR01 [NCT01414933], MOSCATO01 and -02 trials [NCT01566019], SHIVA [NCT01771458], PROFILER [NCT01774409], the EORTC SPECTA initiatives)
Guiding Future Clinical Trials

Table 1 Characteristic of patient entering into Phase I with matched therapy

<table>
<thead>
<tr>
<th>No.</th>
<th>Cancer type</th>
<th>Molecular alteration</th>
<th>Matched therapy</th>
<th>Response</th>
<th>Progression free survival (month)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Bile duct</td>
<td>FGFR2</td>
<td>FGFR inhibitor</td>
<td>PD</td>
<td>0.95</td>
</tr>
<tr>
<td>2</td>
<td>Cervical</td>
<td>PIK3CA E542K</td>
<td>PI3K inhibitor</td>
<td>NE</td>
<td>2.53</td>
</tr>
<tr>
<td>3</td>
<td>Liver</td>
<td>TSC1</td>
<td>mTOR inhibitor</td>
<td>NE</td>
<td>0.82</td>
</tr>
<tr>
<td>4</td>
<td>Breast</td>
<td>BRCA1</td>
<td>PARP inhibitor</td>
<td>PR</td>
<td>8.09</td>
</tr>
<tr>
<td>5</td>
<td>Peritoneal</td>
<td>BRCA1</td>
<td>PARP inhibitor</td>
<td>SD</td>
<td>7.17</td>
</tr>
<tr>
<td>6</td>
<td>Cervical</td>
<td>PIK3CA E542K</td>
<td>AKT inhibitor</td>
<td>PD</td>
<td>0.72</td>
</tr>
<tr>
<td>7</td>
<td>Breast</td>
<td>PIK3CA H1047R</td>
<td>PI3K inhibitor</td>
<td>PR</td>
<td>6.18</td>
</tr>
<tr>
<td>8</td>
<td>Breast</td>
<td>PIK3CA E545K</td>
<td>PI3K inhibitor</td>
<td>SD</td>
<td>2.80</td>
</tr>
<tr>
<td>9</td>
<td>Breast</td>
<td>PIK3CA E545V</td>
<td>PI3K inhibitor</td>
<td>SD</td>
<td>5.72</td>
</tr>
<tr>
<td>10</td>
<td>Breast</td>
<td>AKT1 E17K</td>
<td>AKT inhibitor</td>
<td>PR</td>
<td>14.1</td>
</tr>
<tr>
<td>11</td>
<td>Breast</td>
<td>BRCA1</td>
<td>PARP inhibitor</td>
<td>SD</td>
<td>5.53</td>
</tr>
</tbody>
</table>

*PD* progression disease, *SD* stable disease, *PR* partial response, *NE* not evaluable
Multi-gene Panels

- Multi-gene NGS panels can be performed at multiple companies including Foundation One, Genoptix and Neogenomics
- Turn around time is often around 2 weeks (vs PCR testing can be 3-5 days)
- Many have now been optimized on formalin-fixed
- paraffin-embedded (FFPE) samples (not an issue for AML/MDS, major issue in other malignancies if re-biopsy is not possible).
Tumor Boards

• We have a molecular tumor board that meets q 2 weeks for large NGS panel cases (e.g. Foundation One, Genoptix Nexcourse complete).
  – Also have specific tumor boards with molecular pathologist present
  – Many academic centers with similar setup given growing complexity
Getting help

- How many genes should you test for, what is the right panel for your patient???
- Reports with increasing clinical information but still complex
- Referral to tertiary centers
- Molecular interpretations services (e.g. Pierian Dx; PrecipoDx); virtual tumor boards
Clinical Utility of Molecular Testing in MDS and AML
Somatic Mutations in MDS

Genes Recurrently Mutated in MDS

Tyrosine Kinase Pathway
- JAK2
- KRAS
- BRAF
- NRAS
- RTKs
- PTPN11
- CBL

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

Others
- TP53
- NPM1
- NOTCH?
- MAML?
- ZSWIM4?
- UMODL1?
- BCOR

Epigenetic Dysregulation
- IDH 1 & 2
- DNMT3A
- EZH2
- TET2
- UTX
- ASXL1
- ATRX
- SETBP1

Splicing Factors
- SF3B1
- U2AF1
- ZRSF2
- U2AF2
- PRPF40B
- PRPF8
- SF1
- SRSF2
- SF3A1

Courtesy of Bejar R.
Spliceosome Mutations in MDS

Mutations in SF3B1 Define a Clinical Subgroup

Malcovati L, Blood 2015; Papaemmanuil E, NEJM 2011
SF3B1 VAF Correlates with % of Bone Marrow Ringed Sideroblasts
SF3B1 VAF Correlates with % of Bone Marrow Ringed Sideroblasts

Sallman D, Leukemia 2016.
NGS Impacts Diagnosis in MDS

≥ 15% ring sideroblasts

5-14% ring sideroblasts
### NGS Impacts Diagnosis in MDS

<table>
<thead>
<tr>
<th>WHO Category</th>
<th>Peripheral blood</th>
<th>Bone marrow</th>
</tr>
</thead>
<tbody>
<tr>
<td>MDS with single lineage dysplasia (MDS-SLD)</td>
<td>Cytopenia (1-2 lines)</td>
<td>Dysplasia (1 line)</td>
</tr>
<tr>
<td></td>
<td>&lt;1% blasts</td>
<td>&lt; 5% blasts</td>
</tr>
<tr>
<td></td>
<td></td>
<td>RS &lt;15%/≤5%†</td>
</tr>
<tr>
<td>MDS with ring sideroblasts (MDS-RS)*</td>
<td>Cytopenia (1-3 lines)</td>
<td>Dysplasia (1-3 lines)</td>
</tr>
<tr>
<td></td>
<td>&lt; 1% blasts</td>
<td>&lt; 5% blasts</td>
</tr>
<tr>
<td></td>
<td></td>
<td>RS &gt;15%&gt;5%†</td>
</tr>
<tr>
<td>MDS with multi-lineage dysplasia (MDS-MLD)</td>
<td>Cytopenia (1-3 lines)</td>
<td>Dysplasia (2-3 lines)</td>
</tr>
<tr>
<td></td>
<td>&lt; 1% blasts</td>
<td>&lt; 5% blasts</td>
</tr>
<tr>
<td></td>
<td></td>
<td>RS &lt;15%/≤5%†</td>
</tr>
<tr>
<td>MDS with excess blasts type I &amp; II (MDS-EB-1 &amp; MDS-EB-2**)</td>
<td>Cytopenia (0-3 lines)</td>
<td>Dysplasia (1-3 lines)</td>
</tr>
<tr>
<td></td>
<td>Type I: 2-4% blasts</td>
<td>Type I 5-9% blasts</td>
</tr>
<tr>
<td></td>
<td>Type II: 5-19% blasts</td>
<td>Type II 10-19% blasts</td>
</tr>
<tr>
<td>MDS with isolated del(5q)**</td>
<td>Cytopenia (1-2 lines)</td>
<td>Dysplasia (1-3 lines)</td>
</tr>
<tr>
<td></td>
<td>&lt; 1% blasts</td>
<td>&lt; 5% blasts</td>
</tr>
<tr>
<td>MDS unclassified ( MDS-U)****</td>
<td>Cytopenia (0-3 lines)</td>
<td>Dysplasia (1-3 lines)</td>
</tr>
<tr>
<td></td>
<td>1% or &lt; 1% blasts</td>
<td>&lt; 5% blasts</td>
</tr>
</tbody>
</table>

* Arber D et al., *Blood*; 2016
Somatic Mutations Predict Prognosis in MDS

Table 2. Hazard Ratios for Death in a Multivariable Model.

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age ≥55 yr vs. &lt;55 yr</td>
<td>1.81 (1.20–2.73)</td>
<td>0.004</td>
</tr>
<tr>
<td>IPSS risk group</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intermediate-1 vs. low</td>
<td>2.29 (1.69–3.11)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Intermediate-2 vs. low</td>
<td>3.45 (2.42–4.91)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>High vs. low</td>
<td>5.85 (3.63–9.40)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mutational status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TP53 mutation present vs. absent</td>
<td>2.48 (1.60–3.84)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>EZH2 mutation present vs. absent</td>
<td>2.13 (1.36–3.33)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ETV6 mutation present vs. absent</td>
<td>2.04 (1.08–3.86)</td>
<td>0.03</td>
</tr>
<tr>
<td>RUNX1 mutation present vs. absent</td>
<td>1.47 (1.01–2.15)</td>
<td>0.047</td>
</tr>
<tr>
<td>ASXL1 mutation present vs. absent</td>
<td>1.38 (1.00–1.89)</td>
<td>0.049</td>
</tr>
</tbody>
</table>

MDS sample data collected from 18 centers in Europe, the United States, and Asia

**Clinical Features**
- age and sex
- blast %
- karyotype
- hemoglobin
- platelet count
- neutrophil count

**Overall Survival Data:**
- available for 3359
- 3.6 years follow-up
- 1780 deaths
- median OS 2.65 years

**Gene Mutations**

Courtesy of Bejar R; IWG-PM
Overall Survival by Mutation Number

Papaemmanuil E, Blood 2015
IWG-PM, Bejar R
Prognosis of Mutations in MDS

Figure 2: Kaplan-Meier curve of overall survival in years for the 2504 patients with sequence results for SF3B1 and all six adverse genes (TP53, CBL, EZH2, RUNX1, U2AF1, and ASXL1).

Bejar et al., ASH 2015
Complex Karyotype and TP53 Mutation

<table>
<thead>
<tr>
<th>Three element model</th>
<th>Univariate</th>
<th>Multivariable</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR [95% CI]</td>
<td>p-value</td>
</tr>
<tr>
<td>Monosomal Yes vs. No</td>
<td>2.01 [1.48-2.74]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Number of Abnormalities 5+ vs. 3 or 4</td>
<td>2.33 [1.71-3.17]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TP53 Mutation vs. No mutation</td>
<td>2.55 [1.93-3.35]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>1.34 [0.95-1.89]</td>
<td>0.092</td>
</tr>
<tr>
<td></td>
<td>1.58 [1.11-2.25]</td>
<td>0.011</td>
</tr>
<tr>
<td></td>
<td>2.08 [1.56-2.77]</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Median Overall Survival:

- TP53 Mutated (N=169): 8.1 months
- TP53 Unmutated 5+ Abnl (N=75): 12.8 months
- Double Negatives (N=65): 34.3 months

Courtesy of Bejar R
TP53 VAF Strongly Correlates with Risk of Complex Cytogenetics

**Training Set (n=47)**

- TP53 VAF > 40%
  - Complex: 10 cases
  - Not Complex: 8 cases
  - P = 0.001

- TP53 VAF < 20%
  - Complex: 5 cases
  - Not Complex: 4 cases
  - P = 0.0003

**Validation Set (n=150)**

- TP53 VAF > 40%
  - Complex: 40 cases
  - Not Complex: 30 cases
  - P = 0.0002

- TP53 VAF < 20%
  - Complex: 25 cases
  - Not Complex: 20 cases
  - P = 0.0002

Number of Cytogenetic Abnormalities

Can We Predict Patients for TP53 Mutation

(A)

Chromosome 5 aberrations
N = 55

Isolated del5q
(19%, 5/26)

Complex karyotype with aberrations of chromosome 5
(72%, 21/29)

Aberrations of 5, 7 and 17
(100%, 4/4)

Aberration of 5 and 17
(80%, 4/5)

Aberration of 5 and 7
(73%, 11/15)

Aberration of 5 with other non 7 and 17
(40%, 2/5)

Kulasekararaj A et al. BJH 2013; 160, 660–672
Incorporation of Mutation Data and IPSS-R

TET2 MT/ASXL1 WT Predicts Response to HMA

Table 3. Association of gene mutations with response rate in logistic regression analysis

<table>
<thead>
<tr>
<th>Mutated gene*</th>
<th>Unadjusted OR (95% CI)</th>
<th>P value</th>
<th>Adjusted† OR (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mutations with VAF ≥10%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TET2-mut vs TET2-WT</td>
<td>1.99 (1.05, 3.80)</td>
<td>.036</td>
<td>1.98 (1.02, 3.85)</td>
<td>.044</td>
</tr>
<tr>
<td>ASXL1-mut vs ASXL1-WT</td>
<td>0.69 (0.40, 1.20)</td>
<td>.19</td>
<td>0.68 (0.38, 1.19)</td>
<td>.17</td>
</tr>
<tr>
<td>TET2-mut + ASXL1-WT</td>
<td>3.65 (1.38, 9.67)</td>
<td>.009</td>
<td>3.64 (1.35, 9.79)</td>
<td>.011</td>
</tr>
<tr>
<td>vs other</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TET2-mut + ASXL1-WT</td>
<td>3.40 (1.24, 9.35)</td>
<td>.011</td>
<td>3.36 (1.20, 9.38)</td>
<td>.013</td>
</tr>
<tr>
<td>vs both WT</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TET2-WT + ASXL1-mut</td>
<td>0.77 (0.41, 1.46)</td>
<td>.35</td>
<td>0.80 (0.39, 1.46)</td>
<td>.39</td>
</tr>
<tr>
<td>vs both WT</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TET2-mut + ASXL1-mut</td>
<td>1.11 (0.48, 2.61)</td>
<td>.62</td>
<td>1.07 (0.44, 2.61)</td>
<td>.59</td>
</tr>
<tr>
<td>vs both WT</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CBL-mut vs CBL-WT</td>
<td>0.27 (0.06, 1.29)</td>
<td>.10</td>
<td>0.28 (0.06, 1.40)</td>
<td>.12</td>
</tr>
</tbody>
</table>

TET2 MT/ASXL1 WT Predicts Response to HMA

A  HMA Overall Response Rate

B  Duration of HMA Treatment

Sallman, D ASH 2016.
**TP53 Mutations Predict Outcomes to Treatment**

### Outcomes to Azacitidine

- **A**: Kaplan-Meier survival curve showing the difference between TP53 mutated and TP53 WT groups. The p-value is marked as **p<10^-4**.

- **B**: Overall Survival probability for different TP53 mutation statuses. The curve shows a significant difference between not complex and complex and TP53 unmutated and complex and TP53 mutated groups.

### Outcomes to Allogenic BMT

- **B**: Overall Survival, according to TP53 Mutation Status. The Kaplan-Meier survival curves illustrate the survival rates for patients with and without TP53 mutation.

- **C**: Cumulative Survival (proportion) for different types of AML. The curves distinguish between de novo and secondary AML, and TP53-mutated and wild-type AML.

- **D**: Overall Survival for different combinations of TP53 mutation and complex karyotype.

References:

AML Ontogeny can be Mutationally Defined

Important given recent approval of liposomal daunorubicin/cytarabine for sAML

Lindsay et al., Blood 2015.
sAML with Inferior Response Rates, Overall Survival and higher MRD

Lindsley et al., Blood 2015.
Accumulation of Mutations and MDS Progression

Sperling et al., 2017; Nature Reviews Cancer
## JAK2 V617F Allele Burden (PCR) Impacts Phenotype and Prognosis in MPN

### Table 1. Impact of JAK2 V617F and TP53 VAF on MPN

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Genetic Association</th>
</tr>
</thead>
<tbody>
<tr>
<td>PV versus ET</td>
<td>Homozygous mutation in PV</td>
</tr>
<tr>
<td>ET versus pre-fibrotic PMF</td>
<td>JAK2 VAF &gt; 50% in PMF</td>
</tr>
</tbody>
</table>

### Phenotype

- **Leukocytosis**: ↑ JAK2 VAF
- **Higher hematocrit**: ↑ JAK2 VAF
- **Splenomegaly**: ↑ JAK2 VAF

### Outcomes

- **Fibrotic Transformation (PV and ET)**: ↑ JAK2 VAF/homozygous mutation
- **Thrombosis (ET ± PV)**: ↑ JAK2 VAF (> 75% in PV)
- **Leukemic Transformation**: ↓ JAK2 VAF in PMF (lowest quartile); ↑TP53 VAF
- **Inferior Overall Survival**: ↓ JAK2 VAF in PMF (lowest quartile); ↑TP53 VAF

**Abbreviations:** MPN, myeloproliferative neoplasm; PV, polycythemia vera; ET, essential thrombocythemia; PMF, primary myelofibrosis; VAF, variant allele frequency.

Newer technology is able to find very rare mutations which may have clinical value.

Wong et al., *Nature*; 2015
Molecular Drivers of AML Define Risk Categories (ELN and NCCN)

Good
- CBF (t(8;21)/inv(16)
- NPM1 mutant (no FLT3-ITD)
- Biallelic CEBPA

Bad
- Complex
  - -5/-7
  - Abnl(17p)
  - Inv(3)/t(3;3)
- FLT3-ITD
- TP53 mutation

Patel, et al. NEJM 2012; 366:1079
<table>
<thead>
<tr>
<th>Therapeutic class</th>
<th>Agent</th>
<th>Novel features</th>
<th>Patient population</th>
<th>Stage of development</th>
<th>Preliminary results</th>
</tr>
</thead>
<tbody>
<tr>
<td>IDH inhibitors</td>
<td>AG-221</td>
<td>IDH2-specific inhibitor</td>
<td>IDH2 MT; R/R and frontline (with 7+3 or AZA)</td>
<td>Phase 1–3</td>
<td>ORR 56% (18% complete remission); durable remission</td>
</tr>
<tr>
<td></td>
<td>AG-120</td>
<td>IDH1-specific inhibitor</td>
<td>IDH1 MT; frontline (with 7+3 or AZA)</td>
<td>Phase 1–2</td>
<td>ORR 31% (15% complete remission)</td>
</tr>
<tr>
<td></td>
<td>IDH-305</td>
<td>IDH1-specific inhibitor</td>
<td>IDH1 R132 MT</td>
<td>Phase 1</td>
<td>N/A</td>
</tr>
<tr>
<td>Spliceosome inhibitor</td>
<td>H3B-8800</td>
<td>Synthetic lethality in animal models</td>
<td>SF3B1, SF3F2, U2AF1, ZRSR2 mutant. Unfit or R/R</td>
<td>Phase 1</td>
<td>N/A</td>
</tr>
<tr>
<td>Antibody drug-conjugate (ADC)</td>
<td>SGN-CD33A</td>
<td>Delivers DNA crosslinking agent; effective in MDR AML models</td>
<td>Elderly AML (with HMA); pre/postallo-HSCT</td>
<td>Phase 1–3</td>
<td>33% CRc (60% in frontline setting)</td>
</tr>
<tr>
<td>Other novel agents</td>
<td>Guadecitabine</td>
<td>HMA (cytidine deaminase resistant)</td>
<td>Unfit or elderly AML</td>
<td>Phase 1–3</td>
<td>CRc 57% (complete remission 37%)</td>
</tr>
<tr>
<td></td>
<td>Idasanutlin</td>
<td>MDM2 Inhibitor to increase functional p53</td>
<td>R/R TP53 WT AML (with cytarabine or venetoclax)</td>
<td>Phase 1–3</td>
<td>Complete remission 25%, Improved with high baseline MDM2</td>
</tr>
<tr>
<td></td>
<td>Venetoclax</td>
<td>BCL2 Inhibitor</td>
<td>R/R elderly AML (with cobimetinib (MEKi) or idasanutlin)</td>
<td>Phase 1–2</td>
<td>ORR 19% (higher response in IDH MT)</td>
</tr>
<tr>
<td></td>
<td>Pracinostat</td>
<td>HDACi (I, II, and IV isoforms)</td>
<td>Frontline elderly AML (with AZA)</td>
<td>Phase 3 (planned)</td>
<td>42% complete remission; durable remissions (median OS NR)</td>
</tr>
<tr>
<td></td>
<td>Tosedostat</td>
<td>Aminopeptidase inhibitor</td>
<td>Frontline elderly AML (with AML or DAC)</td>
<td>Phase 1–2</td>
<td>45% complete remission, response predicted by GEP</td>
</tr>
<tr>
<td></td>
<td>Volasertib</td>
<td>Polo-like kinase inhibitor (1–3 (serine/threonine kinase)</td>
<td>Frontline (with 7+3); Unfit /elderly (with DAC or LDAC)</td>
<td>Phase 1–2</td>
<td>CRc 32% (improved EFS/OS vs. LDAC alone)</td>
</tr>
</tbody>
</table>
Acknowledgements

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