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Each Patient is Unique: Personalized Medicine and Myeloma

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Learning Objectives

• There are many different types of multiple myeloma

• Within an individual patient there are often multiple co-existing populations of tumor cells (i.e. clones)
What is Multiple Myeloma?

Normal Bone Marrow

Myeloma Bone Marrow

Goasguen et al. Leukemia Research 1999; 23:1133-1140
There are Two Common Ploidy States

Non-Hyperdiploid Myeloma
(Hypodiploid, Pseudodiploid, Near Tetraploid)

Hyperdiploid Myeloma
Multiple Immunoglobulin Translocations

Four Primary Classes:
- WHSC1/MMSET; t(4;14)
- Cyclin D genes; t(6;14), t(11;14), t(12;14)
- MAF genes; t(8;14), t(14;16), t(14;20)
- MYC; t(8;14)
Gene Expression Profiling is Used for Classification and Prognostication

Complete History of a Patient
Ebb and Flow of Clonal Tides
Even Significant Mutations are Sub-Clonal

Classic Mutations Can Co-Exist BUT...
Tumor Cells Exist in Multiple Populations

What a Difference a Decade Makes

Srivastava et al. Leukemia 2013; 27:2062-2066

Attal et al. NEJM 2003; 349:2495-2502
The Novel Agents

Proteasome Inhibitors

Bortezomib

Carfilzomib

Immunomodulatory Drugs

Thalidomide: 2-(2, 6-dioxopiperidin-3-yl)-1H-isindole-1, 3(2H)-dione

Lenalidomide: 3-(4-amino-1-oxo 1, 3-dihydro-2H-isindol-2-yl) piperidine-2, 6-dione

Pomalidomide: 4-Amino-2-(2, 6-dioxopiperidin-3-yl) isindole-1, 3-dione

Unfolded Protein Response

Bind CRBN, Changes E3 Ligase Specificity, Degrades IKZF1 and IKZF3
What is the MMRF CoMMpass Study

Clinical parameters are collected every 3 months for a minimum of 5(8) years

- DNA Content (DAPI)
- BRAF (V600, V601) Mutation Detection
- 600 Gene Clinical Panel on Relapse Samples*
Getting Patients on Study

Eligible
- >250k CD138pos cells
- Meet trial requirements

Screen Fail
- >250k CD138pos cells
- Do NOT meet trial requirements

Low Recovery
- <250k CD138
- Automatic screen fail

Low Expected
- <100k CD138 expected
- Not Sorted
- Automatic screen fail
Comprehensive Characterization Model

Long-Insert
Shallow Genome
Physical Coverage
Median - 59x

Exome Capture
High-Coverage
75 Mb Capture
Median - 109x

mRNAseq
Reads/Sample
Median - 189M
# Project Status by Interim Analysis

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<td>436</td>
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<td>824</td>
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<td></td>
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<td>925+</td>
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*Current Access: Public Access, Clinical Sites, PMIC*
Comparison To Other Studies - Patients
How Much Data Have We Produced

3,625 mi
Distance from New York, NY to Paris
Consensus Clustering Identifies 12 Classes
Each Tumor is Different
Outgrowth of Subclones

The graph shows the prevalence of subclones over different time points: Untreated, PR, and Progression. The x-axis represents the months (0, 6, 17), and the y-axis represents the prevalence. Different clusters (1 to 5) are color-coded to distinguish their progression trends.
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