Interim Analysis of the MMRF CoMMpass Trial

Identification of Novel Rearrangements Associated with Disease Initiation and Progression

On Behalf of the MMRF CoMMpass Network
**What is the MMRF CoMMpass Study**

Clinical parameters are collected every 3 months for a minimum of 5 years.

**Clinical Assays** - CD13, CD19, CD20, CD27, CD28, CD38, CD52, CD56, CD117, CD138, FGFR3, CD319
- DNA Content (DAPI)
- BRAF (V600, V601) Mutation Detection*
Project Status and Data Availability

Public Access Options: https://research.themmrf.org

dbGAP – Accession Number PHS00748
## Demographics of the IA5 Cohort

<table>
<thead>
<tr>
<th>Demographic Category</th>
<th>n (%)</th>
<th>N=420</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (yrs), median (range)</strong></td>
<td>65</td>
<td>(19-91)</td>
</tr>
<tr>
<td><strong>Gender - Female/Male</strong></td>
<td>170/250</td>
<td>(40.5/59.5)</td>
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<tr>
<td><strong>ISS Stage</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>144</td>
<td>(34.2)</td>
</tr>
<tr>
<td>II</td>
<td>147</td>
<td>(35.0)</td>
</tr>
<tr>
<td>III</td>
<td>130</td>
<td>(30.8)</td>
</tr>
<tr>
<td><strong>Race</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>318</td>
<td>(75.7)</td>
</tr>
<tr>
<td>Black/African American</td>
<td>74</td>
<td>(17.6)</td>
</tr>
<tr>
<td>Others</td>
<td>28</td>
<td>(6.6)</td>
</tr>
<tr>
<td><strong>Treatments</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proteasome + IMID based</td>
<td>242</td>
<td>(57.6)</td>
</tr>
<tr>
<td>bortezomib-lenalidomide-dexamethasone</td>
<td>171</td>
<td>(40.7)</td>
</tr>
<tr>
<td>Proteasome based</td>
<td>115</td>
<td>(27.4)</td>
</tr>
<tr>
<td>bortezomib-dexamethasone-cyclophosphamide</td>
<td>50</td>
<td>(11.9)</td>
</tr>
<tr>
<td>bortezomib-dexamethasone</td>
<td>48</td>
<td>(11.4)</td>
</tr>
<tr>
<td>IMID based</td>
<td>53</td>
<td>(12.6)</td>
</tr>
<tr>
<td>lenalidomide-dexamethasone</td>
<td>31</td>
<td>(7.4)</td>
</tr>
</tbody>
</table>
Comprehensive Characterization Model

Central Dogma: DNA ----> RNA ----> Protein
DNA$^{mt}$ ----> RNA$^{mt}$ ----> Protein$^{mt}$

Long-Insert Shallow Genome
Physical Coverage Median – 59x

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

mRNAseq
Reads/Sample Median – 189M

Median - 109x Reads/Sample
Median – 189M
Immunoglobulin Rearrangements by LI

Only chromosomes involved in a rearrangement are shown.

Common regions are zoomed

Canonical Tx are colored:
t(4;14) – Orange
t(6;14) - Purple
t(8;14) – Green
t(11;14) – Red
t(14;16) – Blue

Random partners are often part of complex canonical events (*)

The only recurrent novel partner is MAP3K14/NIK

Co-existing rearrangement partners are common (**)
Complex Balanced t(11;14)

der(14)
chr14+:chr11-
der(11)
chr11+:chr19+
der(11)
chr19-:chr14-

CCND1 -->

ZSWIM4

LOC284454
MR24-2
Simultaneous Dual IgH Translocation

**MMRF_1286 – t(11;14) and t(14;20)**
- Balanced t(11;14) with a 23 bp deletion between der(11) and der(14)
- Unbalanced t(14;20), with an undefined chr14 breakpoint within 200bp of t(11;14) breakpoints
Overexpression of Both Target Genes

CCND1

BCL2L1
Independent Dual IgH Translocations

- MMRF_1560 - t(4;14) and t(14;17)
  - Balanced t(4;14) dysregulating FGFR3 and WHSC1/MMSET
  - Unbalanced t(14;17) dysregulating MAP3K14/NIK
Overexpression of Both Target Genes

WHSC1 - MMSET

MAP3K14
Recurrent Fusion Partners

Only chromosomes involved in a rearrangement are shown.

Common regions are zoomed

IgH element fusions are grouped into “IgH” group

Two recurrent fusion pairs
- IgH-MMSET (n=19, 10.1%)
- IgH-MYEHOV (n=2)

Several genes are involved in multiple fusions, but with different partners
- NEDD9 (n=2)
- FCHSD2 (n=2)
- ARHGEF12 (n=2)
- CDC42BPB (TRAF3 Deletion)
- BRF1 (n=3)
- MAP3K14 (n=4)
Most Mutations are Not Expressed

Most Mutations are not detectably expressed
Frequently Mutated Genes

- Single nucleotide variants detected by WES in CoMMpass IA5 dataset:
  - There must be at least 5 reads at the position in RNAseq alignments
  - There must be at least one read with the mutant allele observed by WES in RNAseq
  - 156 Patients with Exomes
  - Significant by MutSig (**) 

<table>
<thead>
<tr>
<th>N (%) - Gene</th>
<th>43 (27.6) – KRAS **</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>37 (23.7) – NRAS **</td>
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<tr>
<td></td>
<td>17 (10.9) – FAM46C **</td>
</tr>
<tr>
<td></td>
<td>15 (9.6) – DIS3 **</td>
</tr>
<tr>
<td></td>
<td>13 (8.3) – TRAF3 **</td>
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<tr>
<td></td>
<td>12 (7.7) – BRAF **</td>
</tr>
<tr>
<td></td>
<td>11 (7.1) – PRR14L</td>
</tr>
<tr>
<td></td>
<td>10 (6.4) – ACTG1</td>
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<tr>
<td></td>
<td>9 (5.8) – EGR1</td>
</tr>
<tr>
<td></td>
<td>9 (5.8) – FGFR3</td>
</tr>
<tr>
<td></td>
<td>8 (5.1) – DUSP2</td>
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<tr>
<td></td>
<td>6 (3.8) – BTG1</td>
</tr>
<tr>
<td></td>
<td><strong>Low Frequency but Significant</strong></td>
</tr>
<tr>
<td></td>
<td>2 (1.3) – SP140 **</td>
</tr>
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<td></td>
<td>2 (1.3) – ARID2 **</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>N (%) - Gene</th>
<th>6 (3.8) – MAX **</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>5 (3.2) – FAM111B</td>
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<tr>
<td></td>
<td>5 (3.2) – MCAF1</td>
</tr>
<tr>
<td></td>
<td>5 (3.2) – MAGEC1</td>
</tr>
<tr>
<td></td>
<td>5 (3.2) – NFkBIA</td>
</tr>
<tr>
<td></td>
<td>5 (3.2) – SYNE2</td>
</tr>
<tr>
<td></td>
<td>5 (3.2) – NUP153</td>
</tr>
<tr>
<td></td>
<td>5 (3.2) – TGDS</td>
</tr>
</tbody>
</table>
Are All Mutations Equal?

BRAF
NM_004333

- RBD - Manually Curated...
- C1 - Manually Curated...
- Kinase - Manually Curated...
Clonal Evolution

Diagnosis $\rightarrow$ 6x CyBorD-R $\rightarrow$ Ld Maintenance $\rightarrow$ Relapse (21 Months)

- New at Relapse
- Drug Resistance
- Progression

Enriched at Relapse

- UIMC1/RAP80
- BRAF
- FBXO7

Equal at both visits
- Initiating & Maintenance Events

Lost at Relapse

- ADPRM
- BHLHA15
- DTD1
- GNL3
- GPN2
- FBXO7
- HDGF
- KIAA2026
- SUB1
- TECTA
- TRPC3
- WDR90
- ZNF443

Diagnosis = 36%
Relapse = 88.8%
Structural IKZF3 in Post Len-Dex Patient

17:37,942,194–37,951,042

17:67,236,504–67,245,352

IKZF3

ABCA10

ABCA5
CoMMpass Researcher Gateway

- Enhanced ability to perform gene sets enrichment analyses
- Better analytical and statistical treatment of outcome data
- Bulk download capabilities
- Circulating Multiple Myeloma Cells (CMMC) data incorporated

https://research.themmrf.org/

Raw data is also available from dbGAP (PHS00748)
Conclusions

• The CoMMpass characterization model represents the most comprehensive characterization of the myeloma genome to date
  – The IA5 cohort containing sequencing data from 195 patients will be publically available in the new year.

• We have identified novel IgH translocations targeting MAP3K14, NFKB1, TOP1MT, APOL3, BCL2L1

• MAP3K14/NIK dysregulation occurs through IgH rearrangements and non-IgH gene fusion events in approximately 3% of patients.

• The only highly recurrent fusion transcripts are the IgH-MMSET and MMSET-IgH hybrid transcripts created by t(4;14).

• Current analyses underway to explore:
  – association between somatic events (CNA/structural/mutational/RNA) in primary tumor in patients who had early relapse.
  – association between somatic events (CNA/structural/mutational/RNA) and therapeutic response.
Acknowledgements

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  - Sagar Lonial

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