Clonal heterogeneity and MRD testing in multiple myeloma

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Massive genetic heterogeneity in multiple myeloma

Lohr JG. et al., Cancer Cell, 2014; 25(1):91-101
Treatment With Carfilzomib-Lenalidomide-Dexamethasone With Lenalidomide Extension in Patients With Smoldering or Newly Diagnosed Multiple Myeloma

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Korde N. et al., JAMA Oncology, 2015; 1(6):746-54
Samples and bioinformatic analysis

• DNA isolated from CD138+ cells and whole exome sequencing on HiSeq2500 sequencers with median target coverage of 125x (range 105-185x)

• Tumor only analysis using TGen JetStream analysis pipeline
Samples and bioinformatic analysis

• Somatic mutations identified using variant callers Mutect, Seurat and Strelka

• Variants detected by at least two callers are filtered to remove likely germline variants
Significantly recurrent mutations of individual genes in multiple myeloma

- KRAS
- NRAS
- BRAF
- CYLD
- FAM46C
- TRAF3
- DIS3
- IRF4
- HIST1H1E
- ACTG1
- TP53
- LTB
- PRDM1
- RB1
- MAX

1. Lohr JG. et al., Cancer Cell, 2014; 25(1):91-101
2. Walker BA. et al., JCO, 2015; 33(33): 3911-20
Mutational landscape by treatment response?

Newly diagnosed multiple myeloma → Combination therapy → CR → non-CR
# Patients and treatment response

<table>
<thead>
<tr>
<th>Best treatment response after combination therapy</th>
<th>Newly diagnosed multiple myeloma (N=39)</th>
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<tbody>
<tr>
<td>CR</td>
<td>22 (56%)</td>
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<tr>
<td>non-CR</td>
<td>17 (44%)</td>
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</tbody>
</table>

CR = complete response
Mutational landscape by treatment response?

Multiple myeloma obtaining CR

n/N (%)=7/22 (32%)

Multiple myeloma not obtaining CR

n/N(%)=10/17 (59%)
Patients with significantly recurrent mutations in multiple myeloma genes

- Multiple myeloma obtaining CR: 7/22 (32%)
- Multiple myeloma not obtaining CR: 10/17 (59%)
Recurrent mutations in the NF-kB pathway

Classical NF-kB pathway

Alternative NF-kB pathway

Number of patients with mutations in the NF-kB pathway genes

- Multiple myeloma obtaining CR: 4/22 (18%)
- Multiple myeloma not obtaining CR: 6/17 (35%)
Summary

- Modern therapy produces deep and durable response in patients with multiple myeloma

- Baseline mutations associated with treatment response
Clonal heterogeneity in myeloma

Lohr JG. et al., Cancer Cell, 2014; 25(1):91-101
Patterns of clonal evolution

No change

Patterns of clonal evolution

Differential clonal response

Average time to CR and MRD negativity was 5.5 cycles with KRd therapy.
Average time to CR and MRD negativity was 5.5 cycles with KRd therapy.

Determine the number of cycles of combination therapy by MRD response.

Korde et al. *JAMA Oncology* 2015
Number of cycles of highdose KRd defined by MRD negativity

2  4  6  8  10  12

2+ cycles

Landgren et al. unpublished data
Patterns of clonal evolution

Patterns of clonal evolution

Adding novel agents to overcome clonal heterogeneity

Induction therapy

Consolidation therapy

Novel agents
Myeloma Program at MSKCC

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Thank you to our patients!

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