Hot Topics in Multiple Myeloma Treatment

Webinar 3; November 1, 2017
Precision Medicine

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Multiple Myeloma Research Foundation

Moderator:
- Mary DeRome
  Multiple Myeloma Research Foundation
  Norwalk, Connecticut

www.themmrf.org
https://www.facebook.com/theMMRF
https://twitter.com/theMMRF
https://www.youtube.com/user/TheMMRF

Speakers

- Jeffrey L. Wolf, MD
  University of California, San Francisco
  San Francisco, California

- Amy S. Marsala, RN, MPH, ANP-BC
  University of California, San Francisco
  San Francisco, California
Topics for Discussion

- The potential to adapt therapy to particular subtypes of MM
- The MMRF CoMMpass StudySM results and key precision medicine trials
- What precision medicine mean for patients

Multiple Myeloma Is Not Just One Disease!

MM is a heterogeneous disease even within cytogenetically defined molecular subtypes

Treatment should not be applied in a one-size-fits-all fashion

How do we customize treatment?
How do we match the right myeloma medicines to each patient?

**Precision Medicine**

Personalizing medical care with DNA testing of many different genes (genomics) at the same time

Bone marrow tissue samples
Newly diagnosed → relapse

Genomic testing

- Gene expression profiling (GEP)
- Whole-genome/whole-exome sequencing
- Next-generation sequencing

自私的 treatment

Whole-Genome Sequencing at Diagnosis

<table>
<thead>
<tr>
<th>Complexity</th>
<th>At Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>DNA base-pair substitutions, n</td>
<td>5,286</td>
</tr>
<tr>
<td>Deletions and insertions, n</td>
<td>51</td>
</tr>
<tr>
<td>Rearrangements, n</td>
<td>49</td>
</tr>
</tbody>
</table>

Courtesy of Nikhil Munshi MD, DFCI
Whole-Genome Sequencing at Relapse

<table>
<thead>
<tr>
<th>Complexity</th>
<th>At Diagnosis</th>
<th>At Relapse</th>
</tr>
</thead>
<tbody>
<tr>
<td>DNA base-pair substitutions, n</td>
<td>5,286</td>
<td>12,581</td>
</tr>
<tr>
<td>Deletions and insertions, n</td>
<td>51</td>
<td>606</td>
</tr>
<tr>
<td>Rearrangements, n</td>
<td>49</td>
<td>113</td>
</tr>
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</table>

Significant increase in complexity

The Concept of Clonal Tides

- Five unique clones at diagnosis
- Variable chemotherapy response
- Minor drug-resistant clone lethal

**MMRF CoMMpass℠ Study: Advancing Personalized Medicine Research**

- Landmark study focusing on the genomics of myeloma
- Goals
  - Learn which patients respond best to which therapies
  - Achieve better treatments targeted to each patient’s biological makeup
- 1,000 newly diagnosed patients will be followed for at least 8 years

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**MMRF CoMMpass℠ Study: Advancing Personalized Medicine Research**

<table>
<thead>
<tr>
<th>Age</th>
<th>Gender</th>
<th>Race/ethnicity</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>How old were the people in CoMMpass?</strong></td>
<td><strong>What gender were the people in CoMMpass?</strong></td>
<td><strong>What ethnicity were the people in CoMMpass?</strong></td>
</tr>
<tr>
<td>Average</td>
<td>64</td>
<td>77% Caucasian</td>
</tr>
<tr>
<td>Youngest</td>
<td>27</td>
<td>2% Asian</td>
</tr>
<tr>
<td>Oldest</td>
<td>93</td>
<td>16% African American</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5% Other</td>
</tr>
</tbody>
</table>
Should I be on three drugs?

MMRF CoMMpass\textsuperscript{SM} Study: Advancing Personalized Medicine Research

Should I do a transplant?

MMRF CoMMpass\textsuperscript{SM} Study: Advancing Personalized Medicine Research
Hot Topics in Multiple Myeloma Treatment  
Webinar 3: Precision Medicine

**MMRF CoMMpassSM Study:** Advancing Personalized Medicine Research

### 12 Subtypes of Multiple Myeloma

We’ve identified 12 different molecular types of multiple myeloma, each with its own level of risk. They include:

- MyD88
- IDH1/2
- IGF1R
- ALK
- FGFR3
- PI3K-AKT
- CDKN2C
- CCND1
- BRAF
- KRAS
- NRAS
- Others

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**Molecular Profiling for Precision Therapeutic Strategies in Myeloma**

*BRAF* inhibition (for example, with vemurafenib) has now been clinically validated in multiple myeloma.

PET CT before and after 2 months of vemurafenib treatment in patient with *BRAF* V600E mutation showing significant improvement in bone lesions.

Another Example: Venetoclax Targets BCL-2, an Anti-Apoptotic Protein That Promotes Myeloma Cell Survival

- t(11;14) is associated with sensitivity to venetoclax (Venclexta), a drug approved in CLL
- t(11;14) correlates with higher ratios of $BCL2: MCL1$ and $BCL2: BCL2L1$

From Kumar et al. ASH 2016.
1. Leverson JD et al. S01 Transl Med 2015.

Studies Showing Responses to Venetoclax

- Phase 1 study in relapsed/refractory MM$^1$
  - 66 patients
  - Venetoclax alone
  - Acceptable safety profile
  - Promising single-agent activity in patients with t(11;14)

- Phase 1 study in relapsed/refractory MM$^2$
  - 66 patients
  - Venetoclax + Velcade + dex
  - 67% patients responded
  - Highest responses seen in patients who were not refractory to proteasome inhibitors or immunomodulatory drugs
  - Acceptable safety profile
  - A phase 3 trial is ongoing

<table>
<thead>
<tr>
<th>Cytogenetic abnormality present</th>
<th>t(11;14)</th>
<th>t(4;14)</th>
<th>del(17p)</th>
<th>del(13q)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall response rate (%)</td>
<td>78</td>
<td>65</td>
<td>60</td>
<td>67</td>
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Beyond Single Hypothesis Testing: Master Protocols

- Functional high-risk patients
- Profiling for alterations (NCT02884102)

No detectable actionable alterations → Backbone regimen
- RAF/RAS mutations
- IDH activating mutations
- CCND1 activating alteration
- PI3K/AKT activating alterations
- FGFR3 activating alterations
- t(11;14)

Backbone regimen + immune checkpoint inhibitor
- MAPK + MAPKi
- IDH + IDHi
- CDKi
- AKTi
- FGFRi
- BCLI

Functional high-risk patients

- Backbone regimen + immune checkpoint inhibitor
- MAPKi
- IDHi
- CDKi
- AKTi
- FGFRi
- BCLI

Profiling for alterations (NCT02884102)

Additional Precision Medicine Trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>Patient Population</th>
<th>Gene Mutations Targeted</th>
<th>Primary Site</th>
</tr>
</thead>
<tbody>
<tr>
<td>JNJ-42756493* + dexamethasone</td>
<td>RRMM</td>
<td>FGFR3</td>
<td>University Health Network, Toronto, Canada</td>
</tr>
<tr>
<td>Dabrafenib† + Trametinib†</td>
<td>RRMM</td>
<td>BRAF, NRAS, or KRAF</td>
<td>Massachusetts General Hospital Cancer Center/Dana-Farber</td>
</tr>
<tr>
<td>Idasanutlin* + Ninlaro + dexamethasone</td>
<td>RRMM</td>
<td>17p deletion</td>
<td>Mayo Clinic</td>
</tr>
<tr>
<td>NCI-MATCH</td>
<td>Advanced MM</td>
<td>Various</td>
<td>National Cancer Institute</td>
</tr>
<tr>
<td>GSK-2816126*</td>
<td>Advanced MM</td>
<td>Enhancer of Zeste 2 (EZH2)</td>
<td>Northwestern University</td>
</tr>
<tr>
<td>Targeted Agent and Profiling Utilization Registry Study (TAPUR)</td>
<td>MM</td>
<td>Various</td>
<td>Multiple</td>
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*Experimental therapy not yet FDA approved; †FDA approved for a non-MM indication

Bold = treatments studied in MMRC trials
Trials found at www.clinicaltrials.gov
What new genomic tests are available for patients?

Circulating tumor DNA

- Analysis capabilities:
  - Amplifications and deletions
  - Study of epigenetic modifications
  - Translocations

- Technologies available:
  - NGS
  - Digital PCR
  - RT-qPCR
  - Flow cytometry
  - m in vitro cell culture

Day 0
Day 1–3
Day 4
Day 5–6
Day 6–8
Day 9

Molecular Profiling Initiative: 500 Relapsed and Refractory Multiple Myeloma Patients

Myeloma patients provide their bone marrow and peripheral blood samples at many cancer centers across the US
Tumor Sequencing

- Identifies mutations in genes and the expression levels of these genes in tumor cells

![Diagram showing Tumor Sequencing process]

Getting the Brakes Checked

- Normal Brakes: Front and Back brakes are working
- Some Brakes: Front brake is working, but Back brake is not
- No Brakes: Neither Front nor Back brakes are working

![Cartoon characters and braking systems]

Courtesy of Jonathan Keats, PhD
Today CoMMpass Tells Us

Having no brakes is a bad thing but having half the brakes is okay.  

An Example of the Importance of Personalized Medicine

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<th>CoMMpassMMRF2250</th>
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<td>Age</td>
<td>72</td>
<td>71</td>
</tr>
<tr>
<td>Ethnicity</td>
<td>Caucasian</td>
<td>Caucasian</td>
</tr>
<tr>
<td>ISS stage</td>
<td>II</td>
<td>II</td>
</tr>
<tr>
<td>Baseline treatment</td>
<td>VRD</td>
<td>VRD</td>
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<td>Cytogenetics</td>
<td>t(4;14), del13, del17p</td>
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<td>Time of progression</td>
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<td><strong>p53 status</strong></td>
<td>Mutated</td>
<td>Wild-type</td>
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**Applying Precision to Practice: How can patients help tailor their therapy?**

- Become informed about screening tools and tests that can identify specific features of clonal disease
- Discuss precision medicine practices with primary oncologists (such as availability and timing of testing)
- Be willing to undergo additional biopsies and screening tests to better identify these mutations
- Participate in clinical trials to expand the network of samples to help researchers better understand how to engineer new therapies
Precision Medicine: Lab to Real Life

- Identifying mutations and higher-risk features earlier in disease will hopefully result in superior responses
- Faster disease control will allow recovery of damaged organs and improve overall functional status
- Longer and deeper periods of remission can predict increased progression-free survival and can translate into improved quality of life
- Targeted therapies tend to have few side effects and be better tolerated
- Screening for depths of response can result in possibly shorter time on maintenance therapy or the option of drug holidays

Precision Medicine Summary

- A one-size-fits-all treatment approach for MM is inappropriate due to its heterogeneity
- Efforts are under way to better understand the nature of the disease and to provide patients with a more personalized approach to treatment
- Genomic sequencing and data from MM patients are key to identifying subtype
- Participation in clinical trials to provide bone marrow and peripheral blood paramount
- Precision medicine provides the right treatment at the right time for each myeloma patient
Questions & Answers

Closing
Resources for You!

**MMRF Patient Support Center**
Have questions about the trials or information you heard today?
Call our MMRF Nurse Patient Navigators.

Our MMRF Nurse Patient Navigators can guide you through your multiple myeloma journey every step of the way.
Call Mon–Fri, 9:00 am–7:00 pm ET

Call now
1-866-603-MMCT(6628)

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