The MM Hub were delighted to attend the 59th American Society of Hematology (ASH) Annual Meeting held in Atlanta, Georgia, from 9-12 December 2017. On Sunday 10 December 2017 an oral abstract session was held entitled: Session 651. Myeloma: Biology and Pathophysiology, excluding Therapy: Genomics of The Pathogenesis and Progression of Multiple Myeloma. The first three talks of this session are covered in a separate MM Hub article, and the last three, sharing the common theme of genomic profiling to examine different aspects of Multiple Myeloma (MM), are summarized below.

Abstract 394: High-Risk Cytogenetics in Newly Diagnosed Multiple Myeloma: Prognostic Relevance of Co-Segregations and Analysis of the Role of Double Versus Single Autotransplantation

Nicoletta Testoni, from the Seragnoli Institute of Hematology, Bologna University School of Medicine, Bologna, Italy, spoke about a study in which cytogenetic analysis was performed on a large cohort of Newly Diagnosed Multiple Myeloma (NDMM) patients in order to stratify according to the presence of high-risk abnormalities (HRAs) and the role of double transplant compared with single transplant.

Study Design:

- FISH was performed at diagnosis on patients (pts) enrolled in the phase III EMNO2/H095 study, to establish presence of the following chromosomal abnormalities: t(4;14), t(6;14), t(11;14), t(14;16), t(14;20), deletion of 1p32, 13q14, 17p13, gain of 1q21 and hyperdiploidy (HD)
- HRAs were defined by the presence of one (single or isolated) or more (multiple/co-segregated) of the following: t(4;14), t(14;16), t(14;20), del(17p), gain(1q) and del(1p)
- Pts were divided into two groups to receive either:
  - VMP - standard-dose intensification treatment: bortezomib-melphalan-prednisone OR
  - HDM - high-dose intensification treatment: melphalan at 200 mg/m², and either single autologous stem cell transplant (ASCT-1) or double (ASCT-2)
- Pts were randomized again to either receive consolidation therapy, or none; both arms received lenalidomide maintenance
- Pts (n = 461) were evaluated: VMP (n = 151) and HDM (n = 310)

Key Data:

- HRAs = 233/461 pts (50.5%): gain(1q) = 33.6%, del(1p) = 51 (11.1%), del(17p) = 46 (10.0%), t(4;14) = 58 (12.6%), t(14;16) = 20 (4.3%) and t(14;20) = 6 (1.3%)
- Isolated HRA = 141/461 pts (30.6%): gain(1q) = 76 (53.9%), high-risk translocation (HRT) = 27 (19.1%), del(17p) = 21 (14.9%) and del(1p) = 17 (12.1%)

<table>
<thead>
<tr>
<th>Pts</th>
<th>No HRA</th>
<th>1 HRA</th>
<th>2 HRAs</th>
<th>3 HRAs</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>% Pts</td>
<td>141/461 pts (30.6%)</td>
<td>83/461 pts (17.6%)</td>
<td>11/461 pts (2.4%)</td>
<td></td>
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</tr>
<tr>
<td>3-year PFS</td>
<td>80.3%</td>
<td>51.5%</td>
<td>45%</td>
<td>21.8%</td>
<td>P=0.0001</td>
</tr>
<tr>
<td>OS</td>
<td>95.4%</td>
<td>81.7%</td>
<td>73.5%</td>
<td>40.9%</td>
<td>P=0.0001</td>
</tr>
</tbody>
</table>

- Most common double HRA = HRT co-segregating with a 1q gain: 48.2% of pts
- Median follow-up = 37.8 months
- Strongest impact on OS = del(17p); HR = 3.11; (95% CI = 1.20-8.07) (P = 0.019)
- Isolated gain(1q) vs co-segregation of gain(1q) with a HRT:
  - 3-year PFS = 33.3% vs 57.4%; HR = 1.76; 95% CI, 1.02-3.03; (P=0.041)
  - OS = 56.5% vs 85.7%; HR = 3.33; 95% CI, 1.52-7.30; (P=0.027)
- Gain(1q) plus HRT vs gain(1q) and del(1p) = 68.5% vs 89.6%; HR = 4.78; 95% CI=1.09-20.93; (P=0.038)
- Frequency of HD: pts without HRA = 59.2%; pts with 1 HRA = 53.2%, ≥2 HRAs = 34.8%
- PFS for del(17p) plus HD was significantly longer than del(17) without HD: 43.9 vs 19.4 months, P=0.032.

In this study, 50% of NDMM patients were assessed as having at least one HRA and 20% had two or more, and for these patients, the double transplant option gave added benefit, as assessed by PFS and OS. The most commonly observed co-segregated HRA was a combination of a 1q gain and a HRT and was associated with a lower PFS and OS, compared with isolated gain(1q). Interestingly, the association of HD with del(17p) canceled the adverse effect of having isolated del(17p).

**Abstract 395: Utility of Clinical-Grade Sequencing of Relapsed Multiple Myeloma Patients; Interim Analysis of the Multiple Myeloma Research Foundation (MMRF) Molecular Profiling Protocol**

The next talk was delivered by Daniel Auclair from the Multiple Myeloma Research Foundation, Norwalk, CT, and focussed on the concept of precision medicine (PM) and the existence of directly targetable mutations in MM. In order to identify such targets and to assess the value of such an approach, a large-scale study was established by carrying out molecular
profiling of 500 patients with RRMM.

**Key Highlights:**

- Bone marrow aspirates (BMAs) and matched normal peripheral blood (PB) were collected
- DNA and RNA were isolated from MM cells and deep targeted re-sequencing (>600x) was carried out
- Mutations were searched for and a mutation status report was produced
- 228 consecutive cases were analyzed with 84% of the (192) showing very good tumor content
- Pts with at least one potentially actionable mutation = 76%; of these, the following mutations were found:
  - MAPK pathway = 53%
  - CCND1 and cyclin-dependent kinase (CDK) pathways = 14%
  - activating FGFR3 mutations = 6%
  - A group of events = ≤ 3%; and of this cohort TP53 mutations = 16% (1/4 could be detected in blood)
- Mutations also detected in PB: SF3B1, TET2, ASLX1, ASLX2, and DNMT3A
- 10% of cases with this mutational combination (both BMAs and PB) were associated with MDS, AML, and other myeloid disorders
- In 10% of cases, the treating clinician was able to use this information to treat with a targeted agent
- Analysis of progression-free survival and overall benefit is ongoing

The conclusion of the talk summarized the key finding that actionable mutations were identified in more than 75% of patients analyzed. The importance of sequencing DNA/RNA from both PB and BM samples was emphasized, as these enabled mutations to be identified that might otherwise have been missed. The limitation at present is the lack of relevant drugs to specifically target each mutation, but with this in mind, Dr. Auclair described an initiative called: PMyDRUG, which aims to develop new drugs based on a given genomic MM profile.

**Abstract 396: The Mutational Landscape of Relapse in High Risk Myeloma Is Significantly Impacted by the Depth of Response but Not Maintenance Lenalidomide**

John R. Jones from The Institute of Cancer Research, London, United Kingdom, along with Gareth J. Morgan, from the Myeloma Institute, University of Arkansas For Medical Sciences, Little Rock, AR, who spoke about how the mutational landscape is affected by treatment in high-risk Multiple Myeloma (MM) patients. He began by explaining how understanding the evolutionary pattern of MM is crucial to making effective treatment decisions, and that next generation sequencing (NGS) was an effective tool by which to study this.

- NDMM (n = 56) and high-risk patients: n = 30 who received lenalidomide maintenance (LM) and n = 26 no LM
- Whole exome sequencing (WES) was used to study Newly Diagnosed MM patients (pts) and relapsed pts recruited from the Myeloma XI study
- Relapsed pts had all progressed within 30 months of maintenance and had a median PFS of 19 months (range 8-51)
- NS mutations at relapse = 44 vs whole series = 39 (p=0.005)
Median mutational load at relapse increased from 40 to 59 (p=<0.001) incomplete/near complete responders (CR/nCR)

Pattern in mutational load was the same regardless of LM or not

Mutations in genes known to be significant in myeloma = 84% (47/56) and were both lost and gained at relapse irrespective of maintenance treatment

Proportion of pts with bi-allelic inactivation of important tumor suppressor genes (TSG) increased from 14% (8/56) in NDMM to 18% (10/56) in RRMM

MYC translocations: 27% (15/56) RRMM vs 21% (12/56) NDMM

Mutations in genes involved in immunomodulatory mechanisms = 13% (7/56) regardless of maintenance or relapse

Four evolutionary patterns were identified at relapse: 1) stable progression, 2) stable progression with clonal loss, 3) branching and 4) linear

Branching evolution (gain and loss of mutational clusters at relapse) = 77% (23/30) Len treated and 54% (14/26) observation group

Linear evolution (gain of mutations at relapse) = 13% (4/30) Len treated and 27% (7/26) observation group

Predominant mechanism underlying progression involved dynamic processes (involving gain and loss of mutational clusters) and occurred in 86% (48/56) of cases

35% (n=13/37) of pts with branching evolution gained or lost one or more TSG at relapse vs 18% (2/11) of linear evolution patients and none with stable disease

New bi-allelic inactivation events were only seen in patients with branching evolution

Depth of response was a strong determinant of the pattern of evolution seen at relapse

Stable progression and clonal loss were only noted in the poor responders: 56% (5/9) of PR and 13% (3/23) of VGPR patients

All pts with CR/nCR (0/24) showed branching or linear evolution (p=0.002); none showed signs of stable progression

Therefore, in conclusion, lenalidomide maintenance does not appear to affect the number of mutations or the evolutionary pathways that determine relapse, but the depth of response does seem to be a key determinant.

References

1. N. Testoni et al. High-Risk Cytogenetics in Newly Diagnosed Multiple Myeloma: Prognostic Relevance of Co-Segregations and Analysis of the Role of Double Versus Single Autotransplantation. #Abstract 394, 59th ASH Annual Meeting and Exposition, Atlanta, GA.

2. D. Auclair et al. Utility of Clinical-Grade Sequencing of Relapsed Multiple Myeloma Patients; Interim Analysis of the Multiple Myeloma Research Foundation (MMRF) Molecular Profiling Protocol. #Abstract 395, 59th ASH Annual Meeting and Exposition, Atlanta, GA.

3. J.R Jones et al. The Mutational Landscape of Relapse in High Risk Myeloma Is Significantly Impacted by the Depth of Response but Not Maintenance Lenalidomide. #Abstract 396, 59th ASH Annual Meeting and Exposition, Atlanta, GA.