Myeloma cytogenetics: a personal and historical perspective

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Chromosome abnormalities in myeloma

- Abnormal myeloma karyotypes started to be published in 1970s but many cases throughout the 80s either unrecognised MDS abnormalities or small clones that are not fundamentally disease-associated and can be seen in many B-cell malignancies particularly if stimulated with mitogens.

- 14q32 rearrangements reported fairly early on, particularly t(11;14), but many simply '14q+' and ~30 different partners now known.

- Fundamental division into non-hyperdiploid with common 14q rearrangements and hyperdiploid karyotypes not published until 1998 (Smadja, France).

- First significant association with outcome (del(13) and 11q abnormalities poor) published in 1995 (Little Rock).

- Ross et al 1988 unpublished paper on 5 cases with 45 or 46 chromosomes, gain of 1q or loss of 1p, -13, -14 as poor prognosis. One case t(14;16), other 4 no visible 14q32 abnormality.
Why so late with significant karyotypic abnormalities?

- Relatively low level involvement of bone marrow cf leukaemias in most cases

- Most malignant plasma cells have relatively low mitotic rate and may be dependent on other marrow elements not present in suspension culture of bone marrow aspirate samples

- Aspirating plasma cells is difficult so that many samples are haemodilute

- Together the last 2 factors mean that only ~1/3 cases at diagnosis yield relevant abnormal karyotypes. This rises to ~60% in late stage disease as malignant cells lose their dependence on the bone marrow stroma

- Many myeloma karyotypes are complex; difficulty in achieving accurate karyotypes meant difficulty in identifying recurring patterns
45,X,-X,t(11;14)(q13;q32)
52,XY,+1,der(1;16)(q10;q10),+5,+7,del(8)(q24),+9,+11,t(11;12)(q13;p13),
-13,der(14)t(7;14)(q34;q32),+15,ins(15;14)(26;q32),
der(17)t(17;15;8)(q23;q?;q24),+18,+19,der(19)t(15;19)(q?;p13),+21,-22
Serious interest in myeloma chromosomes

- 1995 Little Rock paper suggesting del(13) was really strong prognostic indicator at a time when no other factors were strongly prognostic

- Development of FISH throughout 90s showing most (now all) myeloma cases have abnormal karyotypes

- Avet-Loiseau's work in particular applying FISH to French myeloma trial patients

- ~ 2000 FISH from several groups confirmed del(13) as significant prognostic factor

- Discovery of t(4;14) (1997) and t(14;16) (1998)
LLR UKMF myeloma cytogenetic database

- Set up in late 2000 with 2 scientists and one technician
- Initial remit to develop techniques for studying chromosome abnormalities in myeloma. Accepted any known/likely plasma cell dyscrasia cases
- Late 2003 to late 2007 essentially restricted to potential MRC Myeloma IX trial patients - maximum of 6 scientists and 3 technicians (but moderate turn-over of scientists)
- ~200 MGUS and SMM cases as well as MM (both trial and non-trial) provided interesting comparisons
Methods

• Magnetic bead purification of plasma cells

• MicroFISH technique

• Cytogenetics on unstimulated and IL6 3 and 6 day stimulated cultures: 200 cells wherever possible and no abns found. Experimented with other growth factors but no improvement

• Arrays - Agilent 244k oligo array
Sampling problems in Myeloma IX

54% of samples sent for Myeloma IX trial contained <10% plasma cells
82% contained <30% plasma cells
Success of purification

Median plasma cell % after purification was 94% but 6% <30% & 2% <10%
<table>
<thead>
<tr>
<th>Primary Genetic Events</th>
<th>Secondary Genetic Events</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>IGH Translocations</strong></td>
<td><strong>Chromosomal architecture</strong></td>
</tr>
<tr>
<td>- t(11;14) <strong>CCND1</strong></td>
<td>- Deletion 1p <strong>CDKN2C, FAF1, FAM46C</strong></td>
</tr>
<tr>
<td>- t(6;14) <strong>CCND3</strong></td>
<td>- Deletion 17p <strong>TP53</strong></td>
</tr>
<tr>
<td>- t(4;14) <strong>FGFR3/MMSET</strong></td>
<td>- Deletion 13q <strong>RB1, DIS3</strong></td>
</tr>
<tr>
<td>- t(14;16) <strong>c-MAF</strong></td>
<td>- Deletion 11q <strong>BIRC</strong></td>
</tr>
<tr>
<td>- t(14;20) <strong>MAFB</strong></td>
<td>- Deletion 14q32 <strong>TRAF3</strong></td>
</tr>
<tr>
<td><strong>Hyperdiploidy</strong></td>
<td>- Deletion 16q <strong>WWOX, CYLD</strong></td>
</tr>
<tr>
<td>- Trisomies of chromosomes 3, 5, 7, 9, 11, 15, 19, 21</td>
<td></td>
</tr>
<tr>
<td><strong>Gain</strong></td>
<td><strong>Gain</strong></td>
</tr>
<tr>
<td>- 1q <strong>CKS1B, ANP32E</strong></td>
<td>- 1q <strong>LTBR</strong></td>
</tr>
<tr>
<td>- <strong>LTBR</strong></td>
<td>- 17p <strong>TP53</strong></td>
</tr>
<tr>
<td>- <strong>TACI</strong></td>
<td>- 16q <strong>WWOX, CYLD</strong></td>
</tr>
<tr>
<td>- <strong>NIK</strong></td>
<td>- Non IGH translocations</td>
</tr>
<tr>
<td><strong>2\textsuperscript{nd} translocations</strong></td>
<td></td>
</tr>
<tr>
<td>- t(8;14) <strong>c-MYC</strong></td>
<td></td>
</tr>
<tr>
<td>- t(14;17) <strong>NIK</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Mutational events and pathways</strong></td>
<td></td>
</tr>
<tr>
<td>- Survival <strong>N-RAS, K-RAS, BRAF</strong></td>
<td></td>
</tr>
<tr>
<td>- PI3k/AKT</td>
<td></td>
</tr>
<tr>
<td>- NF-κB pathway <strong>TRAF, CYLD, IkB</strong></td>
<td></td>
</tr>
<tr>
<td>- DNA repair <strong>TP53, MRE11, PARP</strong></td>
<td></td>
</tr>
<tr>
<td>- RNA editing <strong>DIS3, FAM46C, LRRK2</strong></td>
<td></td>
</tr>
<tr>
<td>- Epigenetic modifiers <strong>UTX, MLL, MMSET, HOXA9</strong></td>
<td></td>
</tr>
<tr>
<td>- PC Differentiation <strong>XBP1, BLIMP, IRF4</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Epigenetic Events</strong></td>
<td></td>
</tr>
<tr>
<td>- Global hypomethylation from MGUS to myeloma</td>
<td></td>
</tr>
<tr>
<td>- Gene specific hypermethylation from myeloma to plasma cell leukaemia</td>
<td></td>
</tr>
</tbody>
</table>
FISH probes

- IgH break-apart, t(4;14), t(11;14), t(14;16), t(8;14) with 8 centromere (Vysis)
- MAFB break-apart for t(14;20), CCND3 break-apart for t(6;14) (in house)
- Rb1 & D13S319 for del(13)
- p53 and 17 centromere
- 5/9/15 (Vysis) for ploidy, along with 3 & 7 centromeres with 22q11 (estimated 98% sensitive and 88% specific)
- chromosome 1 abnormalities (CKS1B, PDZK1, ASPM, 1p12, CDKN2C)
74 different probe combinations used

<table>
<thead>
<tr>
<th></th>
<th>Trial</th>
<th>Non-trial</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with successful FISH results</td>
<td>1074</td>
<td>1299</td>
<td>2373</td>
</tr>
<tr>
<td>Pts with only unsuccessful results</td>
<td>60</td>
<td>93</td>
<td>153</td>
</tr>
<tr>
<td>Samples with at least 1 good result</td>
<td>1242</td>
<td>1743</td>
<td>2985</td>
</tr>
<tr>
<td>Total FISH</td>
<td>12864</td>
<td>21089</td>
<td>33953</td>
</tr>
<tr>
<td>Successful FISH</td>
<td>12566</td>
<td>20315</td>
<td>32881</td>
</tr>
<tr>
<td>% success</td>
<td>97.7</td>
<td>96.3</td>
<td>96.8</td>
</tr>
<tr>
<td>% abnormal FISH cases</td>
<td>96.1</td>
<td>94.6</td>
<td>95.3</td>
</tr>
<tr>
<td>Karyotypes set up</td>
<td>701</td>
<td>1022</td>
<td>1723</td>
</tr>
<tr>
<td>successful</td>
<td>631</td>
<td>956</td>
<td>1587</td>
</tr>
<tr>
<td>% abnormality rate</td>
<td>36.1</td>
<td>31.8</td>
<td>33.6</td>
</tr>
</tbody>
</table>
Comparison between MGUS, SMM & MM by iFISH

- Most routinely tested MM genetic changes are also present in MGUS/SMM.
- The only primary change found at a significantly lower frequency in MGUS than MM (3% vs 12%) is t(4;14).
- MM secondary changes (e.g. del(13), +1q, 17p-) can be found in MGUS/SMM.
- These secondary abnormalities often involved a smaller proportion of clonal PCs in MGUS and SMM.
- No secondary changes investigated by iFISH were responsible for rapid progression to MM, not even those associated with a dismal prognosis in MM.
- However, some (e.g. del(13) in t(11;14) cases, or del(17p13) were only seen in MGUS which then evolved to MM.
17p13 loss

Disease course of MGUS with 17p13 deletion

<table>
<thead>
<tr>
<th>Pt</th>
<th>Age</th>
<th>PP</th>
<th>Diagnosis</th>
<th>IgHt</th>
<th>Δ13</th>
<th>HRD</th>
<th>Proportion of PC with 17p-</th>
<th>Stable</th>
<th>Time to progression (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>684</td>
<td>84</td>
<td>IgGk</td>
<td>MGUS</td>
<td>-</td>
<td>-</td>
<td>yes</td>
<td>60%</td>
<td>√</td>
<td>2*</td>
</tr>
<tr>
<td>2683</td>
<td>54</td>
<td>IgG</td>
<td>MGUS</td>
<td>-</td>
<td>-</td>
<td>yes</td>
<td>42%</td>
<td>No</td>
<td>24</td>
</tr>
<tr>
<td>949</td>
<td>75</td>
<td>IgAλ</td>
<td>MGUS</td>
<td>t(11;14)</td>
<td>-</td>
<td>no</td>
<td>86%</td>
<td>No</td>
<td>32</td>
</tr>
<tr>
<td>1960</td>
<td>72</td>
<td>IgG</td>
<td>MGUS</td>
<td>t(14;?)</td>
<td>√</td>
<td>no</td>
<td>50%</td>
<td>No</td>
<td>15</td>
</tr>
</tbody>
</table>

*Patient 684 died from MM-unrelated causes (age 84 years) 2 months after MGUS diagnosis;

- All MGUS cases with 17p del progressed to MM, suggesting that this abnormality is associated with the clinical manifestation of the disease
- BUT: progression was not rapid in all cases and variation in time to progression was not dependent on the percentage of PCs carrying the abnormality
- 17p13 loss is only found in ~8% MM patients at diagnosis so it cannot represent a ubiquitous mechanism of disease evolution
Array CGH comparison of different stages

- High resolution array CGH showed an increasing level of genomic complexity from MGUS (n=25) to SMM (n=15) to MM (n=47) to PCL (n=11)

- The number of copy number changes per case in MGUS was strongly associated with progression (P=0.003)

- The simplest profiles belonged to MGUS cases with t(6;14), t(11;14) and t(14;20); none of these patients had progressed to MM by the end of this study (median follow-up=72 months)

- A number of chromosomal changes were found to be strongly associated with progression
  * del(1)(p22.3-p23)  
  * del(6)(q25)  
  * del(12)(p13)  
  * del(17)(p13)  
  * MYC changes (MYC signature is activated in 67% of MM)  
  * del(13) in t(11;14) (MGUS, 1/28; SMM, 2/13; MM, 21/53; MGUS vs MM, P<0.001)  
  * abnormalities involving the NF-kB pathway (e.g. TRAF3, NIK, BIRC2/3, TACI)

- All these abnormalities were rare in MGUS/SMM cf MM

- All MGUS/SMM patients positive for these changes progressed to MM

- BUT time to progression was highly variable even for the same abnormalities

- Other factors (genetic or otherwise) must play a role in disease progression
Conclusions about genetics of disease progression

- The evolution of myeloma seems to be characterised by the acquisition of new abnormalities in the majority of cases.
- The timing of these acquisitions can vary from patient to patient.
- The biological impact of these secondary changes also seems to vary from patient to patient.
- In our study, such variation did not appear to depend on the proportion of PCs carrying the abnormality.
- Secondary changes may have different biological implications depending on the primary changes previously acquired by the neoplastic clone.
- iFISH on purified PCs only gives a limited picture of the acquired changes during progression compared to genome-wide methods and does not give reliable information about the level of genomic complexity already established.
- However, iFISH is the best method for assessing the presence of small clones which may be present at various stages of the disease.
Myeloma IX trial design

N = 1960

Intensive

RANDOMISATION

Clodronate CVAD
Zoledronic acid CVAD
Clodronate C-TD
Zoledronic acid C-TD
Clodronate MP
Zoledronic acid MP
Clodronate C-TDa
Zoledronic acid C-TDa

MEL-200 ASCT

RANDOMISATION

–Thal
+Thal

Non-intensive

RANDOMISATION

Clodronate MP
Zoledronic acid MP
Clodronate C-TDa
Zoledronic acid C-TDa

Max Response

RANDOMISATION

–Thal
+Thal

Treatment continued until disease progression
## Incidence of abnormalities in MMIX

<table>
<thead>
<tr>
<th>abnormality</th>
<th>number successful tests</th>
<th>Number abnormal</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>hyperdiploid</td>
<td>1032</td>
<td>603</td>
<td>58</td>
</tr>
<tr>
<td>del(13)</td>
<td>1047</td>
<td>470</td>
<td>45</td>
</tr>
<tr>
<td>IgH rea</td>
<td>1060</td>
<td>464</td>
<td>44</td>
</tr>
<tr>
<td>1q gain</td>
<td>903</td>
<td>351</td>
<td>39</td>
</tr>
<tr>
<td>metaphase abns</td>
<td>639</td>
<td>224</td>
<td>36</td>
</tr>
<tr>
<td>16q loss</td>
<td>938</td>
<td>177</td>
<td>19</td>
</tr>
<tr>
<td>t(11;14)</td>
<td>1053</td>
<td>146</td>
<td>14</td>
</tr>
<tr>
<td>22q loss</td>
<td>838</td>
<td>107</td>
<td>13</td>
</tr>
<tr>
<td>t(4;14)</td>
<td>1055</td>
<td>121</td>
<td>11</td>
</tr>
<tr>
<td>1p32 loss</td>
<td>860</td>
<td>96</td>
<td>11</td>
</tr>
<tr>
<td>del 17p</td>
<td>1017</td>
<td>85</td>
<td>8</td>
</tr>
<tr>
<td>t(14;16)</td>
<td>1048</td>
<td>33</td>
<td>3</td>
</tr>
<tr>
<td>t(14;20)</td>
<td>1043</td>
<td>16</td>
<td>1.5</td>
</tr>
<tr>
<td>t(6;14)</td>
<td>1035</td>
<td>8</td>
<td>&lt;1</td>
</tr>
</tbody>
</table>
Variables that impact prognosis in malignancy

• Patient factors
  – ‘fitness’ (age, PS etc.)

• Tumour stage
  – in myeloma, markers of disease bulk

• Tumour biology
  – Genetic lesions detected by FISH or mapping, gene expression

• Tumour responsiveness to therapy
Patient factors - age

Intensive pathway

Age <55 n=379 ms 85 mo
Age ≥55 n=731 ms 59 mo

p=5.14E-5
Patient factors - performance status

\[ p = 2.39 \times 10^{-21} \]
Patient factors - renal function

Impaired renal function (Cr>110) has a significant impact on OS

Overall Survival

\[ p = 9.8 \times 10^{-10} \]
Tumour bulk variables

Hb

Platelets

Wbc

β2M

CumSurvival vs months

Hb ≥10 n=1245
Hb <10 n=713

P=2.56E-13

Platelets greater than 150 n=1896
Platelets less than 150 n=256

P=1.08E-14

Wbc ≥3.0 n=1692
Wbc <3.0 n=99

P=0.061

β2M less than or equal to 5.5 n=906
β2M greater than 5.5 n=499

P=5.13E-16
The ISS

- Combines tumour and patient factors
- $\beta_2$M is associated with disease bulk and renal function
- Albumin is associated with general condition of patient

**Table 2. New International Staging System**

<table>
<thead>
<tr>
<th>Stage</th>
<th>Criteria</th>
<th>Median Survival (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Serum $\beta_2$-microglobulin $&lt; 3.5$ mg/L and Serum albumin $\geq 3.5$ g/dL</td>
<td>62</td>
</tr>
<tr>
<td>II</td>
<td>Not stage I or III*</td>
<td>44</td>
</tr>
<tr>
<td>III</td>
<td>Serum $\beta_2$-microglobulin $\geq 5.5$ mg/L</td>
<td>29</td>
</tr>
</tbody>
</table>

*There are two categories for stage II: serum $\beta_2$-microglobulin $< 3.5$ mg/L but serum albumin $< 3.5$ g/dL; or serum $\beta_2$-microglobulin 3.5 to $< 5.5$ mg/L irrespective of the serum albumin level.*

Greipp et al, JCO, 2005: 23;3412
Myeloma IX - The ISS

- Cumulative Survival
  - Progression-Free Survival: p=7.26E-14
  - Overall Survival: p=9.36E-23

ISS
- I: n=347 ms 27 mo
- II: n=544 ms 18 mo
- III: n=513 ms 14 mo
del 13q

PFS

OS

p=0.001

p=2.74E-4
Adverse *IGH* translocations

\[ t(4;14) + t(14;16) + t(14;20) \]
Adverse *IGH* translocations

\[ t(4;14) + t(14;16) + t(14;20) \]
17p loss

**PFS**
- Absent: n=930, ms 18 mo
- Present: n=85, ms 14 mo
- p=0.001

**OS**
- Absent: n=930, ms 50 mo
- Present: n=85, ms 27 mo
- p=7.53E-7
1q gain

PFS

OS

p=4.456E-10

p=1.24E-9
Hyperdiploidy

OS p=0.004 in intensive arm but not significant in non-intensive arm
## Multivariate analysis

<table>
<thead>
<tr>
<th>Variable</th>
<th>PFS</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hazard Ratio</td>
<td>95% CI</td>
</tr>
<tr>
<td>Adverse <em>IGH</em> Translocation</td>
<td>1.65</td>
<td>1.31 - 2.07</td>
</tr>
<tr>
<td>+1q21</td>
<td>1.46</td>
<td>1.21 - 1.76</td>
</tr>
<tr>
<td>del(17)(p13)</td>
<td>1.41</td>
<td>1.05 - 1.90</td>
</tr>
<tr>
<td>ISS (I vs II)</td>
<td>1.36</td>
<td>1.07 - 1.74</td>
</tr>
<tr>
<td>ISS (I vs III)</td>
<td>1.55</td>
<td>1.21 - 1.97</td>
</tr>
</tbody>
</table>
Inter-relationship of adverse lesions

- Adverse IGH Translocations: Total = 145
- +1q21: Total = 340
- Del(17p13): Total = 78
Impact of single lesions

- none, n=451, ms 61 mo
- 17p del, n=38, ms 44 mo
- +1q, n=213, ms 41 mo
- advIGH, n=38, ms 39 mo

p=0.002
Impact of combined lesions

\[ p = 4.518 \times 10^{-17} \]

Overall Survival

\begin{align*}
0 & \text{ n=451 ms 61 mo} \\
1 & \text{ n=289 ms 42 mo} \\
2 & \text{ n=113 ms 23 mo} \\
3 & \text{ n=16 ms 9 mo}
\end{align*}
Genetic Risk Groups

**PFS**
- 0 n=451 ms 21 mo
- 1 n=289 ms 18 m0
- >1 n=129 ms 12 mo

**OS**
- 0 n=451 ms 61 mo
- 1 n=289 ms 42 mo
- >1 n=129 ms 21 mo

$p=6.36E-15$

$p=1.08E-15$
Multivariate of genetic groupings and the ISS

<table>
<thead>
<tr>
<th>Variable</th>
<th>PFS</th>
<th></th>
<th>OS</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR</td>
<td>95% CI</td>
<td>p</td>
<td>HR</td>
</tr>
<tr>
<td>Number of adverse lesions (0 vs 1)</td>
<td>1.48</td>
<td>1.21 - 1.80</td>
<td>&lt;0.001</td>
<td>1.3</td>
</tr>
<tr>
<td>Number of adverse lesions (0 vs &gt;1)</td>
<td>2.42</td>
<td>1.89 - 3.09</td>
<td>&lt;0.001</td>
<td>2.59</td>
</tr>
<tr>
<td>ISS (I vs II)</td>
<td>1.34</td>
<td>1.05 - 1.70</td>
<td>0.019</td>
<td>1.79</td>
</tr>
<tr>
<td>ISS (II vs III)</td>
<td>1.53</td>
<td>1.20 - 1.96</td>
<td>0.001</td>
<td>2.72</td>
</tr>
</tbody>
</table>
Genetic groups split by the ISS

Low risk

Intermediate risk

High risk

p=1.02E-8

p=0.042

p=0.009
ISS split by genetic groups

ISS I

Cum Survival

- Low
- Int
- High

months

p=0.086

ISS II

Cum Survival

- Low
- Int
- High

months

p=2.97E-7

ISS III

Cum Survival

- Low
- Int
- High

months

p=8.49E-5
Combining the ISS and genetics

<table>
<thead>
<tr>
<th>Combined Risk Group</th>
<th>Group</th>
<th>Median OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Favourable Risk</td>
<td>ISS I and no adverse lesions</td>
<td>92.3</td>
</tr>
<tr>
<td></td>
<td>ISS I and 1 adverse lesion</td>
<td>68.3</td>
</tr>
<tr>
<td></td>
<td>ISS II and no adverse lesion</td>
<td>61.2</td>
</tr>
<tr>
<td>Intermediate Risk</td>
<td>ISS I and &gt;1 adverse lesion</td>
<td>54.5</td>
</tr>
<tr>
<td></td>
<td>ISS II and 1 adverse lesion</td>
<td>40.4</td>
</tr>
<tr>
<td></td>
<td>ISS III and no adverse lesion</td>
<td>43.3</td>
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<tr>
<td></td>
<td>ISS III and 1 adverse lesion</td>
<td>36.7</td>
</tr>
<tr>
<td>Ultra-High Risk</td>
<td>ISS II and &gt;1 adverse lesion</td>
<td>24.7</td>
</tr>
<tr>
<td></td>
<td>ISS III and &gt;1 adverse lesion</td>
<td>12.6</td>
</tr>
</tbody>
</table>
Combined FISH-ISS

FISH-ISS

- group 1 n=242 ms 70 mo
- group 2 n=299 ms 42 mo
- group 3 n=87 ms 19 mo

p=4.19E-21
What about response?

Intensive pathway

PFS

Non-intensive pathway

OS

- CR
- VGPR
- PR
- SD
- PD
Responses in risk groups

Genetic risk groups

ISS

FISH-ISS
FISH-ISS predicts relapse post achievement of CR

PFS post CR

OS post CR

p=1.11E-6

p=2.98E-6
Is CR important in all risk groups?

Good risk

Intermediate risk

High risk

p=0.024

p=2.31E-5

p=0.360
1p32.3 deletion

Overall Survival

Intensive pathway

- absent n=457 ms 71 mo
- present n=53  ms 41 mo

Non-intensive pathway

- absent n=306 ms 31 mo
- present n=43  ms 42 mo

p=2.52E-4

p=0.051
Multivariate analysis of genetic factors in the intensive pathway

<table>
<thead>
<tr>
<th>Variable</th>
<th>HR</th>
<th>%CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>adverse IGH</td>
<td>1.47</td>
<td>1.06 - 2.02</td>
<td>0.020</td>
</tr>
<tr>
<td>1q gain</td>
<td>1.71</td>
<td>1.32 - 2.23</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>1p loss</td>
<td>1.66</td>
<td>1.15 - 2.24</td>
<td>0.006</td>
</tr>
<tr>
<td>TP53 loss</td>
<td>2.25</td>
<td>1.54 - 3.37</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
Effect of 1p loss on genetic risk groups

**standard genetic risk groups**

- 0 abnormalities
- 1 abnormality
- >1 abnormality

**genetic risk groups inc 1p loss**

- 0 abnormalities
- 1 abnormality
- >1 abnormality

**calling 1p >1 abnormality**

- 0 abnormalities
- 1 abnormality
- >1 abnormality

- p=2.29E-10
- p=1.68E-11
- p=9.79E-13
Conclusions

• Defining prognosis in myeloma is complex, with many variables influencing outcome. It is possible to identify patients at diagnosis with poor prognosis

• The ISS is important

• Tumour genetic lesions are important

• Poor risk lesions are adverse IGH translocations [t(4;14), t(14;16), t(14;20)], +1q, 17p-

• The worst performing patients have >1 of these

• Combining FISH risk with ISS is better than either

• Poor prognostic groups are defined by ISS II or III pts with >1 adverse genetic lesion OR patients with progressive disease

• These 2 groups are distinct, and may have different biology

• Poor risk genetic patients, particularly those with 17p deletion, do particularly badly on thalidomide maintenance
Addendum

• Bortezomib appears to improve prognosis of t(4;14) patients

• Understanding interaction of new drugs with genetic abnormalities will take a long time!

• Clonal diversity also needs to be taken into account when designing treatments

• iFISH probably does still find the most important prognostic genetic factors but it is time to move on to less labour-intensive and more comprehensive methods of detection.
LLR UKMF Cytogenetic Database

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