Rafael Fonseca MD, Mayo Clinic
Michael Morley Memorial Lecture

Genomics and Precision Medicine in Myeloma; Hype or Reality?

Scottsdale, Arizona  |  Rochester, Minnesota  |  Jacksonville, Florida
Disclosures

• Consulting: AMGEN, Genzyme, BMS, Otsuka, Celgene, Medtronic

• Speakers Bureaus: None

• Research: Cylene, Proteolix

• Patent for FISH based prognostication in MM
  • About 1000 BP per year
  • If I am greatly biased maybe can earn 100 more!
Bad Medicine

• Case of using reason and rational principles in medical decisions

• Harm is done by lack of knowledge of options?
  • IGNORANCE

• Harm is done by ignoring evidence or delaying introduction?
  • INEPTITUDE
Genetics and Oncology
Precision Personalized Medicine
Determinants of outcome

- Host features
- Co-morbid conditions
- Disease biology
  - Aggressiveness
  - Responsiveness to Rx
- Tolerance to treatment
  - Genetic heterogeneity
Improved Survival in MM

Greek Myeloma Study Group (GMSG)

Thalidomide available in Greece: 1/1/2000
Group A vs. Group B: 2 (0.2%) vs. 167 (32%) given novel drugs up-front

<table>
<thead>
<tr>
<th>End-point</th>
<th>Group A N=859</th>
<th>Group B N=517</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ PR to first-line therapy</td>
<td>56%</td>
<td>67%</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Median Overall Survival</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 70 years of age</td>
<td>36 months</td>
<td>48 months</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>&gt; 70 years</td>
<td>39 months</td>
<td>74 months</td>
<td>&lt; .001</td>
</tr>
<tr>
<td></td>
<td>26 months</td>
<td>33 months</td>
<td>.273</td>
</tr>
</tbody>
</table>

Group B pts treated with novel agents upfront

4-Year Survival:

ISS Stage I  85%
ISS Stage II 61%
ISS Stage III 26%

Kastritis et al Leukemia. 2009;23(6):1152-7
Survival Has Improved… Even for High Risk MM?

Pre 2000

Post 2000

Kumar et al Blood. 2008;111(5)
Key questions

• How to integrate this information for treatment selection

• Can we tell all patients “myeloma is becoming a chronic disease”?

• What about “novel” agents?
“Now that we have identified a higher risk subset of patients they are candidates for more intensive therapies or clinical trials”

• Detection OK (maybe so, so)
• Treatment not!
Risk of dying from MM

100%
Acute Leukemia

M0  M1  M2  M3  M4  M5  M6  M7

Myeloma

SC  Pre  Pro  Early  Mid  SHM  ICS  PC

Hyperdiploidy

t(11;14)

t(4;14)

t(14;16)

t(6:14)

3 decades
# Classification of MM

<table>
<thead>
<tr>
<th>Ploidy</th>
<th>Prognosis</th>
<th>H</th>
<th>Morph</th>
<th>CD20</th>
<th>ras</th>
<th>-13</th>
<th>Bone DKK1</th>
<th>CCND</th>
</tr>
</thead>
<tbody>
<tr>
<td>t(11;14) (CCND3)</td>
<td>NH</td>
<td>Good</td>
<td>G</td>
<td>κ</td>
<td>+++</td>
<td>++</td>
<td>-/+</td>
<td>++</td>
</tr>
<tr>
<td>t(14;16) (other MAF)</td>
<td>NH</td>
<td>Poor</td>
<td>A</td>
<td>λ</td>
<td>-</td>
<td>-</td>
<td>++</td>
<td>+/-</td>
</tr>
<tr>
<td>t(4;14)</td>
<td>NH/h</td>
<td>Poor</td>
<td>A</td>
<td>λ</td>
<td>-</td>
<td>-</td>
<td>+++</td>
<td>+/-</td>
</tr>
<tr>
<td>Other IgH</td>
<td>H/NH</td>
<td>Poor</td>
<td>?</td>
<td>?</td>
<td>-</td>
<td>-/+</td>
<td>?</td>
<td>+</td>
</tr>
<tr>
<td>Hyper</td>
<td>H</td>
<td>Good</td>
<td>G</td>
<td>κ</td>
<td>-</td>
<td>++</td>
<td>+/-</td>
<td>++</td>
</tr>
</tbody>
</table>
Classification schemes

• Biology classification
  • Pathophysiology
  • Progression events

• Prognostic classification
  • Baseline features
  • Natural history

• Predictive classifications
  • Therapy specific

Translocations
  MGUS to MM

t(4;14)
-17p13

TRAFL3
254 patients with myeloma and abnormal karyotypes

Fonseca Blood 102:25622003
254 patients with myeloma and abnormal karyotypes

- **IgH translocation**
- **No IgH translocation**

Fonseca Blood 102:25622003
Genetic Classification of MM

Primary IgH TRXs
Non Hyperdiploid

Secondary IgH TRX
Ploidy variable

No IgH TRX
Hyperdiploid

Gene expression

Fonseca Blood 102:25622003
Ploidy and Age

Ross et al Leukemia (2005) 19, 1634–1642

![Diagram showing the relationship between ploidy and age]

- High risk cytogenetics
- Less bone disease
- IgA lambda
- Hyperdiploidy
- Bone disease
- IgG kappa

Advancing age at time of diagnosis

![Graph showing the relationship between age and hyperdiploidy]

Log Likelihood Test P=0.001

![Graph showing the relationship between age and IgH translocation]

Log Likelihood Test P=0.004
Molecular Prognostic Model

- Survival probability
- Months
- P<0.001

- All others including t(11;14)
  - Δ13
  - Poor
  - Intermediate
  - Good

- t(4;14)
- t(14;16)
- -17p13

24.7 mos
42.3 mos
51.0 mos

FISH detected Abnormalities

Avet-Loiseau H et al., Blood 2007
# High Risk Disease Bortezomib

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Outcome measured (P value)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>New diagnosis</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vista[^58]</td>
<td>25/142</td>
<td>Same CR 28%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>EFS 19.8 vs. 23.1 (0.5)</td>
</tr>
<tr>
<td>Shaughnessy TT2[^117]</td>
<td>35/341</td>
<td>Hazard ratio of 2.34 (&lt;0.001)</td>
</tr>
<tr>
<td>Shaughnessy TT3[^117]</td>
<td>42/419</td>
<td>Hazard ratio of 1.45 (1.74)</td>
</tr>
<tr>
<td>Avet-Loiseau[^*]</td>
<td>507</td>
<td>t(4;14) PFS 28 vs. 35 (p&lt;0.02)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3 year OS 73% vs 89% (p=0.002)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No difference with VAD</td>
</tr>
<tr>
<td><strong>Relapsed RR</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jagannath (SUMMIT)[^118]</td>
<td>26/147</td>
<td>EFS 24 vs. 33 (NS)*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>EFS 24 vs. 38 (0.36)**</td>
</tr>
<tr>
<td>Jagannath (APEX)[^118]</td>
<td>11/74</td>
<td>EFS 20 vs. 38 (0.2)*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>EFS 25 vs. 35 (NS)**</td>
</tr>
<tr>
<td>Chang[^119]</td>
<td>65</td>
<td>ORR 67 vs. 55% (NS)</td>
</tr>
<tr>
<td>Chang[^120]</td>
<td>85</td>
<td>No difference in OS or PFS</td>
</tr>
<tr>
<td>Pineda-Roman[^121]</td>
<td>85</td>
<td>t(4;14) class was favorable</td>
</tr>
</tbody>
</table>
### VMP and High Risk Disease

<table>
<thead>
<tr>
<th>Response</th>
<th>Total (N=165)</th>
<th>High Risk (N=26)</th>
<th>Std Risk (N=139)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR (IF-)</td>
<td>32%</td>
<td>35%</td>
<td>32%</td>
</tr>
<tr>
<td>≥PR</td>
<td>82%</td>
<td>81%</td>
<td>82%</td>
</tr>
</tbody>
</table>

**TTP**

- **VMP standard risk (N=142):** 23.1 months (34 events)
- **VMP high risk (N=26):** 19.8 months (7 events)

**HR = 1.297 (95% CI: 0.55, 3.06)**

**OS**

- **VMP standard risk (N=142):** not reached (16 events)
- **VMP high risk (N=26):** not reached (3 events)

**HR = 1.009 (95% CI: 0.278, 3.663)**

*San Miguel et al NEJM 2008, 359:906*
**Study design and aim**

**Induction** (x6) Bz weekly except in the 1st

- Bort/Mel/Pred (VMP)
- Bort/Thal/Pred (VTP)

**Maintenance** x3 years; Bz / 3m *

- Bort/Thal (VT)
- Bort/Pred (VP)

**260 pts**

**ORR (CR) rate** .................80% (42% )

**TTP/PFS** .........................35 m/31m; OS (at 3 y) ..........70%

1. No differences in RR between VMP & VTP
2. Increase in CR from 23% to 42% with maintenance without differences between VT/VP
3. No differences in outcome between both induction and maintenance regimens

Mateos et al. Lancet Oncology 2010; 10(11): 934-41
Study population stratified according to cytogenetic abnormalities

- 232 pts
  - Standard-risk
    - no cytogenetic abnormalities ± del (13q) ± t(11;14)
      - 188 pts (80%)
  - High-risk
    - t(4;14) ± t(14;16) ± del(17p)
      - 44 pts (19%)
  - t(4;14) ± del(13q)
    - 17 (7%)
  - del(17p) ± del(13q)
    - 21 (9%)
  - both
    - 3 (1%)
  - t(14;16)
    - 3 (1%)
Outcome according to cytogenetic abnormalities from 1\textsuperscript{st}/2\textsuperscript{nd} randomization

Median follow-up: 32 m

PFS from 1\textsuperscript{st} randomization

Standard risk: 33 m
High risk: 24 m
HR: 1.5, 95% IC: 1.0-2.3
p=0.04

PFS from 2\textsuperscript{nd} randomization

Standard risk: 27 m
High risk: 17 m
HR: 2.0, 95% IC: 1.2-3.5
p=0.01
Overall survival according to cytogenetic abnormalities

Standard risk: NR
High risk: 38m

HR: 2.3, 95% IC: 1.4-4.0
p=0.001
(A) Event-free survival (EFS) and (B) overall survival (OS) in patients with t(4;14) treated with bortezomib-dexamethasone (Vel/Dex) induction (n = 106) or vincristine, doxorubicin, and dexamethasone (VAD) induction (n = 98; EFS and OS in years; P < .001 for EFS and OS).

Avet-Loiseau H et al. JCO 2010;28:4630-4634
(A) Event-free survival (EFS) and (B) overall survival (OS) in patients with t(4;14) (n = 106) or without t(4;14) (n = 401) treated with bortezomib-dexamethasone induction (EFS and OS in years; P < .02 for EFS; P = .002 for OS).
Survival by t(14;16) status

Translocation t(14;16) and multiple myeloma: is it really an independent prognostic factor?

Hervé Avet-Loiseau,1 Florent Malard,1 Loic Campion,2 Florence Magrangeas,1 Catherine Sebba,3 Bruno Lioure,4 Olivier Decaux,5 Thierry Lamy,6 Laurence Legros,7 Jean-Gabriel Fuzibet,8 Mauricette Michallet,9 Bernadette Corront,10 Pascal Lenain,11 Cyrille Hulin,12 Claire Mathiot,13 Michel Attal,14 Thierry Facon,15 Jean-Luc Harousseau,16 Stephane Minvielle,1 and Philippe Moreau,17 for the Intergroupe Francophone du Myélome

![Graph B](image)

\[ P=0.002 \]

![Graph C](image)

\[ P<0.001 \]

\[ n=26, \text{ms 14.4 mo} \]

\[ n=1576, \text{ms 45.1 mo} \]
New Diagnosis MM

Primary genetic factors
Translocations, hyperdiploidy, etc.

Progression factors
p53 deletion, NF-kB

A
MGUS

B
New diagnosis MM

C
Intramedullary disease
Extramedullary progression

Time from disease initiation
Survival by p53 mutation

Log Rank Test p=0.004

<table>
<thead>
<tr>
<th>P53 Mutation</th>
<th>TOTAL</th>
<th>DEAD</th>
<th>ALIVE</th>
<th>MEDIAN</th>
</tr>
</thead>
<tbody>
<tr>
<td>P53 Mutation: No</td>
<td>259</td>
<td>249</td>
<td>10</td>
<td>41.4</td>
</tr>
<tr>
<td>P53 Mutation: Yes</td>
<td>9</td>
<td>9</td>
<td>0</td>
<td>16.7</td>
</tr>
</tbody>
</table>

Chng et al Leukemia 2007, 3:582
TTP and OS del 17p13

Graphs showing time to progression and overall survival by del(17p)

<table>
<thead>
<tr>
<th>Group</th>
<th>No. of subjects</th>
<th>Event</th>
<th>Censored</th>
<th>Median survival (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>no del(17p)</td>
<td>118</td>
<td>60% (81)</td>
<td>31% (37)</td>
<td>8.17 (5.90–11.80)</td>
</tr>
<tr>
<td>del(17p)</td>
<td>12</td>
<td>92% (11)</td>
<td>8% (1)</td>
<td>2.22 (0.90–4.37)</td>
</tr>
</tbody>
</table>

HR = 2.817, P = 0.0014

<table>
<thead>
<tr>
<th>Group</th>
<th>No. of subjects</th>
<th>Event</th>
<th>Censored</th>
<th>Median survival (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>no del(17p)</td>
<td>119</td>
<td>47% (58)</td>
<td>53% (62)</td>
<td>23.70 (14.70–NA)</td>
</tr>
<tr>
<td>del(17p)</td>
<td>12</td>
<td>75% (9)</td>
<td>25% (3)</td>
<td>4.67 (1.73–12.90)</td>
</tr>
</tbody>
</table>

HR = 3.227, P = 0.0013

OS for relapse/refractory MM patients with or without p53 deletion was 4.2 months vs 37.8 months, p <0.01
Studied 8 patients with 17p deletions at RR 7 did not have deletion at diagnosis

FISH (MGUS n=184, SMM n=116, relapsed MM n=62 and PCL n=26)
aCGH (newly diagnosed MM n=224, relapsed MM n=158 and HMCLs n=48)

*p 53 mutational status was evaluated in relapsed MM (n=84) and HMCLs (n=48)

*Tiedemann et al. Leukemia. 2008; 22, 1044-1052
Fonseca. Manuscript in preparation
(A) Event-free survival (EFS) and (B) overall survival (OS) in patients with del(17p) (n = 54) or without del(17p) (n = 453) treated with bortezomib-dexamethasone induction (EFS and OS in years; \( P < .001 \) for EFS and OS).
Staging of MM

**Clinical staging**

1. **Benign disease**
   - MGUS
   - SMM

2. **New diagnosis**
   - MM

3. **First relapse**

4. **Second relapse**

**Molecular staging**

1. **Dormant clone**

2. **Malignant p53 normal**

3. **Malignant p53 abnormal**

4. **Malignant p53 abnormal plus**
**OS New Diagnosis MM Treated RD/d**

**Figure A.** - 18.5 months for high-risk versus 36.5 months for standard-risk patients (P < .001)

Genomic Abnormalities

Avet-Loiseau H et al., JCO 2009

Patients at risk:

<table>
<thead>
<tr>
<th></th>
<th>53</th>
<th>50</th>
<th>44</th>
<th>22</th>
<th>2</th>
<th>0</th>
</tr>
</thead>
<tbody>
<tr>
<td>86</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>46</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Time (months)

Probability of Overall Survival

- $P < .0001$

- **Green**: amp(5q) no del(12p) low S$\beta$M
- **Black**: others
- **Red**: amp(5q) high S$\beta$M del(12p) or no amp (5q) and [high S$\beta$M and/or del(12p)]
(A) Gain of 1q21; (B) amplification of 5p; (C) deletion of CD27; and (D) deletion of CDKN1B.
(A) Gain of 1q21; (B) amplification of 5p; (C) deletion of CD27; and (D) deletion of CDKN1B.
GEP signatures

Shaughnessy et al, Blood 2007, 109(6), 2276-2284
OVERALL SURVIVAL

NEW PROTOCOLS:

Low risk: TT4 (reduce toxicities)
Randomize TT3 v TT3-lite

High risk: TT5 (sustain CR)
MEL80-VTD- PACE
R-VD / M-VD maintenance

EVENT-FREE SURVIVAL

CR DURATION

Bodes well for cure!!!

Courtesy of Dr Barlogie
### Tests

<table>
<thead>
<tr>
<th>Tests</th>
<th>Results</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>TC Class(^1)</td>
<td>D1</td>
<td>Suspect hyperdiploid patient should be confirmed by FISH, generally a good prognosis marker</td>
</tr>
<tr>
<td>UAMS Molecular Group</td>
<td>MY</td>
<td>Can't be classified to many contaminating non-tumor cells</td>
</tr>
<tr>
<td>UAMS 70 Gene Ratio(^2)</td>
<td>-0.13</td>
<td>Good Prognosis; TT2 cutoff was 0.66 and TT3 cutoff was 0.79; (50-60 Percentile)</td>
</tr>
<tr>
<td>Proliferation Indices</td>
<td>PLB12 8.456</td>
<td>nPC range (20-30th Percentile)</td>
</tr>
<tr>
<td></td>
<td>JJK28 7.589</td>
<td>nPC range (20-30th Percentile)</td>
</tr>
<tr>
<td>Centrosome Signature</td>
<td>9.81324312</td>
<td>nPC/Benign range (30-40th Percentile)</td>
</tr>
<tr>
<td>NFKB Indexes</td>
<td>Keats 0.25</td>
<td>Less than normal NFKB activity</td>
</tr>
<tr>
<td></td>
<td>Annunziata 8.92</td>
<td>Less than normal NFKB activity</td>
</tr>
<tr>
<td>Contamination Estimates</td>
<td>Macrophage 233.86</td>
<td>Sample is likely a pure plasma cell population, results should be accurate</td>
</tr>
</tbody>
</table>

Genes of Interest

Therapeutic Antibody Targets

Mechanisms of Therapeutic Resistance

**Quality Control**

<table>
<thead>
<tr>
<th>Percent Kappa</th>
<th>Percent Lambda</th>
<th>RNA Integrity (RIN)</th>
<th>Array QC</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>97</td>
<td>8.5</td>
<td>2/3 Very Good</td>
</tr>
</tbody>
</table>

This test is only done as a research test and is not meant to replace standard clinical testing and analysis. Treatment decisions reside solely on the global interpretation of all information and should be discussed with the treating physician. These tests and results are not done in a clinical laboratory, they are not CLIA certified and are not billed to the patient or insurance company. The patients and treating physician understand these results are provided merely as a courtesy and with no implicit expectations or endorsements of any therapy in particular.
**Tests** | **Results** | **Interpretation**
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Genes of Interest

**Quality Control**

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<th>Percent Kappa</th>
<th>Percent Lambda</th>
<th>RNA Integrity (RIN)</th>
<th>Percent Present</th>
<th>GAPDH Ratio</th>
<th>Actin Ratio</th>
<th>Array QC</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>97</td>
<td>8.5</td>
<td>36.70</td>
<td>1.35</td>
<td>10.44</td>
<td>2/3</td>
</tr>
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Hyperdiploid

Group 1 - Mayo patients (N=53)

CTA / Proliferation
- ASPM
- BIRC5
- C4A
- CDC2
- CENP-A
- CST3
- C1AG2
- DLG7
- FLJ10719
- FLJ21841
- GAGE5
- GAGED2
- KIF20A
- MAGEA1

CTA / Proliferation Signature

HGF / IL6
- HGF
- IL6
- PTP4A3
- SOCS

HGF / IL6

NFkB / Anti-apoptosis
- ABCG2
- BIRC3
- CD74
- CFLAR
- CKIP-1
- FLJ13725
- FLJ23255
- GBA3
- GH1
- KIAA0626
- KIAA0846
- LAPTM4B
- LAPTM5
- MALAT1
- MGC4809
- NSIP2
- OSBL1A
- PCDHG3
- PHF15
- PLEK
- RND1
- Rras
- Rras2
- TNFAIP3
Genetic prognostic factors
## Real Time Report Generated for Patient and Treating Physician

### N of 1

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### UAMS 70 Gene Ratio

-0.13

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<th>Indices</th>
<th>Value</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>JJK28</td>
<td>7.589</td>
<td>nPC range (20-30th Percentile)</td>
</tr>
<tr>
<td>Centrosome Signature</td>
<td>9.81324312</td>
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</tr>
<tr>
<td>Keats</td>
<td>0.25</td>
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</tr>
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<tr>
<td>Macrophage</td>
<td>233.86</td>
<td>Sample is likely a pure plasma cell population, results should be accurate</td>
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</table>

### Quality Control

<table>
<thead>
<tr>
<th>Percent Kappa</th>
<th>Percent Lambda</th>
<th>RNA Integrity (RIN)</th>
<th>Array QC</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>97</td>
<td>8.5</td>
<td>2/3 Very Good</td>
</tr>
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</table>

**Percent Present**

- GAPDH Ratio: 1.35
- Actin Ratio: 10.44

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### Real Time Report Generated For Patient and Treating Physician

**N Of 1**

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<tr>
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<th>Results</th>
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</tr>
</thead>
<tbody>
<tr>
<td>TC Class¹</td>
<td>D1</td>
<td>Suspect hyperdiploid patient should be confirmed by FISH, generally a good prognosis marker</td>
</tr>
<tr>
<td>UAMS Molecular Group</td>
<td>MY</td>
<td>Can't be classified to many contaminating non-tumor cells</td>
</tr>
<tr>
<td>UAMS 70 Gene Ratio²</td>
<td>-0.13</td>
<td>Good Prognosis; TT2 cutoff was 0.66 and TT3 cutoff was 0.79; (50-60 Percentile)</td>
</tr>
<tr>
<td>Proliferation</td>
<td>PLB12 8.456</td>
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### Genes of Interest

#### Therapeutic Antibody Targets

#### Mechanisms of Therapeutic Resistance

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REAL TIME REPORT GENERATED FOR PATIENT AND TREATING PHYSICIAN

**N OF 1**

<table>
<thead>
<tr>
<th>Physician</th>
<th>Sample Date</th>
<th>Mayo Array ID</th>
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<tbody>
<tr>
<td>Rafael Fonseca</td>
<td>6/9/2010</td>
<td>MC1786_MCA0928_BM_CD138pos_U133P2</td>
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Contamination Estimates

Macrophage: 233.86
Poly PC

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Clinical Course - Case Report

- Rev/d (21 Cycles)
- PR-171 (3 Cycles)
- Velcade
- SGN-40
- Cyclo Pred

Graph showing IgA levels and Kappa/Lambda FLC ratio over time with annotations for BM#1 CGH & GEP and BM#2 CGH.
A significant number of differences were detected (The most of any pair studied to date). However, it is possible to sort out the driver events, diagnostic passenger events, and events unique to the relapse sample that may mediate Rev/d resistance.
Common and Unique CNA are Present in the Two Samples
Acquisition of BIRC2/3 Deletion
Laboratory Regulations

• Complex system in the US
• Rules and regulations fall short of state of the art
• Difficulty in converting into clinical tests
• Impossibility of validating every result
  • *e.g.* RT-PCR
  • *e.g.* Direct sequencing
Limitations of promises

- Predictive and prognostic value of tests
- Physician and pt understanding of the HR
- How to integrate this into the clinic
- What will government and commercial insurers will pay
- Medical malpractice risks
Adding up all factors

- So how do we estimate prognosis?

\[
\begin{align*}
I_x &= \frac{4 \cos^2\theta (\sin^2\theta - n^2)}{(1 - n^2) \left[(1 + n^2)\sin^2\theta - n^2\right]} \\
I_y &= \frac{4 \cos^2\theta}{1 - n^2} \\
I_z &= \frac{4 \cos^2\theta \sin^2\theta}{(1 - n^2) \left[(1 + n^2)\sin^2\theta - n^2\right]} 
\end{align*}
\]
The future

- More and more genetic testing will occur
- Results will come more as an interpretation
- Prices will come down
- Better treatments
- Better outcomes
- Cures!
Submarine
In AZ everything is possible!
Acknowledgements

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Leif Bergsagel
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Robert Kyle
SV Rajkumar
Dysproteinemia Group
Joe Mikhael
Craig Reeder
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Syed Jalal
Rhett Ketterling

Mayo Clinic
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Travis Henry
Samar Issa
Angela Mayo
Jacy Spong

TGEN
Jeff Trent
John Carpten
Mike Barrett

Laboratory
Greg Ahmann
Scott Van Wier
Tammy Price-Troska
Rachel Hagerty
Kim Henderson
Laboratory

NUS
Wee Joo Chng