INTERNATIONAL MYELOMA FOUNDATION
presents

Myeloma Updates 2016: Post ASCO / EHA / IMWG

Learn more about current trends in myeloma treatment and research with this update from three major medical meetings held in May and June 2016.

Dr. Brian G.M. Durie will explain what’s new and exciting from the American Society of Clinical Oncology (ASCO), the European Hematology Association (EHA), and the International Myeloma Working Group Summit (IMWG).

You won’t want to miss this free IMF teleconference followed by a 30-minute Q&A session! Save the date, register now!

Date: Thursday, July 7, 2016
Time: 4:00 p.m. Pacific / 5:00 p.m. Mountain / 6:00 p.m. Central / 7:00 p.m. Eastern
Speaker: Dr. Brian G.M. Durie, IMF Chairman of the Board
Duration: 60 minutes (including Q&A)
7th International Myeloma Working Group Summit

June 7–9, 2016 • Copenhagen, Denmark
Let’s start with the IMWG Summit…

… which was a big success!

Keynote topics:

- iSTOP MM
- MRD
- Imaging
- Immune therapies
- CURE
- Sequencing vs. iFISH
- Transplant?
- Cost stratified treatment
All 35 laboratories in Iceland participate
Euro 2016: How tiny Iceland reached Europe's pinnacle

By Motez Bishara

6% of the Icelandic population will be there
deCODE’s whole-genome sequencing project

- **2,600 Icelanders sequenced**
  - Average coverage 20x - Illumina GA and HiSeq
    - Genome Analysis ToolKit calling
  - Individuals from trios, high risk families, and specific diseases
  - Sequence variants identified
    - 36.2 Million markers (SNPs and INDEL’s)
    - 22,000 LOF mutations classified by snpEFF/ANNOVAR
      - 7,016 framshift INDEL’s
      - 5,684 splice acceptor/donor
      - 6,350 stop gained
      - 670 stop or start loss
    - 186,000 Non-Synonymous
    - **DNA samples from 120,000 Icelanders all chip typed**
iSTOP MM Iceland Project

iS T O P
Iceland Screens Treats Or Prevents Multiple Myeloma

Partners
• Sigurdur Kristinsson, University of Iceland
• Binding Site

140,000 adults > Age 40

Screen

Establish criteria for classification/progression

HR SMM

Prevent Multiple Myeloma

CURE Trial

CURE!
Techniques to Monitor MRD

- Flow cytometry
- ASO-PCR / ddPCR
- Next-gen sequencing
- PET/CT

Cellular Imaging
### IMWG Criteria for MRD in Multiple Myeloma

<table>
<thead>
<tr>
<th>Response category</th>
<th>Response criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sustained MRD negative</strong></td>
<td>MRD negative in the marrow (Next-generation flow or Next-generation sequencing) and by imaging as defined below, confirmed one year apart. Subsequent evaluations can be used to further specify the duration of negativity (e.g., MRD negative @ 5 years etc)</td>
</tr>
<tr>
<td><strong>Imaging MRD-negative</strong></td>
<td>MRD negative as defined below (Next-generation flow or Next-generation sequencing) PLUS Disappearance of every area of increased tracer uptake found at baseline or a preceding PET/CT³</td>
</tr>
<tr>
<td><strong>Flow MRD-negative</strong></td>
<td>Absence of phenotypically aberrant clonal plasma cells by next-generation flow cytometry⁴ on bone marrow aspirates using the EuroFlow standard operation procedure for MRD detection in MM (or validated equivalent method) with a minimum sensitivity of 1 in $10^5$ nucleated cells or higher</td>
</tr>
<tr>
<td><strong>Sequencing MRD negative</strong></td>
<td>Absence of clonal plasma cells by next generation sequencing on bone marrow aspirates in which presence of a clone is defined as less than 2 identical sequencing reads obtained after DNA sequencing of bone marrow aspirates using the Lymphosight® platform (or validated equivalent method) with a minimum sensitivity of 1 in $10^5$ nucleated cells⁵ or higher</td>
</tr>
</tbody>
</table>

Kumar SK, et al. Lancet Oncology in press

1. **Optimal antibody panel**
2. **Bulk lyse sample processing**
3. **Novel data analysis strategies**

Standardized sample processing → systematic acquisition of $\geq 10^7$

Infinicyt software (version 1.8.0 RC6): PCA, file merge, automated gating

<table>
<thead>
<tr>
<th>Tube</th>
<th>BV421</th>
<th>BV510</th>
<th>FITC</th>
<th>PE</th>
<th>PerCP</th>
<th>Cy5.5</th>
<th>PECy7</th>
<th>APC</th>
<th>APCC750</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CD138</td>
<td>CD27</td>
<td>CD38</td>
<td>CD56</td>
<td>CD45</td>
<td>CD19</td>
<td>CD117</td>
<td>CD81</td>
<td>cyKappa</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>cyLambda</td>
</tr>
</tbody>
</table>

Flores-Montero, submitted 2016
Groups of events to be reclassified into cell populations

Reference Database

Output for the cluster: Events classified as cell populations

Next generation Flow-MRD monitoring in MM
Includes automated analysis

Flores-Montero J, et al. manuscript in preparation
Next generation Flow-MRD monitoring in MM - immediate and simultaneous sample QC -

7.5% of samples not suited for MRD in multicenter (international) trials
**NEXT GENERATION FLOW-MRD IN MM:**
New flow technique vs Next Generation Sequencing

NGS was applicable in 27/31 (87%) of MM cases

<table>
<thead>
<tr>
<th>Next Generation Flow-MRD</th>
<th>-</th>
<th>+</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Next Generation Sequencing MRD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-</td>
<td>7/27 (26%)</td>
<td>6/27 (22%)*</td>
<td>13/27 (48%)</td>
</tr>
<tr>
<td>+</td>
<td>1/27 (4%)*†</td>
<td>13/27 (48%)</td>
<td>14/27 (52%)</td>
</tr>
<tr>
<td>Total</td>
<td>8/27 (30%)</td>
<td>19/27 (70%)</td>
<td></td>
</tr>
</tbody>
</table>

* 2/6 patients showed disease progression
† This patient is still in remission after 14 months
NEXT GENERATION FLOW:
Impact of MRD on Progression-Free Survival (n=79)

Patients in VGPR, CR/sCR

NGF status

NGF− (n=37), 75% PFS: NR*

NGF+ (n=42), 75% PFS: 10 months

NGF− (n=37), 75% PFS: NR*

NGF+/2nd Generation Flow+ (n=26), 75% PFS: 12 months

NGF+/2nd Generation Flow− (n=16), 75% PFS: 10 months

P = .01

P = .04

Time from MRD assessment (months)

- Relapsed patients in this group corresponded to 1 sample with low acquired cellularity (<5x10^6) PB contamination and a second one also showing clear contamination with PB
# Black Swan Myeloma MRD Consortium

## US Sites

- **Mayo**
  - Research: Kumar (ECOG)
  - **Clinical: Jevremovic (reference)**
- **Roswell Park**
  - Research: McCarthy (Alliance)
  - **Clinical: Wallace (reference)**
- **MDAH:** Manasanch (SWOG)
- **Levine:** Usmani (SWOG)
- **Columbia:** Lentzsch
- **Mt. Sinai:** Jagannath
- **Cornell:** Niesvizky
- **Univ Chicago:** Jakubowiak
- **Ann Arbor:** Cole
- **UCSF:** Martin
- **Seattle:** Bensinger
- **City of Hope:** Krishnan
- **Others pending!**
Immune Therapies at IMWG

• Reviewed by Dr. Joseph Mikhail

• Actively discussed

• Great interest in new technologies
  • CAR-T cells
  • NK cells
  • Check point inhibitors
2015 Was an Amazing Year in Expanding Treatment Options for Multiple Myeloma

What to treat with...at diagnosis or relapse?

- **2015** Daratumumab
- **2015** Ixazomib
- **2015** Elotuzumab
- **2015** Panobinostat
- **2013** Pomalidomide
- **2012** Carfilzomib
- **2007** Doxorubicin
- **2006** Lenalidomide
- **2006** Thalidomide
- **2003** Bortezomib
- **1986** High-Dose Dex
- **1983** Auto Transplantation
- **1962** Prednisone
- **1958** Melphalan
- **1960**
- **1970**
- **1980**
- **1990**
- **2000**
- **2010**

- **1962** Prednisone
- **1983** Auto Transplantation
- **1986** High-Dose Dex

Auto = Autologous; Dex = Dexamethasone
The reality, even for experts in the field…

In 2016: what is the optimal choice for a specific patient?

Discussed by Philippe Moreau

Cost/access stratified guidelines in preparation
Allogeneic transplant: First reports of cure, but…
“investigational approach” (mortality, age, donor)

Autologous stem cell transplant: 5-10% MM patients remain in CR > 10 y…….. “operationally cured”

Novel Drugs: IMIDS & proteasome inhibitors
Up-front setting…………… Survival x 2-3 in last decade

To consider MM a “potentional curable disease” ……
the fraction of patients in cCR (at 10y) should increase to 30-50%
Treatment for Cure for Myeloma

**Induction** (VTD or KRD)+(Dara)

**ASCT** (Bu-MEL) (Tandem)

**CR**

**No CR**

**Consolidation** (Bz-Len-Dx)

**Maintenance** (Len +/- Ixa)

Options:
- KRD+Dar
- KRD+Dar
- KRD+Dar
- ...

International Myeloma Foundation
**Treatment for CURE for HR SMM**
Curative Estrategia Smouldering Alto Riesgo (CESAR trial)

**Induction** 6 cycles of KRd

- MRD → ↓
- ASCT (melphalan 200)

- MRD → ↓
- Consolidation (2 cycles of KRd)

- MRD → ↓
- Maintenance (Len-dex for 2yrs)

- MRD

**Primary objective:** To evaluate the proportion of patients in sustained immunophenotypic response at 5 years

**Hypothesis:** At least 50% of patients will achieve the objective

(n:90) @ 20 centers
PET/CT and FLOW MRD MONITORING BEFORE MAINTENANCE

Moreau P. et al, ASH 2015

- 86/134 evaluated by both PET/CT and flow
- 47.7% both negative
ASCO 2016

Friday, June 3rd – Tuesday, June 7th

• Longer/less intense versus ASH

• Main oral: Friday, 8 abstracts

• Plenary session: Sunday, CASTOR Study

• Each day: Education/Meet Prof/Discussion sessions

• Novel therapies: Tuesday, 3 abstracts
Education/Meet Prof/Discussion Sessions

- Defining/re-defining myeloma: Rajkumar
- Rare subtypes: Treon
- Highlights + post-plenary: Dimopolous/Palumbo/Richardson
- Poster discussions: Martin/Zonder/Landgren/Alliwadi
- Personalized therapy: Lonial/Munshi/Avet-Loiseau
- New novel therapies: Lonial/Fonseca/Cohen
Plenary: CASTOR Study
Abstract: Late-breaking #4: Palumbo, et al

**Figure 2. Castor study design.**

- **Dvd**
  - Bortezomib 1.3 mg/m² SC: Days 1, 4, 8, and 11;
  - Dexamethasone 20 mg PO: Days 1, 2, 4, 5, 8, 9, 11, 12 (1st 8 cycles) +
  - DARA 16 mg/kg IV: weekly x10, q3w until end of Vd, then q4w until disease progression

- **Vd**
  - Bortezomib 1.3 mg/m² SC: Days 1, 4, 8, and 11;
  - Dexamethasone 20 mg PO: Days 1, 2, 4, 5, 8, 9, 11, 12 (1st 8 cycles)

---

**Notes:**
- Dvd, daratumumab, bortezomib, and dexamethasone; SC, subcutaneously; PO, orally; DARA, daratumumab; q3w, every 3 weeks; q4w, every 4 weeks; Vd, bortezomib and dexamethasone.
### CASTOR Study Results

<table>
<thead>
<tr>
<th></th>
<th>DARA Vd</th>
<th>Vd Alone</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median PFS</td>
<td>NR</td>
<td>7.2 months</td>
<td>&lt; 0.0001*</td>
</tr>
<tr>
<td>1 year PPS</td>
<td>61%</td>
<td>27%</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>≥ PR</td>
<td>83%</td>
<td>63%</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>MRD Negative</td>
<td>14%</td>
<td>3%</td>
<td>--------</td>
</tr>
</tbody>
</table>

*HR 0.39 (v 0.53 KRd; 0.72 EloRd)
ASCO: Main Oral Session

- #8000 Upfront ASCT, Cavo et al
- #8001 Revlimid Maintenance/Meta Analysis, Attal et al
- #8002 Ixazomib cd Frontline, Lacy et al
- #8003 Genetics of HR SMM, Mailankody et al
- #8004 New Diagnostic Criteria, Ravi et al
- #8005 SAR at Relapse, Richter et al
- #8006 Plitidepsin at Relapse, Ocio et al
- #8007 CAR/POM/DEX, Rosenbaum et al
- #8008 Ixazomib/POM/DEX, Krishnan et al
Upfront ASCT: VMP vs. CyBorD/ASCT
Abstract #8000: Cavo et al (EMN02/H095)

- 1,503 patients
  - VMP: 512
  - CyBorD/ASCT: 754
- Responses: ≥ VGPR 74% vs. 84%
- PFS superior with upfront ASCT
Meta-analysis of overall survival*

- 3 randomized trials: 1,209 patients
- Median follow up 6.6 years
- Median overall survival: 86 months v. not reached: $P = 0.001$
- At 5 years 66% v. 71%
  - 6 years 58% v. 65%
  - 7 years 50% v. 62%
- Benefit for $\leq$ PR as well as VGPR/CR patients
Genetic plasma cell signatures in high-risk smoldering myeloma versus multiple myeloma patients

June 8, 2016

Sham Mailankody, MBBS, Assistant Attending Physician
Ola Landgren, MD, PhD, Professor of Medicine, Chief Attending Physician

Myeloma Service, Memorial Sloan-Kettering Cancer Center
New York
www.MSKCC.org
Patients with mutations in significantly recurrent multiple myeloma genes

- New diagnosed multiple myeloma: n/N(%)=17/39 (44%)
- Smoldering myeloma: n/N (%)=1/17 (6%)

Fisher’s exact test: P=0.005

Newly diagnosed multiple myeloma versus smoldering myeloma.
• Pembro/Rd: Phase I-II
  (PD-1 MoAb)
  Tolerable safety: ≥ PR (13/17) 76%: 2 VGPRs

• Venetoclax/Vd: Phase 1b
  (Bcl 2 inhibitor)
  Acceptable safety: ≥ PR (21/41) 51%: 17-100%

• Plitidepsin/Vd: Phase 1
  (anti-EF1A2)
  Well-tolerated: ≥ PR 56% : ≥ VGPR 33%
ASCO Focus on Value and Costs

- See blog: http://brianduriemd.myeloma.org/?q=content/asco-2016-more-excitement-about-daratumumab-darzalex%C2%AE-and-tremendous-interest-value-and
  - Routine management most costly
  - Triple therapy (KRd) can reduce costs
  - VRd more costly but better than CyBorD for high risk
  - Pomalidomide base regimens better/less costly versus Carfilzomib combos or vice versa!
- Treating adverse events is expensive

Costs are high!
HIGHLIGHT STUDY AT EHA
POLLUX: STUDY DESIGN*

RRMM patients receiving ≥1 prior line of tx

1:1

Randomize

**RRMM patients receiving ≥1 prior line of tx**

**Stratification factors**
- # prior lines of tx
- ISS staging
- Prior R treatment

---

**DRd (n = 286)**
- Daratumumab 16 mg/kg IV
  - Qw in Cycles 1-2, q2w in Cycles 3-6, then q4w
- R 25 mg PO Days 1-21/cycle
- d 40 mg PO 40 mg qw

Treat to PD or unacceptable toxicity

Interim analysis: ~177 PFS events

**Rd (n = 283)**
- R 25 mg PO Days 1-21/cycle
- d 40 mg PO 40 mg qw

Treat to PD or unacceptable toxicity

---

*aPre-medication for DRd consisted of dexamethasone 20 mg, paracetamol 650 to 1,000 mg, and an antihistamine.*

NCT02076009
Pollux Trial Results*

DARA Rd**

Rd

** MRD $\geq$ 30%  

*HR = 0.35
Key issues for 2016/2017
There is a need for trials testing strategies

• Can we prevent Progression of smoldering multiple myeloma to multiple myeloma?

• Can we use limited-duration combination therapy regimens that are as effective as continuous therapy?

• Can we determine the best triplet to use in the most cost-effective manner at relapse?

• Can we identify molecular subtypes that respond better to one drug versus the other?

• Does modifying therapy based on response or minimal residual disease detection improve outcome?
Final Thoughts

So…

Continue to find new therapies

… but learn how best to use the therapies we have!