Paris Seminar for Patients & Caregivers: BSRI 2017—On the Path to a Cure

Brian GM Durie
Saturday, June 10, 2017
Black Swan: on the way to a cure

1. Decide to seek a cure!
2. Early detection
3. Early Treatment
4. Sensitive, reliable, widely available MRD testing
5. Sustained low level disease
   ➢ Favorable immune signature
Black Swan Key Concepts

Cumulative Driving Mutations

MGUS -> SMM -> MM

Prevention Strategies

Early intervention with curative intent

New therapies for MRD positive
iSTOPMM: Iceland Project

**Partners**
- Sigurdur Kristinsson & team, University of Iceland
- Binding Site

**What causes myeloma?**

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**140,000 adults** > Age 40

- Screen

**CURE Trial**

**HR SMM**

**Prevent Multiple Myeloma**

**Monitor**

**Establish criteria for classification/progression**

**CURE!**
All 35 laboratories in Iceland participate
Importance of deCODE Project

deCODE's whole-genome sequencing project

2,600 Icelanders sequenced
DNA samples from 120,000 Icelanders all chip typed

http://cnn.it/2mMFBi1
Understanding Cure

1990s

Backwards

2017

Forward

Baseline samples → MRD Assessment

Precise F/U Rx

Full Clinical & MRD Testing

1 3 5
CESAR Trial

Curative E strategy Smoldering Alto Risk

- HR SMM
  - KRd x 6 cycles
    - ASCT
      - KRd x 2 cycles
        - Rd x 2 years

Primary Endpoints
MRD Negative at
1 year
3 years
5 years

~50 patients accrued
ASCENT Trial

**Aggressive Smoldering Cure Evaluating Novel Rx Transplant**

- HR SMM
  - KRd + DARA x 4 cycles
    - ASCT
    - KRd + DARA x 4 cycles
      - KRd + DARA x 4 cycles
        - K – DARA x 2 years

- 1st Quarter 2017 set to begin

**Primary Endpoints**
- MRD Negative at
  - 1 year
  - 3 years
  - 5 years
Launch of the NGF Method

2nd International IMF-EuroFlow Workshop on Myeloma MRD

“Next Generation Flow MRD for Treatment Monitoring in Multiple Myeloma”

October 10th & 11th, 2016
NEXT GENERATION FLOW (NGF): IMF-EuroFlow NGF-MRD Approach

**Optimal antibody panel**

**Bulk lye sample processing**

**Novel data analysis strategies**

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

**Infinicyt** software

PCA, file merge, automated gating

* CD38 multi-epitope OK with dara

Flores-Montero, submitted 2016

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<th>BV421</th>
<th>BV510</th>
<th>FITC</th>
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CD117    CD81
CyKappa   CyLambda
Comparison with NGS

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<th>NGF</th>
<th>NGS</th>
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<td>Applicability</td>
<td>31/31 (100%)</td>
<td>27/31 (87%)</td>
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<tr>
<td>Positive</td>
<td>19/27 (70%)</td>
<td>13/27 (48%)</td>
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Less applicable

P < 0.001

P < 0.05

more sensitive
NEXT GENERATION FLOW
Excellent Outcome for MRD Negative Patients

 Patients with adequate marrow sample

NGF negative at 3 years @ 10⁻⁶ level

NGF positive

Progression-free survival (%)

Time from MRD assessment (months)

P=.01
How About a Blood Test?

Liquid biopsy

- NGF detects circulating myeloma cells in SMM and MM: molecular analyses are feasible
- Blood DNA also shows exact mutations and can guide treatment
NGF to Detect Blood Plasma Cells

Frequency (%) of PCN with clonal-PC in PB

- SP: 0%
- Progression from SP: 33%
- MGUS: 65%
- SMM: 100%
- MM: 100%
- MM with >1 plasmacytoma: 0%

n = 6 3 43 6 25 2

* p<0.05
Blood DNA Mutations

- **NRAS Q61K**: 10%
- **KRAS Q61H**: 8%
- **KRAS G13D**: 7%
- **KRAS G12D**: 6%
- **NRAS G12D**: 5%
- **KRAS G13C**: 5%
- **NRAS G13D**: 3%
- **KRAS Q61H**: 3%
- **KRAS Q61L**: 3%
- **KRAS G12R**: 4%
- **KRAS G12V**: 4%
- **KRAS G12A**: 4%
- **TP53 G245D**: 4%
- **TP53 R248W**: 4%
- **KRAS G12T**: 4%
- **KRAS G12R**: 4%
- **KRAS Q61L**: 3%
- **KRAS Q61H**: 3%
- **NRAS G12D**: 3%
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Additional Piece of the Puzzle

Make sensitive, standardized MRD testing available globally
Achieving a Global Standard for MRD Testing

Over 50 researchers in 22 countries!
Current Opportunities

NGF in Blood

CURE Trials

MGUS

SMM

MM

Low MRD Status

New Trial Options

MRD NEG

MGUS Signature

Resistant MRD

1

2

3
Forward Expectations and Plans

- Documenting functional cure
- Validation of clinical correlates
- Expanding cure fraction
- Expanding achievement of MRD-negative
  - Studying MRD-positive; introducing Rx to eradicate
    - Introduce new MRD blood test
    - Understanding MRD-negative @ 1/3/5 years
    - Coordinate MRD testing for "CURE" trials
    - Cross correlate NGS, NGF and imaging
    - Standardized NGF test for bone marrow
Ongoing New Projects