Best of ASCO/EHA/IMWG

Brian GM Durie

Thursday, August 2, 2018

INTERNATIONAL MYELOMA FOUNDATION

IMWG INTERNATIONAL MYELOMA WORKING GROUP
A Research Division of International Myeloma Foundation

BLACK SWAN RESEARCH INITITATIVE

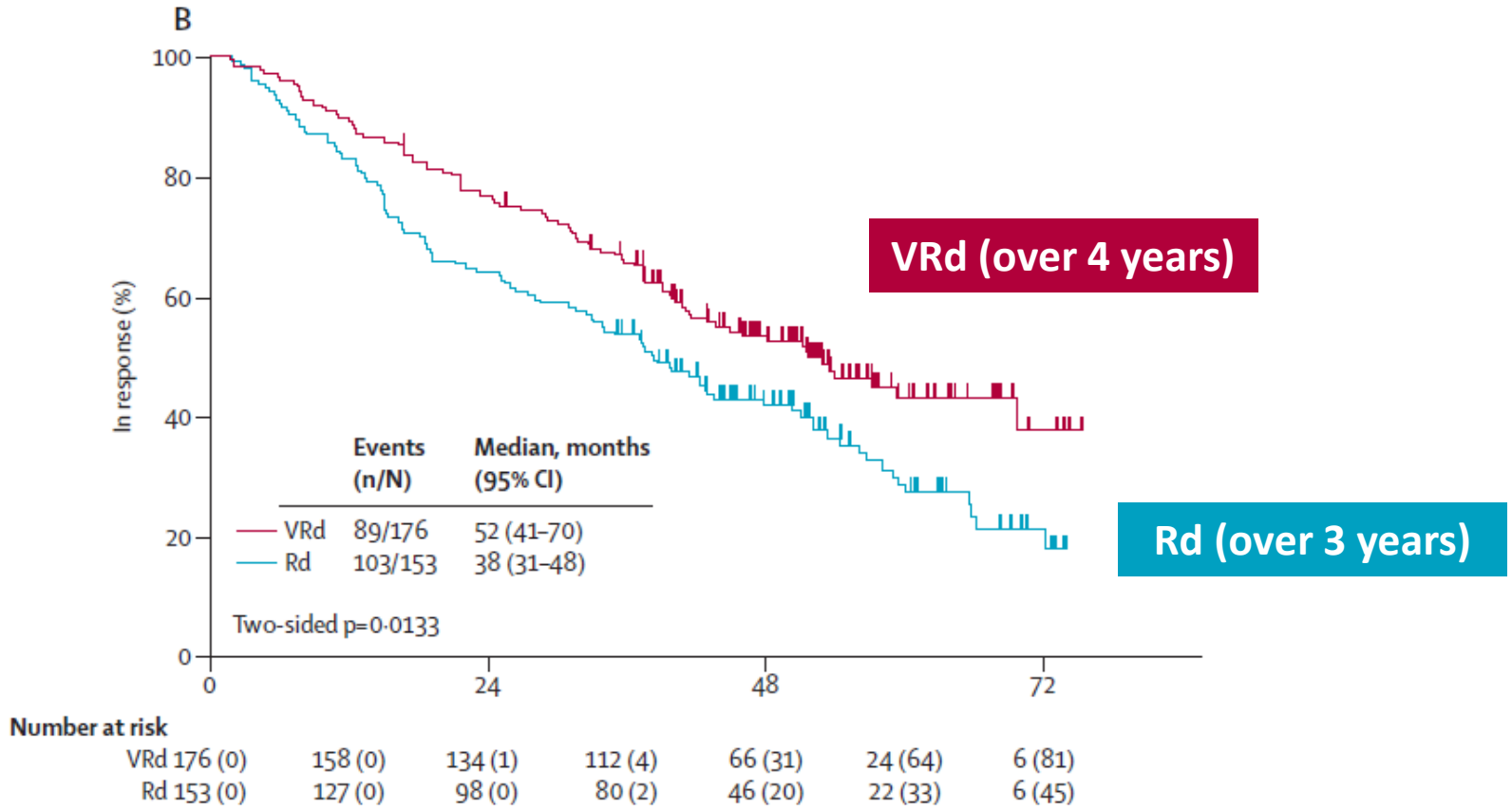
Highlights 2018

- Best outcomes and access
- Role of Mass Spectrometry
- Imaging Guidelines
- Status of MRD Testing and CURE Trials Update
- New Therapies
- CRISPR Gene Editing

Best Outcomes and Access

SWOG 0777: VRd vs Rd

Excellent First Remission Leading to Long Survival



VRd (over 4 years)

Rd (over 3 years)

Frontline Therapy 2018/2019

With Triple Therapy

*VRd– Median length of remission: over 4 years

Median Overall survival: 7-8 years

**KRd– Greater impact with high-risk disease

With 4-Drug Therapy

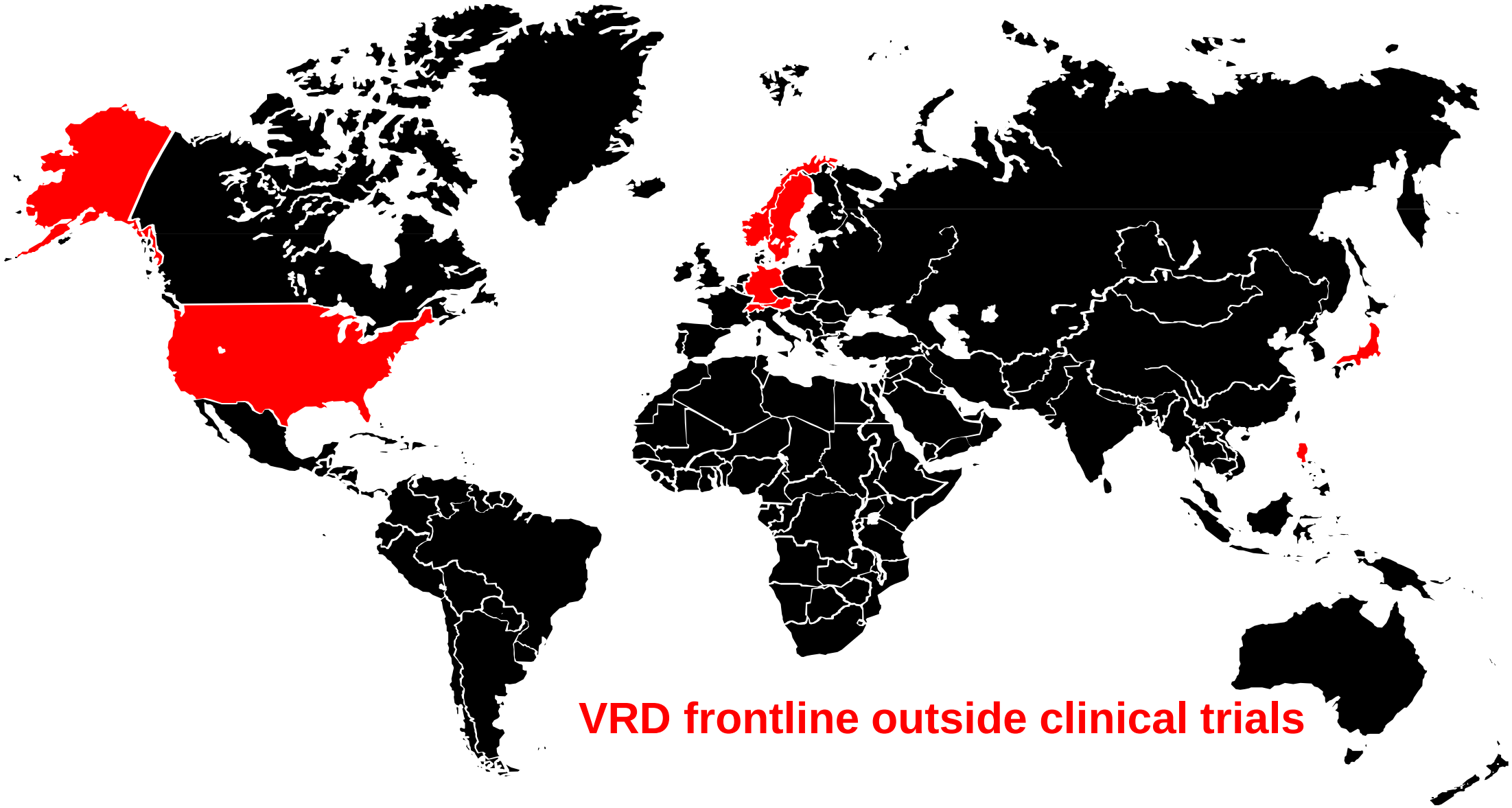
KRd + dara– 62% MRD negative at 10^{-6} in HR SMM

– Anticipated median survival > 10 years

*VRd will be updated at ASH: 2018

**K = Kyprolis (carfilzomib)

Global Access to VRd



Achieving Best Outcomes

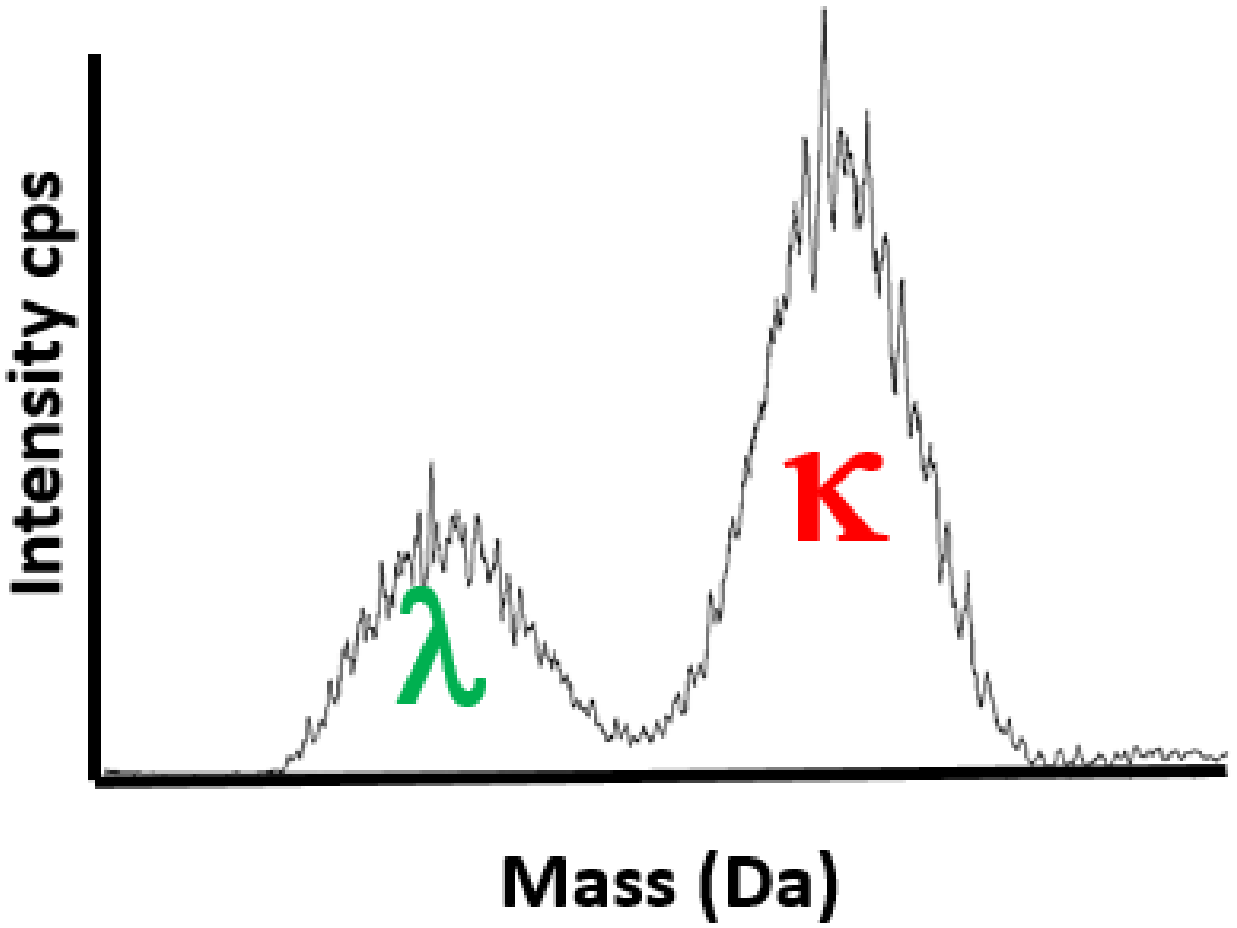
- **Integrating best new drugs**
- **Making new combinations available**

Role of Mass Spectrometry*

*now available as orderable test at **Mayo Medical Labs**

Detecting clonal proteins based upon mass (weight)

Light-chain distributions in normal serum



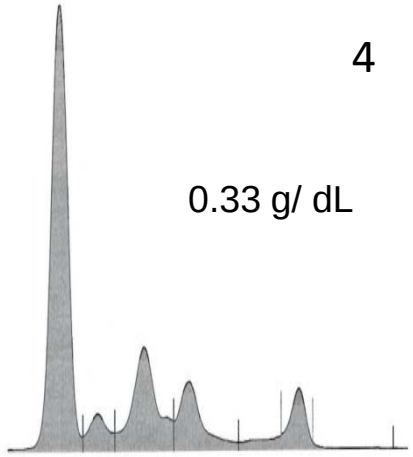
M-Protein and Dara Both Detected

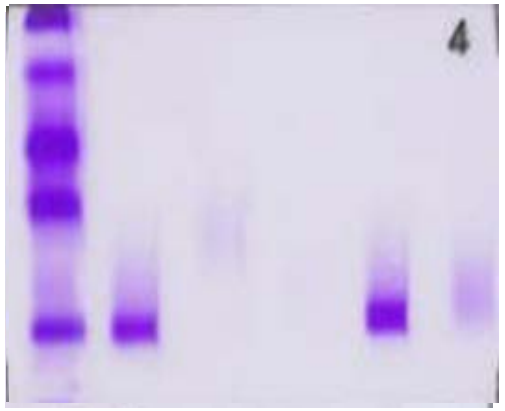
Old

New

SPEP

Serum **P**rotein
Electro**p**horesis

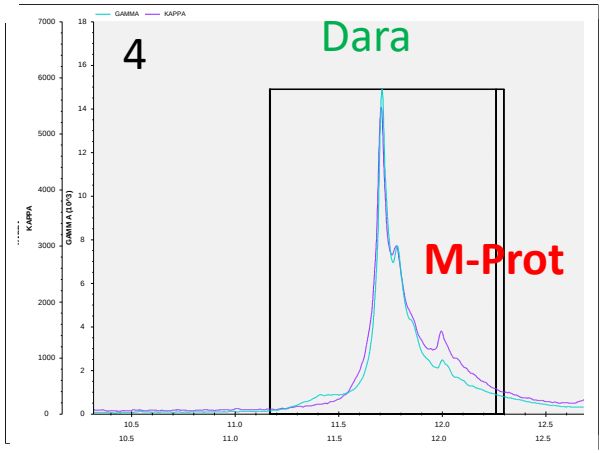


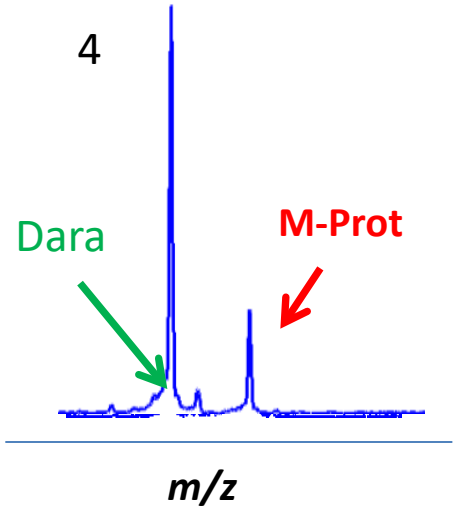


IFE

Immuno**f**ixation

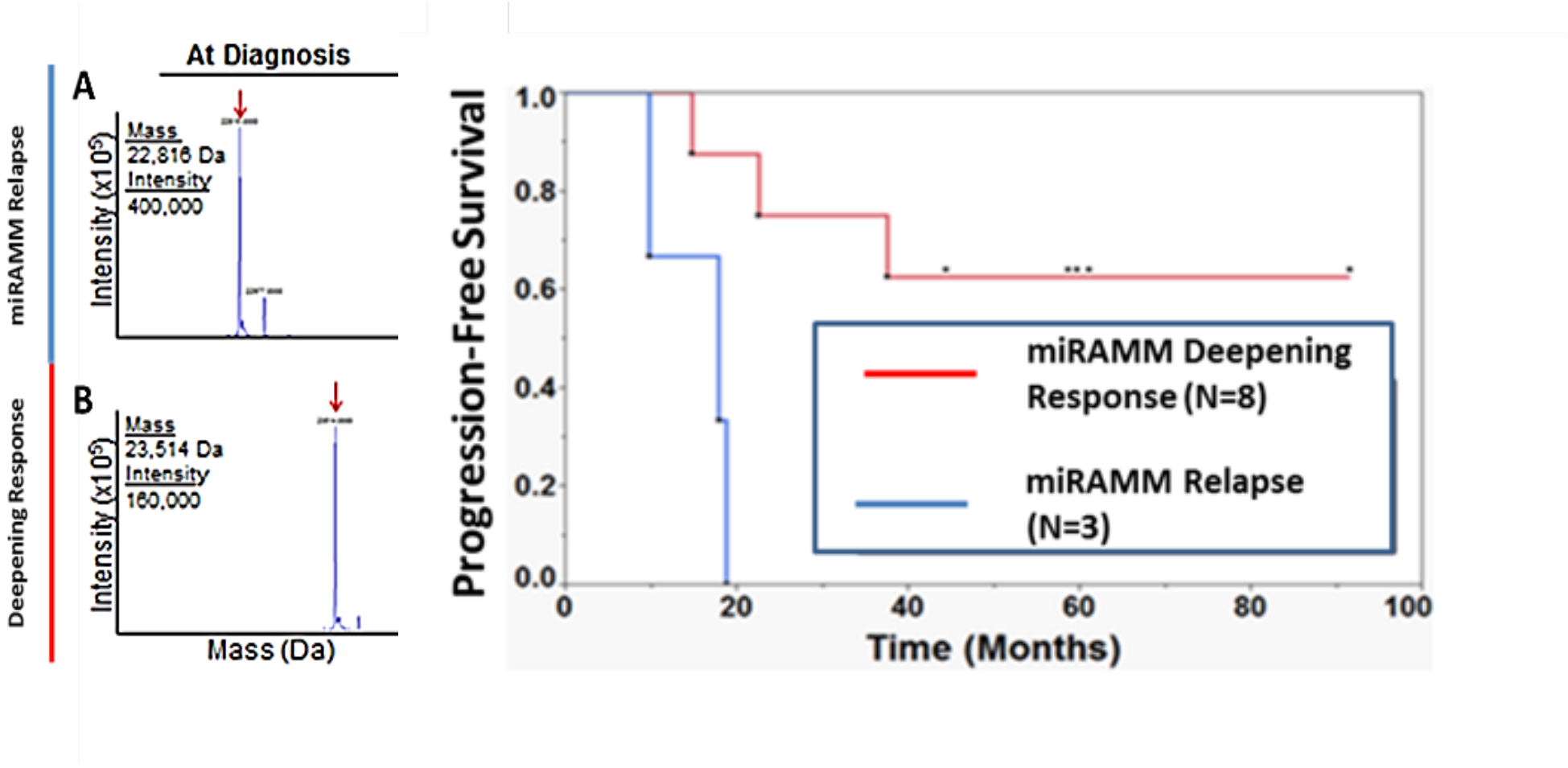
Mass Fix





No Dara 90 M-Protein : 10 Dara 50 M-Protein : 50 Dara 10 M-Protein : 90 Dara

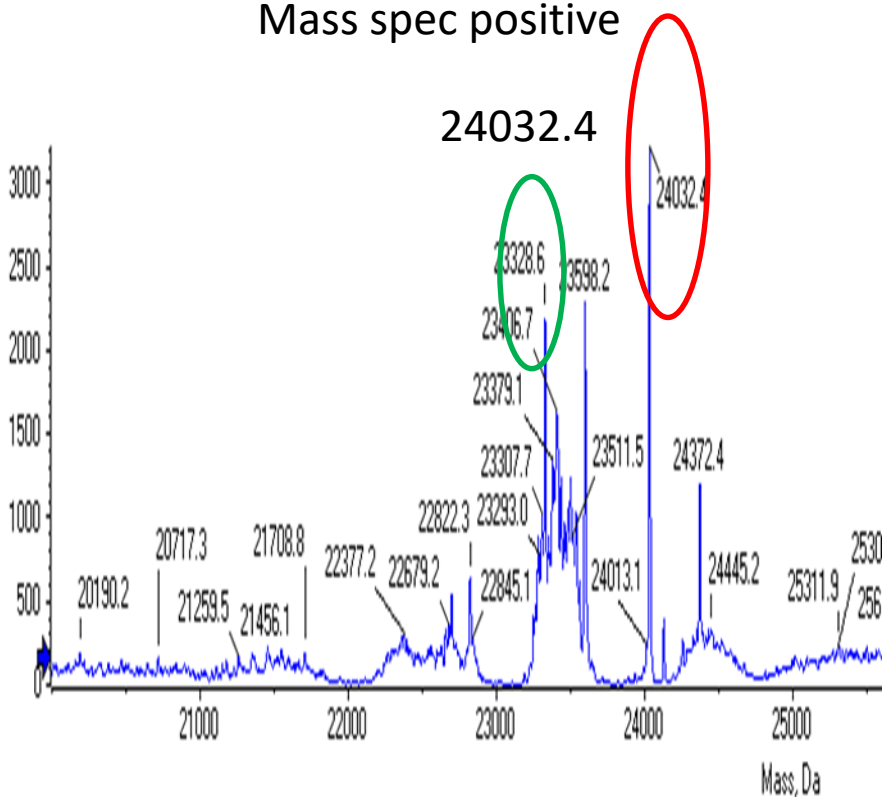
Deepening Response with Mass Spec versus Relapse



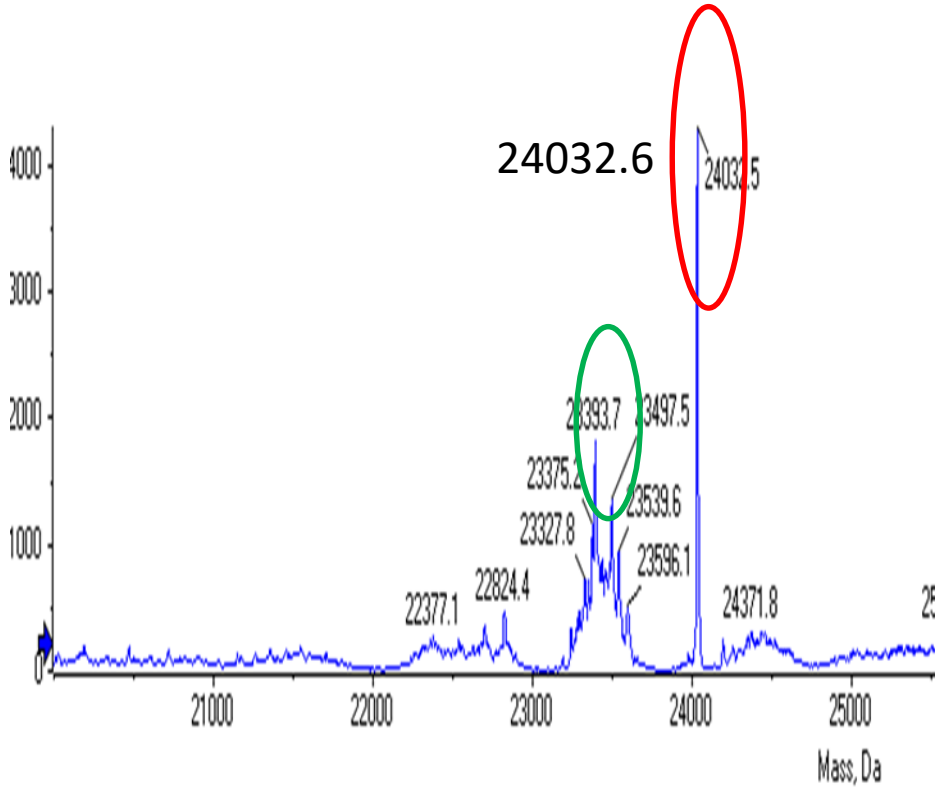
A Glimpse of the Origins of MGUS

12/1997	No MGUS detected

Mass spec positive



MGUS – 8/2006



Dr. Kyle – Olmsted County MGUS Study

Role of Mass Spectrometry

1. Very sensitive test for M-component measurement
2. Practical commercial method
3. Also identifies MoAbs
4. Will change diagnostic/response criteria
5. Affordable (projected: $180) blood test

New Imaging Guidelines

Types of Imaging

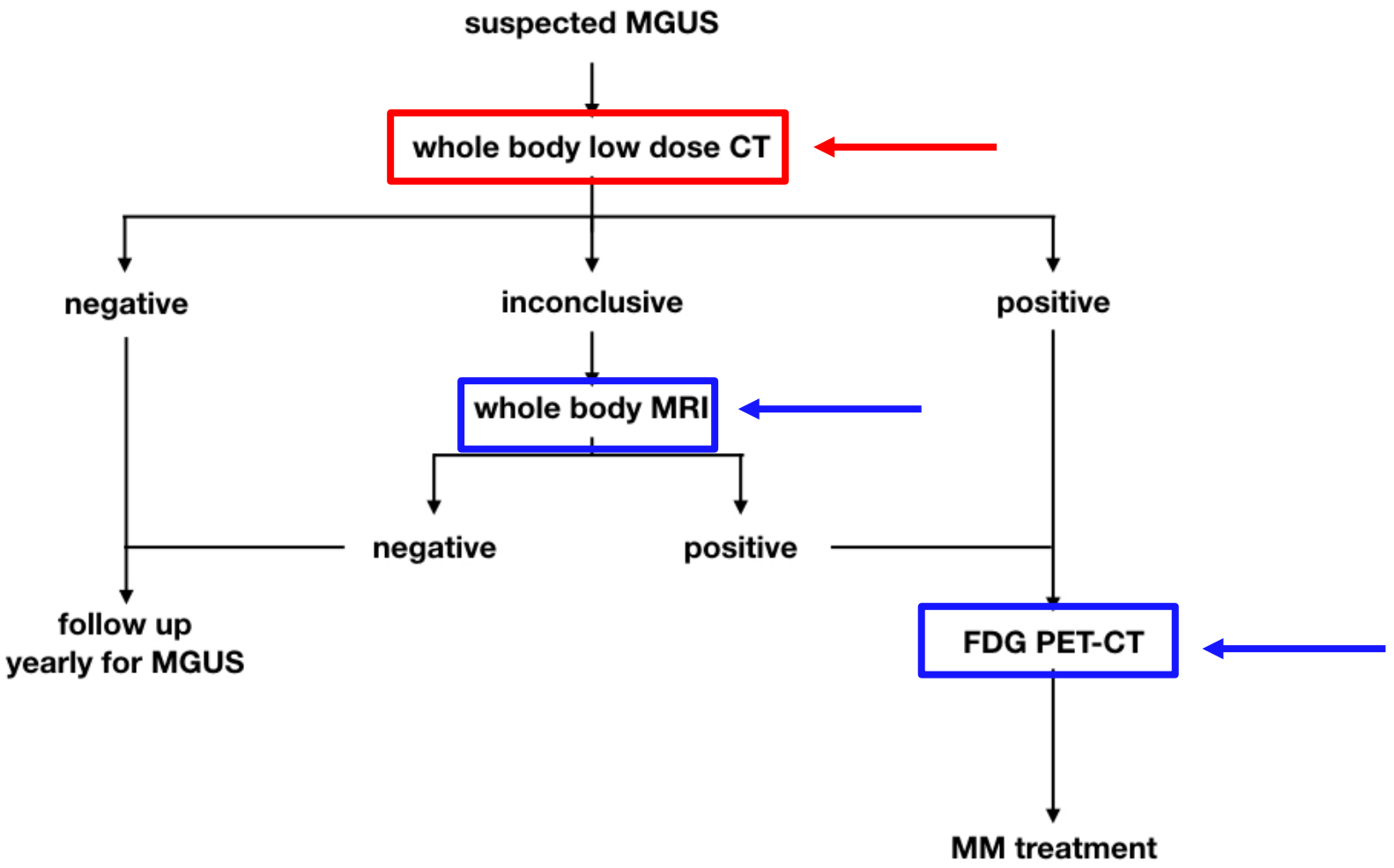
- **X-rays**
- **CT**
- **PET Scan**
- **MRI**

Key Points About Imaging

- X-rays show myeloma lesions
- IF x-rays are negative: ~30% chance other imaging will be positive
- CT can be low dose whole body and shows bone destruction
- PET shows active myeloma (sugar uptake)
- MRI shows myeloma lesions in marrow or elsewhere

Comparisons over time essential

Imaging for MGUS



Status of MRD Testing

MRD Testing in 2018

1. 2 methods
    - NGS: Next Generation Sequencing
    - NGF: Next Generation Flow

2. Sensitivity at 10^{-6} level is key cutoff

3. Strong correlations with improved PFS and OS in trials

4. Routine use controversial

Black Swan Research Initiative Update 2018

Dedicated to Finding a Cure

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MRD Methods

Flow NGF

- Do not need baseline sample
- Results in 100%
- Sensitivity at 10^{-6}
- Widely available
- No false negative
- Also immune monitoring

Sequencing NGS

- Need baseline bone marrow
- Results in ~85%
- Sensitivity at 10^{-6}
- Need reference lab
- False negative rate unknown
- No immune monitoring

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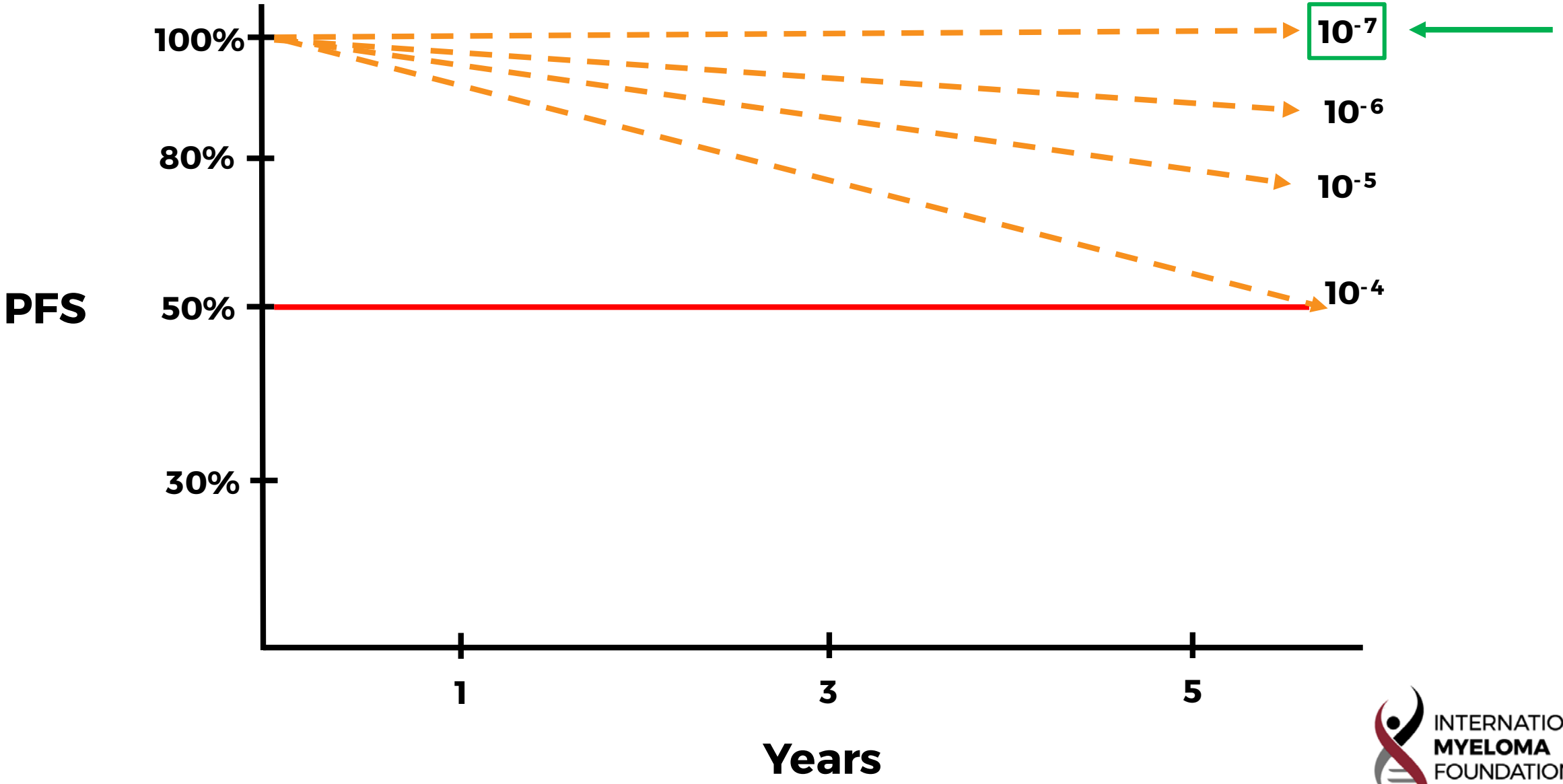
Sensitivity at 10^{-6} Key for CR/ sCR Patients



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CURE Trials

1. CESAR: KRd + ASCT
2. ASCENT: KRd + dara
3. iStopMM: KRd for MM and SMM

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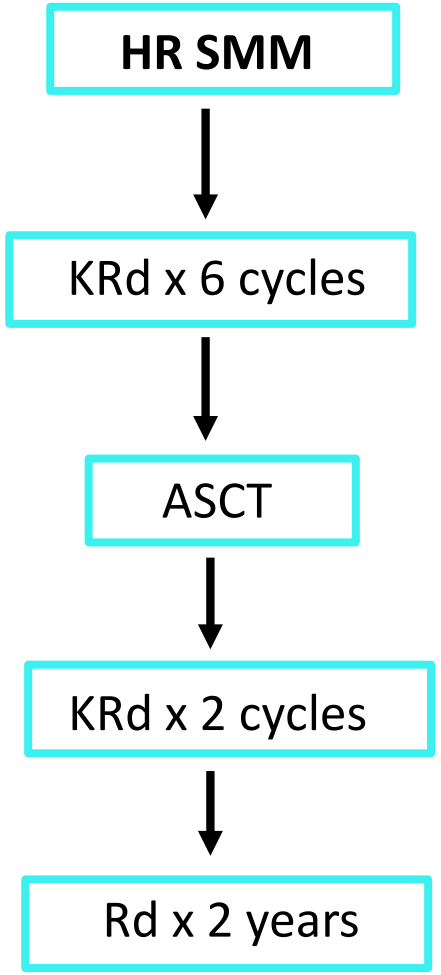
European "CURE" Trials: CESAR

Curative **E**strategy **S**moldering **A**lto **R**isk



MRD at CR

ASH abstract #402: 2017

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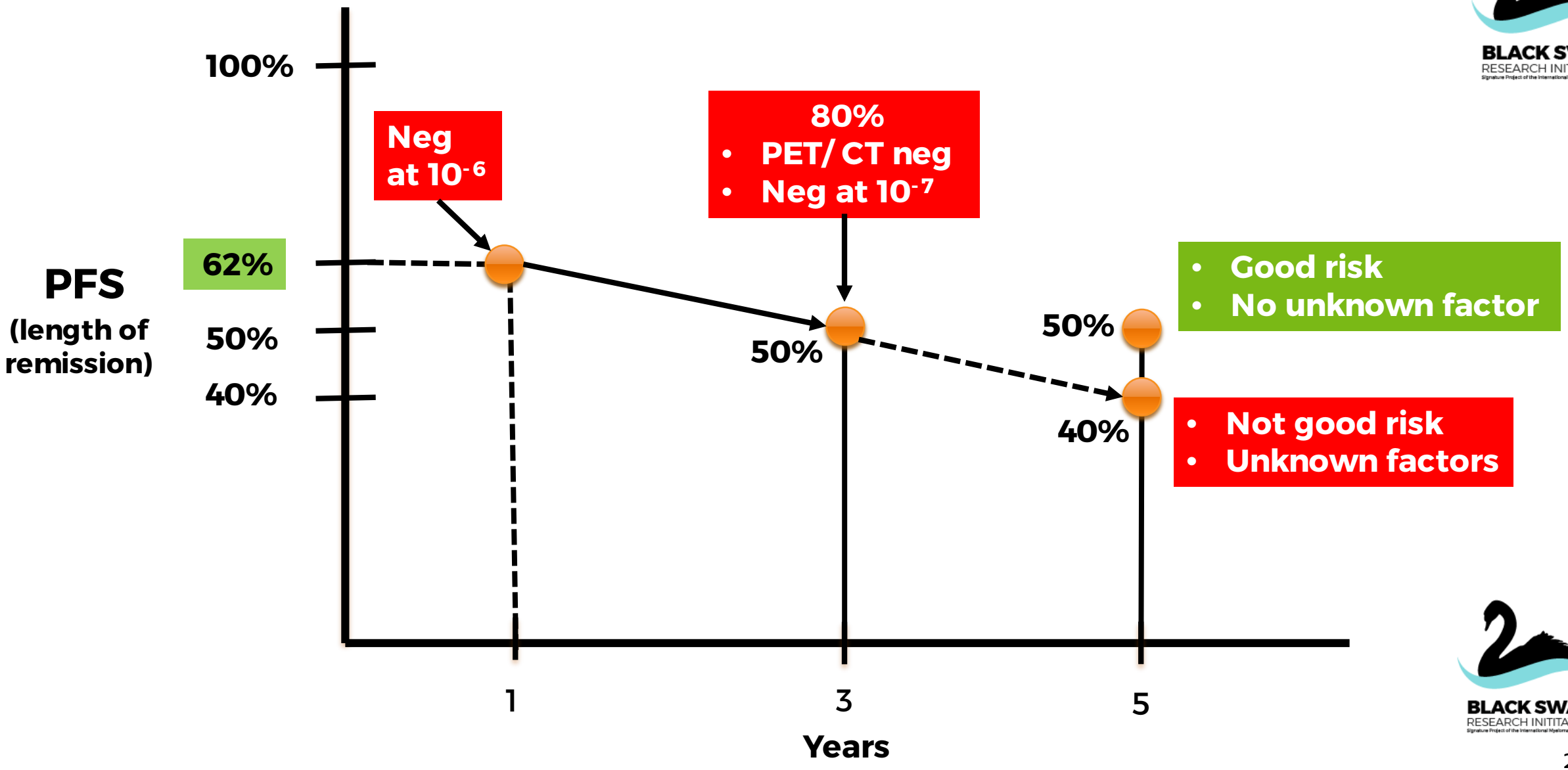
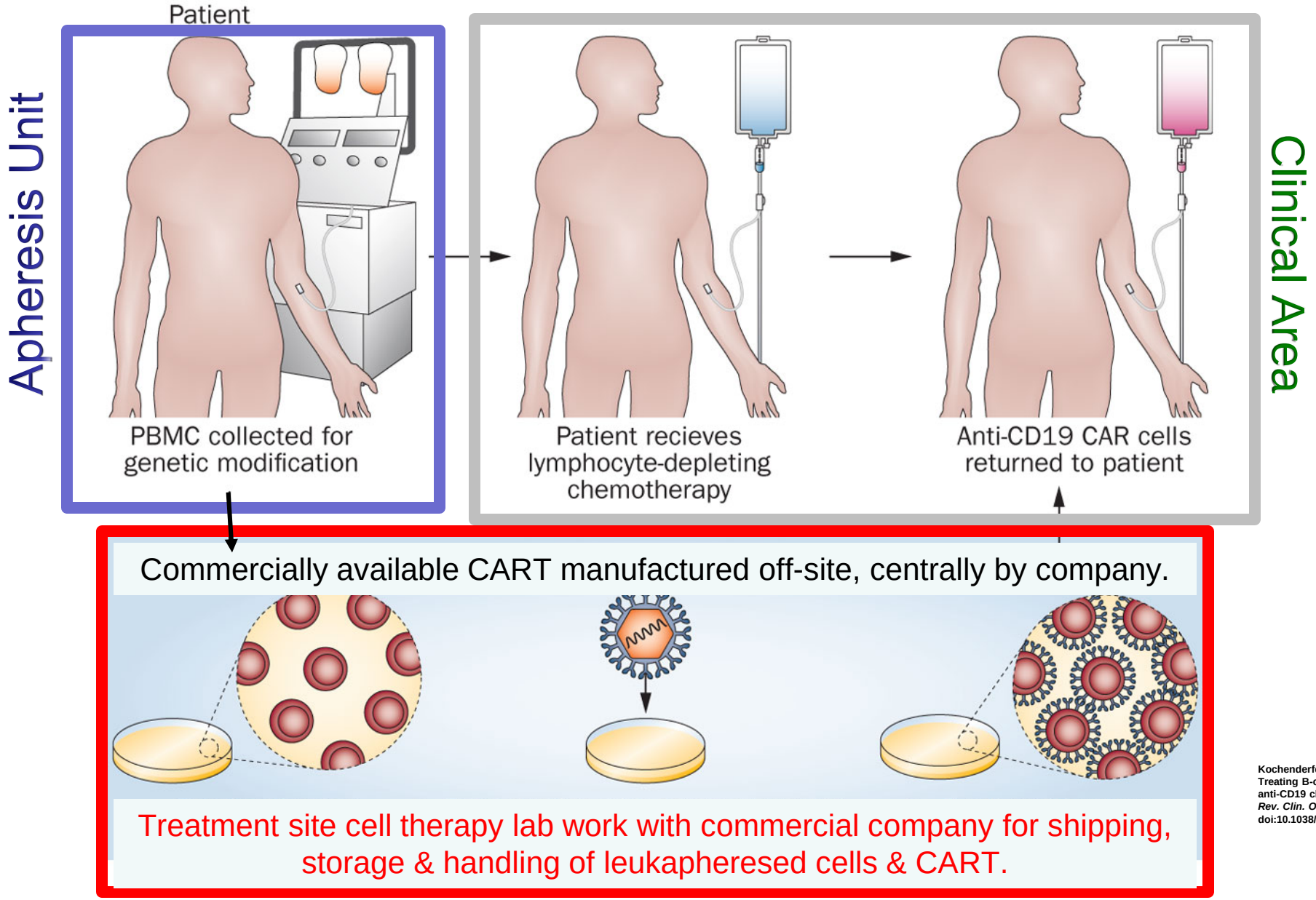
Cure By Numbers



New Therapies

CAR T Therapy

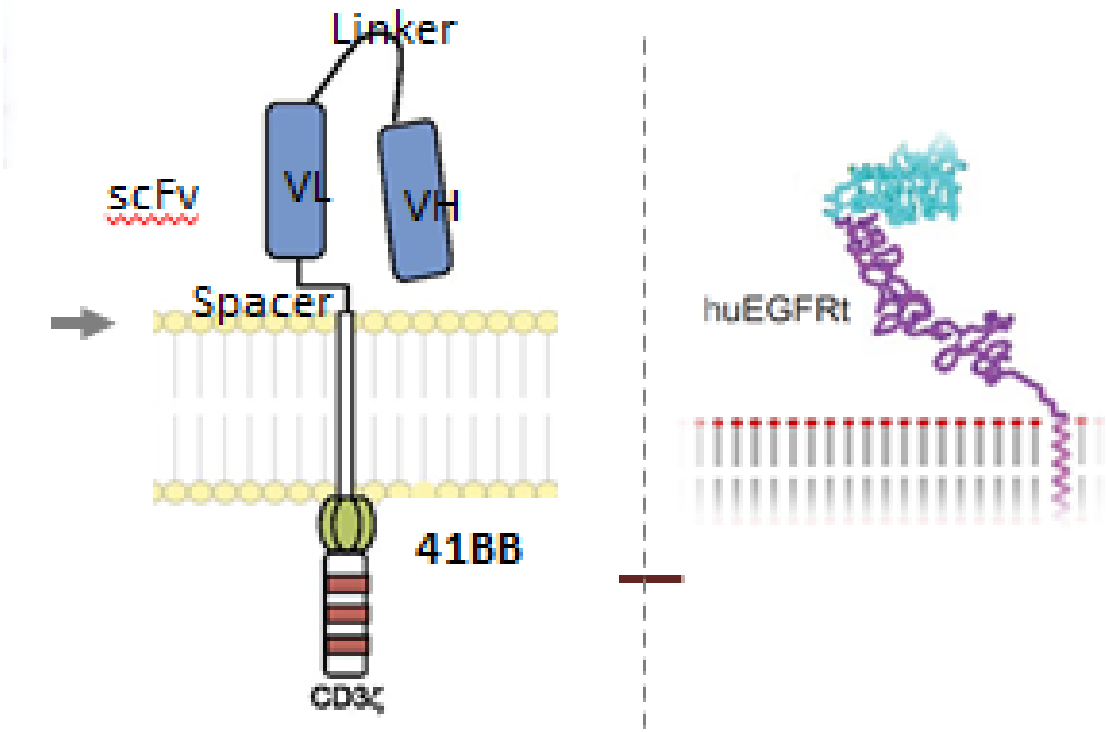


Kochenderfer, J. N. & Rosenberg, S. A. (2013) Treating B-cell cancer with T cells expressing anti-CD19 chimeric antigen receptors. *Nat. Rev. Clin. Oncol.* doi:10.1038/nrclinonc.2013.46

New CAR T Construct

BCMA **CRS Safety Switch**

BCMA-41BB-CD3ζ + **tEGFR**



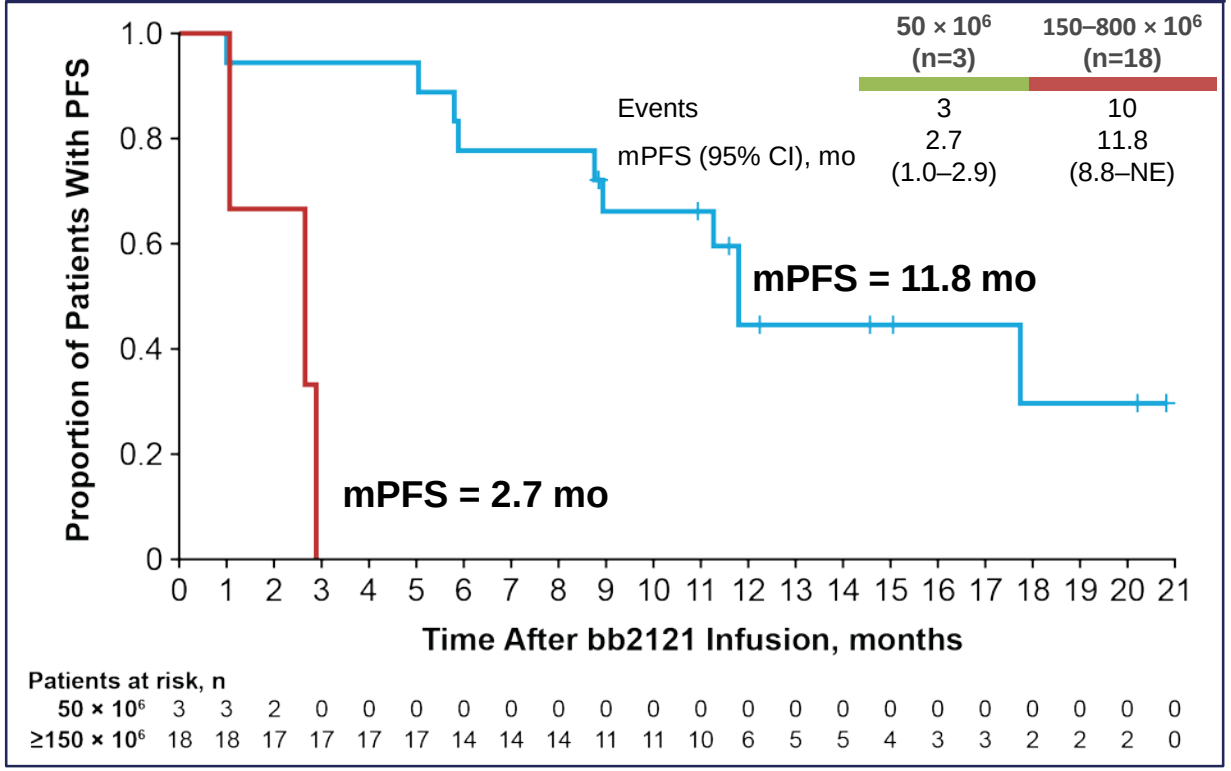
Expressed on cell surface respectively

BCMA CAR T

	bb2121
Source	Phase 1 Interim Analysis ASCO 2018
Enrollment	43 (39 evaluable)
Efficacy	**ORR 30 (77%)** CR/scR 17, VGPR 9
Safety	• Any CRS: 27 (63%) • ≥ Gr 3 CRS: 2 (5%) • ≥ Gr 3 NE: 1
Toci/Steroid Use	Tocilizumab (anti-iL6): 9 Steroids: 4

PFS with BCMA (bb2121) CAR T

PFS at Inactive (50 × 10^6) and Active (150–800 × 10^6) Dose Levels[a]



Status of CAR T Cell Therapy in 2018/2019

1. **Exciting new active therapy**

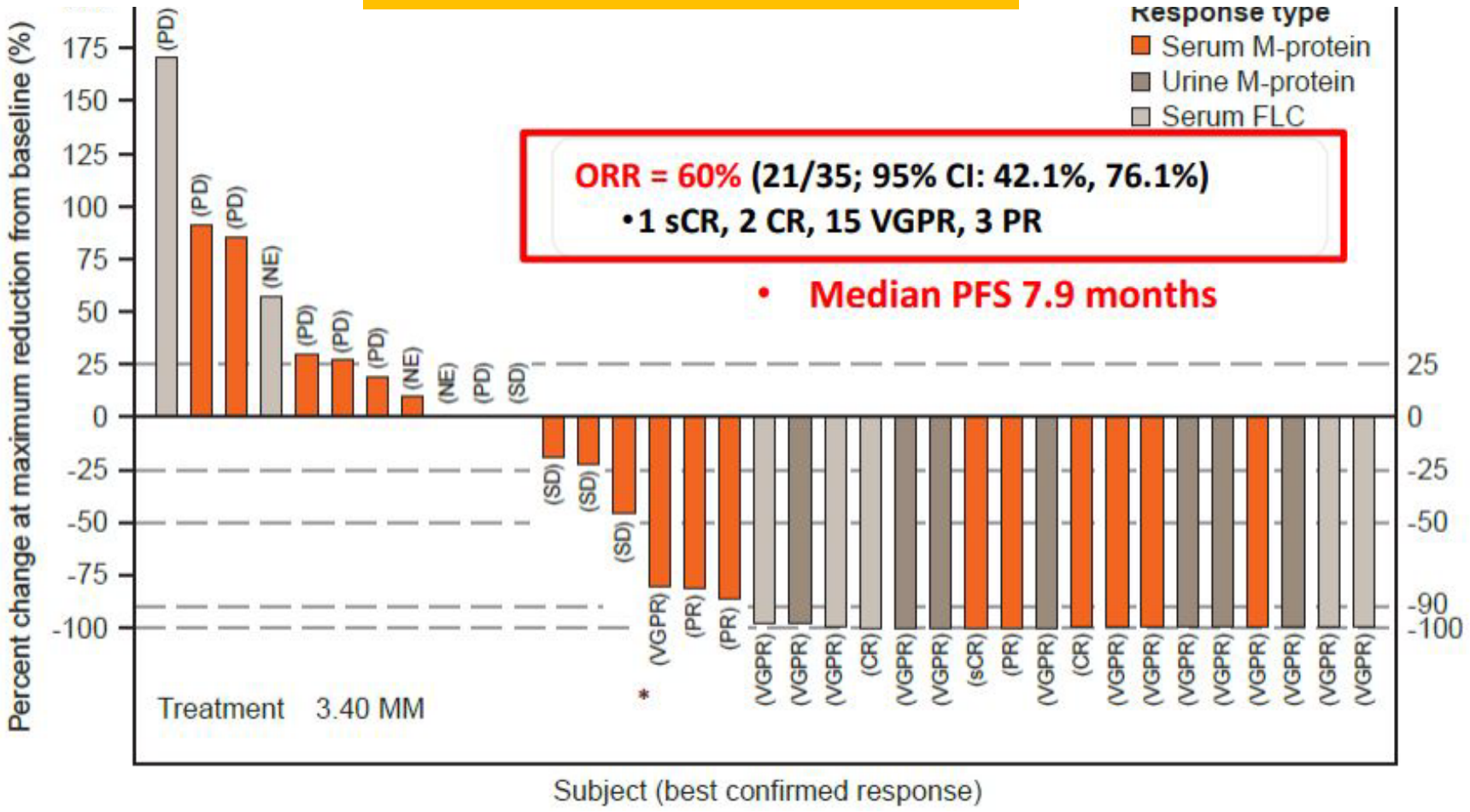
2. **CRS toxicity a concern**

3. **Still much uncertainty re: efficacy**
   - **% response rate?**
   - **Depth of responses and durability?**
   - **Meaning of MRD negative with CAR T?**
   - **Will median PFS be 9-12 months or more?**
   - **Is it safe for earlier use?**

4. **Is salvage therapy of this type worth $1 million?**

GSK 2857916- Another way to target BCMA

DREAMM-1 Study



https://www.youtube.com/watch?v=KxlPGfbst2c&feature=youtu.be

Most Promising New Drugs

Approved/being tested in combinations or new schedules*

- Kyprolis: once/week effective and well-tolerated
- Daratumumab: multiple combinations working well
- Pomalidomide: good outcomes combined with Velcade or elotuzomab
- Ninlaro: Phase 3 trial (MM3) shows maintenance benefit

Still in trials pre-approval: promising phase I – II data

- Selinexor: moving towards FDA approval in “penta refractory”
- Venetoclax: anti-Bcl-2. Active in t(11;14)
- Isatuximab/MOR 202: other anti-CD38 MoAbs

*Kyprolis® is carfilzomib; Darzalex® is daratumumab; Pomalyst® is pomalidomide; Ninlaro® is ixazomib (oral proteasome inhibitor)

Role of CRISPR Gene Editing

CRISPR in Myeloma:
More Than Just Knockouts

Arun Wiita, MD, PhD
Assistant Professor
Dept. of Laboratory Medicine
Director, Multiple Myeloma Translational Initiative Laboratory
University of California, San Francisco
IMWG Stockholm - June 11, 2018

Video: the Basics of CRISPR Editing

- McGovern Institute for Brain Science, MIT
- Cas9 video: https://ytcropper.com/cropped/2p5b16c94f7972e

Big Discovery: You Can Program the Cas9 to Cut Whatever DNA You Want with Easy Changes to "short guide" RNA

RESEARCH ARTICLE

Jennifer Doudna

A Programmable Dual-RNA–Guided DNA Endonuclease in Adaptive Bacterial Immunity

Martin Jinek,[1,2]* Krzysztof Chylinski,[3,4]* Ines Fonfara,[4] Michael Hauer,[2]†
Jennifer A. Doudna,[1,2,5,6]‡ Emmanuelle Charpentier[4]‡

Type II CRISPR-Cas9 *S. pyogenes*

Emmanuelle Charpentier

A Vision for CRISPR in Myeloma Therapy

- Highly-specific, no off target
- Highly-penetrant: edits 100% myeloma
- Specifically kill plasma cells with specific genetic defect/mutation
- CRISPR to repress RNA transcription of specific Ig isoforms in amyloidosis

Time for Questions!

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