Black Swan Sites Globally

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What are we learning from Iceland?

- **Connecting and collaborating works!**
- **Can screening for MGUS prevent and cure myeloma?**
- **Myeloma is myeloma!**

iStopMM
Iceland Screens, Treats and Prevents Multiple Myeloma

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Key Questions

- **What is the quality of life for patients screened in Iceland?**
- **Is early intervention improving outcomes?**

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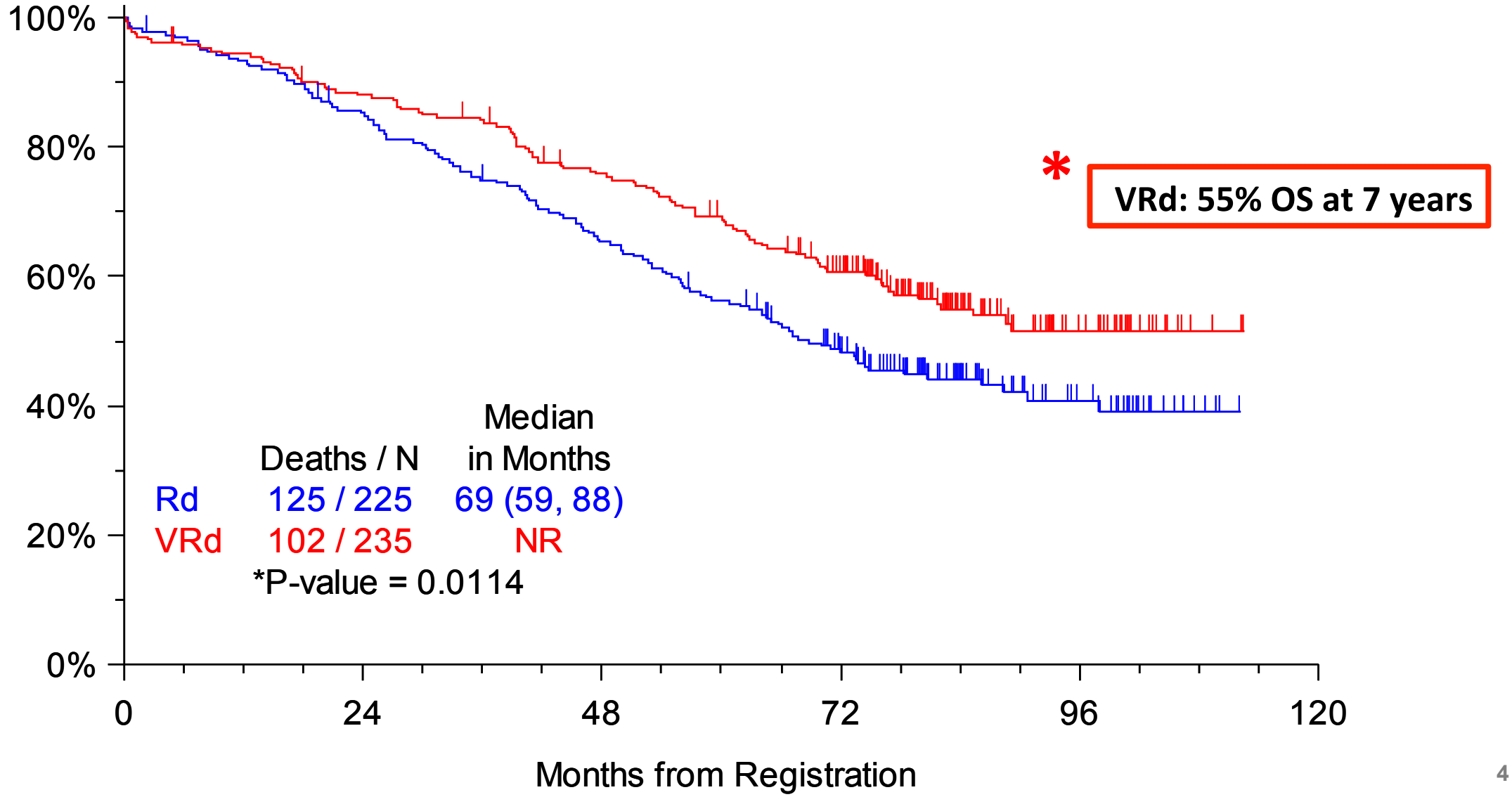
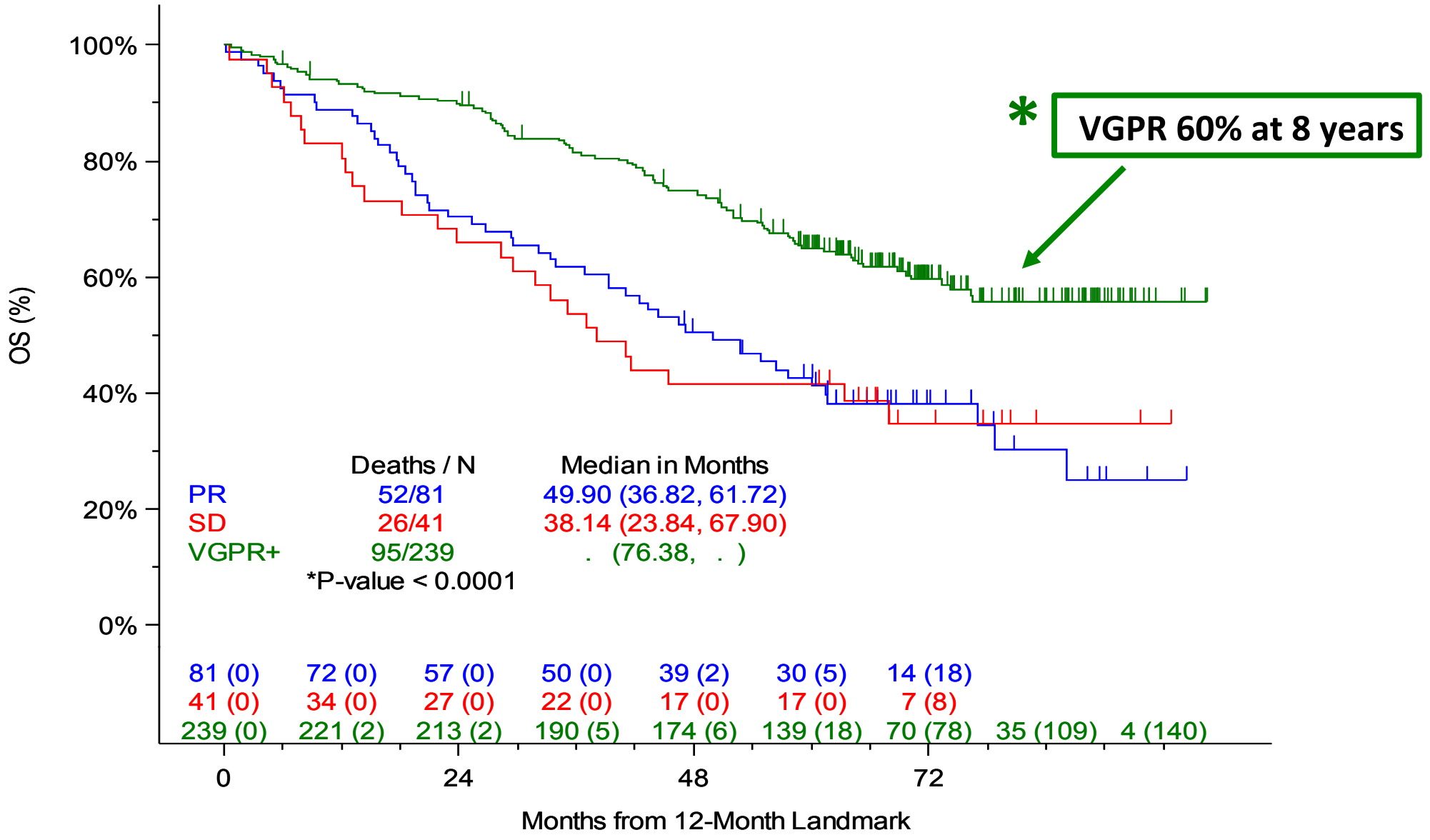
Current best outcome: Overall survival with VRd

CURRENT ELIGIBILITY (N=460) – CURRENT DATA



OS landmarked at 12 months (N = 357)



Adding in ASCT

Frontline VRD* + ASCT: Spanish Trial

	Induction (VRDx6)	HDT/ASCT	Consolidation (VRDx2)
MRD undetected	35%	54%	58%
MRD-positive	65%	46%	42%

Negative at 10^{-6}

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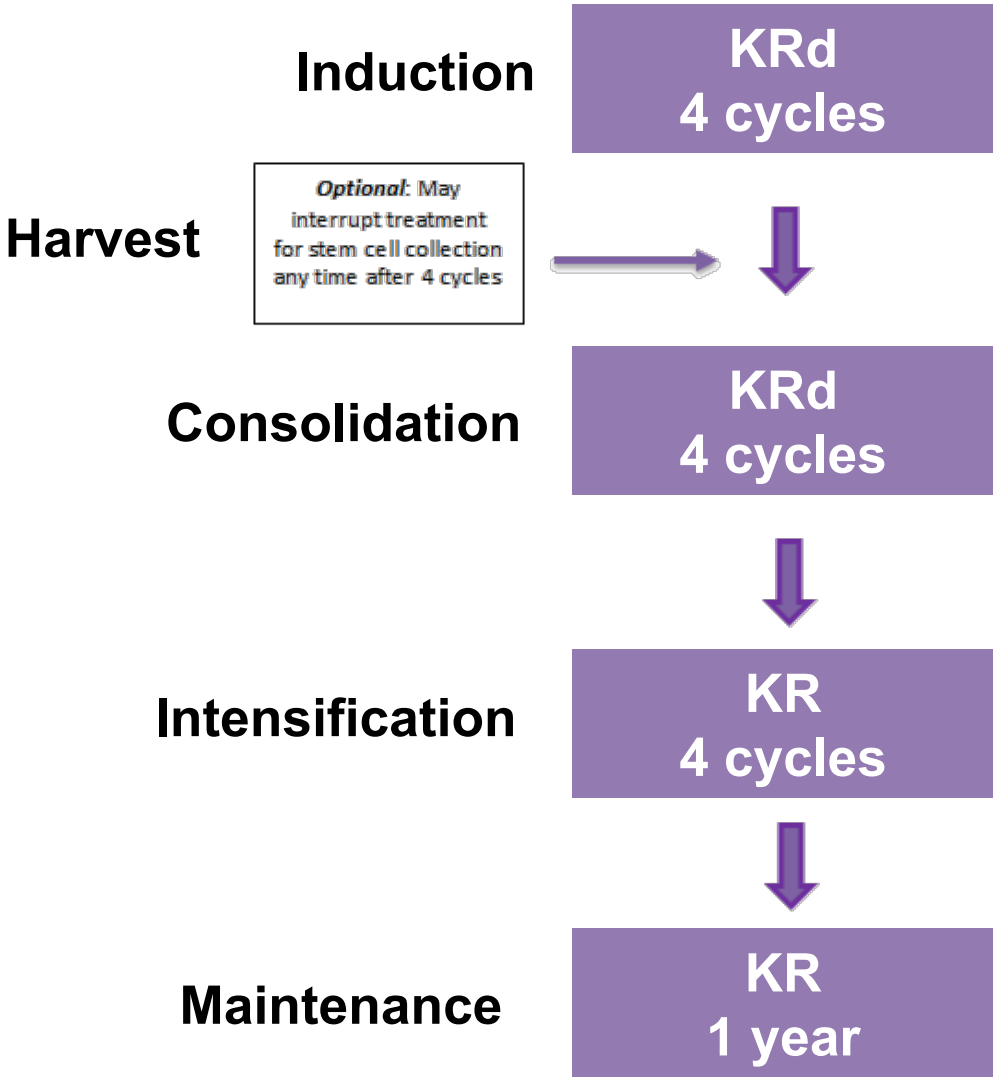
iStopMM Intervention Trials



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Iceland Screens, Treats or Prevents Multiple Myeloma

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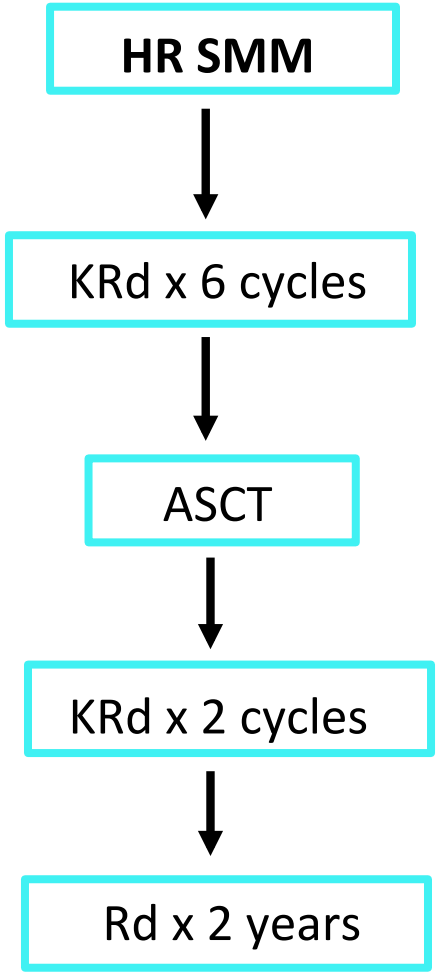
European "CURE" Trials: CESAR

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



MRD at each phase and best response

ASH abstract #402: 2017

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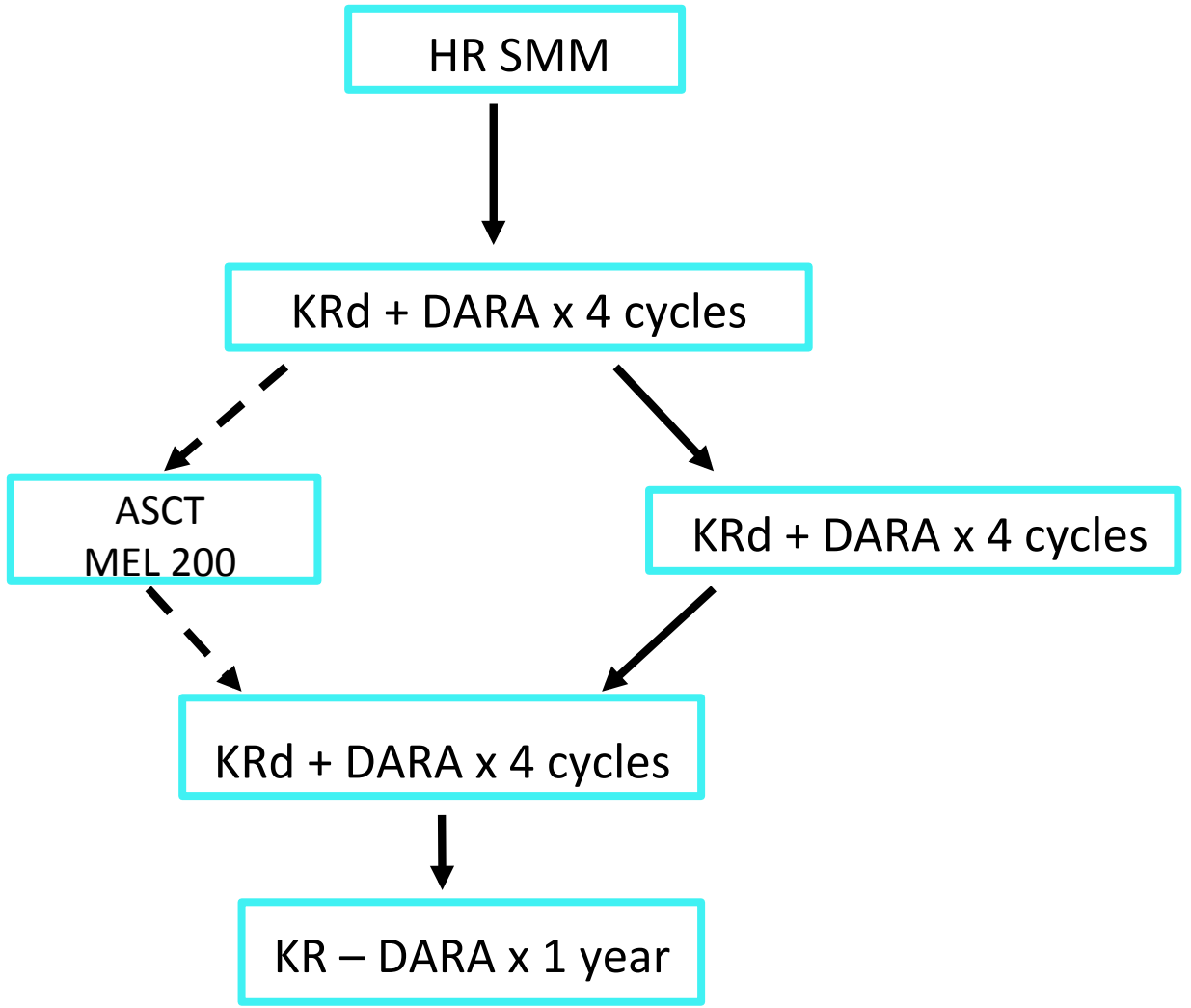
US "CURE" Trial: ASCENT

Accrual ongoing: ~10 patients

US Sites

- Mayo
- University of Indiana
- University of Maryland
- MDAH
- Swedish Seattle
- Emory
- Chicago
- Cornell
- North Carolina
- Columbia
- Wisconsin
- Kansas



MRD at each phase and best response

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New Criteria for HR SMM*

- **M-component level ≥ 2 gm/dl**
- **BMPC ≥ 20%**
- **sFLC ratio (involved/uninvolved) ≥ 20**
- **Presence of 1q+ and/or t(14;16)**

*Mayo team: Blood Cancer Journal 8:59 2018.
Risk stratification based upon 421 patients. Follow up for ~3000 patients being finished.

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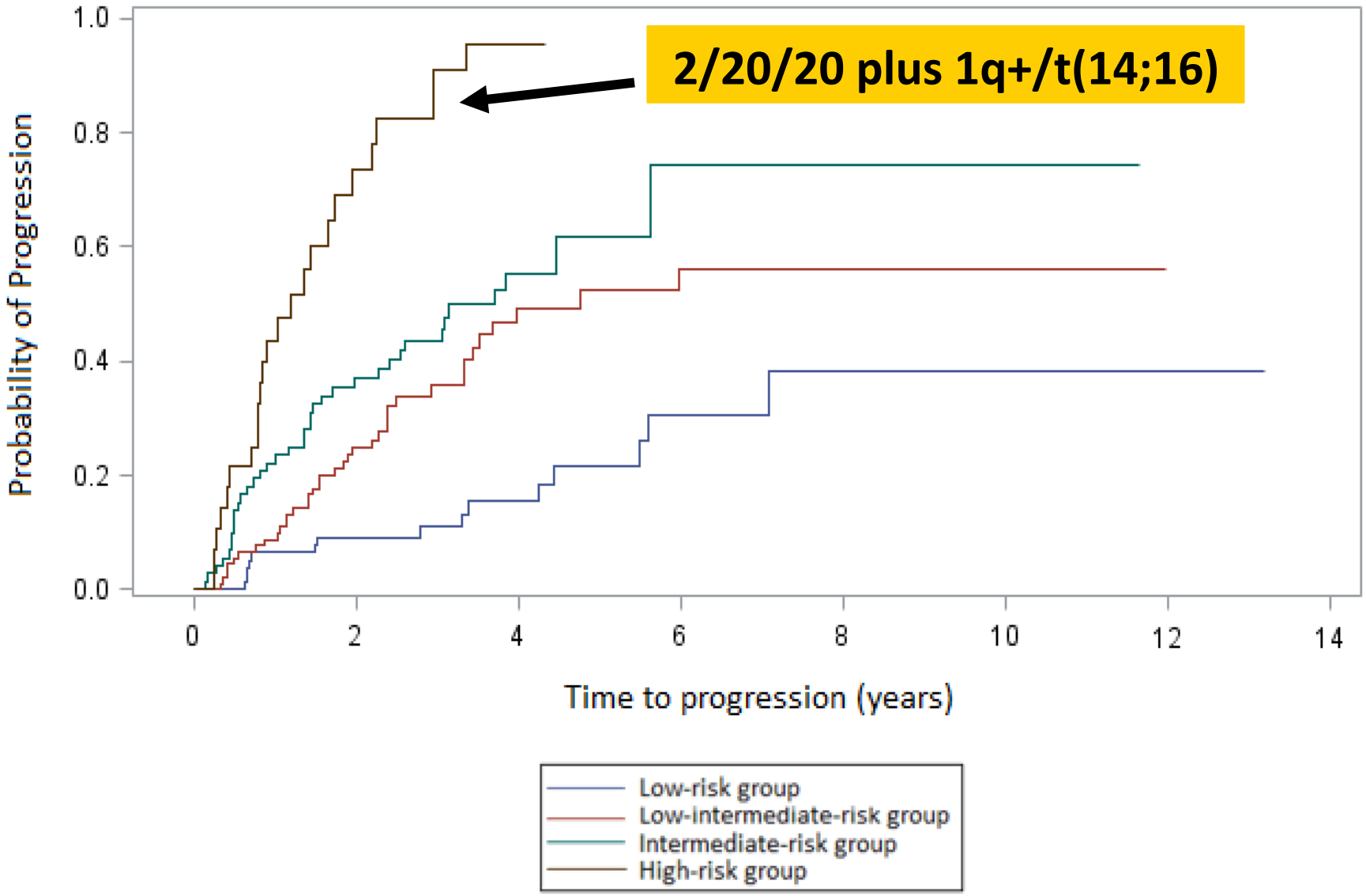
Risk of Progression for SMM



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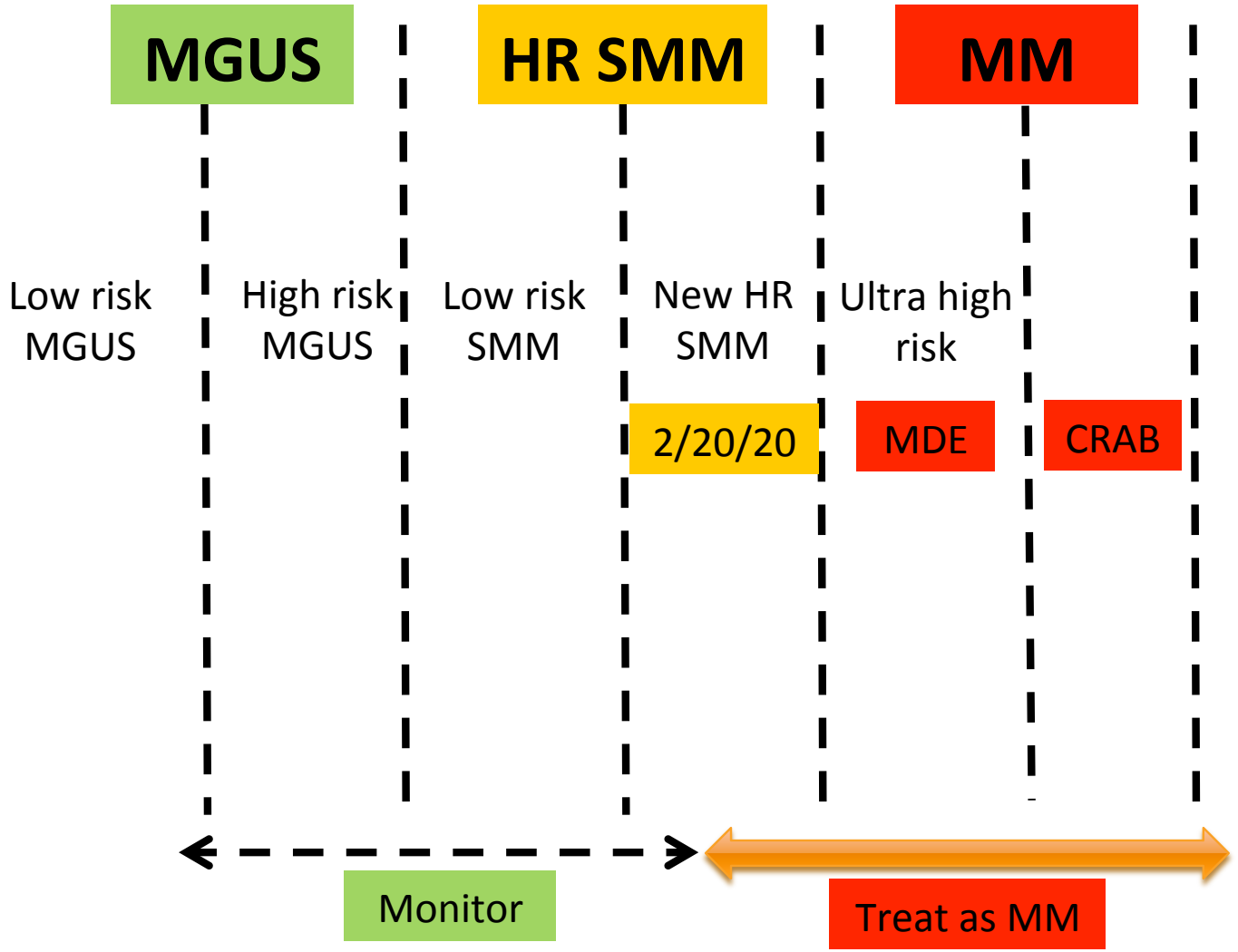
The Future of Myeloma Therapy



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Blood Monitoring to Simplify Testing

Being Studied in Iceland!

- Clonal plasma cells using NGF with molecular/immune testing of cells
- M-component using Mass Spec
- DNA/RNA using ctDNA/RNA

VNiVERSiDAD D SALAMANCA

MAYO CLINIC

Binding Site

MONASH University
Medicine, Nursing and Health Sciences

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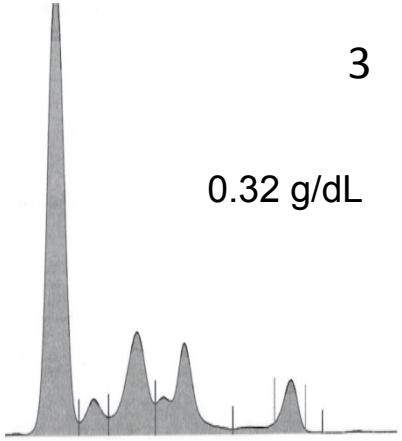
SPEP and IFE versus “Mass Fix”

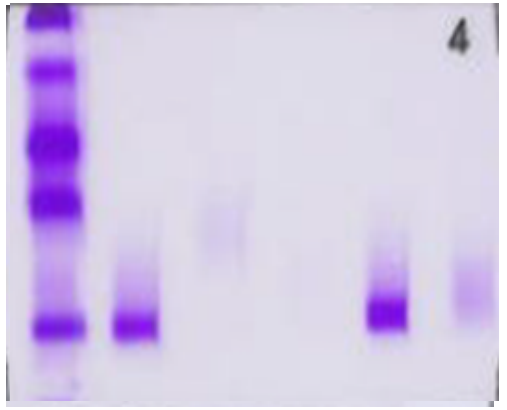
Old

New

SPEP

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

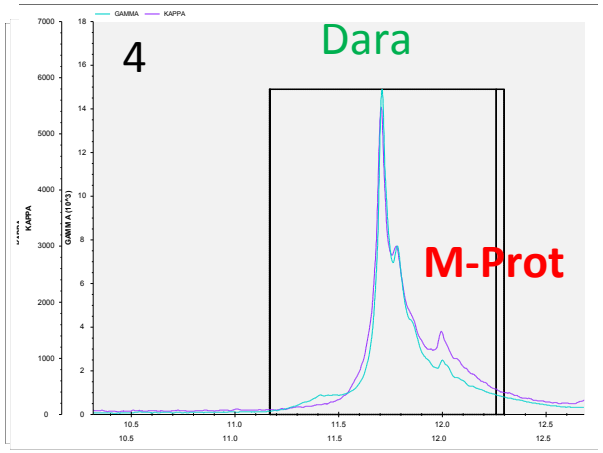


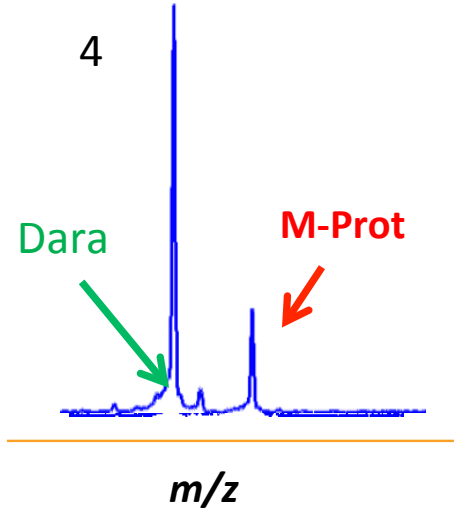


IFE

Immuno**f**ixation

Mass Fix





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

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

… can become new endpoint for response, "biochemical relapse" and maybe MRD testing!

Specific Uses of Mass Spec

Response assessment

- IMWG Work Group established
- Key trials being assessed
- Correlations with MRD negative; CPC; ctDNA, PET/CT…

Biochemical relapse

- Indicator for early intervention
- Integrate with immune molecular classification

MGUS screening/study

- Biology of onset being studied in Iceland

How to Achieve Cure

1

Start early with best available Rx

2

Eliminate residual disease with new approaches

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Selecting Best Therapy for Residual Disease

2

Study MRD + patients:

- Immune phenotype
- Genetics
- Drug sensitivity

Select:

- New monoclonal antibodies
- CAR-T or other approaches

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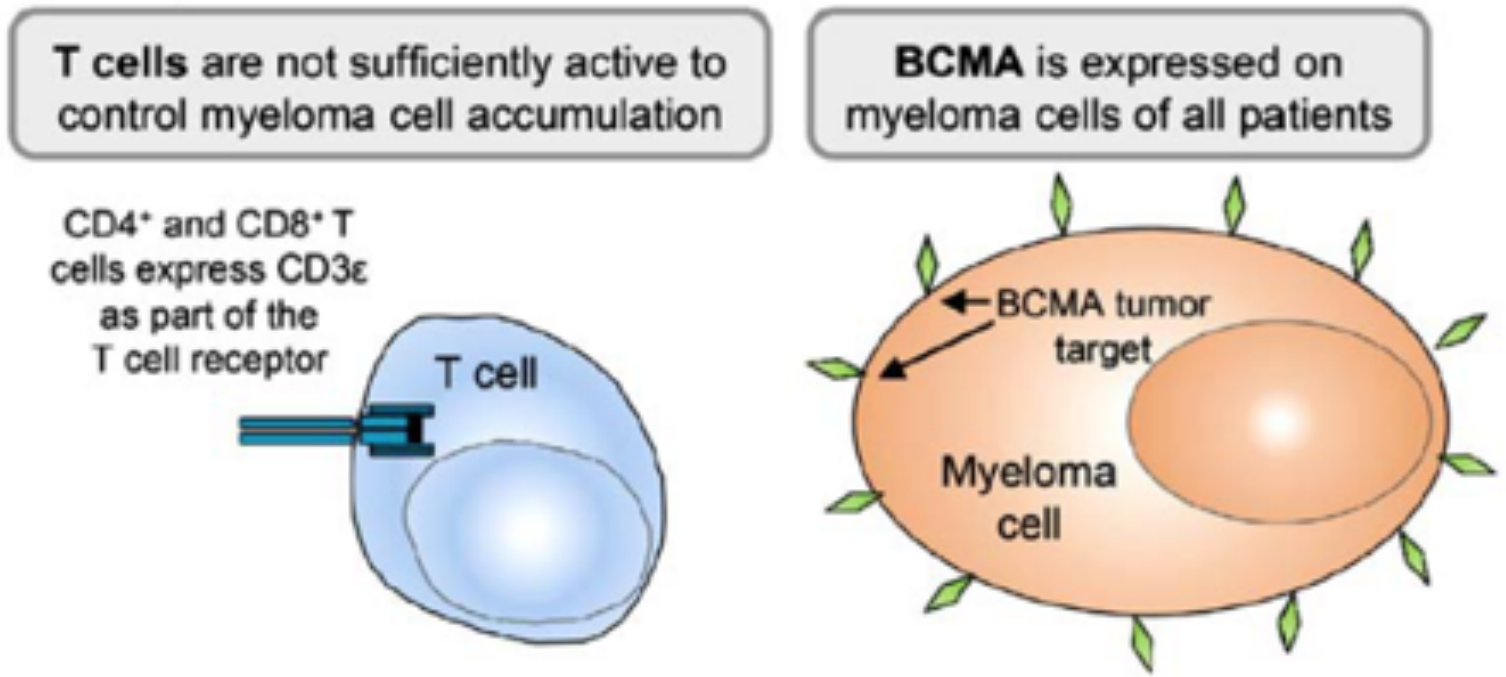
Studies of Immune Microenvironment

Example of Anti-BCMA x CD3 bispecific antibody testing in Black Swan project*

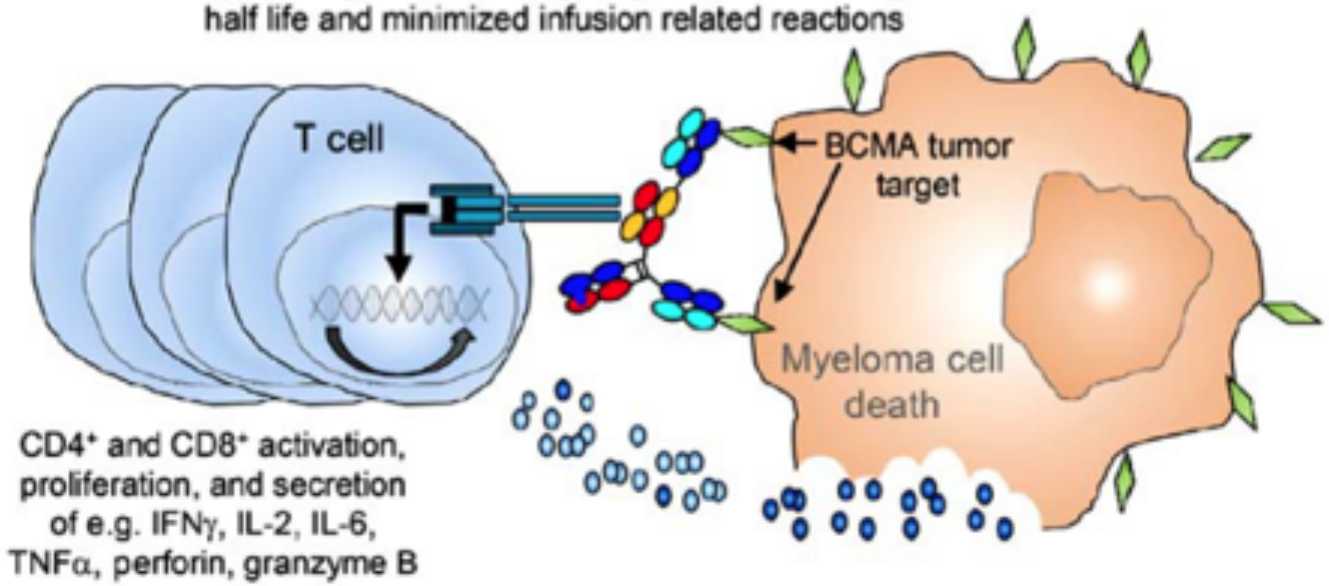


*EngMab 801: CC93269

Impact of EM801 Bispecific Antibody

EM801 redirects (binds) CD4⁺ and CD8⁺ T cells to myeloma cells.
T cells are thereby activated, proliferate, and eliminate myeloma cells.

EM801: One CD3ε but two BCMA binding sites for optimal myeloma cell targeting; silent Fc for long half life and minimized infusion related reactions



Black Swan Research Initiative

Dedicated to Finding a Cure

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Key Steps

Develop MRD tests

Conduct CURE trials with best therapies

Understand and treat resistant disease

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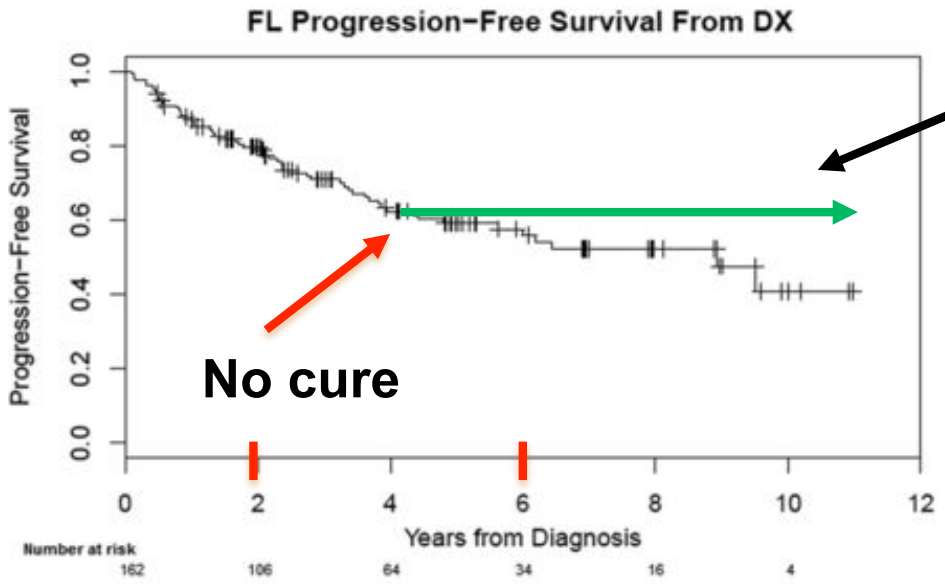
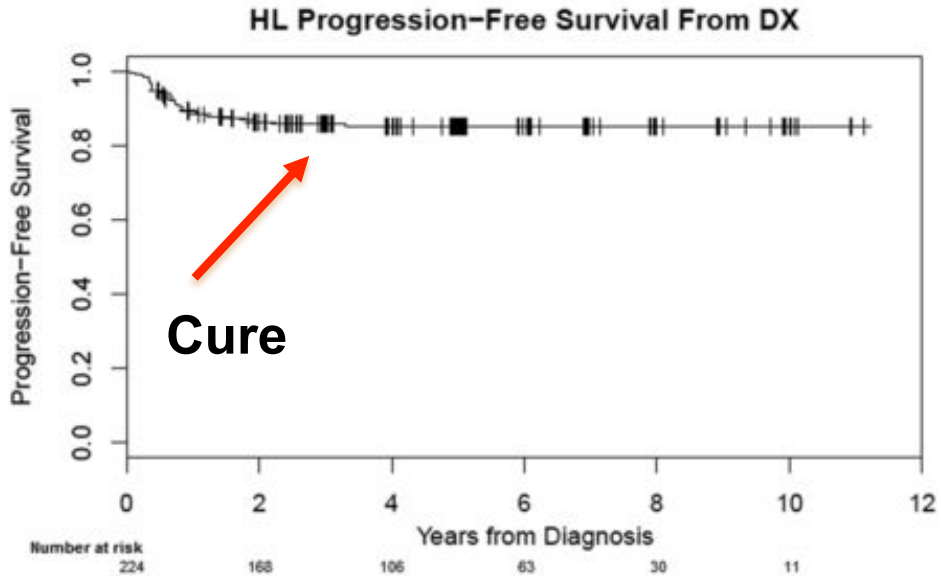
PFS: Myeloma v Hodgkin Lymphoma



Anticipated cure!

No cure

Myeloma



Cure

Hodgkin Lymphoma

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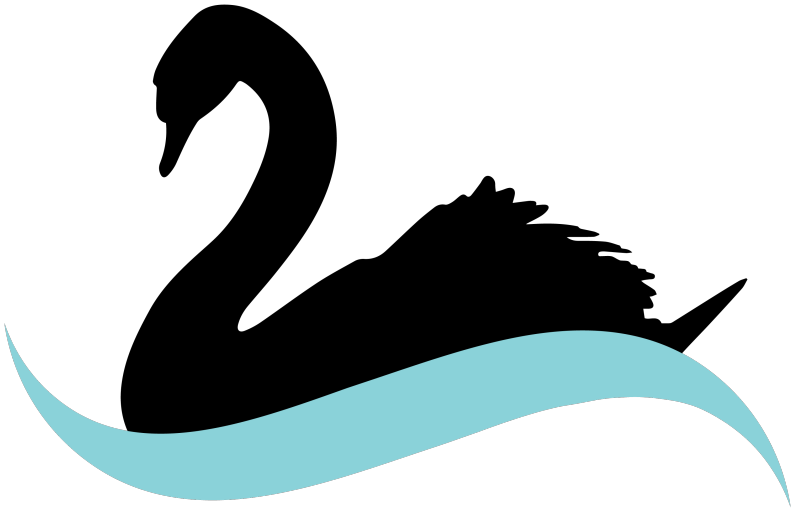

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