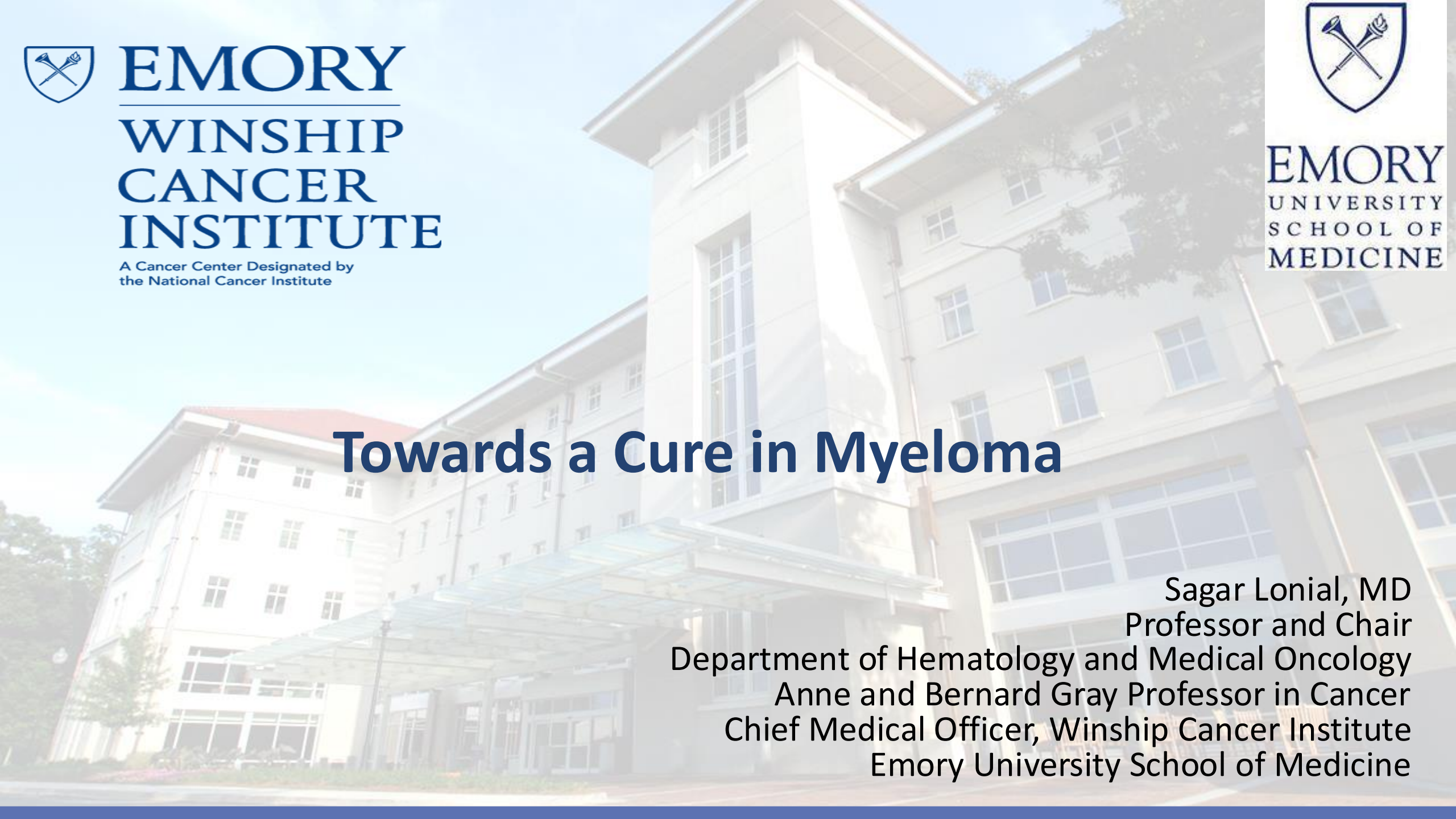

Towards a Cure in Myeloma

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Department of Hematology and Medical Oncology
Anne and Bernard Gray Professor in Cancer
Chief Medical Officer, Winship Cancer Institute
Emory University School of Medicine

First Randomized Trial in MM (Coke won….)

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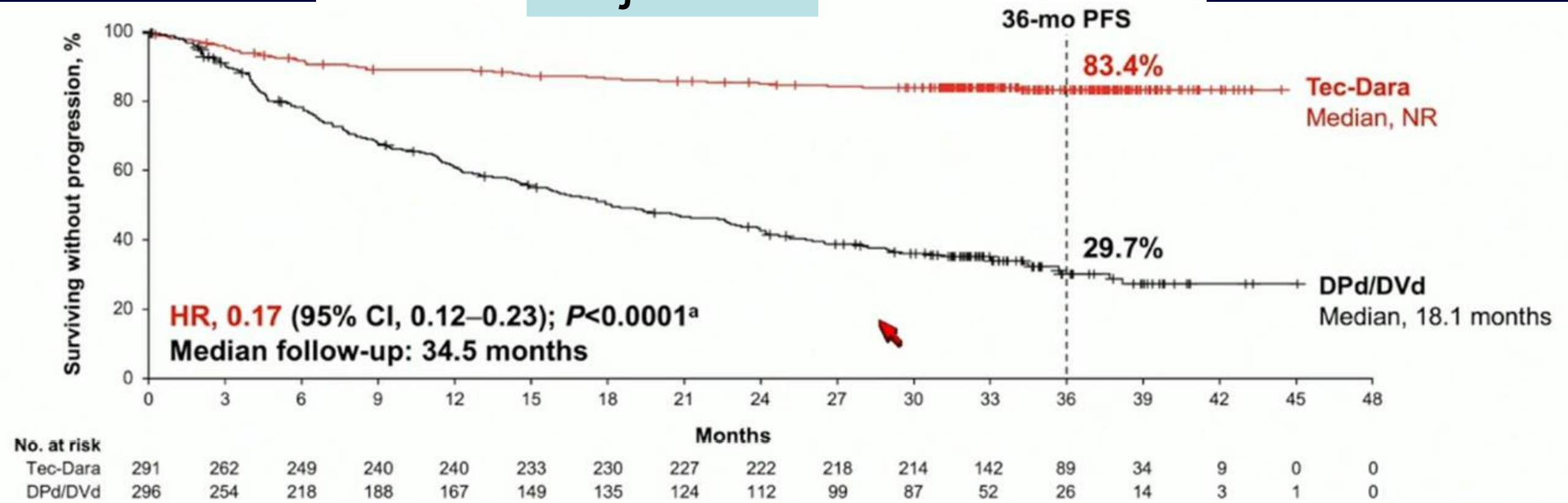
Editorials

A Cure, a Cure, My Kingdom for a Cure…

Sagar Lonial, MD, FAC

DOI https://doi.org/10.1200/

Majestic 3

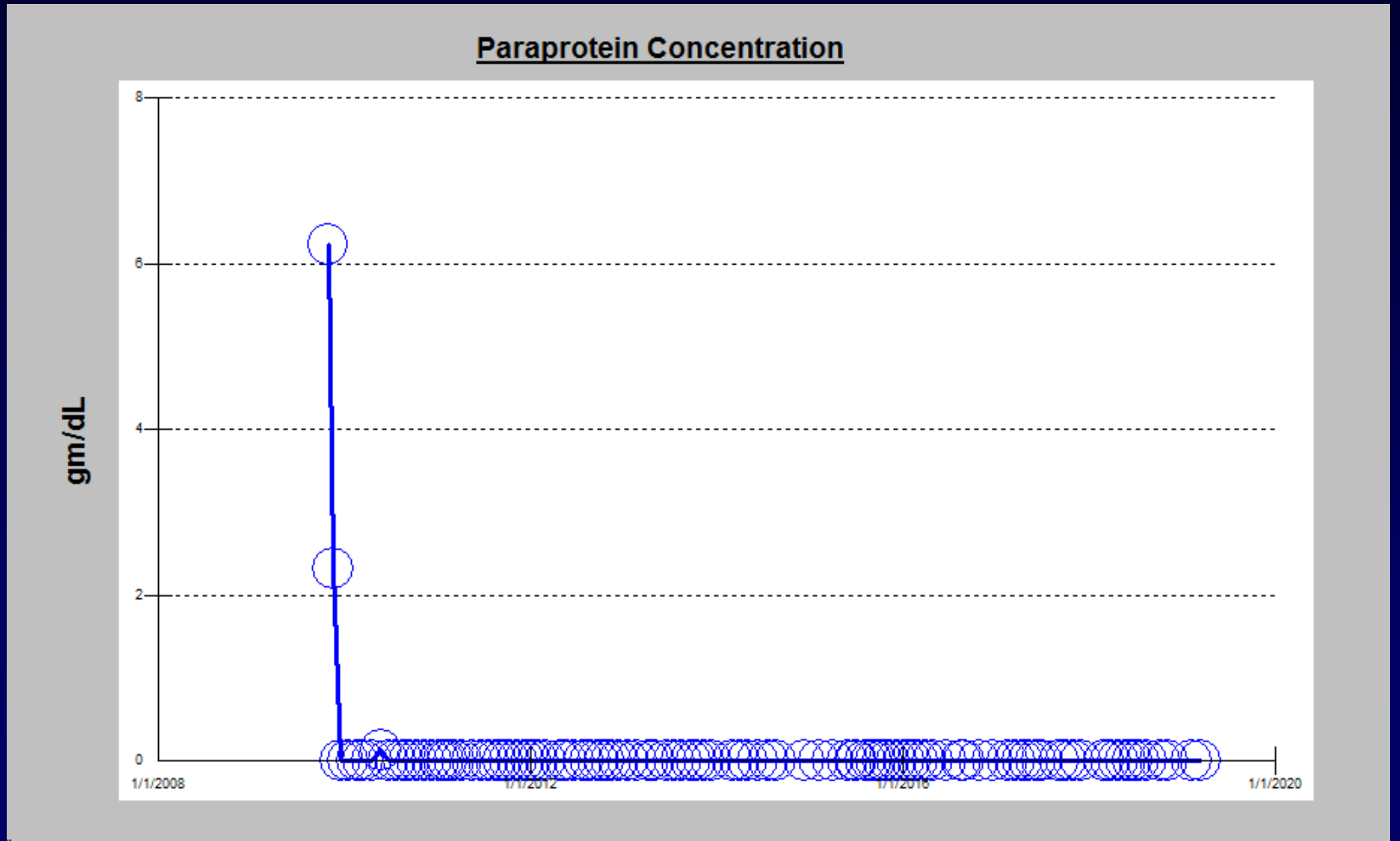


Number at risk
OS 97 91 85 79 74 66 58 53 51 48 36 5 1 0

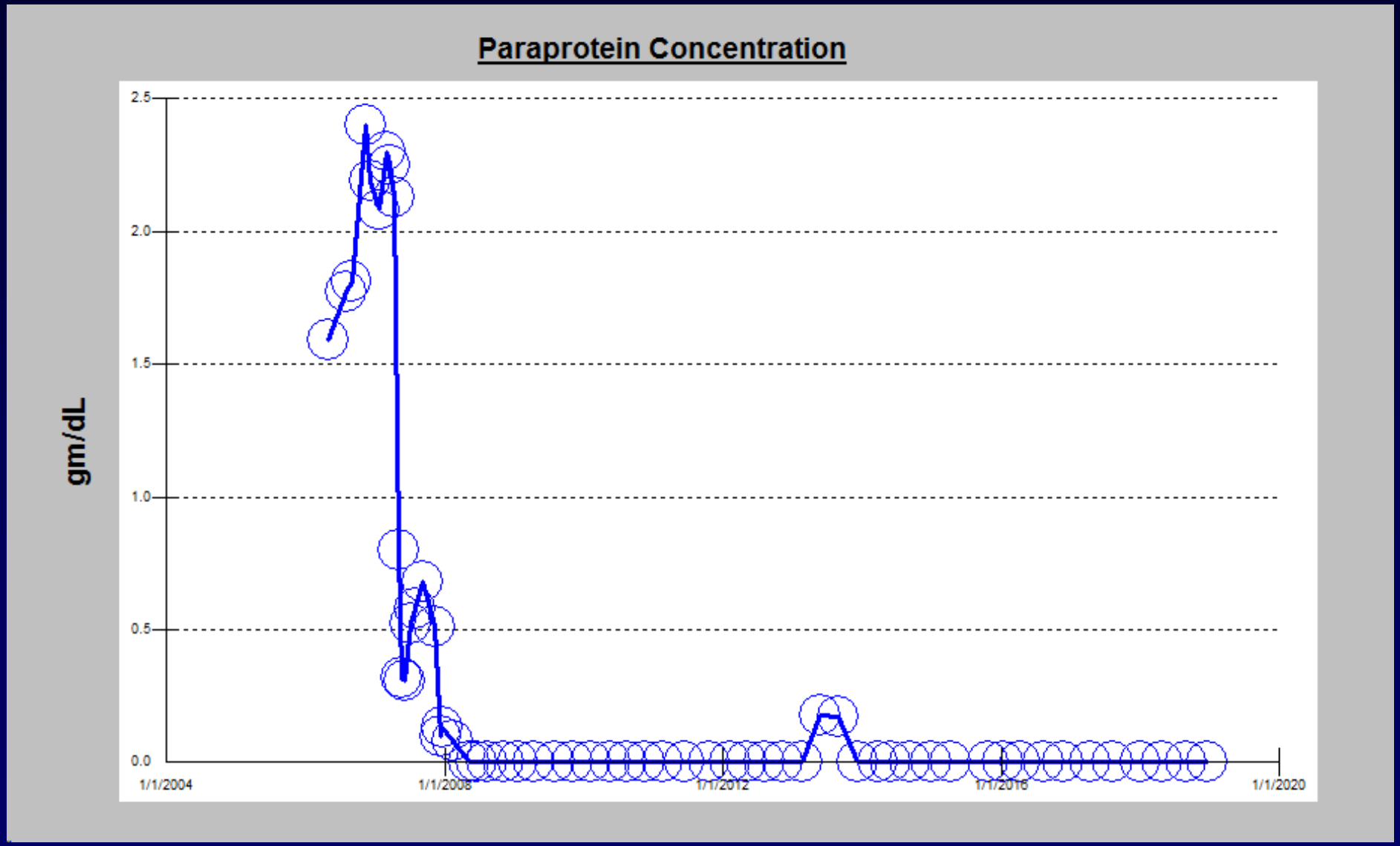
Number at risk
PFS 97 77 63 52 39 36 16 1

FIG 2. (A) OS. (B) Progression-free survival. Cilta-cel, ciltacabtagene autoleucel; OS, overall survival.

60 year old F with PCL



73 year old female, VTD x4, Auto x1 no maintenance



What is Necessary to Get to Cure?

- Elimination of the clone(s)
- Sustained MRD negativity (at least 2 measurements 12 months apart and 10^{-6} minimum)
- Imaging confirmation
- **Avoidance of continuous therapy**
- **Avoidance of drug resistance**

Proposed IMS/IMWG Definition of Cure

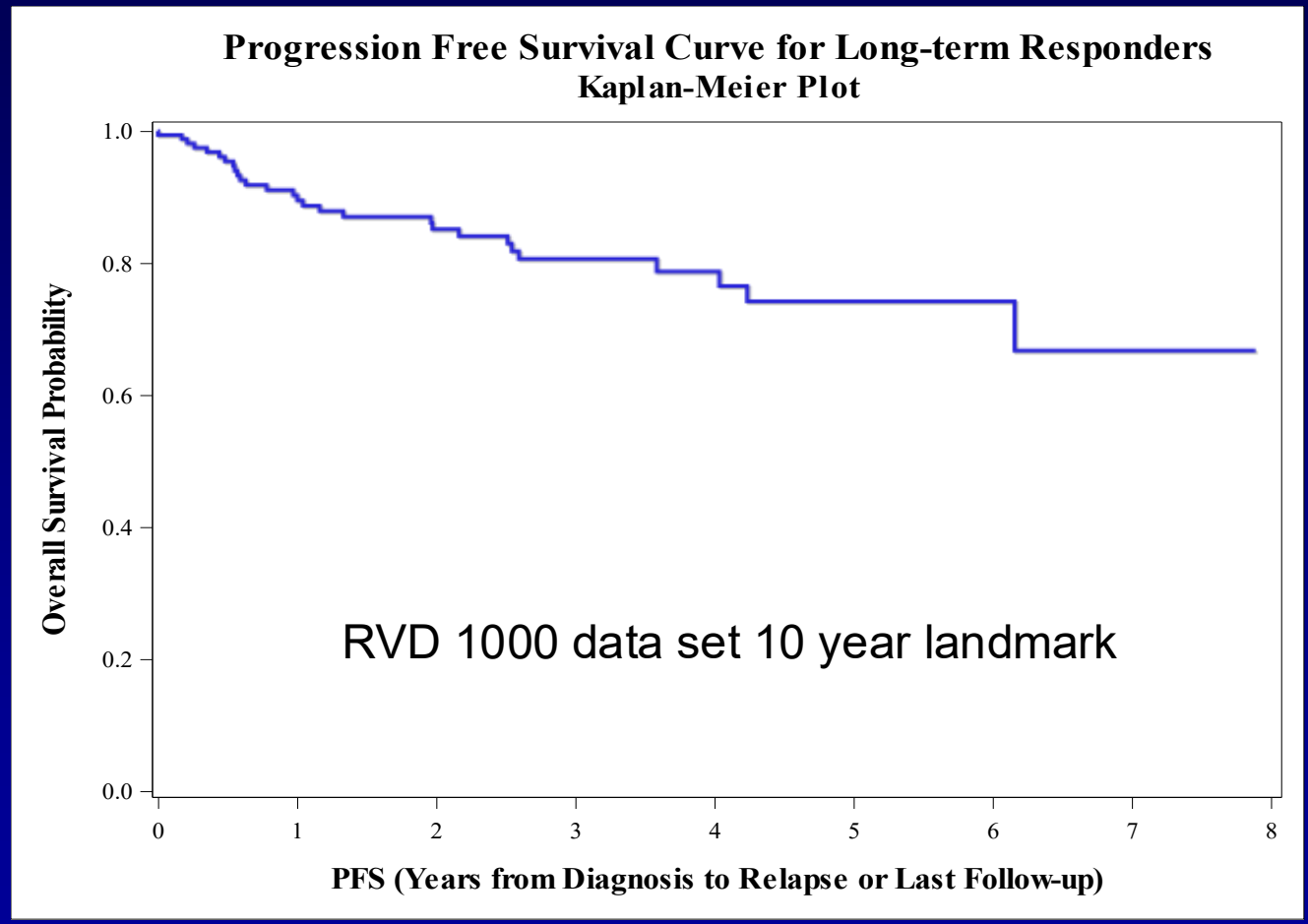
- 5 years off therapy

  And

- MRD negative 10-6

  And

- Imaging negative

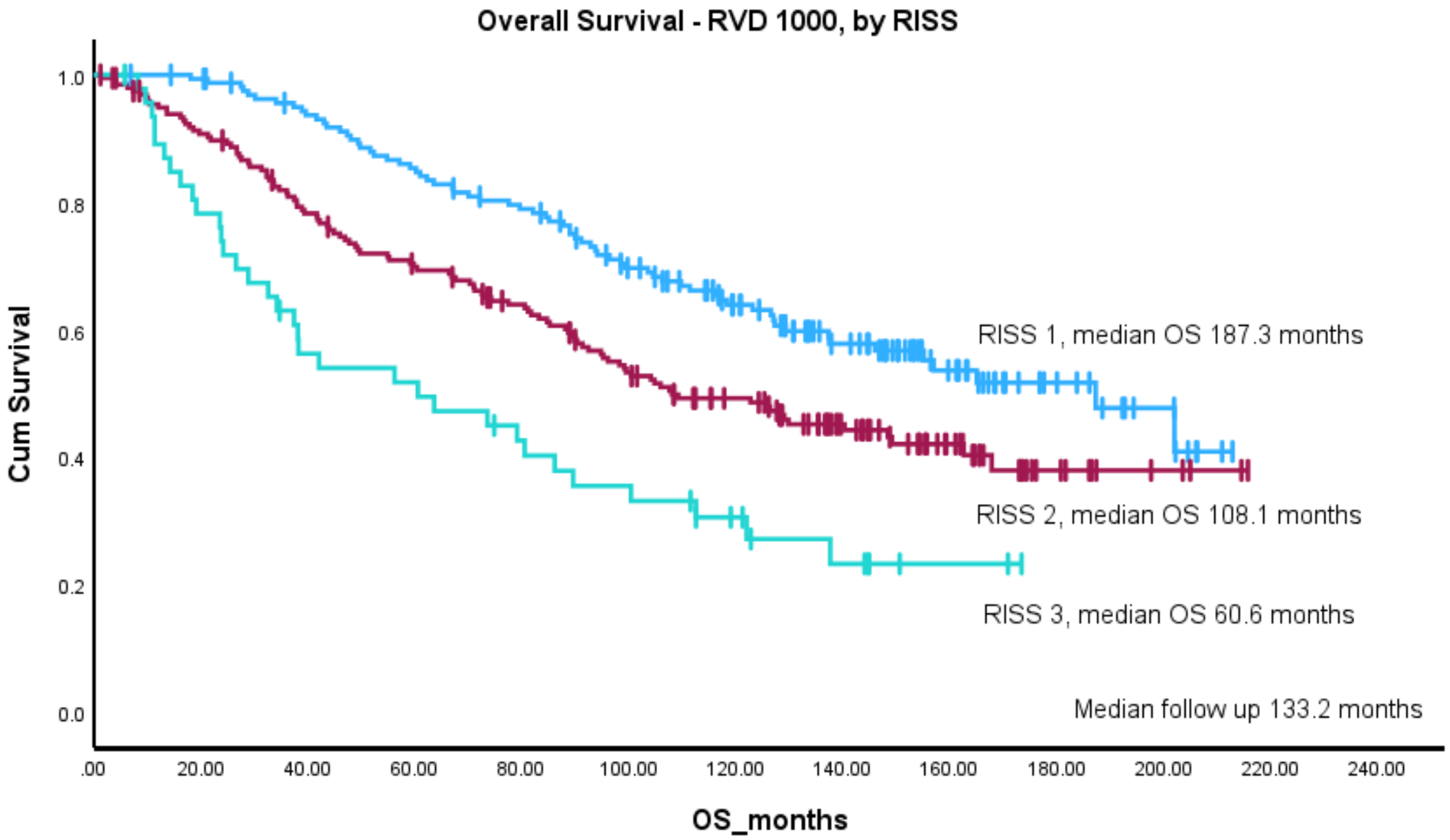


Concept 1

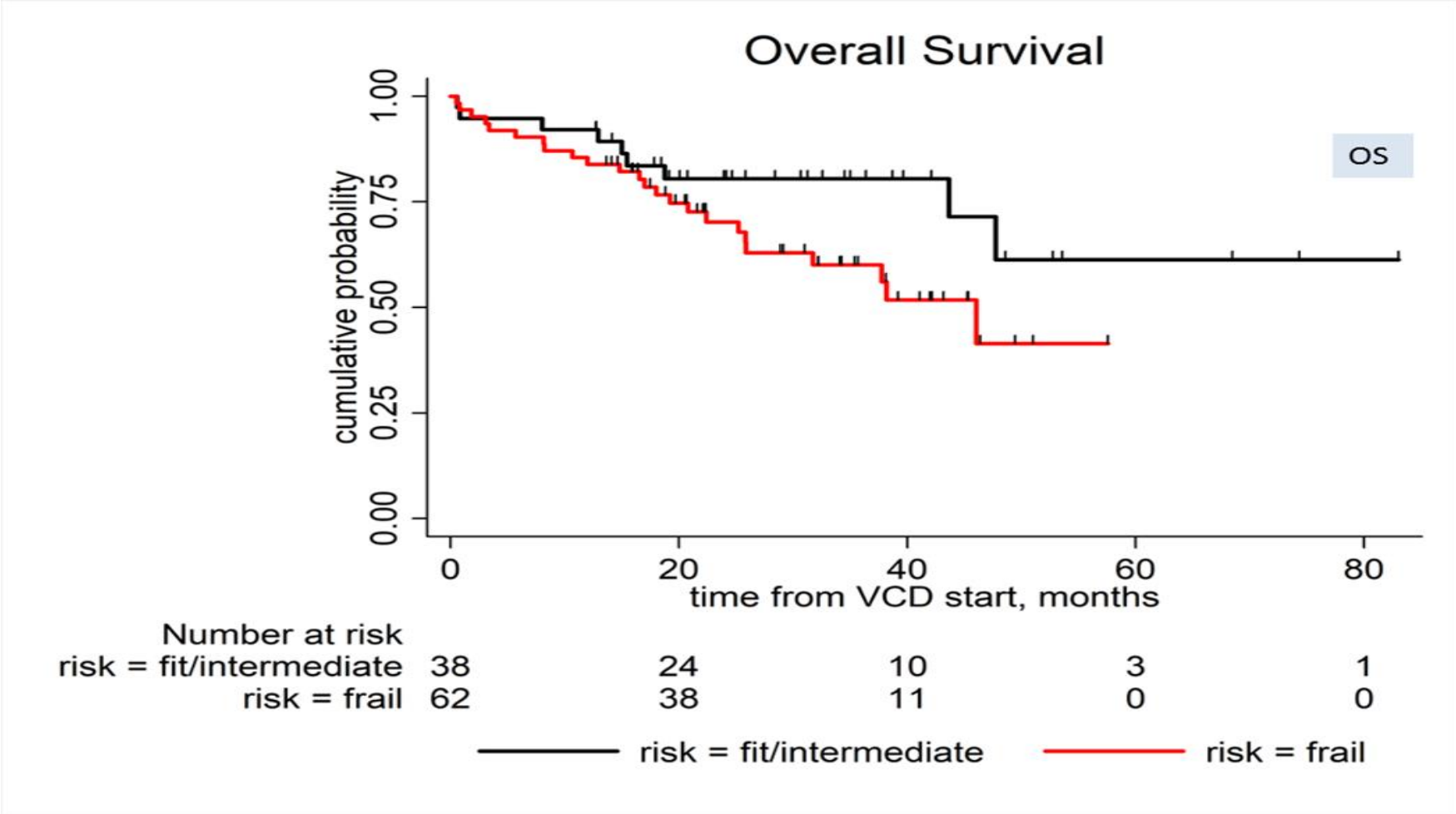
All patients and treatments are not the same

Patient Differences

- High risk vs standard risk
  - In current cohort, nearly all long terms PFS patients are standard risk
- Frail vs Fit
  - Frailty is an independent risk factor as powerful as risk


Overall Survival - RVD 1000, by RISS
Cum Survival
1.0
0.8
0.6
0.4
0.2
0.0
.00
20.00
40.00
60.00
80.00
100.00
120.00
140.00
160.00
180.00
200.00
220.00
240.00
OS_months
RISS 1, median OS 187.3 months
RISS 2, median OS 108.1 months
RISS 3, median OS 60.6 months
Median follow up 133.2 months

Frail vs Fit as an independent predictor



Djebbari et al, *Plos One* 2022

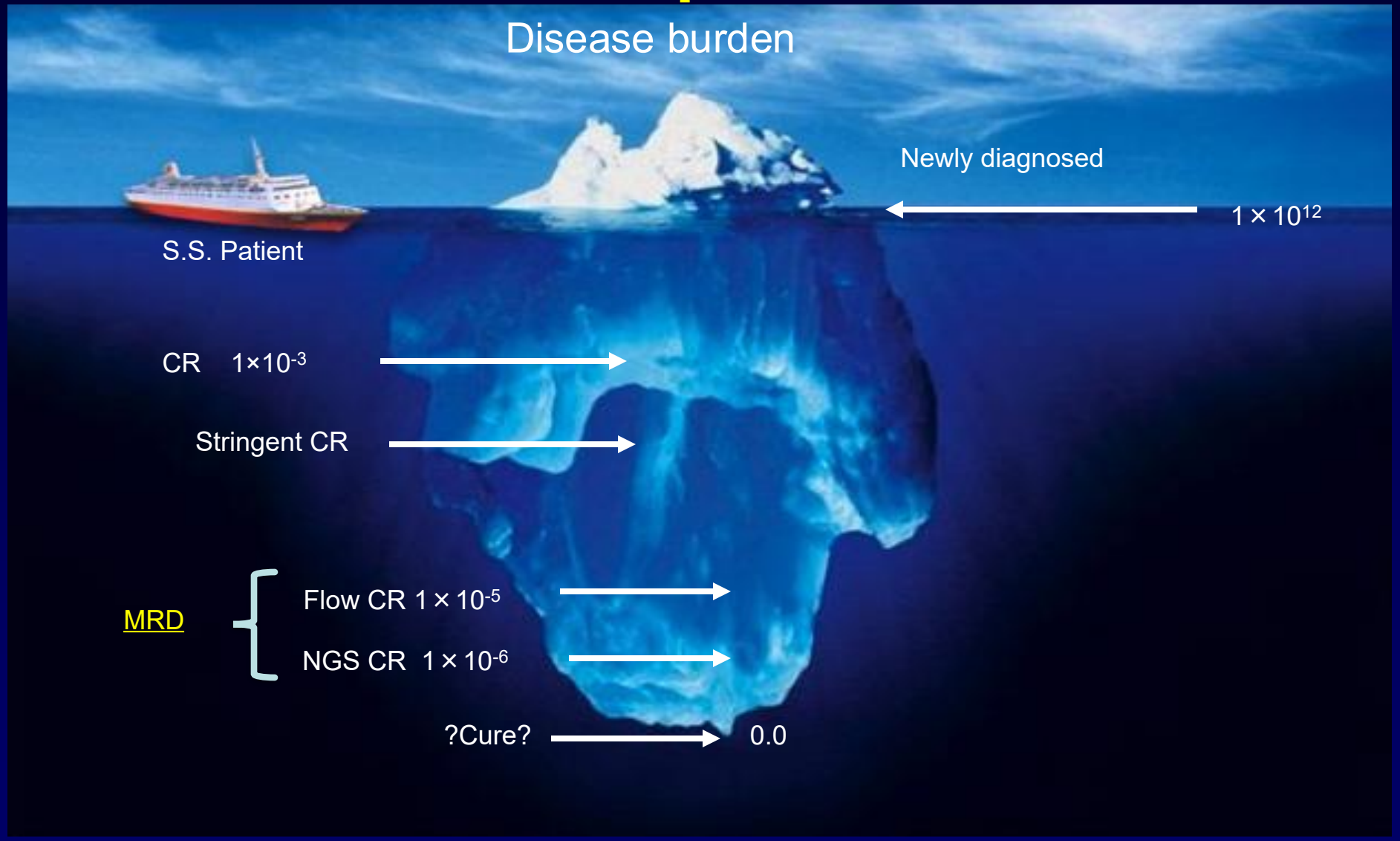
Treatments are different

- Age of Alkylators
  - Rare MRD negative, some CRs
- Age of ‘Novel Agents’
  - Higher CRs, more MRD with continuous therapy
- Age of Immune therapy
  - Higher, faster MRD, need to be smarter about duration

Concept 2

Need to eradicate as much disease as you can and keep it gone

Combination therapy can Achieve Better Depth of response



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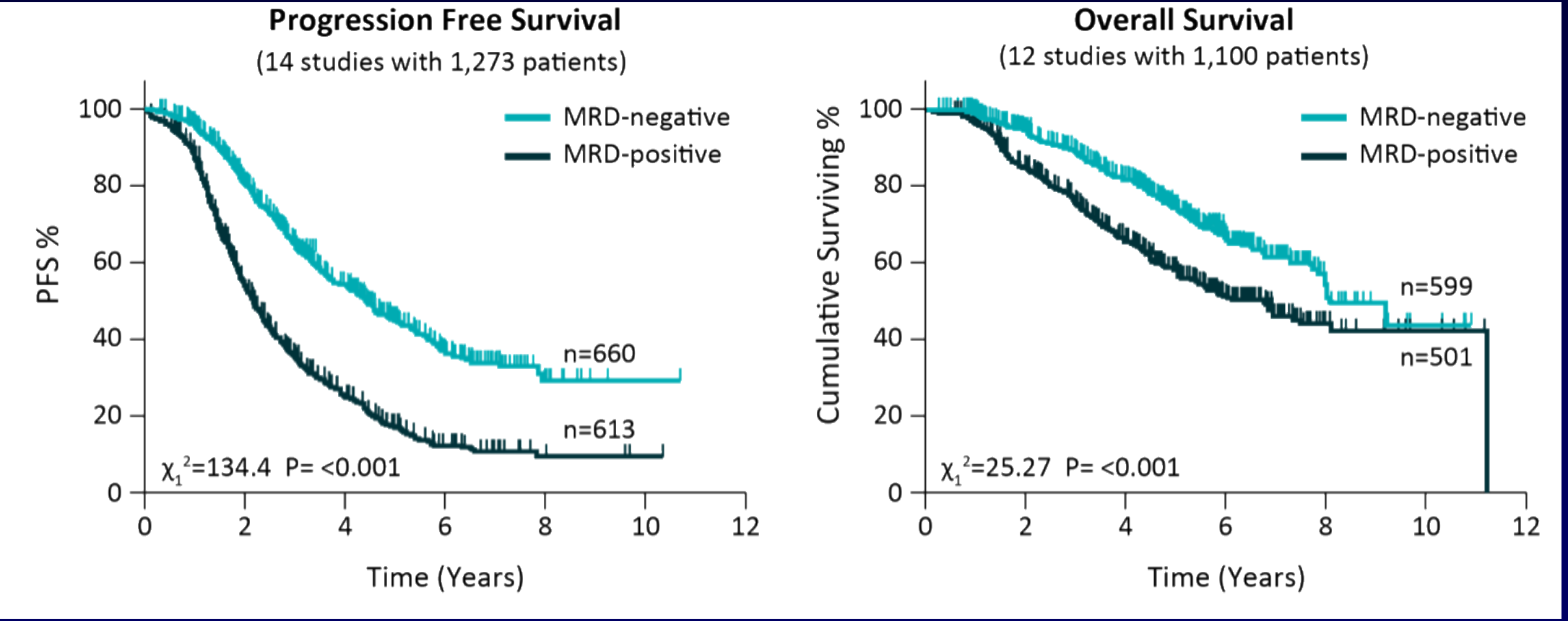
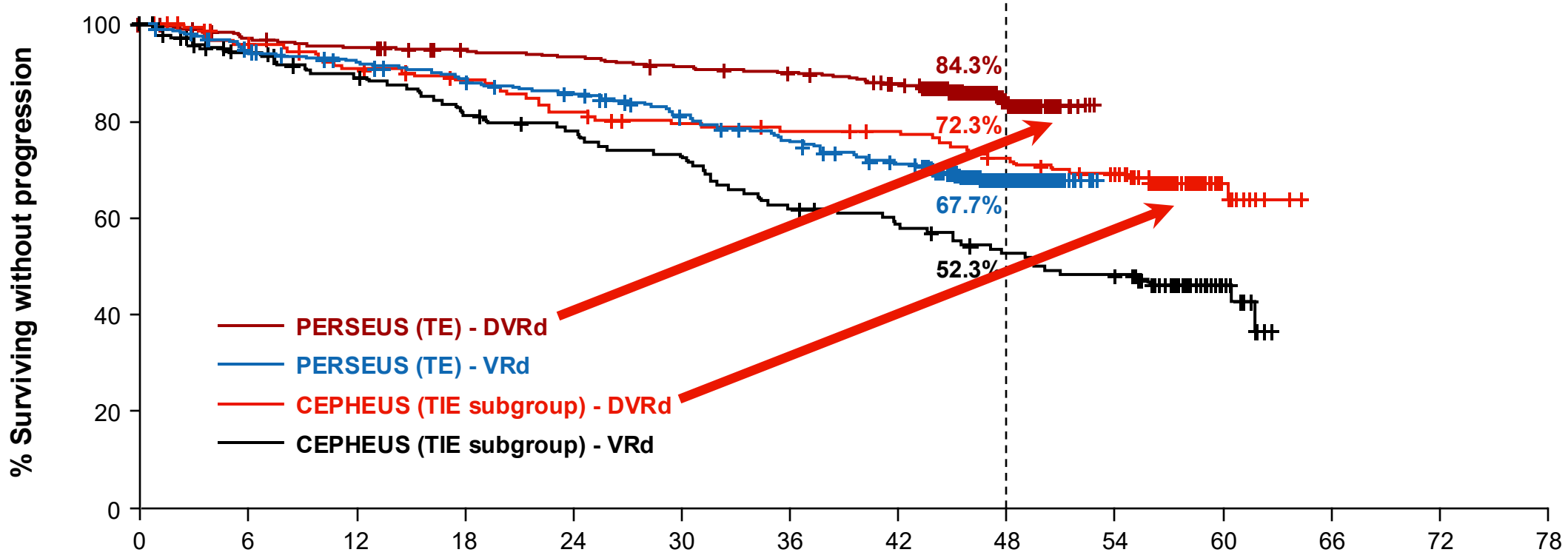
MRD negative dose better, just like CR



Munshi NC, et al. *JAMA Oncol*. 2017;3(1):28-35

Don’t Back Down:
The Addition of HDT improves outcomes, significantly

- **Median PFS with DVRd not reached** in TE patients in PERSEUS and TIE patients in the CEPHEUS trials



No. at risk														
PERSEUS (TE) - DVRd	355	335	327	318	313	305	299	286	90	0	0	0	0	0
PERSEUS (TE) - VRd	354	321	304	291	278	258	238	219	67	0	0	0	0	0
CEPHEUS (TIE) - DVRd	144	133	124	118	109	103	100	98	90	83	23	0	0	0
CEPHEUS (TIE) - VRd	145	125	114	104	96	90	76	70	61	56	18	0	0	0

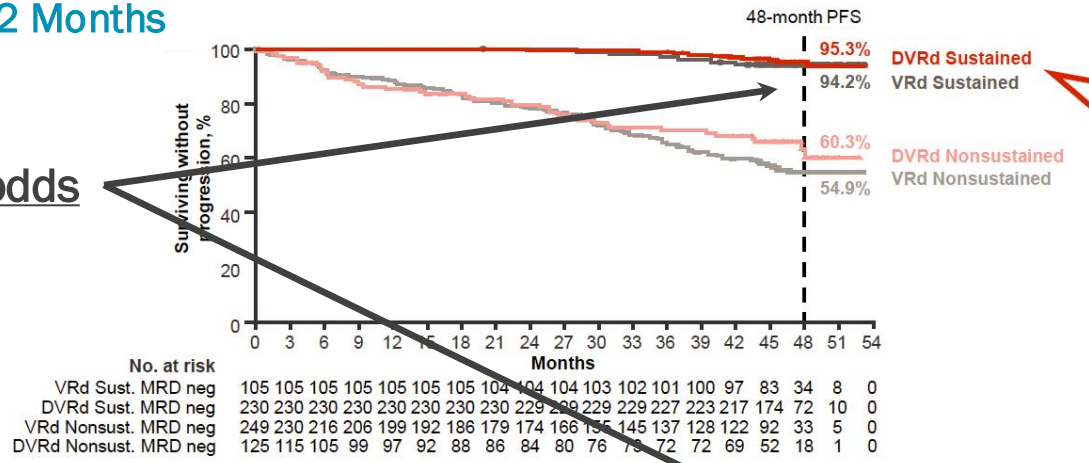
DVRd, daratumumab plus bortezomib, lenalidomide, and dexamethasone; PFS, progression-free survival; TE, transplant-eligible; TIE, transplant-ineligible; VRd, bortezomib, lenalidomide, and dexamethasone

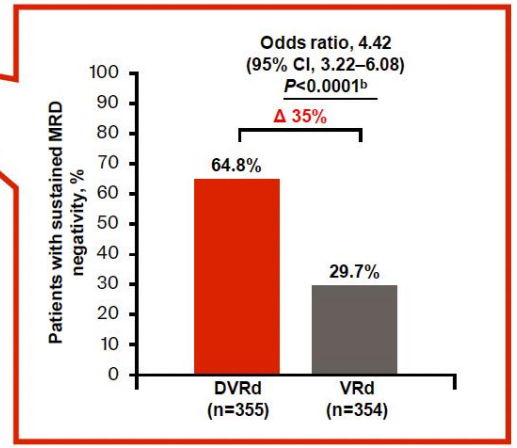
Analysis of Sustained MRD Negativity From the PERSEUS Phase 3 Trial of DVRd vs VRd in TE NDMM: Sustained MRD Negativity ≥CR Rates

PFS by Sustained MRD-Negativity (10^{-5}) ≥CR Status and Rates of Sustained MRD-Negativity (10^{-5}) ≥CR

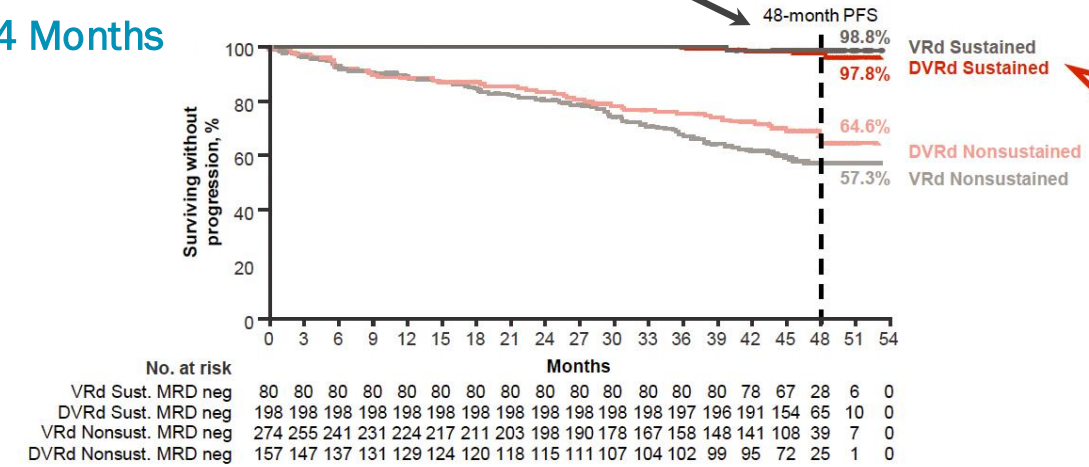
Playing Vegas odds

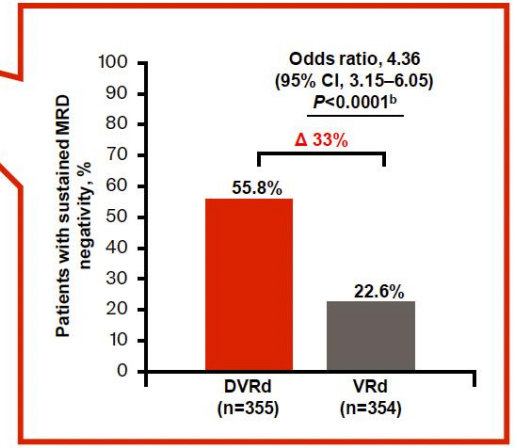
≥12 Months





≥24 Months



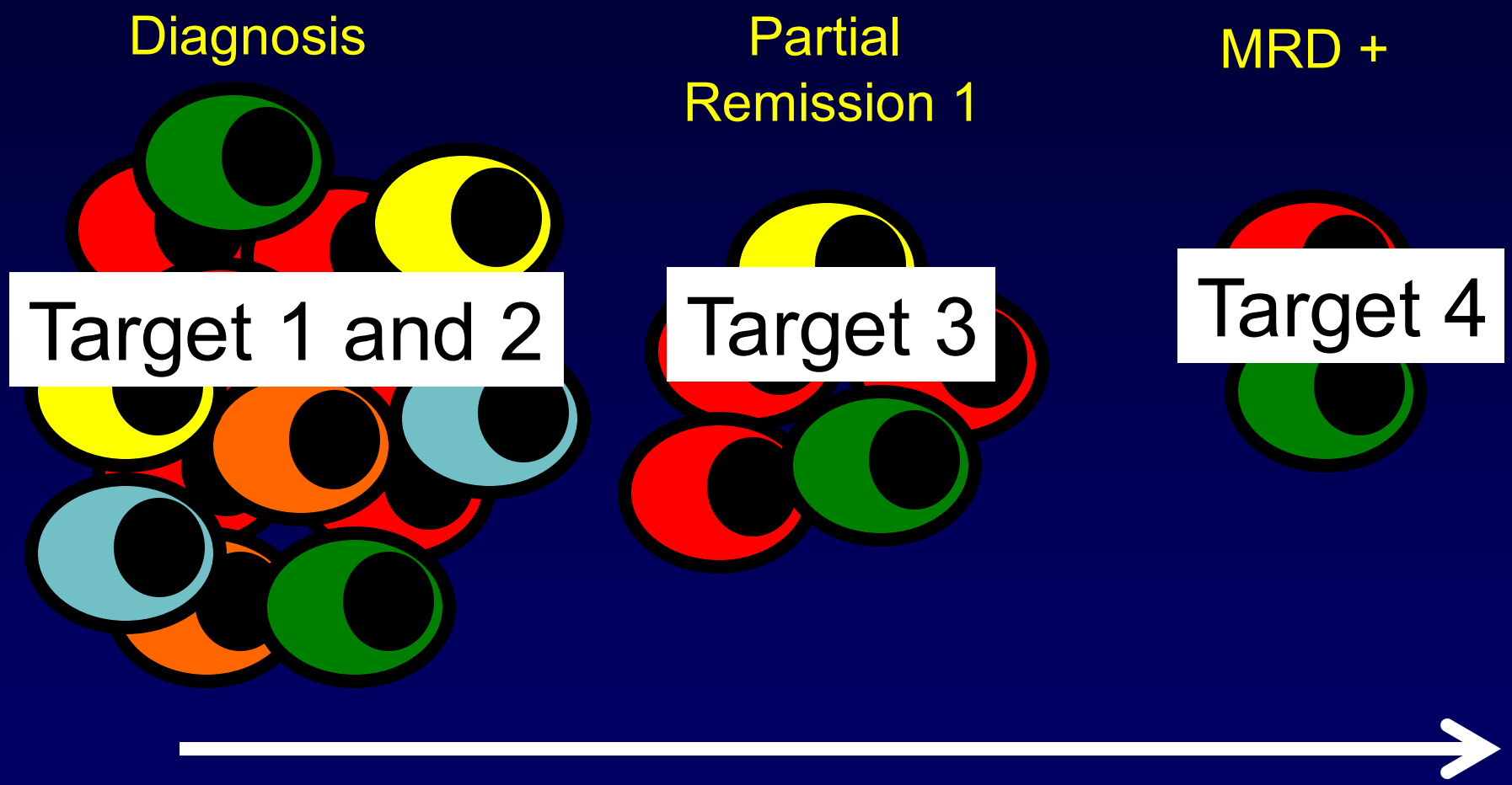


Moreau P, et al. ASCO 2025. Abstract 7501. Moreau P, et al. EHA 2025. Abstract PS1712.

Concept 3

In order to eradicate all the clones, continuous therapy with the same drugs doesn’t make sense….

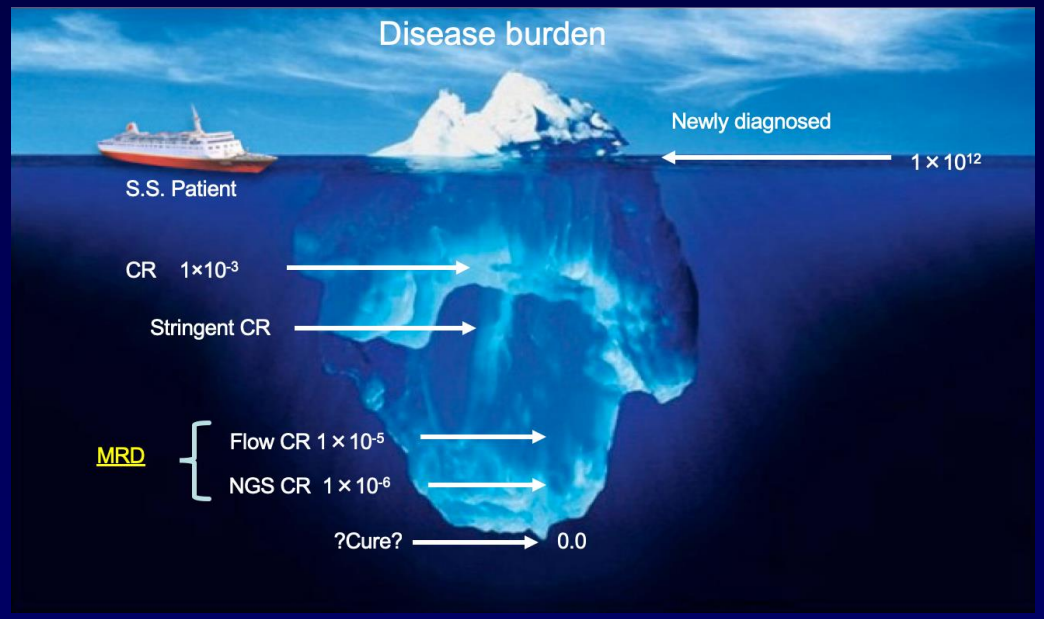
Clonal Evolution During Induction



Model for elimination of the malignant clone

Induction
(goal to achieve deep response)

Depth

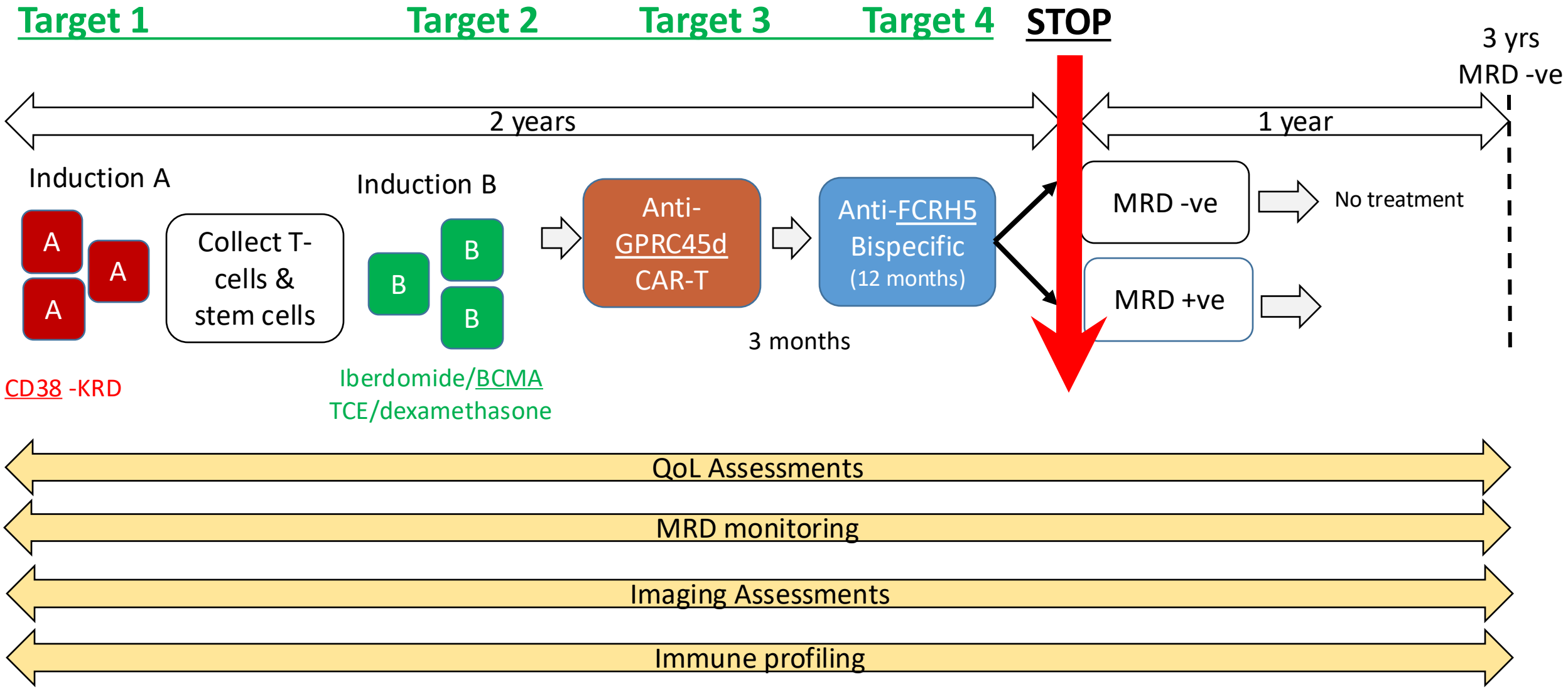


Probably different drugs
To address resistant clones

Duration

Consolidation/Maintenance
(to achieve Cure)

The TiRx Trial



What does the future look like?

- **Combination/sequential** therapy
- **Switching targets** and not treating to **resistance**
- **Limited duration therapy** (another possible benefit of combination therapy)
- The backbones of disease treatment (IMIDS, Pis) will remain important ways to reduce tumor burden quickly but set the stage for immune targets to be more effective
- **NOT dependent** on a single target to do all the work

Patients and Families

Thanks to:

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Vikas Gupta
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Danielle Roberts
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Amelia Langston
Y. Gu
S-Y Sun
Ben Barwick
Mala Shanmugan
Larry Boise
Bryan Burton

sloni01@emory.edu

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T.J. Martell Foundation

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