Curative Therapy for Multiple Myeloma

Andrzej J. Jakubowiak, MD, PhD

Professor of Medicine
Director, Myeloma Program
The University of Chicago

THE UNIVERSITY OF CHICAGO MEDICAL CENTER

Disclosures

- Consultancy and advisory boards for AbbVie, Amgen, BMS, Celgene, GSK, Janssen, Juno, Karyopharm, Millennium-Takeda, Sanofi-Aventis, SkylineDx
- Off-label drug use

- There is no question that we have made tremendous progress
  - Significantly improved overall survival
  - Consistent and deeper responses
  - More and more exceeding 10 years

- However, we are reminded all the time that the general pattern of the disease appears unchanged

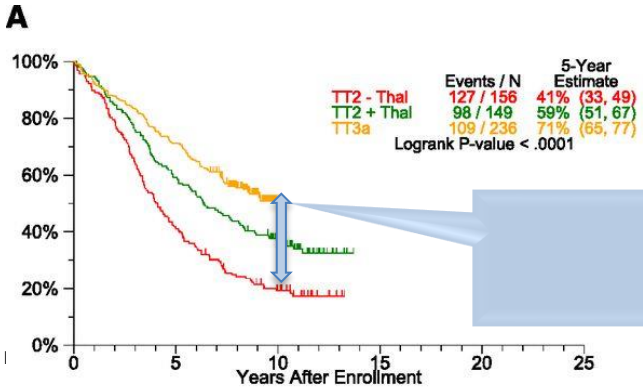
- And that great majority of patient will ultimately relapse

…so, are we at the point that we can talk about curative therapy for myeloma?

…let’s start breaking this down

…first, are we already able to cure at least some patients with myeloma

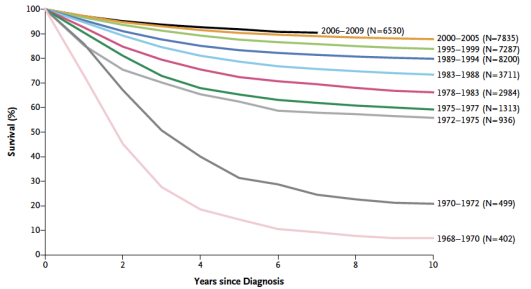
…based on the results of sequential ”Total Therapy” treatments, claim was made that we are not only curing but increasing the rate of cure



. . . With ““the cure fraction” in Total Therapy 3 approaching 50%!!!

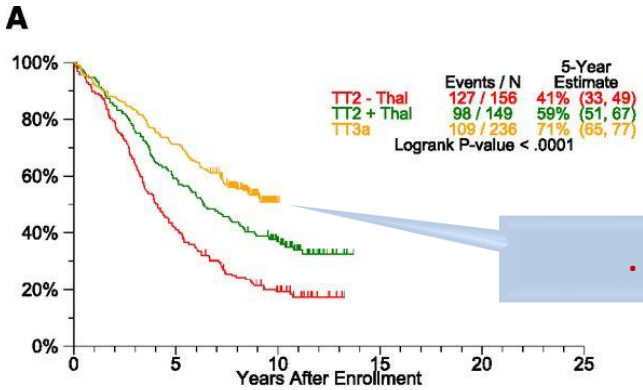
. . . by merely adding new agents and by extending duration of treatment

. . . leading to a proposed “cure strategy” in myeloma similar to the strategy in childhood ALL



Hunger SP, Mulligan CG. *N Engl J Med.* 2015; 373:1541-1552.

But before me move further



. . . Do we know that these patient are actually cured?

Barlogie B, et al. *Blood*. 2014;124:3043-3051.

Proposed in the paper evidence is “indirect,”

…based on sustained CR and overall survival (OS)

…and on overlap of this OS curve with the survival curve of matched population not affected by myeloma

…but this is good starting point for our discussion on “Curative Therapy for Myeloma”

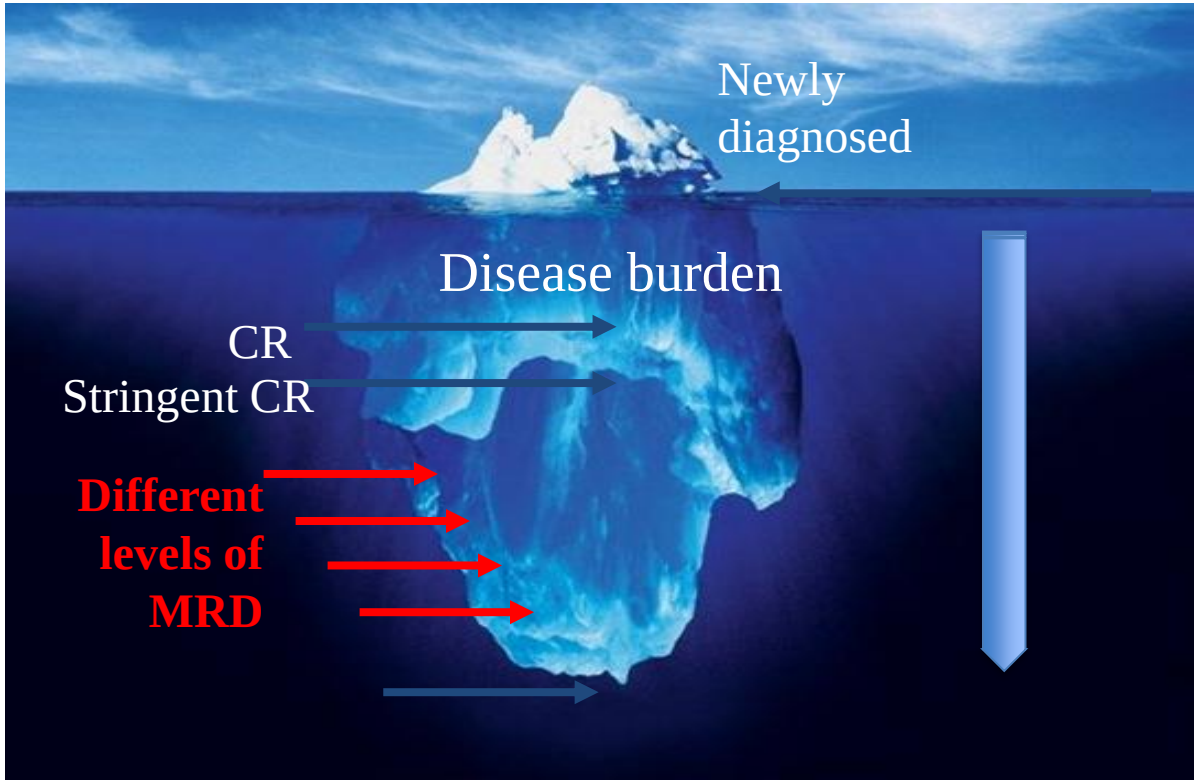
…let’s break our discussion around the following segments

1. What have we learned so far?
2. How based on what we have learned are we advancing curatives strategies in myeloma?
3. Do we need more agents and more therapeutic tools?
4. Is there going to be one or multiple ”curative therapies”
5. How to better define “cure” or at least “presumed cure”?

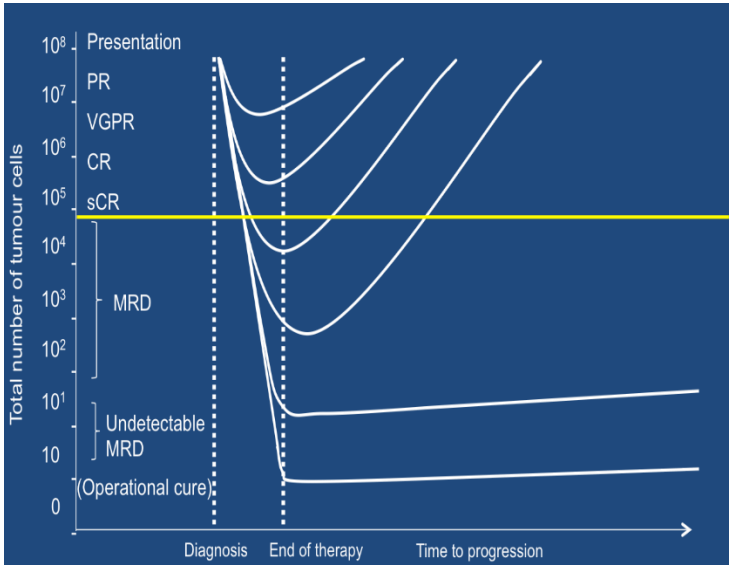
…let’s review them

1. **What have we learned so far?**
2. How based on what we have learned are we advancing curatives strategies in myeloma?
3. Do we need more agents and more therapeutic tools?
4. Is there going to be one or multiple ”curative therapies”
5. How to better define “cure” or at least “presumed cure”?

…first, improvements in MM therapy resulted in deepening of responses to treatment

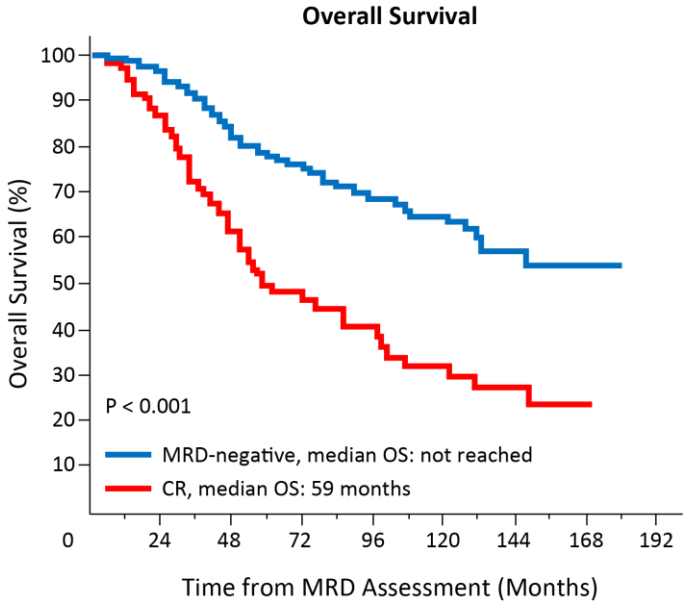


…second,
the deeper the responses, the longer their duration



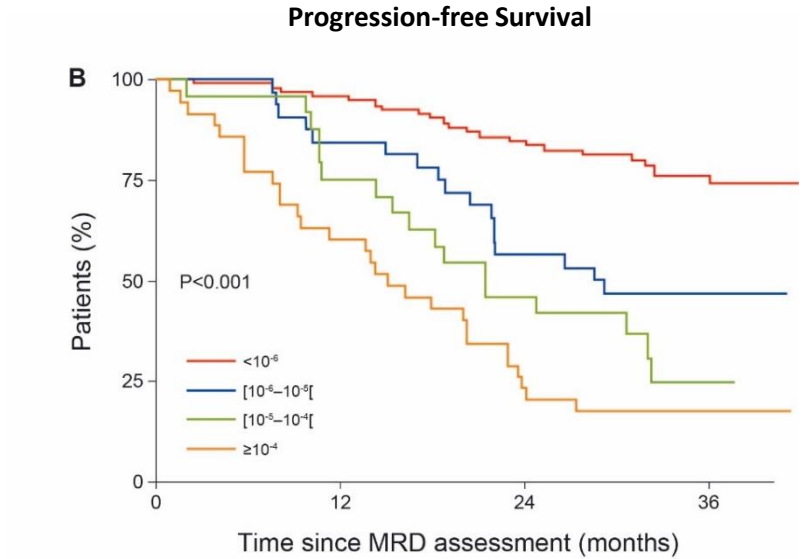
CR, complete response; MRD, minimal residual disease; PR, partial response; sCR, stringent CR; VGPR, very good PR.

Paiva B, et al. *Blood.* 2015;125:3059-3068.



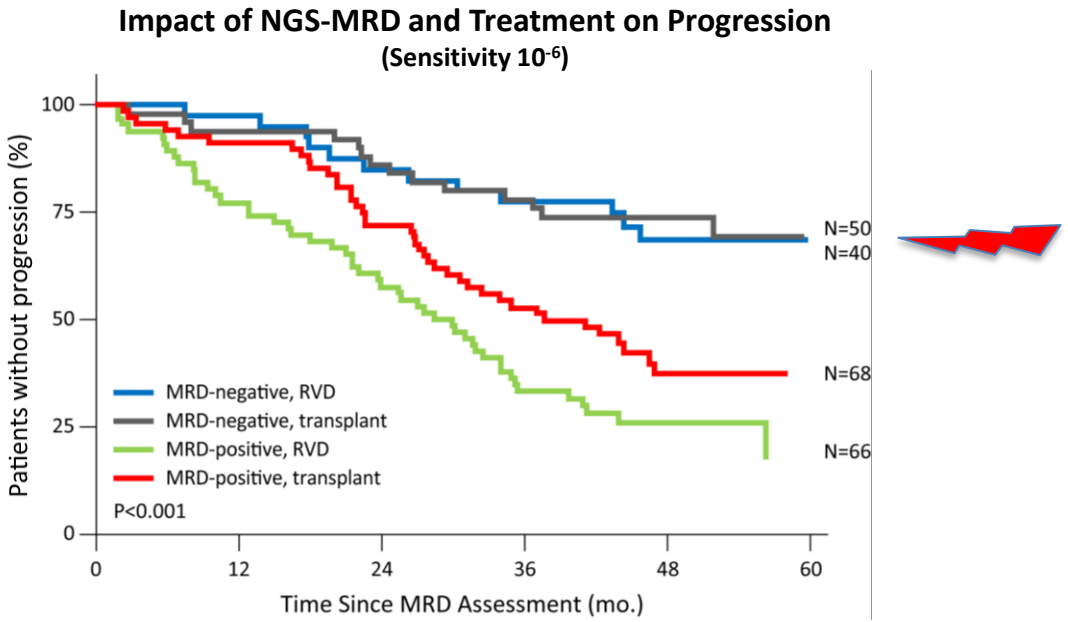
Lahuerta JJ, et al. *J Clin Oncol.* 2017;35:2900-2910.

…third,
the level of MRD – negativity matters



Perrot et al. Blood. 2018 Dec 6;132(23):2456-2464.

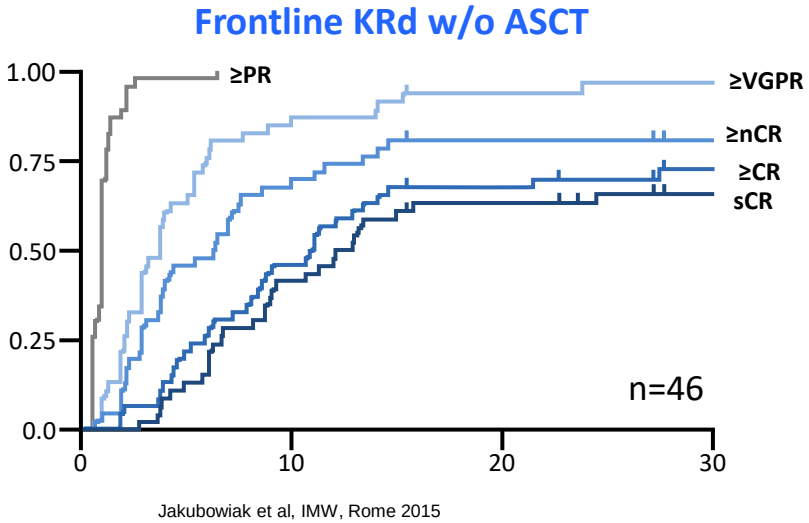
…next, it does not matter with what treatment achieved, the same level of MRD-negativity predicts similar outcome



Patients who achieved MRD-negativity ($<10^{-6}$), regardless of whether they received transplant or not, had the best outcomes ($P<0.001$)

Avet-Loiseau H, et al. ASH 2017: Abstract 435.

…and finally, it takes time to reach deepest responses

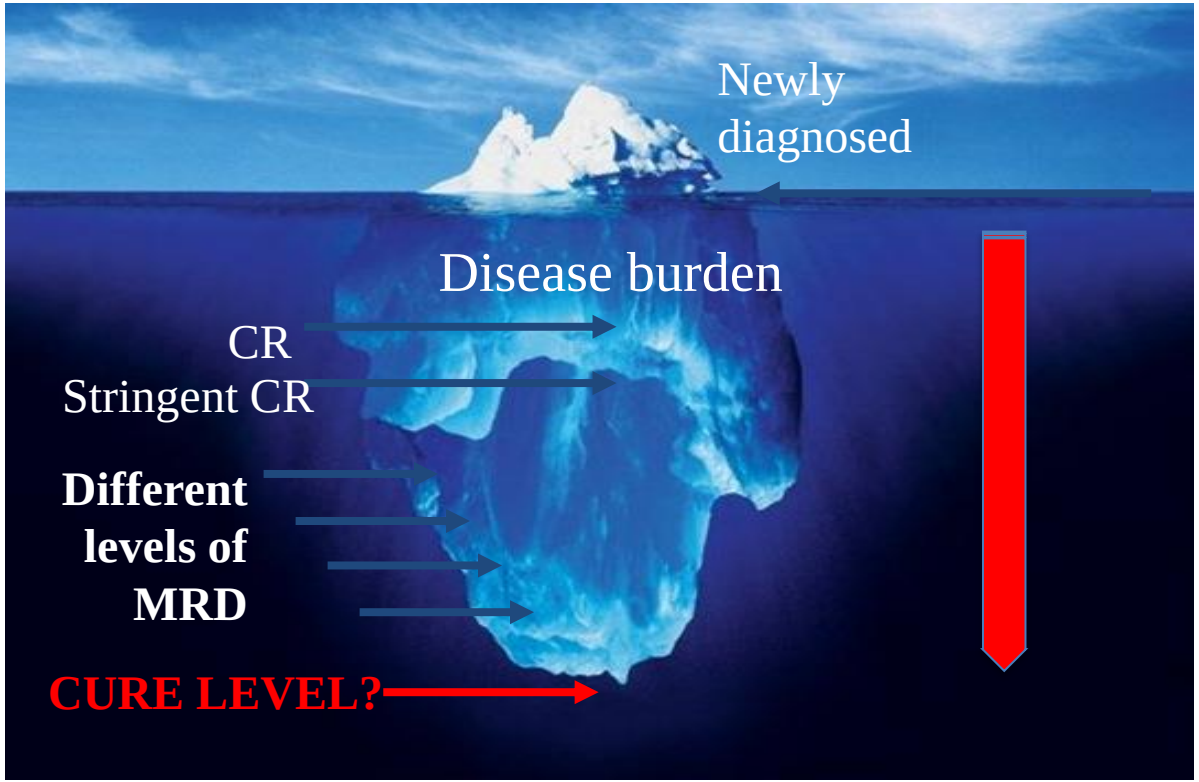


Jakubowiak et al, IMW, Rome 2015

…so “adequate” duration of treatment is important
for the best possible response to even very effective therapy

…to this point, we are working on presumption

that deepening the response brings us closer to a cure



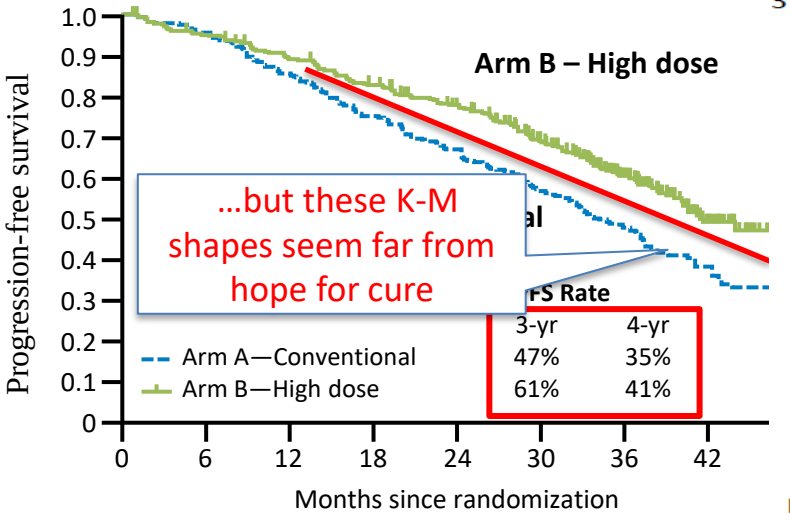
…so, let’s review next

1. What have we learned so far?
2. **How based on what we have learned, are we advancing curatives strategies in myeloma?**
3. Do we need more agents and more therapeutic tools?
4. Is there going to be one or multiple ”curative therapies”
5. How to better define “cure” or at least “presumed cure”?
6. What else is coming and what else is needed to declare victory?

…first, will less toxic than Total Therapy,

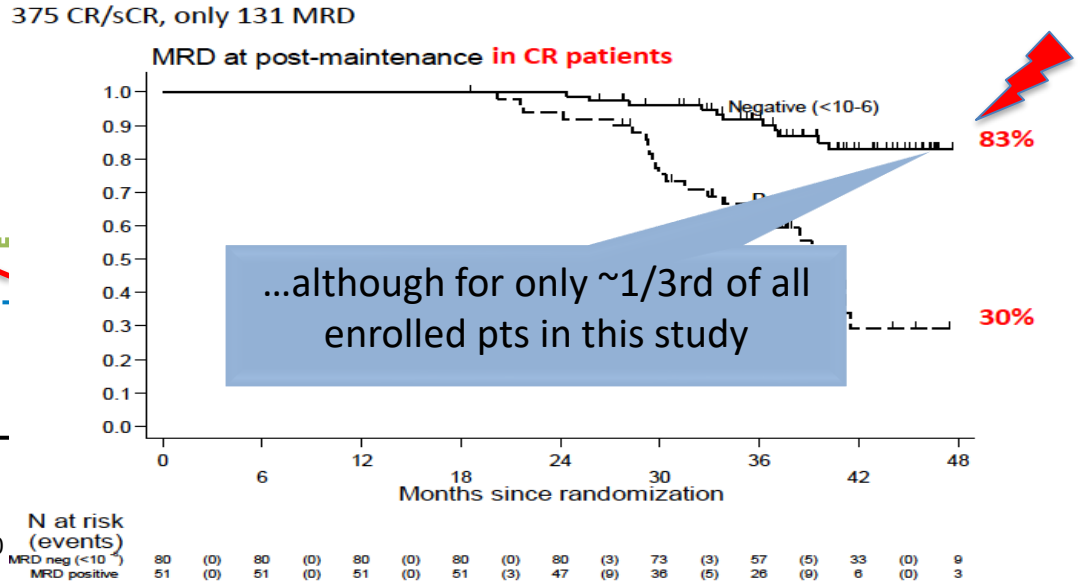
…more modern treatment strategies get us closer to cure?

…like RVd +/- Transplant



Attal M, et al. ASH 2015, Attal M, et al. *N Eng J Med* 2017:376:1311-20

…but it looks that we can achieve very good outcome in a proportion of pts treated with RVd



…but maybe "MRD-readout" is the direction we need to go?

Attal et al, ASH 2015, Abstract 391, Courtesy of Michel Attal; Avet-Loiseau, ASH 2015, Avet-Loiseau, ASH 2017, Abstract 435

…so to make further progress in path to cure

… we need to get more patients to CR/MRD (-) disease,
…as a "cure read-out signal" of being on the right track

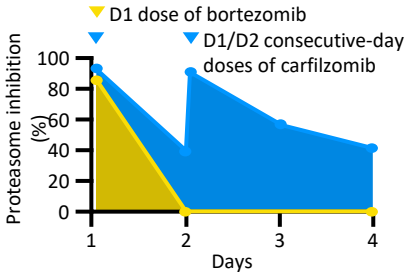
…let's try to tackle next
HOW WE CAN GET THERE?

…maybe first

…by using more effective drugs in the class of drugs we know that work

e.g. by replacing BTZ in RVD with CFZ in KRd

Pre-clinical rationale

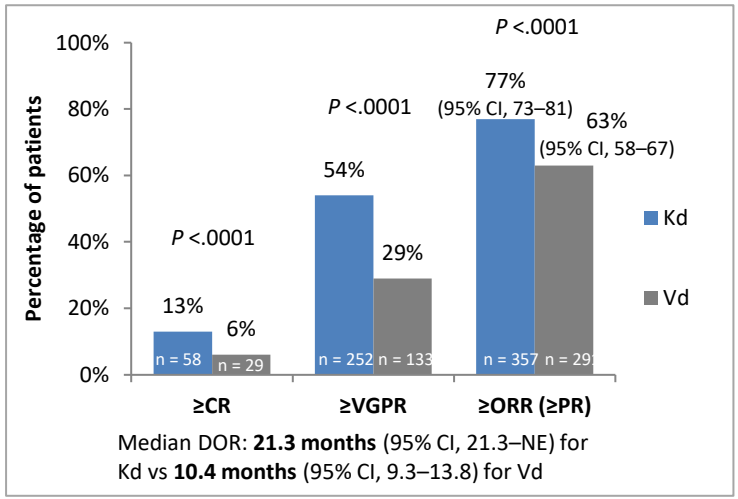


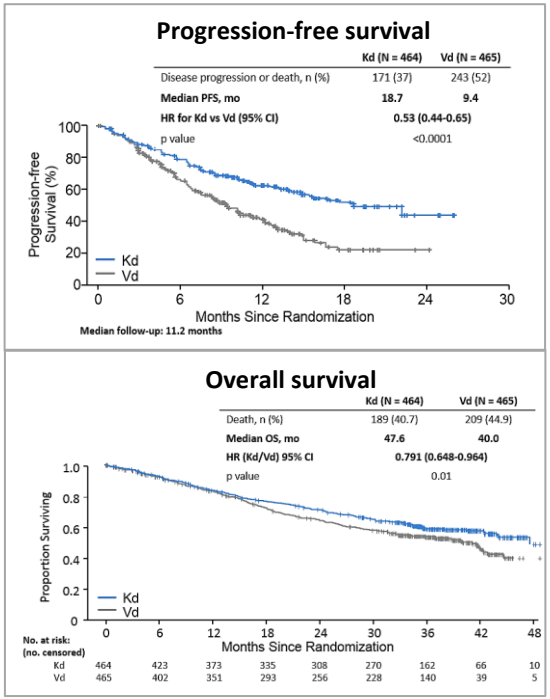
Demo SD, et al. *Cancer Res*. 2007;67:6383.

Clinical rationale

ENDEAVOR TRIAL

CFZ is more active than BTZ





Dimopoulos MA, et al. *Lancet Oncol*. 2016;17:27-38; Dimopoulos MA et al. *Lancet Oncol*. 2017;18;e562.

…and by using this KRd new triplet over an extended 24-months period

The results exceeded our expectations

blood

2012 120: 1801-1809
Prepublished online June 4, 2012;
doi:10.1182/blood-2012-04-422683

A phase 1/2 study of carfilzomib in combination with lenalidomide and low-dose dexamethasone as a frontline treatment for multiple myeloma

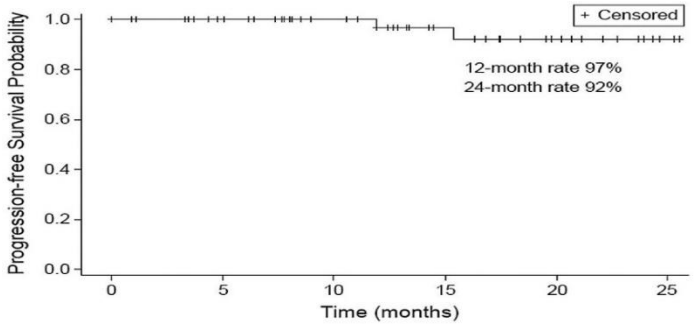
Andrzej J. Jakubowiak, Dominik Dytfeld, Kent A. Griffith, Daniel Lebovic, David H. Vesole, Sundar Jagannath, Ammar Al-Zoubi, Tara Anderson, Brian Nordgren, Kristen Detweiler-Short, Keith Stockerl-Goldstein, Asra Ahmed, Terri Jobkar, Diane E. Durecki, Kathryn McDonnell, Melissa Mietzel, Daniel Couriel, Mark Kaminski and Ravi Vij

CLINICAL TRIALS

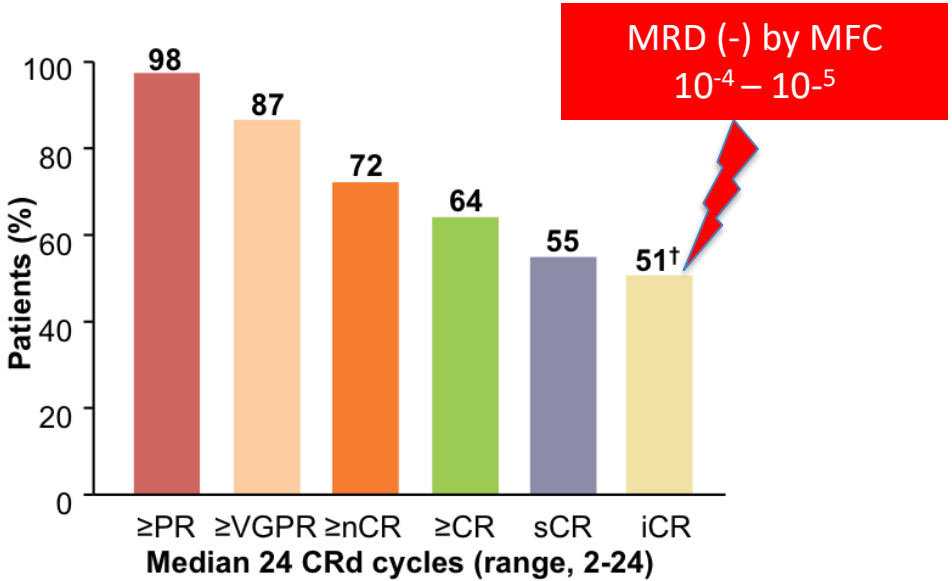
Comment on Jakubowiak et al, page 1801

Treating myeloma: the future is already here!

Ola Landgren and Neha Korde NATIONAL CANCER INSTITUTE



Updated best response rates on ITT

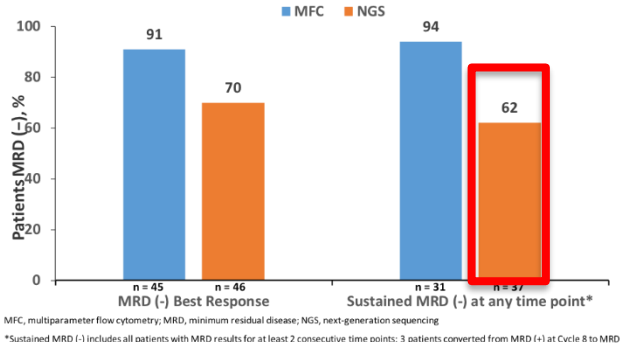


†Estimated rate based on 23 of 26 evaluated pts assessed for MRD by flow cytometry at CR/suspected CR

Zimmerman et al, ASCO 2015, Tandem Transplant, 2016, Jakubowiak et al EHA 2016, manuscript in preparation

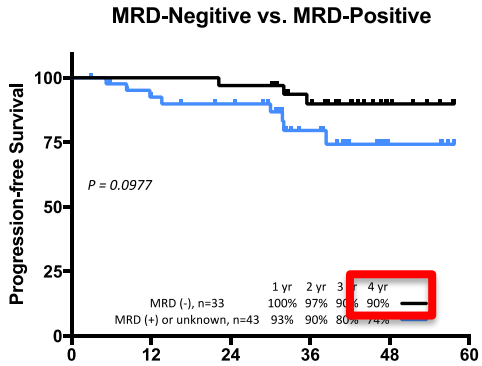
. . . then by combining extend KRd treatment with transplant (ASCT)

MMRC trial KRd + ASCT

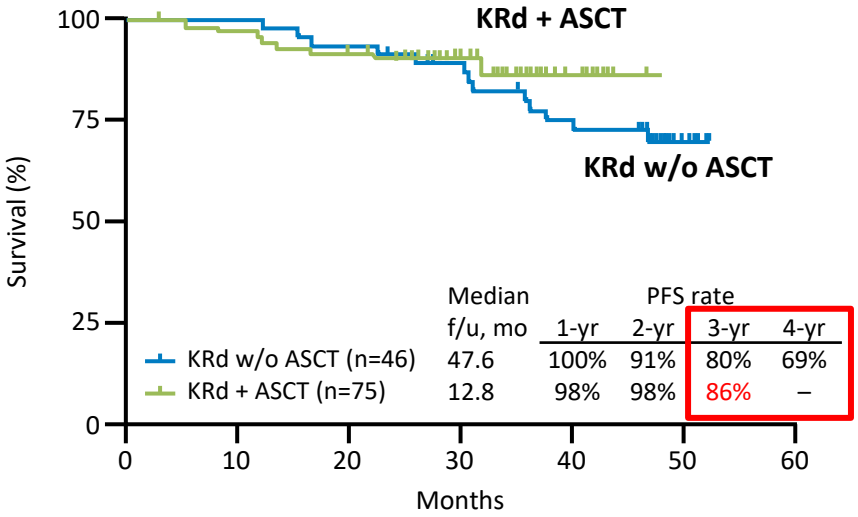


MFC, multiparameter flow cytometry; MRD, minimum residual disease; NGS, next-generation sequencing

*Sustained MRD (-) includes all patients with MRD results for at least 2 consecutive time points; 3 patients converted from MRD (+) at Cycle 8 to MRD



KRd ± ASCT

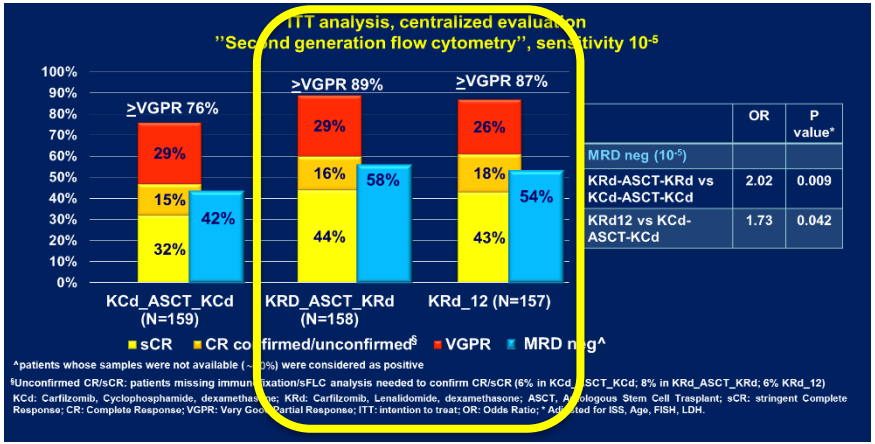


	Median f/u, mo	PFS rate 1-yr	2-yr	3-yr	4-yr
KRd w/o ASCT (n=46)	47.6	100%	91%	80%	69%
KRd + ASCT (n=75)	12.8	98%	98%	86%	–

Jakubowiak et al, IMW 2015, Zimmerman et al, TT Meeting 2016, Jakubowiak et al ASH 2017, manuscript in preparation

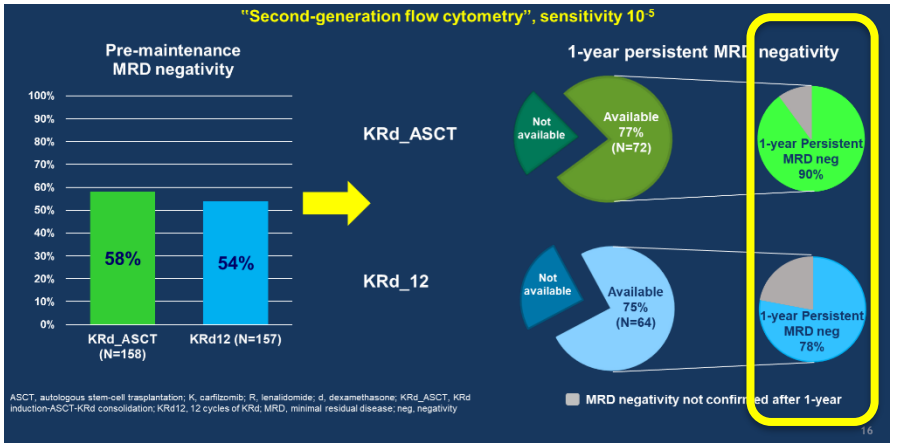
…the KRd +/- ASCT results are now supported by the results of phase III Forte trial (KRd ± ASCT vs KCd + ASCT)

Showing superiority of KRd vs KCd . . .



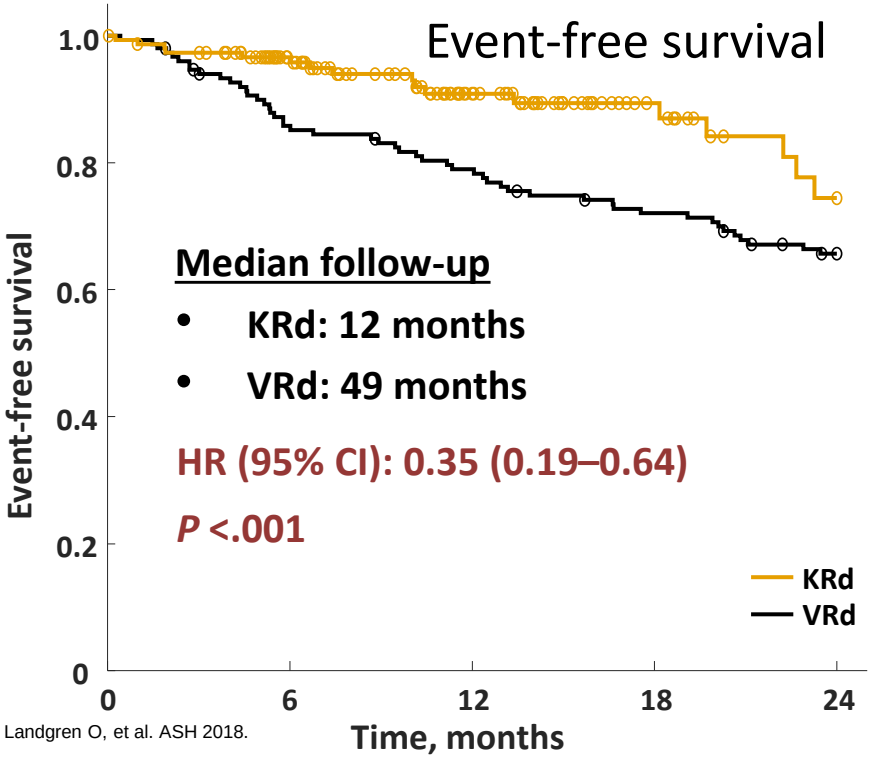
Gay, et al. ASH 2018, oral presentation

. . . and superiority of sustained MRD in KRd + ASCT vs KRd w/o ASCT arm



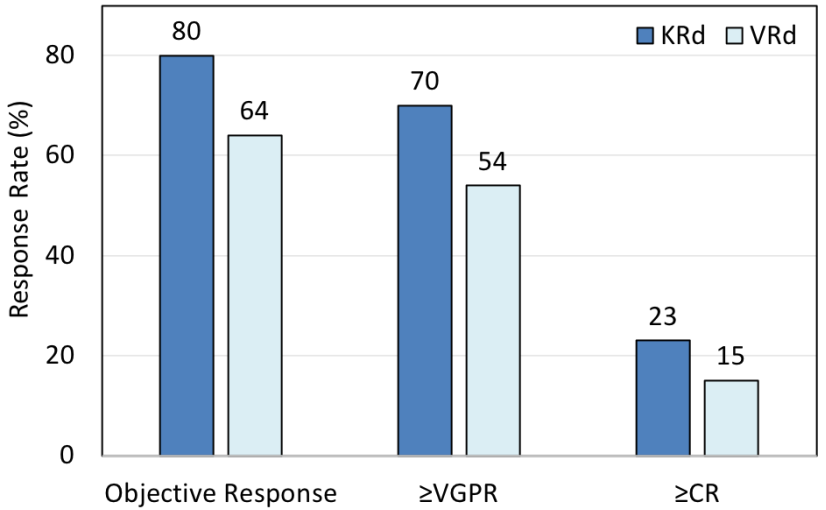
Gay, et al. ASCO 2019, oral presentation

. . . and by the results of the prospective observational KRd vs RVd CoMMpass study



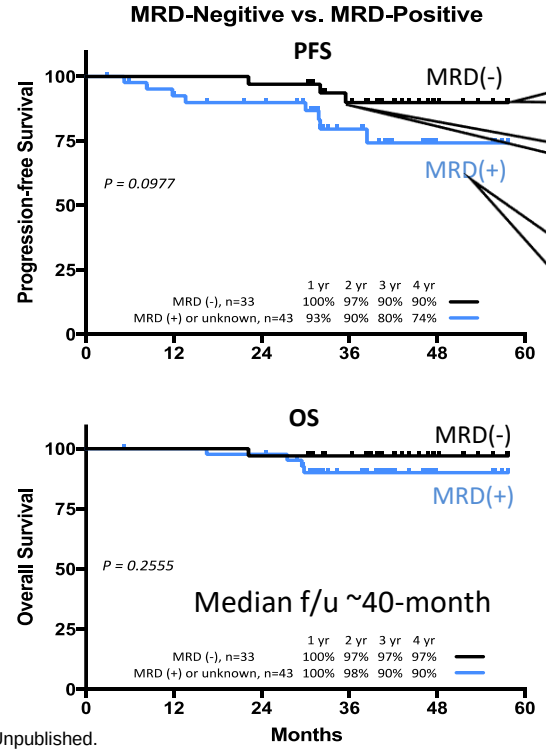
Landgren O, et al. ASH 2018.

Best clinical response at 12 months



…while 2 ongoing phase III KRd vs RVd ENDURANCE and COBRA trials are in progress

MMRC trial KRd + ASCT – are we there?



Jakubowiak J, et al. Unpublished.

. . . while the tail of the curve in the KRd trial is suggestive of potential for cure in a proportion of MRD-negative patients

…even deepest (10^{-6}) MRD-negative status is not a surrogate for cure

…and definitely no cure in close to ~40% who do not achieve MRD negativity

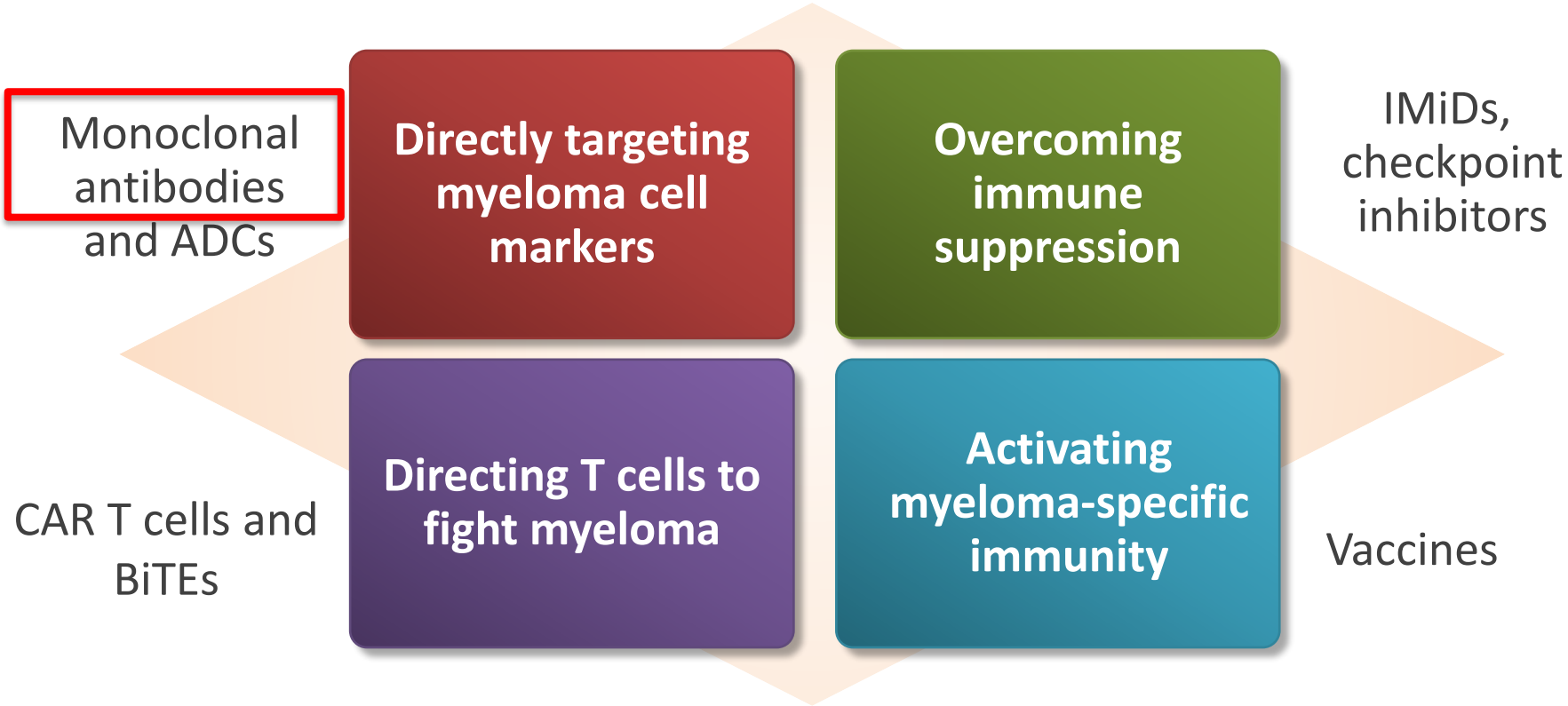
…so probably not for most patients,

if we only use even best available PI+IMID+/-ASCT treatment

…so, we still have work to do to make further improvements in path to cure

1. What have we learned so far?
2. How based on what we have learned, are we advancing curatives strategies in myeloma?
3. **Do we need more agents and more therapeutic tools?**
4. Maybe we need to look not for one but for multiple ”curative therapies”
5. How to better define “cure” or at least “presumed cure”?

an obvious candidate to make further improvements is immunotherapy



Rodriguez-Otero P, et al. *Haematologica*. 2017;102:423.

Let’s start with 2 approved antibodies

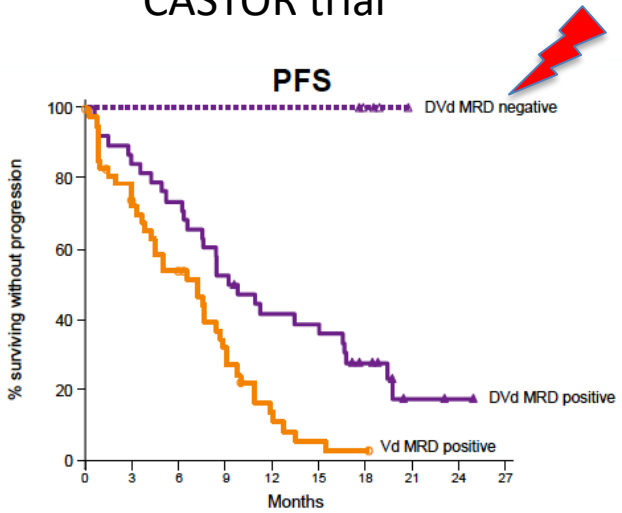
. . . which have generated a preponderance of evidence
that both daratumumab and elotuzumab improve activity
of existing backbone regimens

ELOQUENT-1, VD ± ELO, CASTOR, POLLUX, ALCYONE, MAIA,
CASSIOPEIA, . . . and more coming

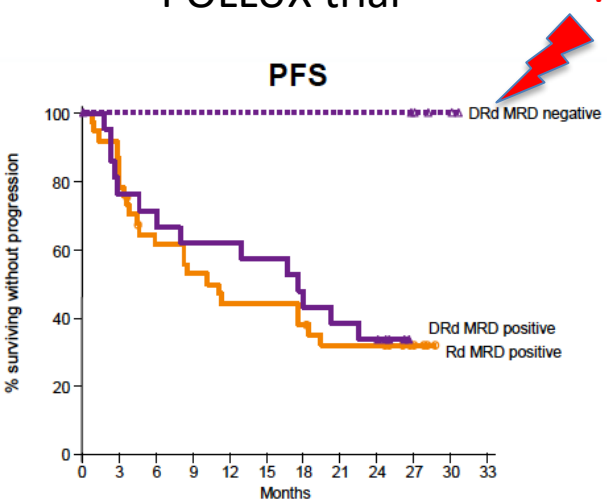
Are these 2 antibodies bringing us closer to a cure?

Let's start with contribution of antibodies to reaching MRD-negative status

CASTOR trial



POLLUX trial



. . . only daratumumab groups achieved MRD negativity,

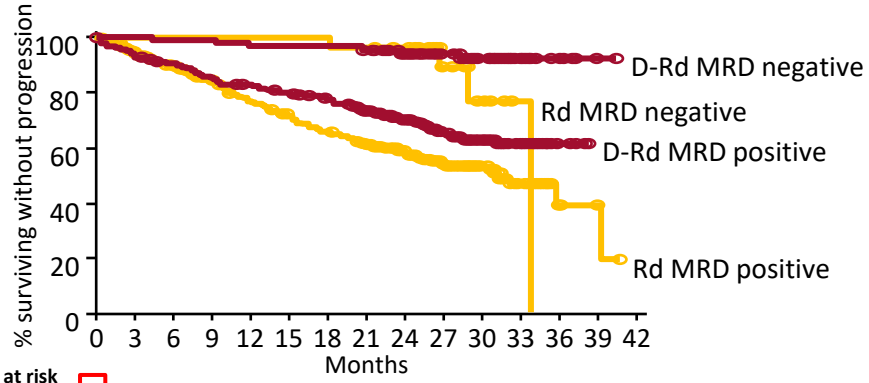
Courtesy Dimopoulos et al. EHA 2017.

. . . showing potential also in RR disease

. . . similarly in MAIA Rd +/- Dara . . . and in ALCYONE VMP ± Dara trial

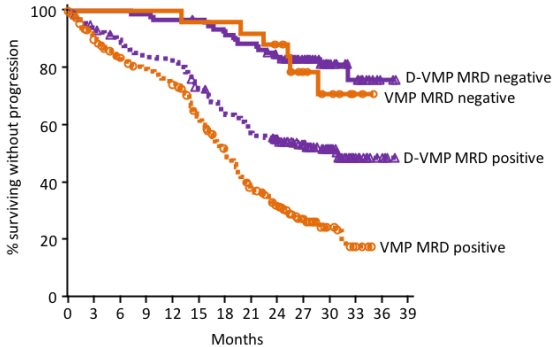
…in non-transplant pts with newly diagnosed myeloma (NDMM)

PFS by MRD status



No. at risk														
Rd MRD negative	27	27	27	27	27	27	27	25	21	12	5	1	0	0	0
D-Rd MRD negative	89	89	88	88	86	86	86	84	70	55	33	12	5	1	0
Rd MRD positive	342	305	280	253	227	209	192	175	128	82	45	17	3	2	0
D-Rd MRD positive	279	258	247	232	223	214	204	187	133	91	53	23	6	0	0

- **>3-fold higher MRD negativity achieved with D-Rd**



No. at risk													
VMP MRD negative	25	25	25	25	25	24	24	23	20	12	6	2	0	0
DVMP MRD negative	96	96	96	95	93	92	89	84	77	57	28	14	2	0
VMP MRD positive	331	279	252	237	220	182	145	104	82	47	21	3	0	0
D-VMP MRD positive	254	226	216	203	199	173	154	136	126	81	45	17	7	0

- **Deep~4-fold higher MRD negativity achieved with D-VMP**

…as well as in 1b arm of KRd+dara trial in NDMM

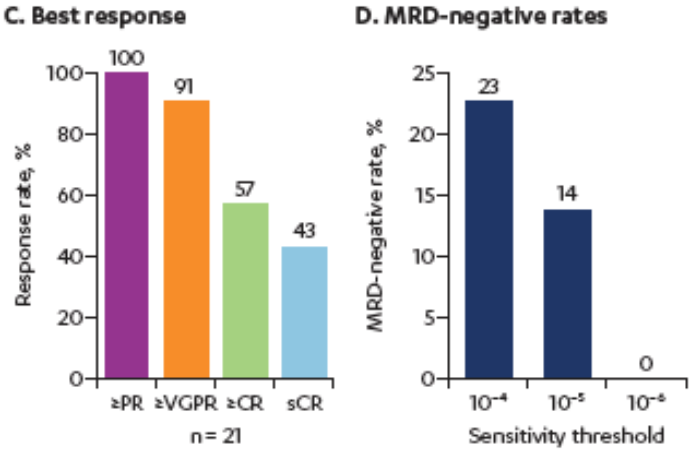
Daratumumab (DARA) in Combination with Carfilzomib, Lenalidomide, and Dexamethasone (KRd) in Patients (pts) With Newly Diagnosed Multiple Myeloma (MMY1001): an Open-label, Phase 1b Study

Andrzej Jakubowiak,[1] Ajai Chari,[2] Sagar Lonial,[3] Brendan Weiss,[4] Raymond L. Comenzo,[5] Kaida Wu,[6] Nushmia Z. Khokhar,[6] Jianping Wang,[7] Parul Doshi,[6] Saad Z. Usmani[8]

[1]University of Chicago Medical Center, Chicago, IL; [2]Tisch Cancer Institute, Mount Sinai School of Medicine, New York, NY, USA; [3]Department of Hematology and Medical Oncology, Winship Cancer Institute, Emory University, Atlanta, GA, USA; [4]Abramson Cancer Center and Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA; [5]Division of Hematology/Oncology, John C. Davis Myeloma and Amyloid Program, Tufts Medical Center, Boston, MA; [6]Janssen Research & Development, LLC, Spring House, PA, USA; [7]Janssen Research & Development, LLC, Raritan, NJ, USA; [8]Levine Cancer Institute/Carolinas HealthCare System, Charlotte, NC, USA.

PRESENTED AT: ASCO ANNUAL MEETING '17 | #ASCO17

…the combination with highest hopes in path to cure



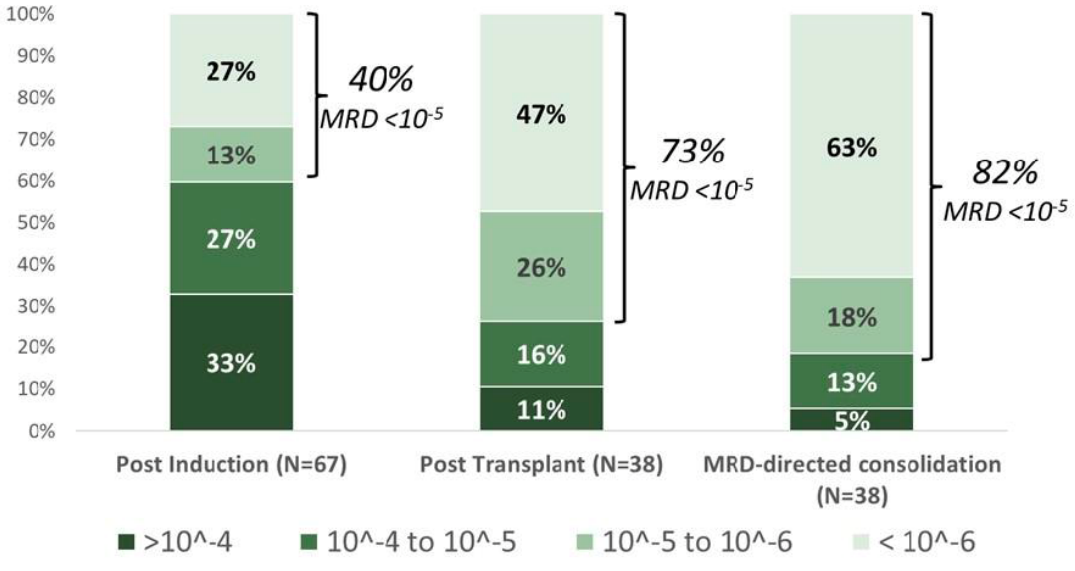
Jakubowiak et al, ASCO 2017, oral presentation, Chari ASH 2017, Abstract 3110 (updated results), manuscript submitted

…with a number of KRd studies, including our 2 studies with daratumumab …and elotuzumab in progress

…some applying adaptive study designs, with the duration of treatment based on MRD status , like in this KRd+Dara+ASCT trial in NDMM

Best MRD response by phase of therapy

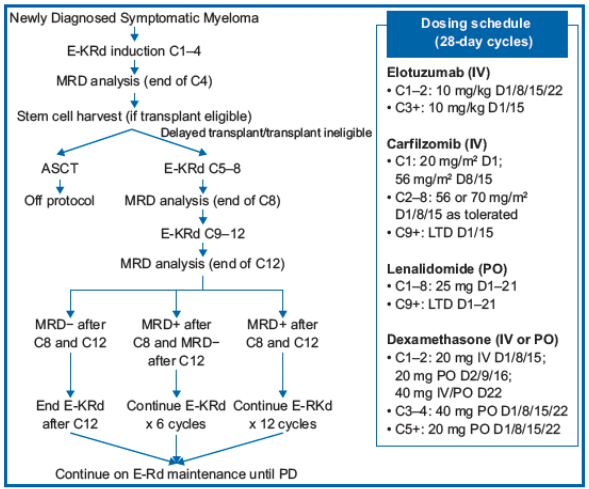
- MRD trackable by NGS clonoSEQ® in 78/81 patients (96%)
- 100% of datapoints obtained in patients with trackable MRD



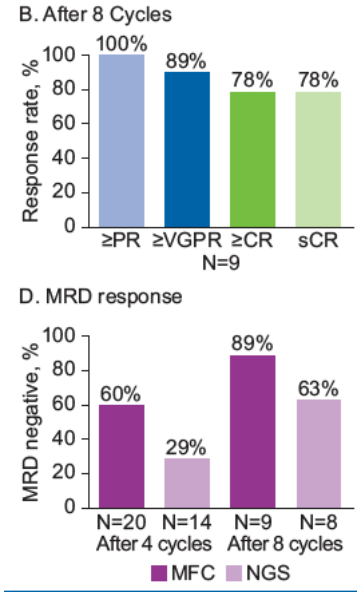
MASTER trial

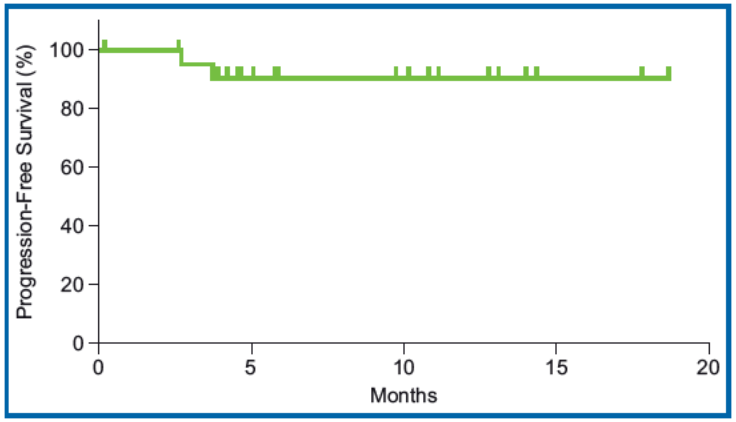
Costa et al, ASH 2019

…or in this KRd+Elotuzumab+/-ASCT our multi-site MMRC trial in NDMM



C, cycle; D, day; E-KRd, elotuzumab, carfilzomib, lenalidomide, dexamethasone; E-Rd, elotuzumab, lenalidomide, dexamethasone; IV, intravenous; LTD, last tolerated dose; MRD, minimal residual disease; PD, progressive disease; PO, orally





Jakubowiak et al, ASCO 2017, oral presentation, Chari ASH 2017, Abstract 3110 (updated results), manuscript submitted

…and indicating that combining
very effective initial Triplet + Immunotherapy +/- ASCT

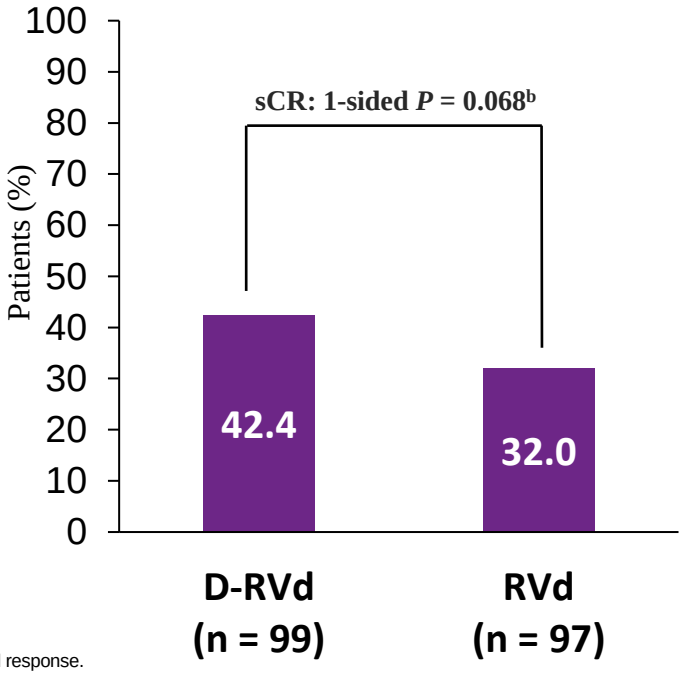
…and using adaptive approach

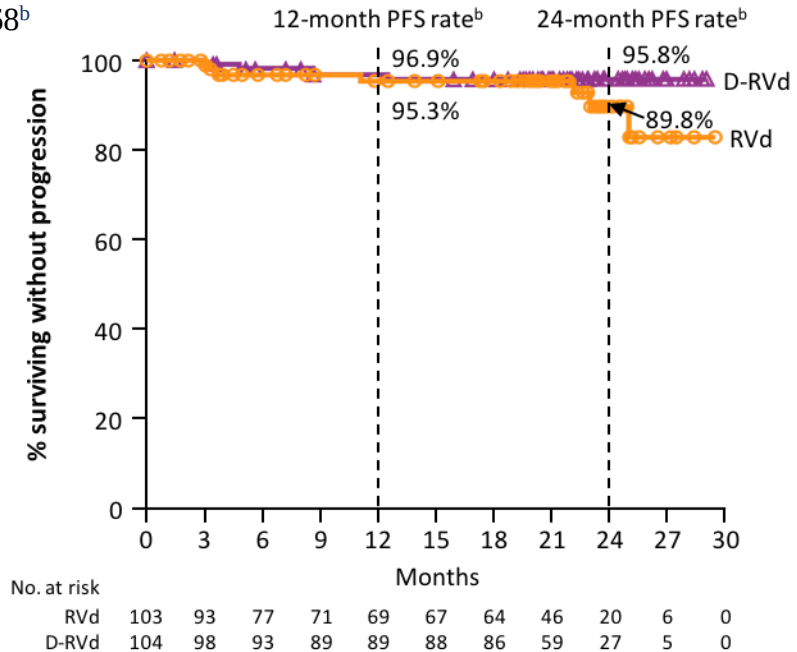
…might bring us closer CURATIVE THERAPY for myeloma

…which is awaiting validation in a number of ongoing
phase III randomized trials in NDMM

…here coming from in GRIFFIN RVD-ASCT +/- Dara Phase II Study

- **Primary endpoint met at pre-set 1-sided alpha of 0.1**
  - sCR by end of consolidation
    - 42.4% D-RVd vs 32.0% RVd
    - Odds ratio, 1.57; 95% CI, 0.87-2.82; 1-sided *P* = 0.068[b]





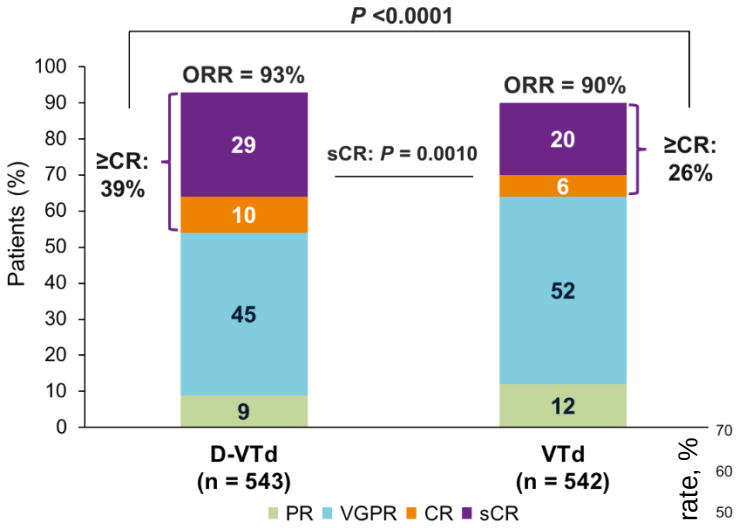
PR, partial response.

[a]Included patients in the response-evaluable population (all randomized patients with a confirmed diagnoses of MM, measurable disease at baseline, received ≥1 dose of study treatment, and had ≥1 post-baseline disease assessment).

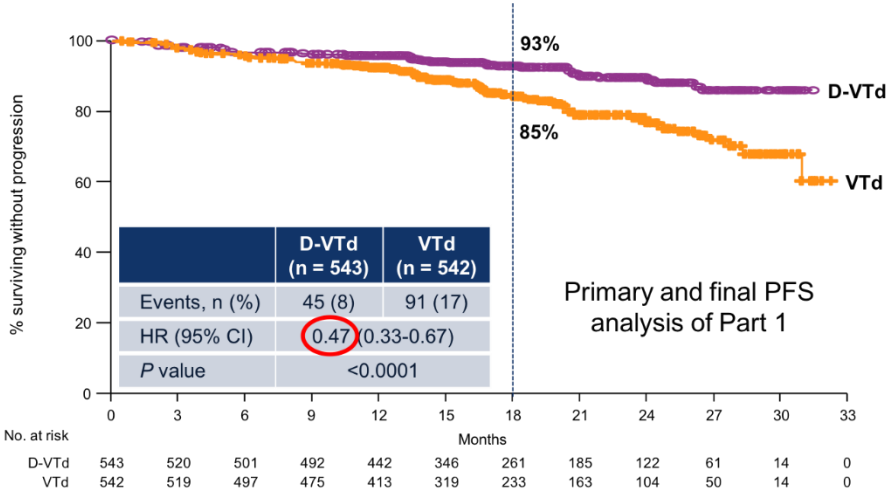
[b]*P* values were calculated with the use of the Cochran–Mantel–Haenszel chi-square test. A 1-sided *P* value is reported for sCR; for all other responses, 2-sided *P* values not adjusted for multiplicity are reported.

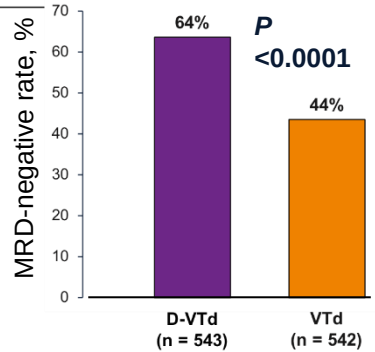
…here in similar Phase III randomized
CASSIOPEIA trial of VTD+ASCT+/- Dara in NDMM

Primary End-point:
Post-consolidation sCR Rate



PFS





Moreau et al, ASCO 2019, Oral Presentation, published on line Lancet June 3, 2019

…the first evidence
of superiority of PI-IMId-based Quadruplet vs Triplet
…with ASCT in both arms

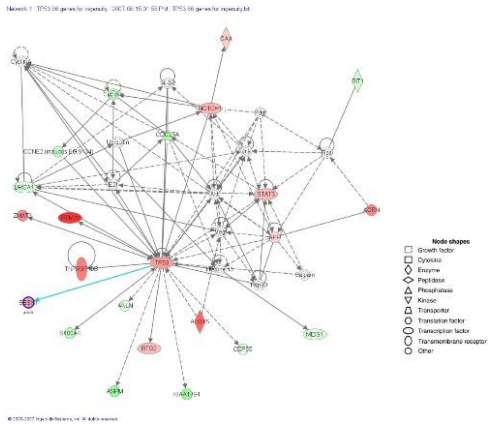
In all, on the basis of the results to date, IO (DARA) is certainly increasing MRD-negative rates – the "cure-readout signal"

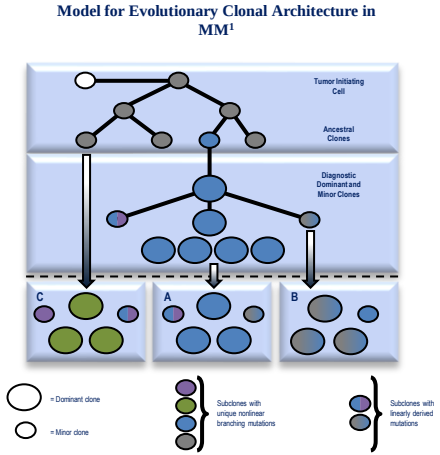
But we need longer f/u to determine whether the margin of improvement for most-effective regimens is sufficient

to count on Dara and/or Elo as agents of cure

…in addition, are Dara or ELO, … or other naked antibodies good enough

to help eliminating complex, multi-clonal disease in majority of patients?



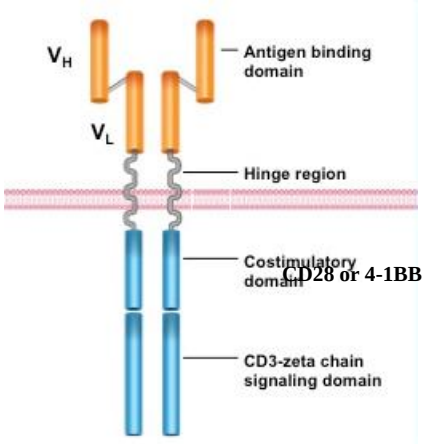


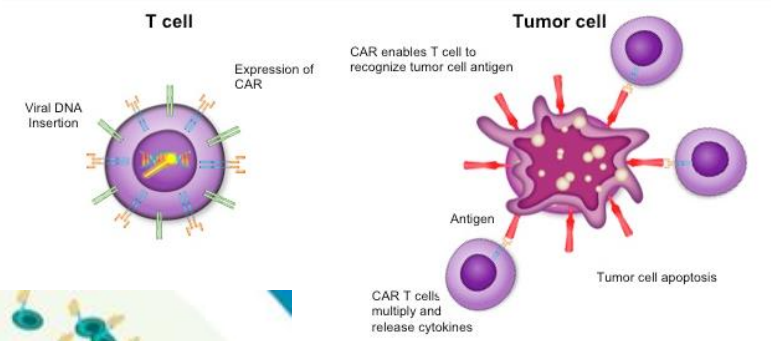
…or we still need to keep working,

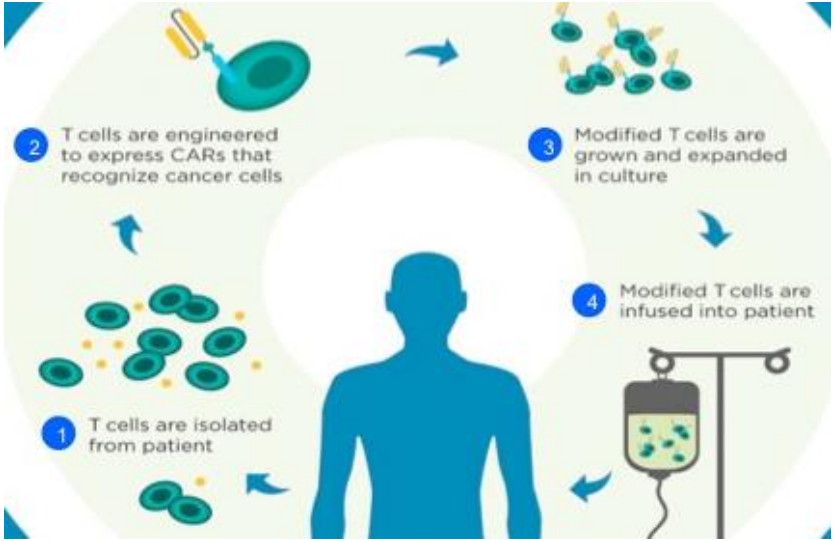
…to make GIANT LEAP in our conquest to cure the disease

…let's look next at CAR modified T cells, which have emerged as such a candidate

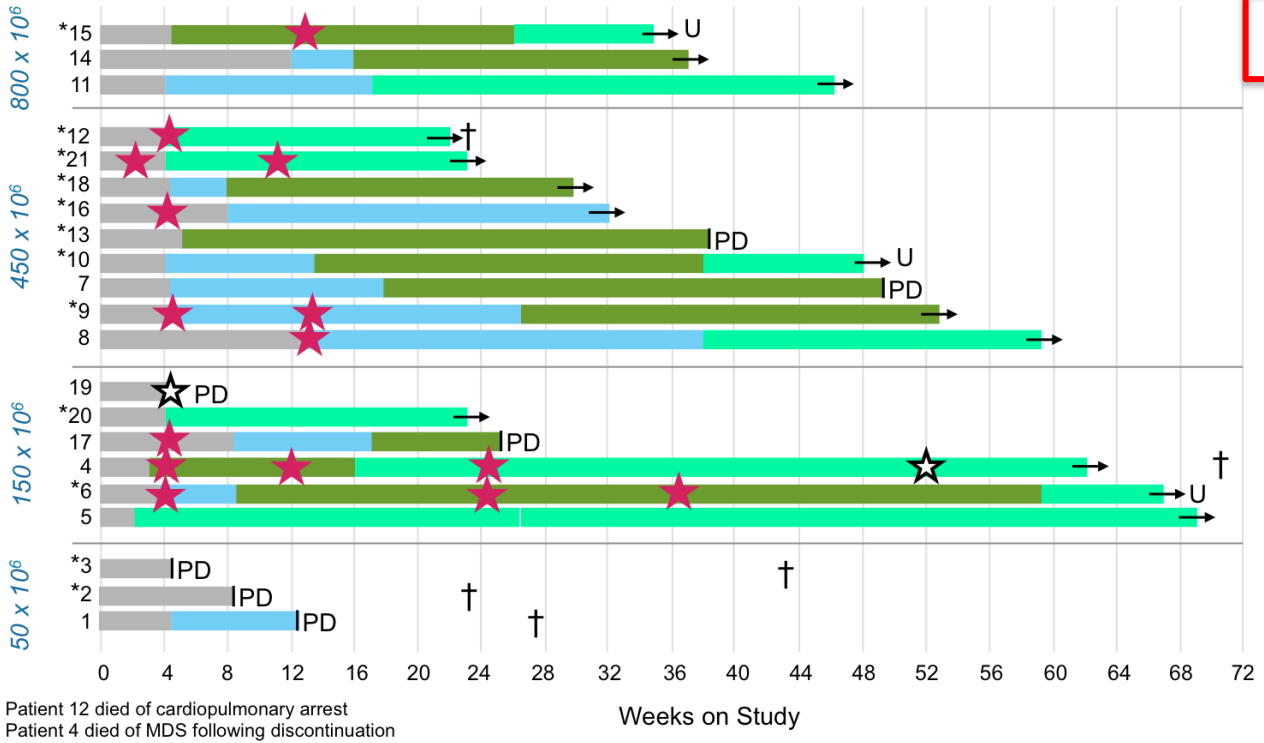
Chimeric Antigen Receptors







…when we saw the first results of the bb2121: Anti-BCMA CART Bluebird trial, it generated hope for CART as a breakthrough treatment



Patient 12 died of cardiopulmonary arrest
Patient 4 died of MDS following discontinuation

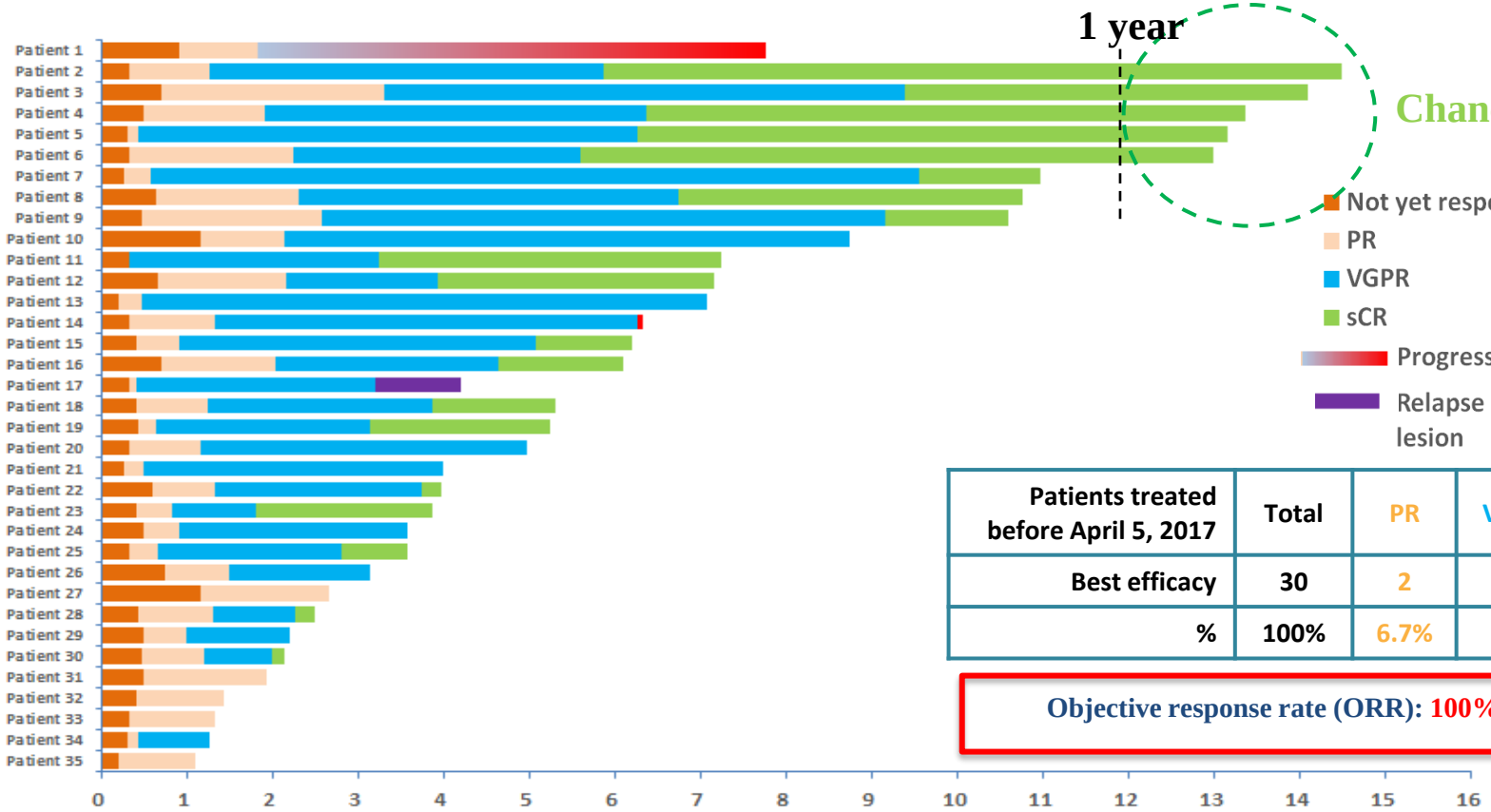
- 17/18 (94%) ORR, 10/18 (56%) CR at active doses
- 9/10 evaluable patients MRD negative
- Durable ongoing responses over 1 year
- Responses continue to improve as late as month 15 (VGPR to CR)
- Median PFS not reached in active dose cohorts
  - 4 patients progressed
  - Median follow up 40 weeks

CR/sCR · VGPR · PR · Stable Disease · PD · MRD- · † Deceased · U Unconfirmed response · MRD+

* High Tumor Burden (>50% Bone Marrow Involvement)

Berdeja et al, ASH 2017, Oral Presentation (Abstract #740)

…LCAR-B38M BCMA CAR-T clinical response persists beyond 4 mo



Patients treated before April 5, 2017	Total	PR	VGPR	sCR
Best efficacy	30	2	9	19
%	100%	6.7%	30%	63.3%

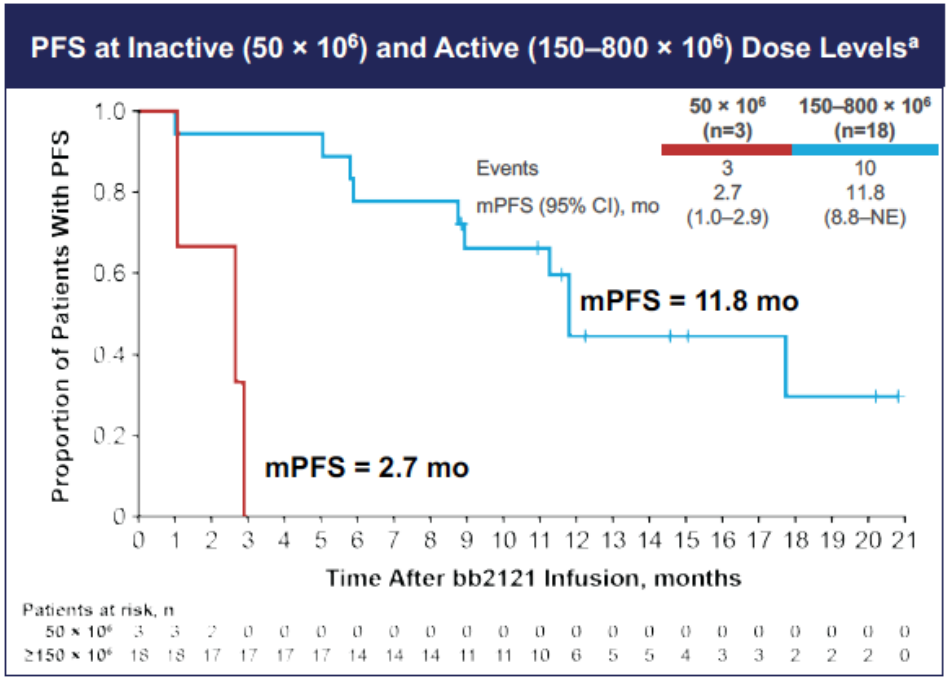
Objective response rate (ORR): 100%

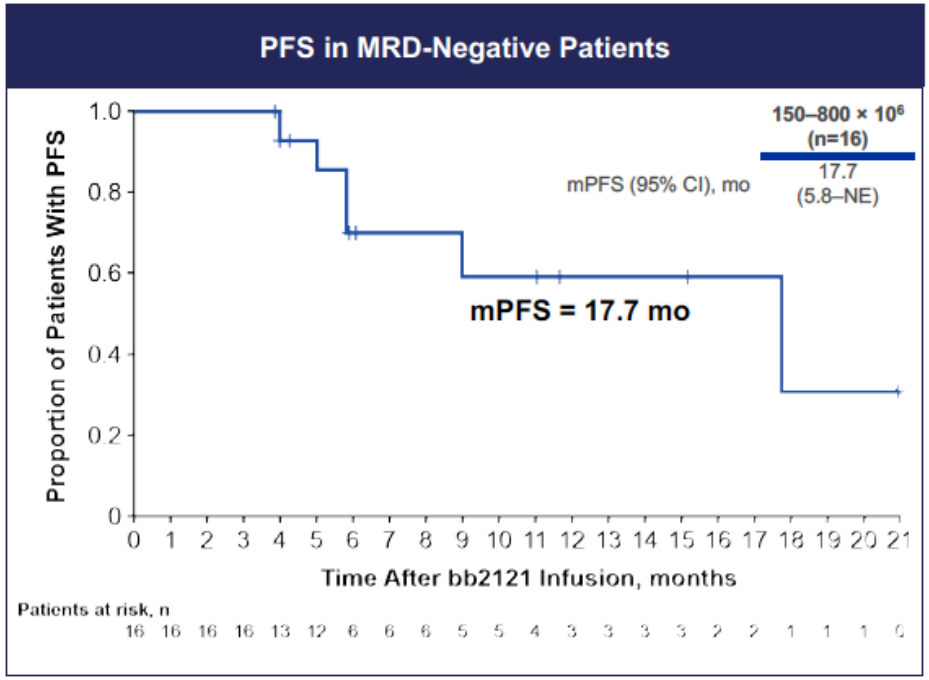
Zhang et al, EHA 2017, Oral Presentation

…at that point, many have thought that BCMA-targeting CART treatment will be not only a big game changer in MM

…but also real candidate for curative strategy

…but when the BlueBird study results were updated

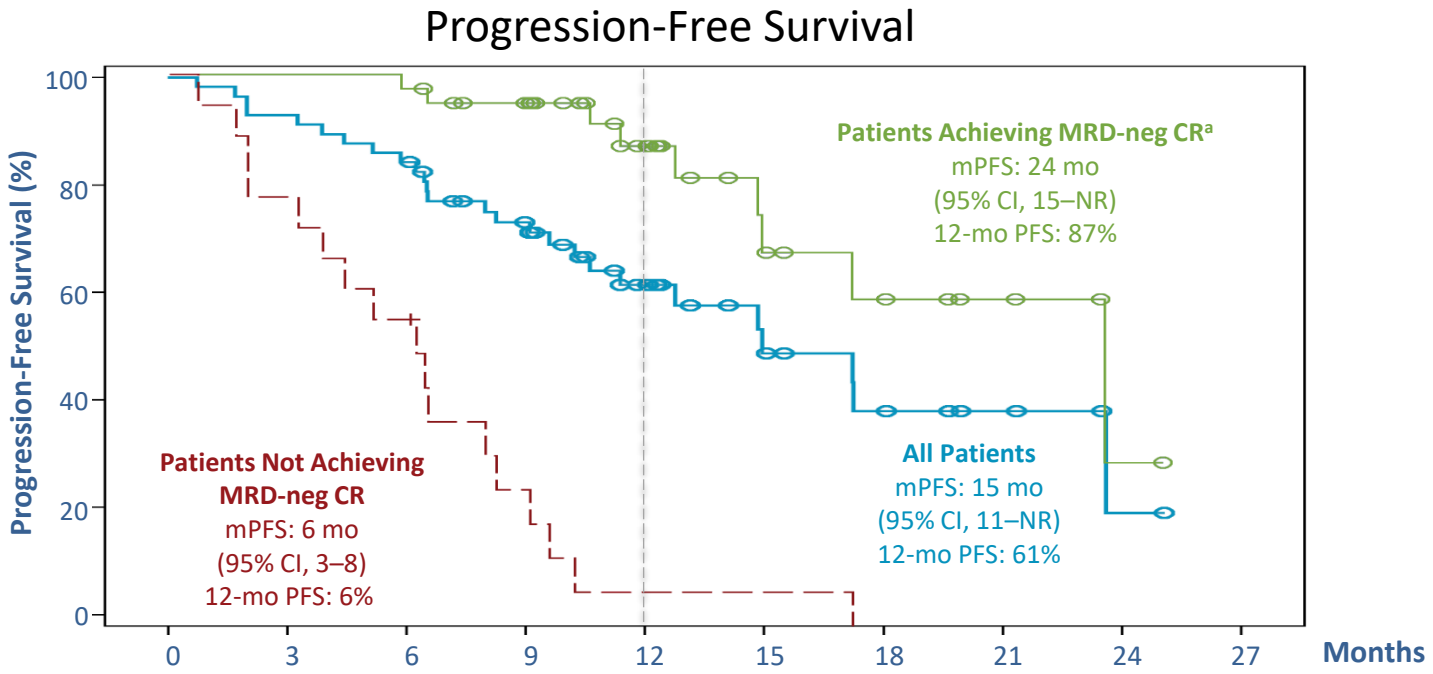




Raje et al, ASCO 2018, Oral Presentation

…the shape of K-M curves was below expectations

…and the updated PFS results from the Legend trial showed similar to BlueBird study K-M curves pattern



…were also quite disappointing to many of us (no cure!)

Zhao et al, ASH 2018 Oral presentation

[a]30/39 patients still in remission

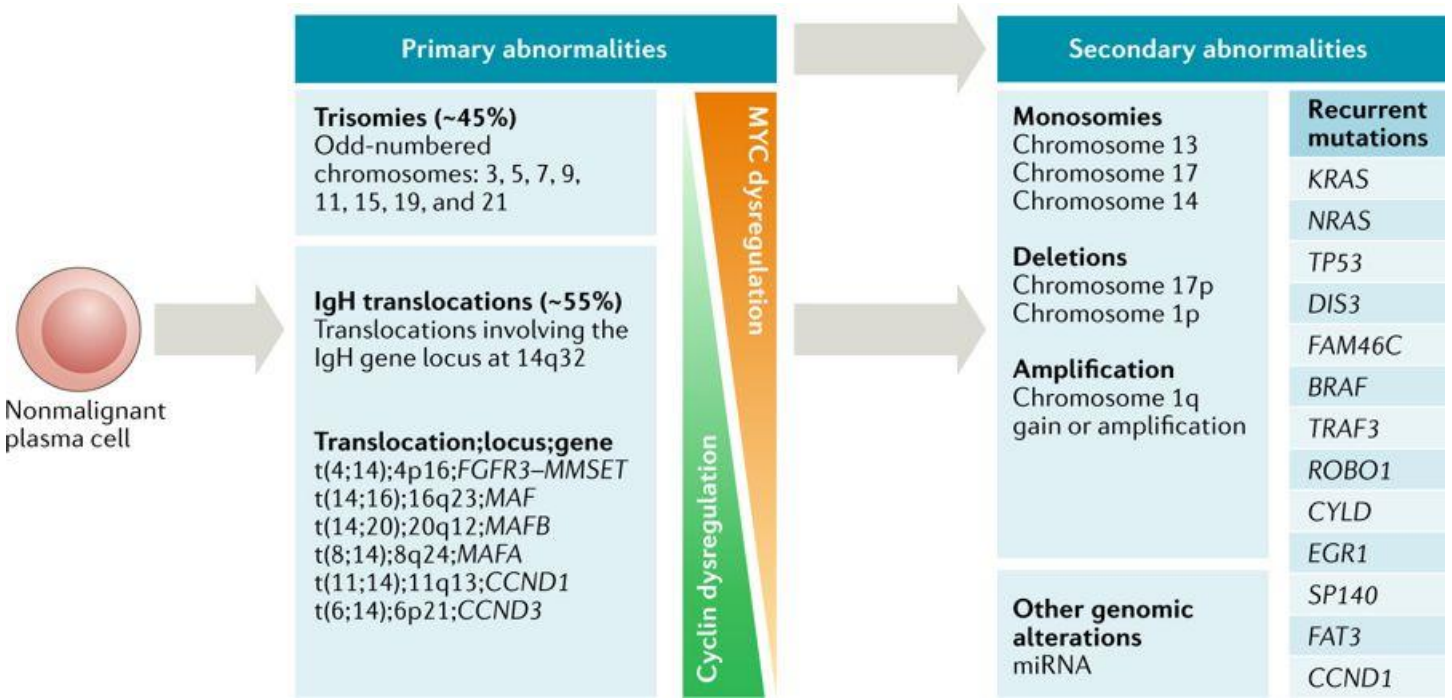
…but with a number of CART and other cellular therapy trials in progress, also in earlier stages of MM

… the jury is out for this strategy as a curative therapy for myeloma

…but is a “sledgehammer approach” of PI+IMiD+IO+/-ASCT or or +/- CART/Cellular therapy going to cure very complex and heterogenous disease

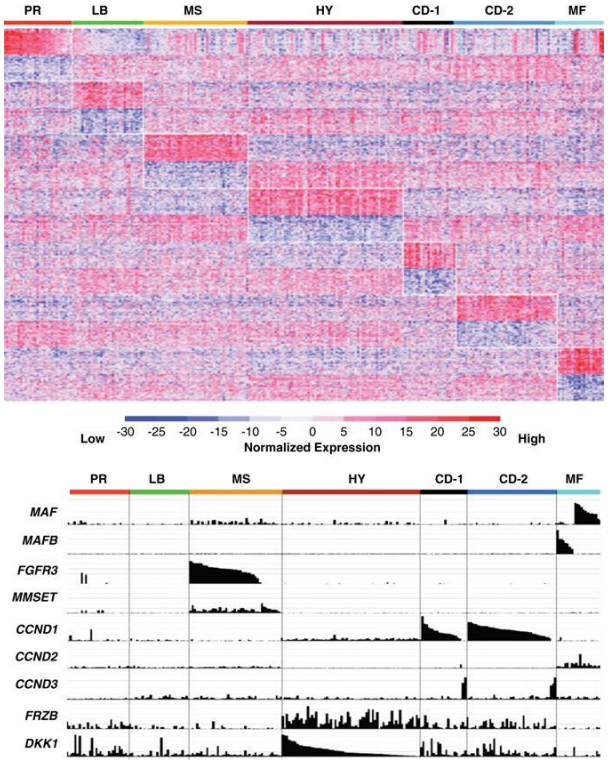
1. What have we learned so far?
2. How based on what we have learned, are we advancing curatives strategies in myeloma?
3. Do we need more agents and more therapeutic tools?
4. **Maybe we need to look not for one but for multiple ”curative therapies”**
5. How to better define “cure” or at least “presumed cure”?

…with heterogeneity of disease reflected by an array of cytogenetic abnormalities



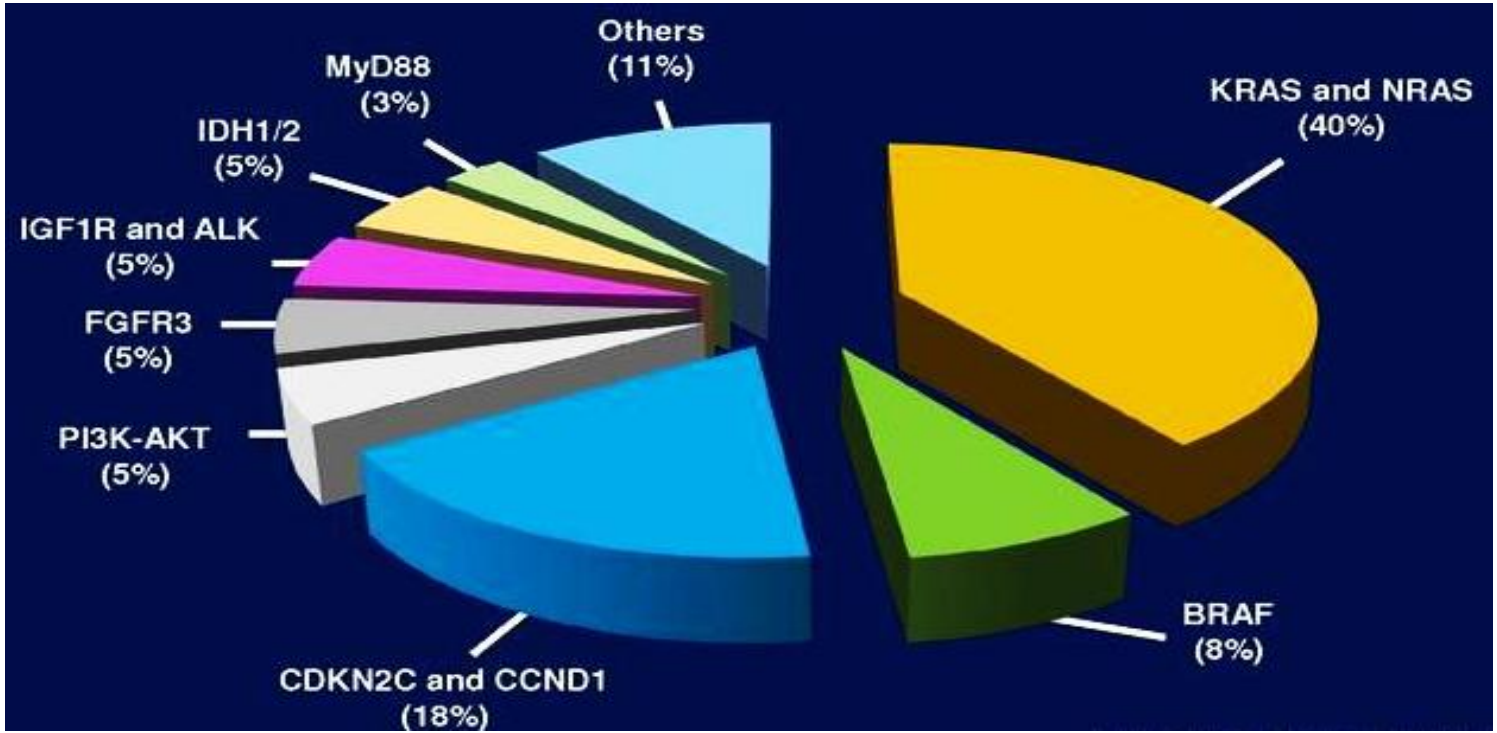
Kumar & Rajkumar, Nature Reviews Clinical Oncology ***2018: 15****, 409–421*

…or by GEP



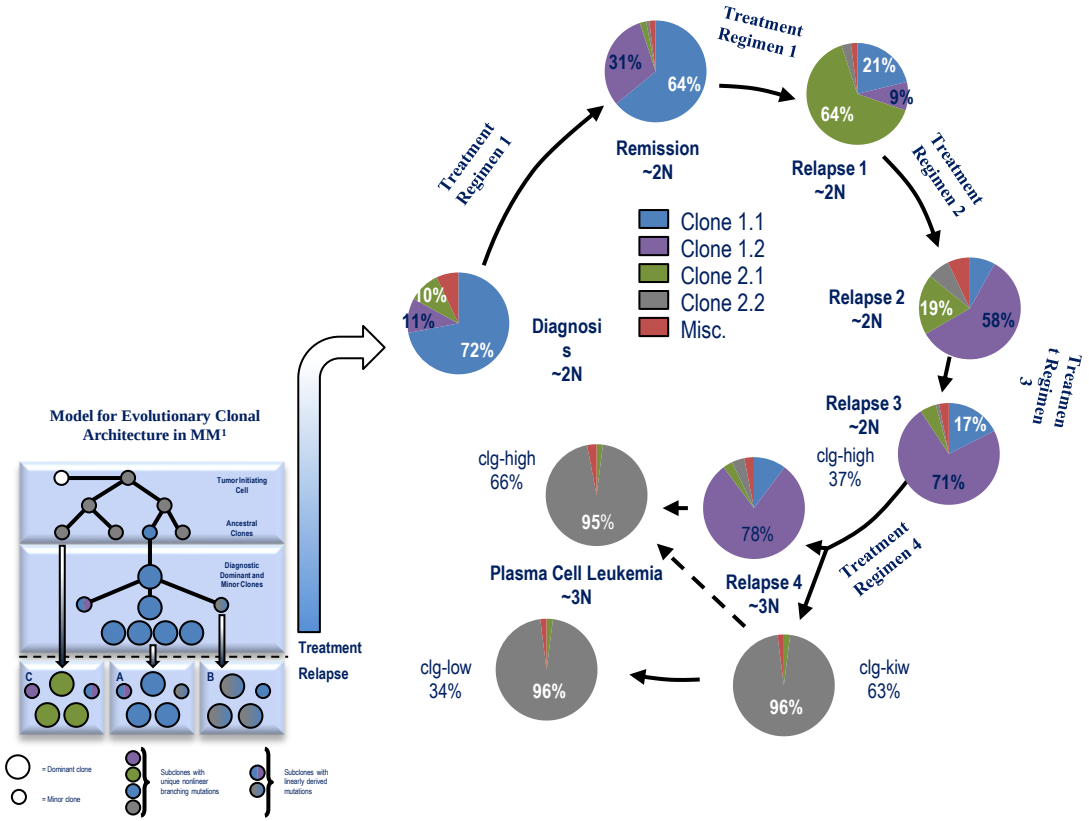
Zhou Y, Barlogie B, Shaughnessy JD Jr. Leukemia. 2009 Nov;23(11):1941-56

..or gene mutations



…and in addition, by significant intra-tumor heterogeneity

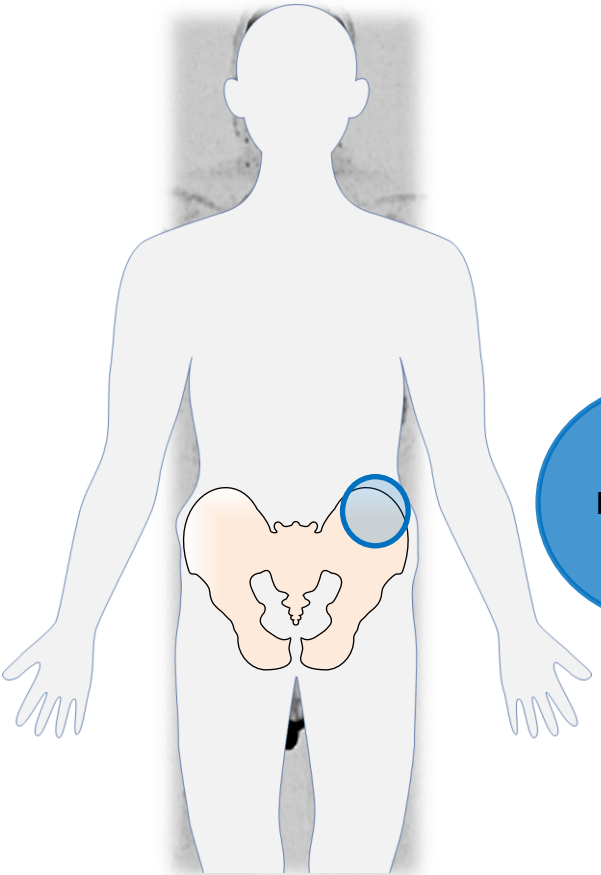
…and clonal evolution under pressure of subsequent treatments



1. Bahlis NJ. *Blood*. 2012;120(5):927-928.
2. Keats JJ et al. *Blood*. 2012;120(5):1067-1076.

cIg=cytoplasmic immunoglobulin

…with fitter clones outcompeting previously dominant clone



HY

30 Mutations

+ 5 Mut

Clone 1

Hyperdipl.

35 Mut

+ 8 Mut

CDKN2C^{biallelic}

gain(1q)

del(17p)

Clone 2D

+ 2 Mut

+ 2 Mut

del(3q)

Clone 2C

Clone 2A

Clone 2B

Rasche et al. *Nature Communications* 2017

…so maybe we need to approach cure in more tailored fashion, taking marker-based selection of regimens

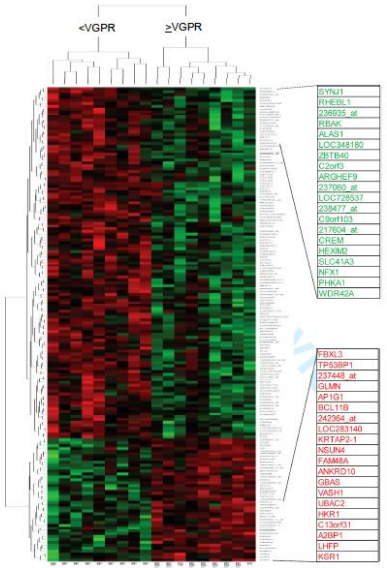
bjh research paper

Proteomic profiling of naive multiple myeloma patient plasma cells identifies pathways associated with favourable response to bortezomib-based treatment regimens

Dominik Dytfeld,[1,2] Shaun Rosebeck,[1] Malathi Kandarpa,[3] Anoop Mayampurath,[4] Dattatreya Mellacheruvu,[5,6] Mattina M. Alonge,[1] Lambert Ngoka,[7] Jagoda Jasielec,[1] Paul G. Richardson,[8] Samuel Volchenboum,[4] Alexey I. Nesvizhskii,[5] Arun Sreekumar[5,*] and Andrzej J. Jakubowiak[1]

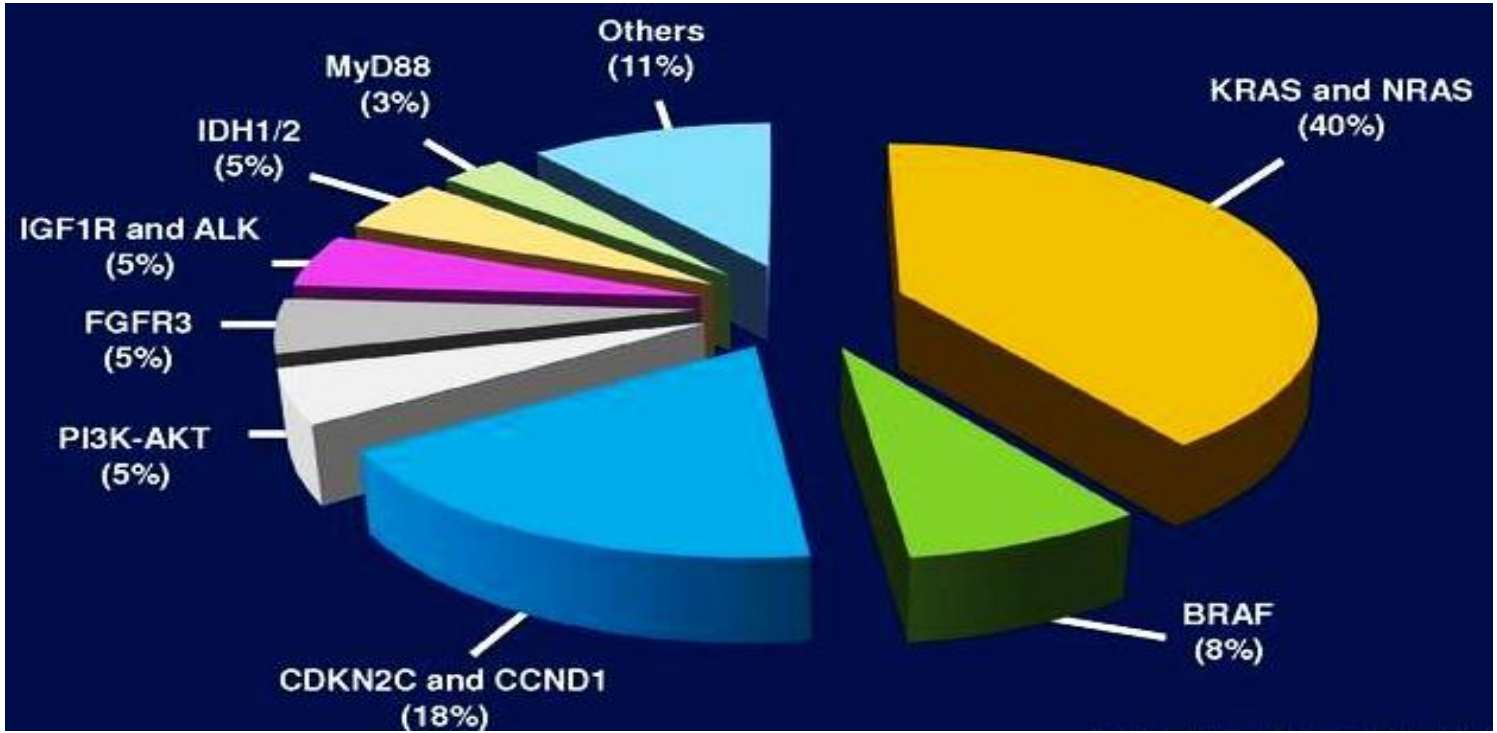
Summary

Toward our goal of personalized medicine, we comprehensively profiled pre-treatment malignant plasma cells from multiple myeloma patients and prospectively identified pathways predictive of favourable response to bortezomib-based treatment regimens. We utilized two complementary quantitative proteomics platforms to identify differentially-regulated proteins indicative of at least a very good partial response (VGPR) or complete



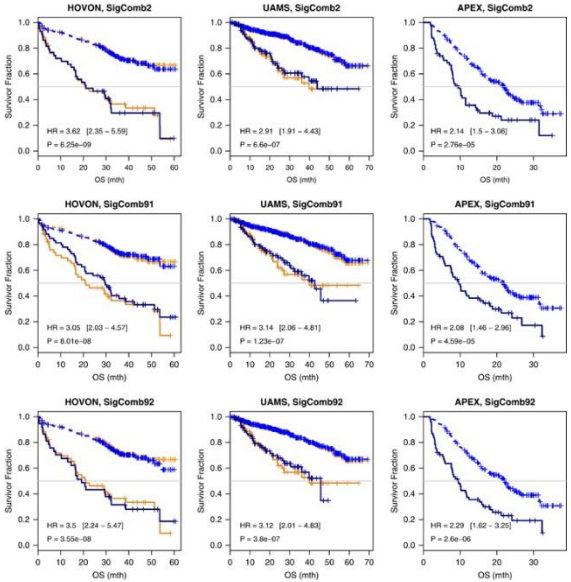
Dytfeld et al, Br J Haematol. 2015 Jul;170(1):66-79

…or by targeting “actionable” genomic alterations



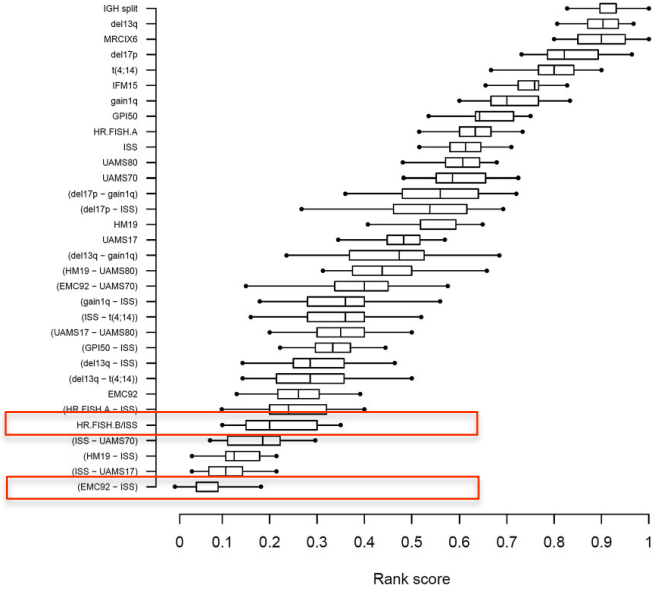
Lohr JG, et al. Cancer Cell. 2014;25(1):91-101.

… and treat differently,
different risk subgroups



Chng et al., Leukemia (2016) 30, 1071–1078

… , regardless of platform
for risk-identification

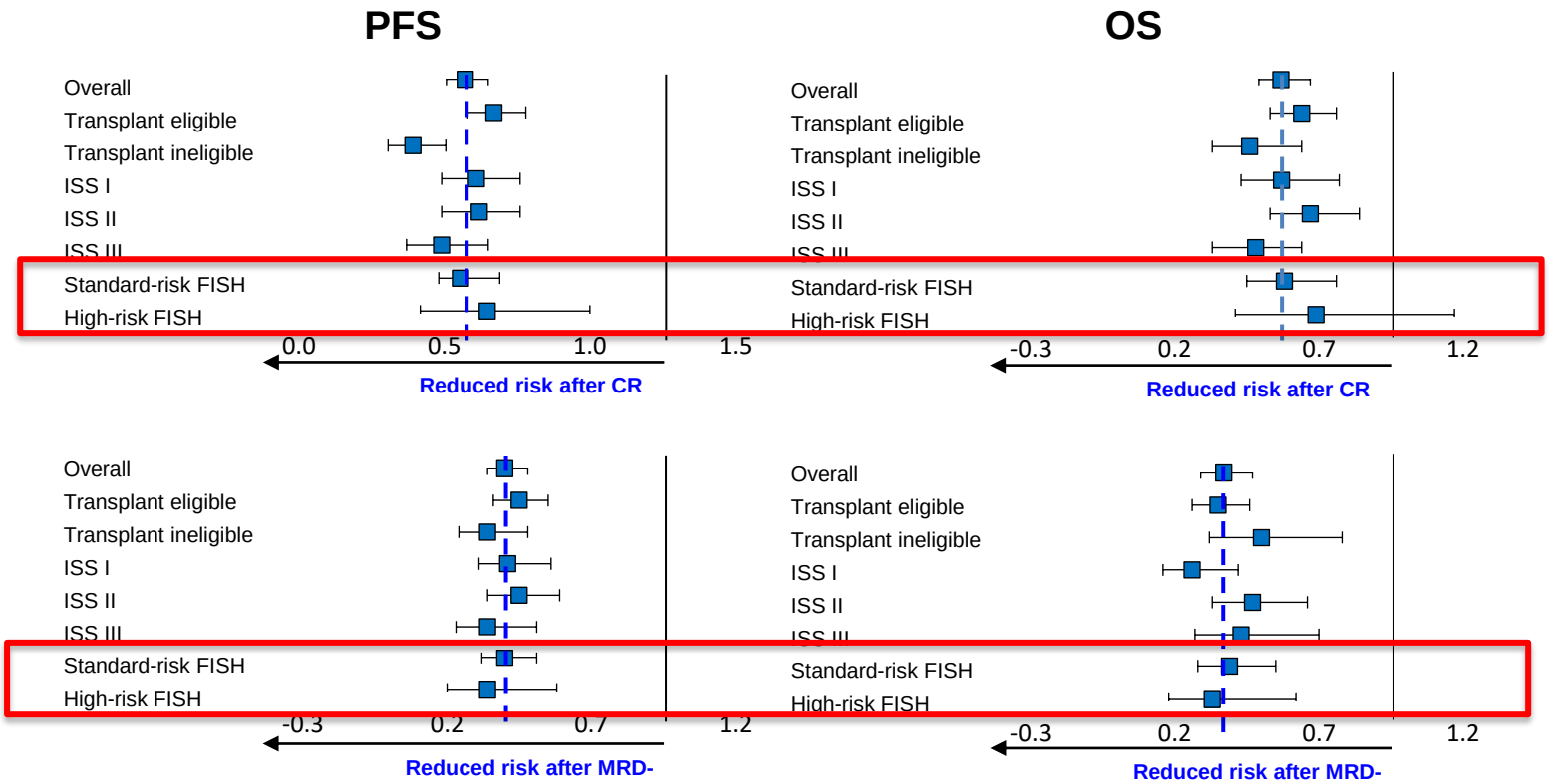


Kuiper et al, Blood 2015 Oct 22; 126(17): 1996–2004

…but so far again

…, more effective regimens
appear to benefit almost equally all risk groups

...and again, the achievement MRD-negative status is most critical for closing the gap between standard- and high-risk myeloma



GEM2000, GEM2005MENOS65, GEM2005MAS65, GEM2010MAS65

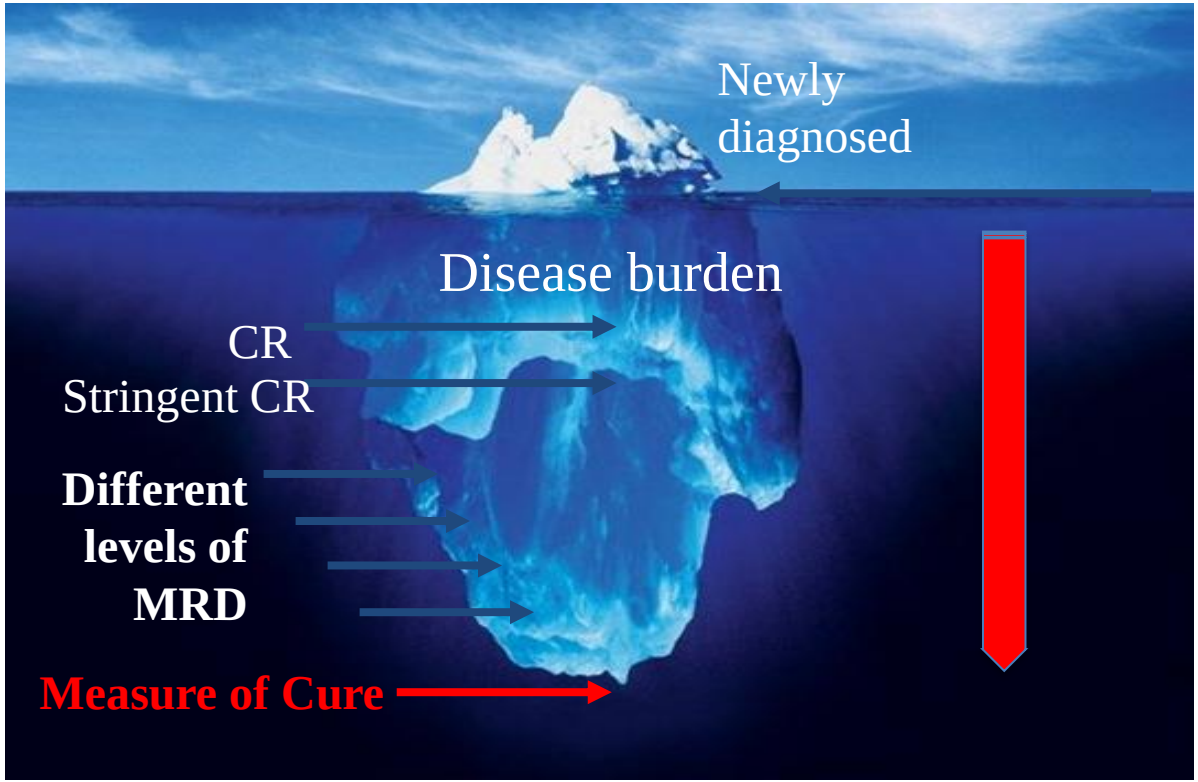
Courtesy Jesus San Miguel, IMW 2017; Lahuerta, Paiva et al manuscript in preparation

…let me close with a discussion on efforts to define early, not after 10+ years, that eliminated the of disease

1. What have we learned so far?
2. How based on what we have learned, are we advancing curatives strategies in myeloma?
3. Do we need more agents and more therapeutic tools?
4. Maybe we need to look not for one but for multiple ”curative therapies”
5. **How to better define “cure” or at least “presumed cure”?**

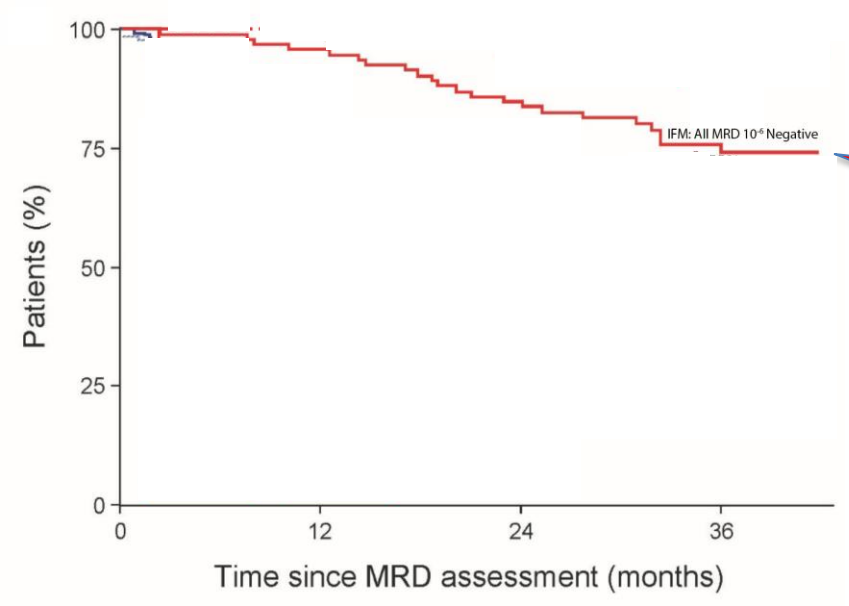
…can we have a “measure” to determine

that disease is already eliminated?



…maybe we just need to use MRD at 10^{-6} MRD-negativity?

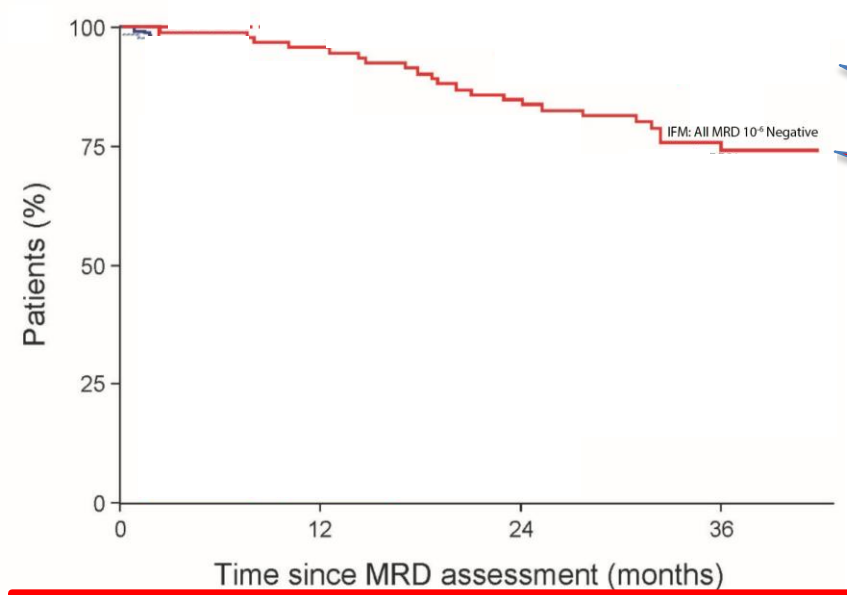
…combined with evaluation of any residual disease using CT/PET, Mass Spectrometry, cfDNA, … and possibly more?



…but pts with MRD (-) even at 10^{-6} sensitivity are still relapsing

Perrot A, et al. *Blood.* 2018;132:2456-2464.

…maybe we need to go deeper to 10^{-7} MRD sensitivity?



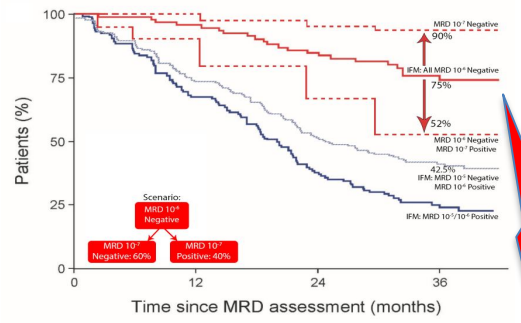
Pts with MRD (-) **at 10^{-7} by (?) New NGS test**

IFM2009 pts with MRD (-) at 10^{-6} by standard Adaptive NGS

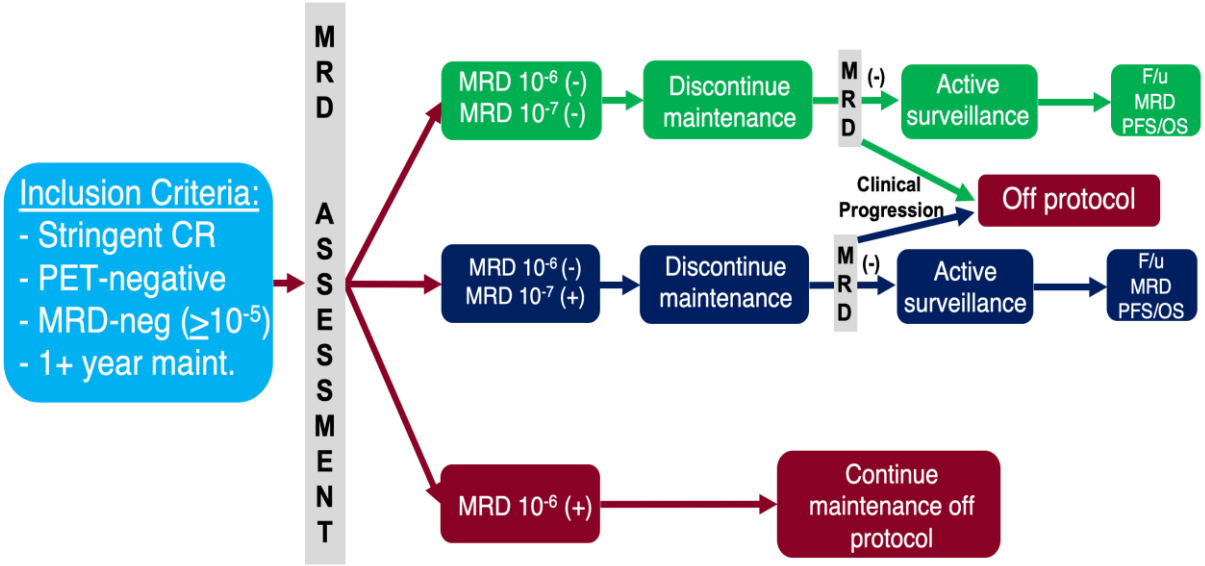
…if we think of cure as an objective,
we do need MRD at 10^{-7} sensitivity

Perrot A, et al. *Blood.* 2018;132:2456-2464.

Using this approach, we have activated MRD2STOP withdrawal trial



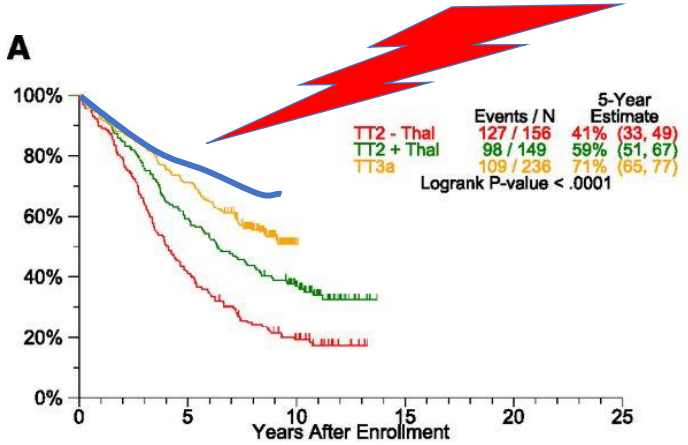
MRD2STOP Schema



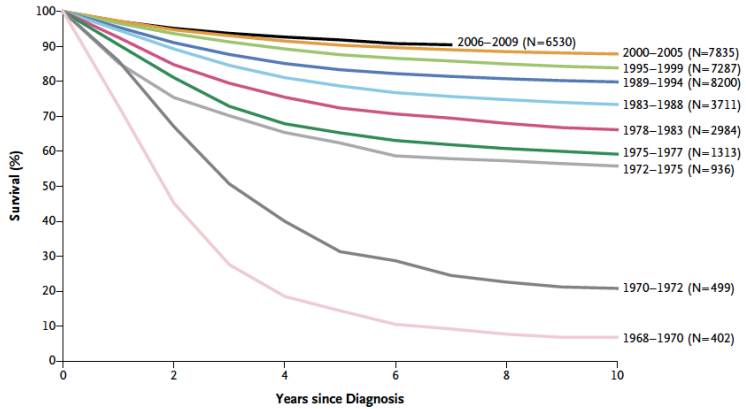
. . . anticipating that the results will inform future studies with adaptive withdrawal designs

ClinicalTrials.gov Identifier: NCT04108624.

…to wrap up,
by using best PI-IMId+/-ASCT+/-IOs
… and maybe +/- CART/Cellular Therapy +/- Targeted Therapy
… we are achieveing MRD-negativity signal of potential cure



Barlogie et al, Blood. 2014 Nov 13;124(20):3043-51



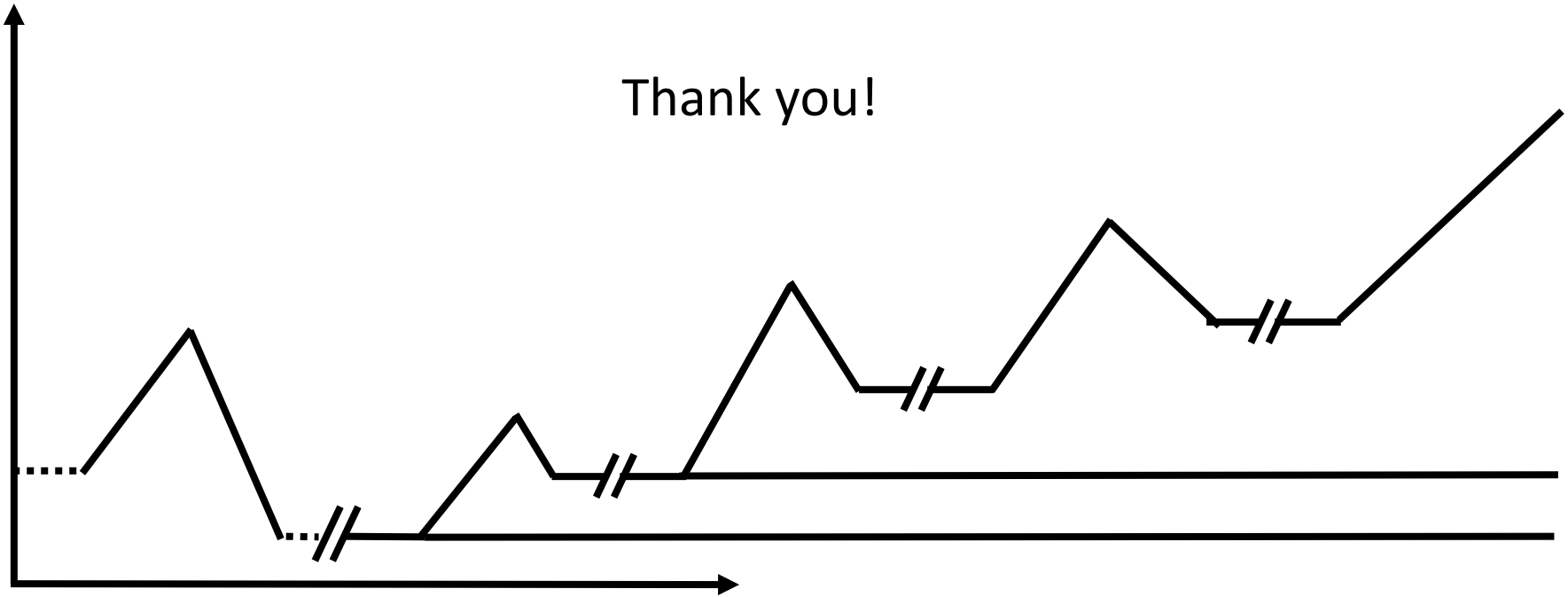
Hunger and Mulligan, N Engl J Med 2015; 373:1541-1552,
Editor Dan L Logo

and we can almost certainly anticipate that we will improve survival curves

. . . so we can not only change the natural history of myeloma,

. . . but also declare treatment strategy to cure the disease

Thank you!



Acknowledgments

I would like to thank:

Members of the Myeloma Program at the University of Chicago

The investigators, nursing staff, and research support staff in participating institutions

The Multiple Myeloma Research Consortium and PCCC, under whom our multisite trials were conducted

And special thanks to my colleagues from collaborating institutions