Norway 2019

Multiple Myeloma – Therapy and Clinical Trials

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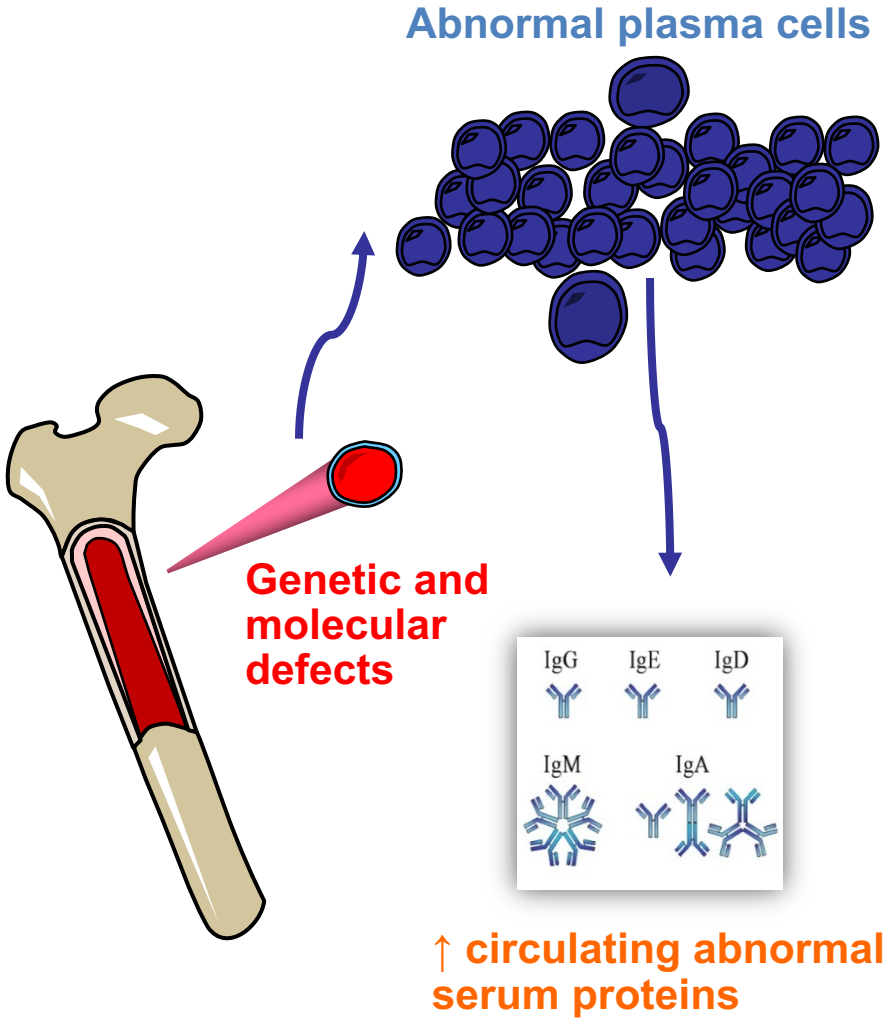
CONFLICT OF INTEREST DISCLOSURES

Anstellungsverhältnis, Führungsposition	Nein
Beratungs-/ Gutachtertätigkeit	Janssen, Celgene, Amgen, BMS, Sanofi
Besitz von Geschäftsanteilen, Aktien oder Fonds	Nein
Patent, Urheberrecht, Verkaufslizenz	Nein
Honorare	Celgene, Janssen, Novartis, Chugai, BMS, Art Tempi
Finanzierung wissenschaftlicher Untersuchungen	Janssen, Celgene, Amgen, BMS, Chugai, Takeda, Sanofi, Mundipharma, Novartis
Andere finanzielle Beziehungen	Keine
Immaterielle Interessenkonflikte	Keine

1 Introduction

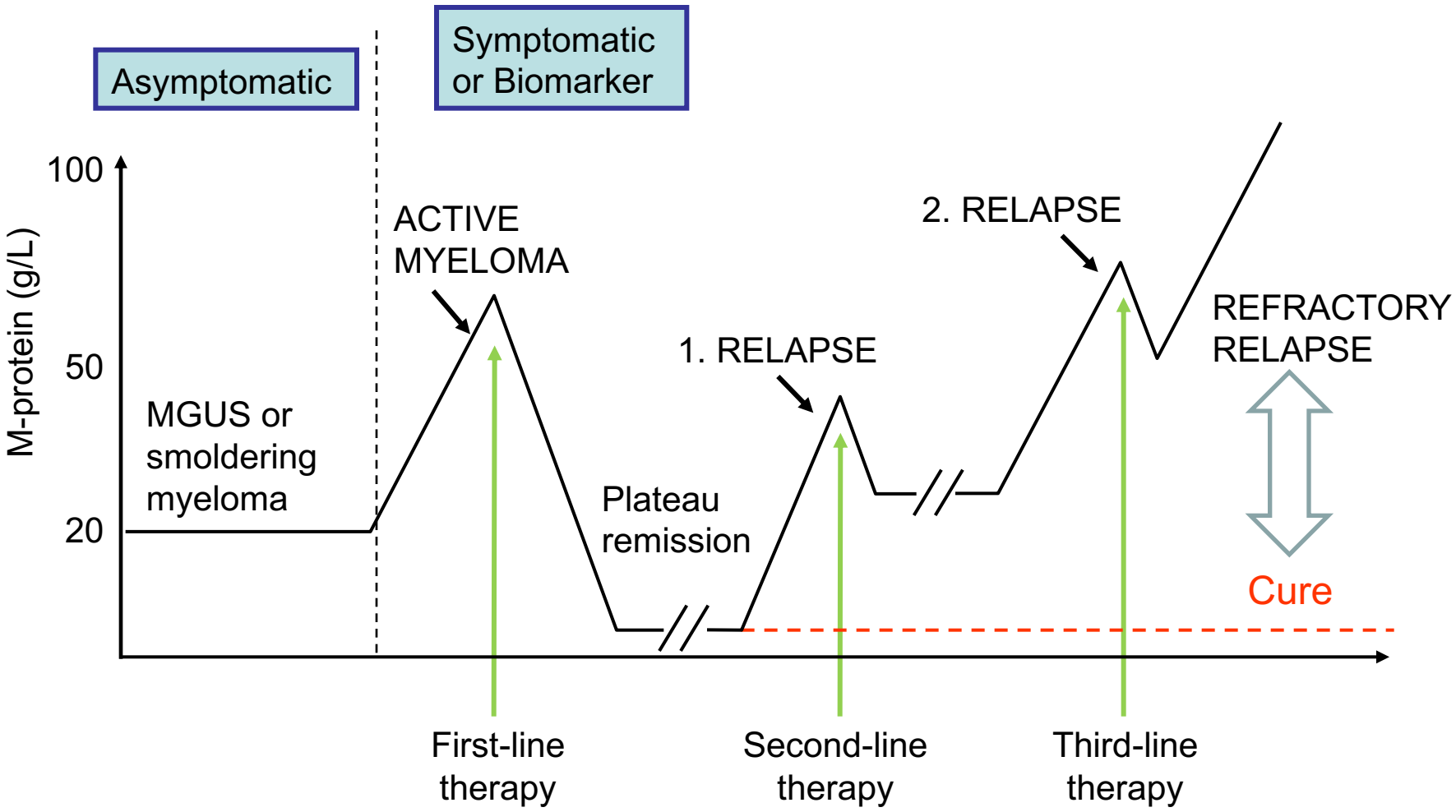
Myeloma Clinical Characteristics

- Cancer of the plasma cells
- 10% of all hematological malignancies[1]
- Europe: 38,900 new cases each year[2]
- Median age: 70 yrs (EU)[1]
- 5-year survival rate: 40-50%[2]
- Newer treatments (Pis, IMiDs and Antibodies) have achieved significant improvement in OS but **MM remains incurable in most patients**



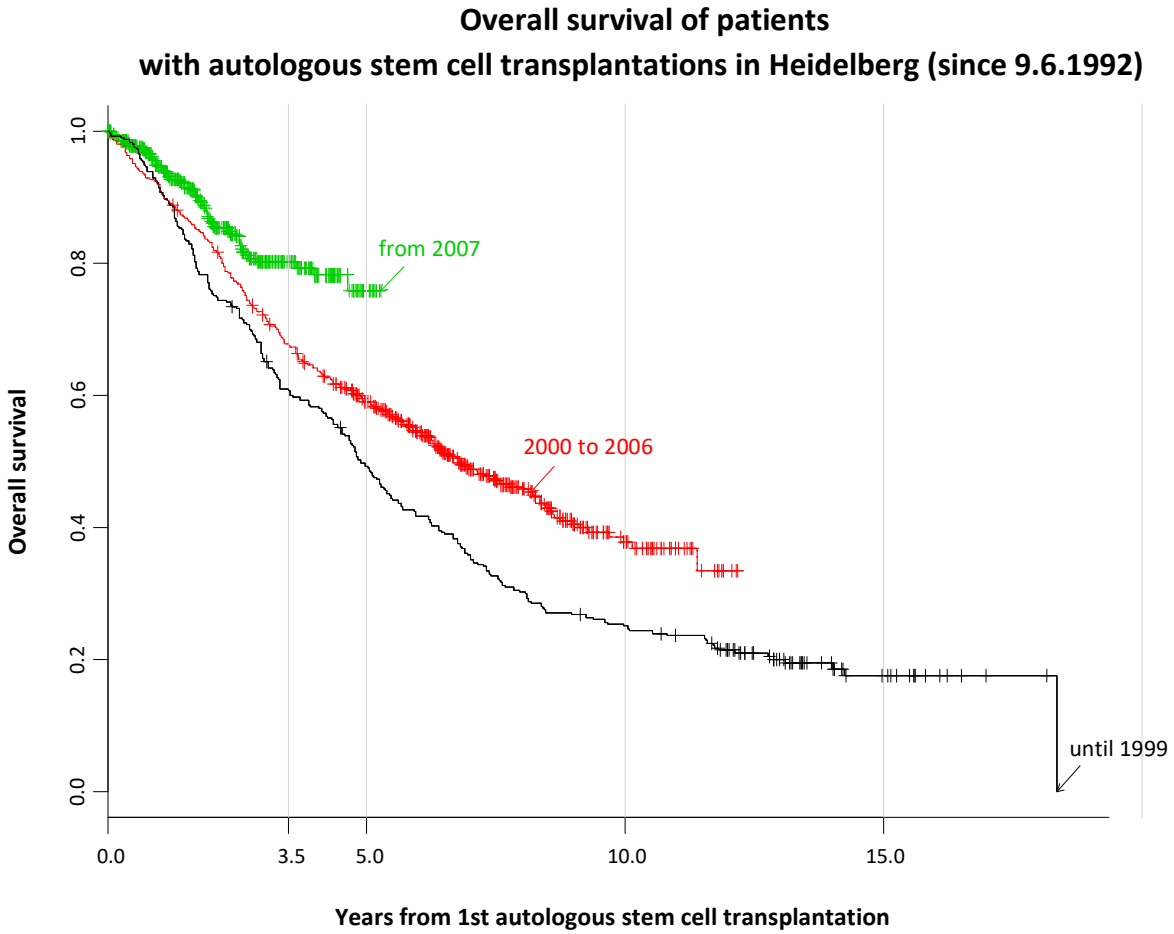
1) Moreau P et al. Ann Oncol. 2013 Oct;24 Suppl 6:vi133-7. Steliarova-Foucher E et al. European Network of Cancer Registries, International Agency for Research on Cancer. Available from http://eco.iarc.fr, accessed on 19/Nov/2015. 2) Cancer Research UK, www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/myeloma/survival#heading-Zero, Accessed 19/Nov/2015.

The Multiple Myeloma Patient Journey



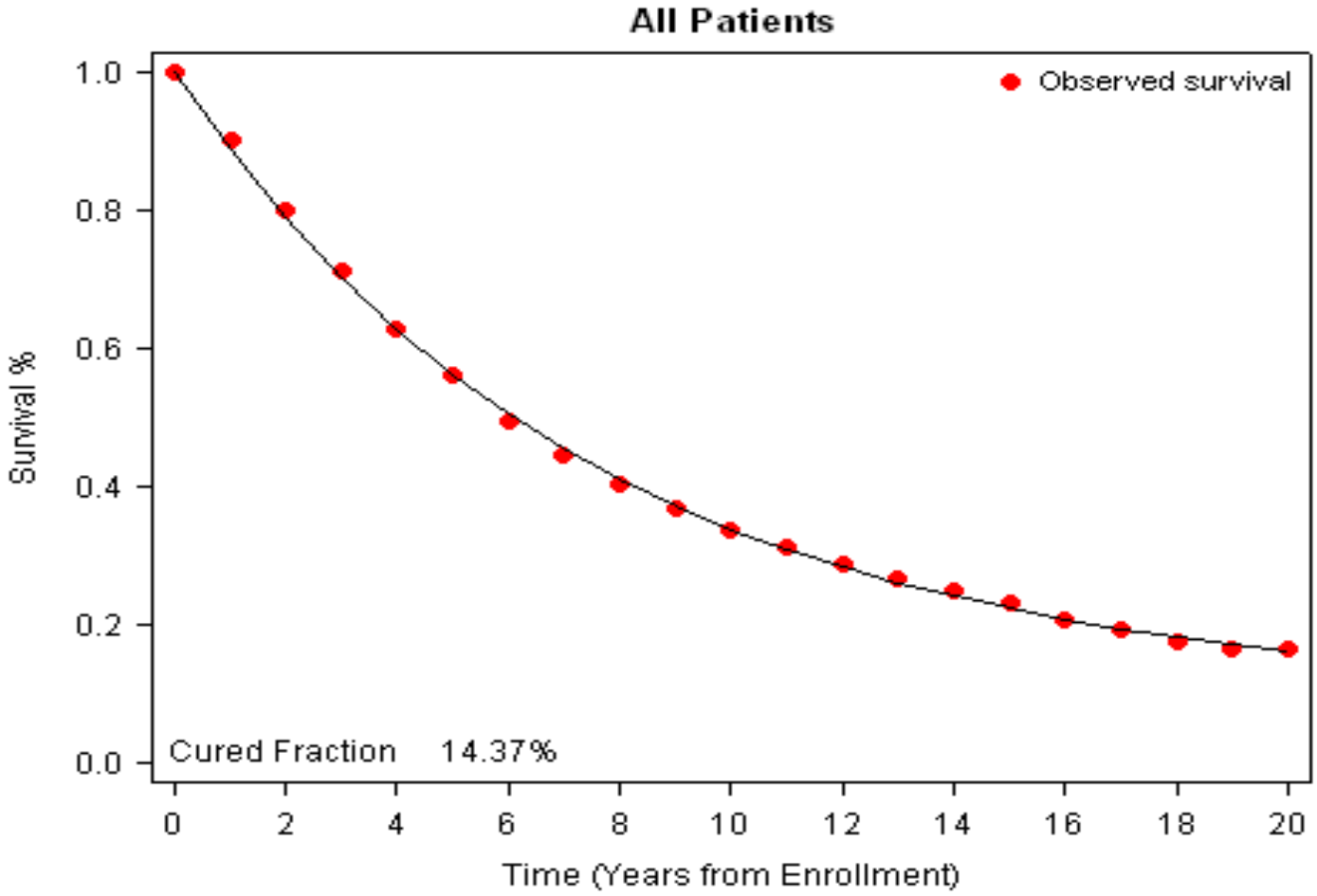
Adapted from Durie 1992, IMF Myeloma Booklet

Multiple Myeloma – Heidelberg Center 20 Years ABSCT (n = 1486 pts)



J. Hillengaß et al., J Cancer Res Clin Oncol. 2013

Cure Fraction NDMM – IMW Project 7,291 Pts. GMMG HD3 Pts. Included



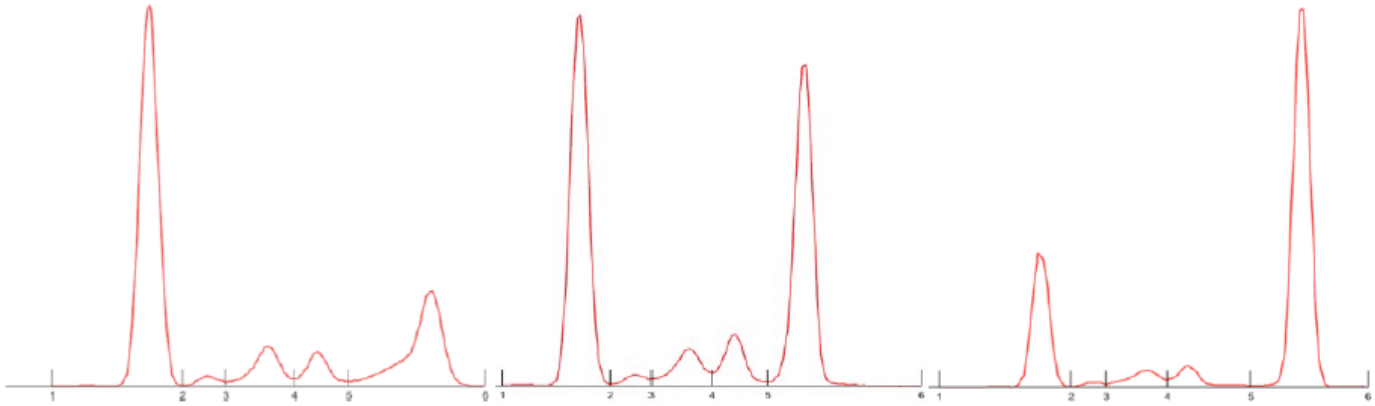
Usmani et al. Blood Cancer J. 2018

Bart Barlogie: MM Control or Cure?

2 New Definitions

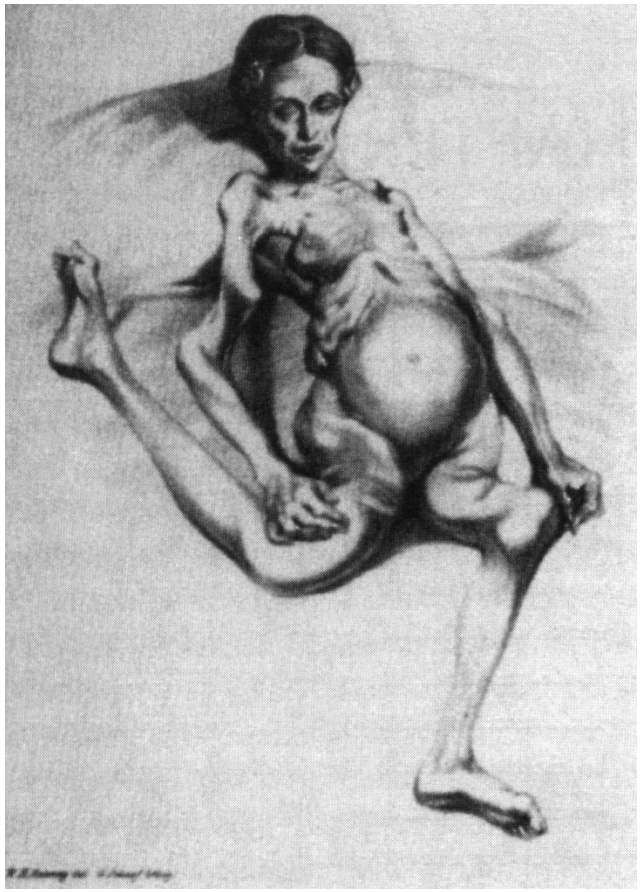
Electrophoresis in MGUS, SMM and Myeloma

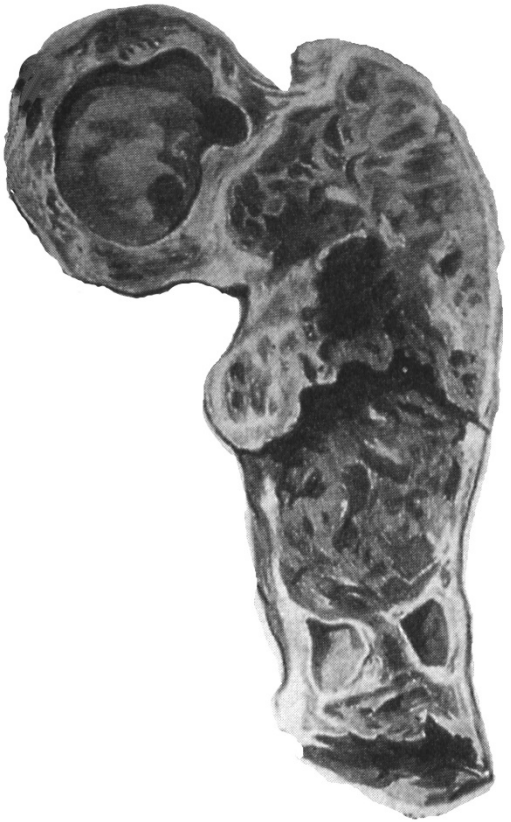
Monoclonal Gammopathy of undetermined Significance (MGUS)	Early Myeloma	Multiple Myeloma



klonale Plasmazellen im Kochenmark	<10%	>10%	>10%
monoklonales Protein	<30g/l	>30g/l	>30g/l
Endorganschädigung	Nein	Nein	Ja

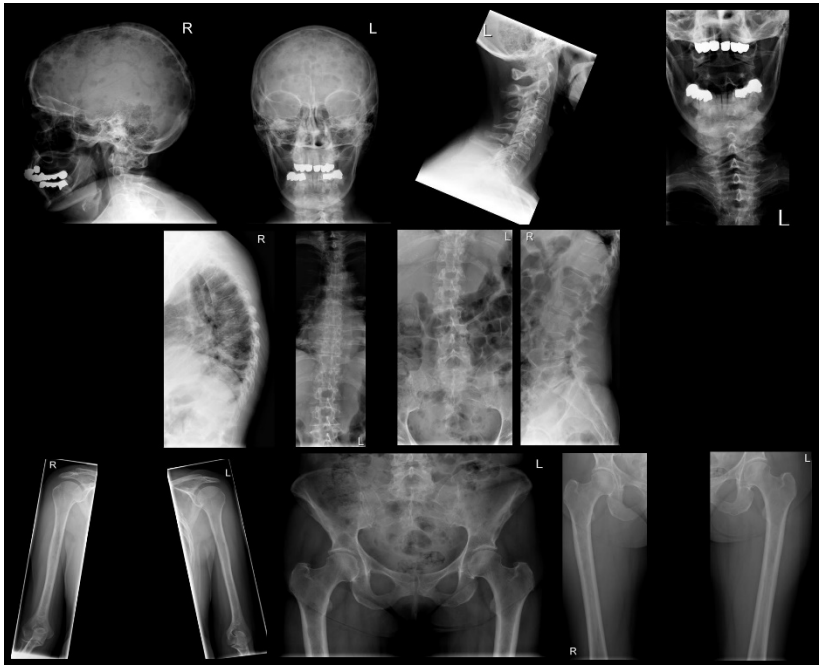
Multiple Myeloma

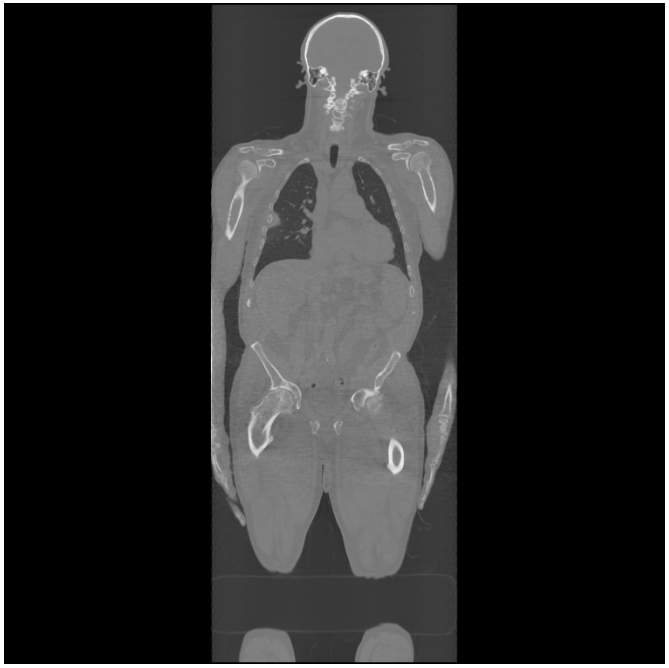


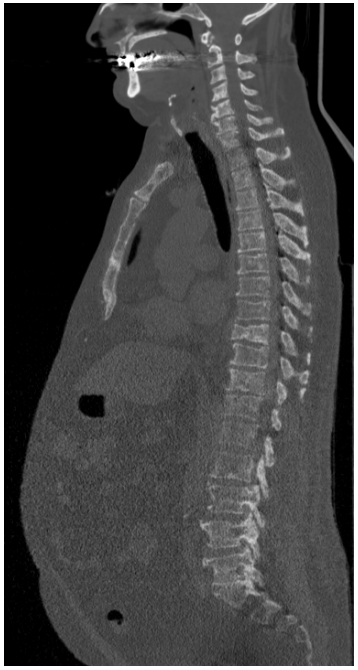


Dr. Solly und Dr. Birkett, St. Guy´s Hospital, London, 1844

Whole Body CT
is the Standard since 10 years



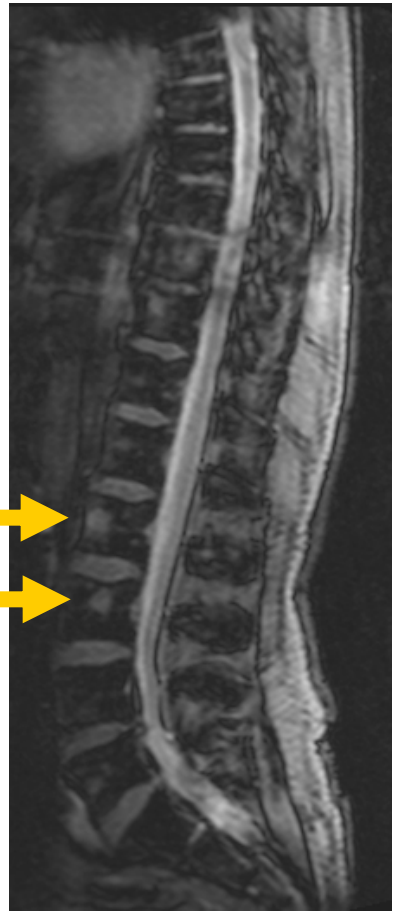


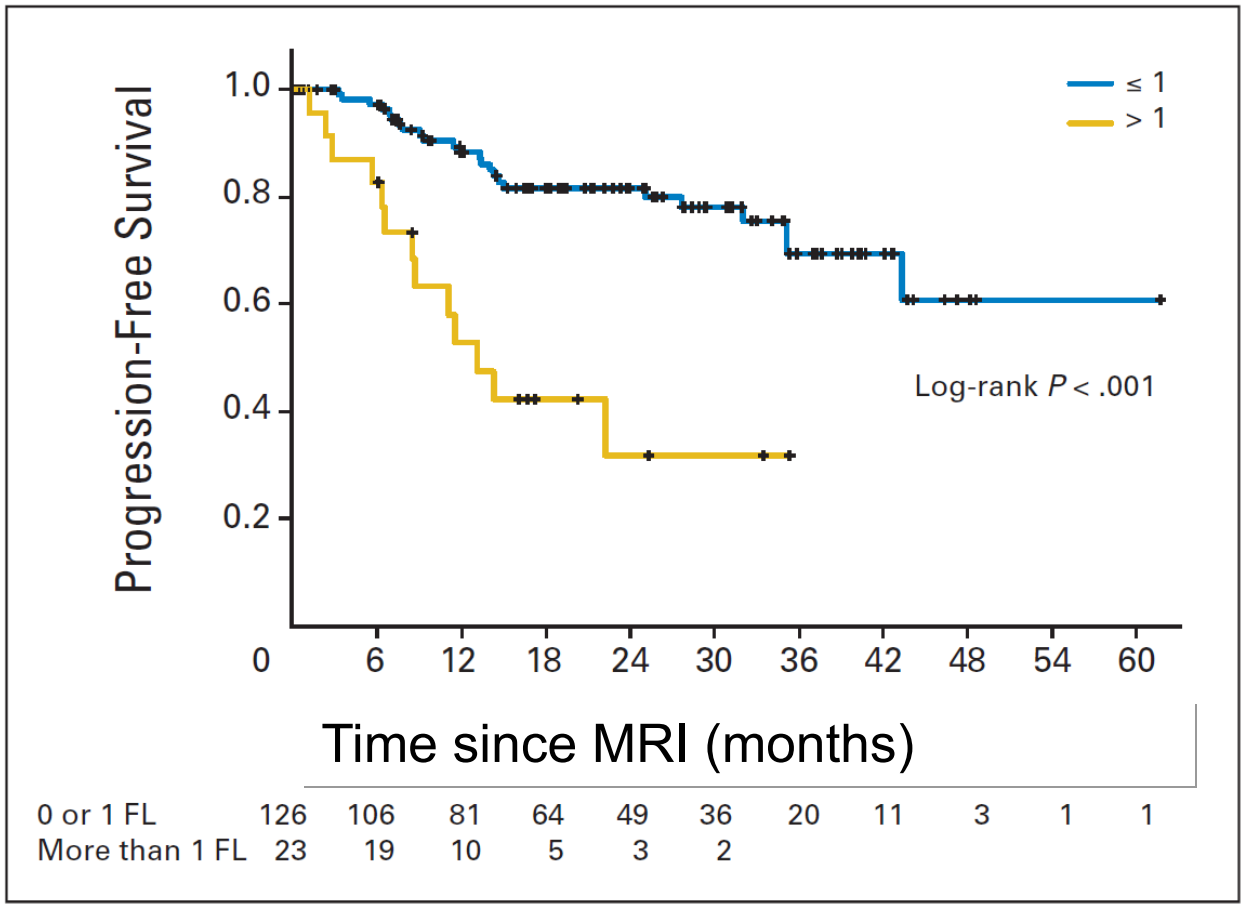


Wolf et al., Eur J Radiol. 2014

Smoldering Myeloma – MRI

Progression Risk → Symptomatic MM

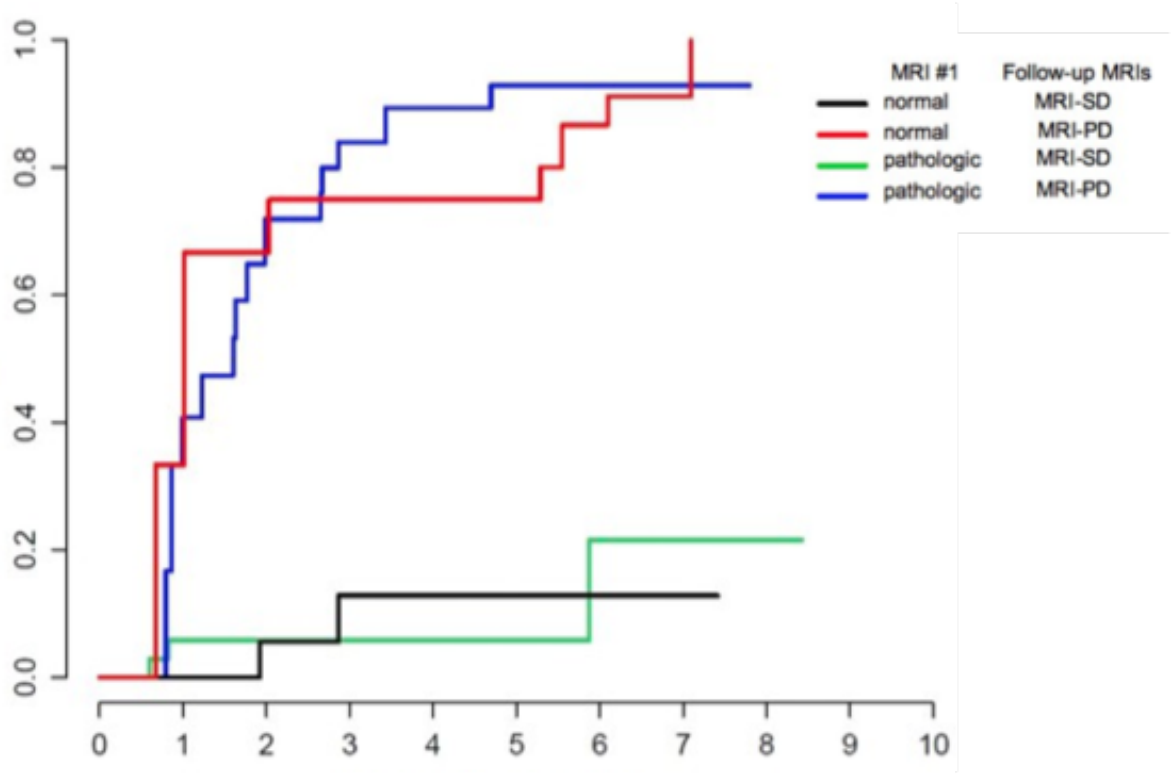




Hillengaß et al, JCO, 2010

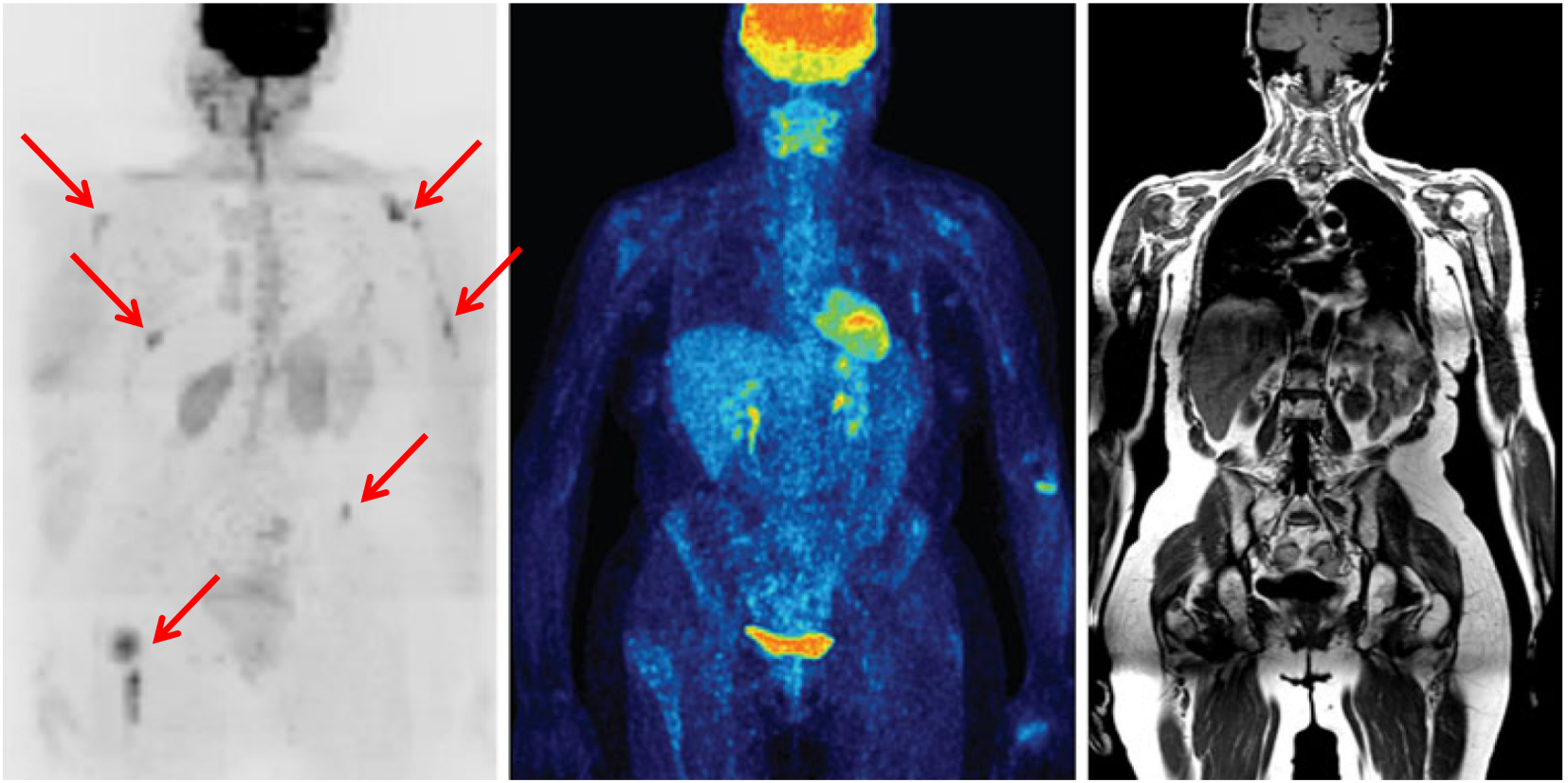
SMM – Dynamics of Focal Lesions

Progression Risk → Symptomatic MM



Merz et al, Leukemia 2014

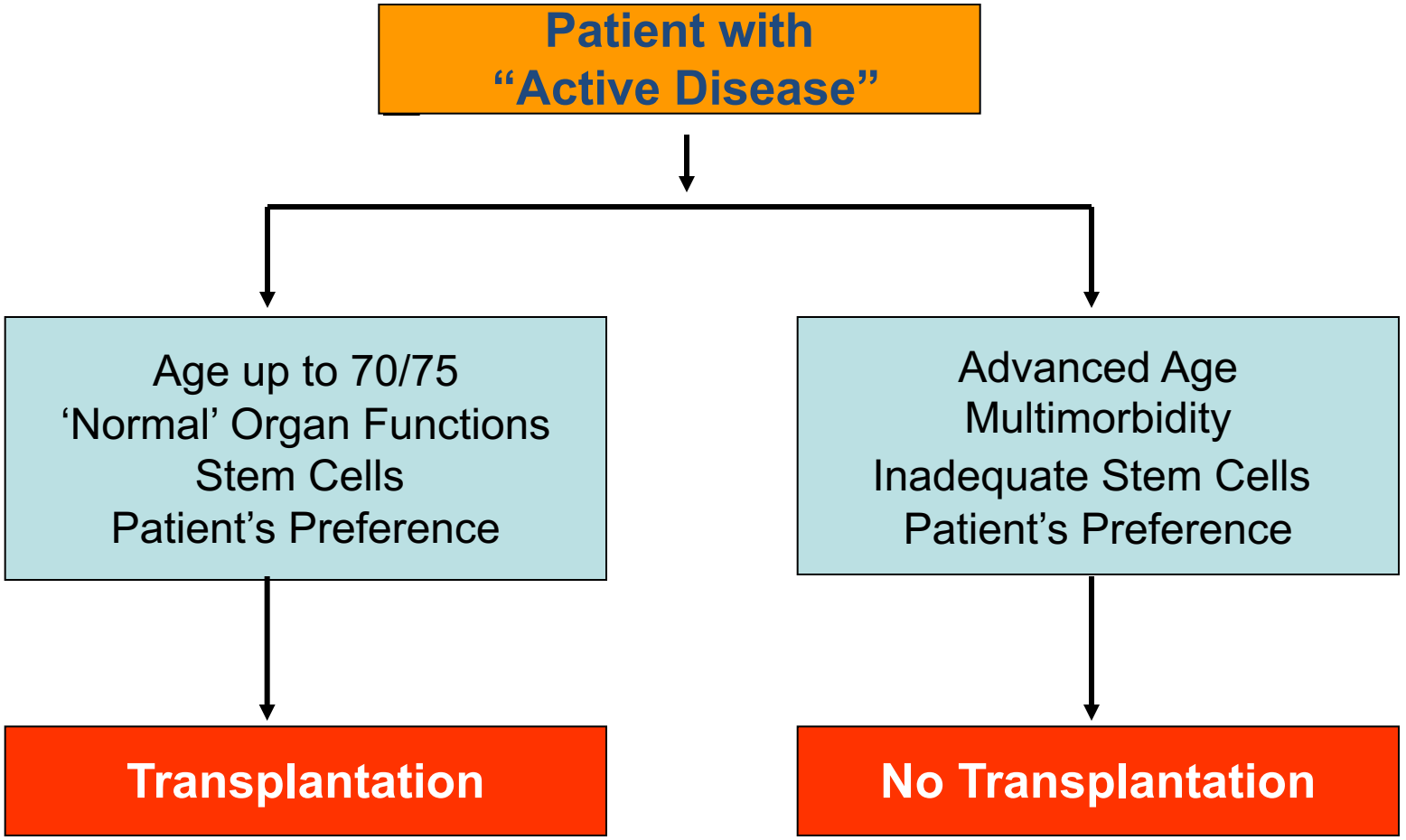
Imaging – Strategy Heidelberg



By courtesy of Hillengaß

3 Treatment of the Myeloma Disease

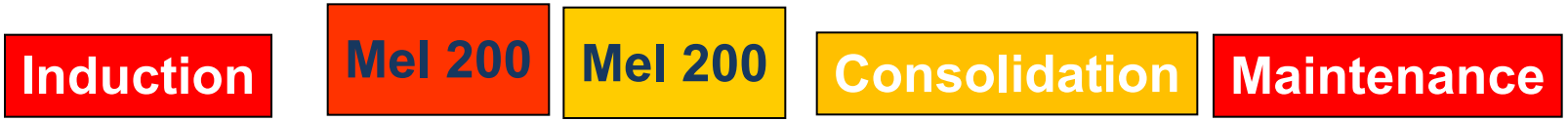
Multiple Myeloma: First Line Treatment



Adapted from Ludwig 2009; Post ASH-Slides

Improving the Response Quality / Increasing CR

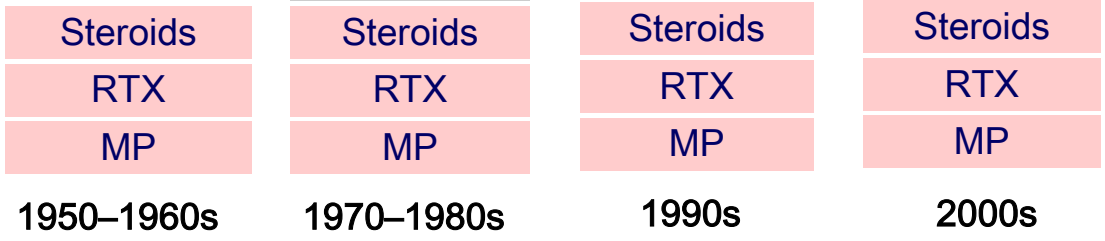
Transplant Eligible



Not Transplant Eligible

Evolving the Therapeutic Armamentarium

Palliation → **Chronic illness** - - - - - - - → **Cure?**



Approved and investigational treatments (2008–2016)[1]	
Targets	**Agent examples**
IMiDs	**Pomalidomide**
Proteasome	**Carfilzomib** ***Ixazomib****
Monoclonal antibodies	**Elotuzumab** **Daratumumab**
HDAC	**Panobinostat**
Akt	Perifosine
XBP-1	XBP-1 peptide
Nitric oxide	JSK
Muc-1	NM3
MEK	AZD6244
NF-κB	NPI1387
Bispecific AB	Multiple
CART-Cells	Multiple
p38MAPK	SCIO469
Telomerase	GRN 163L
Natural products	EGCG

*Ixazomib is approved for treatment of multiple myeloma in the US but is not yet licensed for use in Europe. CHMP positive opinion recommends the granting of a conditional marketing authorisation for ixazomib.[2]

ALLO, allogeneic stem cell transplant; ASCT, autologous stem cell transplant; BP, bisphosphonate; CHMP, Committee for Medicinal Products for Human Use; EGCG, epigallocatechin gallate; HDAC, histone deacetylase; HDC, high-dose chemotherapy; MAPK, mitogen-activated protein kinase; MEK, MAPK/ERK kinase; MP, melphalan, prednisone; NF-κB, nuclear factor kappa B; PKC, protein kinase C; PLD, pegylated liposomal doxorubicin; RTX, radiotherapy; STAT3, signal transducer and activator of transcription 3; VAD, vincristine, Adriamycin (doxorubicin), dexamethasone; XBP-1, X-box binding protein 1.

1. Naymagon L & Addul-Hay M. J Hematol Oncol 2016;9:52–72. 2. EMA 2016 CHMP positive opinion for Ninlaro. Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/003844/smops/Positive/human_smop_000991.jsp&mid=WC0b01ac058001d127. Accessed October 2016. Diagram adapted from Munshi NC. Hematology 2008:297.

MM 2019 – Treatment Options NDMM No TPX

- **Rd** **(EMA approved - DGHO recommended – ESMO First Option)**
- **VMP** **(EMA approved - DGHO recommended – ESMO First Option)**
- **RVd** **(EMA approved - DGHO recommended - ESMO First Option)**

- ***D-VMP*** ***(EMA approved)***

- MPT **(EMA approved – ESMO Second Option)**
- MPR-R **(EMA approved)**
- BP **(EMA approved* – ESMO Third Option)**

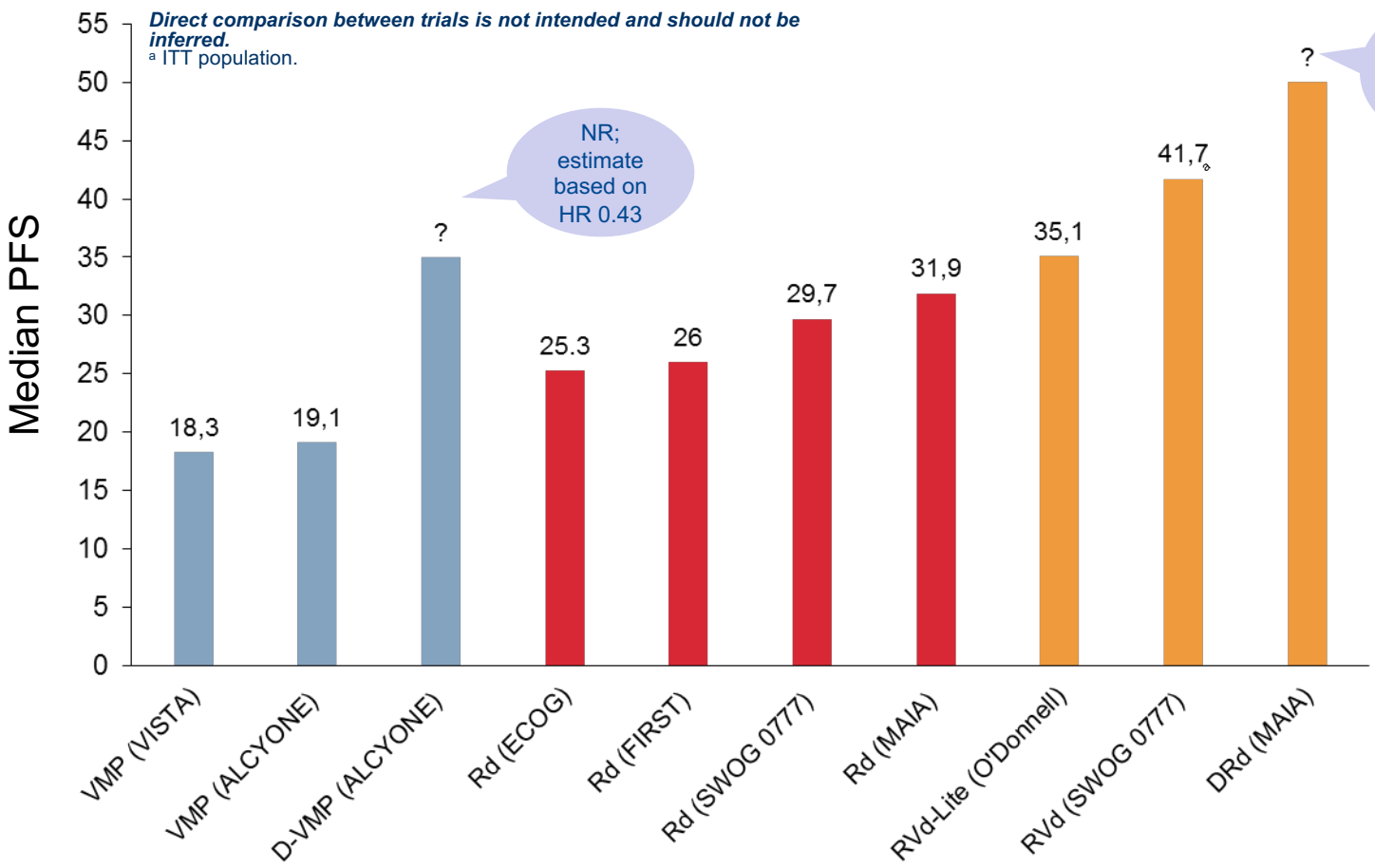
} Keine DGHO-Empfehlung & geringfügige Verwendung in Deutschland

- **VCD** **(not EMA approved - DGHO recommended - ESMO Second Option)**
- **VD** **(not EMA approved)**

*: historic for patients with PNP

adaptiert nach:
Moreau et al., Ann Oncol 2017
Onkopedia Leitlinien „Multiples Myelom“, April 2018

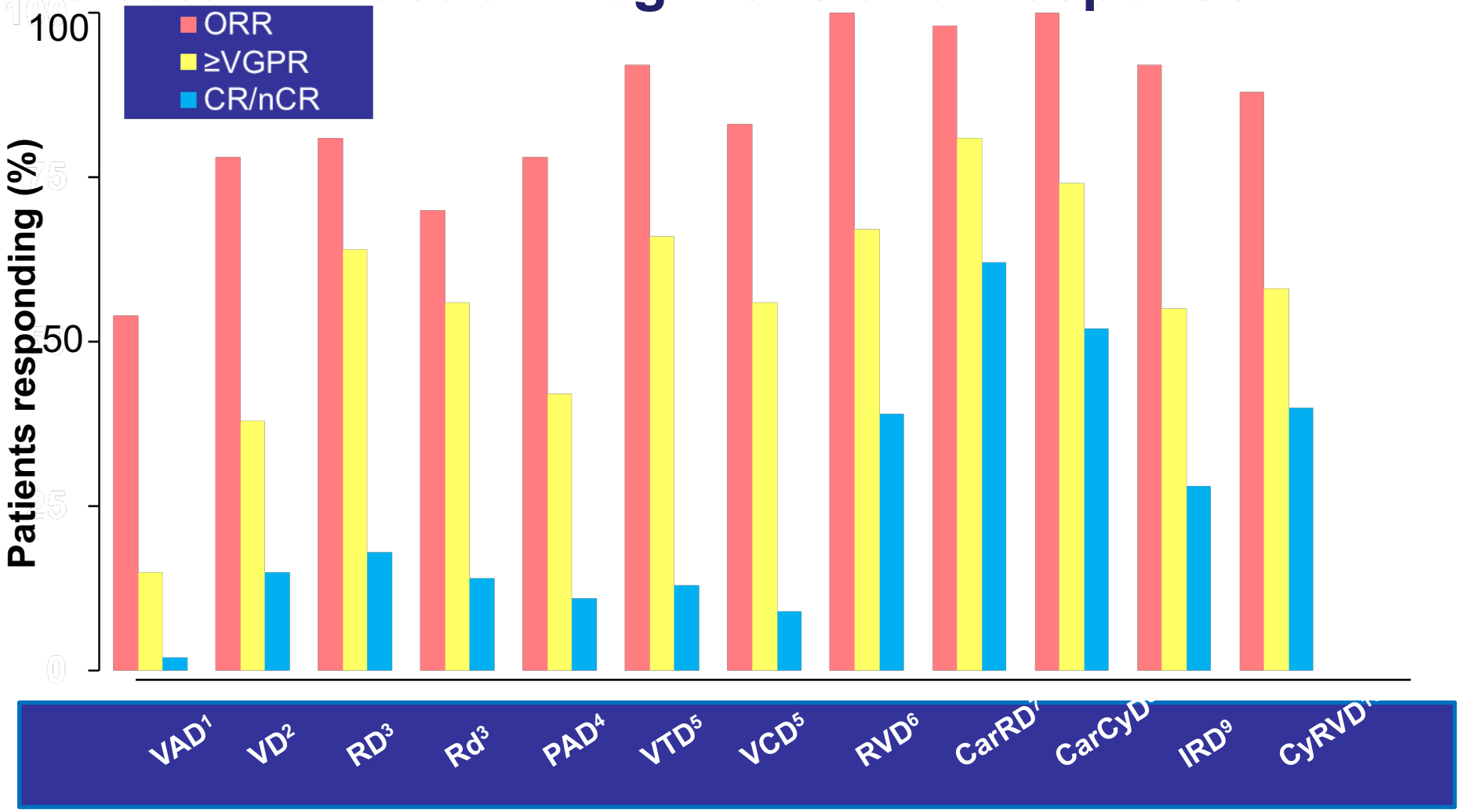
Overview of mPFS in recent phase 3 trials in transplant-ineligible NDMM



Median PFS estimates calculated by dividing the median PFS of the comparator by the HR

1. Velcade [SmPC]. Beerse, Belgium. Janssen-Cilag International; 2014. 2. Dimopoulos M, et al. Blood. 2018;132:156. Presented at ASH 2018. 3. Rajkumar SV, et al. Lancet Oncol. 2010;11:29-37. 4. Facon T, et al. Blood. 2018;131:301-10. 5. REVLIMID [SmPC]. Utrecht, Netherlands. Celgene Europe BV; 2019. 6. Facon T, et al. Blood. 2018;132:LBA-2. Presented at ASH 2018. 7. O'Donnell EK, et al. Br J Haematol. 2018;182:222-30.

Selected Induction Regimens and Response in MM



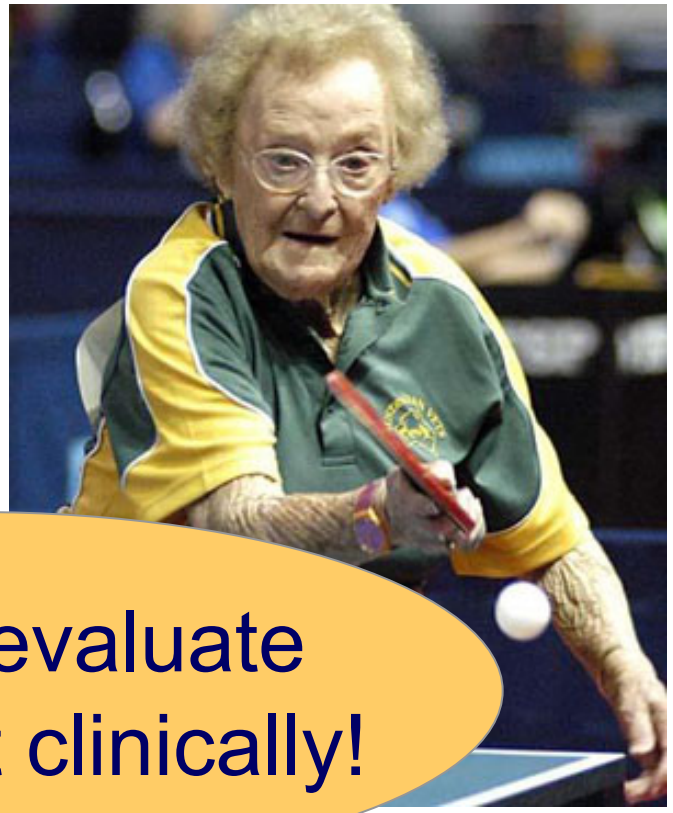
This slide is provided for ease of viewing information from multiple trials. Direct comparison between trials is not intended and should not be inferred.

Adapted, Stewart et al. Blood 2009. Courtesy of Dr. P. McCarthy. ASH Educational 2013. 1. Lokhorst HM, et al. Haematologica. 2008;93:124-7. 2. Harousseau JL, et al 2010 J Clin Oncol 28:4621-4629. 3. Rajkumar SV, et al Lancet Oncol 2010; 11: 29–37. 4. Sonneveld P, et al J Clin Oncol 2012; 30:2946-55. 5. Moreau, P et al. Blood. 2015;126:[abstract 393]. 6. Richardson et al. Blood 2010;116:679-686. 7. Jakubowiak AJ, et al Blood. 2012 30;120:1801-9. 8. Palumbo A, et al. Blood. 2012;120:[abstract 730]. 9. Kumar S, et al . Blood. 2012;120:[abstract 332]. 10. Kumar S, et al. Blood. 2012; 119: 4375-82.

The Patient: Frail versus Fit

Which Dose?

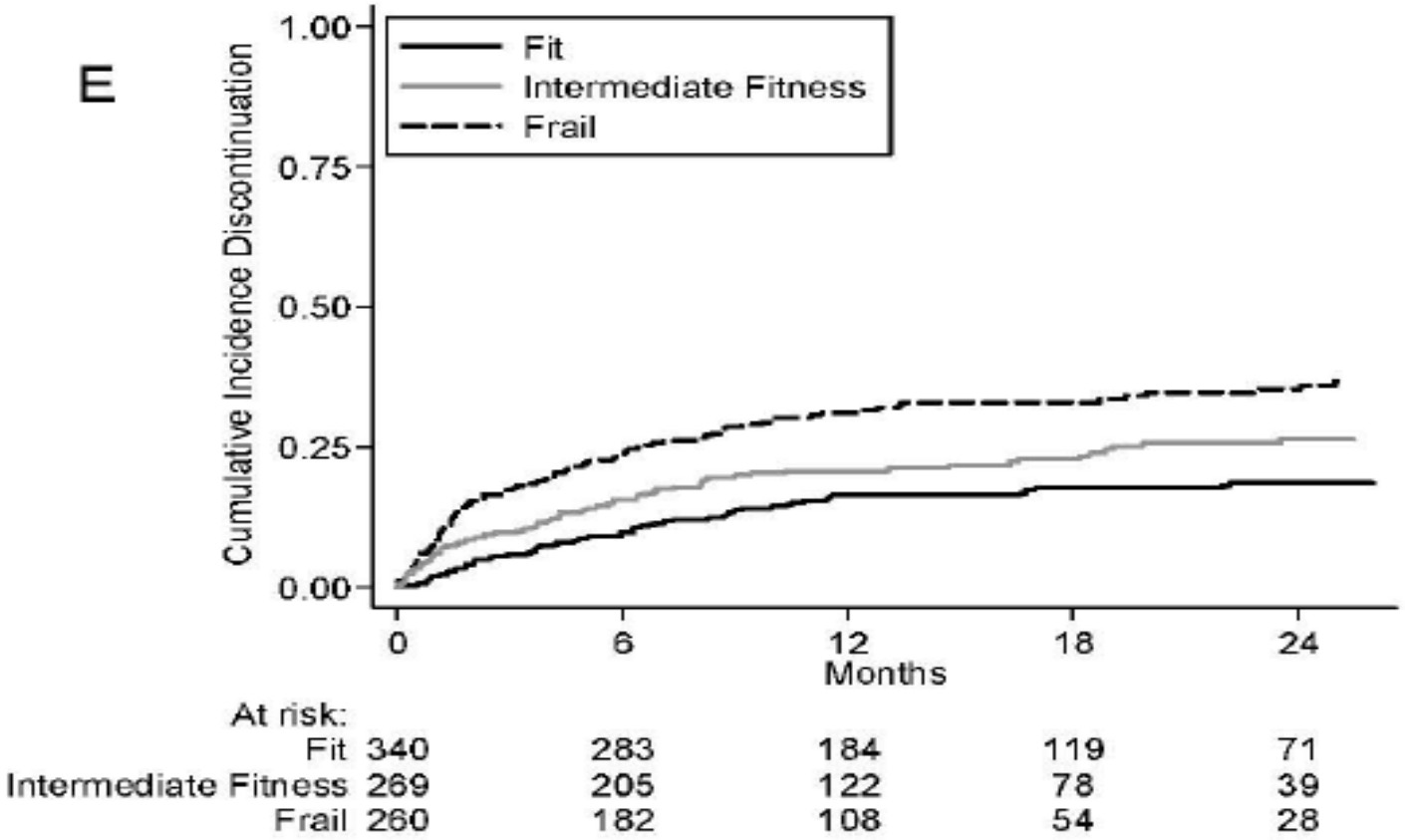
Which of the New Drug(s)?



carefully evaluate
the patient clinically!

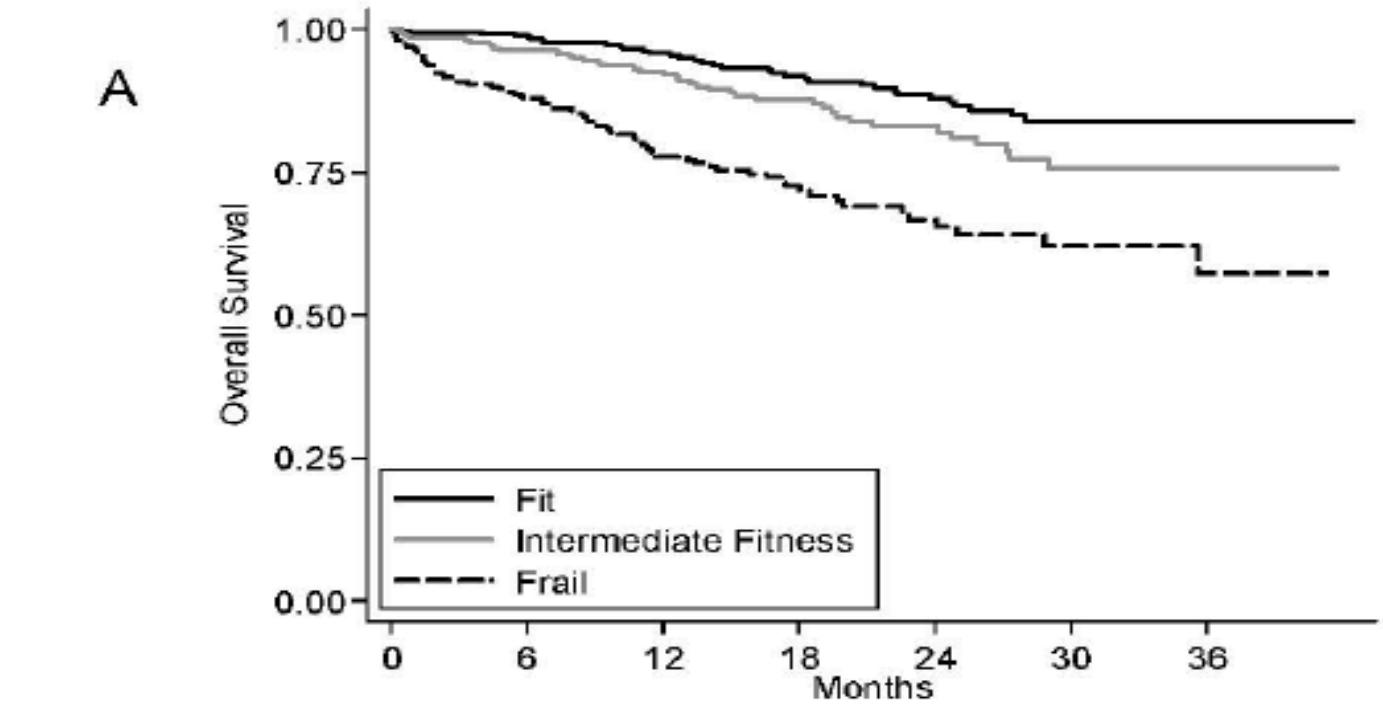
Adapted from Facon/Salwender; IMW 2012

Long Term Outcome - Discontinuation



Antonio Palumbo et al. Blood 2015

Long Term Outcome - Overall Survival



At risk:							
Fit	340	323	248	182	133	84	43
Intermediate Fitness	269	242	183	123	83	47	15
Frail	260	209	151	91	52	27	12

Antonio Palumbo et al. Blood 2015

Recommended Starting Dose and Dose Adjustments According to Age Groups and Vulnerability Status

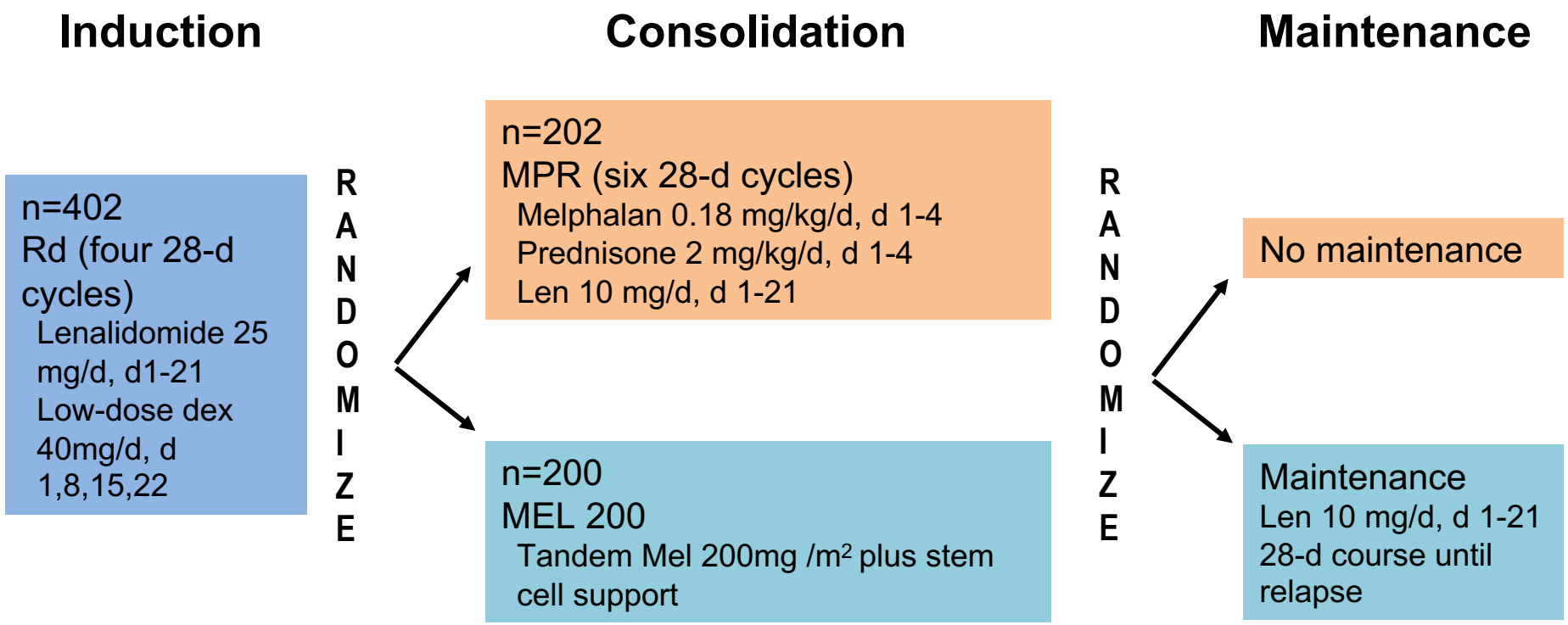
Agent	No Risk Factors*	At least 1 Risk Factor	At least 1 Risk Factor (+ grade 3/4 non-haem AE)
Dexamethasone (mg/day, Weekly)	40	20	10 (or prednisone)
Melphalan (mg/kg, Days 1-4)	0.25	0.18	0.13
Thalidomide (mg/Day)	100	50	50 qod
Lenalidomide** (mg/Day, Days 1-21)	25	15	10
Bortezomib (mg/m^2, Weekly, s.c.)	1.3	1.0	0.7

* Risk factors; age> 75 years, frailty, comorbidities (cardiac, pulmonary, hepatic, renal); ** Dose also adapted according to renal function.

Adapted from Palumbo A, et al. Blood. 2011;118:4519-29.

4 Role of Autologous Blood Stem Cell Transplantation in 2019

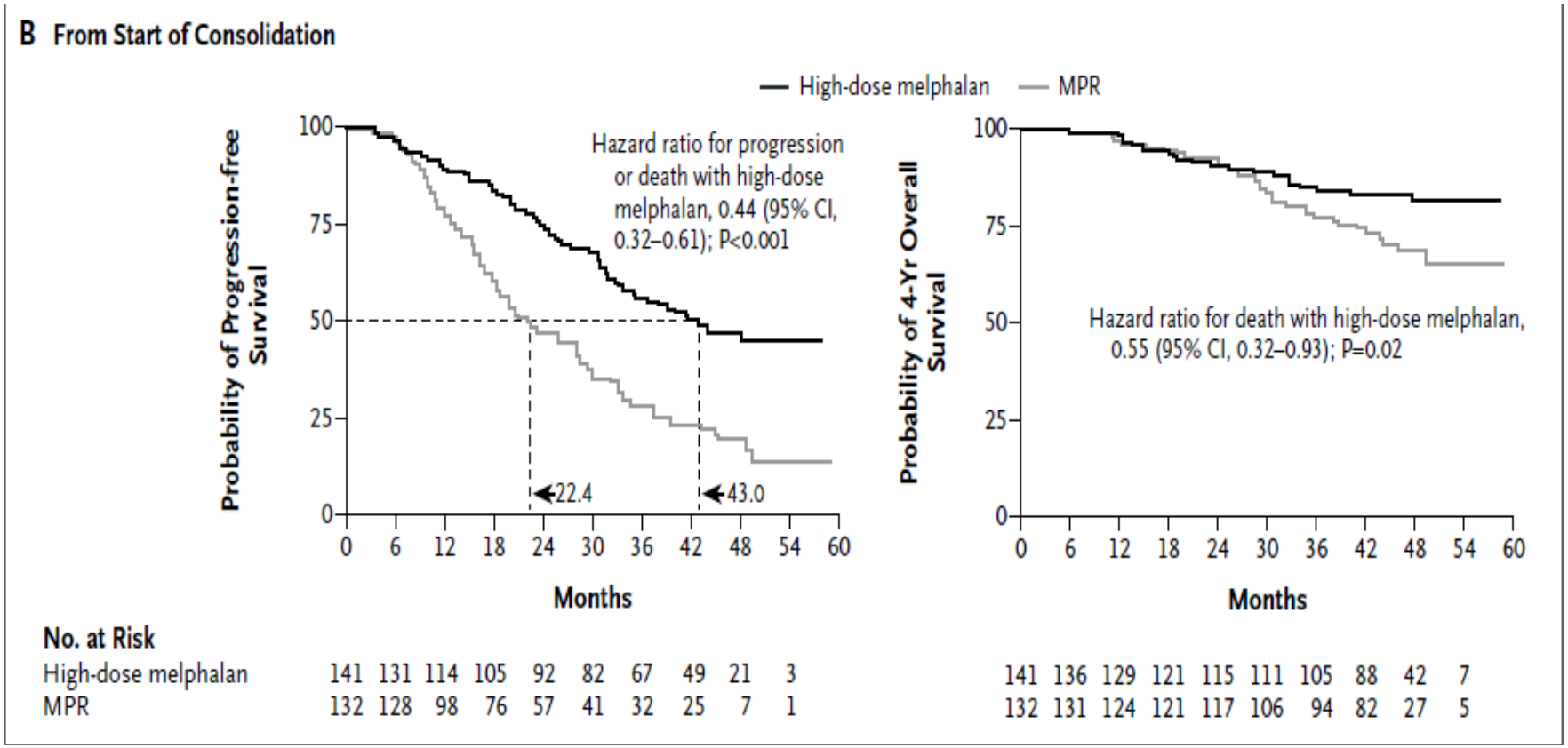
Phase 3: MPR versus Tandem ASCT



Primary end point: PFS

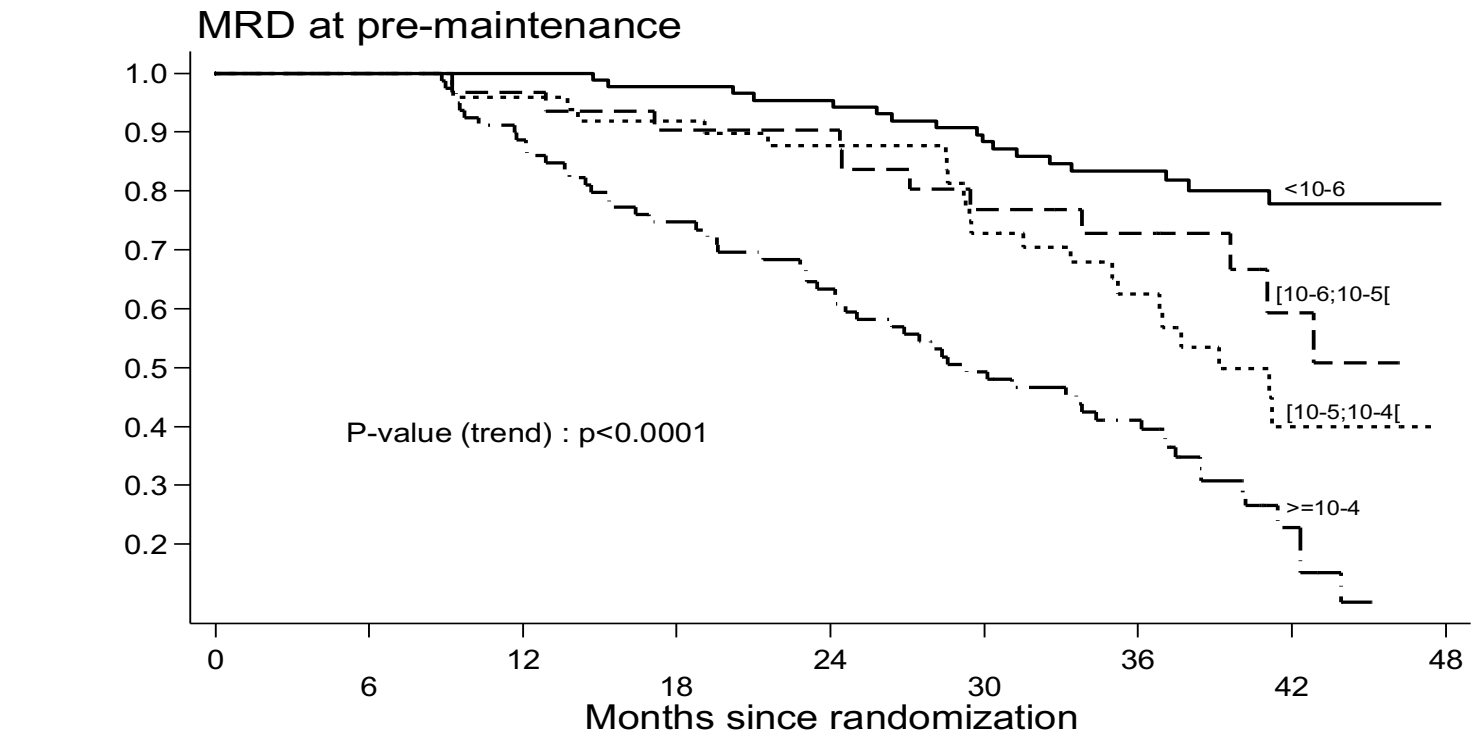
Boccadoro et al. J Clin Oncol 2011;29 (suppl) (Abstract 8020); poster presentation at ASCO 2011
Palumbo et al. Haematologica 2011;96(s2):214 (Abstract 508); oral presentation at EHA 2011

PFS and 4-Year OS from the Start of Consolidation Therapy



Palumbo et al. NEJM 2014

IFM/DFCI 2009 Trial: Role of MRD

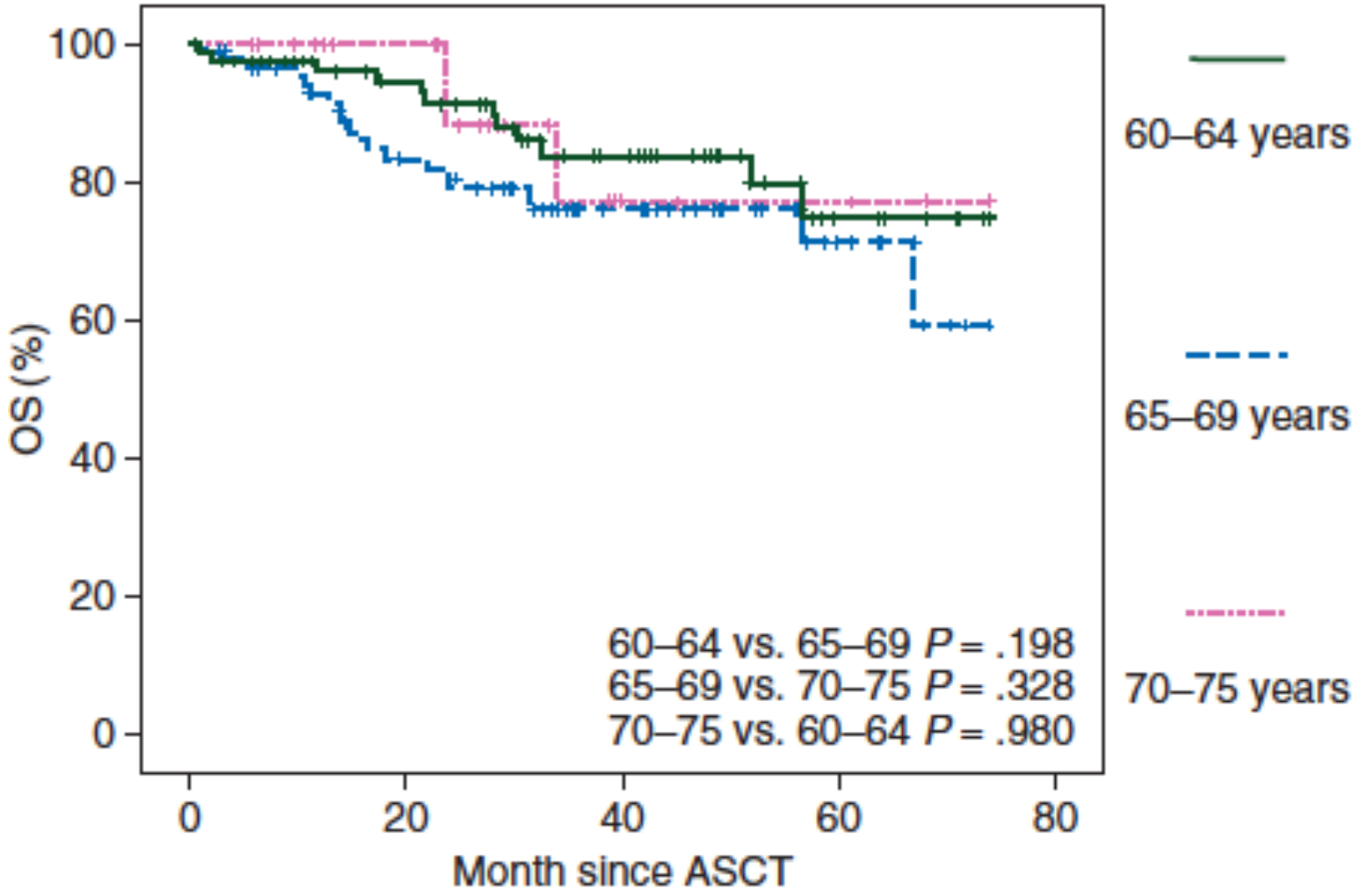


N at risk (events)

$<10^{-6}$	87	(0)	87	(0)	87	(2)	85	(2)	83	(6)	74	(4)	54	(3)	31	(0)	8
$[10^{-6};10^{-5}[$	31	(0)	31	(1)	30	(2)	28	(0)	27	(4)	22	(1)	17	(2)	8	(1)	4
$[10^{-5};10^{-4}[$	49	(0)	49	(2)	47	(2)	45	(2)	43	(7)	34	(4)	22	(6)	8	(0)	2
$[10^{-4};10^{-3}[$	79	(0)	79	(9)	70	(11)	59	(9)	50	(11)	38	(6)	28	(9)	6	(3)	0

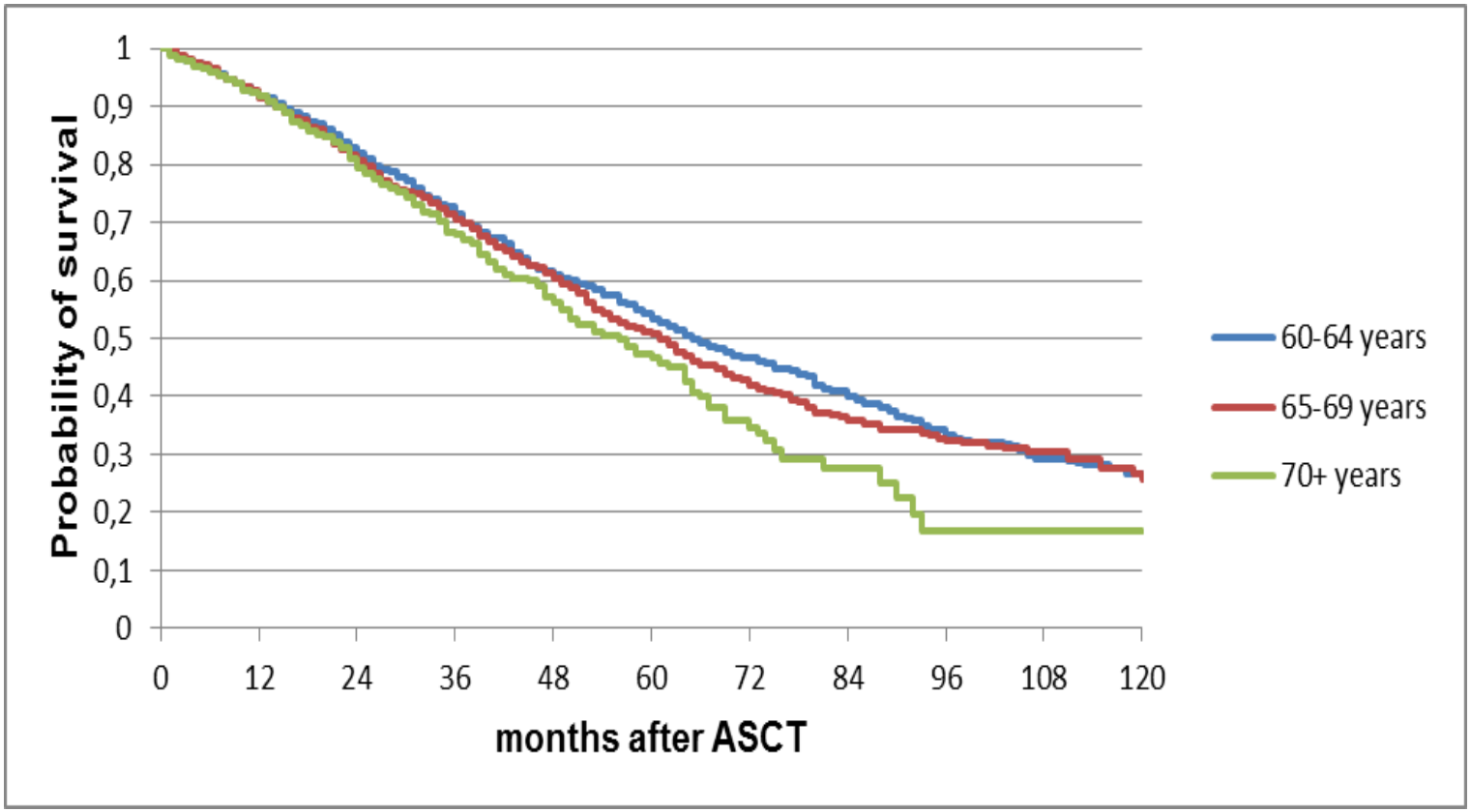
Herve Avet-Loiseau, ASH, 2015

ABSCT: Age is not a Predictive Factor



M. Merz et al., Ann Oncol 2014

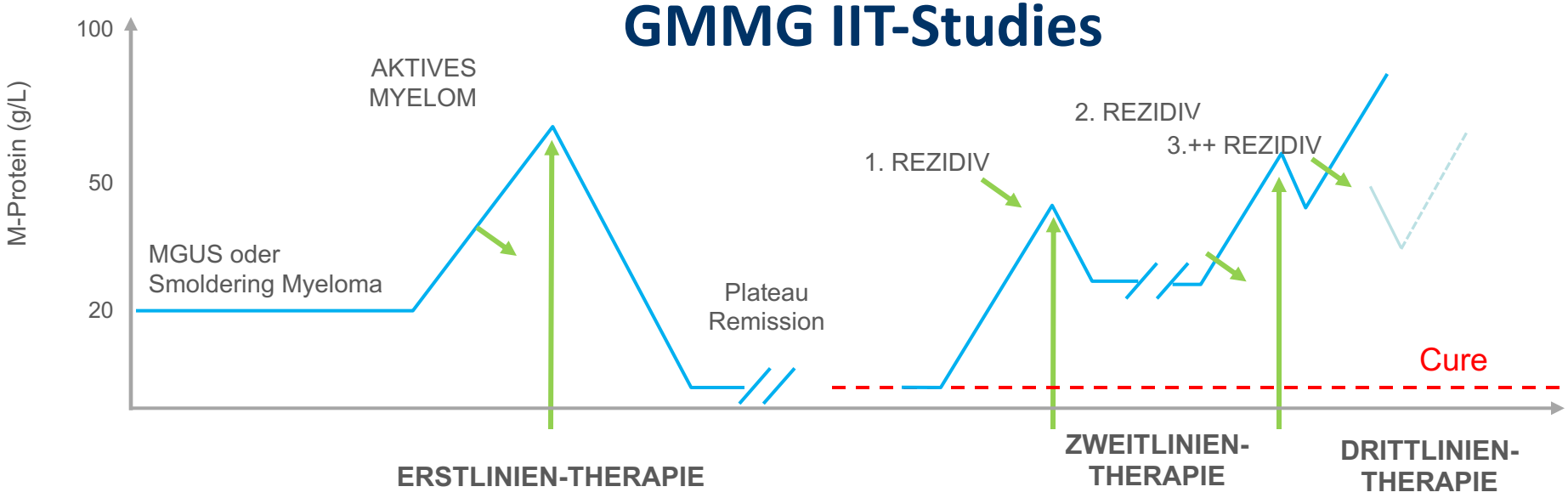
Impact of Age on Outcome after ASCT



Merz et al., Eur J Cancer. 2016

5 Studies in Myeloma – GMMG Trials

GMMG IIT-Studies



MM5 | VCD-Dara | ReLApsE | BIRMA

HD8 | HD6 | BPV | PERSPECTIVE | DANTE

HD7 | CONCEPT

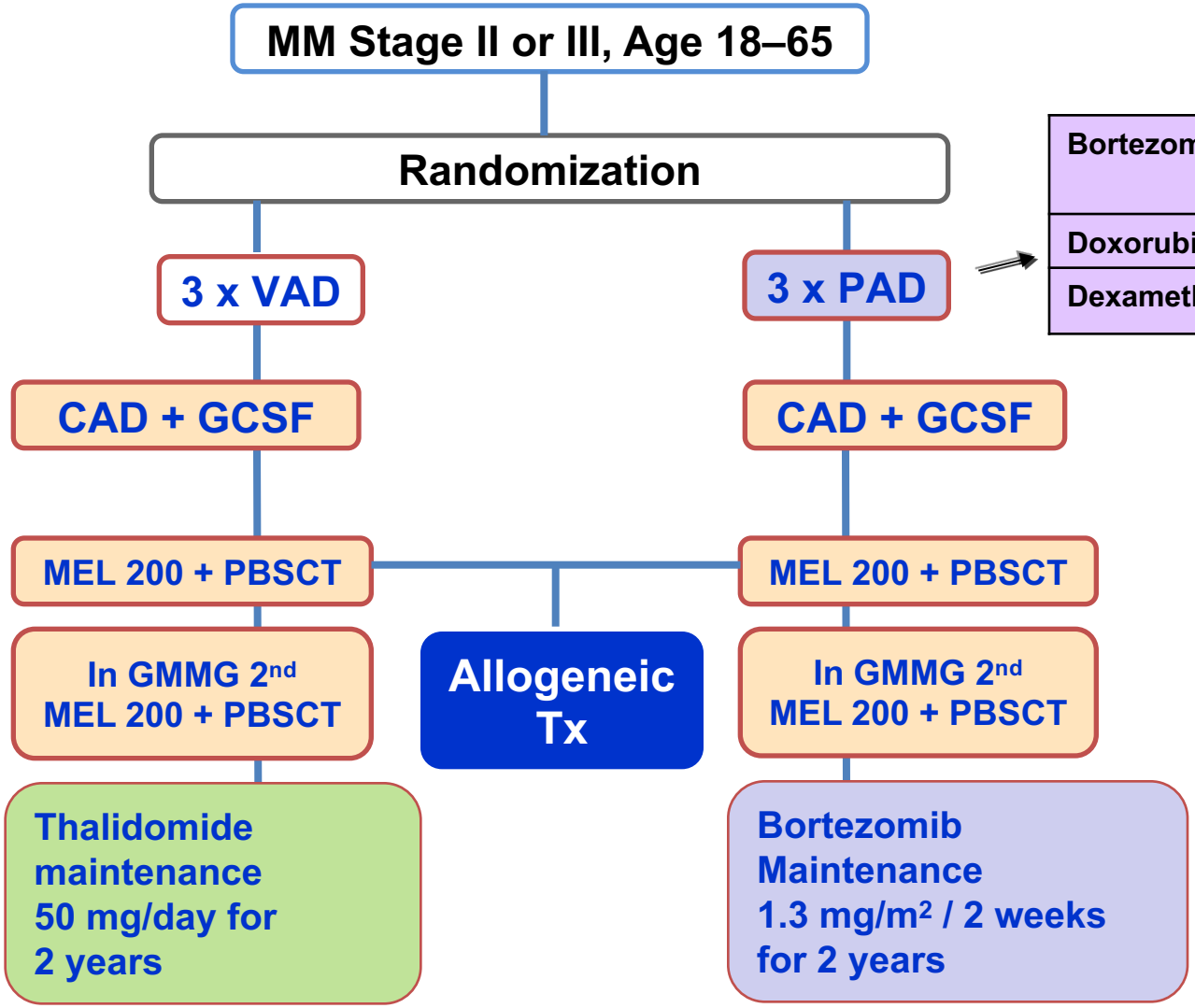
GMMG studies active

GMMG studies in preparation

GMMG studies currently analysed

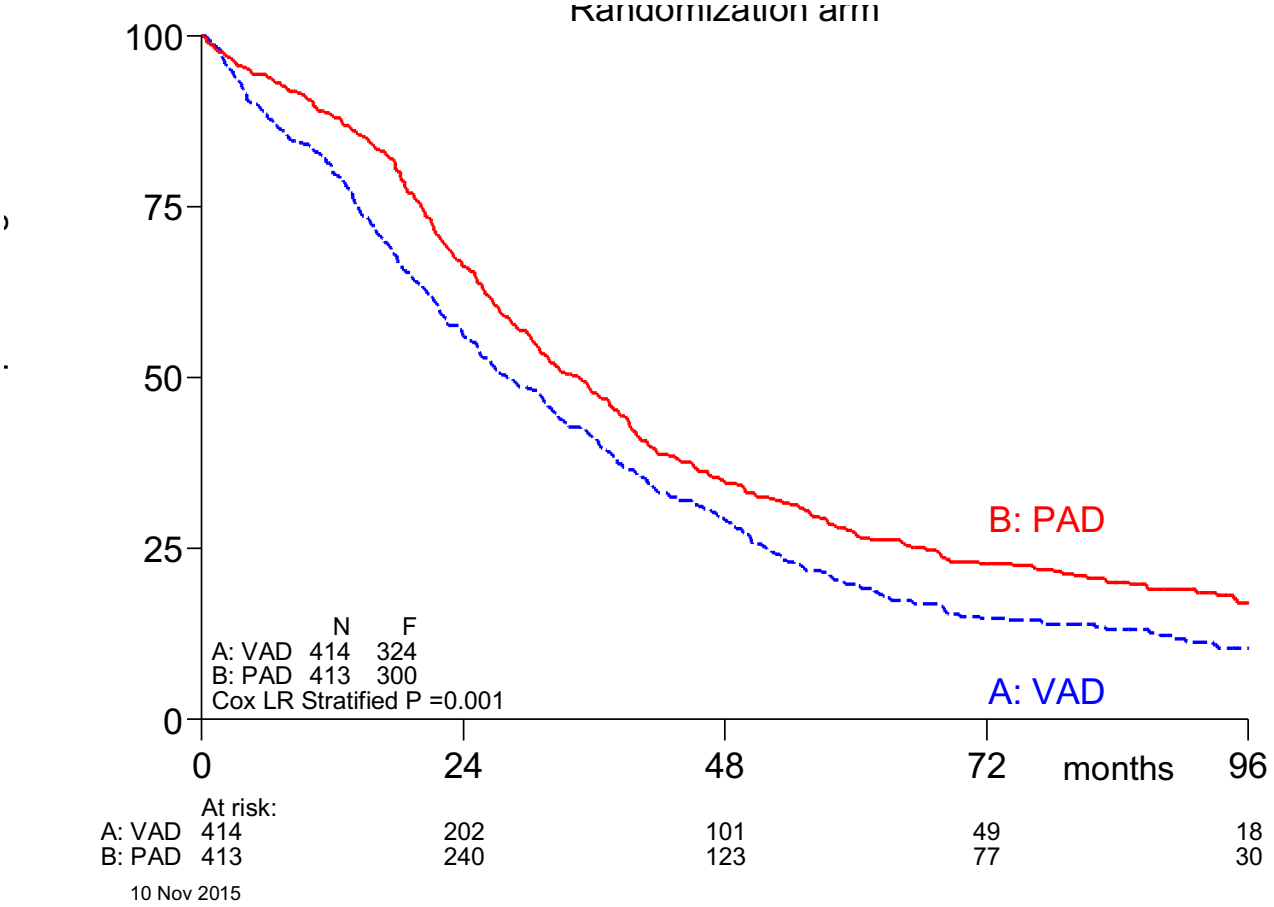
NCT UK HD

HOVON 65/GMMGHD4 Trial design



Goldschmidt et al. Leukemia 2017

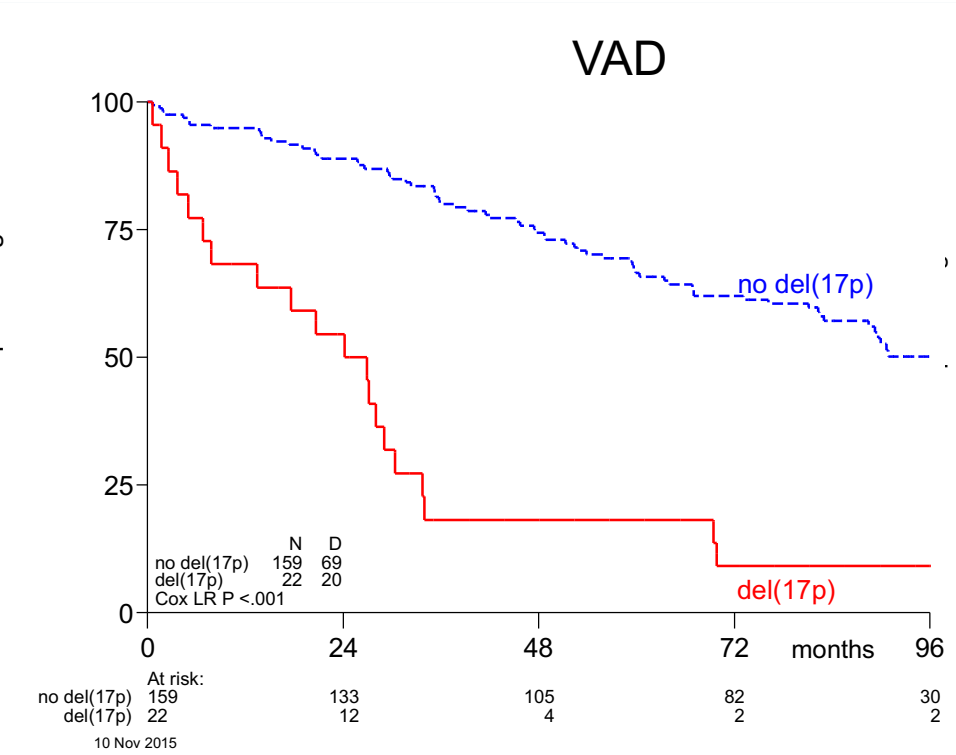
HOVON 65/GMMGHD4 Primary endpoint PFS by treatment arm



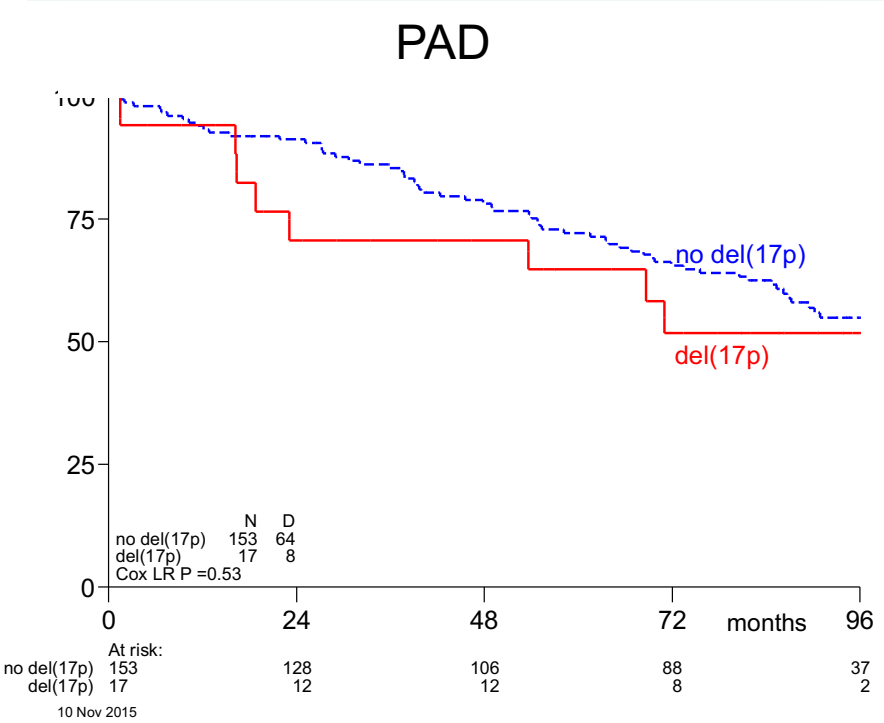
PFS at 96m: 17% vs 10%
HR:0.77, 95% confidence interval (CI) = 0.65-0.90; P = 0.001

Sonneveld et al. ASH Abstract 27,2015

HOVON 65/GMMGHD4: OS by Treatment Arm Subgroup with del(17/17p)



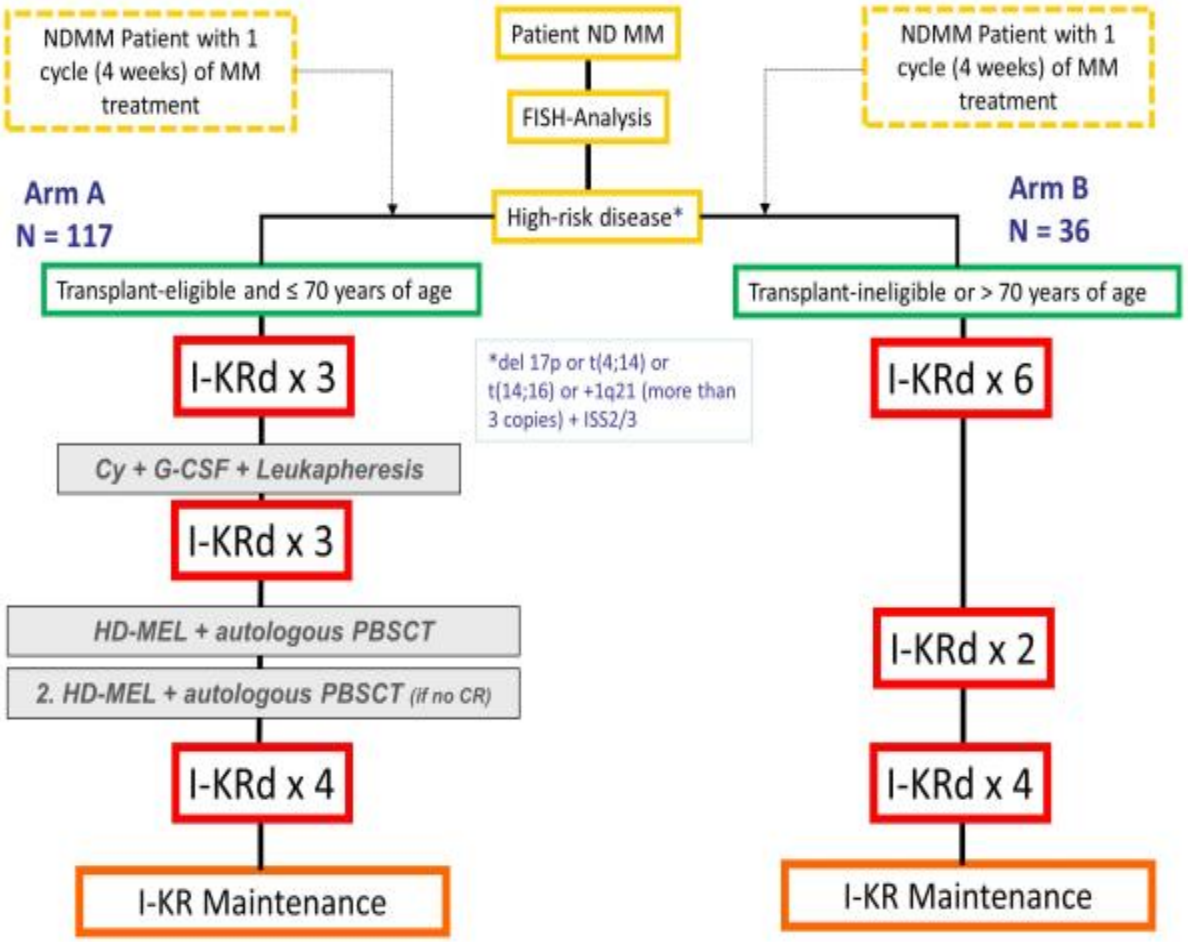
p<0.001



p=0.5

Goldschmidt et al., Leukemia 2017

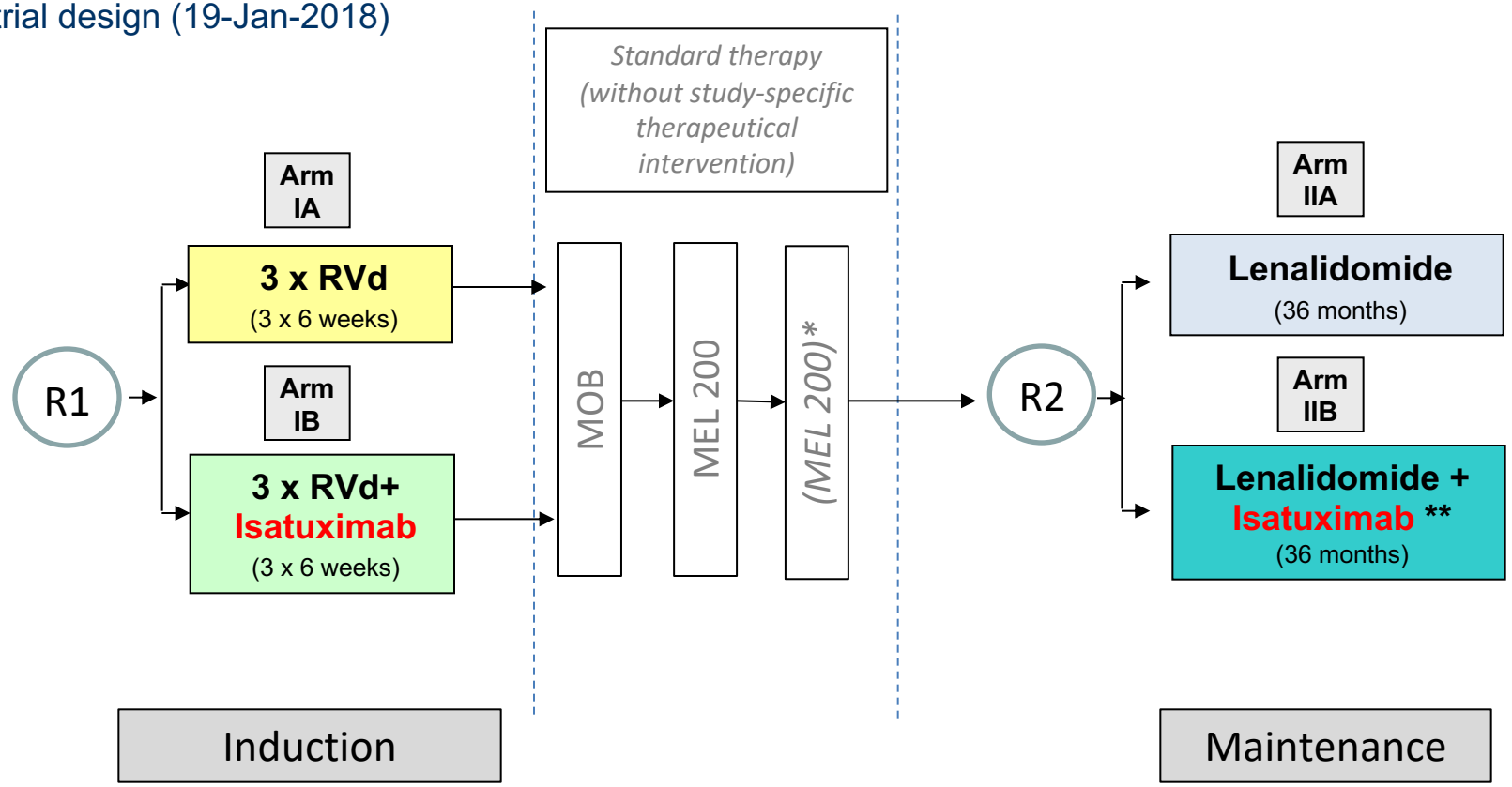
GMMG-CONCEPT-Trial



Lead PI: Katja Weisel, Sponsor: University Medical Center of Hamburg-Eppendorf

GMMG-HD7 Trial

Modified trial design (19-Jan-2018)

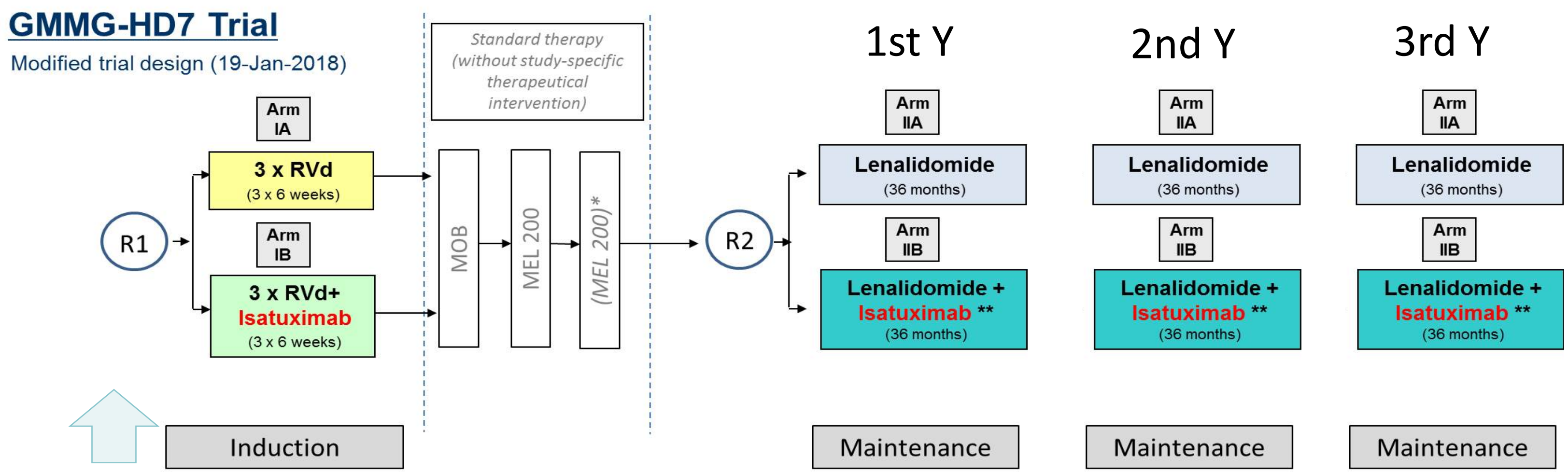


R1 = 1st randomization (at study inclusion); R2 = 2nd randomization (prior to maintenance)

* decision for 2nd high dose therapy response-adapted (in case no CR)

*** Lenalidomide/Isatuximab for 36 months (thereafter, continuation of lenalidomide recommended until PD)*

Biobanking in HD7 - Time Points For Sampling

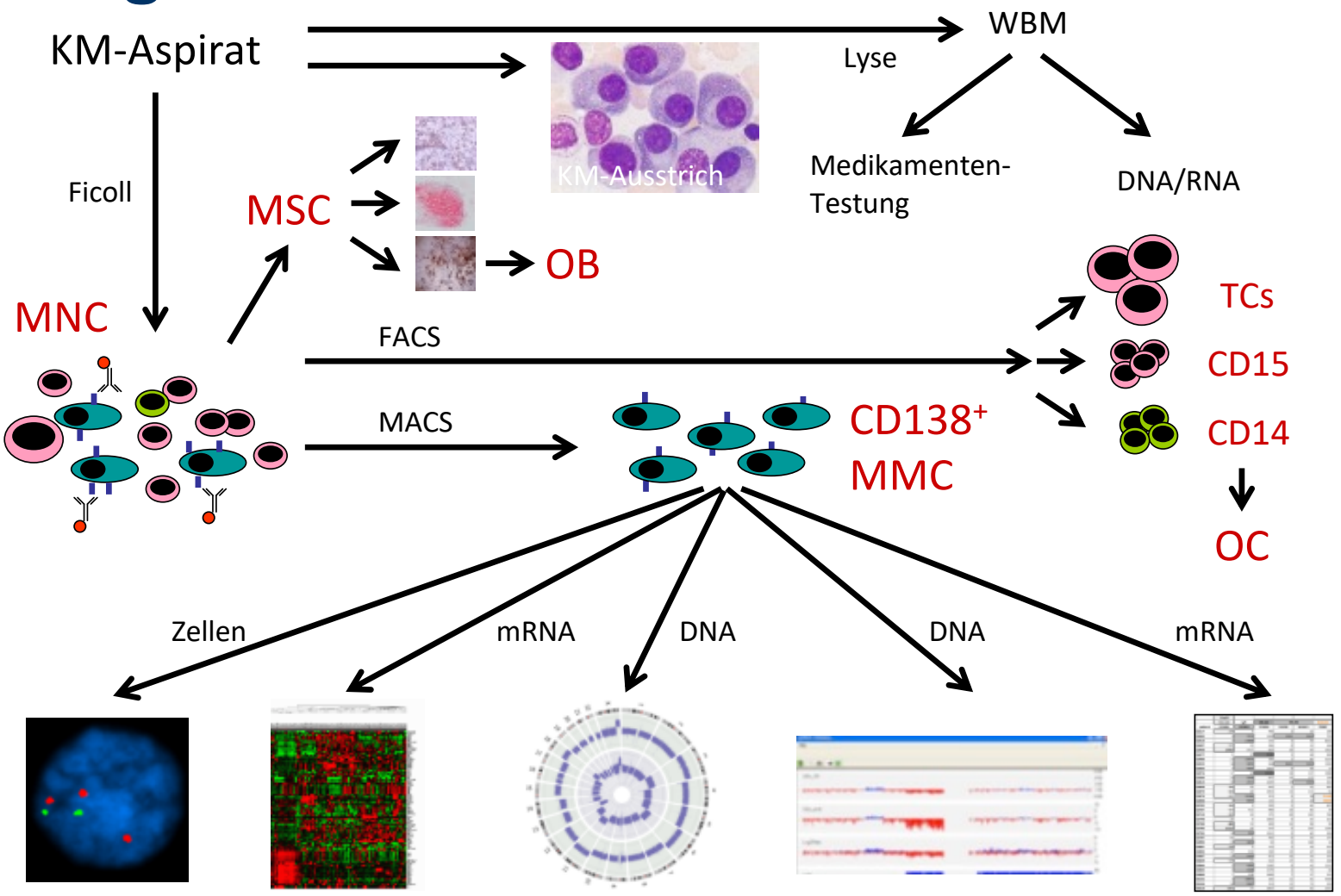


Biopsy	Tumour Genetics Microenvironment					
BM	Immune Phenotype	Immune Phenotype **MRD**	Immune Phenotype **MRD**	Immune Phenotype **MRD**	Immune Phenotype **MRD**	Immune Phenotype **MRD**
BM Sort	MRD ID Tumour Genetics Tumour Heterogeneity Tumour Microenvironment Immune Phenotype Genetic Heterogeneity	Tumour Genetics Tumour Heterogeneity Tumour Microenvironment Immune Phenotype Genetic Heterogeneity	Tumour Genetics Tumour Heterogeneity Tumour Microenvironment Immune Phenotype Genetic Heterogeneity	Tumour Genetics Tumour Heterogeneity Tumour Microenvironment Immune Phenotype Genetic Heterogeneity	Tumour Genetics Tumour Heterogeneity Tumour Microenvironment Immune Phenotype Genetic Heterogeneity	Tumour Genetics Tumour Heterogeneity Tumour Microenvironment Immune Phenotype Genetic Heterogeneity
Focal L.	Tumour Heterogeneity Microenvironment	Tumour Heterogeneity Microenvironment	Tumour Heterogeneity Microenvironment	Tumour Heterogeneity Microenvironment	Tumour Heterogeneity Microenvironment	Tumour Heterogeneity Microenvironment
PB	Tumour Load Peripheral Immune Phenotype	Tumour Load Peripheral Immune Phenotype	Tumour Load Peripheral Immune Phenotype	Tumour Load Peripheral Immune Phenotype	Tumour Load Peripheral Immune Phenotype	Tumour Load Peripheral Immune Phenotype
Serum	Liquid Biopsy Liquid Biopsy Immune Phenotype	Liquid Biopsy Liquid Biopsy Immune Phenotype	Liquid Biopsy Liquid Biopsy Immune Phenotype	Liquid Biopsy Liquid Biopsy Immune Phenotype	Liquid Biopsy Liquid Biopsy Immune Phenotype	Liquid Biopsy Liquid Biopsy Immune Phenotype
Spit	Germline Control					

Flexible Time Points: PD, suspected CR

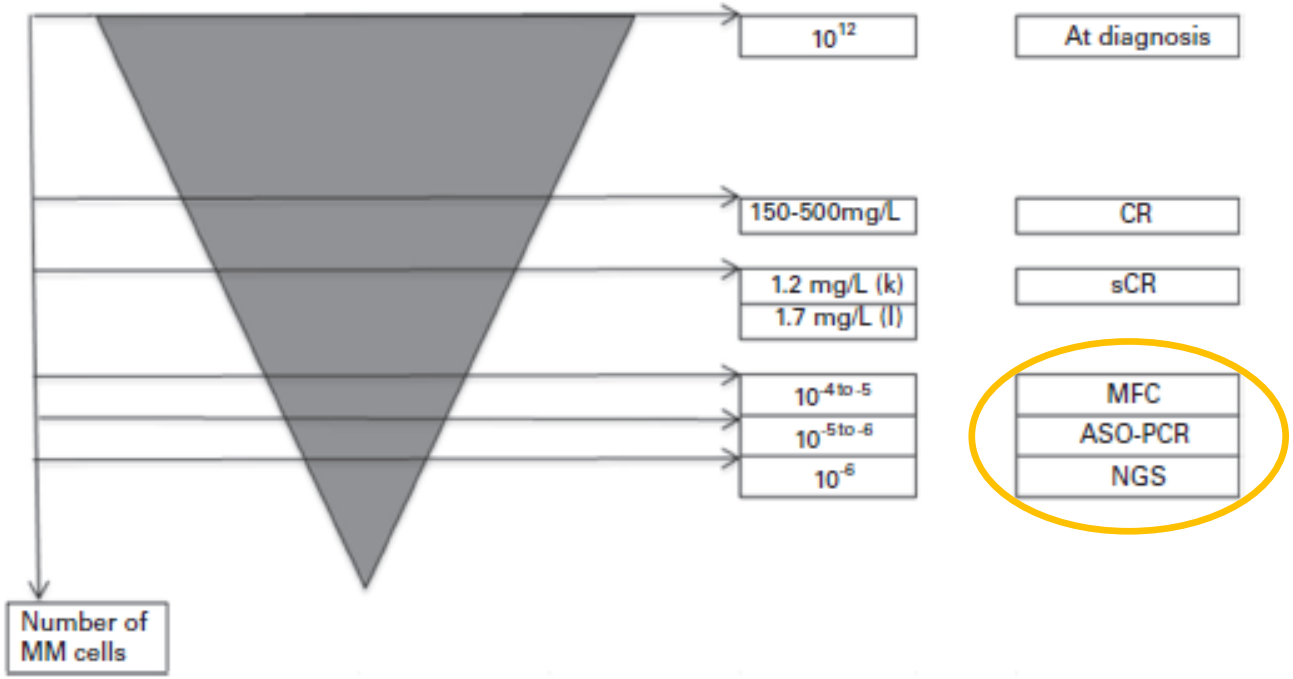
6 Translational Research Activities

MM-Research Lab Heidelberg: Sampling Strategies



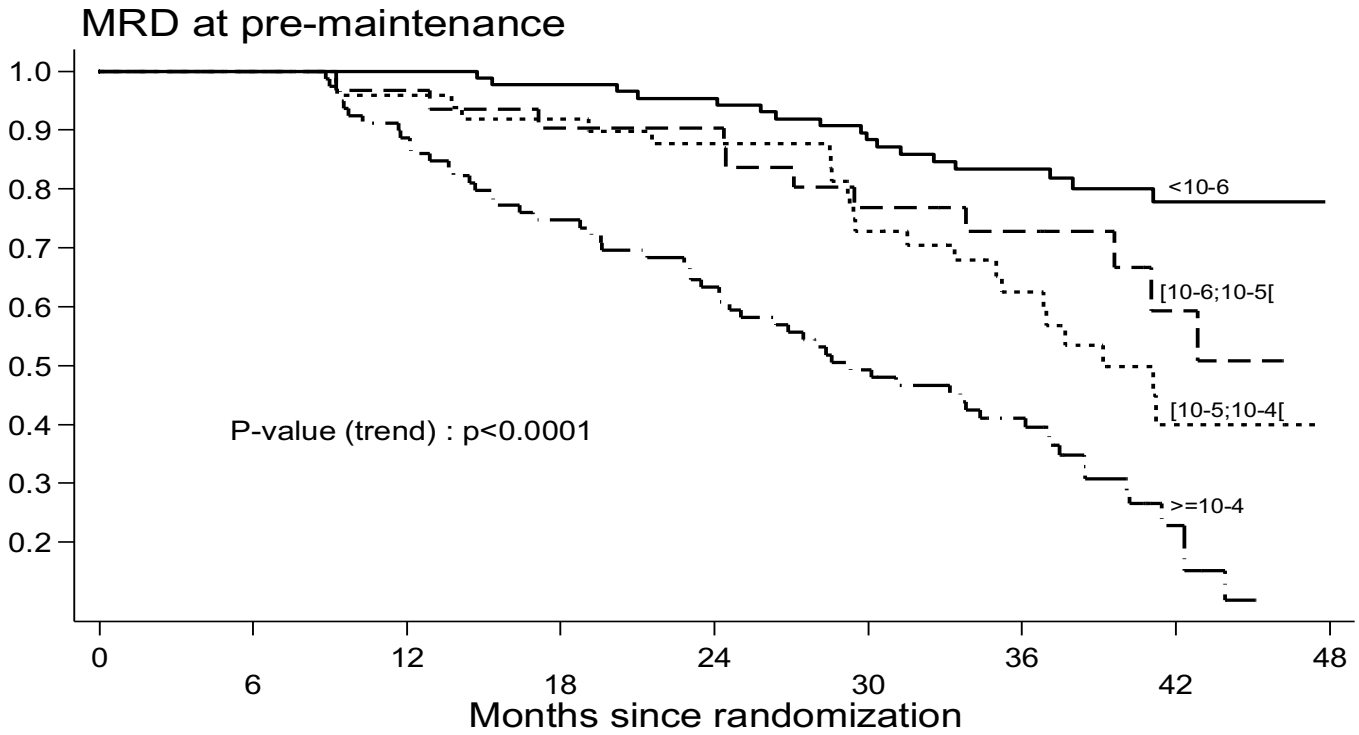
Methods to Measure MRD

- MRD modality and sensitivity of detection
- Increasingly sensitive laboratory techniques



Sherrod et al., BMT, 2015

IFM/DFCI 2009 Trial



N at risk (events)

$<10^{-6}$	87	(0)	87	(0)	87	(2)	85	(2)	83	(6)	74	(4)	54	(3)	31	(0)	8
$[10^{-6};10^{-5}[$	31	(0)	31	(1)	30	(2)	28	(0)	27	(4)	22	(1)	17	(2)	8	(1)	4
$[10^{-5};10^{-4}[$	49	(0)	49	(2)	47	(2)	45	(2)	43	(7)	34	(4)	22	(6)	8	(0)	2
$[10^{-4};10^{-3}[$	79	(0)	79	(9)	70	(11)	59	(9)	50	(11)	38	(6)	28	(9)	6	(3)	0

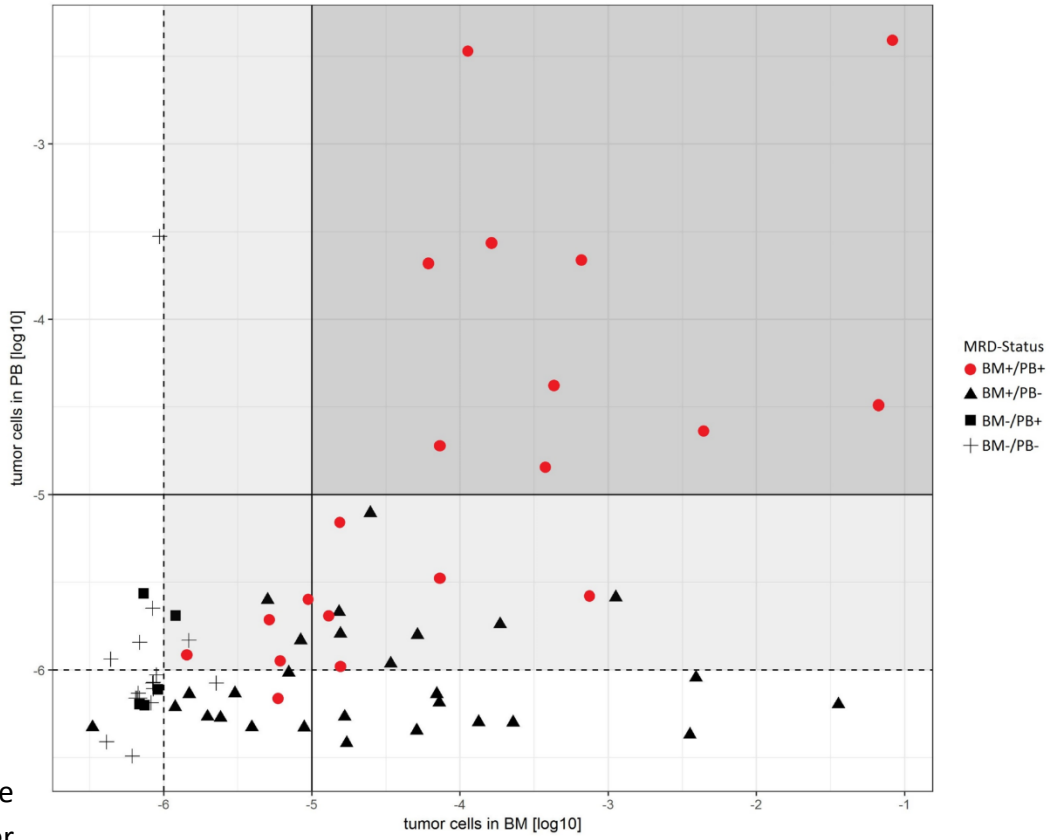
Herve Avet-Loiseau, ASH, 2015

Circulating Tumor Cells as a Surrogate Marker

Results

I. CTCs as surrogate for BM MRD assessment

- Presence of CTCs predicts MRD-positivity in BM with high specificity.



Scatter plot for correlation between the number of tumor cells in BM vs. the number of circulation tumor cells

shades of gray: cut off 10^{-5}, cut off 10^{-6}.

	● BM+/PB+	▲ BM+/PB-	■ BM-/PB+	+ BM-/PB-	N pairs	Sensitivity for MRD+	Specificity for MRD+
Cut off 10^	10	22	0	37	69	31.25%	100%
Cut off 10^	19	19	1	15	54	50.0%	93.75%

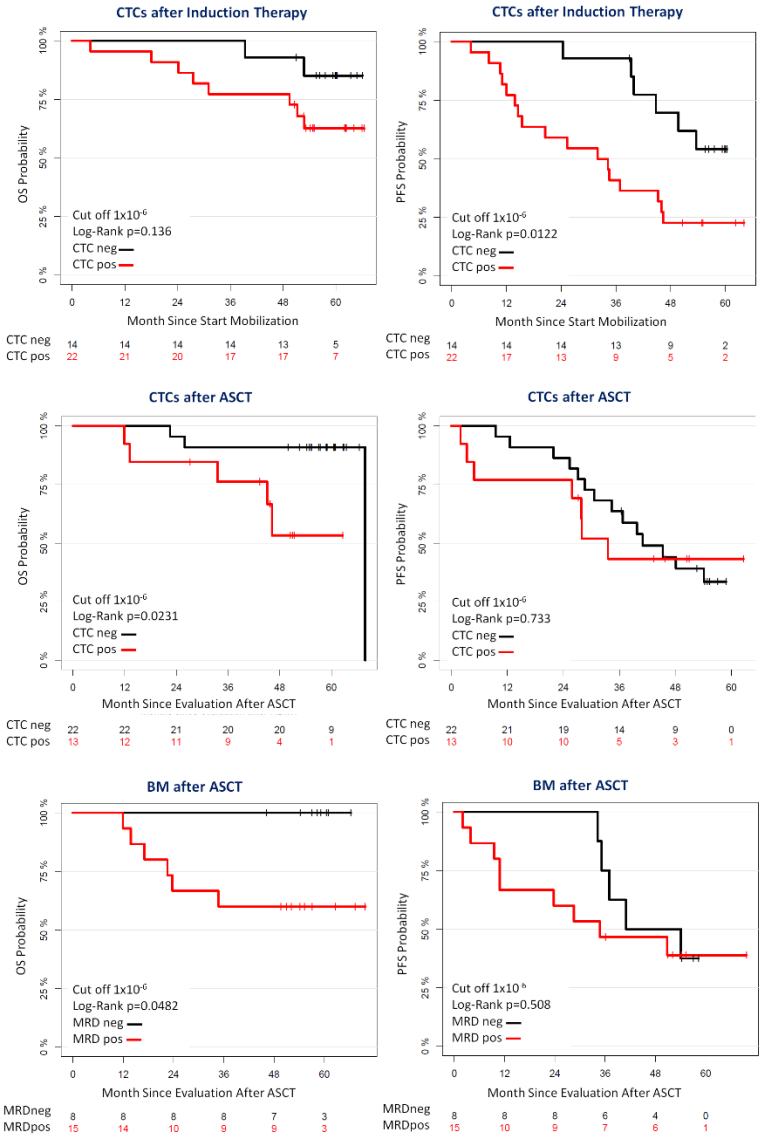
St. Huhn, ASH 2017,Poster Monday, Poster 4359

Circulating Tumor Cells as a Surrogate Marker

Results

II. <u>Prognostic value of CTCs assessment.</u>

- CTCs after IT are associated with poor PFS
- MRD - positivity & CTCs after ASCT are associated with poor OS

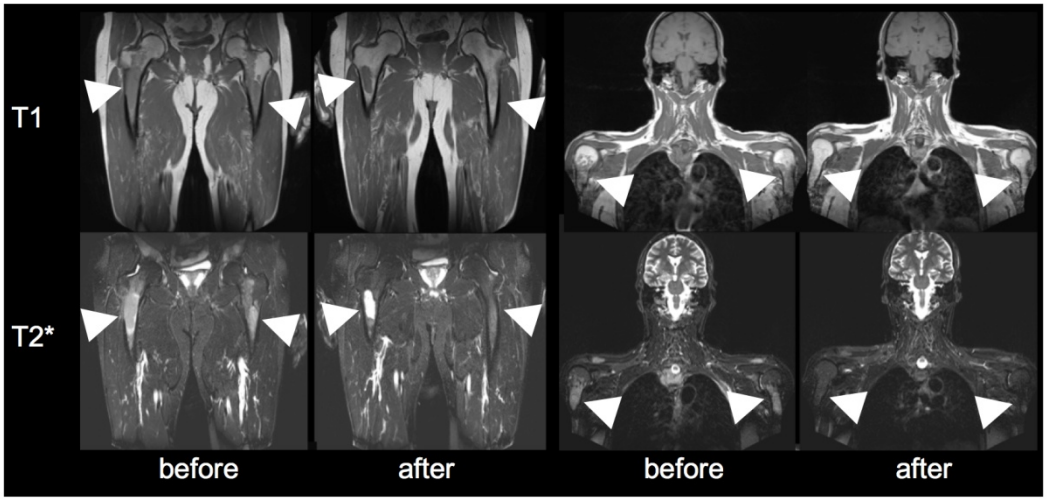


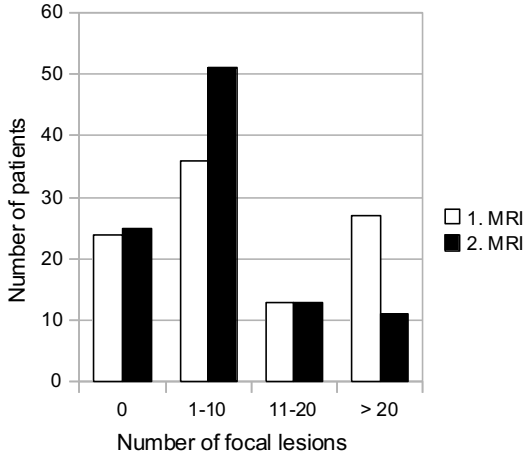
Kaplan-Meier plots and corresponding p-values for CTC/MRD - negativity and OS/PFS.
IT induction therapy, ASCT high dose Melphalan and autologous stem cell transplantation

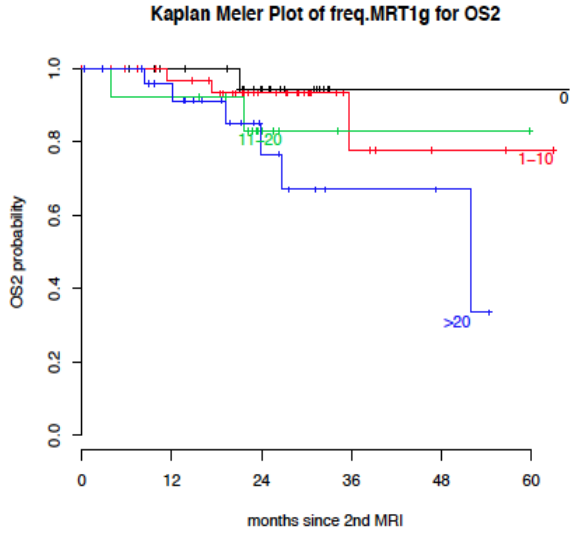
St. Huhn, ASH 2017, Poster Monday, Poster 4359

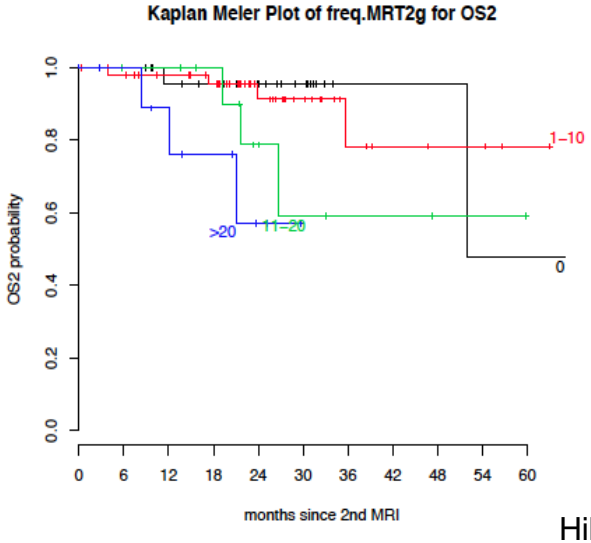
Whole Body - MRI in MM (n=100):

Comparison: Start of Therapy – After ASCT







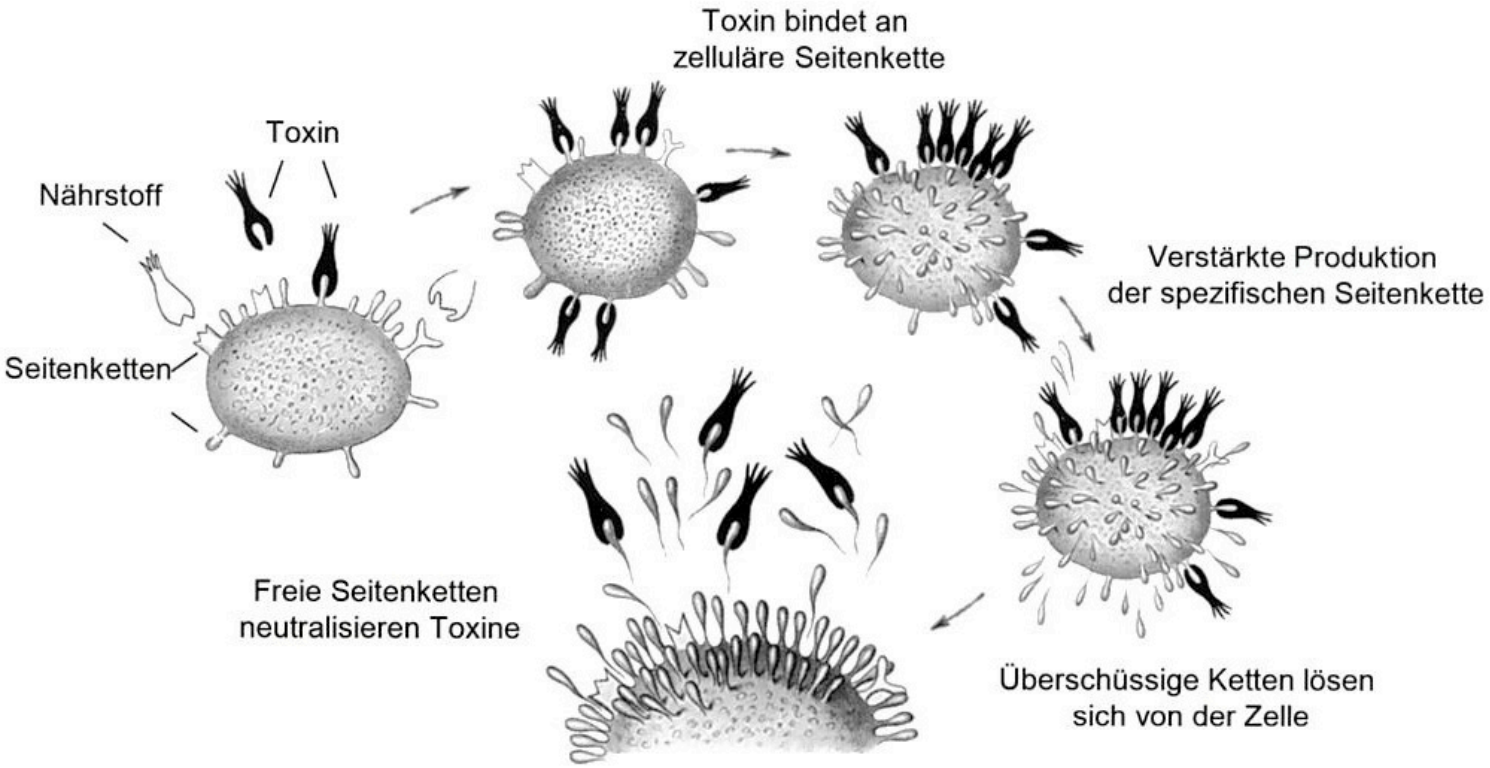


Hillengass et al., Haematolgica 2012

Paul Ehrlich 1854 - 2015

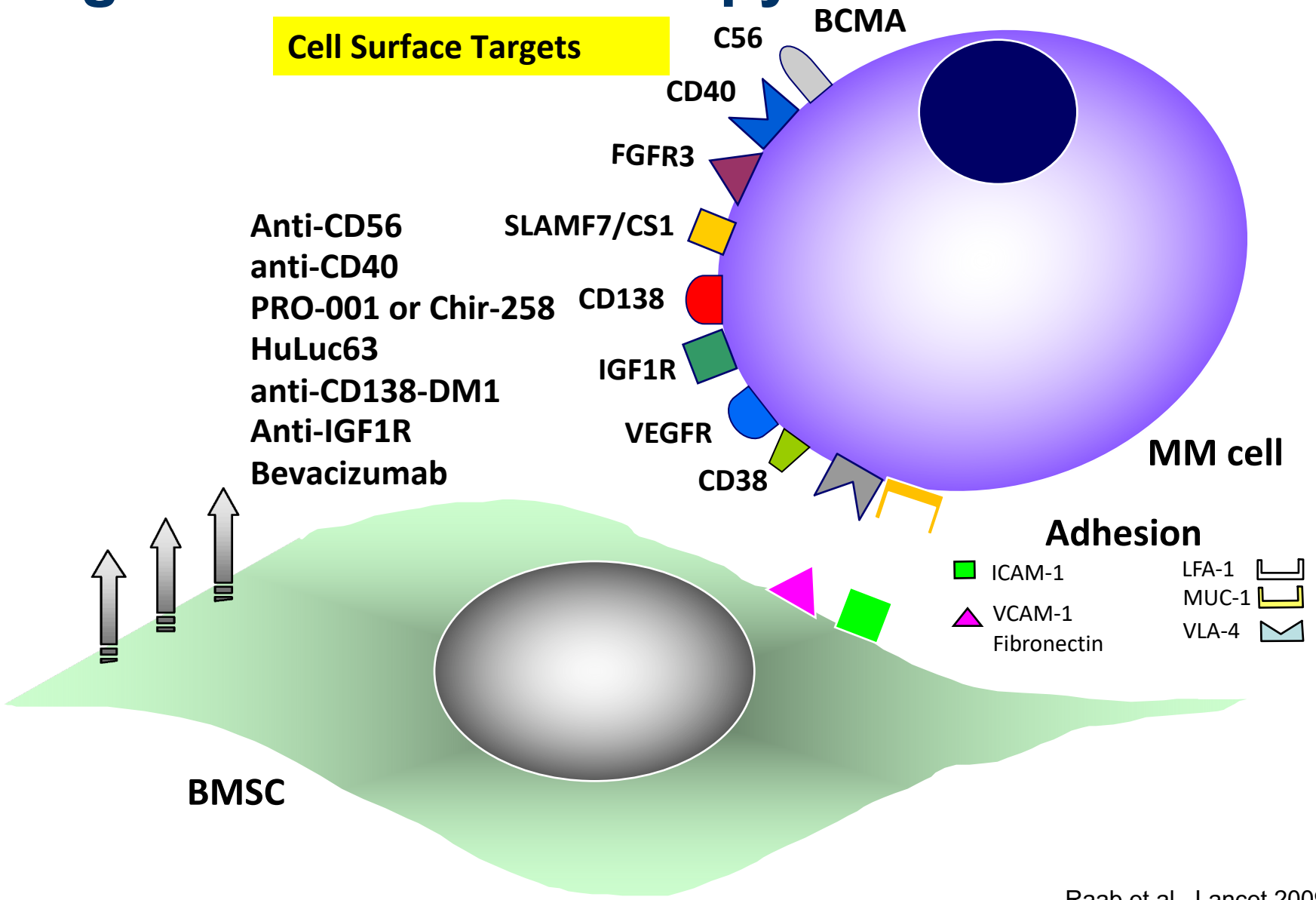
wikipedia

Paul Ehrlich Nobel Prize 1908



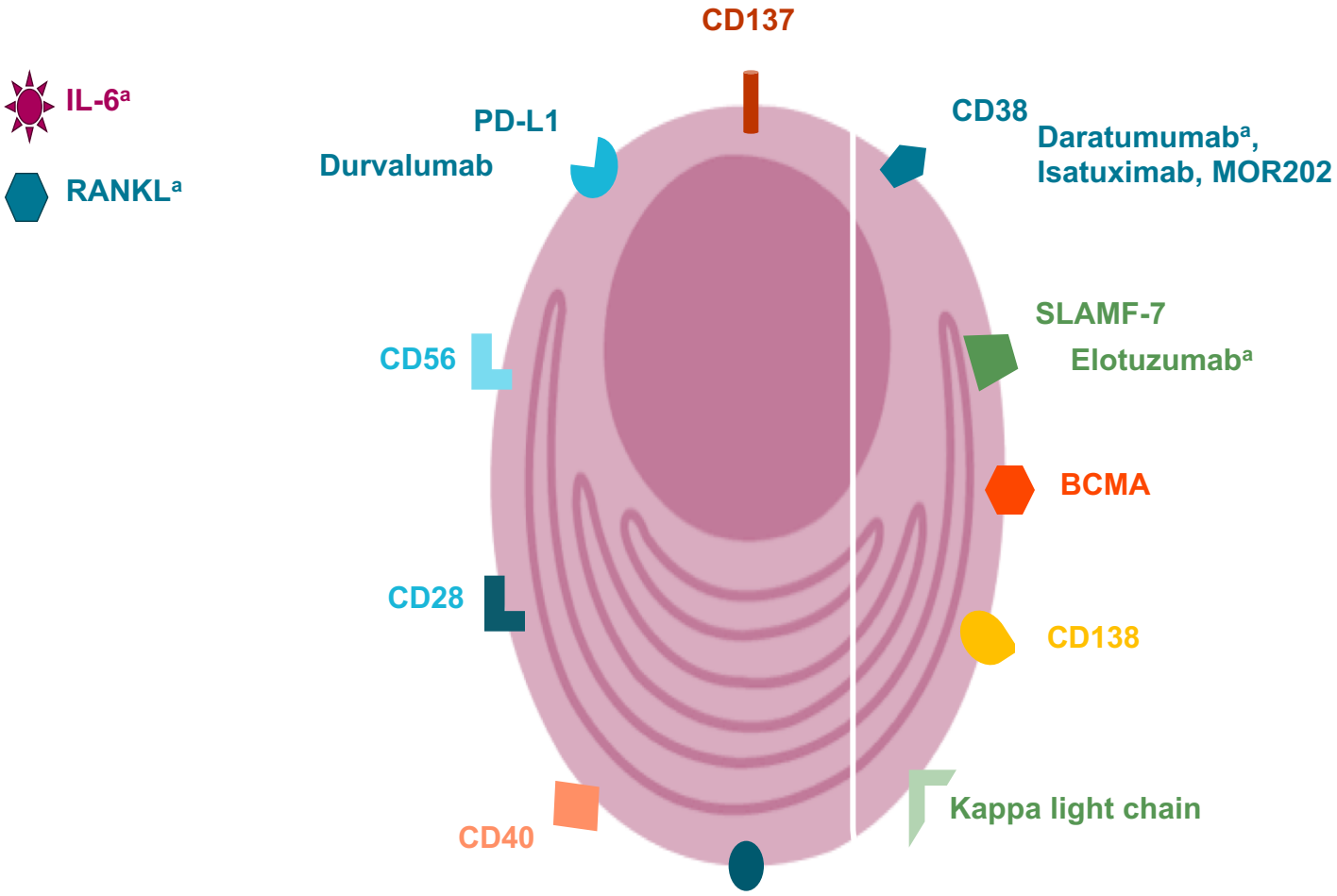
Quelle: Trillium Immunologie 2018; 2(4) – Eine kurze Zeitreise
Von Ehrlichs Seitenkette bis zur Entdeckung der Plasmazelle – Autoren: S.R. Schulz, H-M Jäck, K. Pracht

Targets for MCAB Therapy in MM



Raab et al., Lancet 2009

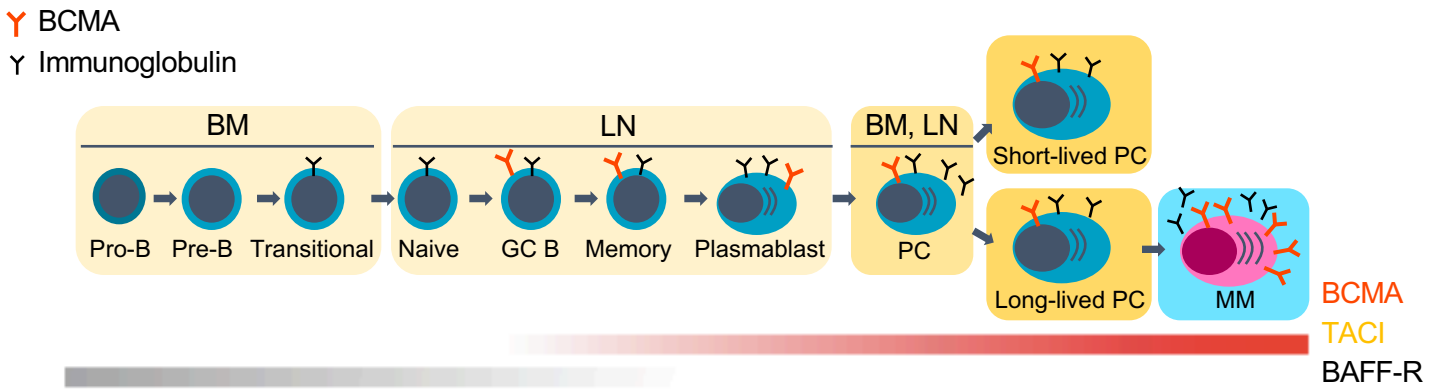
Surface Antigens on Clonal Plasma Cells

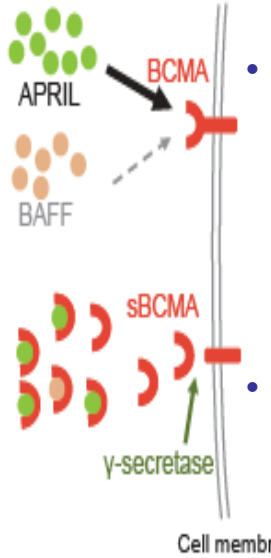


[a] Approved by the FDA and EMA.
BCMA, B-cell maturation antigen; IL-6, interleukin-6; PD-L1, programmed cell death-ligand; RANKL, receptor activator of nuclear factor kappa-B ligand.

Bhatnagar V, et al. Oncologist. 2017;22:1347-53. Gormley NJ, et al. Clin Cancer Res. 2017;23:6759-63.
Jelinek T, et al. Front Immunol. 2018;9:2431. Moreno L, et al. Clin Cancer Res. 2019;25:3176-87.
Raab MS, et al. Blood. 2016;128:1152. Rawstron AC, et al. Haematologica. 2008;93:431-8.

BCMA: A Good Target





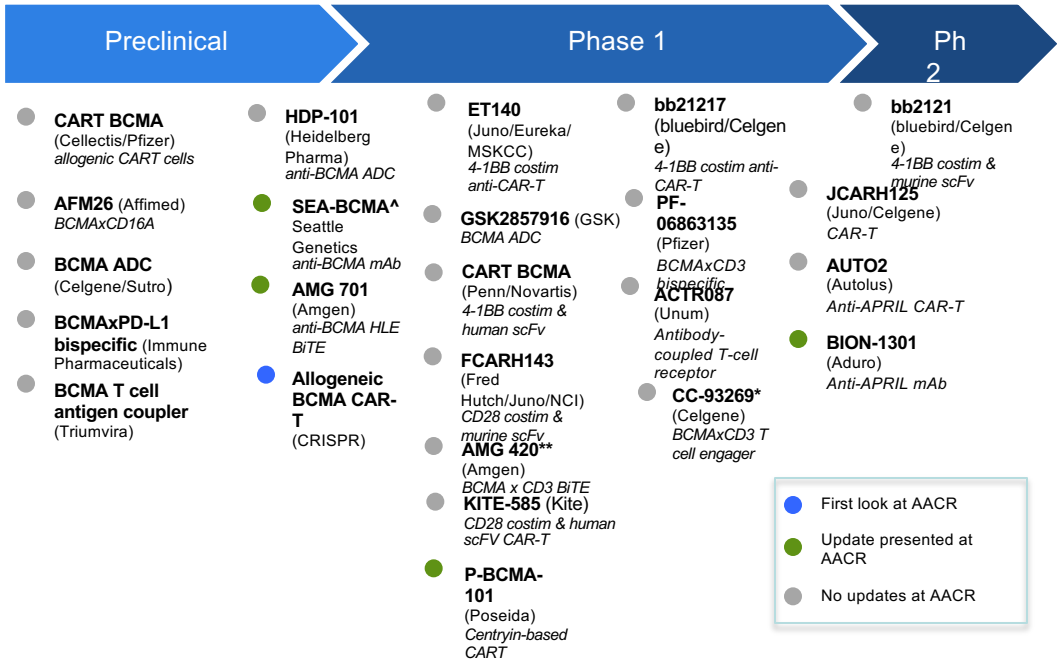
- BCMA is an antigen expressed specifically on PCs and myeloma cells
  - higher expression in myeloma cells than normal PCs
  - key role in B-cell maturation and differentiation
  - promotes myeloma cell growth, chemoresistance, and immunosuppression in the BM microenvironment
- Expression of BCMA increases as the disease progresses from MGUS to advanced myeloma

APRIL, a proliferation-inducing ligand; BAFF-R, B-cell activating factor receptor; GC, germinal centre; LN, lymph node; MGUS, monoclonal gammopathy of unknown significance; sBCMA, soluble BCMA; TACI, transmembrane activator and CAML interactor.

Cho SF, et al. Front Immunol. 2018;9:1821. Moreaux J, et al. Blood. 2004;103:3148-57. Sanchez E, et al. Br J Haematol. 2012;158:727-38.

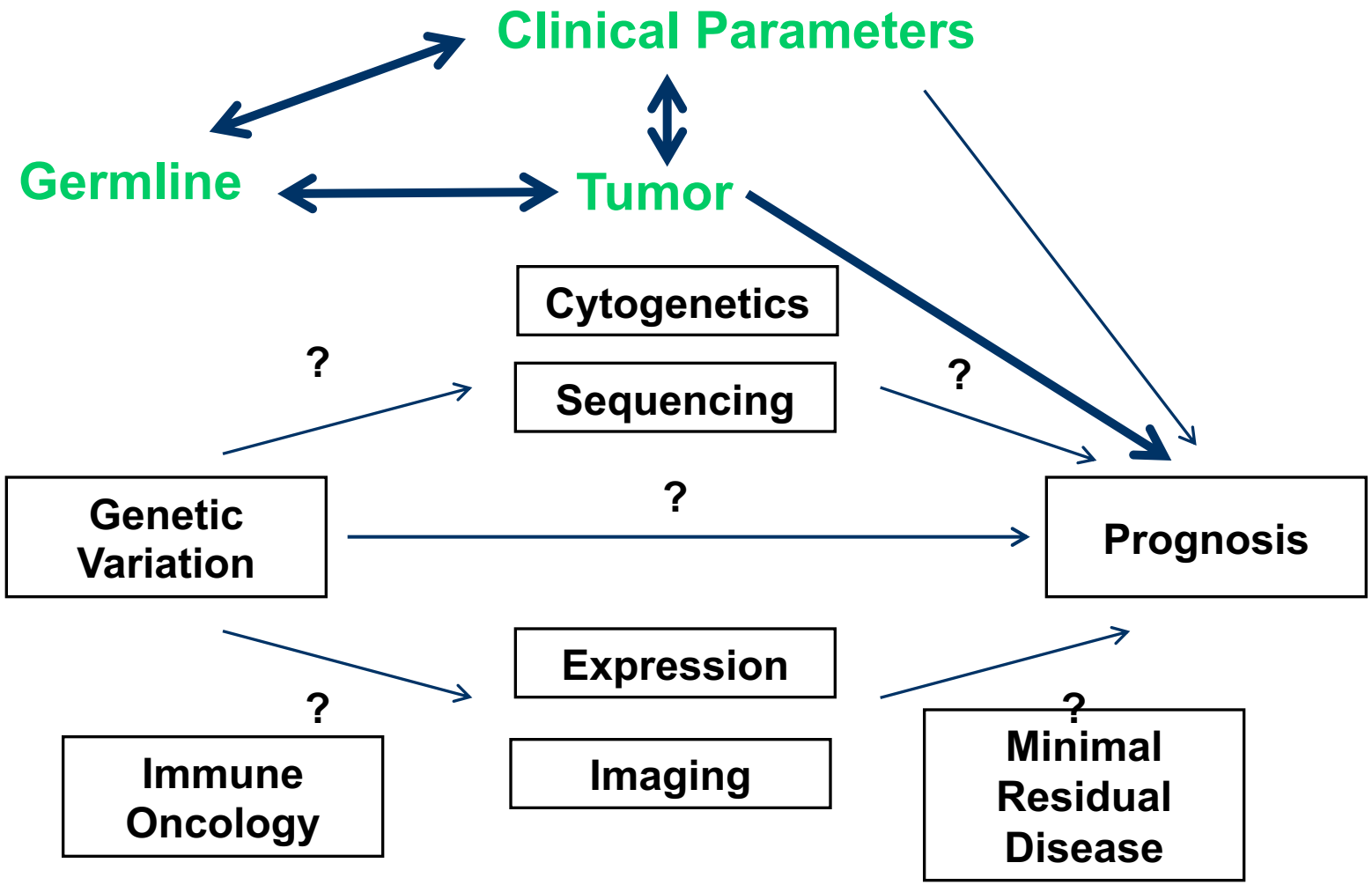
BCMA Key Candidates in Development

Overview about BCMA Trials 5/2018 24 Trials
8/2019 46 Trials

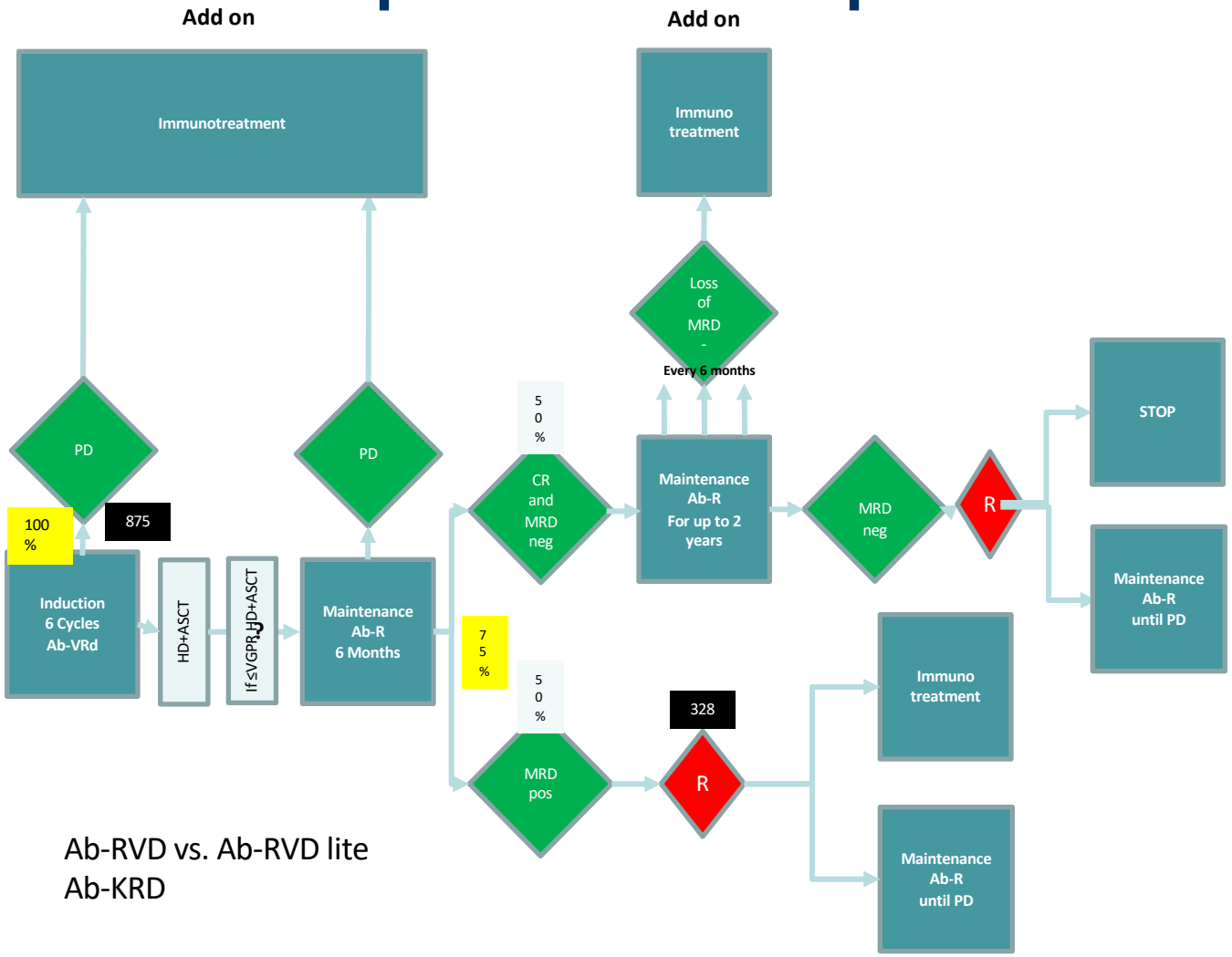


* acquired via EngMab acquisition (formerly called EM901)
** acquired from Boehringer (formerly called BI 836909)
^ Also in development in combination with Unum's ACTR087

Combination of linical Parameters with Omics and Imaging Data => “Systems Medicine”



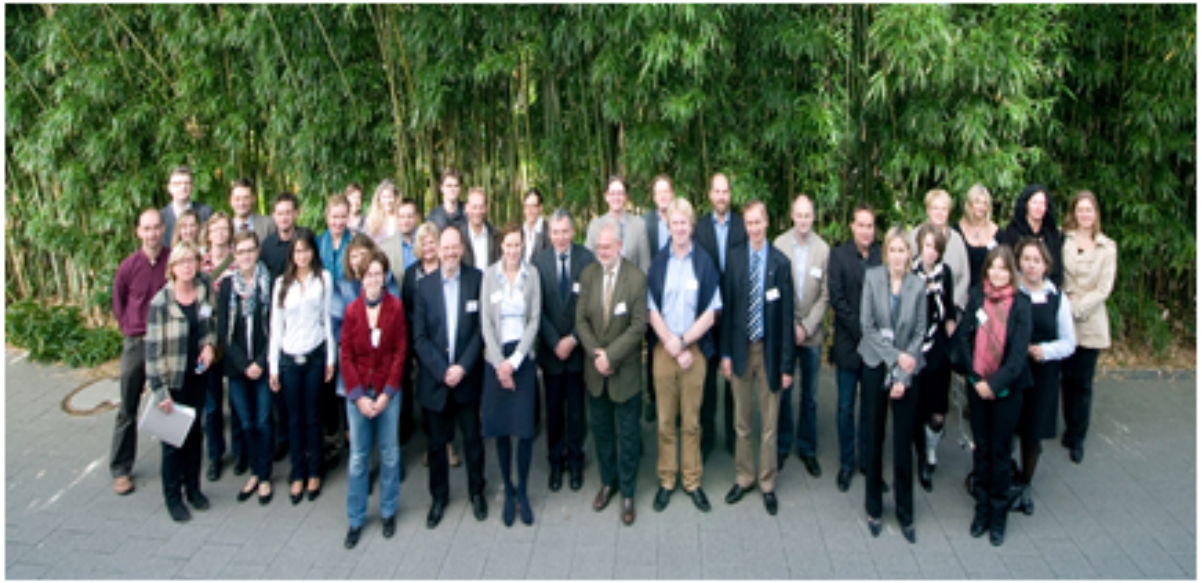
GMMG HD8 Proposal NDMM up to 70 Years



Ab-RVD vs. Ab-RVD lite
Ab-KRD


WORK IN PROGRESS

„Thank You“ to the Heidelberg Myeloma Team and the GMMG Study Group



Thank You for Your Attention