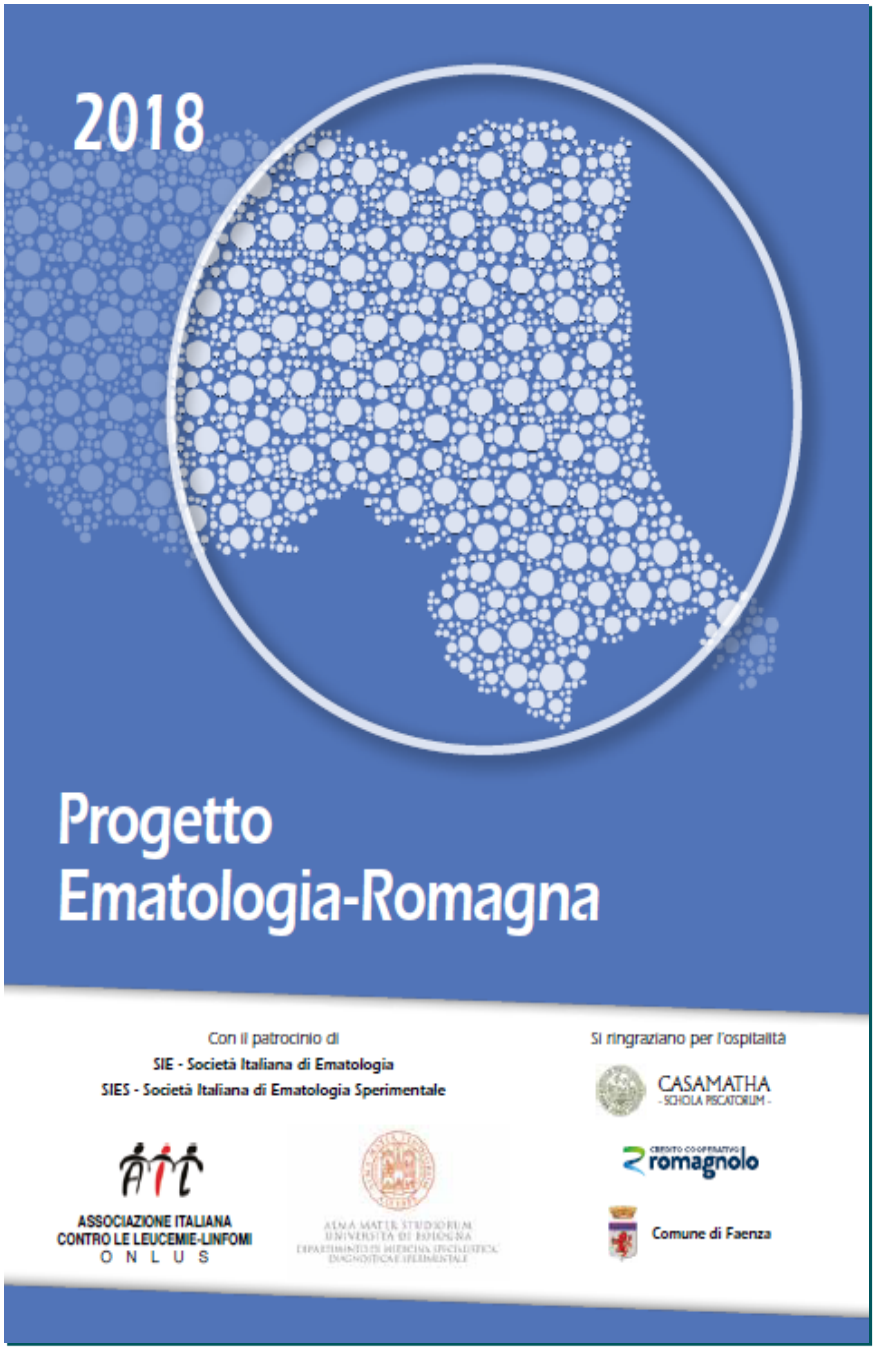

La prognosi del mieloma multiplo oggi: informazioni prognostiche dopo la terapia di induzione

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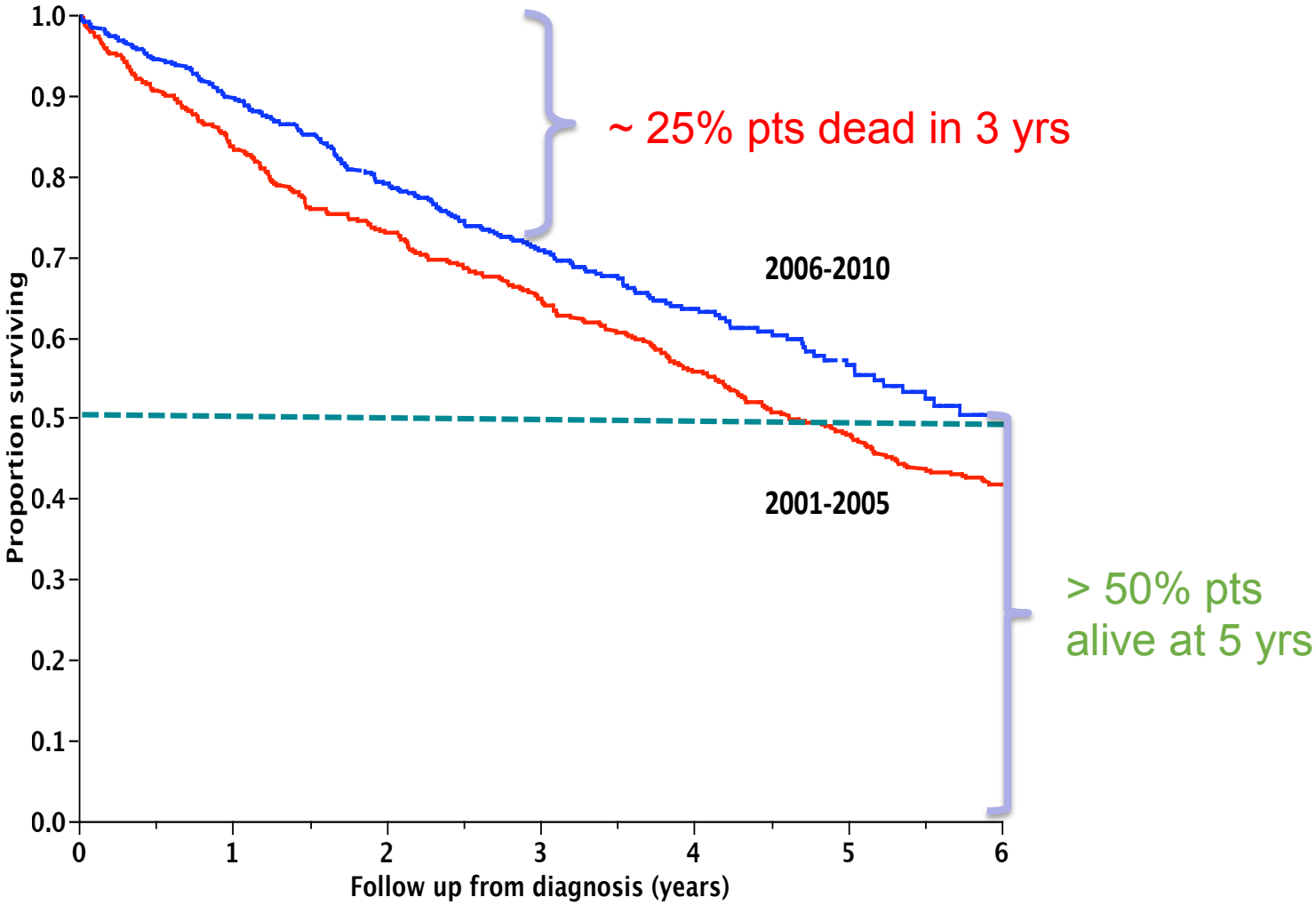
Myeloma Is Not One Disease



Kumar SK, et al. Leukemia. 2014;28:1122-1128

Prognostic factors in MM

Patient-related

- Age
- Performance status, comorbidities

Disease-related

- High β_2 microglobulin
- Low albumin

ISS

Disease burden

- Renal impairment
- LDH above the upper limit

Disease biology

- Cytogenetic abnormalities
- Gene expression profile
- Circulating plasma cells
- Extramedullary disease
- High proliferation rate

At diagnosis

Therapy-related

- **Quality of response**
- **Early relapse**
- **MRD**

Dynamic Model

Why Risk Stratify?

- ***Two important goals***
  - ***Counsel:*** Need to provide pt with realistic expectations based on the currently available treatments
  - ***Therapy:*** Decide if particular therapies can be chosen based on their differential effects on the high-risk and standard-risk disease

Perspectives

blood

Treatment of multiple myeloma with high-risk cytogenetics: a consensus of the International Myeloma Working Group

Consensus statement

- Translocations t(4;14), t(14;16), t(14;20), and del(17/17p) and any nonhyperdiploid karyotype are HR cytogenetics in NDMM regardless of treatment.
- Gain(1q) is associated with del(1p) carrying poor risk.
- Combinations of ≥3CA confer ultra-HR with <2 years survival.
- Routine testing should include t(4;14) and del(17p).
- Clinical classifications may combine these lesions with ISS, serum LDH, or HR gene expression signatures.
- CA may differ in first and later relapse because of clonal evolution, which may influence the effect of salvage treatment.

- **The definition of high-risk is also dynamic, changing over time!**

Sonneveld P, et al. Blood 2016; 127:2955-2962

Perspectives

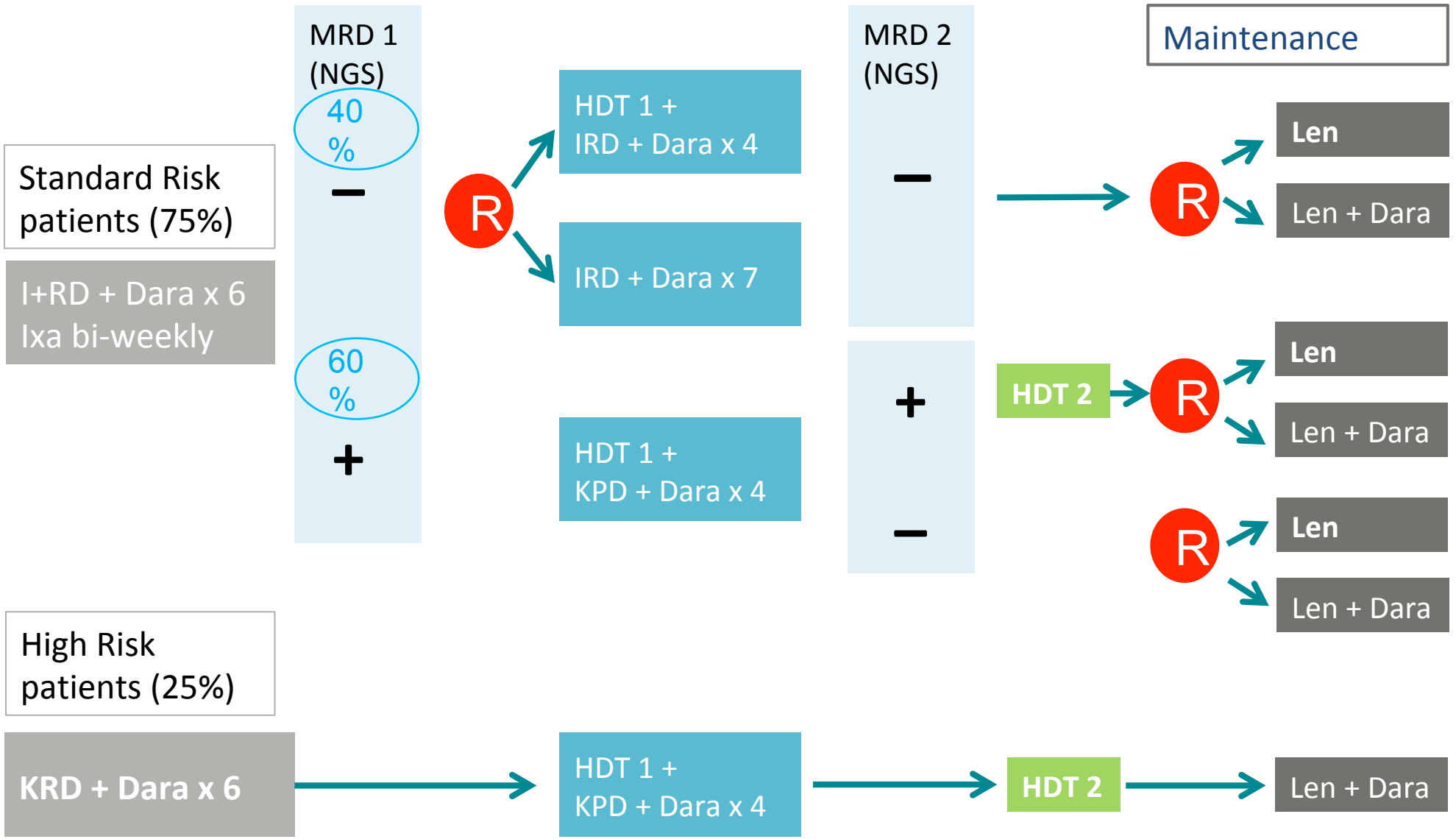
blood

Treatment of multiple myeloma with high-risk cytogenetics: a consensus of the International Myeloma Working Group

- High-risk can refer to many different characteristics and the magnitude of risk can be influenced by different treatmens
- **The short-term goal of therapy is to achieve a rapid and complete response and then to use different treatment strategies to further deepen the level of response and maintain it below the detection level**
- Actual risk-stratification defined by several cooperative groups is not based on prospective randomized trials
- **There is a need of prospective randomized trials which might strongly support choices of therapy in this setting**

Sonneveld P, et al.. Blood 2016; 127:2955-2962

IFM 2019 Project



Courtesy of P. Moreau

Evolvement of Complete Response with effective *novel* treatments

	Alkylators, Steroids HDT/ASCT	Thalidomide Bortezomib Lenalidomide		Carfilzomib Pomalidomide	MoAbs
Year	1998	2006	2011	2013	2015
Response Criteria	EBMT (Blade) [1]	IMWG [2]	IMWGv2 [3]		CR with Moabs4
Depth of response	CR	Stringent CR	MRD Flow CR Molecular CR	Flow CR Molecular CR NGS CR PET/CT	Flow CR NGS CR Imaging CR

Figure 1. In the last two decades, response criteria have changed because novel treatments have improved the quality of response.

Wester R and Sonneveld P Haematologica 2016;101(5):518-20.

IMWG MRD criteria


International Myeloma Working Group consensus criteria for response and minimal residual disease assessment in multiple myeloma

Shaji Kumar, Bruno Paiva, Kenneth C Anderson, Brian Durie, Ola Landgren, Philippe Moreau, Nikhil Munshi, Sagar Lonial, Joan Bladé, Maria-Victoria Mateos, Meletios Dimopoulos, Efstathios Kastritis, Mario Boccadoro, Robert Orlowski, Hartmut Goldschmidt, Andrew Spencer, Jian Hou, Wee Joo Chng, Saad Z Usmani, Elena Zamagni, Kazuyuki Shimizu, Sundar Jagannath, Hans E Johnsen, Evangelos Terpos, Anthony Reiman, Robert A Kyle, Pieter Sonneveld, Paul G Richardson, Philip McCarthy, Heinz Ludwig, Wenming Chen, Michele Cavo, Jean-Luc Harousseau, Suzanne Lentzsch, Jens Hillengass, Antonio Palumbo, Alberto Orfao, S Vincent Rajkumar, Jesus San Miguel, Herve Avet-Loiseau

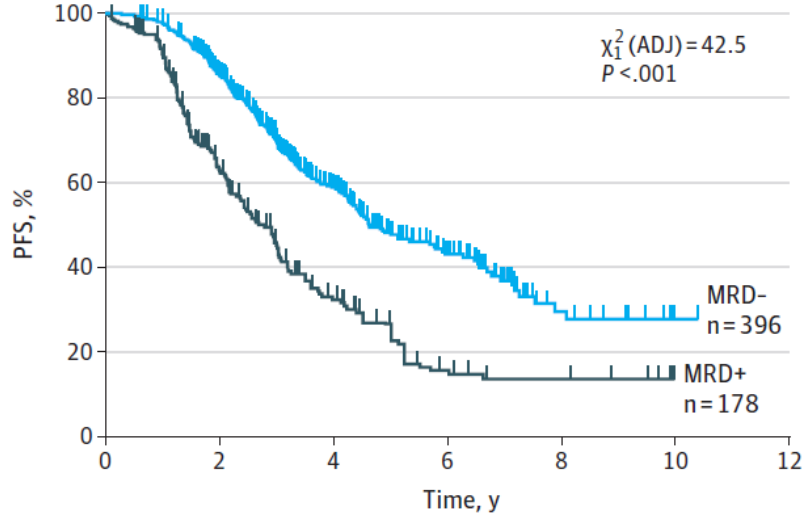
IMWG MRD negativity criteria (requires a complete response)

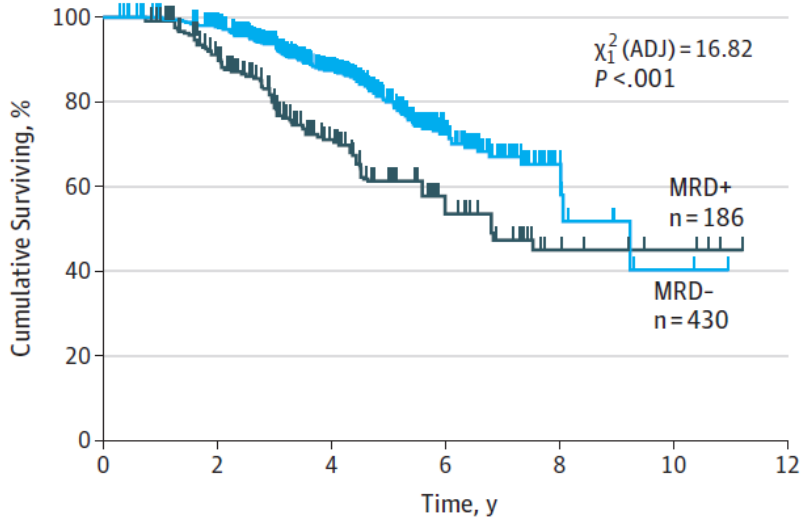
Response SubCategory	Response Criteria
Sustained MRD-negative	MRD negativity **in the marrow** (NGF or NGS, or both) **and** by **imaging** as defined below, **confirmed minimum of 1 year apart**. Subsequent evaluations can be used to further specify the duration of negativity (eg, **MRD-negative at 5 years**)†
Flow MRD-negative	Absence of phenotypically aberrant clonal plasma cells by NGF‡ on bone marrow aspirates using the EuroFlow standard operation procedure for MRD detection in multiple myeloma (or validated equivalent method) with a **minimum sensitivity** of **1 in 10^5** nucleated cells or higher
Sequencing MRD-negative	Absence of clonal plasma cells by NGS on bone marrow aspirate in which presence of a clone is defined as less than two identical sequencing reads obtained after DNA sequencing of bone marrow aspirates using the LymphoSIGHT platform (or validated equivalent method) with a **minimum sensitivity** of **1 in 10^5** nucleated cells§ or higher
Imaging positive MRD-negative	MRD negativity as defined by NGF or NGS plus disappearance of every area of increased tracer uptake found at baseline or a preceding PET/CT or decrease to less mediastinal blood pool SUV or decrease to less than that of surrounding normal tissue

Kumar SK, et al. Lancet Oncology 2016;17(8):e328-e346

Depth of response correlate with survival

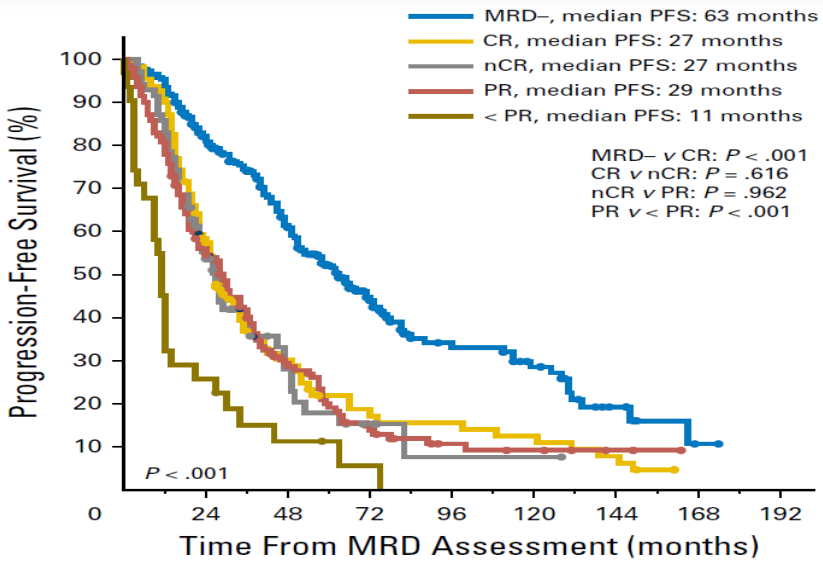
MRD is the best biomarker to predict outcome

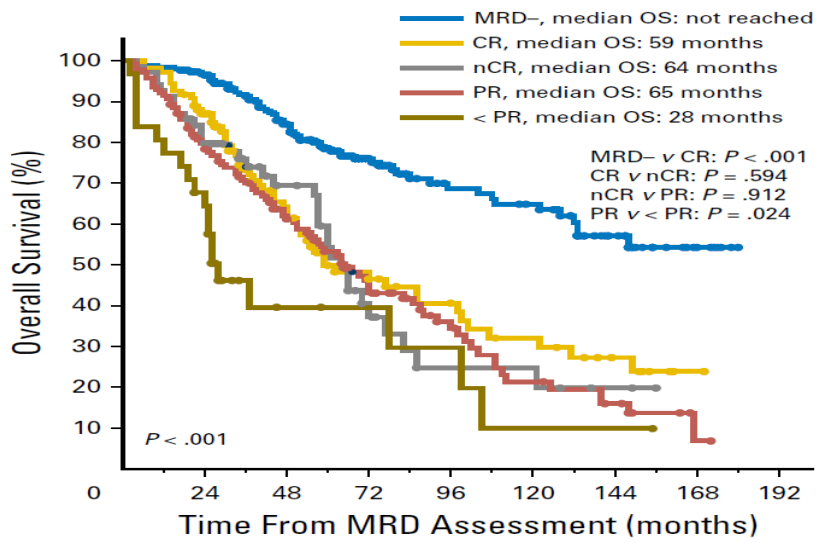




Meta-analysis of MRD studies (CR patients)

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





GEM2000 - GEM2005MENOS65 - GEM2010MAS65

Lahuerta JJ, et al. JCO 2017;35(25):2900-2910

Going beyond the CR criteria with MRD monitoring

< 5% PCs in bone marrow	Negative IFE of serum and urine	Disappearance of soft tissue plasmacytomas

Cellular clonality

- Immunohistochemistry
- ASO-PCR
- **NGS**
- **Flow cytometry (NGF**)

Cellular production

- sFLC
- **Hevylite**
- Isotype specific LC-MS/MS

Cellular dissemination

- **PET/CT**
- **DWI-DCE WB-MRI**

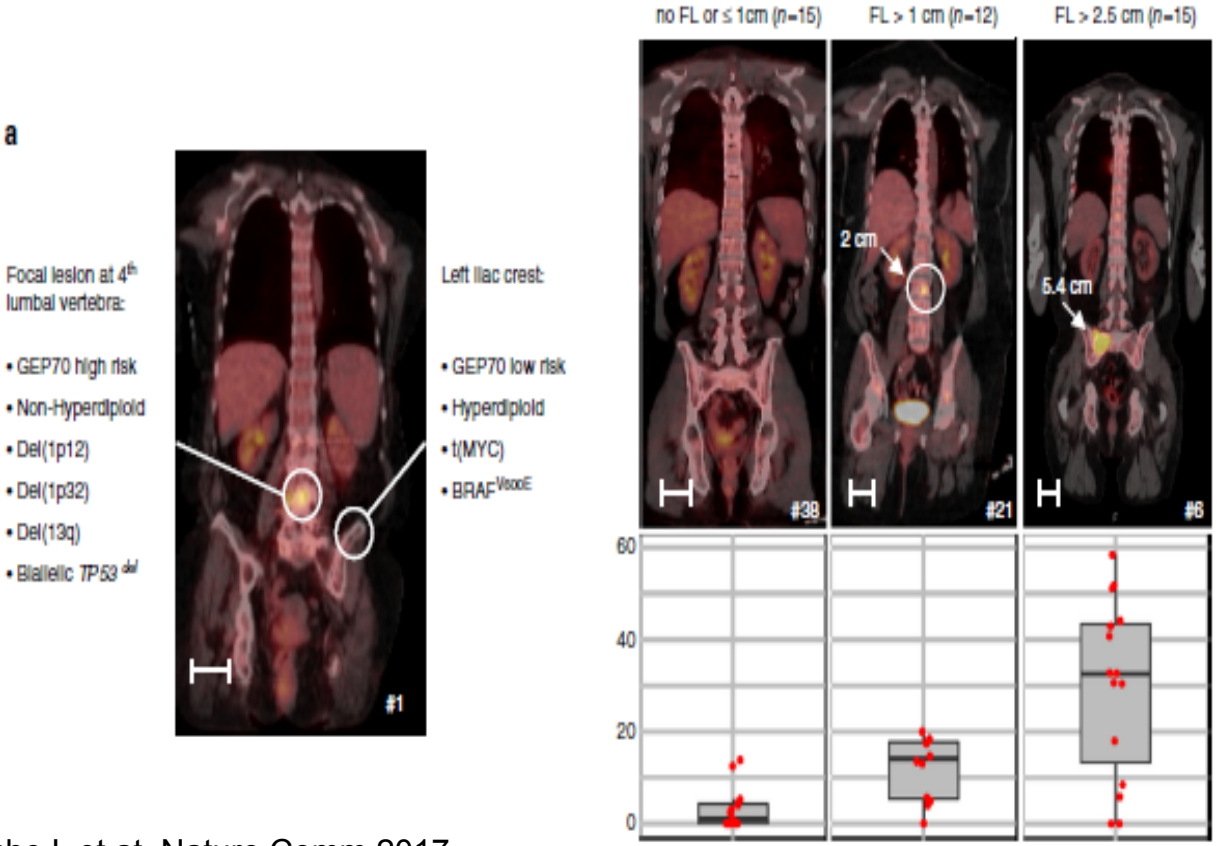
nature COMMUNICATIONS

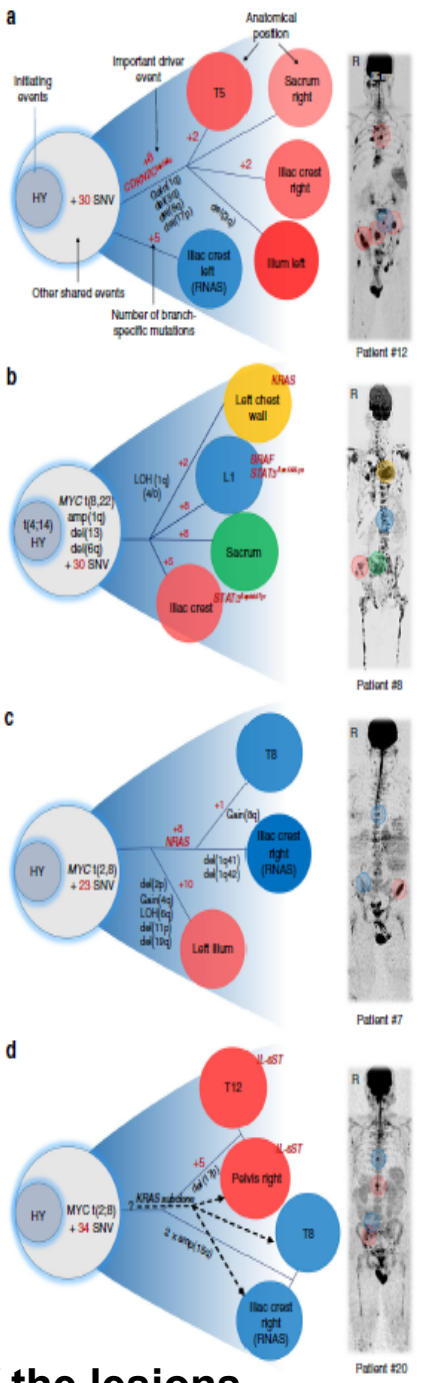
ARTICLE

DOI: 10.1038/s41467-017-00296-y OPEN

Spatial genomic heterogeneity in multiple myeloma revealed by multi-region sequencing

L. Rasche[1], S.S. Chavan[1], O.W. Stephens[1], P.H. Patel[1], R. Tytarenko[1], C. Ashby[1], M. Bauer[1], C. Stein[1], S. Deshpande[1], C. Wardell[1], T. Buzder[1], G. Molnar[1], M. Zangari[1], F. van Rhee[1], S. Thanendrarajan[1], C. Schinke[1], J. Epstein[1], F.E. Davies[1], B.A. Walker[1], T. Meissner[2], B. Barlogie[1], G.J. Morgan[1] & N. Weinhold[1]





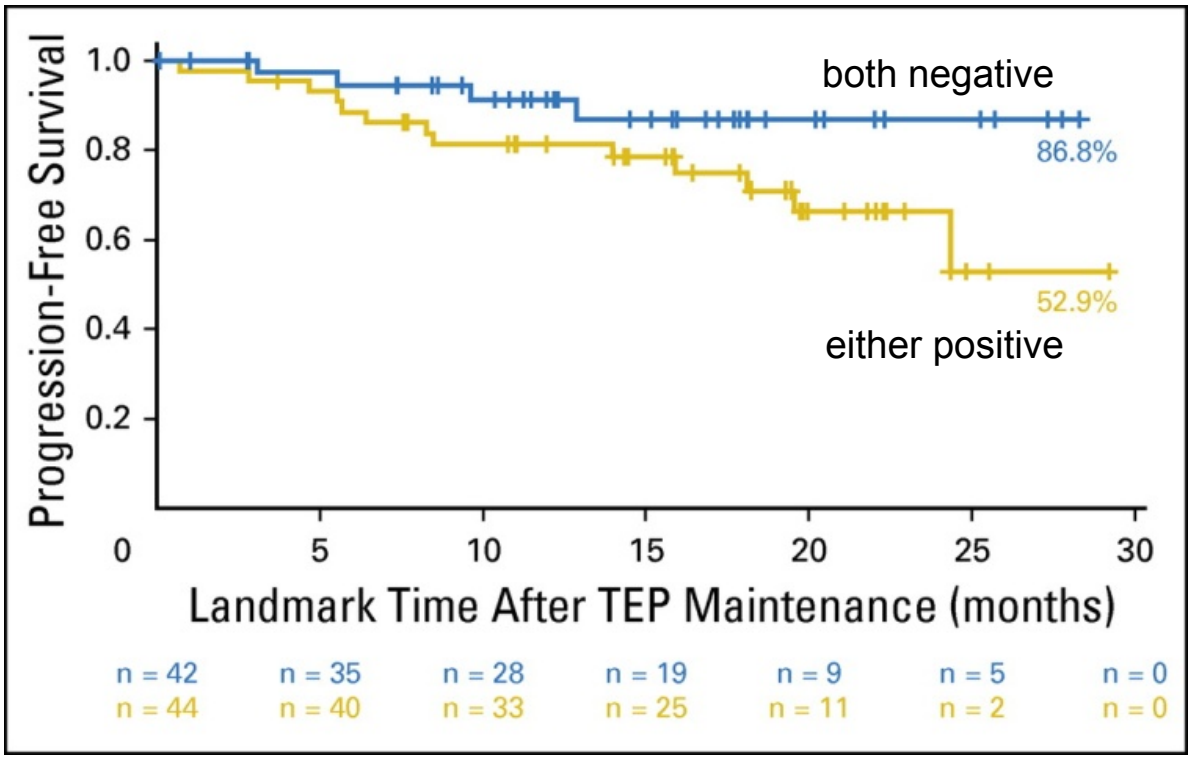
Rasche L et at, Nature Comm 2017
*Rasche L et al, Blood 2018

Growing heterogeneity with growing size of the lesions

Looking for MRD(s) in MM

COMPLEMENTARITY BETWEEN IMAGING AND BM MRD

PET/CT and FLOW MONITORING BEFORE MAINTENANCE

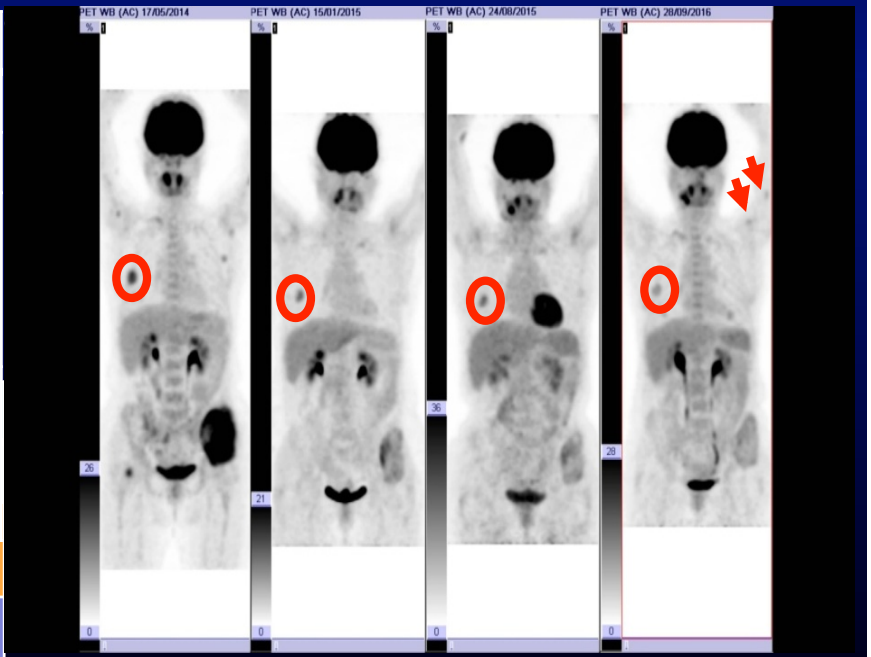


- 86/134 evaluated by both PET/CT and flow
- 47,7% both negative

Moreau P. et al, JCO 2017

- Who are the patients at risk of persistence of disease metabolism in FLs (imaging MRD positivity)?
  - Those with EMD at diagnosis
  - Those with para-skeletal disease

Patient	359	454	502	635	751	767
Diagnosis						
ISS	III	III	I	III	I	I
FISH	1q+(59 %)	del17p(22 %)	1q+(50 %) & 1p-(61%)	1q+(85%) & 1p-(89%)	NE	-
Bone-related plasmacytomas	+	+	+	+	NE	+
10^{-6})	neg	neg	neg	neg	neg	neg
Bone-related plasmacytomas	+	+	+	+	NE	+



Paiva B et al, presented at ASH 2017

Role of ^{18}F-FDG PET/CT in the diagnosis and management of multiple myeloma and other plasma cell disorders: a consensus statement by the International Myeloma Working Group

Michele Cavo, Evangelos Terpos, Cristina Nanni, Philippe Moreau, Suzanne Lentzsch, Sonja Zweegman, Jens Hillengass, Monika Engelhardt, Saad Z Usmani, David H Vesole, Jesus San-Miguel, Shaji K Kumar, Paul G Richardson, Joseph R Mikhael, Fernando Leal da Costa, Meletios-Athanassios Dimopoulos, Chiara Zingaretti, Niels Abildgaard, Hartmut Goldschmidt, Robert Z Orlowski, Wee Joo Chng, Hermann Einsele, Sagar Lonial, Bart Barlogie, Kenneth C Anderson, S Vincent Rajkumar, Brian G M Durie, Elena Zamagni

Table 6: Recommendations for use of 18F-FDG PET/CT in MM

Recommendation	Grade
Active MM:	
18F-FDG PET/CT can be considered as part of the initial workup in patients with newly diagnosed MM since it provides information useful for prognostication and allows to more carefully assess the bulk of the disease, particularly in patients with extramedullary sites of the disease. This latter indication for use of 18F-FDG PET/CT applies also to patients with relapsed/refractory MM	B
In newly diagnosed MM, EMD and >3 FLs on 18F-FDG PET/CT identify subgroups of patients with unfavorable outcomes, particularly those who are candidates to receive upfront ASCT. Controversies exist about the prognostic role of SUV_{max}	B
18F-FDG PET/CT is by now the preferred technique for evaluating and monitoring response to therapy. Metabolic changes assessed by 18F-FDG PET/CT provide an earlier evaluation of response compared to MRI	A
18F-FDG PET/CT should be coupled with sensitive bone marrow-based assays as part of MRD detection inside and outside the bone marrow	B

Cavo M. et al, Lancet Oncology 2017

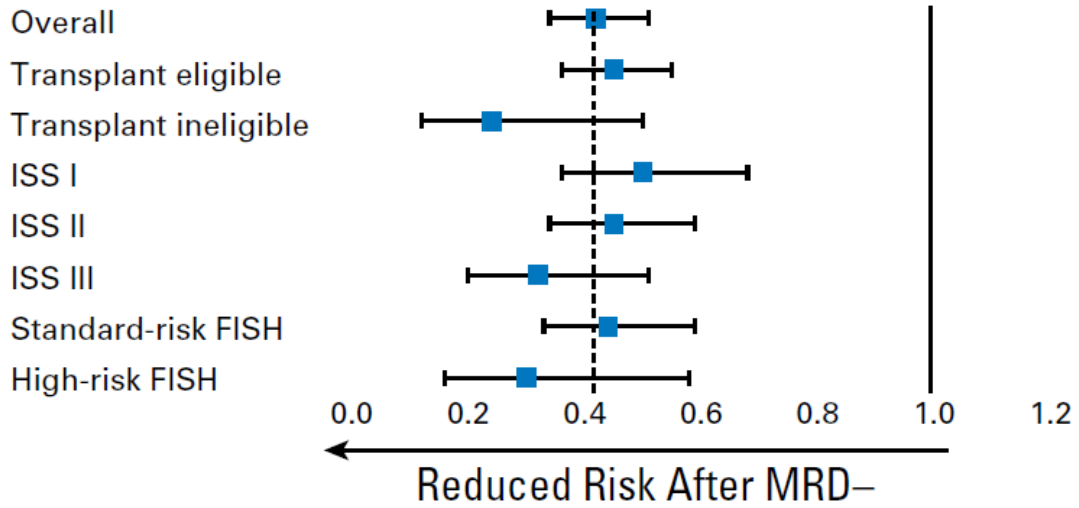
Implications of biology for treatment: how to achieve and maintain MRD

- ✓ **Minor drug-resistant clones lethal**
  - **Complete response/MRD** is required
- ✓ **Multiple clones with variable drug sensitivity**
  - **Combination** chemotherapy a necessity
- ✓ **Resuscitation of drug-sensitive clones**
  - Once resistant, not always resistant
  - Continuous suppressive therapy logical: **maintenance** therapy

Keats JJ, et al. Blood 2012;120(5):1067-1076

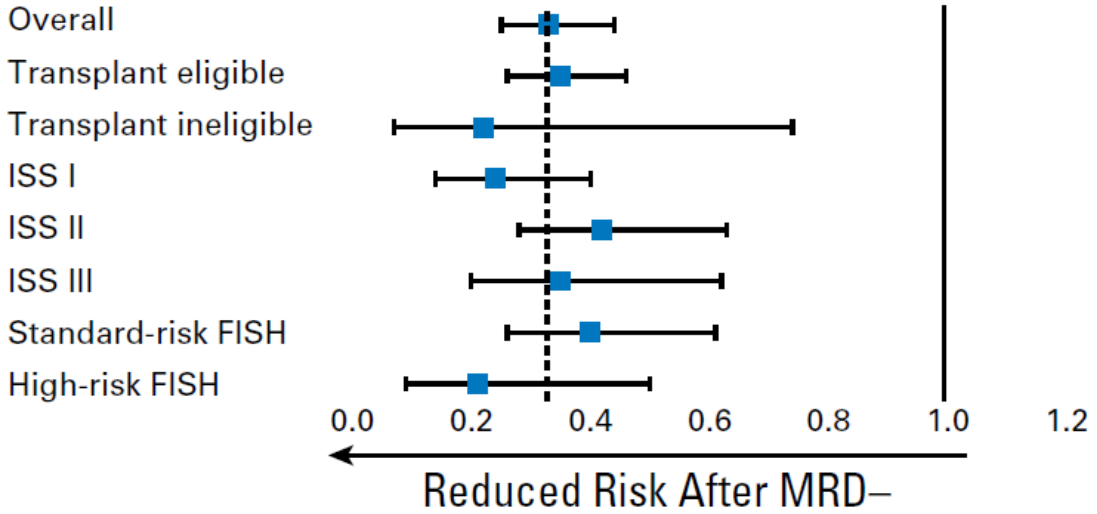
MRD negativity is a prognostic marker for PFS and OS across the spectrum of patients with MM

PFS



	HR	95% CI	*P*
Overall	0.42	0.34 to 0.51	< .001
Transplant eligible	0.45	0.36 to 0.55	< .001
Transplant ineligible	0.24	0.12 to 0.50	< .001
ISS I	0.50	0.36 to 0.68	< .001
ISS II	0.45	0.34 to 0.59	< .001
ISS III	0.32	0.20 to 0.51	< .001
Standard-risk FISH	0.44	0.33 to 0.59	< .001
High-risk FISH	0.30	0.16 to 0,58	< .001

OS

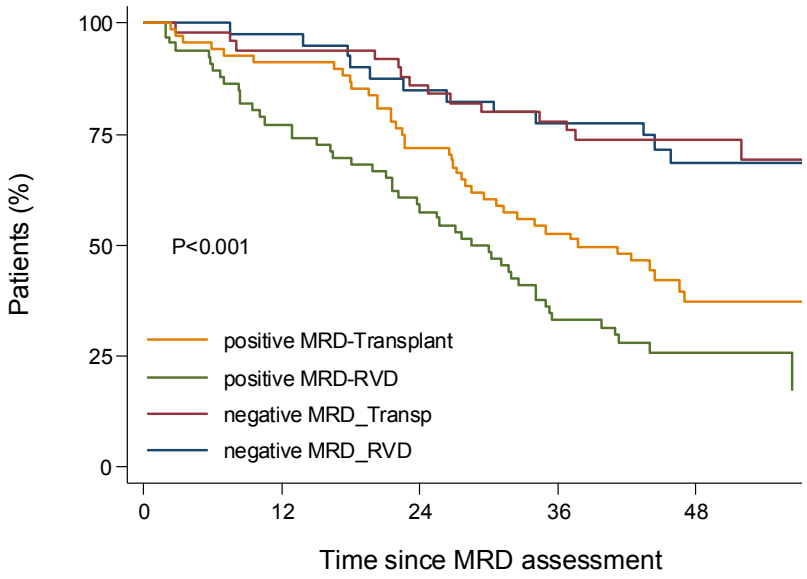


	HR	95% CI	*P*
Overall	0.33	0.25 to 0.44	< .001
Transplant eligible	0.35	0.26 to 0.46	< .001
Transplant ineligible	0.22	0.07 to 0.74	.014
ISS I	0.24	0.14 to 0.40	< .001
ISS II	0.42	0.28 to 0.63	< .001
ISS III	0.35	0.20 to 0.62	< .001
Standard-risk FISH	0.40	0.26 to 0.61	< .001
High-risk FISH	0.21	0.09 to 0.50	< .001

Lahuerta JJ, et al. JCO 2017;35(25):2900-2910

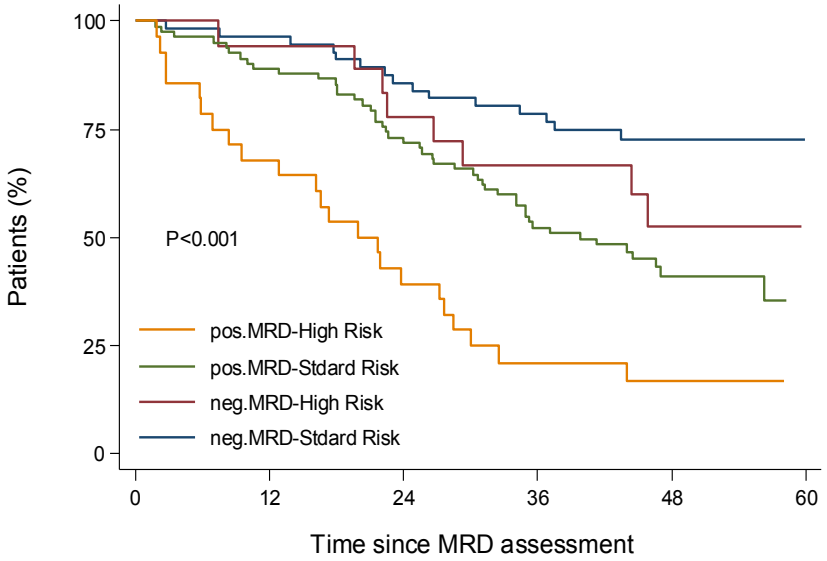
IFM DFCI 2009 trial: MRD by NGS in HIGH-RISK

PFS according to MRD status and treatment arm



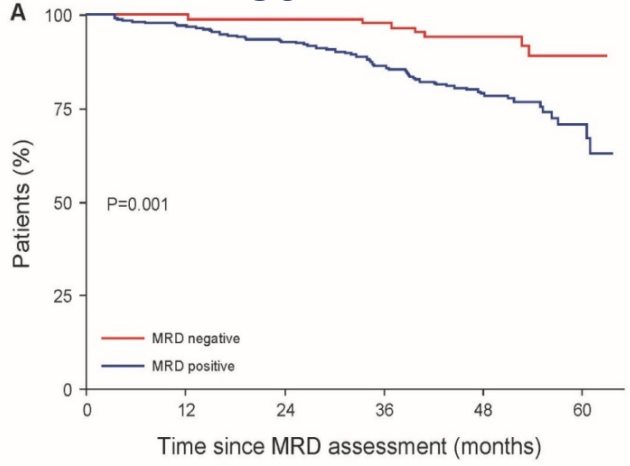
N at risk				
positive MRD-Transplant	68	62	49	11
positive MRD-RVD	66	51	38	5
negative MRD_Transp	50	47	43	4
negative MRD_RVD	40	39	34	0

PFS according to MRD status and cytogenetic risk



N at risk				
pos.MRD-High Risk	59	42	21	3
pos.MRD-Stdard Risk	14	12	5	1
neg.MRD-High Risk	48	43	25	4
neg.MRD-Stdard Risk				

OS

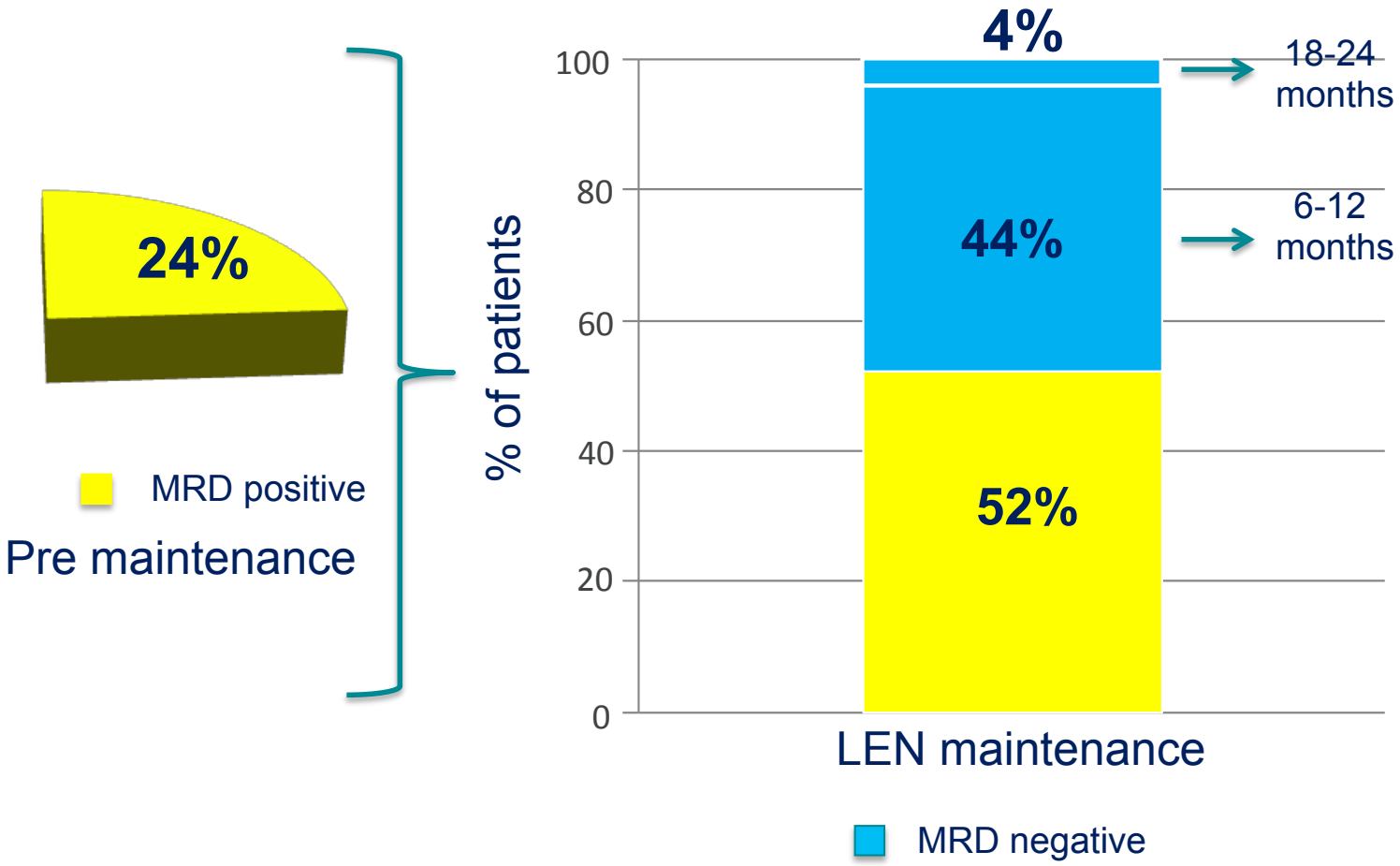


No. at Risk						
MRD negative	90	90	89	85	54	8
MRD positive	276	268	255	237	142	21

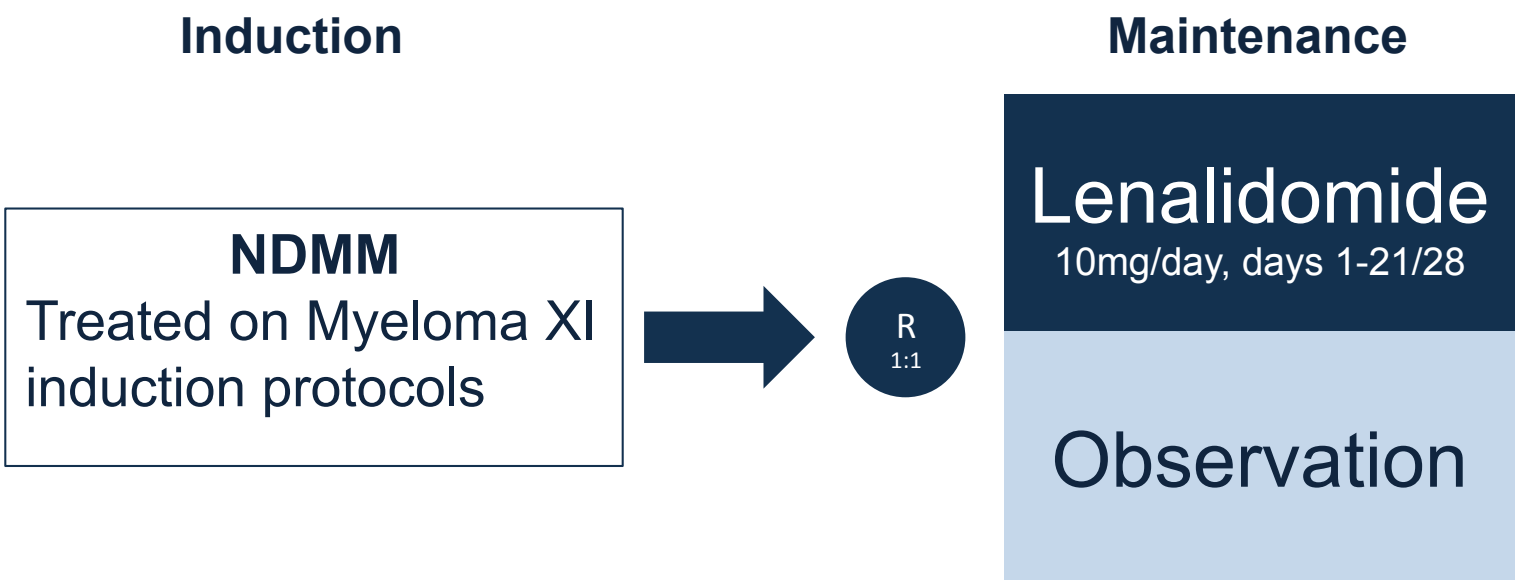
Avet-Loiseau H, et al. ASH 2017

EMN02/HO95 trial: MRD status during maintenance

Sub-analysis on MRD positive patients at pre-maintenance who had a second MRD evaluation >1 year of Lenalidomide



Myeloma XI



N=1971 **TE** = 1248, **TNE** = 723

Median follow up: 30.6 months (IQR 17.9-50.7)

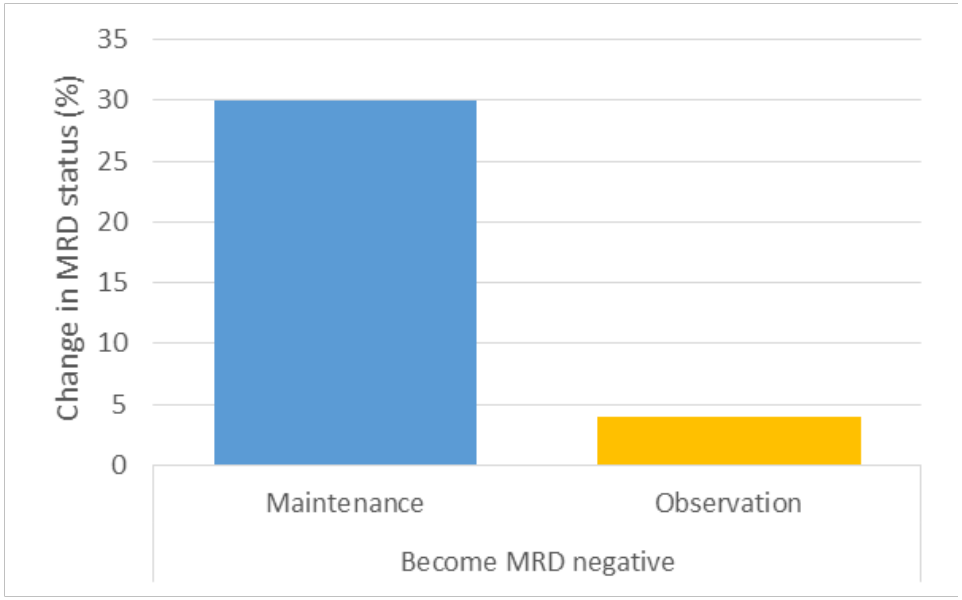
Exclusion criteria

- Failure to respond to lenalidomide as induction IMiD or progressive disease
- Previous or concurrent active malignancies

TE: transplant eligible
TNE: transplant non-eligible

Benefits of **maintenance**

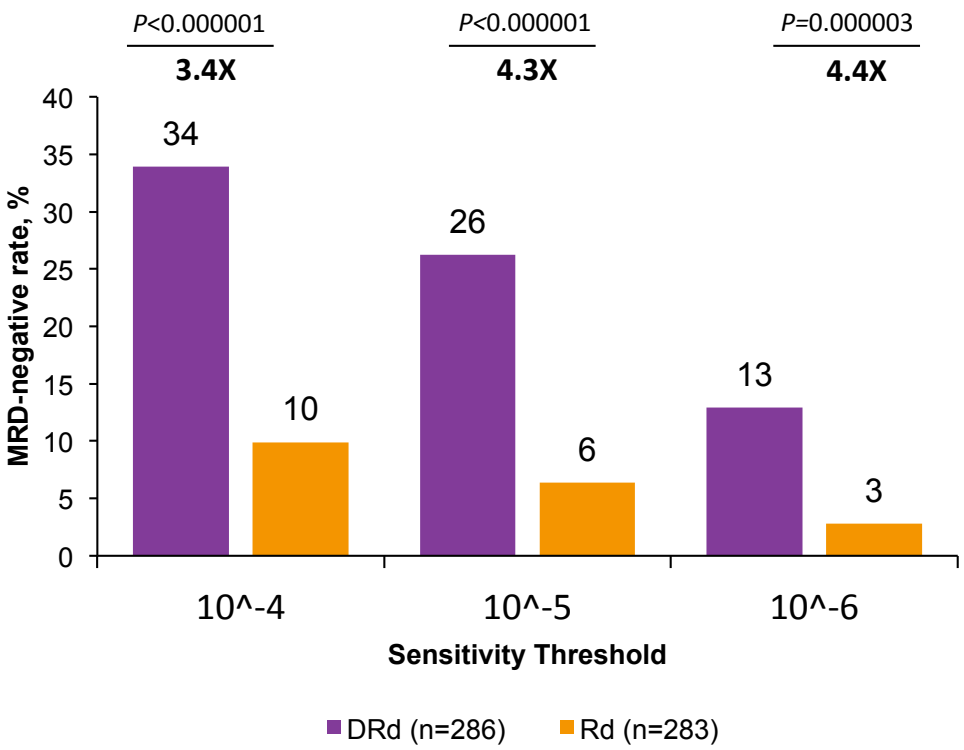
- **Conversions to MRD-negativity were seen in 30% of MRD-positive patients on maintenance** compared to 4% of patients randomised to no further therapy (p=0.0045).
- Conversion noted in all induction therapy groups



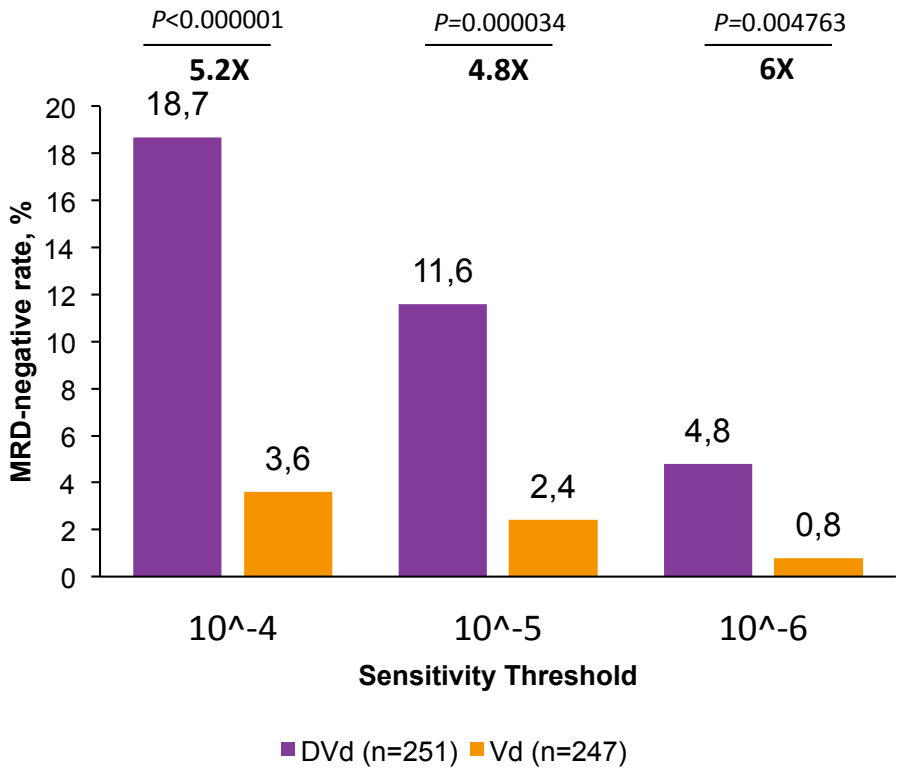
De Tute RM, et al. ASH 2017

Role of MRD negativity in relapsed/refractory patients: DARA-RD and DARA-VD

POLLUX



CASTOR



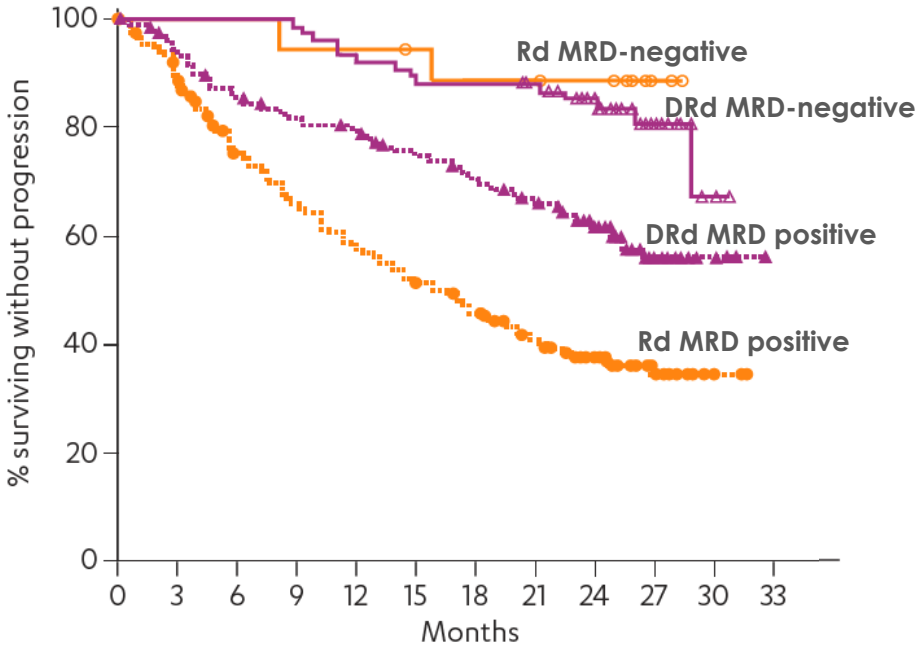
Daratumumab in combination with standard of care significantly improved MRD-negative rates at all thresholds

Avet-Loiseau H et al. ASH 2016
San Miguel J et al. IMWG 2017
Weisel K et al. EHA 2017
Dimopoulos MA et al EHA 2017

MRD is important in the relapse setting as well

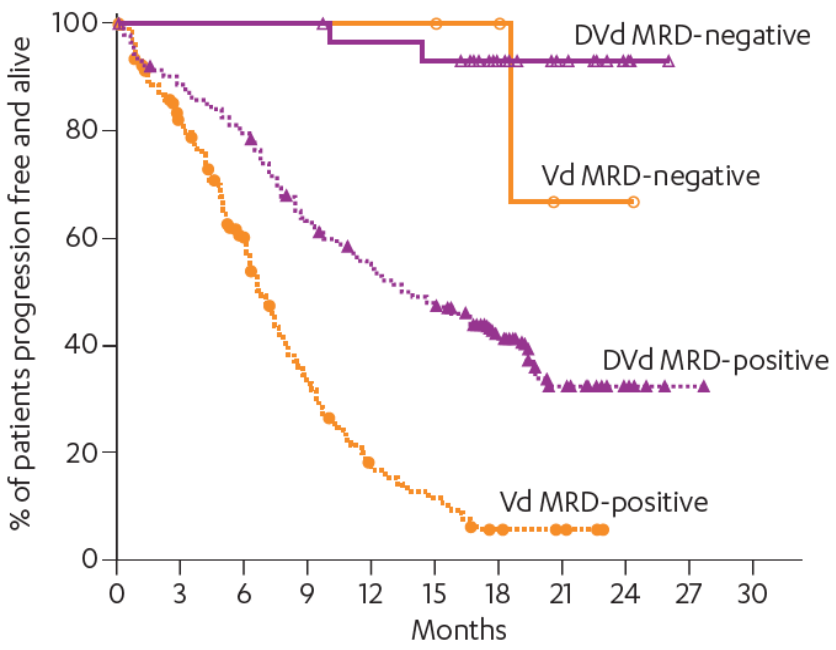
PFS by MRD status (10^{-5})

POLLUX



No. at risk												
Rd MRD negative	18	18	18	17	17	16	15	15	14	4	0	0
DRd MRD negative	75	75	75	74	70	67	66	64	49	18	4	0
Rd MRD positive	265	231	188	164	143	127	112	94	72	19	2	0
DRd MRD positive	211	191	174	164	159	147	137	125	97	28	4	0

CASTOR

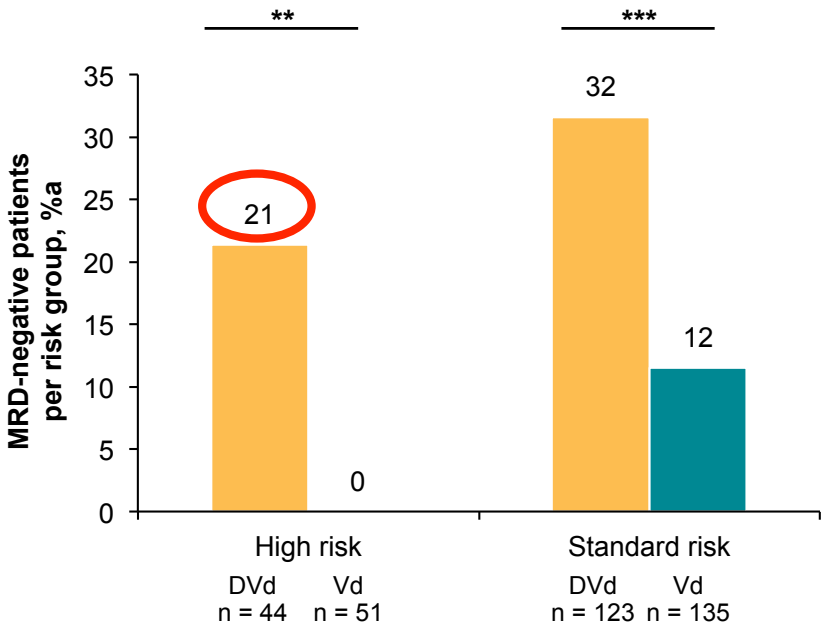


No. at risk											
Vd MRD-negative	6	6	6	6	6	6	5	1	1	0	0
DVd MRD-negative	29	29	29	29	27	26	17	11	3	0	0
Vd MRD-positve	241	176	123	68	33	21	6	4	0	0	0
DVd MRD-negative	222	186	169	132	111	98	62	19	5	1	0

Weisel K et al. EHA 2017
Dimopoulos MA et al EHA 2017

MRD by Cytogenetic Risk Status

POLLUX



**P = 0.0009. ***P = 0.0001.
[a]Percentage of patients within a given risk group and treatment arm.

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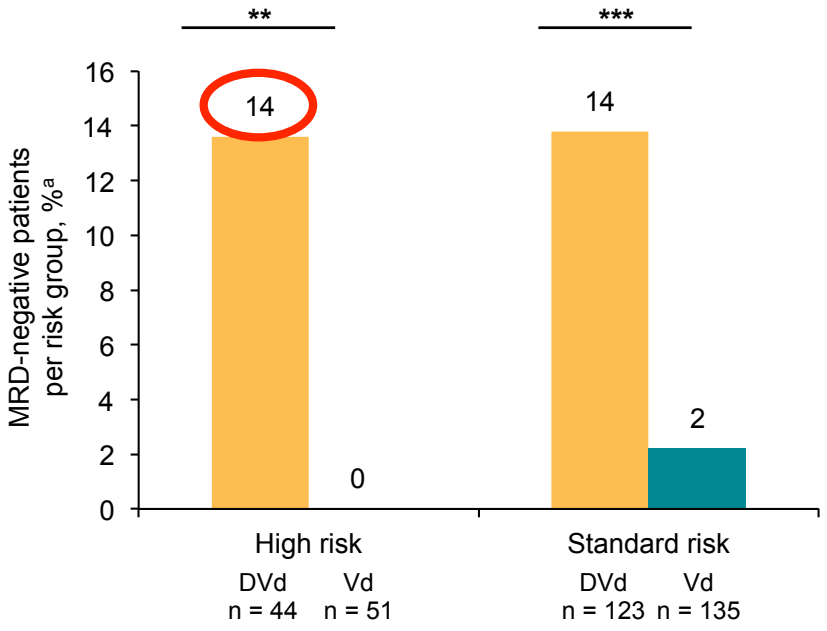


**P = 0.0018. ***P = 0.0003.
[a]Percentage of patients within a given risk group and treatment arm.

In high-risk patients, MRD-negative status was achieved only in those treated with daratumumab-containing regimens

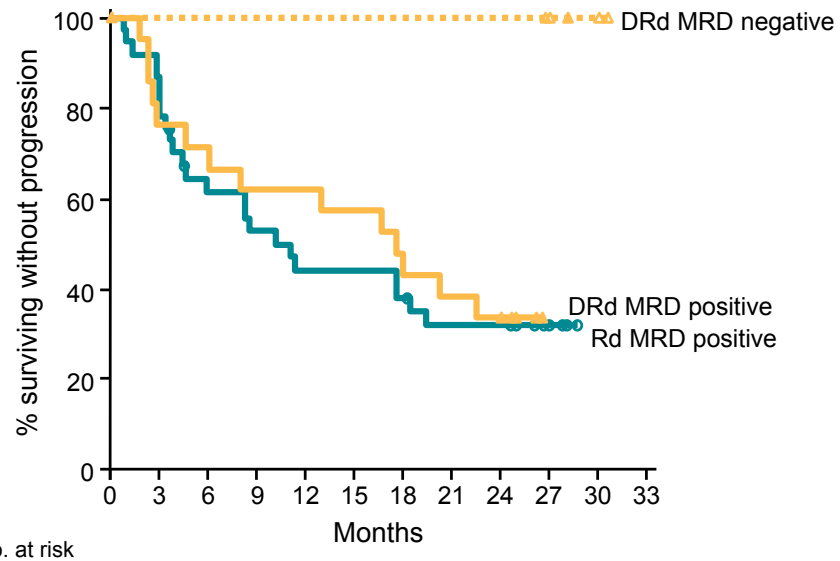
High risk = any of t(4;14), t(14;16), del17p

Standard risk = conclusive absence of all 3 markers

Weisel K, et al. ASCO 2017

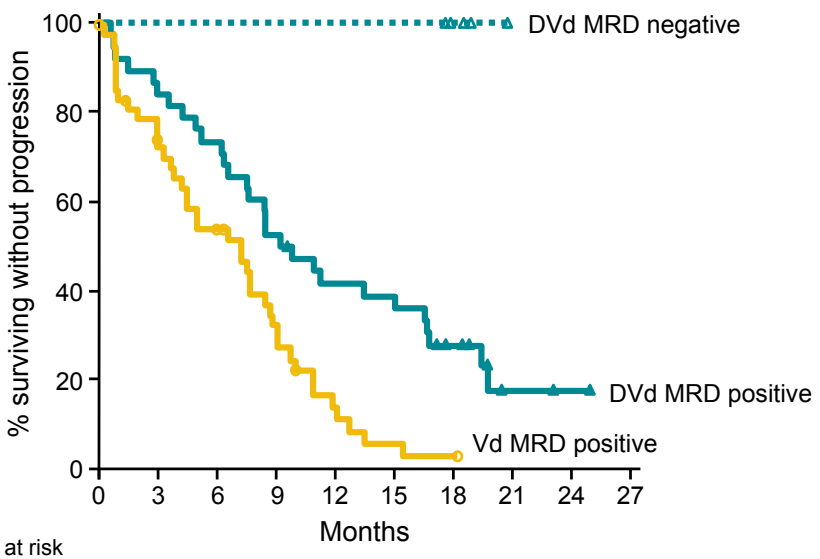
PFS in high-risk patients by MRD

POLLUX



No. at risk												
Rd MRD negative	0	0	0	0	0	0	0	0	0	0	0	0
DRd MRD negative	6	6	6	6	6	6	6	6	6	4	2	0
Rd MRD positive	37	32	21	18	15	15	13	10	10	4	0	0
DRd MRD positive	22	16	15	13	13	12	10	8	7	0	0	0

CASTOR



No. at risk										
Vd MRD negative	0	0	0	0	0	0	0	0	0	0
DVd MRD negative	6	6	6	6	6	6	3	0	0	0
Vd MRD positive	51	32	23	13	4	2	1	0	0	0
DVd MRD positive	38	32	28	20	15	14	8	2	1	0

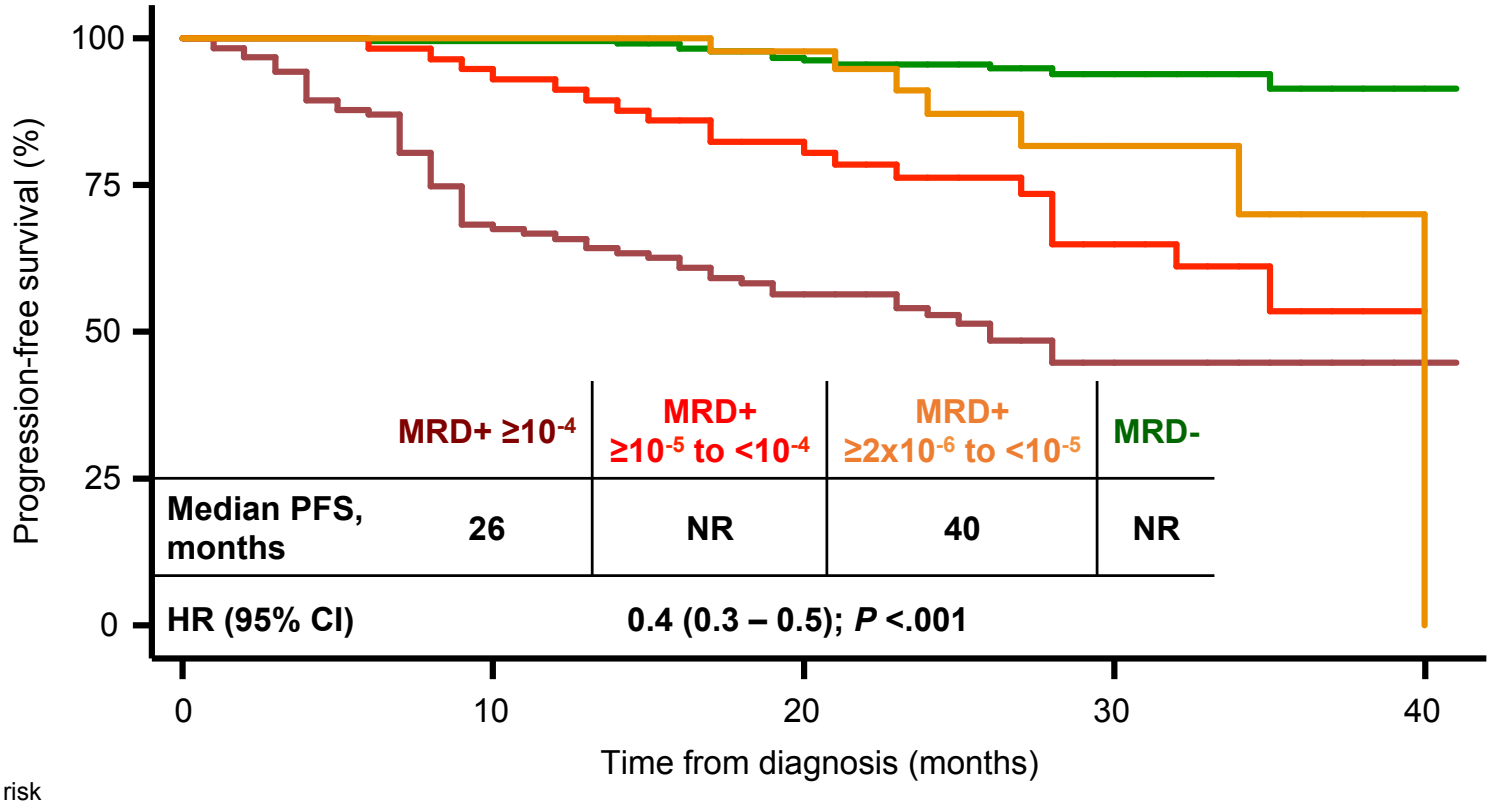
high-risk patients treated with daratumumab achieve MRD negativity and remain progression free

Weisel K, et al. ASCO 2017

MRD: Validated points	MRD: Open issues
MRD negativity is a surrogate for PFS MRD negativity is a surrogate for OS MRD by NGS is standardized MRD by NGF (Euroflow) is standardized MRD by NGS or NGF and PET-CT are complementary MRD useful to compare treatment options Moreau P, Zamagni E. Blood Cancer J 2017	**Optimal threshold for PFS and/or OS prediction by NGS or NGF** Need for both NGS and NGF Time interval to define sustained MRD negativity Definition of loss of MRD-negative status Optimal timing for MRD assessment during and after treatment Meaning of MRD negativity in specific subgroups, i.e., high-risk cytogenetics Standardization of MRD by PET-CT Best tracer for PET-CT Blood-based MRD assessment MRD and detection of clonal evolution MRD and MGUS-like profile MRD as a valid end-point for drug approval MRD to alter therapy: duration of maintenance, change treatment, add agents…

GEM2012MENOS65: MRD assessment by NGF

Progression-free survival according to NGF: MRD log levels



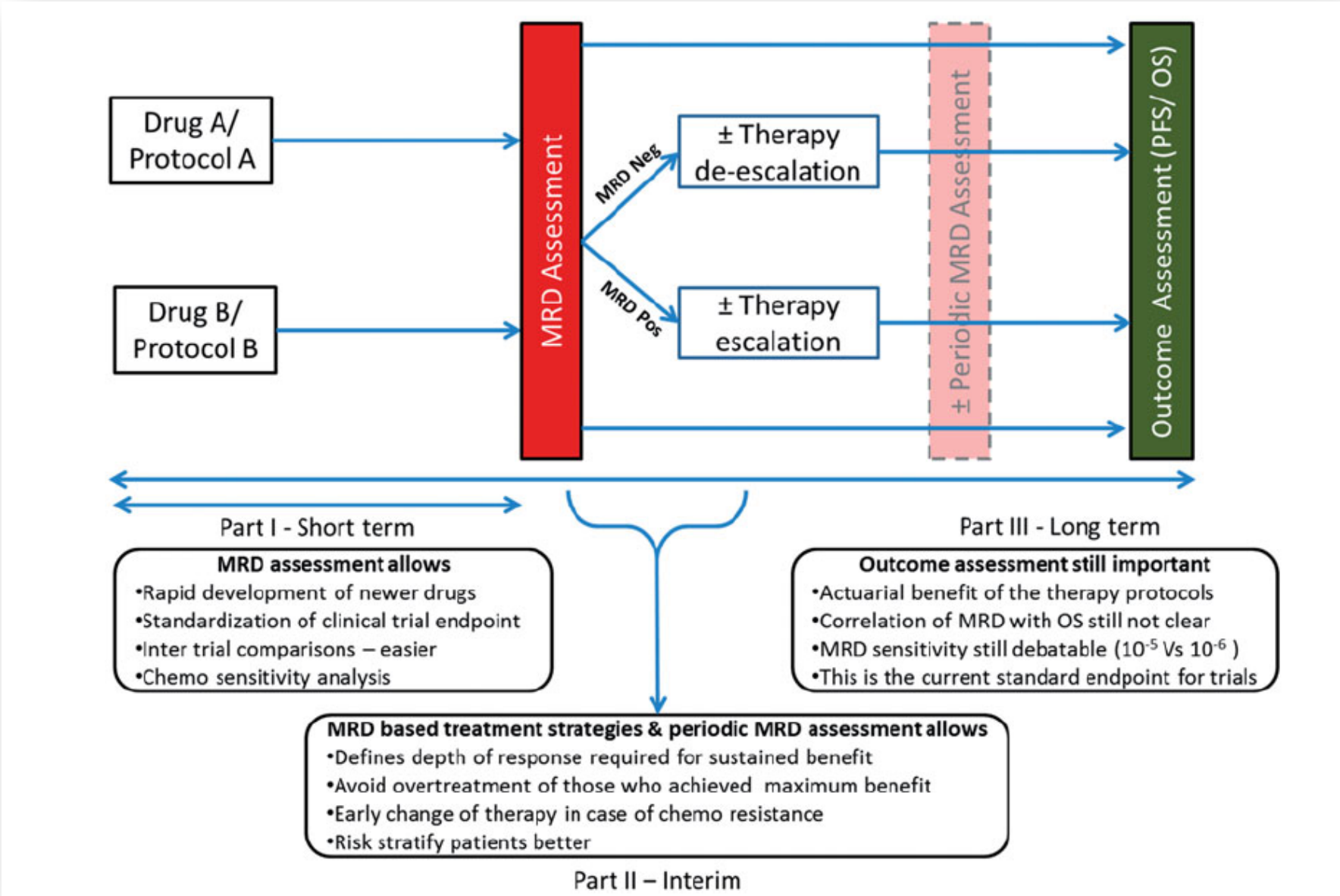
Number at risk					
MRD-neg	0	224	177	86	4
MRD ≥2x10^{-6} to	0	49	36	10	1
<10^{-5}	0	54	43	20	1
MRD ≥10^{-5} to <10^{-4}	458	84	57	20	2
MRD ≥10^{-4}					

Rosiñol L, et al. ASH 2017
Paiva B et al, ASH 2017

MRD: Validated points	MRD: Open issues
MRD negativity is a surrogate for PFS MRD negativity is a surrogate for OS	Optimal threshold for PFS and/or OS prediction by NGS or NGF
MRD by NGS is standardized MRD by NGF (Euroflow) is standardized	Need for both NGS and NGF
MRD by NGS or NGF and PET-CT are complementary	Time interval to define sustained MRD negativity Definition of loss of MRD-negative status Optimal timing for MRD assessment during and after treatment Meaning of MRD negativity in specific subgroups, i.e., high-risk cytogenetics
MRD useful to compare treatment options	Standardization of MRD by PET-CT Best tracer for PET-CT
	Blood-based MRD assessment MRD and detection of clonal evolution MRD and MGUS-like profile MRD as a valid end-point for drug approval
	MRD to alter therapy: duration of maintenance, change treatment, add agents…

Moreau P, Zamagni E. Blood Cancer J 2017

Suggested trial design for the assessing newer drugs/regimens in the future incorporating MRD analysis



Yanamandra U & Kumar SK, Leukemia and Lymphoma 2017

Actions to achieve, maintain and apply MRD negativity to improve the prognosis

- Integrate **all active treatment tools up-front** through:
  - Sequential blocks of therapy
  - Combination regimens

- Inclusion of **new novel-agents**:
  - Second generation PI
  - Monoclonal Ab

- Most effective treatments **at relapse**

- To treat the **disease early on**:
  - In most malignancies early detection and intervention is a pre-requisite for cure

- Design of more **individualized approach** :
  - Risk-adapted treatment strategies
  - MRD-adapted treatment strategies