La MRM oggi: un ausilio per la strategia terapeutica

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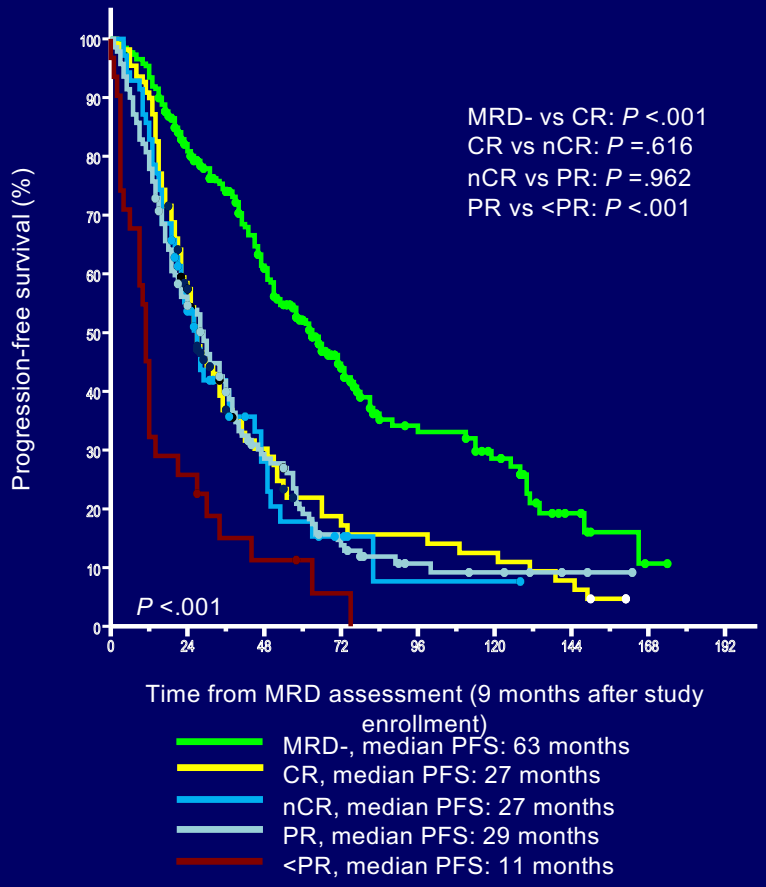
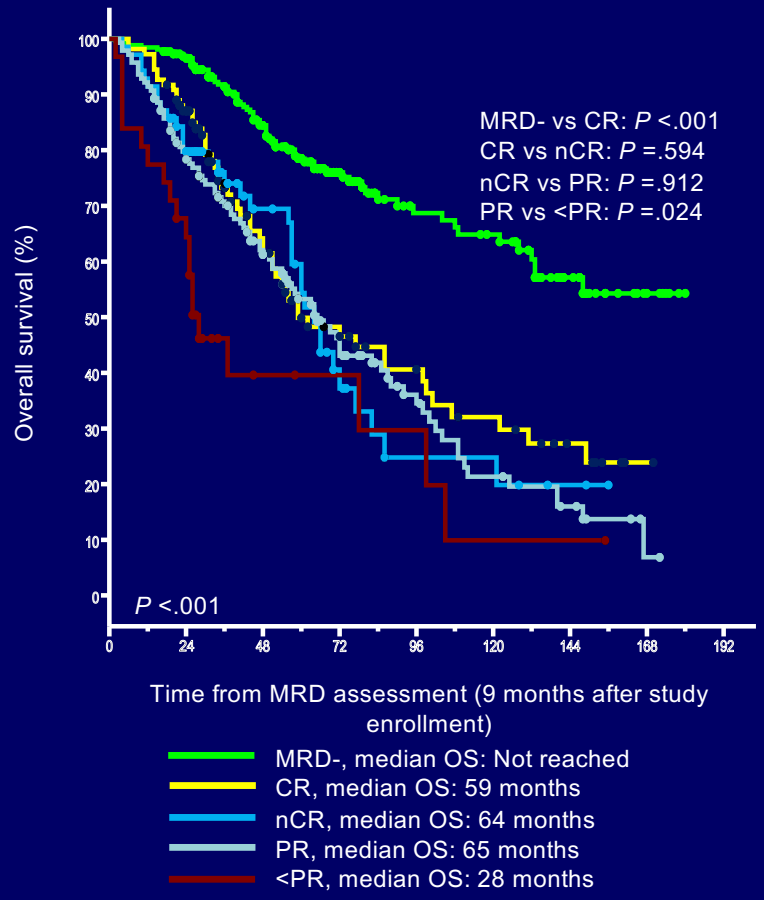
Only achieving MRD-negativity prolongs patients survival

The value of CR relies in the MRD status, and CR w/o MRD is no better than PR

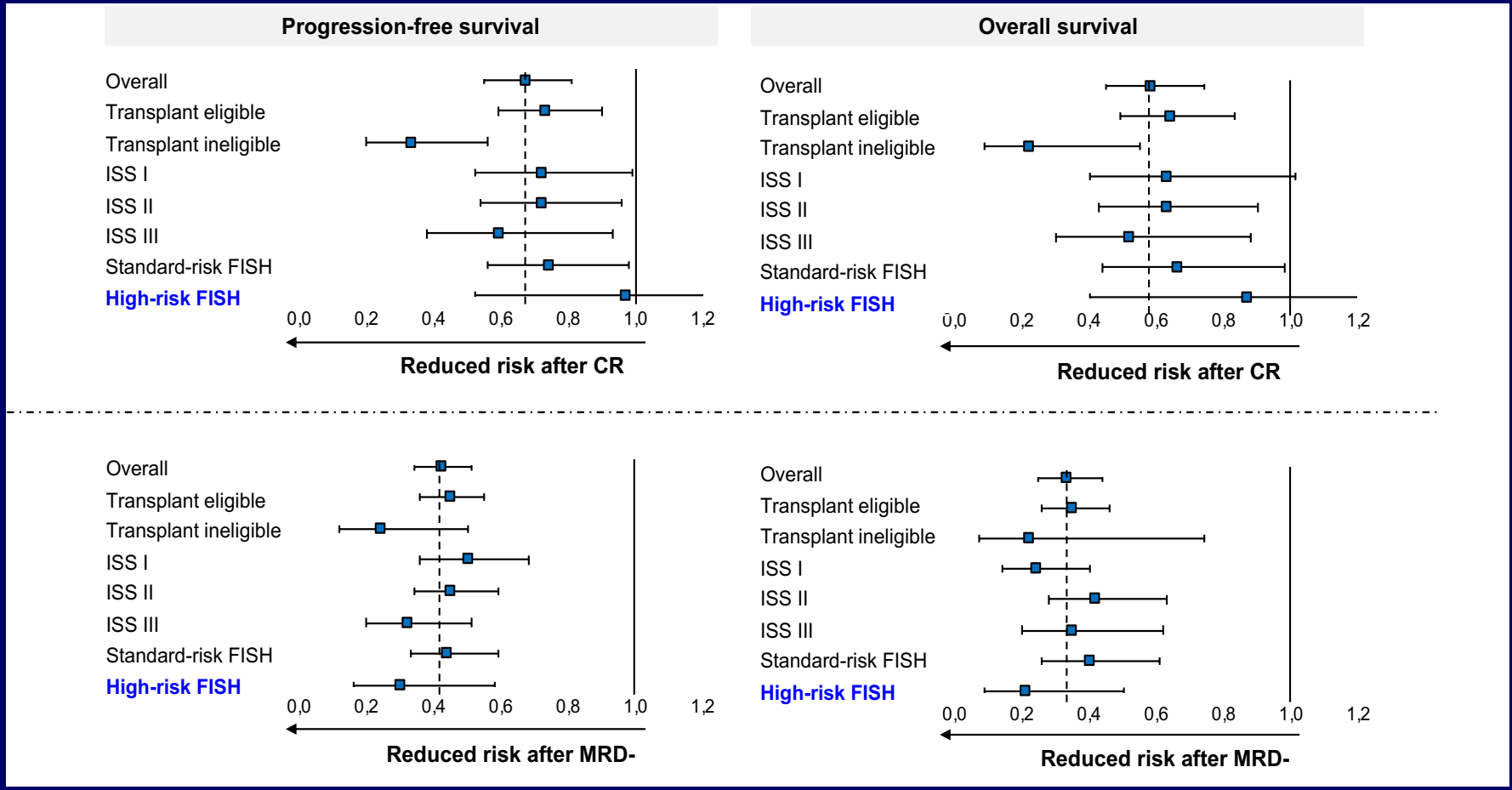




Lahuerta JJ & Paiva B, et al. J Clin Oncol 2017;35(25):2900-2910

CR versus MRD negativity

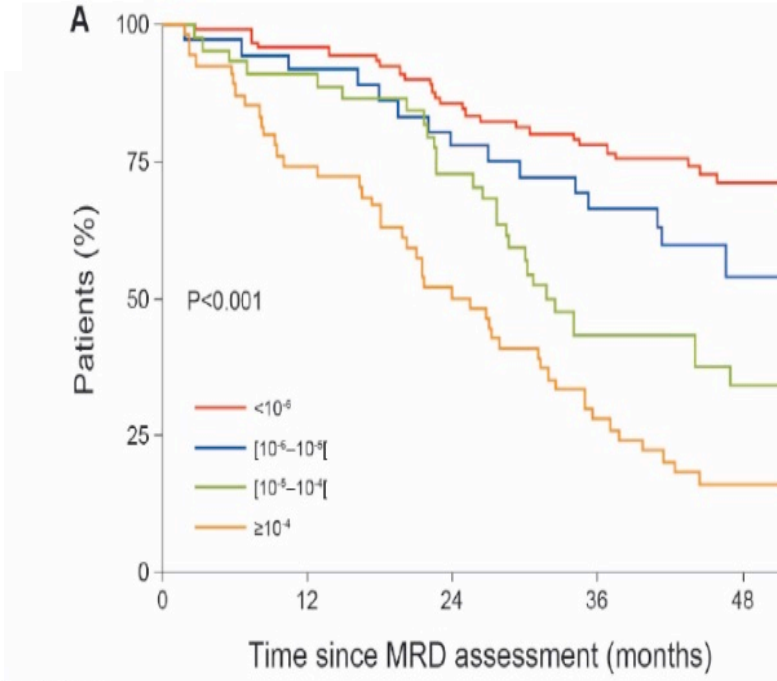
33% versus 58% reduction in the risk of progression and/or death



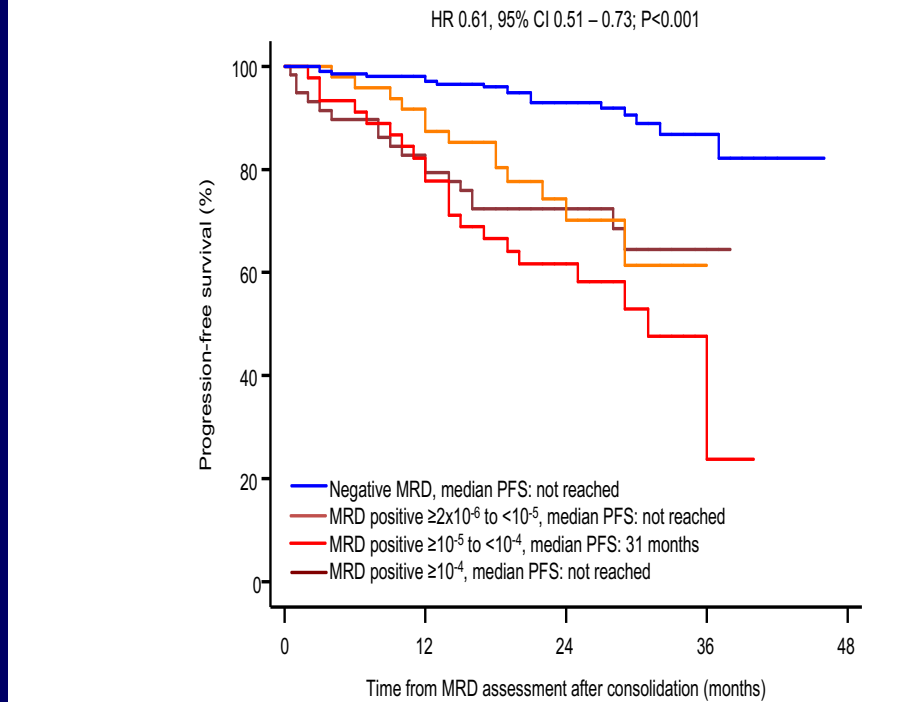
Lahuerta JJ & Paiva B, et al. J Clin Oncol 2017;35(25):2900-2910

MRD assessment with NGS and NGF

Positive MRD in the logarithmic range of 10^{-6} is clinically relevant



No. at Risk					
<10^{-6}	90	86	77	69	49
[10^{-6}–10^{-5}[	36	33	28	22	9
[10^{-5}–10^{-4}[	44	40	32	19	10
≥10^{-4}	54	40	27	15	7



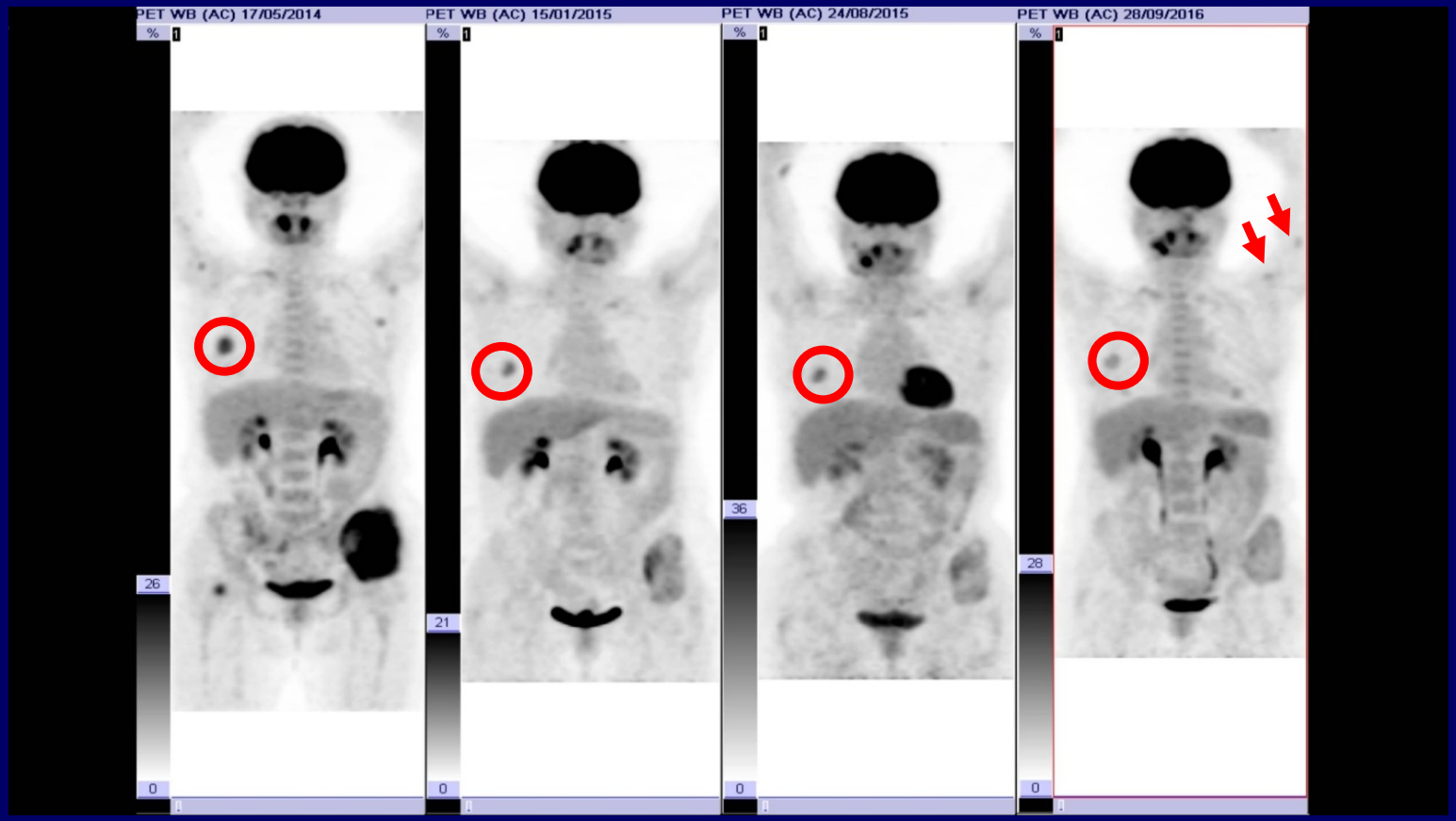
Number at risk					
MRD positive ≥10^{-4}	59	48	26	4	0
MRD positive ≥10^{-5} to <10^{-4}	45	37	20	2	0
MRD positive ≥2x10^{-6} to <10^{-5}	48	43	18	1	0
Negative MRD	205	198	111	19	0

Perrot A, et al. Blood. 2018;132(23):2456-2464.

Courtesy of Paiva B, Presented at IMWG 2019, I. Manuscript in review

GEM2012MENOS65 (VRD + ASCT): MRD assessment by NGF

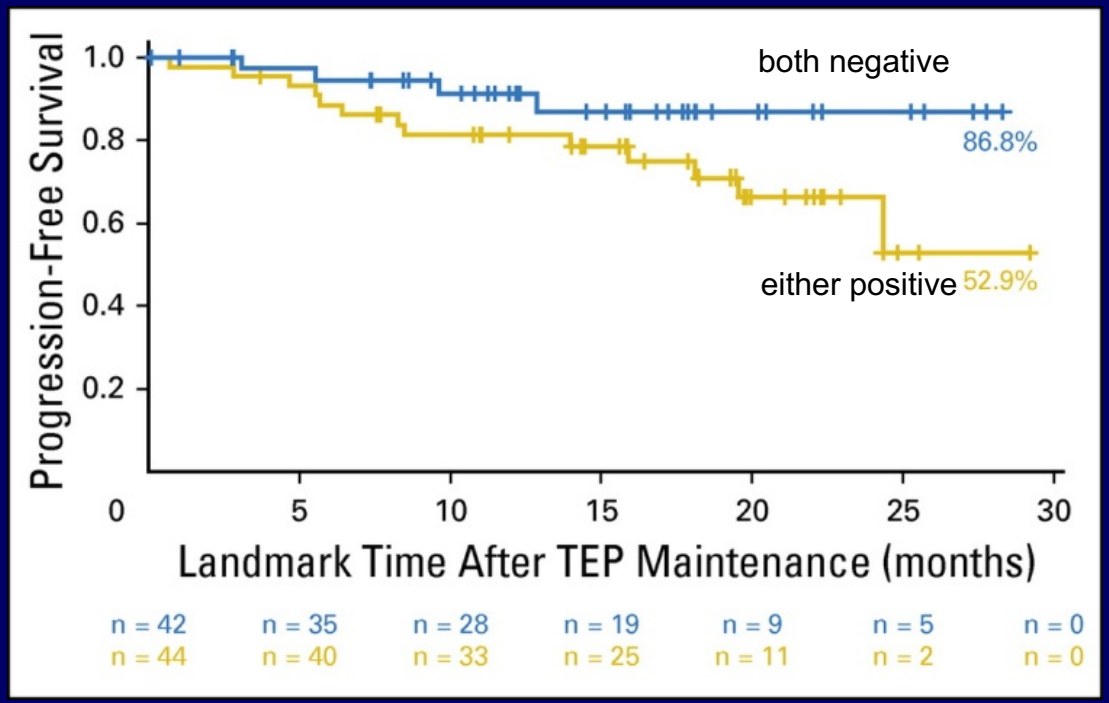
Patients relapsing despite an MRD-^{ve} result



Paiva B et al, ASH 2017

PET/CT and MRD Negativity as Predictor for PFS

PET/CT and FLOW MONITORING BEFORE MAINTENANCE



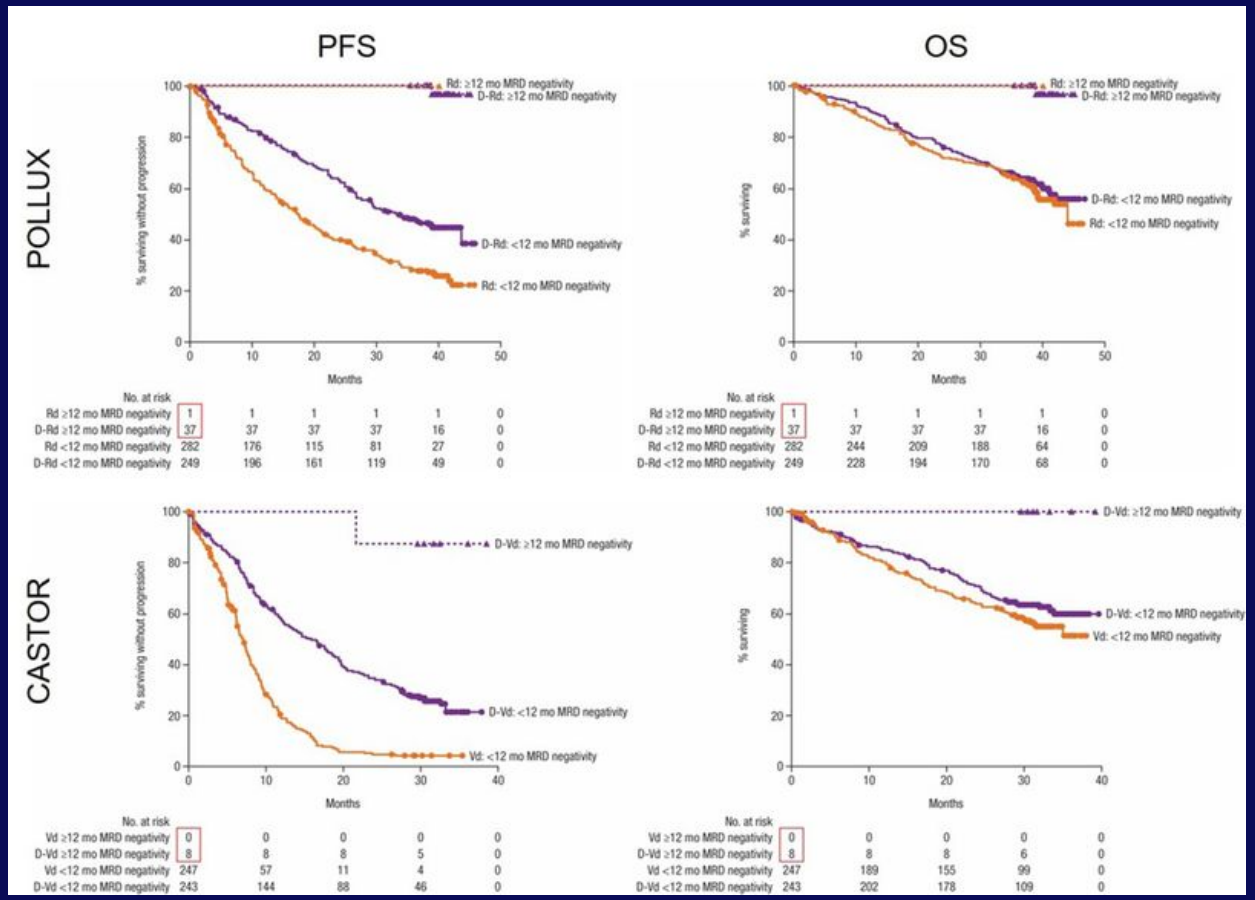
86/134 evaluated by both PET/CT and flow

47,7% both negative

Moreau et al. JCO 2017

Evaluation of Sustained Minimal Residual Disease (MRD) Negativity

PFS and OS based on sustained MRD negativity (> 12 months) in ITT population



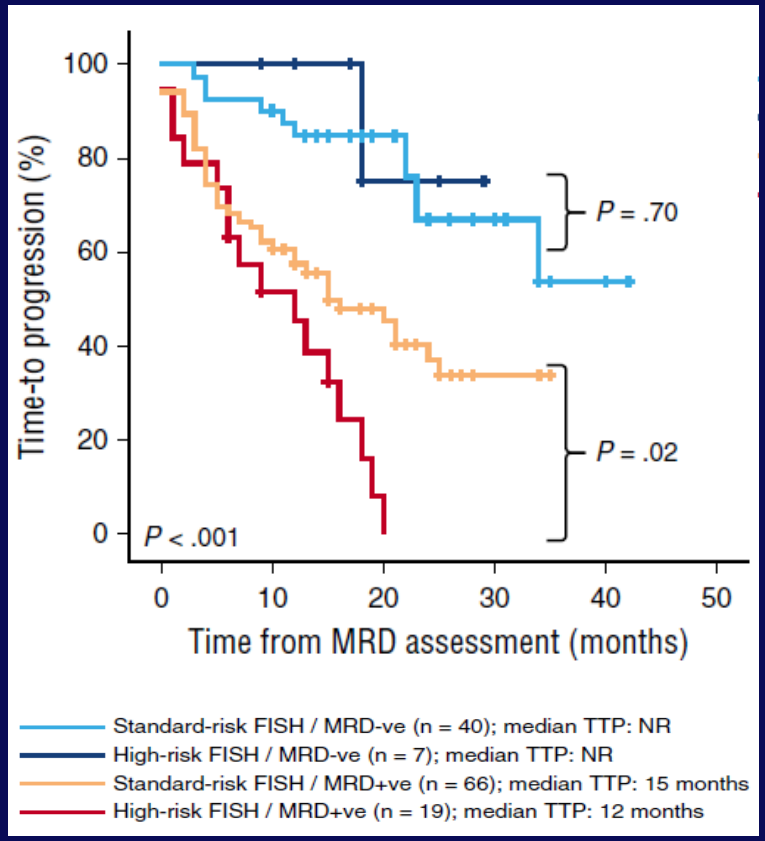
Avet Loiseau H et al. ASH 2018: poster presentation

IMWG Criteria for MRD in Multiple Myeloma

	Response subcategory	Response criteria
IMWG MRD negativity criteria (Requires CR as defined below)	Sustained MRD negative	MRD negative in the marrow (Next-generation flow or Next-generation sequencing) and by imaging as defined below, confirmed one year apart. Subsequent evaluations can be used to further specify the duration of negativity (e.g., MRD negative @ 5 years etc)
	Imaging MRD-negative	MRD negative as defined below (Next-generation flow or Next-generation sequencing) PLUS Disappearance of every area of increased tracer uptake found at baseline or a preceding PET/CT[3]
	Flow MRD-negative	Absence of phenotypically aberrant clonal plasma cells by next-generation flow cytometry[4] on bone marrow aspirates using the EuroFlow standard operation procedure for MRD detection in MM (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 next generation sequencing on bone marrow aspirates in which presence of a clone is defined as less than 2 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[5] or higher

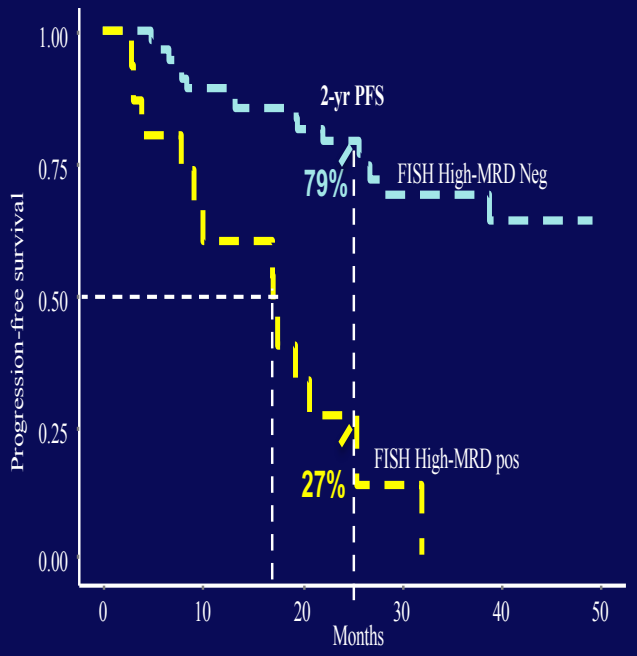
Kumar SK, et al. Lancet Oncology 2016

MRD in high risk

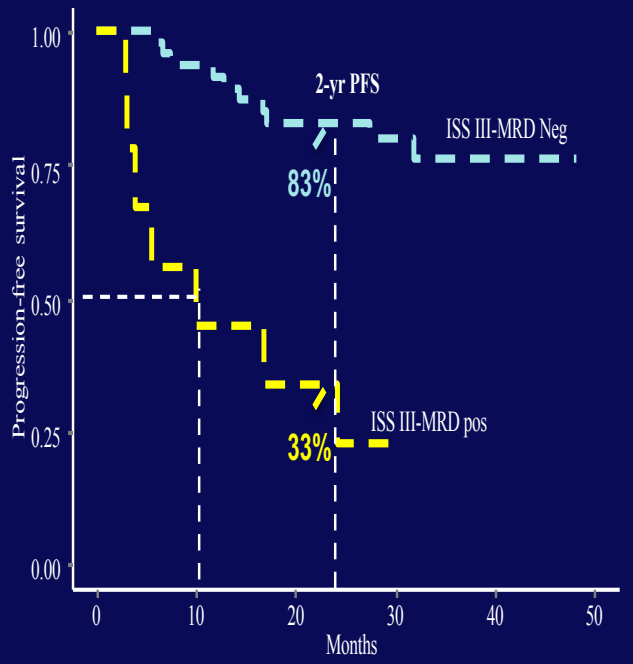


Paiva et al. Blood 2016

FISH – HIGH RISK



ISS III



Oliva S et al EHA 2017

MRD: what we do know

- MRD is prognostic
- Optimal cut off probably 10^{-6}
- Need for sustained MRD
- Imaging plus BM MRD
- Not only standard risk but also High-risk patients benefit from MRD achievement

Is this sufficient to use MRD in clinical practice?

MRD, Minimal Residual Disease; BM, bone marrow.

MRD as a surrogate endpoint

Surrogate Endpoint: used in a clinical trial as a **substitute for** a direct measure of **how a patient** feels, functions or **survives**;
does not measure but **predicts the clinical benefit of primary interest**

Issues to focus on for MRD as a surrogate endpoint:

- **Biological plausibility and causality:** sensitive measure of the clearence of tumor cells
- **Specificity:** evaluates efficacy of a treatment
- **Proportionality:** can the magnitude of change in MRD explain the magnitude of change in PFS/OS?
- **Universality:** is the evidence of surrogacy consistent across different treatments and different populations?

I²TEAMM:

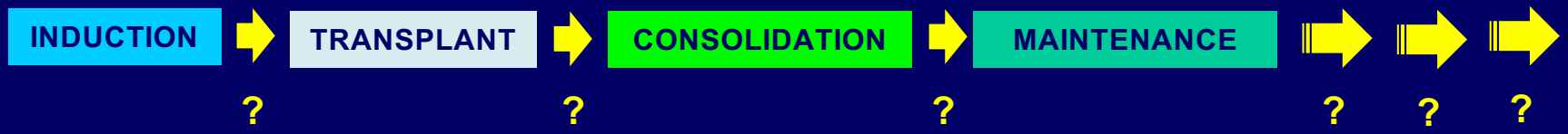
International Independent Team for Endpoint Approval of Myeloma MRD

- Combining all MM research groups in EU and US, pharmaceutical companies and indipendent statisticians
- Patient level data (expected over 4500)

MRD, Minimal Residual Disease; PFS, Progression-Free Survival; OS, Overall Survival.

MRD: open questions

- In **which patients** should we check MRD negativity? *(CR, sCR, VGPR..)*
- **How** should we evaluate MRD? *(NGF, NGS, imaging..)*
- What is the optimal **cut-off**?
- Do we need to perform **imaging** in all patients?
- Is an optimal cut-off enough or do we always need **durability**? And what is the optimal duration?
- What is the optimal **timing** for MRD evaluation? *(sequential treatment and continuous treatment)*

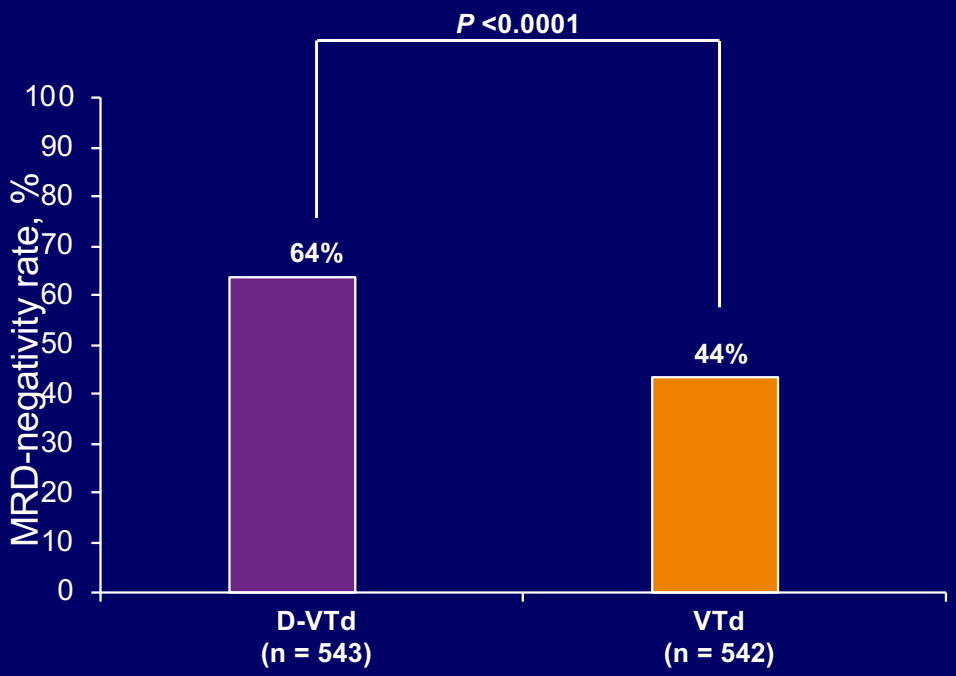


…..STANDARDIZATION!!!!

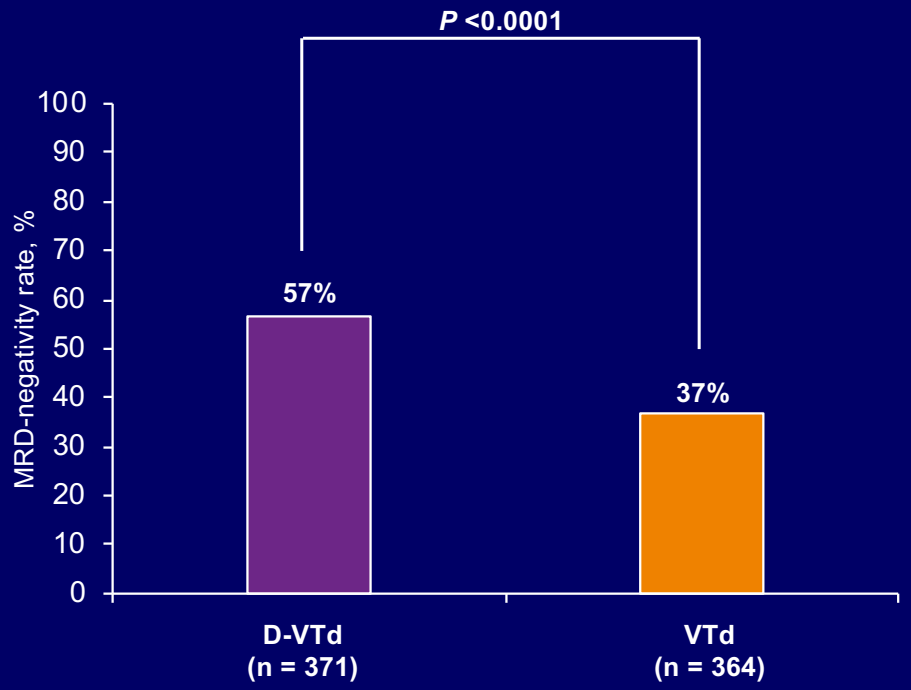
MRD, Minimal Residual Disease; CR, complete response; sCR, stringent complete response; VGPR, very good partial response; NGF, next generation flowcytometry; NGS, next generation sequencing.

MRD-negativity Rates (10^{-5}) (CASSIOPEA STUDY)

Post-consolidation; Flow cytometry[a]



Post-consolidation; NGS[b]



Avet Loiseau H, et al, IMWG 2019

[a]ITT population. [b]NGS-evaluable population.

Concordance: Post-consolidation MRD (10^{-5}; n = 733[a]) by Treatment Arm (CASSIOPEA STUDY)

D-VTd			NGS		
	Flow cytometry	Total	Positive	Negative	Observed agreement[b]
MRD status, n (%)	Positive	114	105 (92.1)	9 (7.9)	82.7%
	Negative	256	55 (21.5)	201 (78.5)	
VTd			**NGS**		
	Flow cytometry	Total	Positive	Negative	Observed agreement[b]
MRD status, n (%)	Positive	201	187 (93.0)	14 (7.0)	84.3%
	Negative	162	43 (26.5)	119 (73.5)	

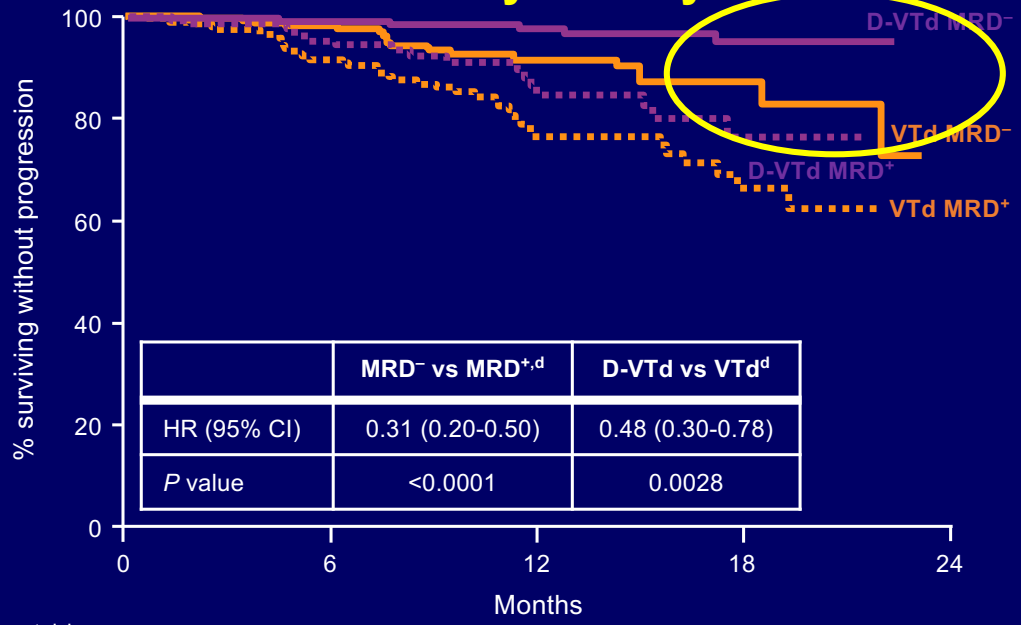
[a]NGS- and flow cytometry-evaluable population.

[b]Calculated as (TP+TN)/Total, where TP = total number of patients positive by both NGS and flow cytometry; TN = total number of patients negative by both NGS and flow cytometry; Total = total number of patients with both NGS and flow cytometry results (positive or negative).

Avet Loiseau H, et al, IMWG 2019

Post-consolidation PFS[a] by MRD Status (10^{-5})

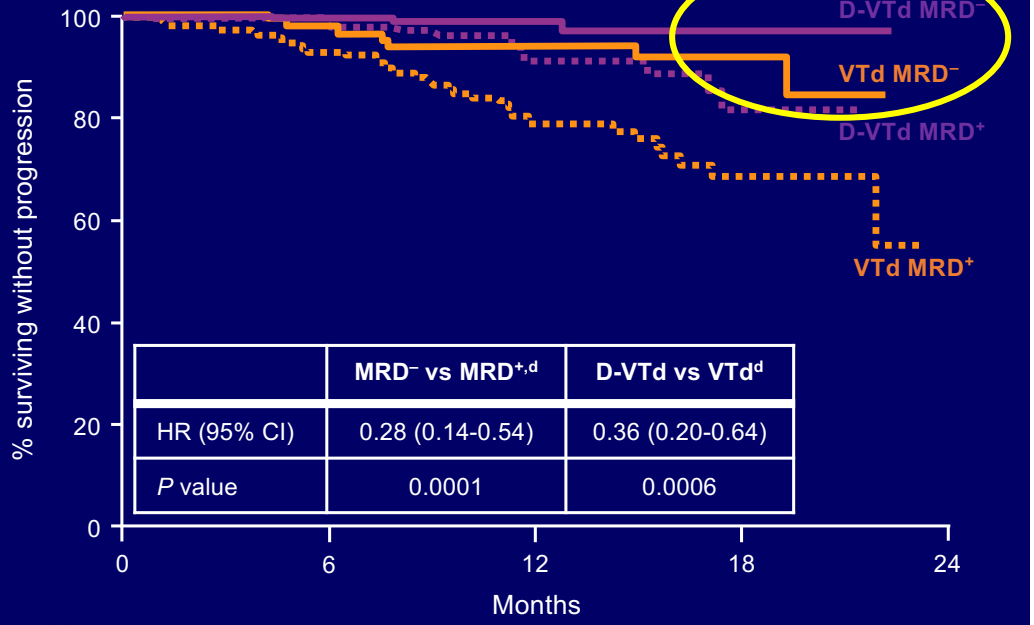
Flow Cytometry[b]



	MRD⁻ vs MRD⁺,[d]	D-VTd vs VTd[d]
HR (95% CI)	0.31 (0.20-0.50)	0.48 (0.30-0.78)
P value	<0.0001	0.0028

No. at risk					
D-VTd MRD⁻	344	241	132	44	0
VTd MRD⁻	232	167	88	27	0
D-VTd MRD⁺	148	105	53	17	0
VTd MRD⁺	243	152	75	23	0

NGS[c]



	MRD⁻ vs MRD⁺,[d]	D-VTd vs VTd[d]
HR (95% CI)	0.28 (0.14-0.54)	0.36 (0.20-0.64)
P value	0.0001	0.0006

No. at risk					
D-VTd MRD⁻	210	147	85	33	0
VTd MRD⁻	133	100	52	16	0
D-VTd MRD⁺	156	123	65	18	0
VTd MRD⁺	220	145	77	23	0

- **PFS benefit in patients achieving MRD negativity**
- **D-VTd showed additional PFS benefit versus VTd**
- **Daratumumab increased the number of patients achieving MRD negativity**

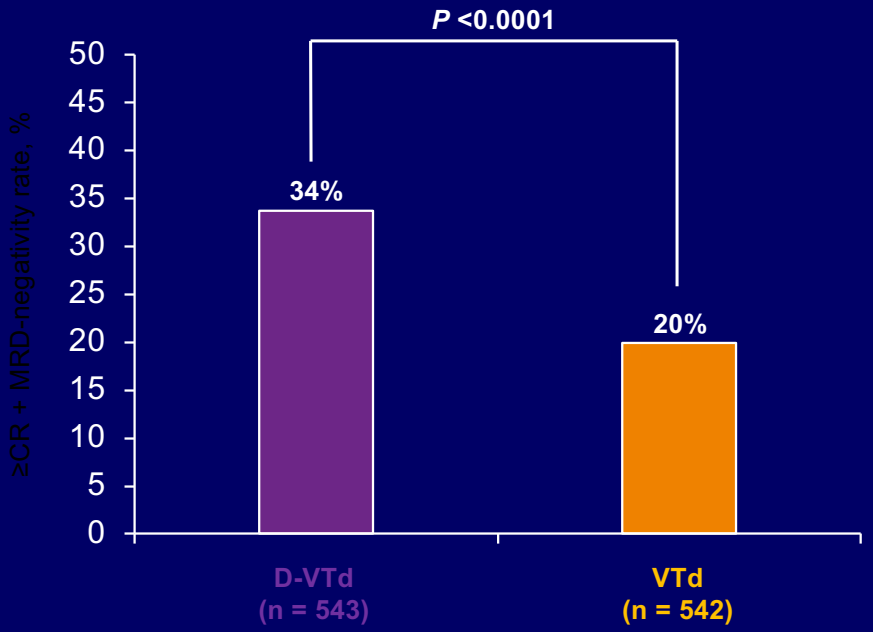
HR, hazard ratio.

Avet Loiseau H, et al, IMWG 2019

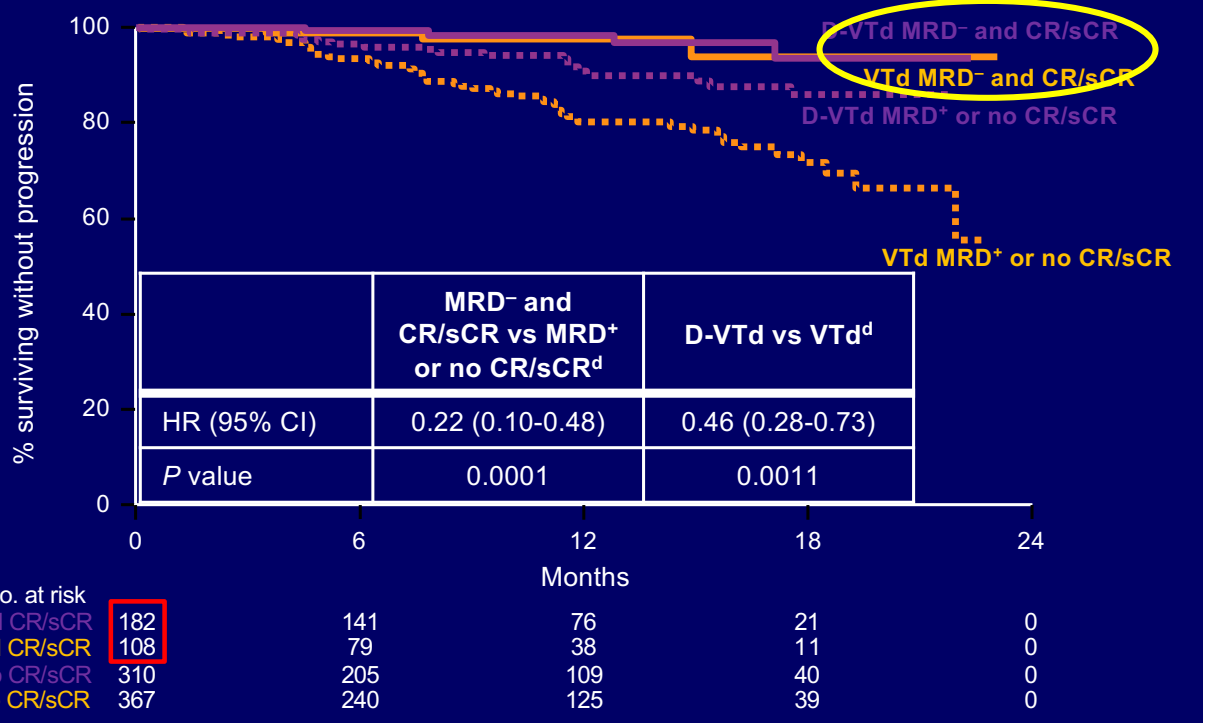
[a]Landmark analysis from post-ASCT Day 100 onward, regardless of second randomization. [b]Patients who had a PFS event or were censored before 9 months (median time to Day 100) were excluded. [c]Patients in the NGS-evaluable population who had a PFS event or were censored before 9 months (median time to Day 100) were excluded. [d]Multivariate analysis accounting for treatment arm and MRD negativity.

Post-consolidation ≥CR[a] + MRD Negativity[b]

≥CR + MRD-negativity Rates



PFS by ≥CR + MRD-negative Status[c]



	MRD⁻ and CR/sCR vs MRD⁺ or no CR/sCR[d]	D-VTd vs VTd[d]
HR (95% CI)	0.22 (0.10-0.48)	0.46 (0.28-0.73)
P value	0.0001	0.0011

No. at risk					
D-VTd MRD⁻ and CR/sCR	182	141	76	21	0
VTd MRD⁻ and CR/sCR	108	79	38	11	0
D-VTd MRD⁺ or no CR/sCR	310	205	109	40	0
VTd MRD⁺ or no CR/sCR	367	240	125	39	0

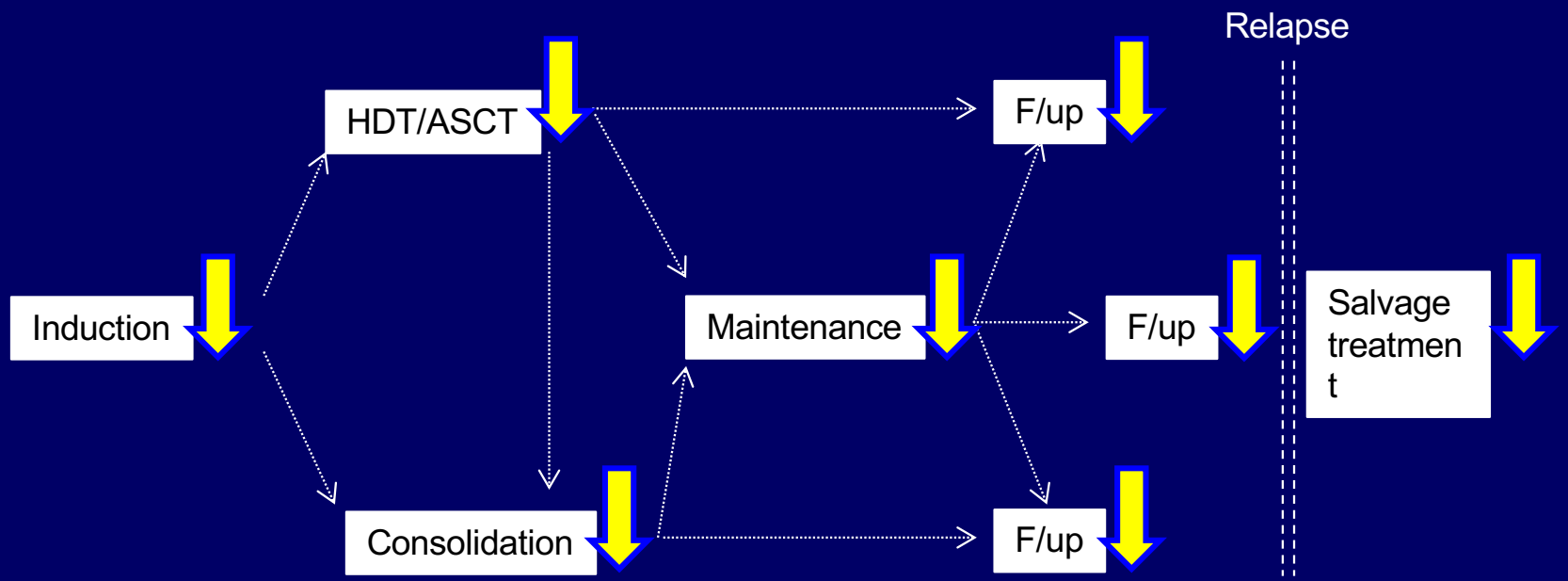
- **Higher proportion of patients achieving both ≥CR and MRD negativity for D-VTd versus VTd**
- **PFS benefit in patients achieving both ≥CR and MRD negativity**
- **D-VTd showed additional PFS benefit versus VTd**

Avet Loiseau H, et al, IMWG 2019

[a]CR criteria: serum immunofixation and urine immunofixation negativity, <5% plasma cells in the bone marrow, and disappearance of all plasmacytomas. sCR criteria: CR criteria + normal free light-chain ratio and 4-color flow negativity. CR and sCR required confirmation at next visit. [b]Flow cytometry; 10^{-5} sensitivity threshold. [c]Landmark analysis from post-ASCT Day 100 onward, regardless of second randomization. Patients who had a PFS event or were censored before 9 months (median time to Day 100) were excluded. [d]Multivariate analysis accounting for treatment arm and MRD negativity.

MRD evaluation is prognostic at any time point. Consider evaluating to:

- Define quality of CR
- Evaluate efficacy of subsequent treatment after CR (eg. Consolidation)
- Predict unsustained CR
- Identify high-risk patients
- …
- Help on treatment decisions



Paiva B, Van Dongen JJ, Orfao A. Blood. 2015;125(20):3059-3068

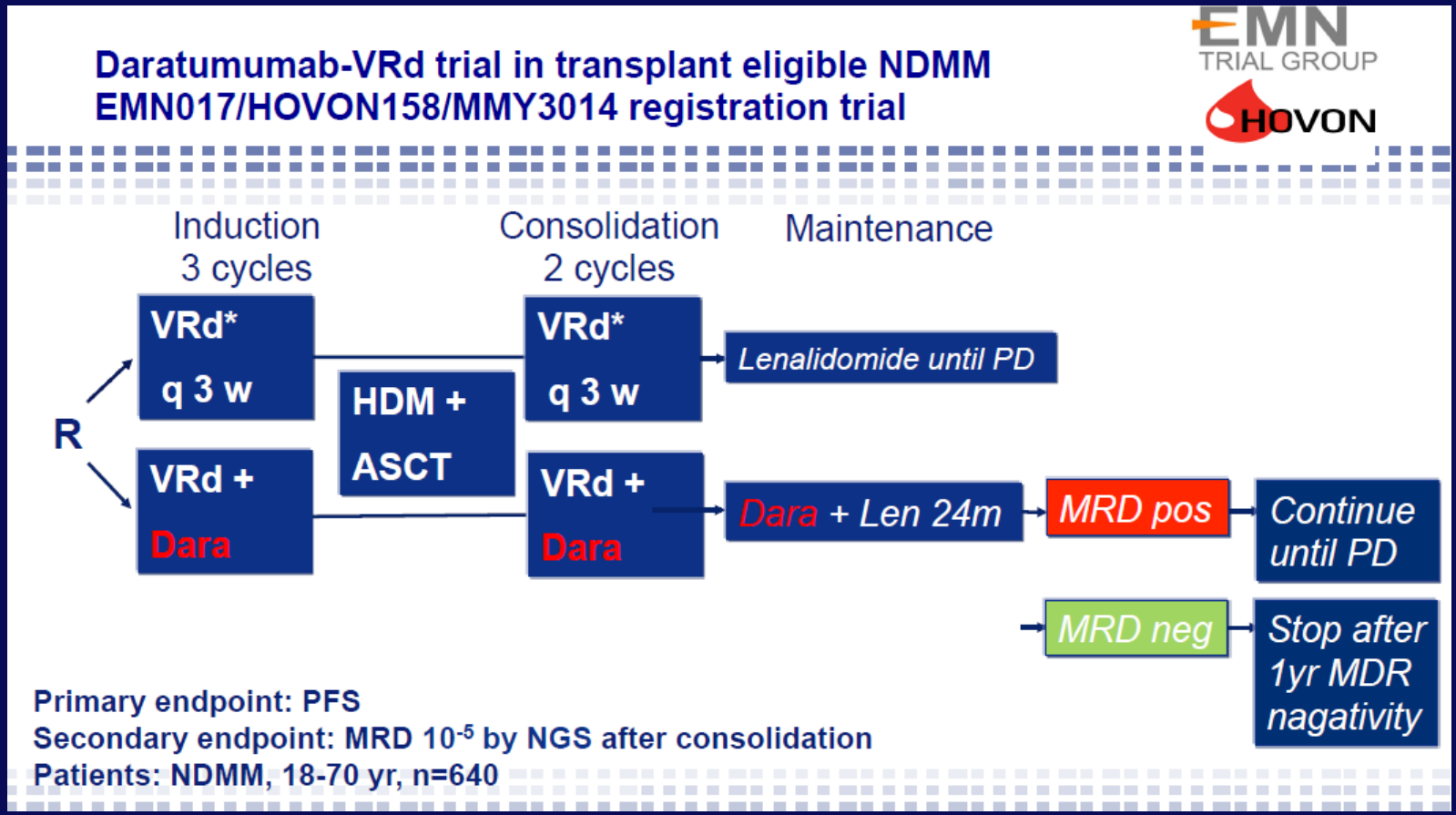
Take Home messages

- **MRD: at present «the most appealing candidate» as a tool to help in treatment decisions**

- **Improve on MRD:**
  - **Sustained MRD**
  - **Feasible MRD**
  - **Algorithm to define when, in which patients and how to evaluate MRD**

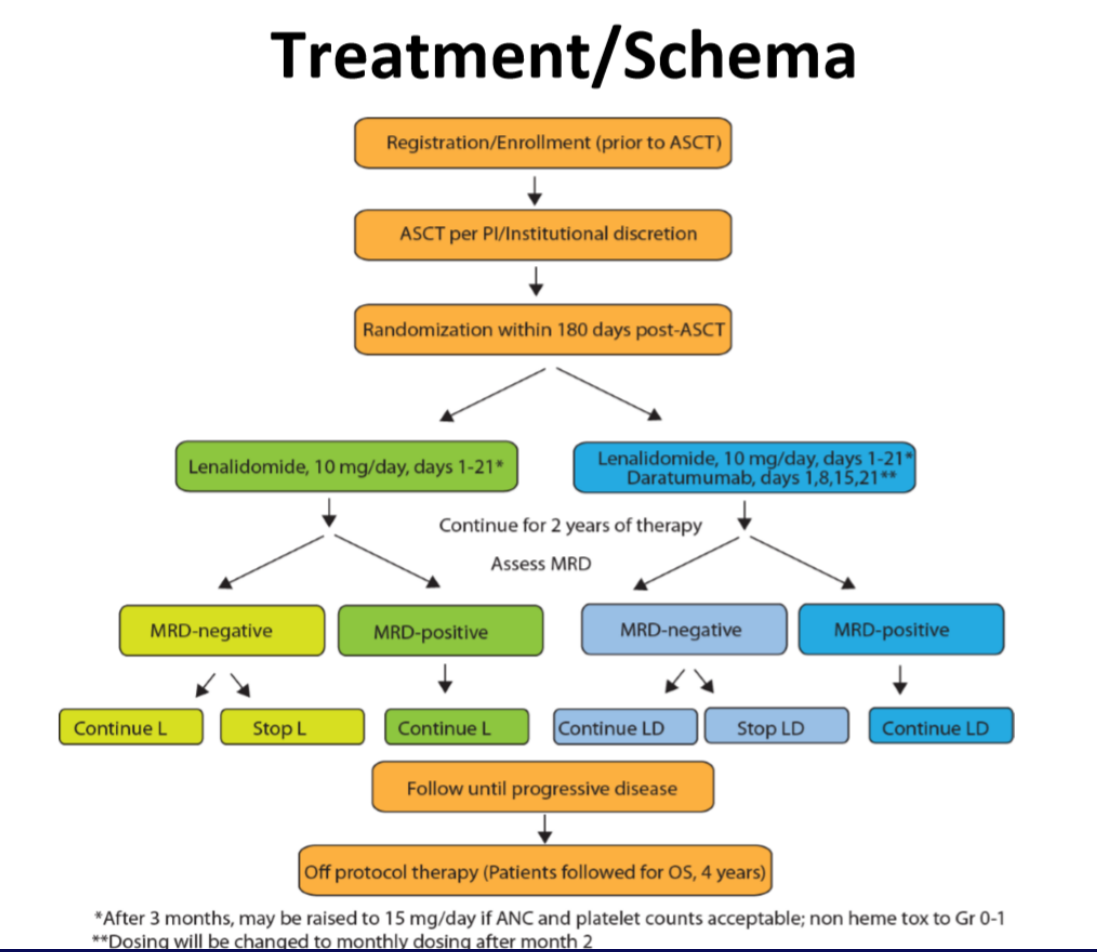
- **We should aim at using MRD to guide treatment decision and to do this :**
  - **Need of prospective trials**
  - **Trials that evaluate if intensify or stop therapy according to MRD**
  - **Trials that evaluate role of MRD and risk factors**

EMN017/Perseus



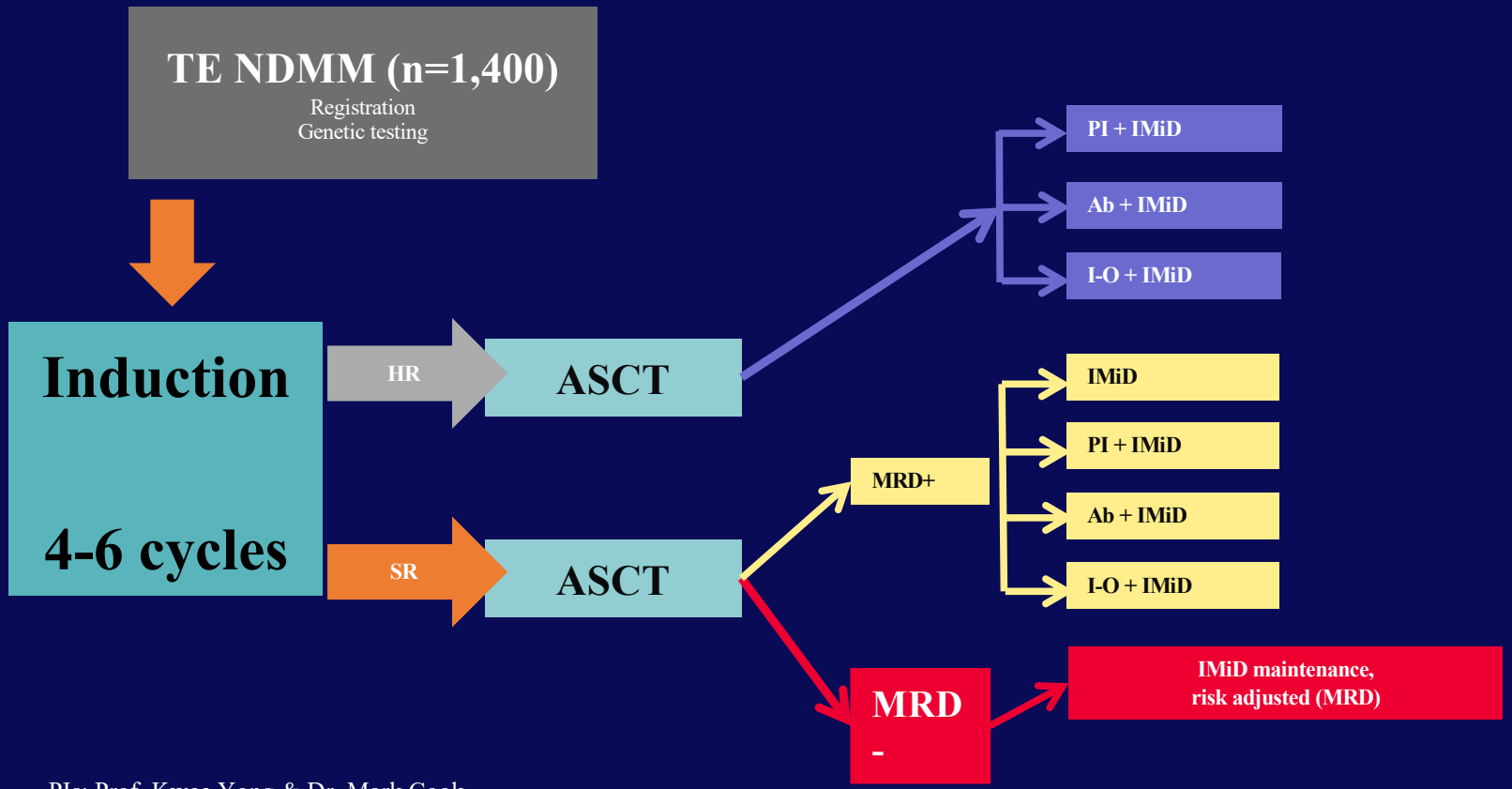
DRAMMATIC STUDY

SWOG1803/BMT CTN 1706: Using Minimal Residual Disease to Direct Therapy Duration



UKMRA Myeloma XV RADAR

Risk Adapted therapy Directed According to Response in transplant-eligibile (TE) NDMM patients



PIs: Prof. Kwee Yong & Dr. Mark Cook.
Moreau P, personal communication, courtesy of Prof. Yong and Dr. Cook.
NDMM, newly diagnosed multiple myeloma; TE, stem-cell translation; KCRD, carfilzomib-cyclophosphamide-lenalidomide-dexamethasone; HR, high risk; SR, standard risk; ASCT, autologous stem-cell transplantation; MRD, minimal residual disease; PI, proteasome inhibitor; IMiD, immunomodulatory drug; Ab, antibody.

Acknowledgments

GIMEMA/European Myeloma Network

**Division of Hematology, University of Torino,
Azienda Ospedaliero-Universitaria Città della Salute e della Scienza,
Torino, Italy**

Prof. Mario Boccadoro

Dr. Sara Bringhen
Dr. Alessandra Larocca
Dr. Stefania Oliva

Dr. Chiara Cerrato
Dr. Roberto Mina

Dr. Luca Bertamini
Dr. Francesca Bonello
Dr. Giusy Cetani
Dr. Mattia D'Agostino
Dr. Marco Salvini

**Dr. Paola Omedé &
Laboratory Staff**

**Dr. Benedetto Bruno &
Transplant Unit**

Nurses

Data Managing Staff