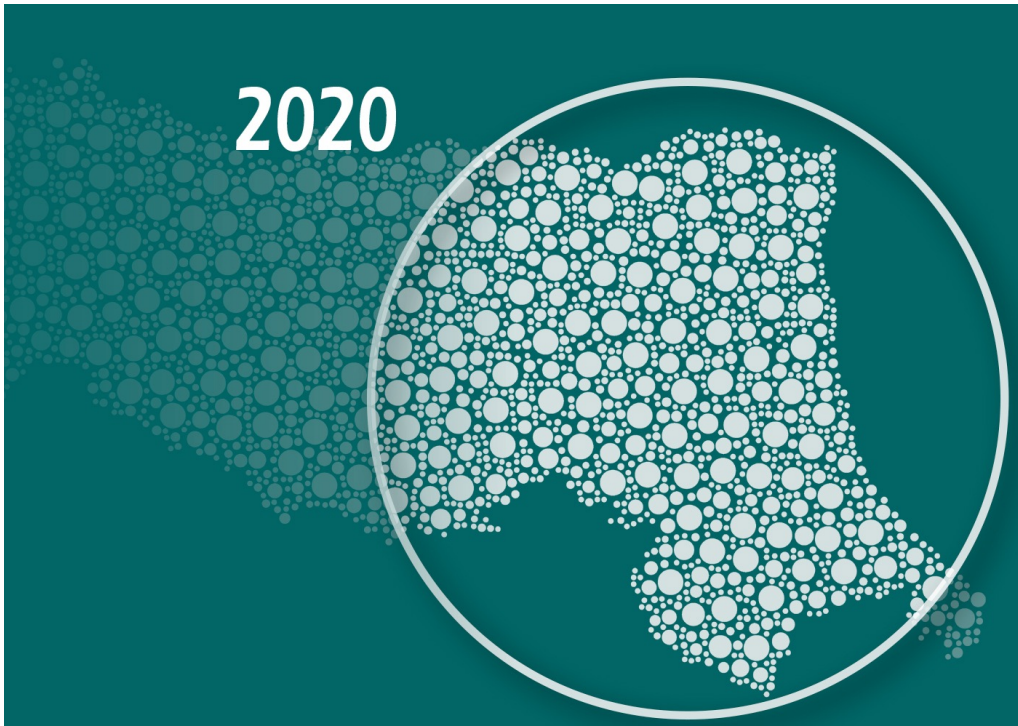


Progetto Ematologia Romagna

Mieloma Multiplo: lunghi sopravviventi o guariti

Paola Tacchetti

Azienda Ospedaliero-Universitaria di Bologna; Istituto di Ematologia “Seràgnoli”;
Dipartimento di Medicina Specialistica, Diagnostica e Sperimentale; Università degli Studi di Bologna

Disclosures of Paola Tacchetti

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Bristol-Myers Squibb/Celgene						x	honoraria
Janssen						x	honoraria
Amgen						x	honoraria
Takeda						x	honoraria
Abbvie							honoraria
Oncopeptides							honoraria

Treating myeloma – The changing landscape

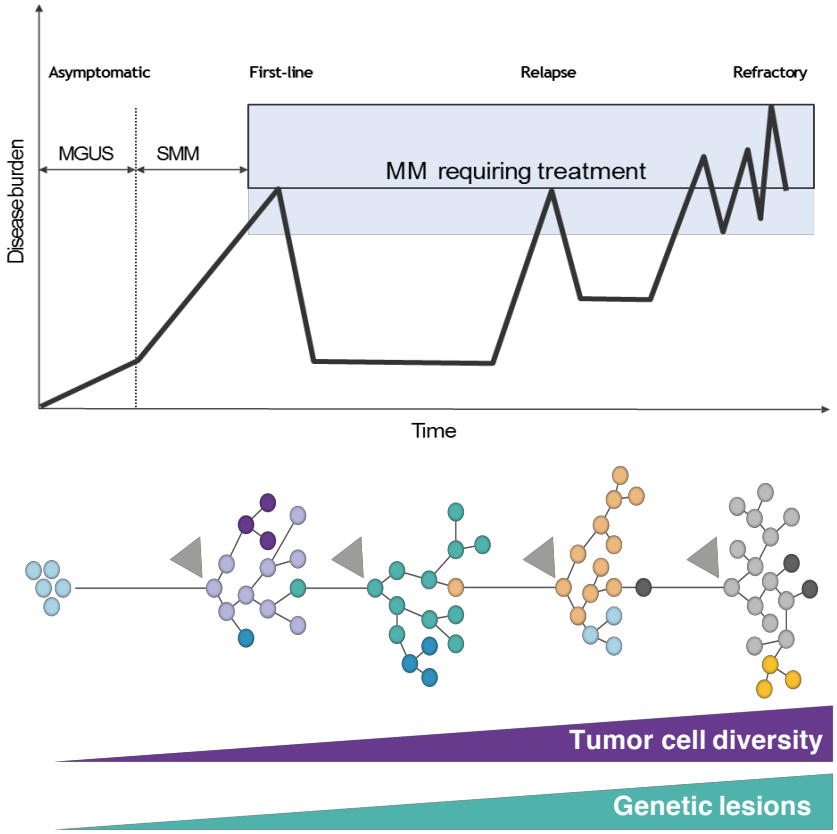
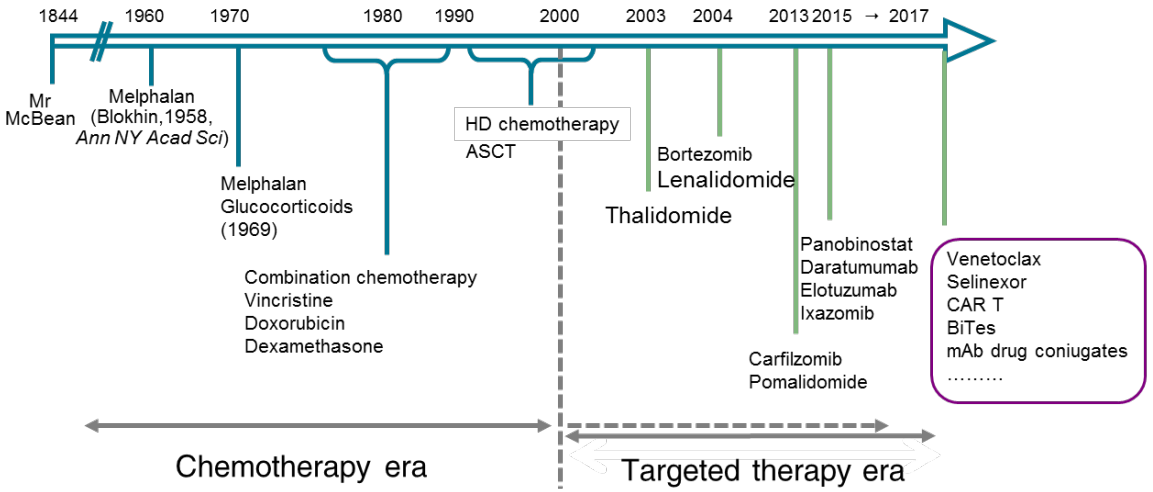
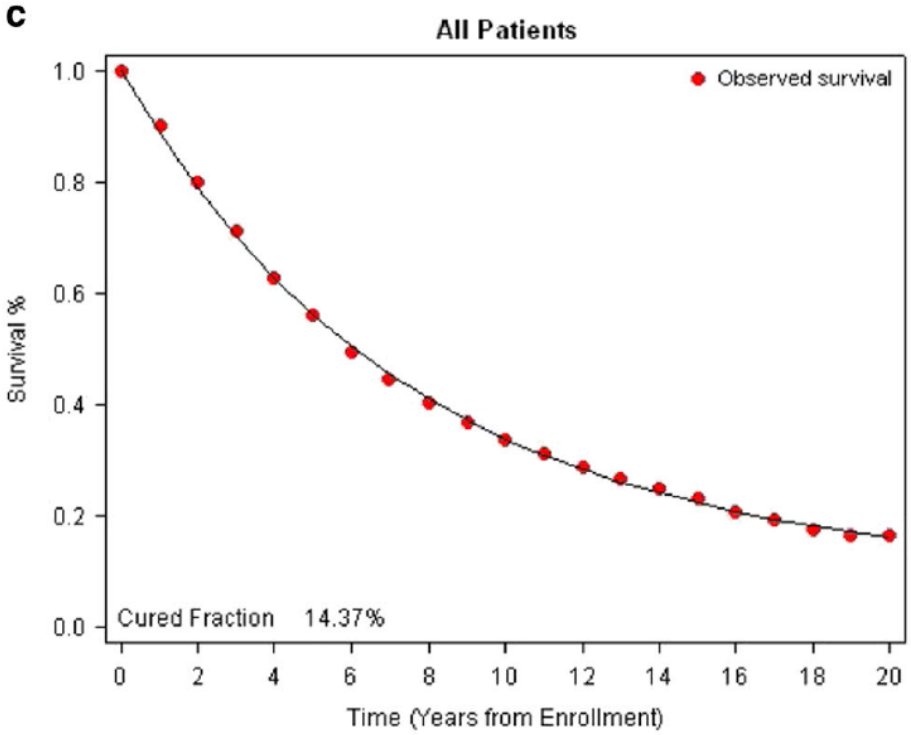


Image adapted from Morgan G et al. Nat Cancer Revs 2012;12:335-348



Is MM "curable"?

Clinical predictors of long-term survival in NDTE MM
An IMWG Research Project



7291 pts enrolled in clinical trials involving ASCT

The **statistical cure fraction** for the whole group appears to be **14.3%**, which signifies the overall proportion of MM pts in this cohort who were able to achieve or exceed expected survival compared to matched general population.

Usmani SZ, et al. Blood Cancer Journal 2018;8:123

IMWG Research Project: OS and PFS by CR status

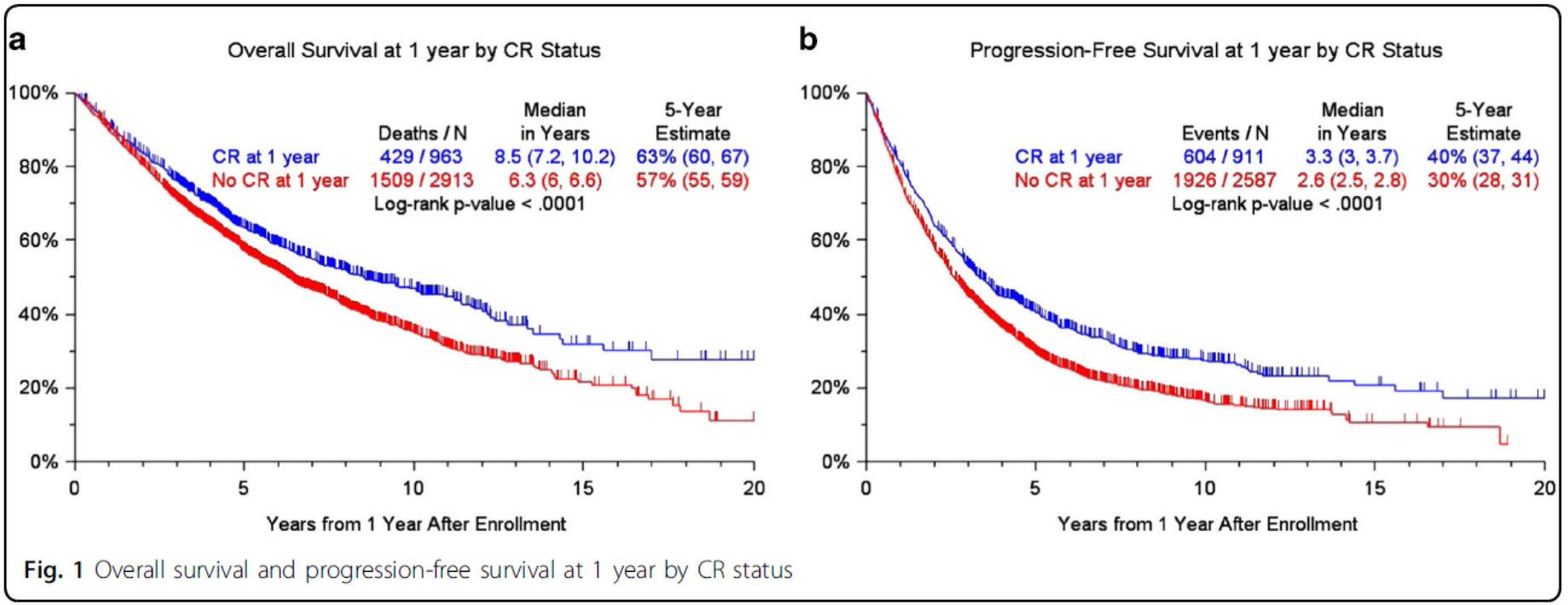


Fig. 1 Overall survival and progression-free survival at 1 year by CR status

Usmani SZ, et al. Blood Cancer Journal 2018;8:123

IMWG Research Project: Logistic regression, 10-yr survival vs 2-yr death

	Factors differentiating 10-year survival vs. 2-year death				
Variable	***N***	**Survival less than 2 years**	**Survival more than 10 years**	**OR (95% CI)**	***P*-value**
Multivariate (stratified by country)					
Age at registration > = 65 yr	1230	98/144 (68%)	525/1086 (48%)	1.87 (1.26, 2.79)	0.002
IgA	1230	180/298 (60%)	443/932 (48%)	1.53 (1.15, 2.04)	0.004
Albumin < 3.5 g/dL	1230	294/474 (62%)	329/756 (44%)	1.36 (1.04, 1.78)	0.023
B2M > = 3.5 mg/L	1230	376/569 (66%)	247/661 (37%)	1.86 (1.41, 2.45)	< 0.001
Creatinine > = 2 mg/dL	1230	130/174 (75%)	493/1056 (47%)	1.77 (1.18, 2.65)	0.005
HGB < 10 g/dL	1230	288/429 (67%)	335/801 (42%)	1.55 (1.16, 2.06)	0.003
Platelet Count < 150 × 10^9/L	1230	163/218 (75%)	460/1012 (45%)	2.26 (1.59, 3.22)	< 0.001

It is important to note that **over 90% of the pts** in the dataset were from the **pre-novel therapy induction era** and ~10% did received thalidomide as part of their upfront therapy (Total Therapy 2 thalidomide arm, GMMG-HD3 thalidomide arm and BO2002).

Usmani SZ, et al. Blood Cancer Journal 2018;8:123

HOVON65MM/GMMG-HD41

Sonneveld et al. JCO 2012;30:2946-55

RANDOM n=827

INDUCTION (3x 28-d cycles)

INDUCTION PAD

INDUCTION VAD

MOBILIZATION

TRANSPLANTATION *
- MEL 200 (ASCT-1)
- MEL 200 (ASCT-2)

* HOVON single / GMMG double ASCT

MAINTENANCE V (2 years)

MAINTENANCE T (2 years)

PETHEMA/GEM

Rosinol et al. Blood 2012;120:1589-96

RANDOM n=386

INDUCTION (6x 28-d cycles)

VBMCP/ VBAD/B

VTD

TD

MOBILIZATION

TRANSPLANTATION MEL 200 (ASCT-1)

RANDOM

MAINTENANCE (3 years)

IFN-α2b

VT

T

GIMEMA MMY-3006

Cavo M et al. Lancet 2010;376:2075-85

RANDOM n=474

INDUCTION (3x 21-d cycles)

INDUCTION VTD

INDUCTION TD

MOBILIZATION

TRANSPLANTATION
- MEL 200 (ASCT-1)
- MEL 200 (ASCT-2)

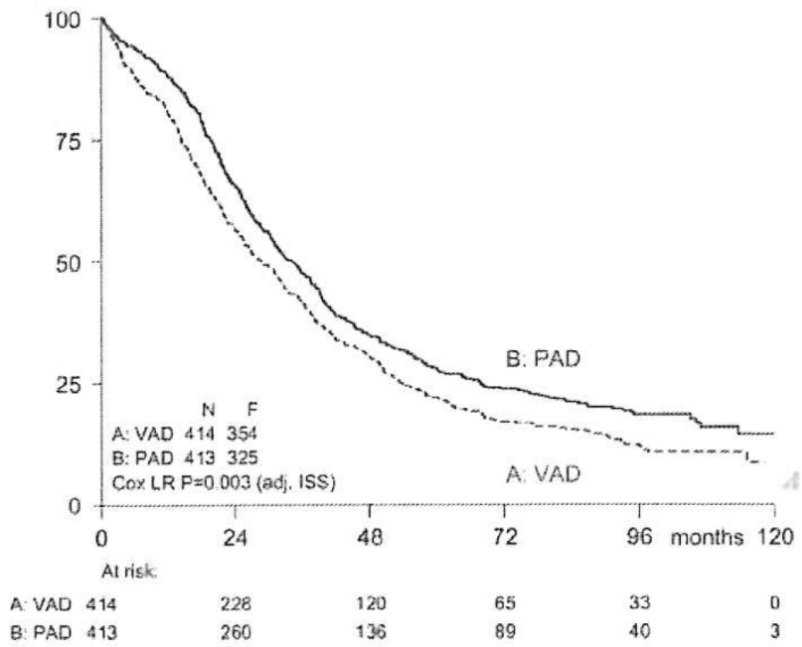
CONSOLIDATION VTD 2x 35-d cycles

CONSOLIDATION TD 2x 35-d cycles

MAINTENANCE DEX

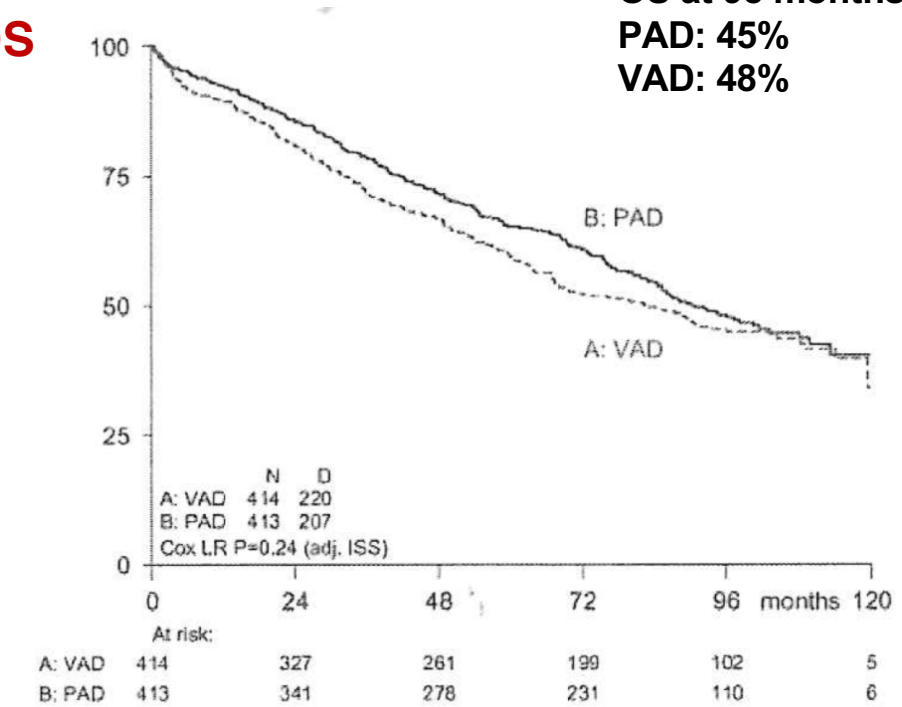
HOVON-65/GMMG-HD4 study: long-term analysis (98-mo follow-up)

PFS



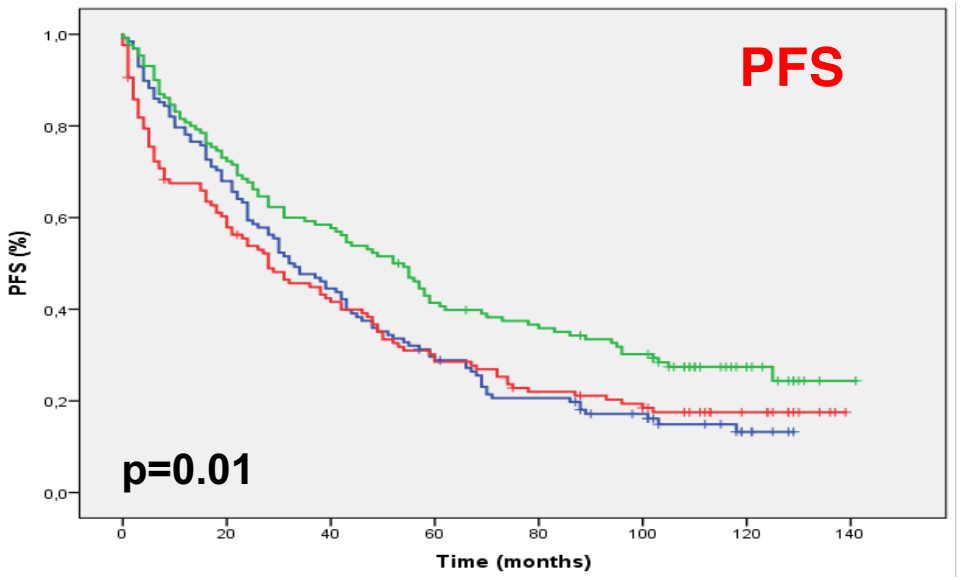
OS

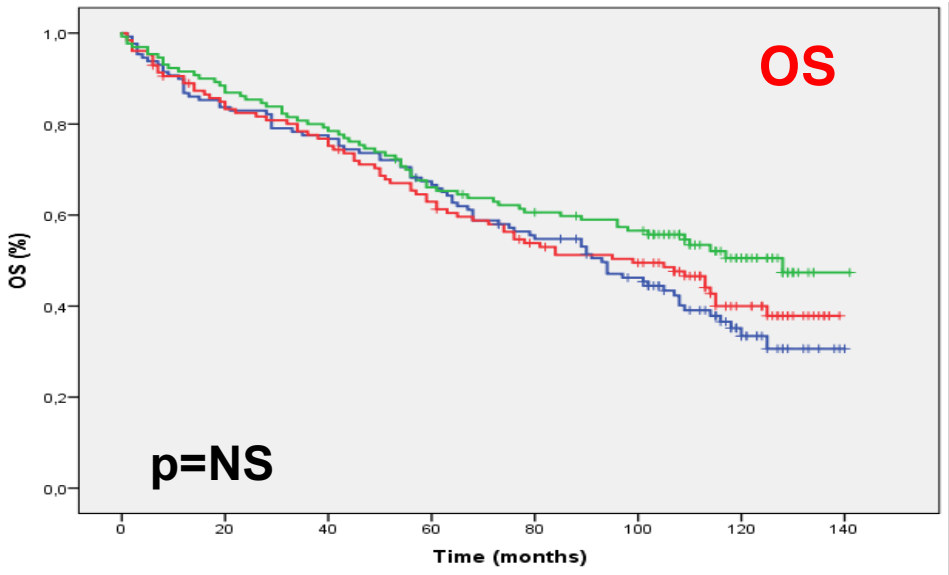
OS at 98 months:
PAD: 45%
VAD: 48%



Goldschmidt H. et al., Leukemia 2018;32:383-390

PETHEMA/GEM study: long-term analysis (10-yr follow-up)



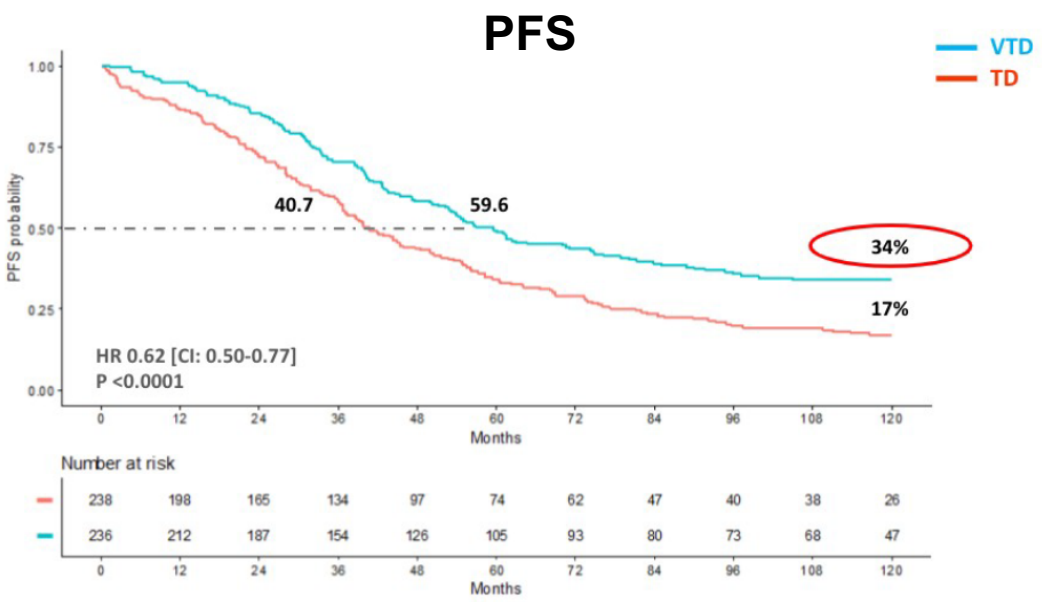


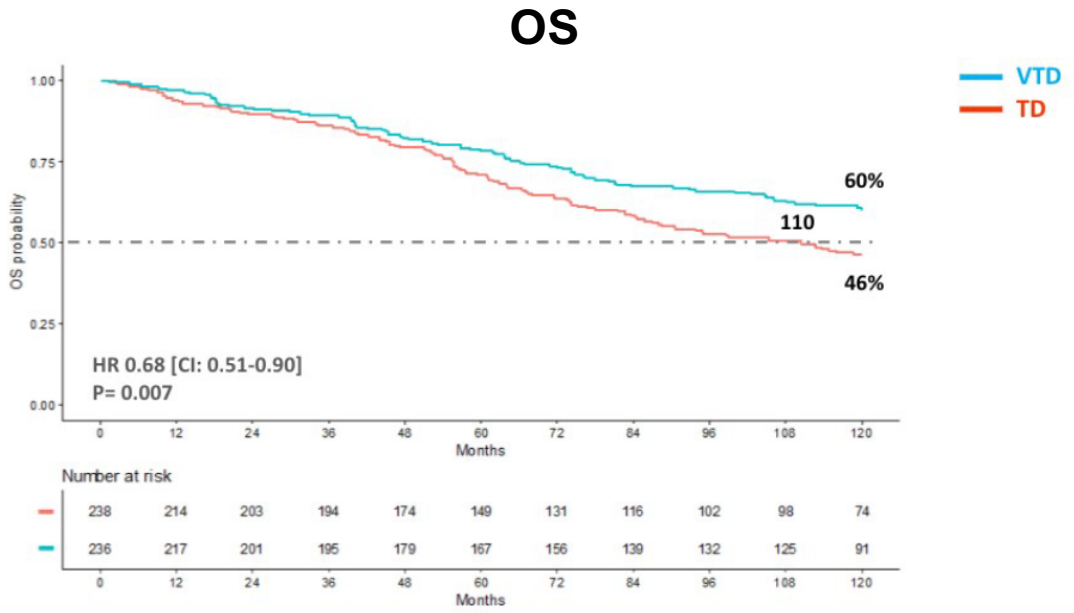
	Median PFS (mos)	10-yr PFS (%)
QT+V	32	13
TD	28	17
VTD	52	24

	Median OS (mos)	10-yr OS (%)
QT+V	93	33
TD	99	40
VTD	128	51

Rosinol L. et al., ASH 2018

GIMEMA-MMY-3006 study: long-term analysis (10-yr follow-up)





HR, hazard ratio; PFS, progression-free survival; OS, overall survival; TD, thalidomide + dexamethasone; VTD, bortezomib + thalidomide + dexamethasone.

Tacchetti P. et al., Lancet Haematology 2020, accepted

HOVON65MM/GMMG-HD41

Sonneveld et al. JCO 2012;30:2946-55

RANDOM n=827

INDUCTION (3x 28-d cycles)

INDUCTION PAD

INDUCTION VAD

MOBILIZATION

TRANSPLANTATION *
- MEL 200 (ASCT-1)
- MEL 200 (ASCT-2)

* HOVON single / GMMG double ASCT

MAINTENANCE V (2 years)

MAINTENANCE T (2 years)

PETHEMA/GEM

Rosinol et al. Blood 2012;120:1589-96

RANDOM n=386

INDUCTION (6x 28-d cycles)

VBMCP/ VBAD/B

VTD

TD

MOBILIZATION

TRANSPLANTATION MEL 200 (ASCT-1)

RANDOM

MAINTENANCE (3 years)

IFN-α2b

VT

T

GIMEMA MMY-3006

Cavo M et al. Lancet 2010;376:2075-85

RANDOM n=474

INDUCTION (3x 21-d cycles)

INDUCTION VTD

INDUCTION TD

MOBILIZATION

TRANSPLANTATION
- MEL 200 (ASCT-1)
- MEL 200 (ASCT-2)

CONSOLIDATION VTD 2x 35-d cycles

CONSOLIDATION TD 2x 35-d cycles

MAINTENANCE DEX

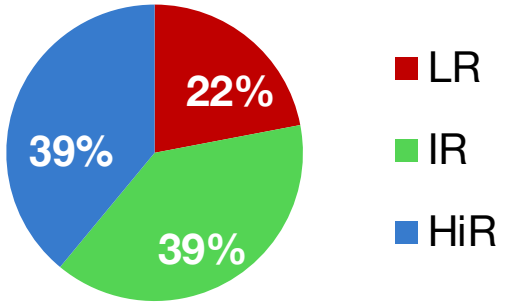
GIMEMA-MMY-3006 study: PROGNOSTIC SCORE

SPECIFIC MULTIVARIABLE REGRESSION ANALYSIS NOT INCLUDING THERAPY

Variables adversely affecting PFS	HR	95% CI	*P*-value
t(4;14) and/or del(17p) pos	1.857	1.452-2.375	<0.001
ISS stage II+III	1.384	1.099-2.743	0.006
Failure to achieve CR* (best response)	2.006	1.593-2.526	<0.001

*time-dependent variable

Risk group	Criteria
Low-risk (LR)	**None** of the three adverse variables
Intermediate-risk (IR)	**1** adverse variable
High-risk (HiR)	**2** or **3** adverse variables



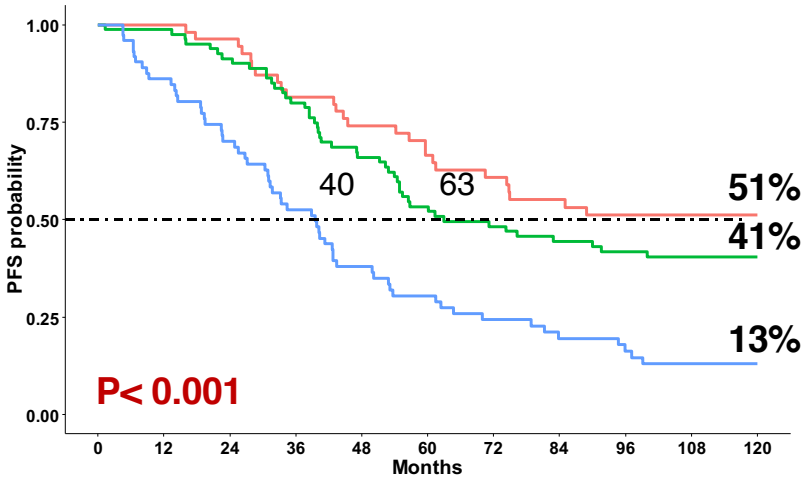
Tacchetti P. et al., Lancet Haematology 2020, accepted

GIMEMA-MMY-3006 study: PFS and OS by risk groups within the VTD arm

LR
IR
HiR

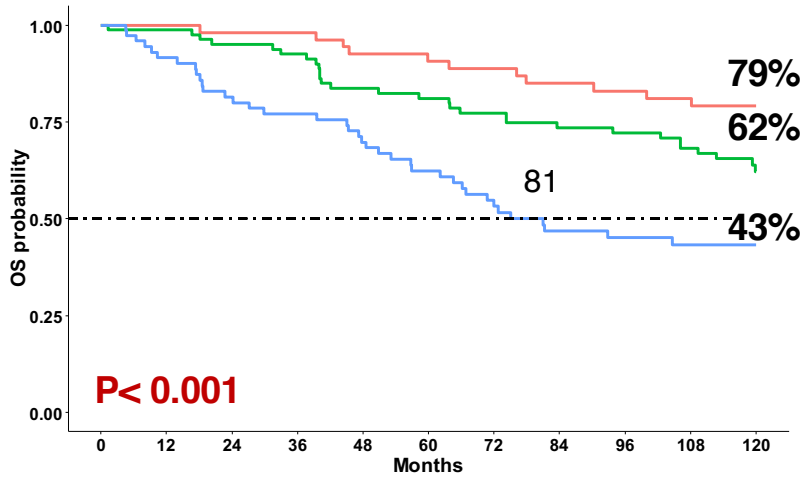
PFS

	HR (95% CI)	P
LR vs HiR	0.32 (0.20-0.51)	<0.001
IR vs HiR	0.44 (0.30-0.54)	<0.001



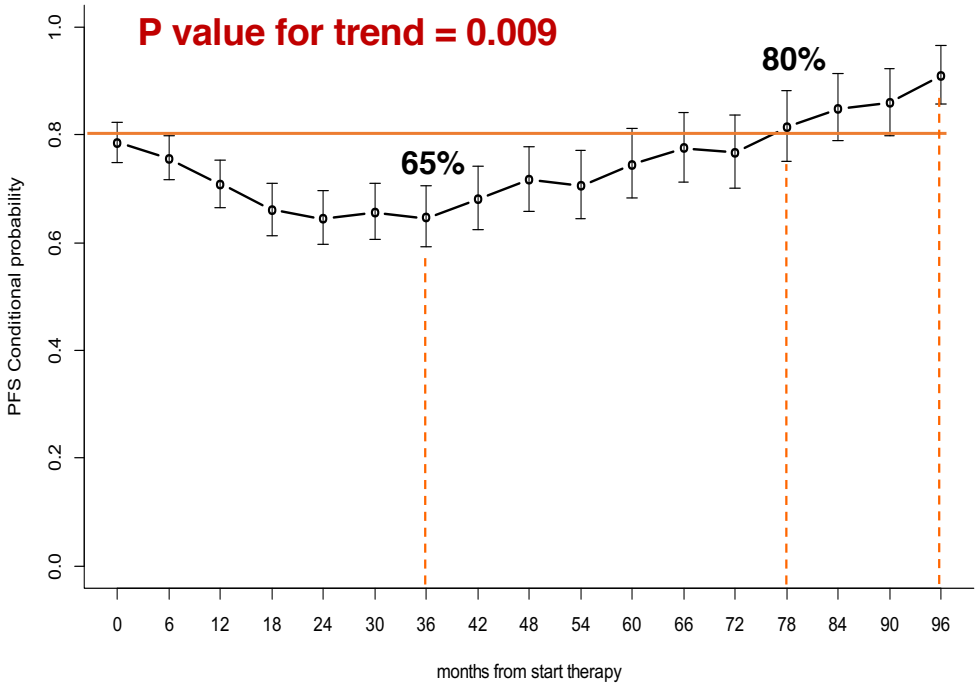
OS

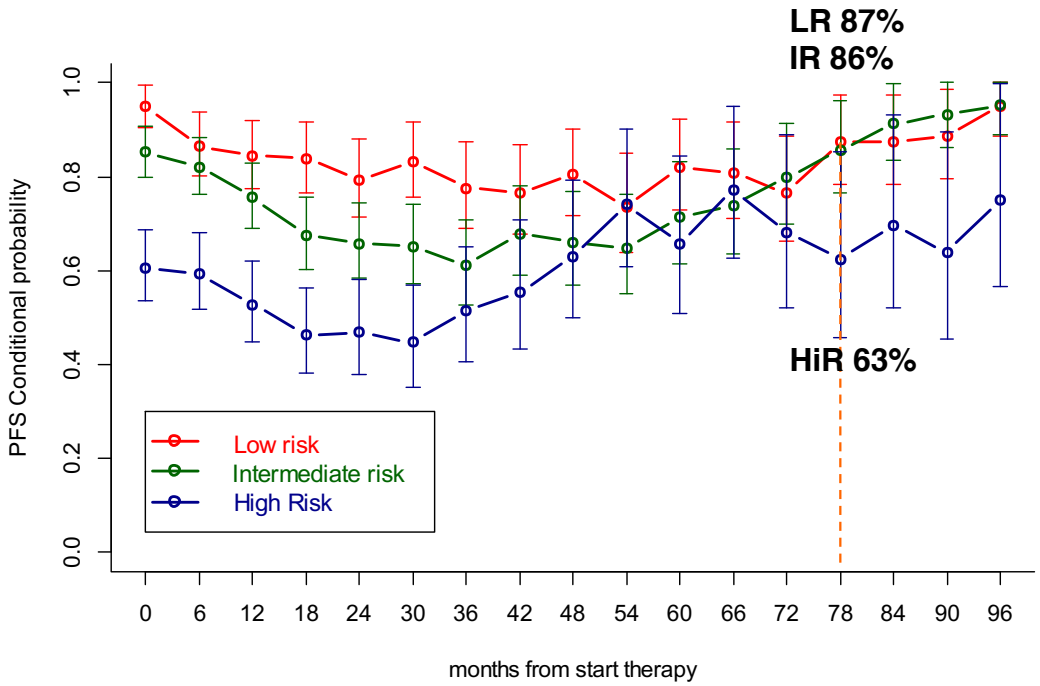
	HR (95% CI)	P
LR vs HiR	0.25 (0.13-0.50)	<0.001
IR vs HiR	0.50 (0.31-0.81)	<0.001



Tacchetti P. et al., Lancet Haematology 2020, accepted

GIMEMA-MMY-3006 study: 2-YRS CONDITIONAL SURVIVAL ESTIMATE FOR PFS

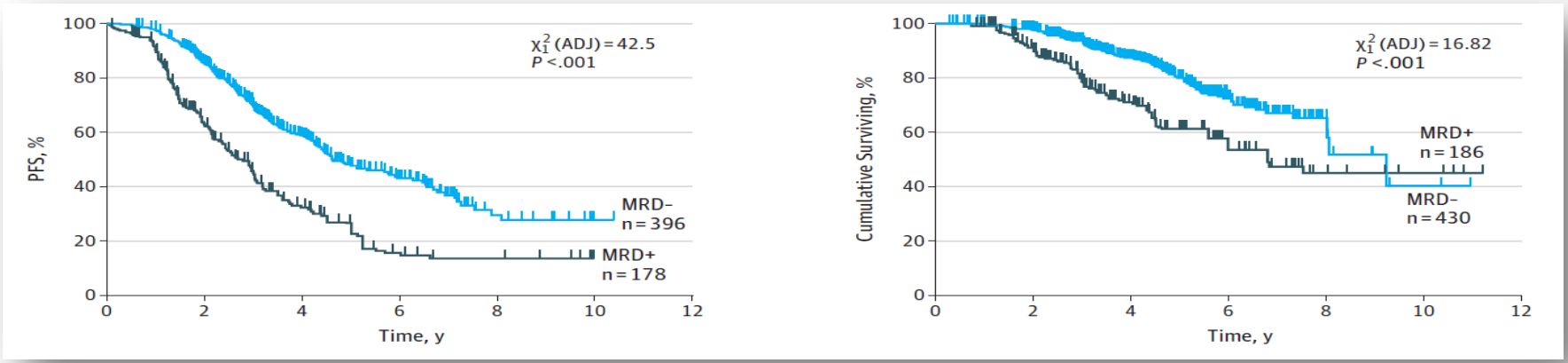




Conditional survival estimate for PFS was calculated as the probability of surviving without progression a further 2 years given the years already survived

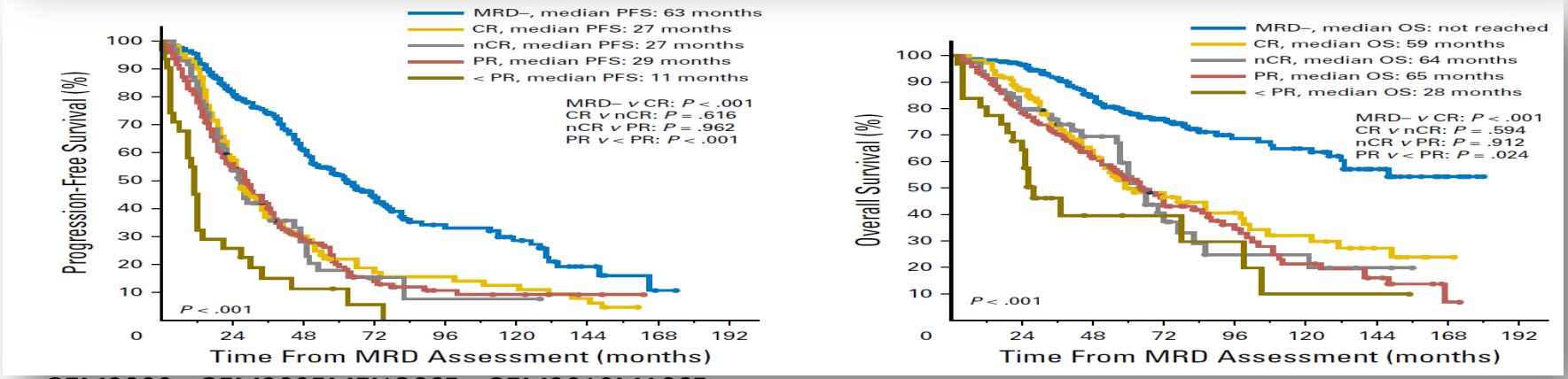
Tacchetti P. et al., Lancet Haematology 2020, accepted

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

PETHEMA/GEM study: Post-transplant negative MRD ($1x10^{-4}$)*

	Negative MRD
Overall series (n=226)	135 (60%)
CT+V (n=85)	48 (56%)
TD (n=50)	27 (46%)
VTD (n=83)**	60 (72%)

*MRD available in 226/ 284 (80%) transplanted patients

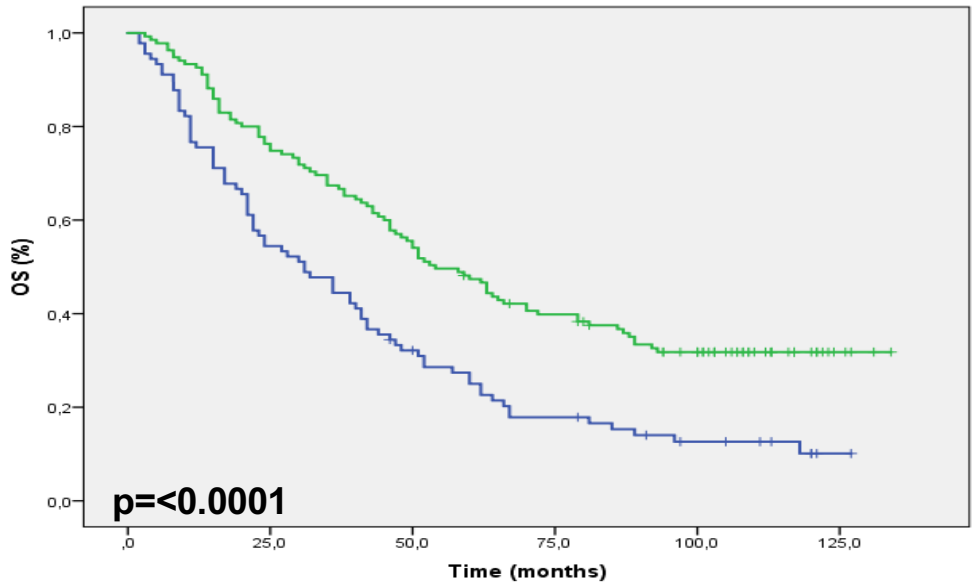
** VTD vs TD, p=0.03; VTD vs CT+V, p=0.04; TD vs CT+V, p= 0.9

Rosinol L. et al., ASH 2018

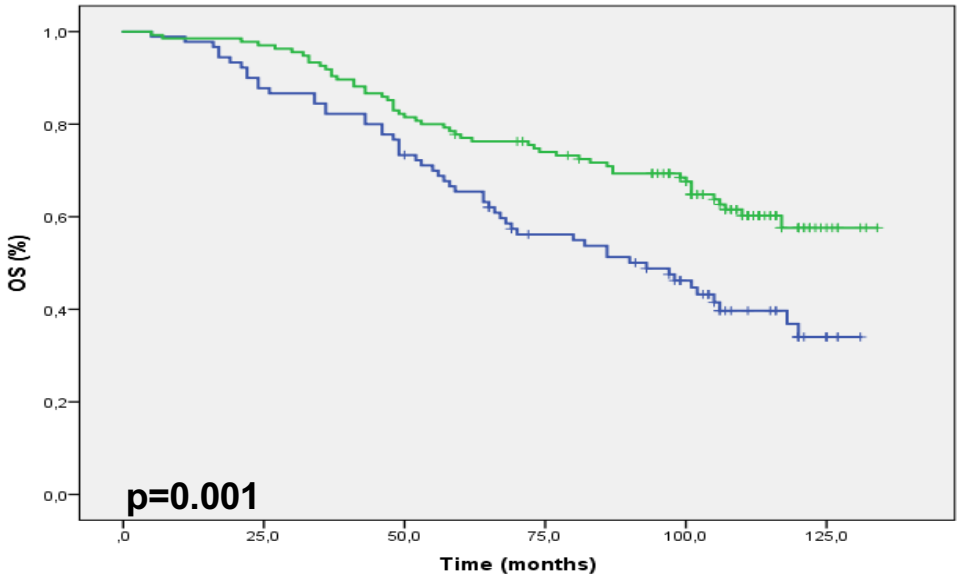
PETHEMA/GEM study: PFS and OS according to post-transplant MRD

(overall series)

PFS



OS

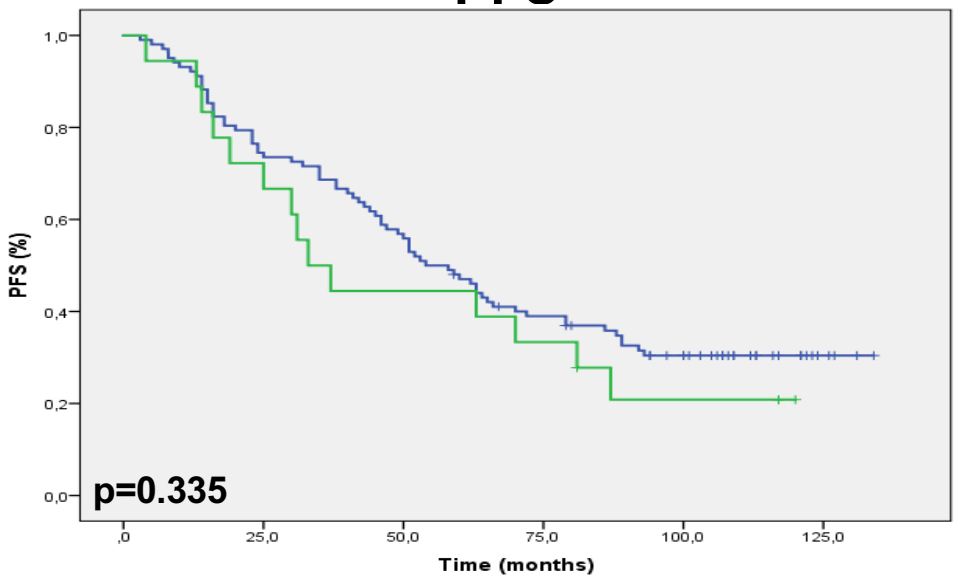


	Median PFS (mos)	Median OS (mos)
Negative MRD	55	NR
Positive MRD	31	93

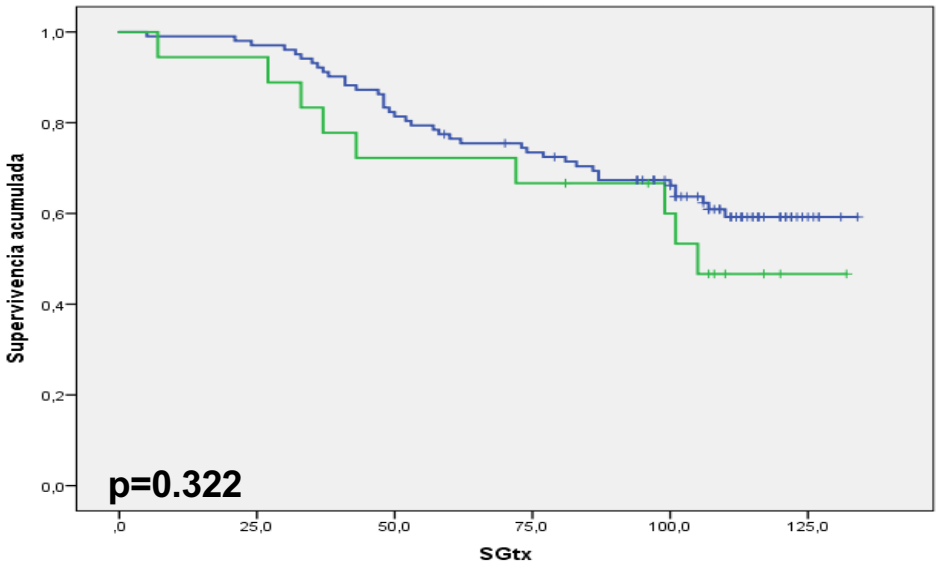
Rosinol L. et al., ASH 2018

PETHEMA/GEM study: Outcome of patients with negative post-transplant MRD according to cytogenetics

PFS



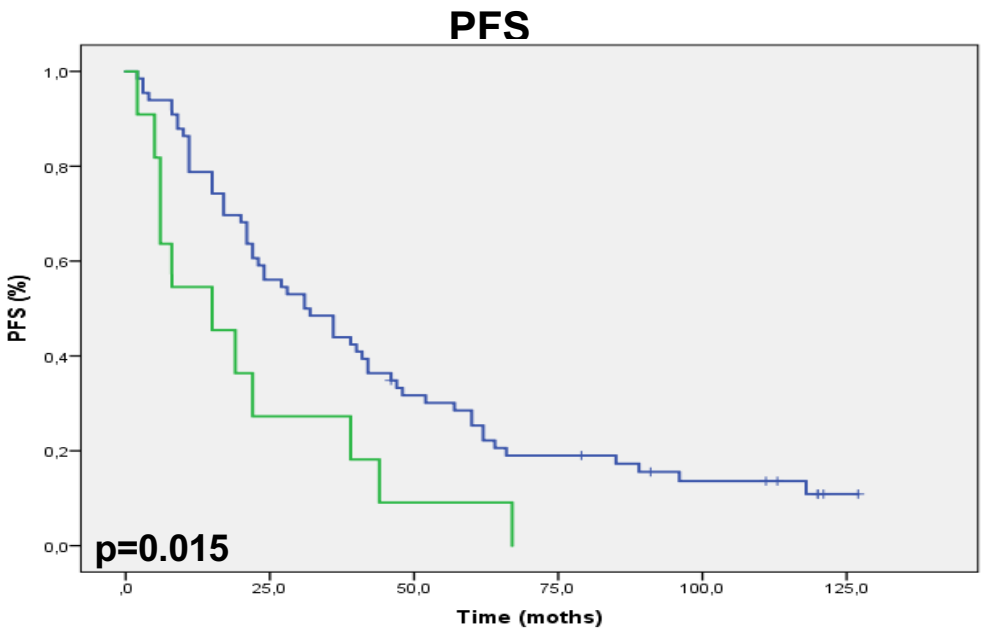
OS

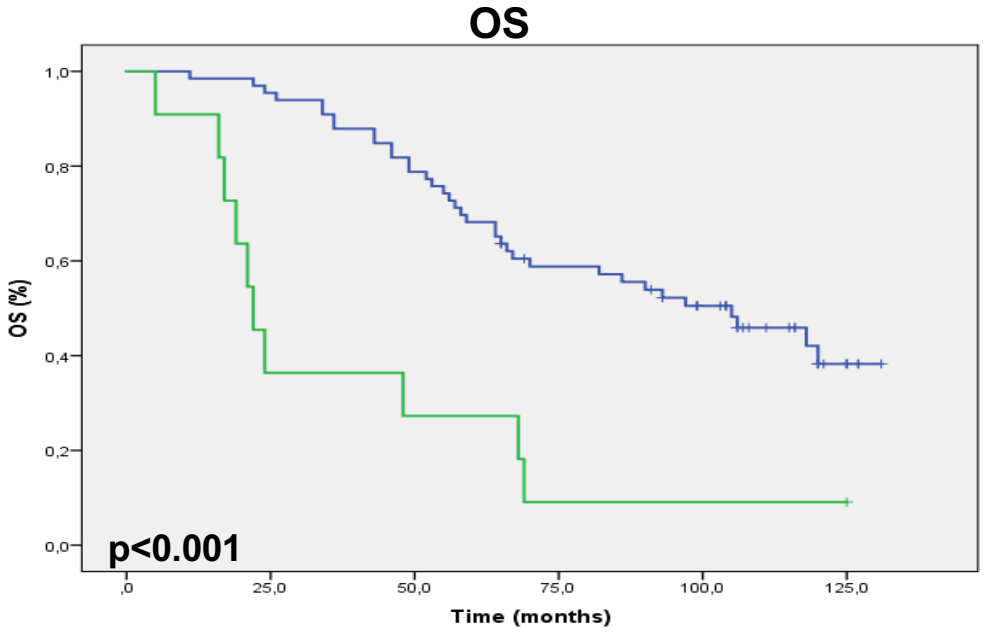


	Median PFS (mos)	Median OS (mos)
Standard- risk cytogenetics	54	NR
High-risk cytogenetics	33	105

Rosinol L. et al., ASH 2018

PETHEMA/GEM study: Outcome of patients with positive post-transplant MRD according to cytogenetics



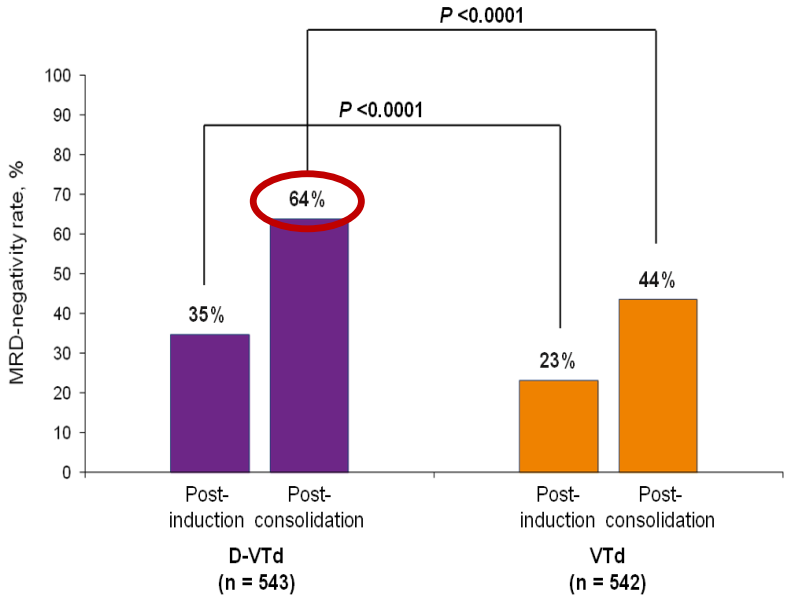


	Median PFS (mos)	Median OS (mos)
Standard- risk cytogenetics	31	105
High-risk cytogenetics	15	22

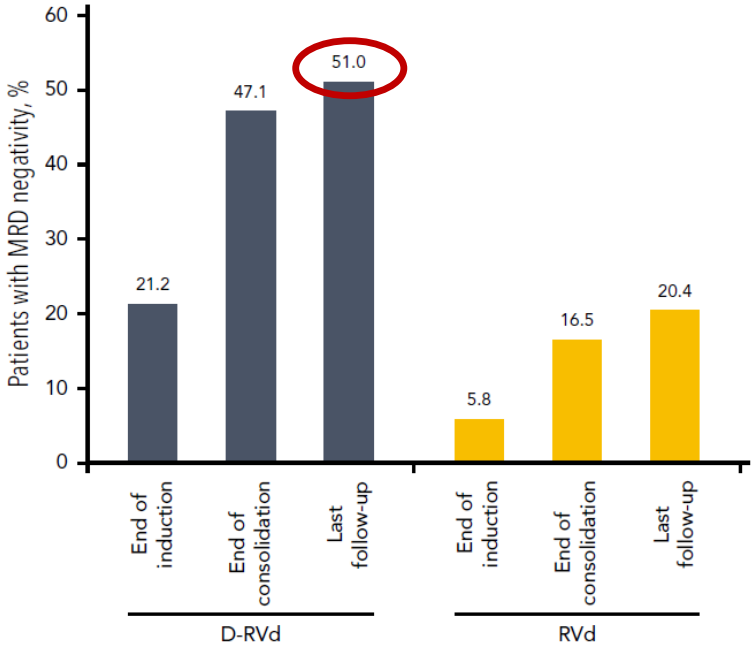
Rosinol L. et al., ASH 2018

Modern treatment strategies for NDTE: MRD data (10^{-5})

CASSIOPEIA ph3 trial

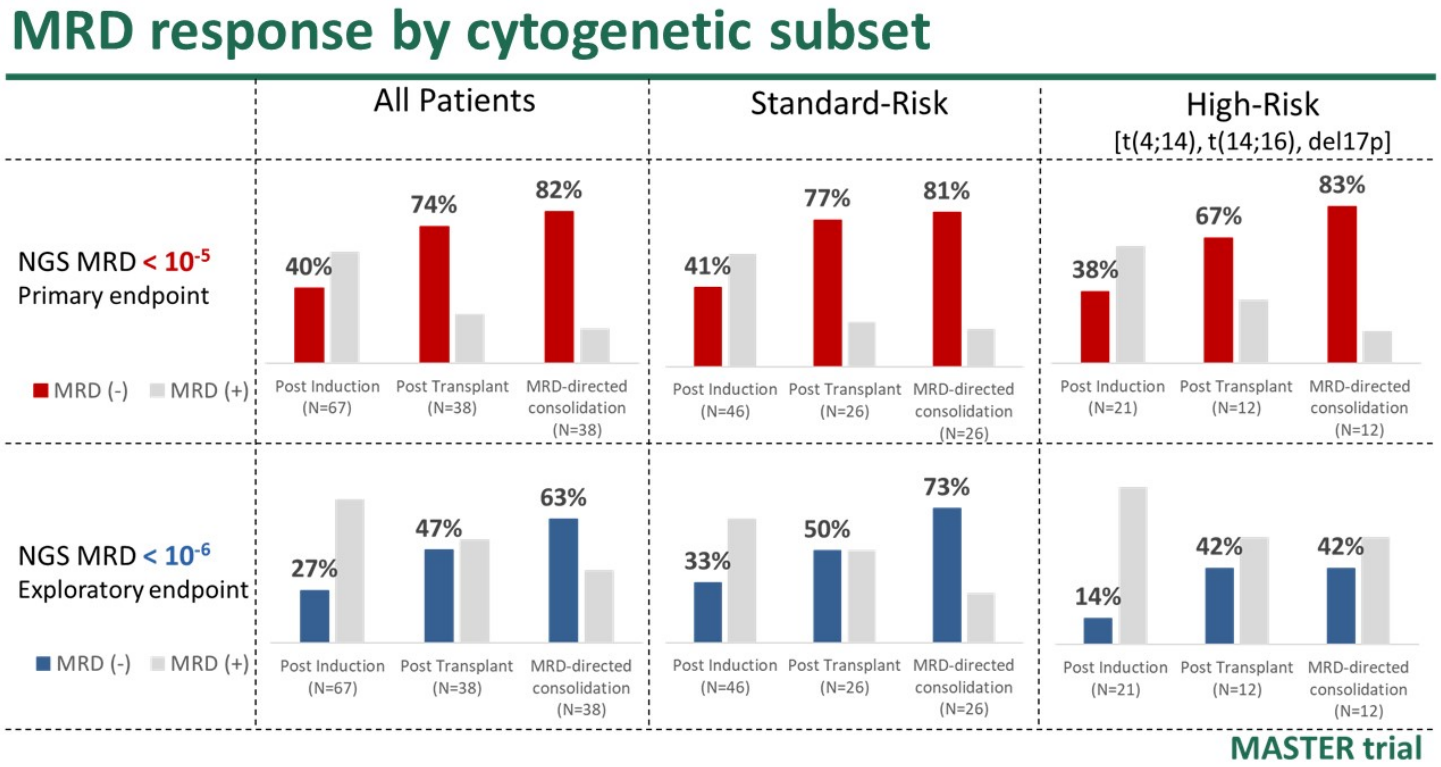


GRIFFIN ph2 trial



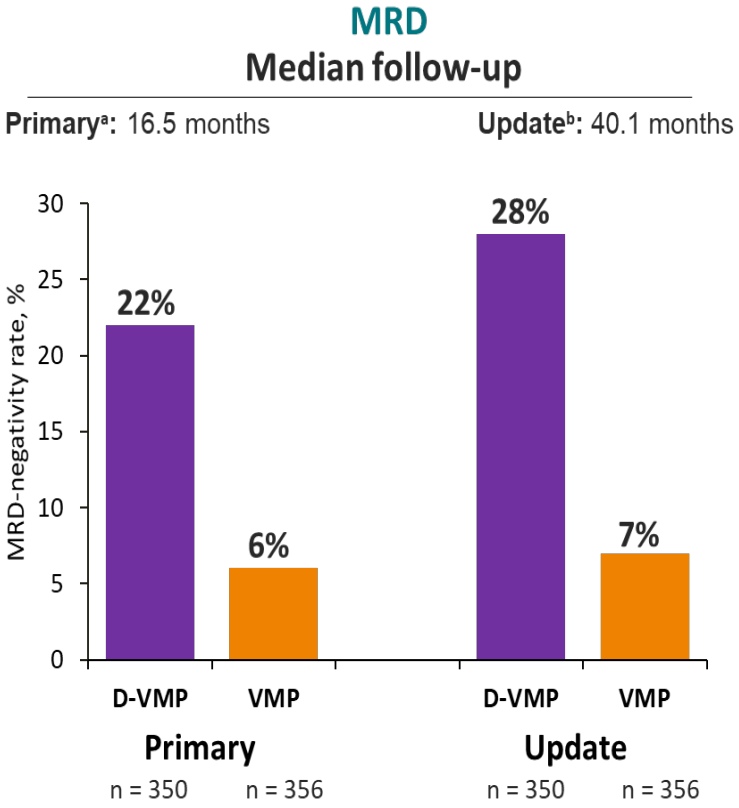
Moreau P, et al. The Lancet 2019;394:29-38; Avet-Loiseau H, et al. IMW 2019,Oral presentation; Voorhees PM et al., Blood. 2020;136(8):936-945

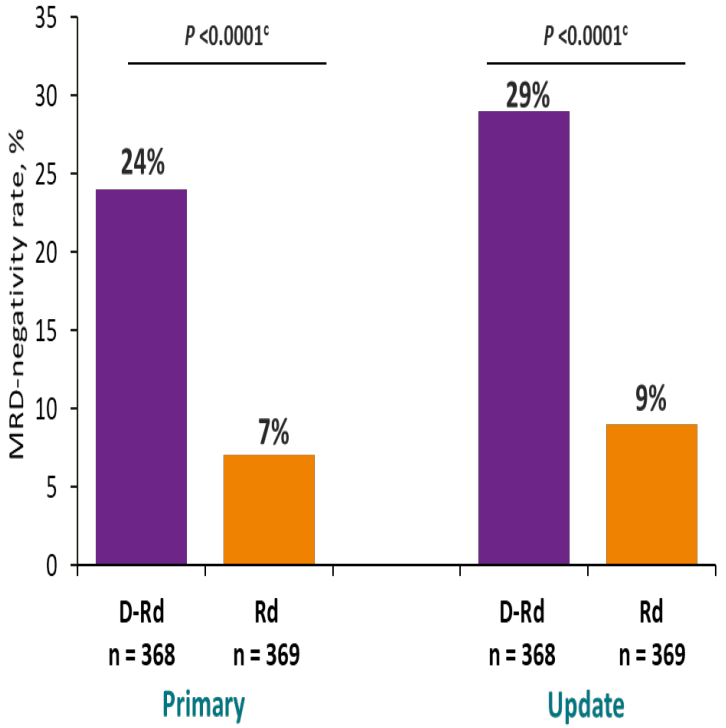
DaraKRd MASTER Trial : Best MRD response by phase of therapy



Costa LJ, et al., ASH 2019; oral presentation

Modern treatment strategies for ND non TE: MRD data (10^{-5})



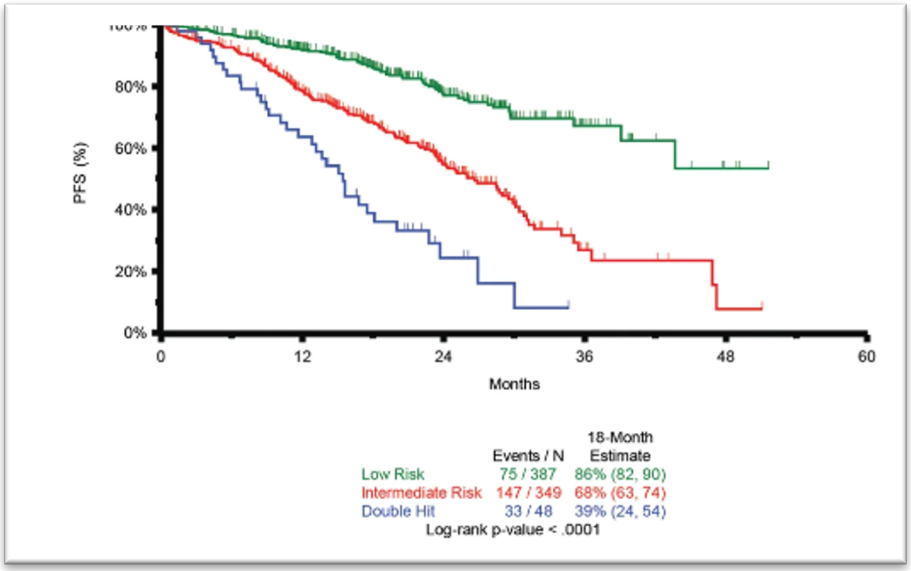


Mateos MV et al., Lancet 2020; Facon T et al. NEJM 2019

What do we know about long-term survivors

They Have	They Do Not
» Low disease burden and minimal end-organ disease » Favorable disease biology » CR or better » Receive optimal up-front therapy (PI + IMiDs, ASCT, maintenance, mAB?)	» High disease burden » Unfavorable disease biology (R-ISS3, HRCA, UltraHR, biallelic p53 del, EMD/PCL) » Suboptimal responses » Multiple co-morbidities

Unmet medical need: High-Risk and Ultra High-Risk Group: Double-Hit MM



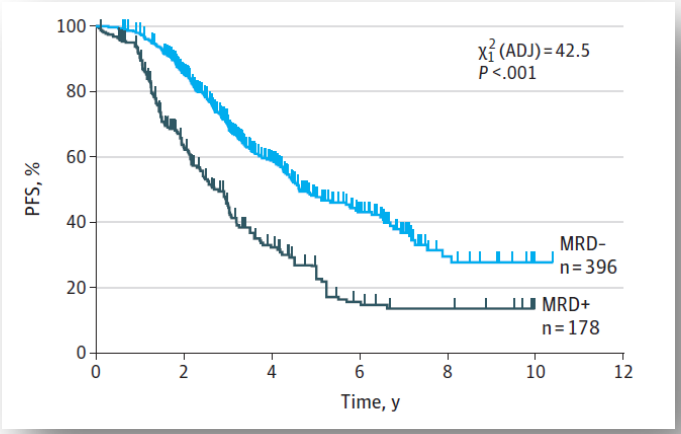
Characteristic: Bi-allelic inactivation of TP53 or ISSIII + amplification of CKS1B
Median PFS = 15.4 mths; OS 20.7 mths

Walker BA, et al., Leukemia 2018;33(1):159-170

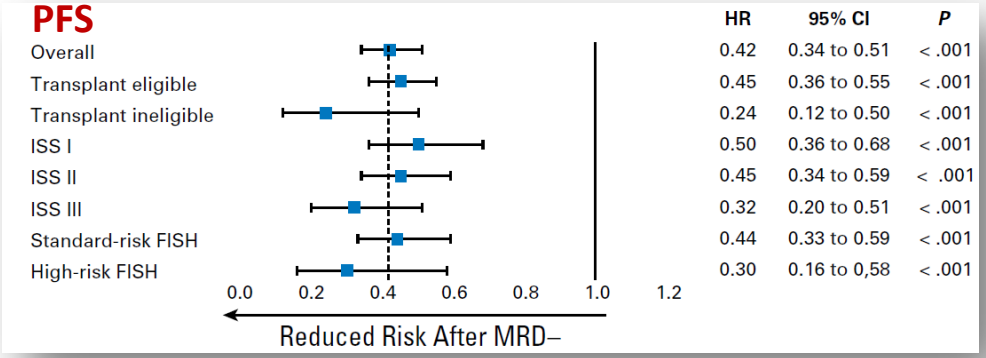
Depth of response correlate with survival MRD is the best biomarker to predict outcome

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

Meta-analysis of MRD studies (CR patients)

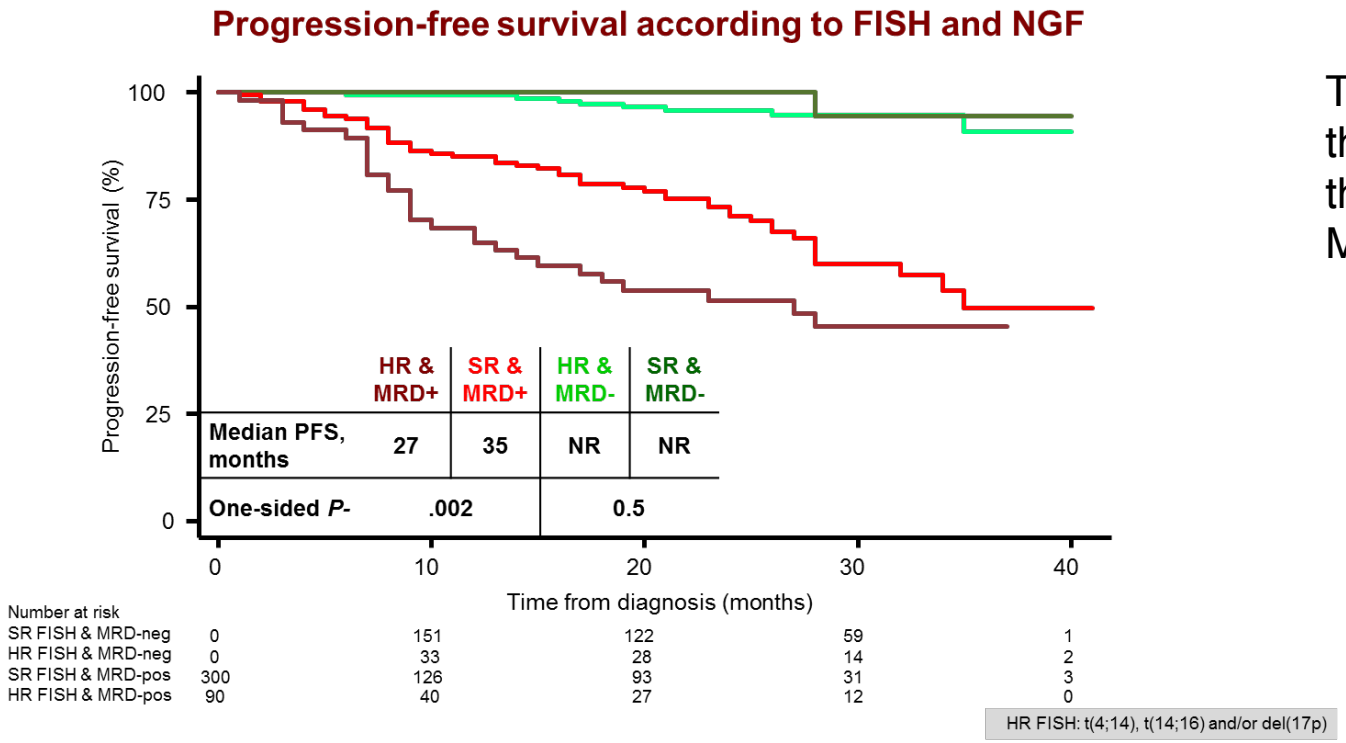


MRD negativity is a prognostic marker for PFS and OS across the spectrum of patients with MM



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

Can MRD-response modulate patients' risk at diagnosis?
Risk in dynamic: patients with adverse prognosis shift into a favorable one upon achieving deep responses to treatment



The best pathway to overcome the poor prognosis of HRCA is through the achievement of MRD-negativity

Paiva B et al. ASH 2017

Conclusions

- There are some known predictors of long-term survivors: depth or response, disease biology, tumor burden
- Not all long-term survivors can be considered effectively cured
- The combination of an extended PFS time (ie 78 months), depth of response and absence of high risk features, can be associated with survival curves potentially reaching a plateau
- MRD negativity is a strong predictor of survival, showing a higher prognostic power than CR, patients with adverse prognosis shift into a favorable one upon achieving deep responses (sustained MRD negativity) to treatment
- Ongoing clinical trials will provide further insights into the role of MRD disease-driven treatment strategies for these patients in the near future