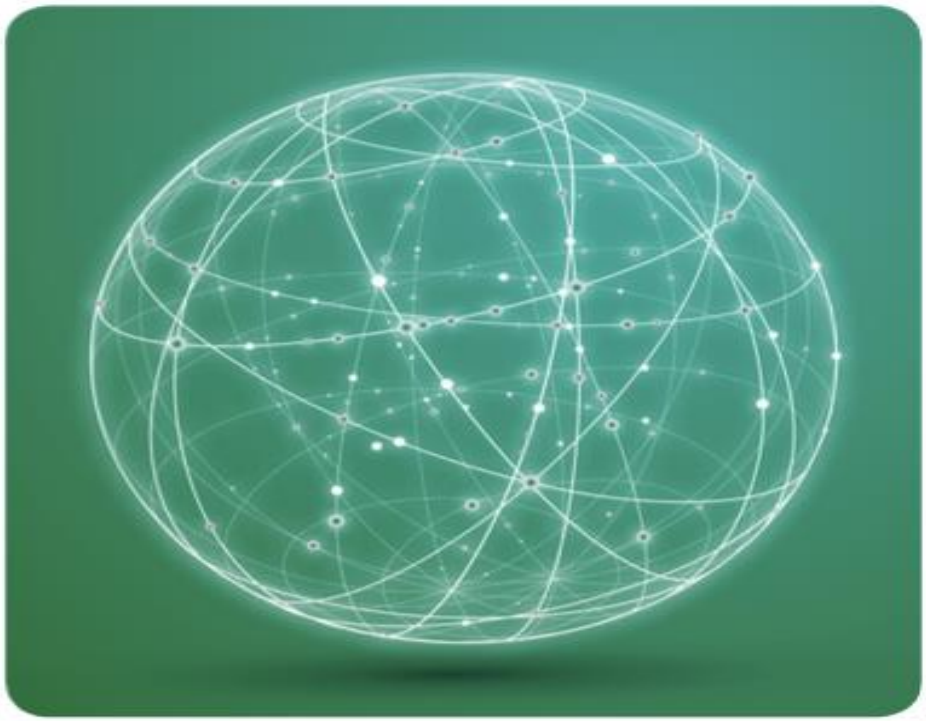


Con il patrocin

AZIENDA OSPEDALIERA UNIVERSITA' PADOVA

PADOVA
AOU PADOVA
AULA MAGNA
PALAZZINA DEI SERVIZI
Via Giustiniani, 2
22 MARZO 2019

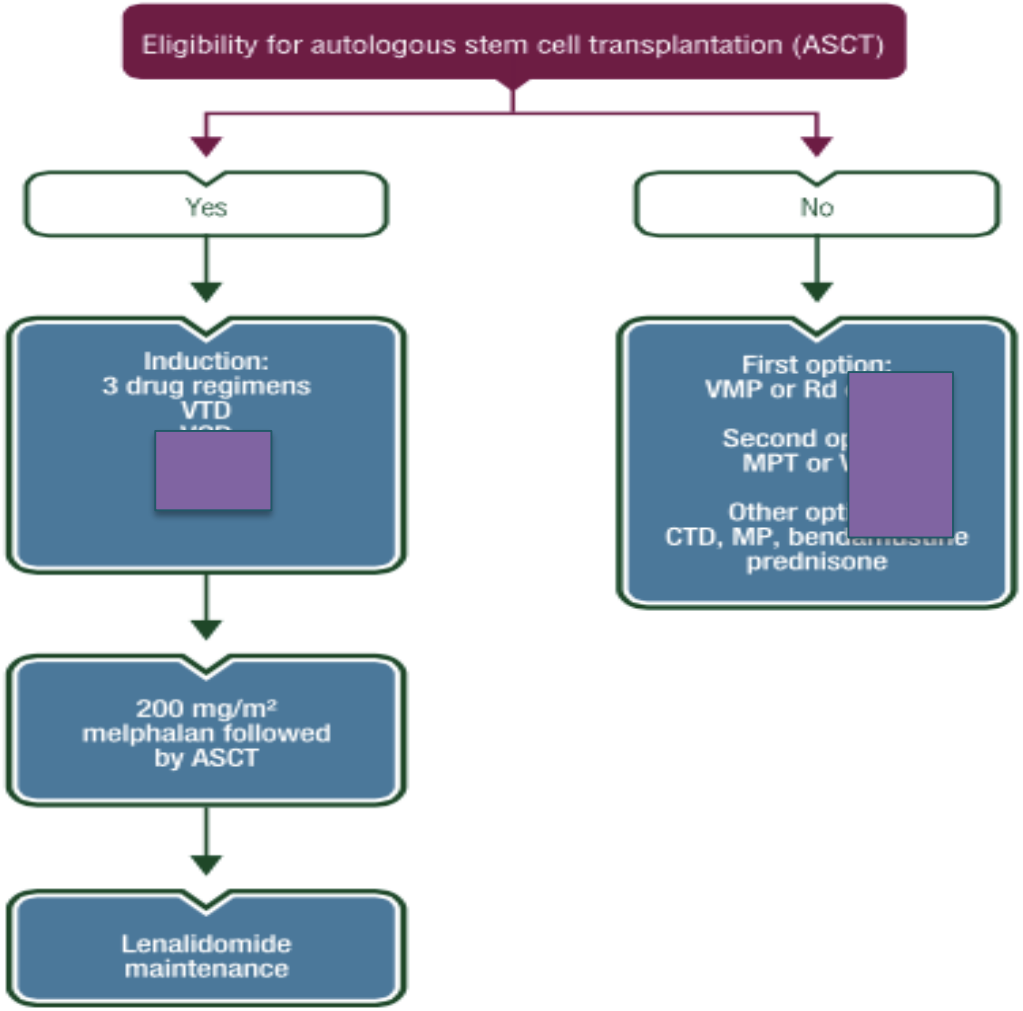
ONCOEMATOLOGIA
TRA SOSTENIBILITÀ E ADERENZA
IL CASO DEL TRIVENETO

TRATTAMENTO DEL PAZIENTE AD ALTO RISCHIO

F. Patriarca
Clinica Ematologica e Centro Trapianti-ASUI Udine
Università di Udine

FIRST LINE TREATMENT IN MM

Annals of Oncology

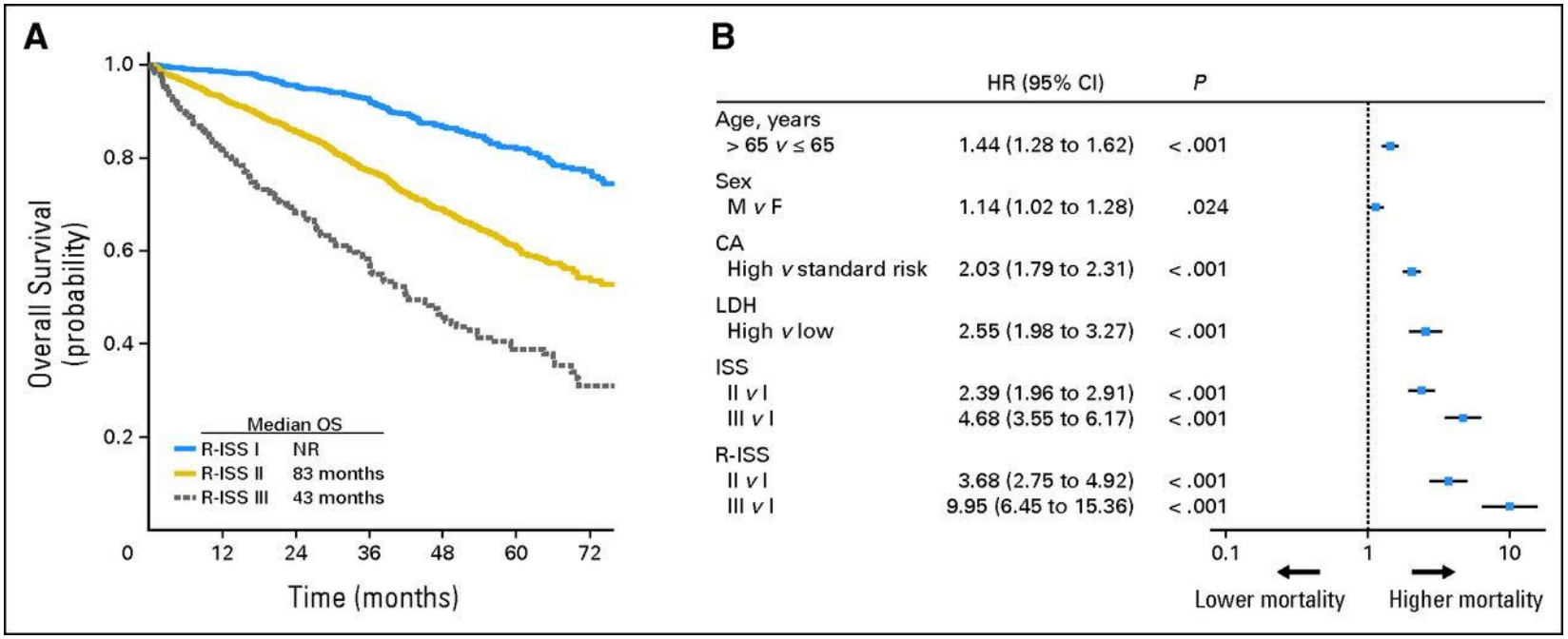


Moreau et al, ESMO guidelines 2017

Prognostic factors in MM

Patient characteristics	Disease characteristics	Tumor burden	Response
Age	ISS stage	D-S stage	CR *vs* other
PS	FISH Cytogenetics	PET scan	MRD
Geriatric assessment	GEP	MRI	
Toxicity	LDH	FLC + HLC	
	High LI		
	Extramedullary disease		
	Renal failure		
	Plasma cell leukemia		

R-ISS
Integration of FISH cytogenetics and clinical staging



R-ISS I: ISS I and standard risk cytogenetic abnormality (CA) by FISH and normal LDH (28%)

R- ISSII: no ISS I or III (62%)

R-ISS III: ISS III and either high-risk CA [del 17, t(4;14) e t (14;16)] by FISH or abnormal LDH (10%)

Antonio Palumbo et al. JCO 2015

ULTRA HIGH-RISK MM
(expected median OS < 2 years)

- presence of two or more adverse cytogenetic features

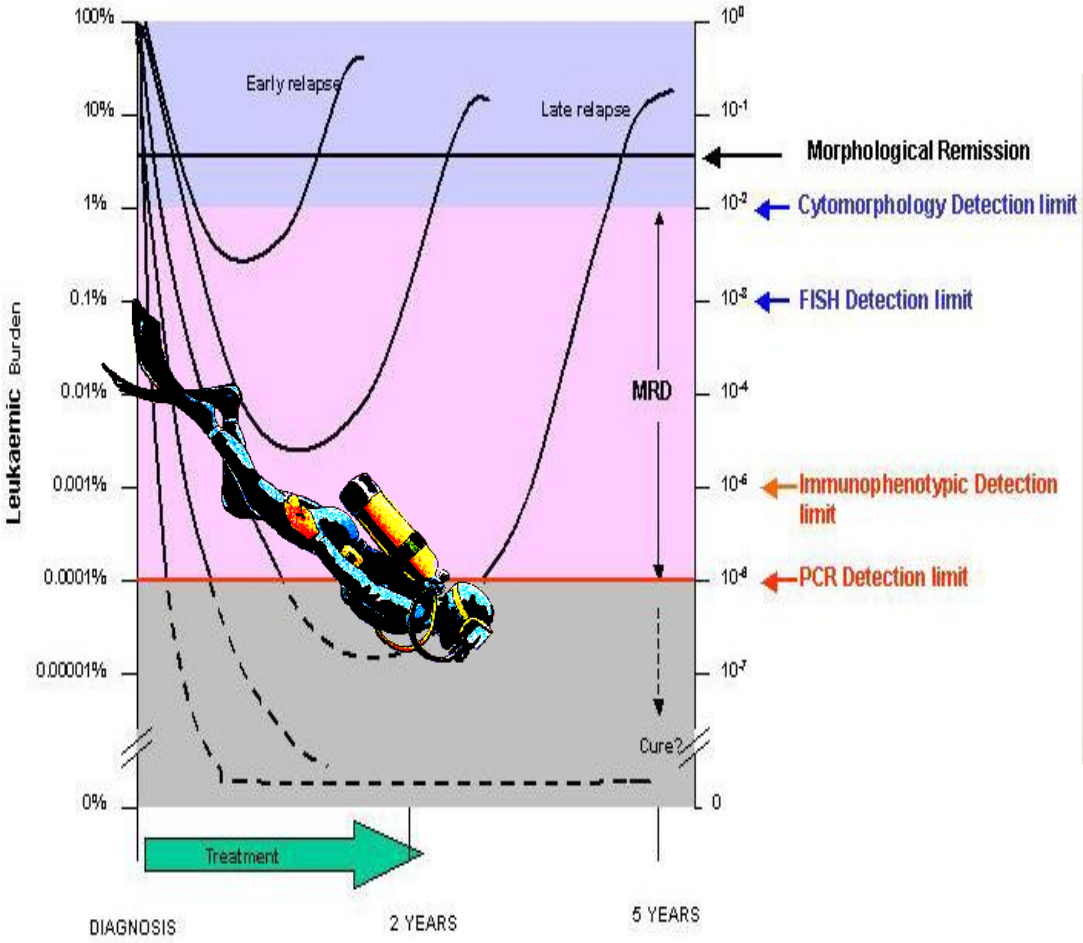
- one cytogenetic adverse feature plus either
  - high LDH or
  - ISS 3 or
  - less then CR after induction or failure to eradicate residual disease after ASCT

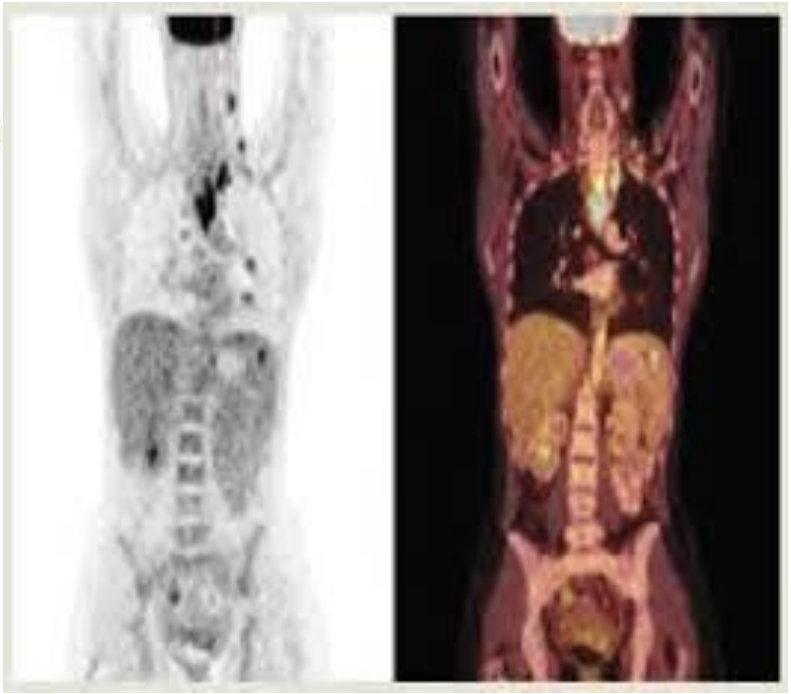
- high number of circulating plasma cells

- less then PR after an optimized induction therapy

Usmani et al, Leukemia 2015

Minimal residual disease (MRD)

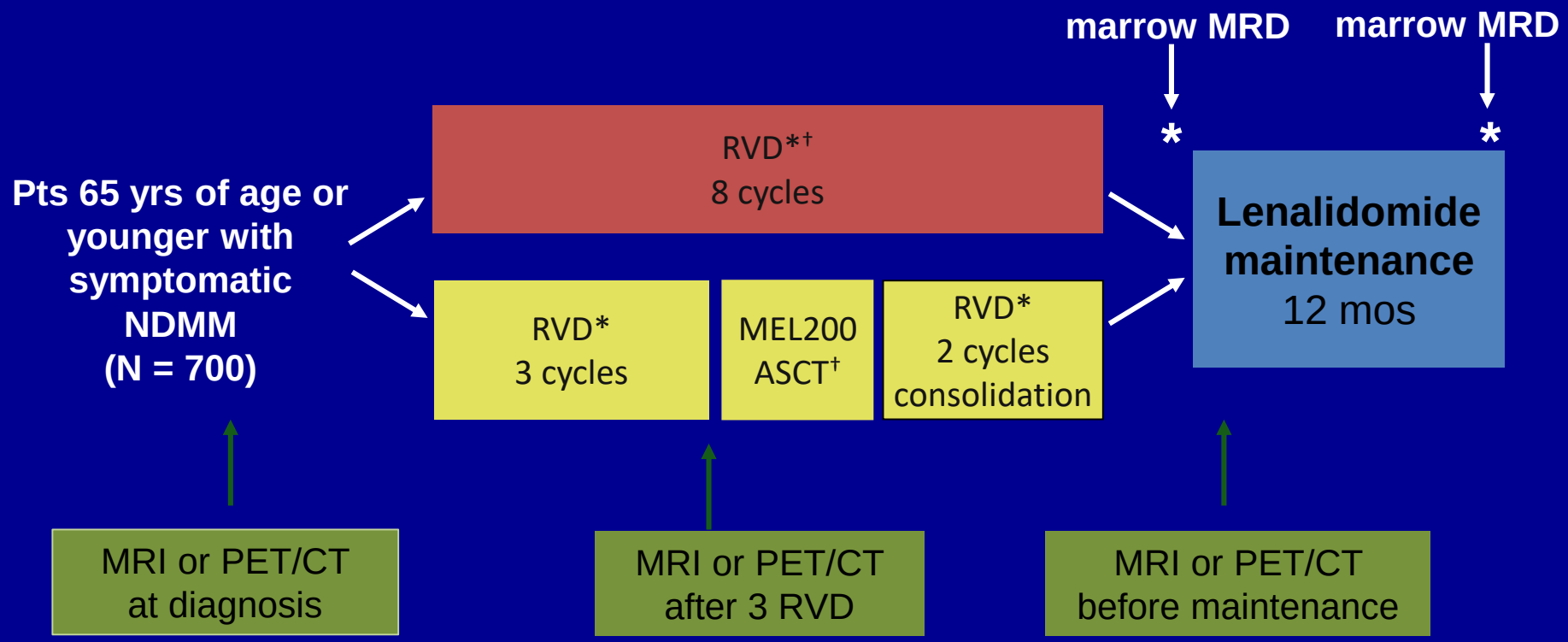




Marrow MRD
NGF: next generation flow
NGS: next generation sequencing

Bone MRD
PET-CT
MRI

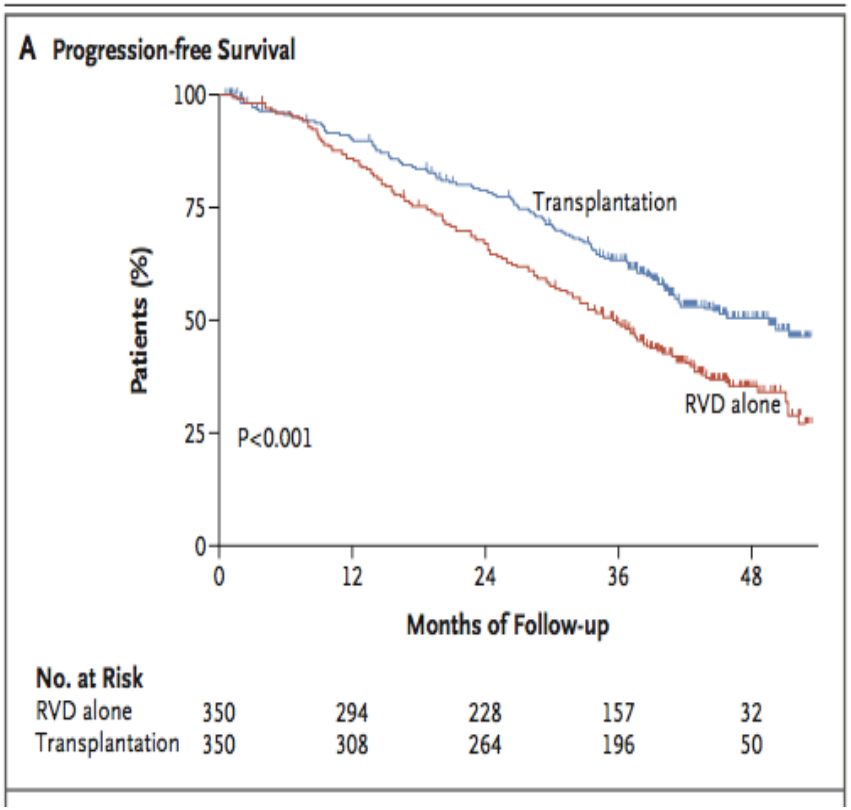
IFM/DFCI 2009: Phase III Study Design

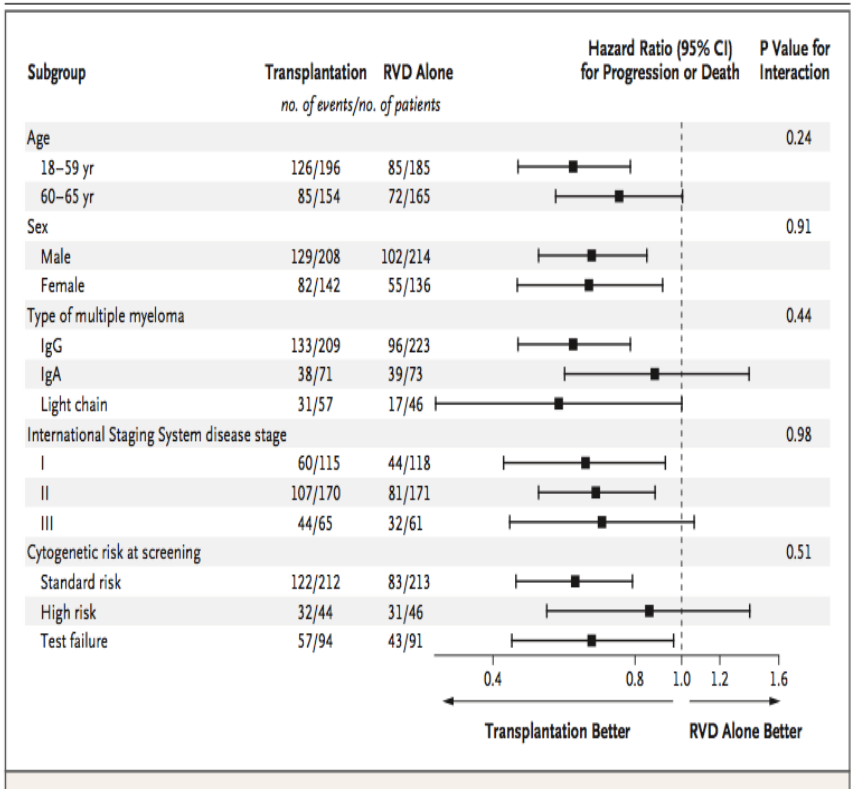


* Bone marrow MRD evaluation for pts achieving ≥ VGPR : **7-colour Flow cytometry and /or next generation sequencing**

Attal M et al ASH 2015. Avet-Loiseau H, et al. ASH 2015. Attal M et al, NEJM 2017.Moreau et al.JCO 2017

CLINICAL RESULTS





Attal M et al, NEJM 2017

MRD RESULTS

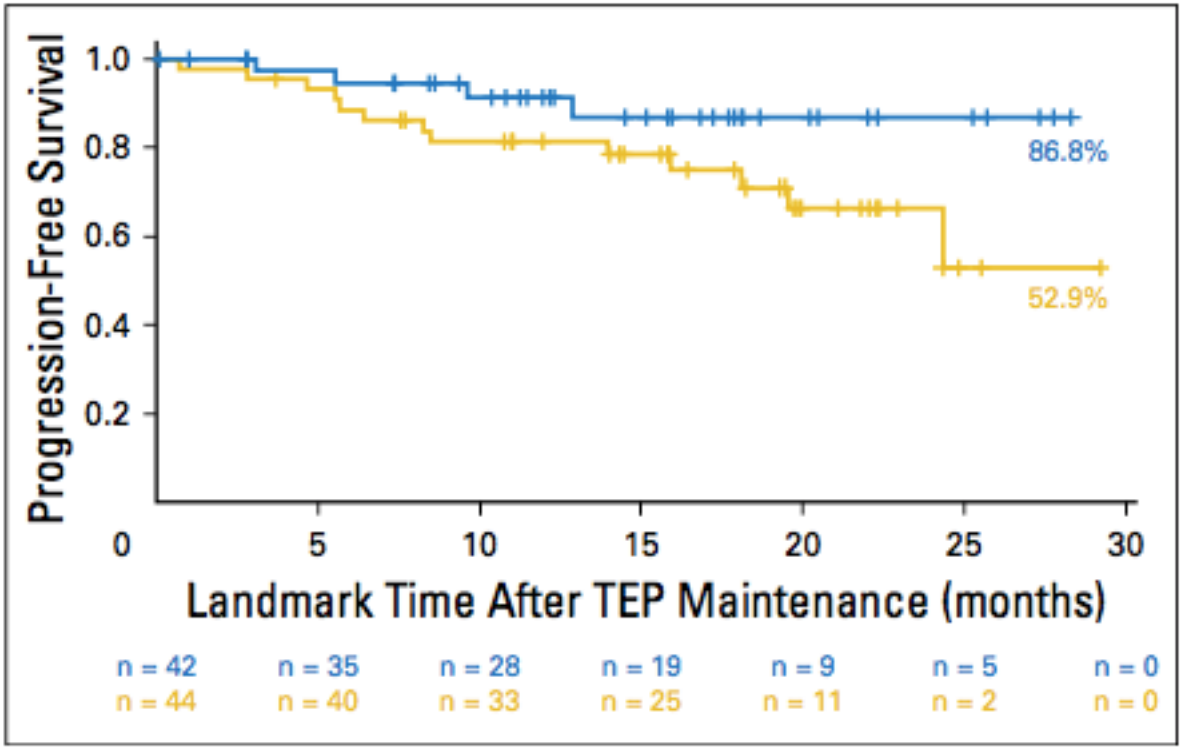


Fig 5. Progression-free survival for patients with negative positron emission tomography-computed tomography and negative minimal residual disease by flow cytometry before maintenance (41 of 86; 48%) versus others (45 of 86; 52%; $P = .05$).

Moreau P et al, JCO 2017

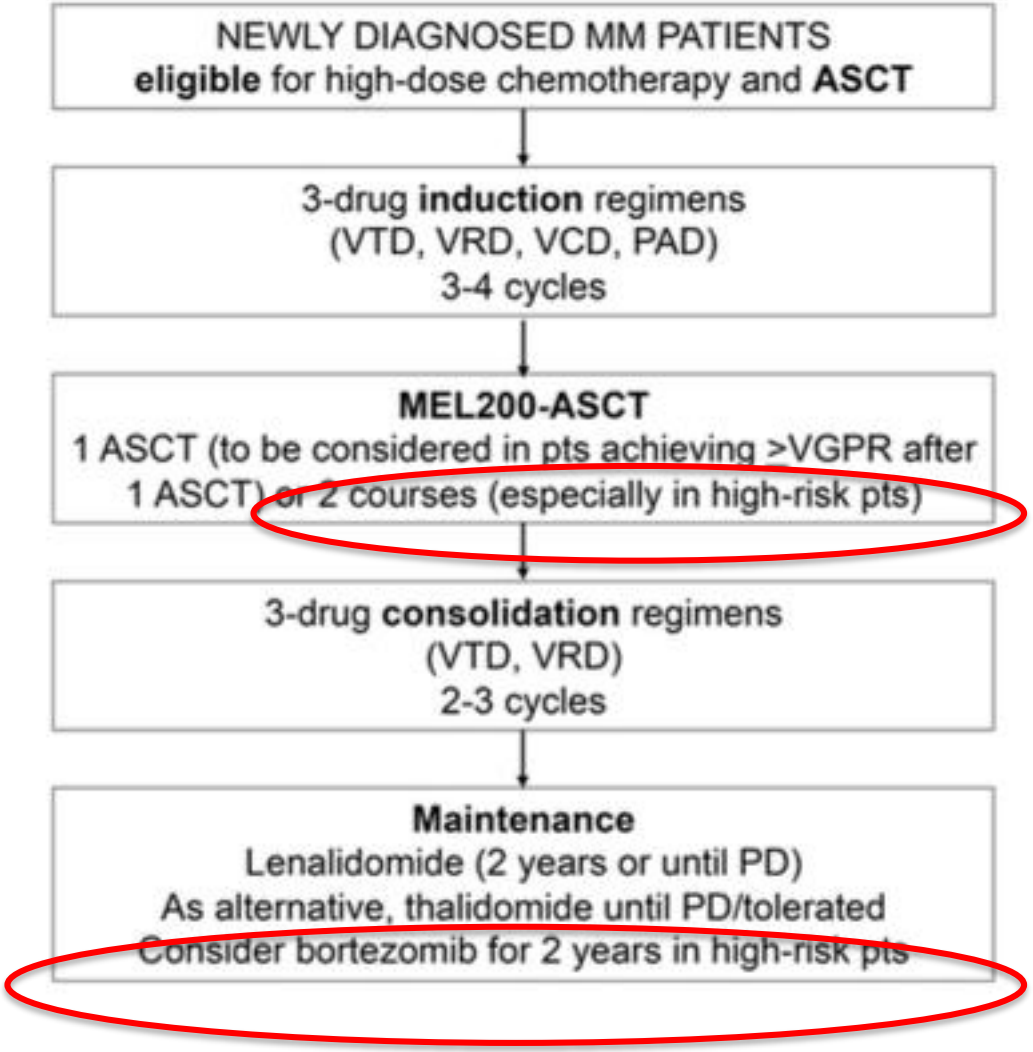
RISK-ADAPTED STRATEGY IN MM

- Investigational

- In transplant candidates: tandem autologous transplant, maintenance, allogeneic transplantation

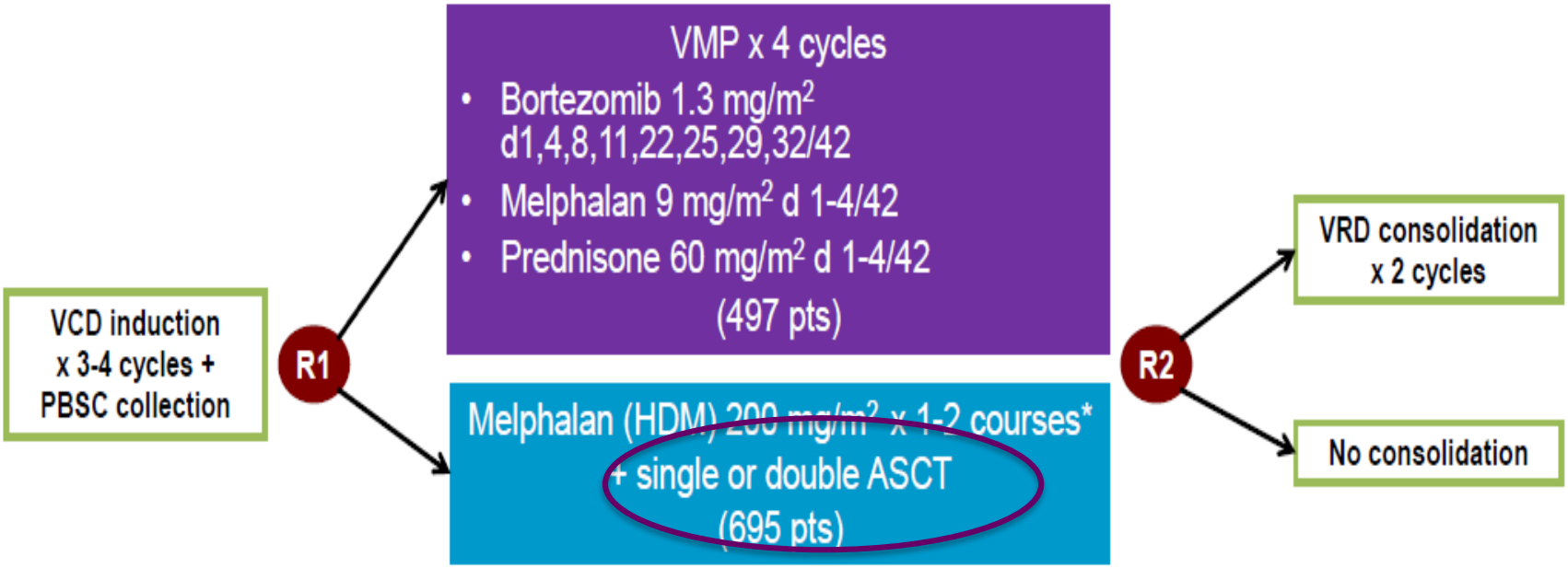
- In non transplant candidates: VMP vr RD

European Myeloma Network guidelines



Gay F, Haematologica 2018

EMN02/HO95 MM Trial: Study Design



All pts received lenalidomide maintenance until R/P

Stratification: ISS I *vs* II *vs* III

Randomization to VMP *vs* HDM (1:1) in centers with a fixed single ASCT policy

Randomization to VMP *vs* HDM-1 vs HDM-2 (1:1:1) in centers with a double ASCT policy

Cavo, ASH 2017

EMN02/HO95 Pts Randomized to ASCT:

PFS at 3 Yrs, % (95% CI)	ASCT-1 (n = 208)	ASCT-2 (n = 207)	HR (95% CI)	*P* Value
All pts	64.0 (57.3-71.5)	72.5 (66.2-79.4)	0.71 (0.50-0.98)	.040
Pts with high cytogenetic risk	44.2 (31.0-63.2)	69.2 (54.7-87.5)	0.42 (0.21-0.84)	.014

- PFS similar for pts with standard-risk vs high-risk MM following double ASCT
- 3-year PFS: 76.4% vs 69.2% (HR: 0.79; 95% CI: 0.41-1.52; *P* = .483)
- Randomization to double ASCT independently associated with better PFS

Variable Assessed in Multivariate Cox Regression Analysis	HR (95% CI)	*P* Value
Randomization to ASCT-2	0.66 (0.45-0.96)	.029
R-ISS I score (vs II/III)	0.61 (0.37-0.98)	.042
Standard-risk cytogenetics (0 of 3 high-risk abnormalities)	0.35 (0.22-0.56)	< .001
Best response ≥ VGPR	0.28 (0.17-0.45)	< .001

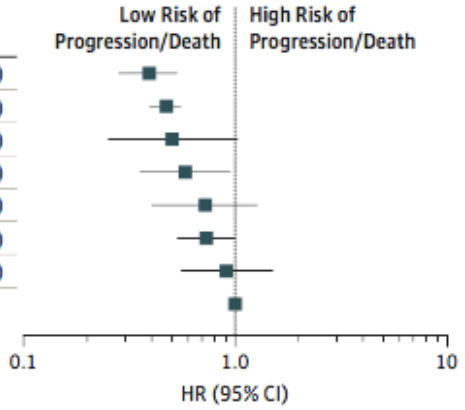
Cavo M, et al. ASH 2017. Abstract 401.

Network meta-analysis on maintenance in MM

Figure 3. Forest Plot of Network Meta-analysis Results (Primary Analysis)

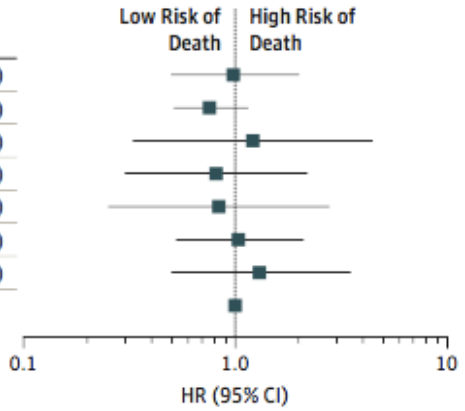
A Progression-free survival

Source	PbBT	MedR	HR (95% CI)
Len-Pred	70	1	0.39 (0.28-0.53)
Len	4	2	0.47 (0.39-0.55)
Thal-IFN	22	3	0.50 (0.25-1.02)
Thal-Bort	3	4	0.58 (0.35-0.95)
Bort-Pred	1	5	0.72 (0.40-1.27)
Thal	0	5	0.73 (0.53-1.00)
IFN	0	7	0.91 (0.55-1.51)
No maintenance/placebo	0	8	1.00



B Overall survival

Source	PbBT	MedR	HR (95% CI)
Len-Pred	8	5	0.98 (0.50-2.03)
Len	38	2	0.76 (0.51-1.16)
Thal-IFN	9	7	1.22 (0.33-4.53)
Thal-Bort	21	3	0.82 (0.30-2.20)
Bort-Pred	21	3	0.84 (0.25-2.80)
Thal	2	5	1.04 (0.53-2.12)
IFN	1	7	1.31 (0.50-3.53)
No maintenance/placebo	1	5	1.00



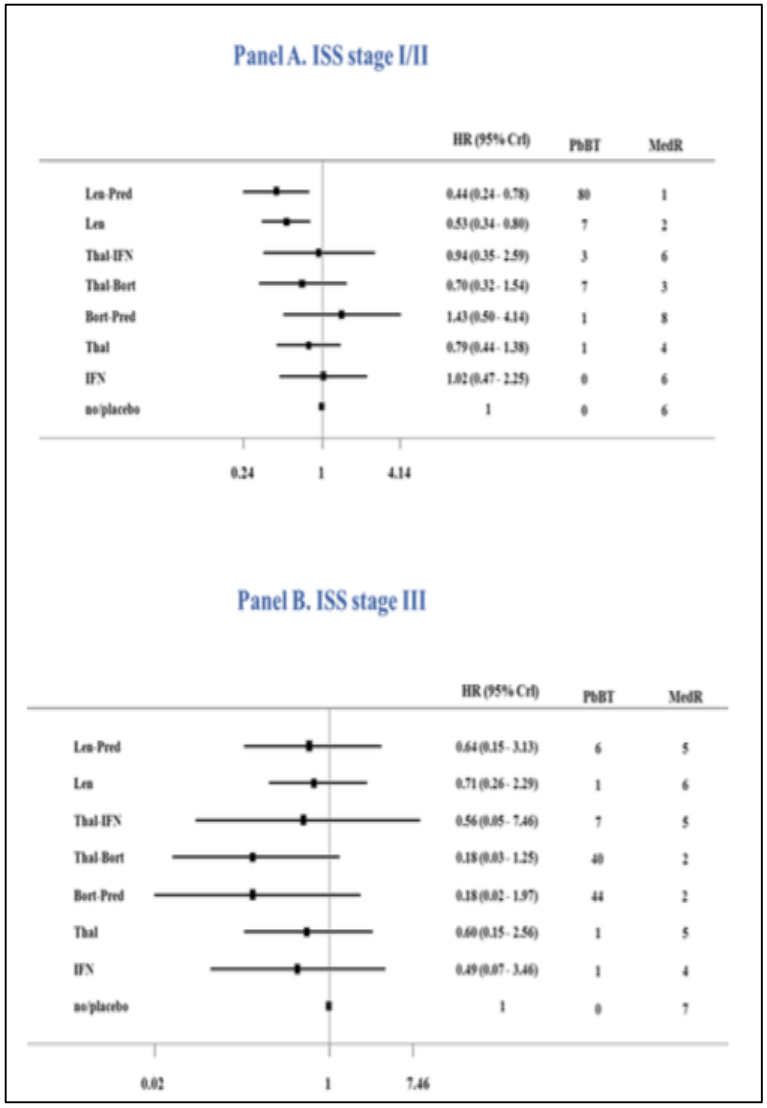
11 phase III randomized studies examined (5073 pts)

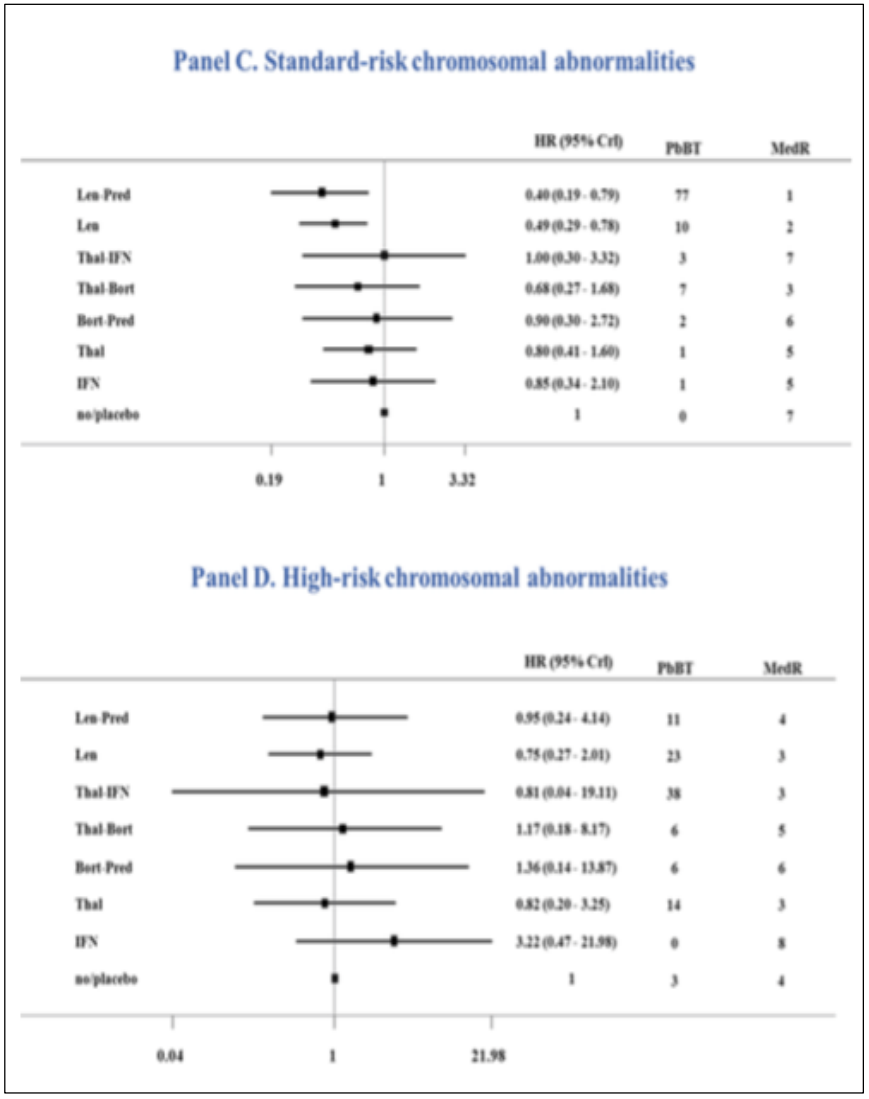
7 studies in transplant eligible patients (2917)

4 studies in transplant ineligible patients (2155)

Gay et al, Jama Oncology 2018

Effect of patient subgroups on PFS

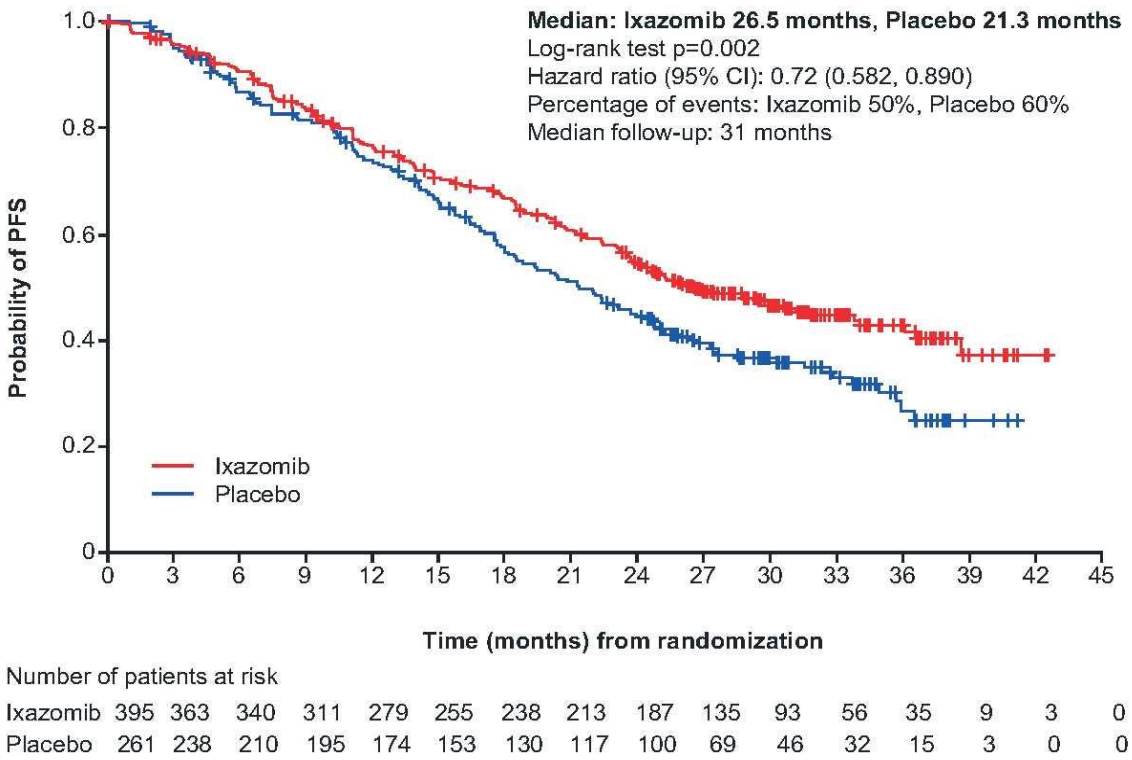




Gay et al, Jama Oncology 2018

Ixazomib as maintenance after ASCT

Phase 3 Tourmaline-MM3 study
656 pts with ≥ PR after induction plus ASCT
Random weekly ixazomib 3 mg (cycles 1-4), 4 mg (from cycle 5) versus placebo



PFS benefit was maintained also in high risk groups (ISS 3 and high risk cytogenetics)

Dimopoulos M et al, ASH 2018, abs 301

Allografting in myeloma: evidence and current indications

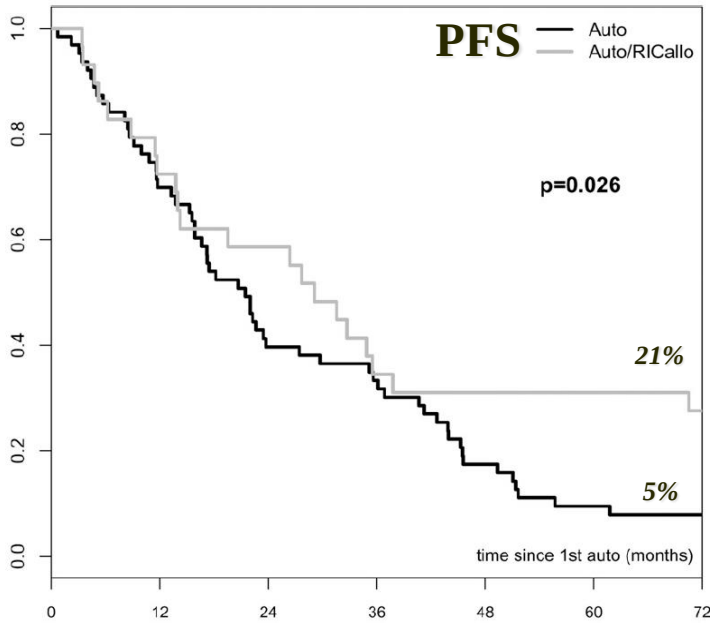
	Level	Practical considerations	Rationale for considerations
At diagnosis	**2C**	**Clinical trial only**	**Discordant results of prospective randomized studies** **Published studies did not include "new drugs"**
At relapse	**2C**	**High risk patients (early relapse/ poor prognosis features)**	**No prospective comparison studies)** **general consensus of panel experts** **Support of retrospective studies** **(better if part of clinical trial)**
Maintenance post-transplant	**-**	**Clinical trial only**	**Lack of studies**

Gay et al. Review Haematologica 2017

Effect of allo on outcome depending on cytogenetic features

	Del(13q)	Del(13q) vs. no del(13q)		t(4;14)	t(4;14) vs. no t(4;14)		Del(17p)	Del(17p) vs. no del(17p)		t(11;14)	t(11;14) vs. no t(11;14)	
		No del(13q)	P		No t(4;14)	P		No del(17p)	P		No t(11;14)	P
	n=84	n=57		n=31	n=92		n=24	n=71		n=24	n=73	
CR+VGPR (%)	59	50	0.17	60	54	0.23	50	51	0.83	43	52	0.11
3-year PFS (%)	38	25	0.18	26	33	0.5	27	22	0.66	25	31	0.45
3-year OS (%)	54	52	0.76	39	52	0.21	34	42	0.35	43	50	0.62
3-year progression (%)	49	62	0.42	55	56	0.67	45	69	0.9	65	56	0.43
2-year TRM (%)	20	28	0.27	29	24	0.36	38	22	0.15	23	27	0.58

Roos Hematologica 2011



Garhton Blood 2013

After a median follow-up of 6 years, overall 5-year progression-free survival was 29%, with no significant difference between del 17p13/t(4;14)-harboring patients and others (24% versus 30%; p=0.70).

Kroger BBMT 2013

Effect of allo on outcome depending on cytogenetic features

Prospective, multicenter

Cytoreduction

↓

Mobilization → Auto (MF 200)

Donor availability
MRD or MURD ≥9/10)

→ Auto (MF 200)

→ Allo-RIC

Flu/MF (+ATG si DNE)

N = 225 → 199

Age = 53 (30-60)

Allo (63%) → 59% URD y 41% MRD

Knop S, Blood 2014 # 43

Effect of allo on outcome depending on cytogenetic features: alloTrx does overcome poor cytogenetic features

	Auto-Allo	Auto-Auto	p
PFS 2 y	**59%***	47%	NS
mPFS	**34.5 m***	21.8 m	0.005
OS 2 y	Not reached	Not reached	NS
NRM 2 y	12%		

del 13q/del 17p (13%)

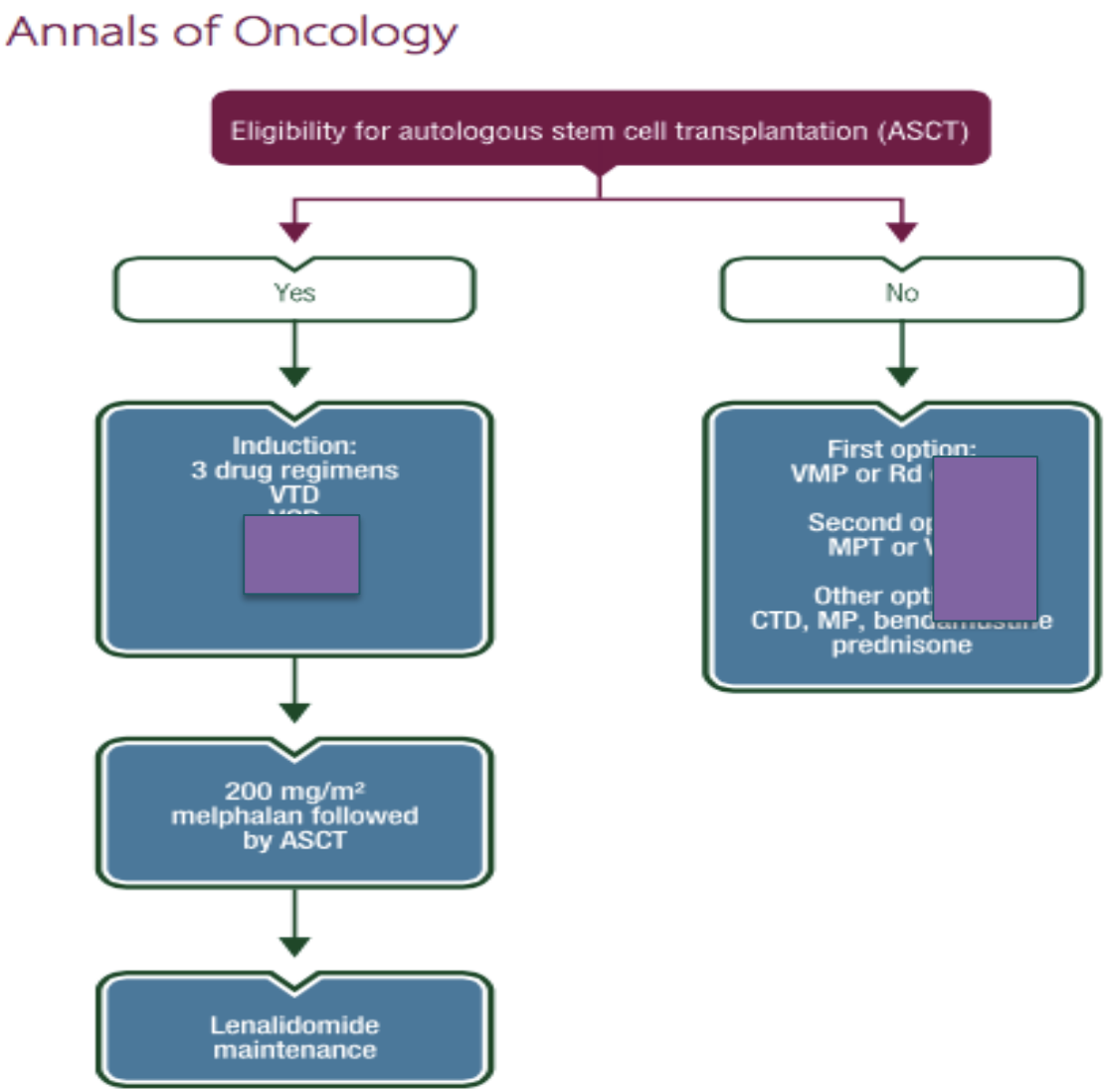
	Auto-Allo	Auto-Auto	p
mPFS	Not reached	6 m	0.0002
mOS	Not reached	23.4 m	0.01

t(4;14)/del 13q (20%)

	Auto-Allo	Auto-Auto	p
mOS	19 m	19 m	NS

Knop S, Blood 2014 # 43

FIRST LINE TREATMENT IN MM



Moreau et al, ESMO guidelines 2017

VMP and Rd in transplant-ineligible patients

	VMP Bortezomib+melphalan+dexa x 9 cycles	Rd Lenalidomide+dexa until progression
Efficacy	CR+VGPR:42%, PFS 22 mo	CR+VGPR:48%, PFS 26 mo
Tolerability	more neuropathy	more neutropenia
Overall outcome/future therapy	rescue with Rd-based regimens	rescue with Vd-based regimens
Renal failure	preferable in severe renal failure	Reduce lena in mild-moderate renal failure
High risk cytogenetics	better outcome	inferior outcome
Logistics		preferable for patients needing caregiver
Age		preferable in older patients ?
Unfit/frail patients		preferable?

Outcomes according to cytogenetics

	n	Standard risk	High risk	n
FIRST[1]: Rd cont (PFS)	205	31,1 months	8,4 months	43
Rd18	209	21,2 months	17,5 months	52
VISTA[2]: VMP (TTP)	142	23,1 months	19,8 months	26

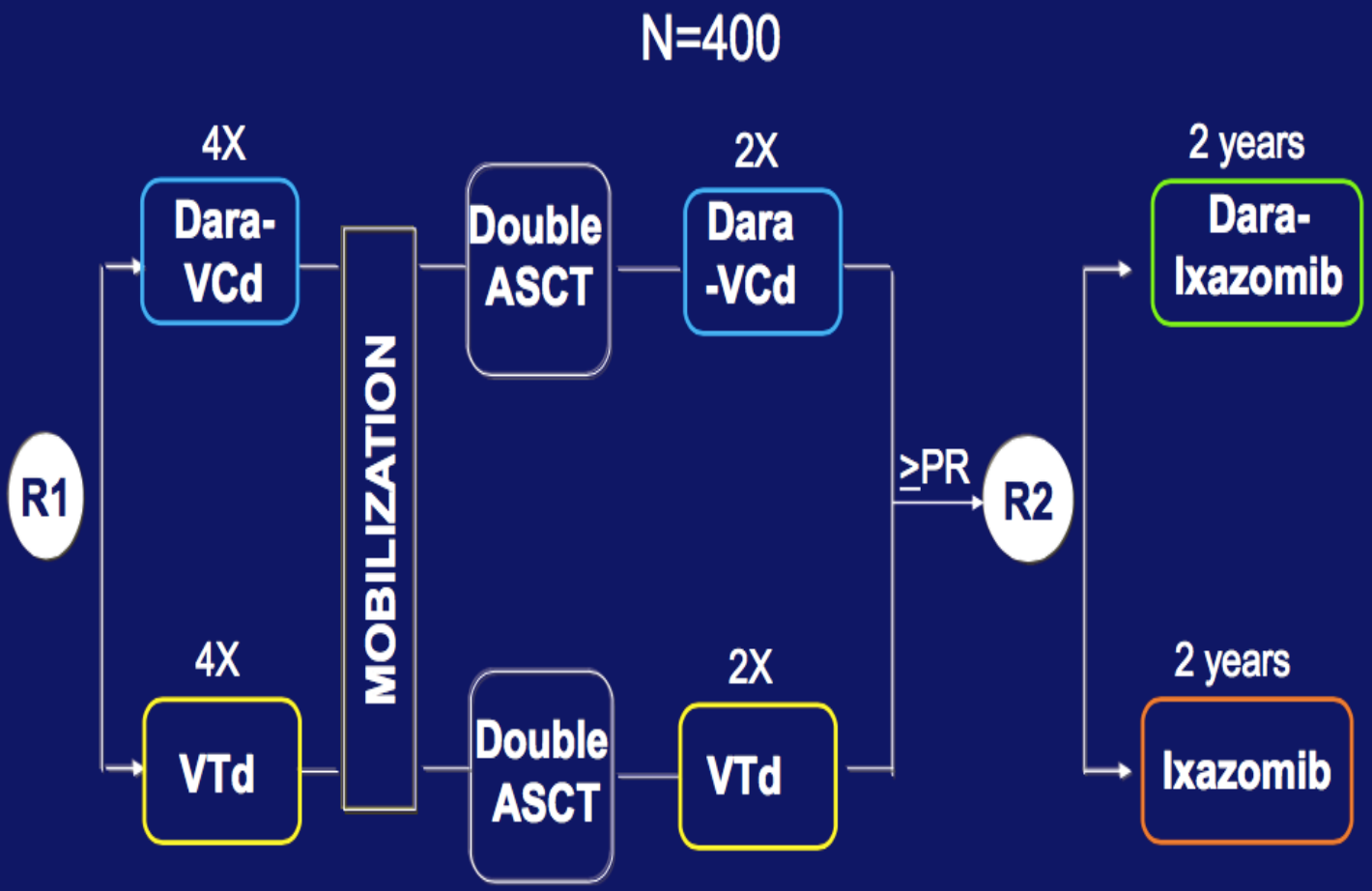
1. Herve Avet-Loiseau et al, Abstract 730 ASH 2015; Facon et al, Blood 2018
2. San Miguel et al, NEJM 2008; 359:906-17

A multicenter, open label, **randomized phase II** study comparing daratumumab combined with bortezomib-cyclophosphamide-dexamethasone (**dara-VCd) vs** the association of bortezomib-thalidomide-dexamethasone **(VTd)** as **pre transplant induction and post transplant consolidation**, both followed by a **maintenance** phase with **ixazomib alone or in combination with daratumumab,** in **newly diagnosed** multiple myeloma young patients eligible for autologous stem cell transplantation

EMN18

PIs Mario Boccadoro, Michele Cavo

Treatment schema



Patients in the first randomization will be stratified according to FISH (standard/missing vs high risk, defined as del17 or t 4;14 or t 14;16) and ISS (I vs II and III)

Patients randomized to maintenance treatment will be stratified according to induction treatment and MRD status by NGF (positive and not evaluable vs negative).

: randomization; Dara-VCd: Daratumumab, Bortezomib, Cyclophosphamide, Dexamethasone; VTd:Bortezomib, Thalidomide, Dexamethasone; ASCT: autologous stem cell Transplant: Dex: examethasone

Aims

Primary endpoints

- PFS at 36 months from first randomization and 24 months from second randomization.
- MRD negativity rate after consolidation by NGS
- MRD negativity rate during maintenance by NGS

Secondary endpoints

-ORR, VGPR, CR rate
-MRD by NGF
-MRD by PET
-DOR, TTP, TNT, PFS2, OS
-Safety and QoL
-Definition of prognostic factors, as assessed by NGS (MM-panel)

CONCLUSIONI

- Alla diagnosi possiamo identificare una frazione di pazienti con MM ad alto rischio in base a caratteristiche cliniche e al cariotipo FISH (20%).

- Un ulteriore criterio dinamico di rischio è la risposta subottimale al trattamento iniziale basato sulla MRD.

- Malgrado la terapia del MM non sia stratificata sul rischio, le linee guida cominciano a suggerire trattamenti differenziati tra pazienti a rischio standard e pazienti ad alto rischio.

- **Pazienti eleggibili al trapianto ad alto rischio** : doppio autotrapianto, mantenimento con inibitori del proteosoma , trapianto allogenico

- **Pazienti non eleggibili al trapianto**: terapia bortezomib -based

PROSPETTIVE E CRITICITA’

- Disponibilità della citogenetica FISH per tutti i pazienti con MM alla diagnosi e alla prima/seconda ricaduta

- Disponibilità delle tecniche di valutazione della MRD durante il trattamento

- Mantenimento con bortezomib nei pazienti ad alto rischio dopo autotrapianto (richiesta di inserimento nella legge 648 da parte di EMN Italy)

- Nuovi inibitori del proteosoma (ixazomib) ed anticorpi monoclonali (daratumumab)