2nd edition

Unmet challenges in high risk hematological malignancies: from benchside to clinical practice

Turin, September 13-14, 2021

Starhotels Majestic

Scientific board:
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How I treat young high-risk multiple myeloma

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Prognostic factors in Multiple Myeloma

Patient-related	Disease burden-related	Disease biology-related	Therapy-related
Age	High B_2 microglobulin*	Cytogenetic abnormalities	Quality of response
Performance status	Low albumin*	GEP	Early relapse
Comorbidities	Renal impairment	Circulating PC	
	LDH above ULN	EMD	
		High proliferation rate	

Cytogenetic abnormalities and relationship with outcomes

Chromosome/region (frequency)	Gene involved/effect	Prognostic implication
14q32 (locus IGH) (45-50%)		
t(11;14) (20%)	Cycline D1 hyperexpression	Neutral
t(4;14) (10-15%)	FGFR3 and MMSET deregulated	Unfavorable (worsened by chromosome 1 alterations, improved by trisomy 5)
t(14; 16) (< 5%)	cMAF	Doubt, mainly unfavorable
t(14; 20) (< 5%)	UK	Doubt, mainly unfavorable
1q21 acquisition (30%)	CKS1B, MCL1	
Gain (3-4 copies)		Partially unfavorable
Amplification (≥ 4)		Unfavorable
1p32 deletion (10%)	FAF1/ CDKN2C	Unfavorable
17p deletion (8-15% according to PCs cutoff)	TP53 and UK	
Single-hit	deletion	Unfavorable
Double-hit	Bi-allelic inactivation (deletion + mutation)	Very unfavorable

Zamagni E et al, «How I treat HR MM», Blood 2021, under revision

Personal recommendations on definition and treatment of HR-NDMM

Newly diagnosed transplant-eligible (NDTE) MM patients		
Risk/estimated frequency	**Definition**	**Suggested treatment**
HR (25-30%)	ISS 3, 1 cytogenetic-molecular aberration*, R-ISS 3, R2-ISS 3 and 2 intermediate-high, > 0.07% circulating PCs, persistent MRD positivity after optimal treatment, renal failure	Quadruplet induction (MoAb + PI + IMiD + dex) Double ASCT Quadruplet consolidation Single/two drugs maintenance (PI + IMiD) for at least 2 years if MRD- Prompt change of therapy if/when MRD+
Ultra-HR (6-10%)	EMD, PCL (PCs > 20% or 2x 10^9), ≥ 2 genetic abnormalities, co-existence of genetic and at least another HR feature (see table 1), primary refractory disease	Innovative strategies, including quadruplet induction (MoAb + PI + IMiD + dex) CAR-T therapy (± ASCT) Innovative maintenance with T-cell engagers. Close MRD follow-up and change of therapy at conversion from – to +

Zamagni E et al, «How I treat HR MM», Blood 2021, under revision

Why Risk Stratify?

- ***Two important goals***
  - ***Counsel:*** Need to provide patients 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

- High-risk can refer to many different characteristics and the magnitude of risk can be influenced by different treatmens
- There is a lack of prospective randomized trials which might strongly support choices of therapy in this setting
- Management of high-risk MM includes a complicated set of steps requiring an aggressive treatment approach
- 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

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

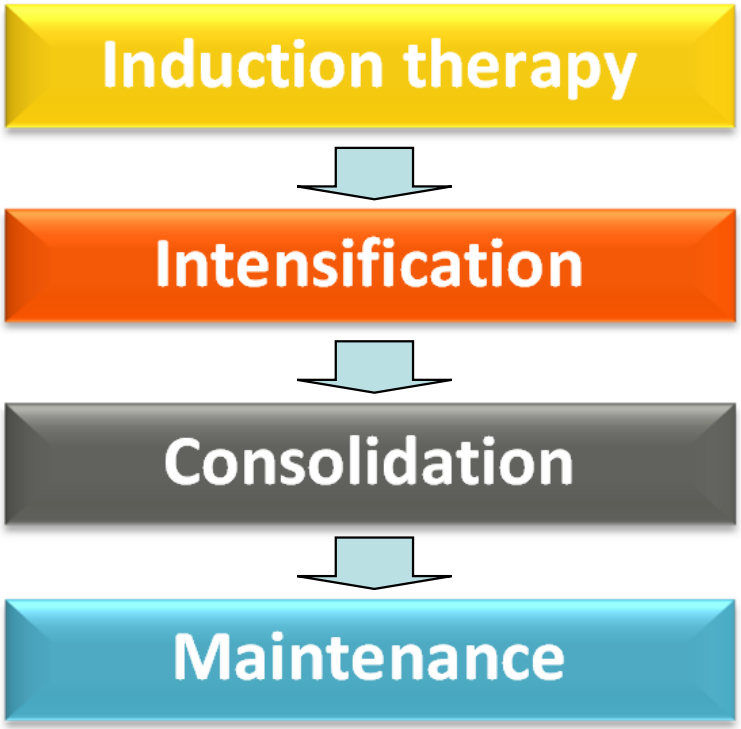
5 years later…..
Pitfalls of treatment of HR patients: the black beast of MM

- Different definitions of HR in different trials
- Most data coming from retrospective analyses
- Guidelines and recommendations (still) poor on HR
- Lack of specific trials dedicated to HR population

Zamagni E et al, «How I treat HR MM», Blood 2021, under revision

Treatment paradigm for transplant-eligible patients

Sequential blocks of therapy



Continued cytoreduction
Sustained suppression of disease burden

Key endpoints

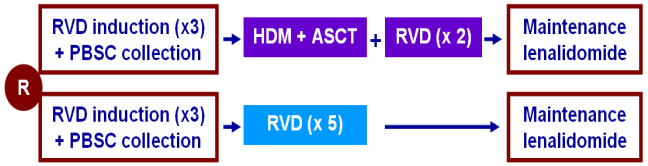
- **Maximize the rate and depth of response, beyond the level of detectable MRD**
- **Sustain MRD negativity and prevent or delay clinical relapse**
- **Increase PFS and OS, possibly offering a chance of cure to a fraction of patients**

Cavo M et al. Blood 2011;117(23):6063-73
Kumar S, et al. Lancet Oncology 2016;17:e328-46
Gay F et al. Haematologica 2018;103(2): 197-211

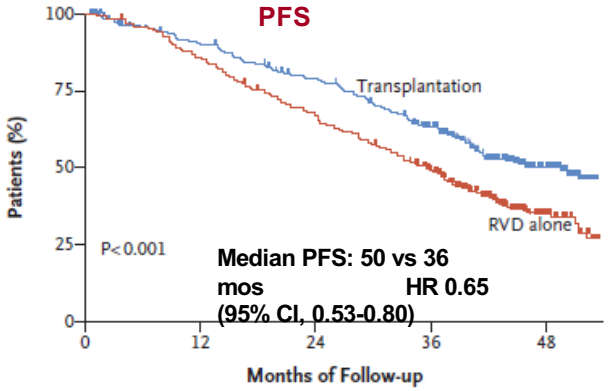
INTENSIFICATION phase: ASCT

Upfront high-dose melphalan with ASCT is still the standard of care for fit patients with NDMM, even in the novel agent era

IFM 2009 phase 3 study



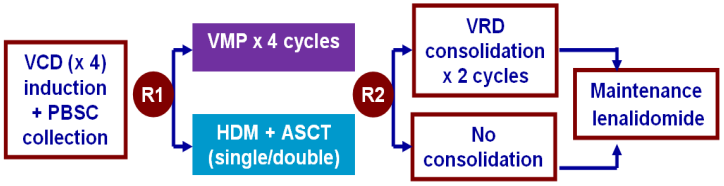
Attal M, et al. NEJM 2017; 376: 1311-1320



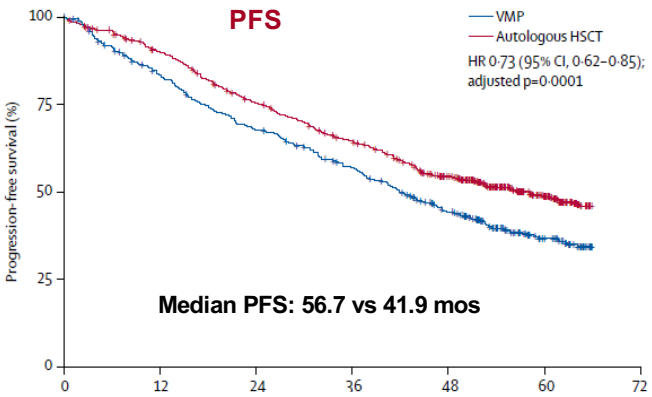
Response

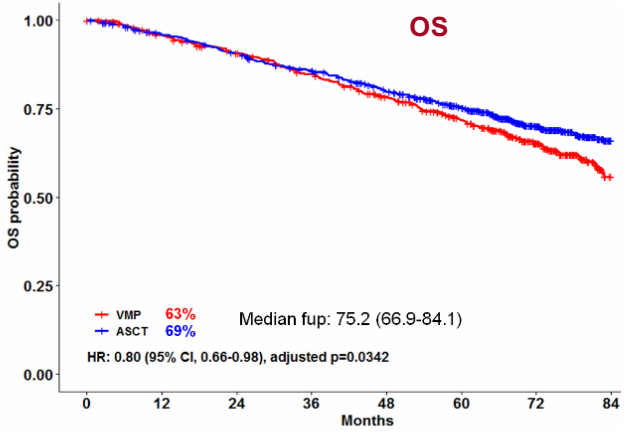
Outcome	RVD-Alone Group (N=350)	Transplantation Group (N=350)	Adjusted P Value†
Best response during the study — no. (%)			0.02
Complete response	169 (48)	205 (59)	
Very good partial response	101 (29)	102 (29)	
Partial response	70 (20)	37 (11)	
Stable disease	10 (3)	6 (2)	
Complete response — no. (%)	169 (48)	205 (59)	0.03
Complete response or very good partial response — no. (%)	270 (77)	307 (88)	0.001
Minimal residual disease not detected during the study — no./ total no. with complete or very good partial response (%)‡	171/265 (65)	220/278 (79)	<0.001

EMN02/HO95 phase 3 study



Cavo et al. Lancet Haematol 2020;7: e456-68
Cavo et al. ASH meeting 2020

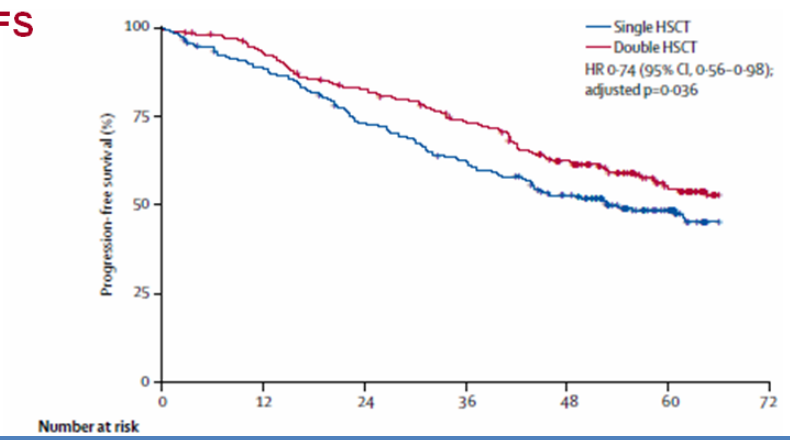




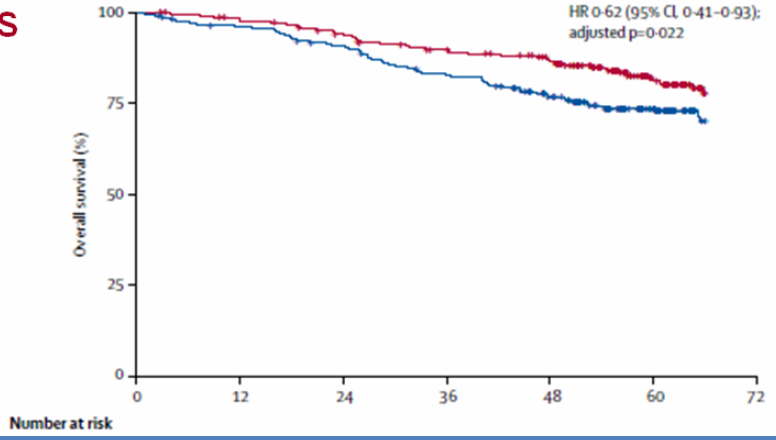
Tandem ASCT: role in HR disease (EMN02/HO95 trial)

EMN02/HO95 phase 3 study (median f up: 75 mos)

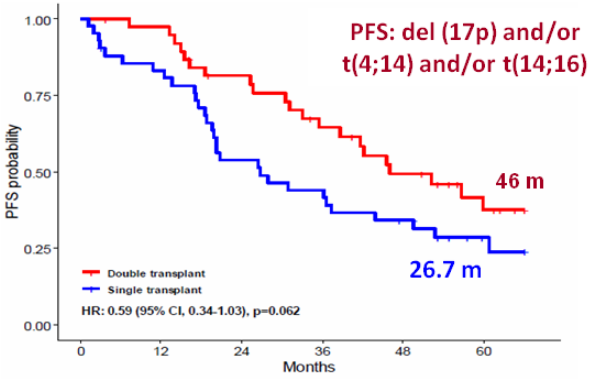
PFS

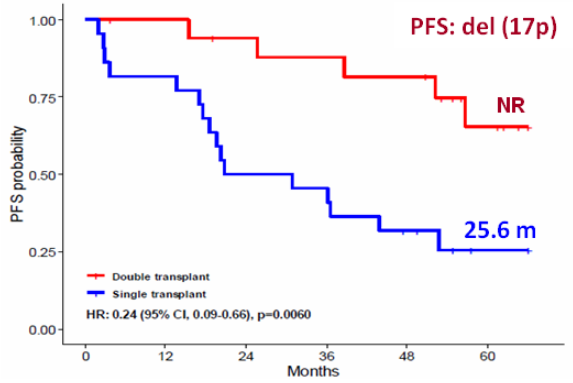


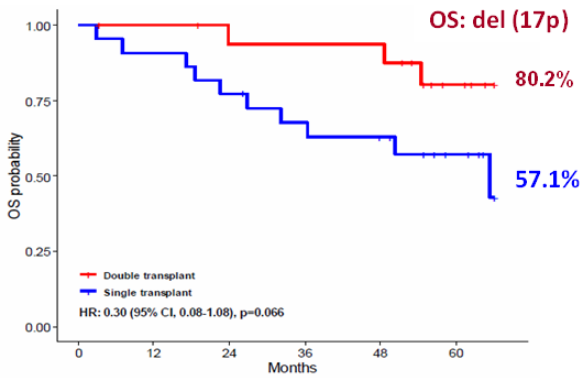
OS



A tandem ASCT is recommended for patients with genetically defined high-risk disease



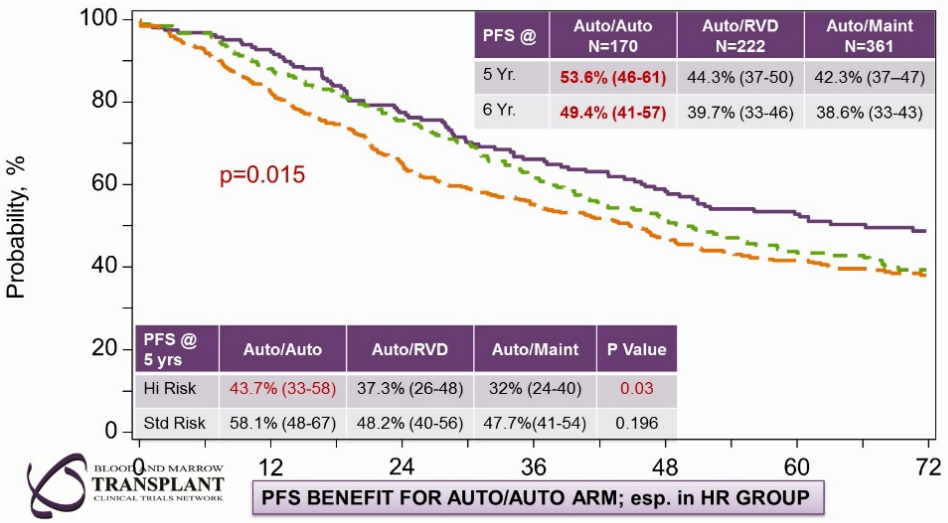




Cavo et al. Lancet Haematol 2020;7:e456–68

Long-term follow-up (median: 6 years) of the STAMINA trial

STaMINA: PFS by Treatment Received



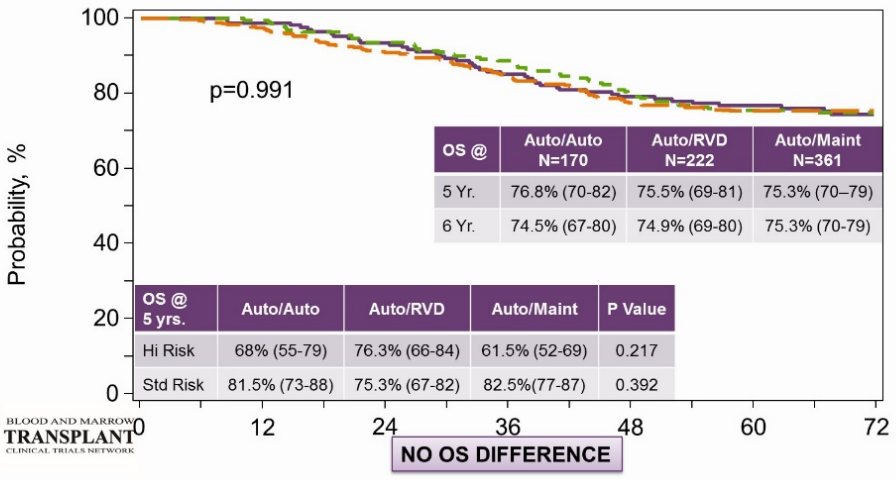
PFS @	Auto/Auto N=170	Auto/RVD N=222	Auto/Maint N=361
5 Yr.	53.6% (46-61)	44.3% (37-50)	42.3% (37–47)
6 Yr.	49.4% (41-57)	39.7% (33-46)	38.6% (33-43)

PFS @ 5 yrs	Auto/Auto	Auto/RVD	Auto/Maint	P Value
Hi Risk	43.7% (33-58)	37.3% (26-48)	32% (24-40)	0.03
Std Risk	58.1% (48-67)	48.2% (40-56)	47.7%(41-54)	0.196

BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

PFS BENEFIT FOR AUTO/AUTO ARM; esp. in HR GROUP

STaMINA: OS by Treatment Received



OS @	Auto/Auto N=170	Auto/RVD N=222	Auto/Maint N=361
5 Yr.	76.8% (70-82)	75.5% (69-81)	75.3% (70–79)
6 Yr.	74.5% (67-80)	74.9% (69-80)	75.3% (70-79)

OS @ 5 yrs.	Auto/Auto	Auto/RVD	Auto/Maint	P Value
Hi Risk	68% (55-79)	76.3% (66-84)	61.5% (52-69)	0.217
Std Risk	81.5% (73-88)	75.3% (67-82)	82.5%(77-87)	0.392

BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

NO OS DIFFERENCE

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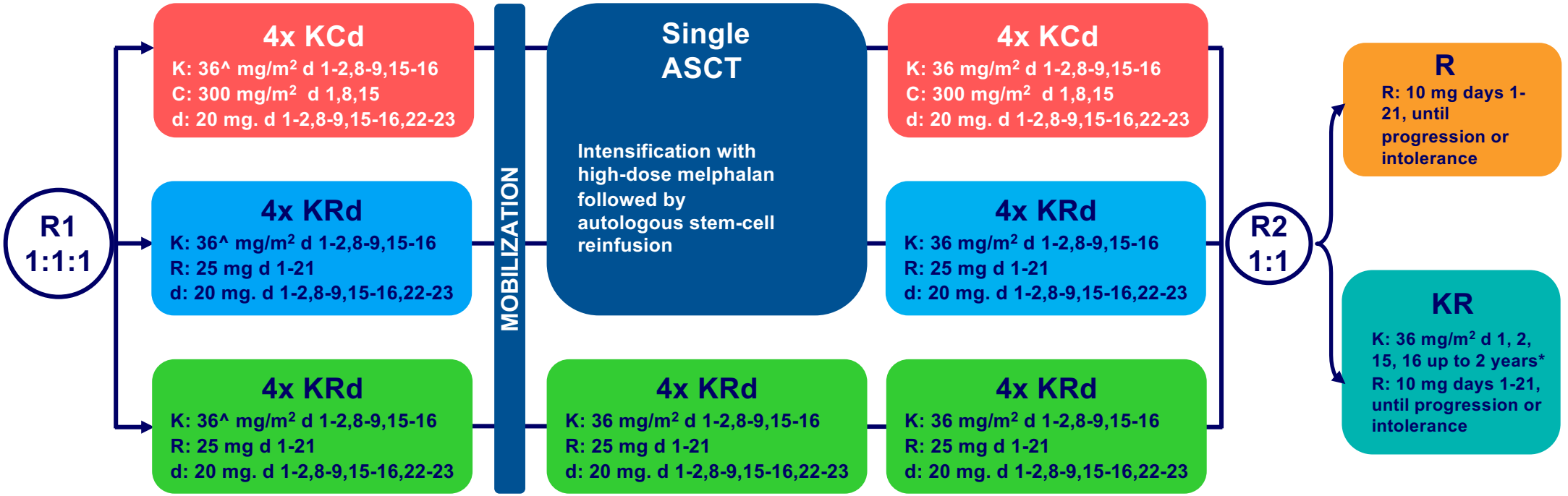
Parameswaran H et al, ASH 2020

FORTE trial: analysis in HR patients

474 NDMM patients, transplant-eligible and younger than 65 years



^20 mg/m^2 on days 1-2, cycle 1 only. *Carfilzomib 70 mg/m^2 days 1, 15 every 28 days up to 2 years for patients that have started the maintenance treatment from 6 months before the approval of Amendment 5.0 onwards.

Mina R et al, EHA 2021

NDMM, newly diagnosed multiple myeloma, R1, first randomization (induction/consolidation treatment); R2, second randomization (maintenance treatment); IQR, interquartile range K, carfilzomib; C, cyclophosphamide; R, lenalidomide; d, dexamethasone; d, days; ASCT, autologous stem-cell transplantation.

Summary of results

- **Patients split in : Standard Risk (no lesion), High Risk (at least 1 chromosomal abnormalities), Double Hit (2 or more chromosomal abnormalities)**
- **KRd+ASCT significantly prolonged PFS vs. KRd12 in:**
  - **SR patients: 4-year PFS → 82% vs. 67%**
  - **HiR patients: 4-year PFS → 62% vs. 45%**
  - **DH patients: 4-year PFS → 55% vs. 33%**
- **KRd+ASCT increased the rate of 1-year sustained MRD negativity vs. Krd12 in patients with both HiR (50% vs 39%) and DH (47% vs 25%) MM.**
- **KR significantly prolonged PFS from the start of maintenance vs. R alone**
  - **SR patients: 3-year PFS → 90% vs. 73%**
  - **HiR patients: 3-year PFS → 69% vs. 59%**
  - **DH patients: 3-year PFS → 67% vs. 42%**
- **The benefit of KRd+ASCT vs. KRd12 and KR vs. R was observed in all subgroups: del(17p), gain(1q), del(1p), and t(4;14), except amp(1q).**

Mina R et al, EHA 2021

PFS, progression-free survival; ASCT, autologous stem-cell trasplantation; K, carfilzomib; R, lenalidomide; C, cyclophosphamide; d, dexamethasone; KCd_ASCT, KCd induction-ASCT-KCd consolidation; KRd_ASCT, KRd induction-ASCT-KRd consolidation; KRd12, 12 cycles of KRd; SR, standard risk; HiR, high risk; DH, double hit; MRD, minimal residual disease; MM, multiple myeloma..

INSTITUTE FOR CANCER OUTCOMES & SURVIVORSHIP
The University of Alabama at Birmingham

#8540

Efficacy of Daratumumab in the treatment of Multiple Myeloma with high-risk cytogenetics: Meta-Analysis of randomized phase 3 trials.

Smith Giri MD MHS[1,2], Alyssa Grimshaw MSLIS[3], Susan Bal MD[2], Kelly Godby MD[2], Benjamin Djulbegovic MD PhD[4], Saad Z Usmani MD[5], Thierry Facon[6], Philippe Moreau[7], Meletios A Dimopoulos MD[8], María-Victoria Mateos MD PhD[9], Luciano J Costa MD PhD[2]
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hematological malignancies:
from benchside to clinical practice

Umberto Vitolo (Candiolo-TO)

Background

- The addition of Daratumumab (D) to backbone multiple myeloma (MM) regimens leads to improved response rates and progression free survival (PFS).
- Whether improved outcomes are also seen among patients with high-risk cytogenetics (HRC) remains unclear, particularly in first line setting

Methods

- We conducted a systematic search of bibliographic databases (Ovid EMBASE, Medline, Pubmed, Scopus, Web of Science Core Collection and Cochrane Library) clinical trials registries and meeting libraries from inception to Jan 2, 2020
- **Eligibility:** phase III randomized trials that compared backbone MM regimens vs. same regimen plus D either in FL or relapsed/refractory (R/R) setting and reported outcomes by cytogenetic risk (HRC vs standard risk cytogenetics, SRC).
- We defined HRC as presence of t(4;14), t(14;16) or del(17p). The primary endpoint was progression free survival. Secondary Endpoint overall survival (OS)

Of 5,194 studies screened, six phase III trials were eligible. Three trials for newly diagnosed MM (ALCYONE, MAIA and CASSIOPEIA, 2,528 patients, 358 HRMM) and 3 trials for relapsed/refractory MM (CASTOR, POLLUX and CANDOR, 1,533 patients, 222 HRMM).

Impact of Daratumumab on PFS among MM patients with high-risk cytogenetics

Study Name	Intervention	Control	Hazard Ratio	95% CI	p-Value
Alcyone	DaraVMP	VMP	0.78	0.43-1.42	0.42
Maia	DaraRD	RD	0.57	0.32-1.03	0.06
Cassiopeia	DaraVTD	VTD	0.67	0.35-1.29	0.23
Pooled Effect Size ($I^2$0%, Cochran's Q p = 0.77)			**0.67**	**0.47-0.95**	**0.025**
Castor	DaraVD	VD	0.41	0.21-0.83	0.01
Pollux	DaraRD	RD	0.37	0.18-0.76	0.01
Candor	DaraKD	KD	0.58	0.30-1.12	0.11
Pooled Effect Size (($I^2$0%, Cochrans Q p = 0.63)			**0.45**	**0.30-0.67**	**< 0.001**

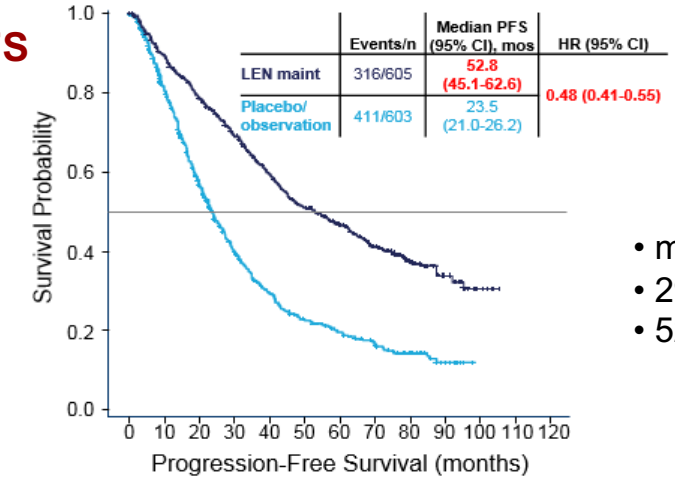
Addition of D to FL backbone regimens among patients with HRC led to improved PFS (pooled HR 0.67; 95% CI 0.47-0.95, p = 0.02)

Similar to R/R setting (Pooled HR 0.45; 95% CI 0.30-0.67, p < 0.01)

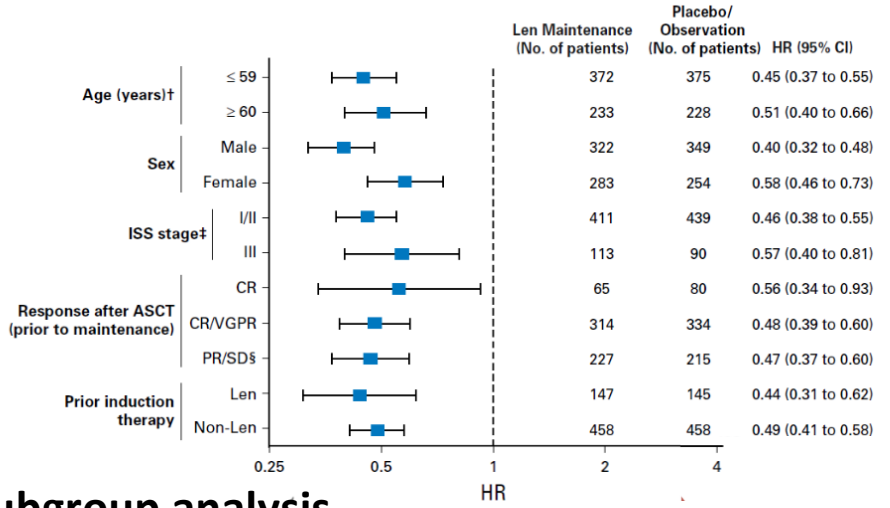
Giri et al, Abstract 8540, ASCO 2020
Smith G et al, JAMA Oncology 2020

MAINTENANCE: Lenalidomide post ASCT: meta-analysis

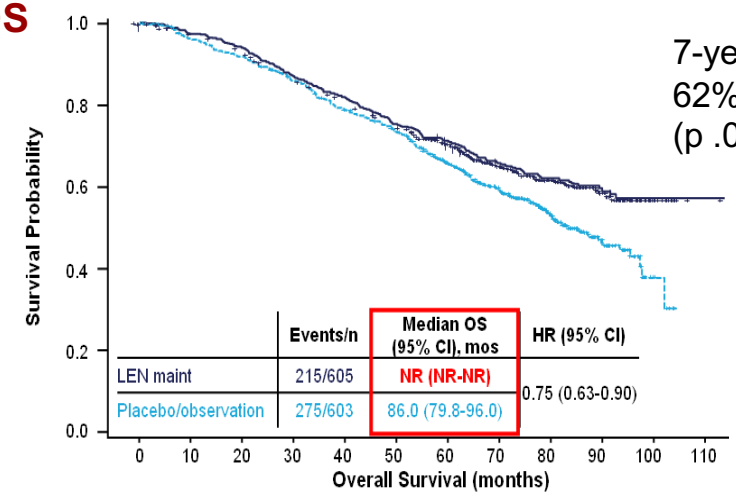
PFS



- median fup 79.5 mos
- 29.3 mos PFS benefit
- 52% reduced risk of PD/death

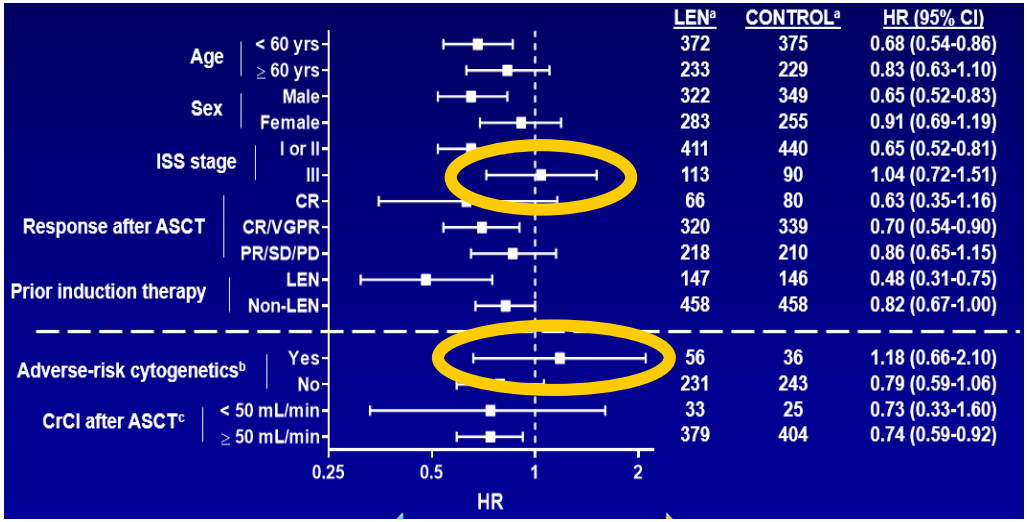


OS



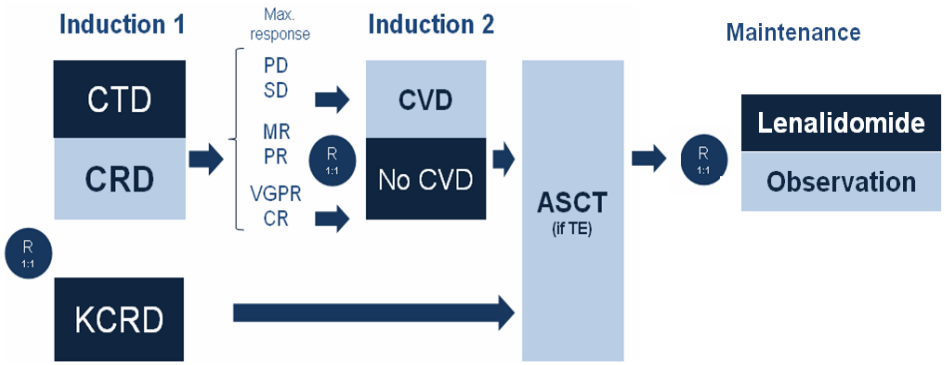
7-year OS rate
62% vs 50%
(p .001)

OS subgroup analysis



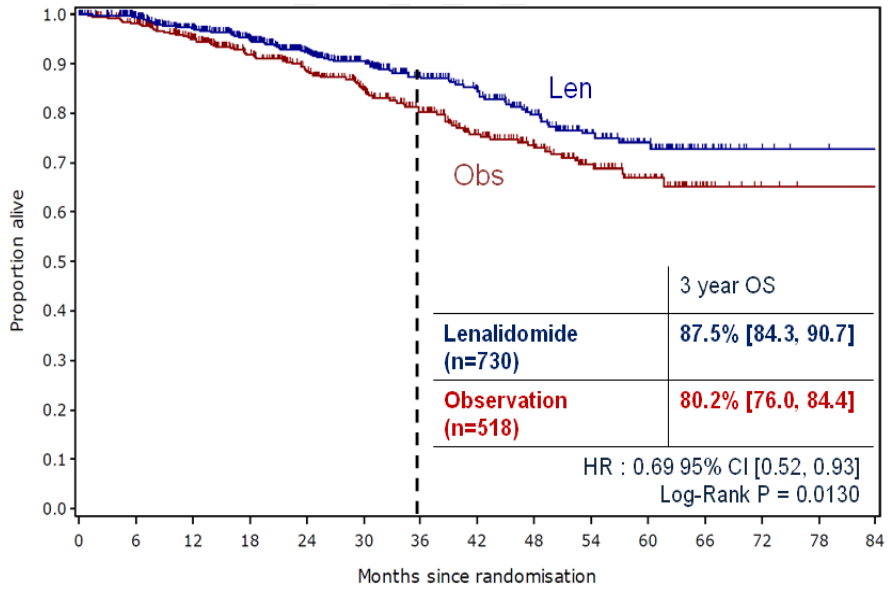
McCarthy, et al. JCO 2017;35:3279-89

MAINTENANCE: Lenalidomide post ASCT: Myeloma XI trial



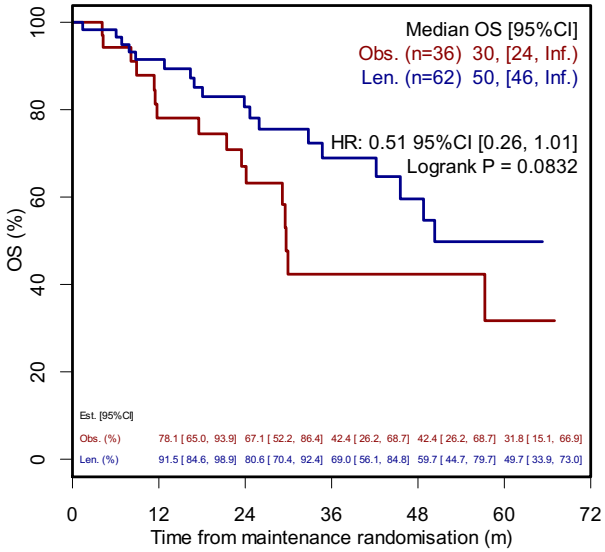
- median fup 79.5 mos
- PFS 57 vs 30 mos (HR 0.48, p < 0.001)
- PFS benefit observed across all prespecified subgroups (cytogenetic risk, age, sex, disease stage, induction therapy, response at baseline…)

OS
(TE pts)



t(4;14) and/or del(17p) present

OS

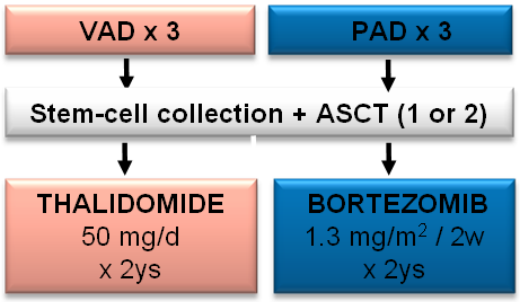


Jackson et al. Lancet Oncol 2019;20:57-73

MAINTENANCE: PIs-based maintenance

- Lack of studies comparing bort vs observation/len, enabling to isolate the contribution of bort as maintenance therapy

HOVON-65/GMMG-HD4 study

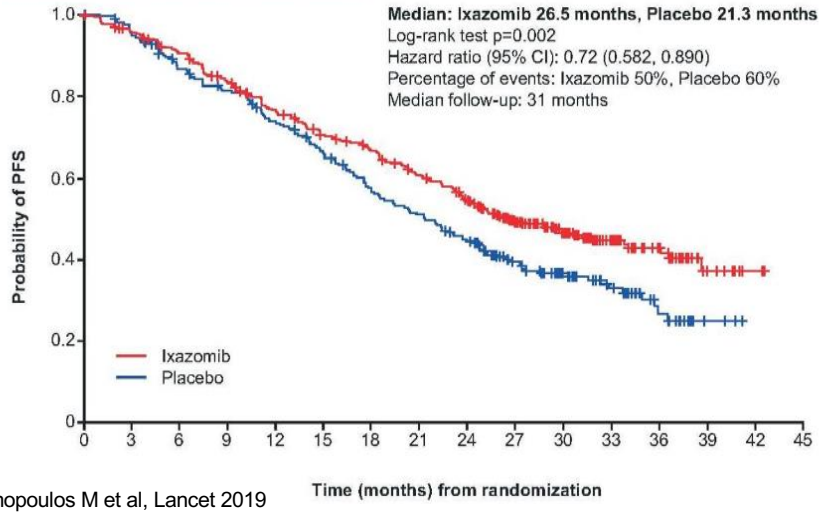


	PAD/bort (= 413)	VAD/thal (= 414)	P value
Response: % CR / ≥ VGPR	36 / 76	24 / 56	<0.001
Upgrade during maintenance	93 (23)	99 (24)	0.64
Median PFS, mos	34	28	0.001
Median OS, mos	90	83	0.22

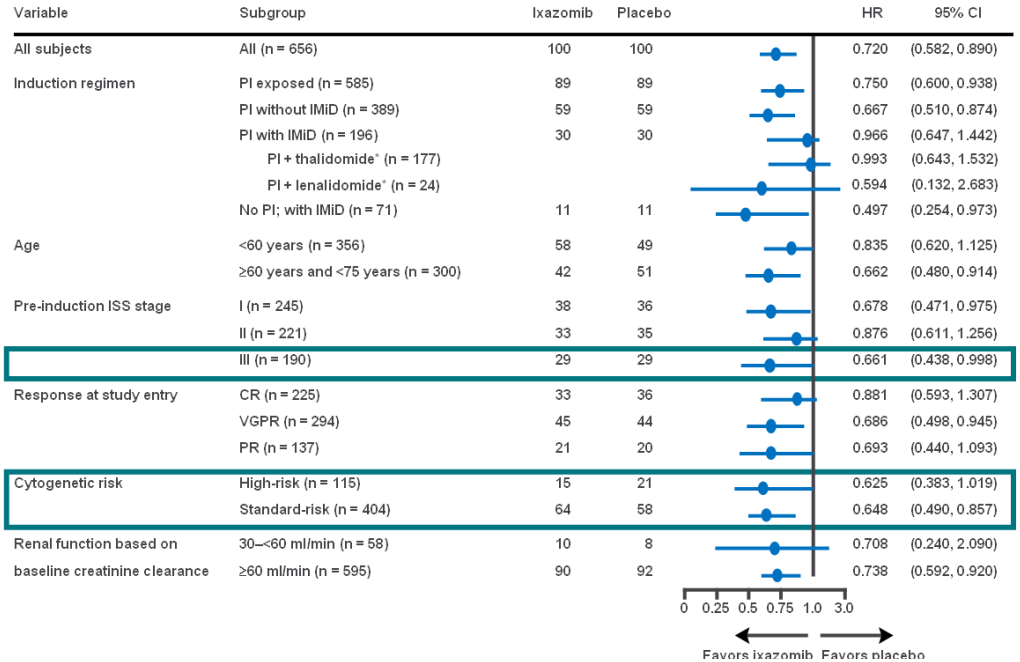
PFS at 60 mo by subtype, %	PAD/Bort		VAD/Thal	
	Yes	No	Yes	No
del(17p)	22	27	5	24
	(*P* = .5)		(*P* < .001)	
OS at 60 mos by subtype, %	**PAD/Bort**		**VAD/Thal**	
	Yes	No	Yes	No
del(17p)	65	72	18	66
	(*P* = .5)		(*P* < .001)	

Sonneveld et al. JCO 2012; Goldschmidt et al. Leukemia 2018; Neben et al. Blood. 2012

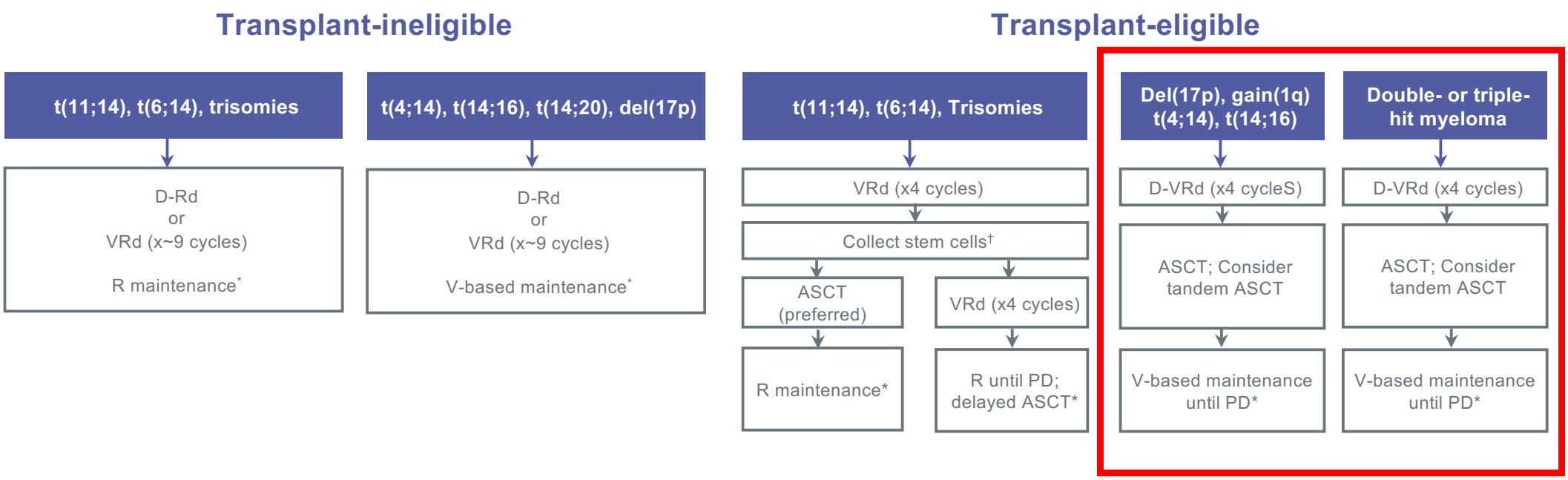
TOURMALINE-MM3 study: PFS



Dimopoulos M et al, Lancet 2019



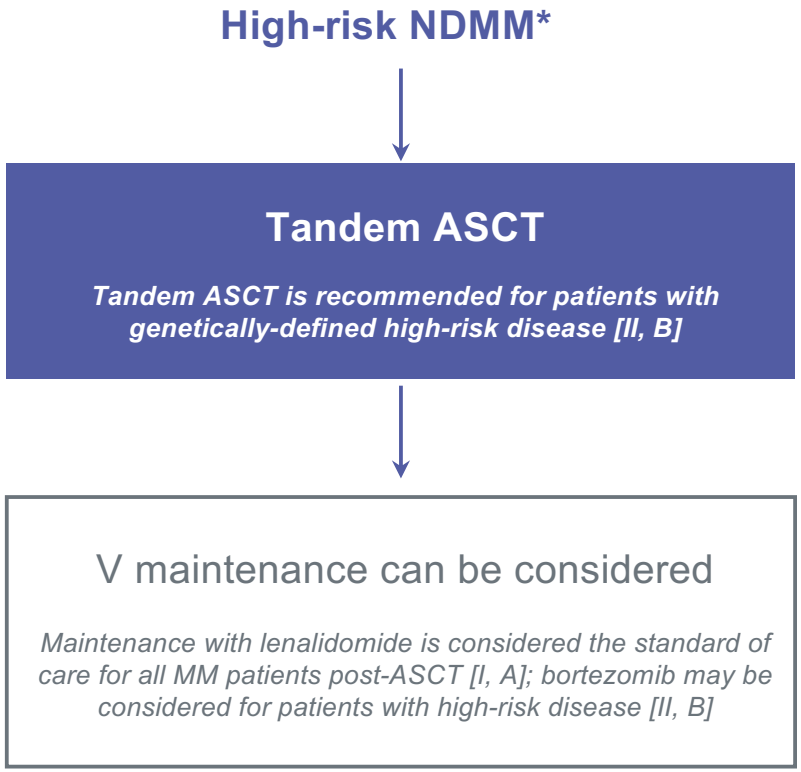
mSMART treatment guideline recommendations regarding common cytogenetic abnormalities



*Duration is usually until progression, based on tolerance; †If age >65 or >4 cycles of VRd, consider mobilization with G-CSF plus cyclophosphamide or plerixafor; d, dexamethasone; D, daratumumab; G-CSF, granulocyte-colony stimulating factor; mSMART, Mayo Stratification for Myeloma And Risk-adapted Therapy; R, lenalidomide; V, bortezomib

mSMART treatment of Newly Diagnosed Myeloma
https://www.msmart.org/mm-treatment-guidelines

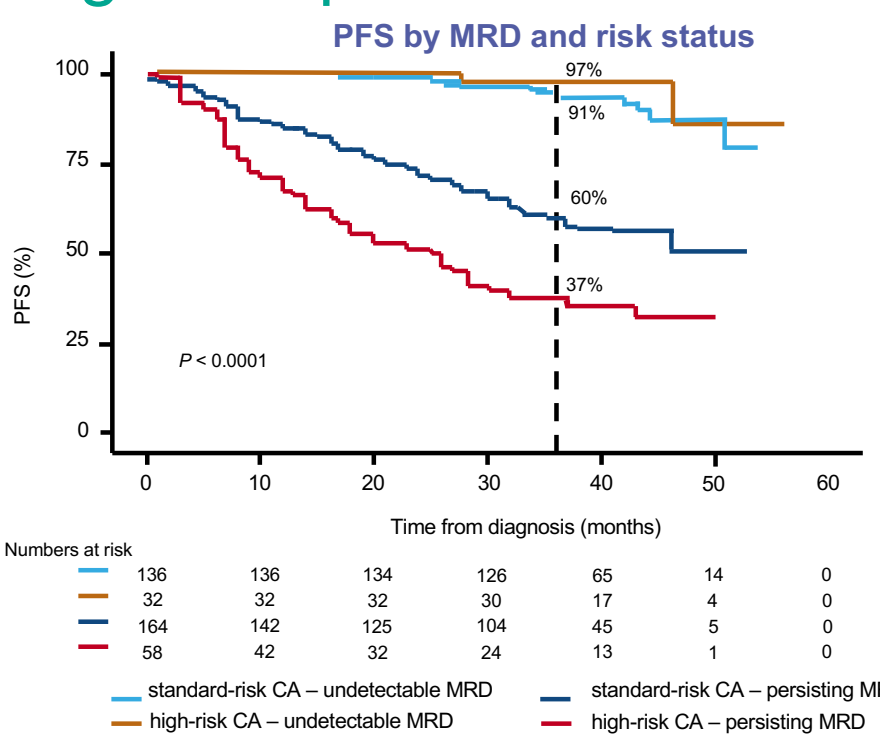
ESMO have limited guidance on treatment of high-risk patients

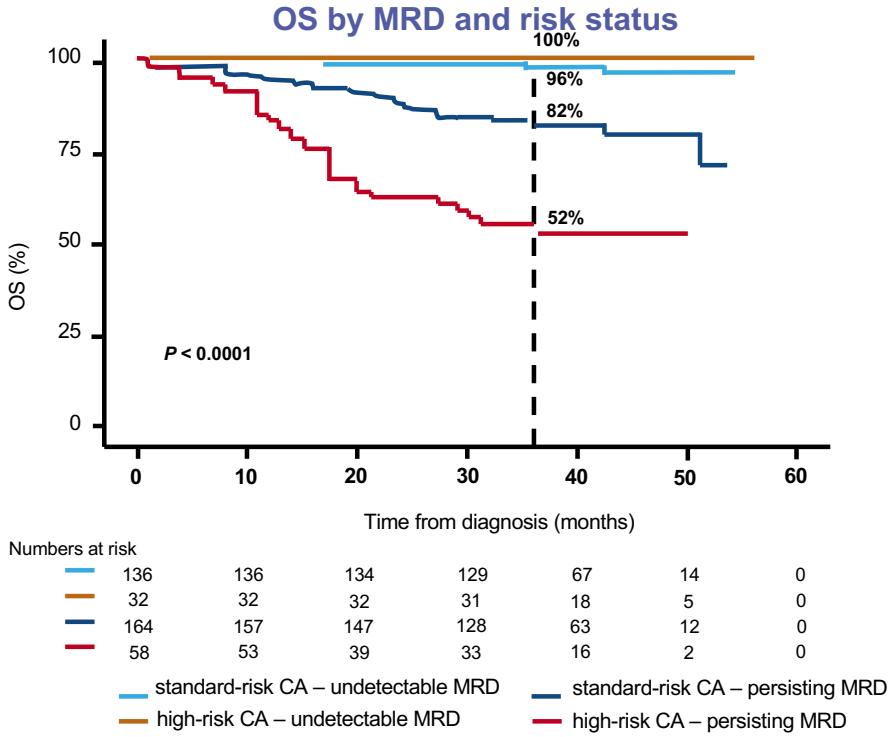


*High-risk NDMM is not specifically defined; ASCT, autologous stem cell transplant; ESMO, European Society of Medical Oncology; NDMM, newly diagnosed multiple myeloma; V, bortezomib

Dimopoulos MA, et al. Ann Onc 2021;32(3):309–22

MRD negativity may overcome poor survival in high-risk patients





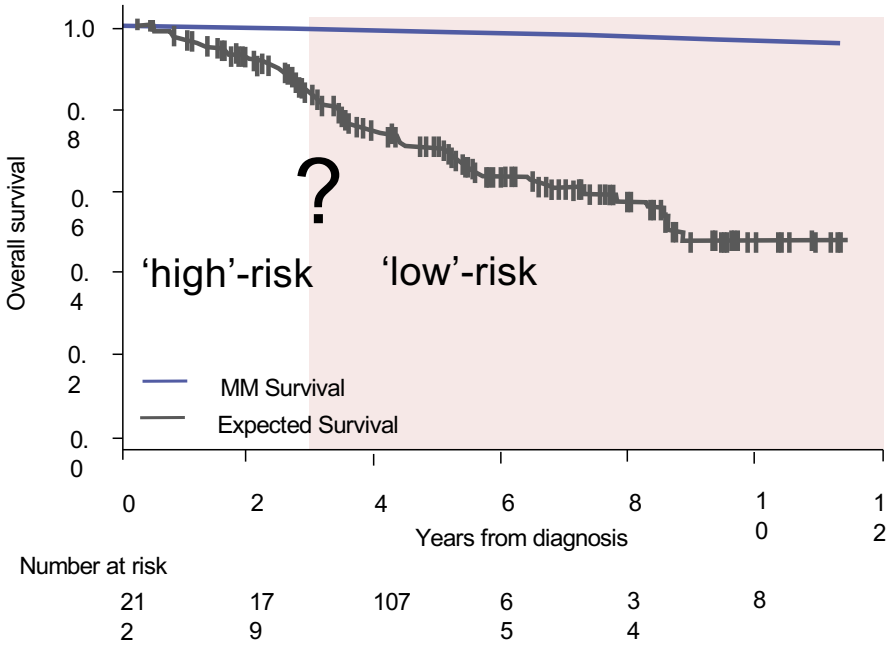
Data from the PETHEMA/GEM2012MENOS65 trial showed patients with high-risk CAs and undetectable MRD after VRd induction/consolidation have similar outcomes to patients with standard-risk disease

High-risk defined as patients with t(4;14), t(14;16), and/or del(17p13) by fluorescent in situ hybridization (FISH)
CA, cytogenetic abnormalities; PFS, progression-free survival; MRD, minimal residual disease; OS, overall survival; VRd, bortezomib, lenalidomide, dexamethasone

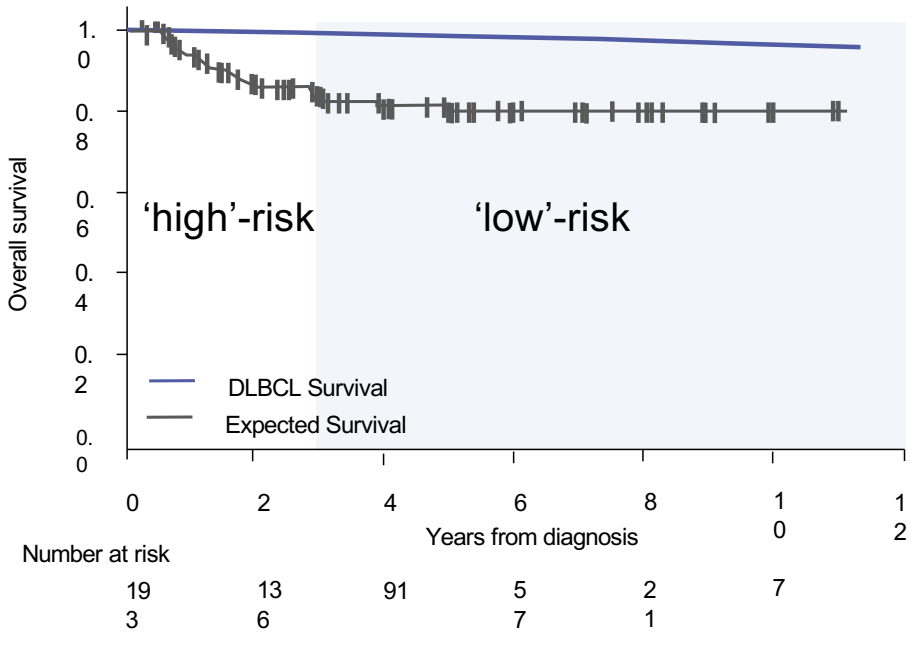
Goicoechea I et al. Blood 2021;137(1):49–60

The definition of ‘risk’ is continuing to evolve

Myeloma



DLBCL

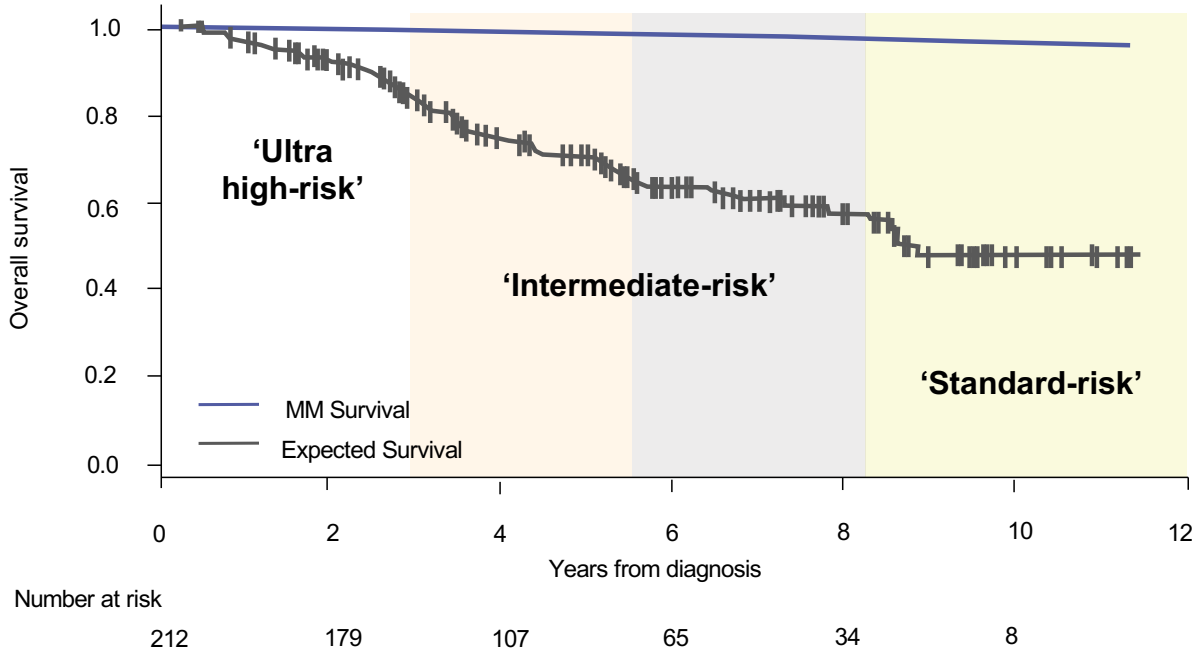


In MM, patients face a persistent risk of relapse with no clear plateau in PFS or OS.
A binary assessment of risk may not be appropriate for MM patients

DLBCL, diffuse large B-cell lymphoma; MM, multiple myeloma; OS, overall survival; PFS, progression-free survival

Ravi P, et al. Blood Cancer J 2018;8:26

A quantitative definition may be more suitable for MM patients

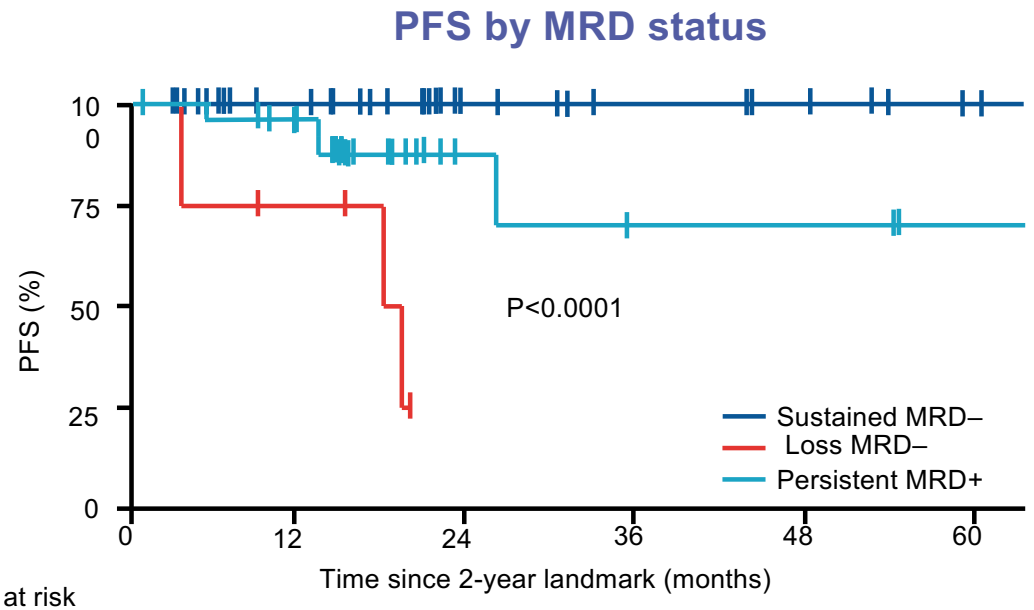


'Ultra high-risk' to describe patients who experience early relapse
'Intermediate-risk' and **'Standard-risk'** groups for patients that experience later relapse

MM, multiple myeloma

Ravi P, et al. Blood Cancer J 2018;8:26

There is a need for prolonged treatment in HRMM:
role of maintenance therapy and SUSTAINED MRD negativity



Number at risk (number censored)						
Sustained MRD–	31 (0)	24 (9)	12	8 (26)	6 (28)	2 (32)
Loss MRD–	4 (0)	4(1)	(22)	0 (3)	0 (3)	0 (3)
Persistent MRD+	28 (0)	24(4)	5 (21)	3 (22)	3 (22)	1 (24)

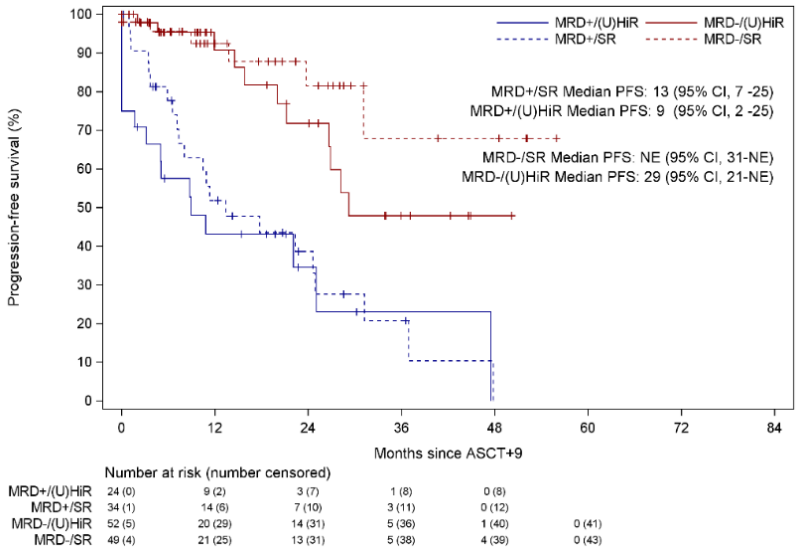
Single agent maintenance may not be enough for some patients with high-risk features to maintain MRD negativity achieved with induction therapy

Patients received up to 5 years of continuous Len maintenance. MRD was assessed from first-pull bone marrow aspirates at baseline and annually by flow cytometry per IMWG criteria, (limit of detection of at least 1×10^{-5})
PFS, progression-free survival; MRD, minimal residual disease

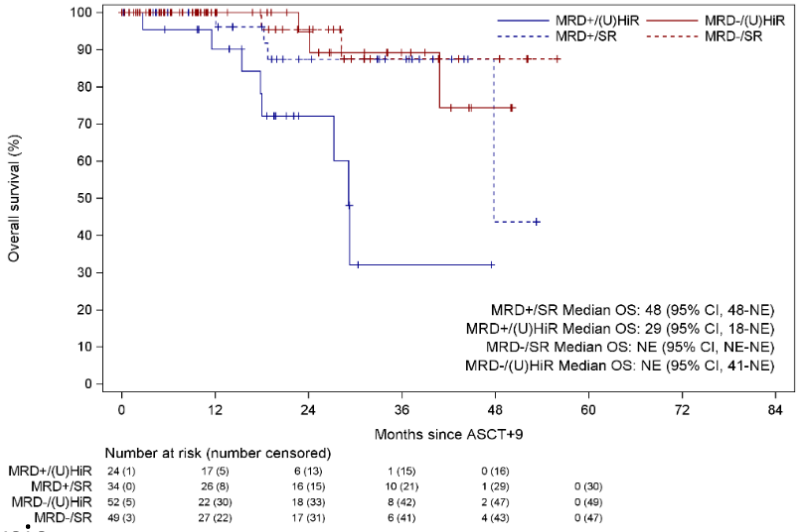
Diamond B, et al. Lancet Haematol 2021;8:e422–32

Impact of MRD status by molecular risk subgroups (HR and ultra HR) during lenalidomide maintenance (MRC XI trial): importance of sensitivity level

PFS



OS



MRD assessment by flow cytometry sensitivity 10^{-5}

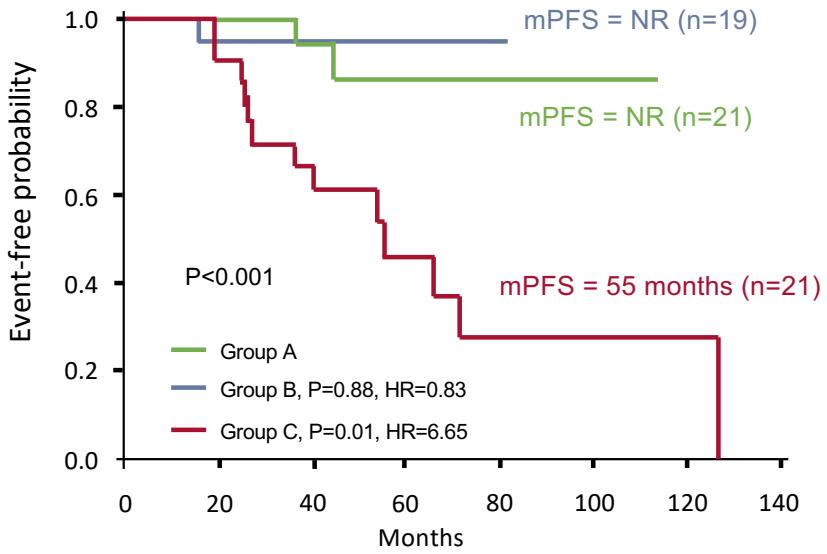
Multivariable analysis

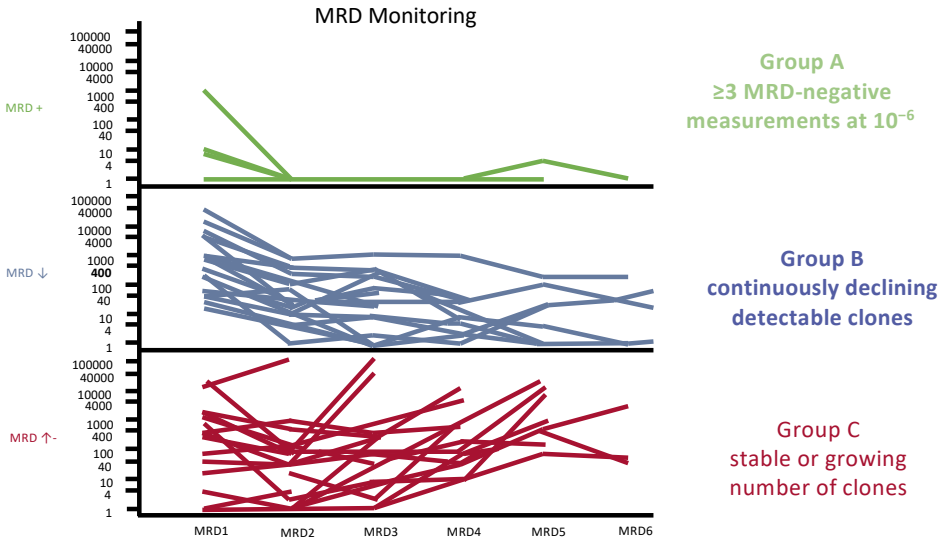
	ASCT+3 PFS			ASCT+9 PFS		
	HR	95%CI	P	HR	95%CI	P
MRD (-ve vs +ve)	0.401	0.271-0.592	<0.0001	0.220	0.102-0.472	0.0001
Treatment (len vs obs)	0.388	0.268-0.561	<0.0001	0.218	0.102-0.463	<0.0001
Cytogenetics (UHiR+HR vs SR)	**2.576**	**1.770-3.748**	**<0.0001**	**2.357**	**1.084-5.126**	**0.0305**
	ASCT+3 OS			**ASCT+9 OS**		
MRD (-ve vs +ve)	0.457	0.246-0.849	0.0132	0.242	0.055-1.073	0.0619
Treatment (len vs obs)	0.528	0.297-0.938	0.0294	0.252	0.070-0.906	0.0347
Cytogenetics (UHiR+HR vs SR)	4.286	2.272-8.086	<0.0001	6.658	1.311-33.82	0.0222

De Tute R et al, IMW 2021

Serial MRD testing may predict clinical relapse

Effect of repeated MRD monitoring on PFS in 61 NDMM patients (up to 6 MRD assessments)





Patients in Group A or Group B had significantly more prolonged PFS than patients in Group C (P<0.001). Serial MRD testing was able to predict clinical relapse in **9 out of 10 cases**

International Harmonization guidelines: *Clinical trials should assess MRD whenever bone marrow examination is performed, and periodically thereafter whilst CR status is maintained*

CR, complete response; m, median; MRD, minimal residual disease; NDMM, newly diagnosed multiple myeloma; PFS, progression-free survival

Martinez-Lopez, et al. Blood Adv 2020;4(14):3295–3301; Costa LJ, et al. 2020; Leukemia 2021;35:18–30

Clinical trials assessing MRD in high-risk NDMM

Trial	Phase	Population	Arms	Definition of high risk	MRD endpoint(s)

GMMG-CONCEPT[1]	2	TE/TI	Isa-KRd ± ASCT	• ISS Stage II or III
				• One or more of:
				  • del(17p)
				  • t(4;14)
				  • > 3 copies gain(1q)
					• MRD– rate (up to approx.1 year) (Primary)

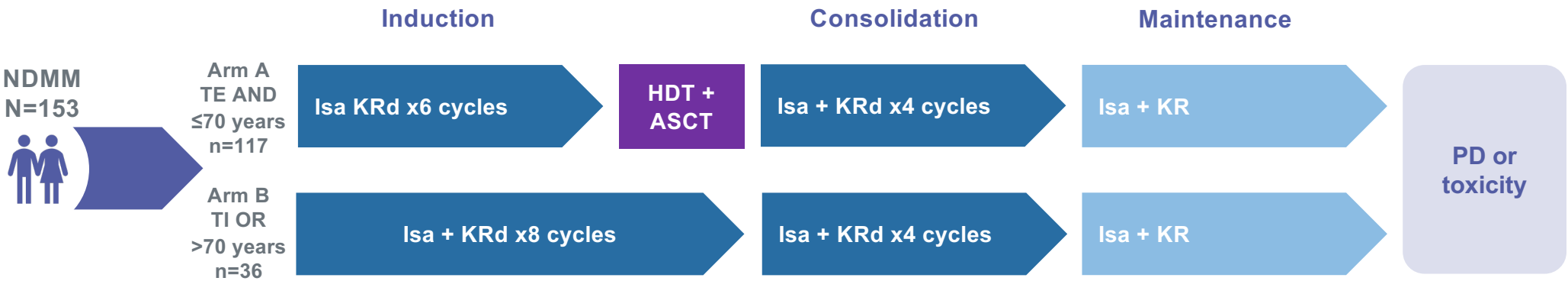
OPTIMUM MUK9[2]	2	TE	D-CVRd + ASCT, D-VRd and D-VR consolidation and DR maintenance	Ultra high-risk NDMM by central trial genetic ≥2 high-risk lesions: • t(4;14) • t(14;16) • t(14;20) • gain(1q) • del(1p) • del(17p) or gene expression SKY92 (SkylineDx) profiling	• MRD– rate (100 days post-ASCT) (Secondary)
IFM 2018-04[3]	2	TE	D-KRd	• del(17p) • or t(14;16) • or t(4;14)	• MRD– rate (48 months) (Secondary)

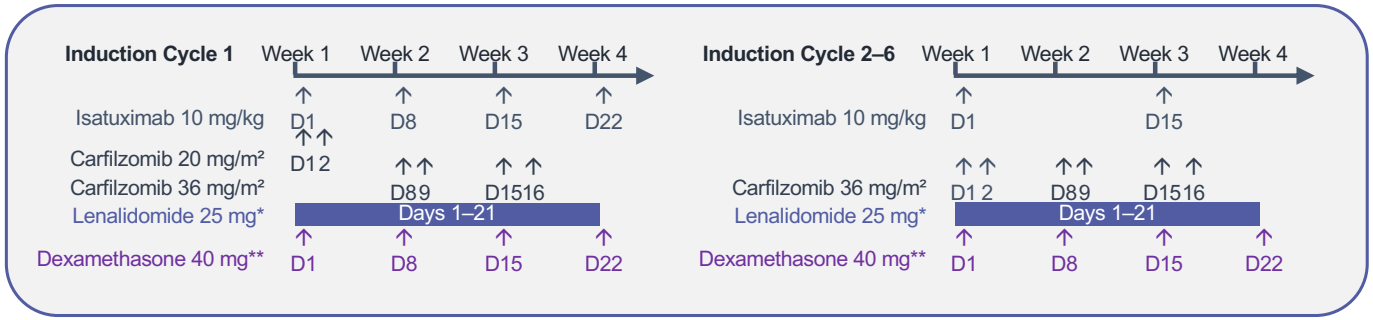
These studies will provide insights into the role of anti-CD38 antibodies added to standard backbone regimens both as induction/consolidation therapy, but also as long-term maintenance in high-risk patients

ASCT, autologous stem cell transplant; MRD, minimal residual disease; NDMM, newly diagnosed multiple myeloma; Te, transplant eligible; Ti, transplant ineligible; D, daratumumab; d, dexamethasone; C, cyclophosphamide; Isa, isatuximab; K, carfilzomib R, lenalidomide; V, bortezomib

1. https://clinicaltrials.gov/ct2/show/NCT03104842
2. https://www.clinicaltrials.gov/ct2/show/NCT03188172
3. https://clinicaltrials.gov/ct2/show/NCT03606577

GMMG-CONCEPT: Study design





*Dose adaption of lenalidomide according to renal function; **20 mg in patients ≥75 years

ASCT, autologous stem cell transplant; d, dexamethasone; GMMG, German Multiple Myeloma Group; HDT, high-dose therapy; Isa, isatuximab; K, carfilzomib; NDMM, newly diagnosed multiple myeloma; PD, progressive disease; R, lenalidomide; Te, transplant eligible; Ti, transplant ineligible

Weisel KC, et al. Presented at ASCO 2020 Virtual meeting; Abstract #8508; ClinicalTrials.gov: NCT03104842

GMMG-CONCEPT: Baseline characteristics

ITT population	N=50
Age, median (range), years	58 (42–82)
Arm A (TE)	58 (42–69)
Arm B (TI)	77 (72–82)
Male / Female, n	21 / 29
ECOG PS, n (%)	
0	21 (42)
1	23 (46)
2	6 (12)
ISS, n (%)	
II	28 (56)
III	22 (44)

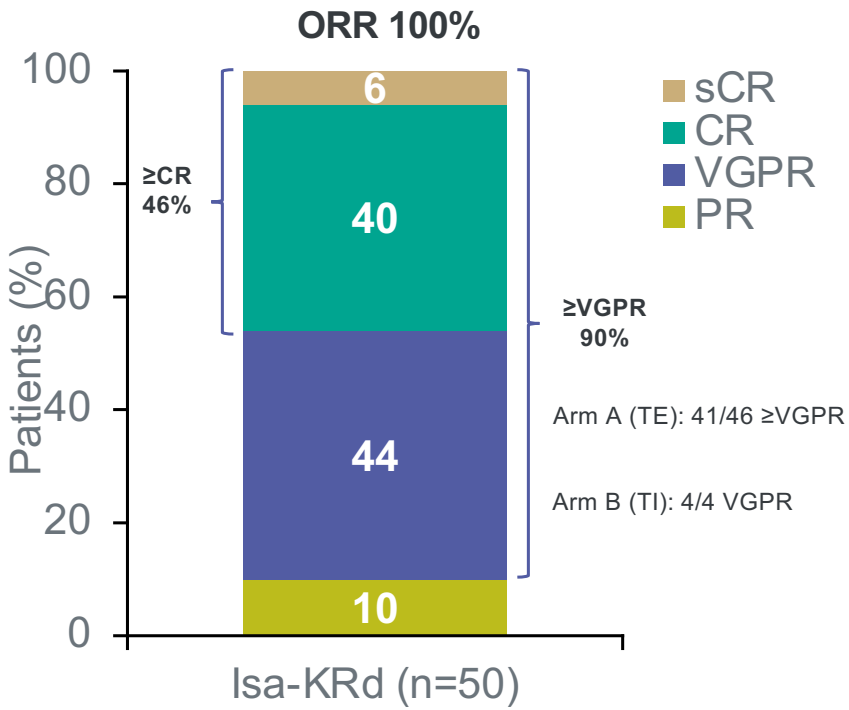
ITT population	N=50
High-risk cytogenetics, n (%)	
del(17p)	26 (52)
t(4;14)	19 (38)
t(14;16)	5 (12)
>3 copies 1q21	21 (42)
Any 2 high-risk aberrations	13 (26)
≥3 high-risk aberrations	2 (4)
LDH, mean (range), U/L	225.5 (190.5–833)
LDH above ULN, n (%)	10 (20)

ECOG, Eastern Cooperative Oncology Group; ISS, International Staging System; ITT, intent to treat; LDH, lactic dehydrogenase; PS, performance status; GMMG, German Multiple Myeloma Group; Te, transplant eligible; Ti, transplant ineligible; ULN, upper limit of normal

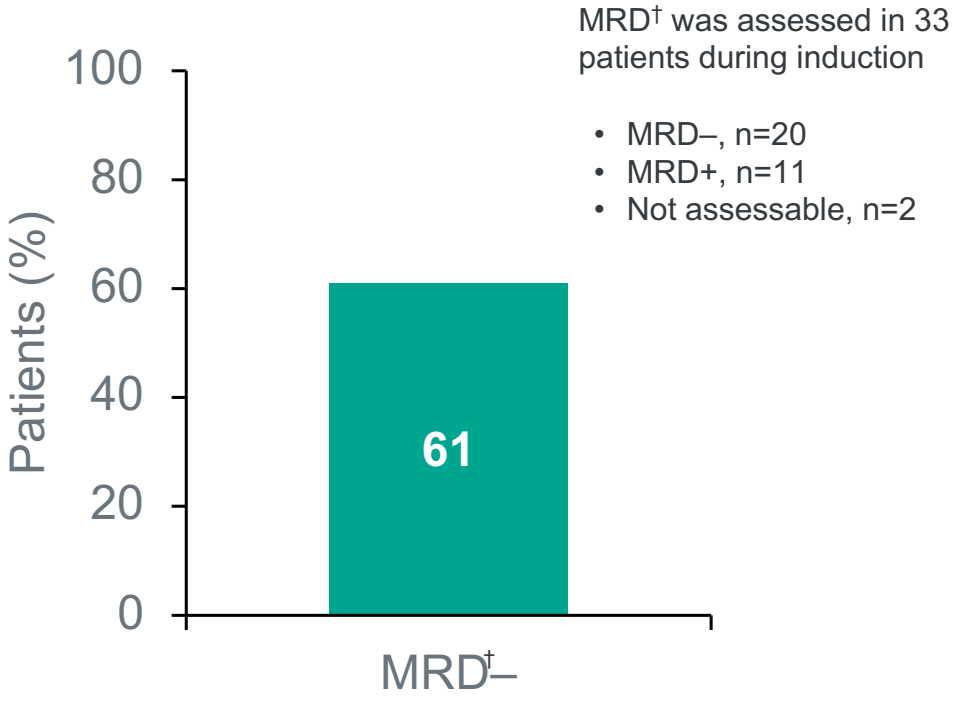
Leypoldt LB, et al. EHA 2021, Presentation S183

GMMG-CONCEPT interim analysis*: Response and MRD

Best response during induction (all evaluable patients)



TE NDMM: MRD (10^{-5}) assessment during induction



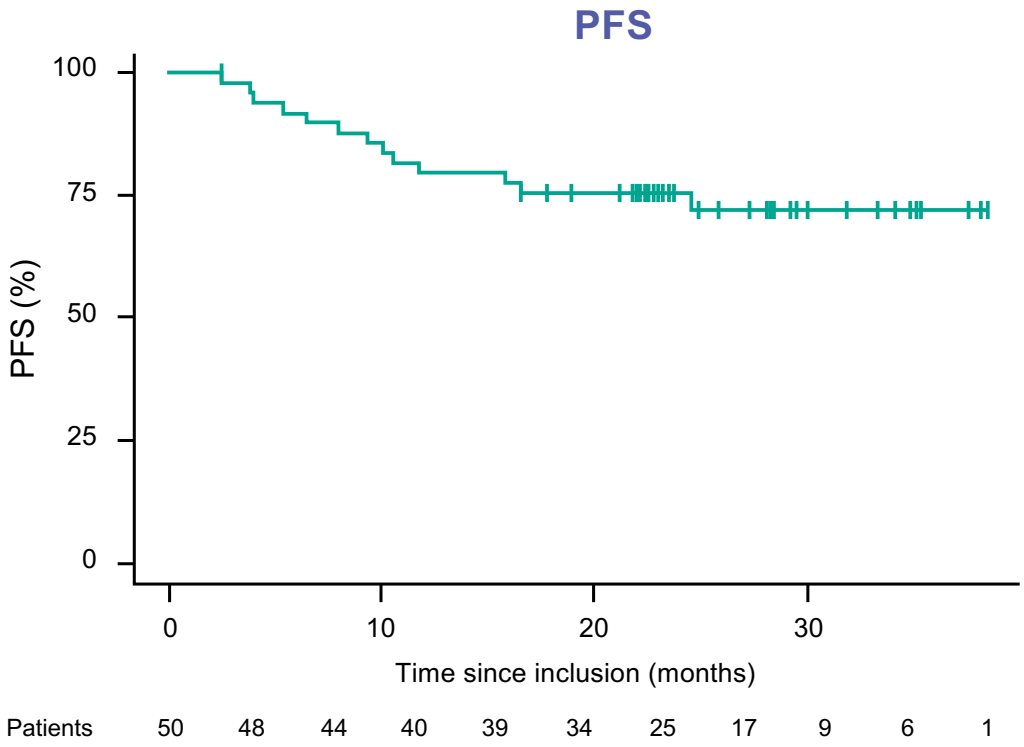
MRD† was assessed in 33 patients during induction

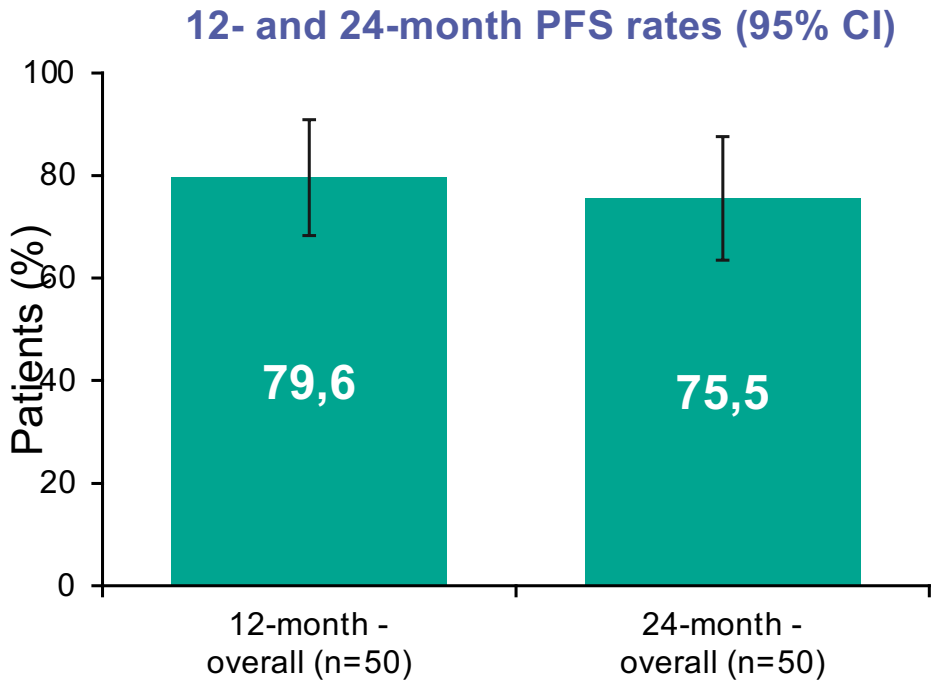
- MRD–, n=20
- MRD+, n=11
- Not assessable, n=2

*Interim analysis of induction treatment of first 50 patients (Arm A n=46, Arm B n=4). †Technique not reported. CR, complete response; d, dexamethasone; Isa, isatuximab; GMMG, German Multiple Myeloma Group K, carfilzomib; MRD, minimal residual disease; ORR, overall response rate; PR, partial response; NDMM, newly diagnosed multiple myeloma; R, lenalidomide; sCR, stringent complete response; TE, transplant eligible; VGPR, very good partial response

Weisel KC, et al. ASCO 2021; Abstract 8508
Leypoldt LB, et al. EHA 2021, Presentation S183

GMMG-CONCEPT interim analysis*: PFS (median follow-up 24.9 months)

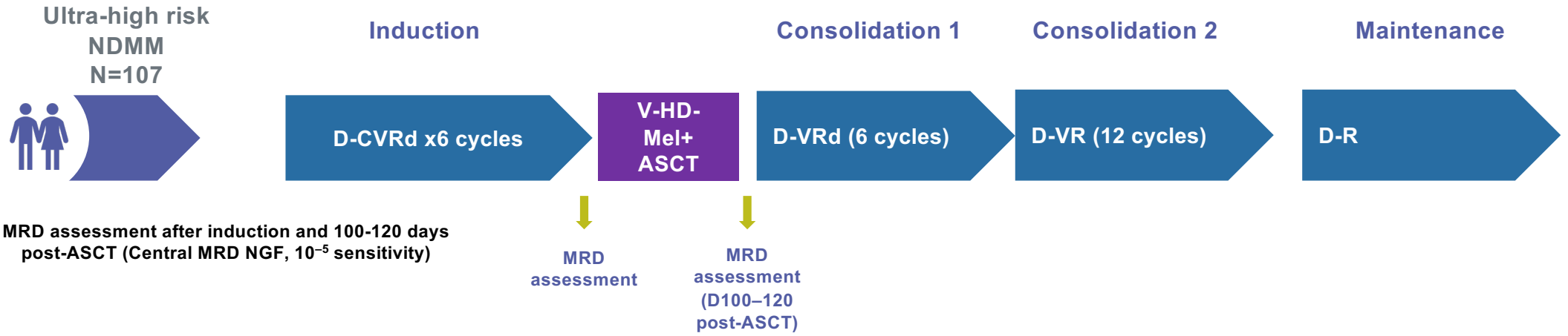




Data cut-off, 26 January 2021.*Interim analysis of induction treatment of first 50 patients (Arm A n=46, Arm B n=4); CI, confidence interval; GMMG, German Multiple Myeloma Group; PFS, progression-free survival; Te, transplant eligible; Ti, transplant ineligible

Leypoldt LB, et al. EHA 2021, Presentation S183

OPTIMUM-MUK9: Study design



*Cycle 1 and 2 only **20mg in patients ≥75 years †Consolidation 1 only

ASCT, autologous stem cell transplant; D-CVRd, daratumumab, cyclophosphamide, bortezomib, lenalidomide, dexamethasone; Mel, melphalan; MRD, minimal residual disease; NDMM, newly diagnosed multiple myeloma; NGF, next generation flow

Kaiser M, et al. Presented at ASCO 2021. Abstract 8001

OPTIMUM-MUK9: Baseline characteristics

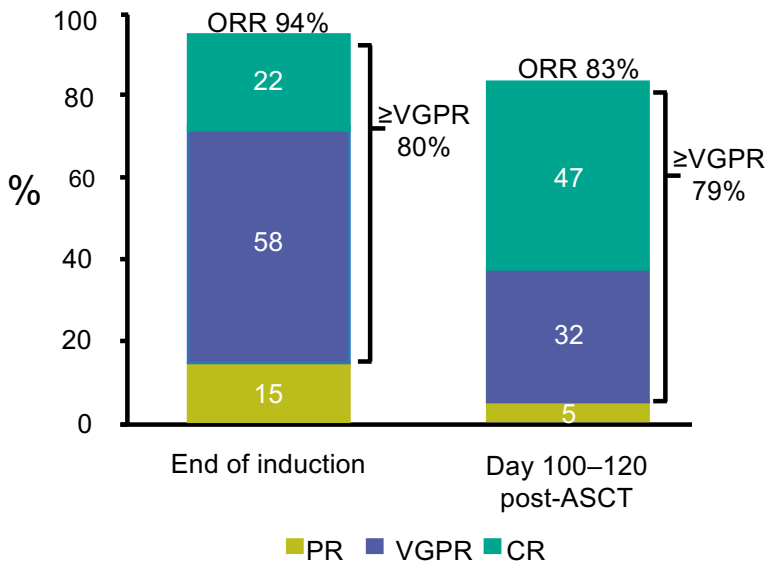
Patient characteristics	Safety population (n=107)
Age, median (range), years	60 (35–78)
ISS, n (%) Stage 1 Stage 2 Stage 3	 29 (27) 44 (40) 34 (32)
ECOG performance status, n (%) 0 1 2	 51 (48) 42 (39) 10 (9)
Received bridging induction therapy, n (%)	86 (80)
Double-hit genetics, n (%)	57 (53)
SKY92 risk signature present, n (%)	83 (77)
Both double hit and SKY92, n (%)	33 (31)

ISS, International Staging System; ECOG, Eastern Cooperative Oncology Group

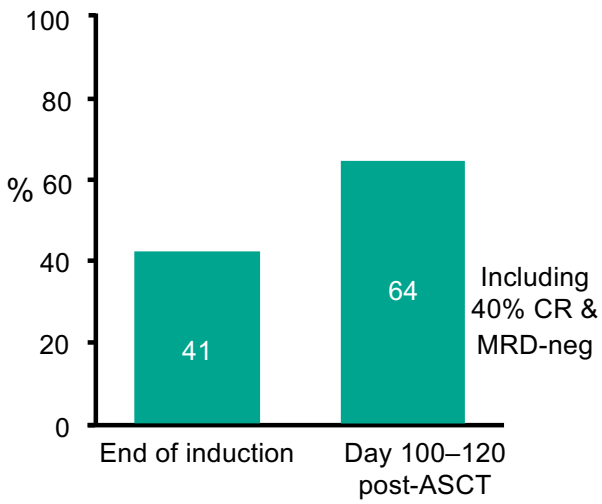
Kaiser M, et al. Presented at ASCO 2021. Abstract 8001

OPTIMUM-MUK9: Response and MRD

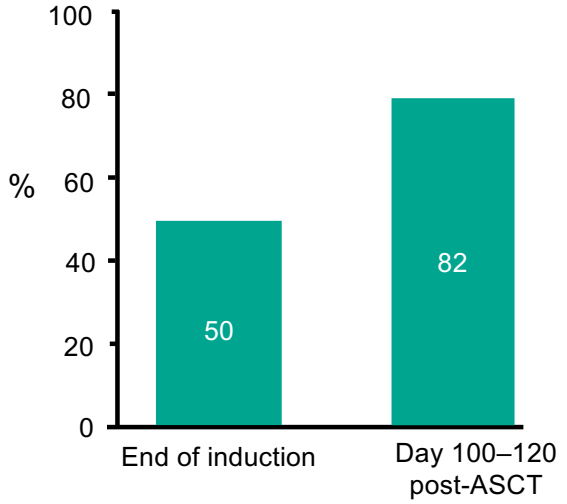
ORR in safety population (n=107)



MRD– (10^{-5}) in safety population (n=107)



MRD– (10^{-5}) in patients with measurable MRD (n=87/n=83)



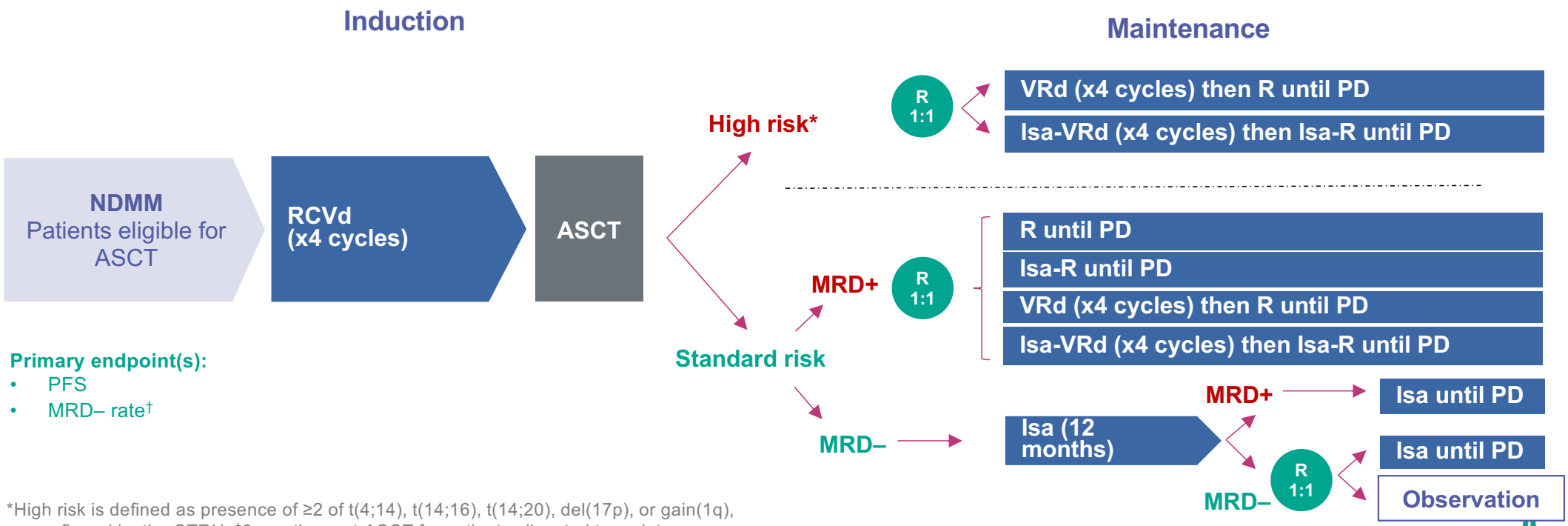
ASCT, autologous stem cell transplant; CR, complete response; MRD, minimal residual disease; PR, partial response; VGPR, very good partial response

Kaiser M, et al. Presented at ASCO 2021. Abstract 8001

MRD and Risk assessment as driver of first-line therapy

Risk-Adapted therapy Directed Accordng to Response (RADAR)

Sponsor: University of Leeds
Estimated primary completion: Not available



Primary endpoint(s):

- PFS
- MRD– rate†

*High risk is defined as presence of ≥2 of t(4;14), t(14;16), t(14;20), del(17p), or gain(1q), as confirmed by the CTRU. †6 months post-ASCT for patients allocated to maintenance only, and 7 months for patience allocated to consolidation then maintenance. MRD assessed at 10^{-5}, confirmed by central lab

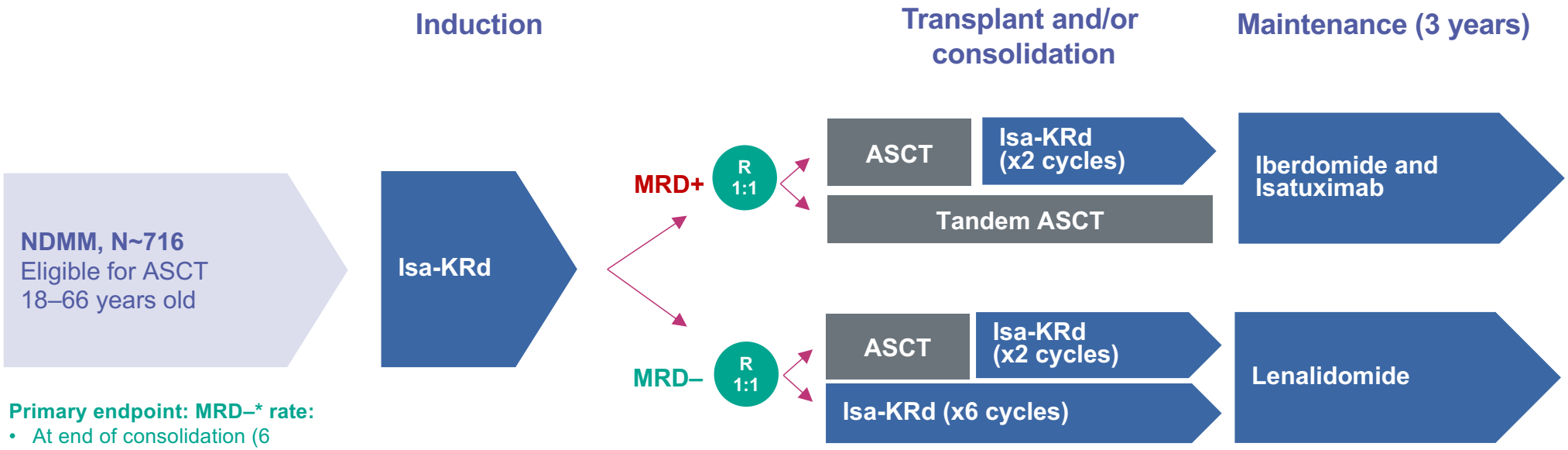
ASCT, autologous stem cell transplant; C, cyclophosphamide; CTRU, clinical trials research unit; d, dexamethasone; Isa, isatuximab; MRD, minimal residual disease; NDMM, newly diagnosed multiple myeloma; PD, progressive disease; PFS, progression-free survival; R, lenalidomide; V, bortezomib

https://www.clinicaltrialsregister.eu/ctr-search/trial/2019-001258-25/GB

MRD status as driver of first-line therapy

Minimal Residual Disease Adapted Strategy (MIDAS)

Sponsor: Intergroupe Francophone du Myelome (IFM)
Estimated primary completion: September 2024



Primary endpoint: MRD–* rate:

- At end of consolidation (6 months)
- 1, 2, and 3 years post induction

*Primary analysis will evaluate MRD (NGS, 10^{-6} threshold)

Isa-KRd is an investigational combination that has not been approved by any regulatory authority. Sanofi does not recommend the use of their products outside the approved indication. Please consult your local label before prescribing

ASCT, autologous stem cell transplant; d, dexamethasone; Isa, isatuximab; K, carfilzomib; MRD, minimal residual disease; NDMM, newly diagnosed multiple myeloma; NGS, next-generation sequencing; R, lenalidomide

https://clinicaltrials.gov/ct2/show/NCT04934475

Summary

- First challenge: **Definition of HR patients**: need for a consensus, maybe classifying **different MM entities**
- Despite advances in treatment, these patients remain an **unmet need**, experiencing primary resistance or early progression
- **Sustained-MRD negativity, at the highest sensitivity level,** can overcome poor prognosis in HR patients; clinical trials are now investigating MRD as an endpoint in HR NDMM patients
- Possible role for **individualize treatment** options/multi-drug regimens, with combined **targeted therapies**

Personal recommendations on definition and treatment of HR-NDMM

Newly diagnosed transplant-eligible (NDTE) MM patients		
Risk/estimated frequency	**Definition**	**Suggested treatment**
HR (25-30%)	ISS 3, 1 cytogenetic-molecular aberration*, R-ISS 3, R2-ISS 3 and 2 intermediate-high, > 0.07% circulating PCs, persistent MRD positivity after optimal treatment, renal failure	**Quadruplet induction (MoAb + PI + IMiD + dex)** **Double ASCT** **Quadruplet consolidation** **Single/two drugs maintenance (PI + IMiD) for at least 2 years if sustained MRD-** **Prompt change/intensification of therapy in patients with persistent MRD + and lost of MRD-**
Ultra-HR (6-10%)	EMD, PCL (PCs > 20% or 2x 10^{9}), ≥ 2 genetic abnormalities, co-existence of genetic and at least another HR feature (see table 1), primary refractory disease	**Innovative strategies, including quadruplet induction (MoAb + PI + IMiD + dex)** **CAR-T therapy (± ASCT)** **Innovative maintenance with T-cell engagers.** **Close MRD follow-up and change of therapy at conversion from – to +**

*t(4;14) if concomitant presence of a second unfavorable genetic abnormality or clinical feature, t(14;16), t(14;20), amplification 1q (≥ 4 copies), del 1p, del 17p in at least 55-60% PCs, TP53 bi-allelic inactivation (double-hit TP53), HR GEP signature

Zamagni E et al, «How I treat HR MM», Blood 2021, under revision