Highlights from IMS 20th meeting 2023

Sara Bringhen, MD, PhD

Terapia di induzione del paziente fit non candidato ad ASCT.

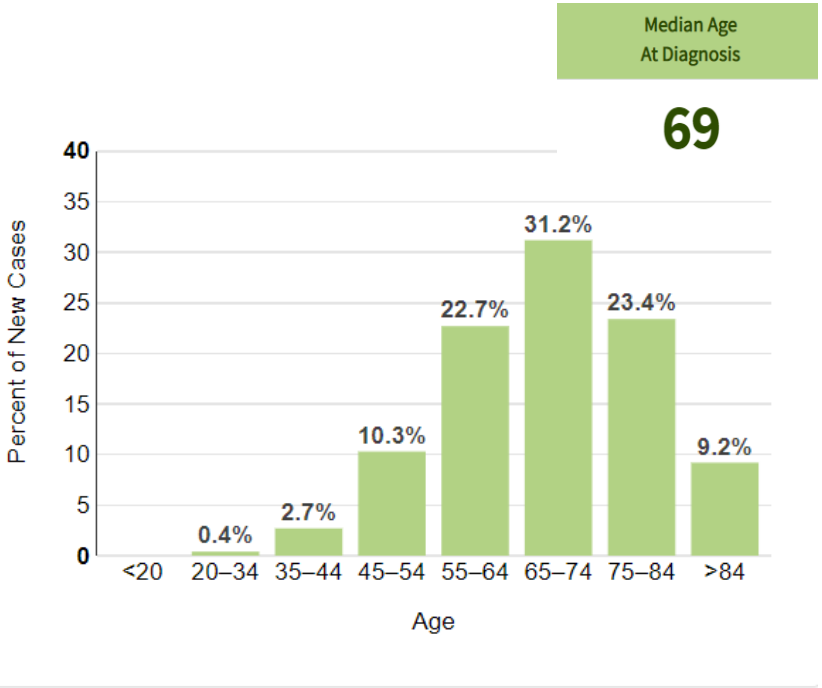
30-31 gennaio 2024
BOLOGNA, Royal Hotel Carlton

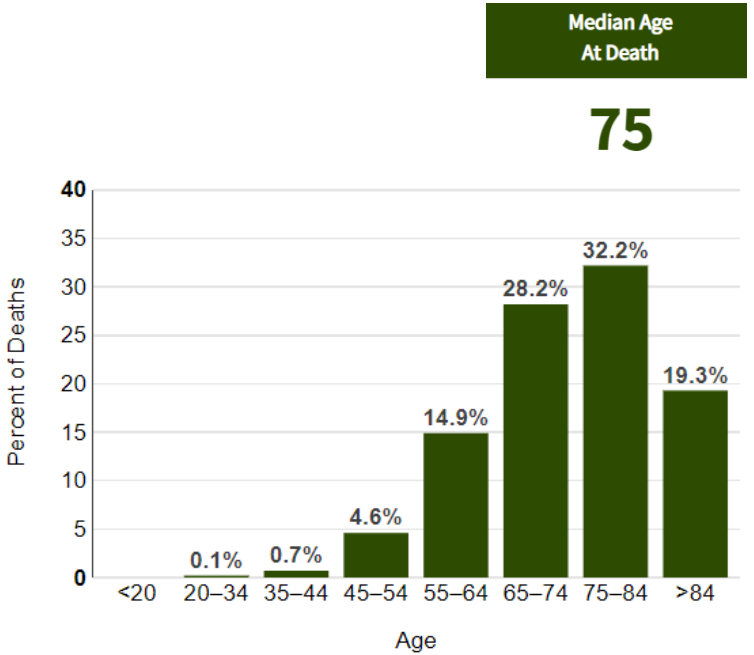
Disclosures

Sara Bringhen, MD, PhD

- **Participation in speakers' bureaus**: Amgen, Bristol Myers Squibb, GlaxoSmithKline, Janssen, Sanofi, and AbbVie
- **Participation in advisory boards**: Bristol Myers Squibb, Janssen, Takeda, Pfizer, Stemline Therapeutics, and Oncopeptides
- **Consultancy fees**: Sanofi.

MULTIPLE MYELOMA: A DISEASE OF THE ELDERLY





U.S. 2014–2018, All Races, Both Sexes

SEER Cancer Stat Facts: Myeloma. National Cancer Institute. Bethesda, MD,

HETEROGENEITY OF THE AGING POPULATION

Fit patients ASCT Eligible

Based on
Age
Performance status (PS)
Comorbidities
(R-MCI score, HCT-CI) and organ function

Fit patients No ASCT Eligible

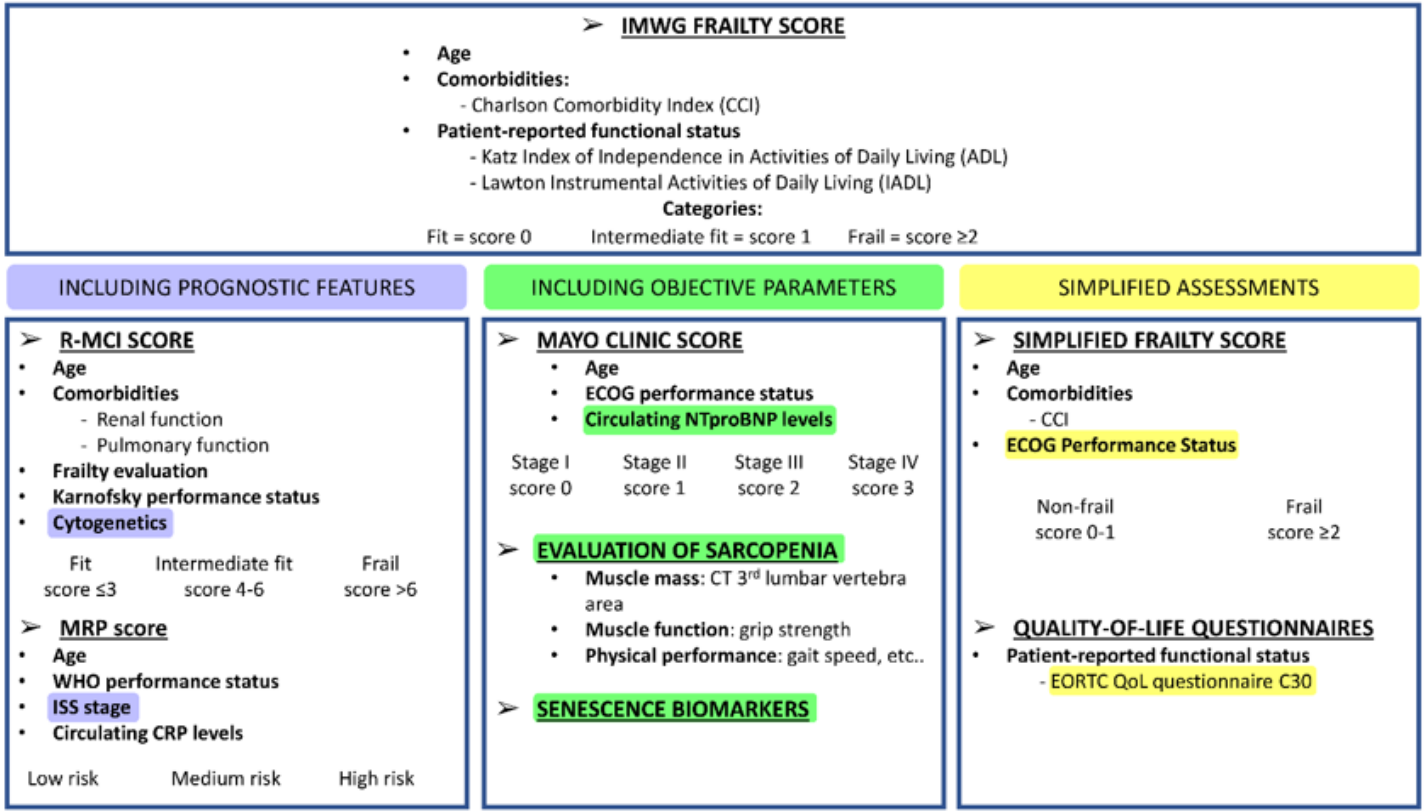
Active, independent, who exercise regularly

Intermediate fit

Can perform limited activities but they don't need any help

Frail

Help for household tasks
Dependent on other people
Partial help for their personal care



Bonello F et al. Cancers 2021, 12(11):3106

IMWG Frailty Score

FIT

Age ≤75 years, ADL >4, IADL >5, *and* CCI ≤1

ASCT eligibility:
cardiac function (LVEF >40%)
liver function (bilirubin <1.5 ULN, AST/ALT <2.5 ULN)
pulmonary function (DLCO/FEV1 >40-80%)

INTERMEDIATE-FIT

Age 76-80 years
or ADL ≤ 4
or IADL ≤ 5
or CCI ≥ 2

FRAIL

Age >80 years regardless of ADL, IADL, CCI
or Age 76-80 years and either ADL ≤ 4, IADL ≤5, CCI ≥2
or Age ≤75 years and at least two of the following: ADL ≤4, IADL ≤5, CCI ≥2

ASCT		No ASCT	Reduced-intensity regimens	Dose-adjusted regimens
MEL200 mg/m^2 if: - age ≤70 years - no renal impairment - rMCI 1-3 - performance status ≥90% (not related to MM)	MEL100-140 mg/m^2 if: - age >70 years - and/or renal impairment - and/or rMCI 4-6 - and/or performance status <90% (not related to MM)	Dara-VMP Dara-Rd VRd VCd VMP* Rd*	Weekly VMP Weekly VCd Vd Rd Rd-R vrd lite°	rd° vd°
				Palliation and supportive care

* If daratumumab-based combinations or VRd are unavailable. ° The lower-case letter indicates a reduced dose. *Abbreviations*: MM, multiple myeloma; IMWG, International Myeloma Working Group; ADL, Activities of Daily Living; IADL, instrumental activities of daily living; CCI, Charlson Comorbidity Index; ASCT, autologous stem-cell transplantation; LVEF, left ventricular ejection fraction; ULN, upper limit of normal; AST/ALT, aspartate aminotransferase/alanine aminotransferase; DLCO, diffusion capacity of carbon monoxide; FEV1, forced expiratory volume in one second; MEL100/140/200, melphalan at 100/140/200 mg/m2; Dara, daratumumab; V, v, bortezomib; M, melphalan; P, prednisone; R, r, lenalidomide; d, dexamethasone; Rd-R, lenalidomide-dexamethasone followed by lenalidomide maintenance; V, bortezomib; rMCI, Revised Myeloma Comorbidity Index.

Iberdomide, bortezomib, and dexamethasone (IberVd) in transplant-ineligible newly diagnosed multiple myeloma: results from the CC-220-MM-001 trial

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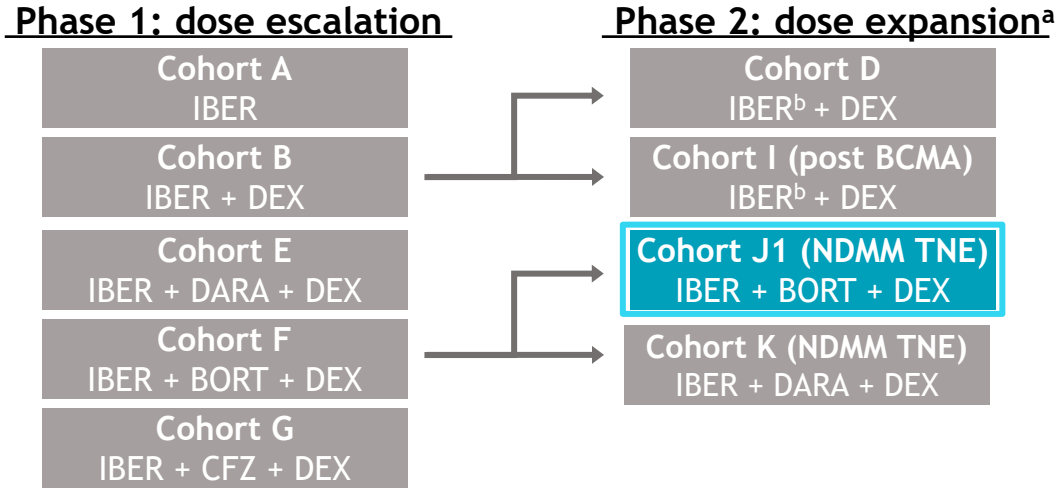
Iberdomide

- IBER is a novel, potent, oral CRBN E3 ligase modulator (CELMoD™) with increased tumoricidal activity and immune-modulatory effects compared with IMiD agents[2–4]
- Preclinically, IBER in combination with BORT and DEX (Vd) demonstrates synergistic antiproliferative activity and deeper apoptosis of myeloma cell lines compared with either LEN or pomalidomide + Vd[2,3]
- IberVd has shown promising preliminary efficacy and safety in patients with relapsed/refractory MM in the ongoing phase 1/2 CC-220-MM-001 trial[4]

- Phase 1/2 trial evaluating IBER with different treatment combinations in MM[1,2]
- **Objective**: to report the first results from the dose-expansion cohort of the CC-220-MM-001 trial evaluating IberVd in patients with NDMM who are TNE or not receiving ASCT as their first therapy



BORT, bortezomib; CRBN, cereblon; c-Myc, cellular Myc; CUL4, cullin 4; DARA, daratumumab; DC, dendritic cell; DDB1, DNA damage-binding protein 1; DEX, dexamethasone; IBER, iberdomide; IberVd, IBER + BORT + DEX; IFN, interferon; IL, interleukin; IMiD, immunomodulatory drug; IRF4, interferon regulatory factor 4; LEN, lenalidomide; MM, multiple myeloma; NDMM, newly diagnosed MM; NK, natural killer; ROC1, regulator of cullins-1; Ub, ubiquitin; Vd, BORT + DEX.

1. Matyskiela ME, et al. *J Med Chem* 2018;61:535–542; 2. Amatangelo M, et al. *Blood* 2018;132(suppl 1). Abstract 1935; 3. Amatangelo M, et al. *Blood* 2020;136(suppl 1):8–9; 4. Lonial S, et al. *Lancet Haematol* 2022;9:e822-e832.

CC-220-MM-001 eligibility, treatments, and endpoints

- NDMM
- Previously untreated symptomatic MM[a]
- No ASCT planned for initial therapy or ASCT-ineligible[b]
- Measurable disease

IBER + BORT + DEX

IBER (oral): 1.0, 1.3, or 1.6 mg on D1–14 in C1-8, and D1-21 in C≥9

BORT (SC): starting at 1.3 mg/m^2 on D1, 4, 8, and 11 in C1-8

DEX (oral): 20 mg[c] on D1, 2, 4, 5, 8, 9, 11, and 12 in C1-8, and 40 mg[d] weekly in C≥9

21-day cycles (C1-8)
28-day cycles (C≥9)

Characteristic[a]	IberVd TNE NDMM (N = 18)
Age, median (range), years	77.5 (57–84)
ECOG PS, n (%)	
0	3 (16.7)
1	11 (61.1)
2	4 (22.2)
ISS stage at study entry, n (%)	
I	7 (38.9)
II	9 (50.0)
III	2 (11.1)
High-risk cytogenetics,[b] n (%)	11 (61.1)[c]

Endpoints

- **Primary:** efficacy and safety
- **Secondary:** additional efficacy parameters (including DOR and PFS)
- **Exploratory:** Pharmacodynamics assessment, MRD evaluation

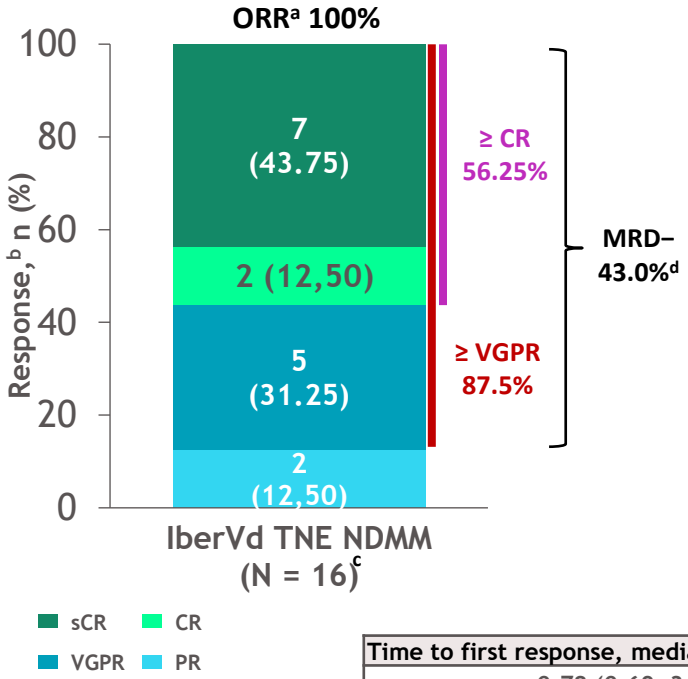
[a]Radiotherapy, bisphosphonates, or a single short course of steroids were permitted; [b]Patients ineligible for ASCT due to age (≥ 65 years of age) or severe comorbidities; [c]DEX was given at a dose of 10 mg in patients > 75 years of age; [d]DEX was given at a dose of 20 mg in patients > 75 years of age.
C, cycle; DOR, duration of response; MRD, minimal residual disease; PD, progressive disease; PFS, progression-free survival; SC, subcutaneous.

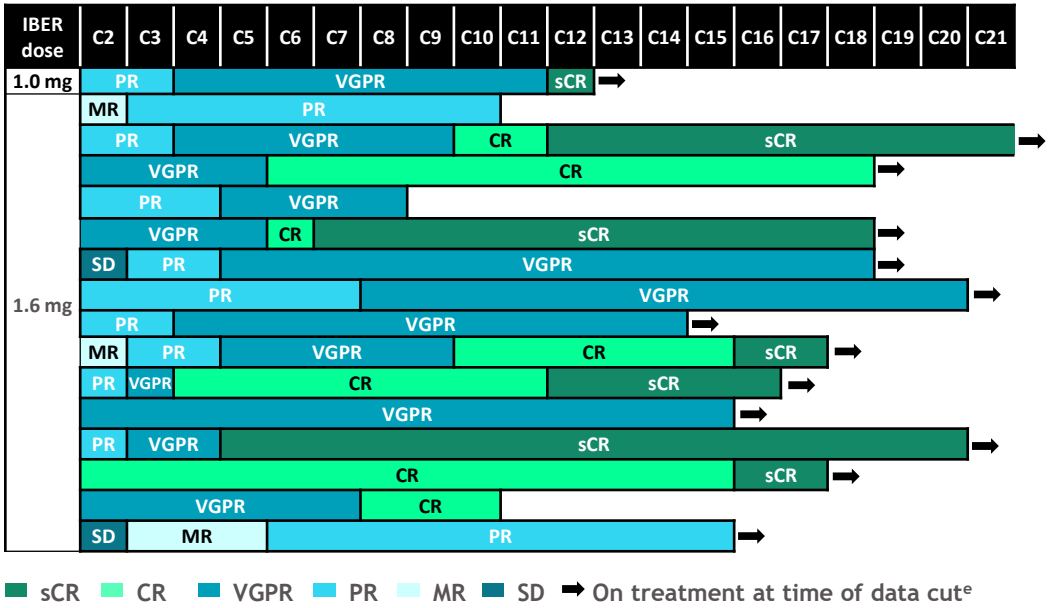
CC-220-MM-001 Safety

Most common (≥ 25% all grade) TEAEs and events of interest,[a] n (%)	IberVd TNE NDMM (N = 17)[b]		
	All grade	Grade 3	Grade 4
Hematologic TEAEs			
Neutropenia	6 (35.3)	2 (11.8)	2 (11.8)
Thrombocytopenia	5 (29.4)	1 (5.9)	1 (5.9)
Anemia	4 (23.5)	1 (5.9)	0
Lymphopenia	4 (23.5)	0	0
Non-hematologic TEAEs			
Peripheral edema	11 (64.7)	1 (5.9)	0
Peripheral sensory neuropathy	11 (64.7)	1 (5.9)	0
Constipation	10 (58.8)	1 (5.9)	0
Insomnia	8 (47.1)	1 (5.9)	0
Fatigue	7 (41.2)	2 (11.8)	0
Pain in extremity	6 (35.3)	0	0
Dyspnea	6 (35.3)	0	0
Decreased appetite	6 (35.3)	0	0
Agitation	5 (29.4)	0	0
Dysgeusia	5 (29.4)	0	0
Infections	13 (76.5)	5 (29.4)	1 (5.9)
COVID-19	5 (29.4)	1 (5.9)	0
Pneumonia	3 (17.6)	2 (11.8)	1 (5.9)

[a]Data cutoff: June 23, 2023; [b]1 patient was enrolled but not included in the safety population due to self-withdrawal (appointment absence).
COVID-19, coronavirus disease 2019.

CC-220-MM-001 Efficacy





Time to first response, median (range), months	Follow-up,[f] median (range), months
0.72 (0.69–3.91)	12.63 (3.91–16.43)

ORR was 100% in the efficacy-evaluable population

[a]ORR (PR or better); [b]Data cutoff: June 23, 2023; [c]Efficacy-evaluable population; [d]At a threshold of 10^{-5}; [e]BORT was administered during C1–8 only; [f]From univariate analysis for all responders without adjusting for censoring.
CR, complete response; MR, minimal response; ORR, overall response rate; PR, partial response; sCR, stringent complete response; SD, stable disease; VGPR, very good partial response.

Carfilzomib-Lenalidomide-Dexamethasone (KRd) Vs. Lenalidomide-Dexamethasone (Rd) in Newly Diagnosed Fit or Intermediate-Fit Multiple Myeloma Patients Not Eligible for Autologous Stem-Cell Transplantation (Phase III EMN20 Trial): Analysis of Sustained Undetectable Minimal Residual Disease (MRD)

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EMN20 Study design

Randomized, multicenter, phase III EMN20 trial (NCT04096066): KRd vs. Rd

NTE NDMM
fit/intermediate-fit
patients
N=82

1:1 Randomization

Stratification for:
- ISS
- Fitness

KRd (n=42)

Carfilzomib (K):
- 20 mg/m^2 IV on day (D) 1 of cycle 1;
- 56 mg/m^2 IV on D 8, 15 of cycle 1; on D 1, 8, 15 of cycles 2–12; on D 1, 15 from cycle 13 onwards

Lenalidomide (R): PO 25 mg D 1–21
Dexamethasone (d): PO 40 mg/day* on D 1, 8, 15, 22
* 20 mg/day on D1, 8, 15, 22 for pts ≥75 years

- MRD Neg → Rd → *Until PD*
- MRD Pos → KRd for 5 years → Rd → *Until PD*

Rd (n=40)

Lenalidomide (R): PO 25 mg on days (D) 1–21
Dexamethasone (d): PO 40 mg/day* on D 1, 8, 15, 22
* 20 mg/day D1,8,15,22 for pts ≥75 years

Until PD

Screening — **After 1 yr** (MRD) — **After 2 yrs** (MRD)

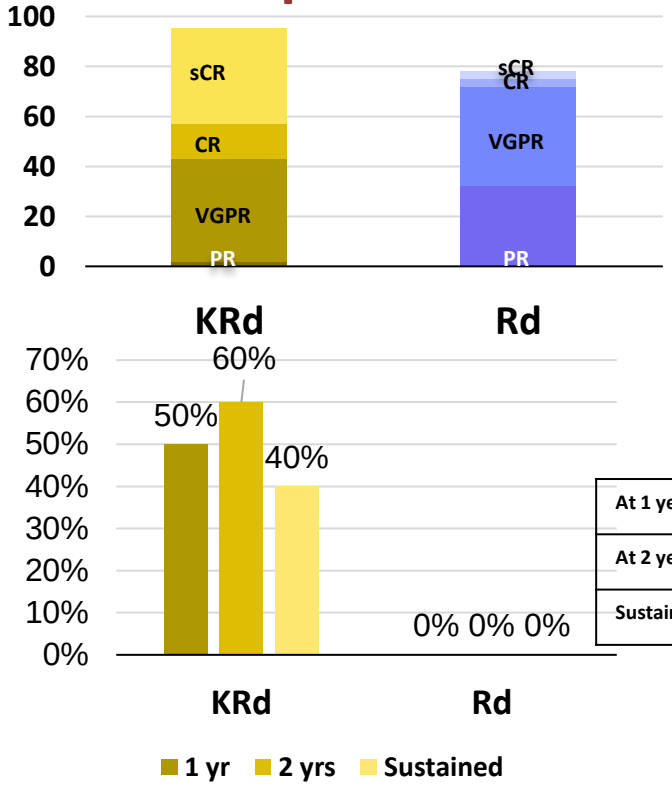
- **Primary endpoints**: MRD after 2 years of treatment and PFS

NTE, transplant-ineligible; NDMM, newly diagnosed multiple myeloma; K, carfilzomib; R, lenalidomide; d, dexamethasone; IV, intravenously; D, days; PO, orally; pts, patients; MRD, minimal residual disease; Neg, negative; Pos, positive; yr, year; PD, progressive disease.

EMN20 Baseline characteristics and Response Rate

	KRd (n=42)	Rd (n=40)
Age		
median, years (IQR)	73 (70–76)	74 (72–76)
76-80 years, n (%)	11 (26)	13 (22)
ISS stage, n (%)		
I	11 (26)	10 (25)
II	17 (40)	18 (45)
III	14 (33)	12 (30)
Cytogenetic risk, n (%)		
Standard	28 (78)	29 (78)
High*	8 (22)	8 (22)
Missing	6	3
Frailty status, n (%)		
Fit	26 (62)	22 (55)
Intermediate-fit	16 (38)	18 (45)
Frail	0	0

Cytogenetic risk was defined as the presence of del(17p) or t(4;14) or t(14;16).



Response rates

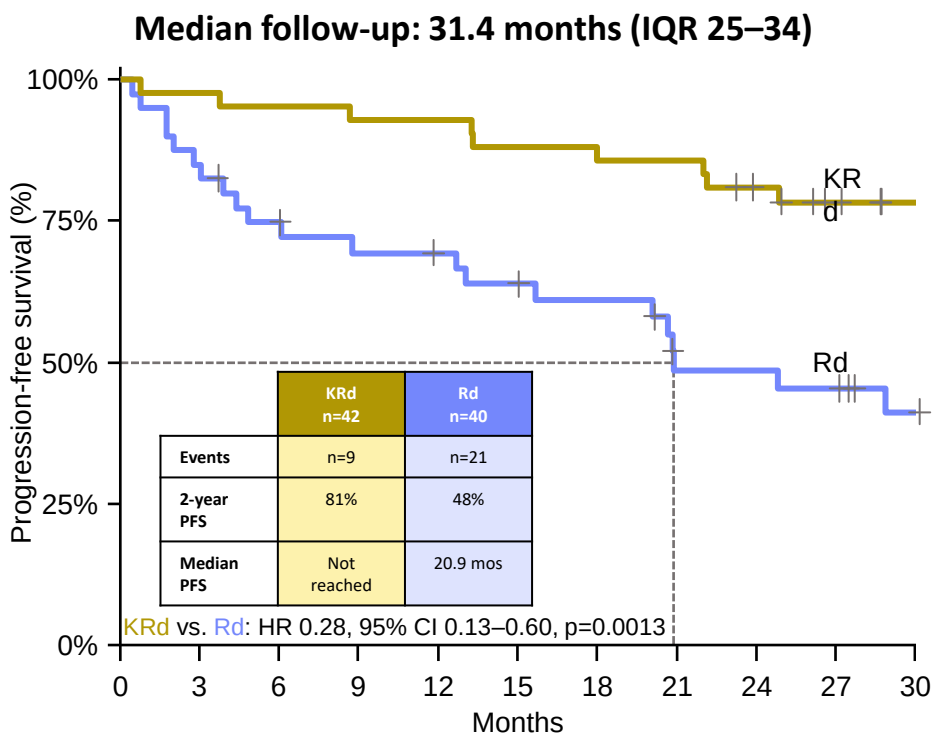
	KRd n=42	Rd n=40	p-value
≥PR	95%	78%	0.04
≥VGPR	93%	45%	<0.0001
≥CR	52%	5%	0.0002

MRD neg rates

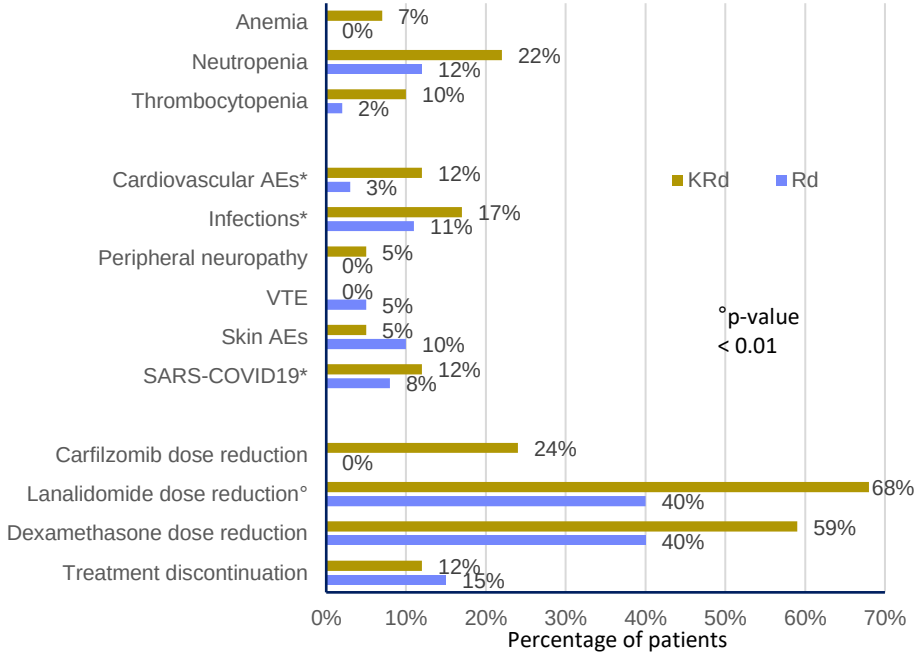
	KRd n=42	Rd n=40	p-value
At 1 year	50%	0	<0.0001
At 2 years	60%	0	<0.0001
Sustained	40%	0	<0.0001

K, carfilzomib; R, lenalidomide; d, dexamethasone; IQR, interquartile range; ISS, International Staging System; del, deletion; t, translocation. PR, partial response; VGPR, very good partial response; CR, complete response; sCR, stringent complete response

EMN20 Progression-free survival and safety



	KRd n=42	Rd n=40
Events	n=9	n=21
2-year PFS	81%	48%
Median PFS	Not reached	20.9 mos

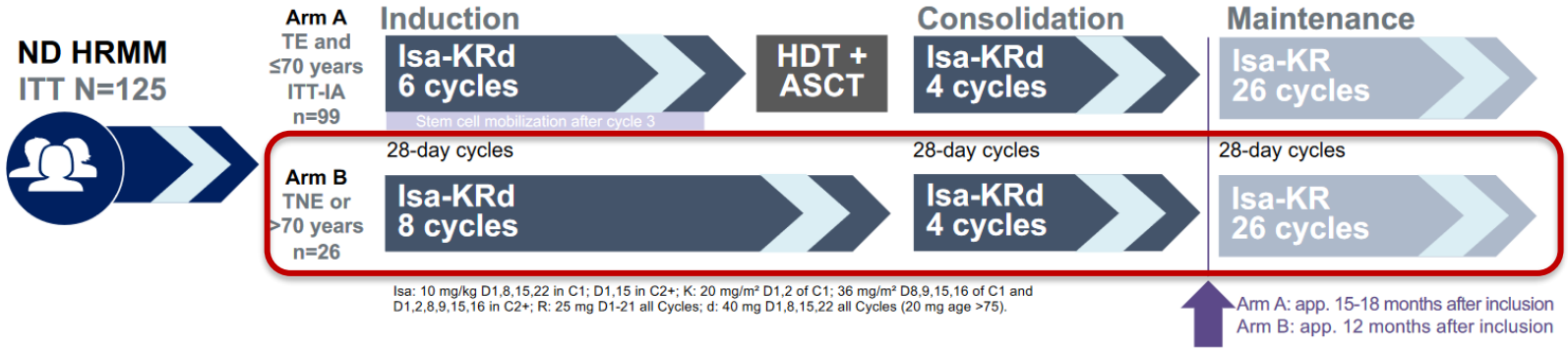


IQR, interquartile range; K, carfilzomib; R, lenalidomide; d, dexamethasone; HR, hazard ratio; CI, confidence interval; p, p-value.; PFS, progression-free survival.; mos, months; ; VTE, venous thromboembolism; G, grade.

*KRd: 3 G5 AEs (3 due to COVID19 infection);
*Rd: 3 G5 AEs (1 due to cardiac AE, 1 due to COVID19 and 1 due to infection)

Analysis of Sustained MRD-Negativity and Progression-Free Survival of Isa-KRd in High-Risk Newly Diagnosed Multiple Myeloma – Additional Data From Planned Interim Analysis of the GMMG-CONCEPT Trial

Lisa B. Leypoldt, Diana Tichy, Britta Besemer, Mathias Hanel, Marc S. Raab, Christoph Mann, Markus Munder, Hans Christian Reinhardt, Axel Nogai, Martin Gorner, Yon-Dschun Ko, Maike de Wit, Hans Salwender, Christof Scheid, Ullrich Graeven, Rudolf Peceny, Peter Staib, Annette Dieing, Hermann Einsele, Anna Jauch, Manola Zago, Axel Benner, Carsten Bokemeyer, Hartmut Goldschmidt, Katja C. Weisel

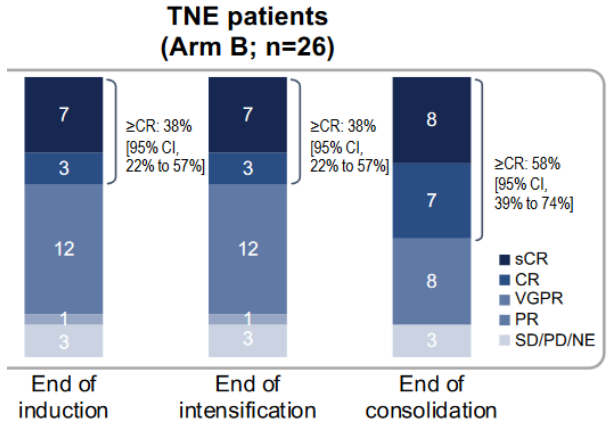


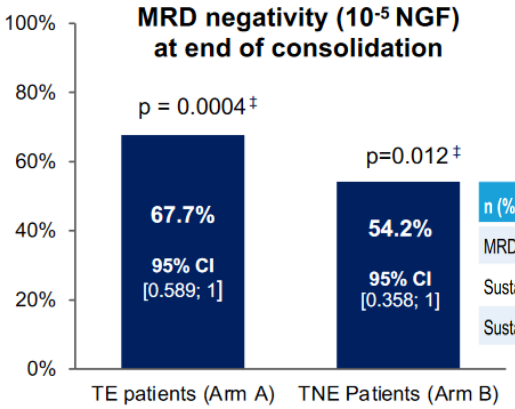
HRMM criteria: ISS stage II or III **PLUS** ≥1 of: del(17p), t(4;14), t(14;16) and/or >3 copies 1q21 (amp1q21)
Primary objective: MRD negativity after consolidation (NGF, 10^{-5})
Secondary objective: PFS; Key tertiary objectives: ORR, OS, safety

ASCT, autologous stem-cell transplant; d, dexamethasone; HDT, high-dose therapy; HRMM, high-risk multiple myeloma; Isa, isatuximab; ISS, International Staging System; K, carfilzomib; MRD, minimal residual disease; ND, newly-diagnosed; NGF, next-generation flow; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; R, lenalidomide; TE, transplant-eligible; TNE, transplant-ineligible.

GMMG-CONCEPT Trial – Arm B

Characteristic		TNE patients (n=26)
Age	Years, median (range)	74 (64–87)
Sex	Female sex, No. (%)	14 (53.8)
ECOG	ECOG 0–1, No. (%)	18 (69.2)
	ECOG 2–3, No. (%)	7 (26.9)
ISS	II, No. (%)	13 (50.0)
	III, No. (%)	13 (50.0)
R2-ISS	I + II, No. (%)	10 (38.5)
	III + IV, No. (%)	15 (57.7)
	Not classifiable, No. (%)	1 (3.8)
FISH	del(17p), No. (%)	11 (42.3)
	t(4;14), No. (%)	6 (23.1)
	t(14;16), No. (%)	2 (7.7)
	amp1q21 (≥4 copies), No. (%)	14 (53.8)
HRCA	1 HRCA, No. (%)	17 (65.4)
	≥2 HRCAs, No. (%)	7 (26.9)
	Not classifiable*, No. (%)	2 (7.7)
LDH	Elevated LDH (>ULN), No. (%)	8 (30.8)
1 prior cycle	Therapy before enrollment, No. (%)	11 (42.3)
BM infiltration	Plasma cell infiltration %, median (range)	50 (5.5–100)



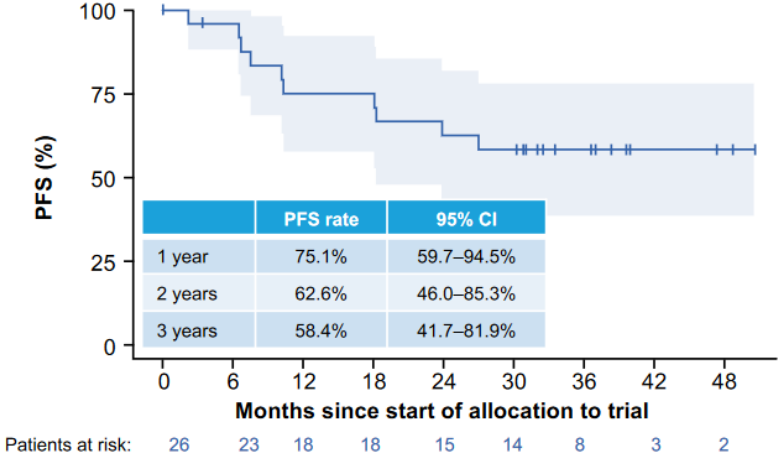


n (%)	TNE patients (n=26)
MRD negative (any time point)	18 (69.2%)
Sustained MRD negativity for ≥6 months	14 (53.8%)
Sustained MRD negativity for ≥12 months	12 (46.2%)

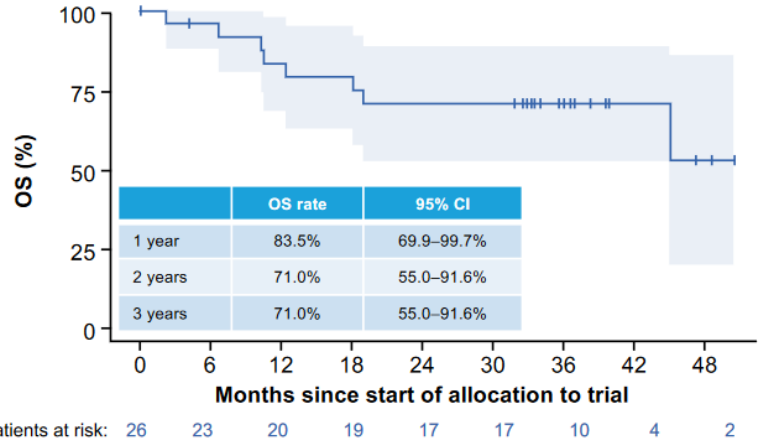
GMMG-CONCEPT Trial – Arm B

Transplant-noneligible patients

- Median PFS and median OS were not reached with a median follow-up of 33 (PFS) and 35 (OS) months
- Secondary endpoint of PFS was met for study arm B



	PFS rate	95% CI
1 year	75.1%	59.7–94.5%
2 years	62.6%	46.0–85.3%
3 years	58.4%	41.7–81.9%



	OS rate	95% CI
1 year	83.5%	69.9–99.7%
2 years	71.0%	55.0–91.6%
3 years	71.0%	55.0–91.6%

P-115

Progression-Free Survival of Daratumumab vs. Bortezomib Triplet Combination with Lenalidomide and Dexamethasone in Transplant Ineligible Newly Diagnosed Multiple Myeloma Patients: A Chart Review Study

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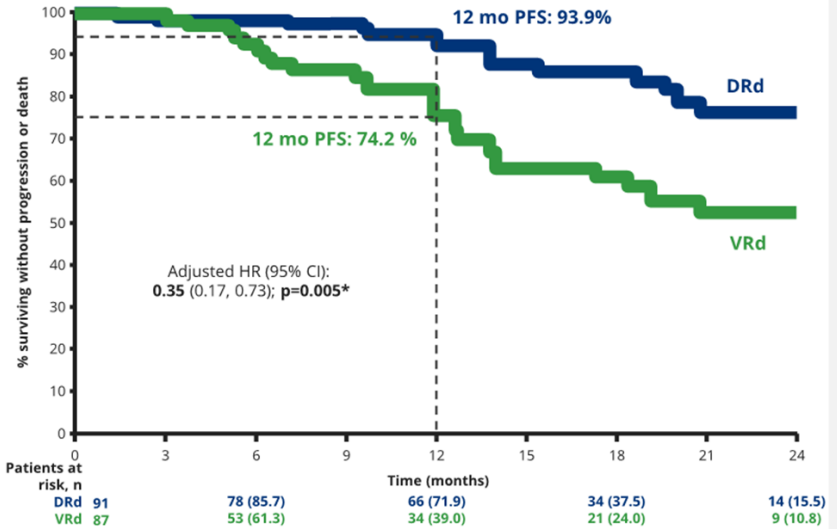
	DRd (n=91)	VRd (n=87)
Age		
median, years (IQR)	76	75
≥ 75 years, n (%)	55 (61)	53 (61)
ISS stage, n (%)		
I	22 (24)	23 (27)
II	27 (30)	21 (24)
III	16 (18)	15 (17)
Cytogenetic risk, n (%)		
Standard	54 (59)	47 (54)
High*	13 (14)	15 (17)
Missing	24	27
ECOG, n (%)		
0	29 (32)	28 (32)
1-2	53 (58)	50 (58)
3-4	2 (3)	3 (4)

FIGURE 2. Adjusted PFS among TIE NDMM patients initiated on 1L DRd or VRd



Ixazomib maintenance in transplant-ineligible patients with newly diagnosed multiple myeloma: Final overall survival analysis from the TOURMALINE-MM4 study

Meletios A. Dimopoulos,[1] Wee Joo Chng,[2] Shinsuke Iida,[3] María-Victoria Mateos,[4] Gareth Morgan,[5] Sagar Lonial,[6] Ivan Špička,[7] Hang Quach,[8] Albert Oriol,[9] Roman Hájek,[10] Mamta Garg,[11] Nicola Giuliani,[12] Meral Beksac,[13] Eirini Katodritou,[14] Sara Bringhen,[15] Cong Li,[16] Xiaoquan Zhang,[16] Richard Labotka,[16] Vincent S. Rajkumar[17]

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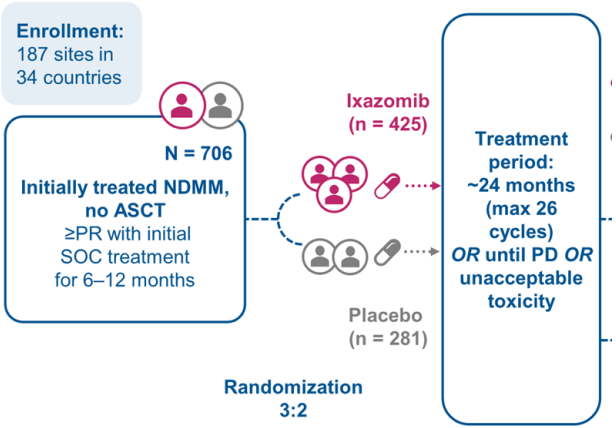
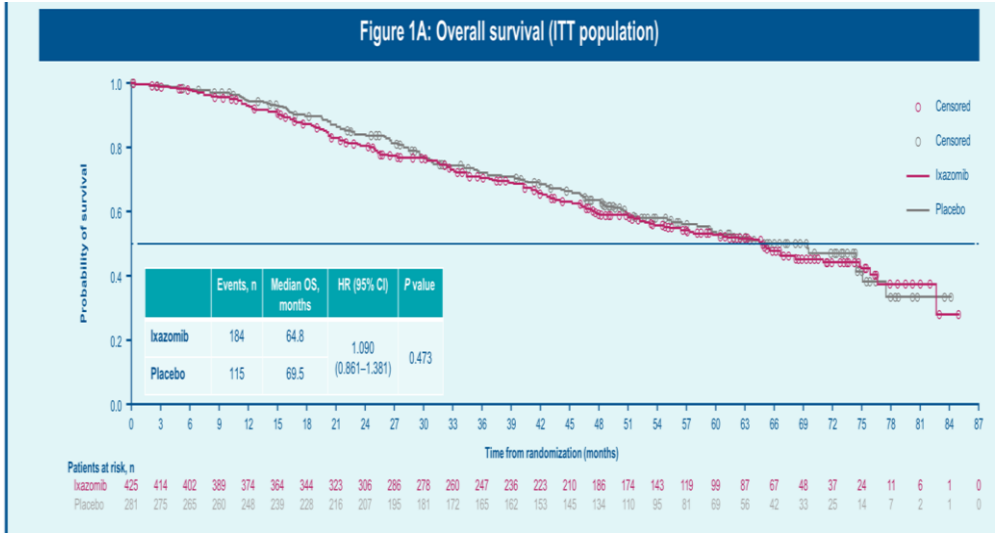
P-110





P-045

Early Treatment With Bispecific T-Cell Redirectors (Teclistamab or Talquetamab) + Daratumumab in Newly Diagnosed High-Risk Multiple Myeloma: an Open-Label, Phase 2, Pilot Study (GEM-TECTAL)

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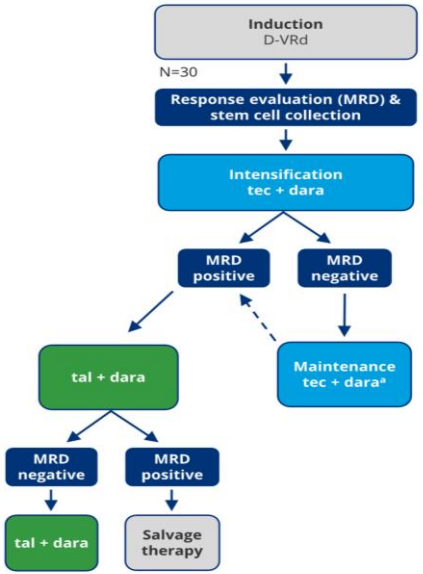
FIGURE: GEM-TECTAL study design

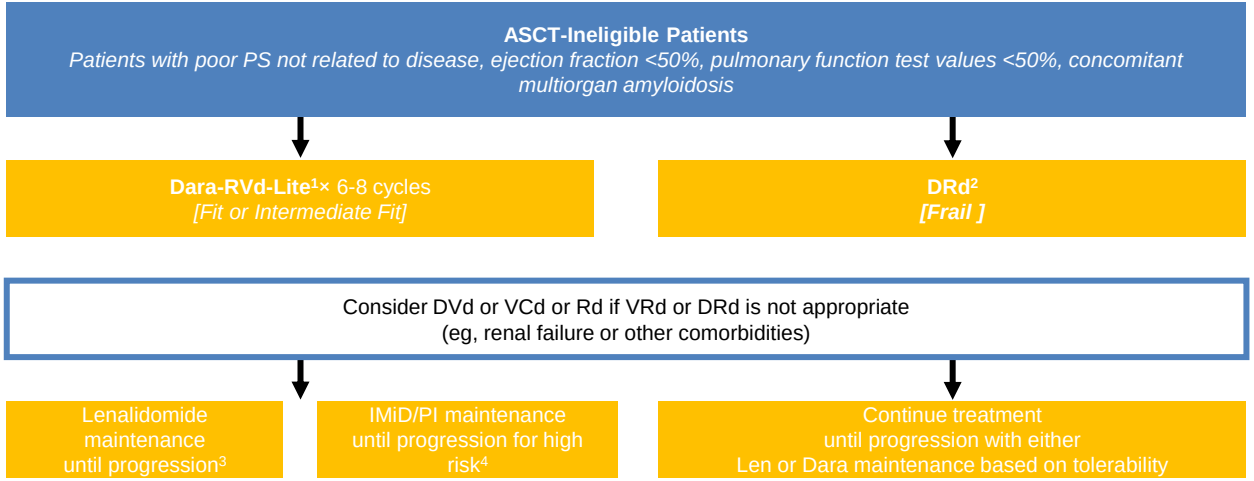


[a]Patients who convert to MRD positive or relapse from CR any time during tec + dara maintenance will be treated as MRD positive (ie, will receive tal + dara early rescue intervention). D-VRd, daratumumab-bortezomib-lenalidomide-dexamethasone.

TABLE: Study endpoints

Primary endpoint	Secondary endpoints	Exploratory endpoints
• MRD-CR rate after 6 cycles of tec + dara intensification measured by NGF 10^{-6} and ^{18}FDG-PET/CT	• Percentage of patients converting from MRD positive to MRD negative after 6 cycles of tal + dara early rescue intervention • Percentage of patients with sustained MRD negativity at 12, 18, and 24 months in both treatment arms • Time to next treatment • Duration of response • Progression-free survival • Event-free survival • Overall survival • Safety	• Immune profiling • Genetic characterization

MSK Approach to Transplant Ineligible NDMM (? 2024)



- DRd, daratumumab, lenalidomide, and dexamethasone; DVd, daratumumab, bortezomib, and dexamethasone; VRd-Lite, modified VRd regimen.
- Adjust dosing of lenalidomide based on renal function. Consider empiric age-adjusted dose reductions for all regimens, as needed.[4]
- 1. O'Donnell. Br J Haematol. 2018;182:222. 2. Facon. ASH 2018. Abstr LBA-2. 3. Larocca. ASH 2018. Abstr 305. 4.Usmani. *Lancet Haematol*. 2021 Jan;8(1):e45-e54.

Presented by: Saad Z. Usmani, MD MBA FACP, @szusmani

Conclusions

- **Improve the treatment strategy of NTE NDMM**
  - Recent trials showed we can improve treatment strategy of NTE NDMM, achieving a deep and durable response especially in fit patients, in which this remains the main goal.
  - Toxicities were predictable and manageable
  - A longer follow-up is needed to evaluate a strategy to reduce the intensity of therapy in MRD-Neg patients
  - Data from ongoing studies will tell us whether quadruplets, such as Isatuximab or Daratumumab plus first or second generation PI and IMIDs as well as novel CELMoD or immunotherapy with bispecific antibodies or CART-cell can be an option