Highlights from IMW 2021

1-2 febbraio 2022
Bologna
Royal Hotel Carlton

Dr.ssa Francesca Bonello

Myeloma Unit, Division of Hematology, AOU Città della Salute e della Scienza, Torino, Italy

Terapia di prima linea nel paziente fit non candidato a trapianto: strategie con anti CD38

Coordinatore Scientifico
Michele CAVO

Comitato Scientifico
Michele CAVO
Maria Teresa PETRUCCI

Disclosures

Research Support/P.I.	No relevant conflicts of interest to declare
Employee	No relevant conflicts of interest to declare
Consultant	No relevant conflicts of interest to declare
Major Stockholder	No relevant conflicts of interest to declare
Speakers Bureau	No relevant conflicts of interest to declare
Honoraria	No relevant conflicts of interest to declare
Scientific Advisory Board	No relevant conflicts of interest to declare

Definition of elderly fit newly diagnosed multiple myeloma patients

Age ≤ 75 years

No multiple severe comorbidities (CCI ≤ 1)

Functionally independent (ADL > 4; IADL > 5)

Transplant eligible

- Age ≤ 70 years
- Normal cardiac/pulmonary/liver function

Transplant ineligible

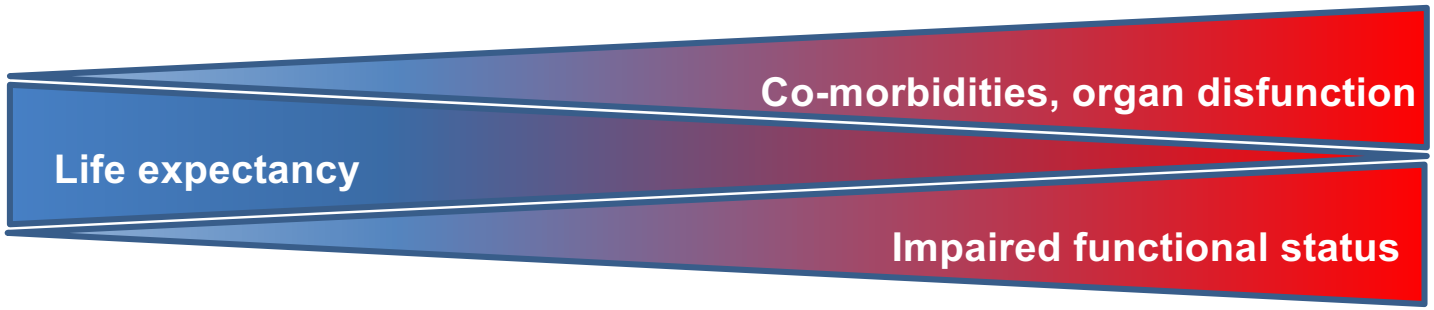
- Age > 70 years (European perspective)
- Inadequate cardiac/pulmonary/liver function
- Personal preference

CCI: Charlson Comorbidity Index; ADL: Activity of Daily Living; IADL: Instrumental Activity of Daily Living

Palumbo et al, Blood 2015; Dimopoulos et al, Hemaspehere 2021

Treatment goal in fit transplant ineligible patients

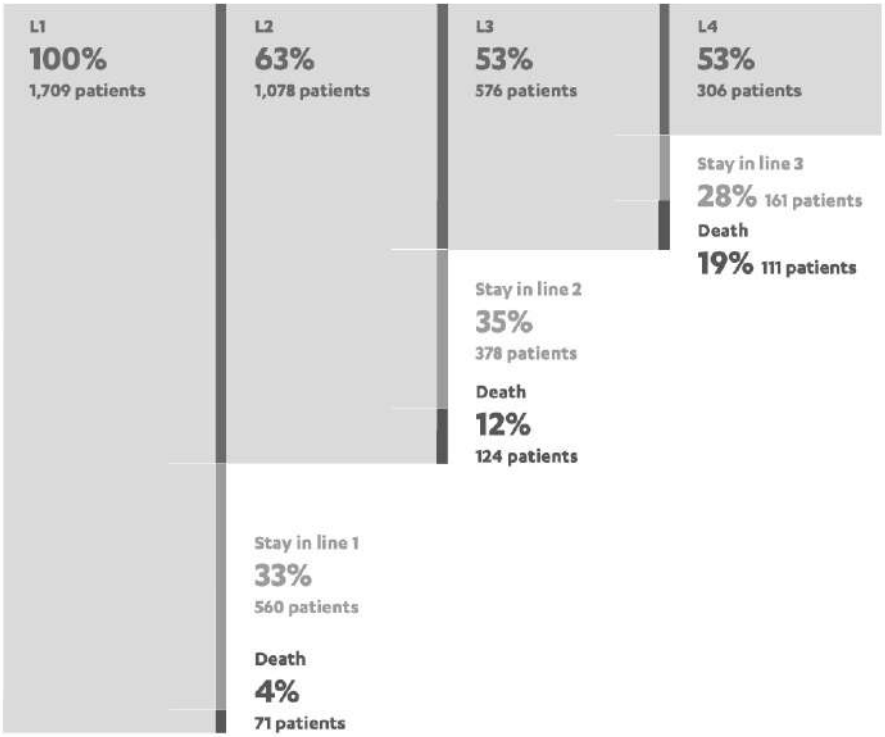
FIT	UNFIT	FRAIL



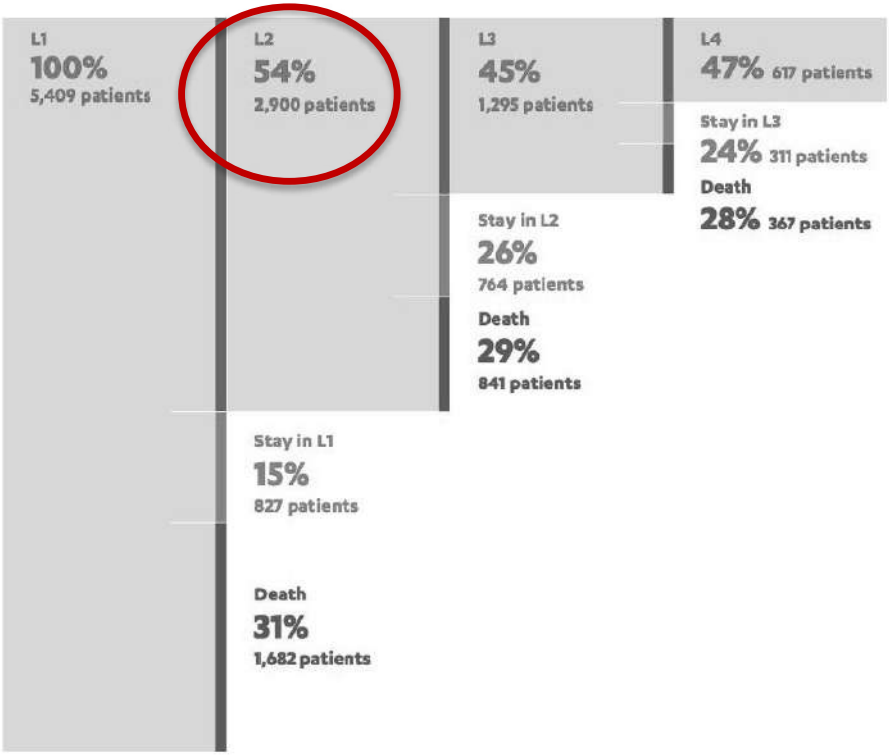
	Deep remission	Balance efficacy/safety	Do not harm
Goal	CR/MRD-negativity	Good response	QoL
Priority	Efficacy	Combination of efficacy/safety	Low toxicity

Treatment pathways in myeloma patients

Patients with transplant



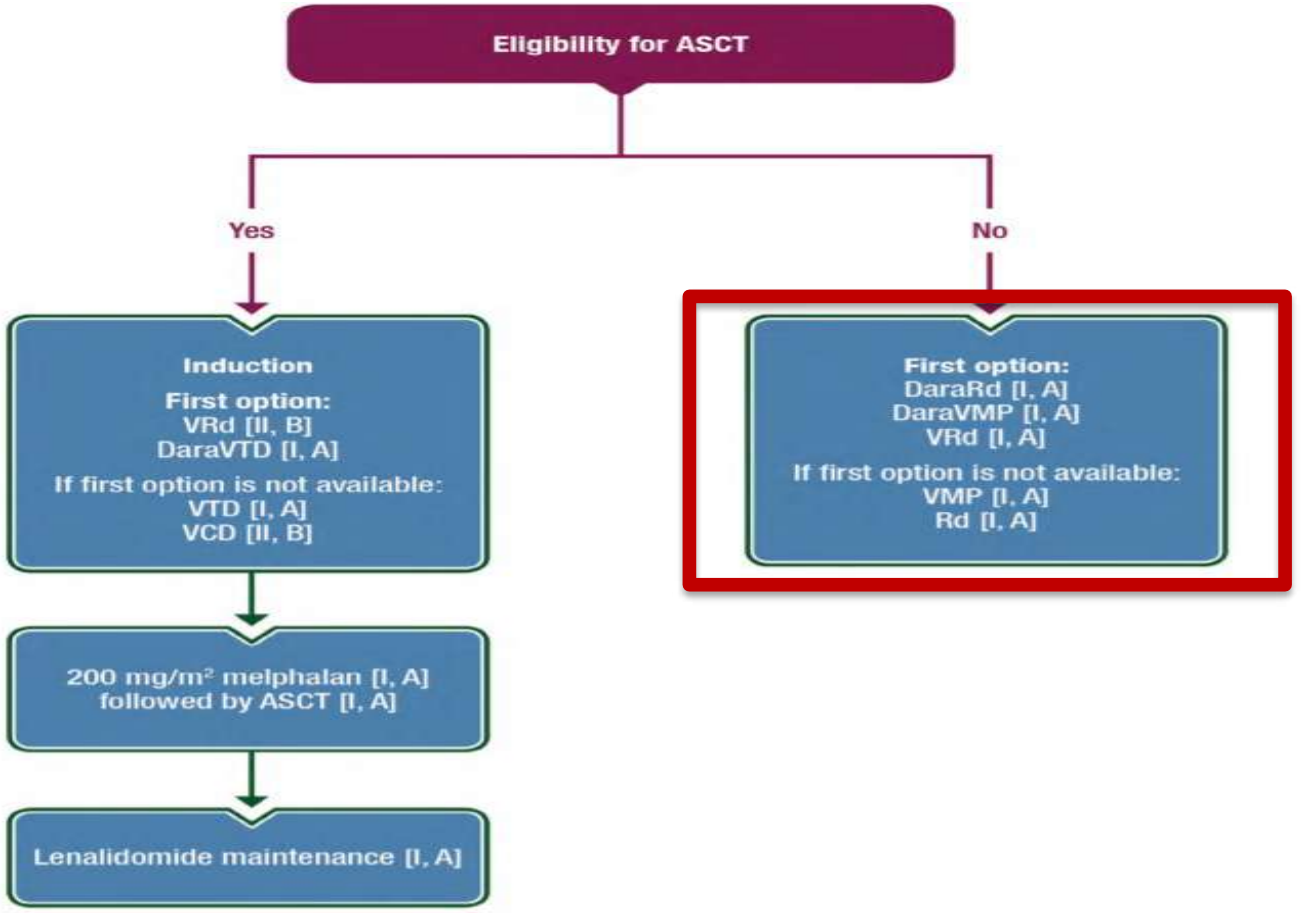
Patients without transplant



Effective first line therapy is crucial in transplant ineligible patients since half of them do not reach subsequent lines

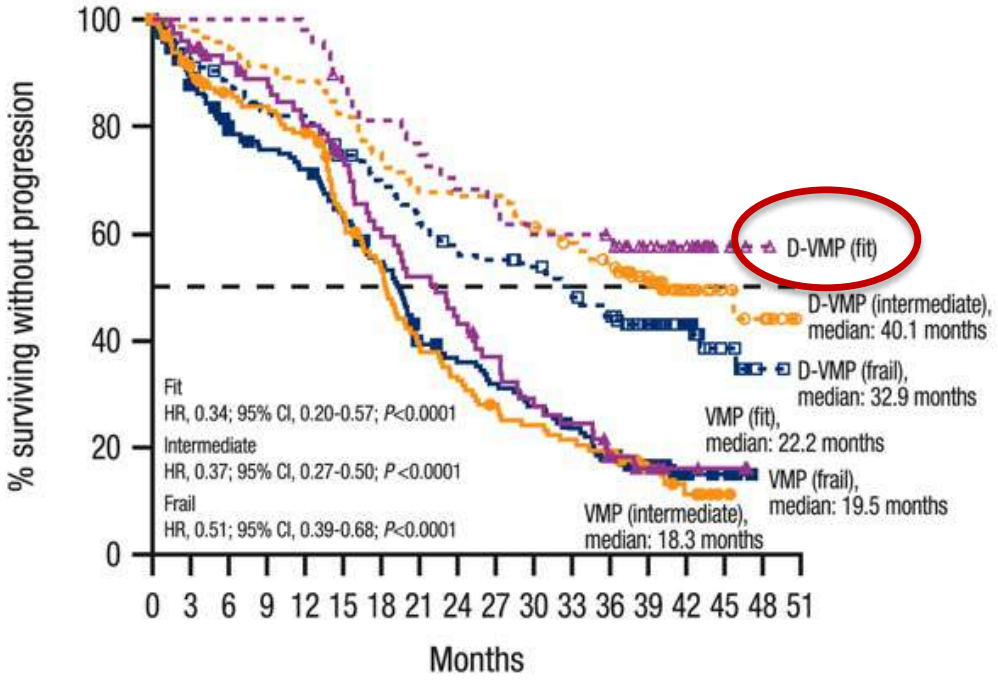
Perrot, IMW 2021

Front-line treatment options for myeloma patients: 2021 ESMO guidelines

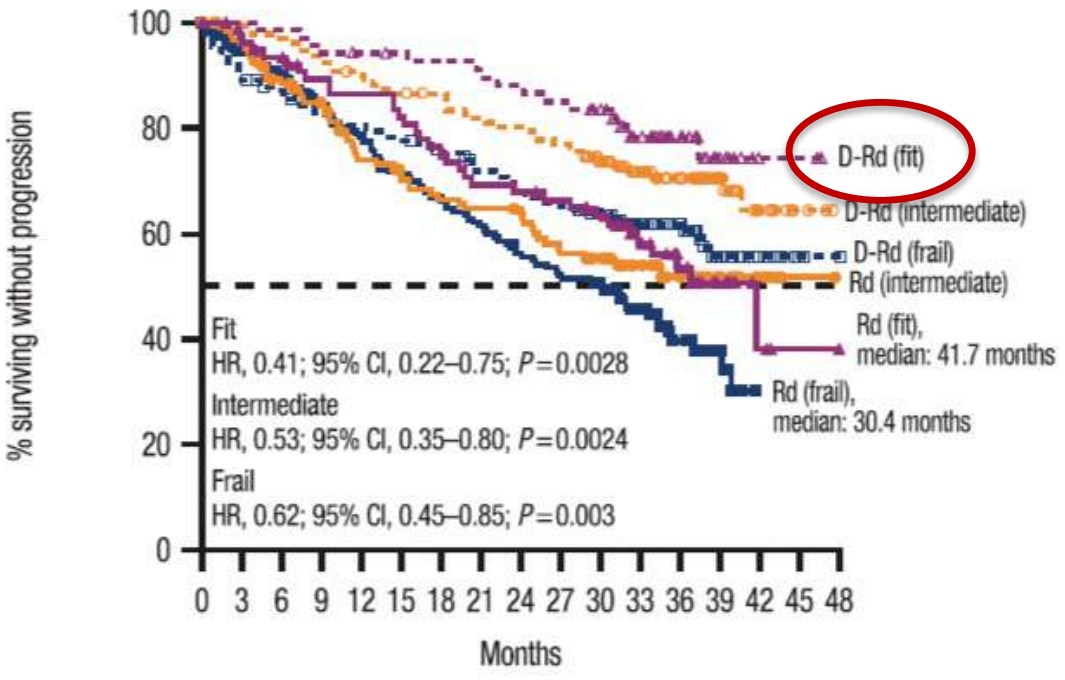


Dimopoulos et al, Hemaspehere 2021

Adding anti-CD38 monoclonal antibodies improves the outcome of NTE patients



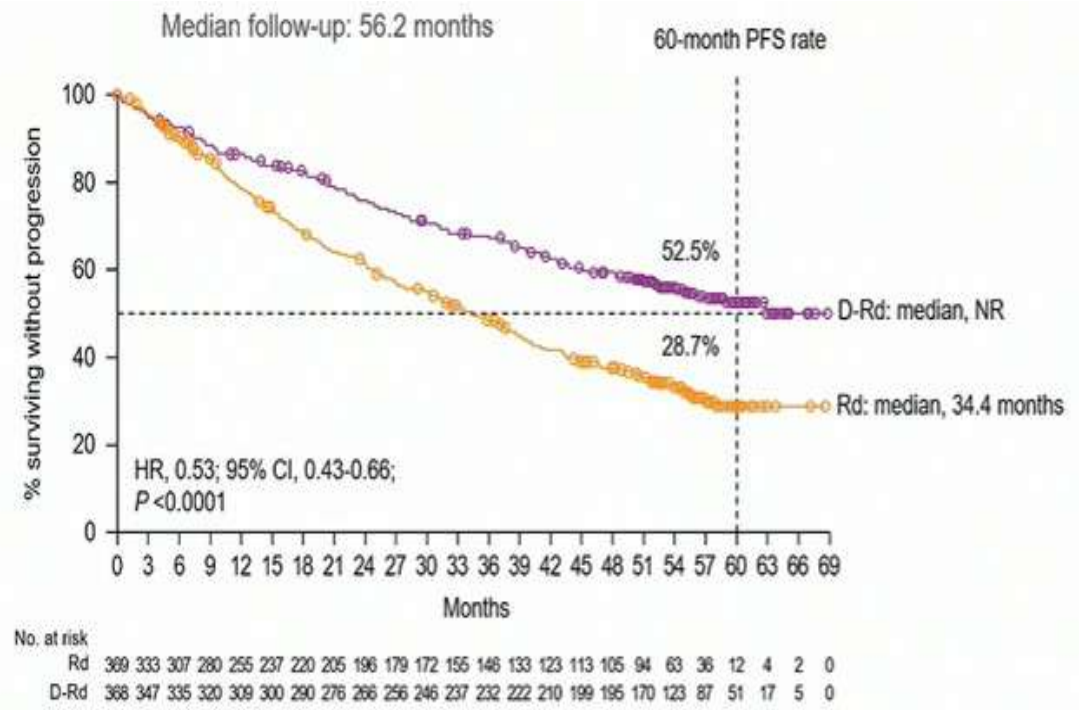
Median follow-up 40 months

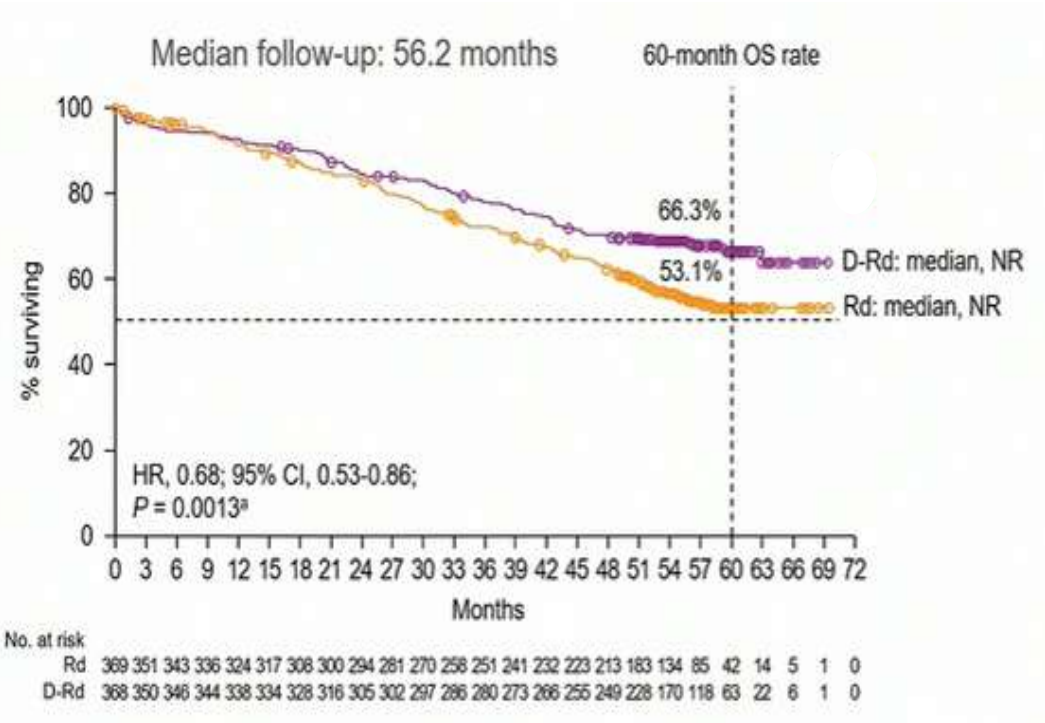


Median follow-up 36.4 months

Mateos MV et al, Clin Lymphoma Myeloma Leuk 2021; Facon et al, Leukemia 2022

Daratumumab + Rd: updated results from the MAIA trial
EFFICACY





Moreau P et al, IMW 2021

Daratumumab + Rd: updated results from the MAIA trial

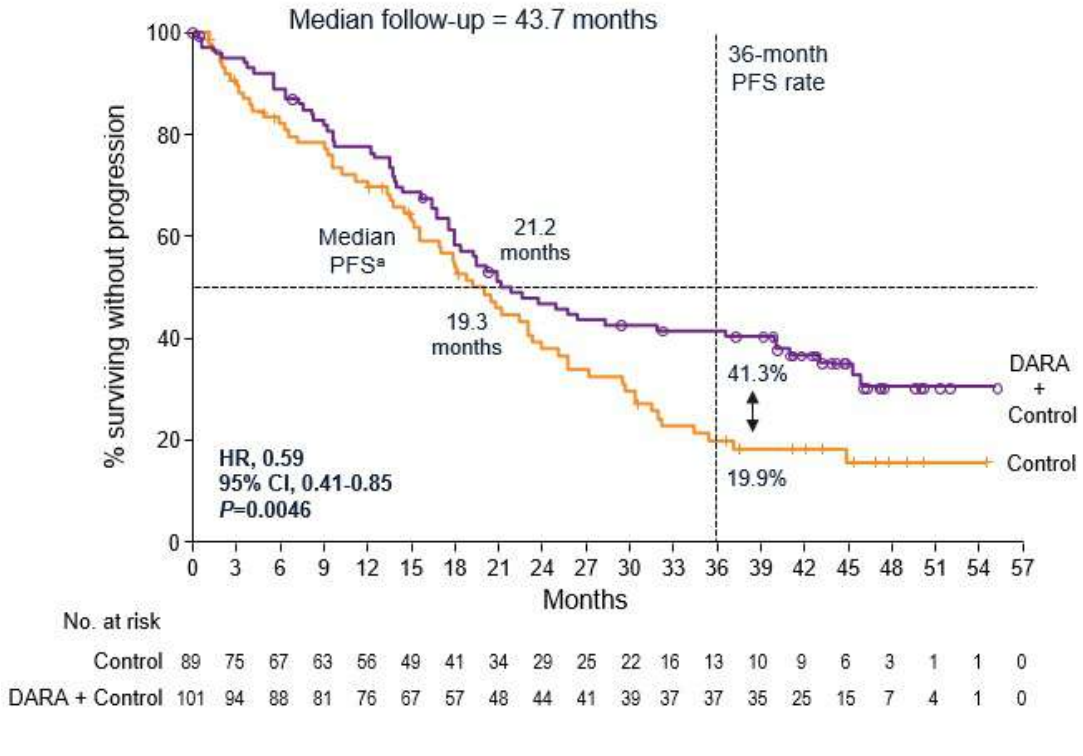
SAFETY

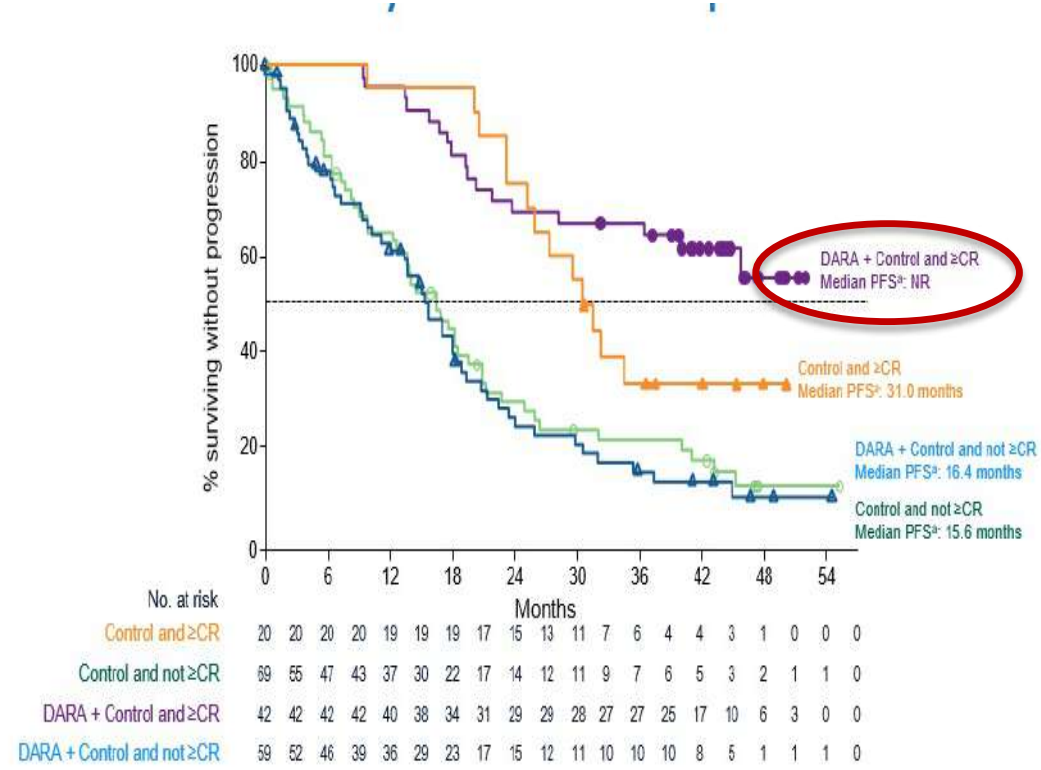
Grade 3/4 AEs	DaraRd (n 364)	Rd (n 365)
Neutropenia	197 (54%)	135 (37%)
Thrombocytopenia	32 (9%)	34 (9%)
Pneumonia	70 (19%)	39 (11%)
Diarrhea	32 (9%)	22 (6%)
Fatigue	32 (9%)	17 (5%)
Pulmonary embolism	26 (7%)	19 (5%)
AKI	19 (5%)	12 (3%)
Discontinuation to AEs	48 (13%)	85 (23%)

Median duration of study treatment: 47.5 months in D-Rd arm and 22.6 months in Rd arm.

Moreau P et al, IMW 2021

Addressing the unmet need: daratumumab in high-risk NTE patients

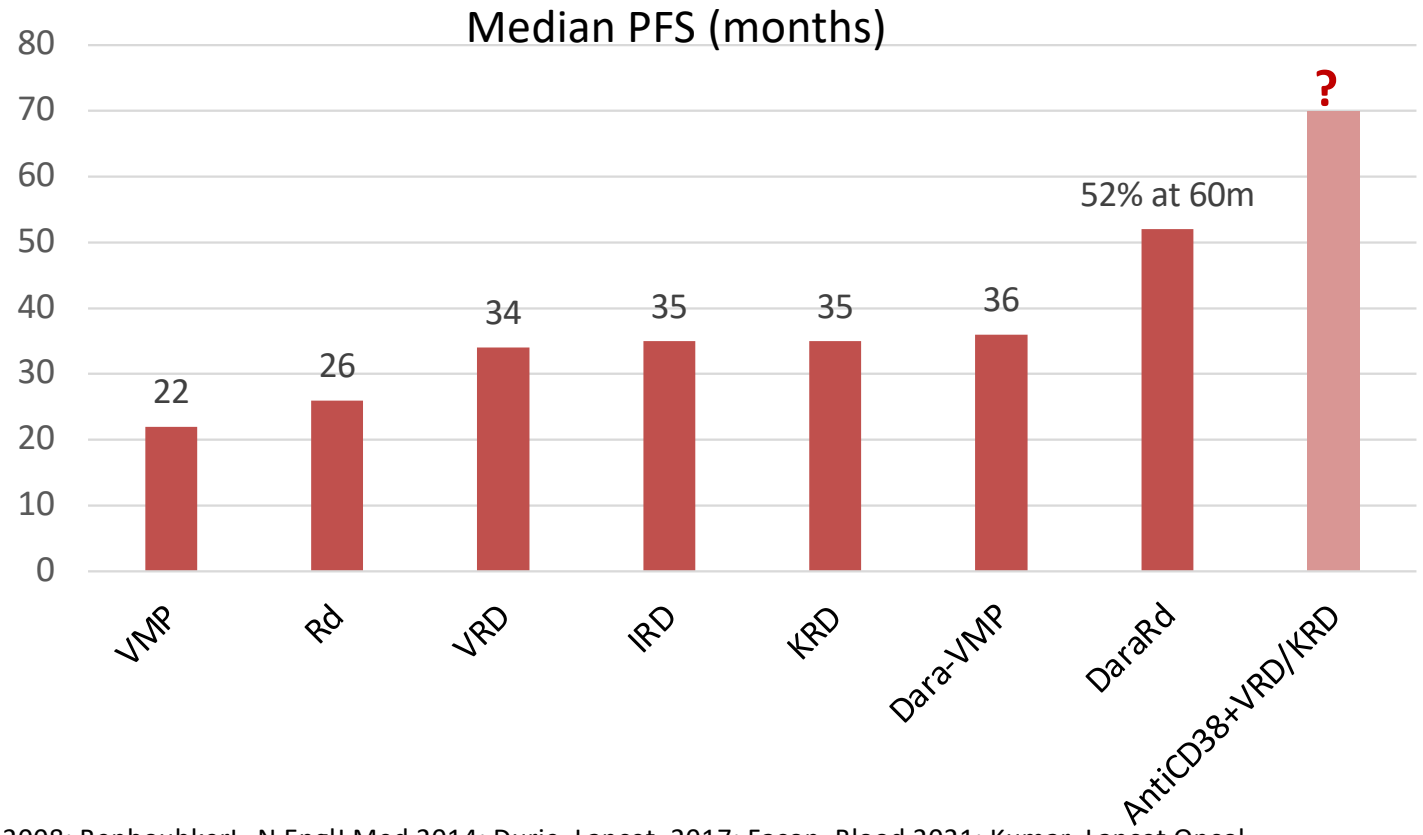




Addition of daratumumab to VMP/Rd increases rate of ≥ CR (42% vs 23%, HR 2.63) in high risk patients
Deeper responses allow longer remissions in high risk patients

Jakubowiak et al, IMW 2021

Roadmap of treatment options for fit NTE patients



San Miguel J, N EnglJ Med 2008; BenboubkerL. N EnglJ Med 2014; Durie. Lancet. 2017; Facon, Blood 2021; Kumar, Lancet Oncol 2020; Mateos. Lancet 2019; Facon. NEJM. 2019;

Adapted from San Miguel, IMW 2021

New anti-CD38 containing quadruplets: preliminary data of Isatuximab-VRD

Isa-VRd
Part A and Part B
N=73

Inclusion criteria:
- NDMM ineligible for ASCT
- Adequate bone marrow reserve and organ function

Induction phase: (4x6-week cycles)

Isa + VRd
Isa IV QW in Cycle 1, then Q2W Cycle 2–4 (10 mg/kg)
V SC Day 1, 4, 8, 11, 22, 25, 29, 32 Cycle 1–4 (1.3 mg/m^2)
R PO Day 1–14 and Day 22–35 Cycle 2–4 (25 mg)
d PO Day 1 and after V administration Cycle 1–4 (20 mg)

Maintenance phase:
(4-week cycles)
Until PD

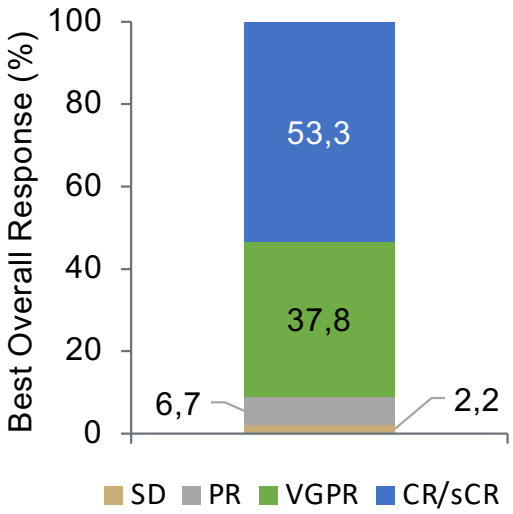
Isa-Rd
Isa IV Q2W (10 mg/kg)
R PO Day 1–21 (25 mg)
d PO QW (40 mg)[c]

Primary endpoint: CR
Secondary endpoints:
- Safety
- ORR
- MRD
- Isa infusion duration

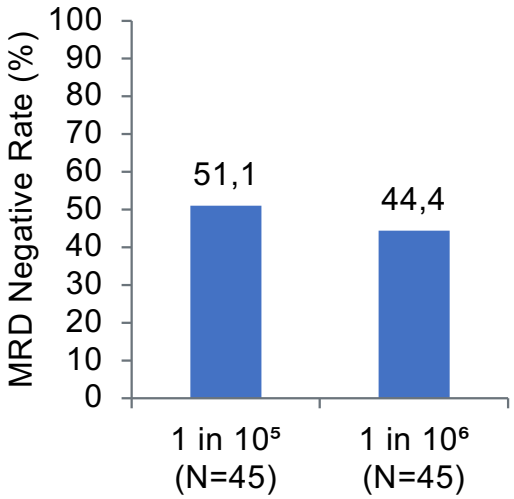
Ocio et al, IMW 2021

New anti-CD38 containing quadruplets: preliminary data of Isatuximab-VRD

ORR: 97.8%



MRD Negative Rate



Median follow-up: 15.24 months

Non hematologic G ≥3	Pts (n 46)
Constipation	1 (2.2%)
Asthenia	3 (6.5%)
Diarrhea	4 (8.7%)
PNP	1 (2.2%)
Peripheral edema	2 (4.3%)
Insomnia	2 (4.3%)
Back pain	1 (2.2%)
Rash	1 (2.2%)
Dyspnea	1 (2.2%)
IRR	0
Hematologic G ≥3	
Neutropenia	19 (41.3%)
Thrombocytopenia	16 (34.7%)
Discontinuation to AE	**8 (17%)**
Death to AE	**5 (11%)**

Ocio et al, IMW 2021

Main ongoing trials with anti-CD38 based quadruplets

TRIAL	REGIMEN	POPULATION	PRIMARY ENDPOINT	STATUS
IMROZ (phase III)	Isatuximab-VRD vs VRD	TNE NDMM ECOG 0-2	PFS	Enrollment completed
CEPHEUS (phase III)	Daratumumab-VRD vs VRD	TNE or TE NDMM Frailty index < 2 ECOG 0-2	MRD	Enrollment completed
IFM2020-05 (phase III)	Isa-Rd vs Isa-VRD	TNE NDMM 65-79 years ECOG 0-2	MRD	Recutiting
NCT04052880 (phase II)	Dara-VRD lite	TNE NDMM ≥ 70 years	≥ VGPR	Enrolling
GMMG CONCEPT (phase II)	TNE arm: Isatuximab-KRD and Isa-KR maintenance	TNE and TE NDMM High-risk	MRD	Enrollment completed (preliminary results at EHA 2021)
TCD13983 (phase I)	Isatuximab-VRD and Isatuximab-VCD	TNE NDMM ECOG 0-2	DLT and ORR	Enrollment completed (preliminary results at ASH 2017, 2018 and ASCO 2020)

CONCLUSIONS AND FUTURE DIRECTIONS

- Upfront deep and durable response is the main treament goal for fit TNE patients
- Dara-VMP and Dara-Rd induce higher rates of CR/MRD negativity and longer PFS and represent the new standard of care for these patients
- Nevertheless about 50% and 70% of fit patients still fail to achieve ≥ CR and MRD negativity
- In this light new quadruplets combining anti-CD38 with VRD/KRD could further ameliorate outcome in fit patients able to tolerate them
- Daratumumab ameliorate te prognosis of high-risk TNE patients that however still show a mPFS < 2 years : new approaches with CART-cell or bispecific antibodies should address this unmet need, particularly in fit patients

TNE: non transplant eligible; dara: daratumumab; VMP bortezomib, melphalan, prednisone; Rd lenalidomide dexamethasone; CR complete response; MRD minimal residual disease; PFS progression free survival VRD: bortezomib-Rd; KRd carfilozmibRd; CART chimeric antigen receptor T cell

Acknowledgements

Myeloma Unit, Division of Hematology

University of Torino

Azienda Ospedaliero-Universitaria Città della Salute e della Scienza, Torino, Italy

Prof. Mario Boccadoro

ProF Dario Ferrero

Dr. Sara Bringhen
Dr. Alessandra Larocca
Dr. Francesca Gay
Dr. Stefania Oliva
Dr. Roberto Mina
Dr. Mattia D'Agostino
Dr Giulia Benevolo

Dr. Luca Bertamini
Dr. Giuseppe Bertuglia
Dr. Lorenzo Cani

Laboratory Staff
Transplant Unit
Nurses
Data Managing Staff
Statisticians