MIELOMA MULTIPLO NEL PAZIENTE NON CANDIDABILE A TRAPIANTO:

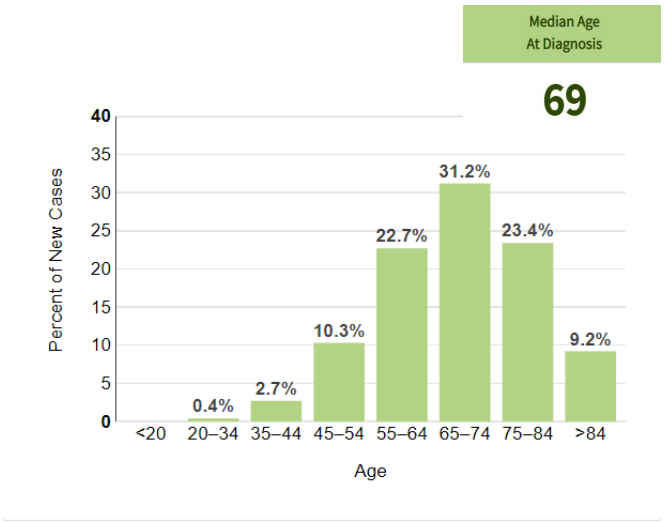
ruolo degli anticorpi monoclonali in prima linea e nel paziente ricaduto/refrattario

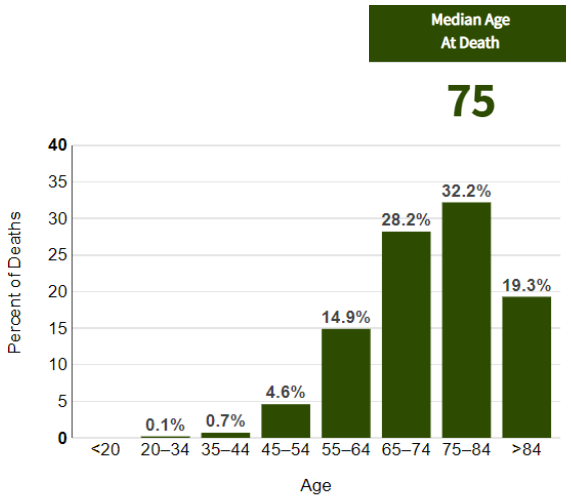
MICHELE CEA, MD

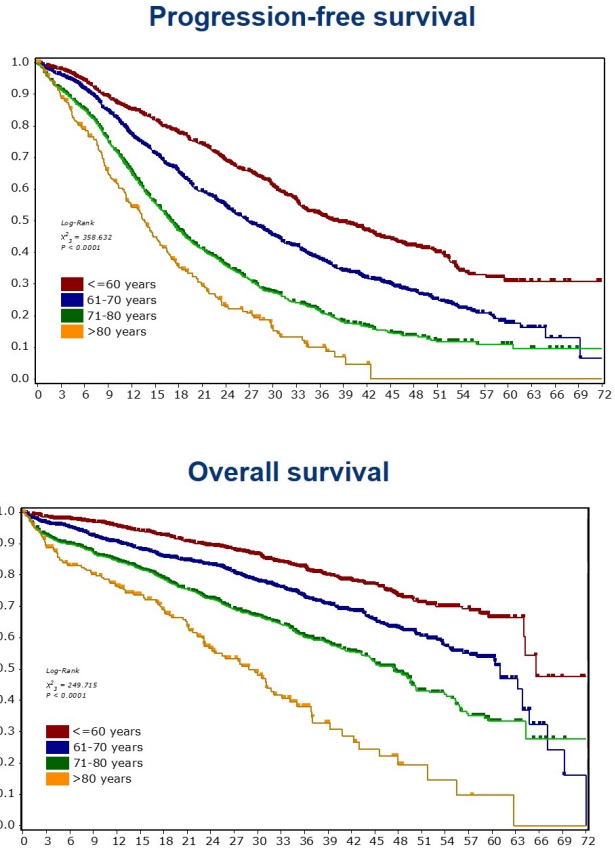
Policlinico San Martino -Università di Genova
Clinica Ematologica
Dipartimento di Medicina Interna e Specialità mediche (DIMI)

Savona 10 novembre 2023

MULTIPLE MYELOMA: A DISEASE OF THE ELDERLY
(age at diagnosis predicts outcome)

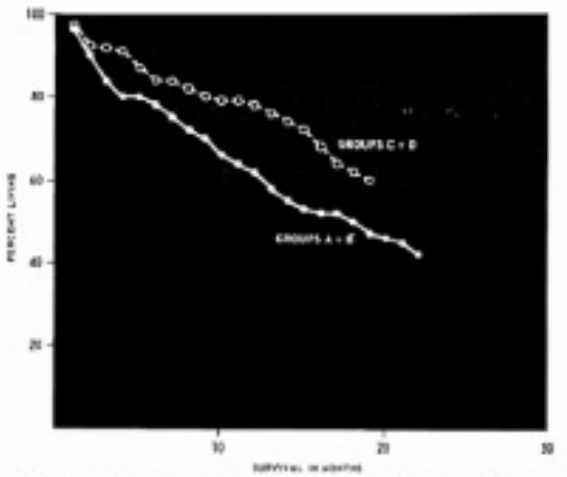






SEER Cancer Stat Facts: Myeloma. National Cancer Institute. Bethesda, MD

Changing Landscape in MM
(prognosis is improving over time in Older patients)



Survival from treatment in all patients receiving melphalan alone (schedules A and B), and melphalan with prednisone (schedules C and D). Nine patients, unresponsive to treatments A or B but responsive to C or D, are included in the curve for A and B with survival measured from their first exposure to melphalan.

Table 4.—Median Survival in Months From Institution of Melphalan Therapy (No. Dead/Total in Parentheses)

	All Patients*	Unresponsive (Includes Early Deaths)	Responsive
Daily melphalan (schedule A)	18 (22/35)†	12 (20/27)†	>32 (1/6)
Intermittent melphalan (schedule B)	18 (38/69)†	13 (31/44)†	>21 (6/20)
Melphalan + prednisone (schedules C and D)	24‡ (33/79)	6 (17/26)	>20 (14/50)
Intermittent melphalan (1958-1965)	17 (135/169)	10 (86/90)	45 (37/64)

1969

Melphalan-based regimes

OS 17-24 months

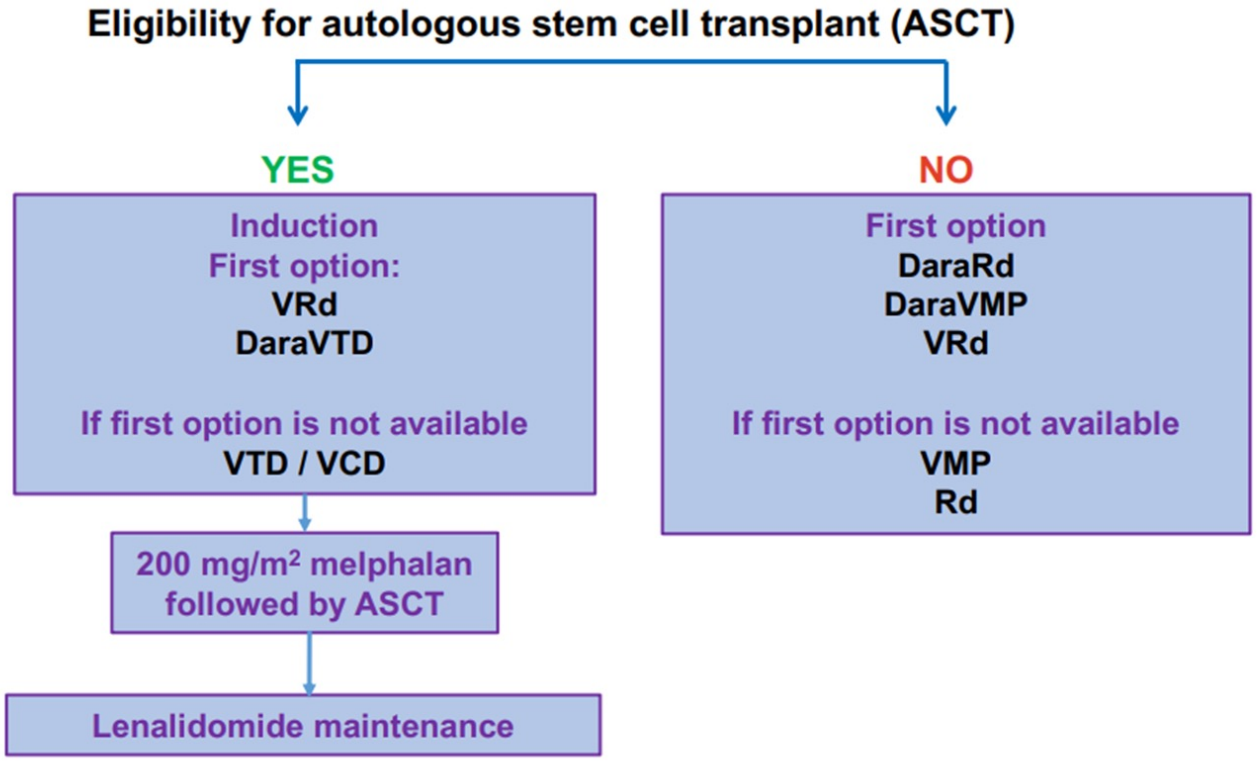
2021

mAb-based regimes
35->50 months

BUT PFS INSTEAD OF OS!

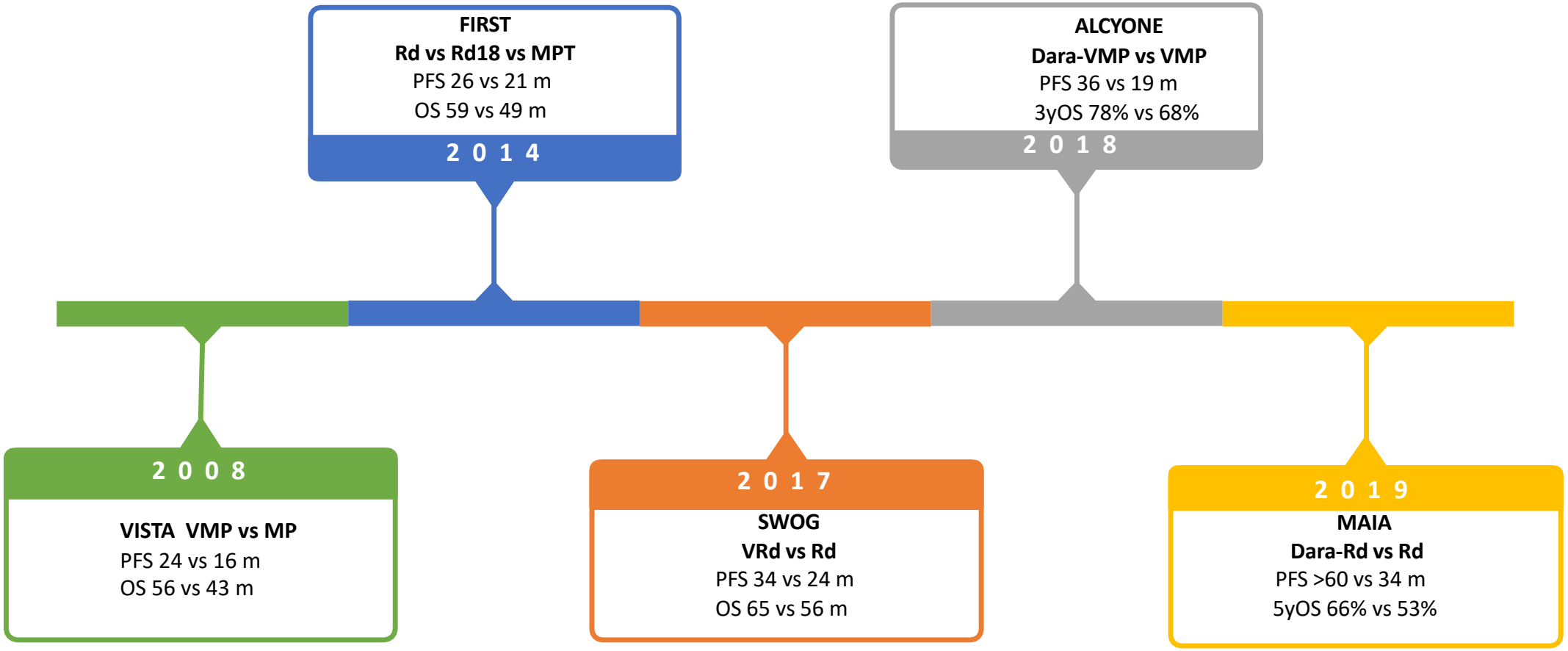
Alexanian R. et al JAMA 1969
Kumar S. et al. ASH 2020: abstract 2276
Mateos M. et al. ASH 2029: abstract 859

Multiple myeloma: EHA-ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up



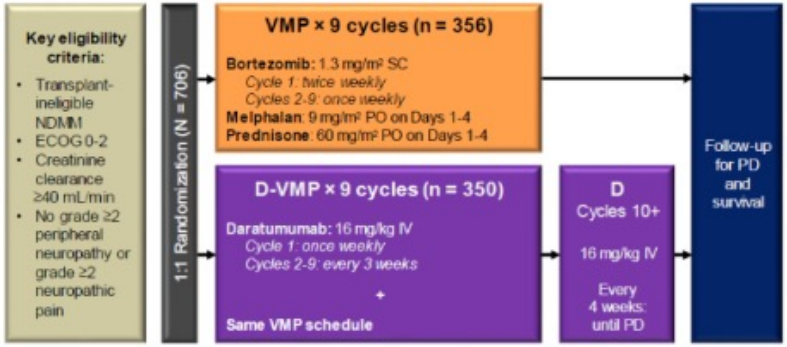
Dimopoulos et al. Annals of Oncology 2021

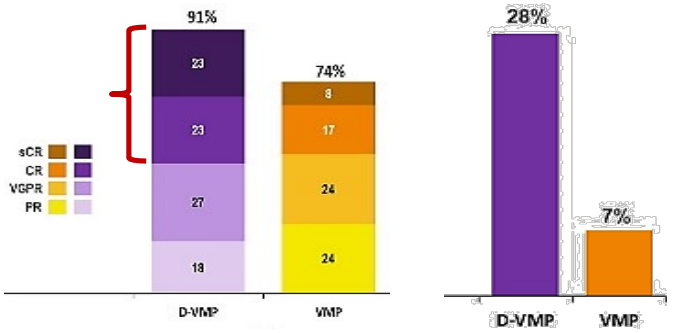
TIMELINE OF REGULATORY TRIALS IN NTE NDMM



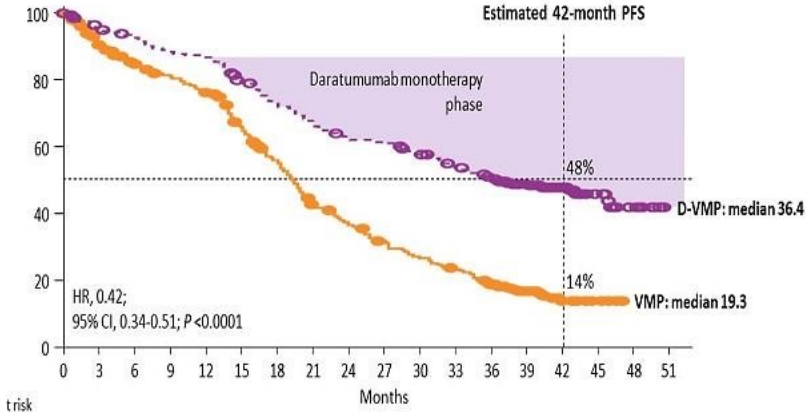
Daratumumab-VMP: ALCYONE phase 3 trial

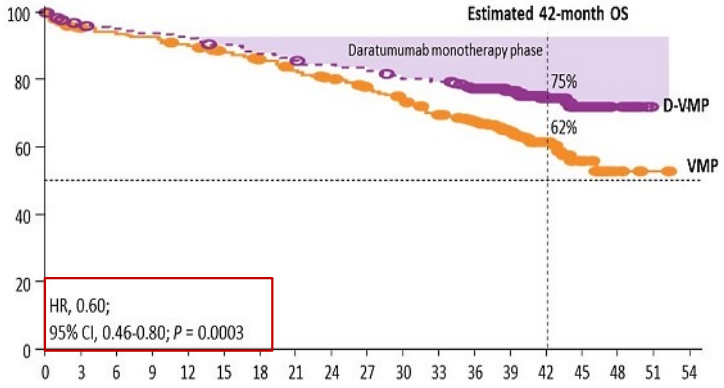
Sum up





- **Significantly higher ORR, ≥VGPR rate, and ≥CR rate with D-VMP**
- **>2-fold increase in sCR rate with D-VMP**
- **4-fold higher MRD negativity achieved with D-VMP**



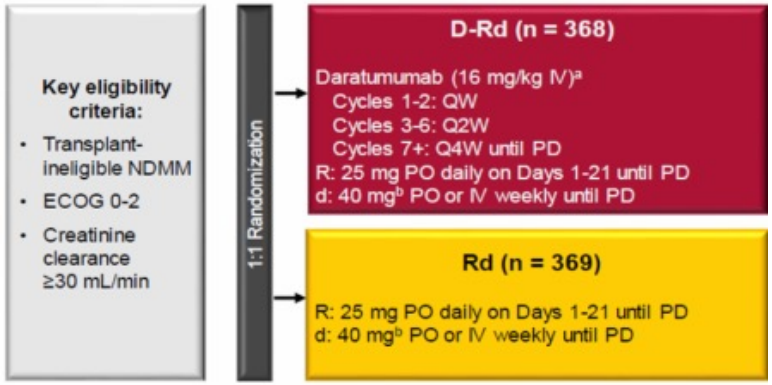


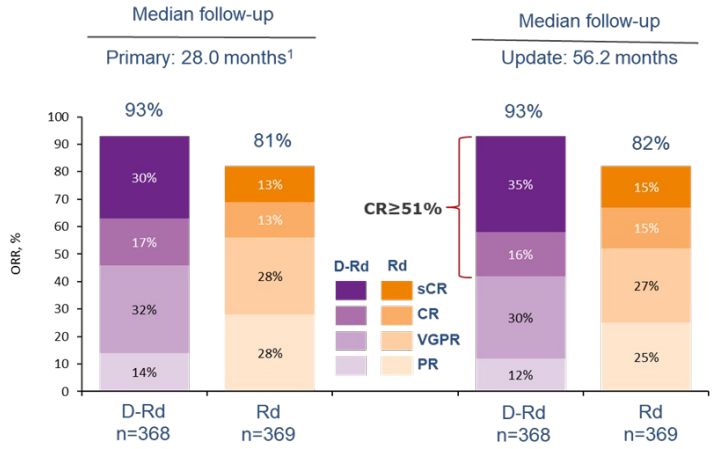
DaraVMP has been approved by FDA and EMA for the treatment of transplant ineligible NDMM patients

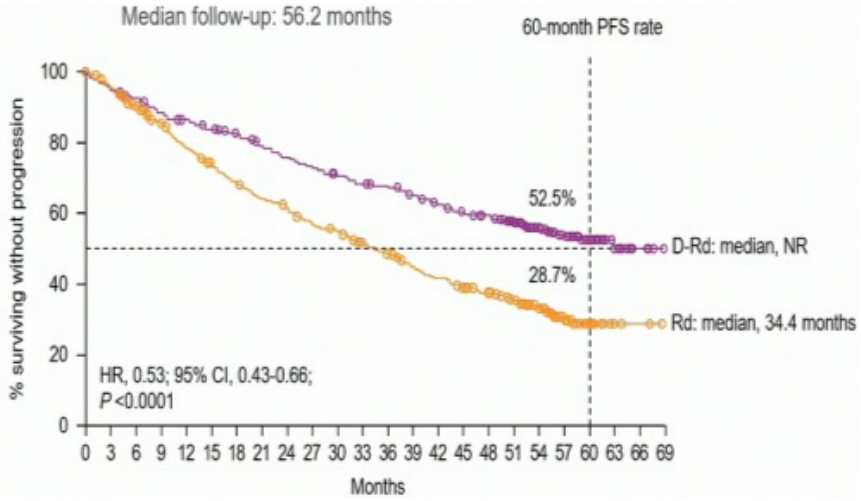
Mateos MV et al. NEJM 2018
Mateos MV et al. Lancet 2020

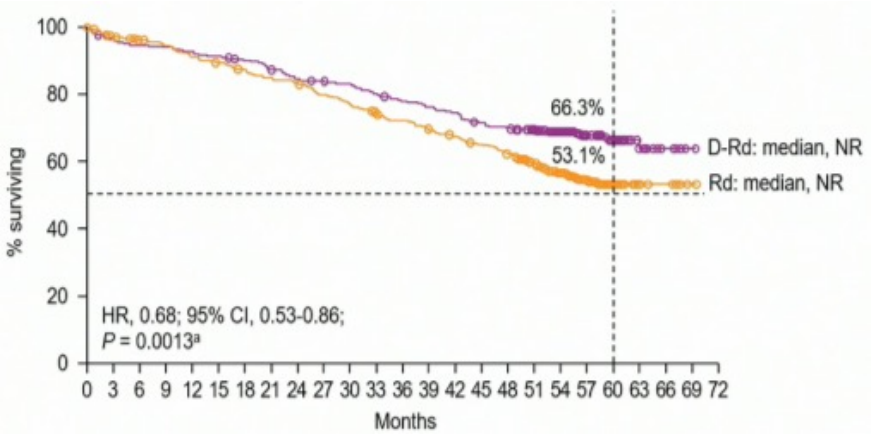
Daratumumab-Rd: MAIA phase 3 trial

Sum up









DaraRd has been approved by FDA and EMA for the treatment of transplant ineligible NDMM patients

Facon T et al. NEJM 2019
Facon T et al. Lancet Oncol 2021

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

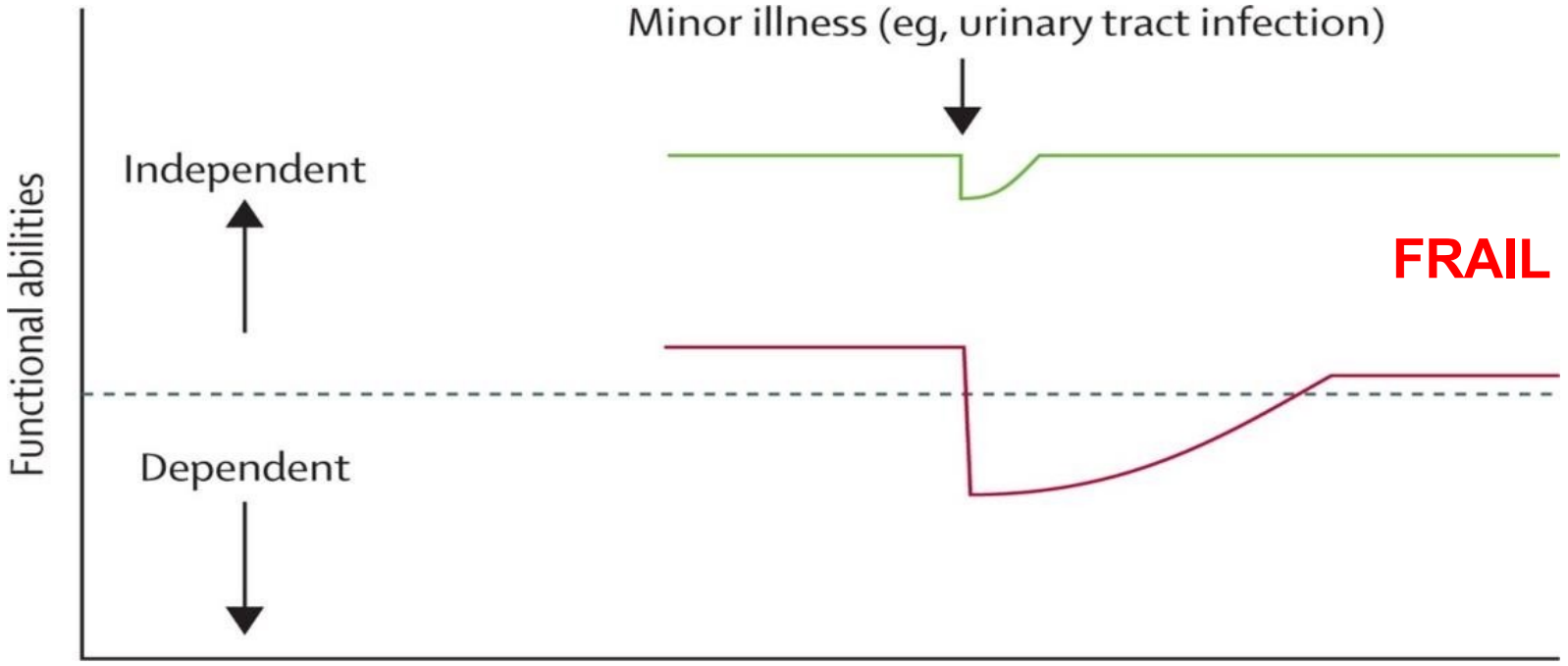
Can perform limited activities but they don't need any help

Frail

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

FRAILTY

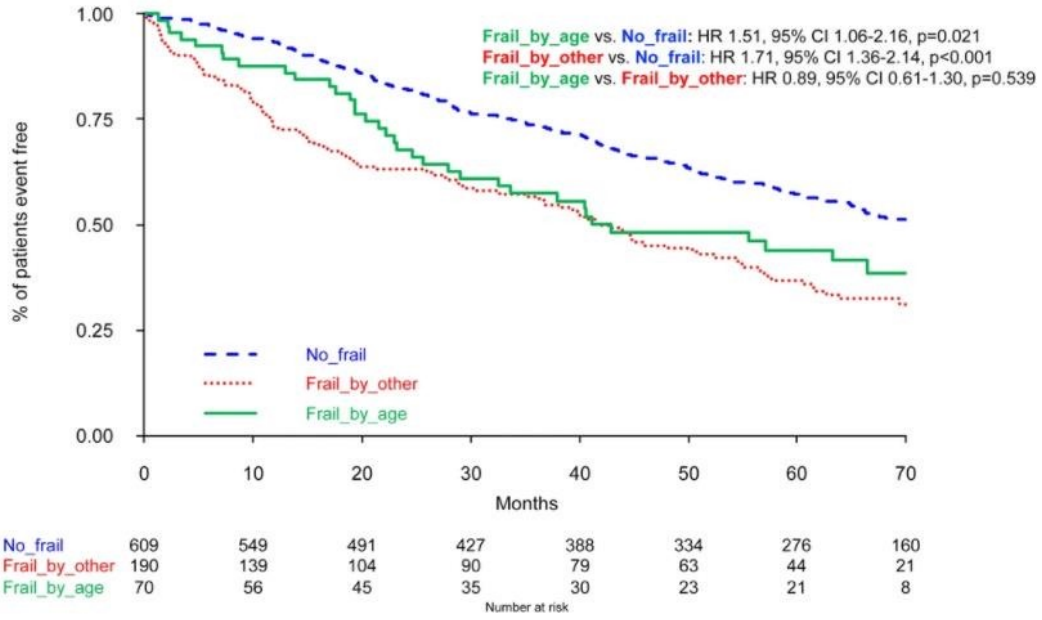
Frailty –state of vulnerability after a stressor event that triggers disproportionate changes in health status



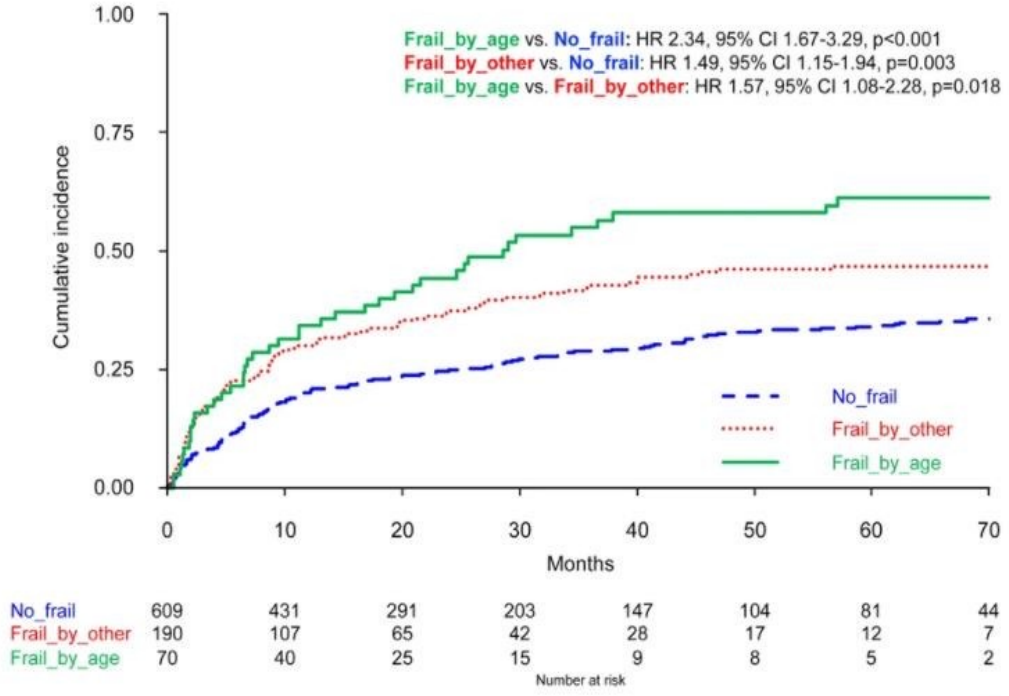
Clegg A, et al. The Lancet 2013

ROLE OF CHRONOLOGICAL AGE IN FRAILTY ASSESSMENT

Overall survival

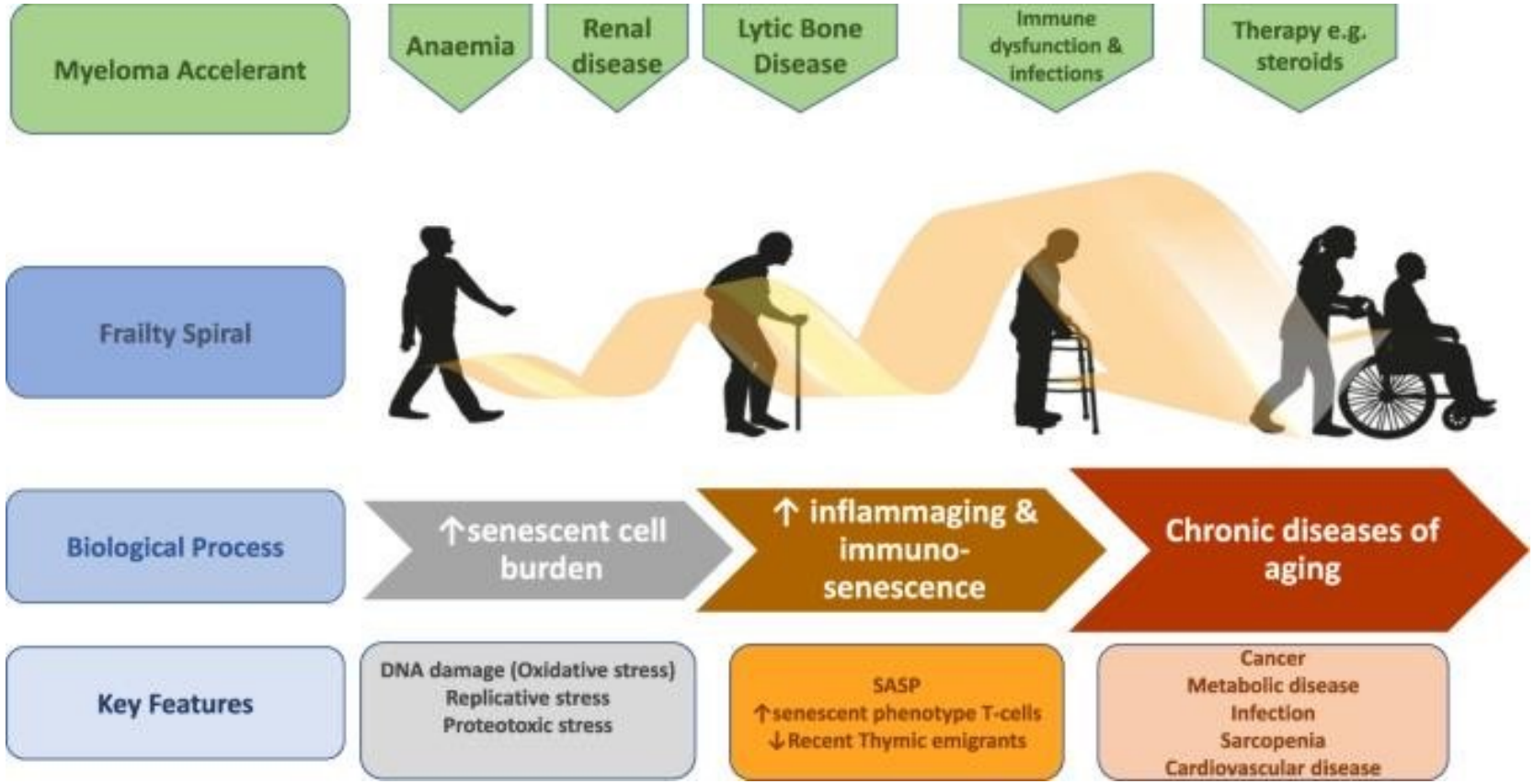


Drug discontinuation



D'Agostino M, et al, Blood Cancer J 2021

THE DETECTION OF FRAILTY IN ELDERLY PATIENTS

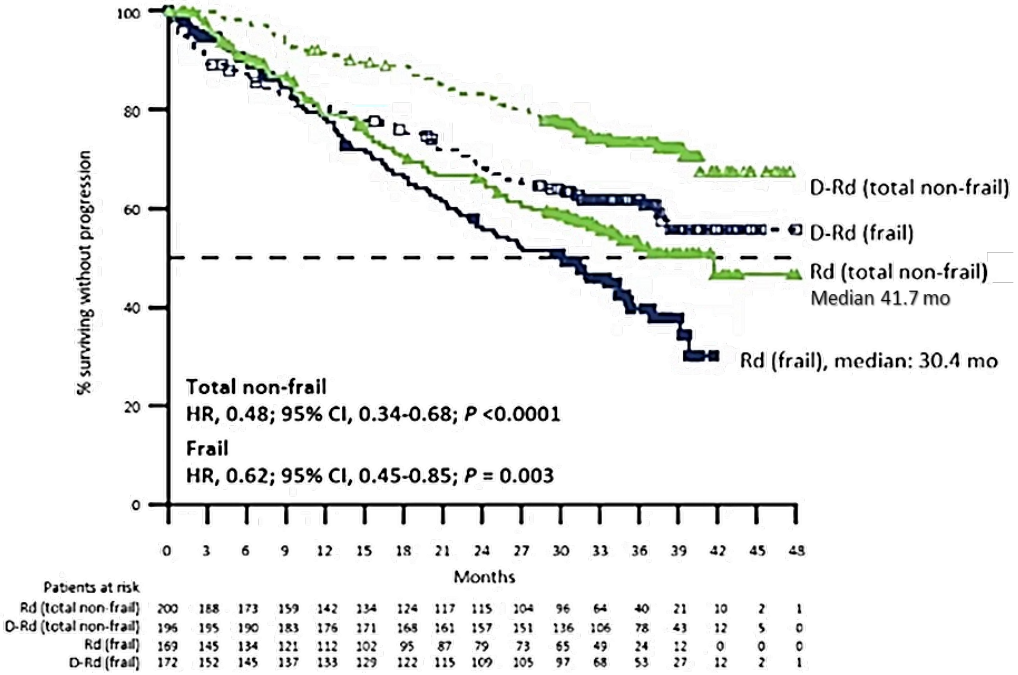


from Cook G et al. Leukemia. 2020;

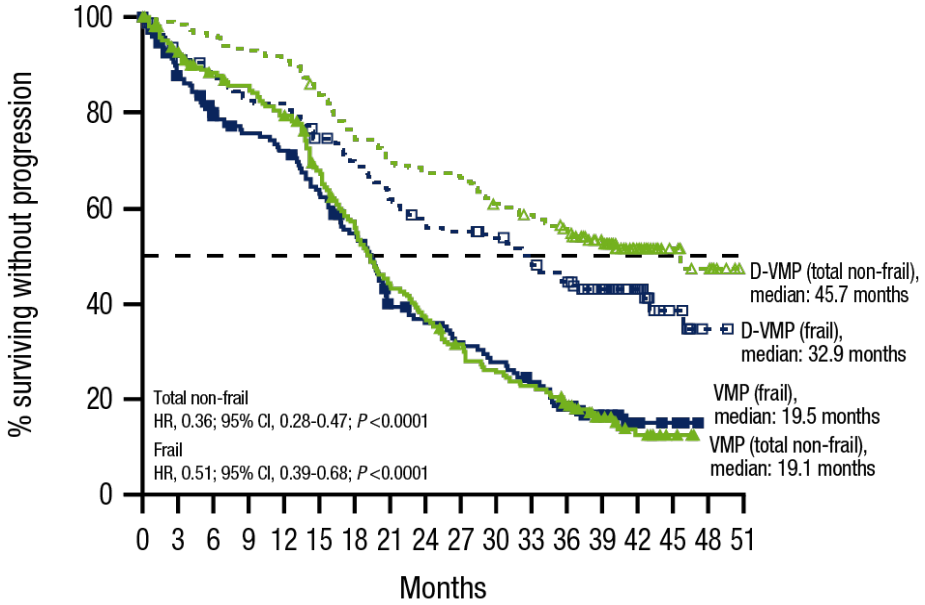
Fup 36.4 mo

PFS by Frailty Subgroup

MAIA



ALCYONE



Patients at risk

VMP (total non-frail)	204	179	166	160	148	122	100	78	66	54	44	39	30	16	9	3	0	0
D-VMP (total non-frail)	187	181	177	171	167	153	139	128	123	121	111	105	98	66	35	15	8	0
VMP (frail)	152	125	112	103	98	85	71	50	44	39	34	28	21	13	6	4	0	0
D-VMP (frail)	163	141	135	127	125	112	104	92	84	81	77	68	62	47	28	11	1	0

Conclusions
Fitness tailored treatment

FRAILTY ASSESSMENT IMWG Frailty Score		
FIT PATIENTS **(score 0)**	**INTERMEDIATE-FIT PATIENTS** **(score 1)**	**FRAIL PATIENTS** **(score ≥2)**
		
age ≤75 + ADL >4 + IADL >5 +CCI≤1	age 76-80 or ADL ≤4 or IADL ≤5 +CCI >1	age >80; age 76-80 + ADL ≤4 or IADL ≤5 or CCI >1; age ≤75 + at least 2 ADL ≤4 or IADL ≤5 or CCI >1
APPROVED REGIMENS **with possibile dose-adjustments according to frailty**		
• Daratumumab-VMP • Daratumumab-Rd • VRd • ASCT: Standard of care in ≤70 years old Consider in 71-75 years old* (*possibly with reduced conditioning)	• (Daratumumab)-VMP, consider weekly V • (Daratumumab)-Rd, consider dex discontinuation • Vd • VRd-lite	• Dose-adjusted Rd ± daratumumab • Dose-adjusted Vd • Palliative care
EXPERIMENTAL REGIMENS		
Daratumumab-VRd (NCT03652064) Isatuximab-VRd (NCT03319667) Belantamab-VRd (NCT04091126) KRD (NCT04096066) Ixazomib-RD (NCT018550524)	Daratumumab-Ixa-dex (NTR6297) Daratumumab-VRd lite (NCT04052880) KRD (NCT04096066) Ixazomib-RD (NCT018550524)	Daratumumab-Ixa-dex (NTR6297) Daratumumab-R (NCT03993912) Ixazomib-RD (NCT018550524)

Bonello F et al. Pharmaceuticals 2020

NTE-NDMM: Practical considerations

- **DaraRd, DaraVMP,** and VRd **are the current standard of care in NTE-NDMM**

- DaraRd is associated with longest median PFS

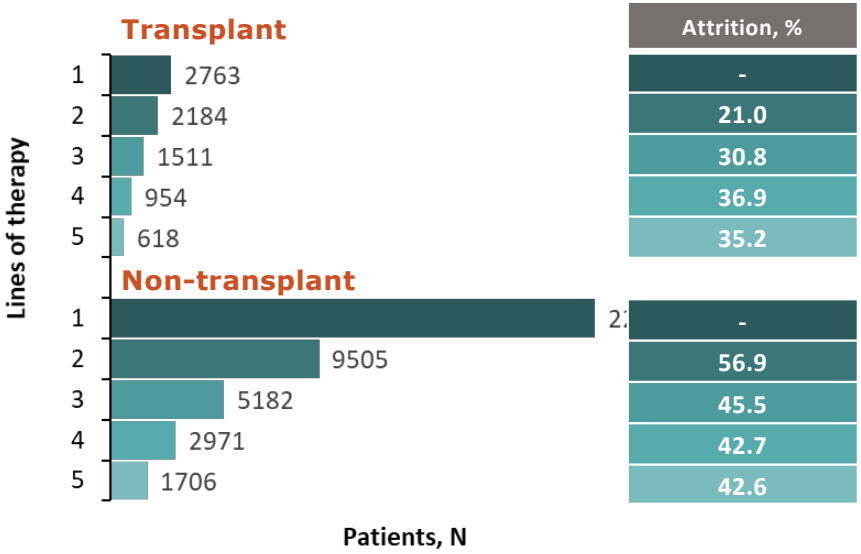
- Frailty-tailored treatment

- Future directions: New combo; Immunotherapy; **Frailty-tailored treatment in clinical practice**; MRD driven treatment: fixed vs continuous treatment; Improving supportive care: antimicrobial prophylaxis in selected patients

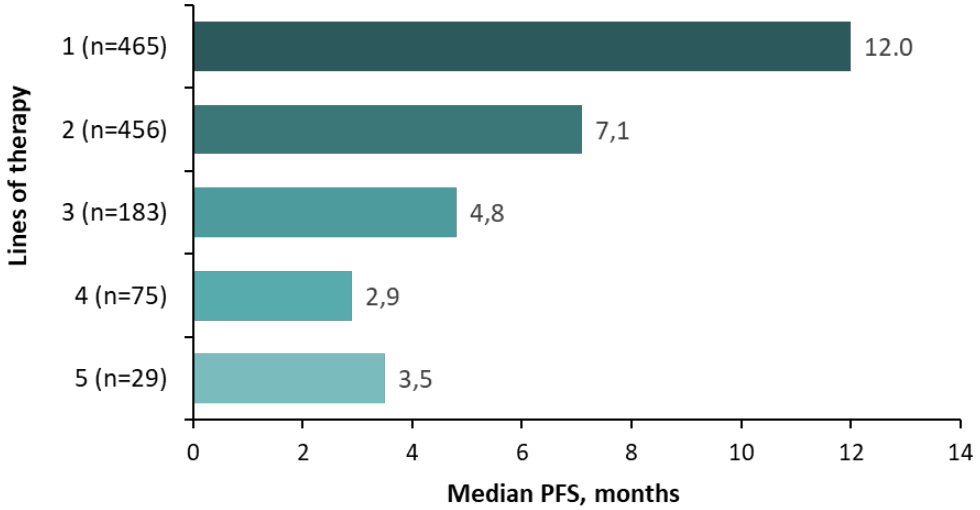
Relapsed Refractory MM patients

Time to progression decreases with each LOT and many patients do not go on to receive a second LOT

Patients reaching each LOT (US)



Median PFS by LOT

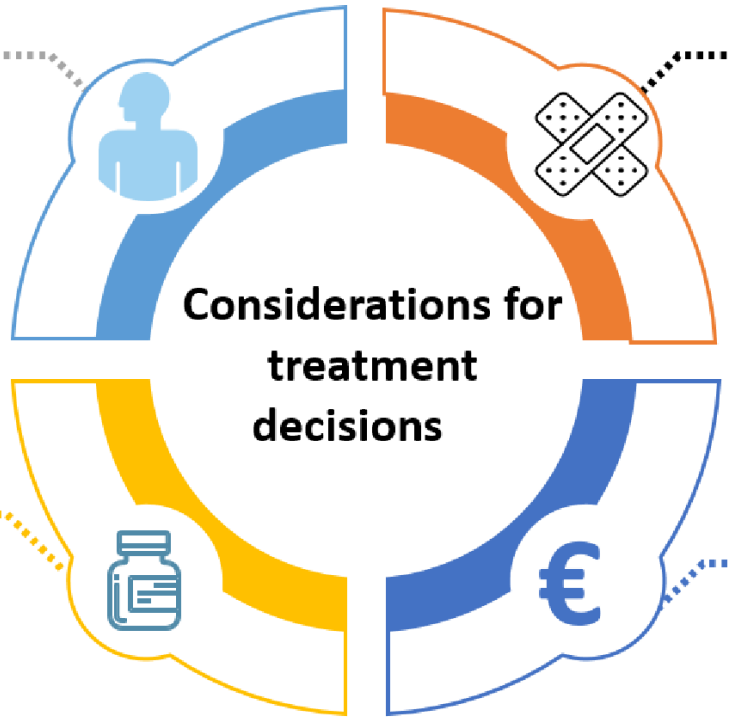


Therefore, the newly diagnosed setting is the most important opportunity to use the most efficacious treatment available

LOT, line(s) of therapy; PFS, progression-free survival

Fonseca R, et al. BMC Cancer 2020;20:1087;
Bruno AS, et al. Exp Rev Hematol 2020;13:1017–25

Treatment choice, in the Real-World setting



Patient

- Age and frailty
- Comorbidities
- Performance status (ISS and R-ISS stage)
- Preference
- Bone marrow reserve

Therapy

- Response to prior therapy
- Toxicity of prior treatment
- Prior ASCT
- Time from prior therapy
- Availability of clinical trials

Disease

- Duration of prior remission
- Disease burden – symptomatic vs asymptomatic
- Aggressive vs indolent disease
- End-organ function
- High- vs standard-risk cytogenetics

Socio-economic

- Support system
- Employment status
- Accessibility of treatment centre

Dimopoulos MA et al. Nat rev Clin Oncol 2015
Baz R et al. Support care cancer 2015
Agarwal A et al. Clin Lymphoma Myeloma Leuk 2017

I pazienti che progrediscono dalla 1L di oggi non rappresentano l'attuale 2L

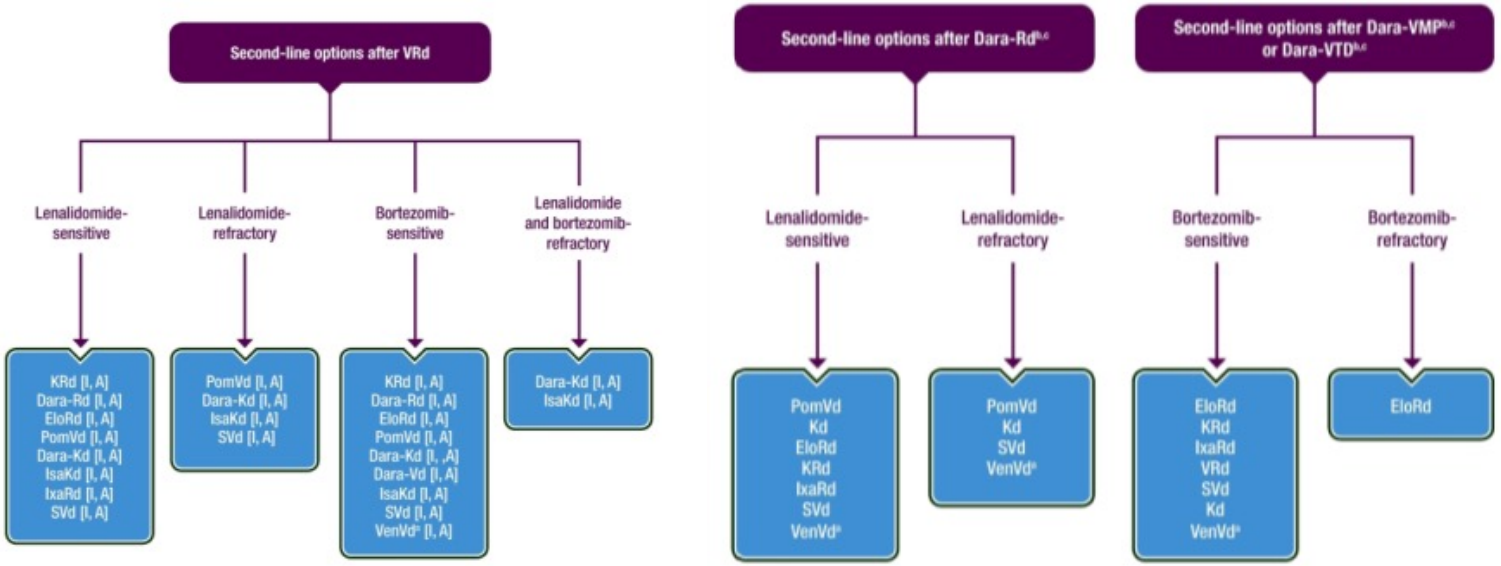
I pazienti attualmente trattati con le nuove opzioni terapeutiche di 1L avranno una ricaduta da questi regimi recentemente approvati non prima del giugno 2024, e la maggior parte di essi dopo il 2025

1L	Gazzetta ufficiale + 3 mesi	mPFS (mesi) Popolazione ITT	Timing mediano recidive
DaraVTd	Dicembre 2021 ▶ Marzo 2022	NR vs 51,5	> 2026
VRd	Febbraio ▶ Maggio 2021	43,0	> 2024
DaraVMP	Gennaio ▶ Aprile 2021	36,4	> 2024
DaraRd	Gennaio ▶ Aprile 2021	NR	> 2024
Mantenimento con lenalidomide	Maggio ▶ Agosto 2018	46,3 (IFM)	Giugno 2022

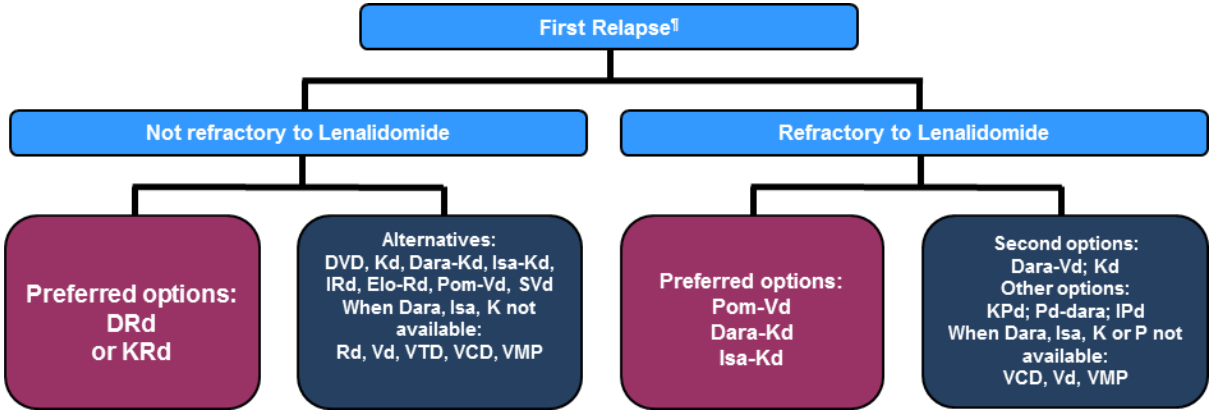
CASSIOPEA-Moreau P et al. EHA 2021 Abstract S180; SWOG-Durie BGM et al. Lancet 2017; 389: 519–527; ALCYONE-Mateos MV et al. Lancet 2020; 395: 132–141; MAIA-Facon T et al. EHA 2021 Abstract LB1901; Attal M et al. N Engl J Med 2012; 366: 1782–1791

Guidelines 2021 for RRMM: first relapse

ESMO
guidelines 2021
Dimopoulos MA et al. Ann Oncol 2021



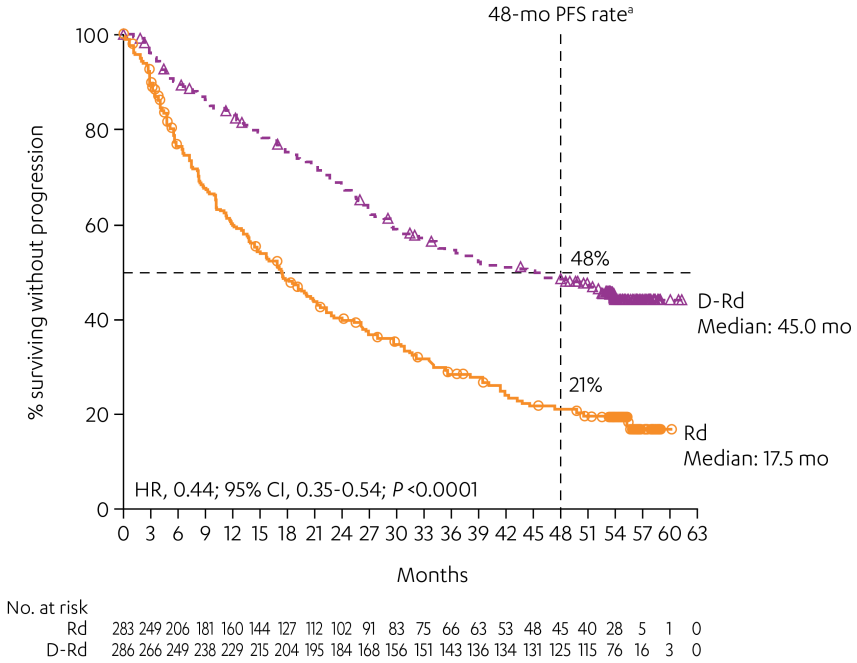
IMWG
guidelines 2021
Moreau P et al, Lancet Oncol 2021



IMiDs based combinations

POLLUX: DRd > Rd

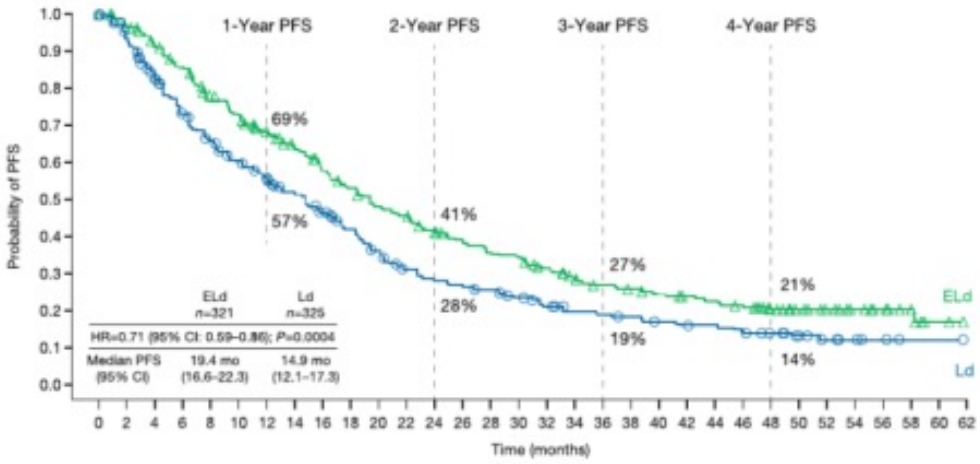
Median follow-up: 54.8 months (≥ 1 prior line)



DaraRd
PFS: 44.5 m, HR: 0.44
CR 56%

ELOQUENT-2: Elo-Rd > Rd

Median follow-up: 46 months (1-3 prior lines)



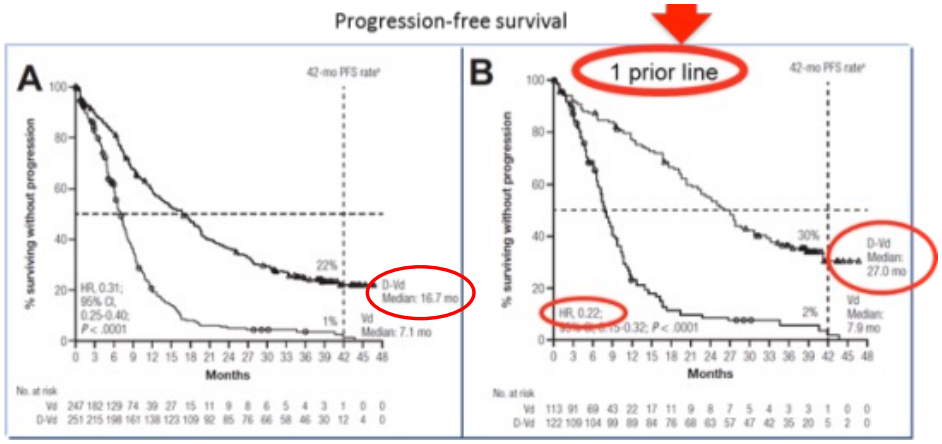
EloRd
PFS: 19.4 m, HR: 0.71
CR 5%

Dimopoulos NEJM 2016
Lonial NEJM 2015

PIs based combinations

CASTOR: DaraVd > Vd

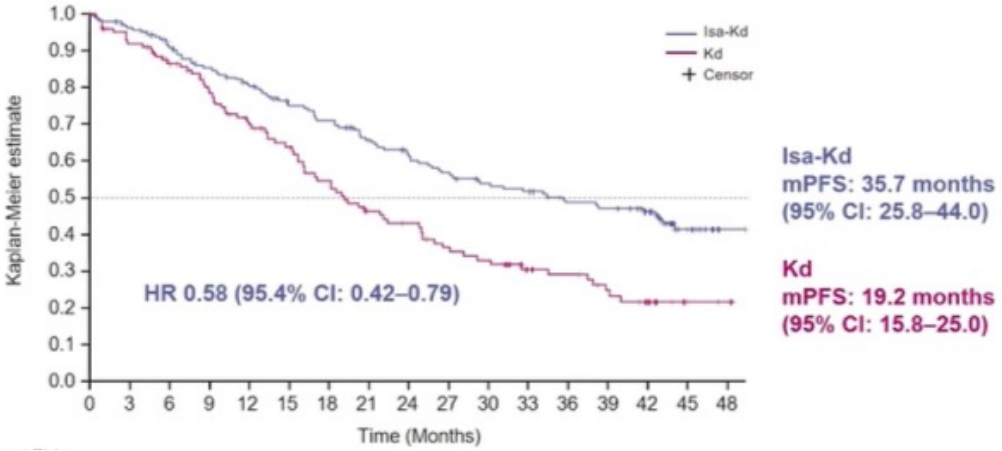
Median follow-up: 40 months (≥1 prior line)



DaraVD
PFS: 16.7 m, HR: 0.32
CR 30%

Ikema: IsaKd > Kd

Median follow-up: 44 months (≥1 prior line)

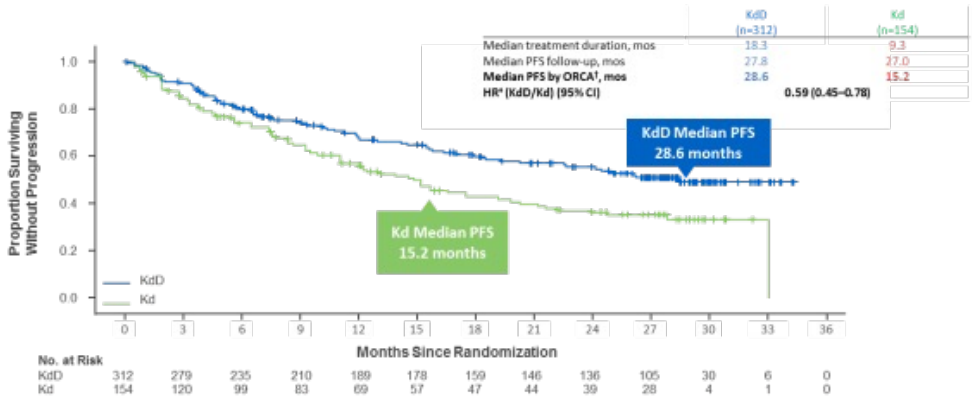


IsaKD
PFS: 35.7 m, HR: 0.32
CR 44.1%

Dimopoulos MA et al, Lancet Oncology 2016
Moreau P et al. Lancet 2021

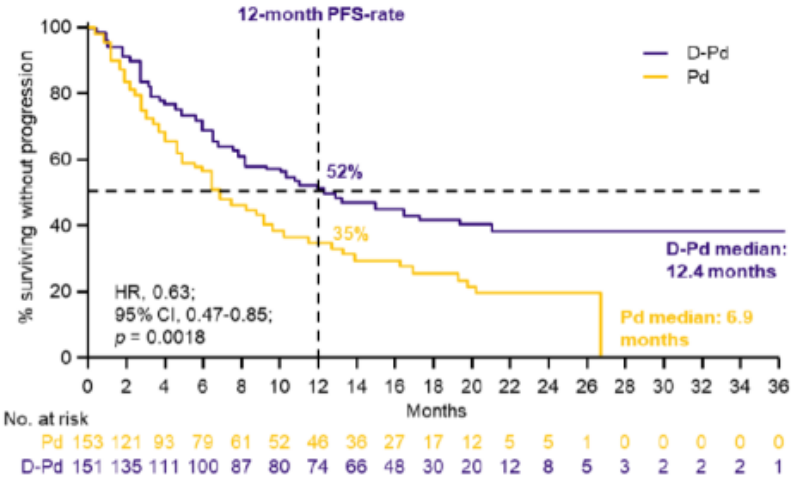
MoAbs based combinations

Candor: daraKd > Kd
Median follow-up: 39 months (≥1 prior line)



DaraKd
PFS: 28.4 m, HR: 0.44
VGPR 69%

Apollo: daraPd > Pd
Median follow-up: 16.9 months (≥1 prior line)



DaraPd
PFS: 12.4 m, HR: 0.71
VGPR 51%

Dimopoulos M, et al. Lancet 2020;396:186-197
Dimopoulos MA et al. ASH 2020; Dimopoulos MA et al, Lancet Oncology 2021

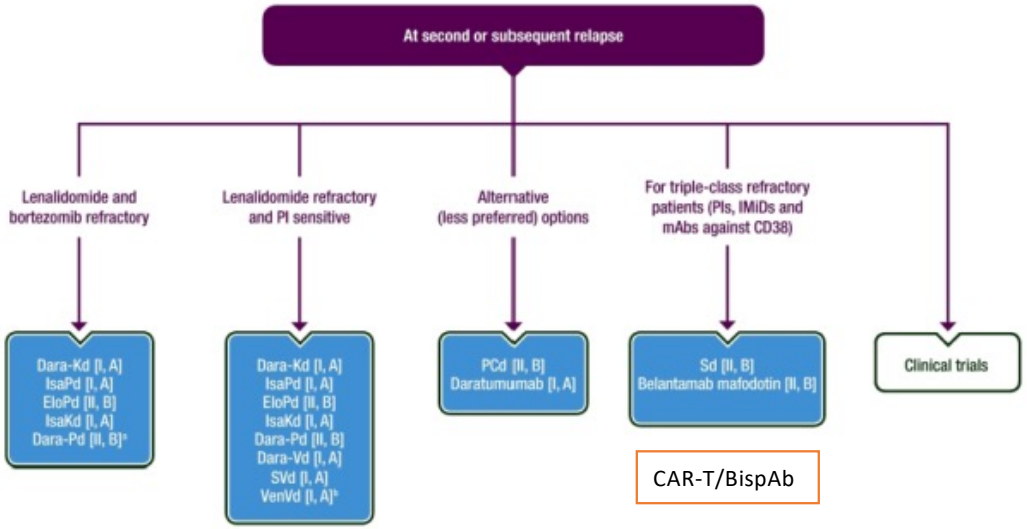
DaraKd vs IsaKd vs DaraPd

	CANDOR Dara-Kd arm	IKEMA Isa-Kd arm	APOLLO Dara-Pd arm
Number of patients	315	179	304
Median age	64y	65y	67y
ISS III	20%	14%	33%
High-risk FISH	**15% (51% missing)**	**23% (13% missing)**	**39% (32% missing)**
Median prior lines of tp	2	2	2
1 prior line of tp	**46%**	**44%**	**11%**
Lenalidomide refractory	**32%**	**32%**	**79%**
Bortezomib refractory	**28%**	**31%**	**47%**
Median duration of follow-up	27,8 months	20,7 months	16,9 months
Median PFS	**28.4 months**	**35.7 months**	**12.4 months**
HR for PFS	**0.59**	**0.58**	**0.63**
Median PFS in len-refractory pts after 1 prior line of therapy/any line	**25.0 months/28.1 months**	**NR/NR**	**23.7 months in MM-014 study after 1 prior LOT/9.9 months**
ORR	84%	87%	69%
CR	**29%**	**44%**	**25%**
MRD negative (10^{-5} sensitivity)	**18% (at 12 mo)**	**33.5% (ITT population)**	**9%**

Dimopoulos et al. Lancet 2021
Dimopoulos M al. Lancet. 2020
Moreau P. et al. Lancet 2021

Guidelines 2021 for RRMM: second or subsequent relapse

ESMO guidelines 2021



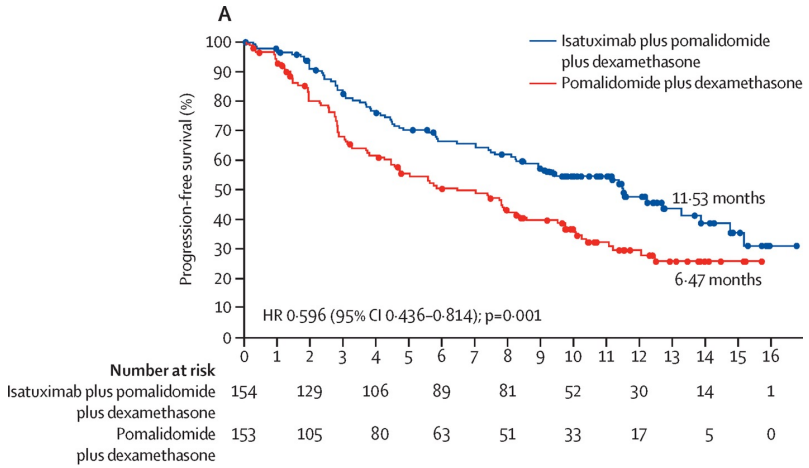
Dimopoulos MA et al. Ann Oncol 2021

IMWG guidelines 2021

Preferred Options	Additional Options
• Any first relapse options that have not been tried • Isa-Pd; Dara-Kd; Isa-Kd (based on phase 3) • Pd-Dara, Elo-Pd, KPd (based on phase 2) • When Dara / K / Elo not available: PCD, PD	• Approved: selinexor, addition of panobinostat to PIs, VTD-PACE, belantamab mafodotin (4 lines) • Investigational agents: melflufen, BCMA-targeting agents including CAR-Ts or bispecific antibodies, vetenoclax in t(11;14) or bcl-2 high expression

Moreau P et al, Lancet Oncol 2021

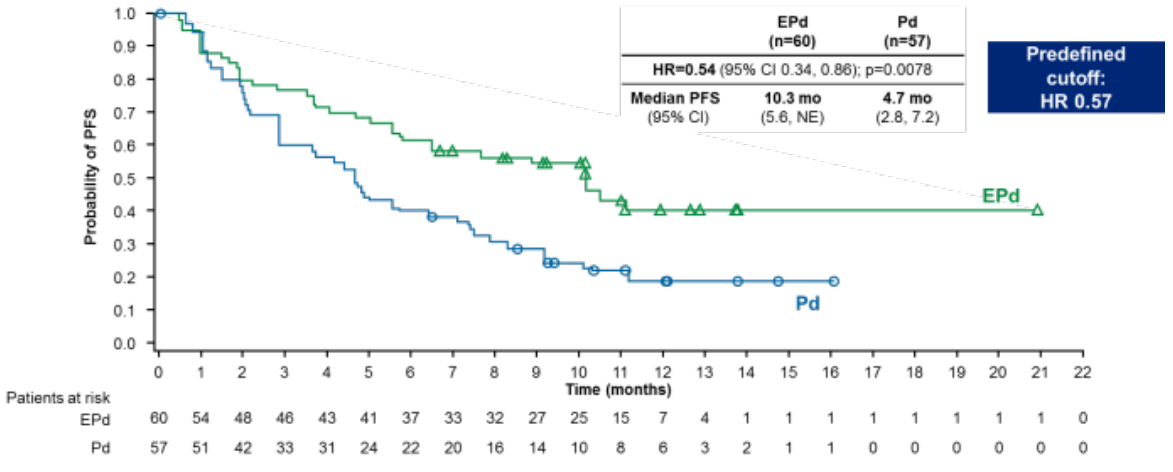
Phase 3 ICARIA trial
Isa-PD vs PD
(response, PFS, trend OS)



Median OS: IsaPd vs Pd: 24.57 mo vs 17.71 mo

Attal M et al, Lancet 2019
Richardson P et al, EHA 2021

Phase 2 ELOQUENT-3 trial
Elo-PD vs PD
(response, PFS, trend OS)



Median OS: EPd vs Pd: 29.8 mo vs 17.4 mo

Dimopoulos MA et al, NEJM 2018
Dimopoulos MA et al, IMW 2021

EloPd versus IsaPd vs DaraPd

	Eloquent-3 Elo-Pd arm	ICARIA Isa-Pd arm	APOLLO Dara-Pd arm
Median prior lines of tp	3	3	2
Prior Lenalidomide	98%	100%	100%
Lenalidomide refractory	90%	94%	79%
PI refractory	78%	77%	47%
Double refractory (len + PI)	68%	72%	42%
Median PFS	10.3 months	11.5 months	12.4 months
HR for PFS	0.54 (p = 0.0078)	0.60 (p = 0.001)	0.63 (p = 0.0018)
Median PFS in len-refractory pts	10.3 months	11.4 months (HR 0.59)	9.9 months (HR 0.66)
Median PFS in double-refractory pts	10.2 months (HR 0.56)	11.2 months (HR 0.58)	9.9 months (HR 0.74)
HR for PFS in High-risk FISH	0.52	0.66	0.85
ORR	53%	63%	69%
CR rate	5%	9% (MRD neg 5%)	25% (MRD neg 9%)
Hematologic toxicity (gr 3-4) **-Neutropenia** **-Thrombocytopenia**	 13% 8%	 85% 31%	 68% 17%
Non hematologic (gr 3-4) **-IRR (all grades)** **-Infections** **-Pneumonia**	 3% 13% 5%	 38% (3% gr≥3) 16%	 5% 28% 13%
Treatment discontinuation due to AEs	18% vs 24%	7% vs 13%	2% vs 3%

Dimopoulos MA et al, NEJM 2018; Dimopoulos MA et al, IMW 2021; Attal M et al, Lancet 2019; Richardson P et al, EHA 2021; Dimopoulos MA et al, ASH 2020, Lancet Oncology 2021

RRMM, first and second relapse: Practical considerations

- Use triplets if possible

- Change mechanism of action, preferably introduce a new target/mechanism

- **DaraRd** → Len sensitive
- **IsaKd** or DaraKd → Len refractory
- **Poma-based triplets** → from 2nd relapse

- Treatment approach should be continuous

- Personalized therapy based on clinical conditions

GRAZIE PER L'ATTENZIONE!

Clinica Ematologica

Direttore Roberto M. Lemoli

Staff medico
Maurizio Miglino
Antonia Cagnetta
Filippo Ballerini
Fabio Guolo
Paola Minetto
Andrea Todiere
Chiara Salvetti

Data manager
Mariagrazia Ciardo

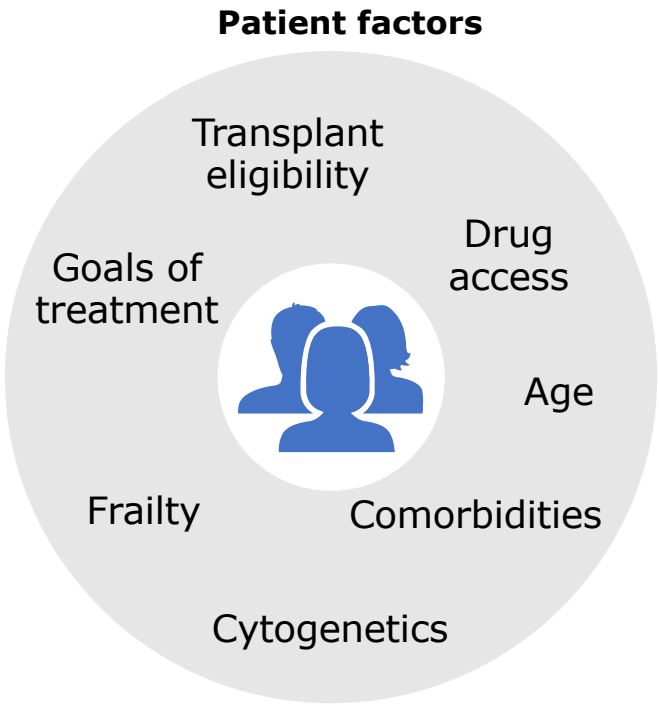
Scuola di specializzazione in Ematologia
Univerisità di Genova

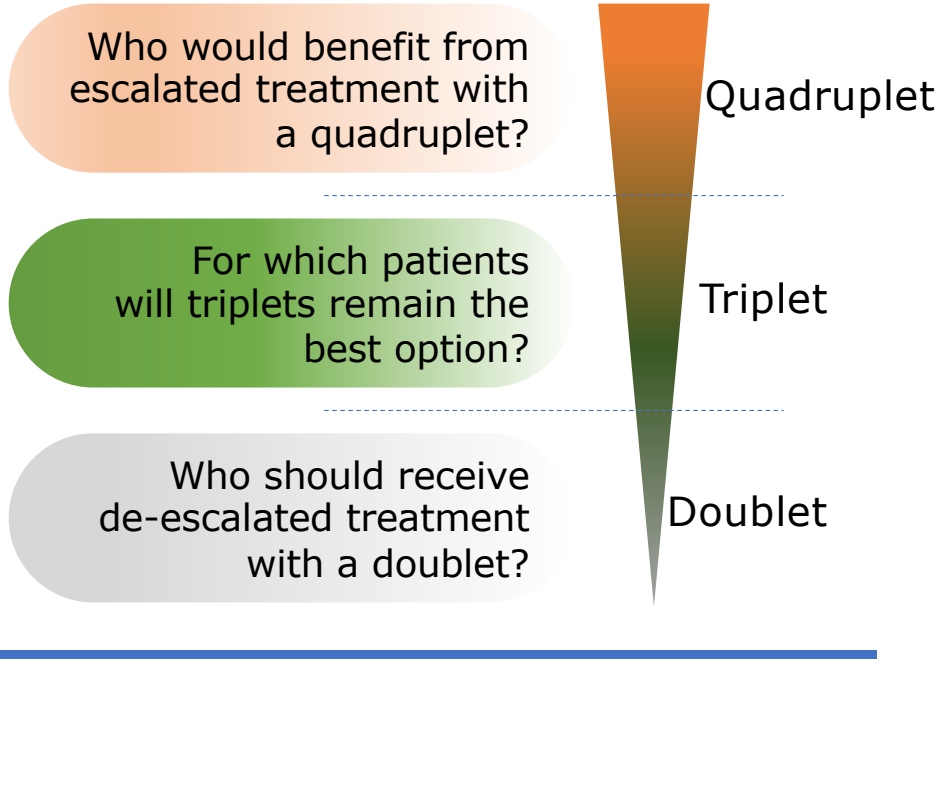
Myeloma research members

Clinicians
Antonia Cagnetta
Matteo Garibotto
Marco Olivieri
Marco Gallo
Elisabetta Catini
Anna Elisa Laserra

Lab members
Soncini Debora
Pamela Becherini
Claudia Martinuzzi
Francesco Ladisa
Giulia Giorgetti
Isabella Traverso

The heterogeneity of NDMM requires upfront treatment to deliver a careful balance of maximal efficacy with tolerability





NDMM, newly diagnosed multiple myeloma

Terpos E, et al. Blood Cancer J 2021;11:40;
Dimopoulos MA, et al. Ann Oncol 2021;32:309–22;
Grant SJ, et al. Hematol Am Soc Hematol Educ Program 2021;1:46-54

NTE-NDMM treatment paradigm

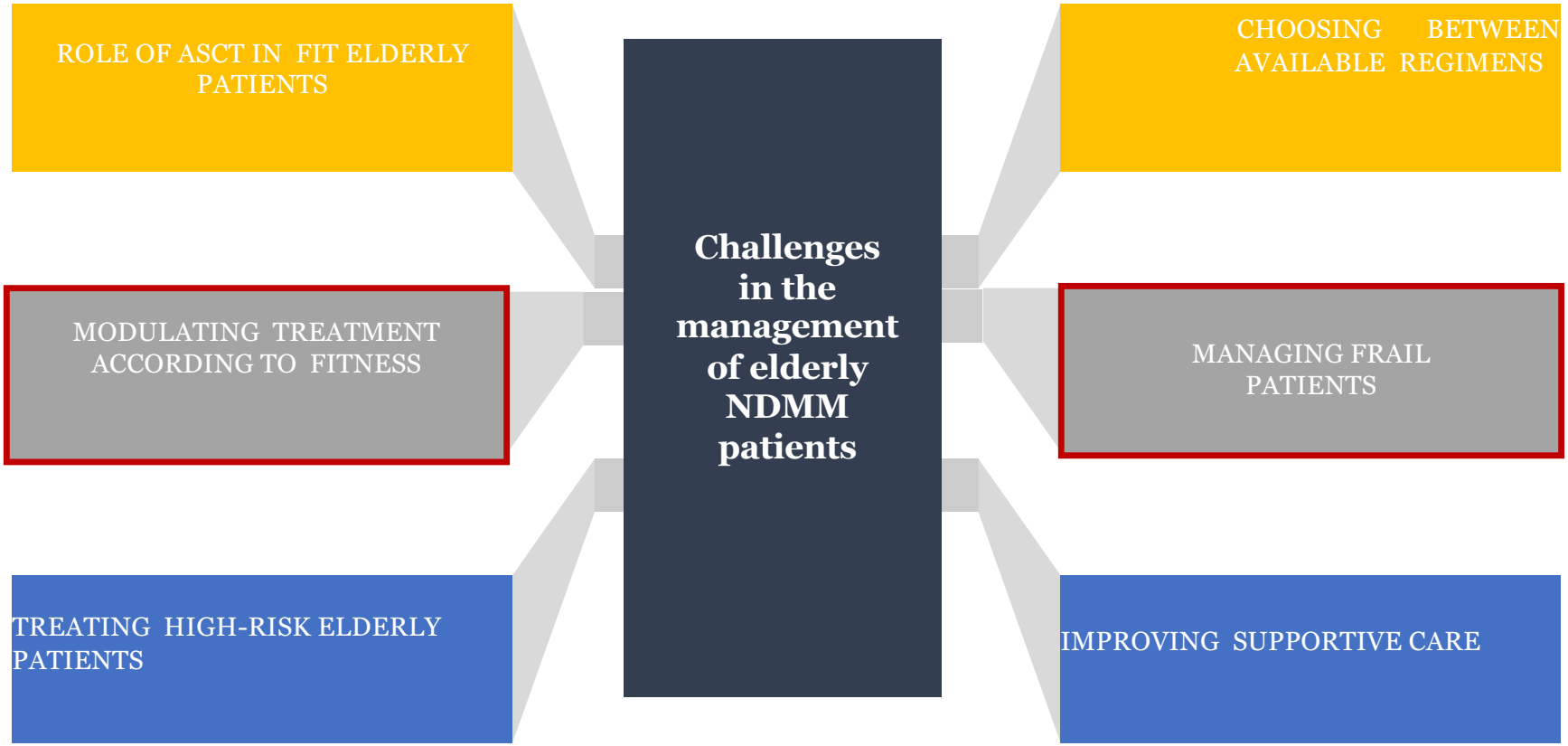
BUT

1. Can study results be translated to older patients in real life?
2. If not, what are the reasons?
3. How to define patients in whom therapy is of added value?
4. How to adapt therapy?
5. Patient preference for independence and QoL versus length of life

How to improve treatments for NTE patients?

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


ROLE OF ASCT IN FIT ELDERLY PATIENTS
MODULATING TREATMENT ACCORDING TO FITNESS
TREATING HIGH-RISK ELDERLY PATIENTS
Challenges in the management of elderly NDMM patients
CHOOSING BETWEEN AVAILABLE REGIMENS
MANAGING FRAIL PATIENTS
IMPROVING SUPPORTIVE CARE

Experimental study versus real-life population

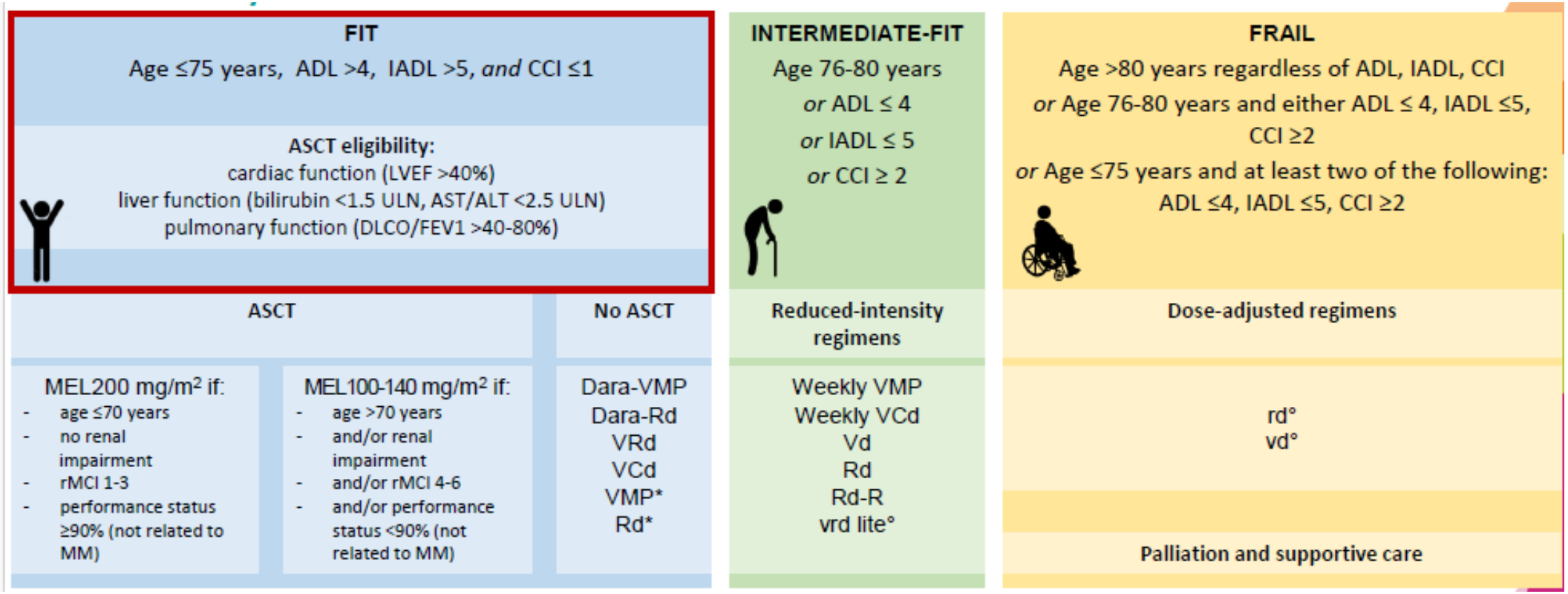
Are patients enrolled in registrational clinical trials comparable to real-world patients?

	ALCYONE	MAIA	SWOG S0777	REAL (Rd vs VMP)
Median age (years) ≥ 75 years >80 years	71 30% Not reported	73 44% Not reported	63 (>65 ys) 43% Not reported	76 (>75 ys) 54% 19%
ECOG PS 0-1 2 >2	 75% 25% Excluded	 83% 17% Excluded	 86% 14% 2-3 Excluded >3	 81% 13% 6%
Creatinine clearance 30-60 ml/min < 30 ml/min	 41% excluded (< 40)	 41% excluded	 5% creatinine > 2mg/dL excluded	 40% 8%
Exclusion criteria Malignancy < 3 years	AST/ALT > 2.5 ULN Malignancy < 5 years Myocardial infarction < 1 year	AST/ALT > 2.5 ULN NYHA III/IV Myocardial infarction < 1 year	Previous malignancy Recent myocardial infarction	None

Durie B et al, Blood 2018; 132;1992; Durie et al; Blood Cancer J; 10:53; Mateos MV et al, Lancet 2020; 395(10218):132-141; Facon T et al, N Eng J Med 2019 380, 2105-15.

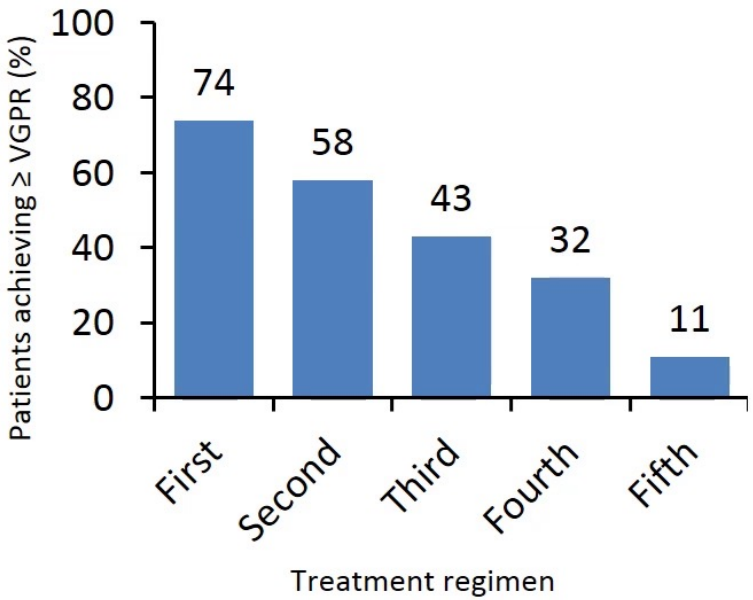
Newly diagnosed MM patients

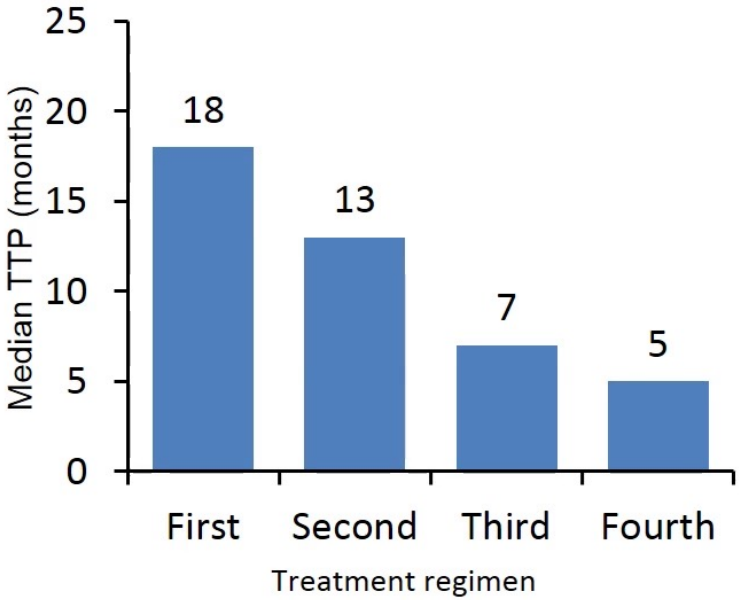
IMWG Frailty Score



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.

Survival prognosis diminishes with each successive relapse





Depth and duration of response are important prognostic factors and decrease with each subsequent line of treatment

Yong K, et al. Br J Haematol 2016;175:252–64.

MM, multiple myeloma; TTP, time to progression; VGPR, very good partial response.