Highlights from IMW 2019

19-20 novembre 2019
Bologna
Royal Hotel Carlton

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SSD Clinical Trials in oncoematologia e mieloma multiplo
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Come orientare la scelta della terapia

DISCLOSURE

Sara Bringhen

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other (Honoraria)
Janssen and Cilag						X	X
Amgen							X
Celgene						X	X
Bristol Meyer Squibb							X

ESMO Guidelines 2017

Eligibility fot autologous stem-cell transplantation (ASCT)

YES

↓

INDUCTION:
3 drug regimens
VTD
VCD
PAD
RVD

↓

200 mg/m^2 melphalan followed by ASCT

↓

Lenalidomide maintenance

NO

↓

FIRST OPTION:
VMP or Rd or VRd

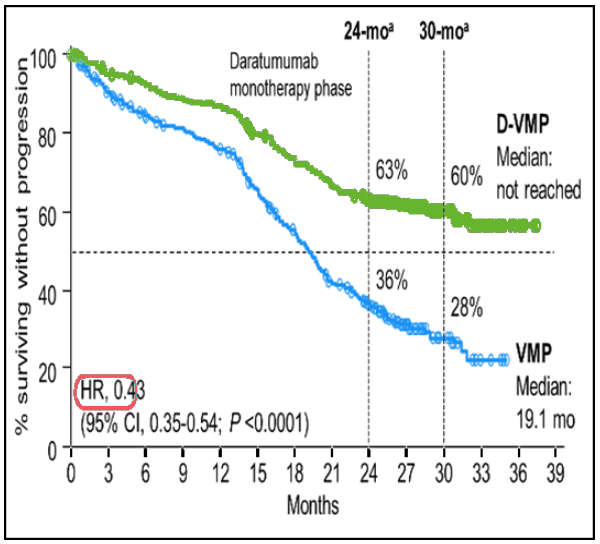
SECOND OPTION:
MPT or VCD

OTHER OPTIONS:
CTD, MP, bendamustine, prednisone

V, bortezomib; T, thalidomide; D, d, dexamethasone; PAD, bortezomib, doxorubicin and dexamethasone; R, lenalidomide; M, melphalan; P, prednisone; C, cyclophosphamide.

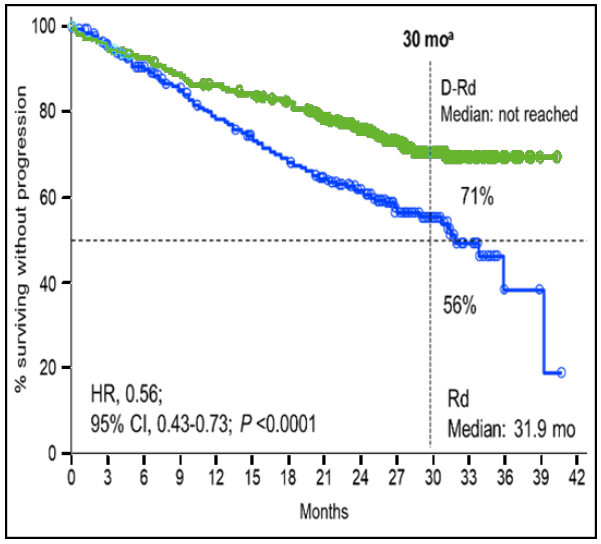
New drug-based combinations

Dara-VMP[1]



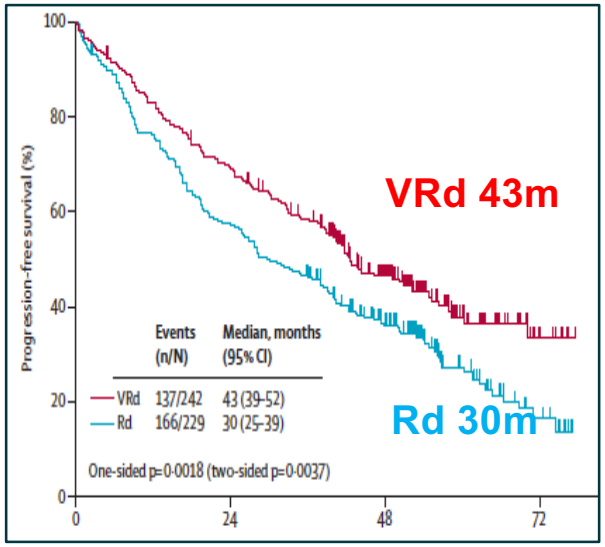
MRD neg 27% vs 7%
30-mo PFS: 60% vs 28%

Dara-Rd[2]



MRD neg 24% vs 7%
30-mo PFS: 71% vs 56%

VRd[3]



Median PFS
34 vs 24 months (≥65 yrs)

- **New standards of care: Dara-VMP, Dara-Rd, VRd**
- **New potential future treatments: Elotuzumab-Rd, Ixazomib-Rd, Carfilzomib-Rd, Dara-KRd, Isatuximab-VRd**

Dara, daratumumab; V, bortezomib; M, melphalan; P, prednisone; R, lenalidomide; K, carfilzomib; MRD neg, minimal residual disease; MRD neg, MRD negative; PFS, progression-free survival; yrs, years.

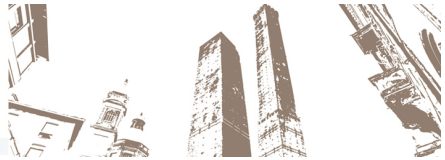
1. Dimopoulos et al., ASH 2018; abstract 156; 2. Facon et al., ASH 2018; abstract LB-2, oral presentation; 3. Durie B, et al. Lancet 2017;389:519-527

How to choose therapy in the elderly?

- Cytogenetic risk
  - Standard vs high risk
- Renal function
- Subsequent lines??
- Level of fitness, IMWG gold standard
  - Fit, unfit or frail

ASCT, autologous stem-cell trnsplantation.

How to choose therapy in the elderly?



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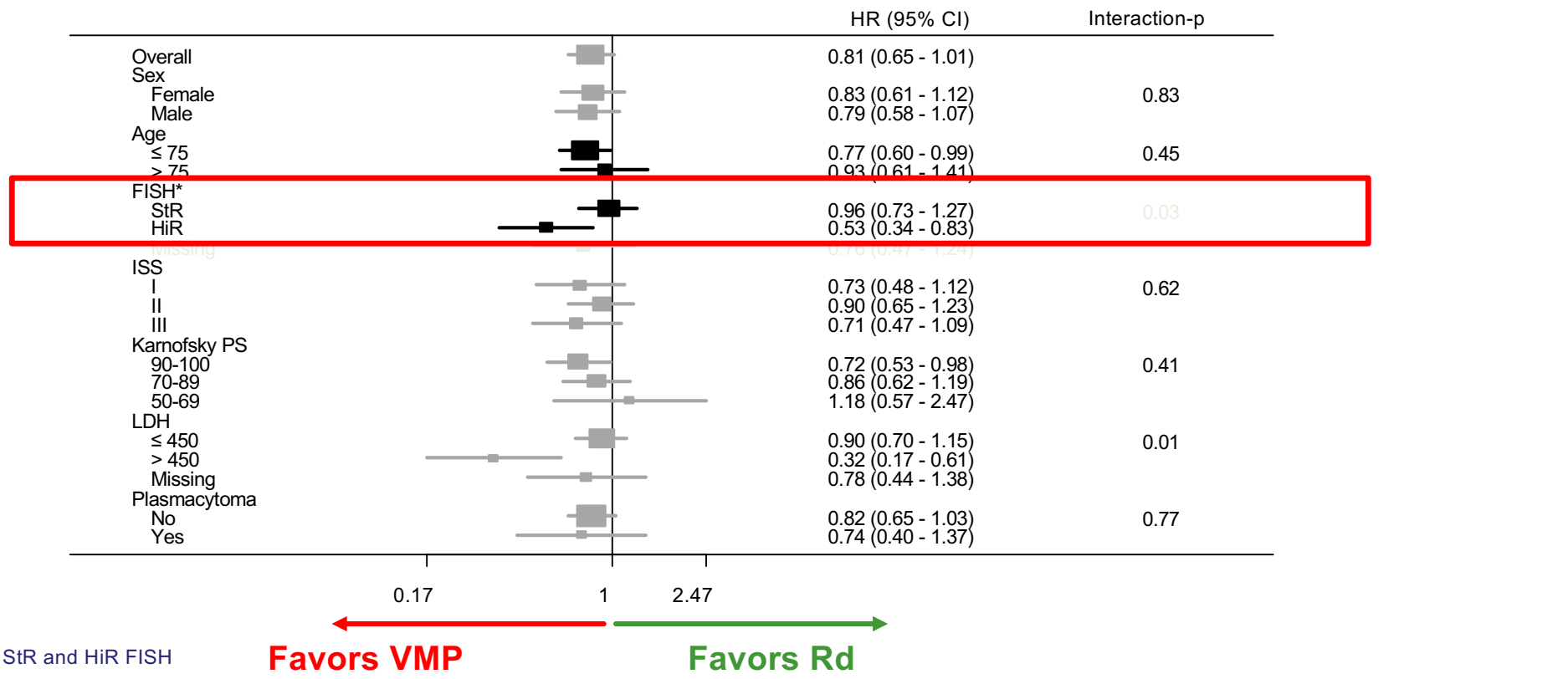
VMP vs Rd:
PFS Subgroup Analysis

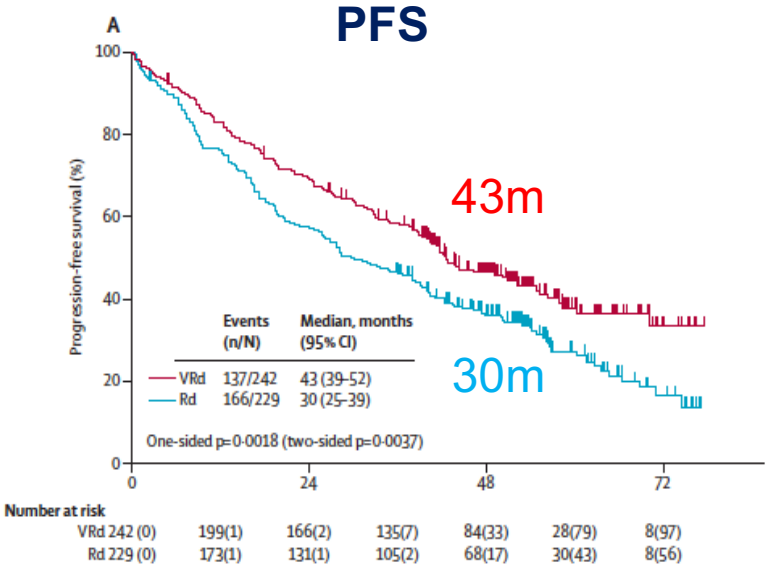


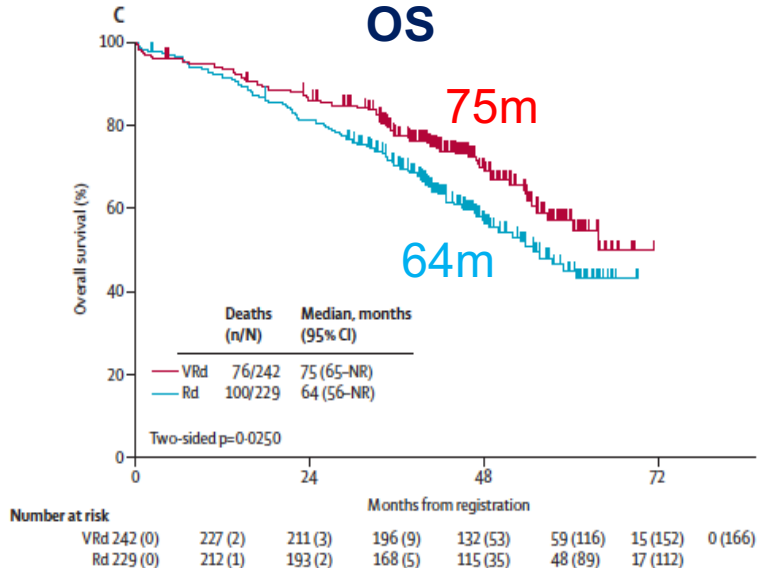
*Interaction-p between StR and HiR FISH

PFS, progression-free survival; VMP, bortezomib-melphalan-prednisone; Rd, lenalidomide-dexamethasone

VRd-Rd vs CONTINUOUS Rd: SWOG TRIAL

- Evaluable high risk cytogenetic patients n=44 (cut-off values 5%).
- Median PFS was 16 vs 38 months with Rd vs VRd in 44 HR patients, and 15 vs 34 months in17 patients with t(4;14) by FISH, respectively.
- These differences were not significant (p=0.19 and 0.96, respectively).





Bortezomib twice a week IV x 8 cycles

Perspectives

blood

Treatment of multiple myeloma with high-risk cytogenetics: a consensus of the International Myeloma Working Group

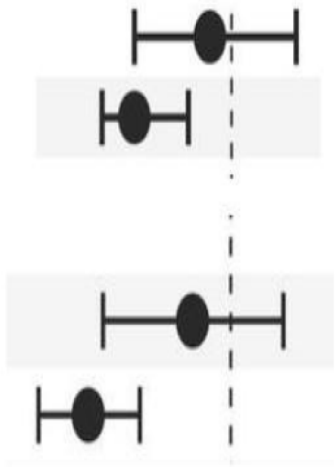
Consensus statement on transplant-ineligible patients

- Data in non TE patients are scarce.
- VMP may partly restore PFS in HR cytogenetics
- There are no data suggesting that lenalidomide may improve outcome with HR cytogenetics
- **The IMWG group advises treating NDMM patients with HR cytogenetics with the combination of a proteasome inhibitor with lenalidomide and dexamethasone.**

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

MONOCLONAL ANTIBODIES

		# of Progression Events or Deaths / total #		HR for PFS
		DARA	CONTROL	
MAIA	High Risk	18/48	17/44	0.85 (0.44 – 1.65)
	Standard Risk	67/271	111/279	0.49 (0.36 – 0.67)
ALCYONE	High Risk	24/53	19/45	0.78 (0.43 – 1.43)
	Standard Risk	54/261	108/257	0.39 (0.28 – 0.55)



- Antibody treatment improves outcome among patients of high-risk (and standard-risk) cytogenetic status
- The poor prognosis of HR status is only partly abrogated

Facon T et al. NEJM 2019, 380: 2104-15; Mateos MV et al., NEJM 2018, 378:518-28

How to choose therapy in the elderly?

- Cytogenetic risk
  - Standard vs high risk
- **Renal function**
- Subsequent lines??
- Level of fitness, IMWG gold standard
  - Fit, unfit or frail

ASCT, autologous stem-cell trnsplantation.

The Oncologist

European Perspective on Multiple Myeloma Treatment Strategies: Update Following Recent Congresses

HEINZ LUDWIG,[a] HERVÉ AVET-LOISEAU,[b] JOAN BLADÉ,[c] MARIO BOCCADORO,[d] JAMIE CAVENAGH,[e] MICHELE CAVO,[f] FAITH DAVIES,[g] JAVIER DE LA RUBIA,[h] SOSANA DELIMPASI,[i] MELETIOS DIMOPOULOS,[j] JOHANNES DRACH,[k] HERMANN EINSELE,[l] THIERRY FACON,[m] HARTMUT GOLDSCHMIDT,[n] URS HESS,[o] ULF-HENRIK MELLQVIST,[p] PHILIPPE MOREAU,[q] JESÚS SAN-MIGUEL,[r] PIA SONDERGELD,[s] PIETER SONNEVELD,[t] MIKLOS UDVARDY,[u] ANTONIO PALUMBO[d]

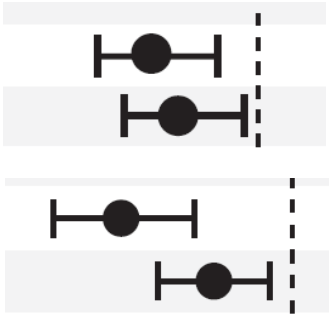
Renal Impairment

Bortezomib-based treatments are effective in patients with renal impairment, and the combination of bortezomib and high-dose dexamethasone may be considered as the treatment of choice, as recently recommended by the IMWG [84]. Reversal of renal insufficiency is observed in a substantial proportion of patients with bortezomib-based treatment. There is limited experience on the use of thalidomide in this setting. Nevertheless, careful administration appears feasible [84]. Lenalidomide-based treatment has been shown to be effective [85]; however, dose modification based on renal function is mandatory because of the renal clearance of the agent [84, 85].

Ludwig H *et* al The Oncologist 2012;17:592–606

MONOCLONAL ANTIBODIES

	creatinine clearance	Progressions or deaths/total DARA	CONTROL	HR for PFS
MAIA	> 60 mL/min	48/206	84/227	0.52 (0.36–0.74)
	≤ 60 mL/min	49/162	59/142	0.60 (0.41–0.87)
ALCYONE	> 60 mL/min	32/150	63/145	0.36 (0.24–0.56)
	≤ 60 mL/min	56/200	80/211	0.63 (0.45–0.88)



Inclusion criteria for creatinine clearance:
≥ 30 mL/min in the MAIA study
≥ 40 mL/min in the ALCYONE study

Facon T et al. NEJM 2019, 380: 2104-15; Mateos MV et al., NEJM 2018, 378:518-28

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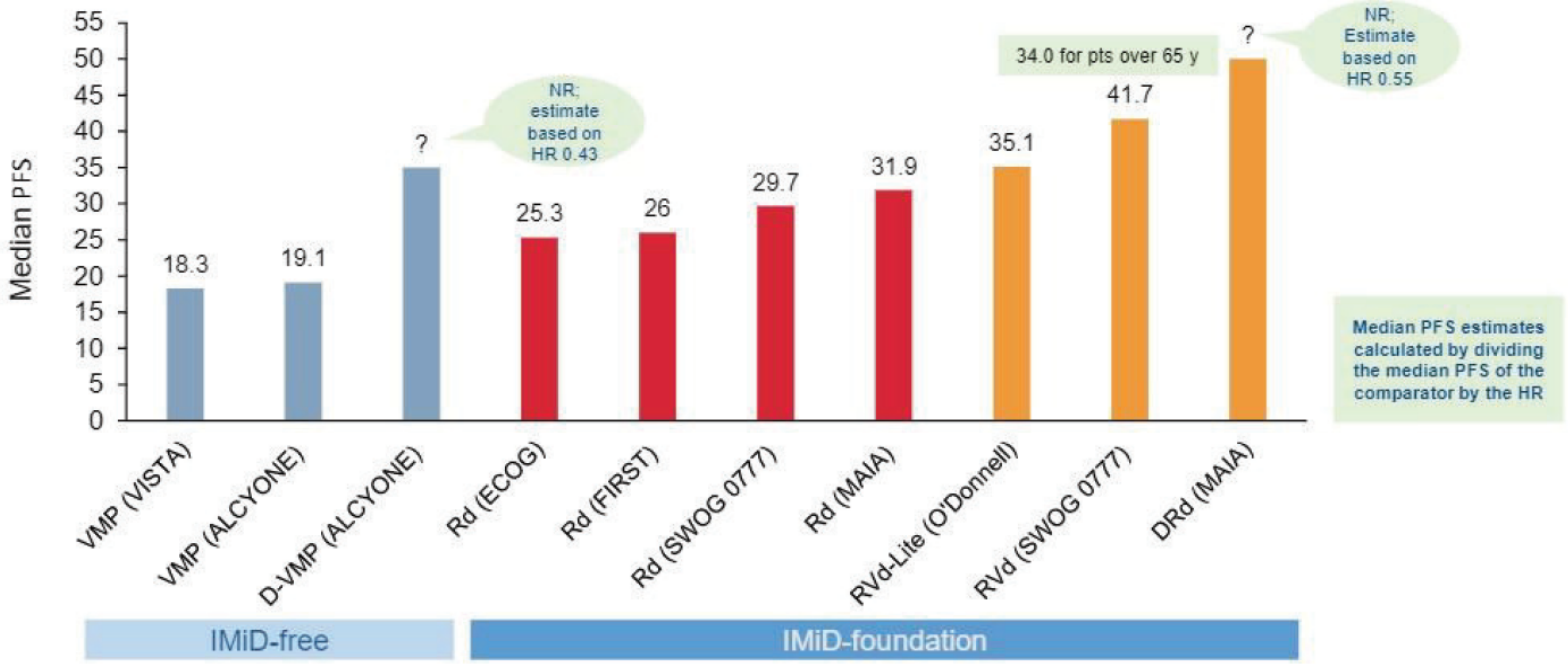
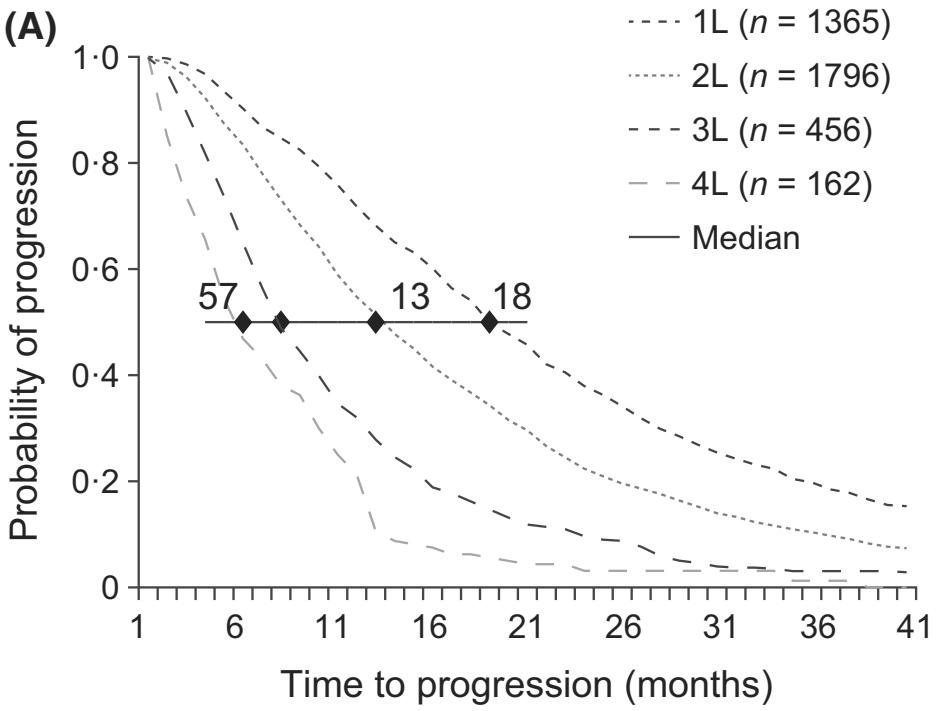
Overview of mPFS in recent phase 3 trials in NTE NDMM



Direct comparison between trials is not intended and should not be inferred.

1. Velcade [SmPC]. Beerse, Belgium. Janssen-Cilag International; 2014.
2. Dimopoulos M, et al. Blood. 2018;132:156. Presented at ASH 2018. 3. Rajkumar SV, et al. Lancet Oncol. 2010;11:29-37.
4. Facon T, et al. Blood. 2018;131:301-10. 5. REVLIMID [SmPC]. Utrecht, Netherlands. Celgene Europe BV; 2019.
6. Facon T, et al. Blood. 2018;132:LBA-2. Presented at ASH 2018. 7. O'Donnell EK, et al. Br J Haematol. 2018;182:222-30.

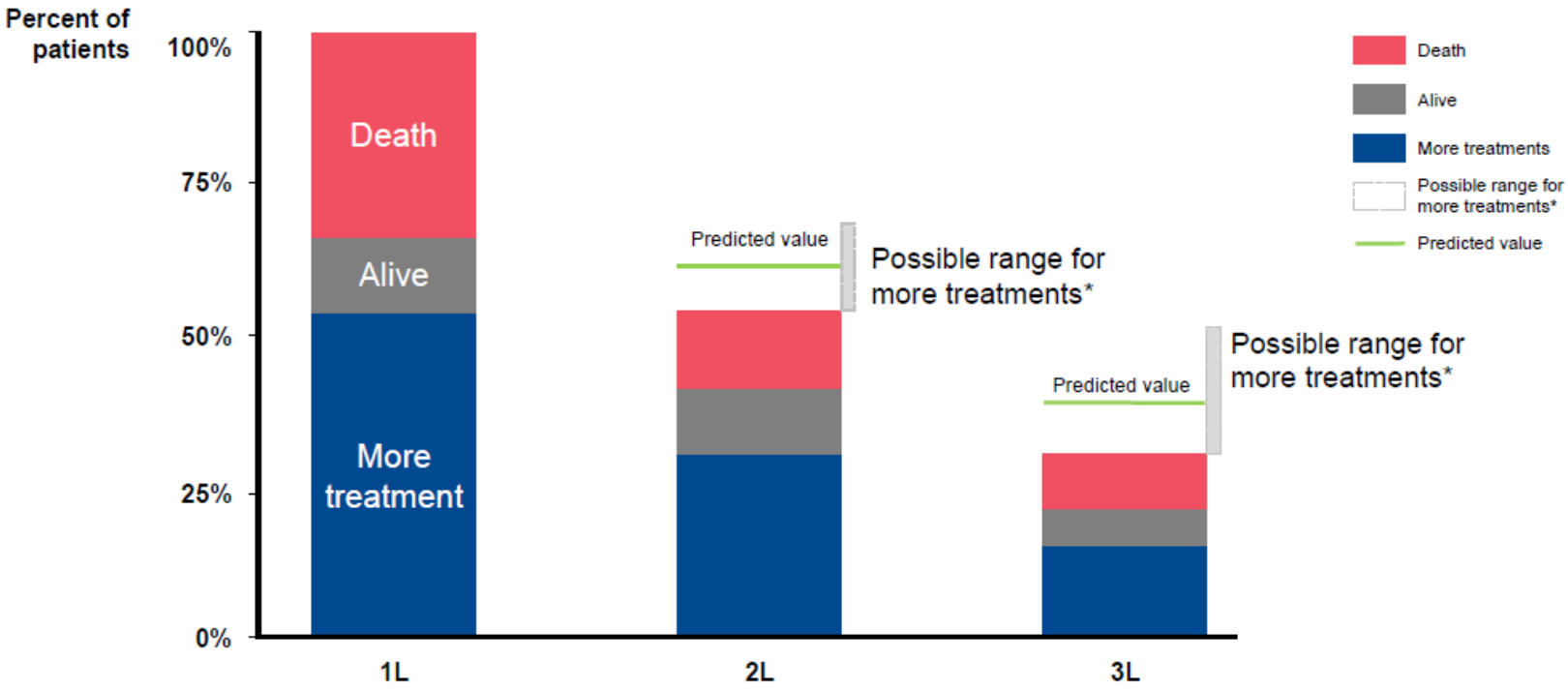
TIME TO PROGRESSION BY LINE OF THERAPY



- **The first remission is the longest one**
- **Duration of remission decreases after each line of therapy**

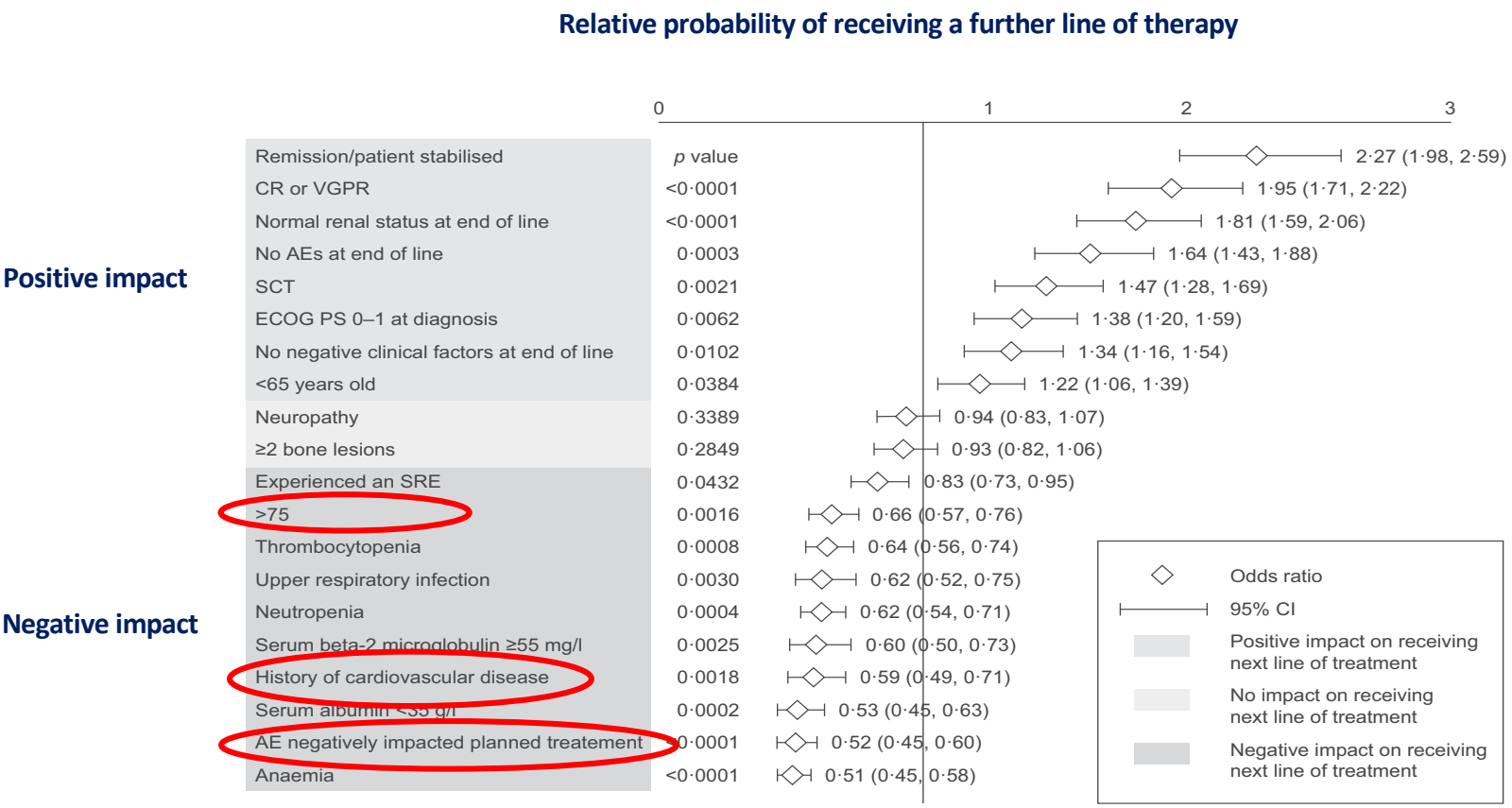
FIRST-LINE TREATMENT IS CRUCIAL – NON-HDT POPULATION

A large number of elderly patients receive only one line of treatment



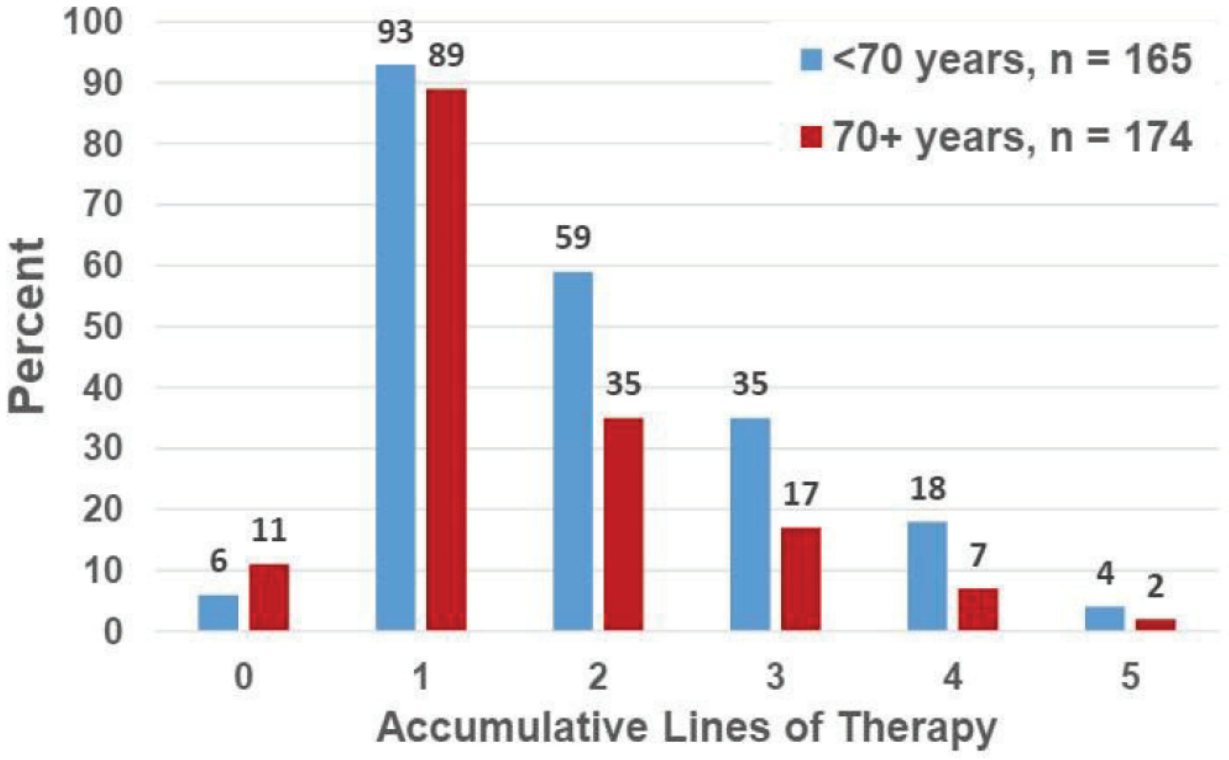
*Possible range for more treatments assumes that all censored patients would live to receive more treatment or die and receive no more treatment. Assumed constant mortality rate in each treatment line.
1L, first line.
Liwing J, *et al. Br J Haematol* 2014;164:684–93.

FIRST-LINE TREATMENT IS CRUCIAL – NON-HDT POPULATION



Yong K, BJM 2016

Accumulative lines of therapy received by age



Courtesy of A Spencer

How to choose therapy in the elderly?

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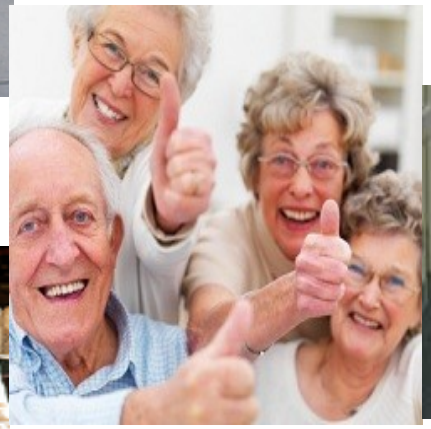
ASCT, autologous stem-cell trnsplantation.

ELDERLY MM PATIENTS ARE AN HETEROGENEOUS GROUP

Moderately fit:
Not regularly active but Routinely walking



Very fit:
active, who exercise regularly

Severely frail:
Dependent on other people

Mildly frail:
Help for household tasks

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

Moderately frail:
Partial help for their personal care

Palumbo A. Blood 2011; 118:4519-29

IMWG FRAILTY SCORE

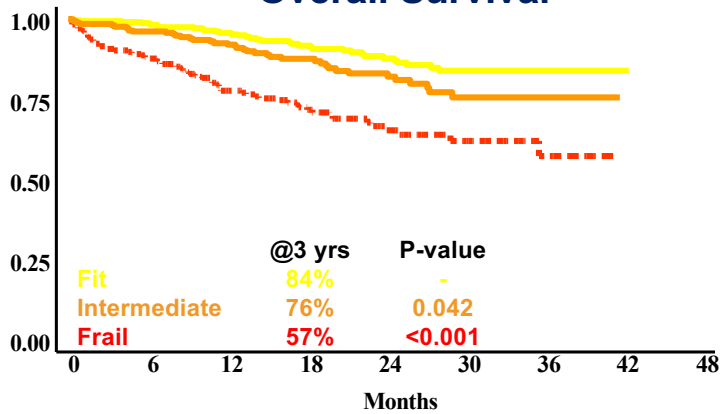
Variable		HR (CI 95%)	P	SCORE
AGE	Age <75 years	1	-	0
	Age 75-80 years	1.13 (0.76-1.69)	0.549	1
	Age >80 years	2.40 (1.56-3.71)	<0.001	2
CHARLSON INDEX	Charlson ≤1	1	-	0
	Charlson ≥2	1.37 (0.92-2.05)	0.125	1
ADL SCORE	ADL >4	1	-	0
	ADL≤4	1.67 (1.08-2.56)	0.02	1
IADL SCORE	IADL >5	1	-	0
	IADL≤5	1.43 (0.96-2.14)	0.078	1

ADDITIVE TOTAL SCORE	PATIENT STATUS
0	FIT
1	INTERMEDIATE
≥2	FRAIL

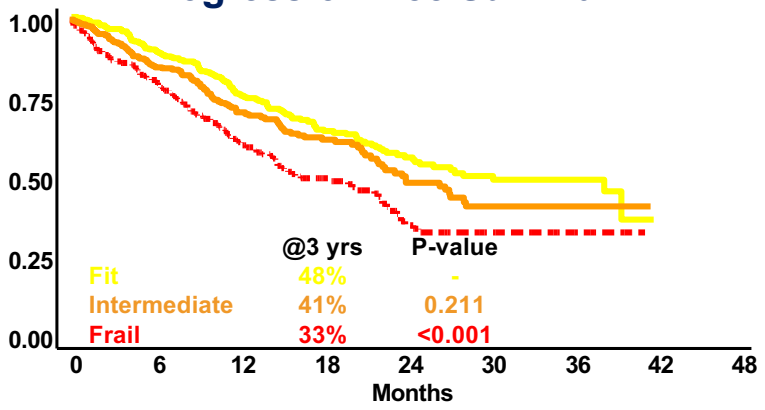
Palumbo A et al, Blood 25(13):2068-74, 2015

IMWG FRAILTY SCORE: LONG-TERM OUTCOME

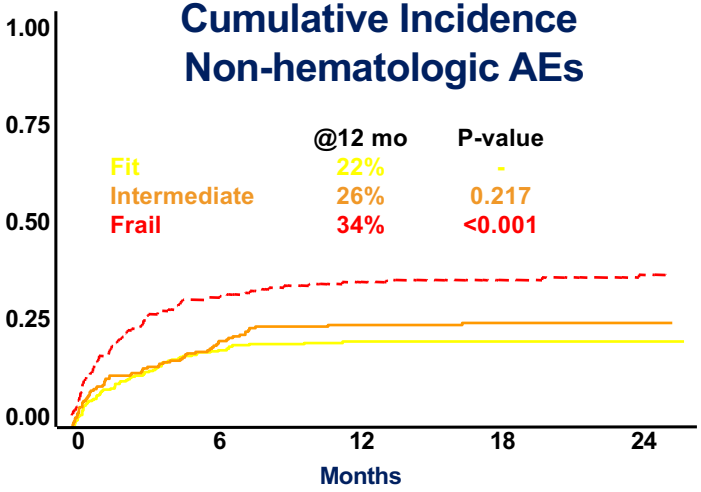
Overall Survival



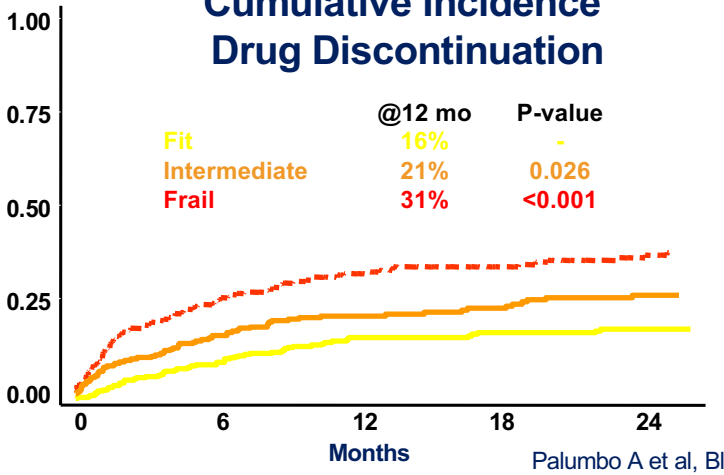
Progression-free Survival



Cumulative Incidence Non-hematologic AEs



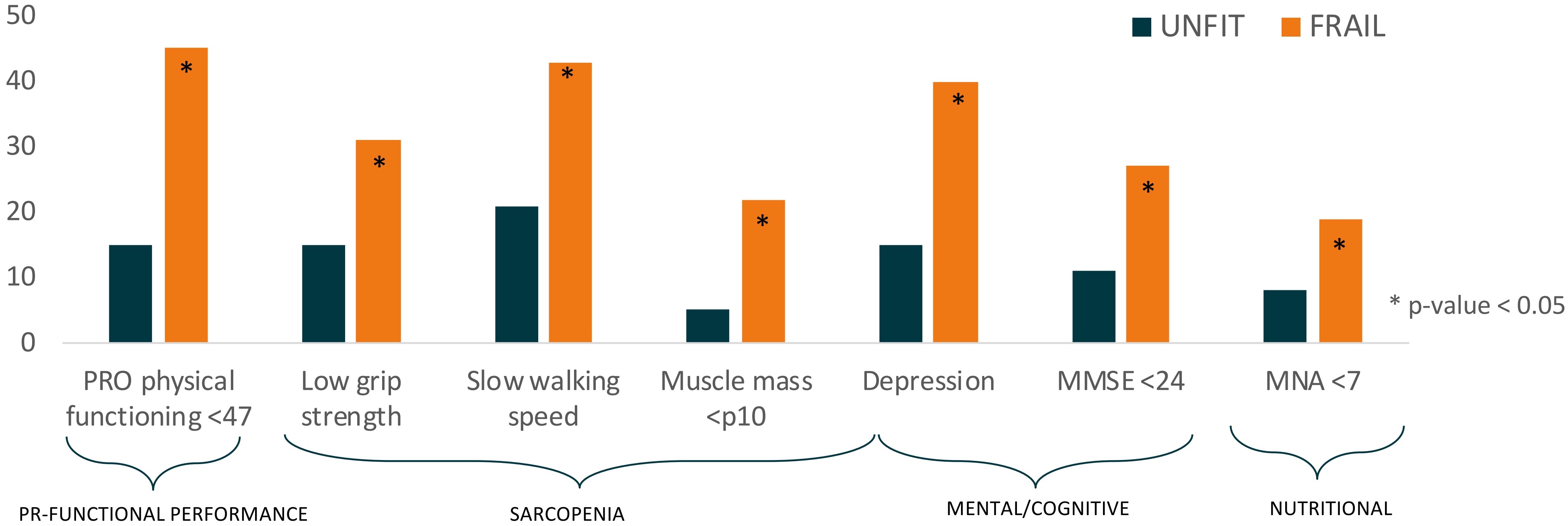
Cumulative Incidence Drug Discontinuation



Palumbo A et al, Blood 25(13):2068-74, 2015

IMWG frailty index reflects biological frailty

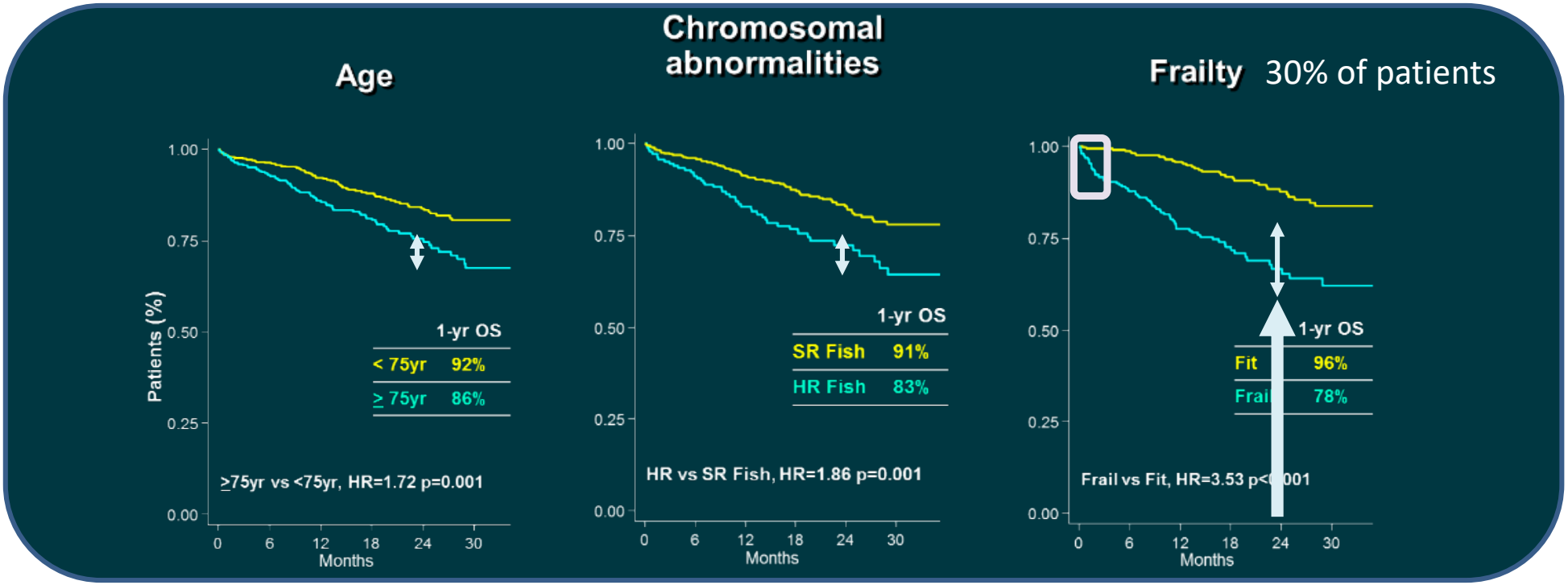
The incidence of functional, cognitive, mental and nutritional impairments is higher in frail compared to unfit



Stege C et al, Blood, 2018, abstract

IMWG Frailty score – the gold standard in MM

But insufficient discriminative power to define who does not benefit
not possible to define those patients who die early



Conclusions

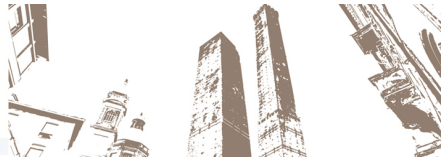
Use of ImiDs, PIs, CD38 in NDMM TNE Patients …accross various regimens and fitness levels

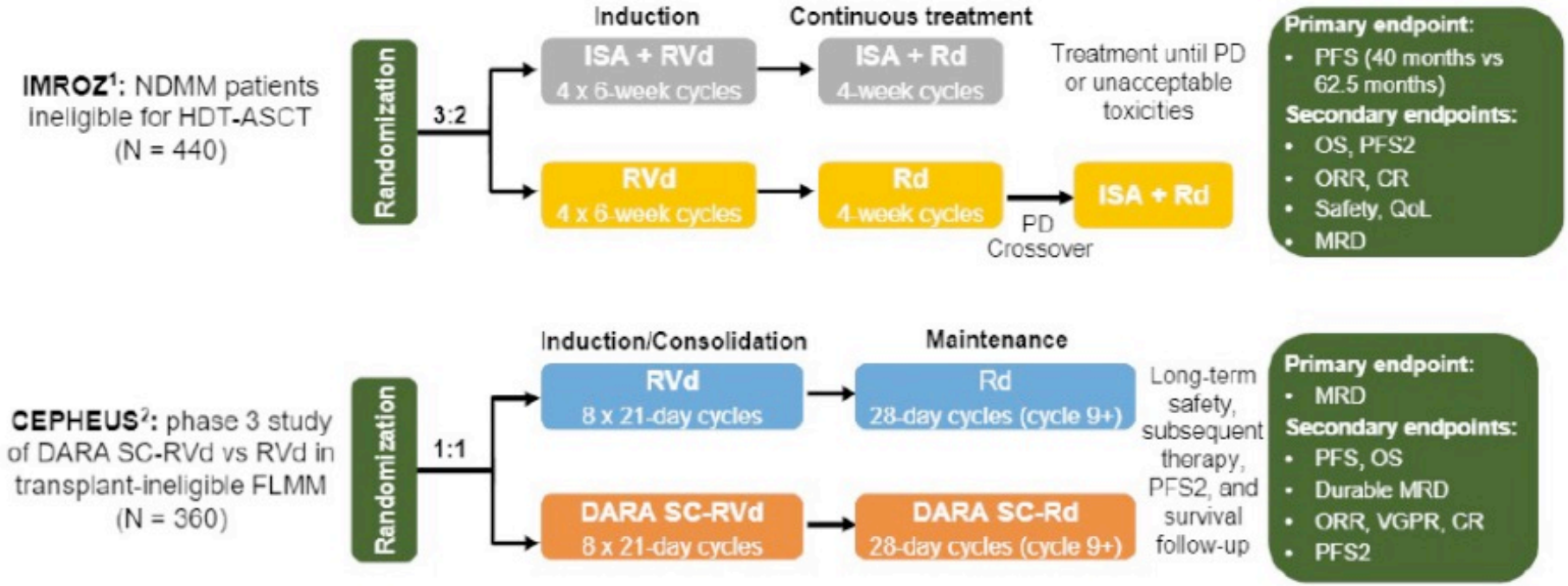
Frail — no ASCT……more ASCT — **Fit**

R-DARA (No/few Dex) → DRd → (VRD/VRD lite) → D-VRD lite → D-VRD/KRD

Continuous Len…before continuous Len and CD38
SC Dara for all patients, other CD38 ?
Iberdomide to replace Lenalidomide ?

IMROZ and CEPHEUS trials: study designs





No cross-trial comparison is intended with this data.
HDT-ASCT, high-dose therapy and autologous stem cell transplantation; ISA, isatuximab; QoL, quality of life.

1. Available from: https://clinicaltrials.gov/ct2/show/NCT03319667. Accessed June 2019.
2. Available from: https://clinicaltrials.gov/ct2/show/NCT03652064. Accessed June 2019.

Treatment of unfit/frail elderly patients

- Despite limitations, the IMWG frailty index is currently the gold standard to detect frail MM patients
- Less duration of induction, less dosed and less dense therapy, but try to maintain in order to reach a long duration of response
- 'Non-frail' drugs such as mAbs

IMWG, International Myeloma Workshop; MM, multiple myeloma; mAbs, monoclonal antibodies.

Concept of 'non-toxic for frail' drugs

HOVON 143 study
Concept of 'non-toxic for frail' drugs

Induction

9 cycles, q 4 weeks

Ixazomib citrate 4 mg
days 1, 8, 15

Dexamethasone 20 mg
days 1, 8, 15, 22, cycle 1
Dexamethasone 10 mg
days 1, 8, 15, 22, cycles 2-9

Daratumumab 16 mg/kg
days 1, 8, 15, 22, cycles 1-2
days 1, 15, cycles 3-6
day 1, cycles 7-9

Maintenance

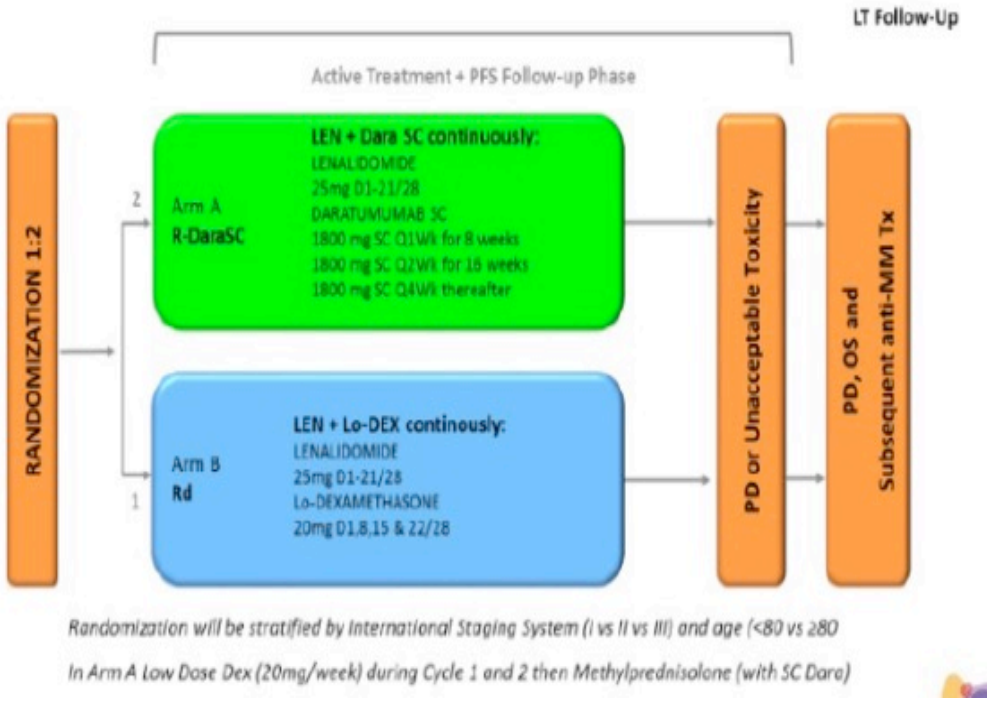
Maximum 2 years until PD
q8 weeks

Ixazomib citrate 4 mg
days 1, 8, 15, 29, 36, 43

Daratumumab 16 mg/kg
day 1

Ix, ixazomib; R, lenalidomide; d, dexamethasone.

IFM 2017-03 study
A dexamethasone-sparing study

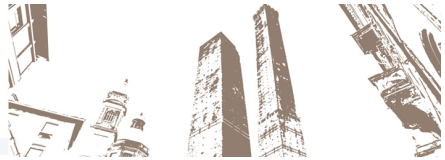


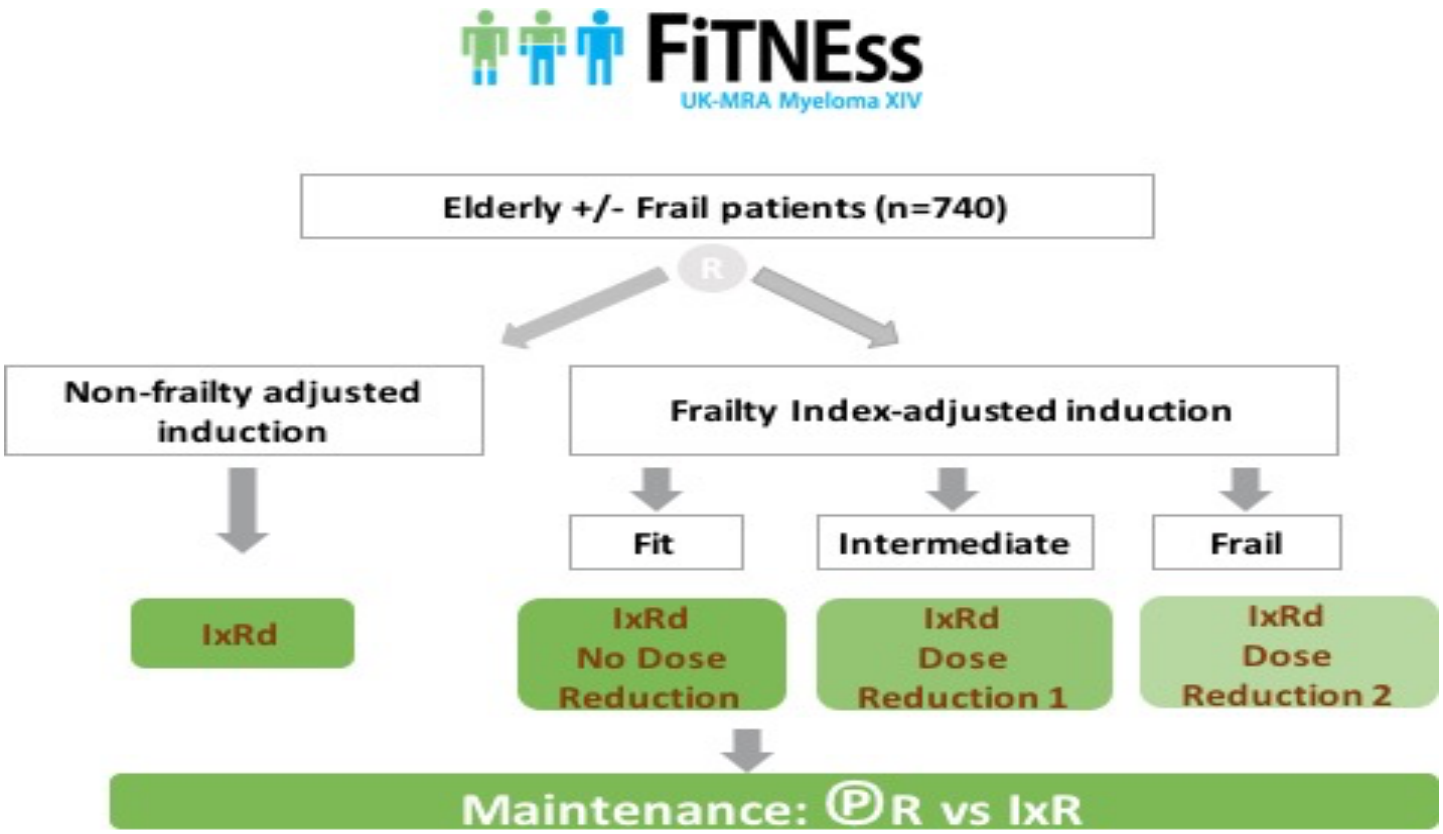
Randomization will be stratified by International Staging System (I vs II vs III) and age (<80 vs ≥80

In Arm A Low Dose Dex (20mg/week) during Cycle 1 and 2 then Methylprednisolone (with SC Dara)

IFM 2017-03 Study - ST 2016-002600-90
Fitness trial - NCT03720041

UK-MRA FitNEss trial: Concept of frailty-adjusted dosing





Ix, ixazomib; R, lenalidomide; d, dexamethasone.

Fitness trial - NCT03720041

We are grateful to all patients, nurses and physicians of the participating centers

1.	**ALESSANDRIA**	Ladetto, Baraldi
2.	**ANCONA**	Leoni, Offidani
3.	**ASCOLI PICENO**	Galieni
4.	**ASTI**	Saracco, Marchetti
5.	**AVELLINO**	Cantore, Volpe
6.	**AVIANO**	Micheli, Rupolo
7.	**BARI**	Silvestris, Ria
8.	**BARI**	Specchia
9.	**BENEVENTO**	Vallone
10.	**BERGAMO**	Rambaldi, Galli
11.	**BIELLA**	Bertinieri, Conconi
12.	**BOLOGNA**	Cavo, Zamagni
13.	**BOLZANO**	Billio, Pescosta
14.	**BRESCIA**	Rossi, Crippa
15.	**BRESCIA**	Russo, Malagola
16.	**BRINDISI**	Melpignano
17.	**CAGLIARI**	Derudas
18.	**CAGLIARI**	La Nasa, Ledda
19.	**CAMPOBASSO**	Storti
20.	**CANDIOLO**	Aglietta, Rota Scalabrini
21.	**CATANIA**	Di Raimondo
22.	**CATANZARO**	Molica, Piro
23.	**CESENA**	Ronconi, Augello
24.	**CIRIÉ/CHIVASSO/IVREA**	Freilone, Falco, Aitoro
25.	**CIVITANOVA**	Centurioni
26.	**COSENZA**	Morabito, Gentile
27.	**CREMONA**	Lanza
28.	**CUNEO**	Massaia, Grasso
29.	**FIRENZE**	Bosi, Nozzoli
30.	**FOGGIA**	Capalbo
31.	**GALLARATE**	Ciambelli
32.	**GENOVA**	Gobbi, Canepa
33.	**GENOVA**	Angelucci, Dominietto
34.	**LATINA**	Cimino
35.	**LECCE**	Di Renzo
36.	**LECCO**	Ardizzoia, Ferrando
37.	**MANTOVA**	Franchini, Zamagni
38.	**MELDOLA**	Ronconi
39.	**MESSINA**	Mannina
40.	**MESSINA**	Musolino, Allegra
41.	**MILANO**	Corradini, Montefusco
42.	**MILANO**	Cairoli, Cafro
43.	**MILANO**	Ciceri
44.	**MILANO**	Cortelezzi, Baldini
45.	**MODENA**	Luppi, Marasca, Narni
46.	**MODENA**	Sacchi
47.	**MONZA**	Passerini, Rossini
48.	**NAPOLI**	Pane,Catalano
49.	**NAPOLI**	Ferrara, Rocco
50.	**NOCERA INF.**	Califano
51.	**NOVARA**	Gaidano, De Paoli
52.	**NUORO**	Latte, Gabbas
53.	**ORBASSANO**	Guerrasio, Guglielmelli
54.	**PADOVA**	Semenzato, Zambello
55.	**PALERMO**	Fabbiano, Cangialosi
56.	**PALERMO**	Siragusa
57.	**PARMA**	Aversa, Giuliani
58.	**PAVIA**	Cazzola, Corso
59.	**PAVIA**	Pavesi, Fregoni
60.	**PERUGIA**	Falini, Ballanti
61.	**PESARO**	Visani
62.	**PESCARA**	Di Bartolomeo, Spadano
63.	**RAVENNA**	Lanza, Cellini
64.	**REGGIO CAL.**	Martino, Vincelli
65.	**REGGIO EM.**	Merli, Gamberi
66.	**RIMINI**	Tosi
67.	**RIONERO**	Musto
68.	**RIETI**	Ceribelli
69.	**ROMA**	Foà, Petrucci
70.	**ROMA**	De Fabritiis, Caravita
71.	**ROMA**	Andriani
72.	**ROMA**	Bagnato, Bongarzoni
73.	**ROMA**	De Stefano
74.	**ROMA**	Mangarelli, Pisani
75.	**ROMA**	Pierelli, De Rosa
76.	**ROMA**	Venditti
77.	**ROMA**	Avvisati, Annibali
78.	**ROMA**	Recine
79.	**ROMA**	Tafuri, La Verde
80.	**ROZZANO**	Santoro, Nozza
81.	**S. G. ROTONDO**	Cascavilla, Falcone
82.	**SASSARI**	Dore, Podda
83.	**SIENA**	Bocchia, Gozzetti
84.	**TERNI**	Liberati
85.	**TORINO**	Boccadoro,Bringhen,Gay,Larocca
86.	**TORINO**	Vitolo, Pregno, Benevolo
87.	**TORINO**	Saglio
88.	**TREVISO**	Gherlinzoni
89.	**TRICASE**	Pavone
90.	**TRIESTE**	Festini, De Sabbata
91.	**UDINE**	Fanin, Patriarca
92.	**VENEZIA**	Bassan
93.	**VERCELLI**	Ardizzone
94.	**VERONA**	Ambrosetti, Meneghini
95.	**VICENZA**	Rodeghiero, Elice

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