Highlights from IMW 2021

1-2 febbraio 2022
Bologna
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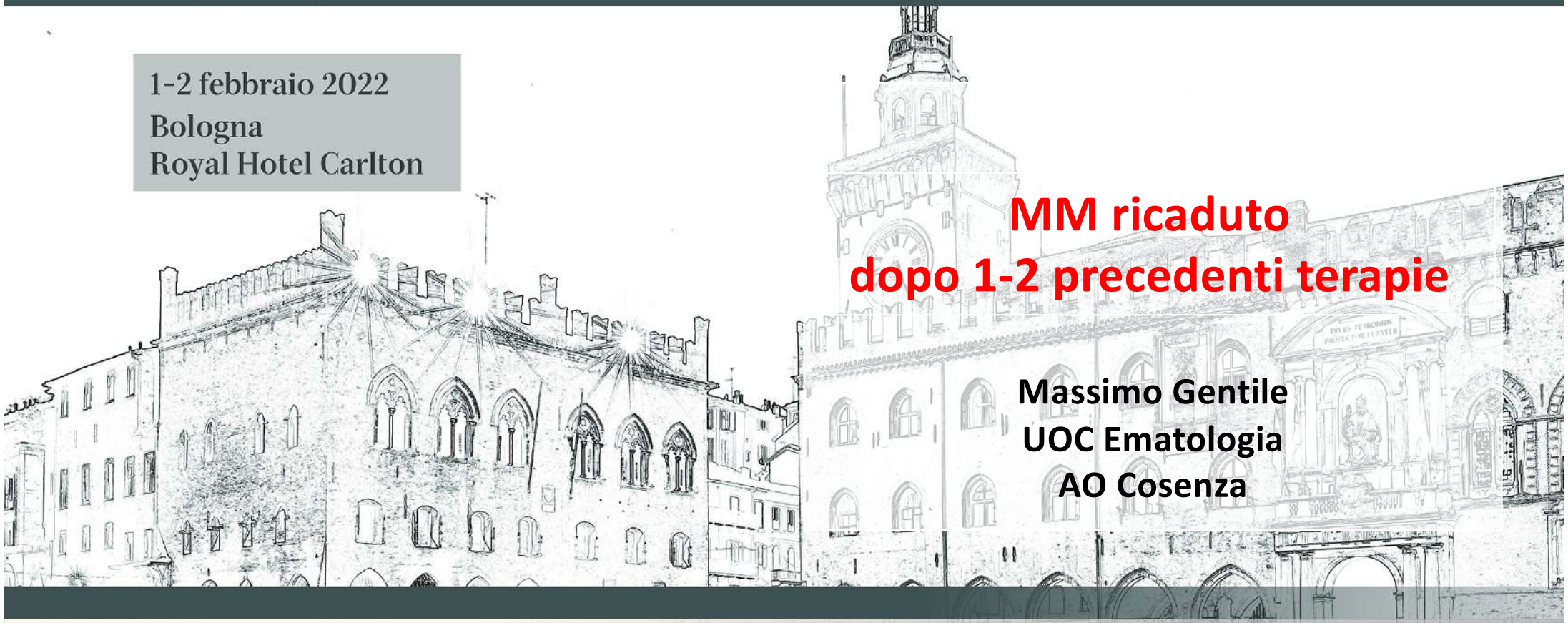


MM ricaduto
dopo 1-2 precedenti terapie

Massimo Gentile
UOC Ematologia
AO Cosenza

Coordinatore Scientifico
Michele CAVO

Comitato Scientifico
Michele CAVO
Maria Teresa PETRUCCI

Patient Journey Through Myeloma Therapy: Results of Chart Review[1–3]

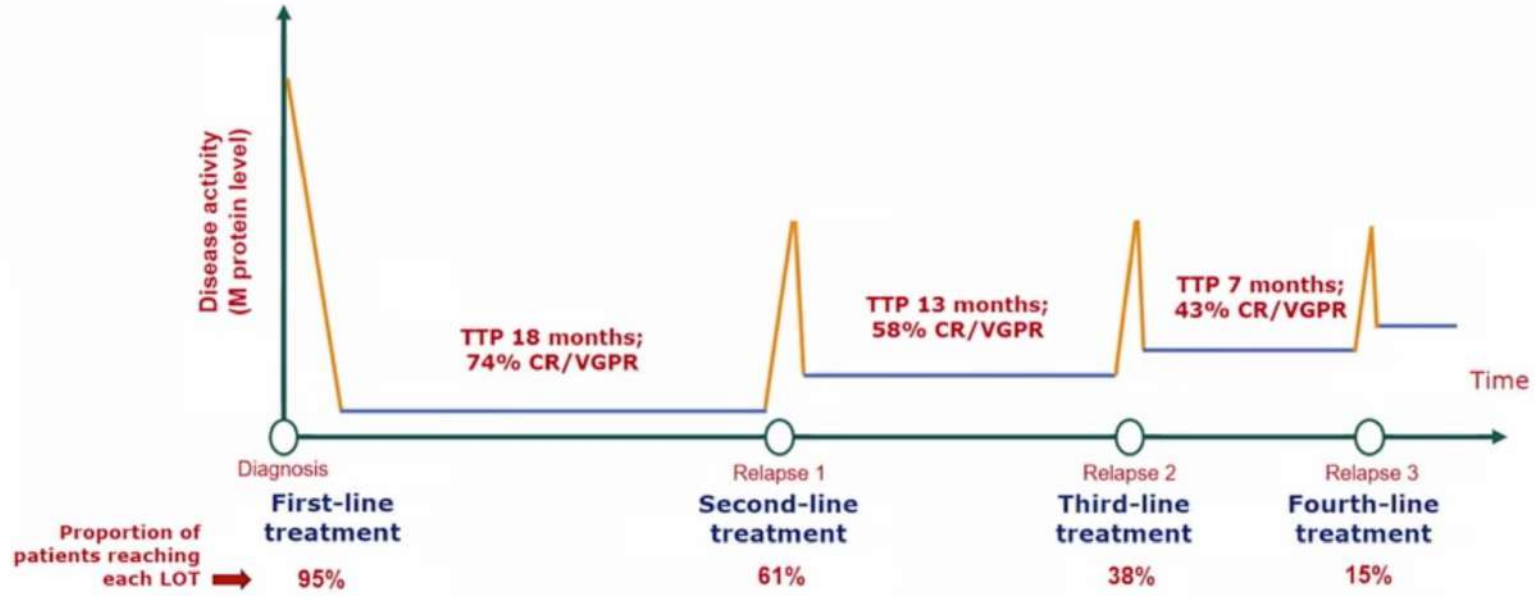
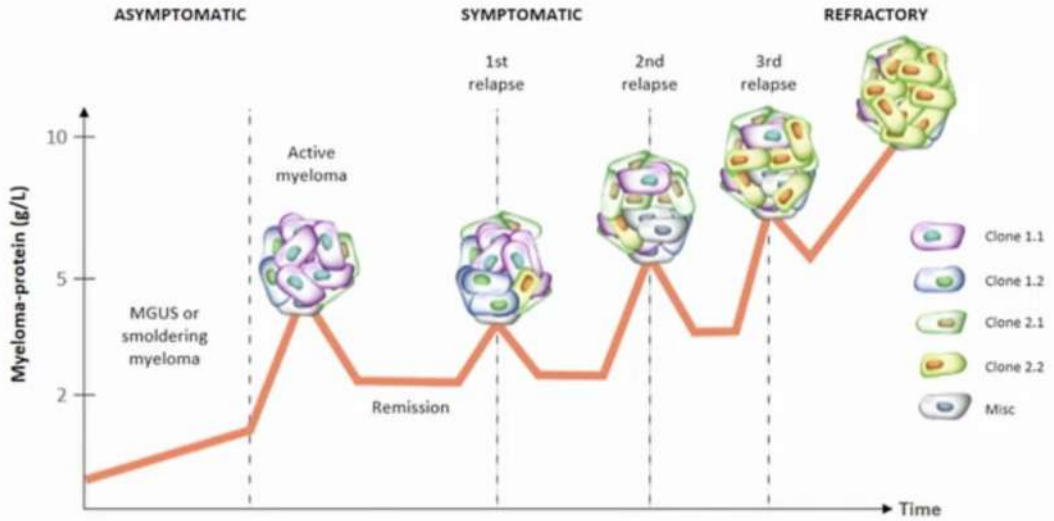


Figure adapted from Durie BGM.[1] Values for duration and response data from Yong K et al.[3]
CR/VGPR, complete response/very good partial response; LOT, line of therapy; TTP, time to progression.
1. Durie BGM. Concise review of the disease and treatment options. International Myeloma Foundation, 2018 (Accessed August 2021); 2. Moreau P, Touzeau C. *Am Soc Clin Oncol Educ Book* 2015:e504–e511; 3. Yong K et al. *Br J Haematol* 2016;175:252–264.

Evolution of Myeloma



Plasma cell genomic instability, antigen loss and microenvironment-related changes are competing events leading to refractoriness

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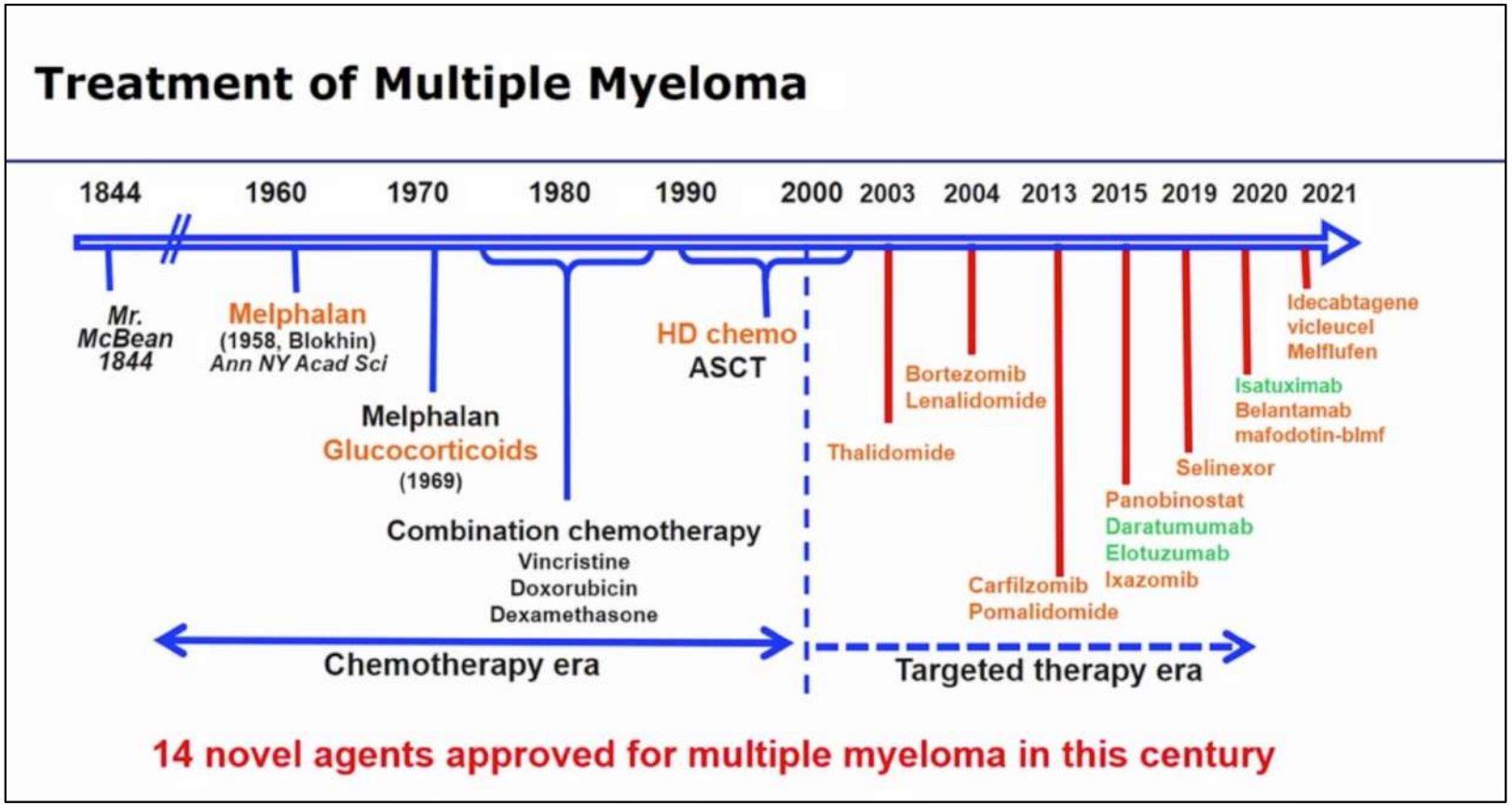
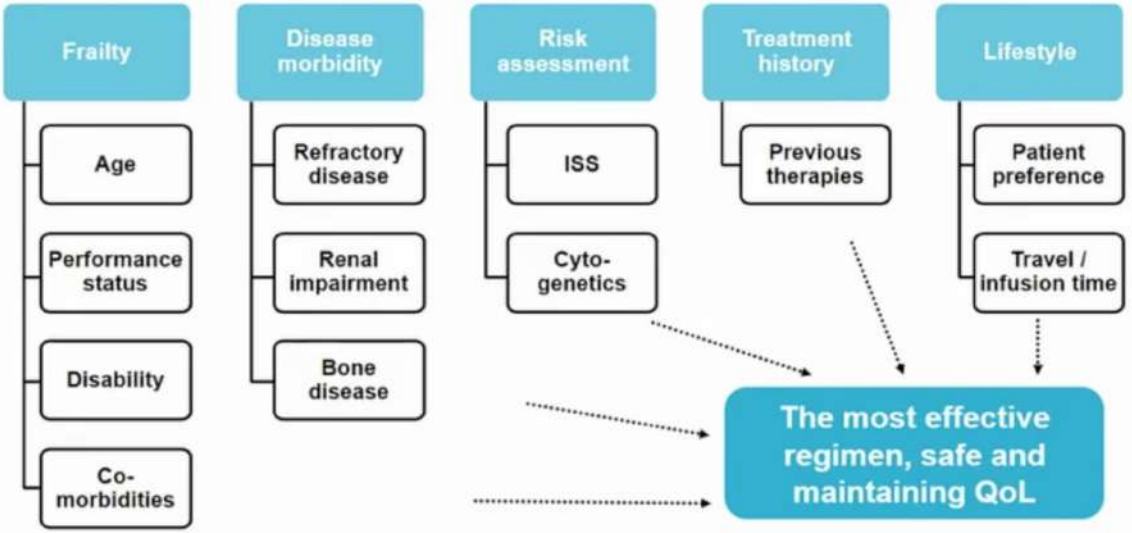
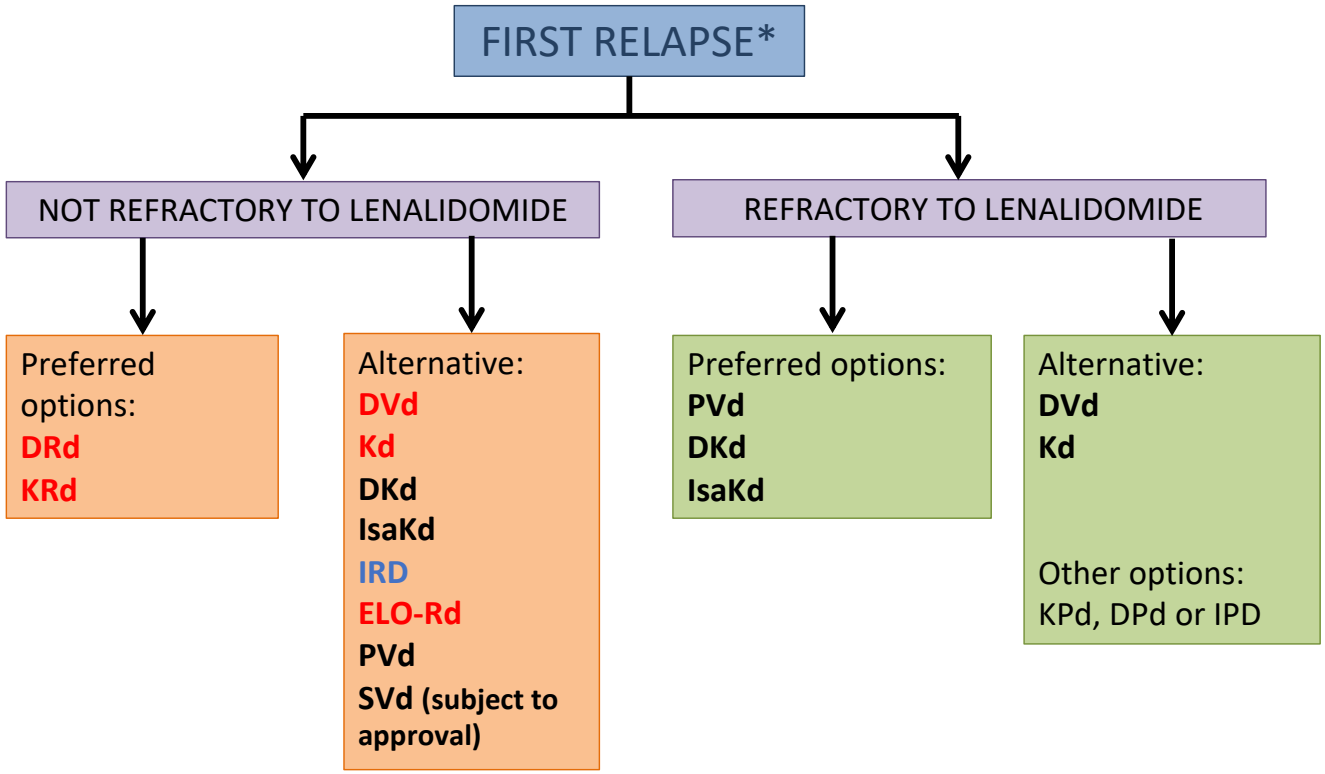


Disease and Patient-Based Factors Influencing the Treatment Decision-Making at the Relapse Setting



ISS, International Staging System; QoL, quality of life.

Clegg A et al. *Lancet* 2013;381:752–762; Handforth C et al. *Ann Oncol* 2015;26:1091–1101; Chen X et al. *Clin Interv Aging* 2014;9:433–441; Palumbo A et al. *Blood* 2015;125:2068–2074; Jhaveri D et al. *Haematologica* 2016;101:1–881 (Abstract E1312); Sonneveld P et al. *Leukemia* 2013;27:1959–1969; Faiman BM et al. *Clin J Oncol Nurs* 2011;15:66–76; Miceli TS et al. *Clin J Oncol Nurs* 2011;15:9–23; Greipp PR et al. *J Clin Oncol* 2005;23:3412–3420; Binder M et al. *Haematologica* 2016;101:P665; Merz M et al. *Haematologica* 2016;101:P650; Chng WJ et al. *Leukemia* 2016;30:1071–1078; Chung TH et al. *PLoS One* 2013;20:e66361; Sonneveld P et al. *Leukemia* 2013;27:1959–1969; Ramsenthaler C et al. *BMC Cancer* 2016;16:427; Williams LA et al. *J Clin Oncol* 2016;34:e18127; Ramasamy K et al. *Haematologica* 2017;102:E1457.



***Consider salvage auto-transplantation in eligible patients**

Moreau, Lancet Oncol, 2021

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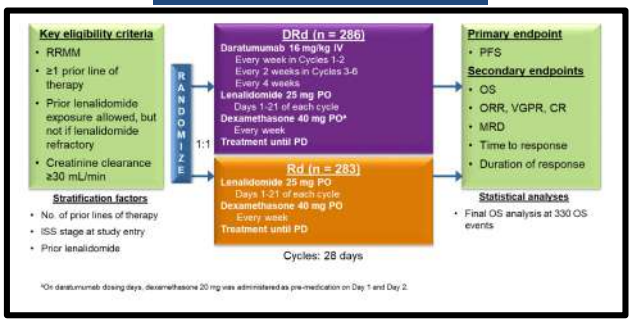
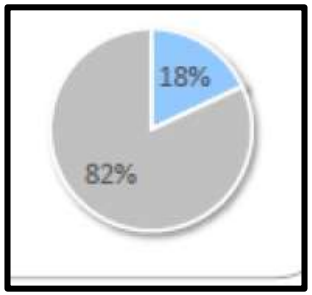
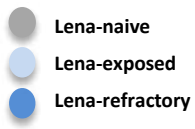
POLLUX

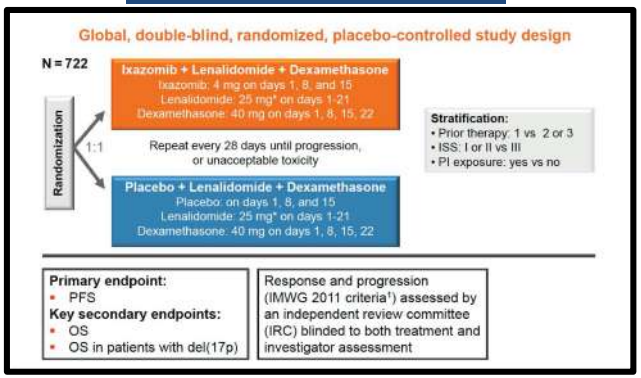


Exclusion per prior therapy: Lena resistant

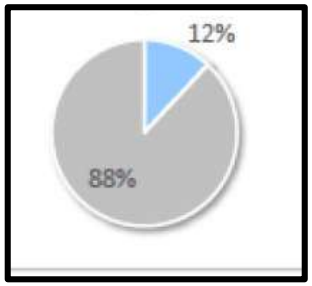


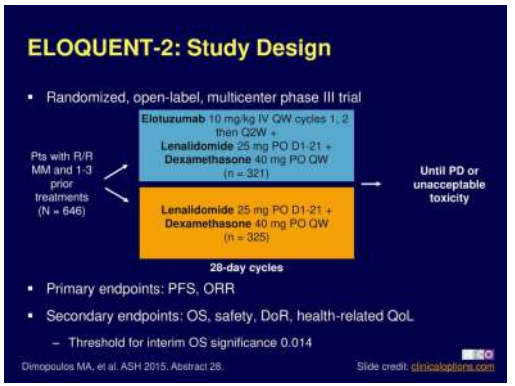


TOURMALINE-MM1

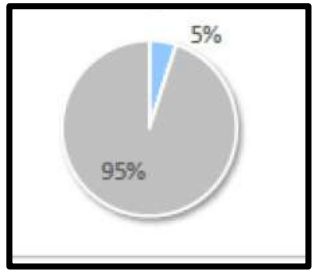


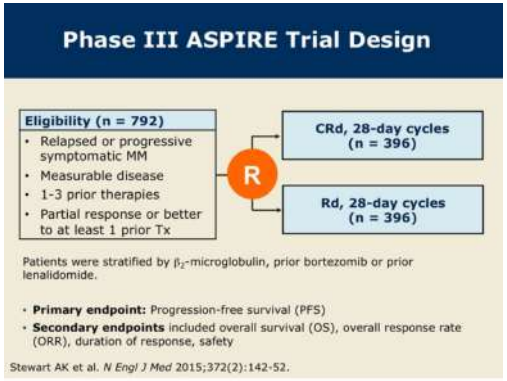
Exclusion per prior therapy: Lena resistant and Bz resistant



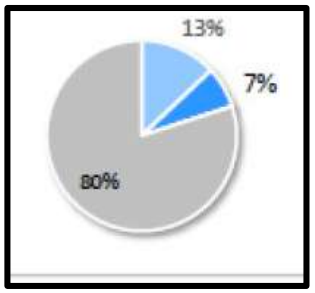


Exclusion per prior therapy: Lena resistant





Exclusion per prior therapy: Lena resistant and Bz resistant if at last line



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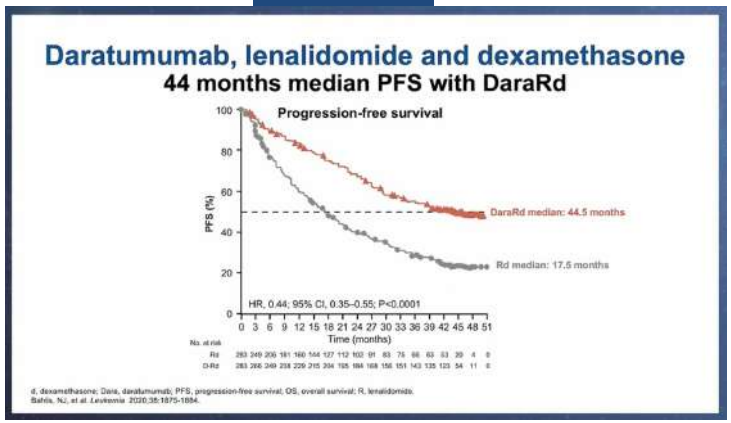
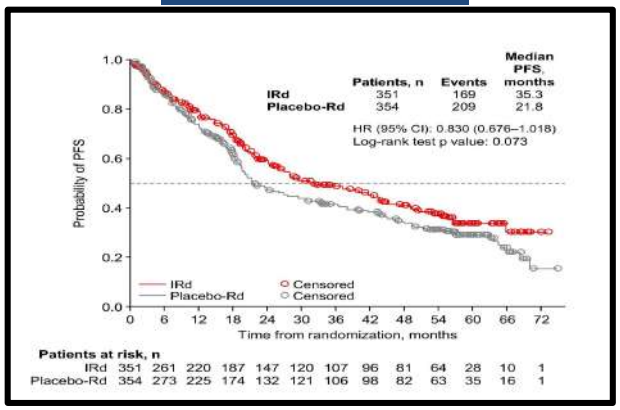
POLLUX



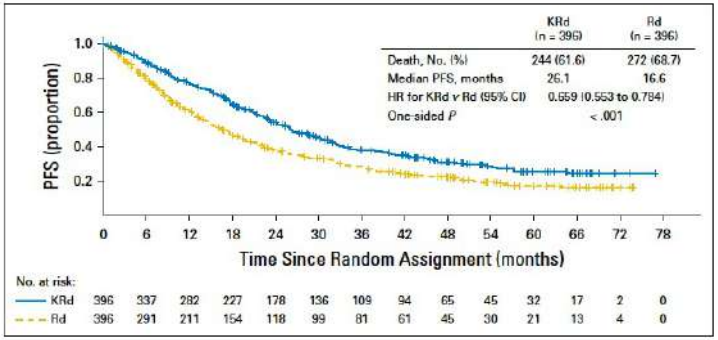
Bahlis, Leukemia 2020

TOURMALINE-MM1



Facon, ASH 2020

ASPIRE



Siegel, JCO 2018

ELOQUENT-2

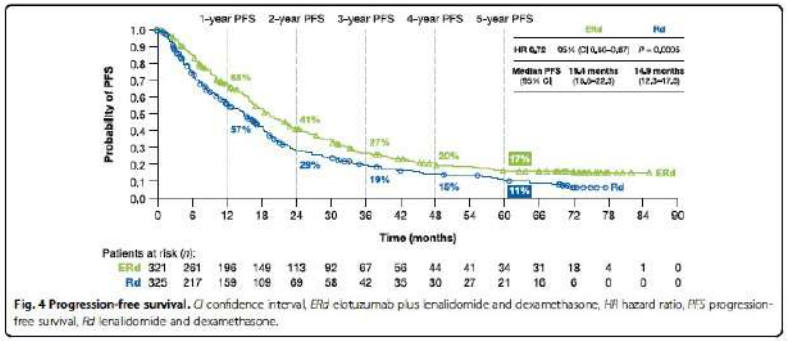


Fig. 4 Progression-free survival. *CI* confidence interval, *ERd* elotuzumab plus lenalidomide and dexamethasone, *HR* hazard ratio, *PFS* progression-free survival, *Rd* lenalidomide and dexamethasone.

Dimopoulos, Blood Cancer Journal 2020

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Treatment of RRMM: recommendations from the IMWG

	Intention-to-treat population			One previous line of therapy		
	n	Median PFS, months (95% CI)	HR (95% CI);* p value	n	Median PFS, months (95% CI)	HR (95% CI);* p value
ASPIRE[11]	..	..	0·69 (0·57–0·83); <0·0001	..	..	0·69 (0·52–0·94); 0·012
Rd group	396	17·6 (15·0–20·6)	..	157	17·6 (15·0–22·2)	..
KRd group	396	26·3 (23·3–30·0)	..	184	29·6 (23·2–33·5)	..
TOURMALINE[12]	..	..	0·74 (0·59–0·94); 0·012	..	..	0·83 (0·63–1·20); NA
Rd group	362	14·7, NA	..	217	NA	..
IRd group	360	20·6, NA	..	224	NA	..
POLLUX[14,39]	..	..	0·44 (0·35–0·54); <0·0001	..	..	0·42 (0·30–0·57); <0·0001
Rd group	283	17·5 (13·9–20·8)	..	146	19·6, NA	..
DRd group	286	44·5 (34·1–NE)	..	149	53·3, NA	..
ELOQUENT-2[13]	..	..	0·70 (0·57–0·85); 0·0004	..	..	0·75 (0·56–1·00); NA
Rd group	325	14·9 (12·1–17·2)	..	159	NA	..
Elo-Rd group	321	19·4 (16·6–22·2)	..	151	NA	..

Moreau, Lancet Oncology 2021

Carfilzomib, lenalidomide, and dexamethasone followed by salvage autologous stem cell transplant with or without maintenance for relapsed or refractory MM

44 pts receiving salvage HDCT/ASCT following re-induction with KRd

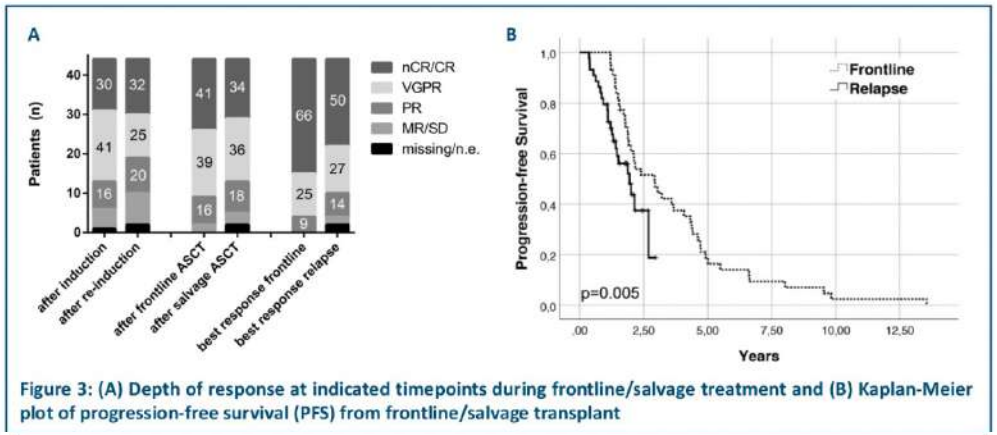


Figure 3: (A) Depth of response at indicated timepoints during frontline/salvage treatment and (B) Kaplan-Meier plot of progression-free survival (PFS) from frontline/salvage transplant

Conclusion: Salvage HDCT/ASCT after triplet re-induction is a safe and effective strategy for RRMM patients that may avoid refractoriness to multiple novel agents at the next relapse. Deep responses and maintenance treatment were associated with prolonged PFS in the range of what is achieved with current triplet regimens administered until progression. Our analysis supports continued use of salvage HDCT/ASCT in combination with triplet regimens and maintenance treatment in patients with sufficient benefit from frontline HDCT/ASCT.

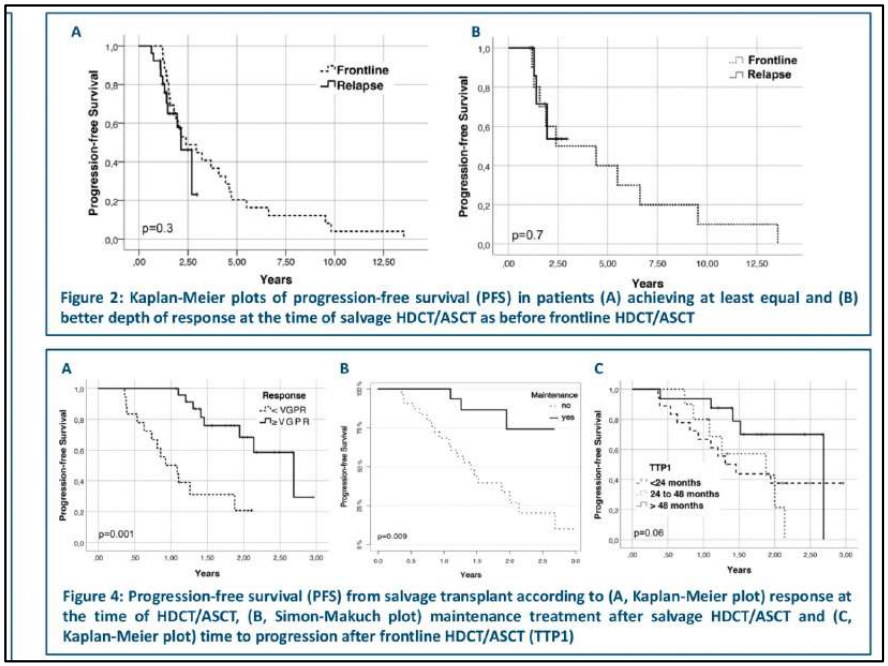
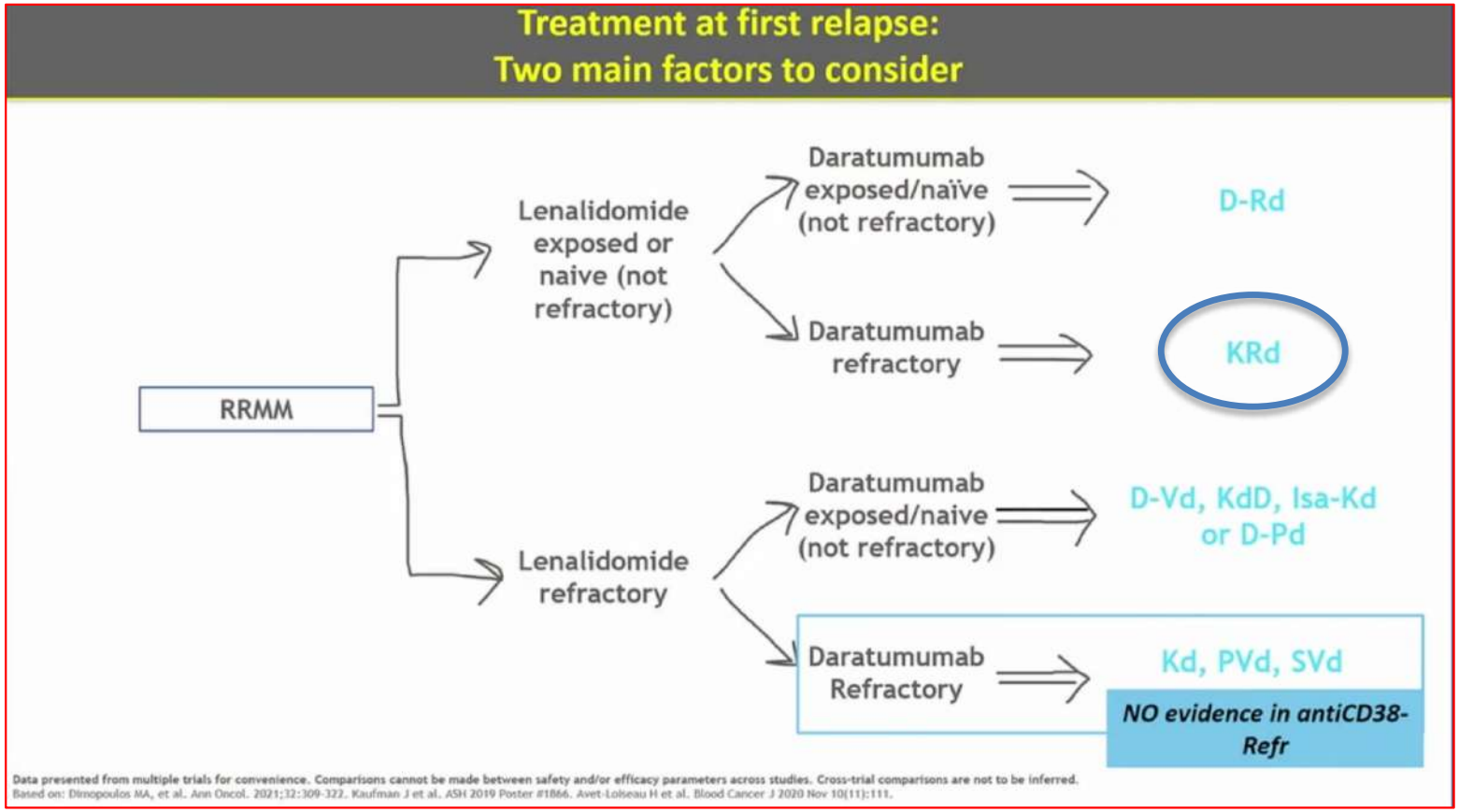


Figure 2: Kaplan-Meier plots of progression-free survival (PFS) in patients (A) achieving at least equal and (B) better depth of response at the time of salvage HDCT/ASCT as before frontline HDCT/ASCT

Figure 4: Progression-free survival (PFS) from salvage transplant according to (A, Kaplan-Meier plot) response at the time of HDCT/ASCT, (B, Simon-Makuch plot) maintenance treatment after salvage HDCT/ASCT and (C, Kaplan-Meier plot) time to progression after frontline HDCT/ASCT (TTP1)

Baertsch, IMW 2021



Rodriguez-Otero, IMW 2021

Use of carfilzomib regimens in patients with multiple myeloma refractory to CD38 antibodies: a subgroup analysis from a prospective observational study

Data for MM received at least one dose of K and anti-CD38 mAb in any prior line were retrieved from a RW study (NCT03091127)

Table 2. Treatment history among patients refractory to anti-CD38 mAbs.

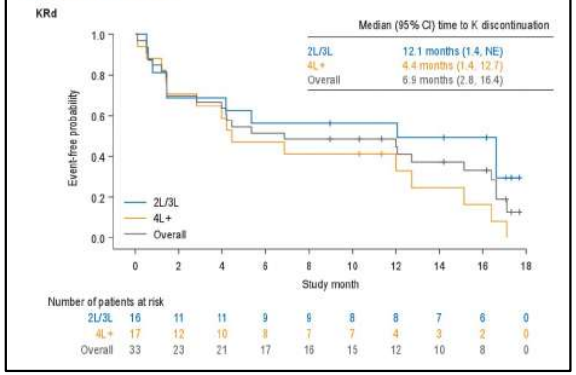
	KRd (n = 33)	Kd (n = 71)
No. of prior treatment lines		
1	9 (27.3)	1 (1.4)
2	7 (21.2)	8 (11.3)
3	4 (12.1)	17 (23.9)
≥ 4	13 (39.4)	45 (63.4)
Median (min, max)	**3 (1, 12)**	**4 (1, 9)**
Previous HSCT	**22 (66.7)**	**40 (56.3)**
Anti-CD38 mAb used		
Daratumumab	32 (97.0)	68 (95.8)
Isatuximab[a]	2 (6.1)	3 (4.2)
Prior anti-CD38 mAb treatment[a]		
Maintenance	**6 (18.2)**	**0 (0.0)**
Induction regimen with anti-CD38	4 (66.7)	0 (0.0)
No induction with anti-CD38	2 (33.3)	0 (0.0)
No maintenance	**28 (84.8)**	**71 (100.0)**
Monotherapy	11 (39.3)	37 (52.1)
Combination	21 (75.0)	37 (52.1)

Table 4. Response to KRd and Kd among anti-CD38 refractory patients in any prior line (overall) and by previous treatment line (2L/3L or 4L+).

Patients with a disease response assessment	KRd			Kd		
	2L/3L refractory (n = 12)	4L+ refractory (n = 15)	Overall refractory (n = 27)	2L/3L refractory (n = 9)	4L+ refractory (n = 53)	Overall refractory (n = 62)
ORR[a]	9 (75.0)	9 (60.0)	18 (66.7)	6 (66.7)	26 (49.1)	32 (51.6)
95% CI	42.8–94.5	32.3–83.7	46.0–83.5	29.9–92.5	35.1–63.2	38.6–64.5
Best overall response						
CR+	4 (33.3)	1 (6.7)	5 (18.5)	0 (0.0)	4 (7.5)	4 (6.5)
VGPR+	8 (66.7)	4 (26.7)	12 (44.4)	4 (44.4)	13 (24.5)	17 (27.4)
PR	1 (8.3)	5 (33.3)	6 (22.2)	2 (22.2)	13 (24.5)	15 (24.2)

All data are n (%), percentages are of patients who had any disease response assessment
[a]ORR is defined as the proportion of patients who had a best overall response of PR or better
2L, second line; 3L, third line; 4L+, fourth line or later; CI, confidence interval; CR+, complete response or better; Kd, carfilzomib in combination with dexamethasone; KRd, carfilzomib in combination with lenalidomide and dexamethasone; ORR, overall response rate; PR, partial response; VGPR+, very good partial response or better

Figure 1. Discontinuation of K in patients refractory to anti-CD38 who were treated with KRd and Kd, overall and by treatment line.



Conclusions

- In this real-world study, patients with MM refractory to an anti-CD38 mAb were heavily pretreated and mostly frail.
  - Patients were also commonly refractory to bortezomib, lenalidomide or pomalidomide.
- Good responses to KRd and Kd were reported in this potentially difficult-to-treat population, particularly in 2L/3L.
  - The estimated time to K discontinuation was 12.1 months in patients treated with KRd in 2L/3L.
- Safety results in this patient population are consistent with those already reported from this study.[5]
- Although in a small population, these results expand on initial reports indicating that K-based regimens are suitable treatment options for patients with anti-CD38 refractory MM, by providing evidence on the use of K from 2L.[3]

Terpos, IMW 2021

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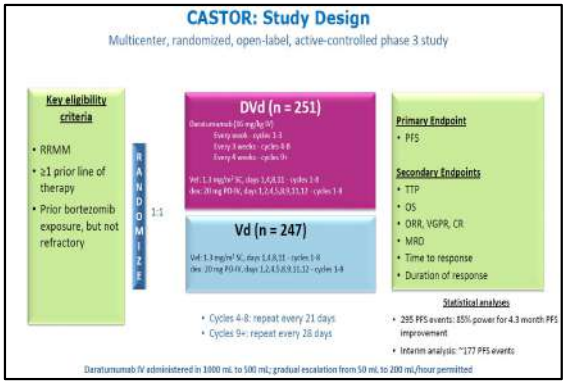
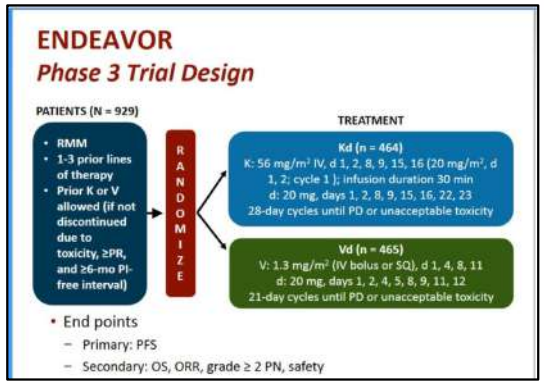
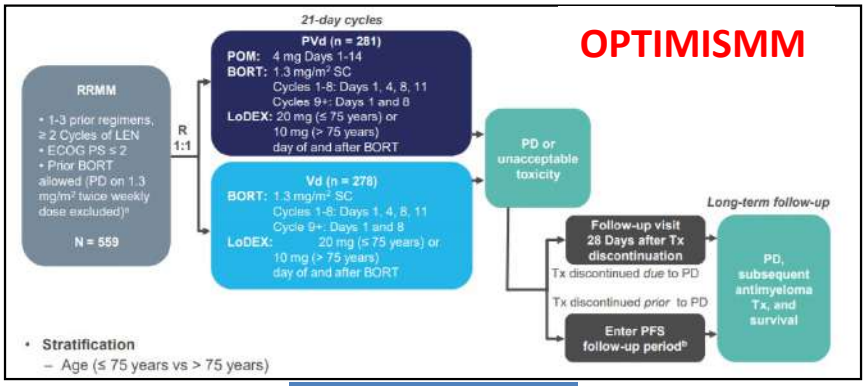


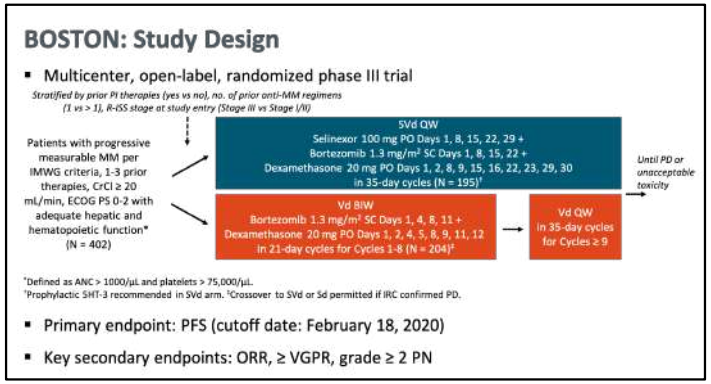
Lena-refr: 28.3%



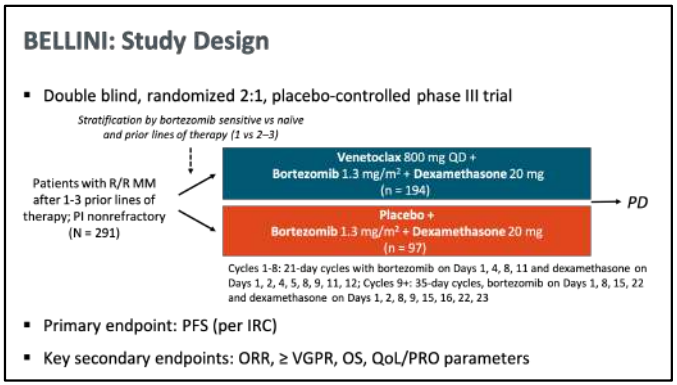
Lena-refr: 14.5%



Lena-refr: 69.9%



Lena-refr: 38.6%



Lena-refr: 22.3%

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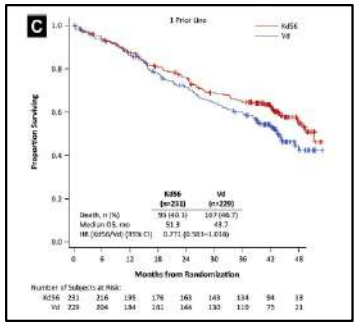
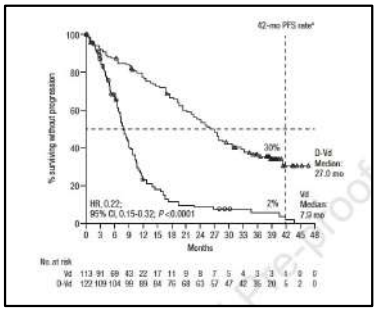
ENDEAVOR



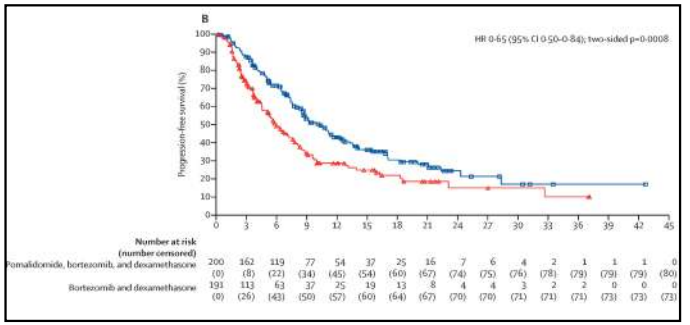
Orlowsky, Clin Lymph, Myeloma & Leuk 2019

CASTOR



Mateos, Clin Lymp, Myeloma & Leuk 2019

OPTIMISMM



Richardson, Lancet Oncology 2019

BOSTON

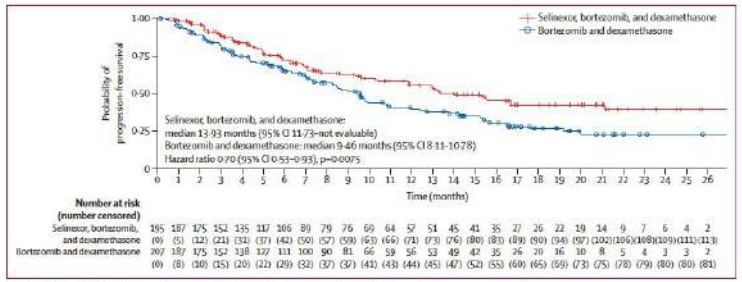
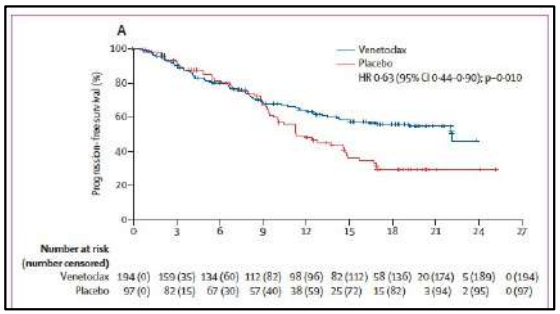


Figure 2: Kaplan-Meier estimates of progression-free survival among patients in the intention-to-treat population

Grosicki, Lancet 2020

BELLINI



Kumar, Lancet 2020

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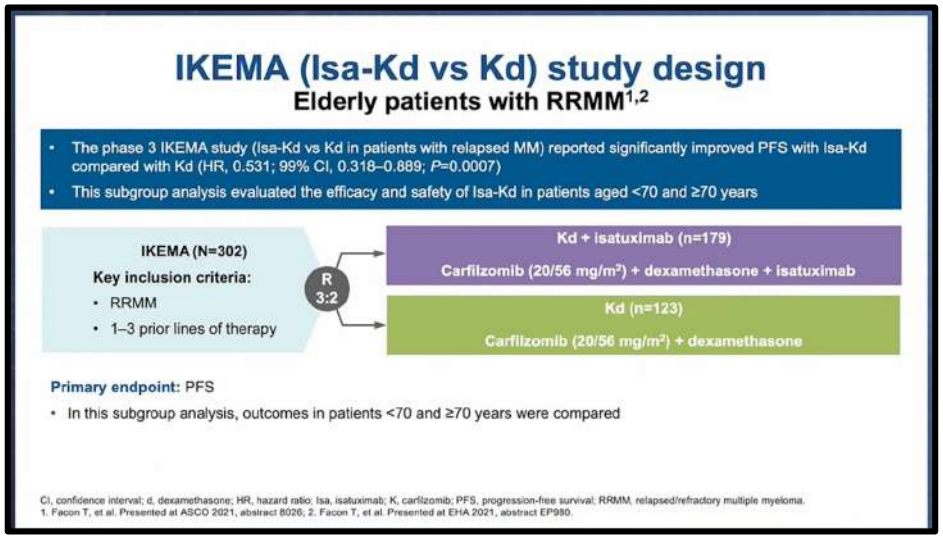
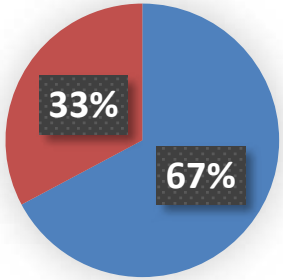
	Intention-to-treat population			One previous line of therapy		
	n	Median PFS, months (95% CI)	HR (95% CI);* p value	n	Median PFS, months (95% CI)	HR (95% CI);* p value
ENDEAVOR[32,33]	..	..	0·53 (0·44–0·65); <0·0001	..	..	0·45 (0·33–0·61); <0·0001
Vd group	465	9·4 (8·4–10·4)	..	229	10·1, NA	..
Kd group	464	18·7 (15·6–NE)	..	231	22·2, NA	..
CASTOR[21,22]	..	..	0·31 (0·25–0·39); <0·0001	..	..	0·22 (0·15–0·31); <0·0001
Vd group	247	7·1 (6·2–7·9)	..	113	7·9, NA	..
DVd group	251	16·7 (12·3 to NE)	..	122	27·0, NA	..
OPTIMISMM[26]	..	..	0·61 (0·49–0·77); <0·0001	..	..	0·54 (0·36–0·82); 0·0027
Vd group	278	7·1 (5·9–8·5)	..	115	11·6 (7·5–15·7)	..
PVd group	281	11·2 (9·7–13·7)	..	111	20·7 (15·1–28·0)	..
BOSTON[39]	..	..	0·70 (0·53–0·93); 0·0075	..	..	0·63 (0·41–0·96); NA
Vd group	207	9·4 (8·1–10·8)	..	99	NA	..
SVd group	195	13·9 (11·7–NE)	..	99	NA	..
BELLINI[40]	..	..	0·63 (0·44–0·90); 0·010	..	..	0·75 (0·45–1·26); NA
Vd group	97	11·5 (9·6–15·0)	..	44	11·4 (9·0–NE)	..
Vd plus venetoclax group	194	22·4 (15·3–NE)	..	91	22·4 (12·2–NE)	..

Moreau, Lancet Oncology 2021

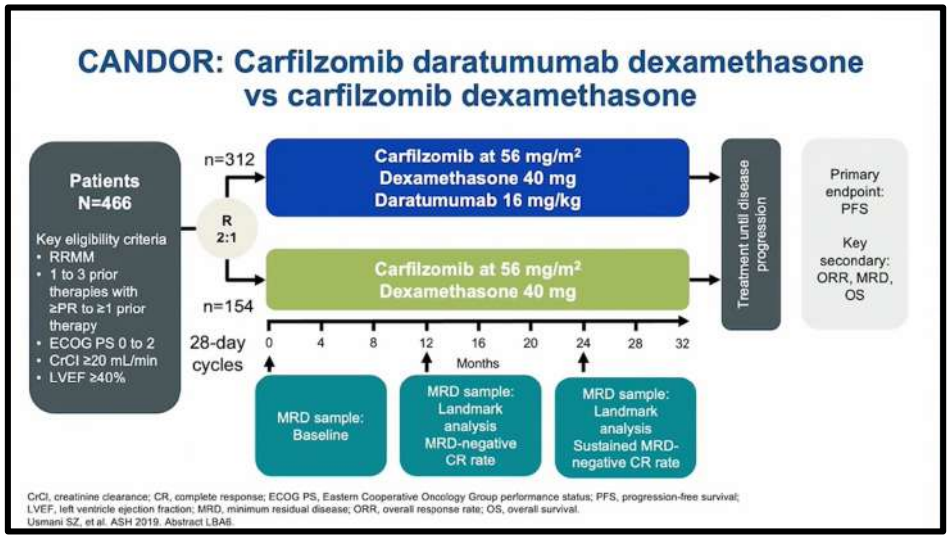
Highlights from IMW 2021

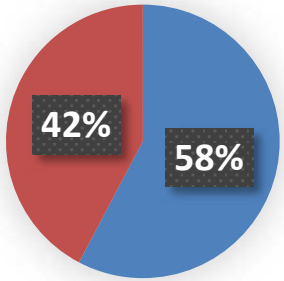
1-2 Febbraio 2022
Bologna
Royal Hotel Carlton





Not Lenarefractory
Lena-refractory





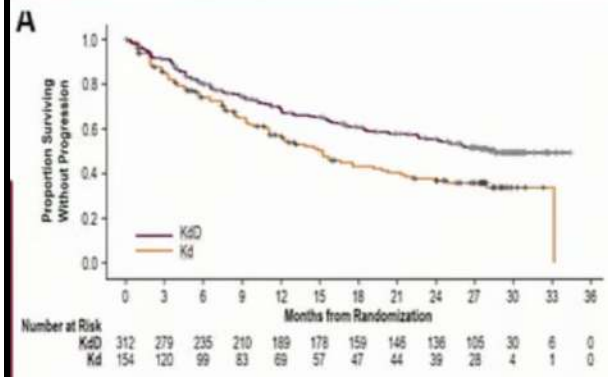
Not Lenarefractory
Lena-refractory

Anti-CD38 MoAb based combinations in second line and not refractory to Lena patients

CANDOR: DaraKD vs Kd

KdD vs Kd: ORR 84% vs 74%; **CR 28% vs 10%**
12m MRDneg rate (10^{-5}): 12.5% KdD vs 1.3% Kd

mPFS 28.6 vs 15.2 (HR 0.59)



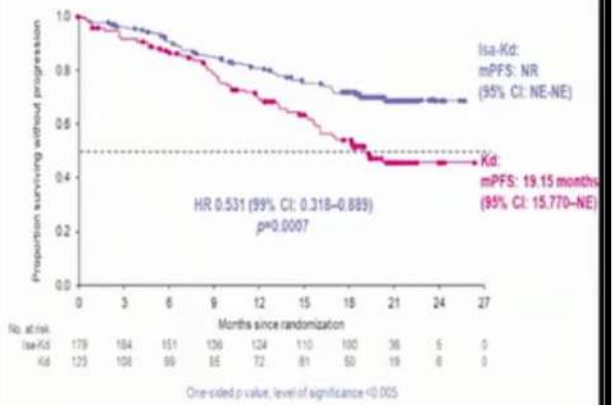
Not refractory to Lena: DKd NE vs Kd 20.3 m
HR 0.543 (0.371-0.795)

Usmani S et al. EHA 2021 ePoster #EP982
Dimopoulos MA et al. ASH2020. Abstract #2325

IKEMA: IsaKD vs Kd

IsaKd vs Kd: ORR 87% vs 83%; **CR 40% vs 28%**
MRDneg rate (10^{-5}) ≥VGPR: 41.4% IsaKd vs 13% Kd

mPFS NR vs 19.15m (HR 0.531)



Not refractory to Lena: IsaKd NC vs Kd NC
HR 0.48 (0.28-0.82)

Moreau P, et al. ASH 2020; abstract #3216
Martin t et al. ASH2020, abstract #414
Facon t et al. EHA 2021. Poster EP980

A matching-adjusted indirect comparison of isatuximab plus carfilzomib and dexamethasone versus daratumumab plus lenalidomide and dexamethasone for relapsed multiple myeloma

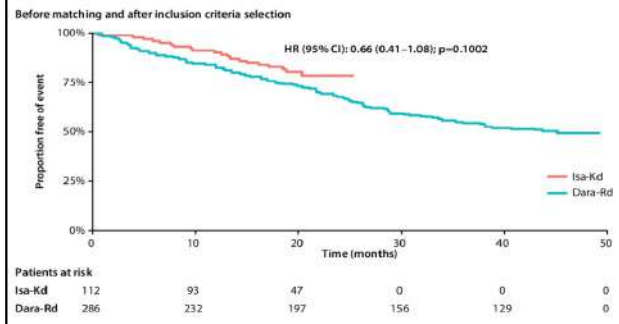
Isa-Kd arm
(IKEMA trial)
vs
DaraRd arm
(Pollux trial)

- In the first step, additional eligibility criteria of POLLUX (creatinine clearance [CrCl] ≥30 mL/min; hemoglobin >7.5 g/dL; platelet count ≥75x10^9/L; non-lenalidomide-refractory) were applied to the IKEMA Isa-Kd individual patient-level data.

Matching average baseline characteristics

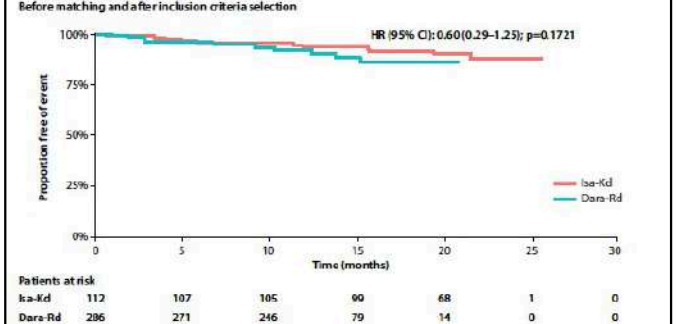
- In the second step, average baseline characteristics were matched between the Isa-Kd and Dara-Rd patients. All baseline characteristics that were available from both trials were included.
- Matched baseline characteristics included:
  - Age (≤64; 65–74; ≥75 years), Eastern Cooperative Oncology Group performance status (0; 1–2)
  - Number of prior therapy lines (1; ≥2), Cytogenetic risk (standard; high; unknown)
  - Disease stage (International staging system) at entry (I or II; III)
  - Prior treatment (proteasome inhibitor [PI]; lenalidomide; immunomodulatory drug [IMiD])
  - Refractory status (PI-refractory only; IMiD-refractory only)

Figure 1. Matching-adjusted indirect comparison results for Isa-Kd versus Dara-Rd in patients with relapsed multiple myeloma: Kaplan–Meier curves of progression-free survival



CI, confidence interval; Dara-Rd, daratumumab + lenalidomide + dexamethasone; HR, hazard ratio; Isa-Kd, isatuximab + carfilzomib + dexamethasone *statistically significant at a 0.05 level

Figure 2. Matching-adjusted indirect comparison results for Isa-Kd versus Dara-Rd in patients with relapsed multiple myeloma: Kaplan–Meier curves of overall survival



CI, confidence interval; Dara-Rd, daratumumab + lenalidomide + dexamethasone; HR, hazard ratio; Isa-Kd, isatuximab + carfilzomib + dexamethasone

Richer, IMW 2021

Myeloma: Second or Higher Relapse

First Relapse Options	Additional Options
• Any first relapse options that have not been tried Isa-Pd, Dara-Pd, Kd-Dara, or Kd-Isa (based on phase III trials data) KPd or EloPd (based on phase II trials data)	• CAR T-cell • Belantamab mafodotin • Selinexor - dex • VDT-PACE like anthracycline containing regimens • Bendamustine-based regimens • Panobinostat + PI • Venetoclax [only t(11;14)] • Cyclophosphamide-dex

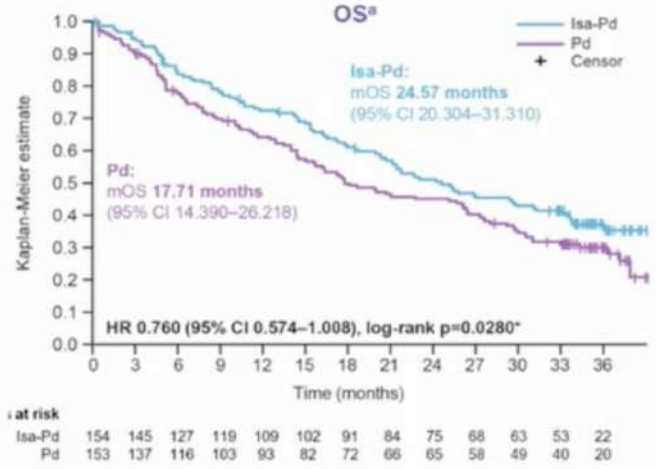
Moreau, Lancet Oncol 2021

Pomalidomide-based combinations approved for 3L + RRMM
Evidence and limitations

ICARIA: IsaPd vs Pd

ORR IsaPD vs Pd: 63% vs 33%. ≥ VGPR: 38.3% vs 10.5

With prolonged follow-up, Isa-Pd continues to improve PFS[a]:
mPFS 11.1 months vs 5.8 months with Pd alone (HR 0.599, p<0.0001)

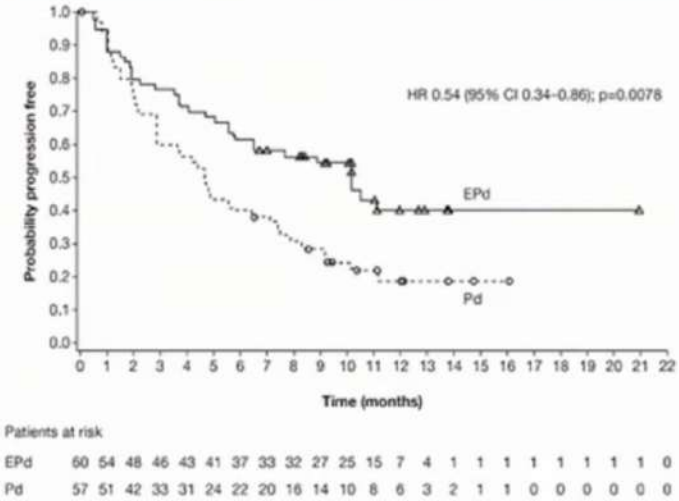


Perrot A et al. EHA 2021. Oral presentation. Abstract #S186

ELOQUENT 3 EloPd vs Pd

ORR EloPd vs Pd: 53% vs 26%. ≥ VGPR: 20% vs 9%

mPFS 10.3 m EloPd vs 4.7 m Pd
HR 0.54 (0.34 – 0.86), p-value 0.0078



Dimopoulos MA et al. NEJM 2018

Elotuzumab plus pomalidomide/dexamethasone for relapsed/refractory multiple myeloma: final overall survival from the phase 2 ELOQUENT-3 trial

Figure 1. ELOQUENT-3 study design (NCT02654132)

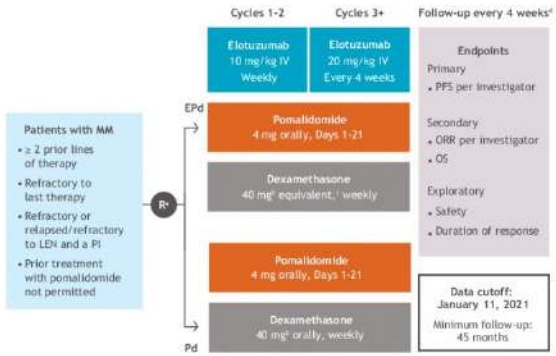
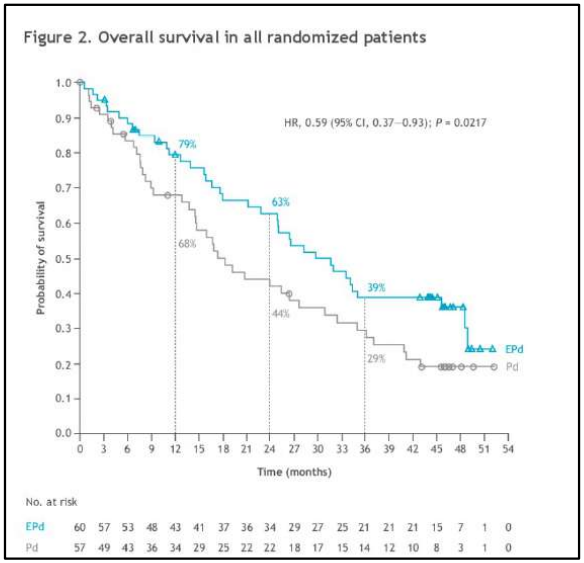


Figure 2. Overall survival in all randomized patients



Conclusions

- In this final analysis of OS from ELOQUENT-3, EPd demonstrated a statistically significant and clinically meaningful improvement in OS versus Pd in patients with RRMM and ≥ 2 prior therapies including LEN and a PI
  - 41% reduction in the risk of death
  - 1-year increase in median OS
- Subsequent therapies were balanced between treatment groups, suggesting that the effect on OS was primarily due to EPd
- OS benefit was consistent in key patient subgroups, including patients who had received LEN as their most recent prior therapy
- The safety profile of EPd was consistent with previous reports and no new safety signals were detected[7,10]
- ELOQUENT-3 is the first randomized controlled study of a triplet regimen incorporating a monoclonal antibody and Pd in RRMM to show both significant PFS and OS benefits

Dimopoulos, IMW 2021

TAKE HOME MESSAGES

- Prefer triplets
- At least two new drugs
- Consider transplant in eligible patients
- Clinical trials