UCLouvain

INSTITUT ROI ALBERT II
CANCÉROLOGIE ET HÉMATOLOGIE
Cliniques universitaires SAINT-LUC | UCL Bruxelles

MM 2023

1 Diagnosis, first line – M.C. Vekemans

2 **First relapse - M.C. Vekemans**

3 Second relapse and beyond - N. Kint

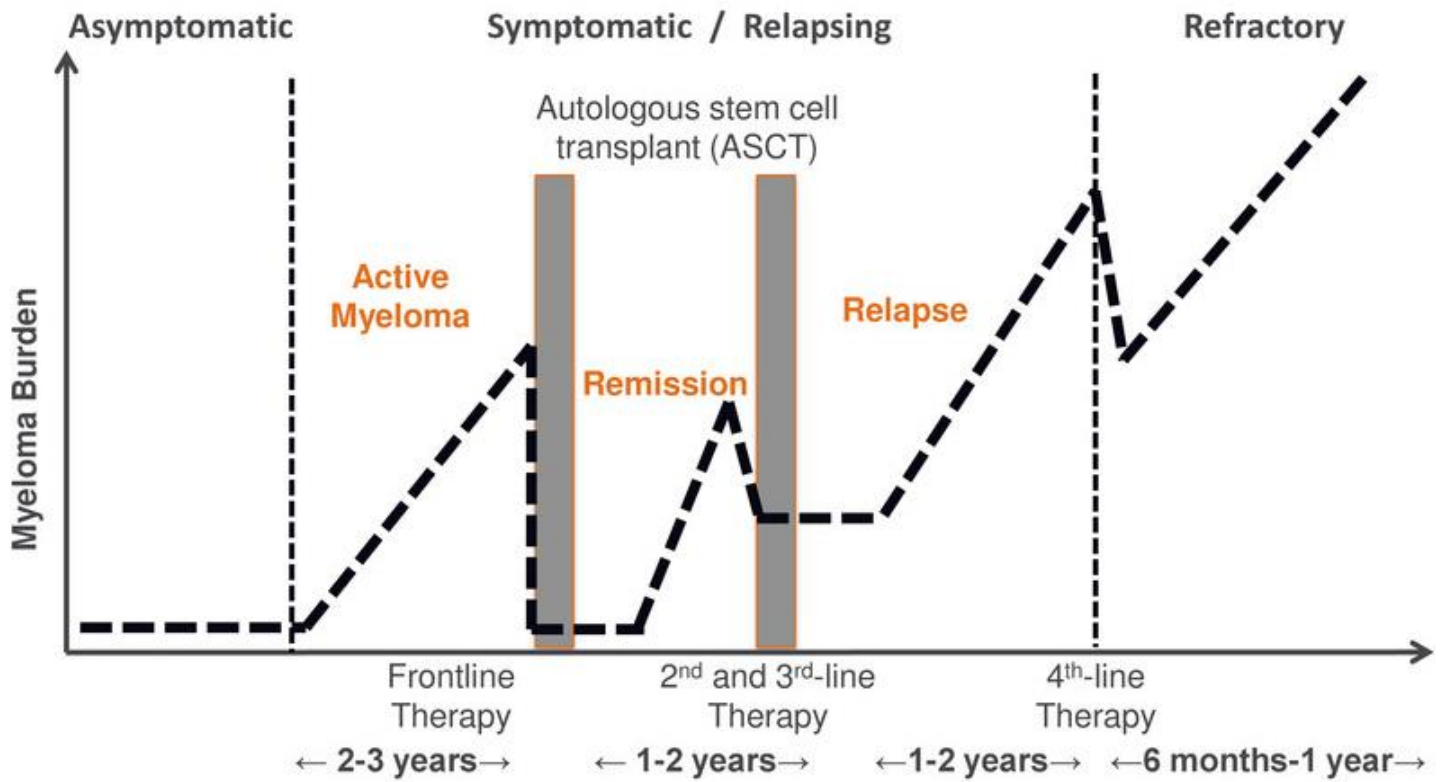
BHS Course

22 April 2023

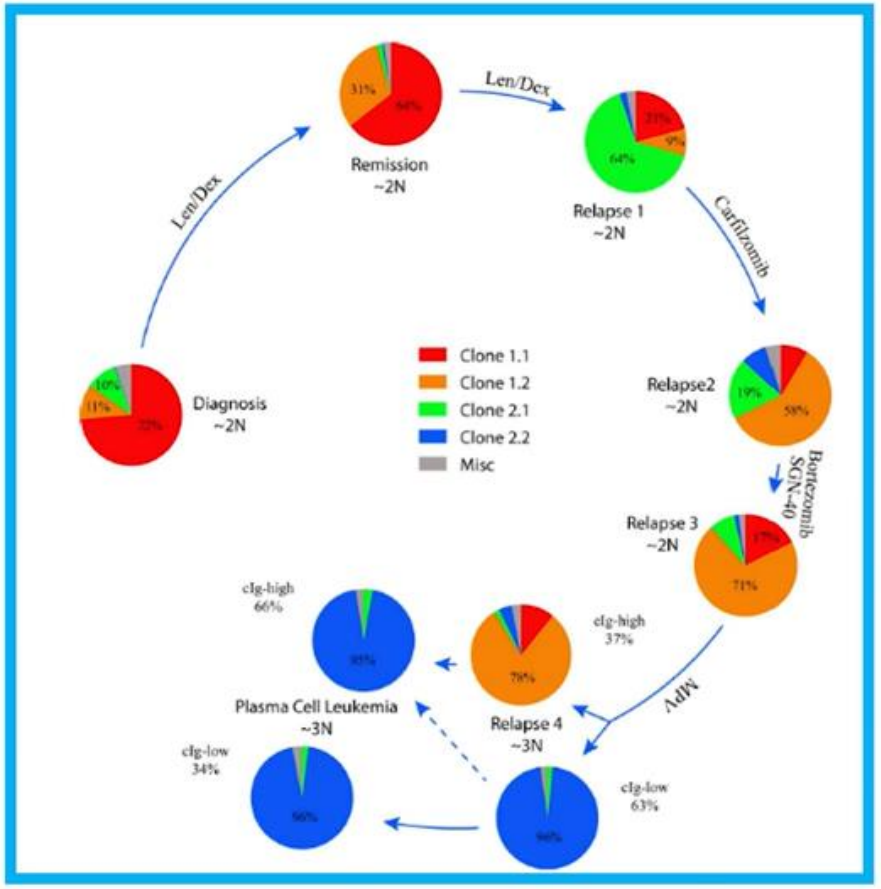
Disclosures

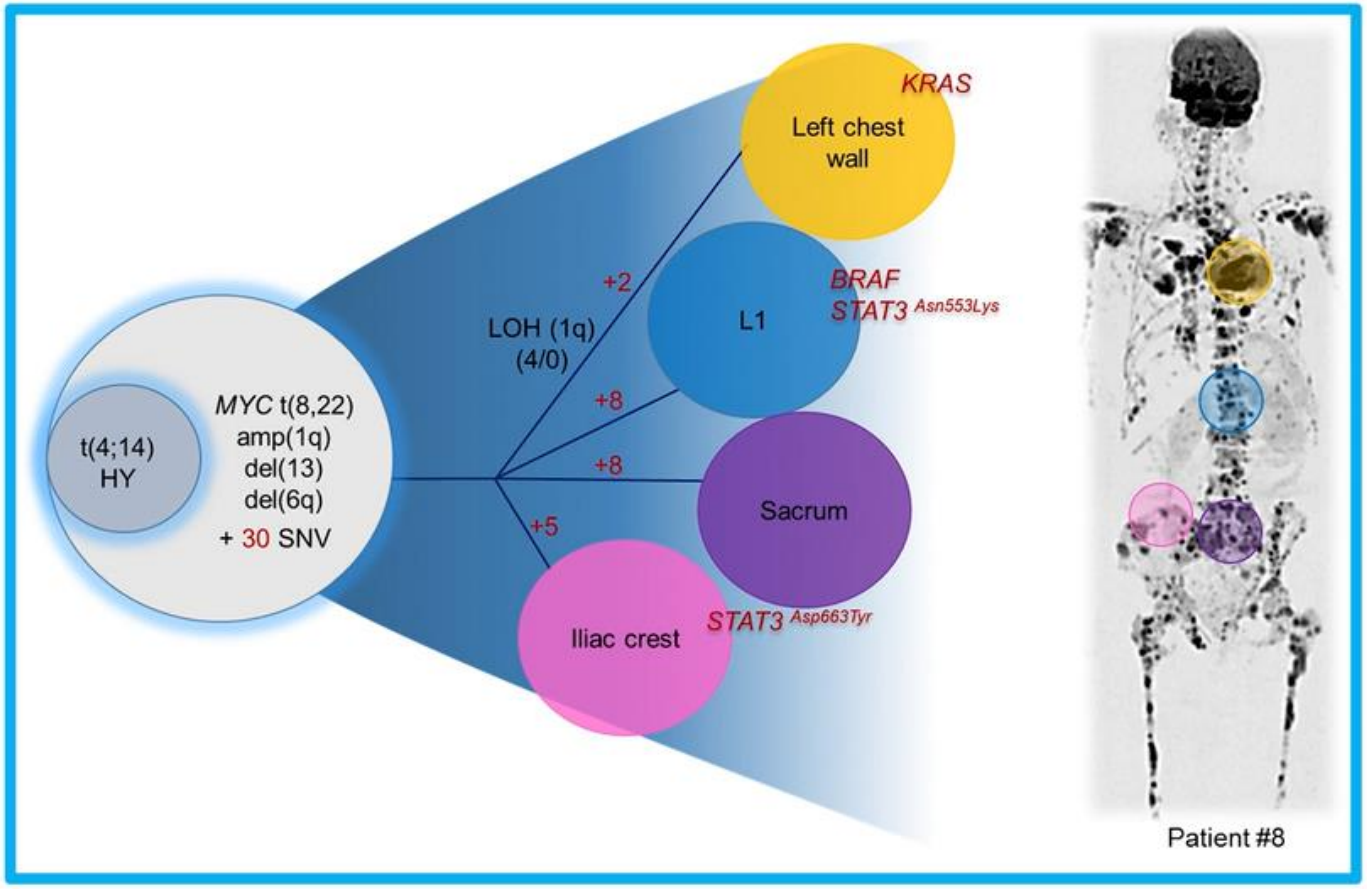
Advisory board of BMS-Celgene, Janssens, Sanofi, Amgen, Takeda, Pfizer, GSK

Natural course of MM



Increasing clonal heterogeneity when MM relapses



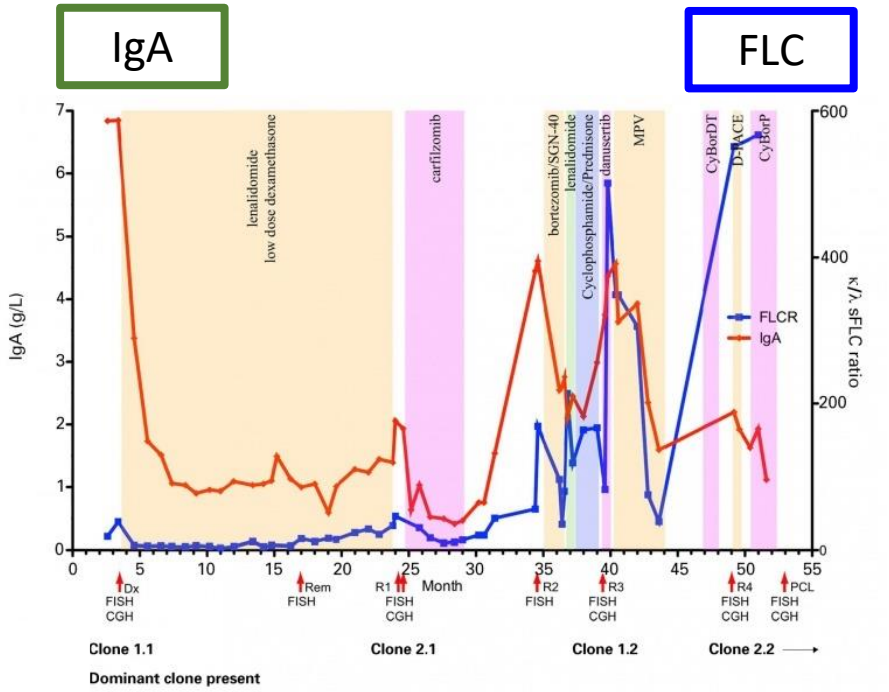


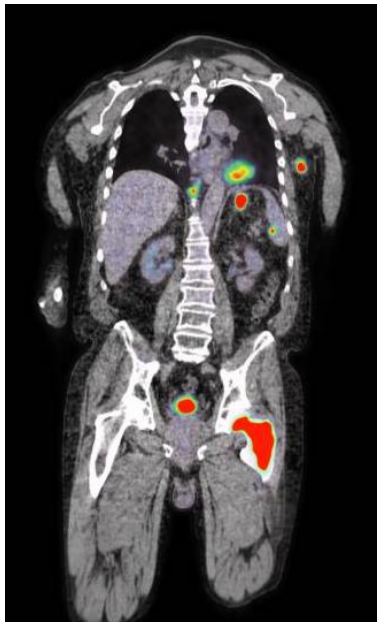
Keats, Blood 2012; Rasche, Nature Communications 2017

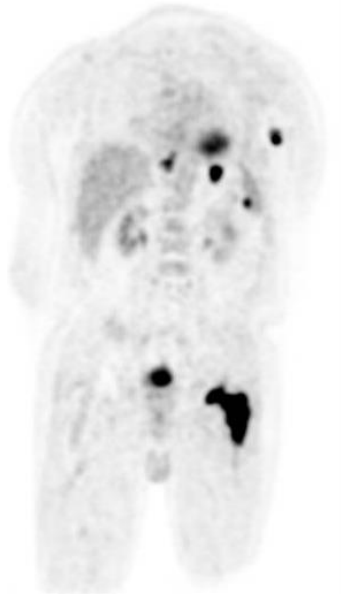
Nature of relapse

Shift on presentation

- Intact Ig to light chain only
- Non secretory relapse
- Extramedullary disease







Agenda

1	Definition
2	Context of relapse
3	Indication of therapy and work up at relapse
4	ASCT
5	ESMO guidelines

Definition of relapse

Progressive disease[4]

Any one or more of the following criteria:

- Increase of 25% from lowest confirmed response value in one or more of the following criteria:
  - Serum M protein (absolute increase must be ≥0.5 g/dL)
  - Urine M protein (absolute increase must be ≥200 mg/24 hours)
  - In patients without measurable serum and urine M protein levels, the difference between involved and uninvolved FLC levels (absolute increase must be >10 mg/dL)
  - In patients without measurable serum and urine M protein levels and without measurable involved FLC levels, BM plasma cell percentage irrespective of baseline status (absolute increase must be ≥10%)
- Serum M protein increase ≥1 g/dL, if the lowest M component was ≥5 g/dL
- Appearance of a new lesion(s), ≥50% increase from nadir in SPD* of >1 lesion, or ≥50% increase in the longest diameter of a previous lesion >1 cm in short axis
- ≥50% increase in circulating plasma cells (minimum of 200 cells/μL) if this is the only measure of disease)

Refractory[5]

Disease that becomes non-responsive or progressive on therapy or within 60 days of the last treatment in patients who had achieved an MR† or better on prior therapy.

Primary refractory[3]

Refractory disease in patients who have never achieved an MR with any therapy. These include patients who never achieve an MR or better, for whom there is no significant change in the M protein concentration and no evidence of clinical progression.

Indication of therapy

2 clear scenarios

Fast, symptomatic relapse

- Symptoms
- Rapidly progressing disease
- High tumor burden
- Organ involvement
- HR cytogenetics
- Poor PS

Prompt treatment initiation

Slow, asymptomatic relapse

- No symptoms
- Slowly progressive disease
- Low tumor burden
- LR cytogenetics
- Good PS

Patients with biochemical progression only may not need immediate therapy

Observation

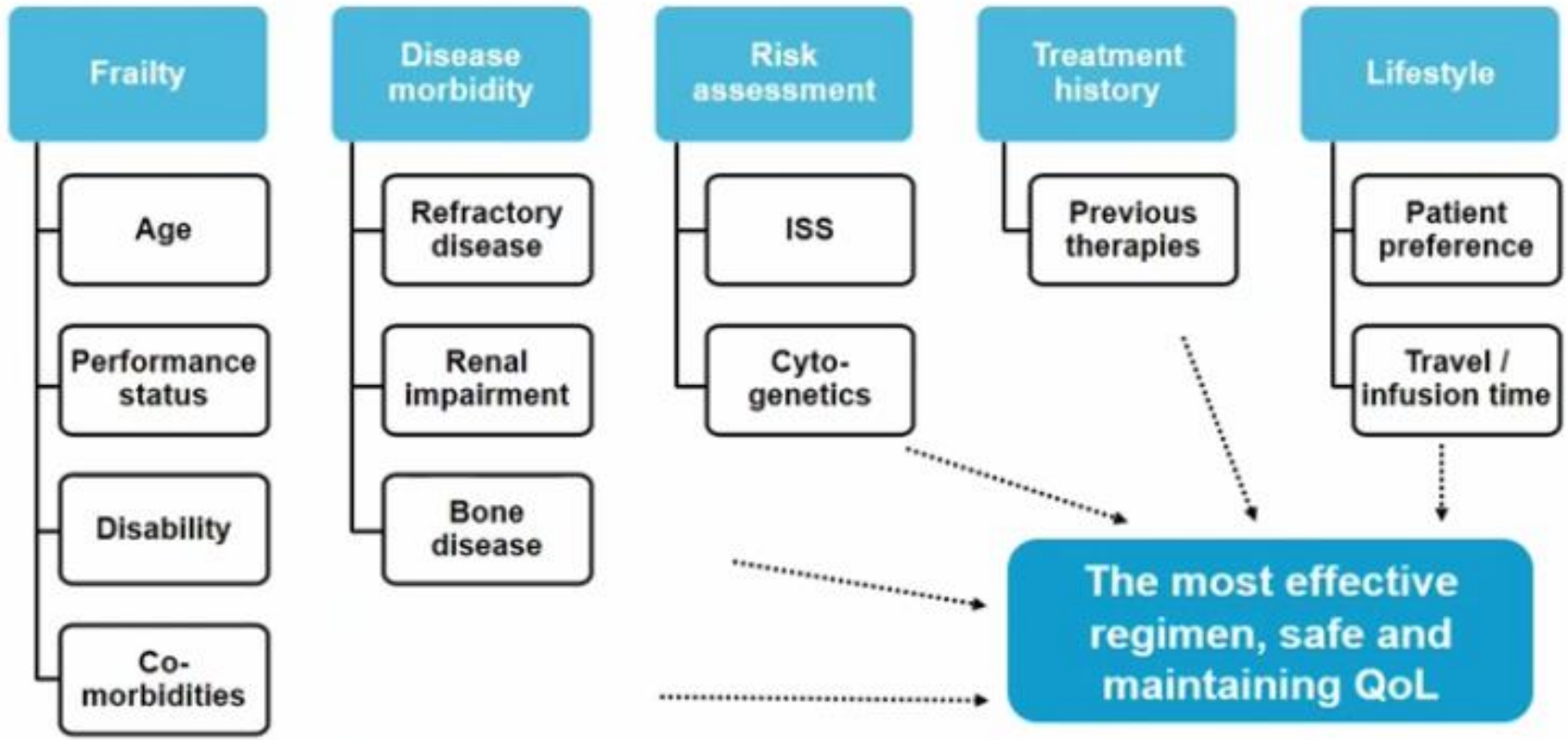
! avoid irreversible **organ damage** or **disease related complications**

Kumar, Blood 2008; Kumar, Leukemia, 2014; Laubach, Leukemia 2016

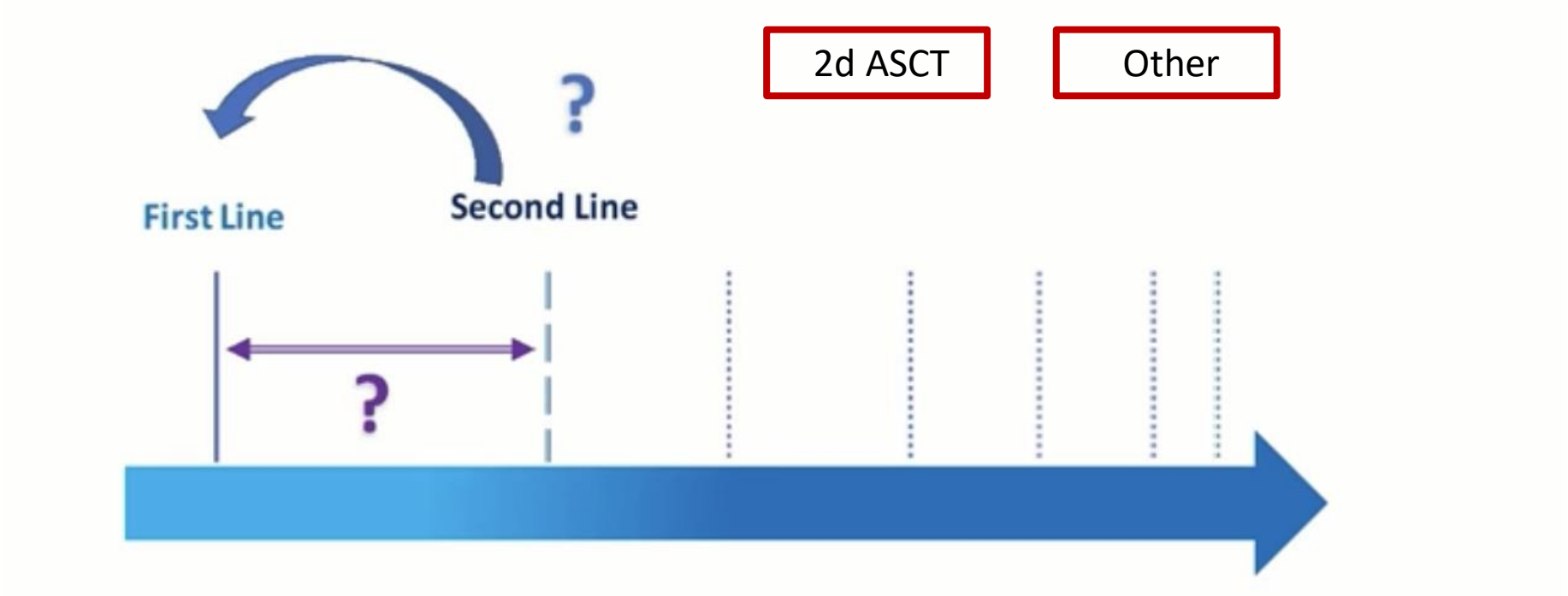
Patient evaluation at relapse

Biology	Complete blood count Renal and liver function Serum and urine paraprotein
Bone marrow	Not mandatory but recommended (cytopenias, non secretory MM) **FISH at physician discretion**
Lytic bone lesions	WBLD-CT (standard) (conventional X-ray) MRI (greater details (focal lesions), cord compression) PET-CT

Factors to consider at relapse



Factors to consider at relapse



How to select the best treatment ?

Second ASCT

ORIGINAL ARTICLE

Early relapse after autologous hematopoietic cell transplantation remains a poor prognostic factor in multiple myeloma but outcomes have improved over time

SK Kumar[1], A Dispenzieri[1], R Fraser[2], F Mingwei[2], G Akpek[3], R Cornell[4], M Kharfan-Dabaja[5], C Freytes[6], S Hashmi[1], G Hildebrandt[7], L Holmberg[8], R Kyle[1], H Lazarus[9], C Lee[10], J Mikhael[11], T Nishihori[5], J Tay[12], S Usmani[13], D Vesole[14], R Vij[15], B Wirk[16], A Krishnan[17], C Gasparetto[18], T Mark[19], Y Nieto[11,20], P Hari[2] and A D'Souza[2]

- 3256 MM patients relapsing after ASCT
- Proportion of patients relapsing early was stable over time

Duration of initial response remains a strong prognostic factor of OS

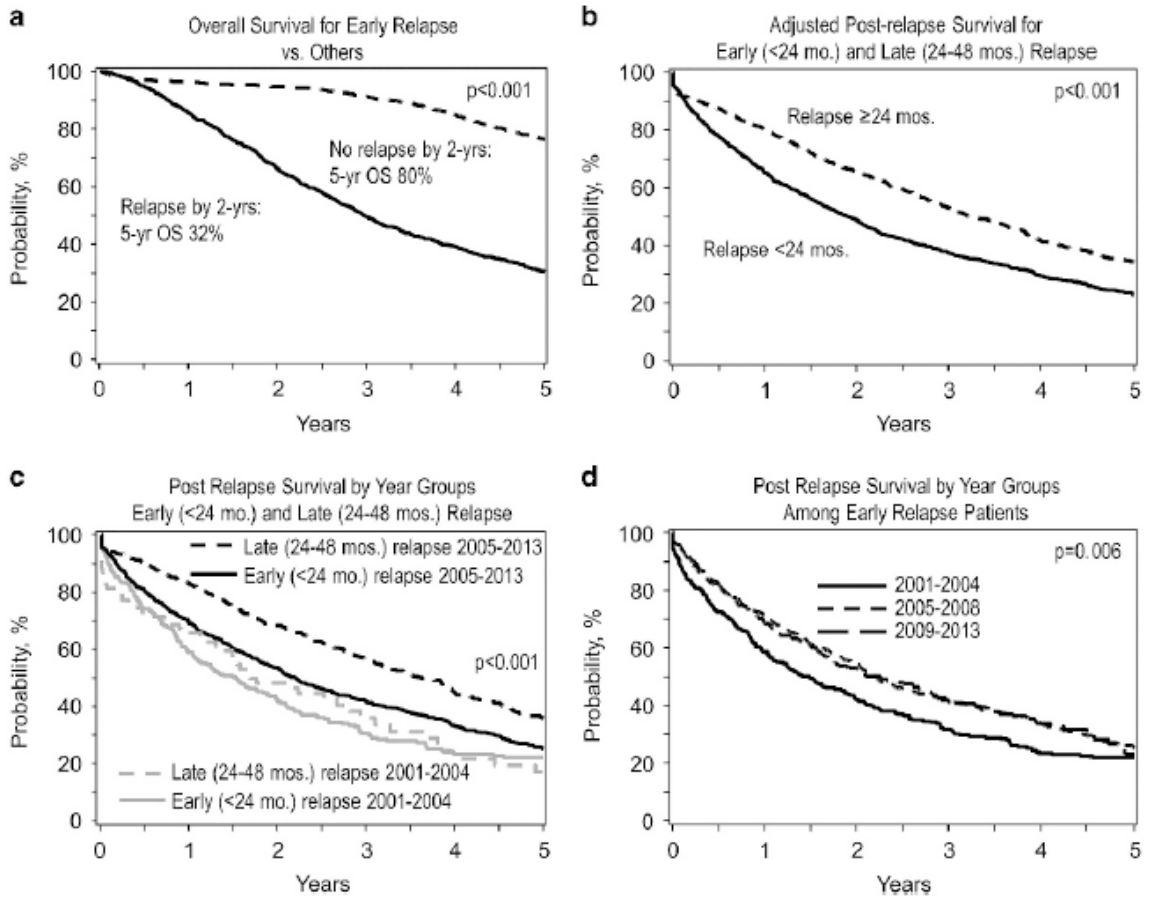
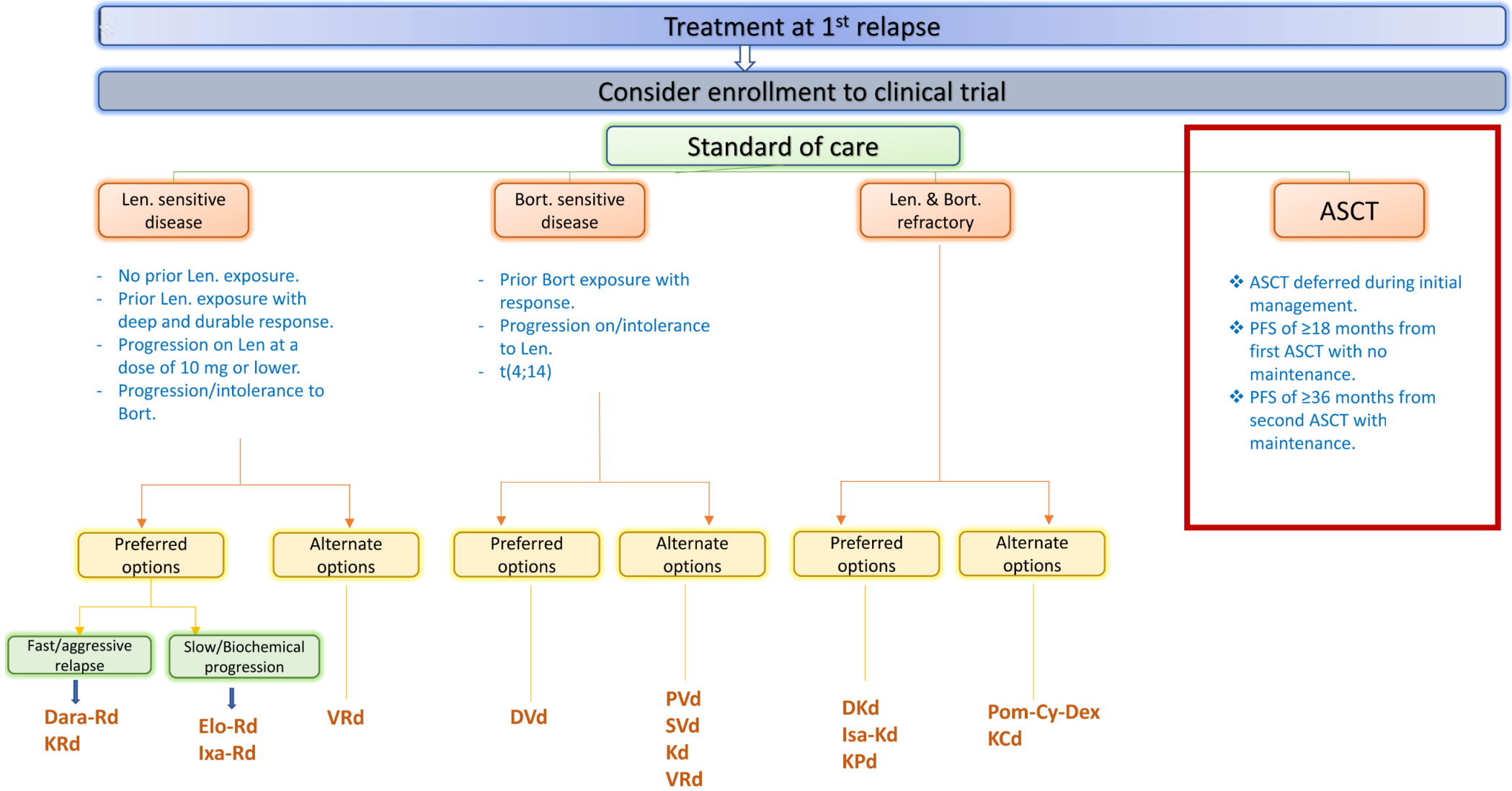


Figure 2. (**a**) Overall survival from diagnosis among patients with early relapse (< 24 months) and late relapse (> 24 months). (**b**) Post-relapse survival for early relapse patients (relapse within 24 months) compared to those with a late relapse. (**c**) Post-relapse survival for early relapse patients who relapsed within 24 months grouped by relapse year 2005. (**d**) Post-relapse survival for early relapse patients who relapsed within 24 months, grouped by the date of AHCT (2001–2004, 2005–2008, 2009–2013).

Kumar, Leukemia 2018

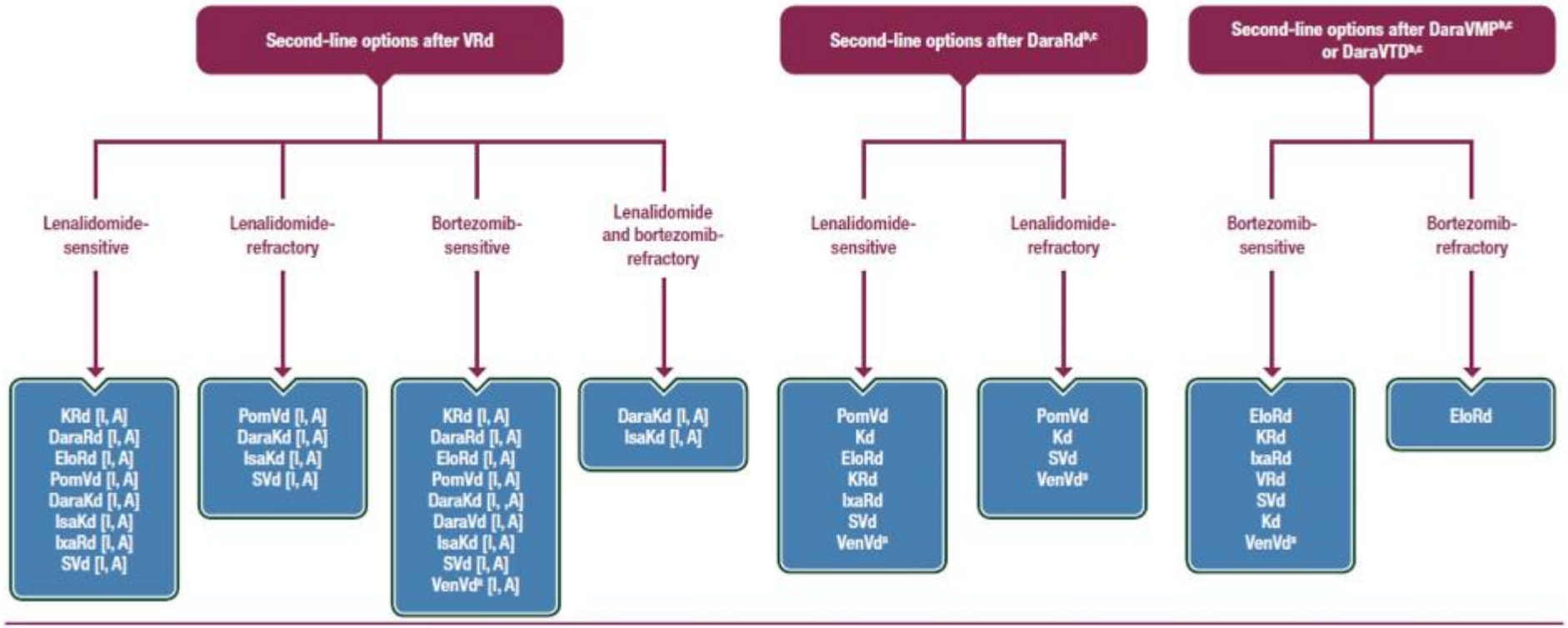
Second ASCT



Deravakonda, ASH 2022

First relapse

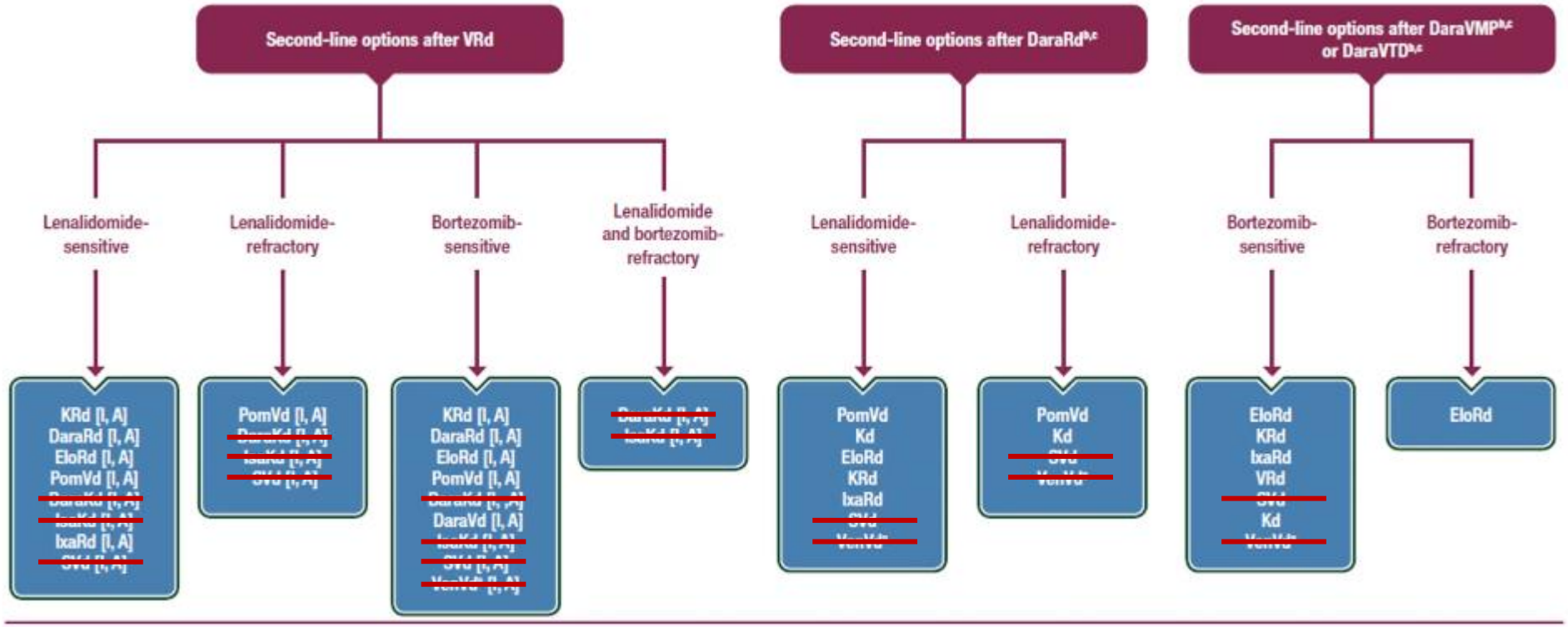
Treatment options ESMO 2021



Dimopoulos, Ann Oncol 2021

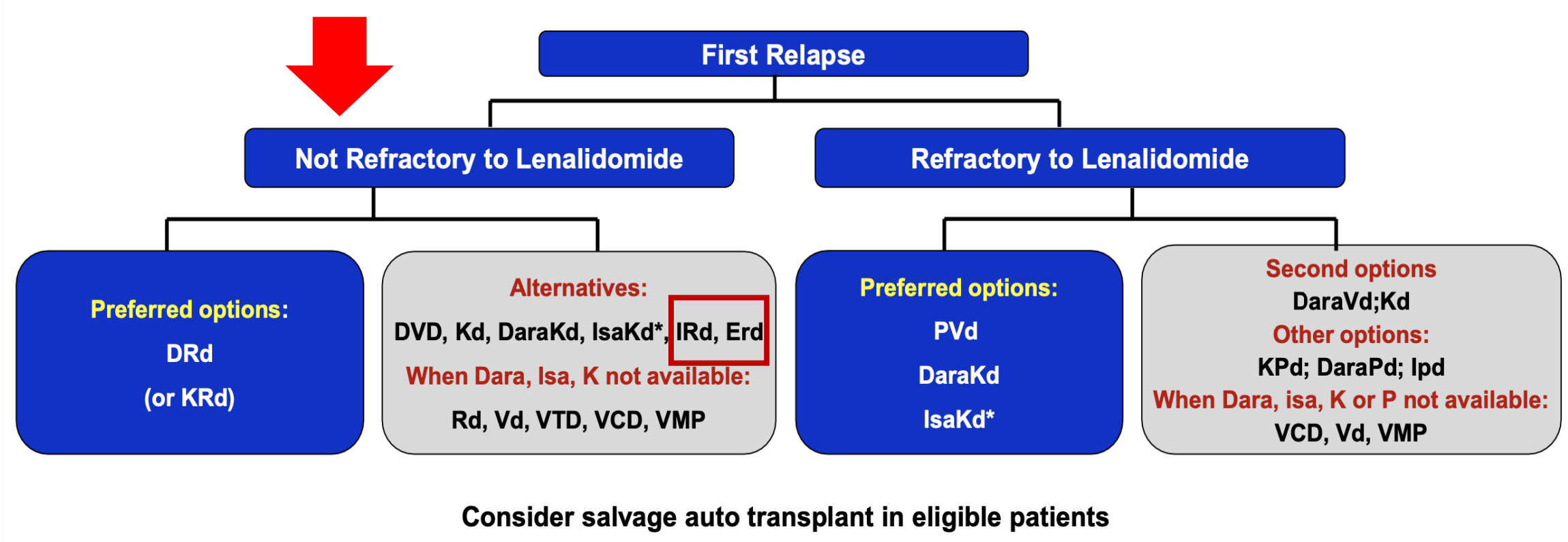
First relapse

Treatment options ESMO 2021



Dimopoulos, Ann Oncol 2021

First relapse | IMW recommendations



Consider salvage auto transplant in eligible patients

Moreau, Ann Oncol 2021

First relapse

LEN-based studies

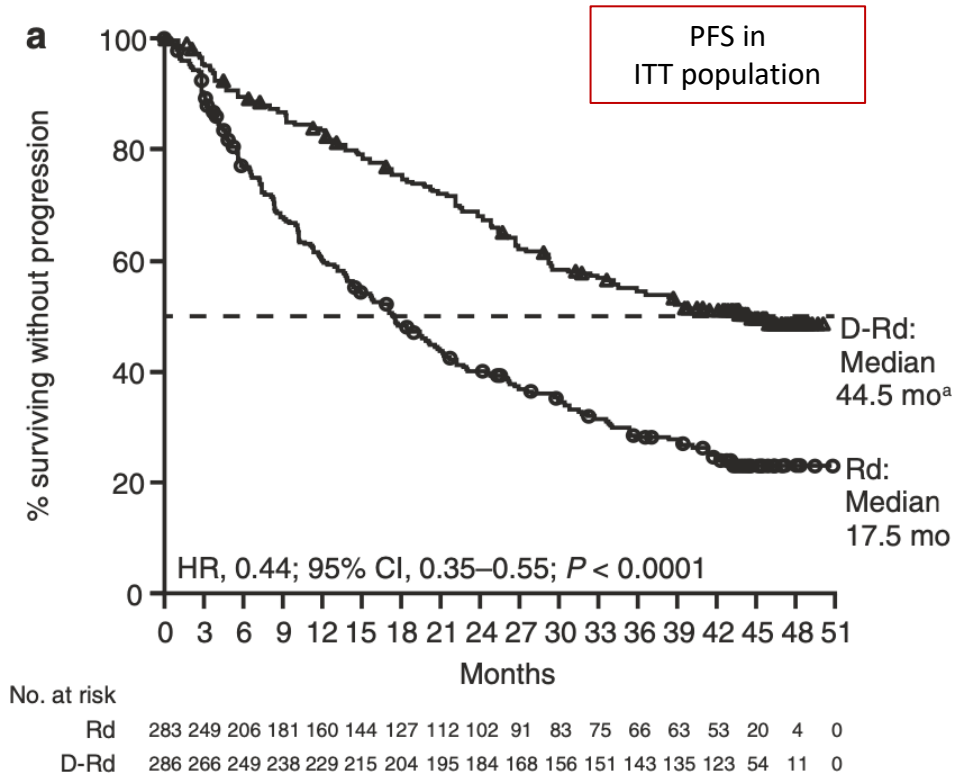
	POLLUX DRd vs. Rd	ASPIRE KRd vs. Rd	ELOQUENT2 EloRd vs. Rd	TOURMALINE IRd vs. Rd
Prior LOT	1 (1-11)	2 (1-3)	2 (1-4)	(1-3)
PFS HR (95% CI)	0.37 (0.27-0.52)	0.69 (0.57-0.83)	0.73 (0.60-0.83)	0.74 (0.59-0.94)
≧CR	43 vs. 19%	32 vs. 14%	14 vs. 7%	12 vs. 7%
PFS months	44.5 vs. 17.5	26.3 vs. 17.6	19.4 vs. 14.9	20.6 vs. 14.7

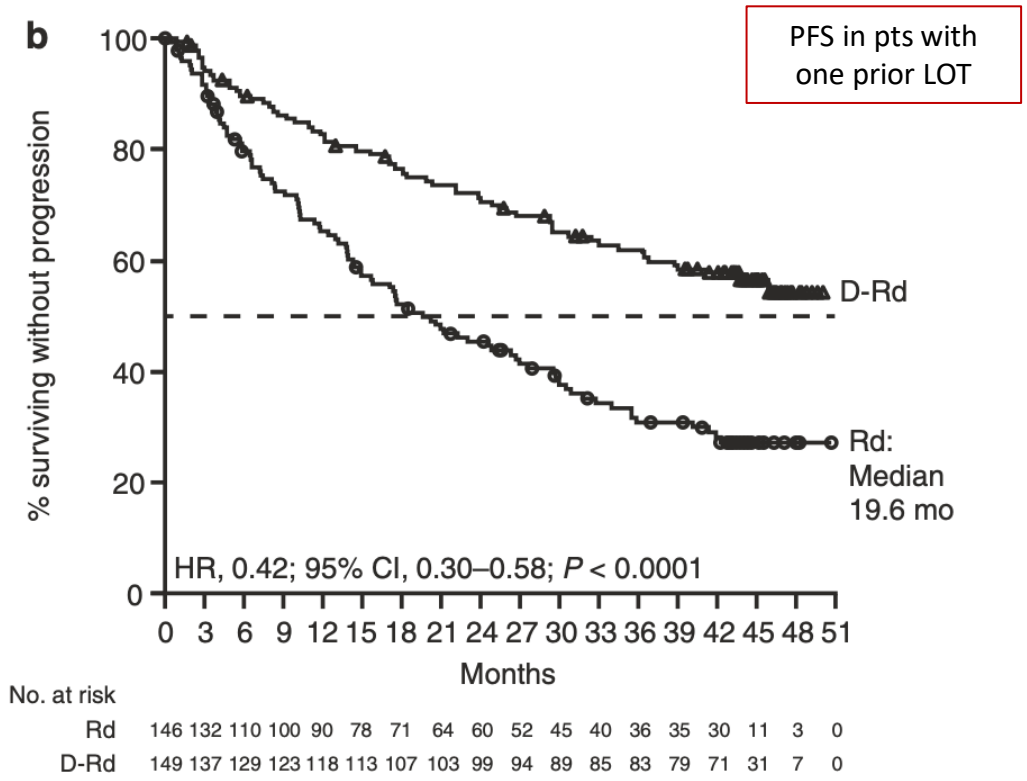
HR PFS of 0.37, the lowest hazard ratio ever seen in a myeloma trial to date

Dimopoulos, Blood Cancer J 2017; Siegel, JCO 2018; Mateos, Haematologica 2017; Lonial, NEJM 2015

POLLUX

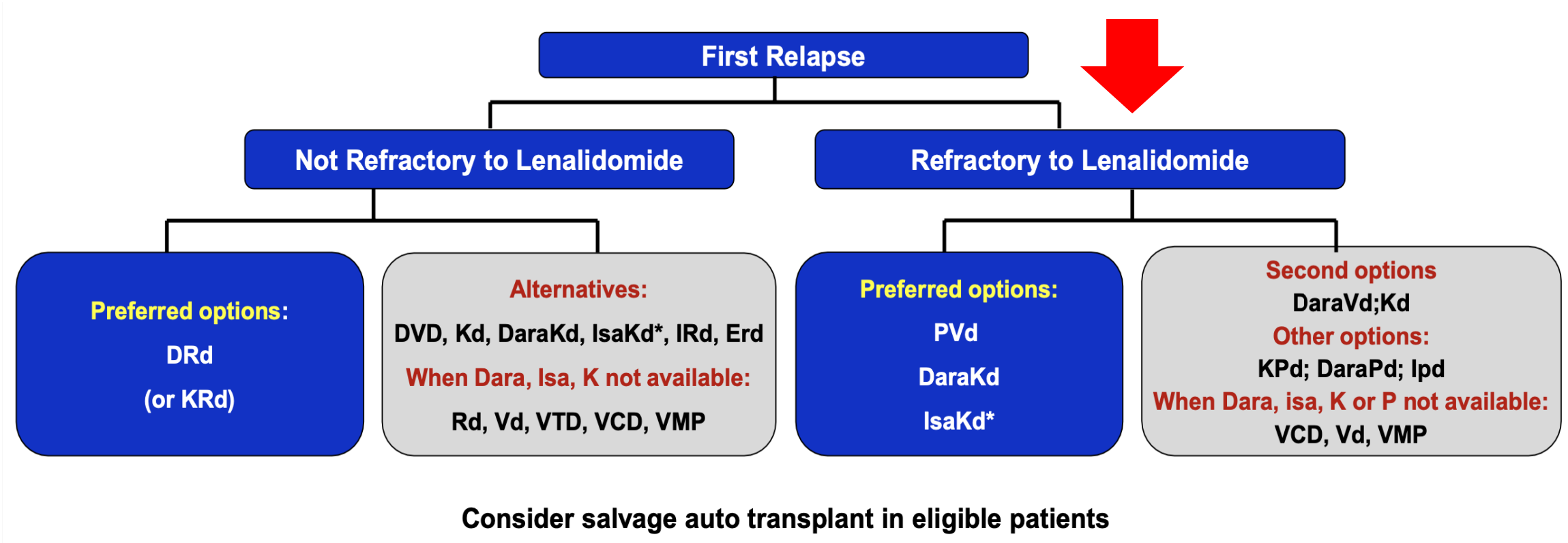
LEN-based studies





Bahlis, Leukemia 2020

First relapse | IMW recommendations

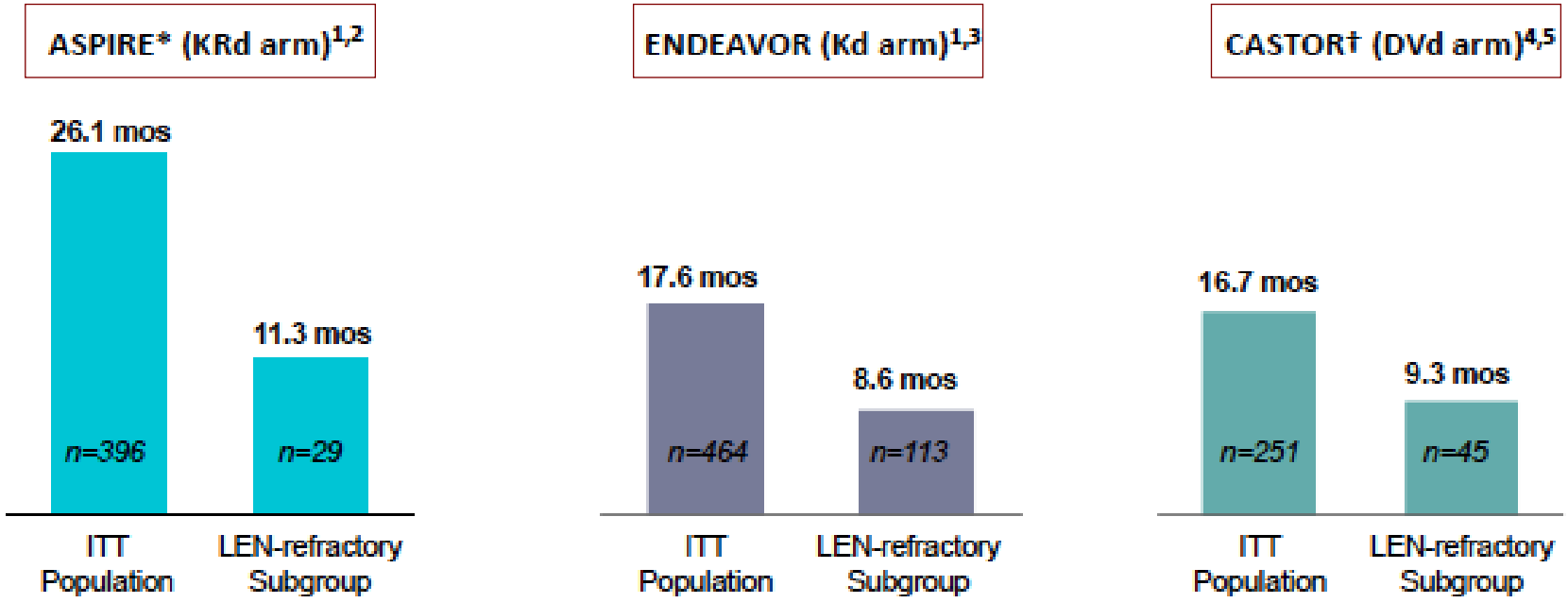


Consider salvage auto transplant in eligible patients

Moreau, Ann Oncol 2021

LEN-refractory

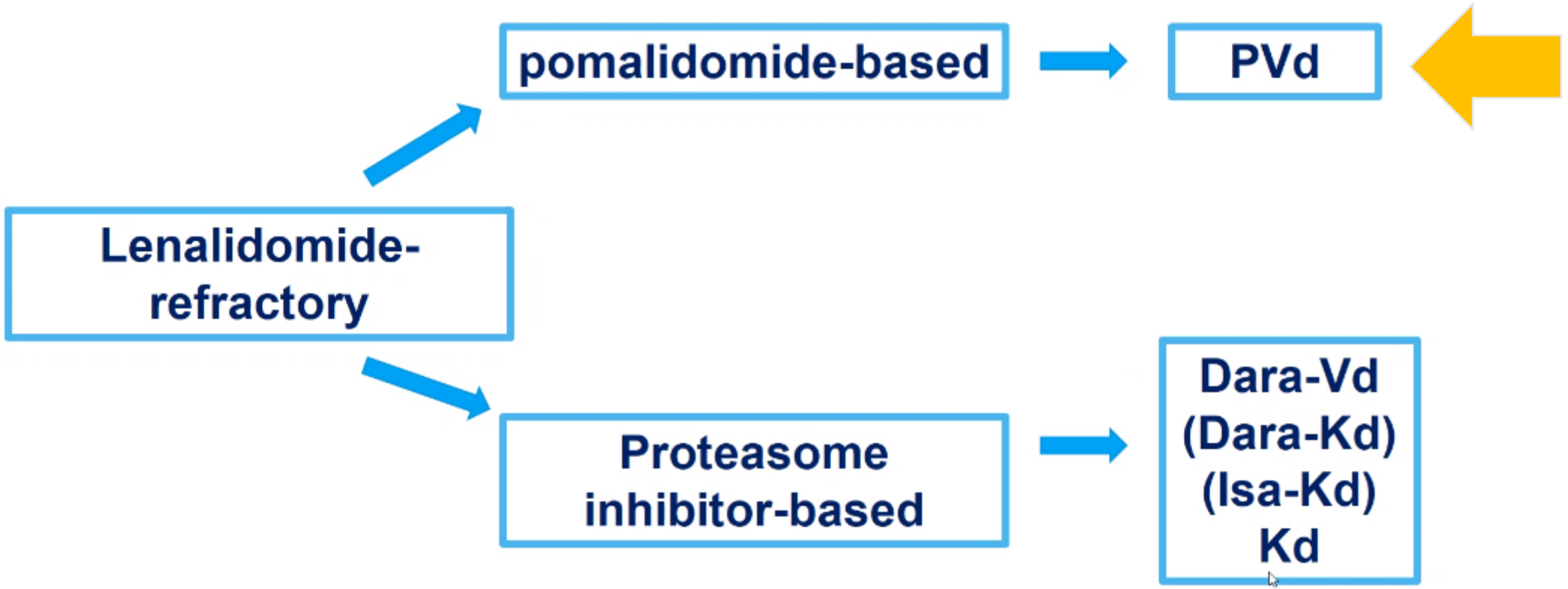
Outcome is poor



After LEN exposure (1-3 prior lines), mPFS in LEN-ref RRMM is low

Siegel, EHA 2017; Stewart, NEJM 2015; Moreau, Leukemia 2017; Spencer, Blood 2017; Chanan-Khan, ASH 2016

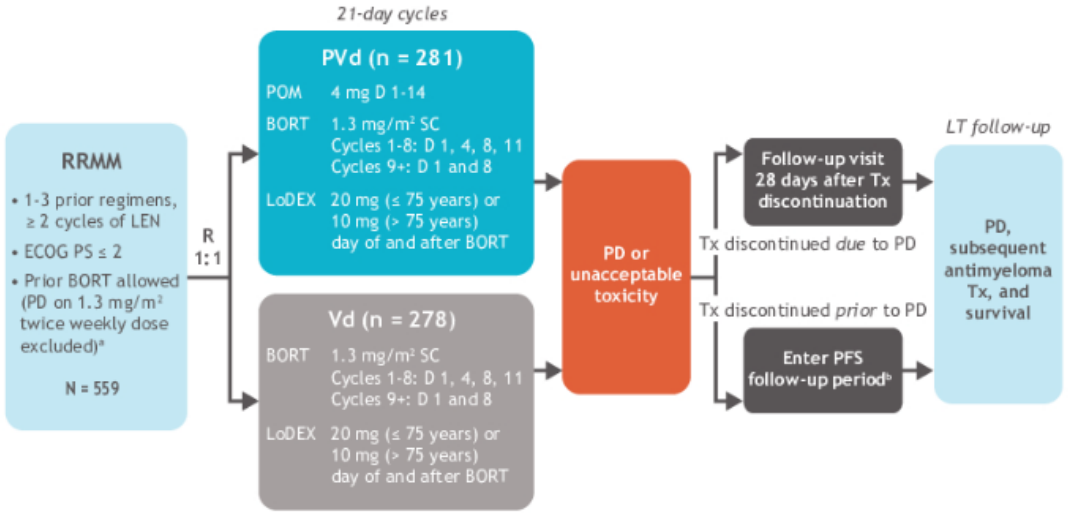
LEN-refractory	POM-based studies



LEN-refractory | OPTIMISMM | PVd vs. Vd

Pomalidomide, bortezomib, and dexamethasone for patients with relapsed or refractory multiple myeloma previously treated with lenalidomide (OPTIMISMM): a randomised, open-label, phase 3 trial

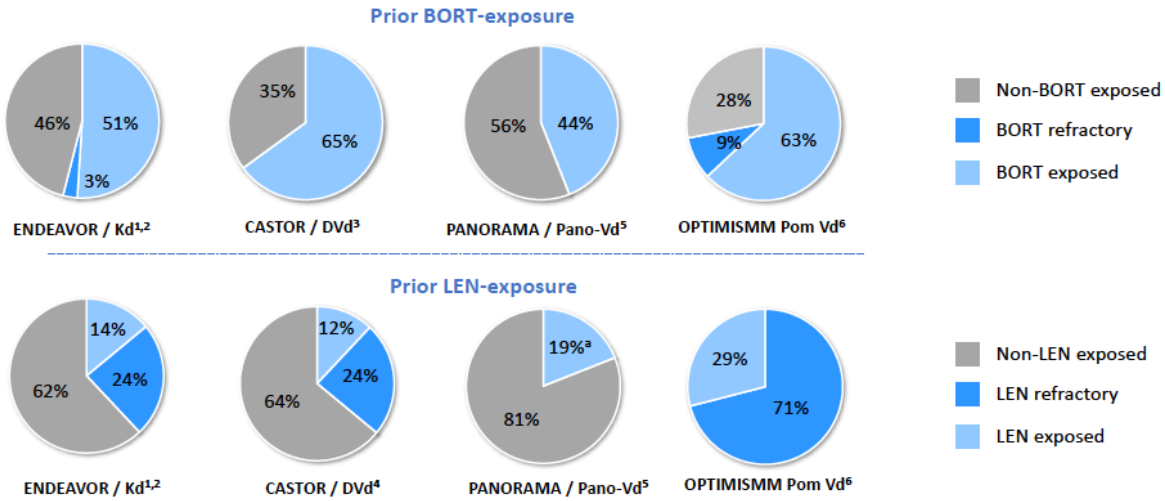
Paul G Richardson, Albert Oriol, Meral Beksac, Anna Marina Liberati, Monica Galli, Fredrik Schjesvold, Jindriska Lindsay, Katja Weisel, Darrell White, Thierry Facon, Jesus San Miguel, Kazutaka Sunami, Peter O'Gorman, Pieter Sonneveld, Pawel Robak, Sergey Semochkin, Steve Schey, Xin Yu, Thomas Doerr, Amine Bensmaine, Tsvetan Biyukov, Teresa Peluso, Mohamed Zaki, Kenneth Anderson, Meletios Dimopoulos, on behalf of the OPTIMISMM trial investigators



Stratification
- Age (≤ 75 y vs > 75 y)
- Prior regimens (1 vs > 1)
- B2-microglobulin at screening (< 3.5 mg/L vs ≥ 3.5 to ≤ 5.5 mg/L vs > 5.5 mg/L)

Study endpoints[c]
- Primary: PFS
- Secondary: OS, ORR by IMWG criteria, DOR, safety
- Key exploratory: TTR, PFS2, efficacy analysis in subgroups[d], and HRQoL

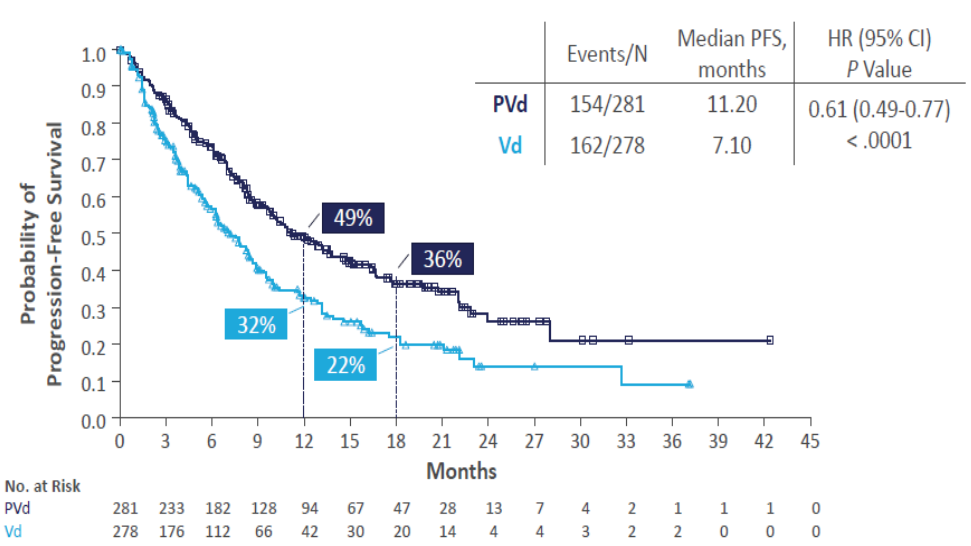
NCT01734928



Richardson, Lancet Oncol 2019

LEN-refractory | OPTIMISMM | PVd vs. Vd

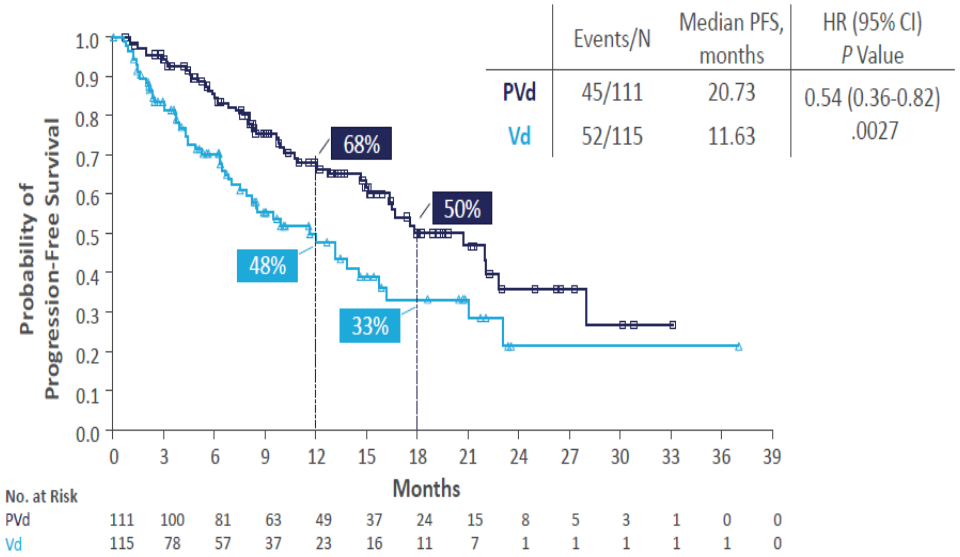
PFS in the ITT population



	Events/N	Median PFS, months	HR (95% CI) *P* Value
PVd	154/281	11.20	0.61 (0.49-0.77)
Vd	162/278	7.10	< .0001

Reduction of the risk of progression/death by 39% compared with Vd

PFS in patients with 1 prior line of therapy



	Events/N	Median PFS, months	HR (95% CI) *P* Value
PVd	45/111	20.73	0.54 (0.36-0.82)
Vd	52/115	11.63	.0027

Reduction of the risk of progression/death by 46% compared with Vd

Richardson, Lancet Oncol 2019

LEN-refractory | OPTIMISMM | PVd vs. Vd

	Pomalidomide, bortezomib, and dexamethasone group (n=281)	Bortezomib and dexamethasone group (n=278)
Overall response*	231 (82·2% [77·2–86·5])	139 (50·0% [44·0–56·0])
Stringent complete response	9 (3·2% [1·5–6·0])	2 (0·7% [0·1–2·6])
Complete response	35 (12·5% [8·8–16·9])	9 (3·2% [1·5–6·1])
Very good partial response	104 (37·0% [31·4–42·9])	40 (14·4% [10·5–19·1])
Partial response	83 (29·5% [24·3–35·2])	88 (31·7% [26·2–37·5])
Stable disease	32 (11·4% [7·9–15·7])	106 (38·1% [32·4–44·1])
Progressive disease	11 (3·9% [2·0–6·9])	16 (5·8% [3·3–9·2])
Not assessable	7 (2·5% [1·0–5·1])	17 (6·1% [3·6–9·6])

Data are n (% [95% CI]). *Defined as patients who achieved either a partial response or a complete response.

Table 2: Responses in the intention-to-treat population

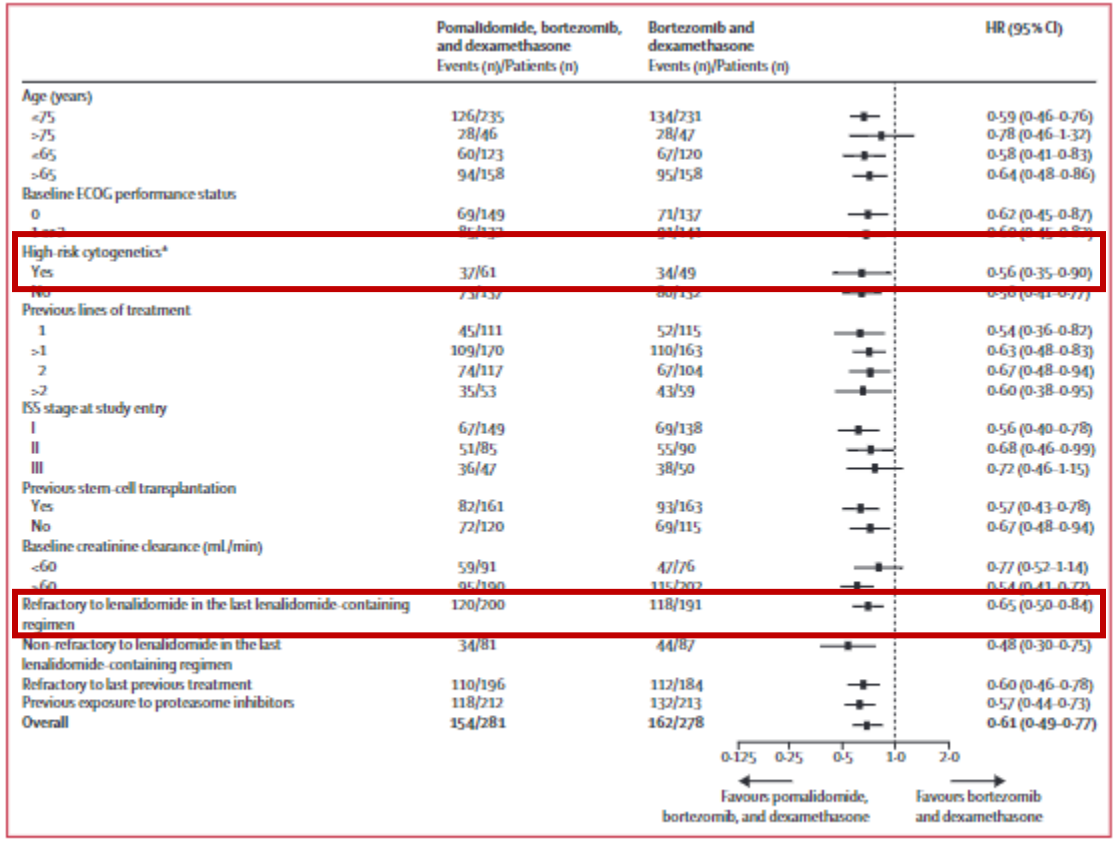
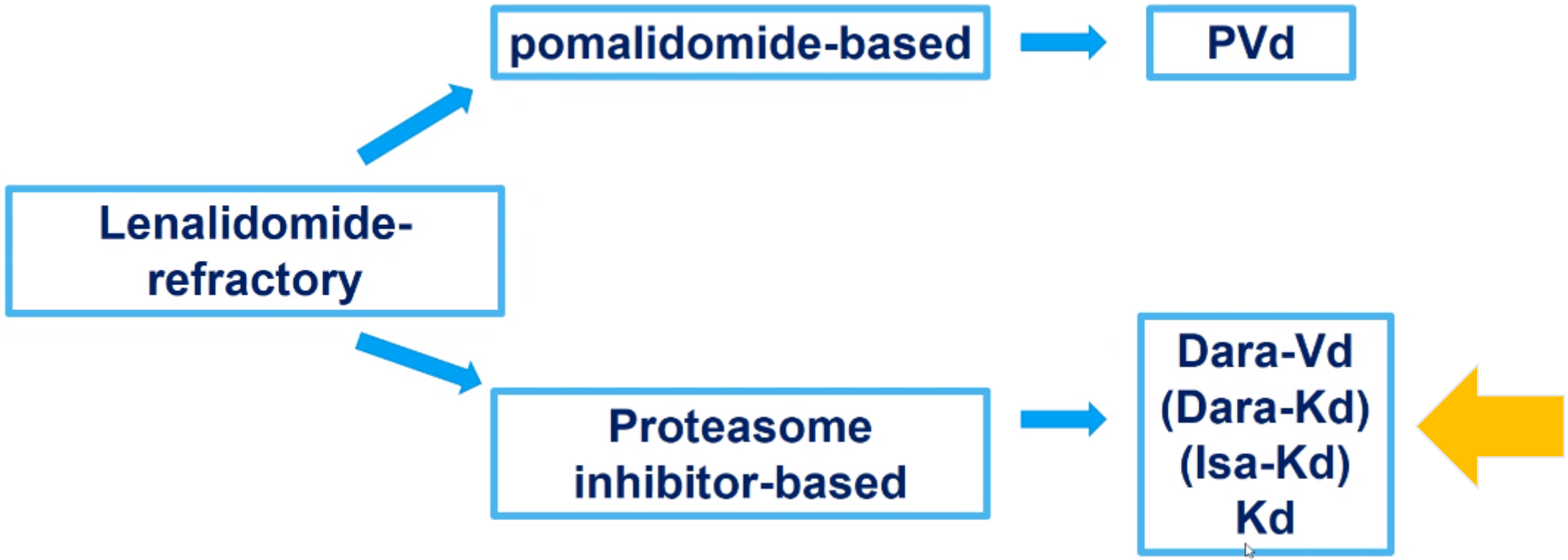


Figure 3: Prespecified subgroup analyses for progression-free survival
HR=hazard ratio. ECOG=Eastern Cooperative Oncology Group. ISS=International Staging System. *Defined as at least one high-risk abnormality—del(17p), t(4;14), or t(14;16).

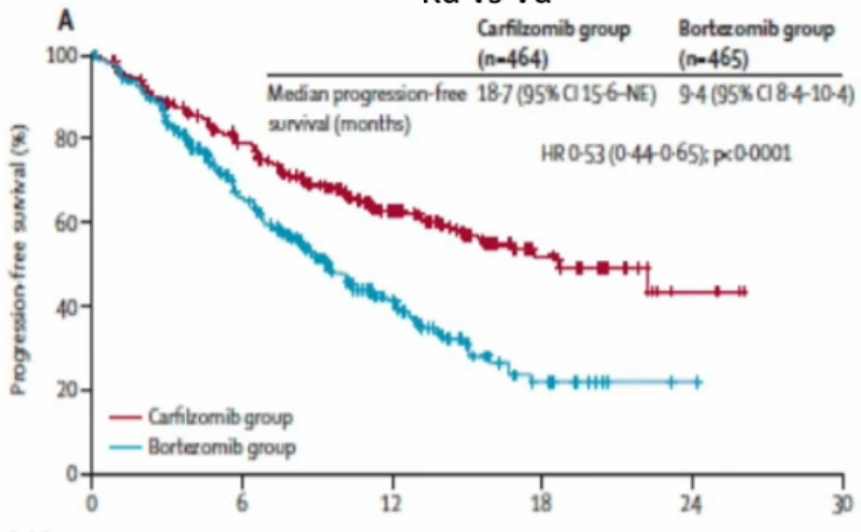
LEN-refractory	PI-based studies



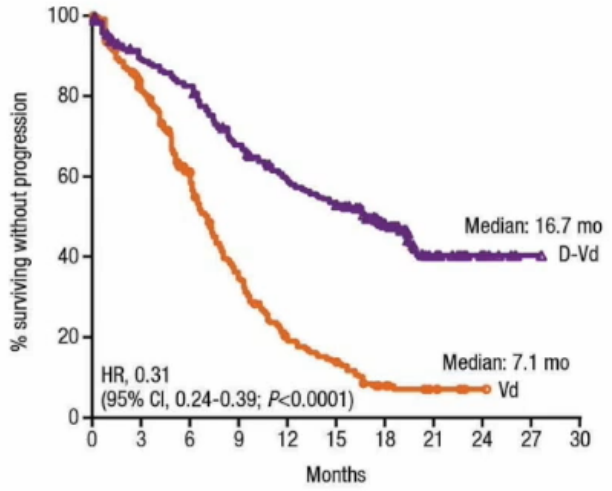
LEN-refractory

PI-based studies

ENDEAVOR[1-2]
Kd vs Vd



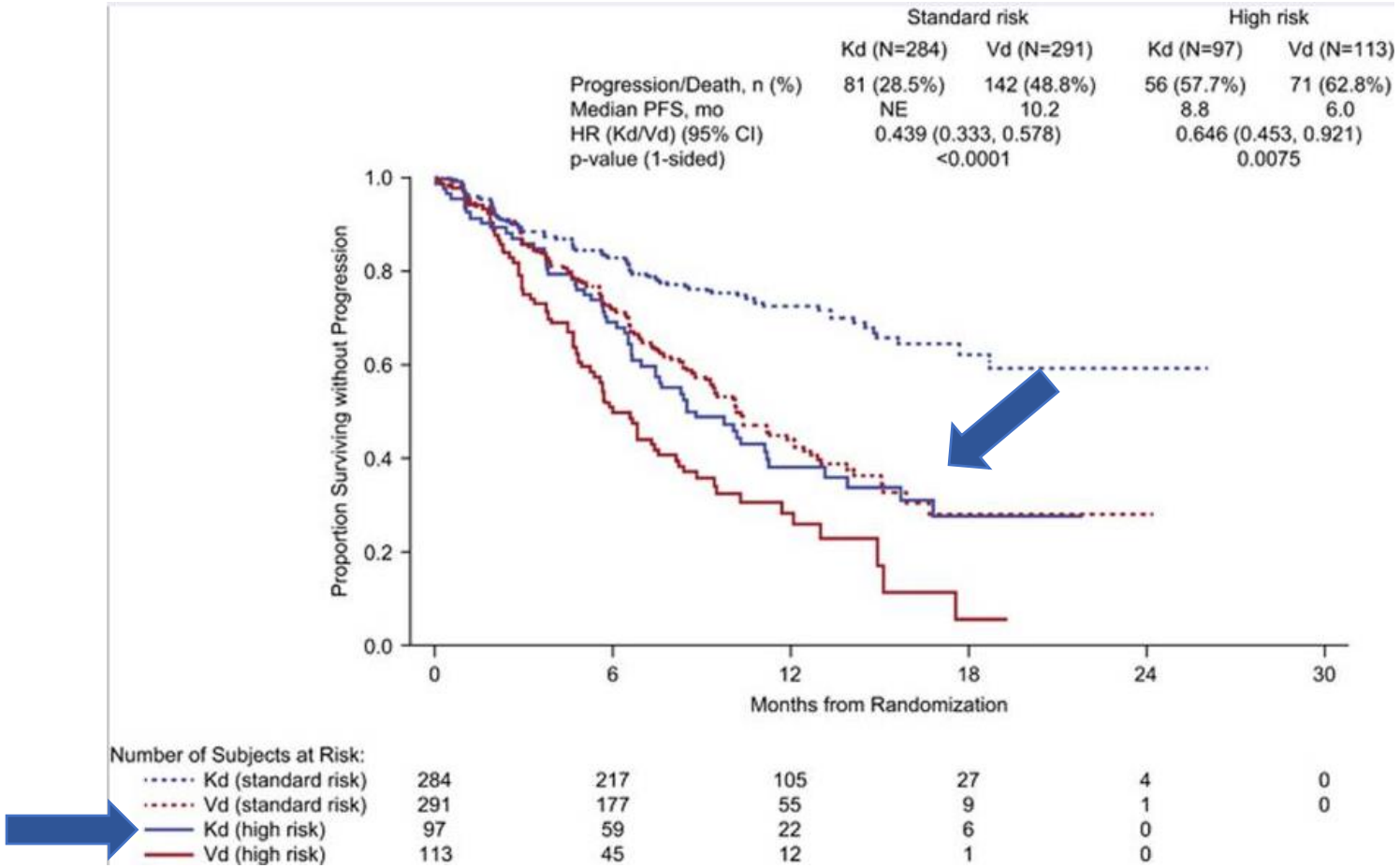
CASTOR[3]
DVd vs Vd



	ENDEAVOR[1-2] Kd vs Vd	CASTOR[3] DVd vs Vd
≥ VGPR	54% vs 29%	63% vs 29%
Median PFS (months)	18.7 vs 9.4, HR 0.53	16.7 vs 7.1, HR 0.31
Median OS (months)	47.8 vs 38.8, HR 0.76	NR
Prior Lena refractory	24% vs 26%	24% vs 33%
Median PFS, (months)	8.6 vs 6.6, HR NR	7.8 vs 4.9, HR 0.44

Dimopoulos, Lancet Oncol 2016; Orlowski, Clin Lymphoma Myeloma Leuk 2019; Spencer, Haematologica 2018

LEN-refractory	ENDEAVOR	Kd vs. Vd



Chng, Leukemia 2018

LEN-refractory

MCRN-003

KCd

Weekly carfilzomib plus cyclophosphamide and dexamethasone in the treatment of relapsed/refractory multiple myeloma: Final results from the MCRN-003/MYX.1 single arm phase II trial

Christopher P. Venner[1] | Richard LeBlanc[2] | Irwindeep Sandhu[1] | Darrell White[3] | Andrew R. Belch[1] | Donna E. Reece[4] | Christine Chen[4] | Sean Dolan[5] | Marc Lalancette[6] | Martha Louzada[7] | Andrea Kew[8] | Arleigh McCurdy[8] | Bethany Monteith[9] | Tony Reiman[5] | Gail McDonald[9] | Max Sherry[9] | Engin Gul[10] | Bingshu E. Chen[9] | Annette E. Hay[9]

PFS

OS

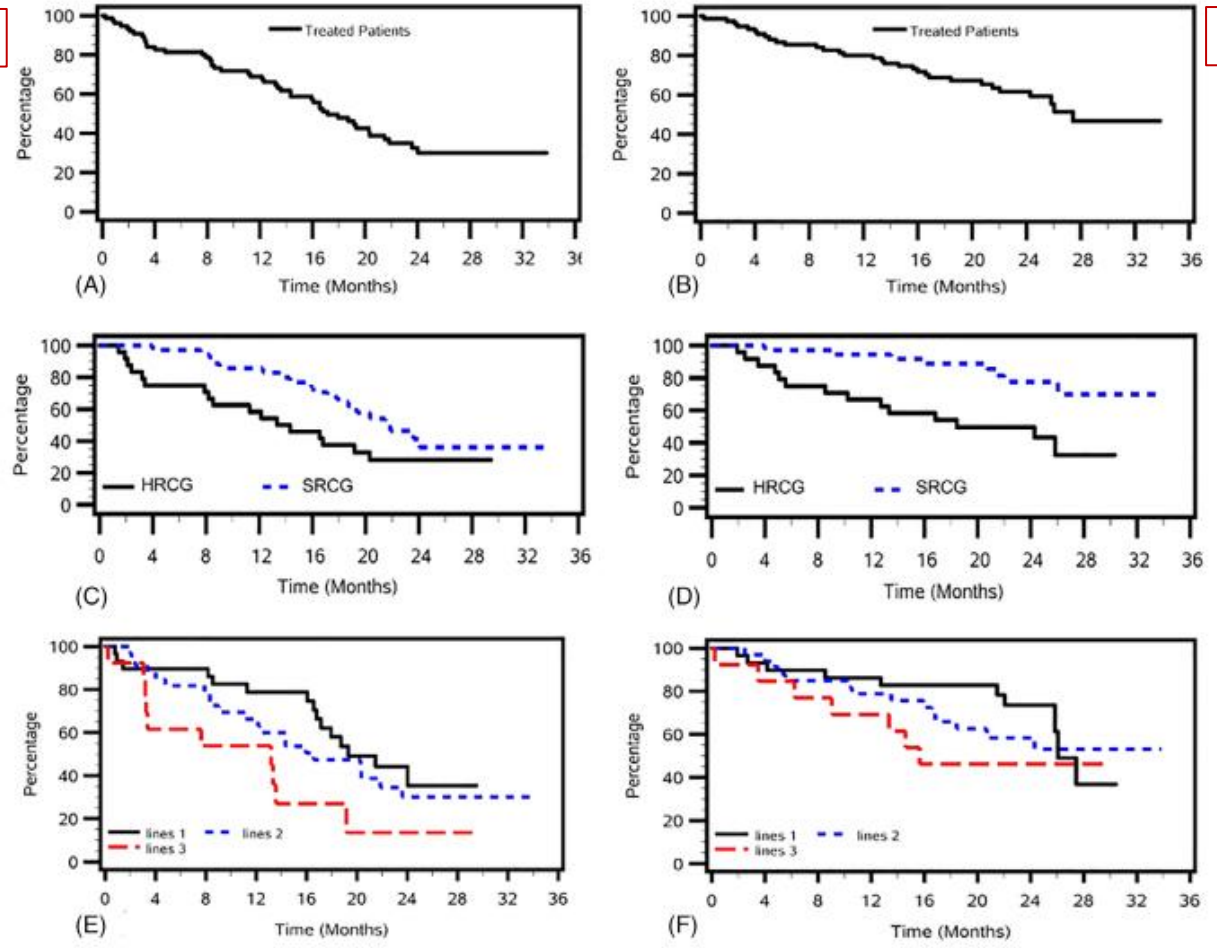


FIGURE 1 Survival outcomes in patients treated with the wKCD regimen examining both (A), progression free survival and (B), overall survival. Patients were further examined based on underlying cytogenetic risk with high risk patients conferring a worse outcome by (C), progression free survival and (D), overall survival. High risk cytogenetics (HRCG) are in solid black lines and standard risk cytogenetics (SRCG) are in dotted blue lines. Lastly, both (E), progression free and (F), overall survival were examined based on prior line of therapy at study entry. Line one patients are in black solid lines, line two patients in dotted blue lines and line three patients are in dotted red lines [Color figure can be viewed at wileyonlinelibrary.com]

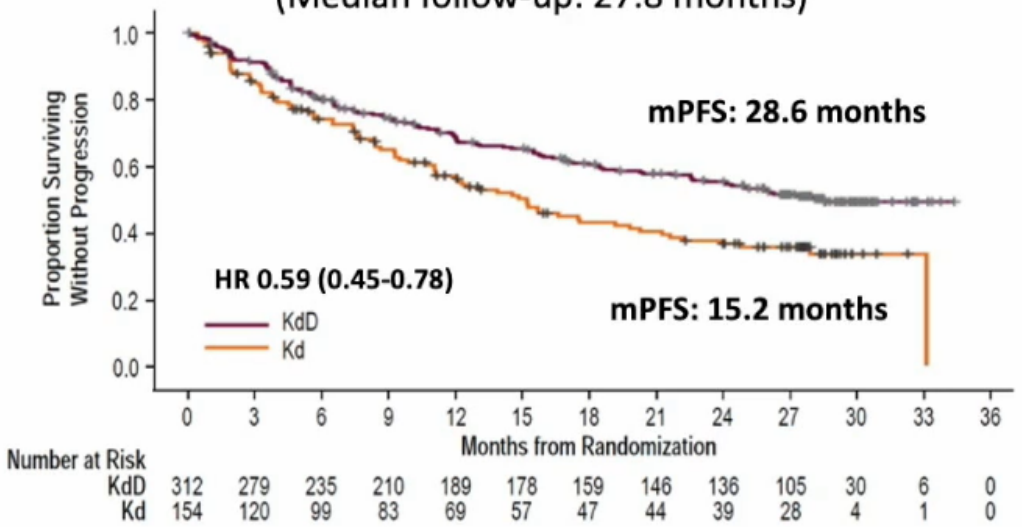
Venner, Am J Hematol 2021

LEN-refractory

PI-based studies

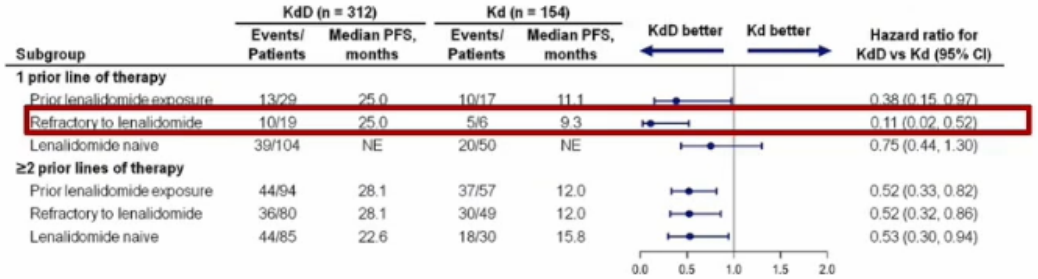
CANDOR: DKd vs Kd

(Median follow-up: 27.8 months)



Number at Risk

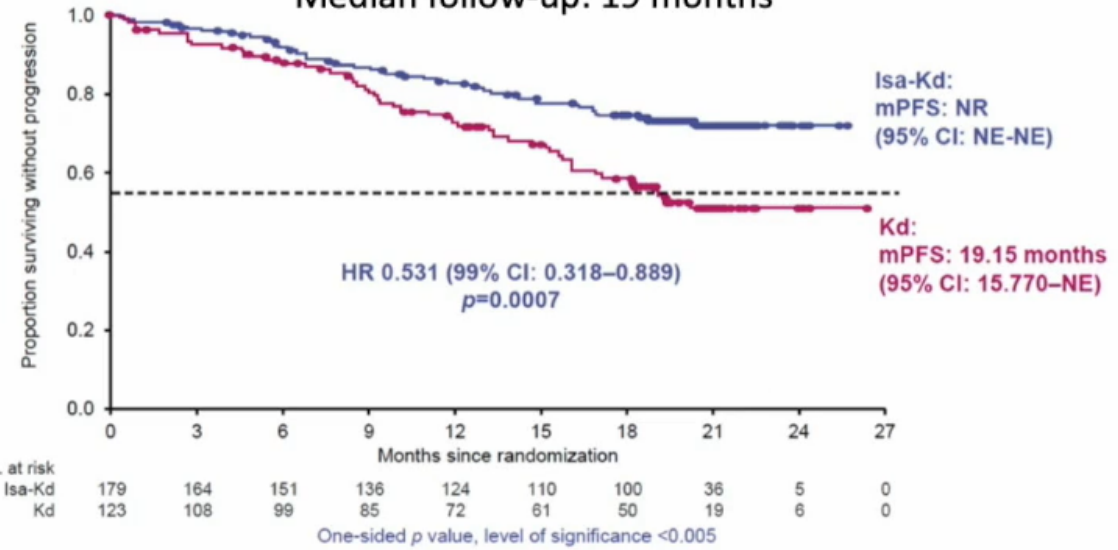
KdD	312	279	235	210	189	178	159	146	136	105	30	6	0
Kd	154	120	99	83	69	57	47	44	39	28	4	1	0



Subgroup	KdD (n = 312) Events/ Patients	KdD (n = 312) Median PFS, months	Kd (n = 154) Events/ Patients	Kd (n = 154) Median PFS, months	Hazard ratio for KdD vs Kd (95% CI)
1 prior line of therapy					
Prior lenalidomide exposure	13/29	25.0	10/17	11.1	0.38 (0.15, 0.97)
Refractory to lenalidomide	10/19	25.0	5/6	9.3	0.11 (0.02, 0.52)
Lenalidomide naive	39/104	NE	20/50	NE	0.75 (0.44, 1.30)
≥2 prior lines of therapy					
Prior lenalidomide exposure	44/94	28.1	37/57	12.0	0.52 (0.33, 0.82)
Refractory to lenalidomide	36/80	28.1	30/49	12.0	0.52 (0.32, 0.86)
Lenalidomide naive	44/85	22.6	18/30	15.8	0.53 (0.30, 0.94)

IKEMA: IsaKd vs Kd

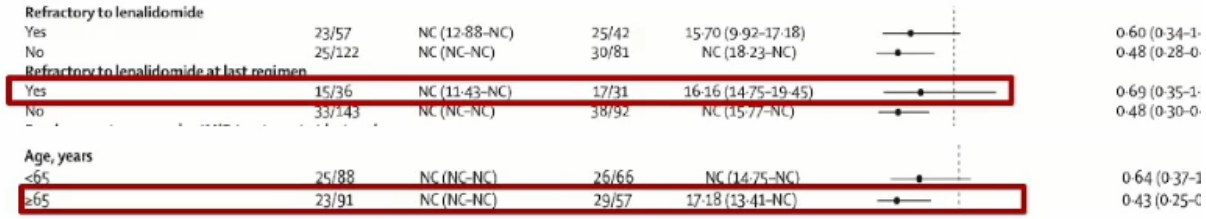
Median follow-up: 19 months



No. at risk

Isa-Kd	179	164	151	136	124	110	100	36	5	0
Kd	123	108	99	85	72	61	50	19	6	0

One-sided *p* value, level of significance <0.005



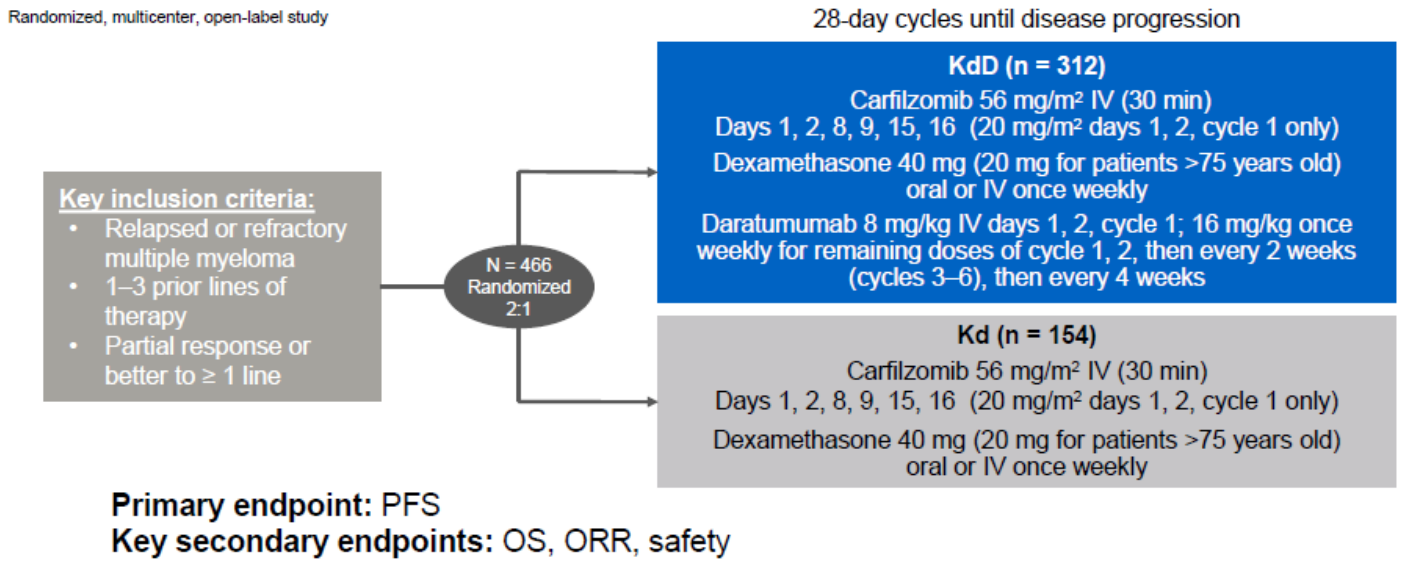
Refractory to lenalidomide					
Yes	23/57	NC (12·88–NC)	25/42	15·70 (9·92–17·18)	0·60 (0·34–1·
No	25/122	NC (NC–NC)	30/81	NC (18·23–NC)	0·48 (0·28–0·
Refractory to lenalidomide at last regimen					
Yes	15/36	NC (11·43–NC)	17/31	16·16 (14·75–19·45)	0·69 (0·35–1·
No	33/143	NC (NC–NC)	38/92	NC (15·77–NC)	0·48 (0·30–0·
Age, years					
<65	25/88	NC (NC–NC)	26/66	NC (14·75–NC)	0·64 (0·37–1
≥65	23/91	NC (NC–NC)	29/57	17·18 (13·41–NC)	0·43 (0·25–0

Dimopoulos, Lancet 2020; Dimopoulos, ASH 2020, #2325; Landgren, ASH 2020, #2282; Moreau, Lancet 2021; Dimopoulos, EHA 2021, #EP986; Martin, ASH 2020, #414; Capra, ASH 2020, #3241

LEN-refractory | CANDOR | DKd vs. Kd

Carfilzomib, dexamethasone, and daratumumab versus carfilzomib and dexamethasone for patients with relapsed or refractory multiple myeloma (CANDOR): results from a randomised, multicentre, open-label, phase 3 study

Meletios Dimopoulos, Hang Quach, Maria-Victoria Mateos, Ola Landgren, Xavier Leleu, David Siegel, Katja Weisel, Hui Yang, Zandra Klippel, Anita Zahlten-Kumeli, Saad Z Usmani



Primary endpoint: PFS
Key secondary endpoints: OS, ORR, safety

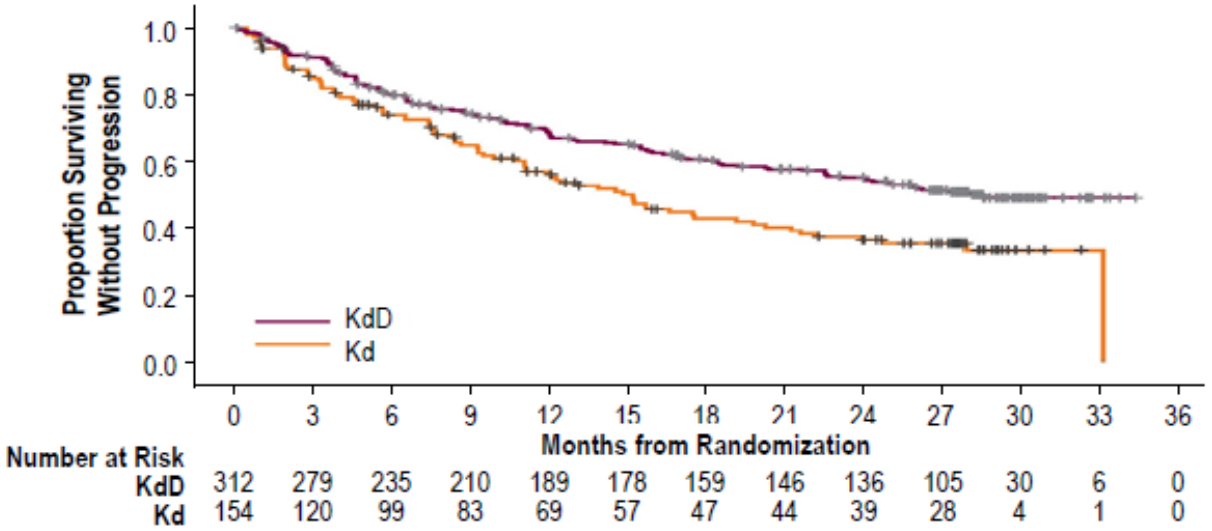
	Carfilzomib, dexamethasone, and daratumumab group (n=312)	Carfilzomib and dexamethasone group (n=154)
(Continued from previous page)		
Previous therapies		
Transplant	195 (63%)	75 (49%)
CD38 antibody therapy†	1 (<1%)	0
Proteasome inhibitor	290 (93%)	139 (90%)
Immunomodulatory drug	206 (66%)	110 (71%)
Bortezomib	287 (92%)	134 (87%)
Refractory to any previous bortezomib-including regimen‡	88 (28%)	47 (31%)
Lenalidomide	123 (39%)	74 (48%)
Refractory to any previous lenalidomide-including regimen‡	99 (32%)	55 (36%)

Data are median (IQR), n (%), or mean (SD). *Fluorescence in-situ hybridisation analysis was conducted by the central laboratory. The high-risk group consisted of patients with the genetic subtypes t(4;14), t(14;16), or deletion 17p. The standard-risk group consisted of patients without t(4; 14), t(14; 16), and deletion 17p. The unknown risk group consisted of patients with fluorescence in-situ hybridisation results that failed or were cancelled. †Based on the Interactive Voice and Web Response System at the time of randomisation. ‡Patients were considered refractory to a drug received in previous regimens if any of the following criteria were met: best response to any regimen containing the drug was stable disease or progressive disease; reason the drug was stopped was progression in any regimen; date of relapse or progression was after start date and within 60 days after stop date of the drug in any regimen.

Table 1: **Baseline characteristics of the intention-to-treat population**

Dimopoulos, Lancet 2020

LEN-refractory	CANDOR	DKd vs. Kd



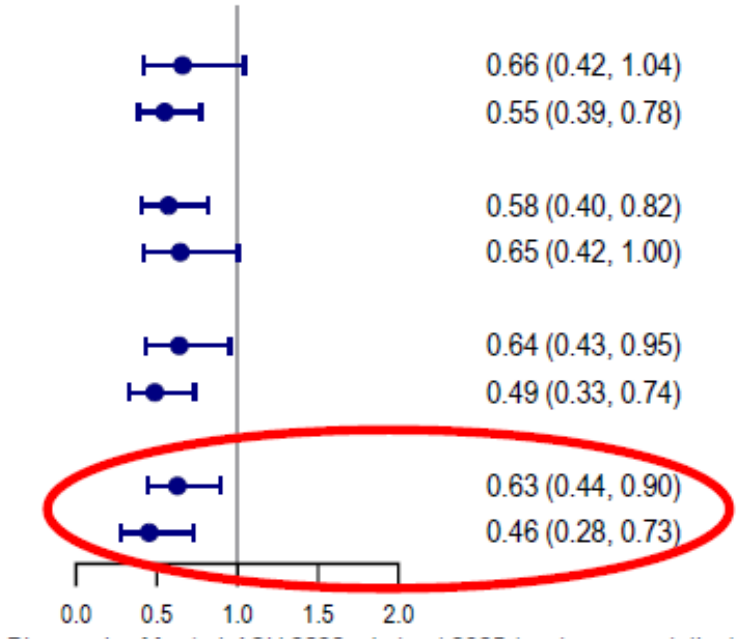
	KdD (n = 312)	Kd (n = 154)
Median treatment duration, months	18.3	9.3
Median PFS follow-up, months	27.8	27.0
Median PFS by ORCA, months	**28.6**	**15.2**
HR (KdD/Kd) (95% CI)	**0.59 (0.45–0.78)**	

41% reduction in risk of progression/death
13.4-month improvement in mPFS with DKd

Dimopoulos, Lancet 2020

LEN-refractory | CANDOR | DKd vs. Kd

Subgroup	KdD (n = 312) Events/ Patients	KdD (n = 312) Median PFS, months	Kd (n = 154) Events/ Patients	Kd (n = 154) Median PFS, months	Hazard ratio for KdD vs Kd (95% CI)
Number of prior lines of therapy					
1	52/133	NE	30/67	21.3	0.66 (0.42, 1.04)
≥2	88/179	24.2	55/87	12.5	0.55 (0.39, 0.78)
Refractory to PI*					
No	86/212	NE	50/99	16.6	0.58 (0.40, 0.82)
Yes	54/100	13.1	35/55	8.7	0.65 (0.42, 1.00)
Prior lenalidomide exposure					
No	83/189	NE	38/80	21.3	0.64 (0.43, 0.95)
Yes	57/123	25.9	47/74	11.1	0.49 (0.33, 0.74)
Refractory to lenalidomide					
No	94/213	28.6	50/99	19.9	0.63 (0.44, 0.90)
Yes	46/99	28.1	35/55	11.1	0.46 (0.28, 0.73)



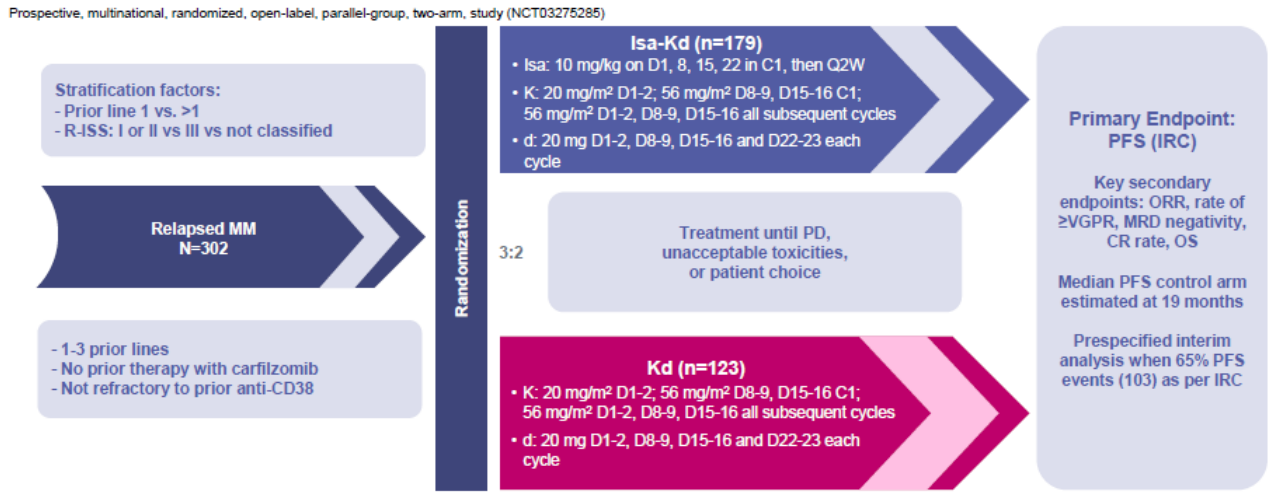
Consistent PFS benefit by prior therapy and refractory disease status

Dimopoulos, Lancet 2020

LEN-refractory | IKEMA | IsaKd vs. Kd

Isatuximab, carfilzomib, and dexamethasone in relapsed multiple myeloma (IKEMA): a multicentre, open-label, randomised phase 3 trial

Philippe Moreau, Meletios-Athanasios Dimopoulos, Joseph Mikhael, Kwee Yong, Marcelo Capra, Thierry Facon, Roman Hajek, Ivan Špička, Ross Baker, Kihyun Kim, Gracia Martinez, Chang-Ki Min, Ludek Pour, Xavier Leleu, Albert Oriol, Youngil Koh, Kenshi Suzuki, Marie-Laure Risse, Gaelle Asset, Sandrine Macé, Thomas Martin*, on behalf of the IKEMA study group†*



Number of previous lines of therapy		
Median (IQR)	2 (1–2)	2 (1–3)
One	79 (44%)	55 (45%)
Two	64 (36%)	36 (29%)
Three	33 (18%)	30 (24%)
More than three	3 (2%)§	2 (2%)
Autologous transplant	116 (65%)	69 (56%)
Main anti-myeloma therapies by class and agent		
Alkylating agents	169 (94%)	101 (82%)
Proteasome inhibitors	166 (93%)	105 (85%)
Immunomodulators	136 (76%)	100 (81%)
Lenalidomide	72 (40%)	59 (48%)
Corticosteroids	179 (100%)	123 (100%)
Monoclonal antibodies	5 (3%)	1 (1%)
Daratumumab	1 (1%)	0
Refractory to immunomodulatory imide drug	78 (44%)	58 (47%)
Refractory to lenalidomide	57 (32%)	42 (34%)
Refractory to lenalidomide in last previous regimen	36 (20%)	31 (25%)
Refractory to proteasome inhibitor	56 (31%)	44 (36%)
Refractory to immunomodulatory imide drug and proteasome inhibitor	35 (20%)	27 (22%)
Refractory to last regimen	89 (50%)	73 (59%)

Moreau, Lancet 2021

LEN-refractory | IKEMA | IsaKd vs. Kd

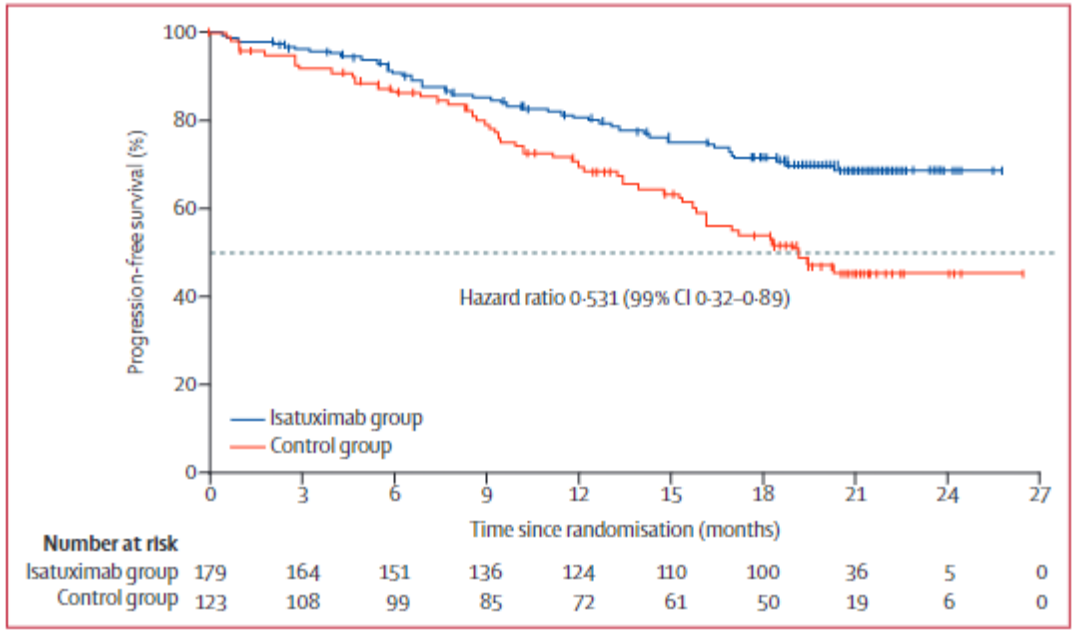
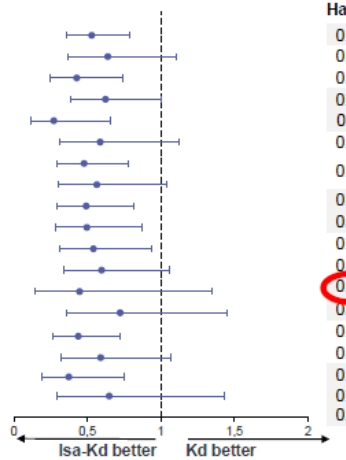


Figure 2: **Progression-free survival**
Kaplan-Meier analysis of progression-free survival among patients in the intention-to-treat population, as assessed by an independent response review committee. Median progression-free survival was not reached (95% CI not estimable) for the isatuximab group and 19·15 months (15·77–not estimable) in the control group. Hazard ratio and 99% CI are derived from Cox proportional hazards model stratified by number of previous lines of therapy and revised International Staging System stage. One sided p value calculated by log-rank test was 0·0007, which was below the nominal significance level at the interim analysis (0·005).

PFS subgroup analyses

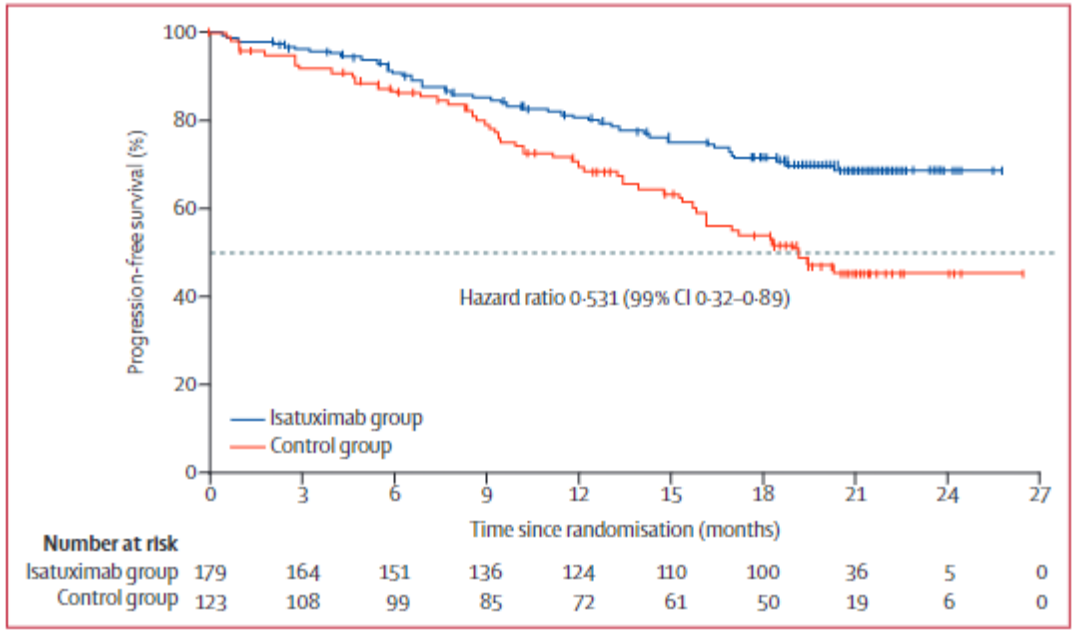
Subgroup		Isa-Kd No. of events/total no.	Kd No. of events/total no.	Hazard ratio (95% CI)
All patients		48/179	55/123	0.531 (0.359–0.786)
Age	<65 years	25/88	26/66	0.640 (0.370–1.109)
	≥65 years	23/91	29/57	0.429 (0.248–0.742)
Baseline eGFR (MDRD)	≥60 mL/min/1.73 m²	32/122	38/93	0.625 (0.391–1.001)
	<60 mL/min/1.73 m²	10/43	10/18	0.273 (0.113–0.660)
Number of prior lines of therapy	1	18/80	19/55	0.589 (0.309–1.123)
	>1	30/99	36/68	0.479 (0.294–0.778)
Prior PI treatment*	Yes	22/81	20/47	0.565 (0.308–1.036)
	No	26/98	35/76	0.493 (0.296–0.819)
Prior IMiD treatment*	Yes	22/81	29/62	0.498 (0.286–0.869)
	No	26/98	26/61	0.542 (0.314–0.933)
Refractory to Len	Yes	23/57	25/42	0.598 (0.339–1.055)
	No	5/15	9/17	0.448 (0.149–1.349)
High-risk cytogenetic status	Yes	17/42	15/31	0.724 (0.361–1.451)
	No	27/114	35/77	0.440 (0.266–0.728)
ISS staging at study entry	I	20/89	24/71	0.592 (0.327–1.071)
	II	17/63	16/31	0.375 (0.188–0.748)
	III	11/26	14/20	0.650 (0.295–1.434)



Consistent treatment effect for Isa-Kd accross all subgroups

Moreau, Lancet 2021

LEN-refractory | IKEMA | IsaKd vs. Kd



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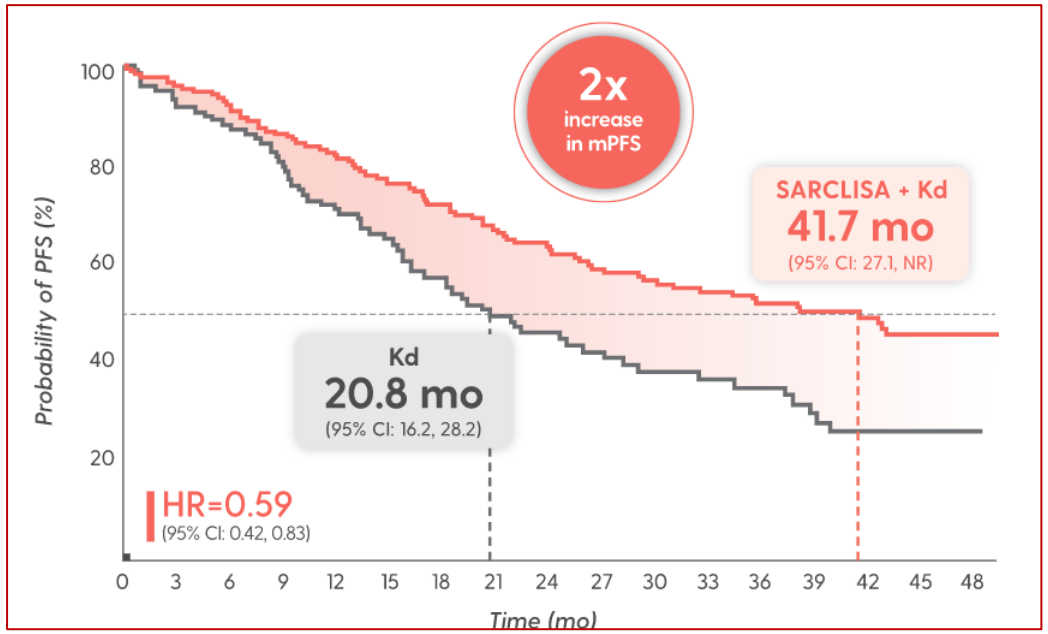

Consistent treatment effect for Isa-Kd accross all subgroups

Moreau, Lancet 2021

First relapse

Treatment options ESMO 2021

	CANDOR DKd vs. Kd	IKEMA IsaKd vs. Kd	APOLLO DPd vs. Pd	OPTIMISMM PVd vs. Pd	ICARIA IsaPd vs. Pd	ELOQUENT 3 EloPd vs. Pd
Lines of therapy	At least 1	At least 1, median 2	At least 1, median 2	At least 1, median 2	At least 2, median 3	At least 2, median 3
PFS HR (95% CI)	0.59 (0.45-0.78)	0.54 (0.37-0.82)	0.63 (0.47-0.85)	0.61 (0.49-0.77)	0.596 (0.43-0.81)	0.59 (0.37-0.93)
PFS, months	28.6 vs. 15.2	35.2 vs. 19.2	12.4 vs. 6.9	11.2 vs. 7.2	11.5 vs. 6.5	11.5 vs. 6.5
PFS first relapse	NR vs. NR HR 0.67 (0.4-1.1)	NR vs. NR HR 0.59 (0.31-1.1)	14.1 vs. 12.6 HR 0.70 (0.3-1.6)	20.7 vs. 11.6		mOS, 29.8 vs. 17.4

Conclusions

- Treatment of RRMM remains **challenging**
- **Salvage ASCT** is an option for patients that received a prior ASCT followed by LEN maintenance and had an **initial remission duration > 36 months**
- **Patients who are refractory to LEN upfront** represent an **emerging population**
  - PVD is the approved indication with best results in terms of PFS as second-line therapy in LEN-refractory patients.
  - Dara-Kd and Isa-Kd have given the best reported PFS to date in LEN-refractory patients
- **Tolerability** is key to efficacy with ‘real world data’ of particular value