



# THE CASE FOR PROTEASOME INHIBITORS AT FIRST RELAPSE IN RRMM

Nisha S. Joseph, MD

Assistant Professor

Department of Hematology and Medical Oncology

Winship Cancer Institute, Emory University



## PATIENT CASE

- ❖ 68-year-old male presented with anemia and renal dysfunction.
- ❖ Work up reveals R-ISS II myeloma, standard risk

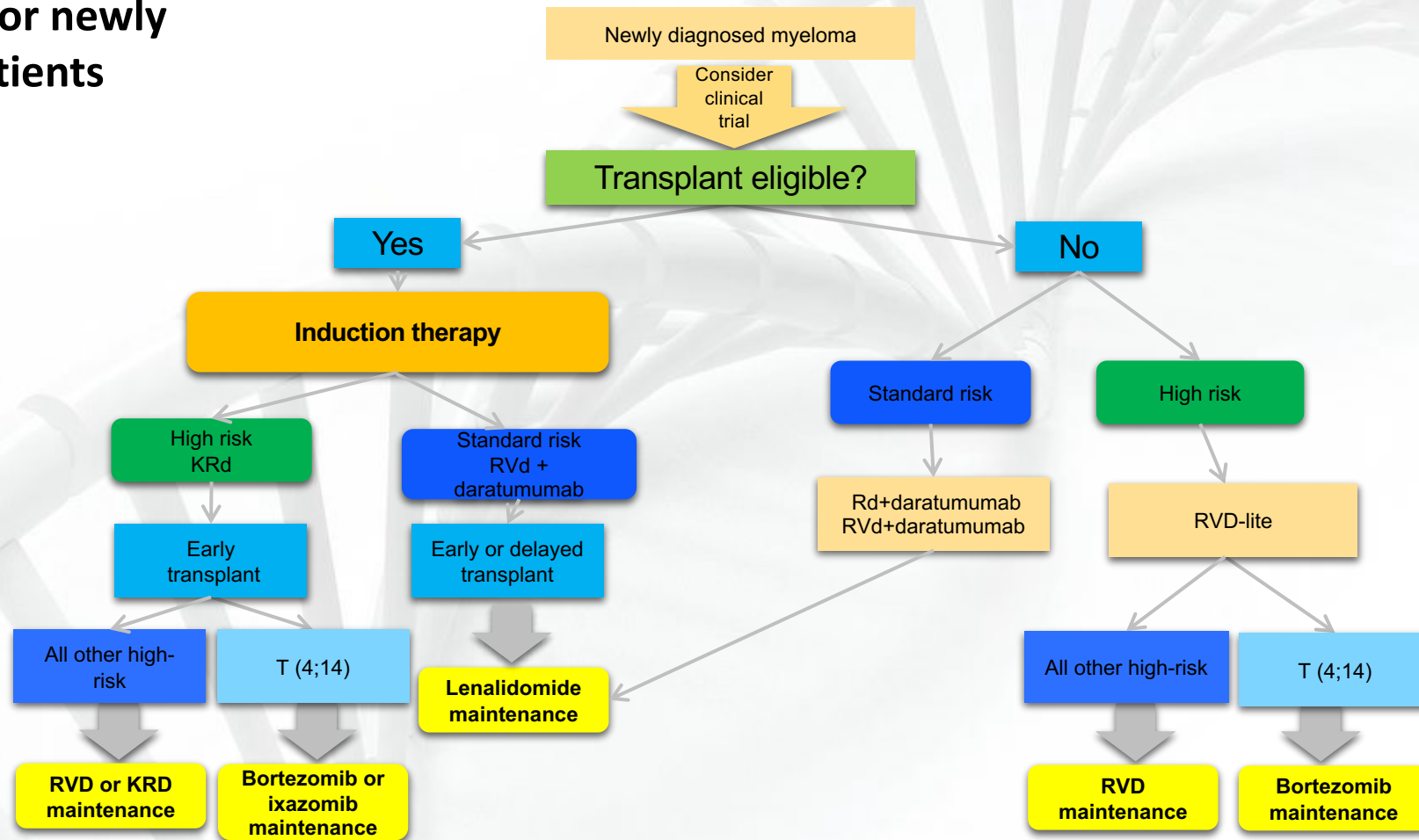
### Treatment:

- ❖ Induction with RVD followed by ASCT conditioning with Melphalan 200 mg/m<sup>2</sup>
- ❖ Post-transplant response = VGPR
- ❖ Started on maintenance therapy with lenalidomide
- ❖ At 4 year restaging, confirmed disease progression.

**What is the best treatment option for this patient?**

# TREATMENT APPROACH TO NDMM

## Emory Algorithm for newly diagnosed MM patients



**Majority of patients are len-refractory at 1<sup>st</sup> relapse**

VD: bortezomib/dexamethasone; Rd: lenalidomide/dexamethasone; RVD: bortezomib/lenalidomide/dexamethasone, RVD-lite: modified RVD; VMP: bortezomib/melphalan/prednisone

# RANDOMIZED TRIALS OF LENALIDOMIDE-DEX COMBINATIONS

Trial	% With Prior Len	% IMiD Refractory/ Len refractory	%First-Relapsed	Response Rates for Triplet vs Doublet (%)	PFS for Triplet vs Doublet, Months	Interim OS for Triplet vs Doublet, Months
<b>ASPIRE<sup>1</sup> KRd vs Rd</b>	19.8	<b>21/7.2</b>	46.5	87 vs 67	<b>26.3 vs 17.6</b> ( <i>P</i> = .0001)	73.3% vs 65% (24 months)
<b>TOURMALINE<sup>2</sup> IRd vs Rd</b>	12	<b>21/NE</b>	62	78 vs 72	<b>20.6 vs 14.7</b> ( <i>P</i> = .012)	--
<b>ELOQUENT-2<sup>3</sup> Elo-Rd vs Rd</b>	5	<b>10/NE</b>	47	79 vs 66	<b>19.4 vs 14.9</b> ( <i>P</i> = .014)	43.7 vs 39.6 ( <i>P</i> = .026)
<b>POLLUX<sup>4</sup> Dara-Rd vs Rd</b>	17.5	<b>3.5/NE</b>	50.5	93 vs 76	<b>44.5 vs 17.5</b> ( <i>P</i> <.0001)	65% vs 57% (42-months)

K=carfilzomib; P=panobinostat; D=daratumumab; E=elotuzumab; d=dexamethasone; NE = not eligible

1. Stewart AK, et al. *N Engl J Med.* 2015;372(2):142-152; 2. Moreau P, et al. *N Engl J Med.* 2016;374:1621-1634; 3. Lonial S, et al. *N Engl J Med.* 2015;373(7):621-631; 4. Bahlis NJ, et al. *Leukemia* 2020 .

Slide courtesy of Dr S Usmani

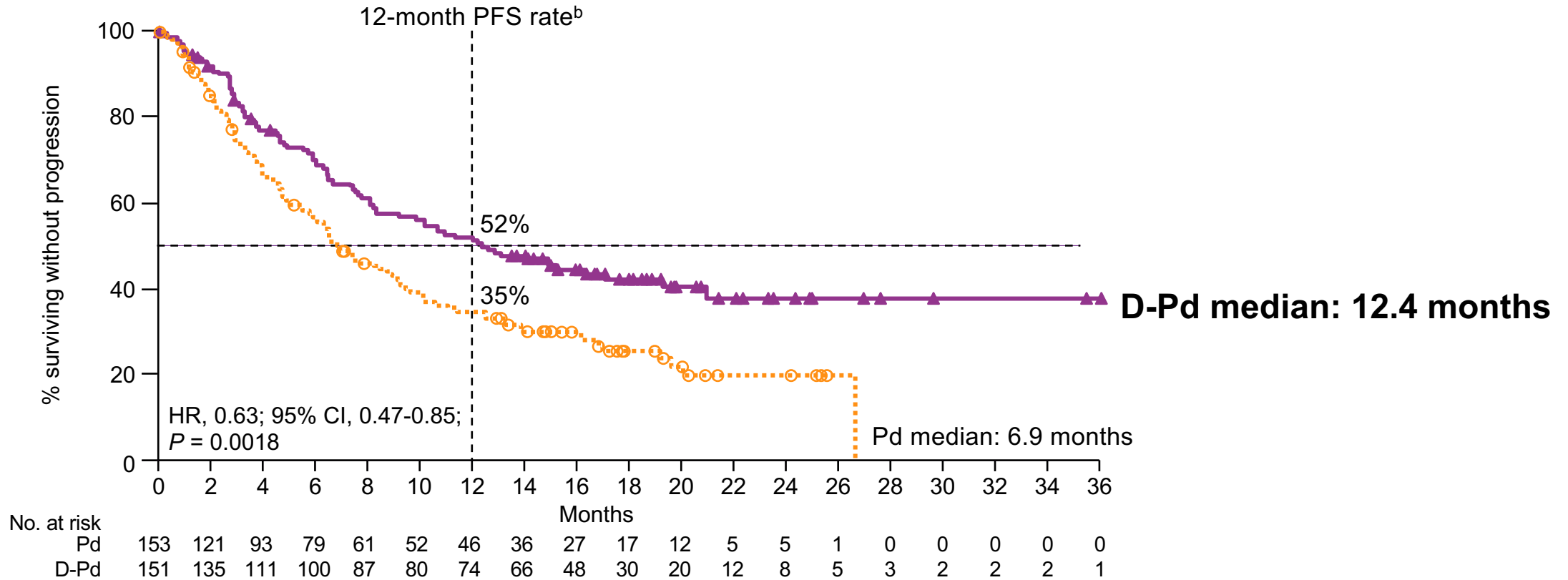
# ROLE OF POMALIDOMIDE IN LEN-REFRACTORY PATIENTS

Trial	Prior regimens	% Len Refractory	% PI Refractory	Response Rates for Triplet vs Doublet (%)	PFS for Triplet vs Doublet, Months
<b>APOLLO<sup>1</sup></b> Dara-Pd vs Pd	2	79	48	69 vs 46	<b>12.4 vs 6.9</b> ( <i>P</i> = .0018)
<b>ICARIA-MM<sup>2</sup></b> Isa-Pd vs Pd	3	94	77	60 vs 35	<b>11.5 vs 6.5</b> ( <i>P</i> = .001)
<b>NCT02654132<sup>3</sup></b> Elo-Pd vs Pd	2	90	78	53 vs 26	<b>10.3 vs 4.7</b> ( <i>P</i> = .008)
<b>OPTIMISM<sup>4</sup></b> V-Pd vs Pd	2	71	44	61 vs 55	<b>11.99 vs 8.08</b> ( <i>p</i> <0.0001)

1. Dimopoulos et al Lancet Oncol 2021, 2. Attal et al Lancet 2019, 3. Dimopoulos et al NEJM 2018, 4. Jesús F San-Miguel et al Lancet Oncol 2014;15: 1195–206. 5. Jatin J. Shah et al Blood (2015) 126 (20): 2284–2290.

Slide courtesy of Dr S Usmani

# PHASE 3 APOLLO STUDY



**Median PFS among patients refractory to lenalidomide was 9.9 months for DPd**

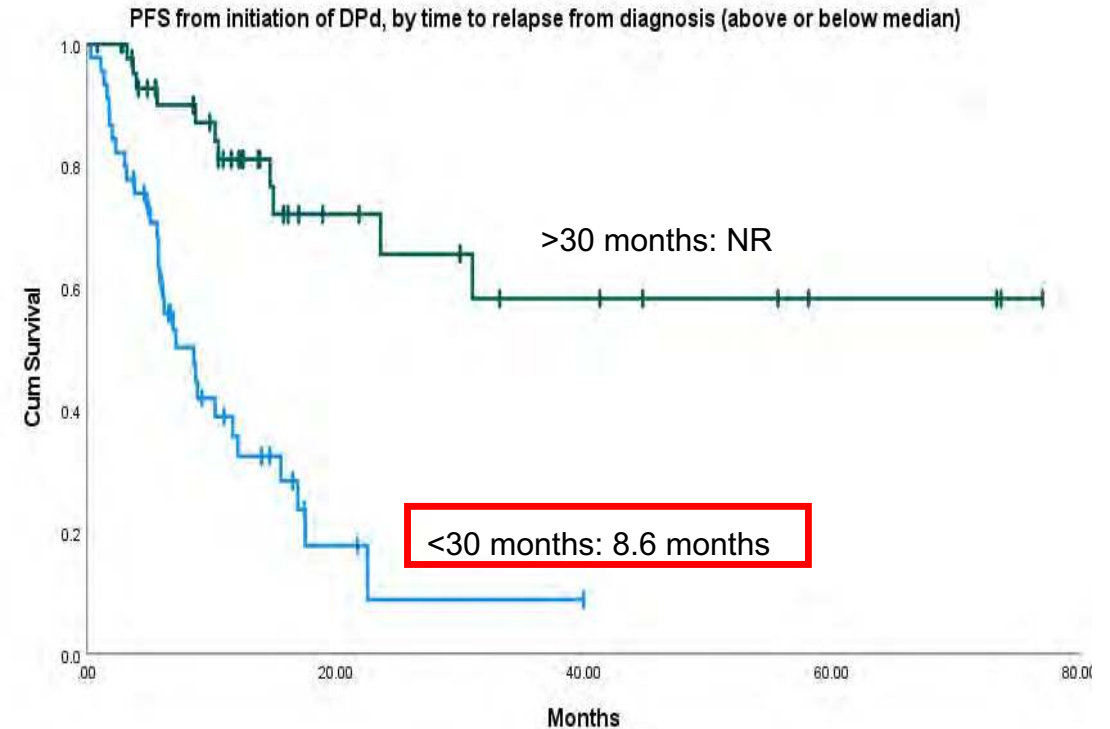
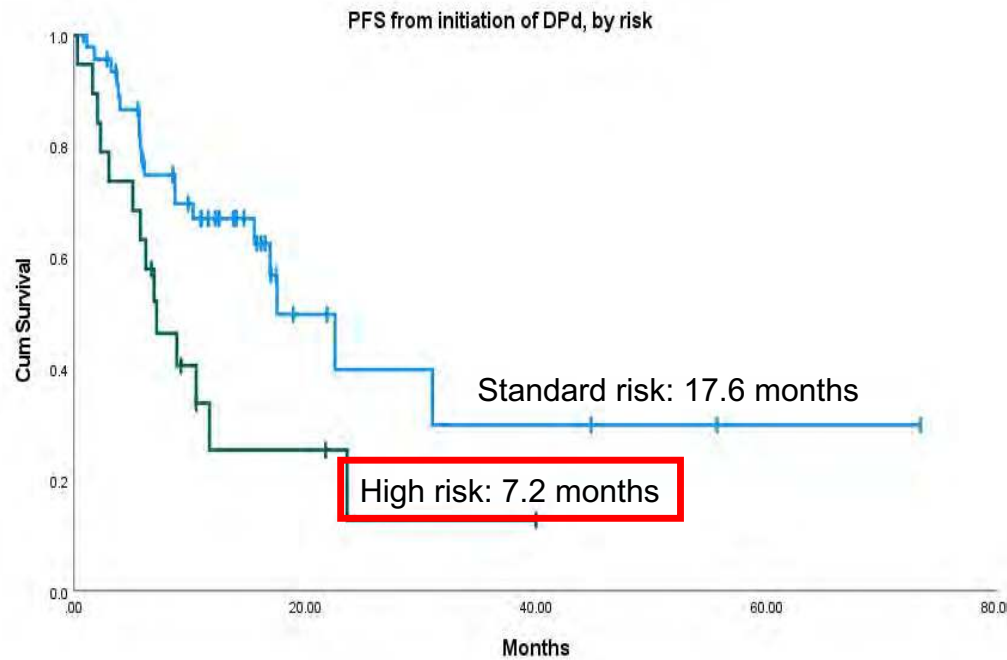
HR, hazard ratio; CI, confidence interval. <sup>a</sup>Intent-to-treat population. <sup>b</sup>Kaplan–Meier estimate.

# DPD AT FIRST RELAPSE: EMORY EXPERIENCE

**mPFS for the entire cohort = 15.6 months**

**mPFS in standard risk vs high risk patients treated with DPD at first relapse**

**mPFS by time to first relapse from diagnosis (<30 months vs >30 months)**



Joseph et al, ASH 2021

PI

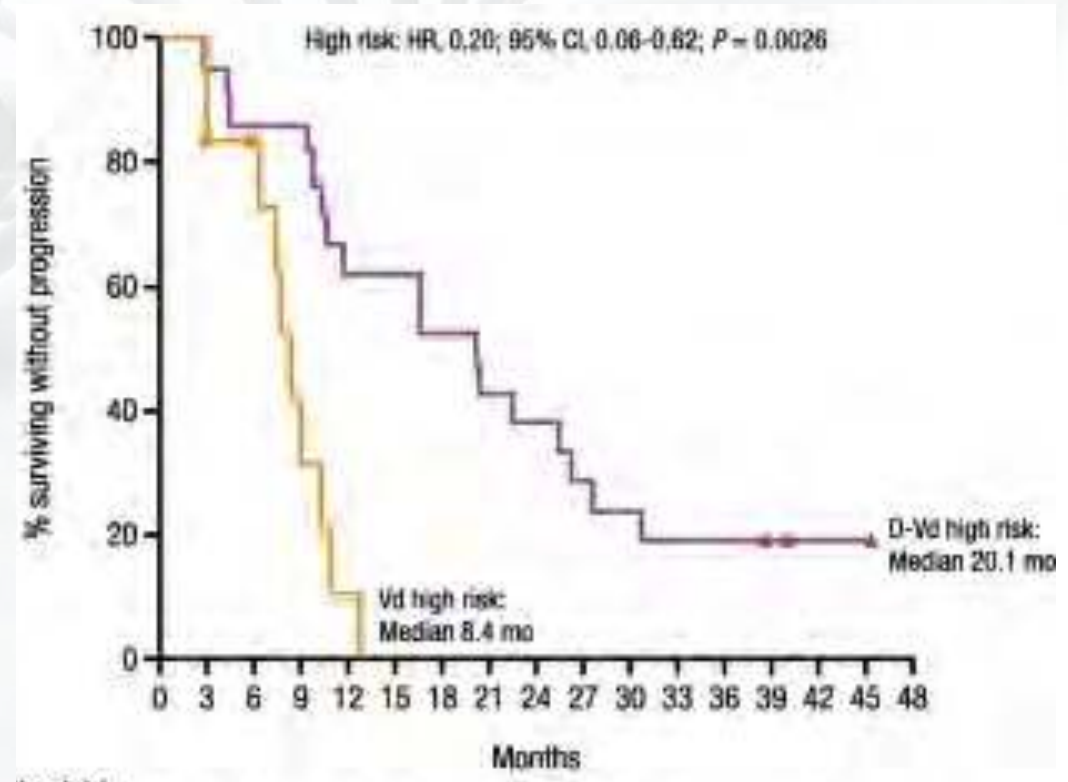
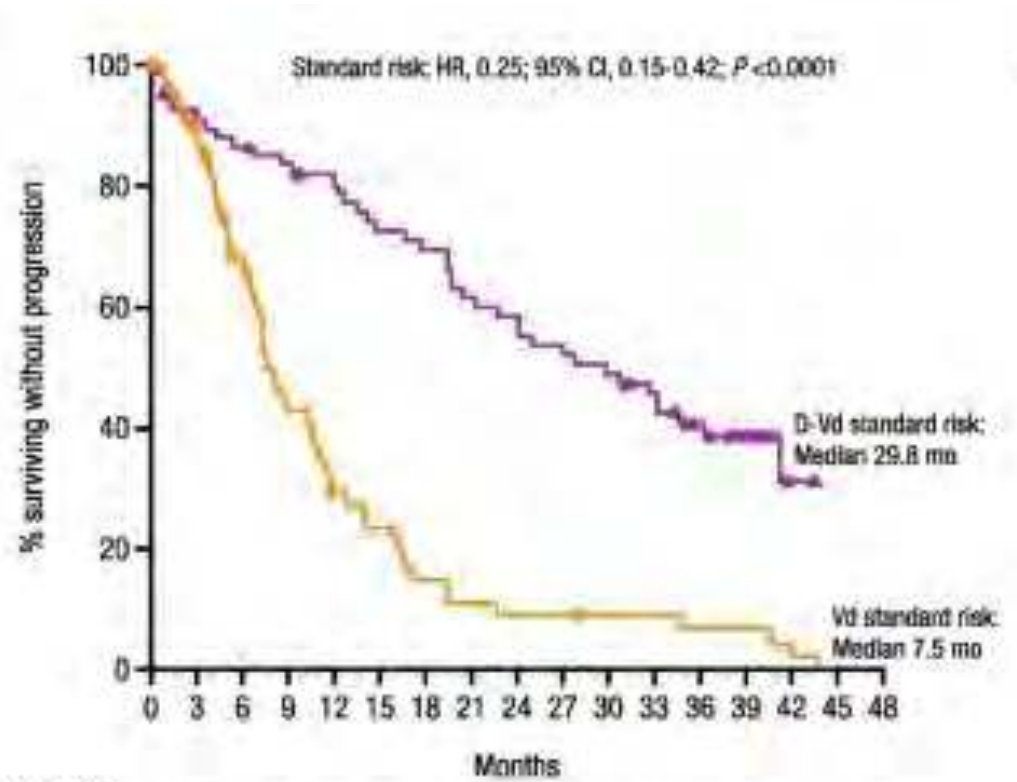


IMID



# PHASE 3 CASTOR<sup>1</sup> TRIAL – DVD VS VD IN R/R MYELOMA

- DVD showed greatest benefit in patients at first relapse with mPFS benefit of **27 mo** versus 7.9 mo
- mPFS **30 mo** in SR and **20 mo** in HR <sup>2</sup>



Palumbo et al, NEJM 2016 <sup>1</sup>; Weisel et al JHO 2020 <sup>2</sup>; Usmani et al ASH 2018 <sup>3</sup>

# CARFILZOMIB-BASED REGIMENS AT RELAPSE

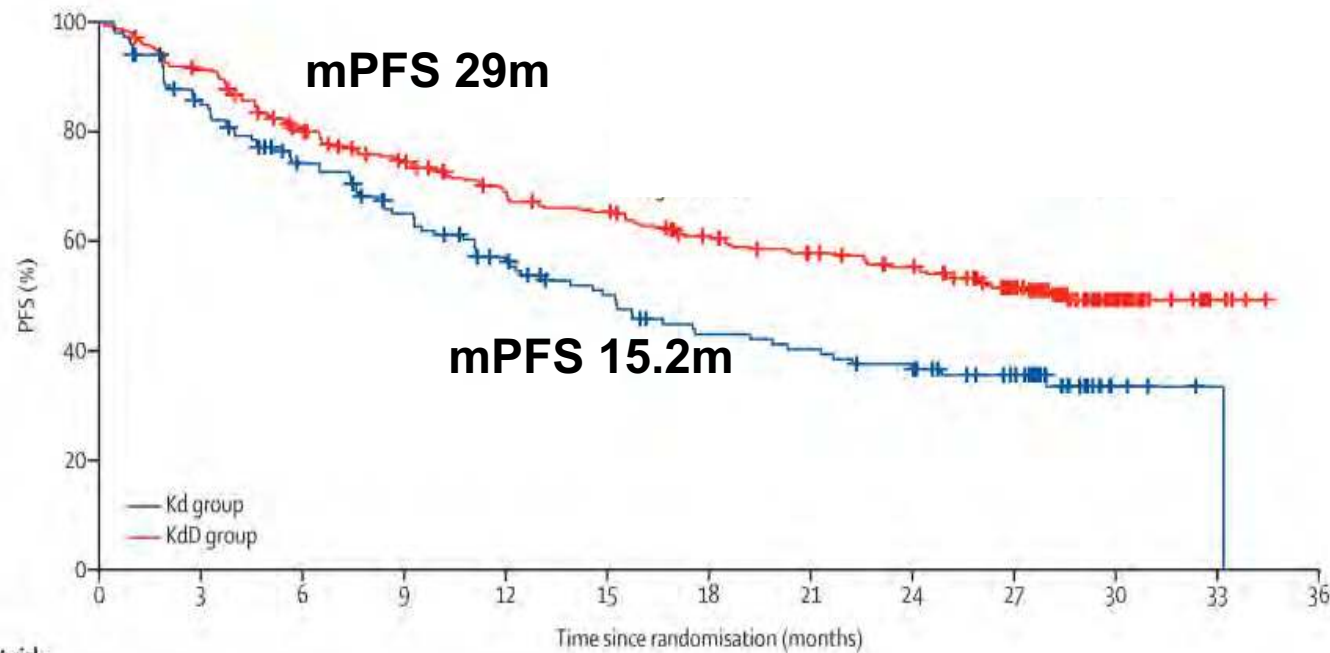
Third Agent	% Len Refractory	% PI Exposed, Refractory	% With High-Risk Cytogenetics	Response Rates for Triplet vs Doublet (%)	PFS for Triplet vs Doublet, Months
<b>Daratumumab<sup>1</sup> Dara-Kd vs Kd (CANDOR)</b>	33	90, 30	15.4 vs 16.9	84 vs 75	<b>28.6 vs 15.2</b> ( <i>P</i> = .0001)
<b>Isatuximab<sup>2</sup> Isa-Kd vs Kd (IKEMA )</b>	33	93, 31	24 vs 25	86 vs 83	<b>35.7 vs 19.2</b> ( <i>P</i> = .0007)
<b>Cyclophosphamide<sup>3</sup> KCd vs Kd</b>	36	100, --	24 vs 23	78 vs 73	<b>20.7 vs 15.2</b> ( <i>P</i> = .24)

1. Dimopolus et al Lancet 2020
2. Martin M et al ASCO 2020; Moreau et al ESMO 2022
3. Mateos MV et al ASH 2020

\*Not reached

# PHASE 3 CANDOR TRIAL

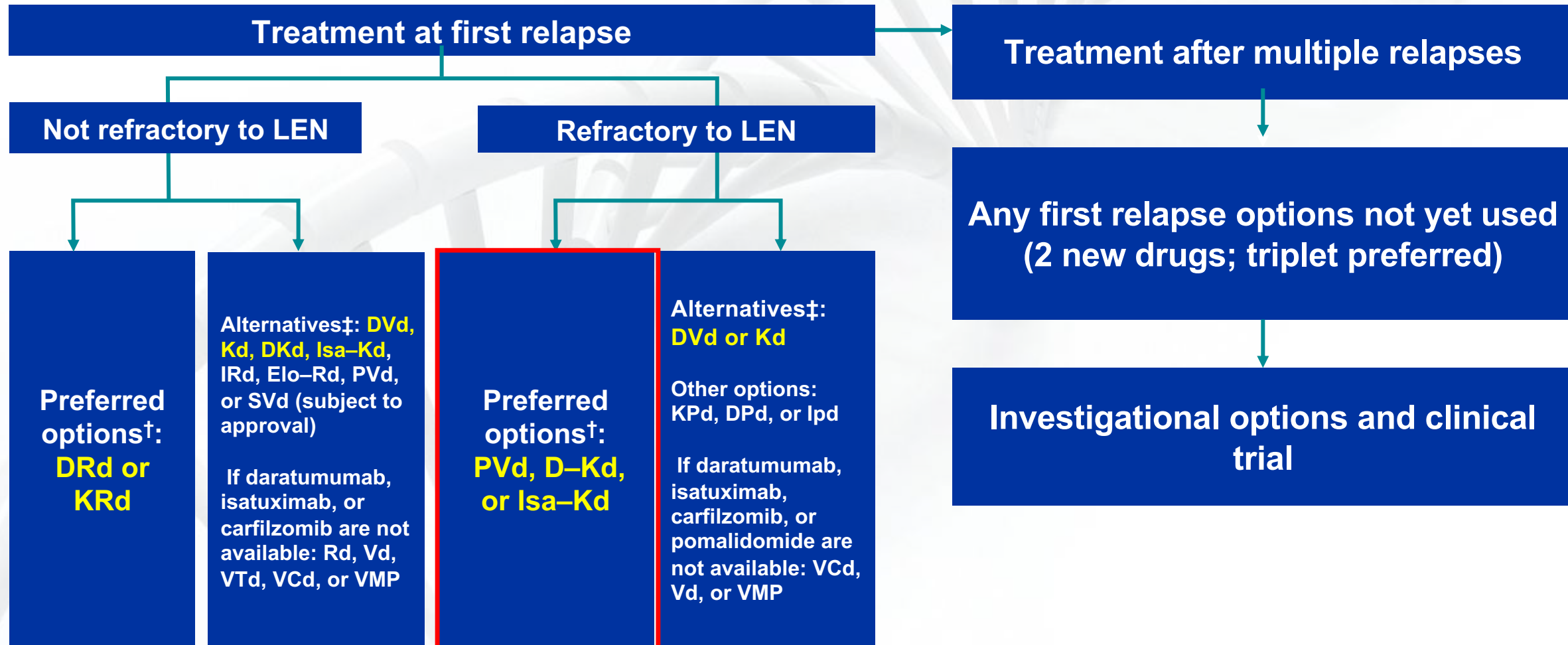
- Phase 3 CANDOR study evaluated KdD vs Kd (2:1) in patients with RRMM (N = 466)<sup>1</sup>
- 43% of patients in the CANDOR trial had received 1 prior line of therapy
- 33% of patients were len-refractory



**In patients with one PLOT and len-refractory, mPFS 25 months**

Dimopolous et al, Lancet 2020; Usmani et al Lancet 2022, Quach et al BJH 2021

# IMWG GUIDELINES : TREATMENT AT 1<sup>ST</sup> RELAPSE



Moreau, et al. Lancet Oncol 2021; 22: e105-18

## CASE PRESENTATION

- ❖ 68-year-old male presented with anemia and renal dysfunction.
- ❖ Work up reveals R-ISS II myeloma, standard risk

### Treatment:

- ❖ Induction with RVD followed by ASCT conditioning with Melphalan 200 mg/m<sup>2</sup>
- ❖ Post-transplant response = VGPR
- ❖ Started on maintenance therapy with lenalidomide
- ❖ At 4 year restaging, confirmed disease progression.

**What is the best treatment option for this patient?**

Started DKd now s/p 24 cycles and continues on therapy with good response and tolerance.

# REFERENCES

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

Saad Z Usmani <sup>1</sup>, Hang Quach <sup>2</sup>, Maria-Victoria Mateos <sup>3</sup>, Ola Landgren <sup>4</sup>, Xavier Leleu <sup>5</sup>, David Siegel <sup>6</sup>, Katja Weisel <sup>7</sup>, Maria Gavriatopoulou <sup>8</sup>, Albert Oriol <sup>9</sup>, Neil Rabin <sup>10</sup>, **Ajay Nooka** <sup>11</sup>, Ming Qi <sup>12</sup>, Meral Beksac <sup>13</sup>, Andrzej Jakubowiak <sup>14</sup>, Bifeng Ding <sup>15</sup>, Anita Zuhlten-Kumeli <sup>15</sup>, Akeem Yusuf <sup>15</sup>, Meletios Dimopoulos <sup>16</sup>


ORIGINAL ARTICLE

**Daratumumab, Bortezomib, and Dexamethasone for Multiple Myeloma**

Antonio Palumbo, M.D., Asher Chanan-Khan, M.D., Katja Weisel, M.D., **Ajay K. Nooka**, M.D., Tamas Masszi, M.D., Meral Beksac, M.D., Ivan Spicka, M.D., Vania Hungria, M.D., Markus Munder, M.D., Maria V. Mateos, M.D., Tomer M. Mark, M.D., Ming Qi, M.D., ...

# Ajay K. Nooka

**Daratumumab, bortezomib, and dexamethasone in relapsed or refractory multiple myeloma: subgroup analysis of CASTOR based on cytogenetic risk**

Katja Weisel , Andrew Spencer, Suzanne Lentzsch, Hervé Avet-Loiseau, Tomer M. Mark, Ivan Spicka, Tamas Masszi, Birgitta Lauri, Mark-David Levin, Alberto Bosi, Vania Hungria, Michele Cavo, Je-Jung Lee, **Ajay Nooka**, Hang Quach, Markus Munder, Cindy Lee, Wolney Barreto, Paolo Corradini, Chang-Ki Min, Asher A. Chanan-Khan, Noemi Horvath, Marcelo Capra, Meral Beksac, Roberto Ovilla, Jae-Cheol Jo, Ho-Jin Shin, Pieter Sonneveld, Tineke Casneuf, Nikki DeAngelis, Himal Amin, Jon Ukropec, Rachel Kobos & Maria-Victoria Mateos [Show fewer authors](#)

**Carfilzomib, dexamethasone and daratumumab in relapsed or refractory multiple myeloma: results of the phase III study CANDOR by prior lines of therapy**

Hang Quach , **Ajay Nooka**, Olga Samoylova, Christopher P. Venner, Kihyun Kim, Thierry Facon, Andrew Spencer, Saad Z. Usmani, Sebastian Grosicki, Kenshi Suzuki, Sosana Delimpasi, Katja Weisel, Mihaela Obreja, Anita Zuhlten-Kumeli, Maria-Victoria Mateos ... [See fewer authors](#)

# SUMMARY

- ❖ Initial therapy and maintenance, response/durability, PS, age and co-morbidities, pattern of relapse, etc., need to be considered while selecting optimal therapy for relapsed MM.
- ❖ Given that a vast majority of patients are len-refractory at first relapse, class switch to an anti-CD38 mAb/PI combination affords best ORR and doubling of PFS in this patient population
- ❖ Better ORR, MRD-ve rates and PFS compared to SOC arms in several P3 trials
- ❖ Infection rates are higher, do not appear to impact survival outcomes and require close monitoring