EHA 2018 Meeting
Abstract S109

Updated Efficacy and MRD Data According to Risk-Status in Newly Diagnosed Myeloma Patients Treated With Carfilzomib plus Lenalidomide or Cyclophosphamide

Results from The FORTE Trial

Francesca Gay[1]*, Delia Rota Scalabrini[2], Angelo Belotti[2], Stefania Oliva[1], Alessandro Rambaldi[2], Elena Zamagni[2], Massimo Offidani[2], Paola Omedé[1], Chiara Cerrato[1], Rossella Troia[1], Alessandro Gozzetti[2], Giuseppe Pietrantuono[2], Vincenzo Pavone[2], Luca De Rosa[2], Salvatore Palmieri[2], Franco Narni[2], Anna Pascarella[2], Renato Zambello[2], Vittorio Montefusco[2], Antonio Palumbo[1,3], Pellegrino Musto[2], Michele Cavo[2], and Mario Boccadoro[1]

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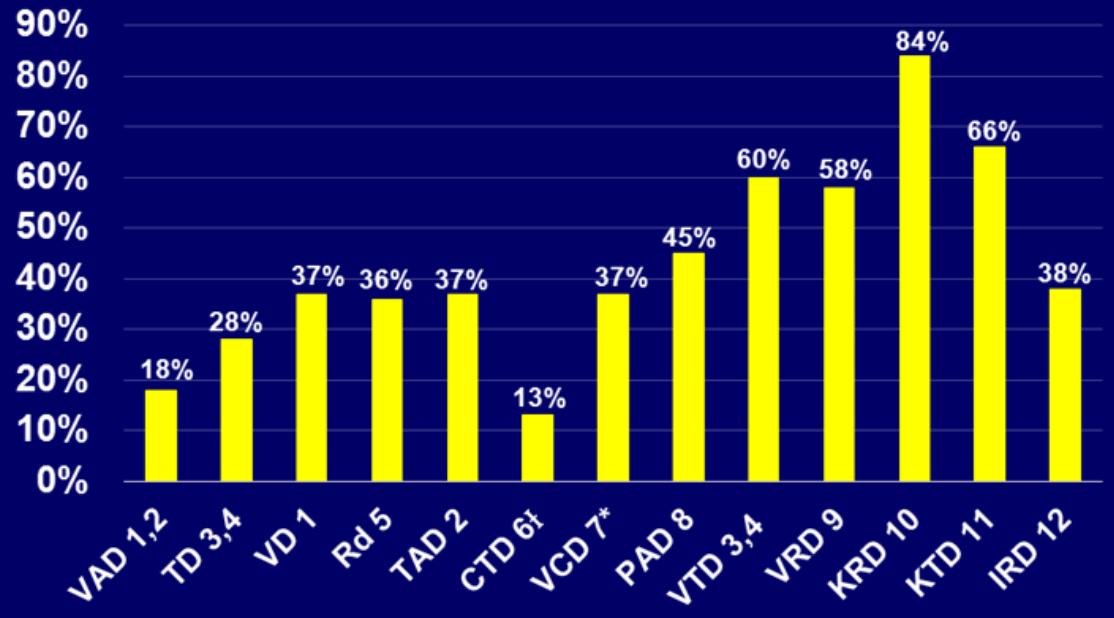
SC-EU-CARFILZOMI-01172-0618

Rationale

Novel agent as pre-transplant induction

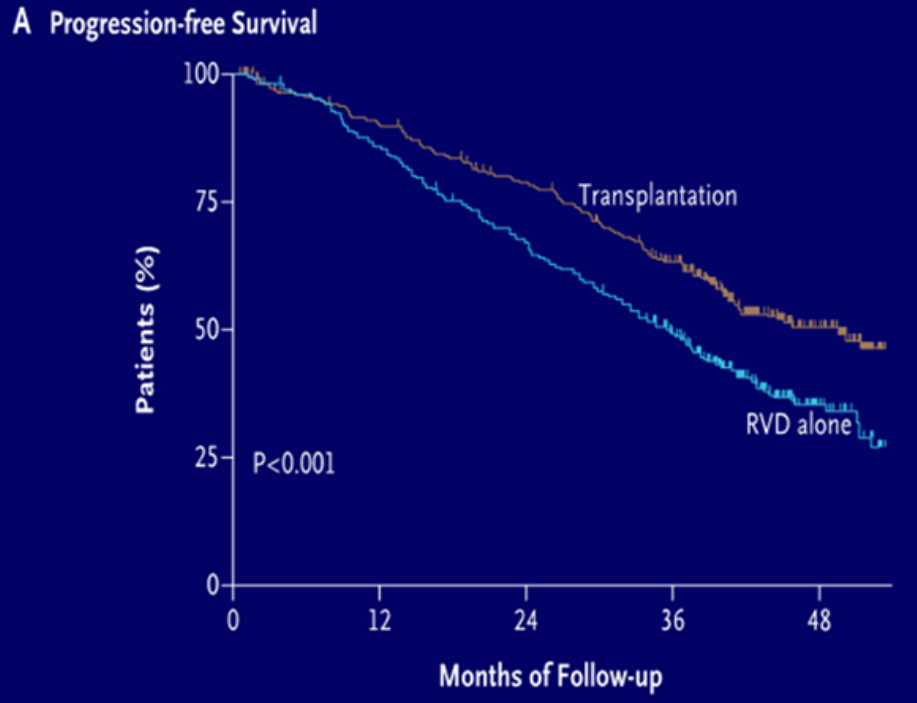
≥ VGPR rates post-induction



1. Harousseau *et al*. *J Clin Oncol*. 2010
2. Lokhorst *et al*. Blood 2010
3. Cavo *et al*. Lancet 2010
4. Rosinol *et al*. Blood 2012
5. Palumbo et al. NEJM 2014
6. Morgan *et al*. Haematologica 2012
7. Einsele *et al*. ASH 2009 (abstract 131); oral presentation
8. Sonneveld *et al*. JCO 2012
9. Roussel et al, JCO 2014
10. Jakuboviak et al Hematologica 2015; oral presentation
11. Wester et al ASH 2016
12. Moreau et al ASH 2016

†CR only

Transplant vs novel agent



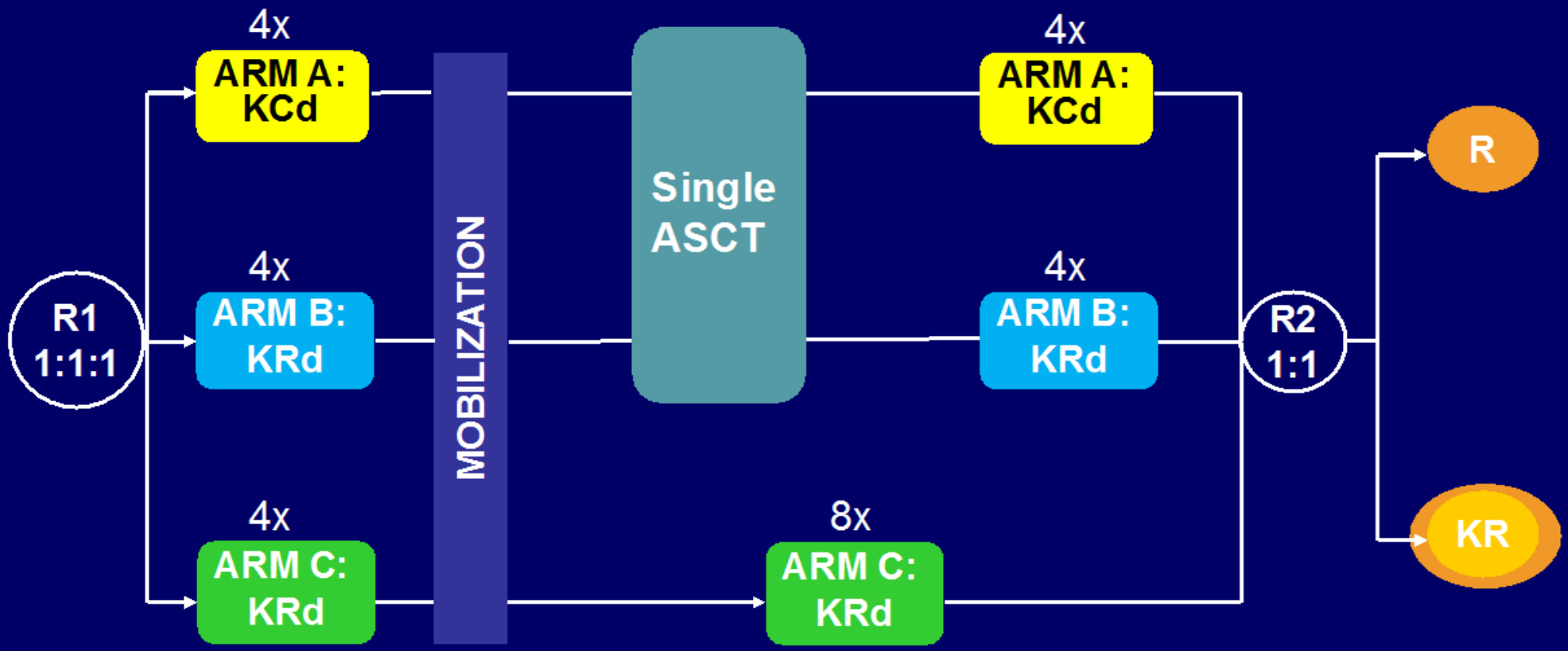
No. at Risk					
RVD alone	350	294	228	157	32
Transplantation	350	308	264	196	50

RVD: lenalidomide, bortezomib, dexametahsone

Attal M et al, NEJM 2017

Treatment schema

- NDMM patients, transplant eligible and younger than 65 years
- Last patients enrolled: March 2017
- Data cut-off May 31st, 2018



R1: randomization1; KCd: Carfilzomib, Cyclophosphamide, dexamethasone; KRd: Carfilzomib, Lenalidomide, dexamethasone; ASCT: Autologous Stem Cell Transplant; R2: randomization2; R: Lenalidomide; KR: Carfilzomib, Lenalidomide. NDMM, newly diagnosed multiple myeloma.

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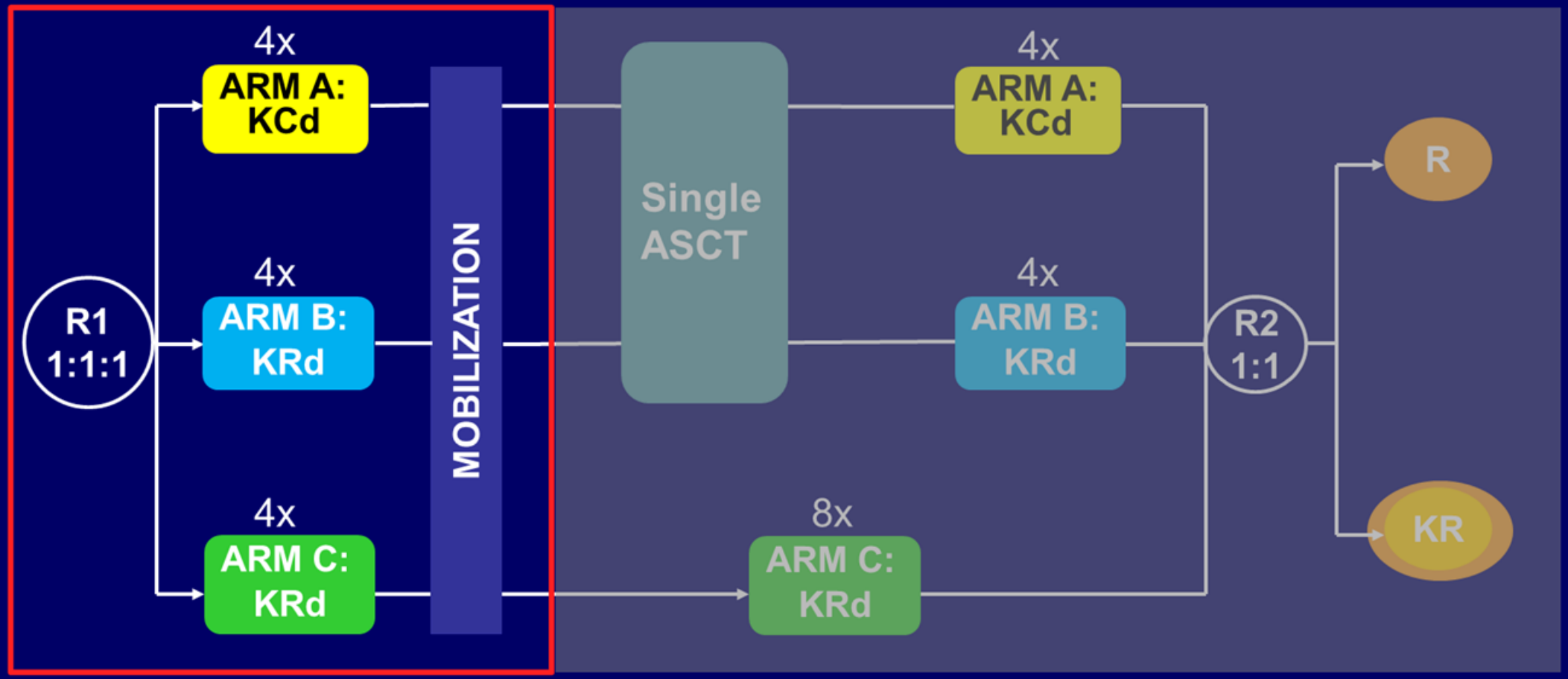

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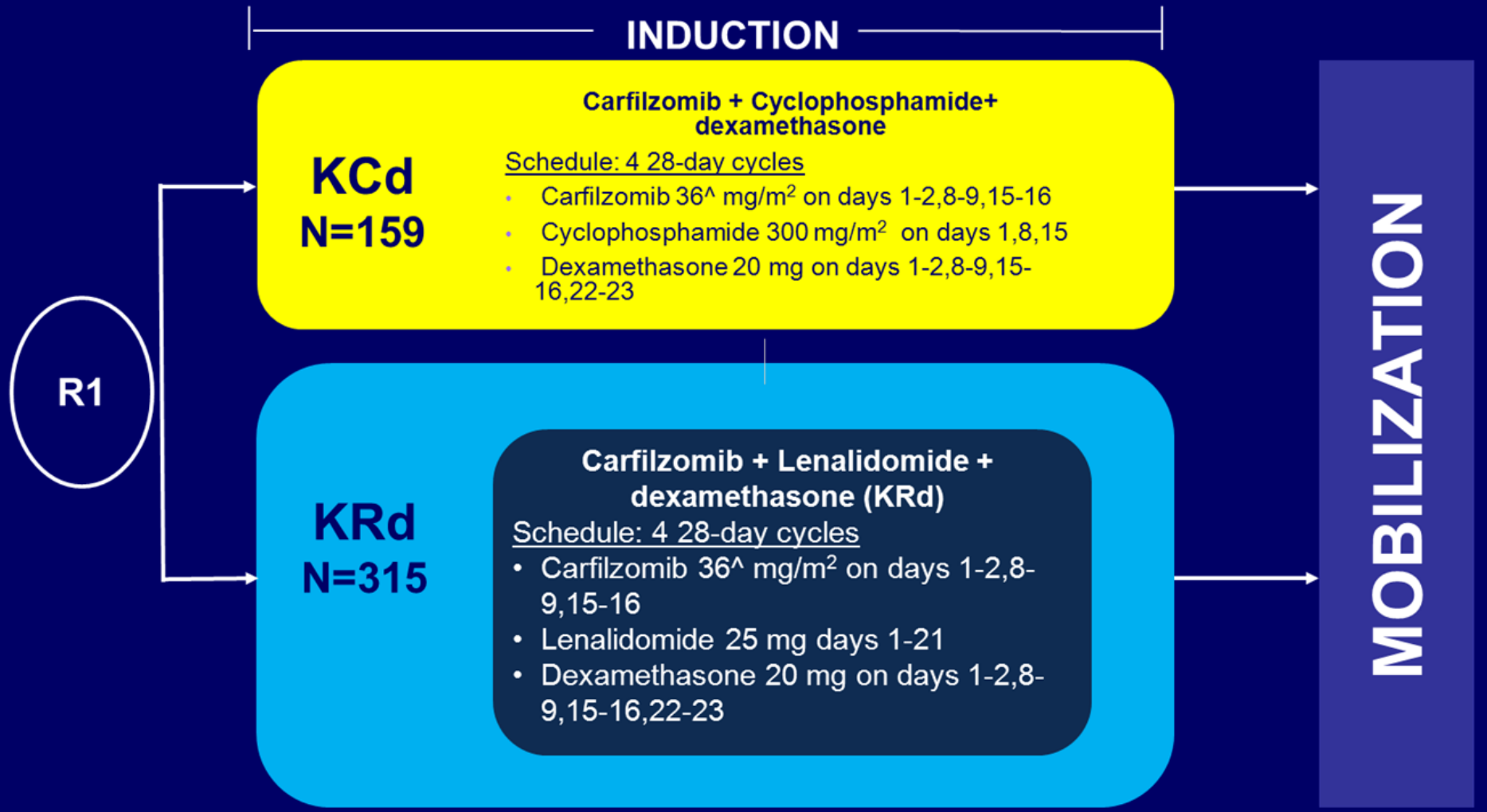
Current analysis



^20 mg/m^2 on days 1-2 cycle 1 only.

KCd: Carfilzomib, Cyclophosphamide, dexamethasone; KRd: Carfilzomib, Lenalidomide, dexamethasone.

Aims

- To compare the **efficacy of KRd vs KCd induction** in patients eligible for transplantation

- To evaluate the **efficacy of KRd vs KCd in different subgroups** of patients according to prognostic features, focusing specifically on **high-risk patients**

KRd: Carfilzomib, Lenalidomide, dexamethasone; KCd: Carfilzomib, Cyclophosphamide, dexamethasone.

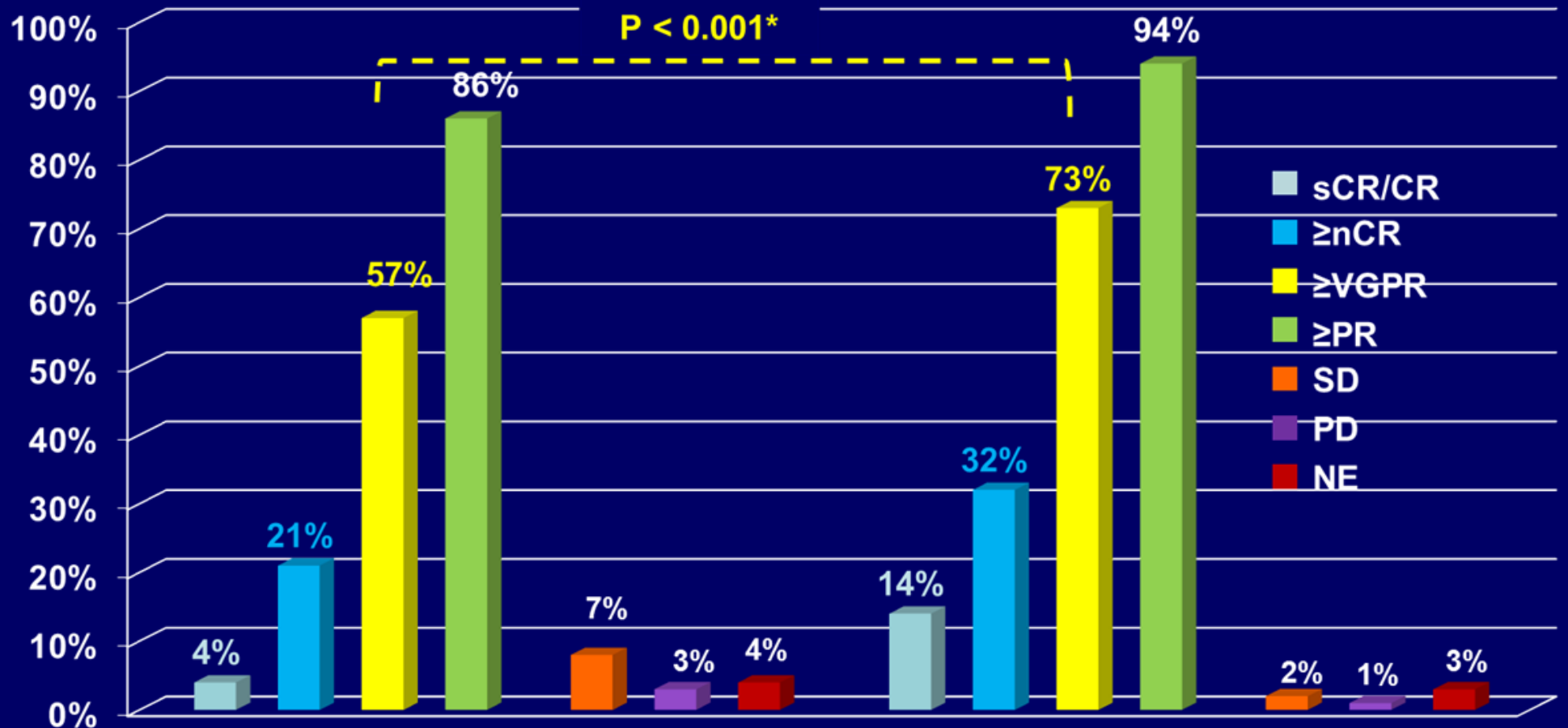
Patient Characteristics

	KCd (N=159)	KRd (N=315)
Age		
Median (IRQ)	57 (52 - 62)	57 (51 - 62)
≥ 60 years	62 (39%)	122 (39%)
Sex		
Male	87 (55%)	176 (55%)
ISS Stage		
I	81 (51%)	160 (51%)
II	51 (32%)	101 (32%)
III	27 (17%)	54 (17%)
LDH		
> upper normal limit*	19 (13%)	36 (12%)
Missing	15	18
Chromosomal Abnormalities (FISH)		
No t(4;14),t(14,16), del17*	92 (65%)	184 (69%)
t(4;14) or t(14,16) or del17*	49 (35%)	82 (31%)
Missing	18	49
R-ISS Stage		
I*	36 (26%)	87 (32%)
II*	92 (66%)	158 (58%)
III*	11 (8%)	27 (10%)
Missing	20	43

IQR: interquartile range; ISS: International Staging System; KRd: Carfilzomib, Lenalidomide, dexamethasone; KCd: Carfilzomib, Cyclophosphamide, dexamethasone. Percentage may not total 100 because of rounding. * % calculated on available patients

Best Responses

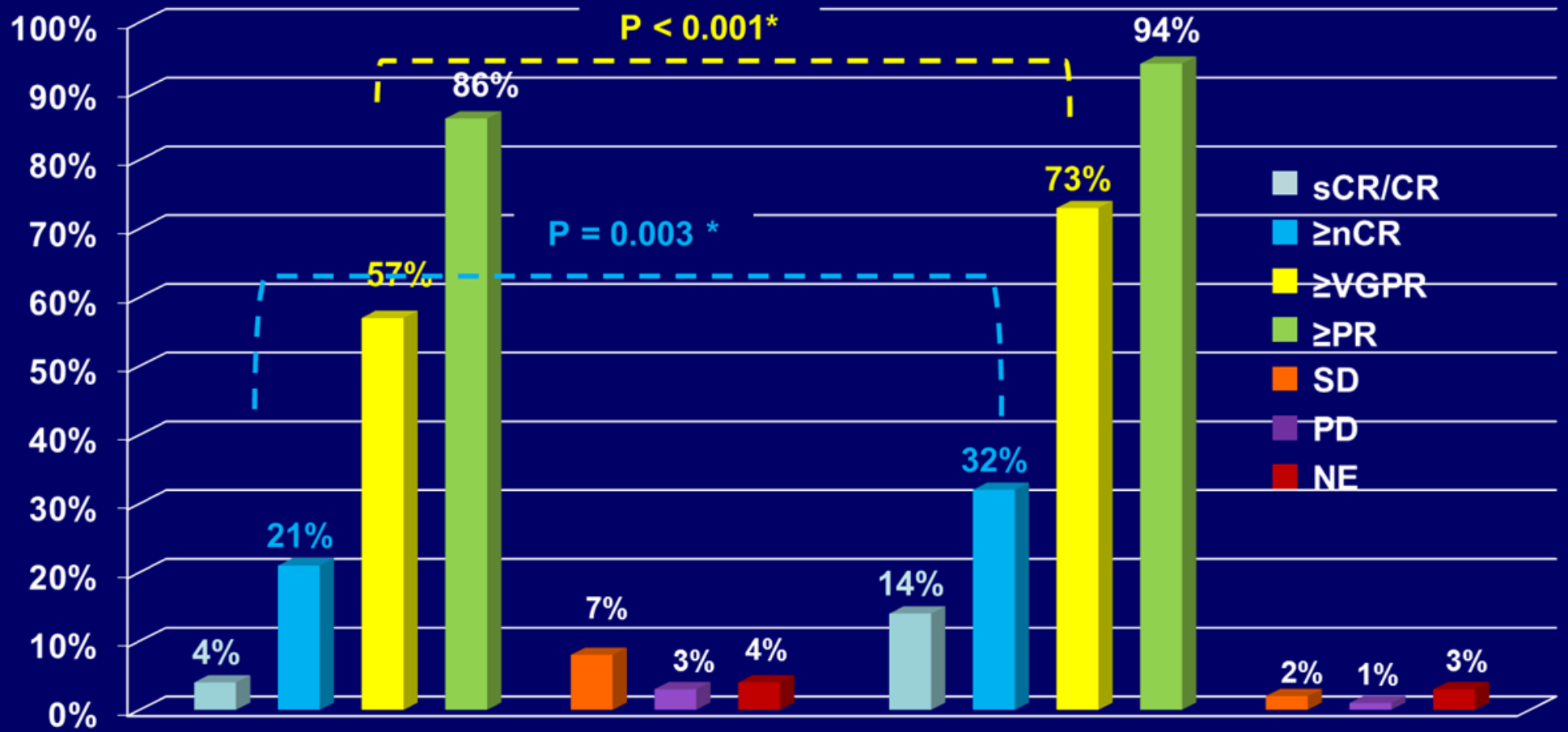
ITT analysis



KCd: Carfilzomib, Cyclophosphamide, dexamethasone; KRd: Carfilzomib, Lenalidomide, dexamethasone; sCR: stringent Complete Response; nCR: near Complete Response; VGPR: Very Good Partial Response; PR: Partial Response; SD: Stable Disease; PD: Progressive Disease, NE: not evaluable; * Adjusted for ISS, Age, FISH.

Best Responses

ITT analysis



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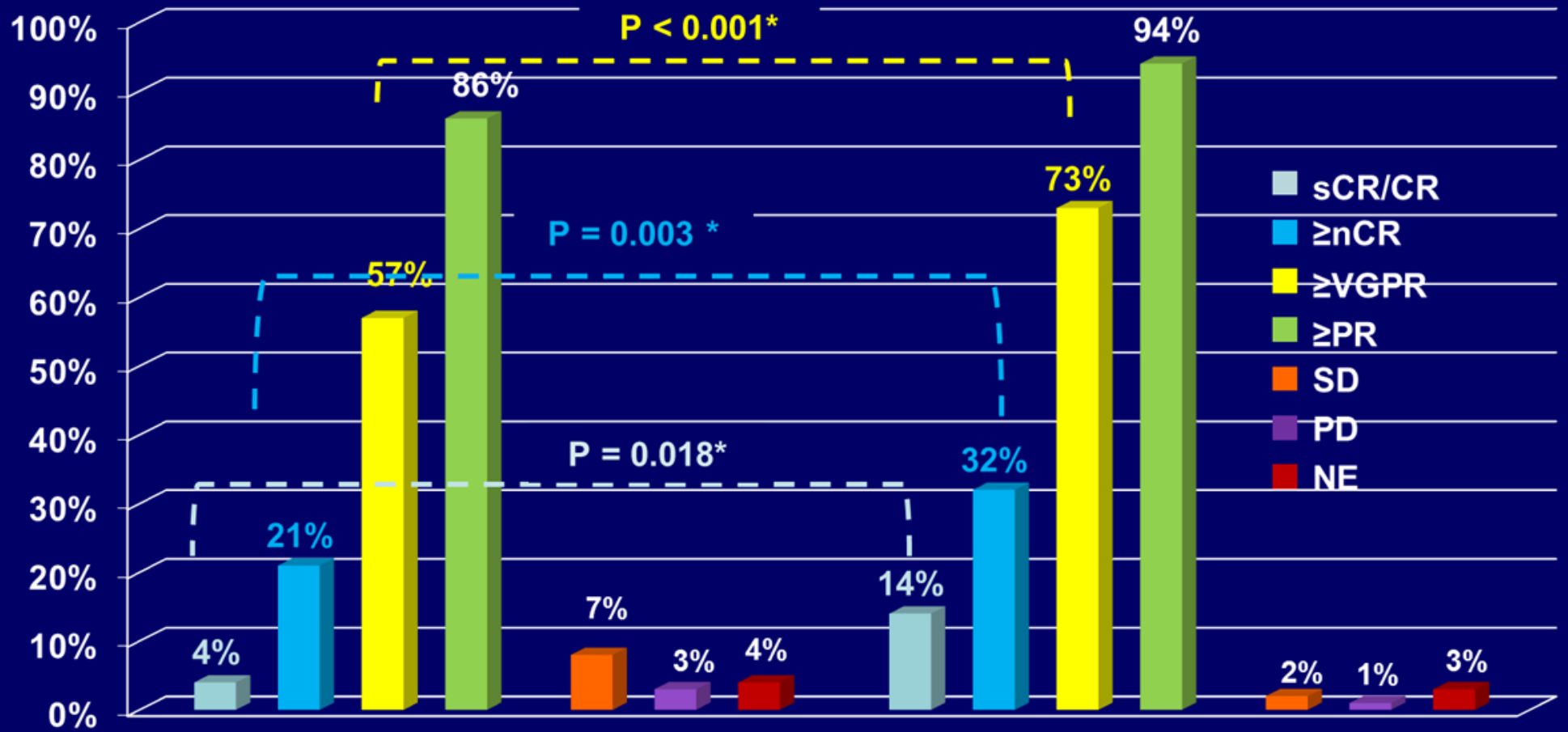
Best Responses

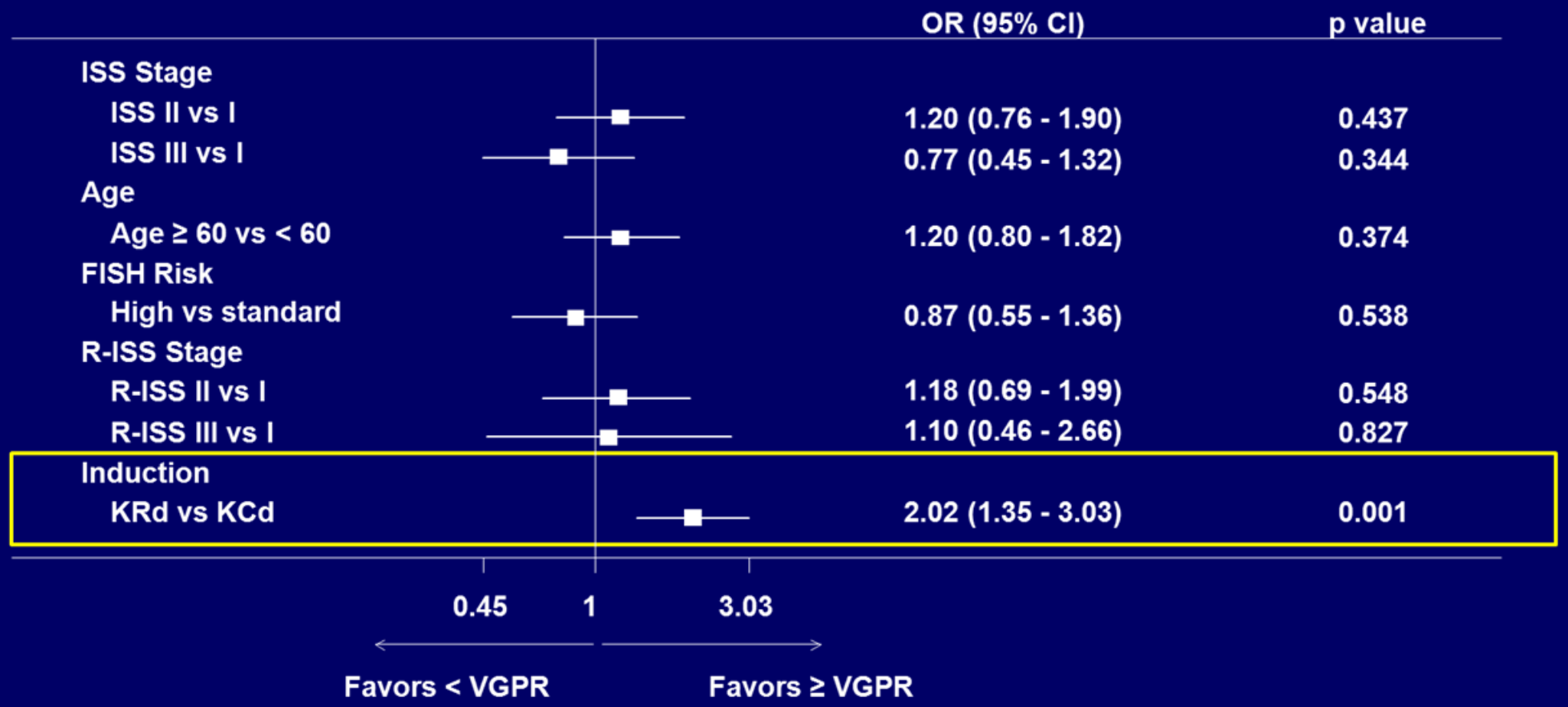
ITT analysis



KCd: Carfilzomib, Cyclophosphamide, dexamethasone; KRd: Carfilzomib, Lenalidomide, dexamethasone; sCR: stringent Complete Response; nCR: near Complete Response; VGPR: Very Good Partial Response; PR: Partial Response; SD: Stable Disease; PD: Progressive Disease, NE: not evaluable; * Adjusted for ISS, Age, FISH.

Predictors of achieving at least VGPR

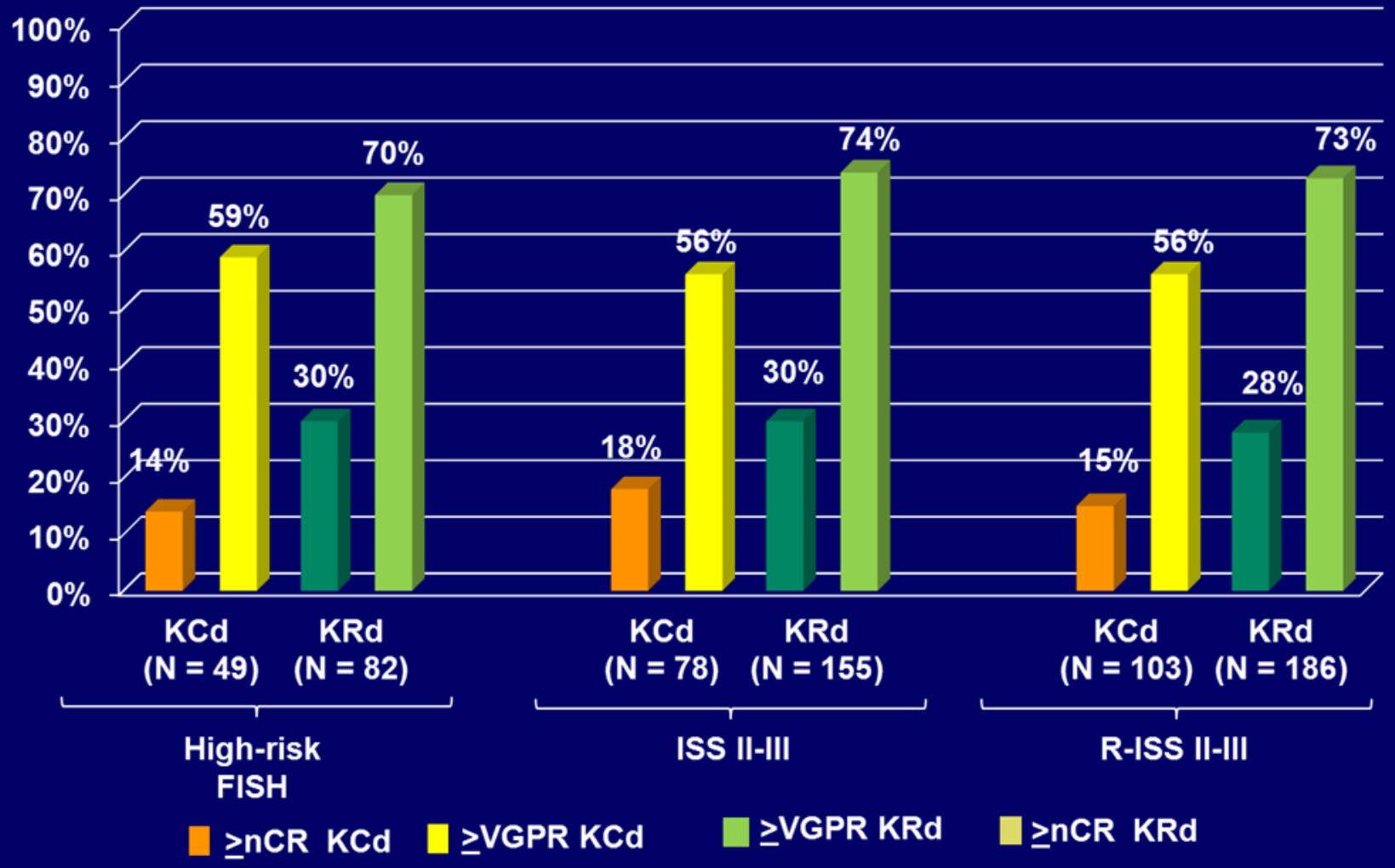
Logistic regression model



high risk FISH: t(4;14) or t(14,16) or del17.
VGPR, very good partial response; ISS: International Staging System; R-ISS, Revised ISS; KRd: Carfilzomib, Lenalidomide, dexamethasone; KCd: Carfilzomib, Cyclophosphamide, dexamethasone; NE, not evaluated.

Subgroups analysis of Response Rate

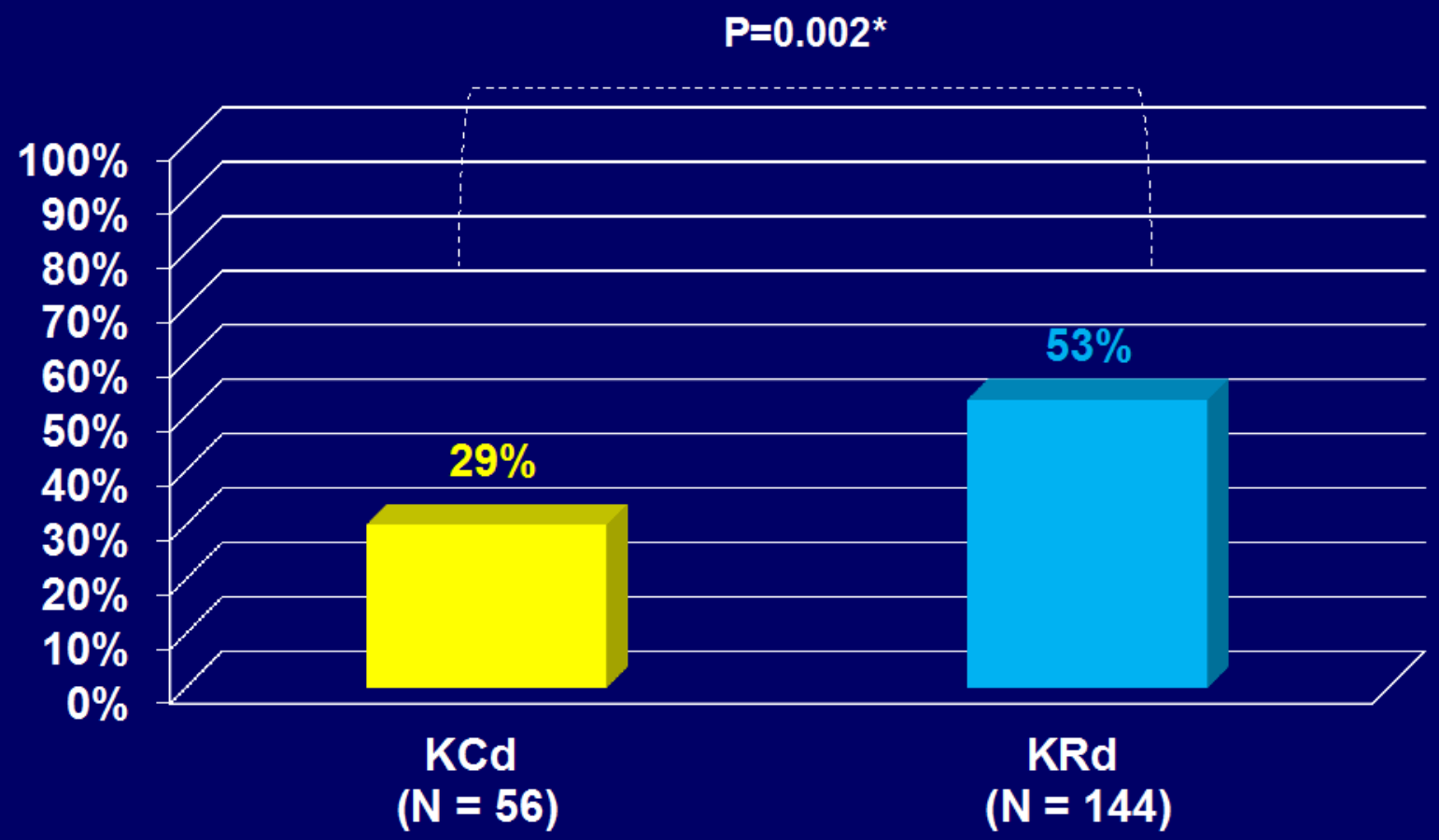
High-risk patients



KCd: Carfilzomib, Cyclophosphamide, dexamethasone; KRd: Carfilzomib, Lenalidomide, dexamethasone; nCR: near Complete Response; VGPR: Very Good Partial Response; ISS: International Staging System; R-ISS: Revised International Staging System; High-risk FISH: del17 and/or t(4;14) and/or t(11;14).

MRD subanalysis

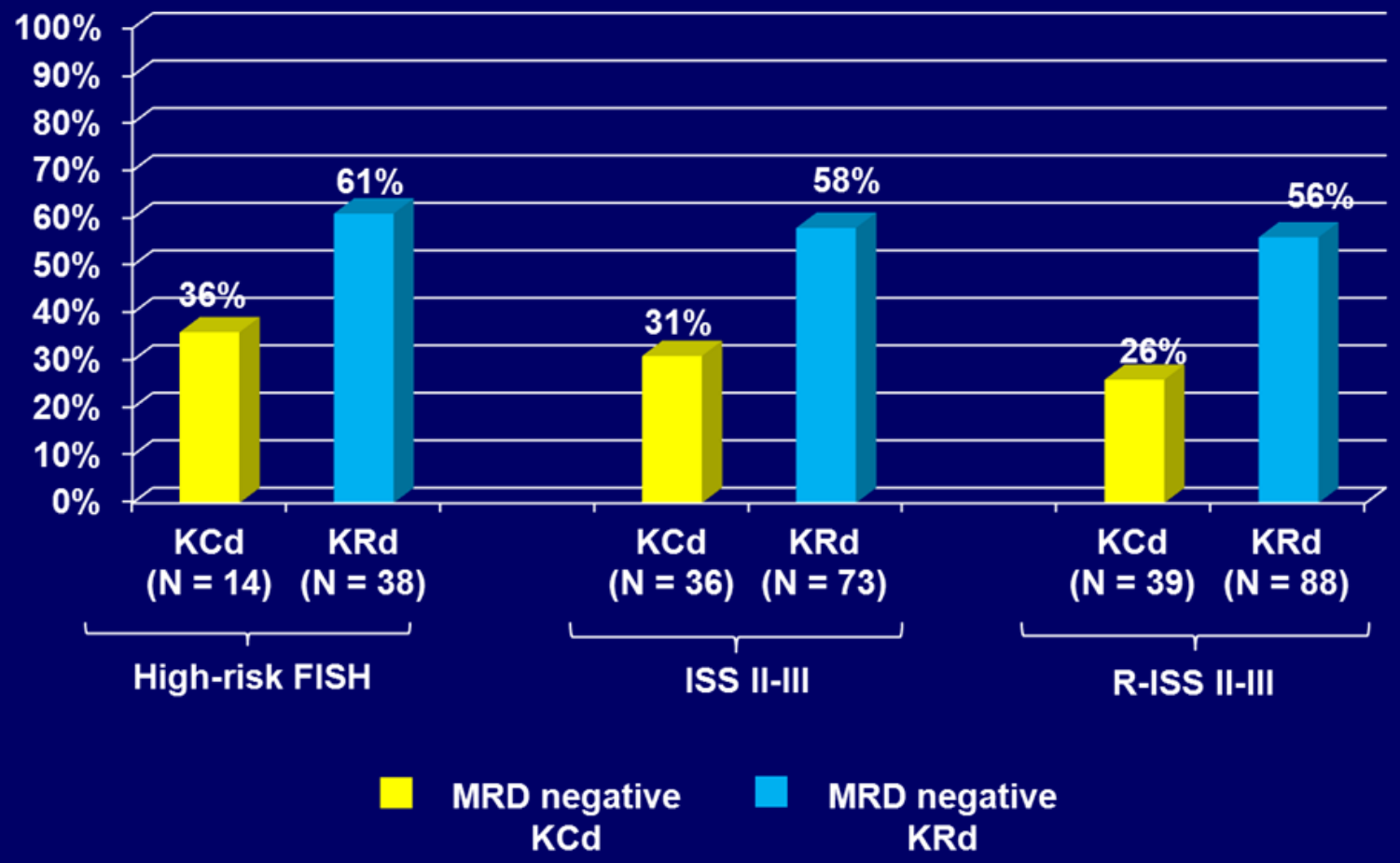
MRD negative
(8 color second generation flow cytometry, sensitivity 10^{-5})



MRD: Minimal Residual Disease; KCd: Carfilzomib, Cyclophosphamide, dexamethasone; KRd: Carfilzomib, Lenalidomide, dexamethasone. *Adjusted for ISS, Age, FISH

Subgroup analyses of MRD

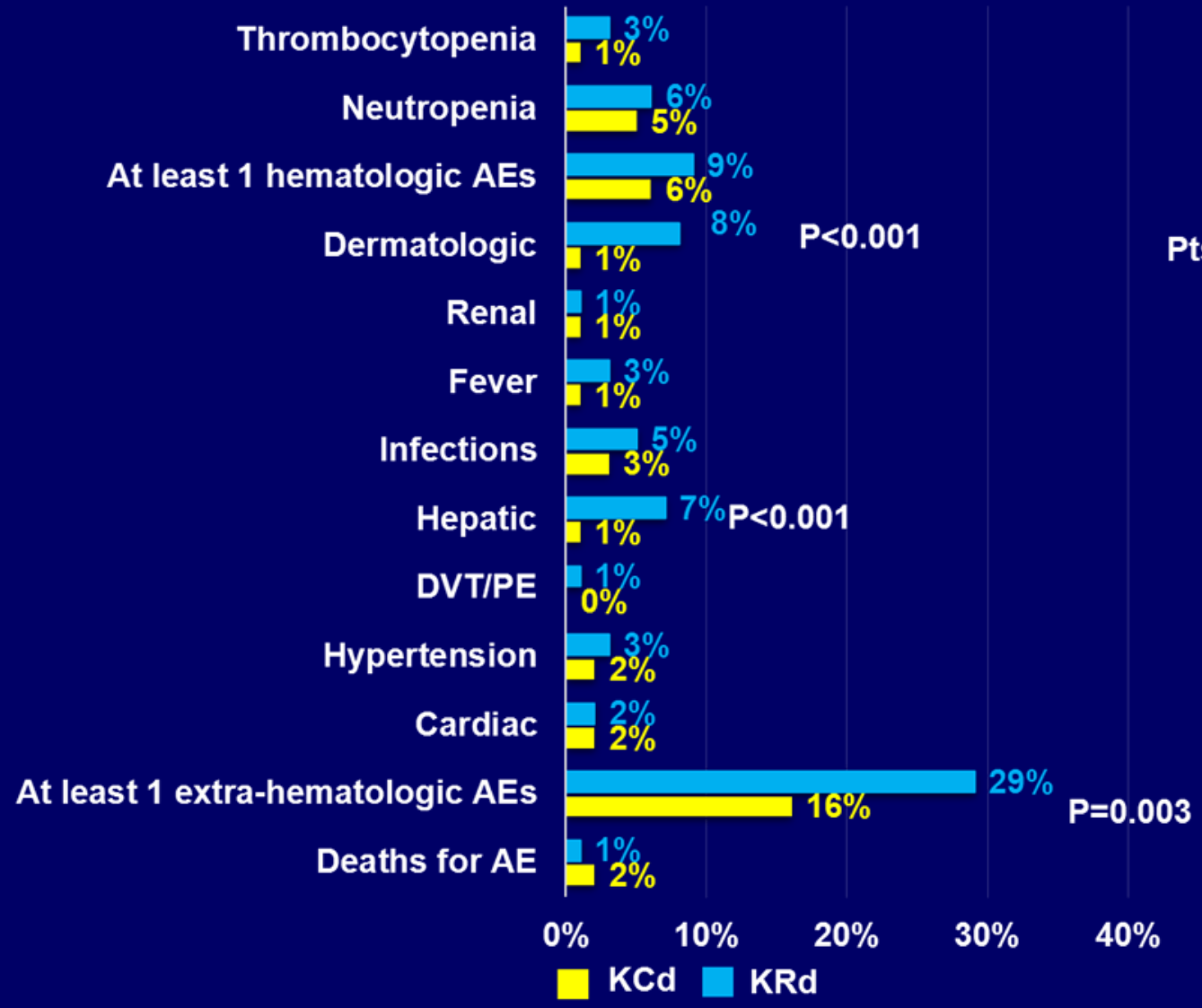
High risk patients



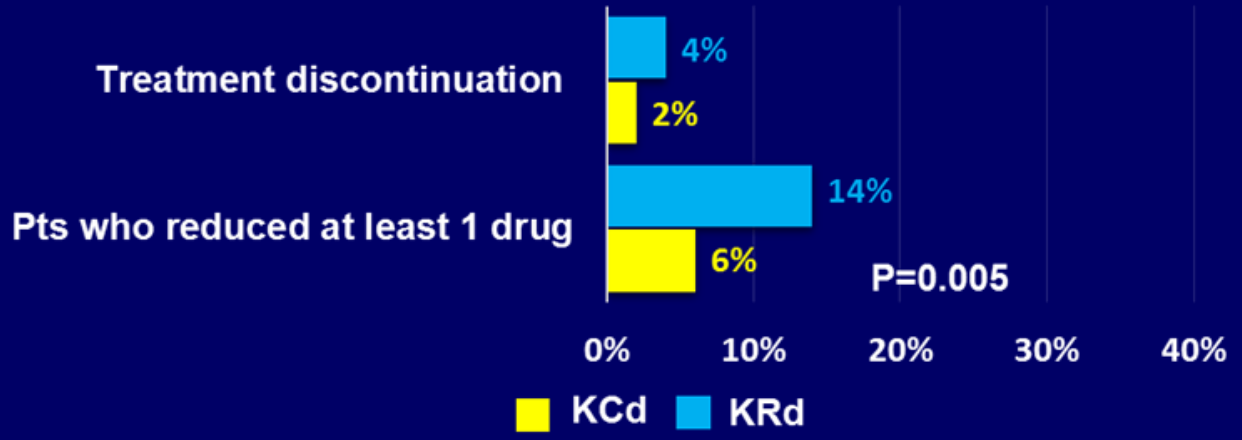
KCd: Carfilzomib, Cyclophosphamide, dexamethasone; KRd: Carfilzomib, Lenalidomide, dexamethasone; nCR: near Complete Response; VGPR: Very Good Partial Response; MRD: Minimal Residual Disease; ISS: International Staging System; R-ISS: Revised International Staging System; High-risk FISH: del17 and/or t(4;14) and/or t(11;14).

Safety

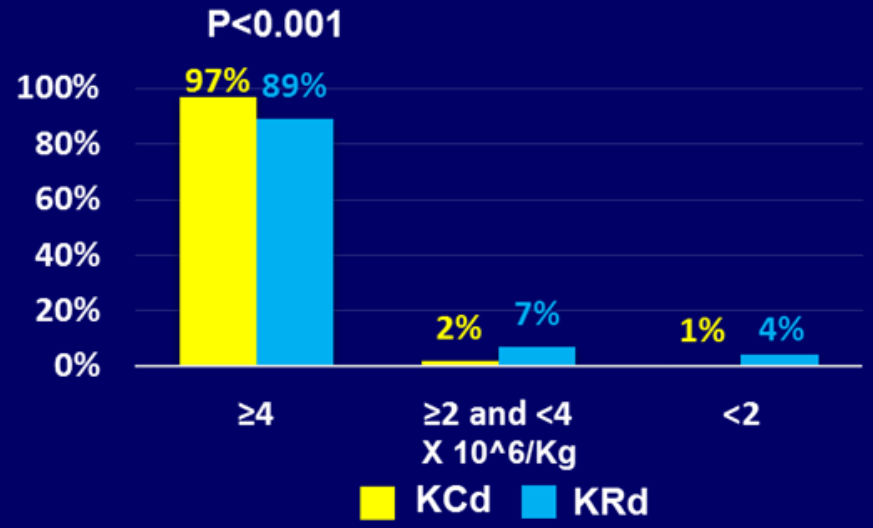
Grade 3-4 AEs/SAEs



Treatment discontinuation and dose reductions



PBSC harvest



KCd: Carfilzomib, Cyclophosphamide, dexamethasone; KRd: Carfilzomib, Lenalidomide, dexamethasone; AE: Adverse Events; SAEs: serious AE; PBSC: peripheral Blood Stem Cells; DVT: deep vein thrombosis; PE: pulmonary embolism.

Conclusions

- **K-based induction induces rapid and high quality response**
- **KRd induction significantly improved sCR/CR, ≥ nCR, ≥ VGPR rates in comparison with KCd**
- **KRd induction significantly improved MRD negativity in comparison with KCd**
- **Response rate and MRD negativity in high-risk patients were comparable to the overall population**
- **Treatment was manageble**

We Are Grateful to All Patients, Nurses and Physicians of the Participating Centers

1. **ALESSANDRIA** Ladetto, Baraldi
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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
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25. **CHIVITANOVA** Centurioni
26. **COSENZA** Morabito, Gentile
27. **CREMONA** Lanza
28. **CUNEO** Massaia, Grasso
29. **FIRENZE** Bosi, Nozzoli
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31. **GALLARATE** Ciambelli
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33. **GENOVA** Angelucci, Dominietto
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35. **LECCE** Di Renzo
36. **LECCO** Ardizzoia, Ferrando
37. **MANTOVA** Franchini, Zamagni
38. **MELDOLA** Ronconi
39. **MESSINA** Mannina
40. **MESSINA** Musolino, Allegra
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42. **MILANO** Cairoli, Cafro
43. **MILANO** Ciceri
44. **MILANO** Cortelezzi, Baldini
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47. **MONZA** Passerini, Rossini
48. **NAPOLI** Pane,Catalano
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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
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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. **9VERONA** Ambrosetti, Meneghini
95. **VICENZA** Rodeghiero, Elice

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Dr. Benedetto Bruno &
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Nurses

Data Managing Staff

Statistician Stefano Spada

Carfilzomib-Lenalidomide-Dexamethasone (KRd) vs Carfilzomib-Cyclophosphamide-Dexamethasone (KCd) induction: Planned Interim Analysis of the Randomized FORTE Trial in newly diagnosed Multiple Myeloma (NDMM)

Gay F.[1], Rota Scalabrini D.[2], Belotti A.[2], Offidani M.[2], Petrucci M.T.[2], Esma F.[1], Palmas AD.[2], Caravita T.[2], Grasso M.[2], Aquino S.[2], Gamberi B.[2], Zambello R.[2], Ledda A.[2], Montefusco V.[2], Omedè P.[1], Galli M.[2], Cavo M.[2], Palumbo A.[3], Musto P.[2] and Boccadoro M.[1]

[1]Myeloma Unit, Division of Hematology, University of Torino, Torino, Italy;

[2]Italian Multiple Myeloma Network, GIMEMA, Italy; [3]Myeloma Unit, Division of Hematology, University of Torino – Currently Takeda Pharmaceuticals Co.

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Rationale

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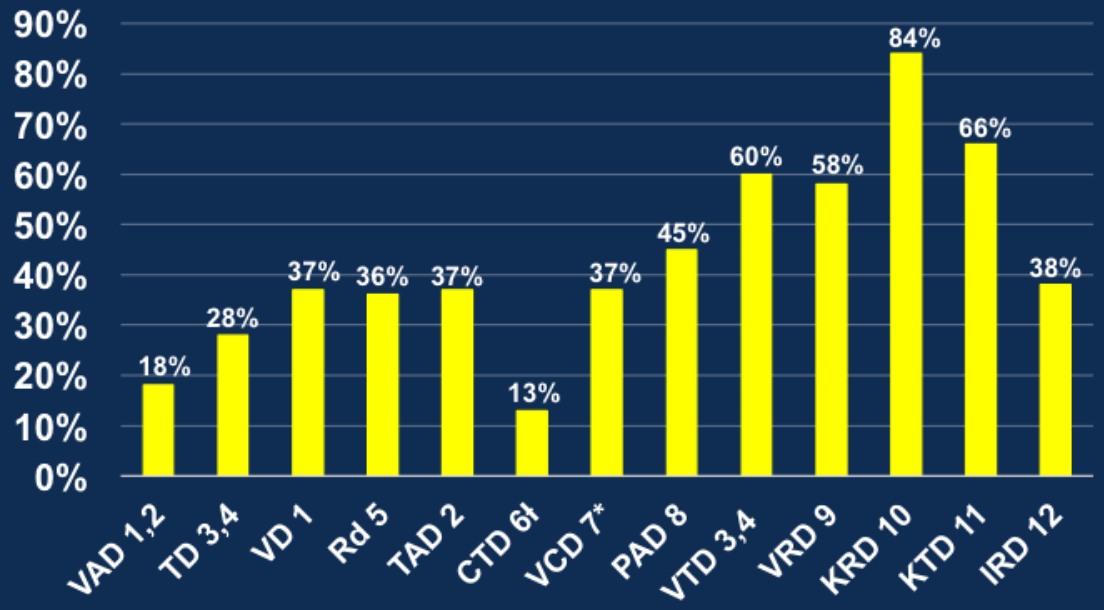

1. Harousseau *et al. J Clin Oncol*. 2010
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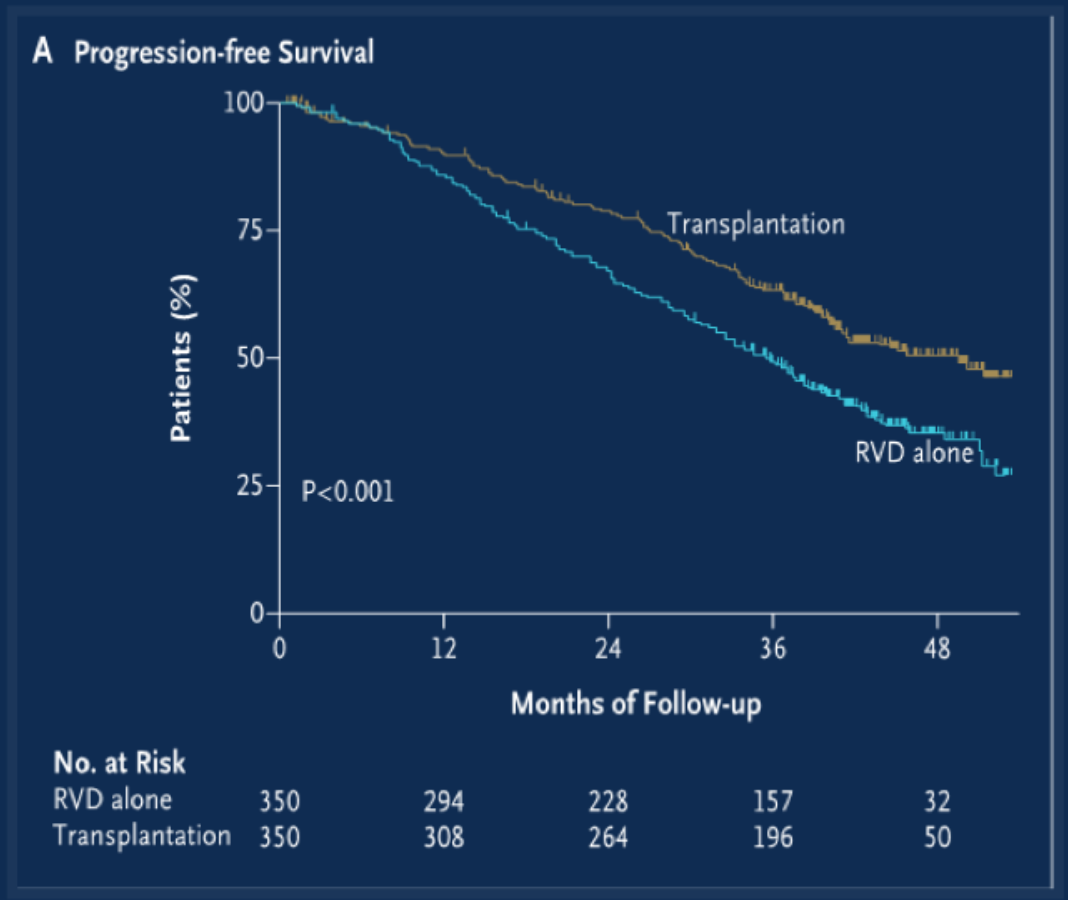
†CR only

Transplant vs novel agent

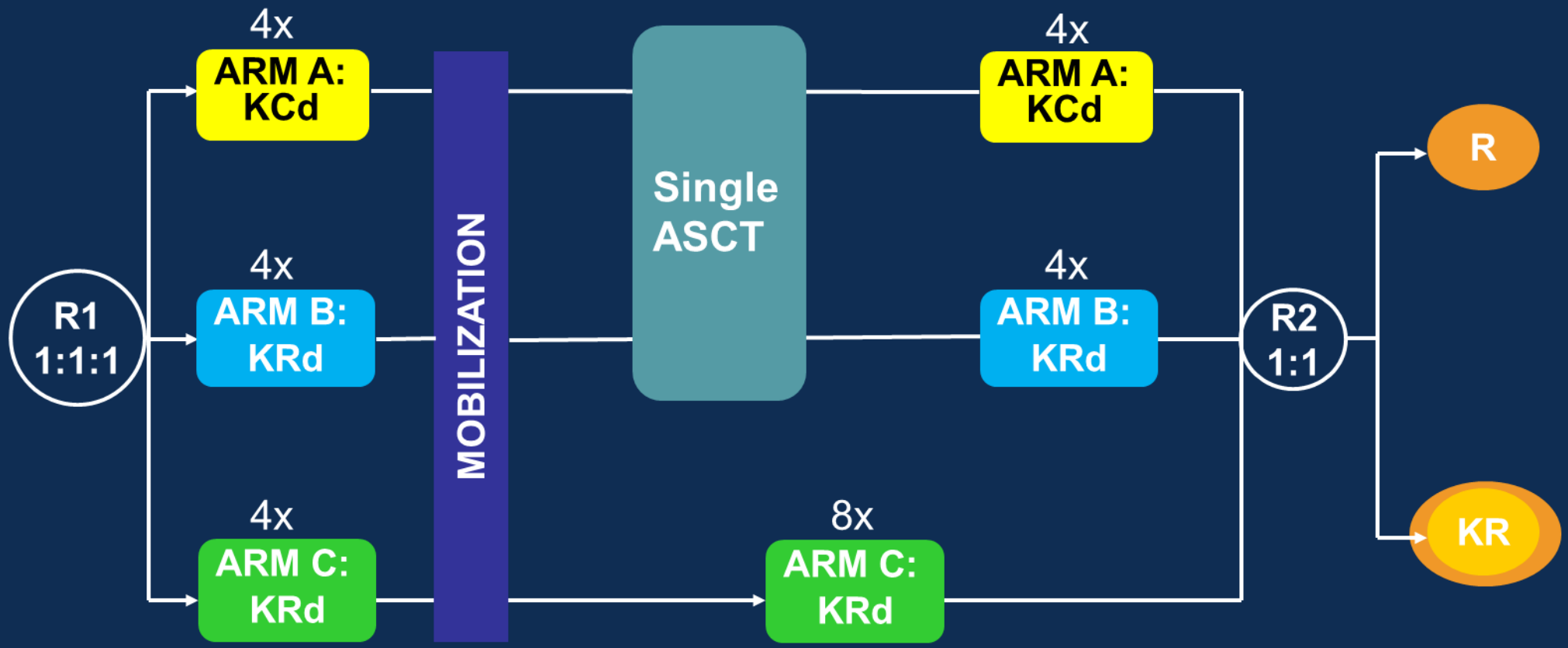


RVD: lenalidomide, bortezomib,dexametahsone

Attal M et al, NEJM 2017

Treatment schema

- 477 NDMM patients enrolled in 46 Italian sites, last patients enrolled in March 2017
- Data cut-off March 31st, 2017



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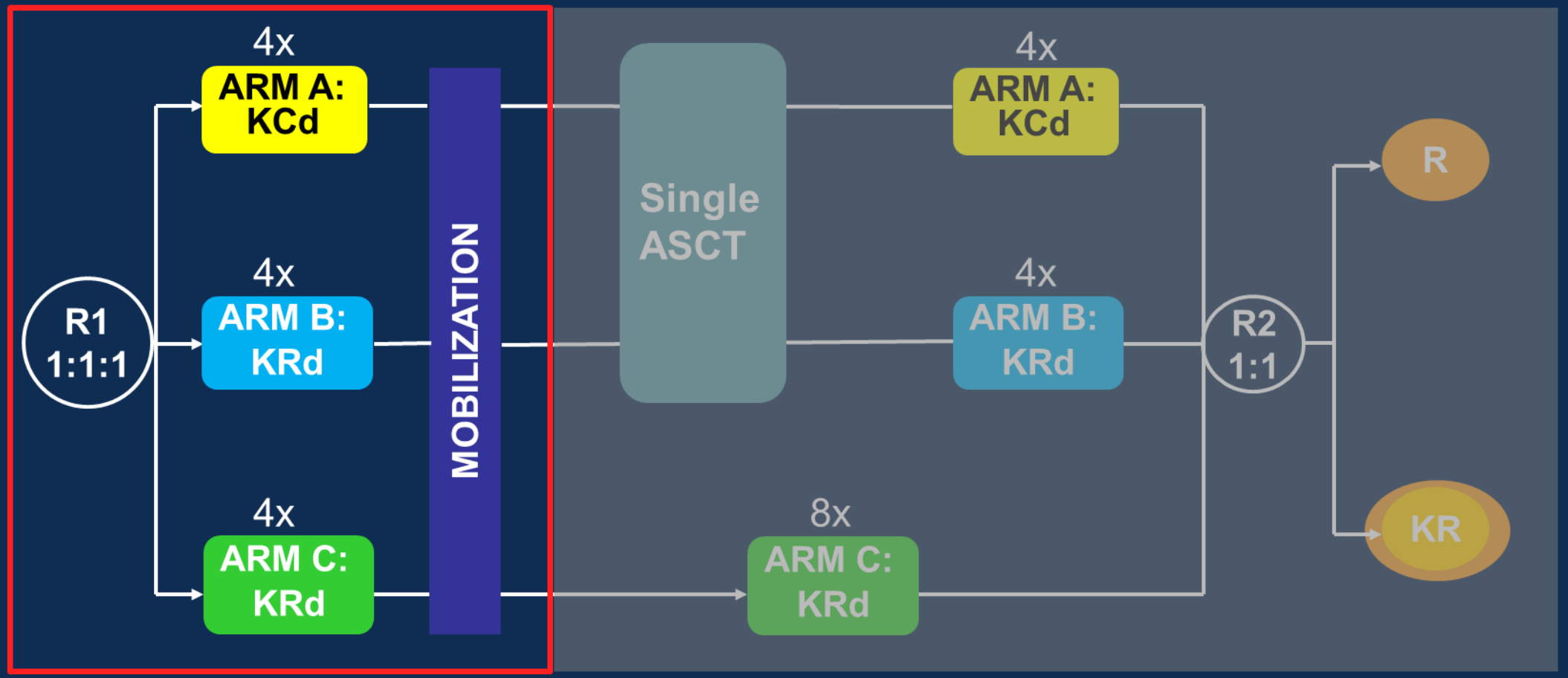

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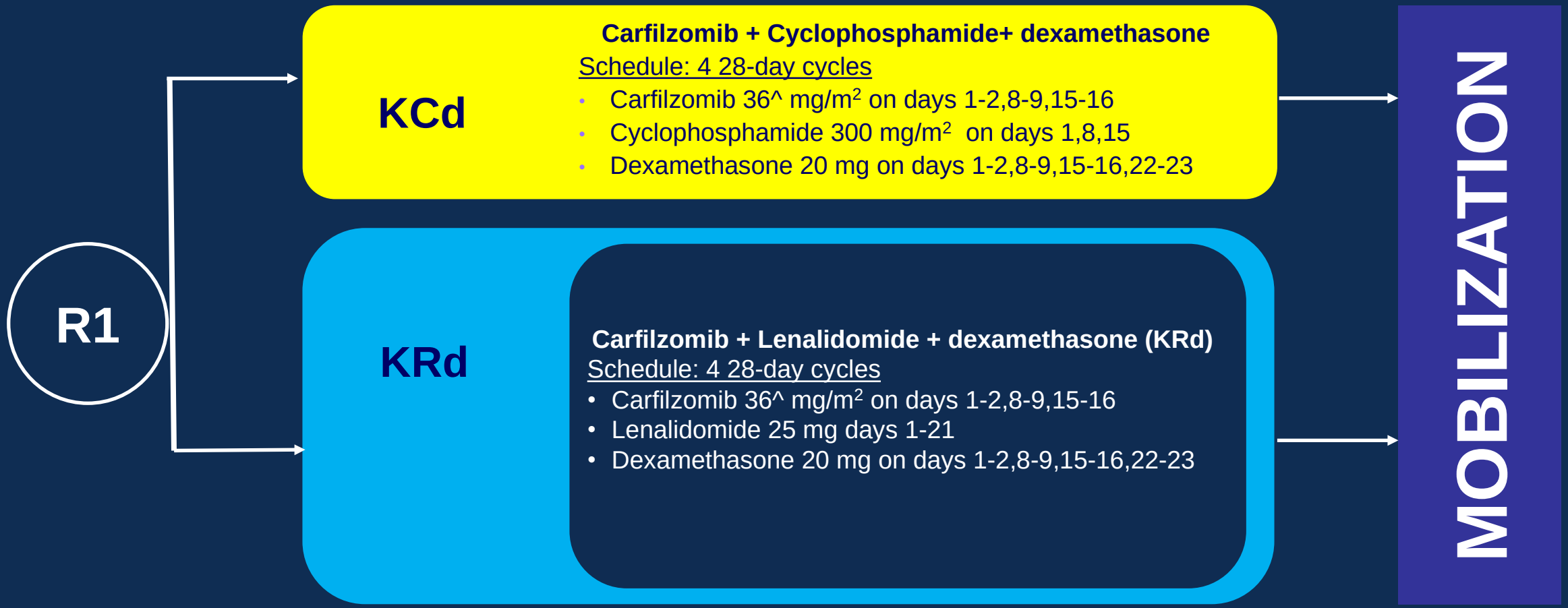
Current analysis of induction



^20 mg/m2 on days 1-2 cycle 1 only

Aims

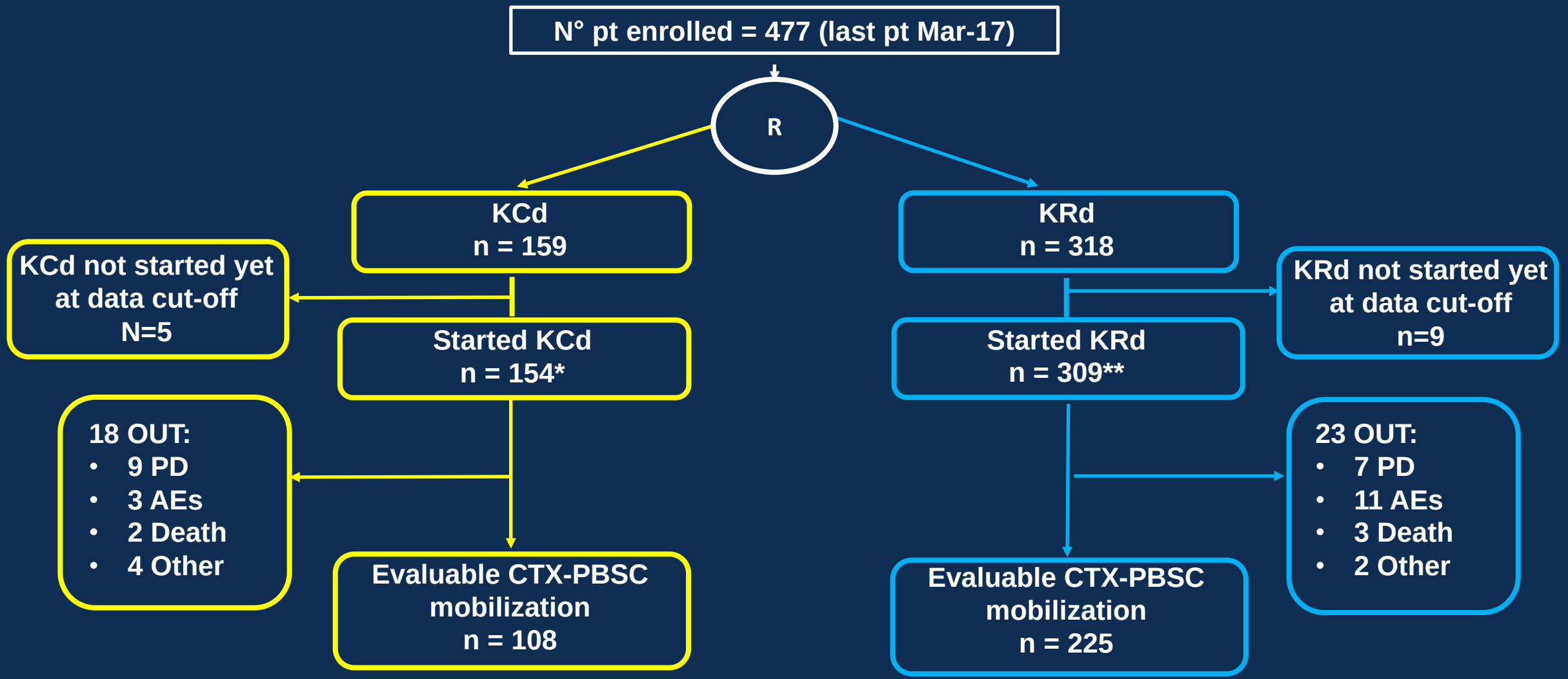
- To evaluate the **Safety** of the **Induction Phase:**
  - grade 1-2 AEs
  - grade 3-4 AEs and SAEs
  - dose reductions
  - discontinuation

- To evaluate **PBSC mobilization**
  - rate of failure
  - rate of poor mobilizers

- To evaluate preliminary **Efficacy**

AEs: Adverse Events; SAEs: Serious Adverse Events;; PBSC, peripheral Blood Stem Cell.

Consort diagram



* In KCD 28 patients are still receiving induction treatment.

** In KRD 61 patients are still receiving induction treatment.

KCd: Carfilzomib, Cyclophosphamide, dexamethasone; KRd: Carfilzomib, Lenalidomide, dexamethasone; PD: Progressive Disease; AEs: Adverse Events; CTX-PBSC: Cyclophosphamide followed by Peripheral blood stem cell mobilization

Patient Characteristics

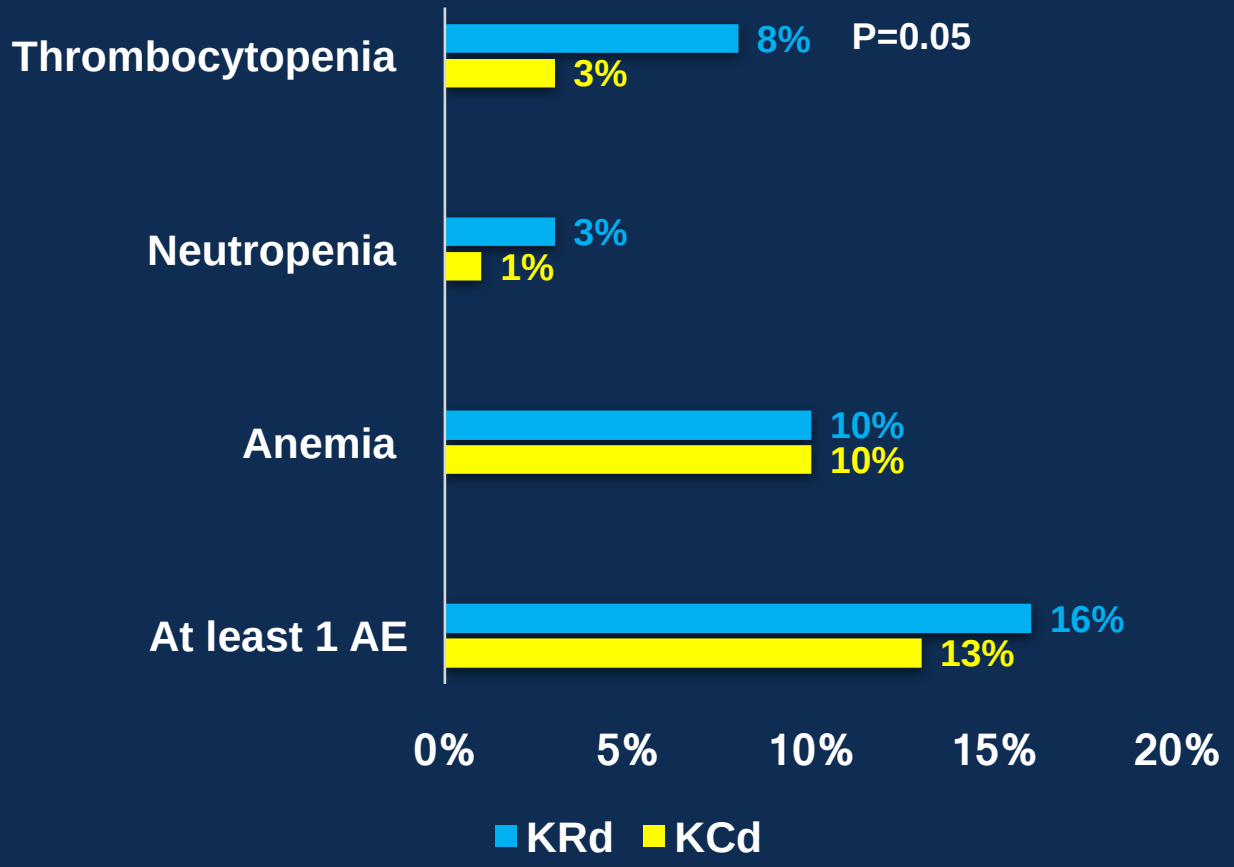
	KCd (N=154)	KRd (N=309)
Age		
Median (IQR)	57 (52 - 62)	57 (51 - 62)
≥ 60 years	57 (37%)	120 (39%)
Sex		
Male	84 (55%)	171 (55%)
ISS Stage		
I	80 (52%)	158 (51%)
II	48 (31%)	97 (31%)
III	26 (17%)	54 (17%)
LDH		
Median (IRQ)	226.5 (156.8 - 321)	241 (163 - 347)
Missing	10 (2%)	10 (2%)
Cytogenetic Risk		
No t(4;14),t(14,16), del17	90 (58%)	181 (59%)
t(4;14) or t(14,16) or del17	47 (31%)	79 (26%)
Missing	17 (11%)	49 (16%)

IQR: interquartile range; ISS: International Staging System; Percentage may not total 100 because of rounding.

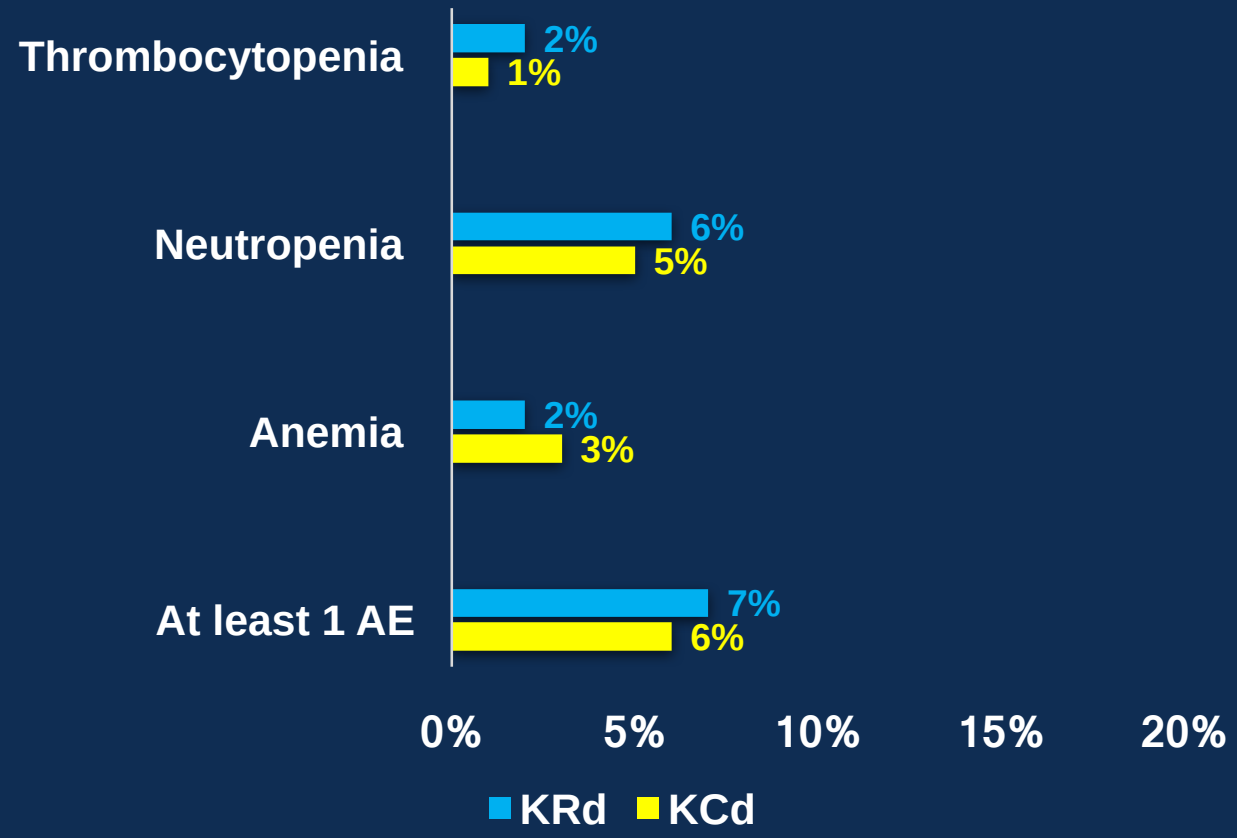
INDUCTION PHASE: SAFETY ANALYSIS

Hematologic Adverse Events

Grade 1-2 AEs



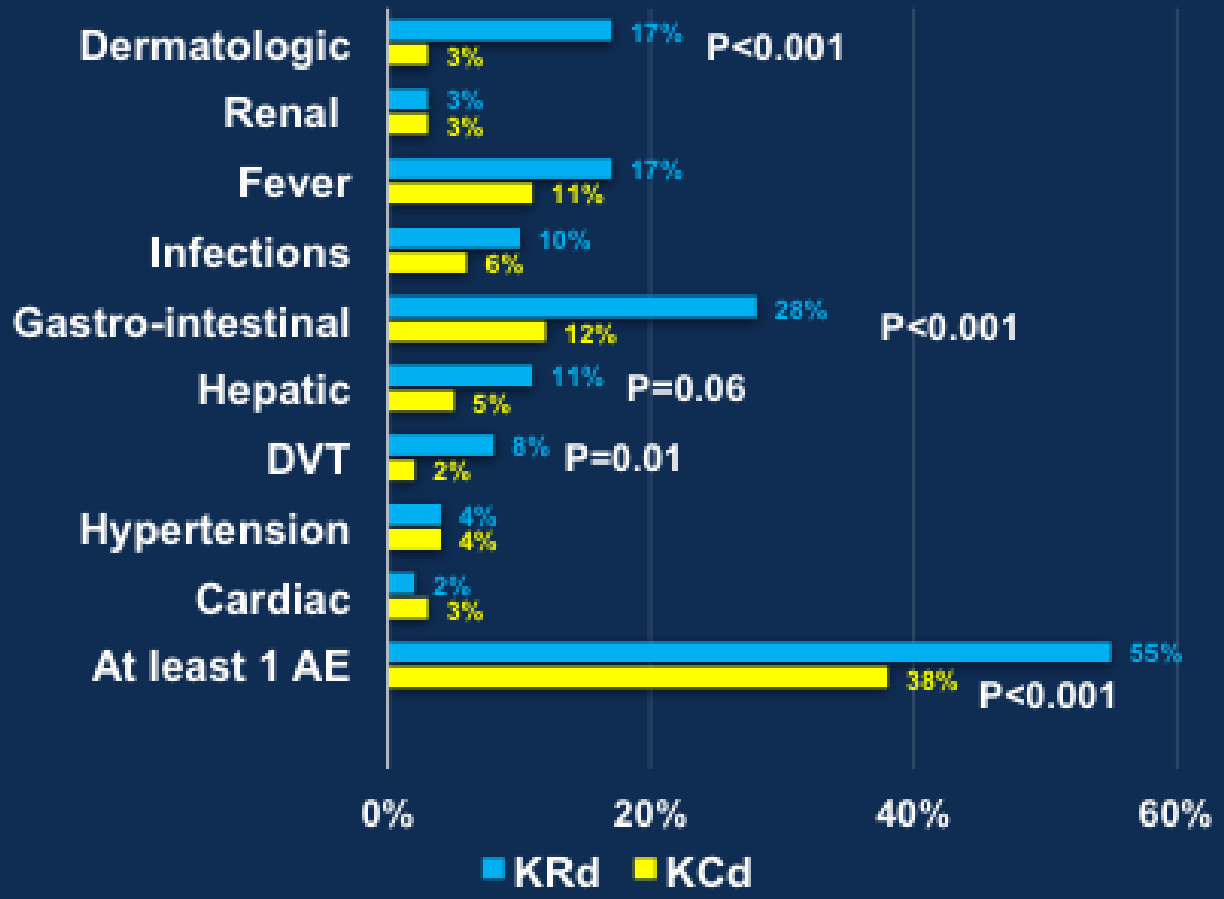
Grade 3-4 AEs/SAEs



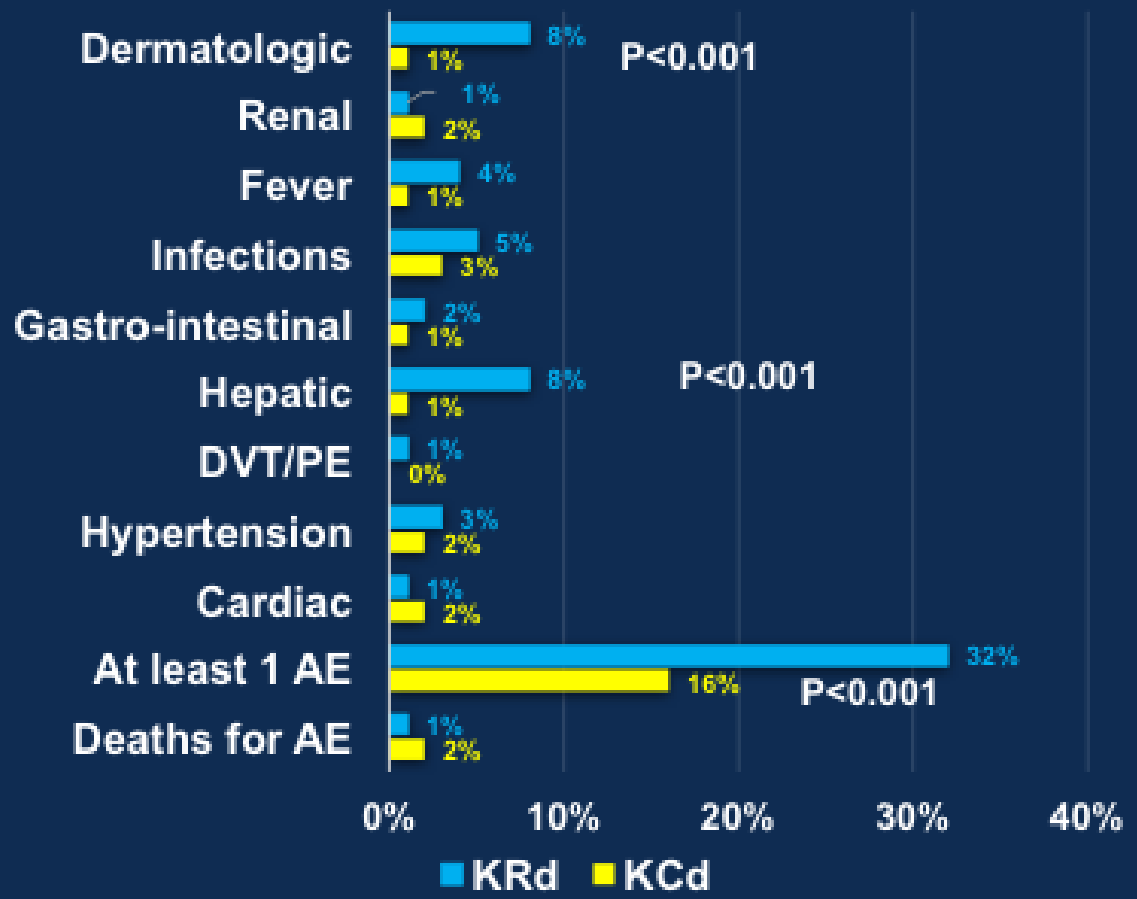
AE: Adverse Events; SAE: Serious Adverse Events;; KRd: Carfilzomib, Lenalidomide, dexamethasone; KCd: Carfilzomib, Cyclophosphamide, dexamethasone.

Non-Hematologic Adverse Events

Grade 1-2 AEs

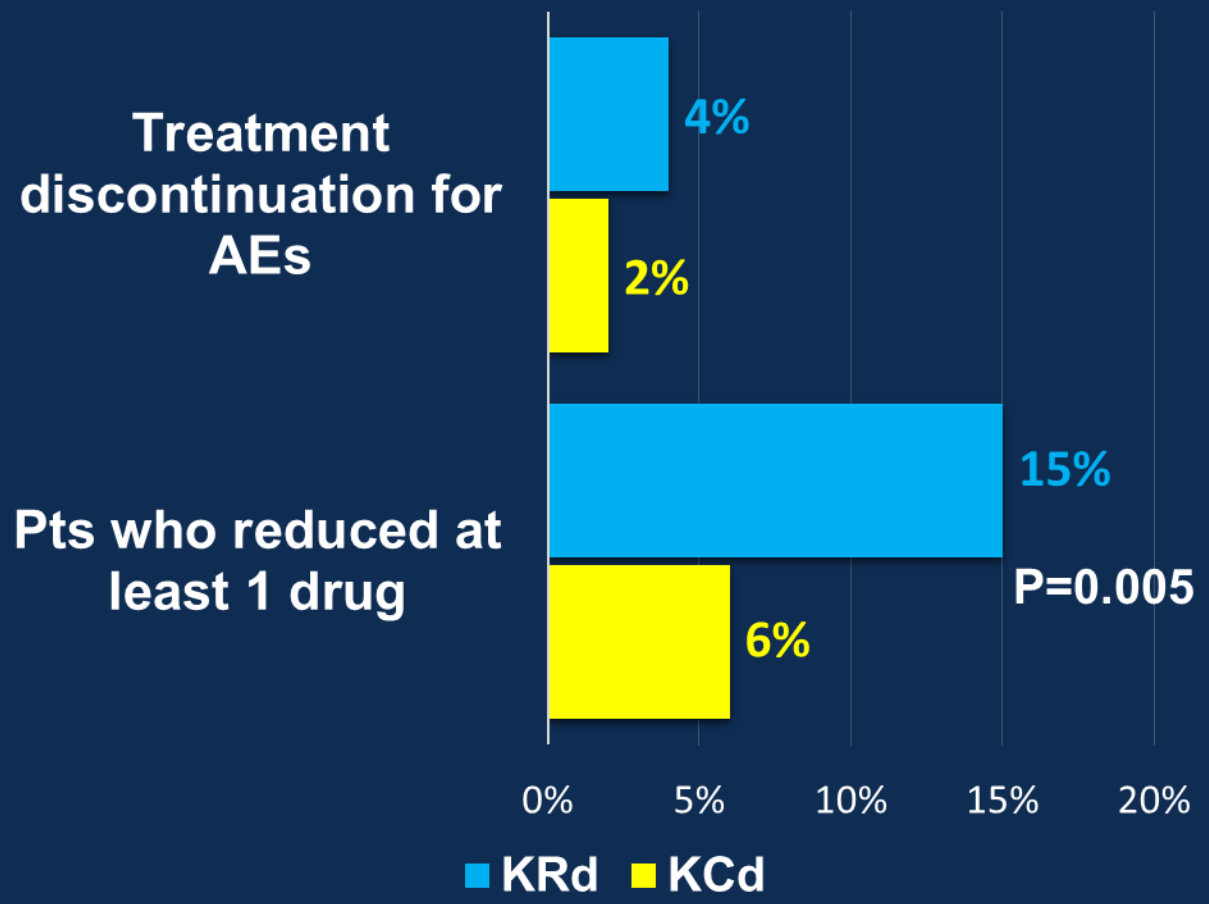


Grade 3-4 AEs/SAEs



Deaths for AEs: KCD: Pneumonia, n=1; Sudden death, n=1; KRD: sudden death (in pt with sepsis), n=1; Infection, n=1; cardiac arrest (in pt who previously discontinued for renal failure), n=1.
AEs: Adverse Events; SAEs: Serious Adverse Events; KRd: Carfilzomib, Lenalidomide, dexamethasone; KCd: Carfilzomib, Cyclophosphamide, dexamethasone; DVT: Deep Vein Thrombosis; PE: Pulmonary Embolism.

Dose Reductions and Discontinuation



Discontinuation for AEs:
KCD: G3 epatotox (related to trimethoprim-sulphamethoxazole), n=1; G3 heart failure, n=1; G3 AKI, n=1;
KRD: G3-4 dermatologic, n=3; G3-4 infections, n=2; G3-4 cardiac, n=2; G2 cardiac, n=1; G2-3 AKI, n=2; G2 Gastrointestinal, n=1; G2 Allergic reaction to K, n=1.
AEs: Adverse Events; KRd: Carfilzomib, Lenalidomide, dexamethasone; KCd: Carfilzomib, Cyclophosphamide, dexamethasone; C: Cyclophosphamide; D: Dexamethasone; K: Carfilzomib; R: Lenalidomide. AKI, Acute Kidney Injury.

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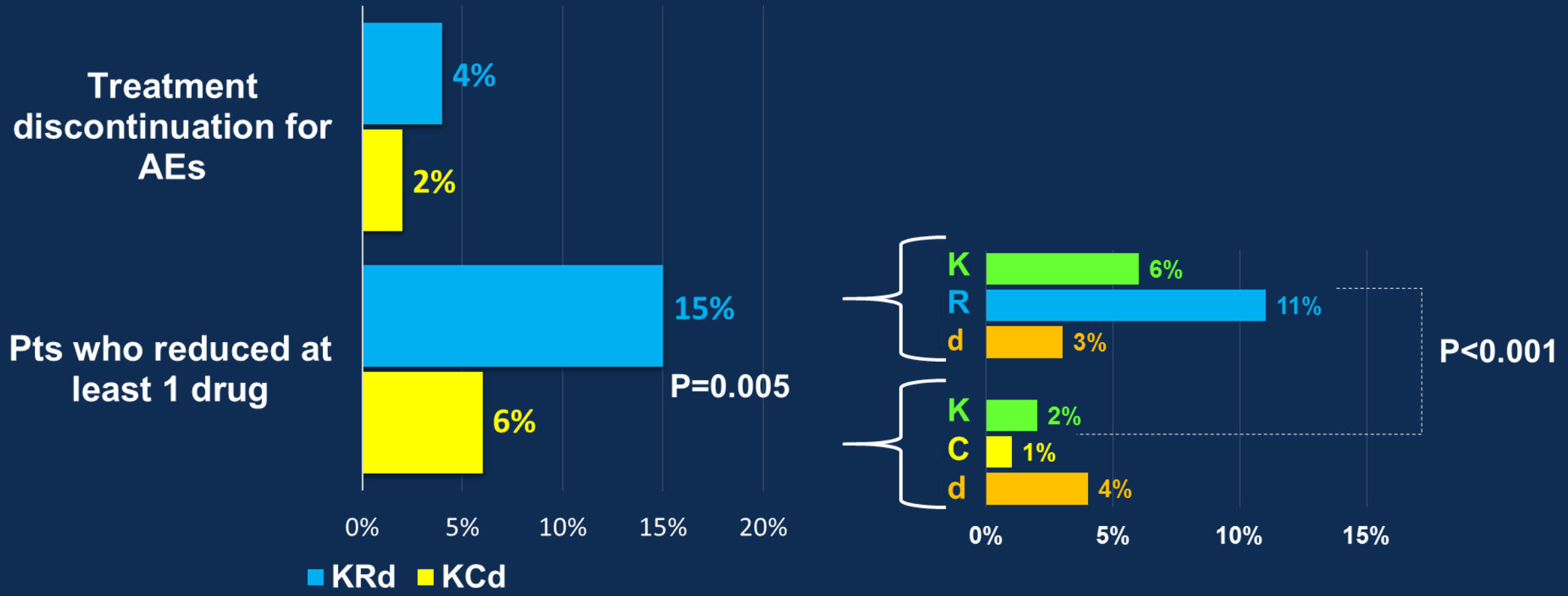

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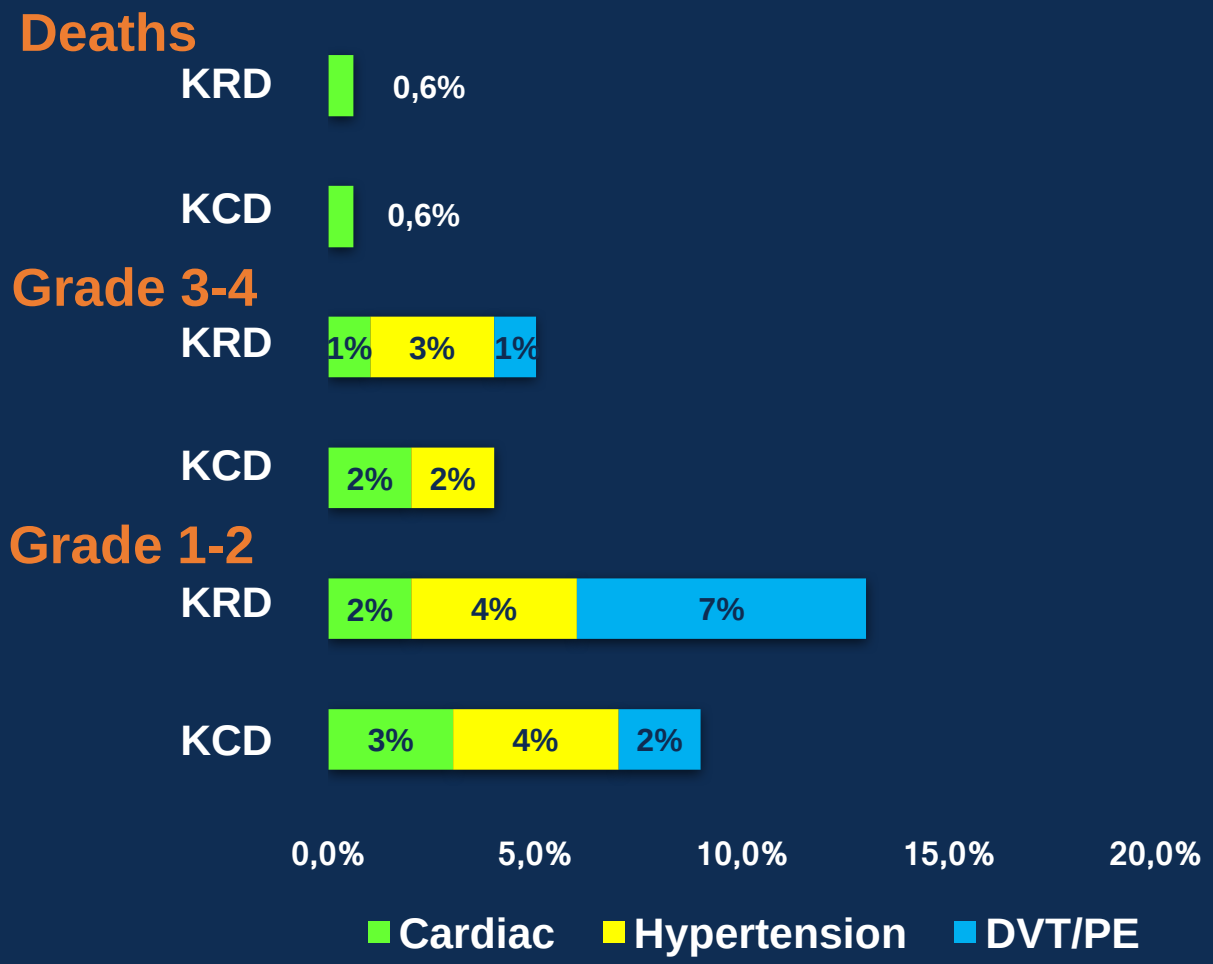
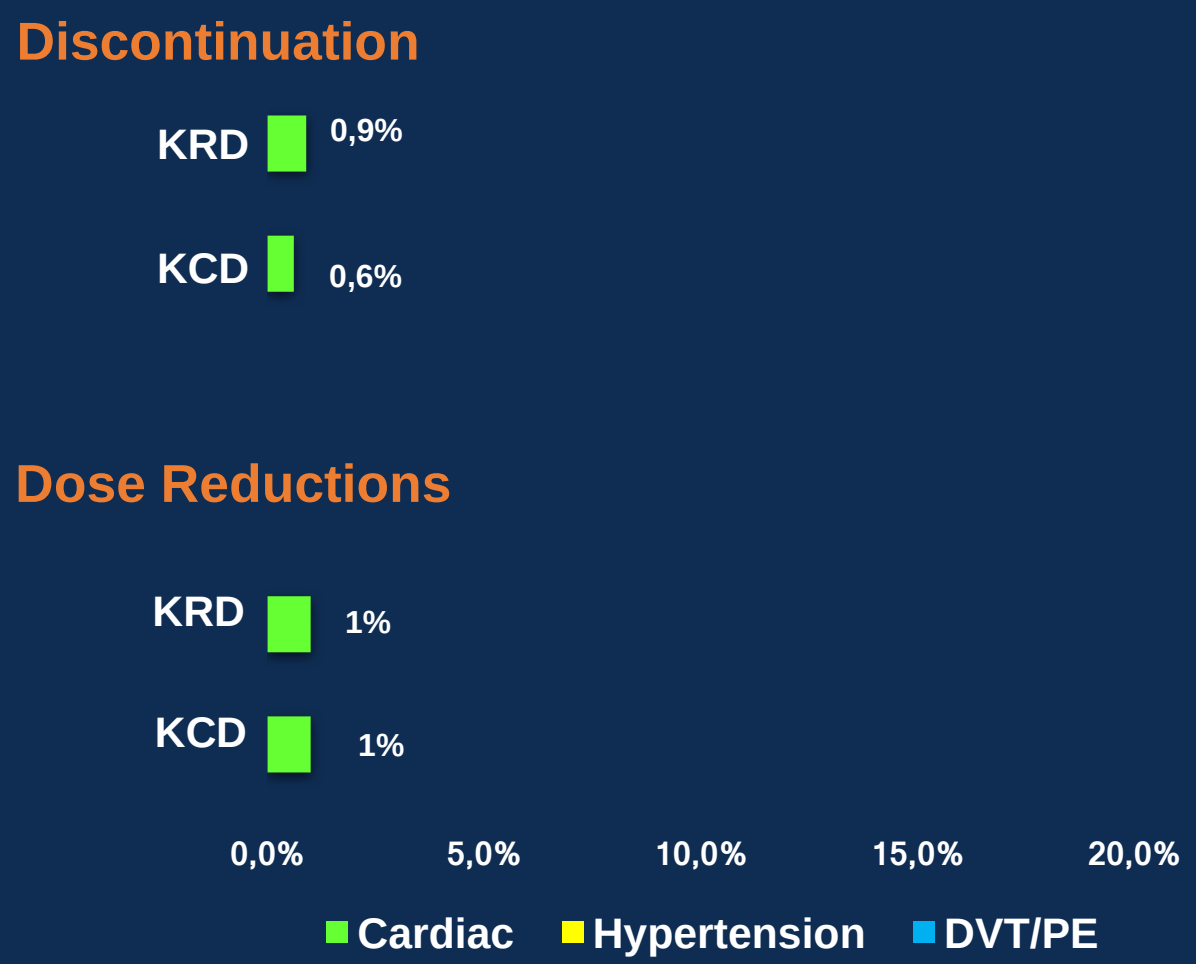
Cardiovascular AEs





AEs: Adverse Events; SAEs; KRd: Carfilzomib, Lenalidomide, dexamethasone; KCd: Carfilzomib, Cyclophosphamide, dexamethasone, DVT/PE: deep vein thrombosis/Pulmunary embolism.

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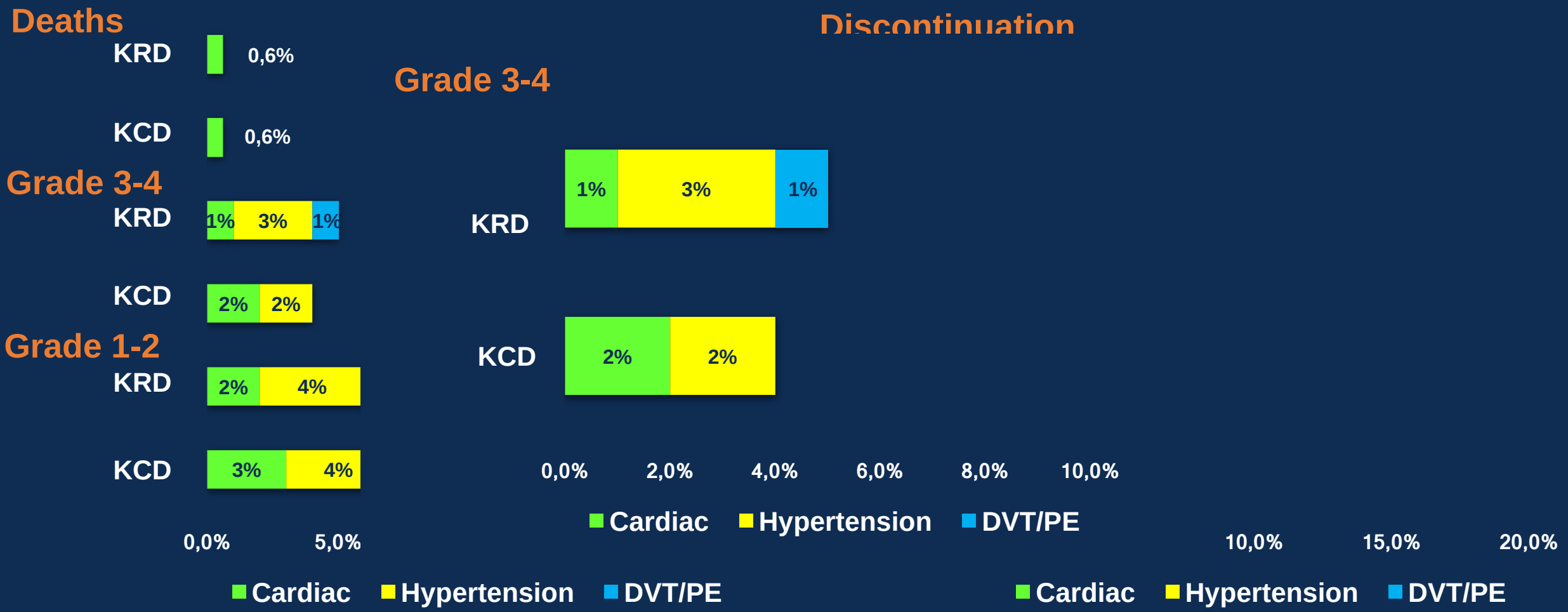

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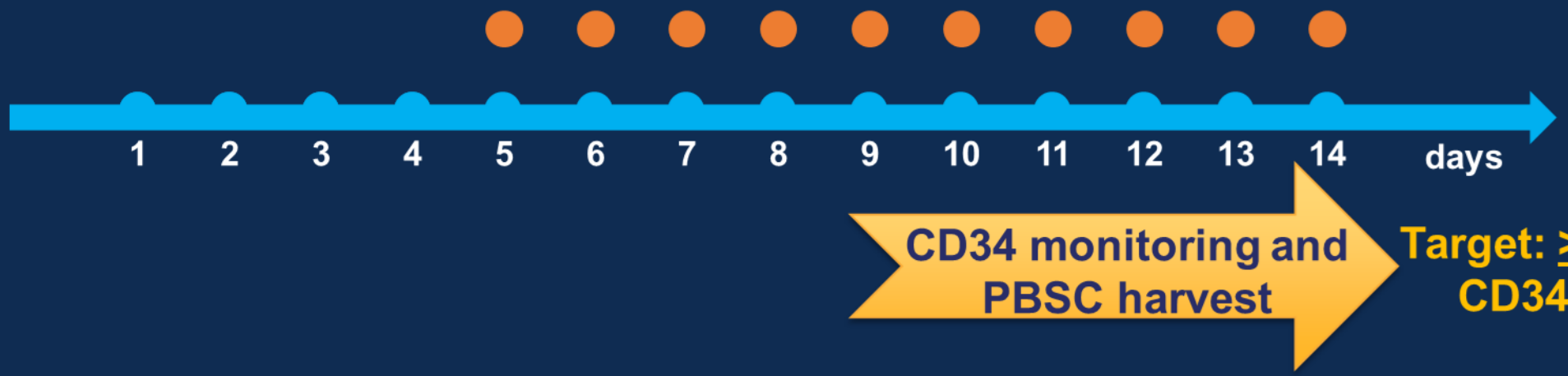
PBSC MOBILIZATION

PBSC mobilization

4-6 weeks after start of 4th induction cycle

Cyphosphamide
2000 mg/m² i.v.

G-CSF (filgastrim)
10 µg/kg s.c.



G-CSF: granulocyte-colony stimulating factor; PBSC: peripheral blood stem cells.

PBSC mobilization

4-6 weeks after start of 4th induction cycle

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10 µg/kg s.c.

CD34 monitoring and PBSC harvest

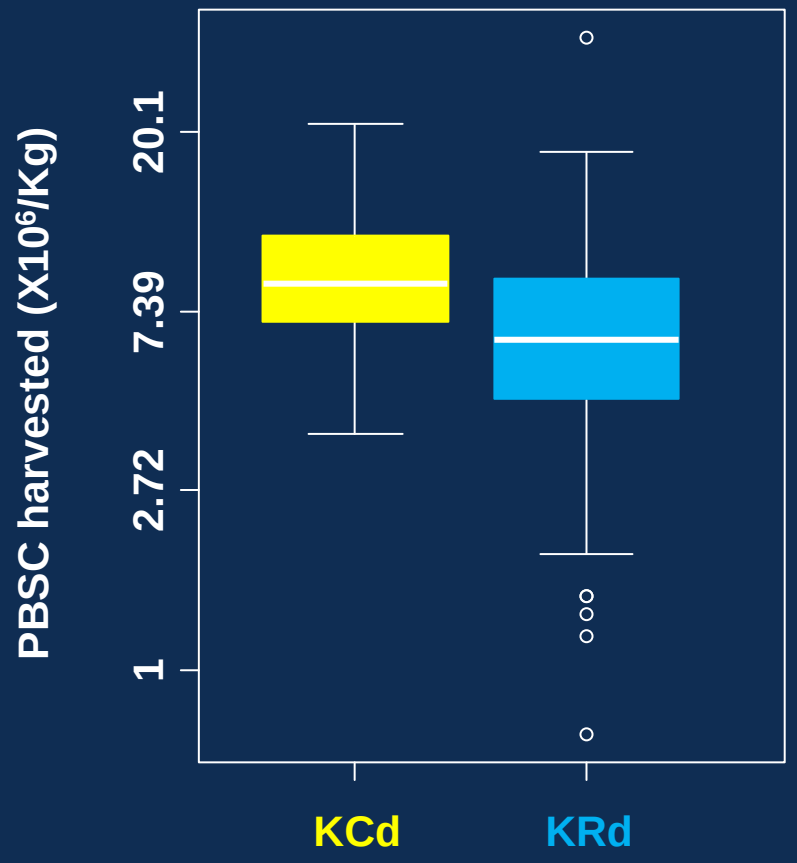
Target: ≥4x10⁶ CD34/Kg

Plerixafor allowed in poor mobilizer patients*

*after >4 days of G-CSF in patients with CD34 <20/µl on the scheduled harvest day, or who failed a previous PBSC harvesting attempt.

G-CSF: granulocyte-colony stimulating factor; PBSC: peripheral blood stem cells.

PBSC mobilization

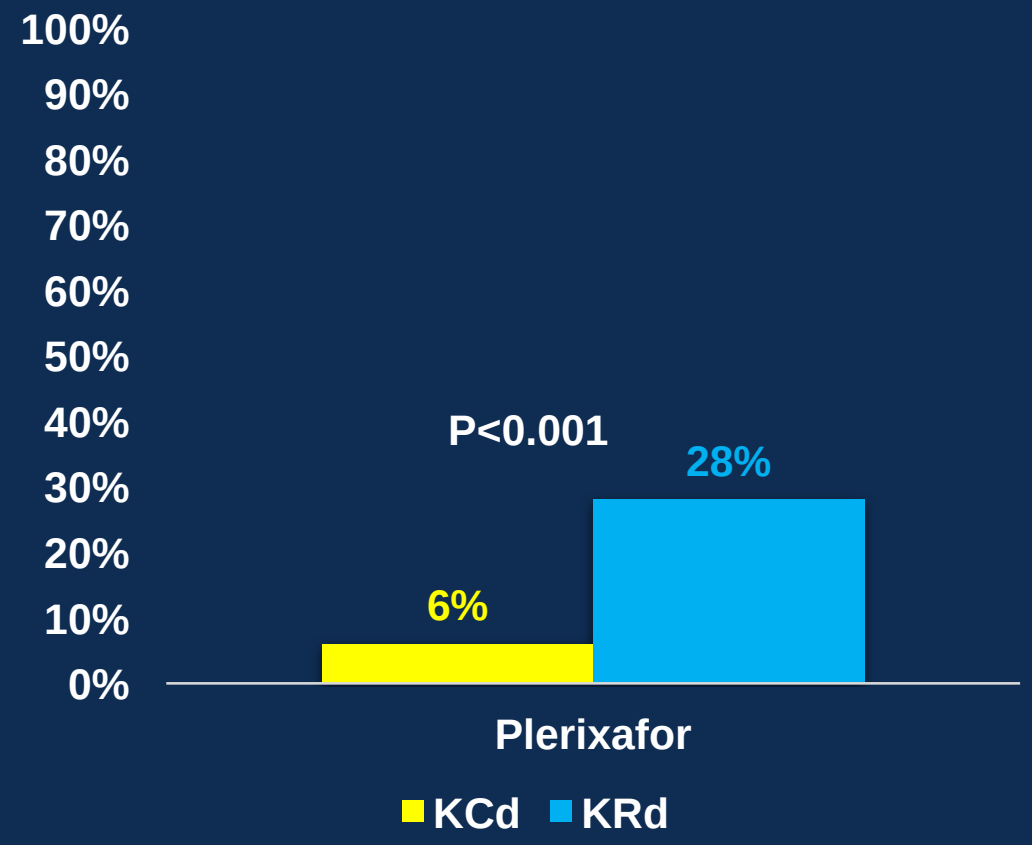


	KCd	KRd	P value
PBSC Median IQR	 8.6x10⁶/Kg 7.0-11.3	 6.3x10⁶/Kg 4.5-8.8	 <0.001
Median days from CTX to leukapheresis	10	10	-
Median days of leukapheresis	1	2	-

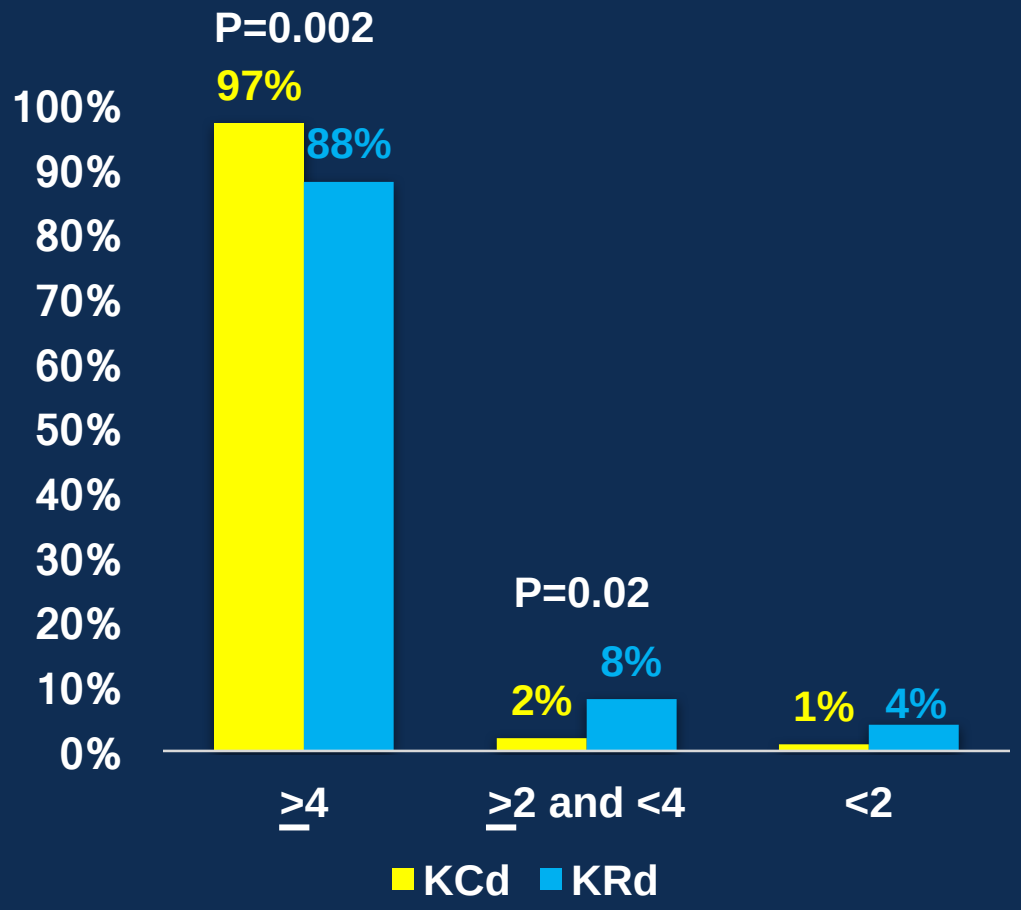
PBSC: peripheral blood stem cell; KRd: Carfilzomib, Lenalidomide, dexamethasone; KCd: Carfilzomib, Cyclophosphamide, dexamethasone; IQR, interquartile range; CTX: cyclophosphamide

PBSC mobilization

Patients requiring Plerixafor



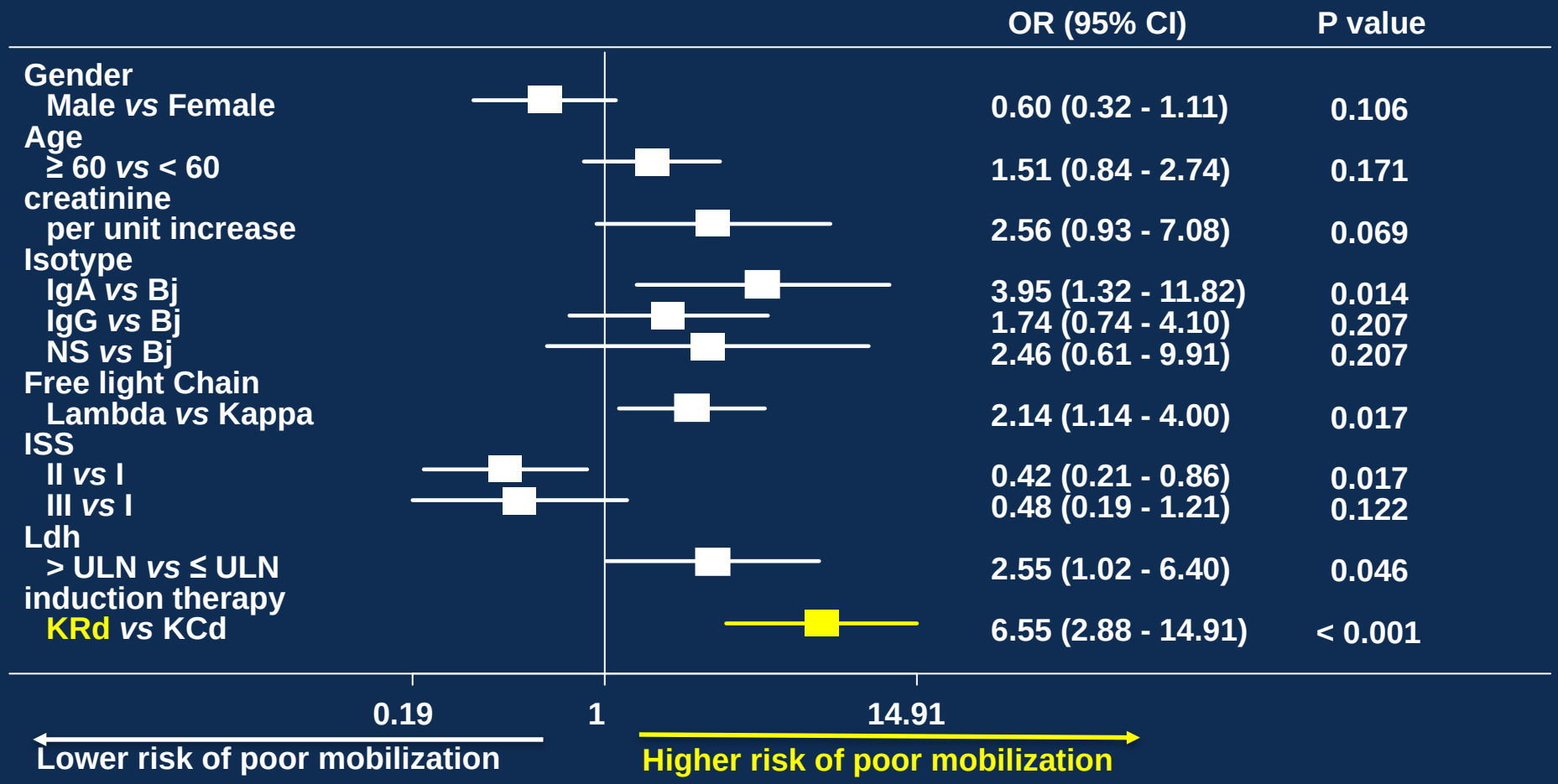
PBSC harvest



KRd: Carfilzomib, Lenalidomide, dexamethasone; KCd: Carfilzomib, Cyclophosphamide, dexamethasone; PBSC: Peripheral Blood Stem Cell.

Poor PBSC mobilization

- **Poor mobilizers** defined as pts who collected <4x10^{6}CD34/Kg and/or required Plerixafor

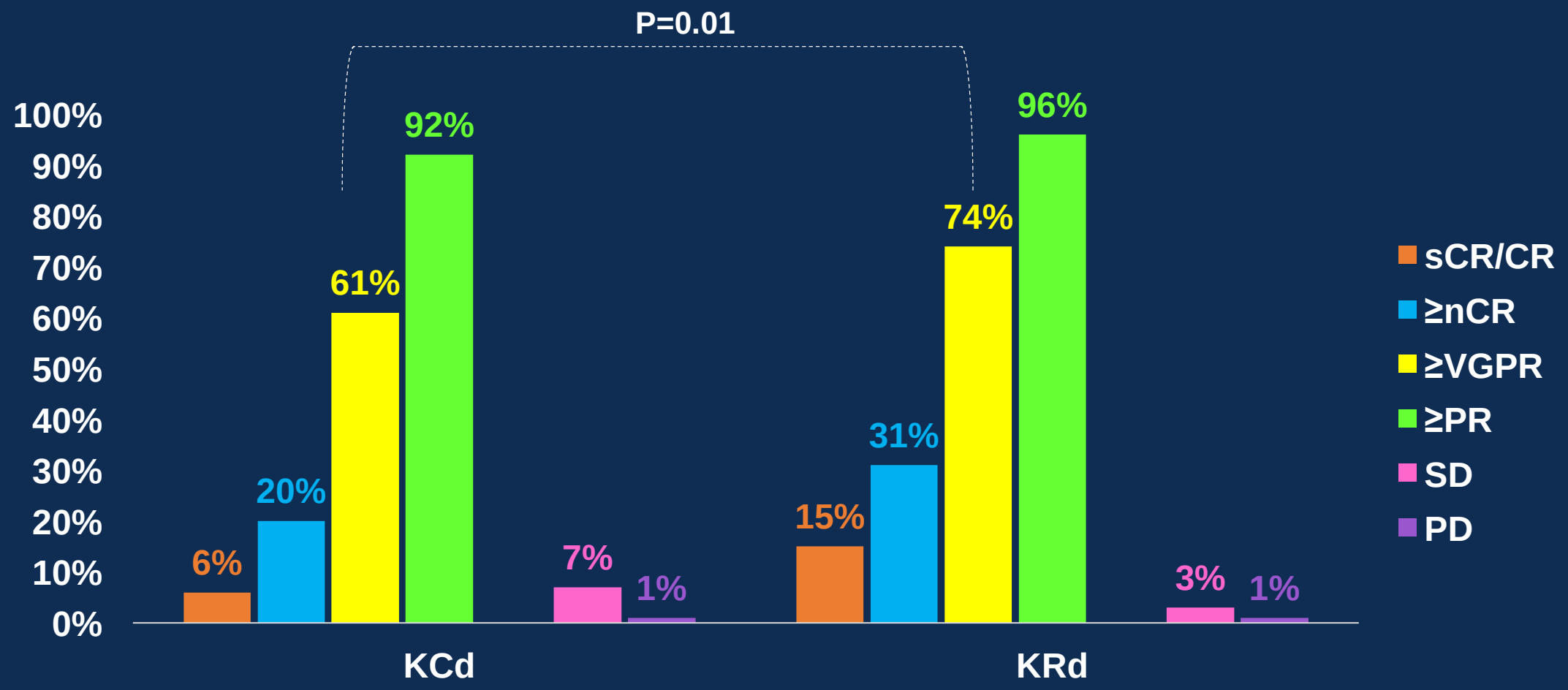


Logistic regression model estimated by backward stepwise algorithm based on AIC

KRd: Carfilzomib, Lenalidomide, dexamethasone; KCd: Carfilzomib, Cyclophosphamide, dexamethasone; PBSC: Peripheral Blood Stem Cell, ISS, International Staging System, ULN, upper limit of normal, OR, Odds Ratio.

EFFICACY: RESPONSE RATE

Best Responses



KCd: Carfilzomib, Cyclophosphamide, dexamethasone; KRd: Carfilzomib, Lenalidomide, dexamethasone; sCR: stringent Complete Response nCR: near Complete Response; VGPR: Very Good Partial Response; PR: Partial Response; SD: Stable Disease; PD: Progressive Disease.

Conclusions 1

- **Induction: Safety**

	KCd	KRd	P value
Grade 3-4 Non-hematologic AEs	16%	32%	<0.001
Hepatic	1%	8%	<0.001
Dermatologic	1%	8%	<0.001
Cardiovascular	4%	5%	ns
Discontinuation	2%	4%	ns
Deaths for AEs	2%	1%	ns

- **Induction: Efficacy**

	KCd	KRd	P value
Response Rate			
≥VGPR	61%	74%	0.01

AEs: Adverse Events; SAEs; KRd: Carfilzomib, Lenalidomide, dexamethasone; KCd: Carfilzomib, Cyclophosphamide, dexamethasone, Cardiovascular include hypertension, deep vein thrombosis and pulmonary embolism, cardiac toxicity, VGPR, very ggod partial response rate.

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Conclusions 2

- **Mobilization**

	KCd	KRd	P value
Median PBSC harvested	8,6x10^{6}CD34/Kg	6,3x10^{6}CD34/Kg	<0.001
Patients who collected ≥4x10^{6}CD34/Kg	97%	88%	0.002
Patients who require Plerixafor	6%	28%	<0.001
Mobilization failure <2x10^{6}CD34/Kg	1%	4%	NS

We Are Grateful to All Patients, Nurses and Physicians of the Participating Centers

ALESSANDRIA	Baraldi, Salvi
ANCONA	Offidani, Gentili
AOSTA	Di Vito
ASCOLI PICENO	Galien
ASTI	Marchetti, Ciravegna
AVELLINO	Cantore
AVIANO	Tirelli, Rupolo
BARI	Dammacco, Ria
BARI	Liso, Specchia
BELLUNO	Pinto, Cimarosto
BENEVENTO	Di Lonardo, Vallone
BERGAMO	Rambaldi, Galli
BOLOGNA	Cavo, Zamagni
BOLZANO	Cortellazzo, Pescosta
BRA	Vanni, Stefani
BRESCIA	Rossi, Crippa
BRESCIA	Russo, Malagola
BRINDISI	Quarta, Melpignano
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CAGLIARI	La Nasa, Ledda
CAMPOBASSO	Storti, Fraticelli
CANDIOLO	Aglietta, Capaldi
CATANIA	Di Raimondo, Palumbo
CATANZARO	Molica, Piro
CATTOLICA	Pasquini
CESENA	Guardigni, Pasini
CIRIE'	Girotto
COSENZA	Morabito, Mazzone
CREMONA	Lanza, Spedini
CUNEO	Massaia, Grasso
FIRENZE	Bosi , Gozzini
FOGGIA	Capalbo
FROSINONE	Sala
GALLARATE	Ciambelli
GENOVA	Gobbi, Canepa
GENOVA	Angelucci, Aquino
GENOVA	Bacigalupo, Dominietto
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LATINA	De Blasio
LATINA	Cimino
LECCE	Di Renzo
MATERA	Fragasso, Ciancio
MESSINA	Mannina, Neri
MESSINA	Musolino, Allegra
MILANO	Corradini, Montefusco
MILANO	Cafro
MILANO	Ciceri, Peccatori
MILANO	Baldini,
MODENA	Luppi, Narni
MODENA	Sacchi, Bari
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POTENZA	Olivieri
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