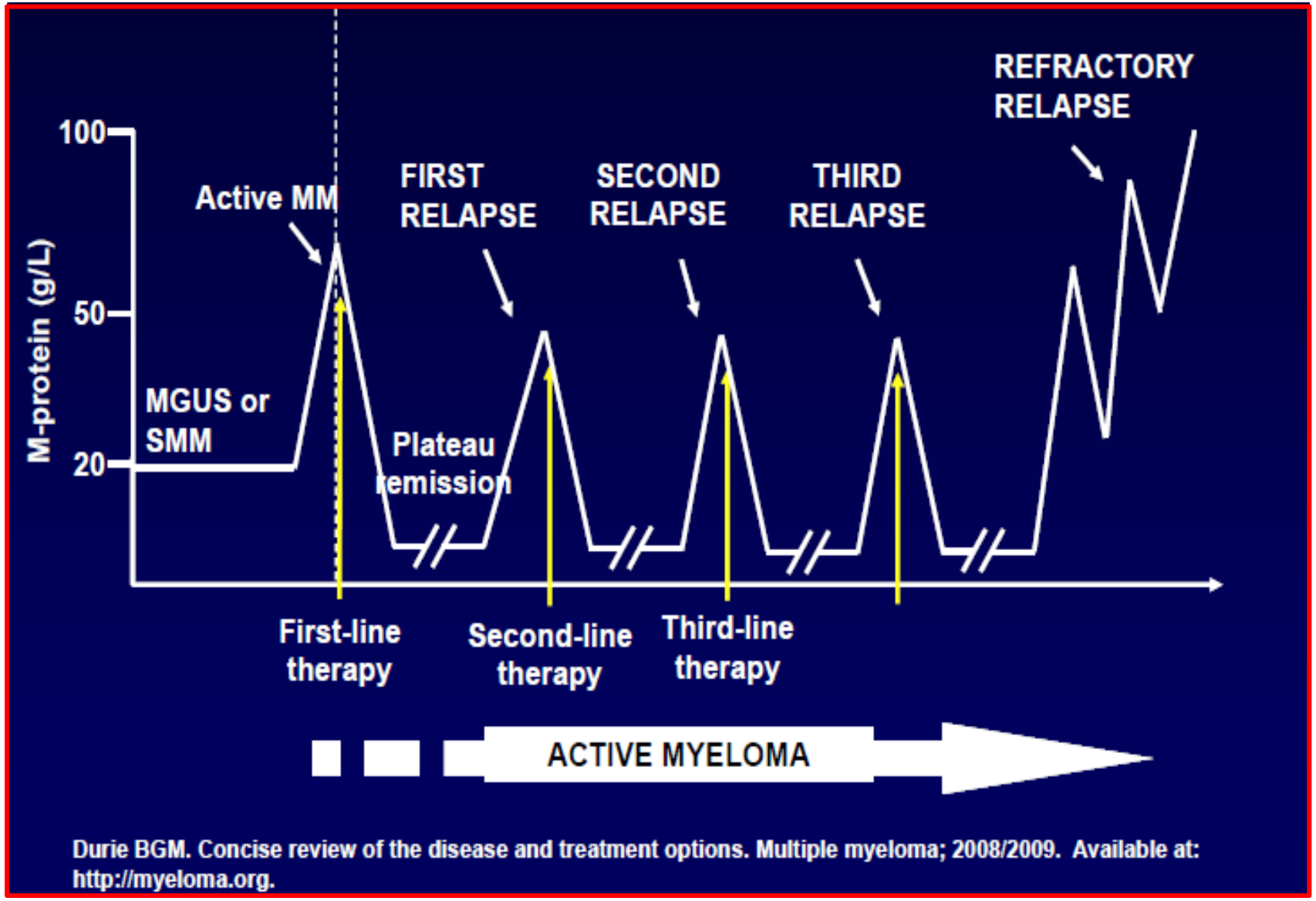
CARDIOTOSSICITA' ED IPERTENSIONE

IL PARERE DELL'EMATOLOGO

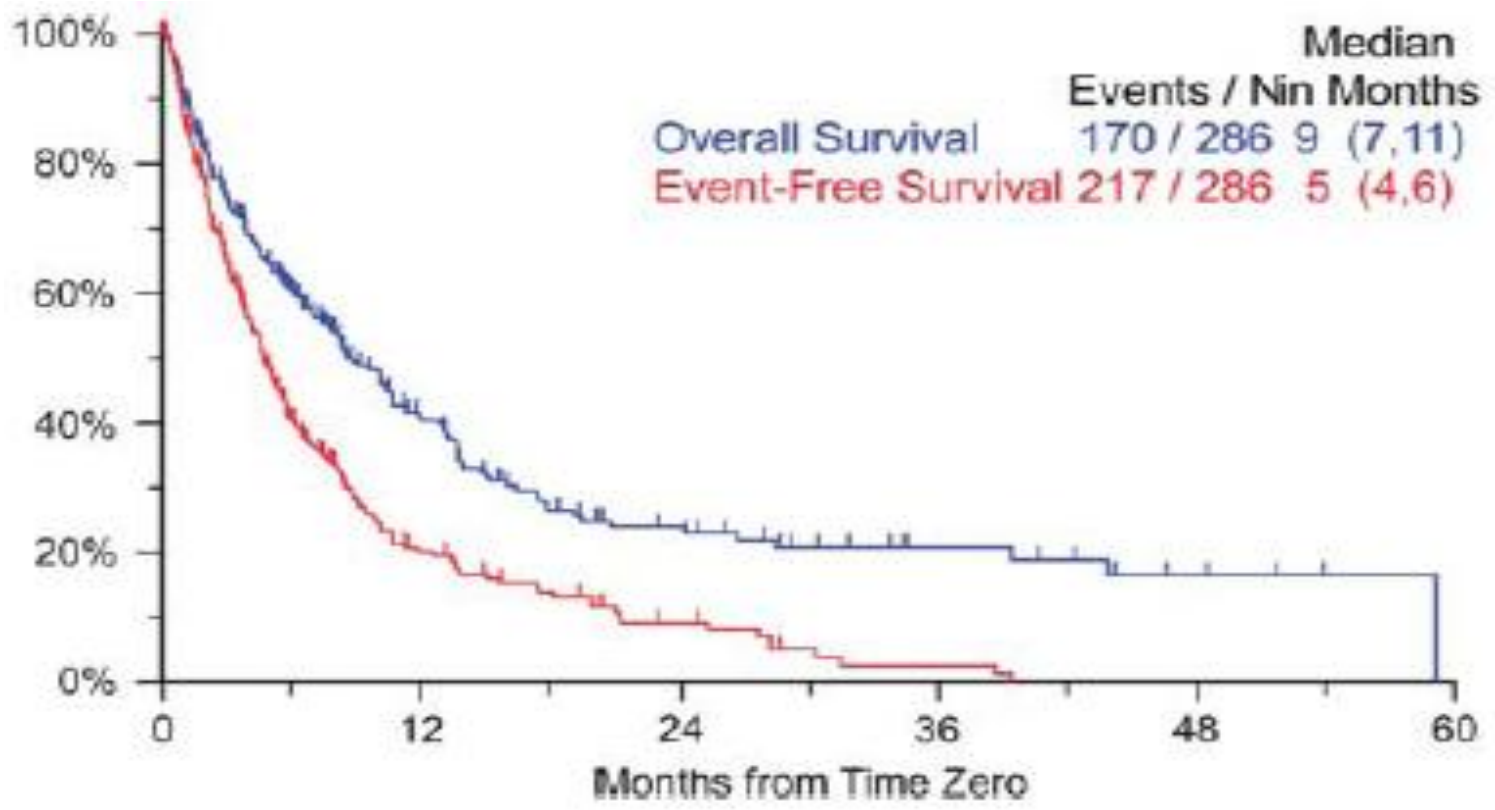
Giulia Benevolo
SC Ematologia
Città della Salute e della Scienza di Torino



Durie BGM. Concise review of the disease and treatment options. Multiple myeloma; 2008/2009. Available at: http://myeloma.org.

Outcome of relapsed/refractory MM

Risk of progression and survival in multiple myeloma relapsing after therapy with IMiDs and bortezomib



New agents effective on R/R patients are required

Kumar SG et al, Leukemia 2012

Quali fattori contribuiscono alla mattia cardiaca nei pazienti con MM?

Factors that contribute to cardiac disease in patients with MM

As of 2012, over 60% of patients with MM in the US have cardiac comorbidities at diagnosis[1]

Age-related[1,2]

Most patients are diagnosed between 65-74 years of age, with a median age at diagnosis of 69[2]

Increased age is associated with cardiac risks and contributes to cardiac comorbidity in patients with MM[1]

Other pre-existing risk factors that can affect cardiac function[3]

Diabetes
Cholesterol
Obesity
Smoking
Hypertension

Disease-related[1]

Pathogenesis and progression:

- Amyloid infiltration
- Hyperviscosity
- A-V shunting
- Renal failure[4]
- Chronic anemia

MM, multiple myeloma; A-V, arteriovenous.

1. Kistler K, et al. ASH. 2012 (abstract 2916); 2. SEER Cancer Statistics Factsheets: Myeloma. National Cancer Institute. Bethesda, MD. http://seer.cancer.gov/statfacts/html/mulmy.html. Accessed 5/13/2016; 3. Centers for Disease Control and Prevention: Heart Disease Risk Factors. http://www.cdc.gov/heartdisease/risk_factors.htm. Accessed February 25, 2016; 4. Korbet SM and Schwartz MM. J Am Soc Nephrol. 2006;17:2533-2545.

Treatment-Related Factors: Antimyeloma Therapy and Cardiac AEs

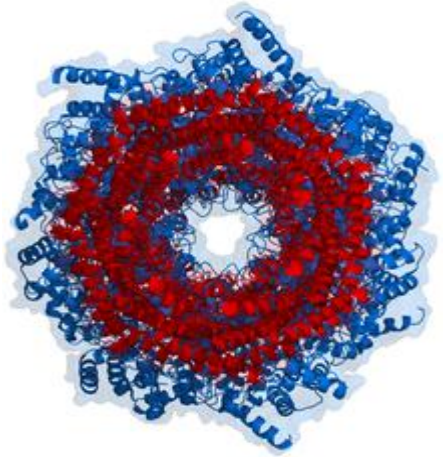
	Drug Class/Name	Reported Cardiac AEs
Chemotherapy[1]	**Anthracyclines** (e.g. doxorubicin, PLD)	Systolic left ventricular dysfunction, heart failure
	Alkylating agents (e.g. cyclophosphamide)	Systolic left ventricular dysfunction, heart failure, pericardial effusion, myopericarditis
Proteasome Inhibitors	**Bortezomib**	Grade ≥3 heart failure*: •Ranged from <1.0% - 4.7% with BTZ-based regimens across NDMM & RRMM[2] •Ranged from <1.0% - 3.9% with non-BTZ-based regimens across NDMM & RRMM[2]
	Carfilzomib	Grade ≥3 cardiac failure†: •ASPIRE: 3.8% (KRd) vs 1.8% (Rd) in RRMM[3] •ENDEAVOR: 4.8% (Kd) vs 1.8% (Vd) in RRMM[4]
	Ixazomib	Heart failure† (Grades 3/4): •TOURMALINE-MM1: 2.5% (IRd) vs 1.7% (Rd) in RRMM[5]
IMiDs	**Pomalidomide**	POM + LoDex vs POM alone in RRMM[6] •Cardiac failure congestive* SAE: 3% vs 0% •Atrial fibrillation* SAE: 3% vs 2%
	Lenalidomide	Rd vs placebo + dexamethasone in relapsed MM[7] •Grade 3/4 cardiac failure congestive*: 1.4% vs 0.3% •Grade 3/4 atrial fibrillation*: 3.7% vs 1.1%
	Thalidomide	Thalidomide + dexamethasone vs placebo + dexamethasone in NDMM[8] •Grade 3/4 atrial fibrillation: 5% vs 3% •Grade 3/4 myocardial ischemia: 3% vs 1%

*Preferred term; †represents multiple preferred terms

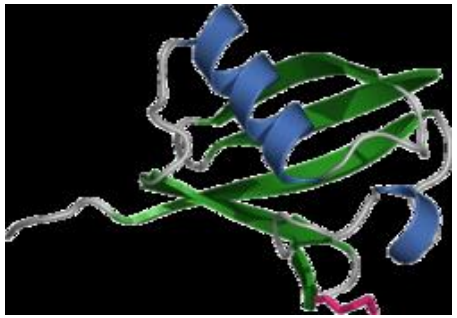
AE, adverse event; BTZ, bortezomib; RRMM, relapsed and/or refractory MM; IMiD, immunomodulatory agent; NDMM, newly diagnosed MM; PLD, pegylated liposomal doxorubicin; POM, pomalidomide; LoDex, low-dose dexamethasone; IRd, ixazomib plus Rd; Rd, lenalidomide plus dexamethasone; PLD, pegylated liposomal doxorubicin; SAE, serious adverse event

1. Wang M, Cheng J. Oncology. 2013;27(Suppl 3):24–30; 2. Laubach J, et al. *ASH*. 2013 (abstract 3187); 3. Stewart, et al. N Engl J Med. 2015;372:142-52;
4. Dimopoulos MA, et al. Lancet Oncol. 2016;17:27-38; 5. Moreau, et al. N Engl J Med. 2016;374:1621-34; 6. POMALYST® [package insert]. Summit, NJ: Celgene Corporation; 2014; 7.REVLIMID® [package insert]; Summit, NJ: Celgene Corporation; 2015; 8. THALOMID® [package insert]. Summit, NJ: Celgene Corporation; 2015

CARFILZOMIB
(proteasome inhibitor)
e malattia cardiovascolare



Pathway Proteasoma-Ubiquitina



2004: premio Nobel Aaron Ciechanover, Avram Hershko and Irwin Rose

Proteasoma: complesso proteico che degrada le proteine attraverso un processo di proteolisi (rottura dei legami peptidici)

Ubiquitina: sequenza aminoacidica, marcatore di proteine

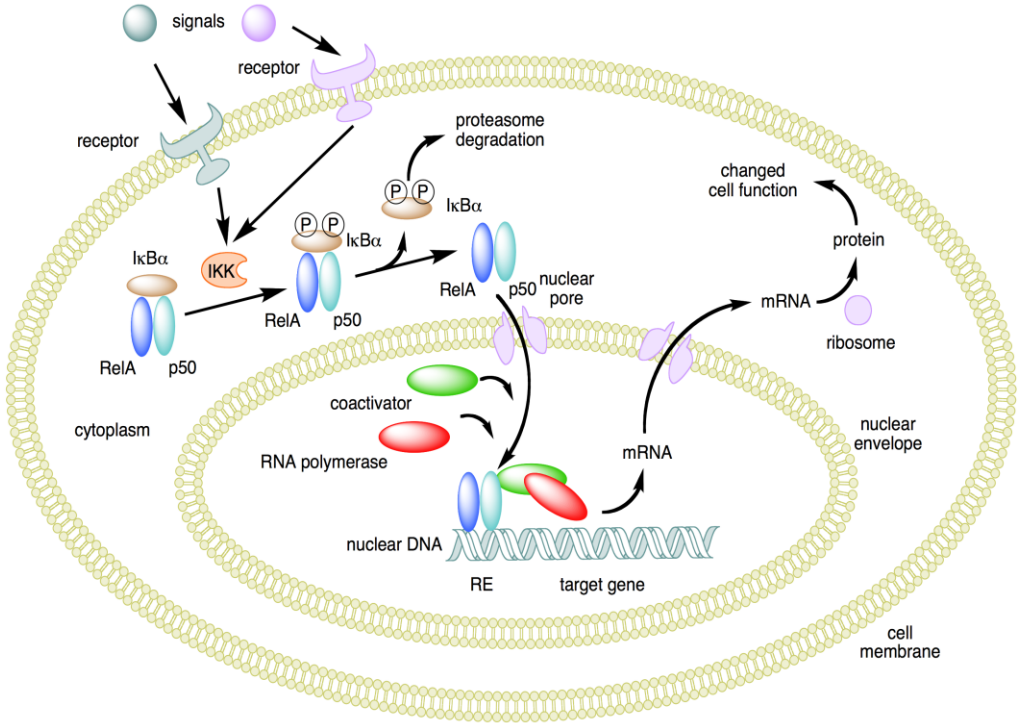
Sistema Proteasoma-Ubiquitina

- aiuta sistema immune: proteolisi di proteine antigeniche
- regola il ciclo cellulare: proteolisi delle cicline
- favorisce la riparazione del DNA: controllo della concentrazione di p53, proteina che blocca il ciclo cellulare se DNA è danneggiato

NF-kB

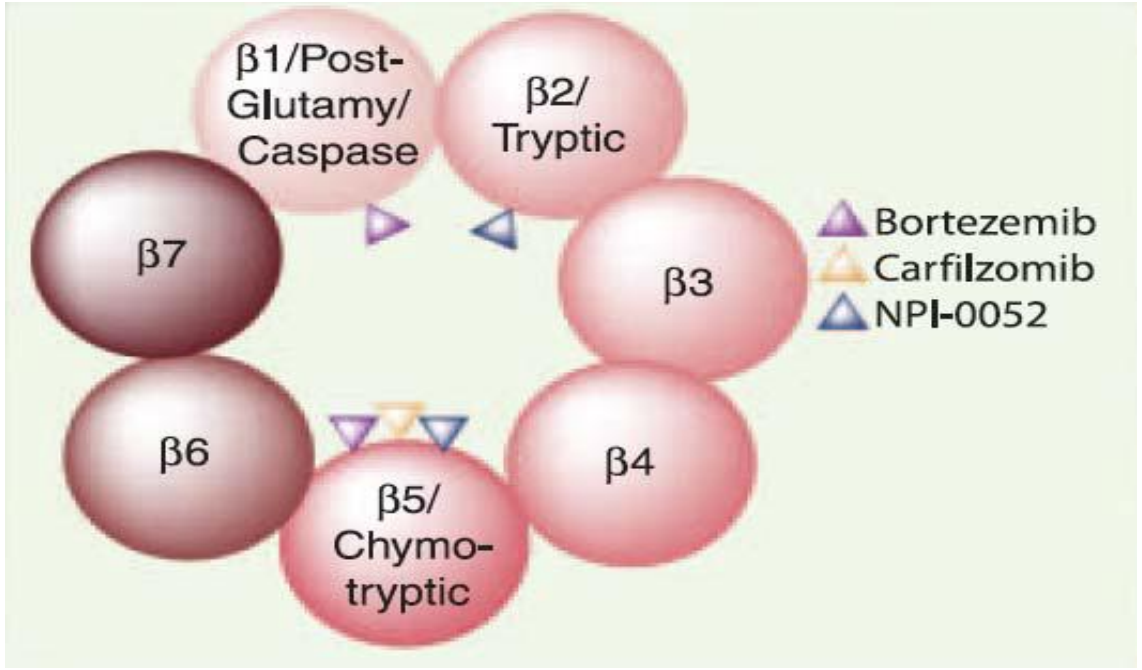
Fattore trascrizionale coinvolto nella fasi della cancerogenesi, compresa la **proliferazione** delle cellule tumorali e la **sintesi di molte citochine**, come l'interleukina-1, l'interleuchina-6 ed il fattore di necrosi tumorale (TNF-a) che regolano la neoangiogenesi e la crescita cellulare

In condizioni normali NF-kB è inattivo nel citoplasma, **legato a I-kB** (fattore inibente)
Se I-kB viene ubiquitinata attraverso la protein chinasi (**I-KK**) ed eliminata dal proteasoma, NF-kB si attiva, entra nel nucleo e attiva la trascrizione del DNA



Carfilzomib (PR-171)

- **Selective** inhibitor of chemotryptic site of proteasome
- **Irreversible** more sustained target inhibition
- Overcomes bortezomib resistence in preclinical models
- In vitro **fewer off-target effects** (lack neurodegeneration)



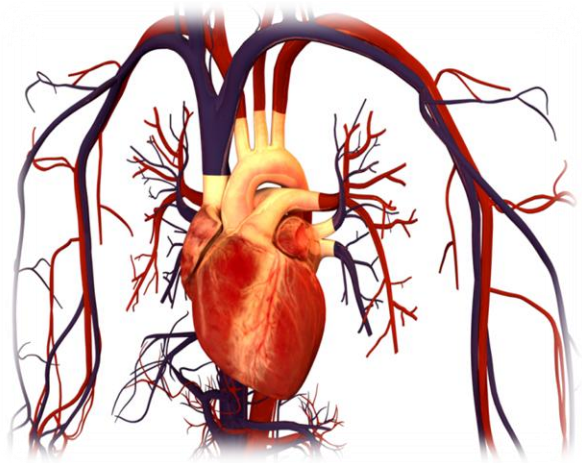
Cardiovascular Disease in Multiple Myeloma:

Hypothesized Mechanisms of Proteasome Inhibitor-Induced Cardiac Adverse Events

Increased apoptosis of endothelial progenitor cells[1]

Impaired endothelial nitric oxide synthase activity[1]

Functional and structural abnormalities in cardiomyocytes due to protein accumulation (decreased proteasomal protein degradation)[2,3]



Potentiation of cardiomyocyte toxicity from other agents (melphalan, doxorubicin)[2]

Left ventricular contractile dysfunction[2]

Disruption of cardiac mitochondrial function[2]

Induction of ER stress in cardiomyoblasts[2]

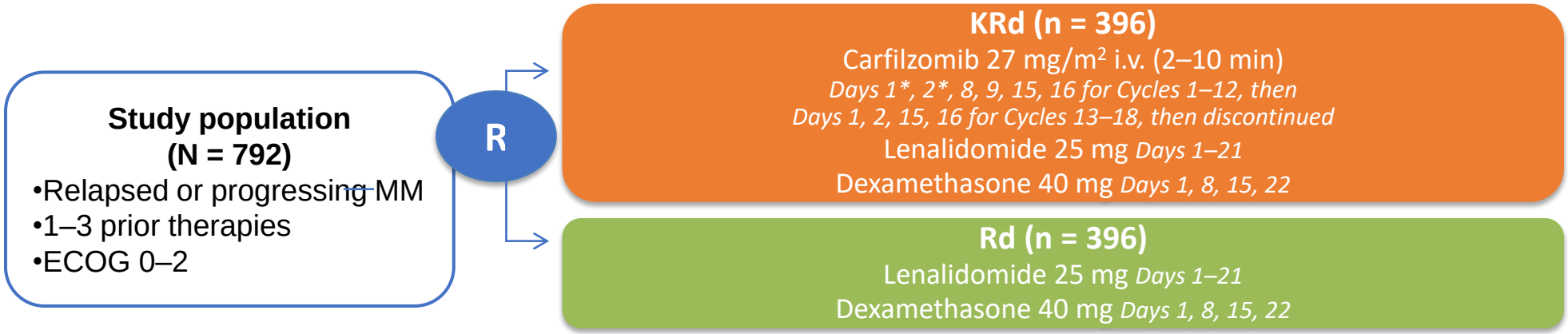
Myocardial scarring and fibrosis[4]

Suppression of adaptive, cytoprotective ubiquitin-proteasome system activity in the setting of baseline cardiomyopathy[5]

ER: Endoplasmic Reticulum

1. Takamatsu H, et al. Int J Hematol. 2010; 91:903-906; 2. Nowis D, et al. Am J Pathol. 2010; 176:2658-2668; 3. Hacihanefioglu A, et al. Int J Hematol. 2008; 88:219-222; 4. Foley P, et al. J Cardiovasc Med. 2010; 11:386-388; 5. Voortman J, et al. BMC Cancer. 2006; 6:129-132

Cardiopulmonary events in the ASPIRE trial

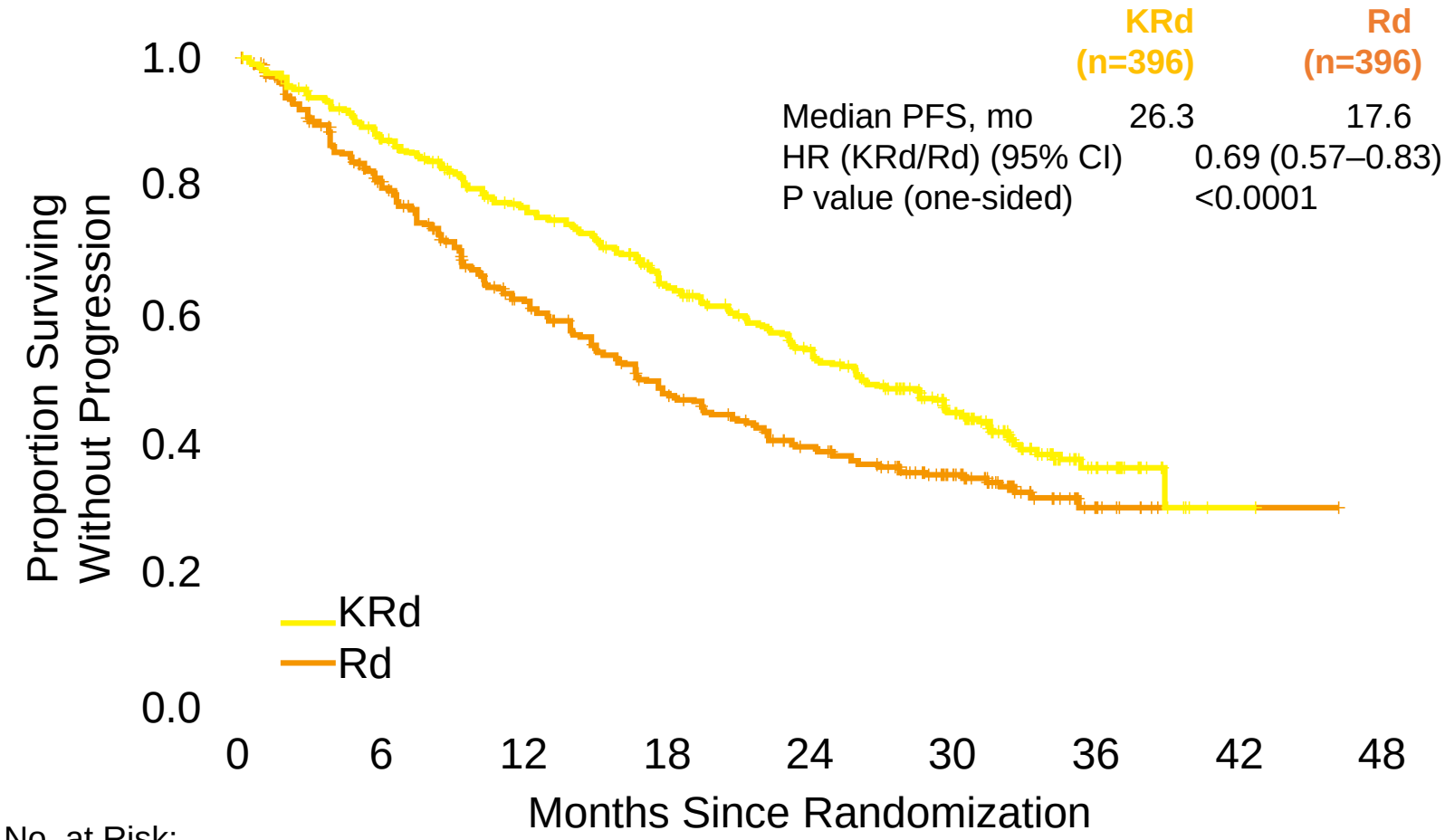


Events, %	KRd		Rd	
Grade	All	Gr 3+	All	Gr 3+
Cardiac failure†	6	4	4	2
Hypertension	**14**	4	**7**	2
Dyspnoea	20	3	15	2
Ischaemic heart disease†	6	3	5	2
Discontinuation due to AEs‡	15	NA	18	NA
Death due to AE‡	7	NA	7	NA

*20 mg/m^2 on Days 1, 2, Cycle 1 only; †cardiopulmonary AEs. ECOG, Eastern Cooperative Oncology Group; NA, not Grouped term; ‡Associated with any AE, not specifically applicable.

Stewart AK, et al. N Engl J Med 2015;372:142–52; Suppl. to: Stewart AK, et al. N Engl J Med 2015;372:142–52.

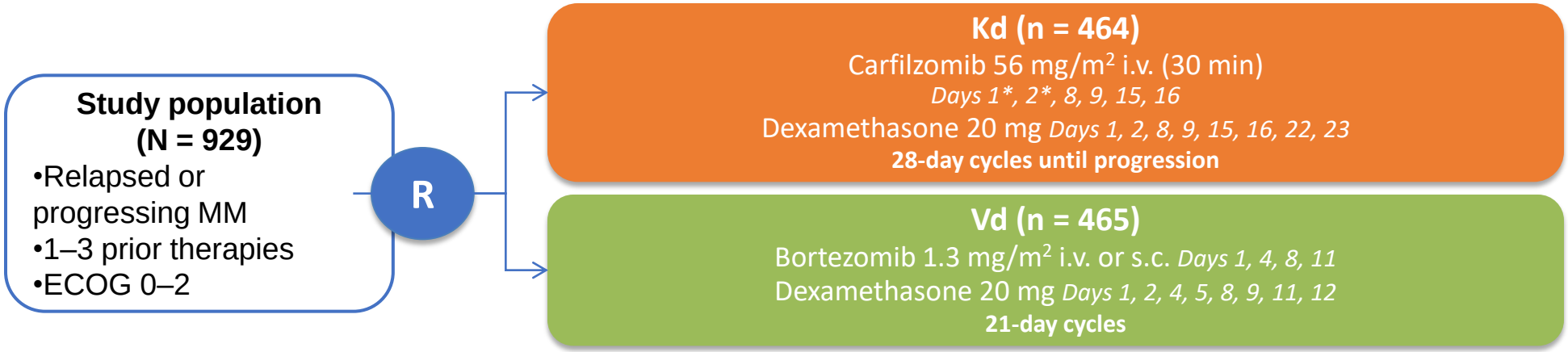
Primary Endpoint: Progression-Free Survival
ITT Population (N=792)



No. at Risk:

KRd	396	332	279	222	179	112	24	1
Rd	396	287	206	151	117	72	18	1

Cardiopulmonary events in the ENDEAVOR trial



Events, %	Kd		Vd	
Grade	All	Gr 3+	All	Gr 3+
Cardiac failure†	8	5	3	2
Hypertension	**25**	9	9	3
Dyspnoea	28	5	13	2
Ischaemic heart disease†	3	2	2	2
Discontinuation due to AEs‡	14	NA	16	NA
Death due to AE‡	4	NA	3	NA

*20 mg/m^2 on Days 1, 2, Cycle 1 only. †Grouped term; ‡Associated with any AE, not specifically cardiopulmonary AEs.

Dimopoulos MA, et al. J Clin Oncol 2015;33(Suppl):Abstract 8509; Dimopoulos MA, et al. Oral presentation at ASCO 2015; 8509.

Dimopoulos MA et al. Lancet Oncol 2016; 17: 27–38; Dimopoulos MA et al. Supplementary appendix, Lancet Oncol 2015

PI-based Studies: Efficacy outcome

	Daratumumab DVd vs Vd	Carfilzomib Kd vs Vd[1]	Panobinostat PVd vs Vd[2,3]	Elotuzumab EVd vs Vd[4]
PFS HR (95% CI)	0.39 (0.28-0.53)	0.53 (0.44-0.65)	0.63 (0.52-0.76)	0.72 (0.59-0.88)
PFS, median mo	NE	18.7	12.0	9.7
≥VGPR	59%	54%	28%	36%
≥CR	19%	13%	11%	4%
Duration of response, mo	NE	21.3	13.1	11.4
OS HR (95% CI)	0.77 (0.47, 1.26)	0.79 (0.58-1.08)	0.94 (0.78-1.14)	0.61 (0.32-1.15)

. Dimopoulos MA, et al. *Lancet Oncol*. 2016;17(1):27-38.
2. San-Miguel JF, et al. *Lancet Oncol*. 2014;15(11):1195-1206.
3. San-Miguel JF, et al. *Blood*. 2015;126(23):Abstract 3026.
4. Jakubowiak A, et al. *Blood*. 2016. Epub ahead of print.

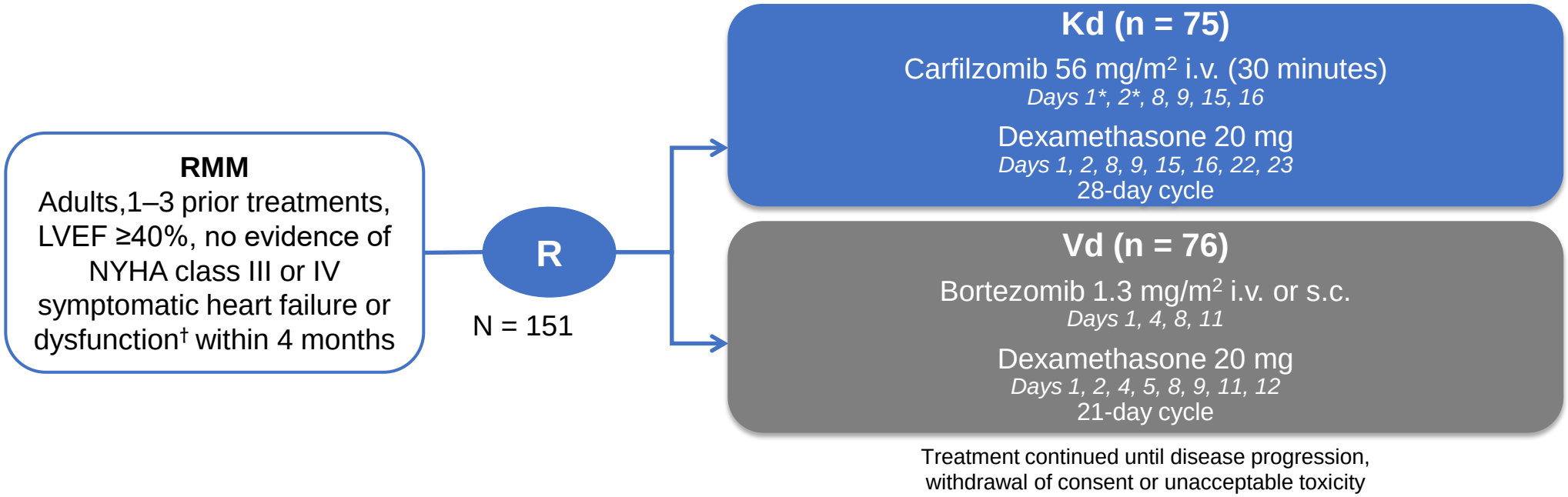
ENDEAVOR vs ASPIRE: Study Design Differences

	ENDEAVOR (N=929)[1]	ASPIRE (N=792)[2]
n	464 (Kd arm)	396 (KRd arm)
Regimen	Doublet (Kd vs Vd)	Triplet (KRd vs Rd)
Dose	20/56 mg/m^2 infused over 30 min	20/27 mg/m^2 infused over 10 min
Treatment duration	• Until PD or unacceptable toxicity	• CFZ through 18 cycles, Rd until PD or unacceptable toxicity
Patient population	• Relapsed or refractory MM	• Relapsed MM
	• 1-3 prior treatments	• 1-3 prior treatments
	• ≥PR to ≥1 line of prior therapy	• Not reported
Inclusion and exclusion criteria	• Prior bortezomib or carfilzomib allowed if at least 6 month treatment-free interval before start of study treatment, patients achieved ≥ PR before relapse or progression, and did not discontinue due to toxicity • Uncontrolled hypertension not excluded	• Prior bortezomib (no PD during treatment) allowed; bortezomib intolerance allowed • Prior lenalidomide and dexamethasone (no PD during first 3 months of therapy or any PD if Rd was most recent line of therapy; no discontinuation due to intolerance) allowed
	• CrCl ≥15 mL/min	• CrCl ≥50 mL/min
	• LVEF ≥40%	• Not specified
Main prophylaxis requirements	• Antiviral agent, proton pump inhibitor	• Antiviral agent, thromboprophylaxis

PD=progressive disease; PR=partial response; CrCl=creatinine clearance; LVEF=left ventricular ejection fraction; MR = minimal response

1. Dimopoulos MA, et al. Lancet Oncol. 2016;17:27-38; 2. Stewart, et al. N Engl J Med. 2015;372:142-52;

ECHO substudy of the ENDEAVOR study



Aim: Substudy to evaluate change from baseline in LVEF, RV function and PASP via echocardiogram in a subset of patients from the ENDEAVOR study

All eligible patients were assessed at baseline and every 12 weeks on D1 of treatment cycles and at the end-of-treatment visit (using 2D transthoracic ECHO)

Primary endpoint: Change in LVEF (≥ 10% absolute decrease from baseline in patients with LVEF ≤ 55% or a reduction < 45% for patients with baseline LVEF > 55%) or no change in LVEF (≤ 24 weeks from baseline)

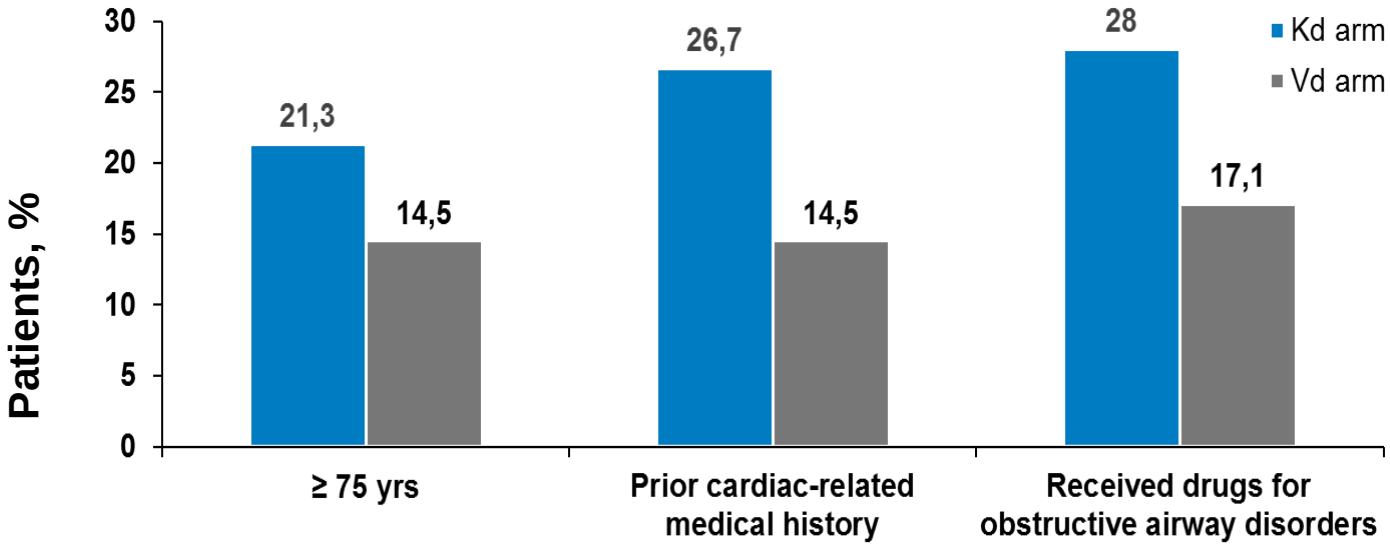
† including ischemia, uncontrolled arrhythmias or recent myocardial infarction; *20 mg/m^2 on Days 1, 2, Cycle 1 only.

ECHO, echocardiogram; i.v., intravenous; Kd, carfilzomib+dexamethasone; LVEF, left ventricular ejection fraction; MM, multiple myeloma; NYHA: New York Heart Association; PASP, pulmonary artery systolic pressure; RMM, relapsed multiple myeloma; RV, right ventricular; s.c., subcutaneous; Vd, bortezomib+dexamethasone.

Hájek R et al. , P664, EHA 2016

More patients in the Kd arm had a history of cardiac disorders

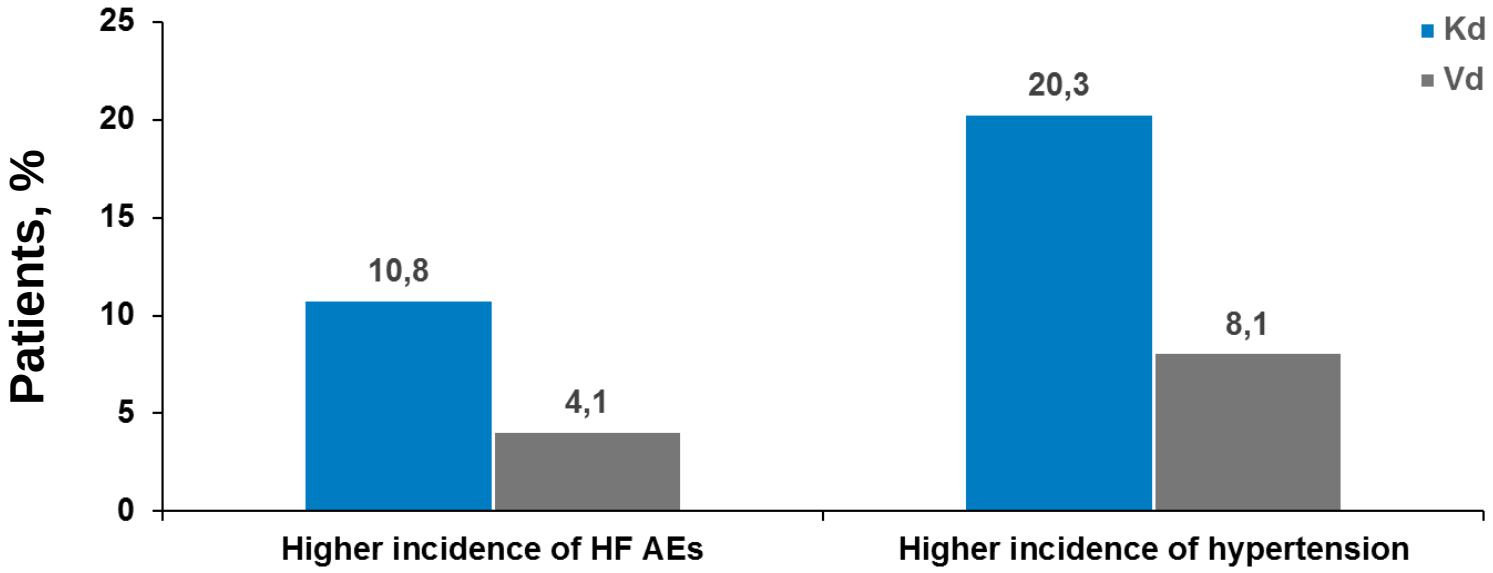
Demographic and baseline characteristics were balanced between the Kd and Vd groups in the cardio-pulmonary substudy with the exception of the proportion of subjects ≥ 75 years of age, those with prior cardiac-related medical history and those receiving drugs for obstructive airway disorder, which were higher in the Kd arm



Kd, carfilzomib+dexamethasone; Vd, bortezomib+dexamethasone.

Hájek R et al. , P664, EHA 2016

Higher incidence for heart failure and hypertension in the Kd arm



A history of cardiac disorders was associated with an elevated (not significant) risk of HF: 3 of 8 Kd patients vs 0 of 3 Vd patients
The **increased HF incidence in the Kd vs Vd arm was consistent** with the overall safety population (**8.2%** vs 2.9%)

AE, adverse event; HF, heart failure; Kd, carfilzomib+dexamethasone; Vd, bortezomib+dexamethasone.

Authors' conclusions

In the overall and cardiac substudy, **HF and pulmonary hypertension** events occurred more frequently with Kd vs Vd

ECHO-detected significant decline in LVEF was low in both treatment arms and with similar frequency

The substudy found limited utility for serial screening with ECHOs to mitigate cardiac risk for unselected patients receiving carfilzomib

Alternative surveillance strategies are needed to detect early cardiotoxicity and prevent treatment interruption or discontinuation

Gestione degli effetti cardiovascolari

nei pazienti trattati con calrfizomib

SUMMARY

BEFORE

What to consider prior to treatment with carfilzomib

Identify and assess potential risk of cardiac AEs in patients at risk:[1]

- Increased age: ≥ 75 years of age may be at increased risk
- Pre-existing cardiac failure (NYHA Class III and IV)
- Recent myocardial infarction (within prior 4 months[1])
- Conduction abnormalities
- Angina
- Arrhythmias uncontrolled by medications

Risk mitigation measures:

- Optimize management of pre-existing hypertension and active cardiac failure and consider cardiologist consultation before initiating Kyprolis treatment[1,2]

Plan fluid management:

- Establish baseline weight of patient[3]
- **Oral:** 30 mL/kg/day fluid at least 48 hours before Cycle 1, Day 1[1,2]
- **IV:** 250-500 mL fluid prior to each dose in Cycle 1[1,2]
- Consider reducing fluid volume in patients with increased cardiac risk[1,2]

1.Kyprolis Summary of Product Characteristics (SmPC).
2.J. Mikhael et al. 2016, Clinical Lymphoma, Myeloma & Leukemia, Vol. 16, No. 5, 241-5

DURING

What to consider during treatment with carfilzomib

SUMMARY

Monitor BP* and cardiac AEs:

- BP regularly measured in all patients[1]
- Monitor for signs/symptoms of active cardiac failure:[1]
    - Dyspnea[3]
    - Cough/wheezing[3]
    - Edema[3]
    - Chest pain[4]
    - Fatigue/weakness[3]
    - Confusion/impaired thinking[4]
    - Nausea/lack of appetite[3]
    - High heart rate[3]
    - Sudden weight change[3]

Monitor and adapt hydration:

- Monitor patients for evidence of volume overload and adjust as clinically appropriate, especially patients at risk for cardiac failure[1,2]

*BP: Blood Pressure

1.Kyprolis Summary of Product Characteristics (SmPC).
2. J. Mikhael et al. 2016, Clinical Lymphoma, Myeloma & Leukemia, Vol. 16, No. 5, 241-5
3.American Heart Association. Get With The Guidelines® - Heart Failure. June 2011;
4. American Heart Association. Self-Check Plan for Heart Failure Management. 2015

ACTION

When a cardiac AE occurs with carfilzomib

SUMMARY

Stop/withhold Kyprolis:[1,2]

- For Grade 3 or 4 cardiac adverse events (including dyspnea) until resolved or returned to baseline
- For pulmonary hypertension until resolved or returned to baseline[1]
- In case of hypertensive crisis until resolved or returned to baseline[1]

Reduce Kyprolis dose:[1]

- If hypertension cannot be controlled

Consider restarting Kyprolis at 1 dose level reduction based on a benefit/risk assessment[1,2]

Consider consulting cardiologist[2]

1.Kyprolis Summary of Product Characteristics (SmPC).
2. J. Mikhael et al. 2016, Clinical Lymphoma, Myeloma & Leukemia, Vol. 16, No. 5, 241-5

EDUCATION & PATIENT DISCUSSION

SUMMARY

Prior to and during treatment with carfilzomib

Contact your treating physician if you develop any of the following events **suddenly or unexpectedly** as these may be signs of cardiac failure:[1,3]

- Shortness of breath with no or minimal activity
- Dizziness/confusion/impaired thinking
- Cough/wheezing
- Swelling of the feet or legs
- Sudden weight change
- High blood pressure
- Systolic reading is 180 mmHg or higher OR a diastolic reading is 110 mmHg or higher after repeated measurement
- Chest pain
- Fatigue/weakness
- Nausea/lack of appetite
- Increased heart beat

1.Kyprolis Summary of Product Characteristics (SmPC).
3.American Heart Association. Get With The Guidelines® - Heart Failure. June 2011;

Prevention and management of cardio-pulmonary events

Evaluation of risk factors to develop cardiac adverse events

Blood pressure monitor before and after Carfilzomib infusion

Blood pressure diary at home

If blood pressure ≥ 140/90 or
increase in diastolic BP ≥ 20 mmHg

Carfilzomib to be held

- RAAS inhibitors (either ACE-inhibitors or Angiotensin 2 receptor blockers)
- Calcium channel blockers and-or Diuretics (thiazide)
- Beta blockers

Blood pressure target:
< 140/90

Mancia G, et al. Eur Heart J. 2013;
James PA, et al. Jama 2013

GRAZIE PER L'ATTENZIONE