Carfilzomib e Ixazomib: l'esperienza real Word della REP

Anna Mele

Carfilzomib - Lenalidomide - Dexamethasone

in Relapsed/Refractory

Multiple Myeloma:

Real-Life Experience of REP

Between December 2015 and August 2018: 120 patients enrolled

	N (%)
TRICASE	29 (24)
SGR	19 (16)
BRINDISI	18 (15)
LECCE	16 (13)
TARANTO	13 (11)
BARLETTA	13 (11)
BARI POLICLINICO	8 (7)
BARI ONCOLOG.	2 (1,5)
FOGGIA	2 (1,5)

Patients' characteristics at enrollment

	N= 120
Median age, years (range)	66 (34-81)
Age ≥ 70 years, n (%)	41 (34)
Age ≥ 75	12 (10)
Type of Myeloma, n (%)	
IgG	63 (52)
IgA / IgD	36 (30) / 1 (1)
Detected in urine only	20 (17)
III Durie Salmon staging, n (%)	80 (70)
III ISS disease staging, n (%)	50 (44)
Extramidollar disease, n (%)	13 (11)
Cytogenetic profile, n (%)	
Unkwown	77 (64)
Standard Risk	35 (29)
High Risk	8 (7)
Elevated LDH, n (%)	51 (46)

Patients' characteristics at enrollment

	N= 120
Median Time since initial therapy, months (range)	40 (0-295)
≤ 18 months	**30 (25)**
Median number of previous lines of therapy (range)	1 (0-11)
Number of previous lines of therapy, n (%)	
0	5 (4)
1	58 (48)
2	24 (20)
≥ 3	33 (29)
Previous autologous transplant, n (%)	**62 (52)**
Previous allogeneic transplant, n (%)	6 (5)
Previous therapy, n (%)	
Proteasome inhibitor (PI)	113 (94)
Lenalidomide	41 (34)
PI and Lenalidomide	39 (33)
plus Pomalidomide	11 (9)
Plus MoAb	3 (2)

Patients' characteristics at enrollment

	N= 115	
Relapsed, n (%)	82 (70)	
Refractory, n (%)	**33 (29)**	
PI	18 (16)	
Lenalidomide	7	11 (10)
Pomalidomide	4	
Dara	2 (2)	
PI and Lenalidomide	2 (2)	
Refractory to last therapy, n (%)	24 (21)	

ASPIRE Key Exclusion	
Revlimid	•if most recent line was Rd and progressed •If progressed in first 3 months of Rd
Velcade	•If progressed at any time during a Velcade based regimen (also after V discontinued)

PRIMARY END POINTS

- ORR
- PFS

SECONDARY END POINTS

- OS
- SAFETY

PRIMARY END POINTS

- ORR
- PFS

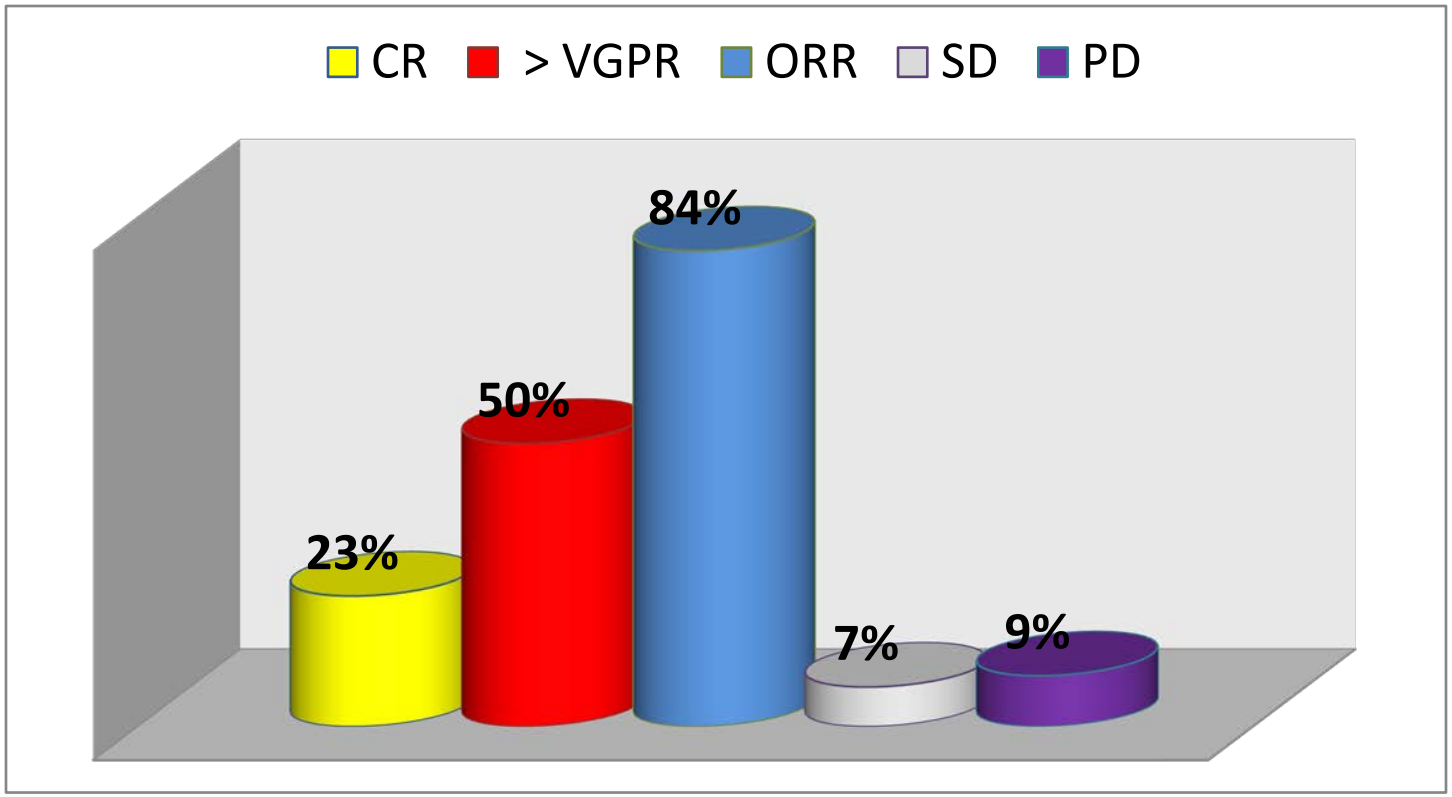
SECONDARY END POINTS

- OS
- SAFETY

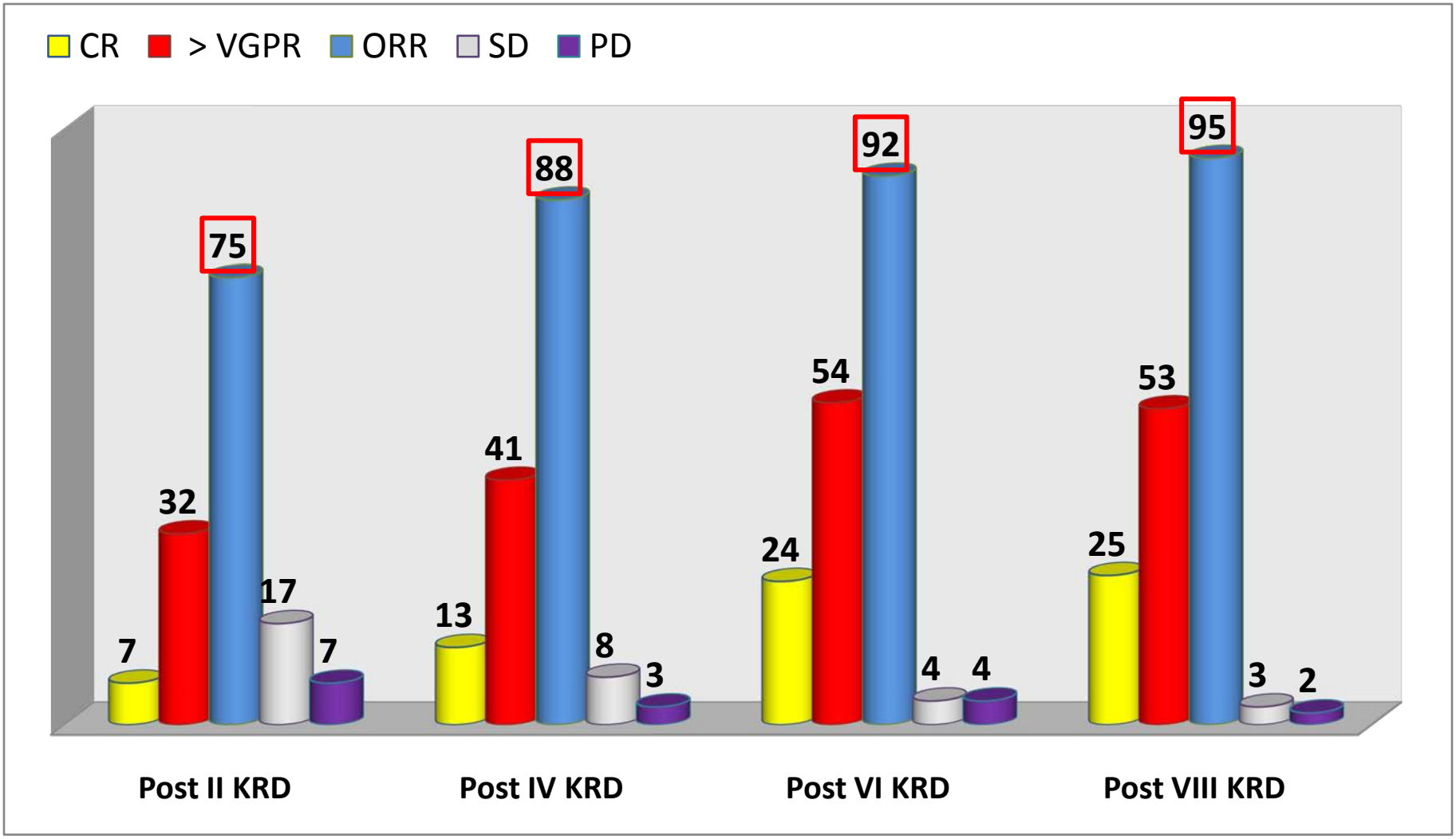
KRd: Treatment Responses

	N (%)	ASPIRE
Overall response rate	**93 (84)**	87%
Best Response		
Complete Response	25 (23)	126 (31,8)
Very good partial response or better	55 (50)	277 (69,9)
Stable Disease	8 (7)	
Progressive Disease	10 (9)	14 (3,5)
Median Time to response, months (range)	1,25 (0,93 – 3,03)	1,0
Duration of response, median (range)	12,9 (3,33 – 27,7)	28,6
Median Follow-up, months (range)	**13,4 (1 – 52)**	**>32**

KRd: Treatment Responses



KRd: Treatment Responses



Analysis of factors associated with ORR

	≥ PR vs. other (%)	Univariate P-value	Multivariate P-value	HR ; IC (95%)
Age ≥70 (years)	31 vs 44	0,21		
≥ III ISS stage	43 vs 46	0,75		
III Durie Salmon stage	71 vs 69	0,90		
Elevated LDH	48 vs 40	0,46		
Entramidollar disease	11 vs 11	0,47		
High Risk Cytogenetic	15 vs 27	0,66		
> 2 previous therapies	29 vs 25	0,33		
PI Lenalidomide PI and Lenalidomide	94 vs 96 36 vs 33 33 vs 30	0,16		
Refractory Disease	31 vs 22	0,39		
Previous ASCT Previous AlloSCT	56 vs 37 5 vs 4	0,08 0,72		
Time to KRd <=18 months	19 vs 44	0,008	0,028	1,8 (0,25-0,29)

Factors associated with time to KRd ≤ 18 months

	≤ 18 months vs. other (%)	Univariate P-value
Age ≥70 (years)	73 vs 38	0,44
≥ III ISS stage	57 vs 40	0,14
III Durie Salmon stage	56 vs 75	0,09
Elevated LDH	71 vs 39	0,001
Entramidollar disease	13 vs 10	0,62
High risk cytogenetic	7 vs 7	0,71
> 1 previous therapies	23 vs 70	0,001
PI Lenalidomide PI and Lenalidomide	87 vs 97 10 vs 42 10 vs 40	0,09 0,001 0,001
Refractory disease	28 vs 29	0,47
Previous ASCT	13 vs 64	0,001
Previous AlloSCT	7 vs 4	0,89
ORR PD	60 vs 83 47 vs 28	0,008 0,05

Leukemia. 2016 November ; 30(11): 2208–2213. doi:10.1038/leu.2016.147.

Early relapse following initial therapy for multiple myeloma predicts poor outcomes in the era of novel agents

N Majithia[1], SV Rajkumar[2], MQ Lacy[2], FK Buadi[2], A Dispenzieri[2], MA Gertz[2], SR Hayman[2], D Dingli[2], P Kapoor[2], L Hwa[2], JA Lust[2], SJ Russell[2], RS Go[2], RA Kyle[2], and SK Kumar[2]

- ❑ Early relapse after first line of therapy (<1y) **have poorer survival outcomes**
- ❑ Median OS : 21 months in early vs (NR) in late relapses
- ❑ The common second-line regimens included :
  - ✓ RD
  - ✓VCD
  - ✓VD

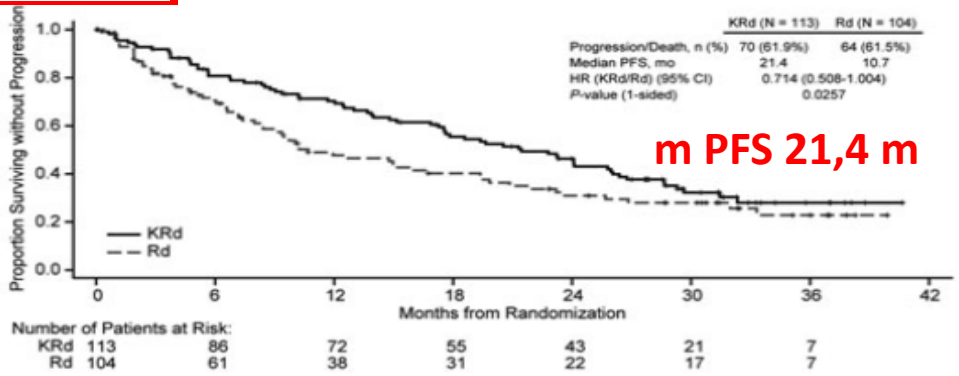
- ❑ **Monoclonal antibody Daratumumab** (POLLUX and CASTOR)
- ❑ **Carfilzomib** (ASPIRE and ENDEVOR)

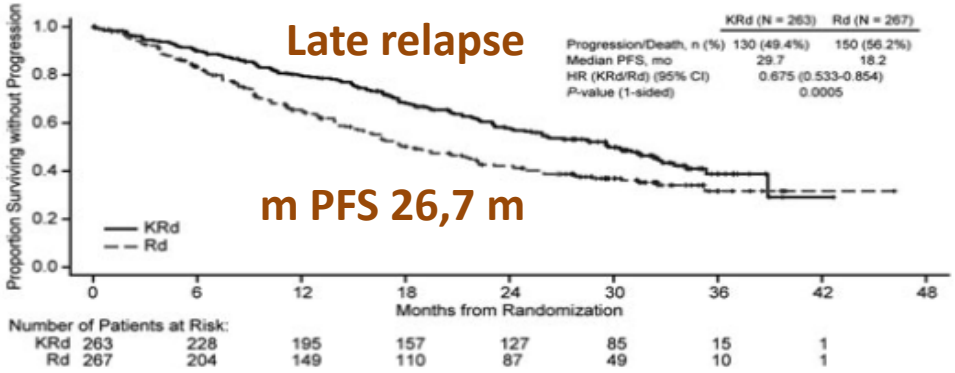
improved

PFS in both early and late relapses

	ASPIRE	
	Early Relapsers	Late Relapsers
	KRd (*n* = 113)	KRd (*n* = 263)
Overall response rate, % (95% CI)	83.2 (75.0–89.6)	89.0 (84.5–92.5)
Complete response or better, *n* (%)	25 (22.1)	97 (36.9)
Best overall response, *n* (%)		
Stringent complete response	10 (8.8)	42 (16.0)
Complete response	15 (13.3)	55 (20.9)
Very good partial response	47 (41.6)	97 (36.9)
Partial response	22 (19.5)	40 (15.2)

Early relapse





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ORIGINAL RESEARCH ARTICLE

WILEY

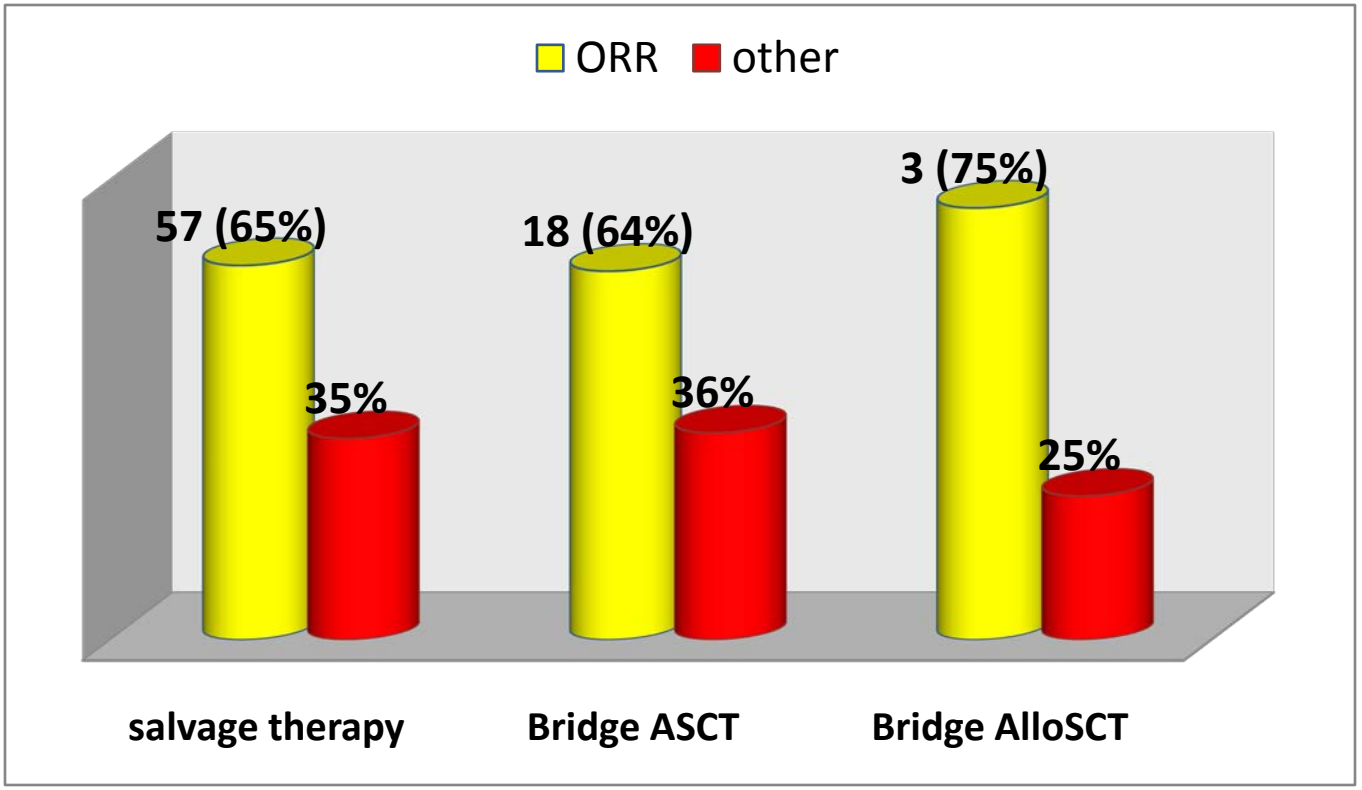
Carfilzomib in relapsed or refractory multiple myeloma patients with early or late relapse following prior therapy: A subgroup analysis of the randomized phase 3 ASPIRE and ENDEAVOR trials

Maria-Victoria Mateos[1] | Hartmut Goldschmidt[2] | Jesus San-Miguel[3] | Joseph Mikhael[4] | Lucy DeCosta[5] | Lifen Zhou[6] | Mihaela Obreja[6] | Julie Blaedel[6] | Zsolt Szabo[7] | Xavier Leleu[8]

Type of therapy

	N (%)
Salvage therapy	88 (73)
Bridge to ASCT	28 (24)
Bridge to AlloSCT	4 (3)

Type of therapy and KRd Response



KRd and Bridge to SCT

	N (%)	SCT post KRd	No SCT
Bridge to ASCT	28 (24)		
≥ ORR	**18 (64)**	**12 (67%)**	**6**
		9 CR	1 PD; 4 MR
		3 VGPR	1 CR
Bridge to AlloSCT	4 (3)		
≥ ORR	**3 (75)**	***I***	**3 CR**

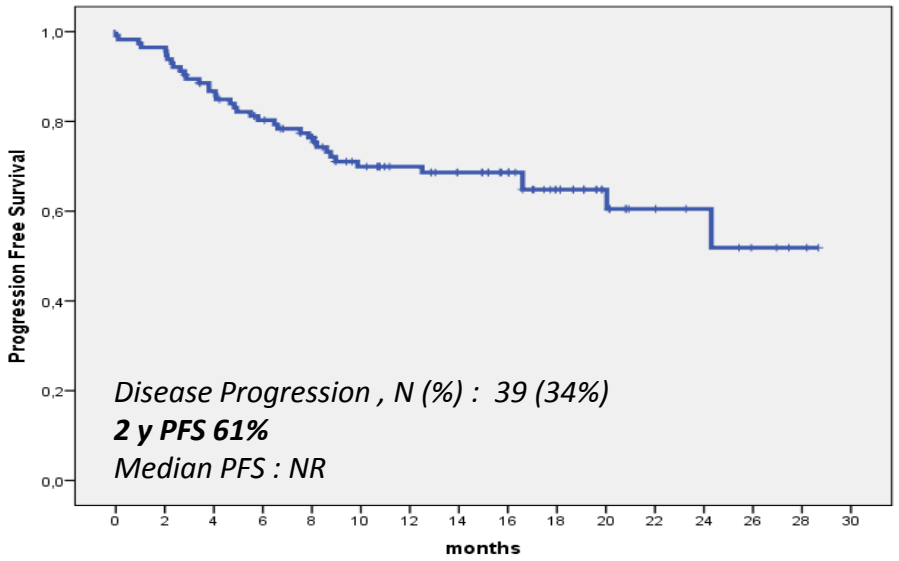
PRIMARY END POINTS

- ORR
- PFS

SECONDARY END POINTS

- OS
- SAFETY

KRd: Progressione Free Survival



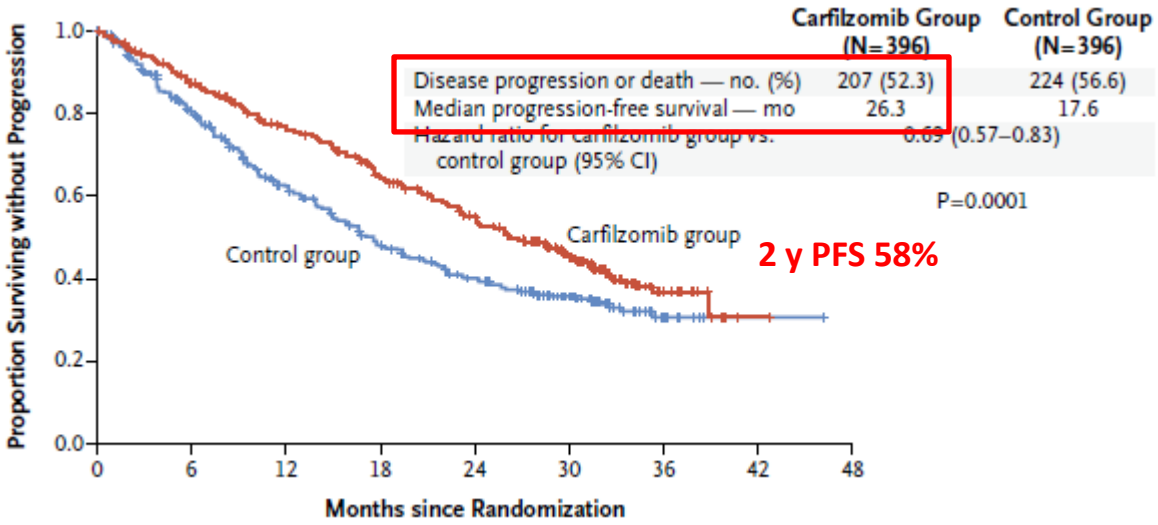
Disease Progression , N (%) : 39 (34%)

2 y PFS 61%

Median PFS : NR

Median Follow-up: 13,4 months (1-52)

ASPIRE: Progressione Free Survival



	Carfilzomib Group (N=396)	Control Group (N=396)
Disease progression or death — no. (%)	207 (52.3)	224 (56.6)
Median progression-free survival — mo	26.3	17.6
Hazard ratio for carfilzomib group vs. control group (95% CI)	0.69 (0.57–0.83)	
	P=0.0001	

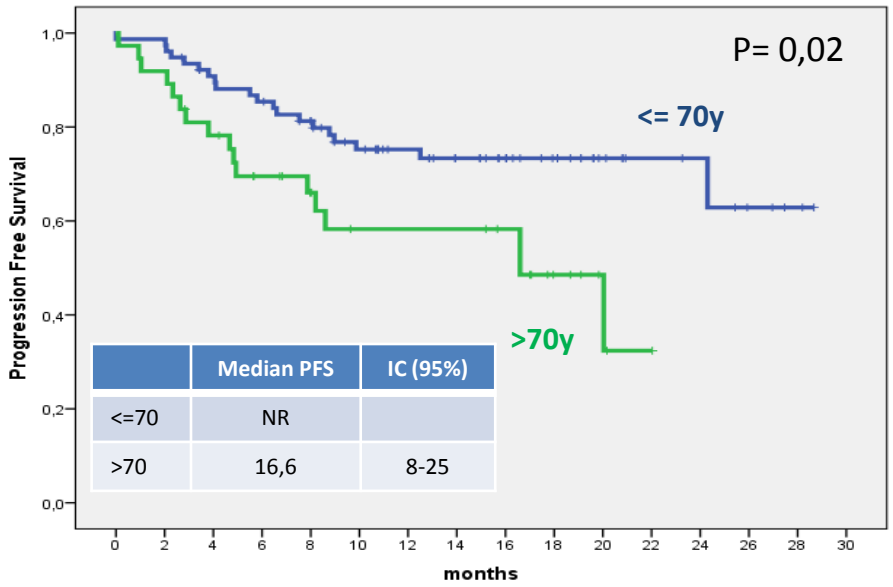
Median Follow-up: over 30 months

Analysis of factors associated with PFS

	PD vs. other (%)	Univariate P-value	Multivariate P-value	HR	IC (95%)
Age ≥70 (years)	46 vs 28	0,05			
≥ III ISS stage	59 vs 36	0,01			
III Durie Salmon stage	77 vs 67	0,25			
Elevated LDH	58 vs 40	0,07			
Entramidollar disease	13 vs 10	0,64			
High Risk Cytogenetic	19 vs 18	0,94			
> 2 previous therapies	33 vs 26	0,43			
PI Lenalidomide PI and Lenalidomide	97 vs 93 49 vs 27 49 vs 25	0,36 0,02 0,008			
Refractory disease	10 vs 90	0,83			
Previous ASCT Previous AlloSCT	31 vs 62 8 vs 4	0,001 0,34	0,002	3,5	0,31 – 0,82
Time to KRd <=18 months	36 vs 20	0,05			
≥ ORR	51 vs 90	0,001			
Post KRd ASCT	0 vs 65	0,001	0,001	5,8	0,10-0,56

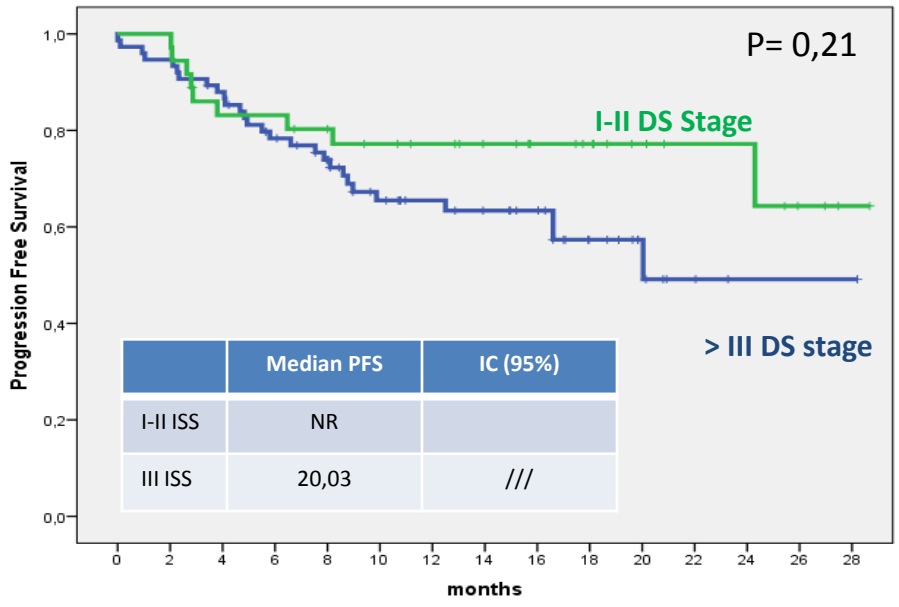
PFS: Subgroup Analysis

Age at enrollment



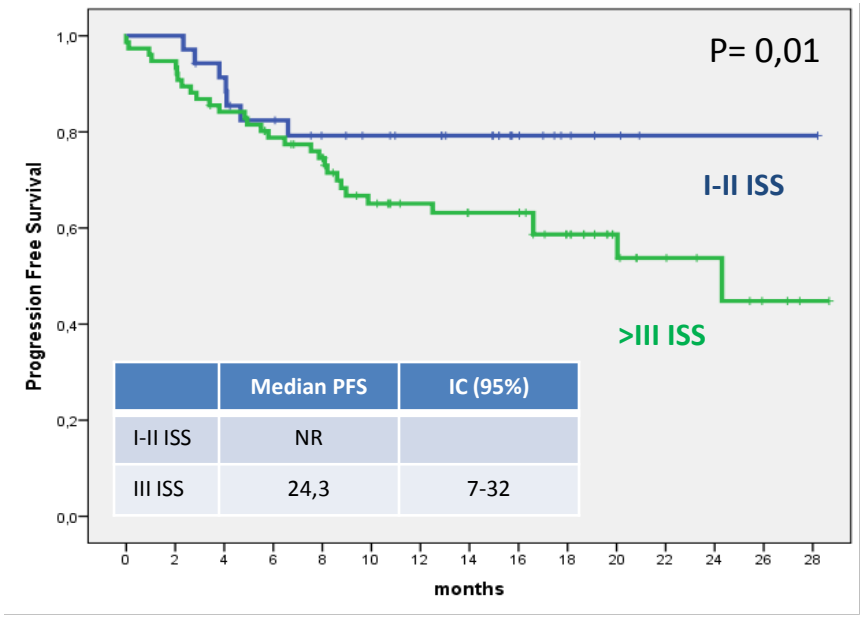
	Median PFS	IC (95%)
<=70	NR	
>70	16,6	8-25

DS Stage at enrollment



	Median PFS	IC (95%)
I-II ISS	NR	
III ISS	20,03	///

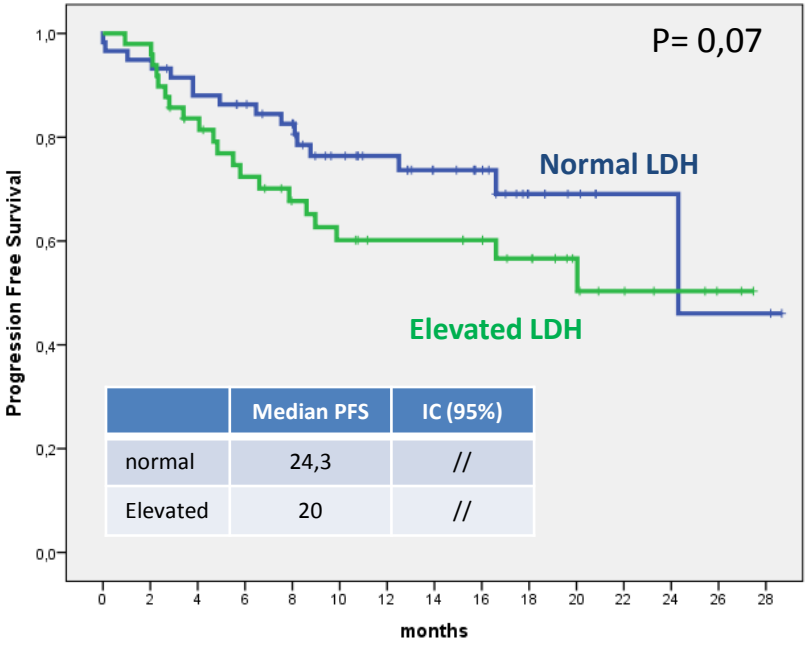
ISS at enrollment



	Median PFS	IC (95%)
I-II ISS	NR	
III ISS	24,3	7-32

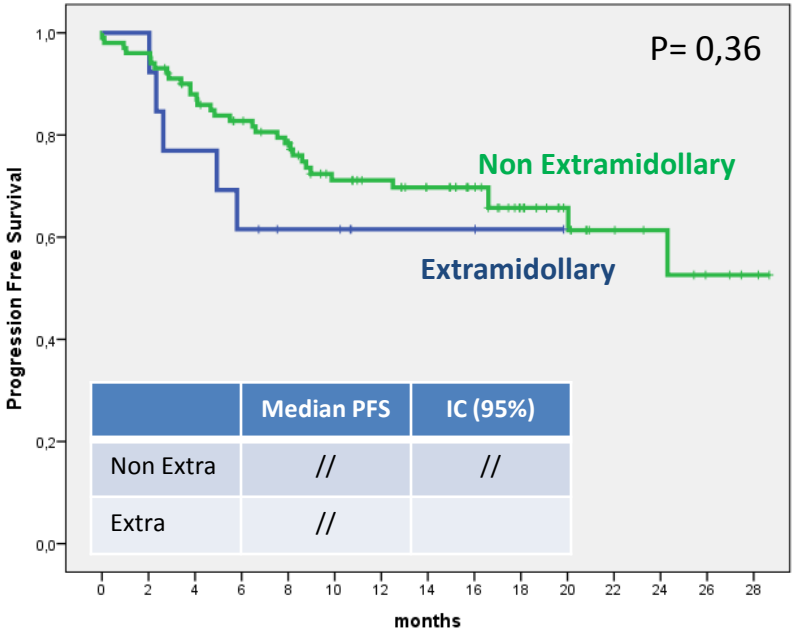
PFS: Subgroup Analysis

LDH at enrollment



	Median PFS	IC (95%)
normal	24,3	//
Elevated	20	//

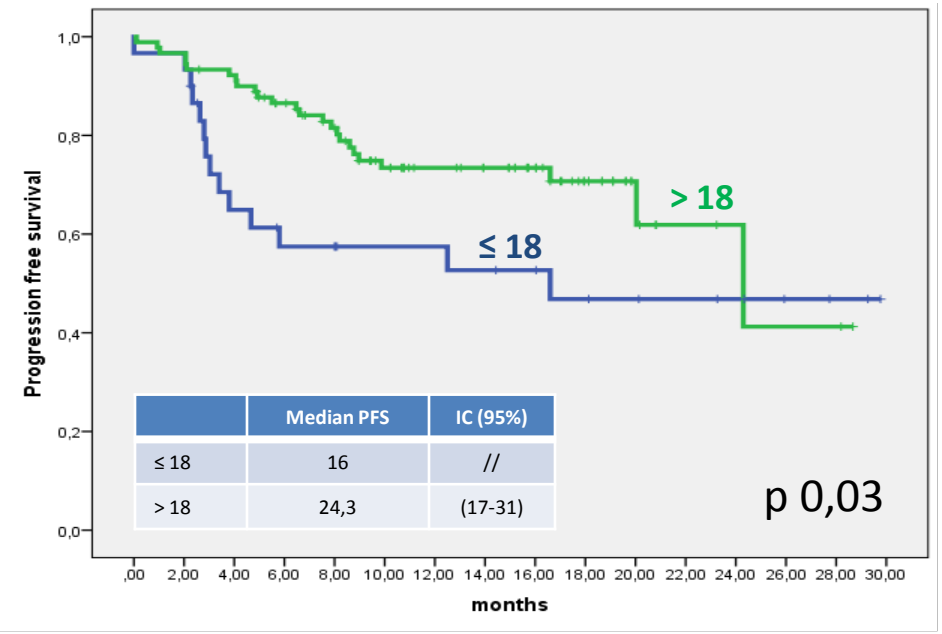
Extramidollary Disease at enrollment



	Median PFS	IC (95%)
Non Extra	//	//
Extra	//	

PFS: Subgroup Analysis

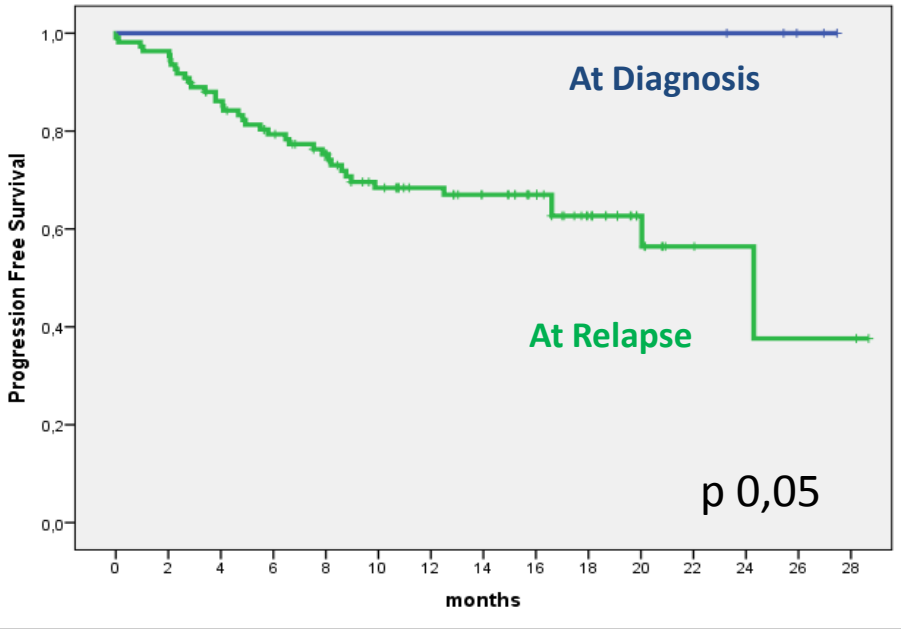
Months to KRD



	Median PFS	IC (95%)
≤ 18	16	//
> 18	24,3	(17-31)

p 0,03

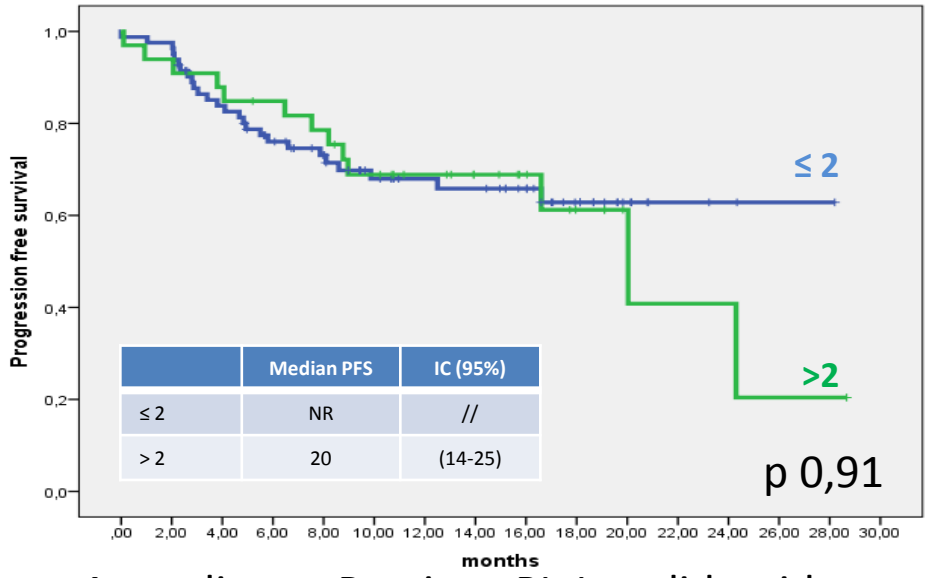
KRd Upfront vs At Relapse Therapy



p 0,05

PFS: Subgroup Analysis

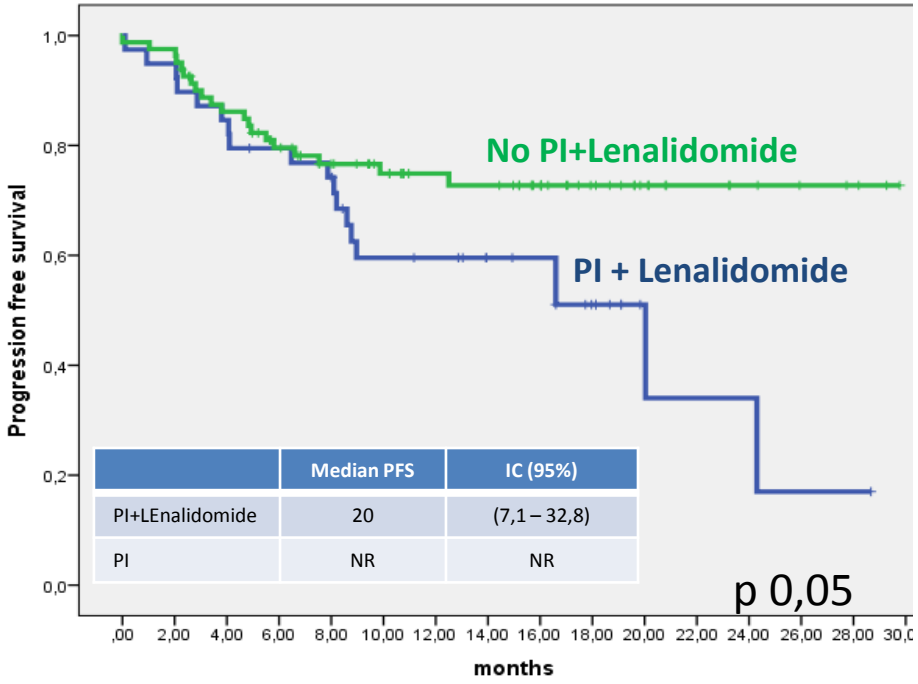
N Previous Therapy



	Median PFS	IC (95%)
≤ 2	NR	//
> 2	20	(14-25)

p 0,91

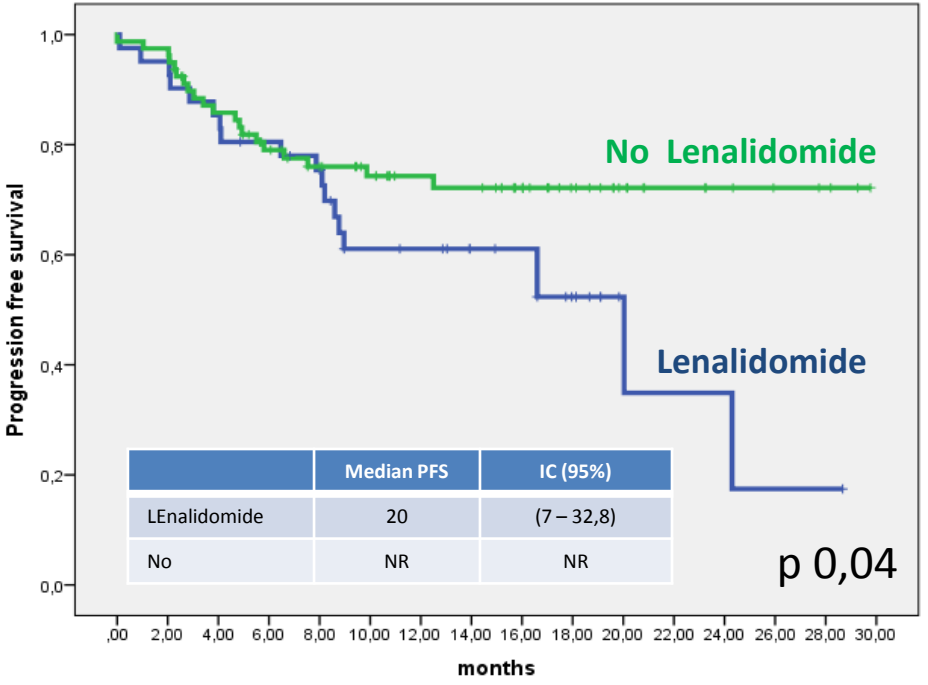
According to Previous PI+Lenalidomide



	Median PFS	IC (95%)
PI+LEnalidomide	20	(7,1 – 32,8)
PI	NR	NR

p 0,05

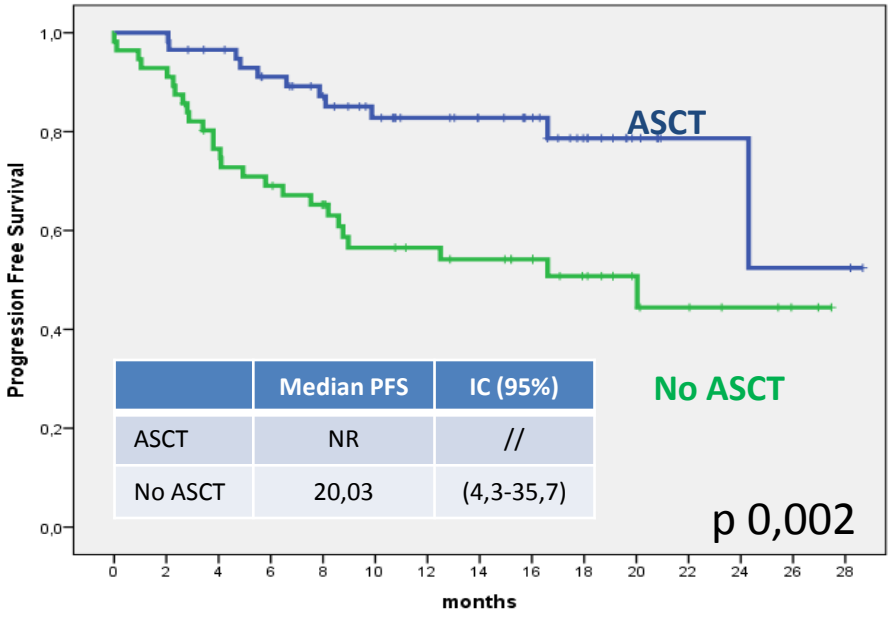
According to Previous Lenalidomide



	Median PFS	IC (95%)
LEnalidomide	20	(7 – 32,8)
No	NR	NR

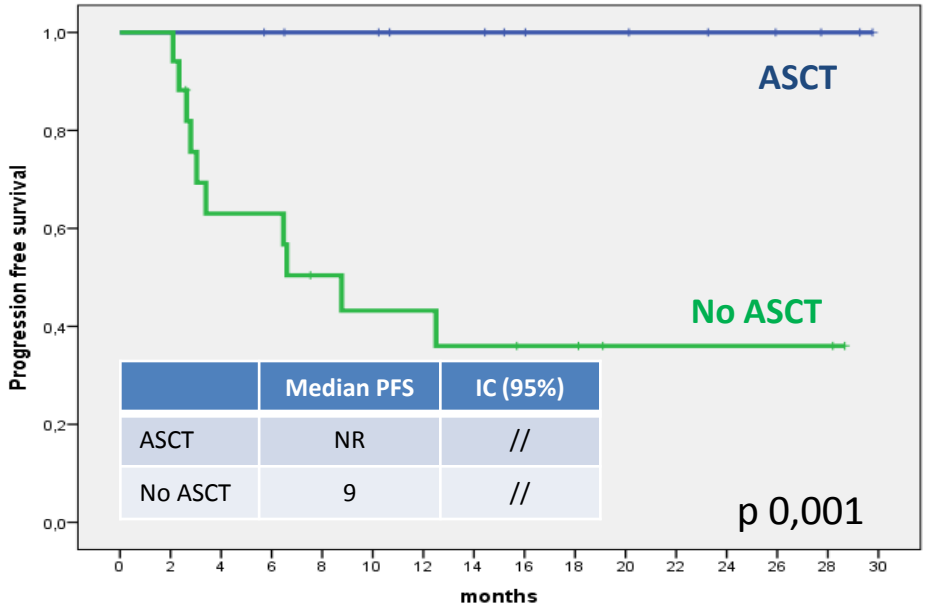
p 0,04

According to Previous ASCT



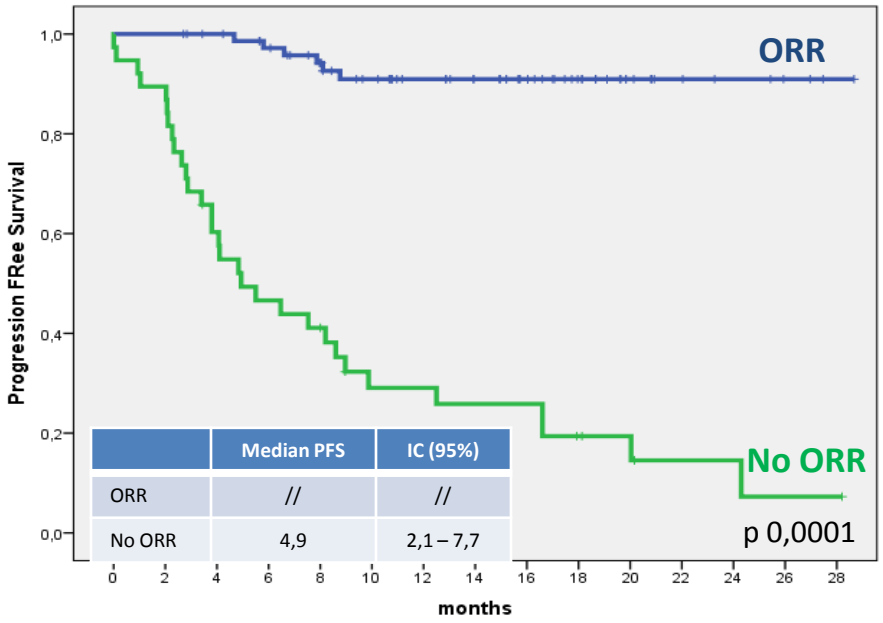
	Median PFS	IC (95%)
ASCT	NR	//
No ASCT	20,03	(4,3-35,7)

According to post KRD ASCT



	Median PFS	IC (95%)
ASCT	NR	//
No ASCT	9	//

According to KRd Response



	Median PFS	IC (95%)
ORR	//	//
No ORR	4,9	2,1 – 7,7

PFS: Subgroup Analysis

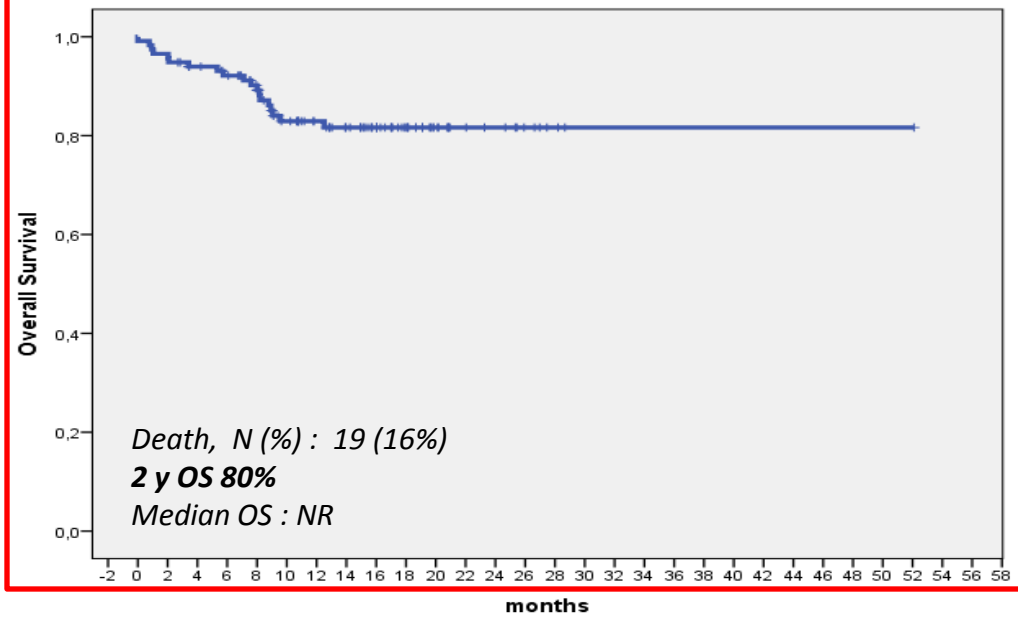
PRIMARY END POINTS

- ORR
- PFS

SECONDARY END POINTS

- OS
- SAFETY

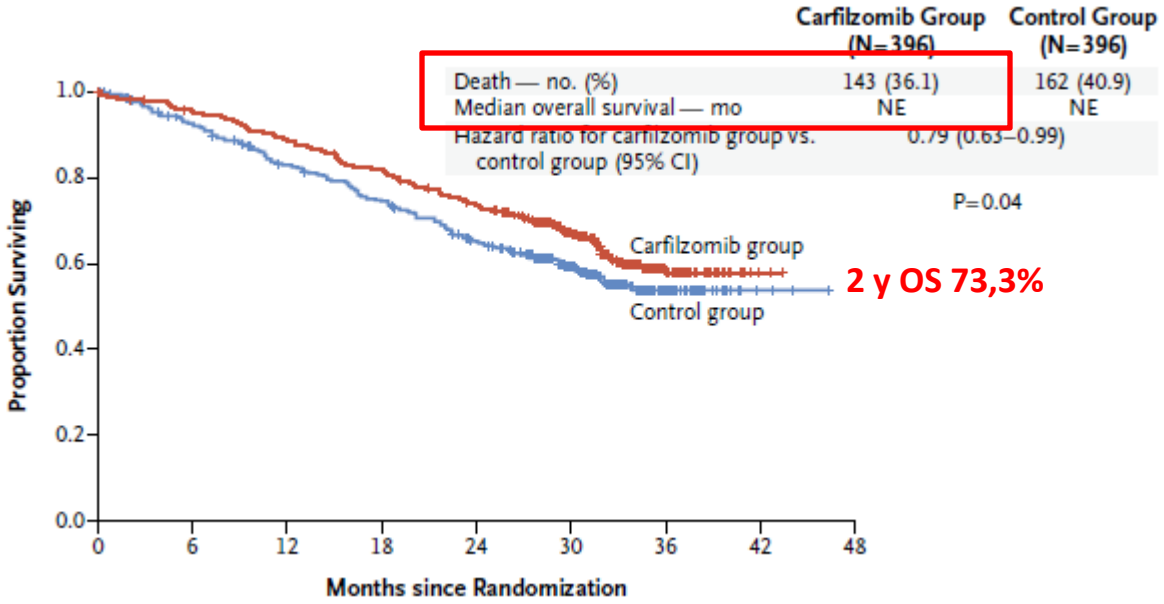
KRd: Overall Survival



Median Follow-up: 13,4 months (1-52)

Cause of Exitus	15 (13%) Progressive disease 1 (1%) Mesotelioma 1 (1%) Sepsis 1 (1%) Ischemic heart disease

ASPIRE: Overall Survival



PRIMARY END POINTS

- ORR
- PFS

SECONDARY END POINTS

- OS
- SAFETY

Hematological toxicity of KRd

Variable	All cases	WHO grade, n (%)			
		1	2	3	4
Anemia	49 (41)	13 (11)	24 (20)	7 (6)	5 (4)
Thrombocitopenia	35 (29)	7 (6)	24 (20)	3 (3)	1(1)
Neutropenia	51 (43)	9 (8)	36 (30)	4 (3)	2(2)

KRd Cycles, median (range): 7 (1-24 courses)

Patients' comorbidity at KRd enrollment

	N 120
Hypertensive Cardiopathy, n (%)	41 (34%)
Normal Cardiac Ecography, n (%) FEV<40% Not evaluated	102 (96%) 4 14
Neuropathy, n (%) III grade	15 (13%) 4

KRd Non hematological toxicity

Event	All Grades	Grade 3 or higher
	N (%)	
Neuropathy	7 (6)	2 (2)
Cardiac Impairment	10 (8)	
Hypertension	2 (1,6)	
Cardiac Failure	1 (1)	1 (1)
Arrhythmia	7 (6)	1 (1)
Deep Venous thrombosis	5 (4)	
Cerebral Ischemia	3 (2,5)	
Cerebral haemorrhage	3 (2,5)	
Acute Renal Impairment	4 (3,5)	
Acute Liver Impairment	2 (1,6)	
Diarrhea	3 (2,5)	1 (1)
Dyspnea	2 (1,6)	
Skin rash	1(1)	

KRd Infection toxicity

Variable	N (%)
Infections	12 (10)
Pneumonia	2 (1,6)
FUO	6 (5)
Microbiologically infections	4 (3,5)
Antimicrobial Prophylaxis	
Oral Ciprofloxacin/Levofloxacin	120
Oral fluconazole	120
Oral aciclovir	104
Oral valaciclovir	16
Oral trimethoprim-sulphamethoxazole	120

KRd Withdrawn or Dose Reduction

	N (%)	Cause of Withdrawn or Dose Reduction	ASPIRE
KRD Withdrawn	66 (55)		69,9%
Toxicity	10 (8)	6 (5) for Carfilzomib; 4 (3) for Lenalidomide	15,3%
Progressive Disease	39 (33)		39,8%
Other	16 (13)		//
Mesothelioma	1 (1)		//
KRD Dose Reduction	3 (2,5)	3 (2,5) for Carfilzomib	11% for Carfilzomib 43,4% for lenalidomide

Analysis of factors associated with ORR and PFS

	ORR		PFS			
	≥ PR vs. other (%)	Univariate P-value	PD vs. no PD (%)	Univariate P-value	Multivariate P-value	HR; IC (95%)
Previous Ipertension Previous neuropaty	36 vs 30 14 vs 7	0,51 0,36	33 vs 35 23 vs 7	0,54 0,01		
Anemia	42 vs 37	0,64	56 vs 33	0,01		
Thrombocytopenia	28 vs 29	0,86	39 vs 24	0,08		
Neutropenia	43 vs 44	0,89	51 vs 40	0,22		
Cardiac Impairment	9 vs 4	0,32	18 vs 4	0,008		
Neuropaty	7 vs 4	0,59	13 vs 3	0,02		
Infections	12 vs 4	0,21	10 vs 10	0,94		
KRD Withdrawn	100 vs 33	0,0001	100 vs 33	0,0001	0,01	2,5 (0,46-0,94)

Conclusions 1

❑ **KRd is safe and effective in this real life experience**

- ❖ORR is 84%
- ❖≥ VGPR is 50%
- ❖Median PFS is NR
- ❖2y PFS is 61%

ASPIRE

- ❖*87%*
- ❖*69,9%*
- ❖*26,3months*
- ❖*58%*

❑ **The ORR was the same across all predefined subgroups**

- ❖Number of previous therapies
- ❖Type of previous therapies
- ❖Refractory disease

❑ **Clinical benefit of PFS in patients with**

- ❖Age ≤ 70 years; without comorbidity
- ❖I-II ISS, I-II DS
- ❖Normal LDH
- ❖No exposure to lenalidomide

Conclusions 2

ASCT is a complementary treatment strategy in the era of novel drug combinations

- Standard of care in first line
- Repeat ASCT for RRMM patients,

  if time to relapse from first ASCT is > 12 months

Conclusions 3

- **The increase of ORR in RR patients**
  - after ASCT *(p<0,08)*
  - later *(p<0,008)*
- **The increase of PFS in patients**
  - with ASCT previous KRd *(p<0,001)*
  - with ASCT post KRD *(p<0,001)*

Suggest that KRd could be an appropriate treatment option

in this setting of patients

Acknowledgments

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- Tricase: Dr S. Citiso; Dr C. De Risi and Colleghi

- SGR : Dr A. La Torre; Dr A. Falcone; Dr N. Cascavilla
- Brindisi : Dr A. Giannotta; Dr G. Mele; Dr D. Pastore
- Lecce : Dr A. Quintavalle; Dr N. Di Renzo
- Taranto: Dr G.Palazzo; Dr S. Sabatelli; Dr P. Mazza
- Barletta : Dr C. Germano; Dr C. Plati; Dr P. Tarantini
- Bari Policlinico: Dr P. Curci; Prof G. Specchia
- Bari Onco : Dr A. Rana; Dr. A. Guarini
- Foggia: Dr S. Capalbo

Rete Ematologica Pugliese

Ixazomib:

l'esperienza real Word della REP

Between August 2016 and October 2017: 5 patients enrolled

SGR 4

TRICASE 1

Patients' characteristics at enrollment

	N= 5
Median age, years (range)	69 (44-75)
Type of Myeloma	
IgG	1
IgA	2
Detected in urine only	2
III Durie Salmon staging	3
II ISS disease staging, n	2
Median Time since diagnosis, months (range)	**120 (36-135)**
Median number of previous lines of therapy (range)	**2 (1-3)**
Previous autologous transplant	5
Previous allogeneic transplant	1
Previous therapy, n (%)	
Proteasome and Immunomodulatory drug	5
plus Pomalidomide	2

IRd: Treatment Responses

	N (%)
Overall response rate	2
Best Response Very good partial response Partial response or better	 1 1 (for 9 months)
Not response	1
Not evaluable	2 (withrawn)

Toxicity of IRd

Variable	All cases	WHO grade, n (%)			
		1	2	3	4
Anemia	3	2	1		
Thrombocitopenia	2		1	1	
Neuropathy	1			1	
Infection	2	1 Fuo ; 1 ocular herpetic infection			

IRd Cycles, median (range): 4 (1-16 courses)

Ixazomib Indications

- In first relapse in high risk patients
- After first relapse in all patients

Thank You