Impact of number of previous treatment lines and pre-treatment with bortezomib or lenalidomide on efficacy of bortezomib-bendamustine-dexamethasone (BBD) in patients with relapsed/refractory multiple myeloma (MM)

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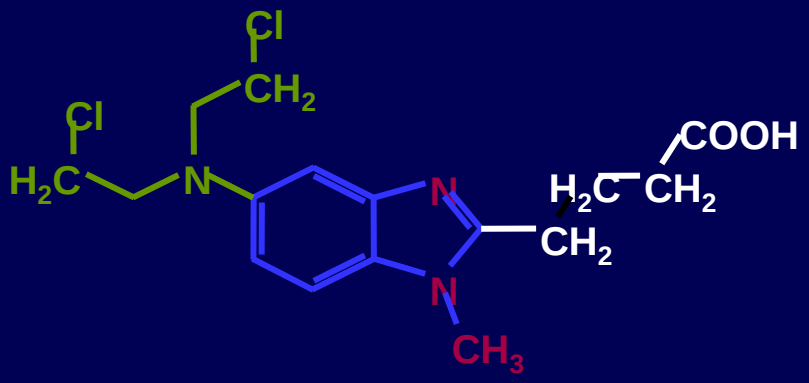
Bendamustine



- Hybrid alkylating agent
- Unique chemical structure containing a
  - purine-like benzimidazol ring as well as
  - a nitrogen mustard group
- Activates proapoptotic genes (NOXA, p21)
- Inhibits cyclin B1 and polo-like kinase (mitotic checkpoints)
- Impacts on DNA repair mechanisms
- No cross resistance with several other alkylators
- Potentially activates p53 (3) and is active in p53 deficient cells

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Bendamustine combinations in MM

Treatment	# of Pts	Response	Publication
Bendamustine-Pred vs. MP	131	Higher CR rate, longer duration of remission	Pönisch et al., J Cancer Res Clin Oncol 2006
Bendamustine single agent phase I	31	ORR: 29%, PFS: 6.5 months	Knop et al., Heamatologca 2005
Bendamustine + Bortezomib	40	ORR: 80%, PFS: 8 months	Hrusovsky I et al., 2007 Blood 110: Abst 4851
Bendamustine+Bortezomib+ Prednisolone	46	ORR: 86%, PFS: 11 months	Pönisch W et al., Blood 2007;110: Abs 2723
Bendamustine+Lenalidomide+Dexamethasone	29	ORR: 86%, PFS: 6.1 months	Lentzsch S et al., Blood 2012
Bendamustine+Thalidomide+ Dexamethasone	23	ORR: 43%, PFS: 3 months	Grey-Davies et al., Br. J Heamatol 2011
Bendamustine+Bortezomib+ Dexamethasone	73	ORR: 67.1%	Rodon Ph et al. ASCO 2012 (abstr 8014)

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Treatment regimen & study objectives

Treatment Regimen

Bendamustine 70 mg/m2, day 1+4

Bortezomib 1.3 mg/m2, days 1, 4, 8, 11

Dexamethasone 20mg, days 1, 4, 8, 11

Cycle was repeated q 4 weeks

Maximum of 8 cycles; in case of no response

or SD after 4 cycles, therapy was discontinued

Primary Objective

Overall response rate

Secondary Objectives

PFS

OS

Time to response

Toxicity

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Patients characteristics

Number of patients	74
Age, median (range)	65 (40-86)
Gender, male/female	34/40
ISS Stage	
I	24 (32.4%)
II	30 (40.5%)
III	20 (27%)
ECOG Status 0-1/≥ 2	71/3
ß2 microglobulin	4.14 mg/l (1.32 – 36.7 mg/l)
IgG	33 (44.6%)
IgA	15 (20.3%)
Light chain myeloma	18 (24.3%)
Oligosecretory myeloma	8 (10.8%)
Prior treatment lines 1-2/3-4/≥5	48/21/5
Prior exposure to Bortezomib	46 (62.2)
Prior exposure to Lenalidomide	38 (51.4%)

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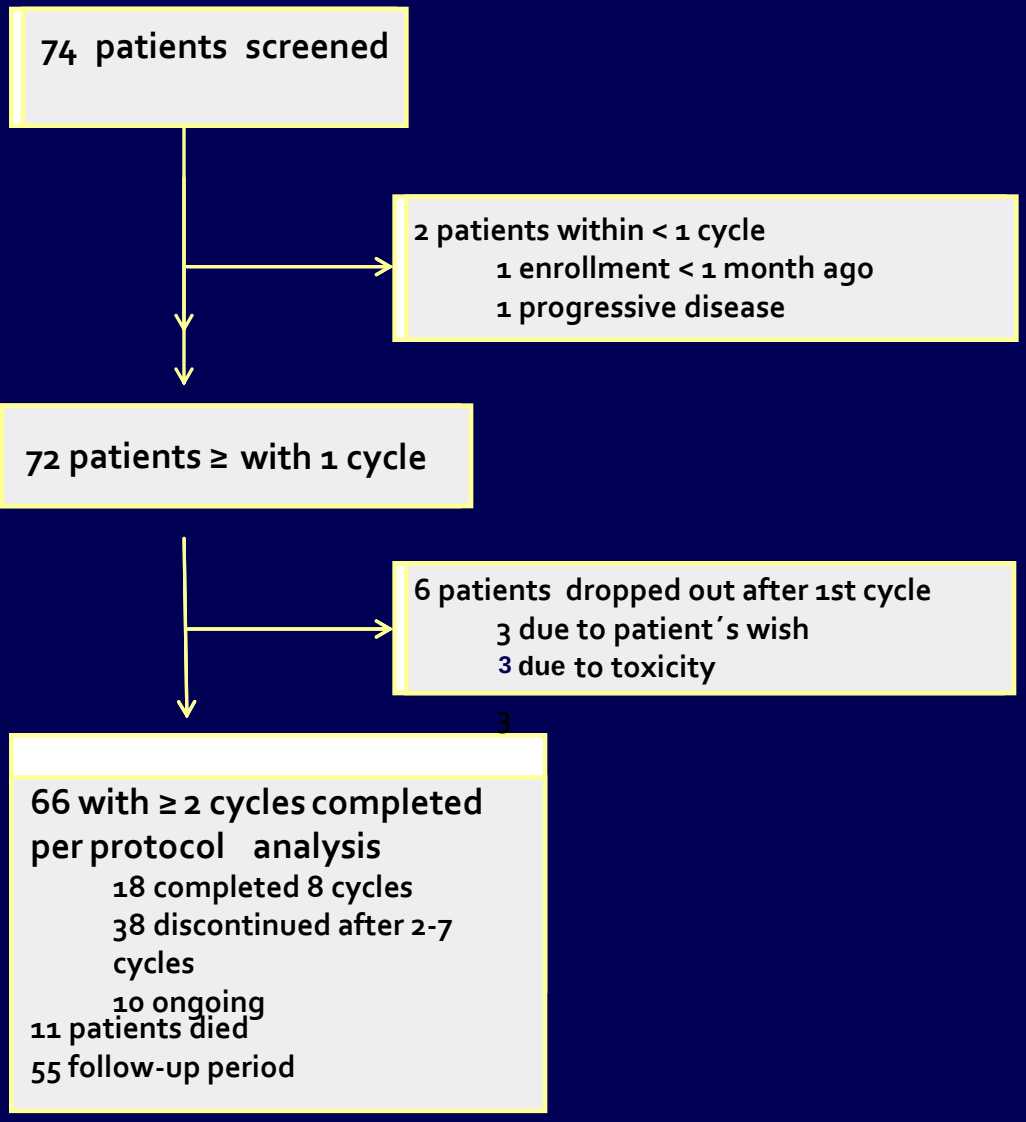
Consort



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Response rates in evaluable patients (≥2 cycles)

sCR/CR/nCR	14 (21.2%)
VGPR	11 (16.7%)
PR	18 (27.3%)
MR	10 (15.2%)
SD	13 (19.7%)
N.A. (<2 cycles completed)	8 (10.8%)
ORR (CR-PR) (CR-MR)	43/66 (65.2%) 53/66 (80.3%)
Previously exposed to bortezomib (42 pts. with ≥2 cycles completed)	CR-PR: 24 (57%) CR-MR: 32 (76%)
Previously exposed to lenalidomide (36 pts. with ≥2 cycles completed)	CR-PR: 19 (53%) CR-MR: 26 (72%)

Median number of cycles in ITT/PP: 5/6

Median time to response (PR): 37 days, (range 22-245 days)

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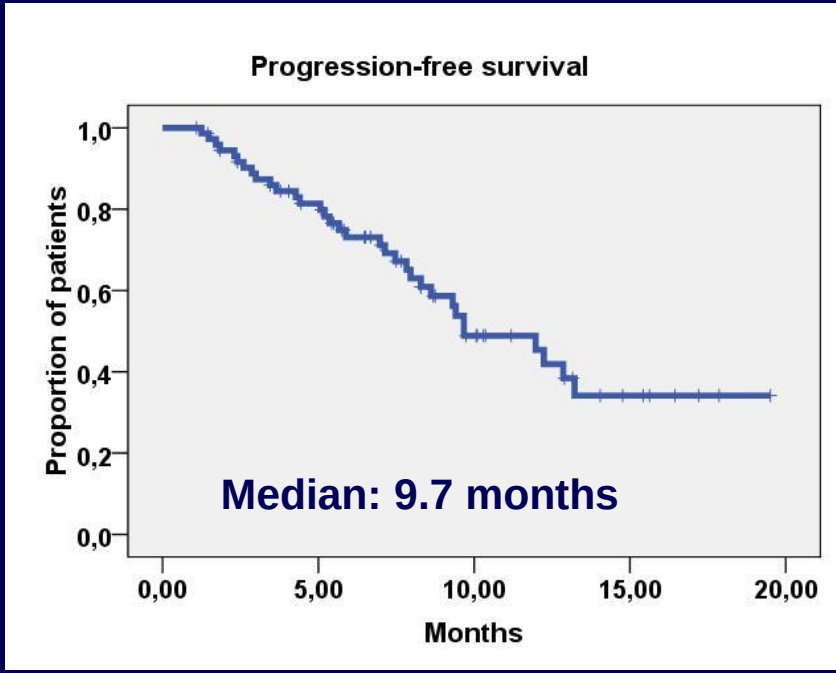
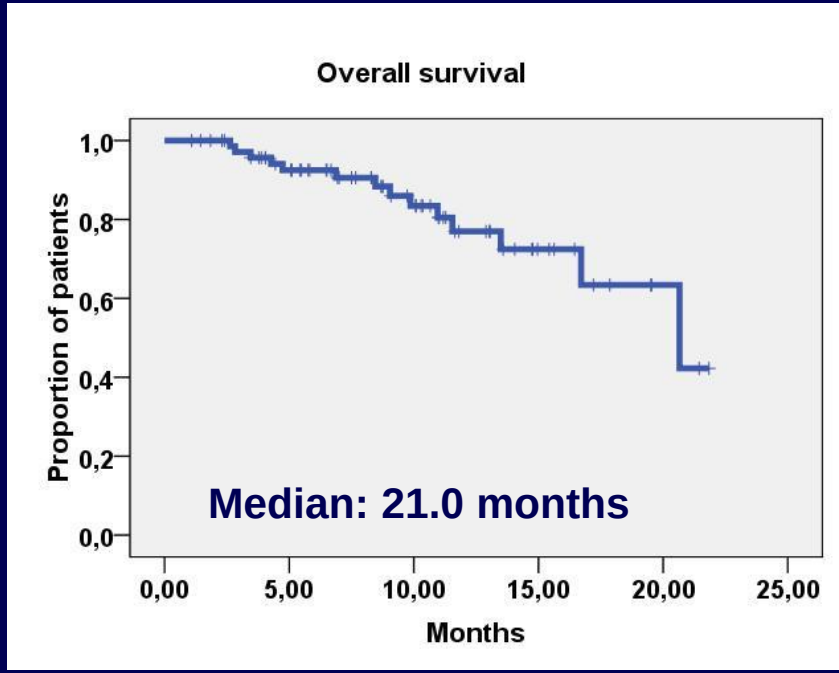
Progression-free survival & overall survival

Progression-free survival



Overall survival



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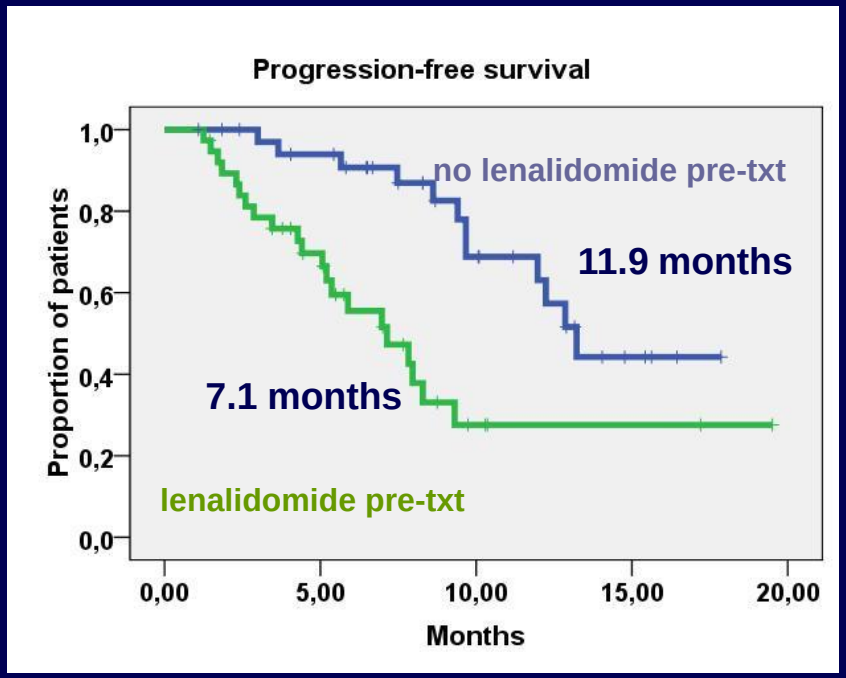
Progression-free survival in relation to pre-treatment

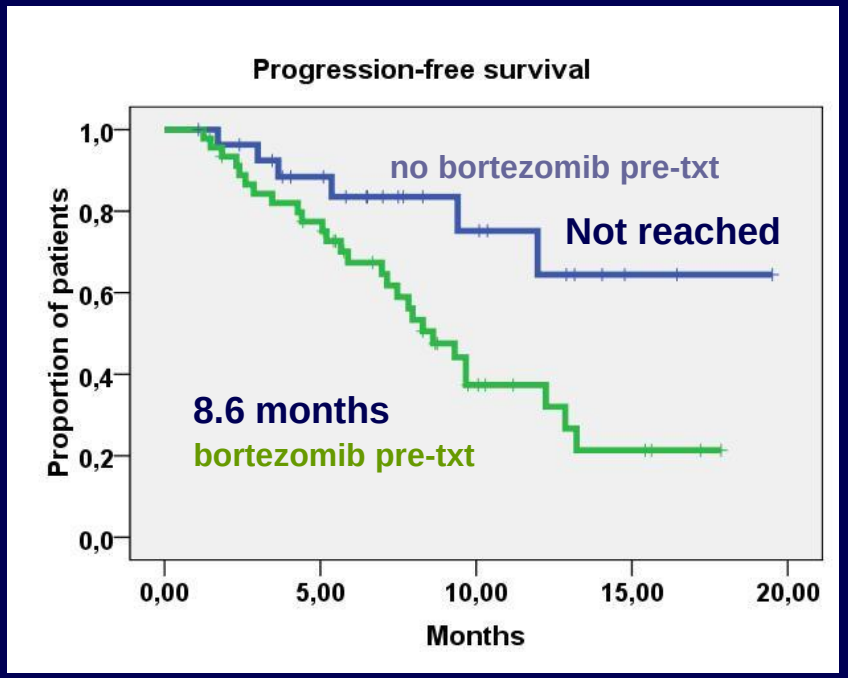
Pre-treatment (≥ 2 cycles) with:

Lenalidomide 36 patients



p=0.000674

Bortezomib 42 patients



p<0.02

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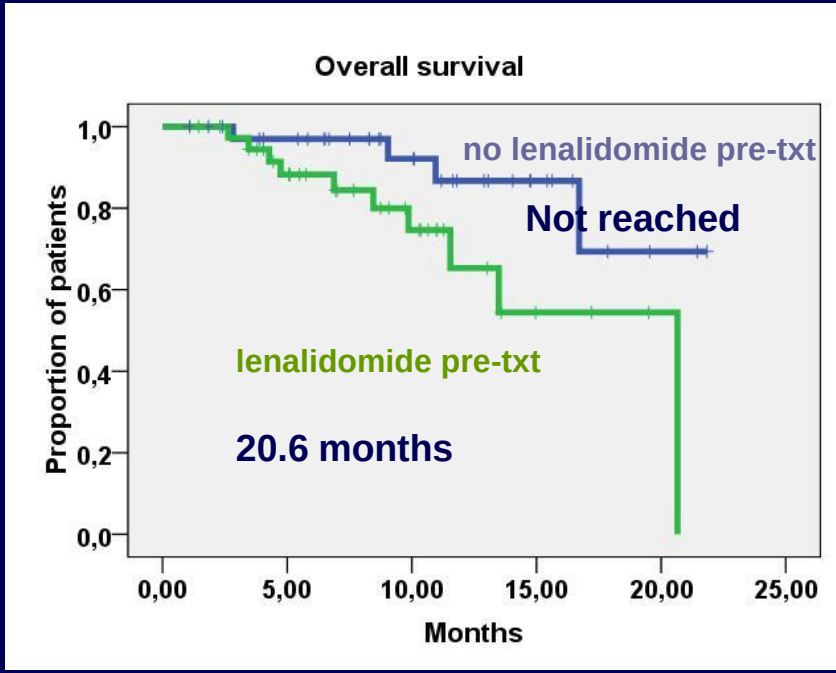
Overall survival in relation to pre-treatment

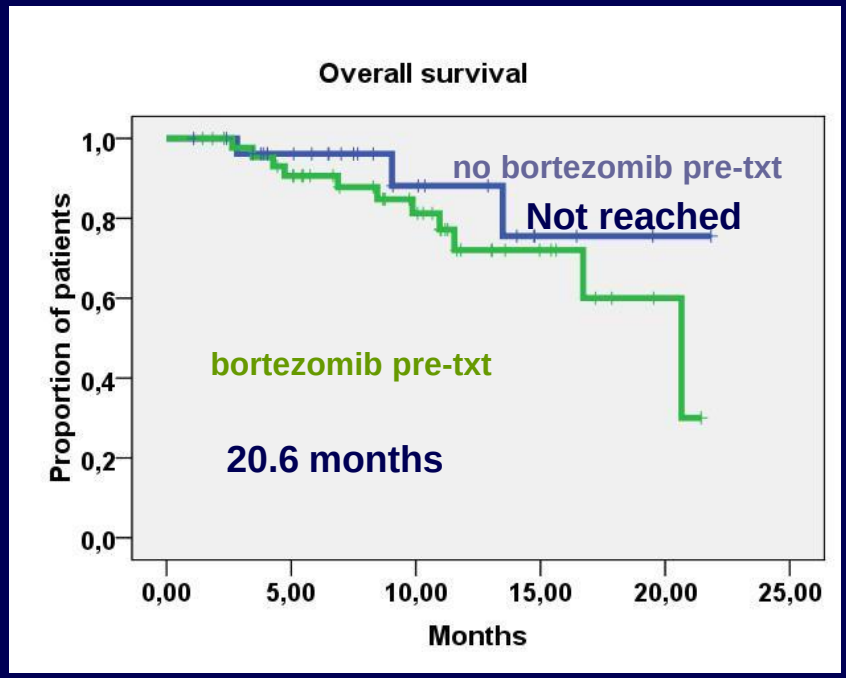
Pre-treatment (≥ 2 cycles) with:

Lenalidomide 36 patients



p<0.04

Bortezomib 42 patients



p=0.341

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Response rates in relation to number of previous treatment lines

Response	1-2 previous treatment lines (41 patients)	3-6 previous treatment lines (24 patients)
CR/nCR	10 (24%)	1 (4%)
VGPR	7 (17%)	3 (13%)
PR	8 (20%)	9 (38%)
CR-PR	25 (61%)	13 (54%)
MR	6 (15%)	5 (21%)
SD	10 (24%)	6 (25%)

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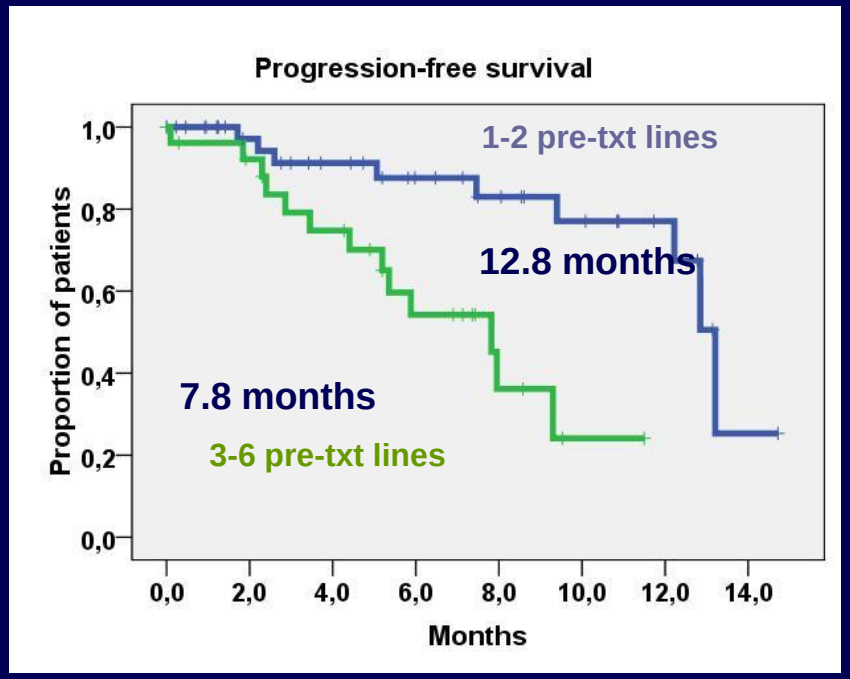
Number of previous treatment lines and outcome

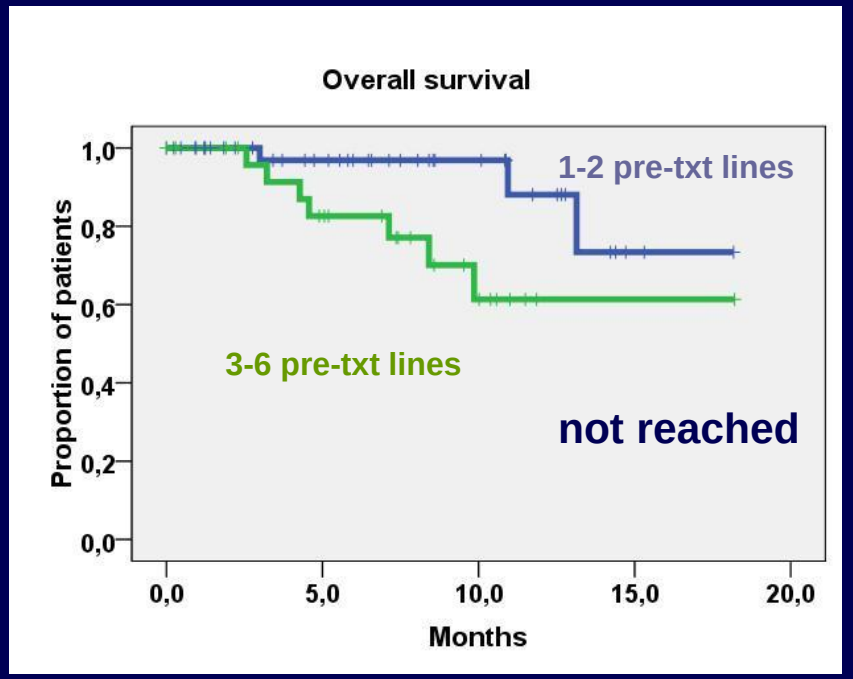
Progression-free survival

Overall survival

1-2 previous treatment lines vs 3-6 previous treatment lines



p=0.001



p=0.024

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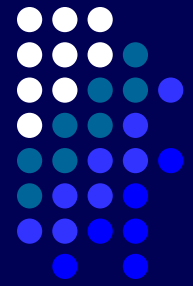
Univariate and multivariate analysis of type of pre-treatmemt and outcome measures



Pre-treatment	Response rate	PFS	OS
Univariate analysis (p value)			
Lenalidomide	0.083	**0.0012**	0.0506
Bortezomib	0.078	**0.0175**	0.3487
Len + Boz	**0.01**	**0.022**	**0.02**
Multivariate analysis (p value)			
Len + Boz	**0.0149**	**0.0979**	**0.0979**

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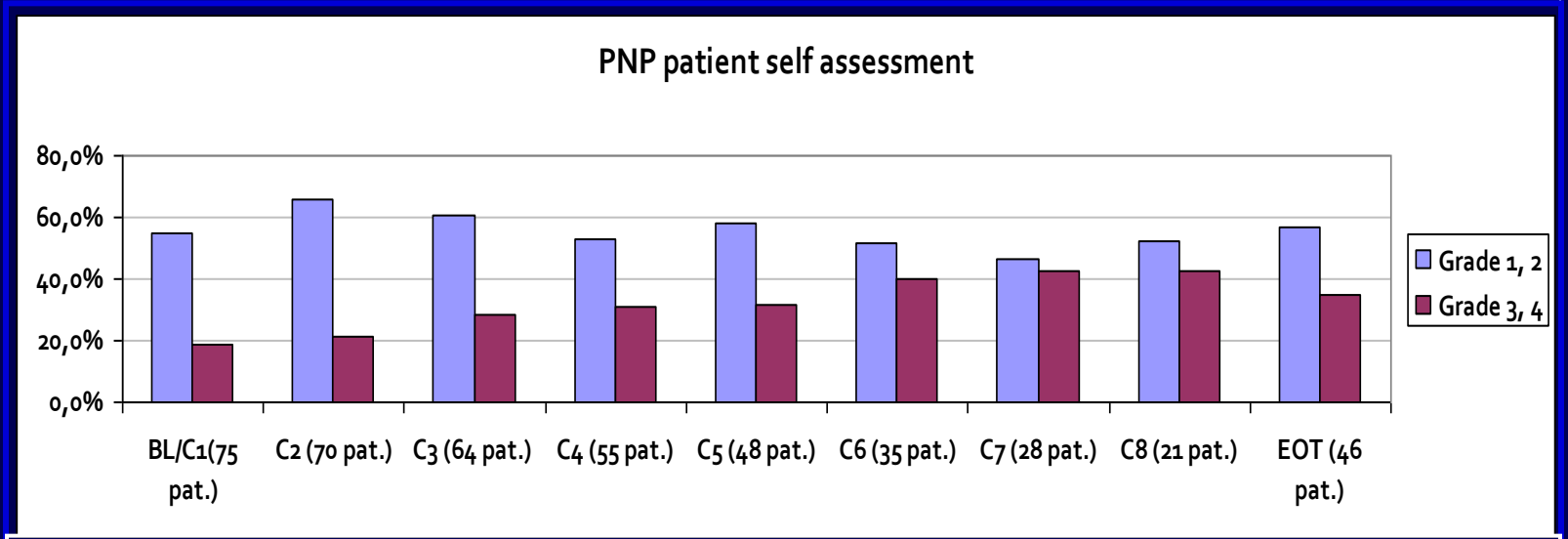
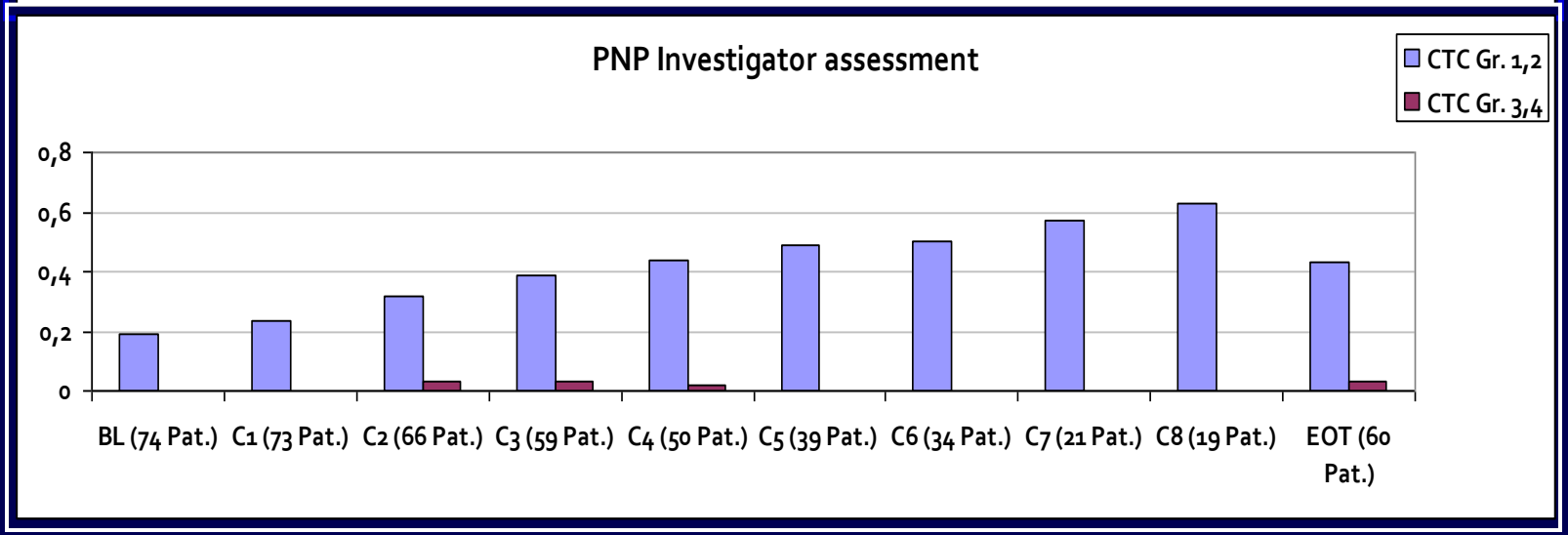
Neurotoxicity





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Hematological & Non-Hematological Toxicity (74 patients)

Hematological		Grade 3	Grade 4/5
Anemia		11(15%)	2 (3%)
Leucopenia		13 (18%)	1(1%)
Thrombocytopenia		24 (33%)	5 (7%)
Non-Hematological	Grade 1/2	Grade 3	Grade 4/5
Infection/sepsis	35 (47%)	7 (9%)	1/2 (1%/3%)
Herpes zoster	3 (4%)	3 (4%)	-
Diarrhea	16 (22%)	5 (7%)	-
Constipation	20 (27%)	3 (4%)	-
Nausea, emesis	20 (27%)	1(1%)	-
Polyneuropathy	32 (43%)	2 (3%)	1/0 (1%/0%)

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Conclusion

The BBD regimen shows significant activity in pre-treated MM patients ORR: 65.2%, PFS was 9.7 and OS 21 months
Pre-treatment with Bortezomib and/or Lenalidomide was associated with lower ORR, shorter PFS. OS was similar in Bortezomib, but shorter in Lenalidomide pre-treated patients
≥ 3 prior TX lines associated with shorter PFS and OS
Multivariate analysis revealed lower ORR in Lenalidomide+Bortezomib pretreated patients only
No impact of high risk cytogenetics on ORR, PFS and OS

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Conclusion

Grade 3/4 hematotoxicity was rare, 2 patients died due to febrile neutropenia
PNP was noted in 46% of patients
The proportion of patients with higher grades of PNP increased during treatment (patient assessment)
Physicians underestimated PNP compared to self assessment by patients
BDD is an attractive option in pre-treated MM patients

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Thank you for your attention