

GIMEMA: Italian Multiple Myeloma Network

POMALIDOMIDE CYCLOPHOSPHAMIDE AND PREDNISONE (PCP) TREATMENT FOR RELAPSED/REFRACTORY MULTIPLE MYELOMA

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Disclosures for Palumbo Antonio, MD

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Presentation includes discussion of the off-label use of a drug or drugs

Rationale

Therapy	N	Time from diagnosis (months)	≥ PR	Median PFS (months)
Pom-Dex ¹	221	NA*	34%	4.6
Pom-Dex ²	34	62	32%	4.8
Pom-Dex ³	41 [#]	70.5	34%	6.3
	43 [°]		35%	
Cla-Pom-Dex ⁴	66	NA*	56%	7.5

*not available. *Pomalidomide 4mg 28/28 days; °Pomalidomide 4mg 21/28 days.

PR, partial remission. PFS, progression-free survival,

1. Richardson PG et al. Blood (ASH Annual Meeting Abstracts) 2011, 118: Abs 634.

2. Lacy MQ et al. Leukemia 2010, 1-6.

3. Leleu XL et al. Hematologica (EHA Annual Meeting) 2012; Abs 0280.

4. Rossi AC et al J Clin Oncol (ASCO Annual Meeting) 2012; Abs 8036.

Eligibility Criteria

Inclusion Criteria

- Patients relapsed* or relapsed and refractory° to lenalidomide
- Patients who received 1-3 lines of therapy
- Measurable disease
- Karnofsky performance status $\geq 60\%$

Exclusion Criteria

- Platelet count $< 50 \times 10^9/L$
- Neutrophil count $< 1.00 \times 10^9/L$
- Serum creatinine $> 2 \text{ mg/dl}$

* Relapsed: previously treated myeloma that progresses and requires the initiation of salvage therapy

° Relapsed and refractory: relapsed while on salvage or progression within 60 days of most recent therapy.

Treatment schedule

Six- 28 day-cycles

1 28 days

Pomalidomide 1-2.5 mg daily continuously*

Cyclophosphamide 50 mg every other day

Prednisone 50 mg every other day

Maintenance (until progression)

Pomalidomide 2.5 mg daily

Prednisone 25 mg every other day

		Pomalidomide mg	Patients
Phase I	Cohort 1	1.5	4
	Cohort 2	1	4
	Cohort 3	2	4
	Cohort 4	2.5	4
	Cohort 5	2.5	4
	Cohort 6	2.5	4

*Thromboprophylaxis with aspirin (100 mg/d) or low molecular weight heparin in high risk patients was given

Phase I: definition of the MTD

Cohort N	Dose mg	Patients N	DLTs*	Type	Updated estimated probability of DLT per dose level			
					1 mg	1.5 mg	2 mg	2.5 mg
1	1.5	4	1	Grade 4 thrombocytopenia	0.237	0.298	0.409	0.553
2	1	4	0	-	0.104	0.145	0.232	0.376
3	2	4	0	-	0.051	0.076	0.136	0.255
4	2.5	4	1	Grade 3 neuropathy	0.052	0.078	0.139	0.259
5	2.5	4	1	Grade 3 hepatic tox	0.052	0.078	0.139	0.259
6	2.5	4	1	Grade 4 thrombocytopenia	0.052	0.077	0.138	0.258

MTD 2.5 mg/d (95% credibility interval 0.101-0.468)

*DLT: dose limiting toxicity. In red the dose level closest to the toxicity target (0.25)

Methods

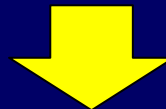
Stage I

- DLT probability (25%) was updated using Bayes theorem*
- 12 patients enrolled in the phase I were treated at the MTD



Stage II

- Additional 43 patients were enrolled in the phase II



55 patients are evaluable after completing at least 1 cycle

Patient characteristics

	All patients N=69	Evaluable patients (2.5 mg) N=55 [°]
Median age (range)	69 (41-84)	69 (41-84)
ISS Stage		
I	49%	51%
II	39%	38%
III	12%	11%
FISH analysis		
High risk*	26%	24%
Standard risk	35%	56%
Not available	23%	20%
Time from diagnosis to enrollment (range)	53 months (11-203)	53 months (11-203)
Prior therapies, median (range)	3 (1-3)	3 (1-3)
Lenalidomide	100%	100%
Bortezomib	84%	84%
Transplant	48%	49%
Refractory/relapsed to lenalidomide	67% / 33%	67% / 33%
Refractory to lenalidomide and bortezomib	32%	29%

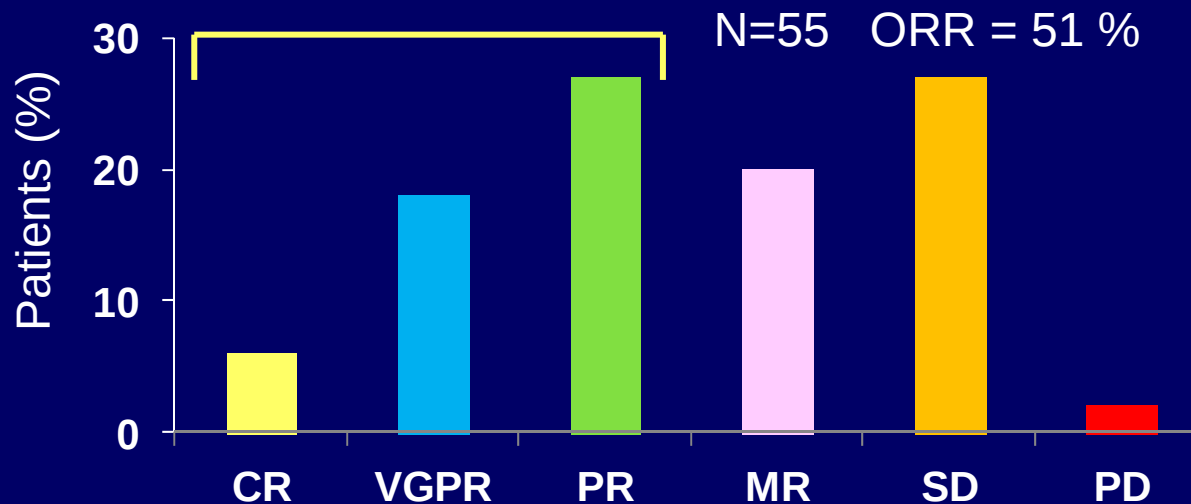
[°] N = 55 including 12 patients of the phase I treated at 2.5 mg and 43 patients of the phase II

* Presence of at least one of the following at baseline t(4;14) or t(14;16) or del 17p13

Phase II: Best Response

Median number of cycles: 6 (1-6)

	Evaluable 2.5 mg N=55	Refractory to lenalidomide N=37	Relapsed after lenalidomide N=18	Refractory to lenalidomide- bortezomib N=16
CR	6 %	5 %	5 %	12%
≥ VGPR	24 %	16 %	39 %	19%
≥ PR	51 %	46 %	61 %	50%
≥ MR	71 %	70 %	72 %	81%

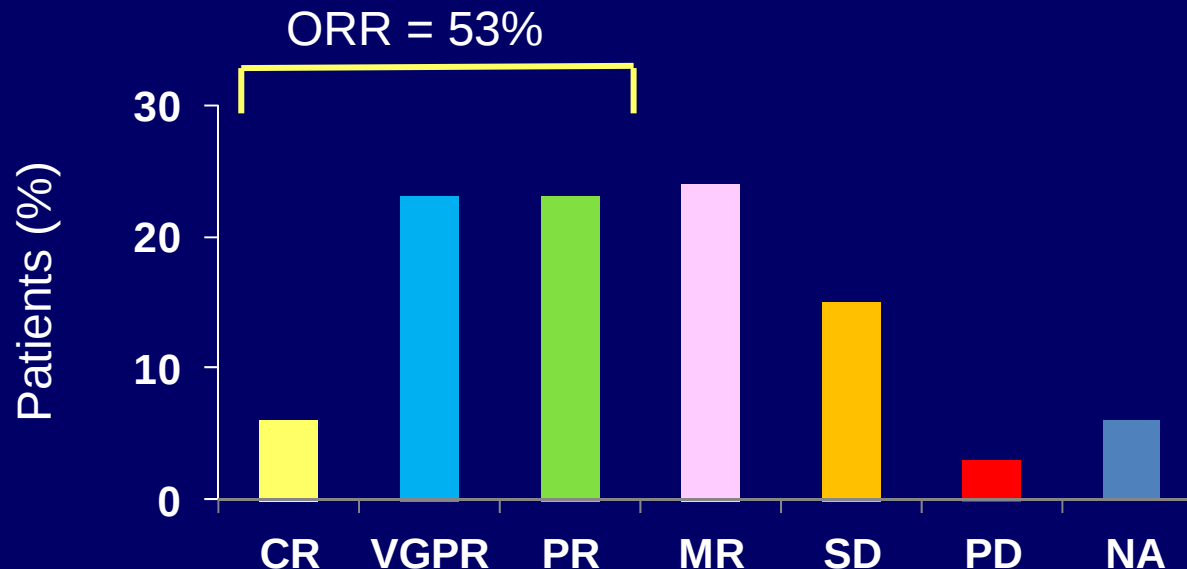


CR complete response, VGPR very good partial response, PR partial response, MR minimal response, SD stable disease, PD progressive disease, ORR overall response rate.

Maintenance: Best Response

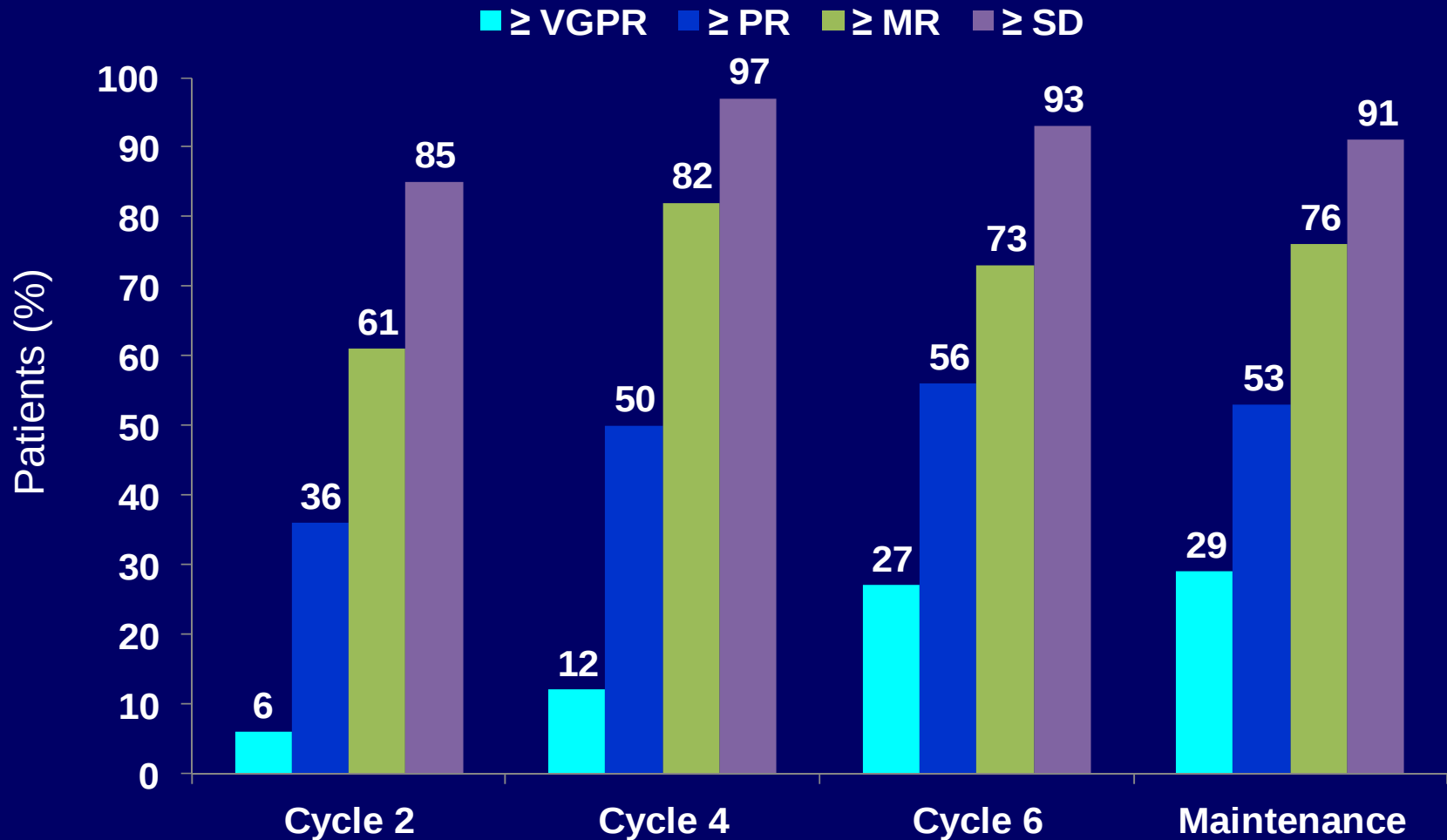
Median duration of maintenance: 3 months (1-15)

All patients, N=34		%
CR	2	6 %
≥ VGPR	10	29 %
≥ PR	18	53 %
≥ MR	26	76 %



CR complete response, VGPR very good partial response, PR partial response, MR minimal response, SD stable disease, PD progressive disease, ORR overall response rate.

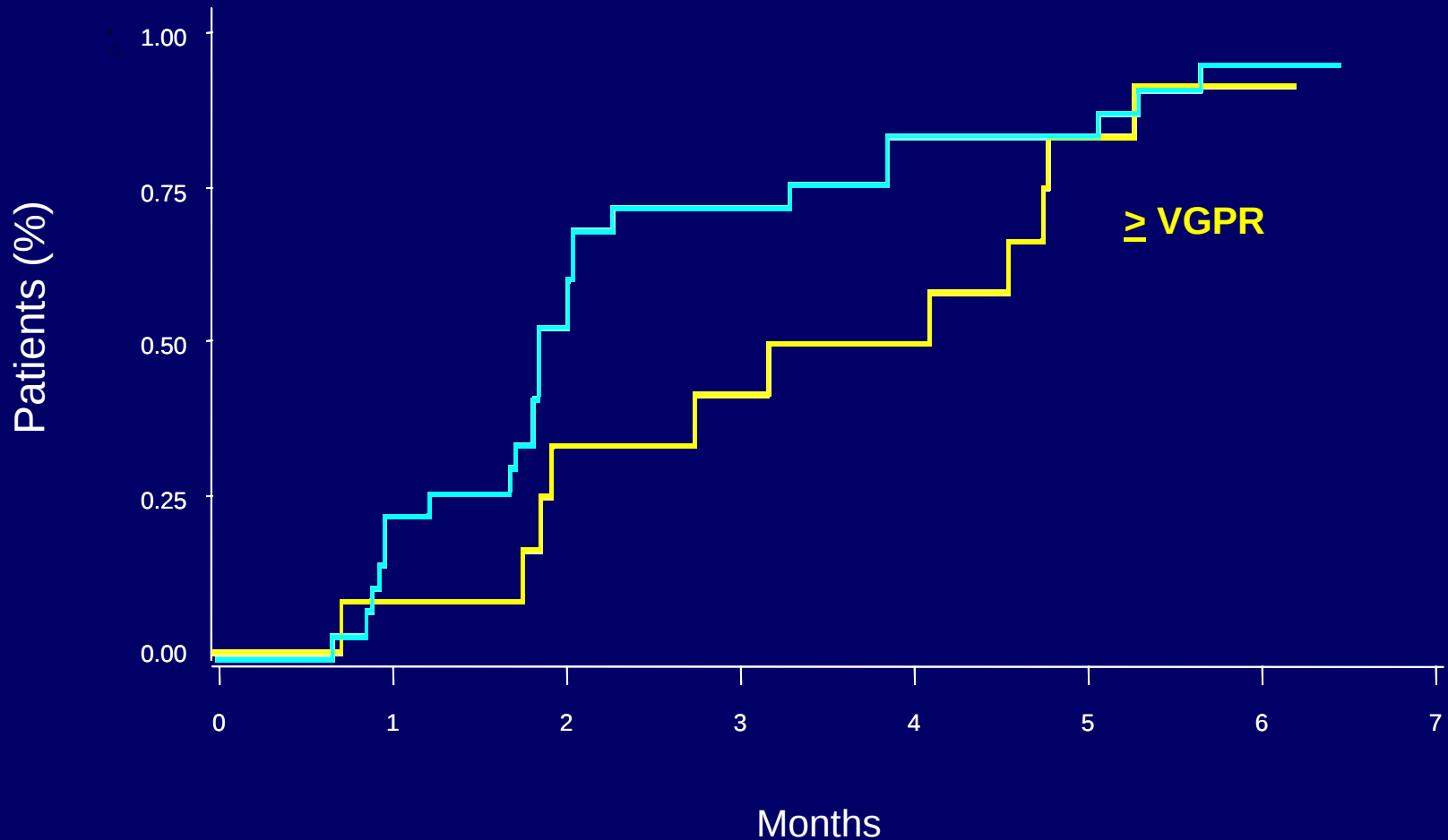
Response rate by treatment duration



VGPR very good partial response, PR partial response, MR minimal response, SD stable disease

Time to at least VGPR and at least PR

N=55



VGPR: very good partial response; PR, partial response

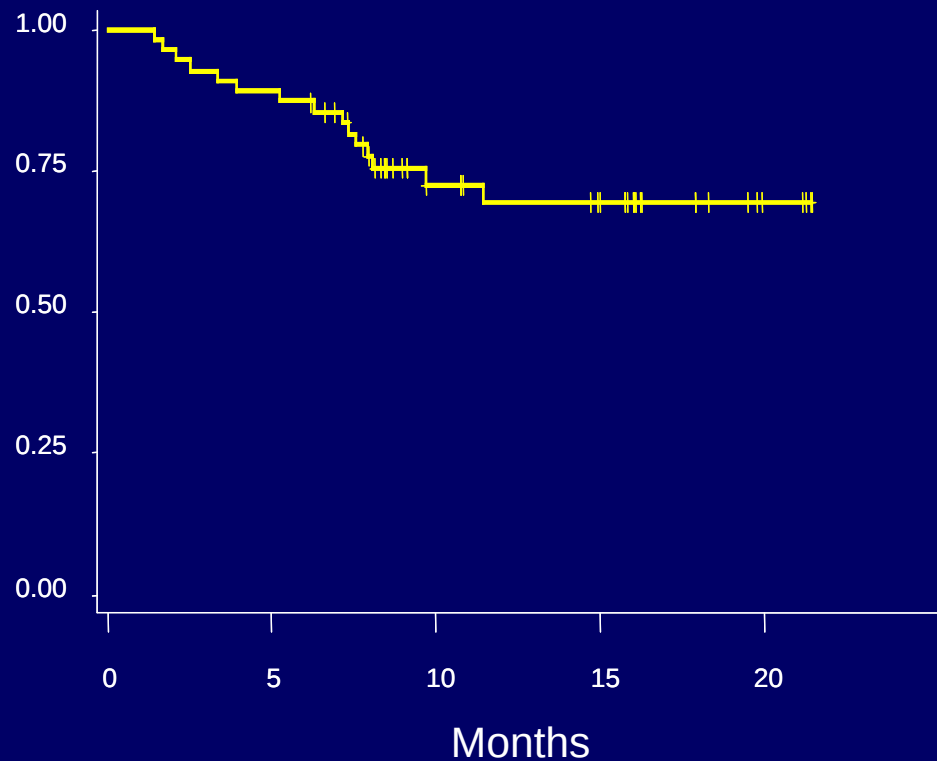
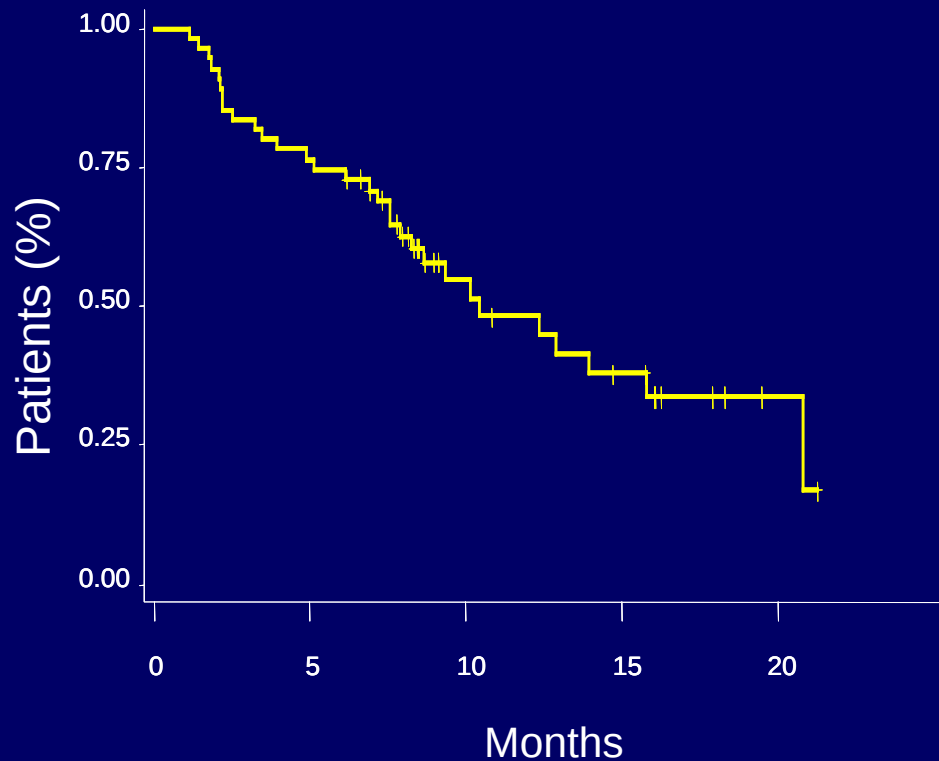
Outcome

N=55

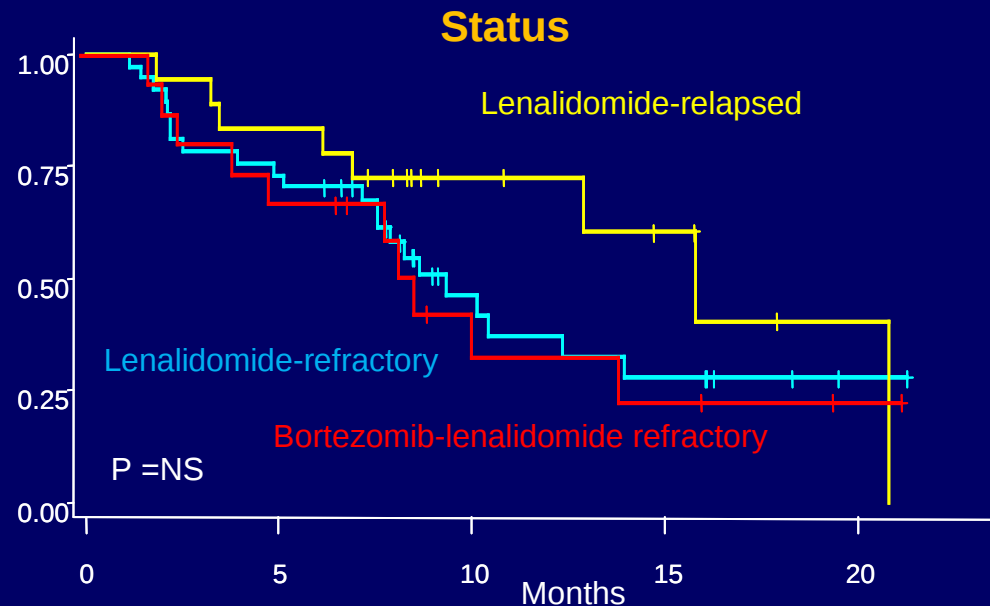
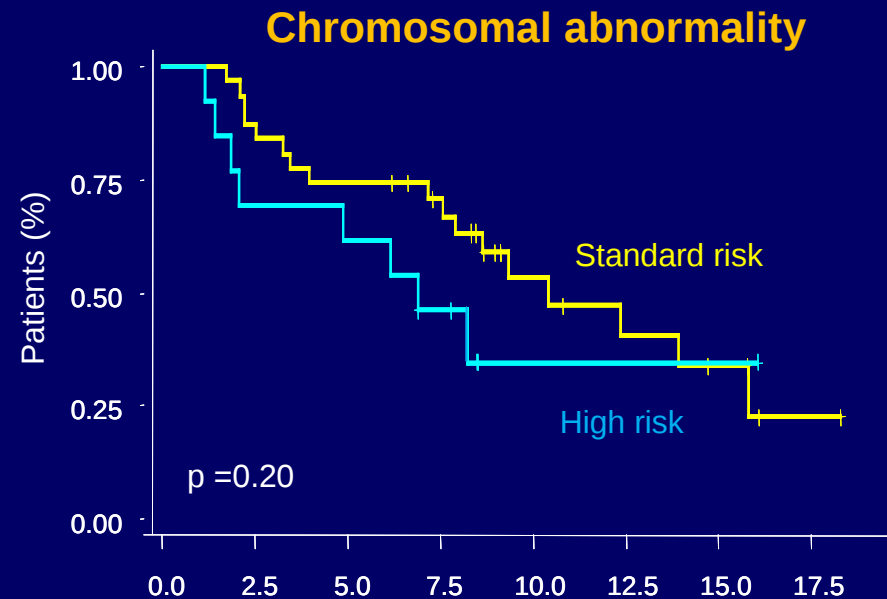
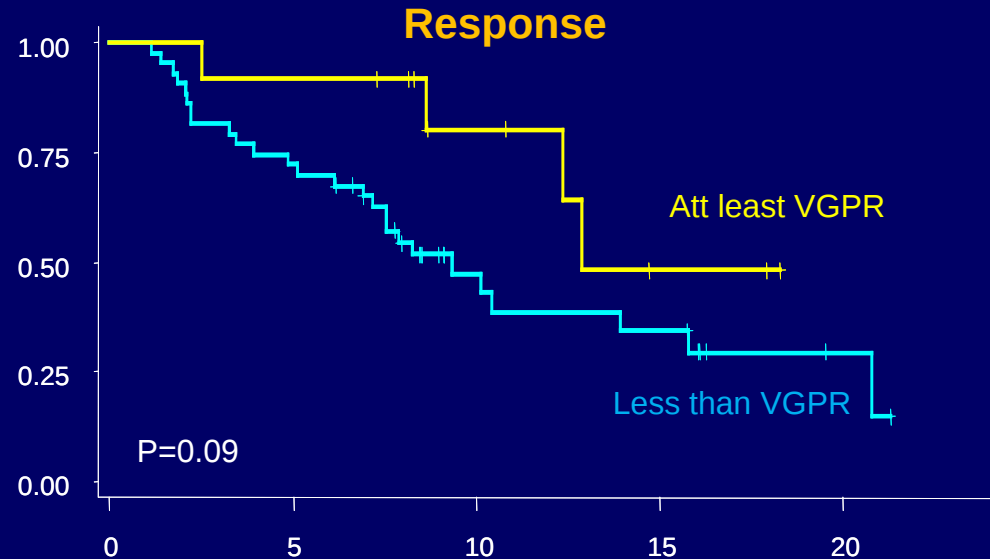
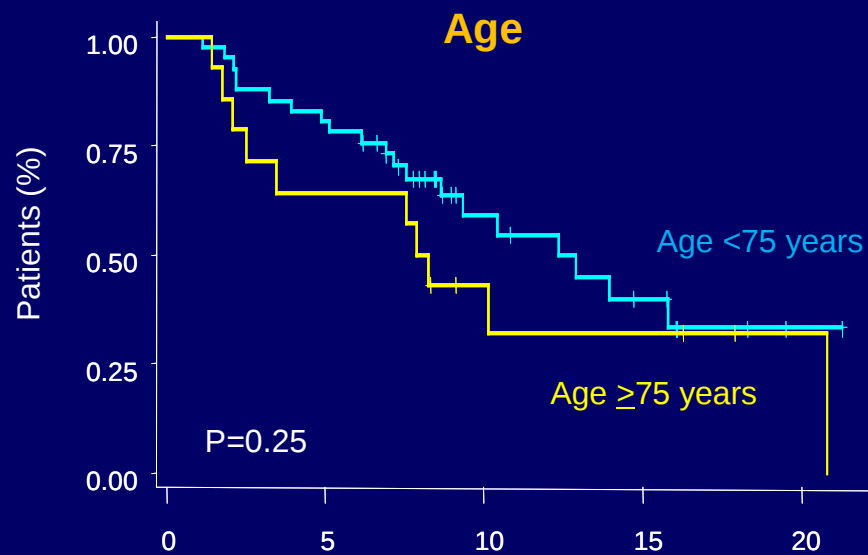
Median follow-up 14.8 months (6-21)

Progression free survival
Median 10.4 months

Overall survival
1 year-OS 69%



Progression free survival



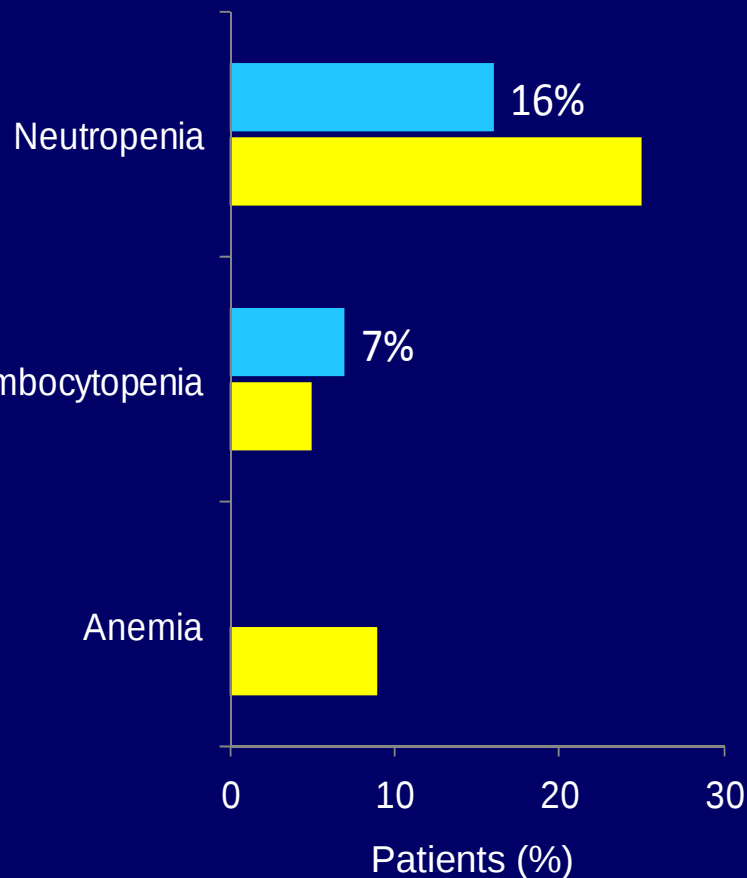
High risk: presence of at least one of the following at baseline t(4;14) or t(14;16) or del 17p13

Toxicities

N=55

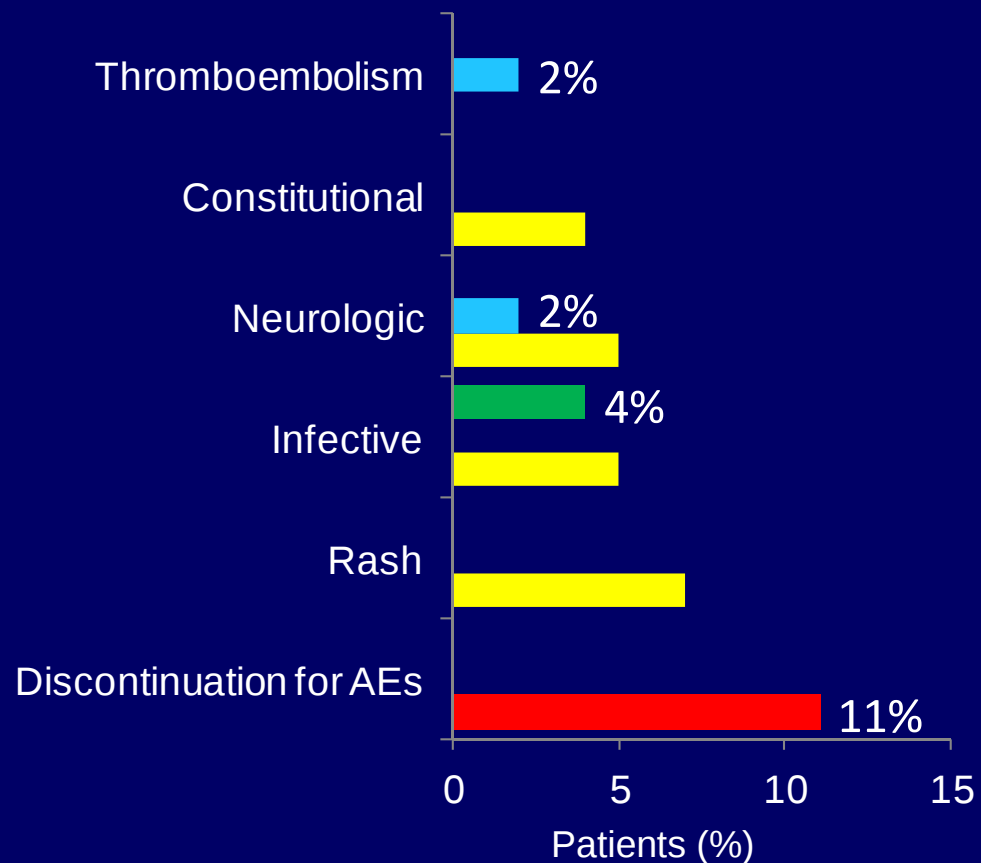
Hematologic toxicity

■ Grade 4 ■ Grade 3



Non-hematologic toxicity

■ Grade 5 ■ Grade 4 ■ Grade 3

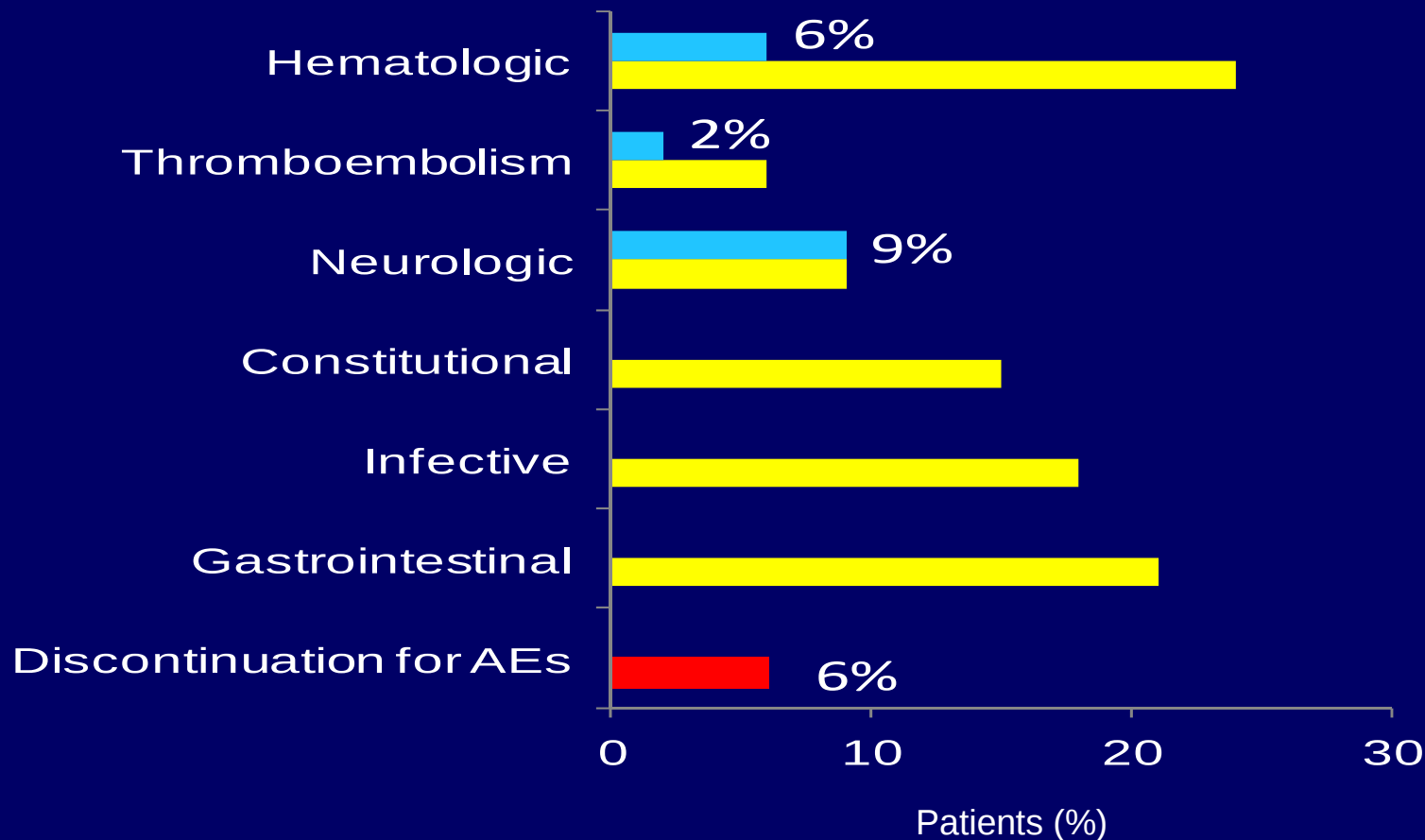


AEs: Adverse Events. Constitutional: fatigue. Neurologic: peripheral neuropathy, confusion. Infective: pneumonia and sepsis. Causes of discontinuation for AEs: pneumonia, rash, pancreatitis, bradycardia, septic shock, deep vein thrombosis, liver failure.

Maintenance: Toxicities

N=34

■ Grade 3-4 ■ Grade 1-2



AEs: Adverse Events. Constitutional: fatigue. Infective : upper respiratory, pneumonia and sepsis. Neurologic : peripheral neuropathy, vertigo, lymbic encephalitis. Gastrointestinal: constipation. Causes of discontinuations for AEs: pulmonary embolism, lymbic encephalitis.

Conclusions

- **MTD** 2.5 mg /day
- **Response rate (median 6 cycles)**
 - CR + VGPR 24%
 - CR + PR 51%
- **Outcome**
 - Median PFS 10.4 months
 - 1 year-OS 69%
- **Grade 4 hematologic AEs (incidence >5%)**
 - Neutropenia 16%
 - Thrombocytopenia 5%
- **Grade 3-5 non-hematologic AEs (incidence >5%)**
 - Rash (grade 3) 7%
 - Infections 9%

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

1. ALESSANDRIA	Levis, Baraldi	39. GENOVA	Carella, Spriano	77. RIMINI	Pasquini, Fattori
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