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Final Results from the Phase IIa Study of the Anti-CXCL12 Spiegelmer® Olaptesed Pegol (NOX-A12) in Combination with Bortezomib and Dexamethasone in Patients with Multiple Myeloma

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Abstract 2111

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Background and Aims

The L-stereo-isomer RNA aptamer (Spiegelmer®) olaptesed pegol (OLA) binds and neutralizes CXCL12. CXCL12 is responsible for trafficking and homing of normal and malignant blood cells to the bone marrow by interacting with the receptors CXCR4 and CXCR7. Preclinical studies have shown synergistic activity of CXCL12-targeting and bortezomib (BTZ).

This single arm study was conducted to assess the activity and safety of i.v. OLA added to the combination of BTZ (1.3 mg/m^2 i.v.) and dexamethasone (DEX, 20 mg p.o) in patients with relapsed / refractory multiple myeloma (MM).

Patients and Methods

From Aug 2012 to Aug 2014, 28 patients were treated according to a dose titration design shown in Figure 1. Ten patients presented with ISS stage 3, 10 had high risk cytogenetic features and 11 were refractory to prior therapy. 15 patients had previous BTZ (Table 1).

OLA was given 1h prior to BTZ, DEX was given on the day of BTZ and the subsequent day. Response was evaluated based on the uniform IMWG response criteria (Rajkumar SV et. al. Blood 2011; 117: 4691-5).

Plasma cell mobilization was studied by flow-cytometry in the first 10 patients before the regular treatment regimen.

Results

The median number of completed treatment cycles was 8. OLA resulted in a significant mobilization of myeloma cells with a 2-fold increase of circulating plasma cells for up to 3 days (Figure 2).

Progression led to treatment termination in 8 patients. Objective responses were observed in 19 (68%) patients of the ITT population. Of note, response rates were similar in patients with high risk and standard risk cytogenetics (70% vs. 67%, Table 2)

The combination of OLA and BTZ dexamethasone was well tolerated without unexpected toxicities (Table 3).

Conclusions

A single dose of OLA effectively mobilized plasma cells. OLA in combination with BTZ and DEX resulted in an ORR rate of 68% in the ITT population and PFS of 6.5 months. Response rates and PFS were similar in patients with or without high risk cytogenetic features or with or without previous exposure to BTZ. The combination regimen was well tolerated. OLA merits further study in randomized controlled trials.

Figure 1: Study Design

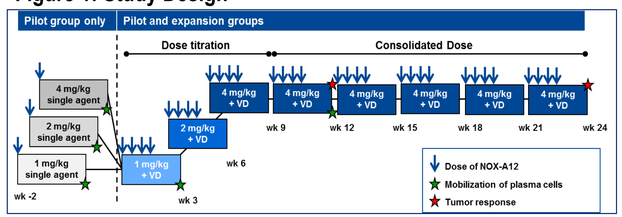

Table 1: Baseline Patient Characteristics

Number of patients	N = 28; (males:females: 14:14)	
Age median (range)	66 years (47- 79)	
MM type	IgG	17 (61%)
	IgA	5 (18%)
	Light chain only	6 (21%)
WHO Performance Score	0	18 (64%)
	1	5 (18%)
	2	5 (18%)
ISS disease stage	I:	4 (14%)
	II:	11 (39%)
	III:	10 (36%)
	Unknown	3 (11%)
Cytogenetic risk group	High risk	10 (36%)
	Standard	11 (39%)
	Not available	7 (25%)
Prior treatment lines median (range)		2 (1 - 5)
Prior treatments (data of 26 patients)	Dexamethasone	25 (89%)
	Lenalidomide	20 (71%)
	Bortezomib	15 (54%)
	ASCT	10 (36%)
	Carfilzomib	1 (3.6%)

Figure 2: Dose-Dependent Plasma Cell Mobilization

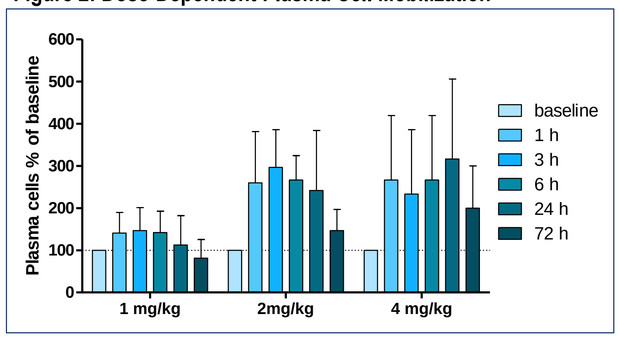

Figure 3: Individual Treatment Durations and Responses

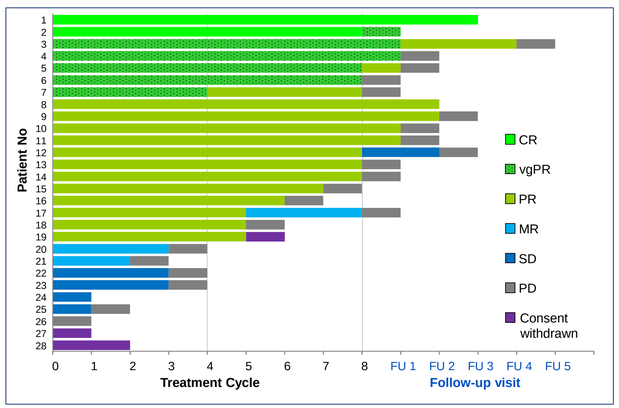

Table 2: Response Evaluation as "Best Response"

	ITT population	Per protocol population	High-risk cytogenetics	Prior BTZ treatment
N	28	25	10	15
ORR	19 (68%)	18 (72%)	7 (70%)	9 (60%)
CR	2 (7%)	2 (8%)	0	1 (7%)
vgPR	5 (18%)	5 (20%)	3 (30%)	0
PR	12 (43%)	11 (44%)	4 (40%)	8 (53%)
MR	2 (7%)	2 (8%)	1 (10%)	1 (7%)
SD	5 (18%)	4 (16%)	1 (10%)	4 (27%)
PD	1 (4%)	1 (4%)	1 (10%)	1 (7%)
Not evaluable	1 (4%)	0	0	0

M-protein decreased by ≥50% in 20 of the 26 evaluable patients (Figure 4).

Figure 4: Waterfall Plot of Maximum M-Protein Change

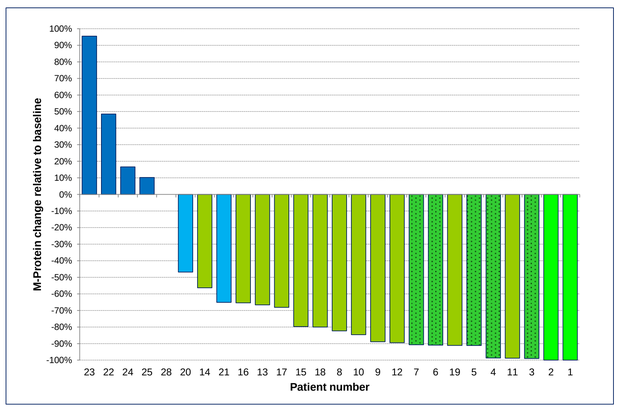

Figure 5: Progression-free Survival

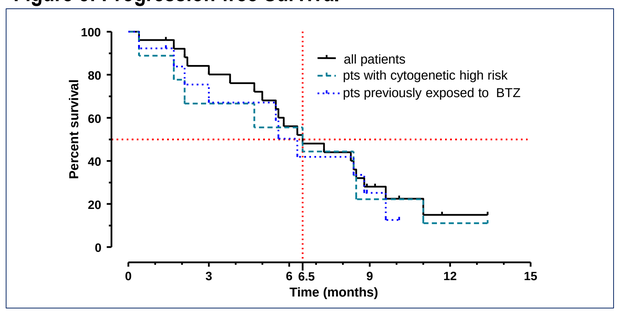

Table 3: Hematologic and non-Hematologic AEs by Severity

	Any grade	Grade 1-2	Grade 3	Grade 4
Hematologic				
Anemia	11 (39.3%)	7 (25.0%)	4 (14.3%)	-
Thrombopenia	11 (39.3%)	5 (17.9%)	4 (14.3%)	2 (7.1%)
Neutropenia	5 (17.9%)	1 (3.6%)	4 (14.3%)	-
Lymphopenia	1 (3.6%)	-	1 (3.6%)	-
Gastrointestinal				
Diarrhea	14 (50.0%)	11 (39.3%)	3 (10.7%)	-
Constipation	9 (32.1%)	7 (25.0%)	2 (7.1%)	-
Infections				
Pneumonia	4 (14.3%)	1 (3.6%)	3 (10.7%)	-
Herpes zoster	3 (10.7%)	3 (10.7%)	-	-
Nervous system				
Polyneuropathy	5 (17.9%)	5 (17.9%)	-	-
General				
Asthenia	5 (17.9%)	4 (14.3%)	1 (3.6%)	-