Phase 2 randomised open label study of 2 modalities of Pomalidomide plus low-dose Dexamethasone in patients with Multiple Myeloma, refractory to both lenalidomide and bortezomib. IFM 2009-02.

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Background

	Phase	Regimen	N	Schema	Doses	PR and better	PFS / DOR / OS, months (m)
Schey et al. JCO 2004	1	Poma	24	28/28	MTD 2 mg	54%	9.7 / - / 22.5
Streetly et al. BJH 2008	1	Poma	20	28/28	MTD 5 mg QOD	50%	10.5 / - / 33
Richardson et al. ASH 2009	1	Poma +/- Dex	32	21/28	2 to 5 mg	28%	- / - / -
Lacy et al. JCO 2009	1/2	Poma + Dex	60	28/28	2 mg	63%	11.6 / 97% at 6m / 94% at 6m
Lacy et al. Leuk 2010 *	2	Poma + Dex	34	28/28	2 mg 4mg (N=8)	32%	9.1 / 4.8 / 13.9
Lacy et al. ASCO 2010 $	2	Poma + Dex	35	28/28	2 mg 4mg (N=9)	31%	TTP 8 m / - / 86% at 6m

* Lenalidomide refractory patients

$ Refractory to both lenalidomide and bortezomib

Study Design

Arm A – Cycle 21 days
- Pomalidomide 4mg oral/d, 1-21
  Dexamethasone 40mg oral/w, 1, 8, 15, 22
- Aspirin/LMWH continue

Arm B – Cycle 28 days
- Pomalidomide 4mg oral/d, d 1-28
  Dexamethasone 40mg oral/w, 1, 8, 15, 22
- Aspirin/LMWH continue

6 pts per arm

STOP #1/DMC – TOLERANCE
Rule: acceptable

Simon stage 1
17 pts per arm

STOP #2 DMC - EFFICACY
Rule: 4 PR and better/arm

Simon stage 2
40 pts per arm

Until Progression
(relapse or refractory)

- Simon two stage design
- 22 IFM centres
- 92 pts included
- N=84 evaluable

Study Objectives

Primary objectives:

- Response rate (PR and better) according to IMWG in either arm

Secondary objectives: In either arm

- Safety of pomalidomide and dexamethasone
- Time to response and Response duration of pomalidomide and dexamethasone
- Time to disease progression and EFS to pomalidomide and dexamethasone
- Overall Survival of pomalidomide and dexamethasone
- Response with regards to cytogenetic of the BM tumor plasma cells

Key Eligibility Criteria

- Relapsed multiple myeloma with one or more prior therapies
- Refractory to at least 2 cycles of both lenalidomide and bortezomib
- Measurable disease: M protein of ≥ 1.0 g/dL in serum; ≥ 0.2 g in 24 hr urine collection sample; freelite >100mg/L (and abnormal K/L ratio)
- ECOG performance status = 0-2
- ANC > 1 $x10^9$/L; Platelets ≥ 75 $x10^9$/L; Hb ≥ 8 g/dL
- Creatinine clearance ≥50 mL/min
- Known Intolerance of thalidomide or lenalidomide
- Neuropathy < Grade 2

Assessments

- Patients continue to participate to the study **until Progression**
- Disease response was assessed according to **IWMG criteria**
  - Efficacy assessments included monthly M-protein measurements in serum and 24-hour urine, and bone marrow examination if CR
  - Assessments of M-protein were objective and performed by a **central laboratory**
- Adverse events (AEs), serious AEs and laboratory values were recorded
  - Toxicities were graded according to NCI-CTCAE version 3.0

Patient Characteristics at diagnosis

Arm	21/28 N = 43	28/28 N = 41
Time from Diag-Screening, months (range)	61 (11-224)	78 (8.8-334)
Median b2m, mg/L (range)	3.9 (1.2-15.7)	2.7 (1.3-6.4)
Median albumin, g/L (range)	37 (25-49)	38 (28-47)
ISS Stage II / III (%)	50 / 18	46 / 11
Bone lesion, presence (%)	60	53
Measurable M component, N (%)		
Serum M spike	36 (84)	33 (82)
Bence Jones	4 (9)	4 (10)
sFLC	3 (7)	3 (8)

Patient Characteristics at entry into IFM2009-02

	Arm	21/28 N = 43	28/28 N = 41
Median age, years (range)		54 (39-78)	53 (36-69)
Gender ratio (M/F)		2	2
Neuropathy (all grades), N (%)		34 (79)	25 (61)
DVT/PE prophylaxis, N (%)	**LWMH**	10 (23)	8 (19.5)
	VKA	7 (16)	4 (10)
Median Hb, g/dL (range)		11 (7-14)	13 (6-14)
Median PNn, $x10^9$/L (range)		2.6 (1.0-10)	2.8 (0.9-8)
Median Plat, $x10^9$/L (range)		168 (51-366)	142 (63-269)
T(4;14), N(%)		0	3 (7)
Del17p, N(%)		5 (12)	4 (10)
Prior line of therapy, N (range)		**4 (1-8)**	**4 (1-8)**
Thalidomide, N (%)		20 (46.5)	24 (58.5)
Revlimid, N (%)		(100)	(100)
Velcade, N (%)		(100)	(100)

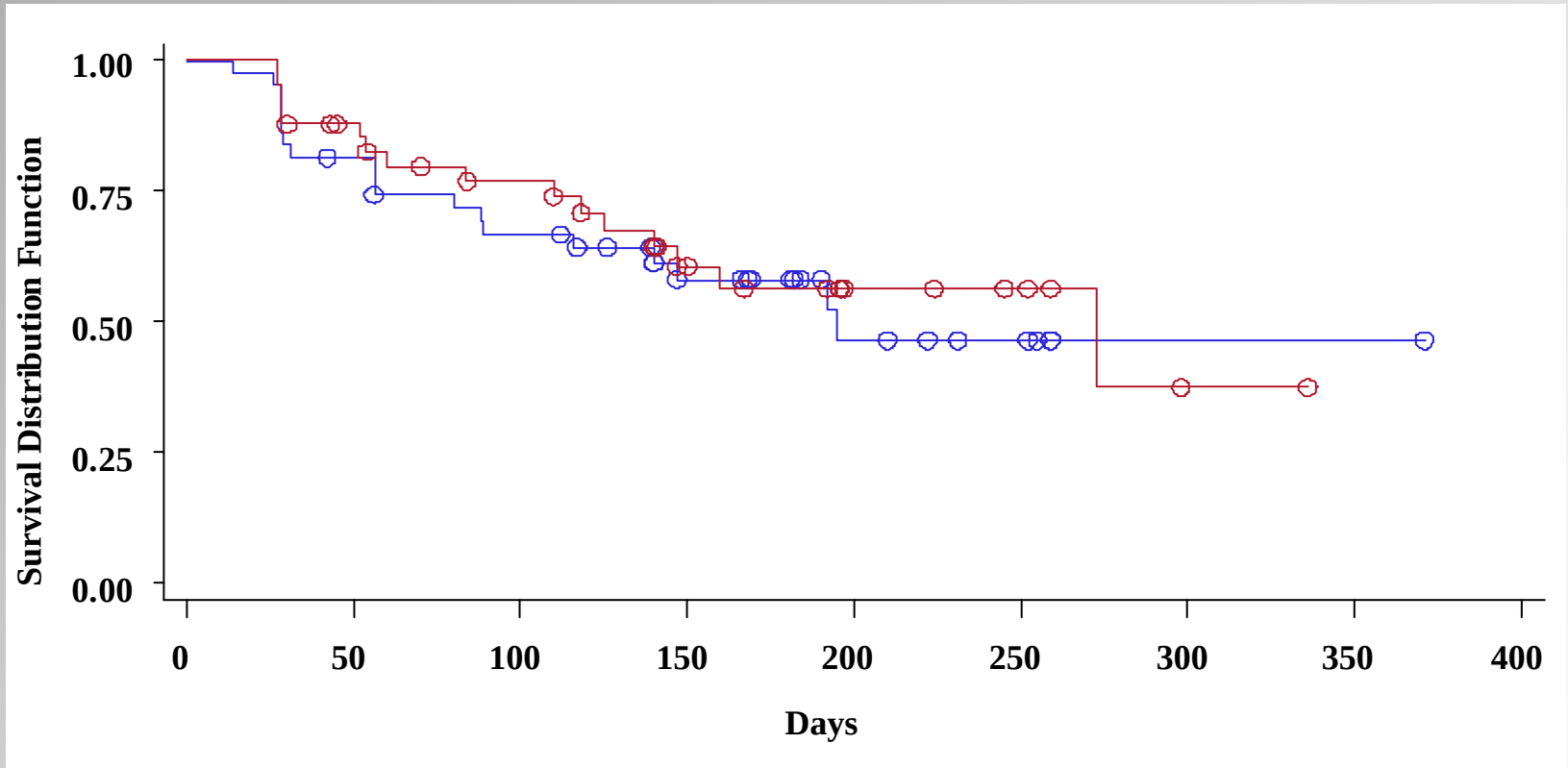
DVT: Deep Veinous Thromboembolism/PE: Pulmonary Embolism; LWMH: Low Weight Molecular Heparin; VKA: Vitamin K antagonist

Response (ITT - Central lab)

Arm	21/28 N=43	28/28 N=41
Number of cycle, median	**5**	**5**
ORR (PR and better), N(%)	**18 (42)**	**16 (39)**
sCR	0	0
CR	1 (2)	0
VGPR	3 (7)	2 (5)
PR	14 (32.5)	14 (34)
Stable disease, N(%)	20 (46.5)	21 (51)
Progression, N(%)	5 (12)	1.7 (10)
Time to best response, months (range)	**2 (1-9)**	**1.7 (1-9)**

Time To Progression (TTP)

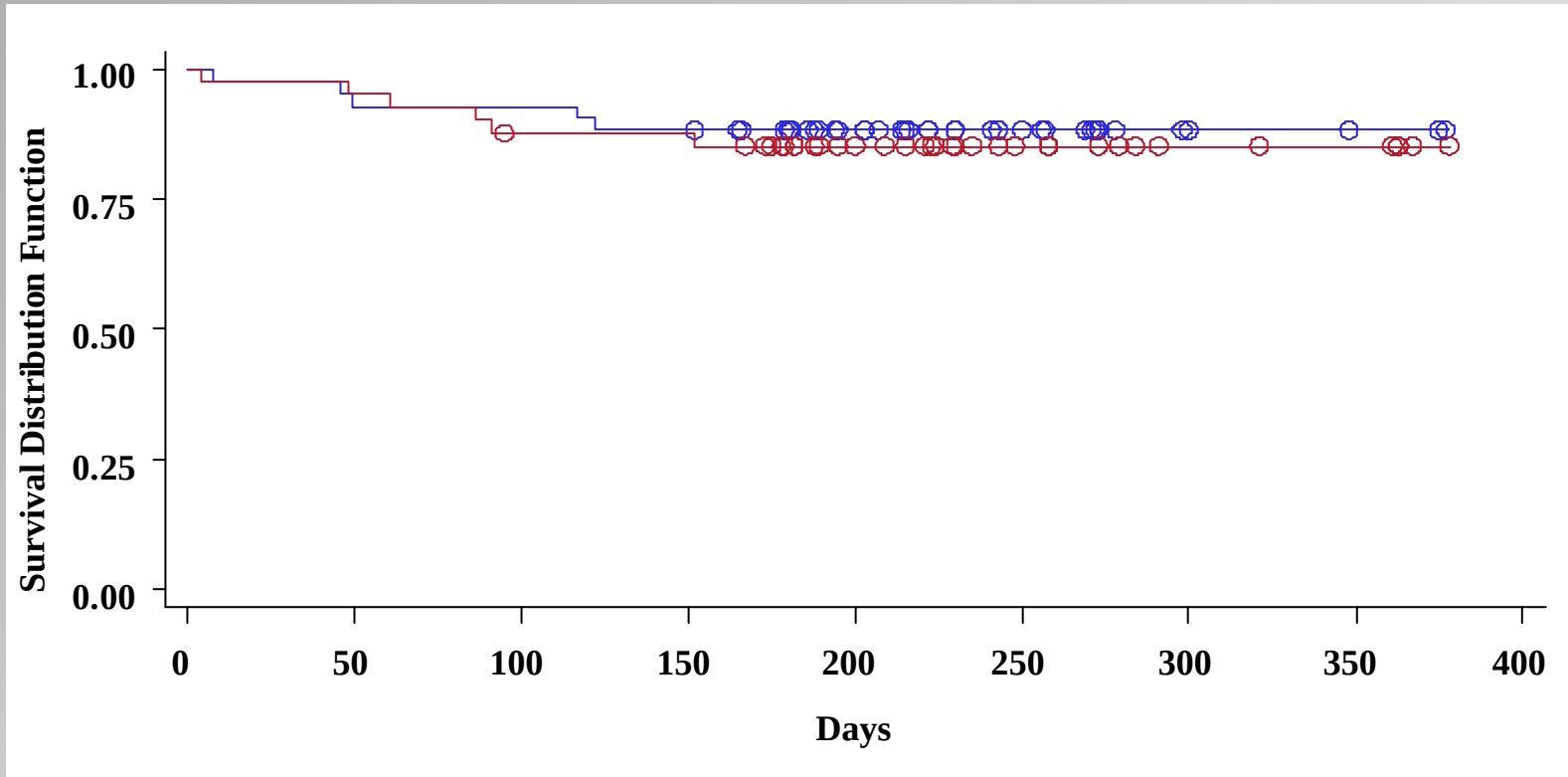
Median follow-up is 6.5 months (arm A 21/28) and 7 months (arm B 28/28)



	Arm	O/N	Median, months	Range
	21/28	19/43	7	(4 -)
	28/28	16/41	9.7	(4 -)

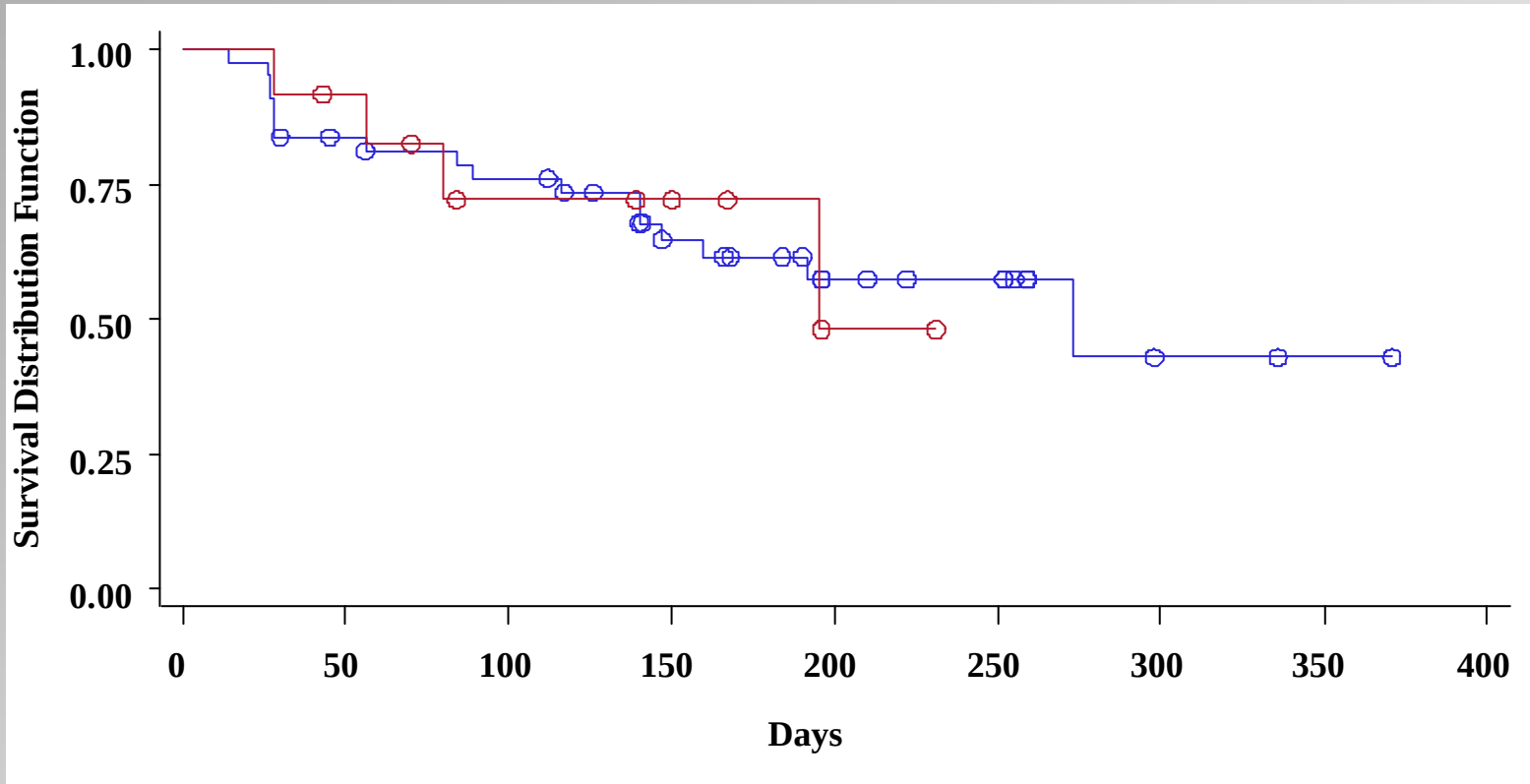
O/N: observed number / total number

Overall Survival



	Arm	O/N	Median
	21/28	5/43	88% at 6 months
	28/28	6/41	85% at 6 months

TTP according to Presence of del17p or t(4;14)



Del17p or t(4;14)	O/N	Median, Months	Range
No	17/43	9.7	(5.2-)
Yes	4/12	7	(2-)

Hematological Adverse Events

Arm	21/28 N = 43	28/28 N = 41
Grade 3 and more,		
% ≥ Grade 3 AE out of all AE	**23.5**	**26.5**
% hematological AE out of ≥ grade 3 AE	**66**	**76**
Hb<= 8 g/dL, %	11	14
PNn<= 1 x10^9/L, %	**34**	**33.5**
Plat<= 50 x10^9/L, %	18	21
Support (at least once per patient), %		
EPO	32.5	34
G-CSF	**30**	**44**
Red cell transfusion	28	34
Platelet transfusion	16	17

Non Hematological Adverse Events of special interest

Arm	21/28 N = 43	28/28 N = 41
Grade 3 and more **% non hematological AE out of all AE**	**12**	**9**
Neuropathy, N	0	0
DVT (with DVT prophylaxis), N	0	0
Asthénia, N	4	2
Cramps, N	0	2
Diarrhea, N	0	2
Hyperglycemia, N	1	0
Bronchitis, N	1	1
Pneumonia, N	1	1

Reduced doses of study treatment

Arm	21/28 N = 43	28/28 N = 41
Reduced dose of Pomalidomide, N (%)	**21 (49)**	**17 (41)**
3 mg	7	5
2 mg	2	4
1 mg	0	1
Dose interruption / discontinuation	12	7
Reduced dose of Dexamethasone, N (%)	21 (49)	22 (54)
20 mg	6	9
10 mg	1	1
Dose interruption / discontinuation	14	12

Conclusions

- The association of Pomalidomide and Dexamethasone is safe and provide responses in patients with advanced and refractory myeloma to bortezomib and lenalidomide
- Pomalidomide 4mg per day is well tolerated
- Pomalidomide 4mg /day 21 days out of 28 days-cycle does not appear inferior to pomalidomide 4mg /day continuous on 28 days-cycle

Acknowledgments

- The authors would like to thank
  - The patients for their participation in this trial
  - Celgene for their help in the design of the study and their financial support
  - IFM centres and study investigators
  - IFM study support teams