Lurbinectedin (PM01183)

An active compound in platinum-resistant/refractory ovarian cancer patients: Results of a two-stage, controlled phase II study

A. Poveda, D. Berton-Rigaud, I. Ray-Coquard, J. Alexandre, M. Provansal, A. Soto-Matos, C. Kahatt, S. Szyldergemajn, A. Nieto, C. Fernández, E. M. Guerra, A. Casado, A. Gonzalez Martin, J. M. Del Campo

Presented By Andres Poveda at 2014 ASCO Annual Meeting

Dr. Andrés Poveda

Instituto Valenciano de Oncología - Valencia - Spain

Disclosure statement:

Has received remuneration from PharmaMar
for a consultant/advisory relationship

PRESENTED AT:

ASCO 50th ANNUAL MEETING SCIENCE & SOCIETY

Ovarian Cancer
Platinum resistant/refractory disease (PROC)

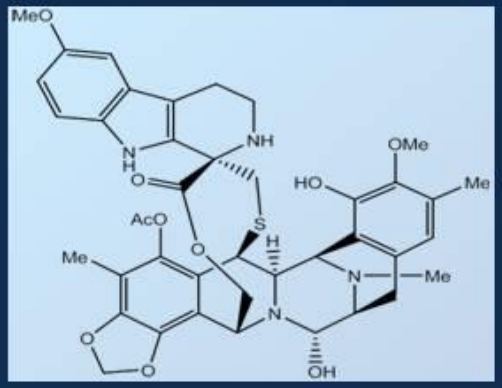
- The treatment of patients with PROC is a challenge and an unmet medical need

- Paclitaxel, PLD and topotecan are approved single agents used in PROC
  - 10-15% of response
  - No difference in terms of PFS and OS

- PROC patients require treatment that can overcome resistance

PRESENTED AT: ASCO 50th ANNUAL MEETING SCIENCE & SOCIETY

Background



- **Lurbinectedin (PM01183)** is a novel synthetic entity, structurally related to trabectedin
- Mechanism of action:
  - Blockade of trans-activated transcription in tumor cells and tumor-associated macrophages
- Broad antiproliferative activity in vitro and in vivo
- Strong preclinical activity in cisplatin resistant epithelial ovarian cancer models*

* Clin. Cancer Res. August 15, 2012

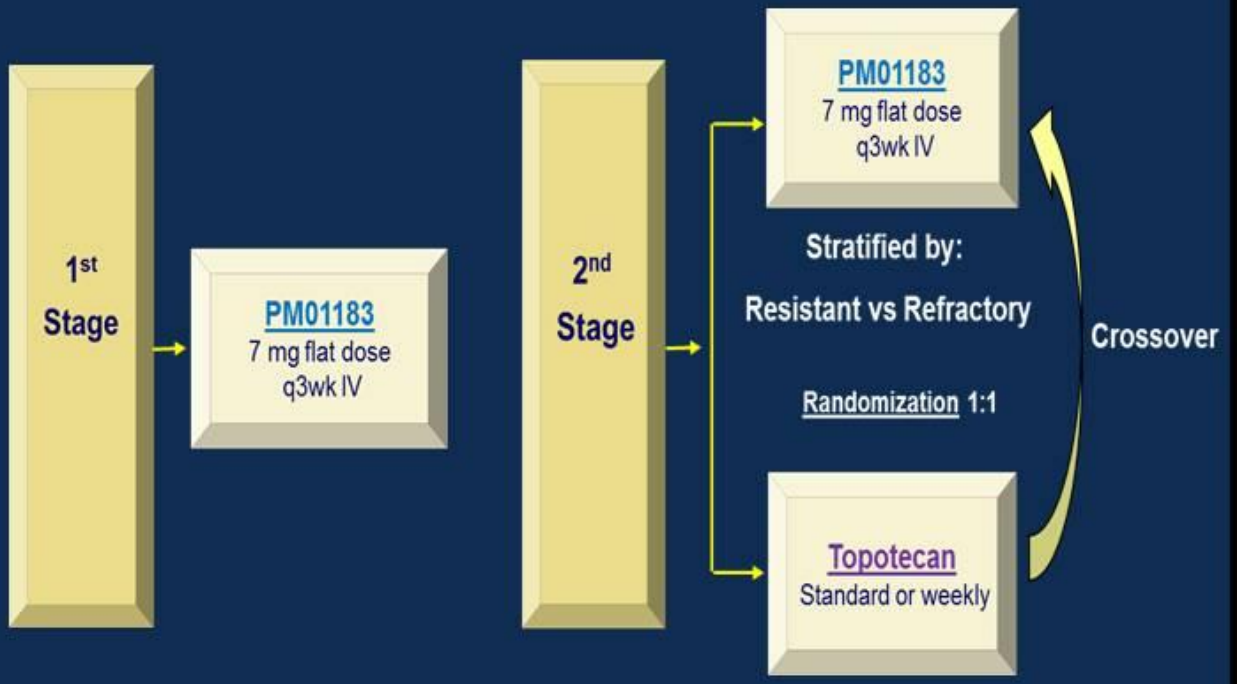
PRESENTED AT:

ASCO 50th ANNUAL MEETING SCIENCE & SOCIETY

Study Design

Phase II, Two-stage design

- Epithelial ovarian, fallopian tube or peritoneal cancer
- Platinum resistant/refractory
- Measurable and/or evaluable disease (RECIST v1.1 or GCIG)
- < 3 prior CT lines
- ECOG-PS 0-2



H0: ORR ≤ 8% vs. H1: ORR ≥ 25%; alpha 0.025 (one-sided) power=90%

- 1st stage: **18** evaluable patients - If ≥2 responders → proceed to the 2nd stage
- 2nd stage: **60** evaluable patients randomized to PM01183 or topotecan
- Both stages: If ≥8 out of 48 **PM01183** evaluable patients respond → **Further Development**

Data cut-off: April 30, 2014

PRESENTED AT: ASCO 50th ANNUAL MEETING SCIENCE & SOCIETY

Presented By Andres Poveda at 2014 ASCO Annual Meeting

Study Endpoints

Primary objective

To evaluate the antitumor activity of PM01183 in terms of

Overall Response Rate (RECIST v1.1 and/or GCIG) in PROC

Secondary objectives

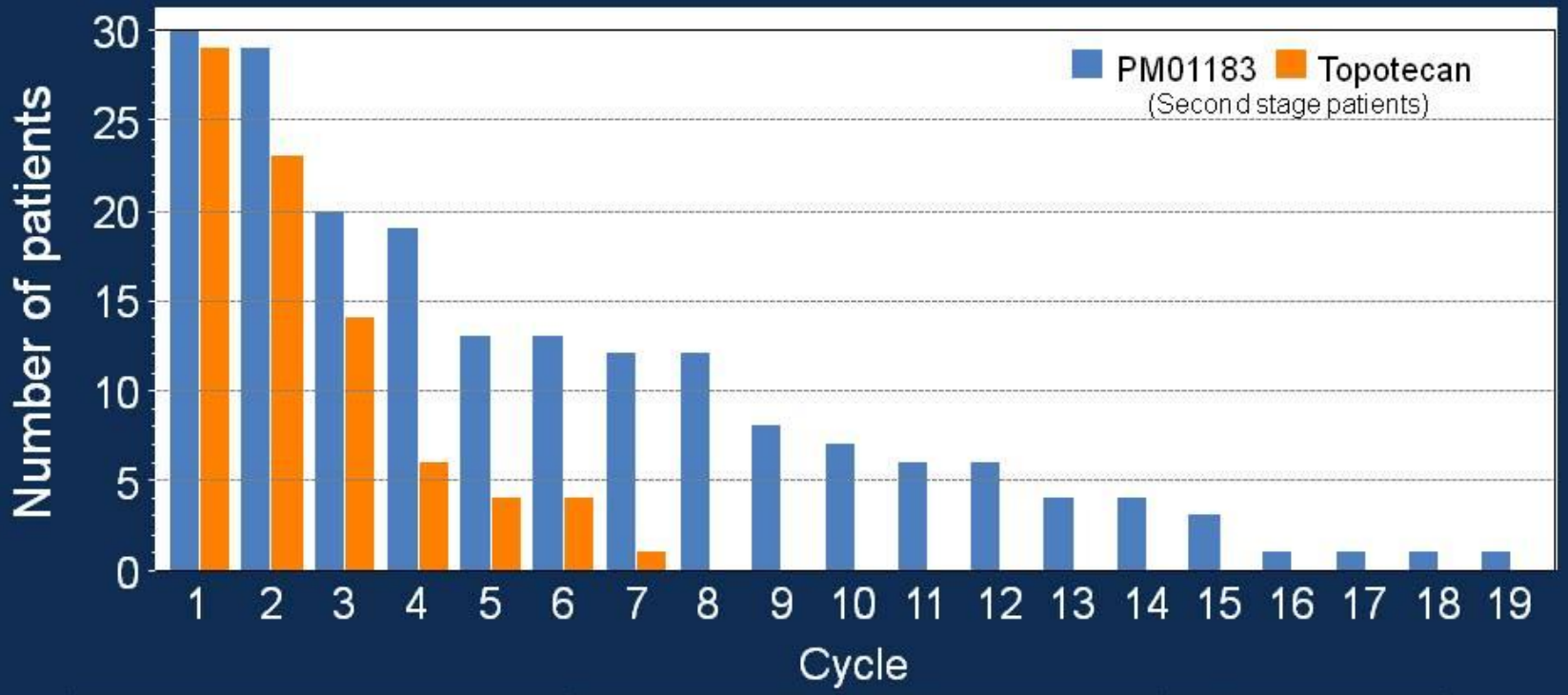
To analyze:

- Progression free survival
- Overall survival
- PM01183 safety profile
- Antitumor activity of topotecan as control arm

Patient Characteristics

		PM01183		Topotecan
		Overall (1st & 2nd stage) n= 52	Randomized (2nd stage) n = 30	n=29 (standard, n=8; weekly, n=21)
Age years	Median range	59 (35-81)	60 (35-81)	61 (35-80)
ECOG PS	0 - 1 / 2	96% / 4%	97% / 3%	86% / 14%
Primary tumor site	Ovarian	83%	90%	79%
Histology type	Serous	72%	74%	66%
	Endometrioid	8%	3%	3%
	Clear cell	2%	-	10 %
	Other/unspecified	18%	23%	21%
Disease	Visceral	38%	30%	21%
	Ascites	19%	20%	34%
RECIST	Measurable	85%	90%	76%
Platinum status	Resistant	64%	57%	55%
	Refractory	36%	43%	45%
Platinum-free interval	PFI < 3 months	38%	43%	52%
Prior CT lines	Median	2	2	2

Treatment Exposure



	PM01183		Topotecan
	Overall (1st & 2nd stage) n=52	Randomized (2nd stage) n= 30	n=29
Total cycles	310	190	81
Cycles administered median, range			
- All patients	5 (1-19)	4 (1-19)	2 (1-7)
- Platinum resistant patients	6 (1-19)	8 (2-19)	3 (1-6)

PRESENTED AT:

ASCO 50th ANNUAL MEETING SCIENCE & SOCIETY

Presented By Andres Poveda at 2014 ASCO Annual Meeting

Overall Response Rate (ORR)

	PM01183		Topotecan	p-value
	Overall (1st & 2nd stage) n=52	Randomized (2nd stage) n=30	n=29	
ORR (n [%])				
CR	1 (2)	1 (3)	0 (0)	
PR	&10 (19)	4 (13)	0 (0)	
SD	26 (50)	14 (47)	15 (52)	
PD	15 (29)	11 (37)	14 (48)	
ORR (%) (95% CI)	**21 (11-35)**	17 (6-35)	0 (0-11)	0.006
- Platinum resistant	30 (16-49)	24 (7-50)	0 (0-21)	0.020
- Platinum refractory	5 (0-26)	8 (0-36)	0 (0-25)	1

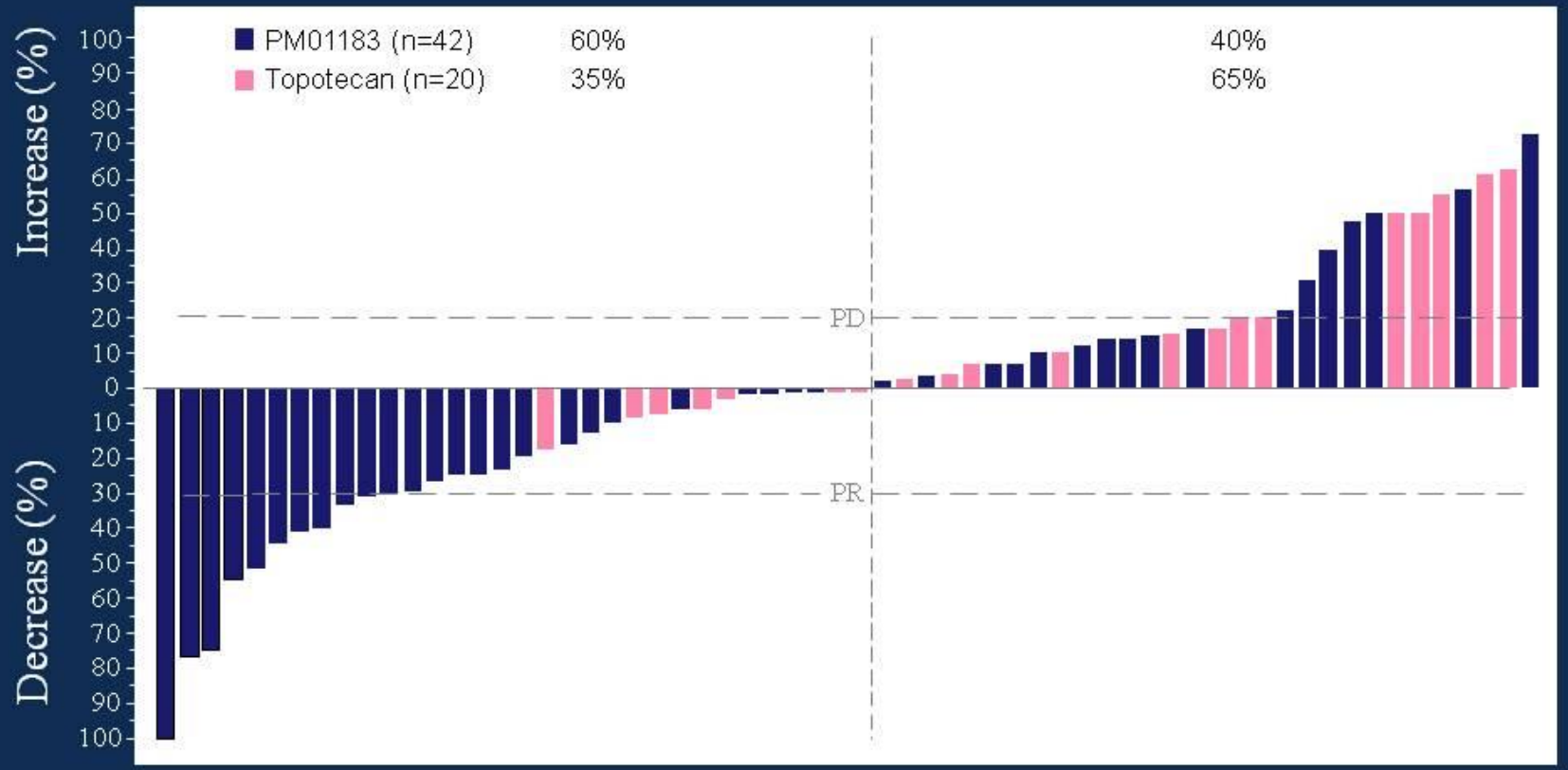
&2 PRs by Rustin criteria

PRESENTED AT: ASCO 50th ANNUAL MEETING SCIENCE & SOCIETY

Presented By Andres Poveda at 2014 ASCO Annual Meeting

Waterfall Plot (RECIST)

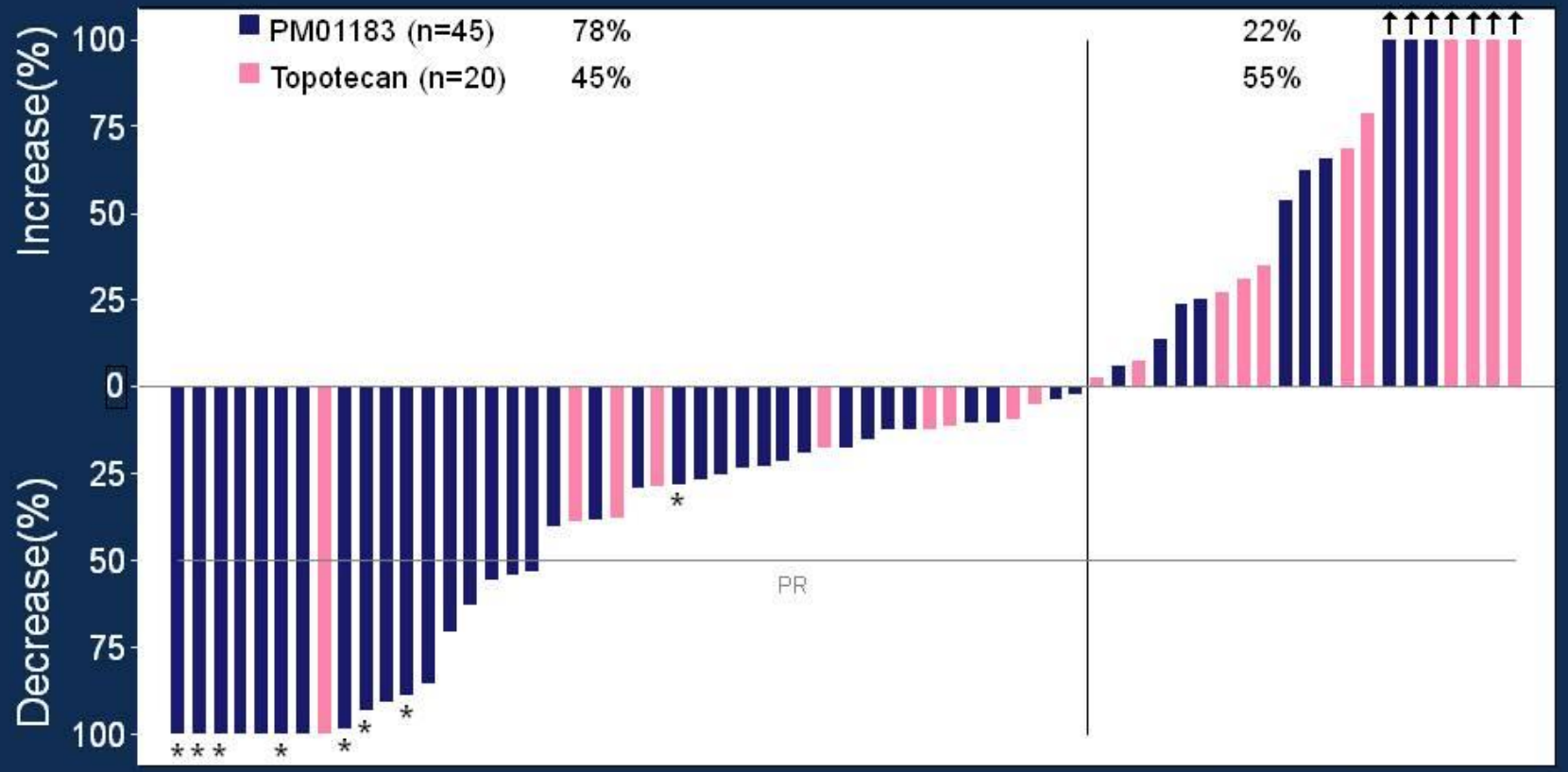
Maximal variation in target lesions according to RECIST (n=62)



PRESENTED AT: ASCO 50th ANNUAL MEETING SCIENCE & SOCIETY

Waterfall Plot (CA-125)

Maximal variation of CA-125** (n=65)



* RECIST responder

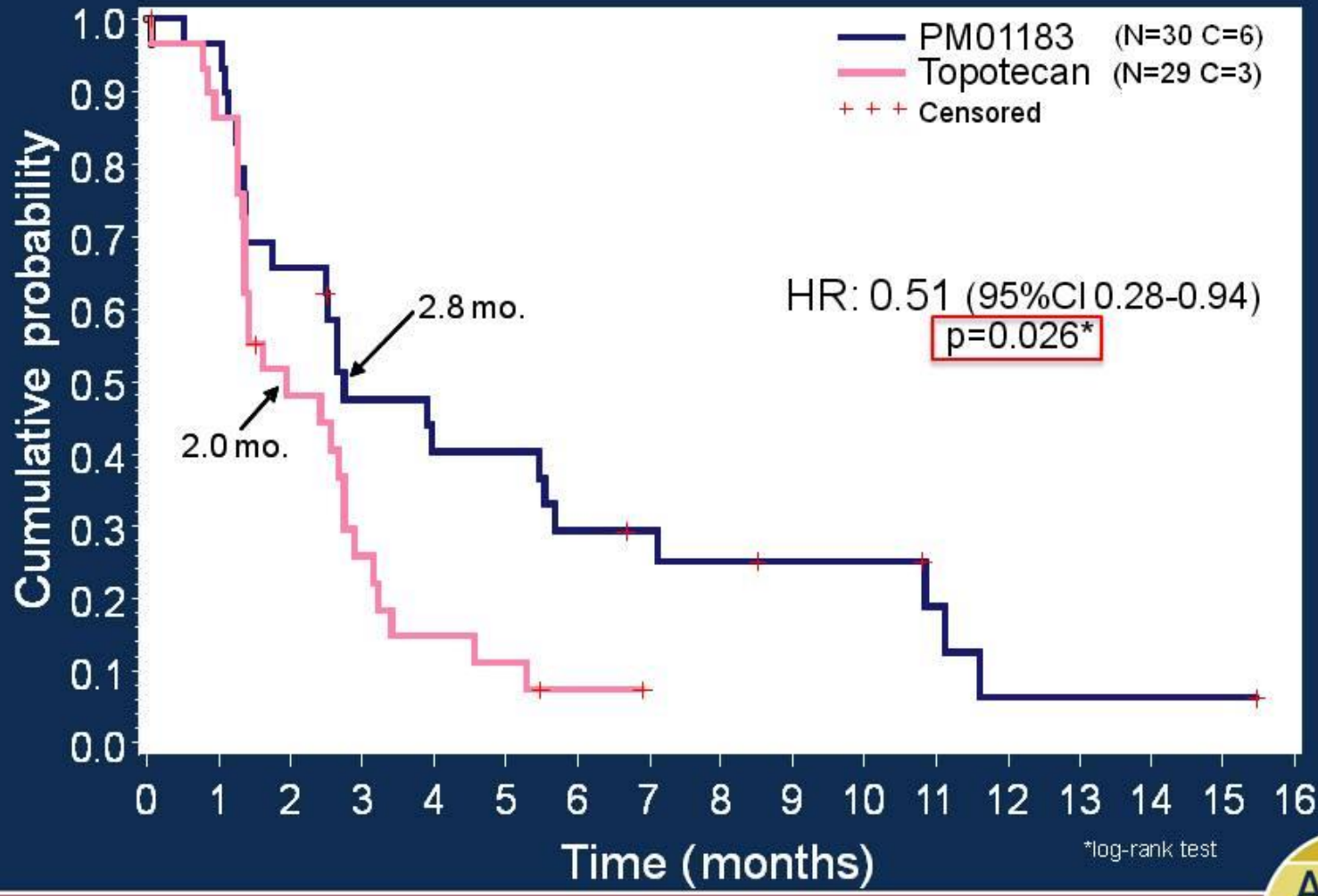
**Patients with abnormally elevated CA-125 levels at baseline. Patients with value normalized (<35 UI/ml) in treatment, imputed as 100% decrease

PRESENTED AT: ASCO 50th ANNUAL MEETING SCIENCE & SOCIETY

Presented By Andres Poveda at 2014 ASCO Annual Meeting

Progression-free Survival – 2nd stage

Platinum Resistant/Refractory

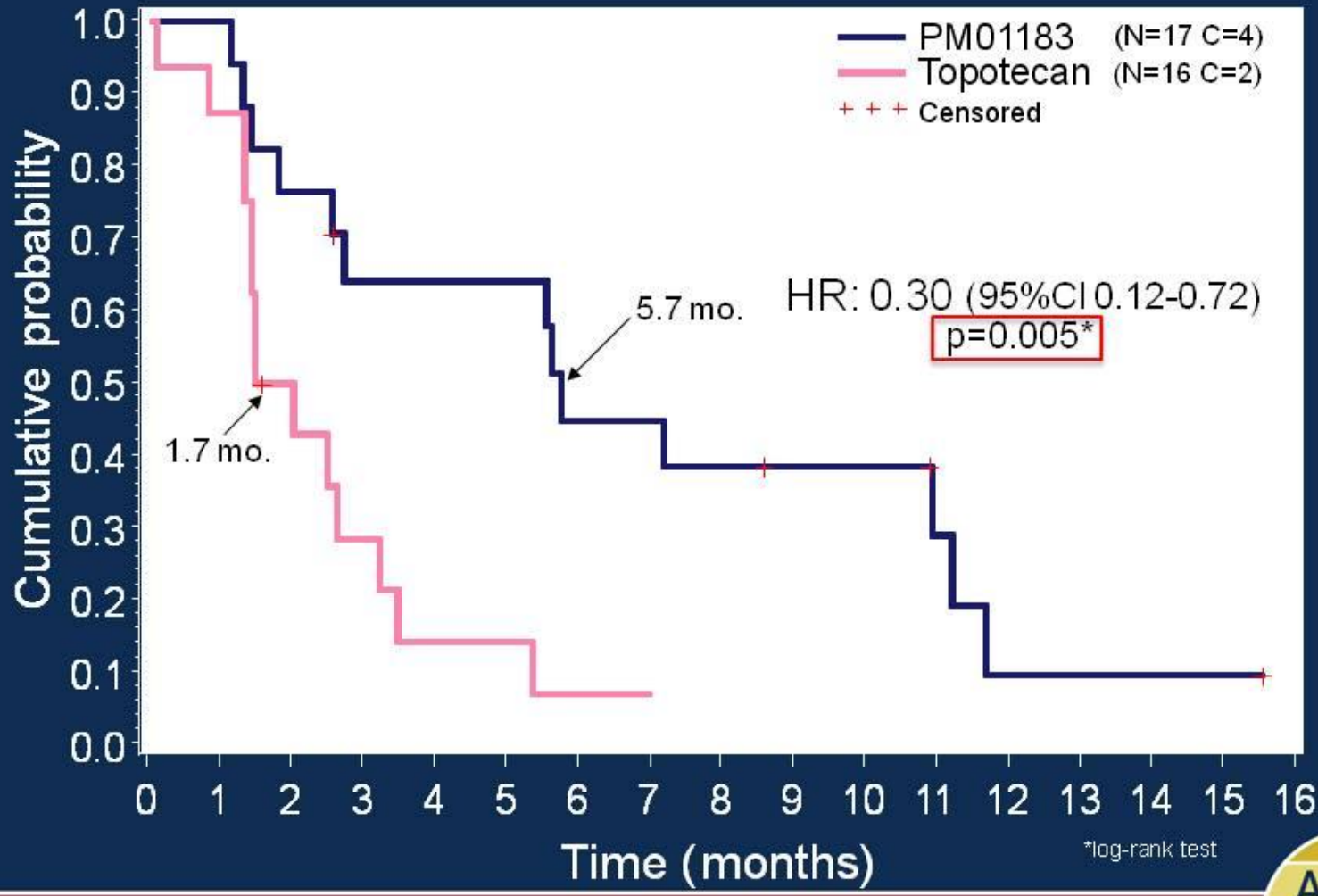


PRESENTED AT: ASCO 50th ANNUAL MEETING SCIENCE & SOCIETY

Presented By Andres Poveda at 2014 ASCO Annual Meeting

Progression-free Survival – 2nd stage

Platinum Resistant

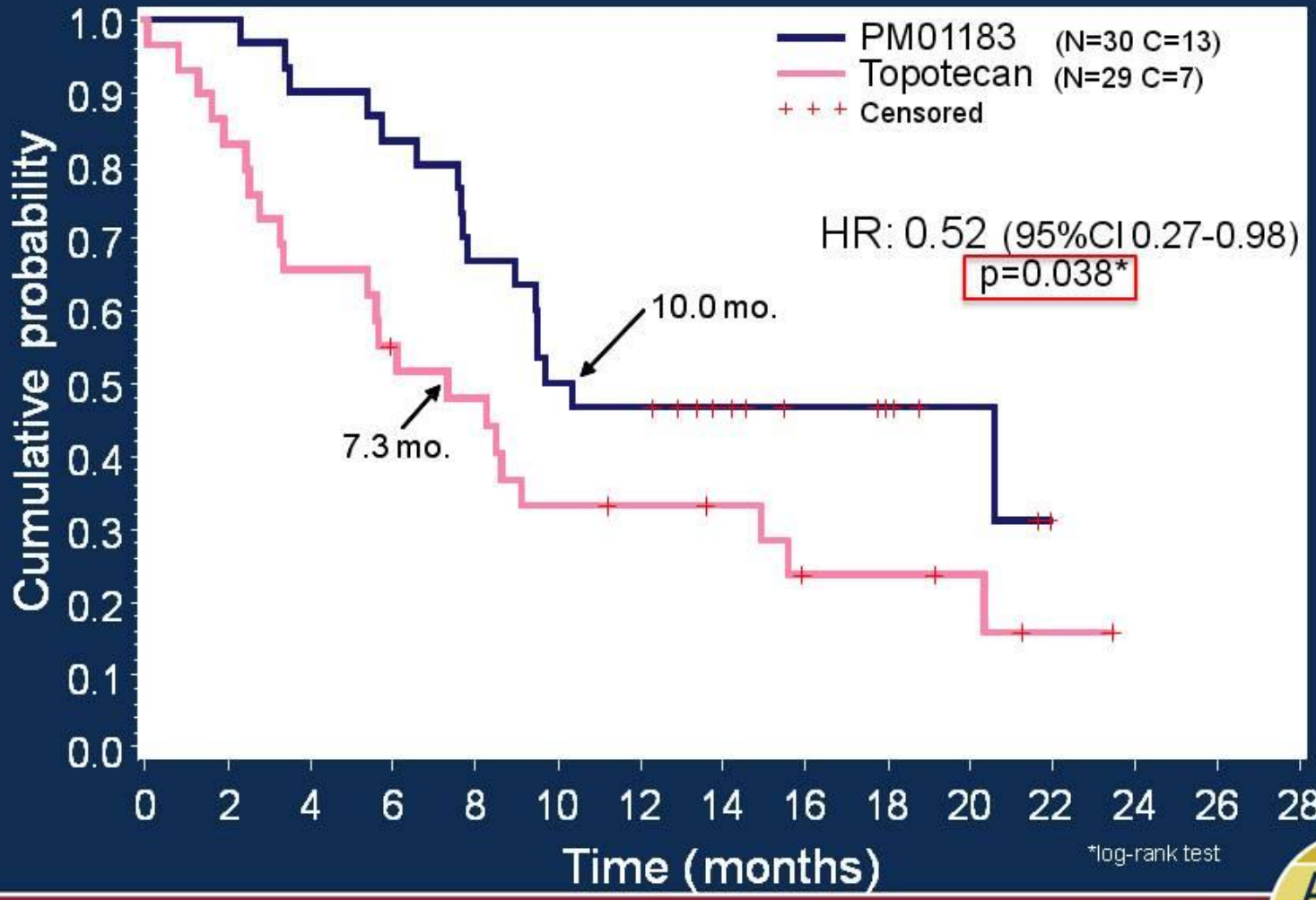


PRESENTED AT: ASCO 50th ANNUAL MEETING SCIENCE & SOCIETY

Presented By Andres Poveda at 2014 ASCO Annual Meeting

Overall Survival - 2nd stage

Platinum Resistant/Refractory

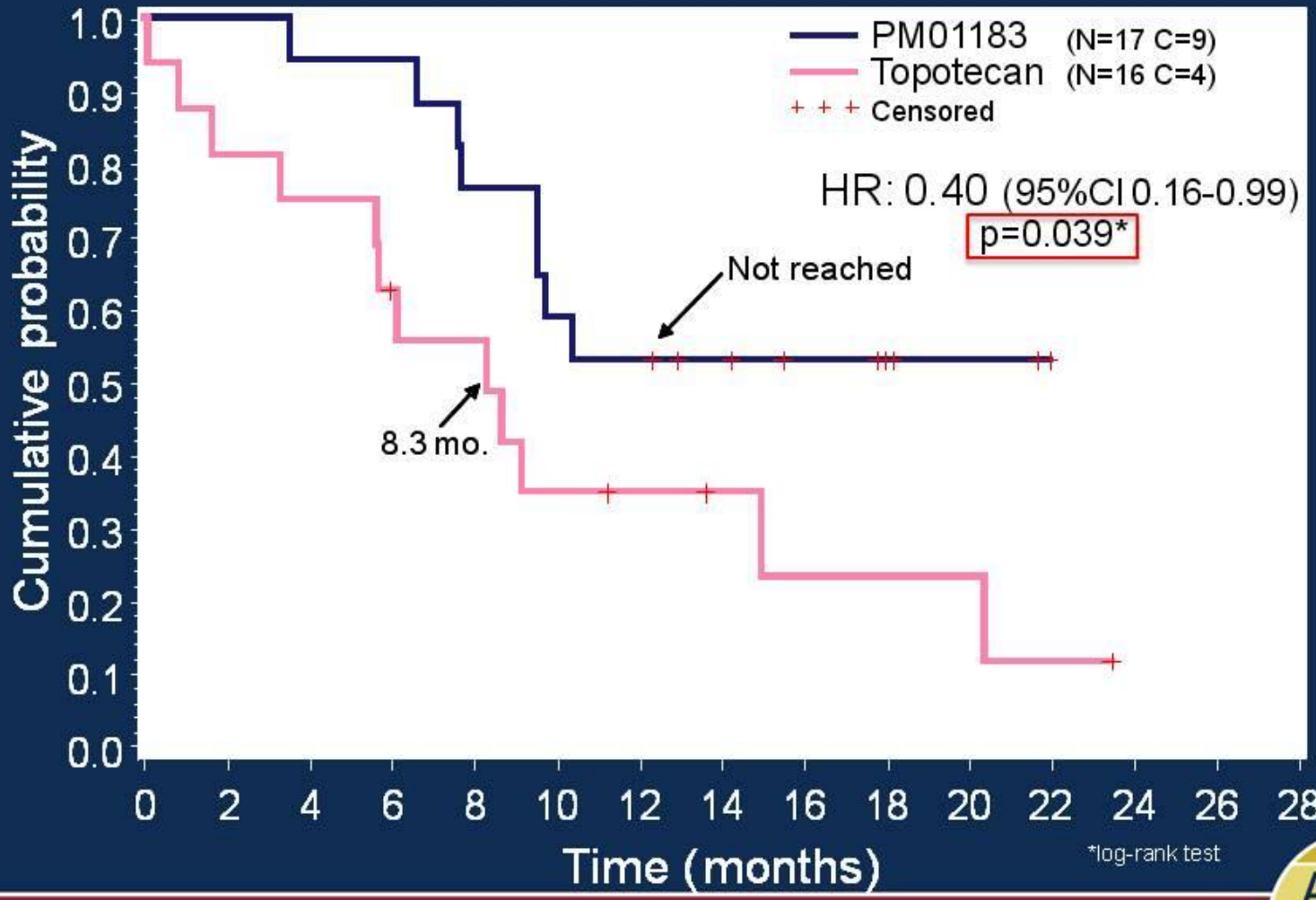


PRESENTED AT: ASCO 50th ANNUAL MEETING SCIENCE & SOCIETY

Presented By Andres Poveda at 2014 ASCO Annual Meeting

Overall Survival - 2nd stage

Platinum Resistant

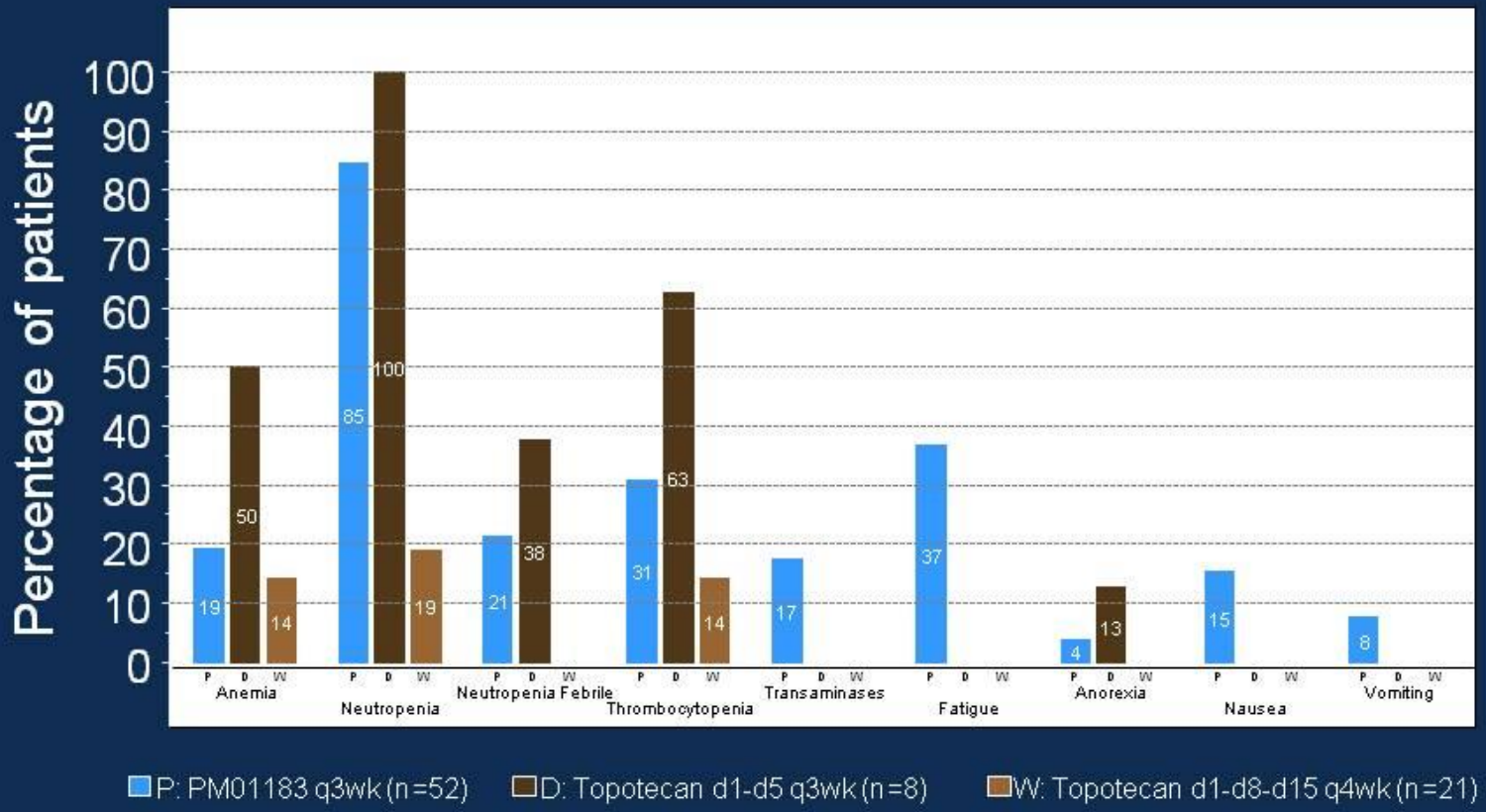


PRESENTED AT: ASCO 50th ANNUAL MEETING SCIENCE & SOCIETY

Presented By Andres Poveda at 2014 ASCO Annual Meeting

Safety G3-4 Adverse Events (AEs)

Worst per Patient



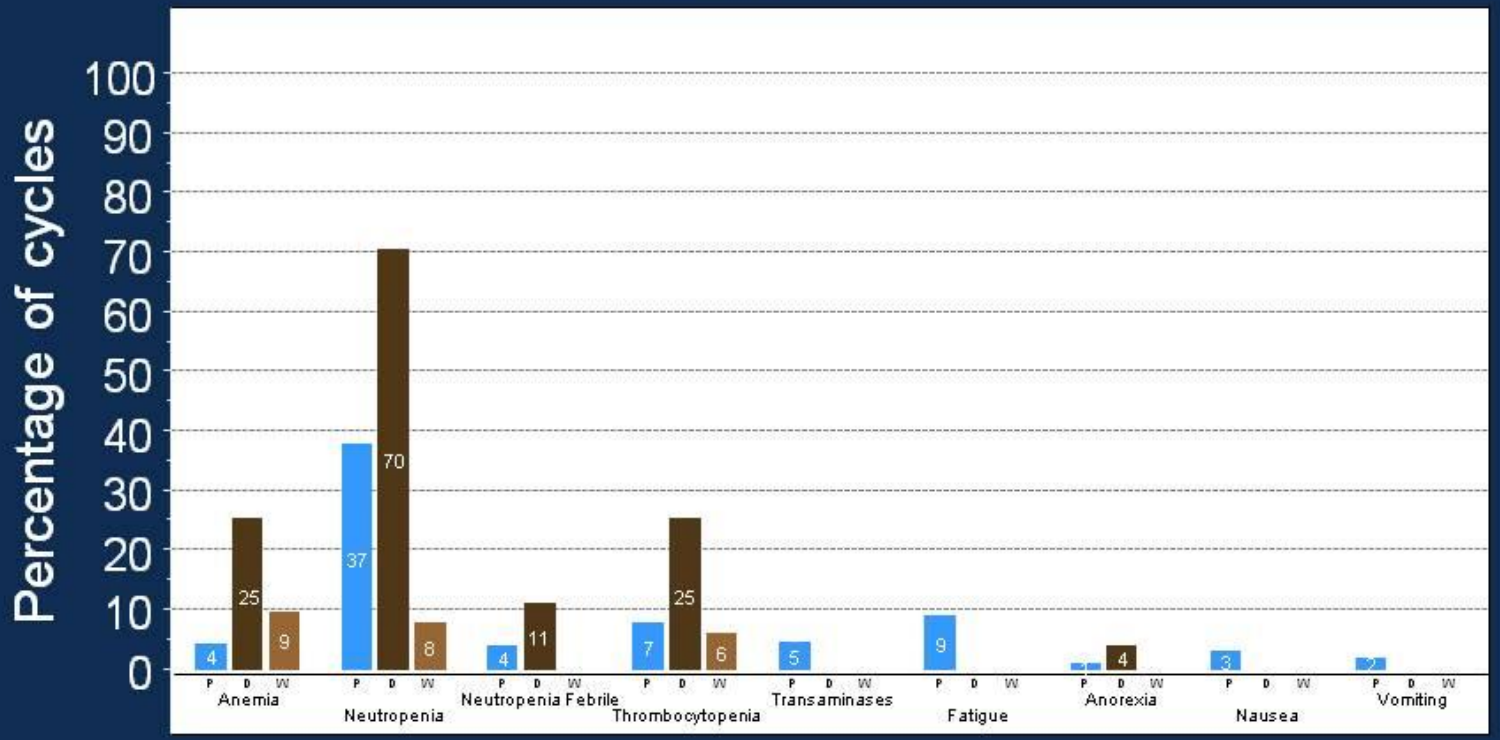
	PM01183 (n= 52)	Topotecan (n= 29)
Treatment discontinuation – AEs related	5 (10%)	0 (0%)
Treatment related deaths	0 (0%)	0 (0%)

PRESENTED AT: ASCO 50th ANNUAL MEETING SCIENCE & SOCIETY

Presented By Andres Poveda at 2014 ASCO Annual Meeting

Safety G3-4 Adverse Events (AEs)

Worst per Cycle



	PM01183 (n= 52)	Topotecan (n= 29)
Treatment discontinuation – AEs related	5 (10%)	0 (0%)
Treatment related deaths	0 (0%)	0 (0%)

PRESENTED AT:

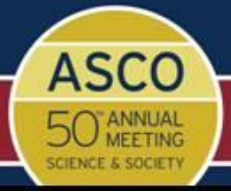
ASCO 50th ANNUAL MEETING SCIENCE & SOCIETY

Presented By Andres Poveda at 2014 ASCO Annual Meeting

Conclusions

- PM01183 is active in Platinum Resistant/Refractory Ovarian Cancer
  - ORR 30% in platinum resistant patients
- PM01183 showed statistically significant superiority in PFS/OS over topotecan, particularly in the platinum resistant population
- PM01183 safety profile was predictable, manageable and non-cumulative
  - Primary GCSF prophylaxis is supported by current data in this population
- A phase III trial in platinum resistant ovarian cancer patients is underway

PRESENTED AT:



Acknowledgments to:

Patients and their families, and their caregivers team

Intituto Valenciano de Oncologia, Valencia-Spain
Dr. Romero
Calabuig L
Mallol P

ICO Centre Rene Gauducheau, Nantes-France
Dr. Frenel
Dr. Bourbouloux
Bourcier C

Cochin - Hotel-Dieu Hospital, Paris-France
Dr. Pujade-Lauraine
Dr. Chauvenet
Gaudon C

Hospital Ramón y Cajal, Madrid-Spain
Dr. Martínez
Dr. Martinez-Jañez
Domingo P

MD Anderson Cancer Center, Madrid-Spain
Dr. Marquez
Dr. Bratos
López MJ

Hosp Univ. Vall d` Hebrón, Barcelona-Spain
Dr. Rodriguez-Freixinos
Gonzalez C

Centre Leon Berard, Lyon-France
Dr. Tredan
Dr. Guastalla
Linard P

Institut Paoli Calmettes, Marseille-France
Karsenty J

Hosp Clínico San Carlos, Madrid-Spain
Domínguez MJ

PM01183 PharmaMar team
Arias Parro M
García A
Luque M
Parra C

PRESENTED AT: