#671P: Safety and Efficacy of PM060184 plus Gemcitabine in Advanced Solid Tumors

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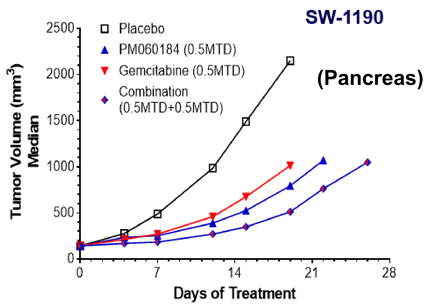
Background

PM060184 induces de polymerization of tubulin fibers with disorganization and fragmentation of the microtubule network leading to mitosis. Gemcitabine is a pyrimidine analog used in multiple cancers. PM060184 was safe in a single agent phase 1 dose escalation study and pre clinically is synergistic with gemcitabine. Here, we present the safety, efficacy, and pharmacokinetics (PK) of PM060184 combined with gemcitabine in a Phase I trial.



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PharmaMar data on file

Objectives

The primary objective was to evaluate the safety and pharmacokinetics profile of PM060184 combined with gemcitabine, and secondary end points included efficacy.

Methods

Designa	**Standard phase I dose escalation**
Population	Eligible patients (pts) with advanced or metastatic solid tumors who had prior standard of care anti-cancer therapy
Dose	PM060184: 6-10.5 mg/m^2 , 10 min infusion Gemcitabine: 800-1000 mg/m^2 , 30 min infusion
Administration	PM060184: Twice weekly in a 3-week cycle D1,8 q3w Gemcitabine: Twice weekly in a 3-week cycle D1,8 q3w
Infusion	Gemcitabine: 30-minute IV infusion, followed by PM060184: 10-minute IV Infusion
PK	D1 up to 5 hr EOI, and D2
CT Scan recist 1.1	At 0,6,12,21,29,38,47,56,68,75… weeks
AEs	CTCAE version 4.0

Results

Baseline characteristics

	Total n=57
Gender	
Male	15 (26.3)
Female	42 (73.7%)
Age (Median)	62 (25-80)
Race	
White	26 (45.6%)
Black or African-American	12 (21.1%)
Asian	1 (1.8%)
Other/Unknown	18 (31.6%)
ECOG PS score:	
0	15 (26.3%)
1	42 (73.7%)
Primary Tumor Type	
NSCLC	18 (31.6%)
Gynecological (Endometrial or Cervical)	13 (22.8%)
Epithelial ovarian cancer	13 (22.8%)
Metastatic Breast Cancer (MBC)	4 (7.0%)
Gastrointestinal Stromal Tumor (GIST)	3 (5.3%)
Head and Neck Cancer (HN)	3 (5.3%)
Germ cell tumor (GCTs)	2 (3.5%)
Carcinoma unknow primary (CUP)	1 (1.8%)
Most Common Lesions at Baseline	
Lymph nodes	40 (70.2%)
Lung	38 (66.7%)
Liver	26 (45.6%)
Peritoneum	19 (33.3%)
Prior systemic anticancer therapy	
Median Prior Lines (range)	3 (1-7)
Patients with ≥4 Prior Lines (%)	29.8%
Most Common Anti-Cancer agents	
Taxanes	
Paclitaxel	42 (73.7%)
Docetaxel	12 (21.1%)
Platinum Compounds	
Carboplatin	37 (64.9%)
Cisplatin	26 (45.6%)
Monoclonal Antibodies	
Bevacizumab	18 (31.6%)
Folic Acid Analogues	
Pemetrexed Disodium	14 (24.6%)
Other Prior Anticancer Therapies	
Oncological Surgery	38 (66.7%)
Radiotherapy	36 (63.2%)

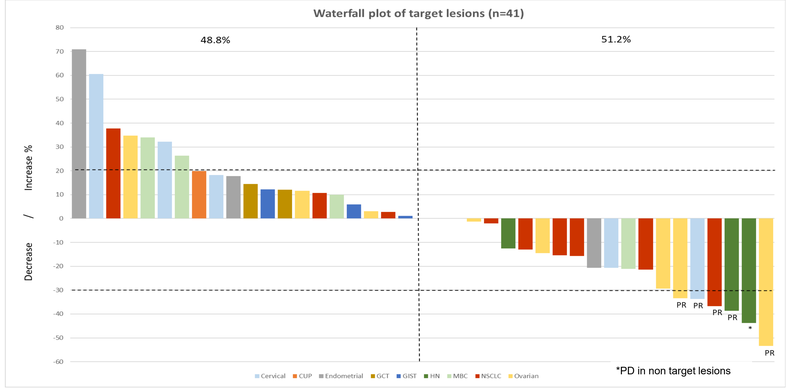
Adverse Events

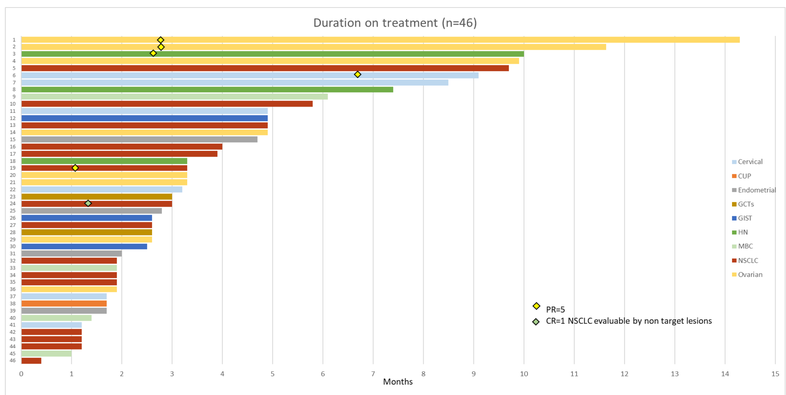
DOSE LEVEL Treated patients (n=55)	1 n=4			2 n=7			3 n=4			4 n=5			5 n=5			6 n=9			7 n=16			8 n=5	
Grade	G2			G2	G3		G2	G3		G2	G3		G2	G3		G2	G3		G2	G3		G2	G3
Diarrhea																1			3	1		1	
Dyspepsia	1																						
Nausea				1						1			3						2	2			
Vomiting								1					1	1		1						1	
Abdominal Pain								1								1				1		1	
Constipation																1							
Hematochezia																1							
Dry mouth																			1				
Intestinal obstruction																							1
Fatigue				2			3			2			2	1		3			4	1		2	1
Pyrexia	1									1													
Weight decreased																			1				
Urinary tract infection	1																						
Decreased appetite							1												3				
Muscular weakness														1					1				
Musculoskeletal pain																			1				
Arthralgia																						1	1
Musculoskeletal stiffness																						1	
Pain in extremity																						1	
Headache																			1				
Neurotoxicity					1														1				
Peripheral sensory N.		1					1						1			1			1			1	
Peripheral Neuropathy																1			2				
Paresthesia																			1				
Alopecia										1												1	
Rash maculo-papular										1													
Skin disorder																			1				
Dyspnea											1												
Pneumonitis																							1
Palpitation										1													

PM060184 PK

Study ID	Infusion Duration	Dose mg/m^2	#	Cmax (µg/L)	AUC last (h*µg/L)	CL (L/h)	HL (h)	Vss (L)
PM060184 –A-003-14	10 min	10	16	665 (524)	430 (241)	49 (20)	4 (1)	131 (57)

Efficacy





Dose Levels and DLT

Dose level	Dose GEM (mg/m^2)	Dose PM060184 (mg/m^2)	No. of patients with DLTs / no. of evaluable patients		DLT
I	800	6.0	0/3		.
II	800	7.0	1/6		Grade 3 neurotoxicity [a,b]
III	1000	7.0	0/3		.
IV	1000	8.0	0/3		.
V	1000	9.0	0/4		.
VI	1000	9.3	1/7		Grade 4 thrombocytopenia [c]
VII	1000	10.0	Overall: 1/13	0/7	.
				Cohort expansion: 1/6	Grade 3 abdominal pain [a]
VIII (MTD)	1000	10.5	1/5		Grade 3 intestinal obstruction [a]

[a] Related to PM060184 [b] G3 peripheral sensory neuropathy [c] Related to both GEM and PM060184

Conclusions

- **The tolerability of the combination of PM060184 and GEM was acceptable.**
- **Main adverse events included nausea, diarrhea, fatigue and peripheral neuropathy.**
- **The MTD was PM060184 10.5 mg/m^2 + GEM 1000 mg/m^2.**
- **The mean CL and Cmax observed for PM060184 at all dose levels were similar to the mean values found for these parameters in previous phase I and II studies (ref 1,2,3), suggesting that GEM had no major effects on the PK of PM060184.**
- **Signs of activity were observed in NSCLC, cervical cancer, and ovarian cancer at different dose levels**

References:
[1] Hidalgo M, et al. Phase I, open-label, dose-escalating clinical and pharmacokinetic study of the novel antimicrotubulin agent PM060184 administered over 10 Minutes on day 1 and 8 every three weeks to patients with advanced malignant solid tumors. Eur J Cancer.
[2] Elez E, et al. First-in-human phase I study of the microtubule inhibitor plocabulin in patients with advanced solid tumors. Invest New Drugs.
[3] Hidalgo M, et al. Phase I, open-label, dose-escalating clinical and pharmacokinetic study of the novel antimicrotubulin agent PM060184 administered over 10 minutes on days 1-3 and 15-17 every 28 days to patients with advanced malignant solid tumors Eur J Cancer.

Contact Information

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