

Abstract #: 210

Phase II Study of a Novel Micellar Paclitaxel Formulation for Treatment of Pancreatic Cancer

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Updated Abstract

Background: Genexol-PM (GPM) is a novel micellar formulation of paclitaxel in a low molecular weight biodegradable synthetic polymer. MTD for GPM in both preclinical and phase I clinical trials is higher than that for Cremophor-based paclitaxel (CBP). Differences in vehicle toxicity and in pharmacokinetics and tissue distribution of paclitaxel may be responsible for the higher MTD. At MTD for each formulation, GPM was more effective than CBP or gemcitabine against several tumor models, including 2 pancreatic cancer (Ca) xenografts.

Methods: Patients (pts) with advanced pancreatic Ca were treated with 3 hr GPM infusions every 21 days. Pts had measurable disease, ECOG PS ≤ 2, no prior chemotherapy and adequate organ function. Initial pts were treated at 435 mg/m² (n=11), which was reduced for subsequent pts to 350 (n=6) or 300 (n=39) mg/m². Response was evaluated by RECIST criteria; pts without disease progression for ≥ 6 weeks were considered to have SD. Pts were considered efficacy evaluable if they received ≥ 2 cycles GPM or progressed at 1 cycle. Time to tumor progression (TTP) was time from first dose to documentation of progression or symptomatic deterioration or death due to disease, whichever occurred first. Progression-free survival (PFS) was time from first dose to documentation of progression or symptomatic deterioration or death, whichever occurred first.

Results: To date of 56 treated pts., all have received ≥ 2 cycles or discontinued. Median age was 64.2 years (range 43.4 to 80.7). 40 (71.4%) were male; 47 (83.9%) were white; 45 (80.4%) had metastatic disease. Adverse events were generally those expected with paclitaxel or related to the patient's underlying condition; they were manageable with standard supportive measures.

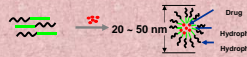
	Dose level, mg/m ²	
	435	300 or 350
N entered	11	45
N available for response	5	37
Cycles therapy, median (range)	1 (1-3)	3 (1-10)
Discontinued due to toxicity, N (%)	7 (63.6)	9 (25.0) [†]
Discontinued due to PD [‡] , N (%)	4 (36.4)	27 (47.2) [†]
Ongoing, N (%)	0	4
Best response: CR, N (%)	0	1 (2.7)
PR, N (%)	0	2 (5.4)
SD, N (%)	2 (40)	21 (56.8)
TTP, months, median (95% CI)	1.3 (0.6, 3.7)	3.0 (1.4, 3.9)
PFS, months, median (95% CI)	1.3 (0.6, 3.7)	2.8 (1.4, 3.9)
OS, months, median (95% CI)	2.5 (2.0, 7.9)	10.0 (5.4, not reached)

[†] Including symptomatic deterioration, death due to disease
[‡] Data regarding discontinuation are available for only 36 patients in the 300/350mg/m² group.

Conclusions: Treatment of advanced pancreatic Ca with GPM was generally well tolerated and resulted in PFS similar to that seen historically with gemcitabine. Confirmation of activity awaits combination and/or comparison studies.

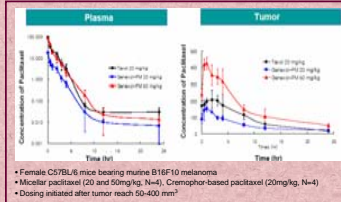
Background

- Advanced pancreatic cancer is poorly responsive to chemotherapy.
- Cremophor-based paclitaxel, as well as docetaxel, have been tested for treatment of advanced pancreatic cancer, with occasional responses but considerable toxicity.
- A novel polymeric micellar (PM) formulation of paclitaxel (GPM) has been developed.
 - Hydrophilic shell, Hydrophobic core
 - methoxypoly(ethylene glycol)-block-poly(D,L-lactide) (mPEG-PDLLA)



- GPM does not use Cremophor and avoids certain toxicities of that excipient.
- GPM increases the ratio of paclitaxel tumor/blood concentration.
- GPM allows use of a higher dose of paclitaxel as compared to Cremophor formulation.

Pharmacokinetics of Polymeric Micellar Paclitaxel



• Female C57BL/6 mice bearing murine B16F10 melanoma
 • Micellar paclitaxel (20 and 50mg/kg, N=4), Cremophor-based paclitaxel (20mg/kg, N=4)
 • Dosing initiated after tumor reach 50-400 mm³

Materials and Methods

- Patients:
 - Unresectable or metastatic cancer of the exocrine pancreas
 - No prior chemotherapy
 - ECOG PS 0 through 2
- Treatment
 - 3 hour infusions every 21 days
 - First 11 patients received 435 mg/m²
 - 6 received 300 mg/m²
 - 6 received 350 mg/m²
 - 33 subsequent patients received 300 mg/m²
 - Starting with patient 36, all patients received dexamethasone prophylaxis prior to each infusion.
- Periodic safety labs, physical examinations
- Tumor assessment by RECIST criteria at the end of every 2 cycles

Demographics and Disease Characteristics

	Dose level, mg/m ²	
	435	300 or 350
N entered	11	45
Age, median (Range)	68.3 (49.2 - 80.2)	63.6 (43.4 - 80.7)
Gender, male, N (%)	9 (81.8)	31 (68.9)
Ethnicity, white, N (%)	9 (81.8)	38 (84.4)
Duration of disease, median (Range)	0.6 (0.3 - 11.7)	0.8 (0.2 - 9.0)
Melanistic disease, N (%)	10 (90.9)	35 (77.8)
ECOG PS, 0 or 1, N (%)	11 (100.0)	41 (91.1)
Prior radiation therapy, N (%)	1 (9.1)	1 (2.2)
Prior therapeutic surgery, N (%)	3 (27.3)	10 (22.2)

Treatment Administered

	Dose level, mg/m ²	
	435	300 or 350
N entered	11	45
Discontinued due to toxicity, N (%)	7 (63.6)	9 (25.0) [†]
Discontinued due to PD [‡] , N (%)	4 (36.4)	27 (47.2) [†]
Duration of GPM treatment (weeks), median (range)	3.0 (3 - 9)	9.0 (3 - 30)
Cumulative dose of GPM (mg/m ²), median (range)	435 (431 - 1,065)	730 (131 - 3,002)
Dose intensity of GPM (mg/m ² /week), median (range)	144 (116 - 145)	100 (44 - 124)
Relative dose intensity of GPM, median (range)	99.3 (81 - 100)	100 (38 - 124)

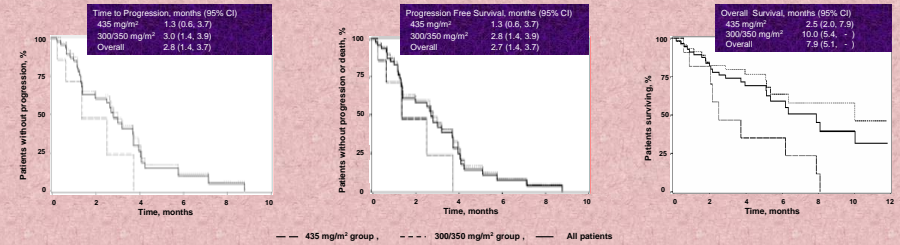
[†] Including symptomatic deterioration, death due to disease
[‡] Data regarding discontinuation are available for only 36 patients in the 300/350mg/m² group.

Response to Therapy

	Dose level, mg/m ²	
	435	300 or 350
N entered	11	45
Complete Response (CR), N (%)	0	1 (2.2)
Partial Response (PR), N (%)	0	2 (4.4)
CR+PR, N (%)	0	3 (6.7)
Stable disease (SD), N (%)	2 (18.2)	23 (51.1)
Progressive disease (PD), N (%)	3 (27.3)	36 (80.0)
Inevaluable, N (%)	8 (54.5)	8 (17.8)
CR or PR or SD, N (%) (95% CI)	2 (18.2) (2.3, 51.8)	26 (57.8) (42.2, 72.3)

[†] EE: Efficacy Evaluable

Time to Progression, Progression Free Survival, Overall Survival



Time to Progression, months (95% CI)
 435 mg/m²: 1.3 (0.6, 3.7)
 300/350 mg/m²: 3.0 (1.4, 3.9)
 Overall: 2.8 (1.4, 3.7)

Progression Free Survival, months (95% CI)
 435 mg/m²: 1.3 (0.6, 3.7)
 300/350 mg/m²: 2.8 (1.4, 3.9)
 Overall: 2.7 (1.4, 3.7)

Overall Survival, months (95% CI)
 435 mg/m²: 2.5 (2.2, 7.9)
 300/350 mg/m²: 10.0 (5.4, -)
 Overall: 7.9 (5.1, -)

Adverse Events Occurring in ≥ 20% of Study Patients

	Dose level, mg/m ²		Overall	
	435 (N=11)	300 or 350 (N=45)	(N=56)	
Neutropenia	6 (54.5)	18 (40.0)	14 (31.1)	24 (42.9)
Abdominal pain	1 (9.1)	4 (8.9)	4 (8.9)	15 (26.8)
Constipation	3 (27.3)	11 (24.4)	14 (25.0)	0
Diarrhea	1 (9.1)	2 (4.4)	17 (30.4)	2 (3.6)
Nausea	6 (54.5)	17 (37.8)	23 (41.1)	3 (5.4)
Vomiting	6 (54.5)	2 (4.4)	23 (41.1)	2 (3.6)
Fatigue	1 (9.1)	20 (44.4)	21 (37.5)	8 (14.3)
Pruritus	4 (36.4)	7 (15.6)	11 (19.6)	0
Hypersensitivity	1 (9.1)	12 (26.7)	13 (23.2)	4 (7.1)
Anorexia	3 (27.3)	14 (31.1)	17 (30.4)	2 (3.6)
Dehydration	2 (18.2)	11 (24.4)	13 (23.2)	6 (10.7)
Antralgia	1 (9.1)	10 (22.2)	11 (19.6)	0
Dysgeusia	0 (0.0)	11 (24.4)	11 (19.6)	0
Neuropathy	4 (36.4)	26 (57.8)	30 (53.6)	9 (16.1)
Dyspnea	0 (0.0)	11 (24.4)	11 (19.6)	3 (5.4)
Alopecia	0 (0.0)	23 (51.1)	23 (41.1)	1 (1.8)
Rash	4 (36.4)	8 (17.8)	12 (21.4)	1 (1.8)

Time to Development of Neurotoxicity ≥ Grade 2

	Dose level, mg/m ²		Overall
	435	300 or 350	56
N entered	11	45	56
N developed ≥ grade 2 neuropathy (%)	4 (36.4)	13 (28.9)	18 (32.1)
Cumulative dose (mg/m ²) to development of grade 2 neuropathy, median (95% CI) Range	431 [†] - 790 [†]	1,757 (1,056 - 3,002) - 131 [†] - 3,002	1,757 (1,020 - 3,002) - 131 [†] - 3,002
Time (months) to development of grade 2 neuropathy, median (95% CI) Range	0.0 - 2.5 [†]	4.7 (2.8 - 6.5) - 0.0 [†] - 6.5	3.6 (2.8 - 6.5) - 0.0 [†] - 6.5

[†] Censored observation

Conclusion

- Micellar paclitaxel at a dose of 300 mg/m² every 3 weeks was well tolerated:
 - 350 mg/m² was tolerable but more toxic than the lower dose.
 - 435 mg/m², used initially in the study, was poorly tolerated.
- Efficacy endpoints in patients treated with 300 or 350mg/m² (ITT population):
 - Median TTP: 3.0 months (95% CI: 1.4, 3.9)
 - Median PFS: 2.8 months (95% CI: 1.4, 3.9)
 - Median overall survival: 10.0 months (95% CI: 5.4, not reached)
- Common toxicities qualitatively similar to Cremophor-based paclitaxel
- In patients receiving 300 or 350mg/m²:
 - Most common acute toxicity: neutropenia, grade 4 in 15.6% of patients
 - Grade 2 neuropathy developed after a median dose of 1,757 mg/m² or approximately 6 courses of therapy.
- TTP similar to single agent gemcitabine but median survival longer, as compared to historical data:
 - Many patients censored for survival, but lower end of 95% CI for current study similar to median survival for single agent gemcitabine.
 - Several patients received subsequent therapy with gemcitabine and other agents.
- Overall survival and other efficacy parameters show efficacy compared to historical controls, suggesting further study of micellar paclitaxel for the treatment of pancreatic cancer.