



# Dose-ranging study of the combination of paclitaxel poliglumex and pemetrexed in advanced non-small cell lung cancer (NSCLC)

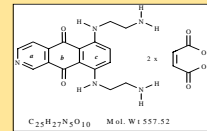
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## BACKGROUND AND OBJECTIVES

Lung cancer remains the leading cause of cancer-related death in the U.S. Five-year survival rates are less than 7%, and have improved little over the past two decades despite the introduction of newer agents. Patients with advanced NSCLC and a good performance status benefit from chemotherapy, with platinum plus paclitaxel considered standard front-line treatment and docetaxel-platinum also showing activity. However, these combinations are not without substantial toxicity. Myelosuppression and peripheral neuropathy are common, and alopecia is nearly universal. Because paclitaxel is not water-soluble, it must be delivered in polyoxyethylated castor oil and alcohol (Cremophor EL), which can cause life-threatening hypersensitivity reactions. Docetaxel does not require the Cremophor vehicle, but grade 3 hypersensitivity reactions occur in about 9% of patients despite dexamethasone premedication.

This study evaluated pemetrexed and paclitaxel poliglumex, a unique regimen with potentially improved efficacy and reduced toxicity in advanced NSCLC. Pemetrexed (Alimta, Eli Lilly & Company) is a multitargeted antifolate approved for treating mesothelioma in combination with cisplatin and as single-agent therapy for NSCLC.

Paclitaxel poliglumex (formerly CT-2103; Xyotax™, Cell Therapeutics, Inc.) is an ester conjugate of paclitaxel bound covalently to  $\alpha$ -poly-L-glutamic acid (PG), a biodegradable polymer of the natural amino acid L-glutamic acid.



Drug delivery advantages of paclitaxel poliglumex include:

- Soluble in aqueous solution - does not require Cremophor or ethanol
- Not significantly released from PG backbone in plasma
- Higher concentration delivered to tumor tissue with prolonged clearance

Paclitaxel poliglumex has shown promising activity in preclinical and clinical studies and is currently in phase III development for ovarian cancer, lung cancer, and hematologic malignancies. Treatment-related hematologic adverse events are common, but generally manageable. Cardiac adverse events have occurred, primarily in patients heavily pretreated with anthracyclines, but clinical review to date has not demonstrated a clear pattern of treatment-related causality.

## STUDY OBJECTIVES

**Primary Objective:** Evaluate the safety and adverse event profile of this combination therapy.

**Secondary Objectives:** Evaluate duration of response (RECIST criteria), TTP and overall survival

## STUDY METHODS AND ELIGIBILITY

This was a single-arm, single-institution, open-label dose escalation study. An initial-dose-limiting toxicity (IDLT) was defined as a clinical observation in the first 2 cycles that, in the investigator's judgment, was attributable to the administration of paclitaxel poliglumex and pemetrexed and necessitated reduction, suspension or discontinuation of study drug because of a NCI CTC grade 3 or 4 toxicity or serious adverse event.

Dose Levels		
	Cohort 1 (n=6)	Cohort 2 (n=6)
<b>21-day cycles</b>		
paclitaxel	135 mg/m <sup>2</sup>	175 mg/m <sup>2</sup>
poliglumex (day 1)		
pemetrexed (day 1)	500 mg/m <sup>2</sup>	500 mg/m <sup>2</sup>

Six patients were initially to be enrolled in Cohort 1. If 2 or more patients in the first cohort had an IDLT with 2 cycles of therapy, the MTD was considered to have been surpassed and the study was to be terminated. If 0-1 patients had an IDLT, the dose was to be escalated for the next cohort provided the safety and monitoring committee gave approval.

The recommended phase 2 dose (MTD) was defined as the highest dose at which no more than 1 of 6 patients experienced an IDLT. Safety assessments were scheduled prior to each treatment and 5-10 days after each cycle. Efficacy was evaluated with CT/MRI scans after every 2 cycles and response characterized per RECIST criteria. Patients who progressed were withdrawn. Patients without progression who withdrew because of toxicity were to be assessed every 8 weeks until progression. All patients were followed for overall survival.

## ELIGIBILITY CRITERIA

- Able to provide written informed consent
- Histologically or cytologically confirmed diagnosis of locally advanced and/or metastatic NSCLC (stage IIIB or IV)
- Bidimensionally or unidimensionally evaluable lesion; at least one measurable target lesion as defined by RECIST not previously treated with local therapy
- Age  $\geq$  18 years and ECOG performance status 0-2
- Prior chemotherapy (including taxanes) for advanced NSCLC permitted
- Life expectancy > 12 weeks
- No active infection
- Adequate liver and bone marrow function
- Treated brain metastases must be neurologically stable
- At least 3 weeks since last chemotherapy and/or radiotherapy and all treatment-related adverse events recovered to  $\leq$  grade 1
- Negative pregnancy test for WOBBCP; fertile couples must use contraception
- Bisphosphates already begun could be continued but not initiated on study

## RESULTS

### Patient Demographics and Baseline Disease Characteristics

	Cohort 1 (n=6)	Cohort 2 (n=6)	Overall (N=12)
Male	4	4	8 (67%)
Female	2	2	4 (33%)
Stage IIIb	1	0	1 (8%)
Stage IV	5	6	11 (92%)
PS 0	1	1	2 (17%)
PS 1	4	5	9 (75%)
PS 2	1	0	1 (8%)
Age - Median	68.5	59	64.25
Age Range	54-73	48-74	48-74

Twelve patients were enrolled, 6 to each dose level. Four patients were female, median age was 65 years (48-74), 11 were PS 0-1, and only 1 patient had prior chemotherapy. None of the 6 patients in the initial dose cohort had an IDLT with 2 cycles of therapy, and the next 6 patients were enrolled at the second dose level.

A median of 4.5 cycles was delivered in each cohort.

There was one IDLT of infection with neutropenia at the 2<sup>nd</sup> dose level. Aside from grade 3 fatigue in 2 patients, there were no grade 3 or greater nonhematologic toxicities. Common nonhematologic toxicities included peripheral neuropathy, constipation, fatigue, and alopecia.

The best response was stable disease in 9 patients. Two patients remain without evidence of disease progression, and 6 patients are alive to date. Median progression free survival was 3.3 months (range 0.7-10.7 months).

Drug Exposure			
	Cohort 1 (n=6)	Cohort 2 (n=6)	Overall (N=12)
Median Cycles Received	4.5	4.5	4.5
Range	2-12	1-7	1-12
$\leq$ 2 cycles	2	2	4 (33%)
3-6 cycles	2	3	5 (42%)
$\geq$ 7 cycles	2	1	3 (25%)

Response			
	Cohort 1 (n=6)	Cohort 2 (n=6)	Overall (N=12)
<b>Best Response</b>			
SD	5	4	9 (75%)
PD	1	2	3 (25%)
Median PFS and range (months)	3.795 1.5-9.25	2.865 0.7-10.5*	3.22 0.7-10.5

\* Two patients in cohort 2 remain with stable disease

Safety and Toxicity			
	Cohort 1 (n=6)	Cohort 2 (n=6)	Overall (N=12)
Treatment-related AEs $\geq$ grade 3	0	4	4 (33%)
<b>Reasons for Discontinuing Study</b>			
clinical deterioration or progressive disease	5	4	9 (75%)
withdrew consent	1	1	2 (17%)
physician discretion	0	1	1 (8%)
Deaths $\leq$ 30 days of study treatment	5	1	6 (50%)
	2	1	3 (25%)

## CONCLUSIONS

The combination of paclitaxel poliglumex and pemetrexed was well tolerated at the proposed phase II dose of 175 mg/m<sup>2</sup> and 500 mg/m<sup>2</sup>. The PFS is encouraging and future studies of this combination are recommended.