Phase I Study of Intravenous (IV) Milataxel in Adult Patients with Advanced Malignant Tumors

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Abstract

Background: M (TL139, MAC-321) is a novel taxane with activity in human xenograft models against tumors resistant to paclitaxel. The maximum tolerated dose (MTD) when given IV every 3 weeks was 35 mg/m². The current study was designed to determine if the dose intensity of M could be increased by a weekly IV schedule.

Methods: The primary objective of the study was to determine the maximum tolerated dose (MTD), the dose limiting toxicity (DLT) and the recommended dose (RD) for phase II. Secondary objectives were pharmacokinetic (PK)/pharmacodynamic (PD) parameters of M given IV weekly and a preliminary estimate of efficacy in an expanded cohort at the RD. Key pt eligibility criteria included in adult pts with refractory malignant tumors, ECOG PS <3 and adequate hematologic, hepatic and renal function. Patients were not allowed concurrent strong inhibitors of cytochrome p450 3A4. Dose escalation was based on Fibonacci method. At the RD, additional pts with tumors that typically respond to taxane treatment were added. PK data were obtained on day 1 and 15.

Results: A total of 32 pts were treated, 15 (6 females, 9 males) in the dose escalation part and 17 (15 females, 2 males) in the MTD confirmation part. The median number of doses was 11 (range 1-18). In the dose escalation phase, 3, 4, and 3 pts were treated at 8, 12, and 16 mg/m² IV weekly without DLT. At 20 mg/m², 2 of 5 pts developed DLT (1 pt - myalgia and neuropathy, 1 pt grade 4 neutropenia > 5 days in duration). The RD was 16 mg/m² weekly. 17 more pts were treated at the RD. The most frequent grade 3 or 4 adverse events were asthenia (19%), nausea (9%), parethesia (9%) and neuropathy (9%). Of the 10 pts with breast cancer who were evaluable for response, one had a PR. Another breast cancer pt with a PR was a protocol violation and was not evaluable. In 20 pts at the MTD, the Tmax was 4 hr, the Cmax was 51.97 ng/mL, AUC 2711 ng*hr/mL, and the Vss was 1496 L/m².

Conclusions: Milataxel had an RD of 16 mg/m² IV per week. Objective responses were observed in pts with metastatic breast cancer.

Background

- Milataxel is a novel taxane that is more potent than the currently marketed taxanes *in vitro*, with a lower IC_{50} against most tumor cell lines, including cell lines with resistance to paclitaxel and docetaxel.
- Milataxel is highly effective in mouse tumor models (using human xenografts) compared with paclitaxel and docetaxel, often producing curative effects after a single dose.
- Milataxel is more soluble than either paclitaxel or docetaxel and thus may be administered in less toxic vehicles which do not require pre-medications.

Methods

Study Objectives

Primary

- To determine the MTD and the DLT of weekly IV administration of milataxel when given as a 4-hour infusion (Part 1).

Secondary

- To assess the safety and pharmacokinetic profiles of single-agent milataxel when given as a weekly infusion.
- To obtain preliminary information on the antitumor activity of weekly infusions of milataxel in patients with advanced malignant tumors.
- To confirm the safety and tolerability at the MTD.
- To determine the MTD, DLTs and clinical activity of weekly IV administration when given as a shortened (i.e., 1-hour) infusion (Part 2) to patients with advanced malignant tumors, if elected by the sponsor.

Key Inclusion Criteria

- Adult patients with refractory malignant tumors
- Measurable disease (per RECIST)
- ECOG PS=0, 1, or 2
- Adequate hematologic, hepatic and renal function

Key Exclusion Criteria

- Symptomatic CNS metastases
- More than 2 lines of chemotherapy for metastatic disease (beyond any adjuvant/neoadjuvant chemotherapy)

Results

Three Populations Were Defined for Analysis

1. MTD1: all patients treated at the MTD dose level defined during the dose escalation phase, the objective of this group was to confirm the MTD
2. All Treated: all patients that received at least one dose of milataxel
3. Breast cancer evaluable: all patients from MTD1 with metastatic breast cancer evaluable for response according to the criteria prospectively defined in the protocol. (While 13 patients with breast cancer were treated in this cohort, three of the patients had adjuvant only and therefore were not included in this population.)

Demography

Characteristic	Treated N=32 (%)	MTD1 N=17 (%)	Breast Cancer Evaluable N=10 (%)
Gender			
Female	21 (66)	15 (88)	10 (100)
Male	11 (34)	2 (12)	--
Race			
Caucasian	32 (100)	17 (100)	10 (100)
Age (years)			
Mean (± SD)	60.94 (± 9.33)	60.82 (± 10.33)	62.8 (± 10.02)
Minimum	41	41	48
Maximum	76	76	76
Weight (kg)			
	N=26	N=13	N=8
Mean (± SD)	68.62 (± 17.11)	66.74 (± 13.37)	68.06 (± 12.47)
Minimum	46	48	49.9
Maximum	112	92	84

Primary Cancer Diagnosis

Primary Diagnosis	Treated N=32 (%)	MTD1 N=17 (%)	Breast Cancer Evaluable N=10 (%)
Breast	15 (47)	13 (76)	10 (100)
Colorectal	3 (9)		
Gastric	2 (6)	1 (6)	
NSCLC	1 (3)	1 (6)	
Esophagus	1 (3)		
Suspect for bronchus	1 (3)		
Thyroid	1 (3)		
Vaginal melanoma	1 (3)		
Small cell lung	1 (3)		
Ovarian	2 (6)	2 (12)	
Prostate	1 (3)		
Renal	2 (6)		

Baseline Disease Characteristics

Characteristic	Treated N=32 (%)	MTD1 N=17 (%)	Breast Cancer Evaluable N=10 (%)
ECOG Performance Status			
0	15 (47)	10 (59)	6 (60)
1	15 (47)	6 (35)	3 (30)
2	2 (6)	1 (6)	1 (10)
Liver Lesions (baseline)			
No	15 (47)	8 (47)	5 (50)
Yes	17 (53)	9 (53)	5 (50)
Prior Chemo/Immuno/Hormone Therapy			
No	1 (3)		
Yes	31 (97)	17 (100)	10 (100)
Number of Prior Chemo Regimens			
0	8 (25)	5 (29)	
1	10 (31)	5 (29)	4 (40)
2	13 (41)	6 (35)	
3	1 (3)	1 (6)	6 (60)
Prior Taxane Therapy			
No	21 (66)	8 (47)	5 (50)
Yes	11 (34)	9 (53)	5 (50)
Prior Radiotherapy			
No	12 (37)	5 (29)	1 (10)
Yes	20 (63)	12 (71)	9 (90)
Prior Cancer-Related Surgery			
No	4 (12)	1 (6)	1 (10)
Yes	28 (88)	16 (94)	9 (90)

Dose Escalation

Dose Level (mg/m²)	Number of Patients
8	3
12	4
16	20
20	5

- During the dose escalation phase, no dose limiting toxicity was seen at dose levels of 8 mg/m², 12 mg/m² or 16 mg/m². Two of five patients treated with milataxel 20 mg/m² every week had dose limiting toxicity. One patient had grade 4 neutropenia in excess of 5 days and a second patient developed grade 3 neuropathy and myalgia. A second portion of the study enrolled an additional 17 patients to confirm the maximum tolerated dose of 16 mg/m² every week and to obtain a preliminary efficacy assessment. The maximum tolerated dose was confirmed as 16 mg/m² every week.
- Patients with evidence of clinical benefit at the end of cycle 6 (stable disease or better) could continue to receive additional cycles of milataxel after consultation with the sponsor.

Efficacy by Subgroup

Parameter	Treated N (%)	Breast Cancer Evaluable N (%)
Number of Patients	32	10
PR	3 (9%)	2 (20%)
SD	14 (44%)	4 (40%)
PD	11 (34%)	4 (40%)
Unknown/NA	4 (13%)	--

Neutropenia

Cycle	ANC Grade 3 or 4	ANC Grade 4
Cycle 1 N=32 (%)	2 (6%)	1 (3%)

- Of the patients who developed grade 3 or 4 neutropenia during cycle 1 or 2, one patient (0019) developed grade 3 neutropenia without fever and one patient (0028) developed grade 4 neutropenia with fever and discontinued from treatment due to neutropenic fever.

Neuropathy

- Patients had a neurological examination performed and recorded at each cycle.
- Of the 32 patients treated, 19 patients had parethesia or neuropathy reported.
  - One patient (0006) with grade 2 neuropathy due to Horner's syndrome, not related to treatment.
- 5 patients developed grade 3 neuropathy.
  - All of these patients were discontinued from treatment, 4 for neuropathy and 1 for asthenia.
  - In the 4 patients discontinued due to neuropathy, the neuropathy improved in 3 cases (1 pt to grade 1 one month after last dose, 2 patients to grade 2 two months after last dose). One patient died 30 days later with persisting paresthesia.
- 6 patients with grade 2 neuropathy, 1 patient required a dose reduction and was not withdrawn from study and 4 patients were discontinued due to neuropathy without dose reduction.
- 7 patients reported paresthesia or neuropathy with a worst severity of grade 1.

Summary of Adverse Events

Adverse Event	Related TEAEs N=32 (%)	Related Grade 3/4 TEAEs N=32 (%)
Asthenia	19 (59)	6 (19)
Nausea	14 (44)	3 (9)
Diarrhea	14 (44)	1 (3)
Paresthesia	13 (41)	3 (9)
Anorexia	11 (34)	2 (6)
Vomiting	11 (34)	2 (6)
Neuropathy	8 (25)	3 (9)
Myalgia	8 (25)	1 (3)

Secondary Parameters

- The number of patients demonstrating clinical benefit (i.e., CR, PR, and SD) was 17/32 (53%).

Exposure to Test Medication

- Thirty-two patients in the study received at least one dose of milataxel. The median number of continuous doses received was 11 (range 1-30). Twenty-four patients completed at least 6 cycles of treatment. The median total dose received was 144 mg/m² (range 16-360 mg/m²).

Pharmacokinetics

- In 20 patients treated at the MTD:
- T_{max} = 4 hrs
- C_{max} = 51.97 ng/mL
- AUC = 2711 ng•hr/mL
- Vss = 1496 L/m²

Discussion

- The maximum tolerated dose was confirmed as 16 mg/m² every week.
- The incidence of neutropenia was low at the MTD; only one patient developed grade 3 or 4 neutropenia during the first two cycles.
- The major dose limiting toxicity was peripheral neuropathy. The event was primarily sensory with only two patients with motor neuropathy.
- The relatively low rate of neutropenia compared to the higher incidence of neuropathy is consistent with data on other taxanes. In the current study, milataxel was given every week without break. In clinical studies with other taxanes given weekly, breaks have been added to the schedule to reduce the incidence of the non-hematological toxicities.
- Objective responses were observed in three patients in the study. A total of ten breast cancer patients were considered evaluable for response as per the protocol specific criteria. Two of these patients had partial responses for an overall response rate of 20%.

Conclusions

- Milataxel had a recommended dose of 16 mg/m² IV per week. Objective responses were observed in patients with metastatic breast cancer.

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