MBP-426, a novel liposome-encapsulated oxaliplatin, in combination with 5-FU/leucovorin (LV) – Phase I results of a Phase I/II study in gastro-esophageal adenocarcinoma, with pharmacokinetics

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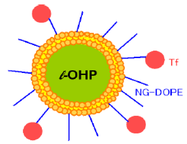
Abstract #C36

Introduction

MBP-426 is a liposomal drug product in which the drug substance oxaliplatin is encapsulated within a liposome, and human transferrin is attached to the liposome surface. The lipid is organized as a bilayer with an acceptable range of the principal peak between 50-200 nm.
The transferrin-conjugated liposomal oxaliplatin formulation MBP-426 was developed to improve the safety and efficacy of oxaliplatin through the prolongation of drug circulation time in plasma and by targeting transferrin receptors on tumor cells.



50 – 200 nm

MBP-426 has shown efficacy in non-clinical *in vivo* studies using the following human xenograft tumor models: MX-1 (breast), HCT-116 (colon), HT-29 (colon), MKN45 (gastric), COLO 205 (colon), NCI-N87 (gastric), and PANC-1 (pancreas).

A previous phase I clinical study (Sankhala et al, 2009) reported the exploration of MBP-426 as a single agent in solid tumors. MBP-426 was administered by 2-hr IV infusion q3w. This dose-finding study explored doses from 6 mg/m² to 400 mg/m² in 39 patients. Thrombocytopenia was the dose limiting toxicity, with DLTs reported in one patient treated at 226 mg/m² (grade 4 thrombocytopenia), and 2 patients at 400 mg/m² (grade 4 thrombocytopenia, and grade 2 thrombocytopenia lasting >14 days); 226 mg/m² was the recommended dose for phase II studies.

The current phase I-II study was designed to establish the RD of MPB-426 in combination with 5-FU/LV (de Gramont schedule) and assess the efficacy of this combination in second-line patients with gastro-esophageal (GE) adenocarcinoma. Here we report the phase I data.

Study Objectives

Primary Objective

Phase Ib: To determine the RD of MBP-426 in combination with 5-FU/LV (de Gramont schedule) administered every 21 days.

Phase II: To measure the objective tumor response rate (RECIST) in patients with second line metastatic gastric, gastro-esophageal junction, or esophageal adenocarcinoma.

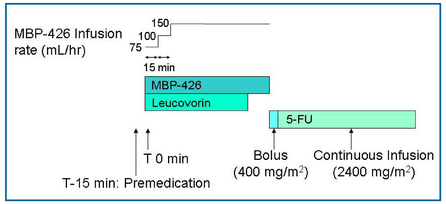
Secondary Objectives

Phase Ib: • To characterize the safety profile
• To undertake a preliminary exploration of anti-tumor activity of
• To determine the plasma and urine pharmacokinetics of MBP-426 in combination with 5-FU/LV

Phase II: • To characterize the safety profile of the combination therapy

Study Design

- Phase Ib/II, open-label, non-randomized, single arm study of MBP-426 in combination with 5-FU/LV (de Gramont regimen).
- MBP-426 is administered every 21 days as an IV infusion with a starting dose of 226 mg/m².
- MBP-426 is provided in 30 mL vials containing 24 mg. No dilution is required. MBP-426 infusion rate will start at 75 mL/hr for 15 minutes, will increase to 100 mL/hr for the next 15 minutes, and then increase to a maximum of 150 mL/hr for the remainder of drug administration.
- Following MBP-426 administration, leucovorin (400 mg/m²) is administered with an IV bolus of 400 mg/m² fluorouracil, followed by 2400 mg/m² fluorouracil continuous IV (CIV) infusion over 46 hours.



Prophylactic medication
Patients are premedicated 15 minutes prior to MBP-426 infusion as follows: 10 mg dexamethasone (IV), 8 mg Zofran, and 25 mg Benadryl.

Dose escalation
In the Phase Ib portion of this study, the first cohort of patients were to receive MBP-426 at a dose of 226 mg/m². Subsequent patients were to be treated at doses in accordance with the table below.

Dose escalation was to follow a standard 3+3 paradigm. The MTD is defined as the dose level below that which produces DLTs in at least one-third of evaluable patients during Cycle 1.

-1 Dose de-escalation	170 mg/m²
MBP-426 STARTING DOSE	**226 mg/m²**
Intermediate dose	263 mg/m²
+1 Dose Escalation	301 mg/m²

Dose Limiting Toxicity (defined during Cycle 1)
Grade 4 neutropenia persisting for at least 5 days;
Grade 3 to 4 neutropenia associated with fever ≥38.5°C, IV antibiotics, or hospitalization for infection;
Grade 4 thrombocytopenia persisting for at least 5 days or Grade 3 thrombocytopenia with bleeding and need for platelet transfusions;
Grade ≥ 3 diarrhea persisting for more than 24 hours in spite of optimal medical management
Any other Grade ≥ 3 non-hematological toxicity considered related and clinical relevant

Dose Modification and Re-Treatment
On the planned day of treatment, chemotherapy may only be administered if:
•the neutrophil count is >1.5 x10⁹/L
•the platelet count is >100 x10⁹/L
•other chemotherapy-related toxicity < grade 1 (except for alopecia and acne-like rash)
If dosing is delayed for longer than 2 weeks, the patient will be removed from study.

Eligibility Criteria

Inclusion criteria

Phase Ib:
- Advanced or metastatic solid tumor malignancy that is refractory to standard therapy or for which conventional therapy is not reliably effective, or no effective therapy is available.
- Measurable disease as defined by RECIST.
- Age 18 years or older.
- ECOG PS of 0, 1, or 2.
- Adequate organ and system function defined by the following parameters:
  - Bone marrow: (ANC of ≥1500/mm³, platelet count ≥100,000/mm³, and HB ≥9 g/dL;
  - Coagulation: PT <1.3 x ULN, PTT >LLN, <1.1 x ULN;
  - Renal: Serum creatinine of ≤1.5 x ULN or calculated creatinine clearance ≥60 mL/min/1.73m²;
  - Hepatic: Total bilirubin ≤1.5 mg/dL, ALT and AST ≤2.5 x ULN (or 5 x ULN in the case of liver metastases), and alkaline phosphatase ≤2.5 x ULN (or 5 x ULN in the case of liver metastases)
- Recovered to ≤Grade 1 from all acute toxicities
- If of childbearing potential, agree to use an effective method of contraception.
- Provide written informed consent.

Phase II:
- Inoperable, histologically, or cytologically confirmed, locally advanced or metastatic gastric, gastro-esophageal junction, or esophageal adenocarcinoma that has recurred or progressed following 1 prior chemotherapy.
- Measurable disease as defined by RECIST.

Exclusion Criteria

Phase Ib and II:
- Radiotherapy or major surgery within 14 days prior to study enrollment.
- Anticancer therapy (chemotherapy, radiotherapy, hormonal therapy, immunotherapy, or investigational agents) within 30 days of enrollment (6 weeks for mitomycin C).
- Known or clinical evidence of central nervous system (CNS) metastases.
- Receiving high-dose steroids (more than a dexamethasone-equivalent dose of 4 mg per day).
- Current active infections or significant intercurrent illnesses.
- Documented or known hematologic malignancy and/or bleeding disorder.
- Peripheral neuropathy ≥ grade 2 (NCI-CTCAE, Version 3.0).
- Any requirement(s) for therapeutic anticoagulation (low dose deep vein thrombosis [DVT] or line prophylaxis is allowed).
- History of allergy to any of the treatment components (oxaliplatin, 5-FU, folinic acid, liposome, ferritin).

Study Design (continued)

Pharmacokinetic assessments
Clinical PK studies were performed for all patients treated in the phase Ib part.

Sampling schedule
- Cycle 1: Baseline, end of infusion, then 0.5, 1, 2, 4, 8, 24, 48, and 72 hr after the end of the infusion
- Cycle 2: Baseline, end of infusion, then 0.5, 1, 2, 4, and 8 hr after the end of the infusion

Efficacy assessment
Efficacy was assessed according to RECIST at the end of every 2 cycles. Confirmatory scans were obtained > 4 weeks after documentation of an objective response.

Safety

PATIENT CHARACTERISTICS
Between May and September 2009, a total of 10 patients were included and treated in the phase I part of the study. A total of 14 cycles were administered at the starting dose of 226 mg/m², and 16 cycles were administered at the lower dose of 170 mg/m². Most of the treated patients had received some prior platinum-based treatment, and 4 patients were oxaliplatin resistant.

Table 1. Patient characteristics

	N
N patients included / treated	10 / 10
Dose Level 226 mg/m²	6
Dose Level 170 mg/m²	4
Age, median (range)	60.5 (44-67)
Sex M / F	5 / 5
PS 0 / 1 / 2	2 / 8 / 0
Primary tumor	
CRC	5
Pancreas	2
Cervix	1
HyN	1
Bladder	1
N metastatic sites, median	2
Number of previous systemic lines, median (range)	4 (2-10)
Previous platinum-based treatment	9
Oxaliplatin resistant	4

DLTs AND DETERMINATION OF THE MAXIMUM TOLERATED DOSE

Two dose levels were explored: 226 and 176 mg/m². Two patients experienced DLT at the starting dose level of 226 mg/m² MBP-426. Enrollment continued at the next lowest dose level (170 mg/m²); 6 patients were included and treated at this dose level, with no DLTs observed. Thus 170 mg/m² is the recommended dose to be used with FU/Leucovorin (de Gramont regimen), and is currently being explored in the phase II part of the study.

Table 2. Incidence of DLT

Patient	Tumor	Cycles	DLT	Reason for Discontinuation
Dose level 226 mg/m²				
#01	CRC	4	NO	G3 Erythema Multiforme at Cycle 4
#02	Bladder	1	G3 Nausea-Vomiting	GI toxicity
#03	Pancreas	5	NO	Progression
#04	CRC	4	G3 Back and Abdominal Pain	Progression
Dose level 170 mg/m²				
#05	Cervix	4	NO	On Study
#06	Pancreas	3	NO	Progression
#07	CRC	2	NO	Progression
#08	CRC	4	NO	On Study
#09	HyN	1	NO	Non-compliance with protocol
#10	CRC	2	NO	On Study

Safety (continued)

At dose level 226 mg/m², during the first cycle, an episode of back pain (probably related to the liposomal formulation) and grade 3 nausea-vomiting were the dose limiting toxicities. However, the observation of more cycles showed that the most frequent severe toxicity was thrombocytopenia, with three out of four patients experiencing grade 3-4 thrombocytopenia. The grade 4 events were documented during the second cycle. No febrile neutropenia was observed.

At the recommended dose level of 170 mg/m² no grade 3-4 non hematological adverse events were observed, while one out of 6 patients had grade 3 thrombocytopenia.

Table 3. Treatment-Related Adverse Events (CTCAE v3) – Maximum grade per patient

MBP-426 Dose Level	226 mg/m² 4 Patients 14 Cycles		170 mg/m² 6 Patients 16 Cycles	
	Grade 1-2	Grade 3-4	Grade 1-2	Grade 3-4
Febrile Neutropenia	-	-	-	-
Neutropenia	1	2	2	2
Thrombocytopenia	-	3	1	1
Anemia	3	-	3	1
Diarrhea	3	-	3	-
Nausea-vomiting	3	1	3	-
Back pain	-	1	-	-
Fatigue	2	-	2	-
Skin	-	1	-	-
Anorexia	2	-	1	-
Abdominal Pain	2	-	1	-
Headache	1	1	-	-
Bilirubin (↑)	-	1	-	-
Transaminases (↑)	-	1 (ALT)	1 (AST)	-
Creatinine (↑)	1	-	-	-

No treatment-emergent peripheral neurotoxicity was reported, despite significant cumulative doses of oxaliplatin in 4 patients (see below); grade 1 peripheral neurotoxicity was reported by one patient who exhibited this at baseline.

Table 4. Peripheral neurotoxicity in patients with significant cumulative dose

Patient	Disease	Cycles	MBP-426 Cumulative Dose (mg/m²)	Peripheral Neurotoxicity Grade
#01	CRC	4	900	G1 *
#03	Pancreas	5	1070	-
#04	CRC	4	900	-
#05	Cervix	4	680	-

Efficacy

Stable disease was documented as best objective response (RECIST) in 4 patients:
- two patients with CRC, both of whom were oxaliplatin-resistant, and who each received a total of 4 cycles of treatment
- one patient with pancreas cancer, who received 5 cycles of treatment
- one patient with cervical cancer, who was cisplatin-resistant, and who is still on treatment after 4 cycles

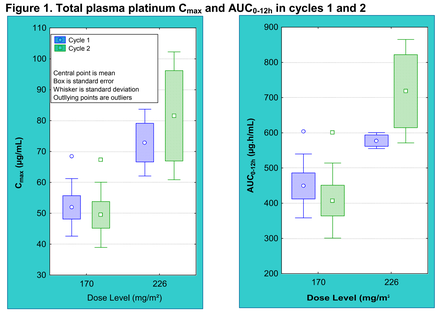
Pharmacokinetics

- The pharmacokinetics of MBP-426 when combined with 5-FU and LV are comparable to single-agent administration.
- Results of cycle 1 and 2 were broadly consistent, when the difference in the sampling schedule is taken into account.
- At a dose of 170 mg/m², MBP-426 results in C_{max} and AUC exposure approximately 10 times higher than oxaliplatin 130 mg/m² (Graham et al, 2000).
- The reported half-lives do not provide an accurate estimate, given that sampling did not cover a sufficiently long period, and are provide for information only.

Table 5. Total plasma platinum pharmacokinetic parameters

DL (mg/m²)		170	170	226	226
Cycle		1	2	1	2
N patients		6	6	3	2
C_{max} (µg/mL)	Mean	51.27	48.61	72.36	80.24
	CV	17	21	15	26
$T_{½}$ (h)	Mean	29.6	24.3	45.5	25.8
	CV	30	54	66	54
$AUC_{0\text{-}12h}$ (µg.h/mL)	Mean	441.7	402.3	577.4	710.7
	CV	20	22	20	21
$AUC_{0\text{-}last}$ (µg.h/mL)	Mean	1674	453	2114	711
	CV	49	26	55	21
$AUC_{0\text{-}\infty}$ (µg.h/mL)	Mean	2212	1707	3720	3076
	CV	36	42	58	72
Clearance (mL/h/m²)	Mean	76.84	99.58	60.76	73.46
	CV	36	42	58	72
V_z (L/m²)	Mean	3.29	3.49	3.99	2.74
	CV	32	19	23	14

Figure 1. Total plasma platinum C_{max} and $AUC_{0\text{-}12h}$ in cycles 1 and 2



Conclusions

- MBP-426 at 170 mg/m² is the recommended dose for use in combination with 5-FU/LV (de Gramont schedule) every 3 weeks.
- Treatment at this dose level was well tolerated
- No peripheral neurotoxicity has been reported with this new oxaliplatin formulation
- Hints of efficacy were reported in patients with previous disease progression and platinum resistance
- The co-administration of 5-FU and LV did not appear to alter the pharmacokinetics of MBP-426
- The phase II part has already started, looking for proof of concept in second-line gastric and esophageal adenocarcinoma

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