Unexpected Pharmacokinetics of Evofosfamide Observed in Phase III MAESTRO Study

Jack P. Higgins, Nenad Sarapa, Jason Kim, Eric Poma; Molecular Templates, Inc., Austin, TX; Molecular Templates, Inc., Jersey City, NJ

Abstract # 2568

MOLECULAR TEMPLATES

Molecular Templates, Inc. | Austin, Texas

Introduction

- Evofosfamide (Evo) is a prodrug of bromo-isophosphoramide mustard (Br-IPM) only activated under low levels of oxygen (hypoxia). Evofosfamide has been clinically investigated both as monotherapy and in combination with chemotherapy or other targeted cancer therapies in over 1,700 patients.
- In a randomized phase II trial (TH-CR-404) of patients with advanced pancreatic cancer, two hundred fourteen patients were randomized to receive either gemcitabine (Gem) alone, Gem plus Evo at 240 mg/m², or Gem plus Evo at 340 mg/m². The Gem plus Evo at 340 mg/m² showed statistically superior response rates compared to Gem (26% vs 12%, P = 0.04) and improved median overall survival times (9.2 vs 6.9 months, P = not significant).
- On the basis of these phase II findings, a global phase III clinical trial (MAESTRO) comparing Gem plus Evo at 340mg/m² versus Gem plus placebo was initiated in treatment-naive patients with advanced unresectable or metastatic pancreatic cancer. In the MAESTRO study, the regimen of Gem plus Evo failed to show a statistically significant improvement in overall survival (OS) compared to Gem plus placebo (P = 0.0589). The response rate, progression-free survival, and overall survival results for Gem plus Evo at 340 mg/m² in the MAESTRO study underperformed the same endpoints observed for Gem plus Evo at 340 mg/m² in the prior phase II study. Specifically, the MAESTRO response rate, progression-free survival and overall survival Gem plus Evo at 340 mg/m² were comparable to the phase II Gem plus Evo at 240 mg/m² arm and underperformed what had been observed in the phase II (“404”) study with Gem plus Evo at 340 mg/m² (Table 3).
- The formulation for Evo was altered after the phase II (“404”) study and before the phase III MAESTRO study. Evo drug product was initially formulated for the phase II (“404”) study as a lyophilized parenteral drug product without ethanol (stored at -20°C ± 10°C). Subsequently, a liquid parenteral ethanol-based drug product formulation was developed for the phase III MAESTRO study.
- The C_{max} and AUC for Evo and C_{max} for its active form (Br-IPM) in the MAESTRO study were 48%, 48%, and 63% lower, respectively, than what was observed in the phase II (“404”) study (Table 4). The PK parameters for both Evo and Br-IPM in the MAESTRO Gem plus Evo 340 mg/m² arm were comparable to the phase II (“404”) Gem plus Evo 240 mg/m² arm (Table 4). Additionally, infusion time in the phase II study was not limited to 30 mins as in the MAESTRO and the longer infusion time in the phase II study may have contributed to the observed PK differences. This reduced PK profile suggests that MAESTRO subjects may have had suboptimal Evo exposure.
- Interestingly, Japanese patients (N=59) in the MAESTRO showed Br-IPM C_{max} values that were substantially higher than patients from the rest of the world (ROW) in the MAESTRO study (Table 4). Japanese patients also had substantially better clinical outcomes than those seen in ROW (Table 6).

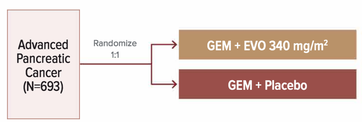
Methods

- Gem was evaluated alone or with Evo (240 mg/m² or 340 mg/m²) in a randomized phase II (“404”) study (N=214) in US patients with advanced PDAC (TH-CR-404: NCT01144455).
- MAESTRO was an international, randomized, double-blind, placebo-controlled phase III trial (N=693) of Evo + Gem versus Placebo (Pbo) + Gem in patients with locally advanced unresectable or metastatic PDAC (MAESTRO; NCT01746979) using the same phase II schedule and 340 mg/m² Evo dose.
- An ethanol-based liquid formulation to improve drug product solubility (previously a lyophilized formulation) was introduced after the phase II study and before the start of the phase III MAESTRO study.

Figure 1. TH-CR-404 phase II study in advanced pancreatic cancer

GEM = Gemcitabine at 1000mg/m²; EVO = Evofosfamide
- Patients - Metastatic or locally advanced unresectable pancreatic cancer
- Primary endpoint - Progression free survival
- Secondary endpoints - Overall response rate, overall survival, event-free survival, CA 19-9 response rate as well as various safety parameters

Figure 2. MAESTRO phase III study in advanced pancreatic cancer



GEM = Gemcitabine at 1000mg/m²; EVO = Evofosfamide
- Patients - Metastatic or locally advanced unresectable pancreatic cancer
- Primary endpoint – Overall survival (OS)
- Secondary endpoints - Overall response rate, PFS, CA19-9, QOL, pain, safety

Results

- Median OS in the MAESTRO phase III study was 8.7 mo with Evo + Gem vs 7.6 mo with Gem + placebo; HR = 0.84 (P = 0.059). Median PFS was 5.5 mo with Evo + Gem vs 3.7 mo with Gem + placebo; HR = 0.77 (P = 0.004) (Table 3).
- The outcomes observed in the MAESTRO study in the Gem + Evo 340 mg/m² arm were similar to the outcomes in the 240 mg/m² arm of the phase II (“404”) study (median OS = 8.7 mo; median PFS = 5.6 mo) (Table 3).
- The PK parameters for both Evo and its active metabolite Br-IPM in the Gem + Evo 340 mg/m² arm in the MAESTRO phase III study were similar to that of the Gem + Evo 240 mg/m² in the phase II study (Table 4, Figure 3).
- Japanese patients in the MAESTRO phase III study treated with Gem + Evo 340 mg/m² showed significantly greater levels of the metabolite (Br-IPM) than rest of world patients (Table 4), which likely contributed to better clinical outcomes (OS, PFS, ORR) for Japanese patients treated with Gem + Evo 340 mg/m² compared to Gem + Placebo (Table 4-6, Figure 3-4).

Table 1. Patient disposition and baseline characteristic between Phase IIb (“404”) study and Phase III MAESTRO study

		Phase II TH-CR-404			Phase III MAESTRO	
		Gem Alone	Gem + Evo 240 mg/m²	Gem + Evo 340 mg/m²	Gem + Placebo	Gem + Evo 340 mg/m²
N		69	71	74	347	346
Median age, years (range)		67 (41-83)	63 (41-81)	65 (29-86)	65 (35-84)	66 (27-87)
ECOG	0	24 (35%)	35 (49%)	26 (36%)	117 (34%)	113 (33%)
	1	45 (65%)	36 (51%)	46 (64%)	230 (66%)	233 (67%)
Locally advanced disease		15 (22%)	15 (21%)	20 (27%)	74 (21%)	75 (22%)
Metastatic disease		54 (78%)	56 (79%)	54 (73%)	273 (79%)	271 (78%)

Table 2. Grade ≥ 3 AEs in >10% of patients in Phase IIb (“404”) study and Phase III MAESTRO study

	Phase II TH-CR-404			Phase III MAESTRO	
	Gem Alone	Gem + Evo 240 mg/m²	Gem + Evo 340 mg/m²	Gem + Placebo	Gem + Evo 340 mg/m²
N	69	71	74	347	346
Anemia	20 (29%)	24 (34%)	32 (43%)	41 (12%)	75 (22%)
Leukopenia	0 (0%)	6 (8.5%)	10 (13.5%)	32 (9.4%)	75 (22%)
Neutropenia	12 (17%)	24 (34%)	32 (43%)	88 (26%)	152 (45%)
Thrombocytopenia	8 (12%)	21 (30%)	41 (55%)	26 (7.6%)	160 (47%)

Table 3. Comparison of Phase IIb (“404”) study and Phase III MAESTRO study outcomes

	Phase II TH-CR-404			Phase III MAESTRO	
	Gem Alone	Gem + Evo 240 mg/m²	Gem + Evo 340 mg/m²	Gem + Placebo	Gem + Evo 340 mg/m²
N	69	71	74	347	346
Median OS (months)	6.9	8.7	9.2 (P = NS)[a]	7.6	8.7 (P = 0.0588)[b]
Median PFS (months)	3.6	5.6	6.0 (P = 0.008)[a]	3.7	5.5 (P = 0.001)[b]
Best ORR	12%	17%	26%	17%	22% (P = 0.227)[b]

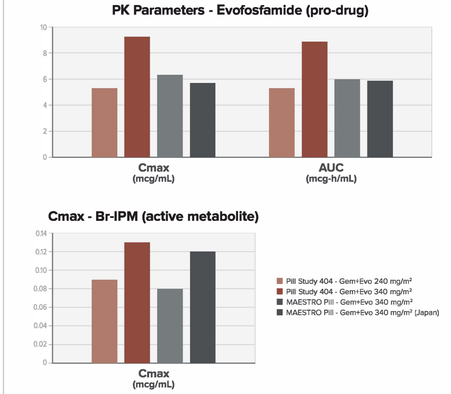
NS = not significant
a Compared to Gem alone
b Compared to Gem + placebo

Table 4. Comparison of evofosfamide and Br-IPM PK parameters in Phase IIb (“404”) study and MAESTRO study (with Japan subset)

		Phase II TH-CR-404		Phase III MAESTRO	
		Gem + Evo 240 mg/m²	Gem + Evo 340 mg/m²	Gem + Evo 340 mg/m²	Gem + Evo 340 mg/m² (Japan)
N		71	74	346	59
Evo (Pro-drug)[a]	C_{max} (mcg/mL)	5.3	9.3	6.3	5.7
	AUC (mcg-h/mL)	5.3	8.9	6.0	5.9
Br-IPM (Active Metabolite)[a]	C_{max} (mcg/mL)	.09	.13	.08	.12 (P < 0.001)[b]

a Geometric means
b Statistically significant compared to ex-Japanese patients in MAESTRO

Figure 3. Comparison of evofosfamide and Br-IPM PK parameters in Phase IIb (“404”) study and MAESTRO study (with Japan subset)



Abbreviations: N = number of patients; AUC = area under the curve; Cmax = maximum serum concentration; Evo = evofosfamide; GEM = gemcitabine
Geometric means used for Cmax and AUC values

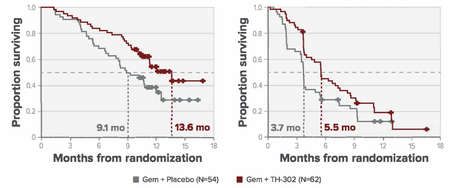
Table 5. Grade ≥ 3 AEs in >10% of patients Phase III MAESTRO study (Japan subset)

	Phase III MAESTRO (Japan subset)	
	Gem + Placebo	Gem + Evo 340 mg/m²
N	54	59
Anemia	6 (11%)	20 (34%)
Leukopenia	6 (11%)	34 (58%)
Neutropenia	12 (22%)	43 (73%)
Thrombocytopenia	2 (3.7%)	37 (63%)

Table 6. Phase III MAESTRO study outcomes in Japan subset

	Phase III MAESTRO (Japan subset)	
	Gem + Placebo	Gem + Evo 340 mg/m²
N	54	59
Median OS (months)	9.1	13.6 (P = 0.0106)
Median PFS (months)	3.7	5.5 (P = 0.019)
ORR	2%	31% (P < 0.001)

Figure 4. Overall survival and progression free survival in Japan subset of MAESTRO study



Conclusions

- **Evo is a chemotherapeutic prodrug that is activated under hypoxic conditions to its active form Br-IPM. It has been studied in over 1,700 patients.**
- **The phase II (“404”) study (N=214) in unresectable pancreatic ductal adenocarcinoma in combination with Gem at two different doses of Evo (240 mg/m² or 340 mg/m²) compared to Gem alone showed promising response rates, progression-free survival, and overall survival outcomes.**
- **MAESTRO, a phase III study (N=693) in the same patient population comparing Gem to Gem pus Evo at 340 mg/m² failed to replicate the clinical benefit seen in the phase II study.**
- **A new ethanol-based formulation was introduced before the initiation of the phase III MAESTRO study, and C_{max} values in MAESTRO were substantially lower for Evo and Br-IPM compared to the phase II (“404”) study at the same dose.**
- **In the Japanese patients (N=59) tested in MAESTRO, substantially higher C_{max} values of Br-IPM were observed with correspondingly better clinical outcomes versus ROW patients.**
- **We surmise that the formulation change may have adversely affected the PK of Evo, and its active form Br-IPM, and reduced the clinical benefit of the Evo 340 mg/m² dose in MAESTRO.**
- **Evo is currently being evaluated in a phase I study, in combination with ipilimumab, at higher doses in the current formulation (ethanol-based) in an attempt to replicate the PK seen with the previous formulation at 340 mg/m².**

bd@mtem.com | www.mtem.com

MOLECULAR TEMPLATES