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A randomized phase II study of PEP02 (MM-398), irinotecan or docetaxel as a second-line therapy in patients with locally advanced or metastatic gastric or gastro-oesophageal junction adenocarcinoma†

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Background: PEP02 is a novel highly stable liposomal nanocarrier formulation of irinotecan. This randomized phase II study evaluated the efficacy and safety of single agent PEP02 compared with irinotecan or docetaxel in the second-line treatment of advanced oesophago-gastric (OG) cancer.

Patients and methods: Patients with locally advanced/metastatic disease who had failed one prior chemotherapy regimen were randomly assigned to PEP02 120 mg/m^2, irinotecan 300 mg/m^2 or docetaxel (Taxotere) 75 mg/m^2 every 3 weeks. The primary end point was objective response rate (ORR). Simon's two-stage design was used and the ORR of interest was 20% ($\alpha = 0.05$, type II error $\beta = 0.10$, null hypothesis of ORR was 5%).

Results: Forty-four patients per arm received treatment, and 124 were assessable for response. The ORR statistical threshold for the first stage was reached in all arms. In the intent-to-treat (ITT) population, ORRs were 13.6% (6/44), 6.8% (3/44) and 15.9% (7/44) in the PEP02, irinotecan and docetaxel arms, respectively. The median progression-free survival (PFS) and overall survival were similar between the trial arms. Commonest grade 3–4 adverse event reported was diarrhoea in the PEP02 and irinotecan groups (27.3% versus 18.2%).

Conclusion: The ORR associated with PEP02 was comparable with docetaxel and numerically greater than that of irinotecan. PEP02 warrants further evaluation in the advanced gastric cancer setting.

Key words: docetaxel, irinotecan, liposomal irinotecan, oesophago-gastric cancer, phase II, second line

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introduction

Oesophago-gastric (OG) cancer represents a significant global health problem with an estimated one million cases diagnosed every year worldwide [1]. Several randomized trials and meta-analyses have established the role of combination chemotherapy in the first-line treatment of advanced OG cancer with prolongation of OS and improvement in the quality of life [2].

Currently there are no standard second-line treatments in this setting [3, 4], although a trend exists towards increased use of second- and third-line treatments, with a significant geographical variation seen in both the therapeutic approach and the uptake of second-line treatment. In large first-line clinical studies, the rates of uptake of subsequent chemotherapy were 14% in the UK REAL 2 study, 42% in the international ToGA trial and 75% in the Japanese SPIRITS trial [5–7]. Recent phase III trials have demonstrated a survival benefit associated with the use of irinotecan or docetaxel (Taxotere) compared with best supportive care (BSC) alone in patients who have failed one or two prior lines of treatment [8, 9]. More recently, a randomized study from Japan demonstrated comparable results with either weekly paclitaxel (Taxol) or irinotecan in second-line therapy [10].

PEP02

PEP02, also known as MM-398 (Merrimack Pharmaceuticals, Inc.), is a highly stable liposomal nanocarrier formulation of irinotecan hydrochloride (CPT-11) [11]. This liposomal formulation is associated with preferentially increased tumour exposure to irinotecan and therefore, local release and conversion to SN-38 as a result of prolonged circulation in the bloodstream, longer half-life, increased area under the curve (AUC), slower clearance and reduced volume of distribution compared with the free drug [11]. In a phase 1 study of a variety of solid tumours, the maximum tolerated dose (MTD) of PEP02 as a single agent was found to be 120 mg/m^2 once every 3 weeks [12].

This randomized three-arm phase II study was designed to assess objective response rate (ORR) with single agent PEP02, or irinotecan or docetaxel in patients with locally advanced or metastatic gastric and gastro-oesophageal (GEJ) adenocarcinomas in the second-line setting.

methods

patients

Eligible patients were aged ≥18 years of age with histologically or cytologically confirmed locally advanced or metastatic gastric or GEJ junction adenocarcinoma. Patients had to have at least one measurable lesion and have failed one prior systemic chemotherapy (including patients with disease recurrence within 6 months of (neo)adjuvant chemotherapy).

Additional eligibility criteria included Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0–2, adequate organ function, life expectancy >3 months, no concurrent uncontrolled medical condition, no other active malignancy, no known brain metastasis, no prior irinotecan/taxane treatment and no history of allergic reactions to liposomal products. The trial was conducted in accordance with the Declaration of Helsinki and had ethical approval. A written informed consent was obtained from each patient before study entry. The institutional review boards of all participating centres reviewed and approved the protocol (ClinicalTrials.gov identifier NCT00813072).

treatment

Eligible patients were randomly assigned 1:1:1 to receive PEP02: 120 mg/m^2 (90-min infusion on day 1 of each cycle), irinotecan: 300 mg/m^2 (90-min infusion on day 1 of each cycle) or docetaxel (Taxotere): 75 mg/m^2 (60-min infusion on day 1 of each cycle) intravenously as monotherapy administered every 3 weeks. In the PEP02 arm, a protocol-specified dose level increase to 150 mg/m^2 was allowed for patients who did not have a ≥grade 1 adverse event. Treatment was continued until disease progression, unacceptable toxicity or withdrawal of consent. Treatment was delayed by 1 week (maximum of 2 weeks) if the neutrophil count was $<1.5 \times 10^9$/l or the platelet count was $<100 \times 10^9$/l. The severity of adverse events was graded according to NCI-CTCAE v 3.0.

assessments

Medical history, vital signs and PS were documented within seven days before randomization, and the patients underwent ECG, urinalysis and routine blood tests (including creatinine clearance) during this timeframe. Physical examination, haematology, biochemistry and urinalysis were repeated at the beginning of each cycle.

Baseline tumour assessment [computed tomography (CT) scan of chest, abdomen, and pelvis] was carried out within 28 days before randomization and CT scans were repeated after every two treatment cycles until disease progression. Response and progression were evaluated using the RECIST version 1.0 [13] criteria and all responses were confirmed with a second CT scan carried out 1 month later. The survival status was assessed every 2 months following the completion of trial treatment. Safety assessments were carried out on the day of treatment administration and at 30 days following the last exposure to trial treatment. The severity of adverse events was graded according to NCI-CTCAE v 3.0. An independent data monitoring committee regularly reviewed study safety and efficacy data.

pharmacokinetic and pharmacogenetic analysis (non-UK sites)

Pharmacokinetic (pK) studies were carried out in the PEP02 and irinotecan arms (supplementary Appendix SA. I. 1, available at *Annals of Oncology* online). An optional pharmacogenetic (pGx) study was also conducted, with analysis being carried out on samples from consenting patients in the PEP02 or irinotecan arms (see supplementary Appendix SA. I. 2, available at *Annals of Oncology* online).

statistical considerations

The primary end point was ORR and was analysed in both the intent-to-treat (ITT) and assessable populations (AP). The ITT population was defined as all recruited subjects who received any study medication. The AP, a subset of ITT, was defined as patients who had received at least two cycles of treatment and were assessable for response.

The study was not powered to allow statistical comparison of efficacy and toxicity between the three treatment arms. For the primary end point, a Simon's two-stage design was used and the response rate of interest was set at 20% ($\alpha = 0.05$, type II error $\beta = 0.10$) with a null hypothesis rate of 5%. For each arm, two responses within the first 21 assessable patients were required to proceed to the second stage, and five responses among 41 assessable patients in both the stages were required to reject the null hypothesis. Based on these calculations, 41 assessable patients were planned to be enrolled in each arm of the study.

The secondary end points included progression-free survival (PFS; time from the date of first study treatment to the date of disease progression or death, overall survival (OS; time from the date of first study treatment to the date of death), and 1-year survival rate.

results

Between January 2008 and June 2010, 135 patients were randomly assigned from 19 sites in the UK, Spain, Taiwan, Croatia, Korea and Bosnia. Overall, 54% (73/135) of the patients were recruited from Europe and 46% (62/135) were recruited from Asia. Three patients (one per arm) were ineligible and were withdrawn before receipt of any study medication, leaving 132 patients (44 in each arm) in the ITT population (Figure 1). Eight patients did not receive at least one post-treatment tumour assessment, leaving 124 patients in the AP (PEP02 $n = 41$, irinotecan $n = 43$, docetaxel $n = 40$). The baseline characteristics were well balanced between the treatment arms, the majority of patients were male (78%), had metastatic disease (94%) and PS 0–1 (92%). (Table 1)

The mean number of treatment cycles was 4.4 in the PEP02 arm (range 1–18), 4.6 in the irinotecan arm (range 1–12) and 4.7 in the docetaxel arm (range 1–12). In the PEP02 arm, five patients without ≥grade 1 toxicity received a dose of 150 mg/m^2. The median relative dose intensity by cycle was high in all the three treatment arms (>0.90) and the proportion of patients requiring dose reduction was also similar between the treatment arms [20.5% (9 of 44) with PEP02, 25% (11 of 44) with irinotecan and 22.7% (10 of 44) with docetaxel]. The primary reason for treatment discontinuation was disease progression (68.9%) followed by adverse events (13.6%) and investigators' decision (9.8%).

efficacy

Within the first assessable 21 patients recruited to each arm, responses were noted in 4, 2 and 5 patients treated with PEP02, irinotecan and docetaxel, respectively. The ORR threshold for the first stage of Simon's two-stage was, therefore, reached in all the three arms and the trial continued to full accrual. In the ITT population, the ORR was 13.6% (6/44; 95% CI 5.2–27.4) in the PEP02 arm, 6.8% (3/44; 95% CI 1.4–18.7) in the irinotecan arm and 15.9% (7/44; 95% CI 6.6–30.1) in the docetaxel arm. (Table 2) Additionally, the response rate of PEP02 at 150 mg/m^2 ($n = 5$) was 60% (3 PR). The DCRs for the three arms were PEP02 59.1% (26/44), irinotecan 61.4% (27/44), and docetaxel 52.3% (23/44), respectively. A pre-specified subgroup analysis demonstrated a numerically better ORR in Asian versus European patients in the PEP02 and docetaxel arms [20% versus 8.3% for PEP02 and 26.3% versus 8.0% for docetaxel (supplementary Table SA.1, available at *Annals of Oncology* online)].

survival

In the ITT population, the median OS was 7.3 months (95% CI; 3.84–9.17) in the PEP02 arm, 7.8 months (95% CI; 4.90–9.20) in the irinotecan arm and 7.7 months (95% CI; 5.32, 12.32) in the docetaxel arm. Kaplan–Meier estimates of 1-year survival rates were 21.3%, 30.8% and 40.4% in those three treatment arms, respectively (Table 2, Figure 2A). Median PFS was similar in all the three arms [2.7 months (95% CI; 1.54–3.65) with PEP02, 2.6 months (95% CI; 1.48–4.34) with irinotecan and 2.7 months (95% CI; 1.41–5.45) with docetaxel] (Table 2, Figure 2B). A trend towards better overall survival was observed in Asian patients (median OS 8.9 m versus 6.0 m, HR 1.40, 95% CI 0.97–2.16, $P = 0.065$) (supplementary Figure S1, available at *Annals of Oncology* online). Median PFS and OS of patients who received PEP02 at 150 mg/m^2 were numerically higher than patients who received that at 120 mg/m^2 group (PFS: 6.0 m versus 2.5 m; OS: 7.8 m versus 6.0 m, respectively).

toxicity

Table 3 demonstrates treatment-related grade 3–4 toxic effects. Treatment was well tolerated; the overall incidence of grade

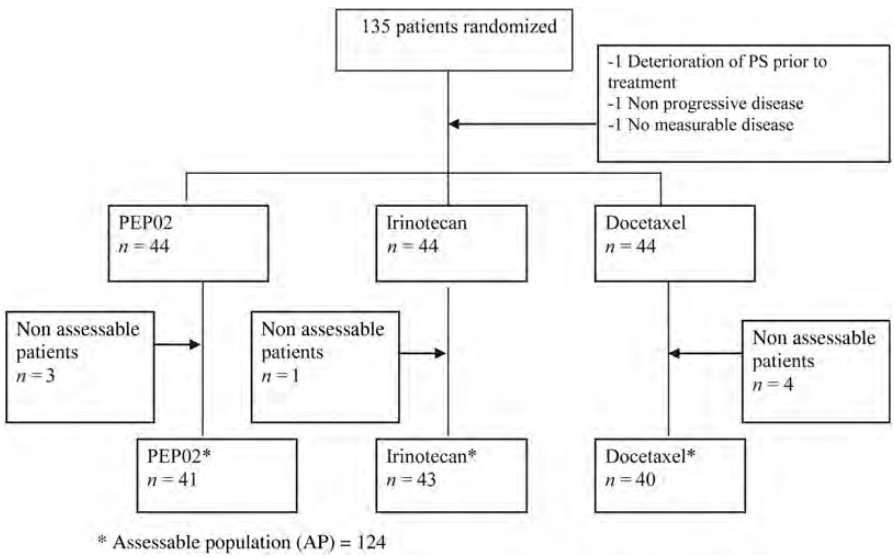

Figure 1. Consort diagram.

Table 1. Baseline characteristics

Baseline characteristics	PEP02, $N = 44$		Irinotecan, $N = 44$		Docetaxel, $N = 44$	
	n	%	*n*	%	*n*	%
Sex						
% of males	35	79.5%	34	77.3%	34	77.3%
Age						
Median	56		62		58	
Range	38–81		33–79		33–81	
Eastern Cooperative Oncology Group performance status (ECOG PS)						
0–1	41	93%	41	93%	40	91%
2	3	7%	3	7%	4	9%
Geographical region ($n = 45$ each group)						
Asia	21	47%	21	47%	20	44%
Europe	24	53%	24	53%	25	56%
Previous treatment						
Prior Radiotherapy	9	20.5%	6	13.6%	7	15.9%
Prior Surgery	31	70.5%	31	70.5%	37	84.1%
Prior Chemotherapy	44	100%	44	100%	44	100%
Primary tumour site						
Gastric	37	84%	35	80%	30	68%
GO Junction	7	16%	9	20%	14	32%
Extent of disease						
Metastatic	43	97.7%	40	91%	43	97.7%

3–4 adverse events was 38.6% in the PEP02 arm, 34.1% in the irinotecan arm and 15.9% in the docetaxel arm. No treatment-related deaths were observed. Diarrhoea was the most common toxicity noted in the PEP02 and irinotecan arms (all grade toxicity 72.7% versus 68.2%, respectively). The most frequent toxicity in the docetaxel group was alopecia (52.3% all grade toxicity). Overall, PEP02 was associated with an increased frequency of grade 3–4 diarrhoea and nausea, with similar rates of vomiting, neutropaenia and febrile neutropaenia compared with irinotecan and docetaxel. In the five patients treated at the dose of 150 mg/m^2, no clinically relevant toxicity difference was noted. Treatment-related toxic effects led to discontinuation of the study drug in six patients in each arm.

pharmacokinetic/pharmacogenetic evaluation

Sixty-four patients were included in the pK analysis. The effect of treatment on pK parameters is summarized in supplementary Table SA.1, available at *Annals of Oncology* online (supplementary Appendix, available at *Annals of Oncology* online). The pGx sub-study was undertaken in 71 patients of which 37 were treated with PEP02 and 34 with irinotecan.

pharmacokinetics of the active metabolite, SN-38

The mean T_{max} values of SN-38 were 10.2 and 2.1 h after infusion of 120 mg/m^2 PEP02 and 300 mg/m^2 irinotecan, respectively. The dose-normalized C_{max} value following PEP02 treatment was lower than that of irinotecan, and correspondingly the dose-normalized C_{max} value for the formation of SN-38 from CPT-11 following infusion of PEP02 was ∼50% less than after infusion of irinotecan. However, the dose-normalized AUC_{0-t} and $AUC_{0-\infty}$ values of SN-38 in the PEP02 treatment group were 3.30 and five times higher, respectively, than those seen with irinotecan. The mean $T_{1/2}$ and $MRT_{0-\infty}$ values of PEP02 treatment were four and five times higher, respectively, than those associated with irinotecan. The pK parameters of CPT 11 and SN-38G are detailed in the supplementary Appendix, available at *Annals of Oncology* online (see supplementary Appendix SA.II, available at *Annals of Oncology* online).

pharmacogenetic analysis

The genotype frequencies of the genetic polymorphisms of the UGT1A family were analysed. Forty-three (61.4%) patients were found to be wild type for *UGT1A1*28* (TA_6TA_6), 26 (37.1%) patients had a heterozygous polymorphism (TA_7TA_6) and only one (1.4%) patient was found to have homozygous mutation (TA_7TA_7). Genotype frequencies for the other UGT1A polymorphisms are summarized in supplementary Table SA, available at *Annals of Oncology* online. 2 (supplementary Appendix, available at *Annals of Oncology* online).

UGT1A1 variants were correlated with toxicity. Thirty-six patients from the PEP02 group and 34 patients from the irinotecan group were included in this analysis. In the PEP02 arm, the frequency of grade 3–4 neutropaenia was higher for *UGT1A1*6* heterozygotes compared with the wild-type genotype [3% (1 of 30) for wild type versus 40% (2 of 5) for heterozygotes, $P = 0.0220$]. Higher rates of grade 3–4 neutropaenia was also observed in heterozygotes for the genotype *UGT1A1*27* in the irinotecan arm, when compared with wild type [13% (4 of 31) for wild type versus 66% (2 of 3) for heterozygotes, $P = 0.0197$]. No other association between gene polymorphisms and toxic effects was significant. No correlation between UGT1A gene polymorphism and PEP02/irinotecan pK was demonstrated. (supplementary Appendix SA II. 4, available at *Annals of Oncology* online)

Table 2. Summary table of main efficacy results (ITT, $n = 132$)

	ITT population	Disease response		1-Year survival rate	PFS	OS
		CR + PR *n* (%)	DCR *n* (%)	% (95% CI)	Median 95% CI	Median 95% CI
PEP02	44	6 (13.6)	26 (59.1)	21.3% (6.6, 36.0)	2.7 (1.54, 3.65)	7.3 (3.84, 9.17)
Irinotecan	44	3 (6.8)	27 (61.3)	30.8% (16.6, 45.1)	2.6 (1.48, 4.34)	7.8 (4.90, 9.20)
Docetaxel	44	7 (15.9)	23 (52.3)	40.4% (25.8, 55.1)	2.7 (1.41, 5.45)	7.7 (5.32, 12.32)

ITT, intent to treat; CR, complete response; PR, partial response; DCR, disease control rate (CR + PR + SD).

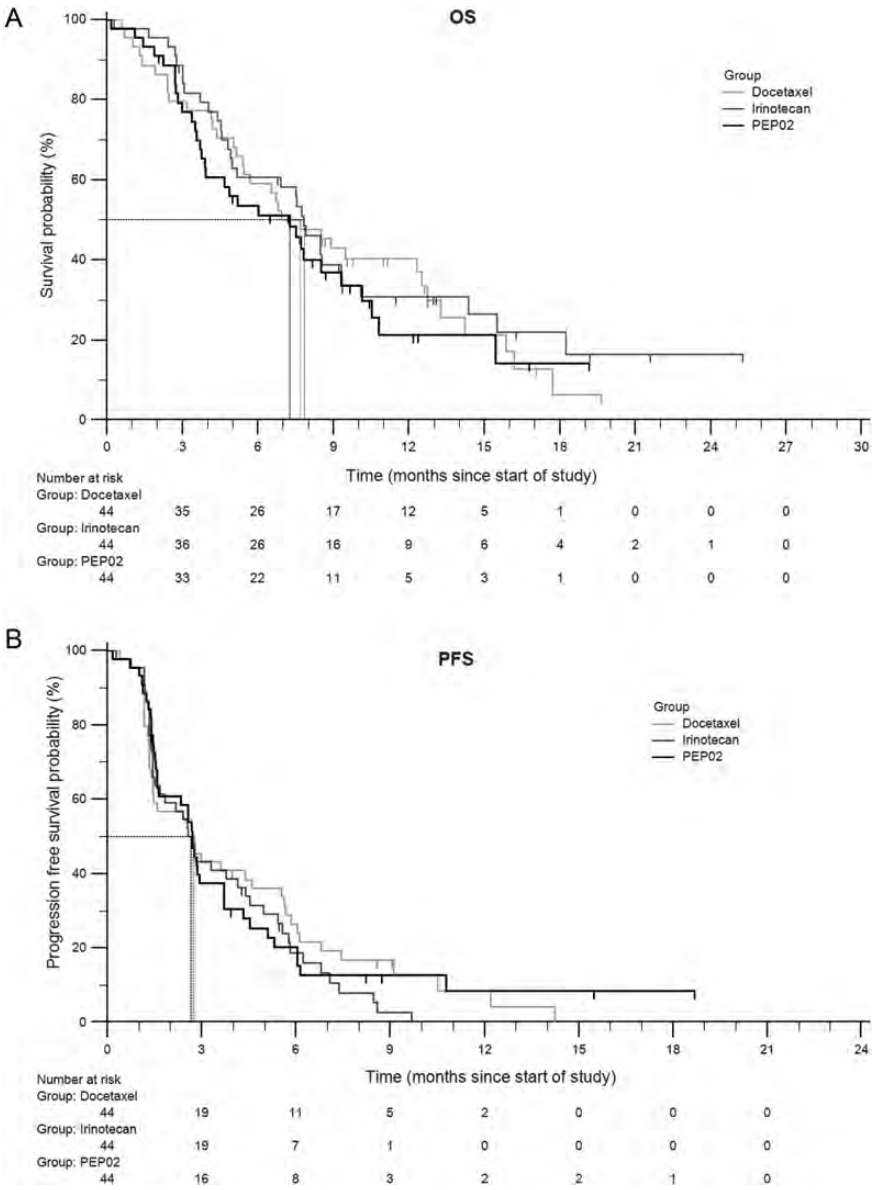

Figure 2. (A) Kaplan–Meier estimates of OS in the intent-to-treat population. (B) Kaplan–Meier estimates of PFS in the intent-to-treat population.

Table 3. Most common grade 3–5 adverse events

	Most common grade 3–4 adverse events					
	PEP02		Irinotecan		Docetaxel	
	N	%	*n*	%	*n*	%
Anaemia	2	4.5	2	4.5	3	6.8
Neutropaenia	5	11.4	7	15.9	2	2.6
Thrombocytopaenia	1	2.3	1	2.3	0	0
Febrile neutropaenia	3	6.8	5	11.3	2	2.6
Diarrhoea	12	27.3	8	18.2	1	2.3
Nausea	5	11.4	2	4.6	0	0
Vomiting	2	4.6	6	13.6	3	6.8
Anorexia	3	6.8	3	6.8	0	0
Fatigue	2	4.6	1	2.3	1	2.3

discussion

This randomized phase II trial represents the first study comparing a novel highly stable liposomal nanocarrier formulation of irinotecan (PEP02, MM-398) with docetaxel and irinotecan in the treatment of locally advanced or metastatic OG cancer after failure of first-line treatment.

The study's primary end point was ORR and in Simon's two-stage design only the PEP02 and docetaxel arms met the protocol-specified primary end point of five or more patients with confirmed tumour response in a total of 41 assessable patients. PFS, 1-year survival rate and OS were similar in the three arms. Other stratification factors such as geographical region, gender, ECOG and disease status (locally advanced versus metastatic) did not affect ORR or survival outcomes.

CPT-11 is mainly present in encapsulated form in the plasma after administration of PEP02 [12, 14]. In our study, pK results were consistent with previously reported profiles of PEP02 and free irinotecan [14, 15]. This study also confirms that following infusion of PEP02, there is a higher AUC, lower clearance and smaller volume of distribution for total and encapsulated irinotecan compared with the published pharmacokinetic data for free irinotecan [15, 16]. Multiple preclinical models have demonstrated that extended circulation of PEP02 leads to increased tumoural drug retention which permits local release and enzymatic conversion of irinotecan into SN-38. This sustained-release effect of the drug provides longer effective concentrations and AUC of the active metabolite (SN-38) in plasma and consequently a potentially beneficial longer duration of anti-tumour activity. Although the mechanism of release is not fully understood, it is assumed that once irinotecan is released from the liposomes either passively or from active breakdown potentially by Kupffer cells in the liver, it is metabolized in a similar fashion to the conventionally administered irinotecan. Therefore, genetic polymorphisms affecting toxicity and efficacy of irinotecan should be relevant to the study drug PEP02.

In this study, the percentages of observed toxic effects were consistent with the previously reported toxicity profiles of irinotecan and PEP02 while lower rates of PEP02 related diarrhoea were observed in other studies [8, 9, 12, 14, 17]. Of note, irinotecan and docetaxel doses used in our study were higher than those in the Korean and the German Arbeitsgemeinschaft Internistische Onkologie (AIO) studies. However these doses were based on the available evidence and expert clinical recommendation at the time of trial design [18, 19]. Liposomal irinotecan is not known to accumulate in many of the target organs and therefore, theoretically results in lower tissue exposure to the free drug and reduced toxicity while maintaining a greater anti-tumour potency [11]. However, overall toxicity and rates of grade 3–4 diarrhoea in our study were numerically higher than expected. We speculate that the lower clearance and higher AUC of PEP02 and SN-38 could explain this unexpected toxicity.

The frequency of homozygosity for *UGT1A1*28* allele is higher in Caucasians (5.8%–9.0%) and is associated with decreased UGT1A1 expression and activity [20–22]. The presence of homozygous mutation is known to critically impact on the glucuronidation of SN-38 resulting in severe neutropenia and diarrhoea in patients who receive irinotecan [21]. The majority of patients in this study were wild type (TA_6TA_6) for this mutation and only 1 (1.4%) Caucasian patient was found to harbor the homozygous mutation (TA_7TA_7). In Asian patients, the *UGT1A1*28* is a rare allele [23, 24] and genetic polymorphisms of *UGT1A1*6* are more frequent that may have an association with irinotecan-related grade 3–4 neutropenia and other toxic effects [25]. In this study, we found no significant associations between gene polymorphisms and pK parameters; however as previously described [26], there did seem to be an association between the heterozygote alleles of the prominent genetic polymorphisms and treatment-related grade 3–4 toxicity.

The recent phase III trial results reported by the AIO and the South Korean groups confirm the benefits associated with second-line chemotherapy in an advanced OG cancer population [8, 9]. The AIO study randomized metastatic OG cancer patients who had failed one prior line of treatment to irinotecan or BSC. The trial was terminated prematurely due to poor accrual. However, irinotecan was associated with a statistically significant OS benefit of 1.6 months (hazard ratio, HR 0.48, 95% CI 0.25–0.92, $P = 0.012$). Similarly, Kang et al. randomized 202 previously treated advanced OG cancer patients with a good PS in a 2:1 fashion to salvage chemotherapy (docetaxel or irinotecan as per investigators' choice) or BSC. In the ITT population, an OS benefit was noted in favour of chemotherapy (5.1 months versus 3.8 months, HR 0.63; $P = 0.004$) and more patients in the chemotherapy arm received further salvage chemotherapy compared with the BSC arm (40% versus 22%, respectively; $P = 0.011$). Median OS with PEP02 in this study is comparable and therefore encouraging. However, clearly with trial results demonstrating median OS of consistently <10 months, there are still significant improvements required to improve the outcomes for this patient group.

The potential advantages of nanoparticle liposomal delivery of irinotecan are several, and include bypassing solubility limitations of irinotecan, extending the circulation time, increasing tumour accumulation via the enhanced permeability and retention effect, and decreased organ toxicity. The results from recent phase I studies and this phase II study demonstrate that PEP02 is well tolerated and also has a comparable efficacy to docetaxel and irinotecan in patients with prior treatment of advanced gastric and GEJ cancer. Interestingly, patients who received PEP02 at 150 mg/m^2 had a numerically better response rate and PFS/OS compared with the patients who received 120 mg/m^2, suggesting a higher antitumour activity and this dose is worthy of further evaluation in future studies of PEP02. However, due to small numbers in this cohort and a potential selection bias for good PS patients, a significant conclusion cannot be made from these data at this time. Although toxicity especially diarrhoea associated with PEP02 appears to be high in this study, the results from ongoing studies of PEP02 as monotherapy and in combination with other cytotoxic [27] or targeted agents in other tumour types will be crucial to establish this novel agent's utility in the cancer therapeutics armamentarium.

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funding

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Scientific and Ethical committee as well as regulatory approvals were obtained at each institute and country.

PEP02 is designated as MM-398 by Merrimack Pharmaceuticals, Inc. (Cambridge, MA, USA).

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disclosure

ADG and LTC are consultants or have received honorarium from PharmaEngine. CGY holds stock of PharmaEngine, the makers of PEP02. ACR, SRP, DC, YKK, YC, CR, HYL, JT, FJR, MK and MBC have no relevant competing interest to declare.

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