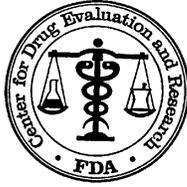


**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

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STATISTICAL REVIEW(S)



U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA Serial Number: 207,793

Drug Name: Onivyde[®] (irinotecan liposome injection, MM-398)

Indication(s): Metastatic adenocarcinoma of the pancreas

Applicant: Merrimack Pharmaceuticals, Inc.

Date(s): Submission: 4/24/2015
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1 EXECUTIVE SUMMARY

In this original New Drug Application (NDA), the applicant is seeking an approval of irinotecan liposome injection (MM-398) in combination with 5-fluorouracil (5-FU) and leucovorin (LV) in patients with metastatic pancreatic cancer who had failed prior gemcitabine-based therapy.

The trial MM-398-07-03-01 (NAPOLI-1) to support the application was a randomized, open-label, three-arm multinational phase 3 study evaluating the efficacy and safety of MM-398 with or without 5-FU and LV relative to 5-FU and LV (5-FU/LV) in metastatic pancreatic cancer patients previously treated with gemcitabine based therapy. The trial was originally designed with two treatment arms, comparing MM-398 monotherapy with a control of 5-FU/LV. Subjects were randomized in a 1:1 ratio. After 63 patients had been randomized to the MM-398 monotherapy arm and the 5-FU/LV arm, the trial was amended to add a third arm of a combination treatment of MM-398 with 5-FU/LV (MM-398 + 5-FU/LV) with a 1:1:1 randomization ratio. The amended trial had two pair-wise comparisons: MM-398 versus 5-FU/LV and MM-398 + 5-FU/LV versus 5-FU/LV. The primary endpoint was overall survival (OS). The key secondary endpoints included investigator-assessed progression-free survival (PFS) and objective response rate (ORR) as assessed by investigator. A total of 417 patients were randomized (MM-398: 151; 5-FU/LV: 149; MM-398 + 5-FU/LV: 117). Among the 149 patients in the 5-FU/LV arm, 119 enrolled after the trial amendment were included in the comparison of MM-398 + 5-FU/LV with 5-FU/LV. In this trial, since there was an imbalance in the number of patients who had censored OS times due to withdrawal of consent from follow-up, FDA requested the applicant to provide dates of death from public records for the patients who were censored due to consent withdrawal. The primary efficacy results based on the data cut-off date of February 14, 2014 using the amended dataset with additional information are:

- The data and analyses from the trial NAPOLI-1 demonstrated that MM-398 + 5-FU/LV had a statistically significant improvement in the OS when compared with 5-FU/LV. The unstratified log-rank test p-value for OS comparison was 0.014. The median OS was 6.1 months (95% CI: 4.8, 8.5) for MM-398 + 5-FU/LV and 4.2 months (95% CI: 3.3, 5.3) for 5-FU/LV. The Cox proportional hazard ratio (HR) was 0.68 with 95% CI (0.50, 0.93).
- MM-398 + 5-FU/LV also demonstrated an improvement in the PFS when compared with 5-FU/LV. The median PFS was 3.1 months (95% CI: 2.7, 4.2) for MM-398 + 5-FU/LV and 1.5 months (95% CI: 1.4, 1.8) for 5-FU/LV. The Cox proportional hazard ratio (HR) was 0.55 with 95% CI (0.41, 0.75). The nominal p-value was <0.0001 based on an unstratified log-rank test.
- In addition, MM-398 + 5-FU/LV demonstrated an improvement in the ORR when compared with 5-FU/LV (MM-398 + 5-FU/LV: 7.7%; 5-FU/LV: 0.8%). The nominal p-value was 0.010 based on the Fisher's exact test.

- However, the data and analyses from the trial NAPOLI-1 showed that MM-398 monotherapy did not demonstrate a statistically significant improvement in the OS when compared with 5-FU/LV. The unstratified log-rank test p-value for OS comparison was 0.971. The median OS was 4.9 months (95% CI: 4.2, 5.6) for MM-398 and 4.2 months (95% CI: 3.6, 4.9) for 5-FU/LV. The Cox proportional hazard ratio (HR) was 1.00 with 95% CI (0.77, 1.28).

Whether the data and analyses from the current submission demonstrated an overall favorable benefit vs. risk profile is deferred to the clinical team reviewing this application.

2 INTRODUCTION

Onivyde[®] (irinotecan liposome injection, MM-398) is a topoisomerase 1 inhibitor. This original New Drug Application (NDA) submission provided the clinical efficacy and safety data that intend to support the use of MM-398 in combination with 5-fluorouracil and leucovorin for the treatment of patients with metastatic pancreatic cancer who have failed prior gemcitabine-based therapy. This submission was primarily supported by results from a randomized, open-label, multinational phase 3 trial MM-398-07-03-01 (NAPOLI-1) under Investigational New Drug (IND) 102, 799. This is a 505(b)(2) application under 21CFR 314.54, relying on data from the Camptosar[®] Irinotecan Injection NDA approval.

2.1 Overview

2.1.1 Class and Indication

Pancreatic cancer is a malignant neoplasm of the pancreas. It is estimated that in 2015 in the United States, about 48,960 new cases of pancreatic cancer will be diagnosed and about 40,560 people will die of pancreatic cancer. Pancreatic cancer often has a poor prognosis. It typically spreads rapidly and is seldom detected in its early stages. Signs and symptoms may not appear until pancreatic cancer is quite advanced and complete surgical removal isn't possible.

Onivyde[®] (irinotecan liposome injection, MM-398) is a topoisomerase 1 inhibitor. In the current NDA submission, the indication proposed by the Applicant is for treatment of patients with metastatic pancreatic cancer who have failed prior gemcitabine-based therapy. This indication was supported by a single trial, MM-398-07-03-01 (NAPOLI-1), under Investigational New Drug (IND) 102, 799.

2.1.2 History of Drug Development

Trial NAPOLI-1 was titled “A randomized, open label phase 3 study of MM-398, with or without 5-fluorouracil and leucovorin, versus 5-fluorouracil and leucovorin, in patients with metastatic pancreatic cancer who have failed prior gemcitabine-based therapy”. The original protocol was issued on October 6, 2011, and the last protocol amendment was Protocol Version 2.2 dated October 19, 2012. The Statistical Analysis Plan (SAP) was finalized on April 16, 2014 based on Protocol Version 2.2 (October 19, 2012).

Table 1 shows the protocol amendments regarding statistical issues that were more relevant to this NDA statistical review and some important milestones.

Table 1: Protocol Milestones for Trial NAPOLI -1

	Date	Major Amendments
Protocol Version 1.1 (Original version)	October 6, 2011	<ul style="list-style-type: none"> • 2-arm study comparing MM-398 and 5-FU/LV • 1:1 ratio • Planned to enroll 270 patients with final OS analysis conducted when 220 deaths occurred • Planned to conduct an interim analysis for safety and futility by an independent data monitoring committee (DMC) when at least 60 patients had been randomized and had received at least one dose of study drug
Study initiation	January 11, 2012	First patient enrolled
Protocol Version 2	April 9, 2012	Interim analysis was removed. Four patients had been randomized at this time.
Protocol Version 2.1	June 14, 2012	<ul style="list-style-type: none"> • Added the third arm of MM-398 + 5-FU/LV based on safety data of the combination therapy from a separate study (safety data received on March 31, 2012) • Increased total number of patients to 405 • Planned to conduct the primary analysis for OS once 305 death events had occurred <p>At this time, 63 patients had been randomized: 33 in the MM-398 arm and 30 in the 5-FU/LV arm.</p> <p>This is the version that was finally submitted to the sites, IRBs/ECs and regulatory authorities.</p>
Protocol Version 2.2	October 19, 2012	<ul style="list-style-type: none"> • Clarified that all patients enrolled in the study NAPOLI-1, including the patients enrolled under all versions of the protocol, would count towards the overall study population of 405 patients, and the primary analysis for overall survival would take place once 305 events occurred in patients enrolled in the study, under any version of the protocol • Clarified that all efficacy comparisons between Arm A and Arm B would include all patients randomized to either arm, under all versions of the protocol. The efficacy comparisons between Arm B and Arm C would include only patients randomized under protocol version 2.1 or later
Enrollment completion	September 11, 2013	The last patient enrolled.
Data cut-off date	February 14, 2014	
Statistical Analysis Plan 2.0 (Final version)	April 16, 2014	Based on Protocol Version 2.2
NDA submission	April 24, 2015	

Reviewer's comments:

1. Following the initiation of the trial with enrollment of 63 patients, without discussion with the Agency, the Applicant amended the protocol to include the third arm, consisting of MM-398 in combination with 5-fluorouracil and leucovorin.
2. Though the Statistical Analysis Plan (SAP) was finalized after the data cut-off date of February 14, 2014, the SAP was based on the Protocol Version 2.2 dated October 19, 2012. The statistical methods for the analyses of the primary endpoint OS and secondary endpoints PFS and ORR in the SAP are consistent with those in the Protocol Version 2.2.

2.1.3 Study Reviewed

The current NDA submission is based primarily on the phase 3 study NAPOLI-1. This reviewer will focus on the trial NAPOLI-1 outlined in Table 2 for a full statistical review and evaluation.

Table 2: Overview of Trial NAPOLI-1

Study Design	Phase 3, randomized, open-label study of MM-398, with or without 5-fluorouracil and leucovorin (5-FU/LV), versus 5-FU/LV, in the treatment of patients with metastatic pancreatic cancer who have failed prior gemcitabine-based therapy
Treatment Period	Arm A (MM-398, Experimental Arm): MM-398 120 mg/m ² IV over 90 minutes, every 3 weeks Arm B (5-FU/LV, Control Arm): - 5-FU 2000 mg/m ² IV over 24-hours, administered weekly for 4 weeks (days 1, 8, 15 and 22), followed by 2 weeks of rest, in a 6 weekly cycle - Leucovorin <i>l</i> + d racemic form 200 mg/m ² , or <i>l</i> form 100 mg/m ² , IV over 30 minutes, administered weekly for 4 weeks (days 1, 8, 15 and 22), followed by 2 weeks of rest, in a 6 weekly cycle Arm C (MM-398 + 5-FU/LV, Experimental Arm): - MM-398 80 mg/m ² IV over 90 minutes, every 2 weeks - 5-FU 2400 mg/m ² IV over 46 hours, every 2 weeks - Leucovorin <i>l</i> + d racemic form 400 mg/m ² , or <i>l</i> form 200 mg/m ² IV over 30 minutes, every 2 weeks - MM-398 should be administered prior to 5-FU and leucovorin; leucovorin should always be administered prior to 5-FU Patients were treated until progressive disease (radiologic or clinical deterioration) or unacceptable toxicity.
Follow-up Period	Tumor responses were measured and recorded every 6 weeks (+/- 1 week) by using Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. Patients were followed until death or study closure, whichever occurred first.
Treatment Arms	Arm A: MM-398 (N=151)

(Number of Subjects)	<p>Arm B: 5-FU/LV (N=149*)</p> <p>Arm C: MM-398 + 5-FU/LV (N=117)</p> <p>*: 119 patients in the 5-FU/LV arm enrolled under protocol version 2.1 or later.</p>
Enrollment Period	<p>First patient randomized: January 11, 2012</p> <p>Last patient randomized: September 11, 2013</p> <p>Patients were from 76 study sites in 14 countries.</p>
Primary Endpoint	Overall survival

The trial NAPOLI-1 was a randomized, open-label, multinational phase 3 study evaluating the efficacy and safety of MM-398, with or without 5-fluorouracil and leucovorin (5-FU/LV), versus 5-FU/LV, in the treatment of patients with metastatic pancreatic cancer who had failed prior gemcitabine-based therapy. This trial was conducted at 76 study sites within 14 countries. Patients were randomized into the trial between January 11, 2012 and September 11, 2013. The data cut-off date for the efficacy analyses was February 14, 2014.

The trial NAPOLI-1 was originally designed with two treatment arms, comparing MM-398 monotherapy (Arm A) with a control of 5-FU/LV (Arm B). Subjects were randomized in a 1:1 ratio to the treatment arms. After 63 patients had been randomized to Arm A and Arm B, the trial was amended to add a third arm of a combination treatment of MM-398 with 5-FU/LV (MM-398 + 5FU/LV) with a 1:1:1 randomization ratio. A total of 417 patients were randomized in the trial NAPOLI-1 (MM-398: 151; 5-FU/LV: 149; MM-398 + 5-FU/LV: 117). The trial had two pairwise comparisons: MM-398 vs. 5-FU/LV and MM-398 + 5-FU/LV vs. 5-FU/LV. The primary endpoint was overall survival (OS), and the key secondary endpoints included investigator-assessed progression-free survival (PFS) using Response Evaluation Criteria in Solid Tumors (RECIST) 1.1, and objective response rate (ORR) as assessed by investigator. No interim analysis was planned for this trial.

Reviewer's comments:

The trial NAPOLI-1 used different 5-FU regimens in the combination arm (Arm C) and control arm (Arm B). Therefore, it is difficult to conclude that the treatment effect is attributed to MM-398 alone for the comparison of Arm B to Arm C. Please refer to Clinical Review of this application for further discussion of this issue.

2.2 Data Sources

The electronic submission including protocols, statistical analysis plan, clinical study reports, analysis datasets, and SAS programs for this submission are located on the network with network path

<\\cdsesub1\evsprod\nda207793\0002>.

In the clinical study report, since there was an imbalance in the number of patients who had censored OS times due to withdrawal of consent from follow-up, FDA requested the applicant to provide dates of death from public records for the patients who were censored due to consent withdrawal. The amended dataset with additional information is located at <\\cdsesub1\evsprod\nda207793\0015>.

This reviewer considers the analyses of OS and PFS based on the amended dataset with additional information as the primary analyses for OS and PFS.

3 STATISTICAL EVALUATION

Part of the text, tables and figures presented in this review were adapted from clinical study report (CSR).

3.1 Data and Analysis Quality

The data and analysis quality of the submission was acceptable for the reviewer to be able to perform the statistical review.

3.2 Evaluation of Efficacy

3.2.1 Objective

The primary objective of the trial NAPOLI-1 was to compare the OS when treated with MM-398, with or without 5-FU/LV, versus 5-FU/LV. The key secondary efficacy objective included comparisons for PFS and ORR.

3.2.2 Study Design and Endpoints

3.2.2.1 Overall Study Design

The trial NAPOLI-1 was a multinational, multicenter, randomized, open-label phase 3 study comparing the efficacy and safety of MM-398, with or without 5-FU/LV, versus 5-FU/LV in patients with metastatic pancreatic cancer who had failed prior gemcitabine-based therapy.

The trial NAPOLI-1 was originally designed with 2 treatment arms, comparing MM-398 monotherapy (Arm A) with a control of 5-FU/LV (Arm B). Subjects were randomized in a 1:1 ratio to the treatment arms. Per Clinical Study Report (CSR), after 63 patients had been randomized to Arm A and Arm B under the original two-arm protocol, when clinical safety data for a combination treatment of MM-398 with 5-FU/LV (MM-398 + 5FU/LV) became available

from a separate study, the trial NAPOLI-1 was amended (protocol version 2.1) to add the third arm of MM-398 + 5FU/LV (Arm C), and patients were planned to be randomized in a 1:1:1 ratio.

Treatment was administered in 3-weekly cycles for Arm A, 6-weekly cycles for Arm B, and 3-weekly cycles for Arm C. Patients were treated until disease progression (radiologic or clinical deterioration), intolerable toxicity or other reasons for study termination. All patients who discontinued study treatment were requested to continue to be followed-up as required by the protocol unless the patient had withdrawn consent.

Tumor assessments were to be performed every 6 weeks (\pm 1 week) by using the RECIST guidelines (version 1.1). Patients who withdraw from study treatment due to reasons other than objective disease progression should continue to be assessed every 6 weeks during the follow-up period for radiologic progression (including patients who discontinued due to symptomatic deterioration). Following treatment discontinuation, all patients were to be followed-up every 1 month for overall survival (by phone or visit to the study site) until death or study closure, whichever occurred first.

Approximately 405 patients in total were planned to be randomized in an open-label fashion via an Interactive Web Response System (IWRS) in order to observe 305 death events in the intent-to-treat (ITT) population. Randomization were stratified by baseline albumin levels ($<$ 4.0 g/dL vs. \geq 4.0 g/dL), Karnofsky Performance Status (KPS) (70 and 80 vs. $>$ 90), and ethnicity (Caucasian vs. East Asian vs. All Others).

For all efficacy comparisons, the MM-398 arm (Arm A) was planned to be compared to the 5-FU/LV arm (Arm B) using all patients randomized to either arm, while the MM-398 + 5-FU/LV arm (Arm C) was planned to be compared to the 5-FU/LV arm (Arm B) using patients randomized to either arm after protocol amendment (under protocol version 2.1 or later) only.

The main inclusion criteria were:

- Histologically or cytologically confirmed adenocarcinoma of exocrine pancreas
- Documented metastatic disease; disease status may be measurable or non-measurable as defined by RECIST v1.1 guidelines
- Documented disease progression after prior gemcitabine or gemcitabine containing therapy, in locally advanced or metastatic setting. Examples of permitted therapies included, but were not limited to:
 - Single agent gemcitabine
 - Any one gemcitabine-based regimen, with or without maintenance gemcitabine
 - Single agent gemcitabine to which a platinum agent, a fluoropyrimidine, or erlotinib was subsequently added
 - Gemcitabine administered in the adjuvant setting if disease recurrence occurred within 6 months of completing the adjuvant therapy
- Karnofsky Performance Status (KPS) \geq 70
- Adequate bone marrow reserves as evidenced by:
 - ANC $>$ 1,500 cells/ μ l without the use of hematopoietic growth factors; and

- Platelet count > 100,000 cells/μl; and
- Hemoglobin > 9 g/dL (blood transfusions were permitted for patients with hemoglobin levels below 9 g/dL)
- Adequate hepatic function as evidenced by:
 - Serum total bilirubin within normal range for the institution (biliary drainage was allowed for biliary obstruction)
 - Albumin levels \geq 3.0 g/dL
 - Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) \leq 2.5 x ULN (\leq 5 x ULN was acceptable if liver metastases were present)
- Adequate renal function as evidenced by a serum creatinine \leq 1.5 x ULN
- Normal ECG or ECG without any clinically significant findings
- Recovered from the effects of any prior surgery, radiotherapy or other antineoplastic therapy
- At least 18 years of age
- Able to understand and sign an informed consent (or had a legal representative who was able to do so)

3.2.2.2 Efficacy Endpoints

Overall survival (OS) was defined as the time from the date of patient randomization to the date of death or the date last known alive. Patients who were not known to have died at the time of data cut-off date were censored at the date of last contact prior to the data cut-off date.

Progression-free survival (PFS) was defined as the time from the date of randomization to the date of progression or death, whichever occurred earlier (per RECIST 1.1). Disease progression was based on investigator's assessment.

Objective response rate (ORR) for each treatment group was defined as the proportion of patients with a best overall response of confirmed CR or PR per RECIST 1.1 as assessed by investigator.

Patient-reported outcomes (PROs) used the European Organization for Research and Treatment of Cancer (EORTC) quality-of-life core questionnaire (EORTC-QLQ-C30). This patient recorded outcome consists of 15 subscales in 3 independent domains: global health-related quality of life (HRQoL), functional scales (cognitive, emotional, physical, role and social functioning), and symptom scales (appetite loss, constipation, diarrhea, dyspnea, fatigue, insomnia, nausea and vomiting, and pain). Scoring was carried out as described in the EORTC QLQ-C30 Scoring Manual. Linear transformations were applied to the raw scores so that the reported score had range 0-100 for all scales.

Reviewer's Comments:

1. *Per the protocol and the SAP, ORR analysis was based on confirmed CR or PR.*

2. *Patient-reported outcome endpoints are subject to bias in an open-label study. Therefore, this reviewer considers these endpoints as exploratory.*

A sequential testing procedure was planned to control the overall type I error rate at the two-sided 0.05 level for the primary and secondary endpoints. The order of the sequence was: OS, PFS, and ORR. A pairwise treatment comparison for a secondary endpoint was conducted only if the prior pairwise comparisons in the hierarchy were significant.

3.2.3 Statistical Methodologies

3.2.3.1 Sample Size Consideration

The trial was originally designed as a two-arm study comparing the overall survival in the MM-398 monotherapy arm and the 5-FU/LV arm. Patients were planned to be randomized 1:1 to receive either MM-398 monotherapy or 5-FU/LV. In protocol version 2.1 or later, after 63 patients had been randomized to the MM-398 monotherapy arm and the 5-FU/LV arm, the trial was amended to include a third arm of MM-398 + 5-FU/LV and patients were planned to be randomized in a 1:1:1 ratio. In the amended protocol, the primary objective of the trial involved two pair-wise comparisons of OS between the three treatment arms: MM-398 vs. 5-FU/LV, and MM-398 + 5-FU/LV vs. 5-FU/LV.

It was assumed that the median OS times were 4.5 months for the MM-398 monotherapy arm, 3 months for the 5-FU/LV arm and 6 months for the MM-398 + 5-FU/LV arm. The trial was designed to have at least 85% power to detect a hazard ratio (HR) of 0.67 for the OS comparison of the MM-398 arm to the 5-FU/LV arm and at least 95% power to detect a HR of 0.5 for the OS comparison of the MM-398 + 5-FU/LV arm to the 5-FU/LV arm. For the planned two pair-wise comparisons of OS, a Bonferroni-Holm adjustment was used to control the family-wise Type I error rate at the two-sided 0.05 level. Accounting for the 63 patients enrolled before the addition of the third arm to the trial, assuming 14 month patient accrual period, and up to 3 months follow up, it was estimated that 305 death events were needed for the OS analysis, which could be expected from a total accrual of 405 patients.

3.2.3.2 Interim Analysis

No Interim analysis was planned for the primary endpoint of OS.

3.2.3.3 Efficacy Analysis

For all efficacy comparisons, the MM-398 arm was compared to the 5-FU/LV arm using all patients randomized to either arm, and the MM-398 + 5-FU/LV arm was compared to the 5-FU/LV arm using patients randomized to either arm under protocol version 2.1 or later.

Analysis Population

Intent-to-Treat (ITT) population was defined as all randomized patients. Patients were included in all ITT analyses according to the treatment to which they were randomized. This population was the primary population for evaluating efficacy results.

PRO population was defined as all ITT patients that have provided baseline and at least one subsequent assessment on EORTC-QLQ-C30 instrument.

Analysis Method

Efficacy Analysis Method for OS

The analysis for OS was performed using an un-stratified log-rank test. The median OS with corresponding 95% CIs and survival curves were estimated using the Kaplan-Meier (KM) method. The Cox regression of HR with 95% CI was planned.

Efficacy Analysis Method for PFS

The PFS analysis method was identical to OS analysis.

Efficacy Analysis Method for ORR

The analysis for ORR was performed using a Fisher's exact test. ORR estimates and exact 95% CIs were to be estimated for each treatment arm.

Efficacy Analysis Method for PROs

Figures were produced showing the proportions of patients with improvement, stability, or decrease by treatment group and subscale.

3.2.4 Patient Disposition, Demographic and Baseline Characteristics

3.2.4.1 Patient Disposition

There was an imbalance in the number of patients who were randomized but not treated among the three treatment arms. More patients in the 5-FU/LV arm were never treated (n=14) compared with those in the MM-398 arm (n=3) and MM-398 + 5-FU/LV arm (n=2). Thirteen out of the 14 patients in the 5-FU/LV arm were enrolled in Protocol Version 2.1 or later.

Reviewer's comments:

This imbalance could have influenced the assessment of OS. Sensitivity analyses were conducted to evaluate the robustness of the primary OS analysis (see Section 3.2.5.1 for more details).

Table 3 presents patient disposition which included all randomized patients.

Table 3: Patient Disposition

	MM-398 Mono (N=151)	5-FU/LV Mono Control (N=149)	MM-398+5- FU/LV Combo (N=117)	5-FU/LV Combo Control (N=119) [‡]	All ITT (N=417)
	n (%)	n (%)	n (%)	n (%)	n (%)
Subjects who terminated treatment	148 (98.0)	143 (96.0)	103 (88.0)	113 (95.0)	394 (94.5)
Reason for treatment termination:					
Adverse event	17 (11.3)	10 (6.7)	11 (9.4)	7 (5.9)	38 (9.1)
Clinical deterioration	21 (13.9)	17 (11.4)	13 (11.1)	12 (10.1)	51 (12.2)
Death	9 (6.0)	5 (3.4)	2 (1.7)	5 (4.2)	16 (3.8)
Investigator decision	7 (4.6)	5 (3.4)	4 (3.4)	4 (3.4)	16 (3.8)
Other	0	3 (2.0)	1 (0.9)	2 (1.7)	4 (1.0)
Progressive disease based on RECIST v1.1 criteria	77 (51.0)	83 (55.7)	57 (48.7)	64 (53.8)	217 (52.0)
Sponsor decision	0	0	1 (0.9)	0	1 (0.2)
Subject decision	17 (11.3)	20 (13.4)	14 (12.0)	19 (16.0)	51 (12.2)
Time from randomization to treatment termination					
Median (weeks)	7.6	6.3	10.1	6.1	7.1
(95% CI)	(6.7, 12.1)	(6.1, 6.9)	(7.3, 12.7)	(6.1, 6.9)	(6.7, 8.0)
Overall Study Disposition					
Death	128 (84.8)	107 (71.8)	70 (59.8)	78 (65.6)	305 (73.1)
Lost to follow-up	3 (2.0)	1 (0.7)	1 (0.9)	1 (0.8)	5 (1.2)
Subject withdrew consent from follow-up	2 (1.3)	12 (8.1)	8 (6.8)	12 (10.1)	22 (5.3)
Other reasons	0	1 (0.7)	1 (0.9)	1 (0.8)	2 (0.5)
Subjects on study at analysis cut-off date (February 14, 2014)	18 (11.9)	28 (18.8)	38 (32.5)	27 (22.7)	84 (20.1)

RECIST= Response Evaluation Criteria in Solid Tumors, CI=confidence interval, ITT=intent-to-treat, 5-FU= 5-fluorouracil; LV=leucovorin

* This group is a subset of 5-FU/LV mono control group that was enrolled in the study after protocol Version 2 was activated.

[Source: CSR Table 6-2]

Reviewer's Comments:

The reasons for treatment termination were imbalanced among the three treatment arms. Both the MM-398 arm and the MM-398 + 5-FU/LV arm had more AE and less PD compared to the 5-FU/LV arm.

3.2.4.2 Demographic and Baseline Characteristics

Table 4 presents the baseline demographics.

Table 4: Baseline Demographics (ITT Population)

	All randomized patients in Arms A and B		Randomized patients in Arms C and B under protocol version 2.1 and later	
	MM-398 N = 151	5-FU/LV N = 149	MM-398 + 5-FU/LV N = 117	5-FU/LV N = 119
Age (years)				
Mean (SD)	63.6 (10.1)	61.8 (9.7)	63.2 (9.1)	61.0 (9.5)
Median (min – max)	65 (31 – 87)	63 (34 – 83)	63 (41 – 81)	62 (34 – 80)
Age group				
≤ 65	82 (54%)	94 (63%)	65 (56%)	81 (68%)
> 65	69 (46%)	55 (37%)	52 (44%)	38 (32%)
Race				
White	89 (59%)	92 (62%)	72 (62%)	76 (64%)
Black or African American	3 (2%)	3 (2%)	4 (3%)	3 (3%)
Asian	52 (34%)	50 (34%)	34 (29%)	36 (30%)
Other	7 (5%)	4 (3%)	7 (6%)	4 (3%)
Gender				
Female	64 (42%)	68 (46%)	48 (41%)	52 (44%)
Male	87 (58%)	81 (54%)	69 (59%)	67 (56%)
Height				
Mean (SD)	166.6 (10.7)	166.2 (10.1)	167.5 (9.6)	166.7 (10.1)
Median (min-max)	167 (144 – 193)	166 (145 – 193)	168 (142 – 189)	166 (147 – 193)
Weight				
Mean (SD)	64.7 (14.2)	65.6 (17.7)	65.9 (14.9)	66.1 (18.3)
Median (min-max)	64 (38 – 118)	63 (37 – 151)	64 (40 – 123)	63 (37 – 151)
Region				
North America	25 (17%)	26 (17%)	19 (16%)	19 (16%)
Asia	48 (32%)	50 (33%)	34 (29%)	35 (29%)
Europe	55 (37%)	54 (36%)	47 (40%)	49 (41%)
Other	21 (14%)	21 (14%)	17 (15%)	16 (13%)

Table 5 summarizes the IWRS stratification factors.

Table 5: Summary of Stratification Factors at Randomization (ITT Population)

	All randomized patients in Arms A and B		Randomized patients in Arms C and B under protocol version 2.1 and later	
	MM-398 N = 151	5-FU/LV N = 149	MM-398 + 5-FU/LV N = 117	5-FU/LV N = 119
Baseline albumin levels				
< 4.0 g/dL	88 (58%)	83 (56%)	64 (55%)	65 (55%)
≥ 4.0 g/dL	63 (42%)	66 (44%)	53 (45%)	54 (45%)
KPS				
70 and 80	66 (44%)	65 (44%)	51 (44%)	52 (44%)
≥ 90	85 (56%)	84 (56%)	66 (56%)	67 (56%)
Ethnicity				
Caucasian	90 (60%)	90 (60%)	75 (64%)	75 (63%)
East Asian	53 (35%)	50 (34%)	34 (29%)	36 (30%)
All others	8 (5%)	9 (6%)	8 (7%)	8 (7%)

Table 6 summarizes the important baseline disease characteristics in the ITT population.

Table 6: Baseline Characteristics (ITT Population)

	All randomized patients in Arms A and B		Randomized patients in Arms C and B under protocol version 2.1 and later	
	MM-398 N = 151	5-FU/LV N = 149	MM-398 + 5-FU/LV N = 117	5-FU/LV N = 119
Measurable lesions at baseline	144 (95%)	144 (97%)	113 (97%)	114 (96%)
Measurable metastatic lesions at baseline	128 (85%)	129 (87%)	97 (83%)	103 (87%)
Prior Gemcitabine therapy				
Gemcitabine only	67 (44%)	66 (44%)	53 (45%)	55 (46%)
Gemcitabine in combination	84 (56%)	83 (56%)	64 (55%)	64 (54%)
Anatomical location of lesion at baseline				
Distant lymph node	44 (29%)	40 (27%)	32 (27%)	31 (26%)
Liver	101 (67%)	108 (73%)	75 (64%)	83 (70%)
Lung	49 (32%)	44 (30%)	36 (31%)	36 (30%)
Pancreas	99 (66%)	97 (65%)	75 (64%)	72 (61%)
Peritoneal	48 (32%)	39 (26%)	28 (24%)	32 (27%)

Regional lymph node	19 (13%)	20 (13%)	13 (11%)	14 (12%)
Other	38 (25%)	48 (32%)	27 (23%)	39 (33%)
Prior lines of treatment				
Neoadjuvant/adjuvant therapy only	17 (11%)	19 (13%)	15 (13%)	15 (13%)
Neoadjuvant/adjuvant + 1 line in advanced/metastatic setting	18 (12%)	16 (11%)	13 (11%)	14 (12%)
Neoadjuvant/adjuvant + 2 or more lines in advanced/metastatic setting	12 (8%)	4 (3%)	8 (7%)	4 (3%)
1 line in advanced/metastatic setting only	68 (45%)	70 (47%)	49 (42%)	53 (45%)
2 or more lines in advanced/metastatic setting only	36 (24%)	40 (27%)	32 (27%)	33 (28%)
Number of measurable metastatic lesions				
0	23 (15%)	20 (13%)	20 (17%)	16 (13%)
1	36 (24%)	26 (17%)	19 (16%)	22 (18%)
2	63 (42%)	72 (48%)	49 (42%)	58 (49%)
3	22 (15%)	21 (14%)	22 (19%)	15 (13%)
4	6 (4%)	9 (6%)	7 (6%)	8 (7%)
5	1 (1%)	1 (1%)	0	0
Baseline KPS	n = 151	n = 148	n = 117	n = 118
50	0	0	1 (0.9%)	0
60	0	0	2 (1.7%)	0
70	15 (9.9%)	11 (7.4%)	7 (6.0%)	10 (8.5%)
80	50 (33.1%)	61 (41.2%)	38 (32.5%)	51 (43.2%)
90	64 (42.4%)	54 (36.5%)	51 (43.6%)	40 (33.9%)
100	22 (14.6%)	22 (14.9%)	18 (15.4%)	17 (14.4%)
Baseline albumin (g/dL)	n = 149	n = 146	n = 114	n = 116
Mean (SD)	4.0 (0.4)	4.0 (0.5)	4.0 (0.5)	4.0 (0.5)
Median (min – max)	4.0 (2.9 – 4.8)	4.0 (2.4 – 5.1)	4.1 (2.6 – 5.1)	4.0 (2.4 – 5.0)

Reviewer's comments:

1. *There were no apparent differences with respect to baseline demographics except age and the age group. Patients in the 5-FU/LV arm were younger than those in the MM-398 arm and the MM-398 + 5-FU/LV arm. More patients in the 5-FU/LV arm were older than 65 compared with those in the MM-398 arm and MM-398 + 5-FU/LV arm. A sensitivity analysis for OS adjusting for the age group was performed by this reviewer to evaluate the robustness of the primary OS analysis (see Section 3.2.5.1 for more details).*

2. *There were no apparent differences with respect to stratification factors at randomization.*
3. *There were no apparent differences with respect to baseline disease characteristics except the baseline KPS categories. A sensitivity analysis for OS adjusting for KPS categories was performed by this reviewer to evaluate the robustness of the primary OS analysis (see Section 3.2.5.1 for more details).*

3.2.4.1 Protocol Deviations

Table 7 summarizes the protocol deviations.

Table 7: Summary of Protocol Deviations

	MM-398 Mono (N=151)	5-FU/LV Mono Control (N=149)	MM-398+ 5-FU/LV Combo (N=117)	5-FU/LV Combo Control (N=119)*	All ITT (N=417)**
	n (%)	n (%)	n (%)	n (%)	n (%)
Subjects with any major protocol deviation	40 (26.5)	39 (26.2)	45 (38.5)	32 (26.9)	124 (29.7)
Administrative criteria	2 (1.3)	1 (0.7)	0	1 (0.8)	3 (0.7)
Efficacy criteria	0	1 (0.7)	0	1 (0.8)	1 (0.2)
Eligibility and entry criteria	5 (3.3)	4 (2.7)	2 (1.7)	3 (2.5)	11 (2.6)
Informed consent	15 (9.9)	8 (5.4)	3 (2.6)	5 (4.2)	26 (6.2)
IP compliance	19 (12.6)	20 (13.4)	38 (32.5)	17 (14.3)	77 (18.5)
Laboratory assessment criteria	1 (0.7)	0	1 (0.9)	0	2 (0.5)
Randomization criteria	2 (1.3)	1 (0.7)	1 (0.9)	1 (0.8)	4 (1.0)
Source document criteria	3 (2.0)	9 (6.0)	7 (6.0)	9 (7.8)	19 (4.6)
Study procedures criteria	0	1 (0.7)	3 (2.6)	1 (0.8)	4 (1.0)

* This group is a subset of 5-FU/LV mono control group that was enrolled in the study after protocol Version 2 was activated.

** Rows do not add across because of the presentation of the control groups. Patients are counted only once in the All column.

5-FU= 5-fluorouracil; LV=leucovorin; IP=Investigational Product

[Source: Clinical Study Report Table 6-4]

Reviewer's comments:

1. *The major protocol violations for the comparison of the MM-398 arm to the 5-FU/LV arm were comparable between the two treatment arms.*
2. *The major protocol violations for the comparison of the MM-398 + 5-FU/LV arm to the 5-FU/LV arm were comparable between the two treatment arms except for the investigational product compliance. More patients in the MM-398 + 5-FU/LV arm (n=38) had deviations related to investigational product compared with those in the 5-FU/LV arm (n=17). Twenty-three of the 38 patients in the MM-398 + 5-FU/LV arm had deviations related to receiving a lower dose of leucovorin.*

3.2.5 Results and Conclusions

3.2.5.1 Primary Efficacy Endpoint – OS

Per protocol, patients who withdrew consents would not be followed for study endpoints in the trial NAPOLI-1. In the Clinical Study Report, since there was an imbalance for the number of patients who had censored OS time due to withdrawal of consent from follow-up, FDA requested the applicant to provide dates of death from public records for the patients who were censored due to consent withdrawal. The amended data with additional information will be used for all efficacy analyses in this review.

Reviewer's comments:

- 1. In the original dataset, 16 patients had censored OS times due to withdrawal of consent from follow-up: 1 in the MM-398 arm, 11 in the control arm and 4 in the MM-398 + 5-FU/LV arm. In the amended dataset with additional information, among the 16 patients, retrieved public records were not available for 1 patient in the MM-398 arm, 3 patients in the 5-FU/LV arm and 2 patients in the MM-398 + 5-FU/LV arm.*
- 2. The OS and PFS analyses based on the amended dataset with additional information are considered the primary analyses for OS and PFS by this reviewer.*

Table 8 presents the applicant's efficacy analyses for the pair-wise comparisons of OS between MM-398 and 5-FU/LV and between MM-398 + 5-FU/LV and 5-FU/LV, respectively, using the amended dataset with additional information.

There were a total of 244 death events for the comparison of MM-398 vs. 5-FU/LV. The trial did not show a difference in OS for the comparison of MM-398 vs. 5-FU/LV. The unstratified log-rank test p-value is 0.971. The median OS was 4.9 months (95% CI: 4.2, 5.6) for the MM-398 arm and 4.2 months (95% CI: 3.6, 4.9) for the 5-FU/LV arm. The unstratified Cox HR was 1.00 with 95% CI (0.77, 1.28).

There were a total of 163 death events for the comparison of MM-398 + 5-FU/LV vs. 5-FU/LV. The MM-398 + 5-FU/LV demonstrated a statistically significant improvement in the OS compared with the 5-FU/LV based on the unstratified log-rank test with a p-value 0.014. The median OS was 6.1 months (95% CI: 4.8, 8.5) for the MM-398 + 5-FU/LV arm and 4.2 months (95% CI: 3.3, 5.3) for the 5-FU/LV arm. The unstratified Cox HR was 0.68 with 95% CI (0.50, 0.93).

Table 8: Applicant’s Overall Survival Results Based on the Amended Dataset with Additional Information (ITT Population)

	All randomized patients in Arms A and B		Randomized patients in Arms C and B under protocol version 2.1 and later	
	MM-398	5-FU/LV	MM-398 + 5-FU/LV	5-FU/LV
Subjects randomized	151	149	117	119
Death	129 (85.4%)	115 (77.2%)	77 (65.8%)	86 (72.3%)
Censored	22 (14.6%)	34 (22.8%)	40 (34.2%)	33 (27.7%)
Overall survival (months)				
Median (95% CI)	4.9 (4.2, 5.6)	4.2 (3.6, 4.9)	6.1 (4.8, 8.5)	4.2 (3.3, 5.3)
p-value ^a	0.971		0.014	
Hazard ratio (95% CI) ^b	1.00 (0.77, 1.28)		0.68 (0.50, 0.93)	

^a p-value is from an unstratified log-rank test.

^b Hazard ratio is from an unstratified Cox proportional hazards model.

Figure 1 and Figure 2 present the Kaplan-Meier (K-M) curves for the two pair-wise comparisons of OS using the amended dataset with additional information.

Figure 1: Kaplan-Meier Survival Curves for Overall Survival (ITT Population, MM-398 vs. 5-FU/LV)

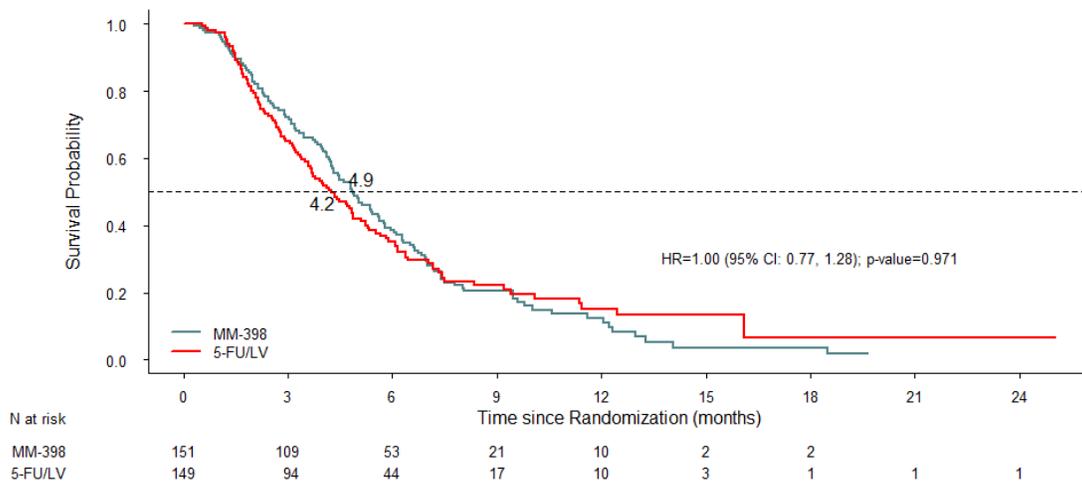
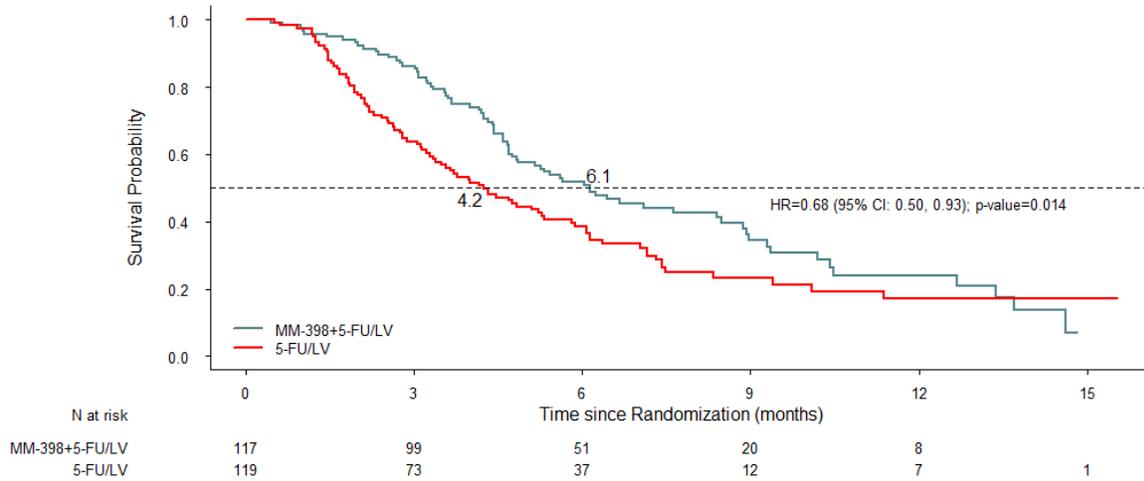


Figure 2: Kaplan-Meier Survival Curves for Overall Survival (ITT Population, MM-398 + 5-FU/LV vs. 5-FU/LV)



Based on the pre-specified Bonferroni-Holm adjustment for the planned 2 pair-wise comparisons of OS, the trial showed a statistically significant improvement in OS between the MM-398 + 5-FU/LV arm and the 5-FU/LV arm. However, the trial did not show a difference in OS between the MM-398 arm and the 5-FU/LV arm.

Reviewer's comments:

This reviewer will focus on the efficacy evaluation for the comparison of MM-398 + 5-FU/LV versus 5-FU/LV.

Table 9 shows the applicant's original efficacy analyses for the pair-wise comparisons of OS between MM-398 and 5-FU/LV and between MM-398 + 5-FU/LV and 5-FU/LV, respectively.

Table 9: Applicant's Original Overall Survival Results (ITT Population)

	All randomized patients in Arms A and B		Randomized patients in Arms C and B under protocol version 2.1 and later	
	MM-398	5-FU/LV	MM-398 + 5-FU/LV	5-FU/LV
Subjects randomized	151	149	117	119
Death	129 (85.4%)	109 (73.2%)	75 (64.1%)	80 (67.2%)
Censored	22 (14.6%)	40 (26.8%)	42 (35.9%)	39 (32.8%)
Overall survival (months)				
Median (95% CI)	4.9 (4.2, 5.6)	4.2 (3.6, 4.9)	6.1 (4.8, 8.9)	4.2 (3.3, 5.3)
p-value ^a	0.942		0.012	

Hazard ratio (95% CI) ^b	0.99 (0.77, 1.28)	0.67 (0.49, 0.92)
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^a p-value is from an unstratified log-rank test.

^b Hazard ratio is from an unstratified Cox proportional hazards model.

Reviewer's comments:

The OS results based on the original dataset are consistent with the primary findings based on the amended dataset with additional information.

All subsequent analyses are based on the amended dataset with additional information.

Table 10 shows the sensitivity analyses results for OS.

Table 10: Sensitivity Analyses of Overall Survival (MM-398 + 5-FU/LV vs. 5-FU/LV)

Sensitivity Analysis Description	MM-398	5-FU/LV	HR (95% CI)
	+ 5-FU/LV Median OS	Median OS	
1. Stratified analysis on ITT population ^a	6.1	4.2	0.58 (0.42, 0.80) ^a
2. Per Protocol (PP) population	8.9	5.1	0.58 (0.38, 0.89)
3. ITT population, adjusted for baseline age group	6.1	4.2	0.68 (0.50, 0.93)
4. ITT population, adjusted for baseline KPS ^b	6.1	4.2	0.69 (0.50, 0.93)

^a Stratified by the same stratification factors as used for randomization per IWRS.

^b Baseline KPS is categorized as ≤ 80, vs. 90 vs. 100.

Reviewer's comments:

The sensitivity analyses presented above show that the OS results are robust. The hazard ratios ranged from 0.58 to 0.69.

There was an imbalance in the number of patients who were randomized but not treated among the three treatment arms. More patients in the 5-FU/LV arm were never treated (n=14) compared with those in the MM-398 arm (n=3) and MM-398 + 5-FU/LV arm (n=2). Thirteen out of the 14 patients in the 5-FU/LV arm were enrolled in Protocol Version 2.1 or later. This imbalance could have influenced the assessment of OS. The applicant conducted an exploratory Bayesian analysis to impute the OS time for the patients in 5-FU/LV arm who did not received treatment drugs. The results of the Bayesian analysis are consistent with the primary findings of OS.

Additional sensitivity analyses were conducted by this reviewer to evaluate the influence of the imbalance in number of subjects who were randomized but not treated. Results are shown in Table 11.

Table 11: Additional Sensitivity Analyses of Overall Survival (MM-398 + 5-FU/LV vs. 5-FU/LV)

Sensitivity Analysis Description	MM-398	5-FU/LV	HR (95% CI) ^a
	+ 5-FU/LV Median OS	Median OS	

1. Excluding patients never treated	6.1	4.2	0.66 (0.48, 0.91)
2. Censoring patients who were not treated at the median OS times ^a	6.2	4.8	0.71 (0.52, 0.98)
3. Censoring patients who were not treated at the 25 percentile OS times ^b	6.1	4.3	0.68 (0.49, 0.93)

^a 6.1 months for patients in the MM-398 + 5-FU/LV arm and 4.2 for the patients in the 5-FU/LV arm

^b 3.7 months for patients in the MM-398 + 5-FU/LV arm and 2.2 for the patients in the 5-FU/LV arm

Reviewer's comments:

The sensitivity analyses presented above are consistent with the primary OS findings for the comparison of MM-398 + 5-FU/LV vs 5-FU/LV.

3.2.5.2 Key Secondary Endpoint – Progression-free Survival

Table 12 presents the applicant's efficacy analysis for PFS based on the updated information.

Table 12: Progression-Free Survival Results (ITT Population, MM-398 + 5-FU/LV vs. 5-FU/LV)

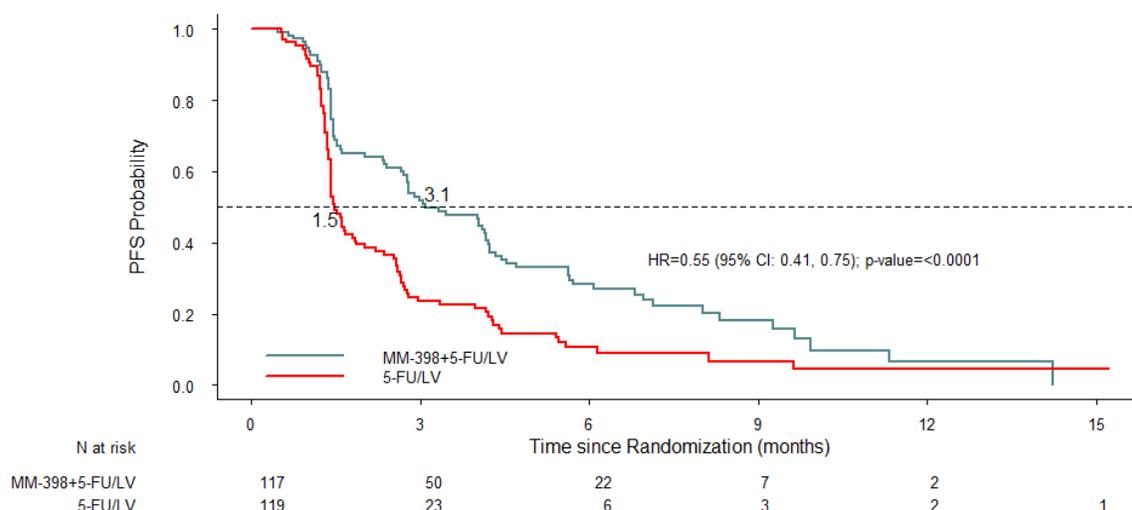
	MM-398 + 5-FU/LV	5-FU/LV
Subjects randomized	117	119
PD or Death	83 (70.9%)	94 (79.0%)
Censored	34 (29.1%)	25 (21.0%)
PFS (months)		
Median (95% CI)	3.1 (2.7, 4.2)	1.5 (1.4, 1.8)
p-value ^a	< 0.0001	
Hazard ratio (95% CI) ^b	0.55 (0.41, 0.75)	

^a p-value is from an unstratified log-rank test. This p-value is nominal.

^b Hazard ratio is from an unstratified Cox proportional hazards model.

Figure 3 presents the Kaplan-Meier (K-M) curves for PFS based on the updated information.

Figure 3: Kaplan-Meier Survival Curves for Progression-Free Survival (ITT Population, MM-398 + 5-FU/LV vs. 5-FU/LV)



3.2.5.3 Key Secondary Endpoint – Overall Response Rate

Table 13 presents the ORR analysis based on the confirmed complete response (CR) or partial response (PR).

Table 13: ORR Results (ITT Population, MM-398 + 5-FU/LV vs. 5-FU/LV)

	MM-398 + 5-FU/LV (N=117)	5-FU/LV (N=119)
Overall Response	9 (7.7%)	1 (0.8%)
Complete Response (CR)	0	0
Partial Response (PR)	9 (7.7%)	1 (0.8%)
Fisher's Exact Test p-value ^a	0.010	

^a This p-value is nominal.

Reviewer's comments:

1. For Bonferroni-Holm procedure, unless both hypotheses of the planned two pair-wise comparisons for the primary endpoints were rejected, no type I error rate can be transferred from the primary endpoints to the secondary endpoints for either comparison. Since the trial NAPOLI-1 failed to demonstrate statistically significant improvement in OS between the MM-398 arm and the 5-FU/LV arm, p-values for the secondary endpoints PFS and ORR are not interpretable for either comparison.

2. *The ORR analysis based on the unconfirmed CR or PR shows that 19 patients (16.2%) had achieved PR in the MM-398 + 5-FU/LV arm and 1 patient (0.8%) had achieved PR in the 5-FU/LV arm. No CRs were observed in either arm.*
3. *Per the protocol Section 12 (Statistical Analyses) and the SAP, the primary ORR analysis was based on the confirmed CR or PR (Table 13).*

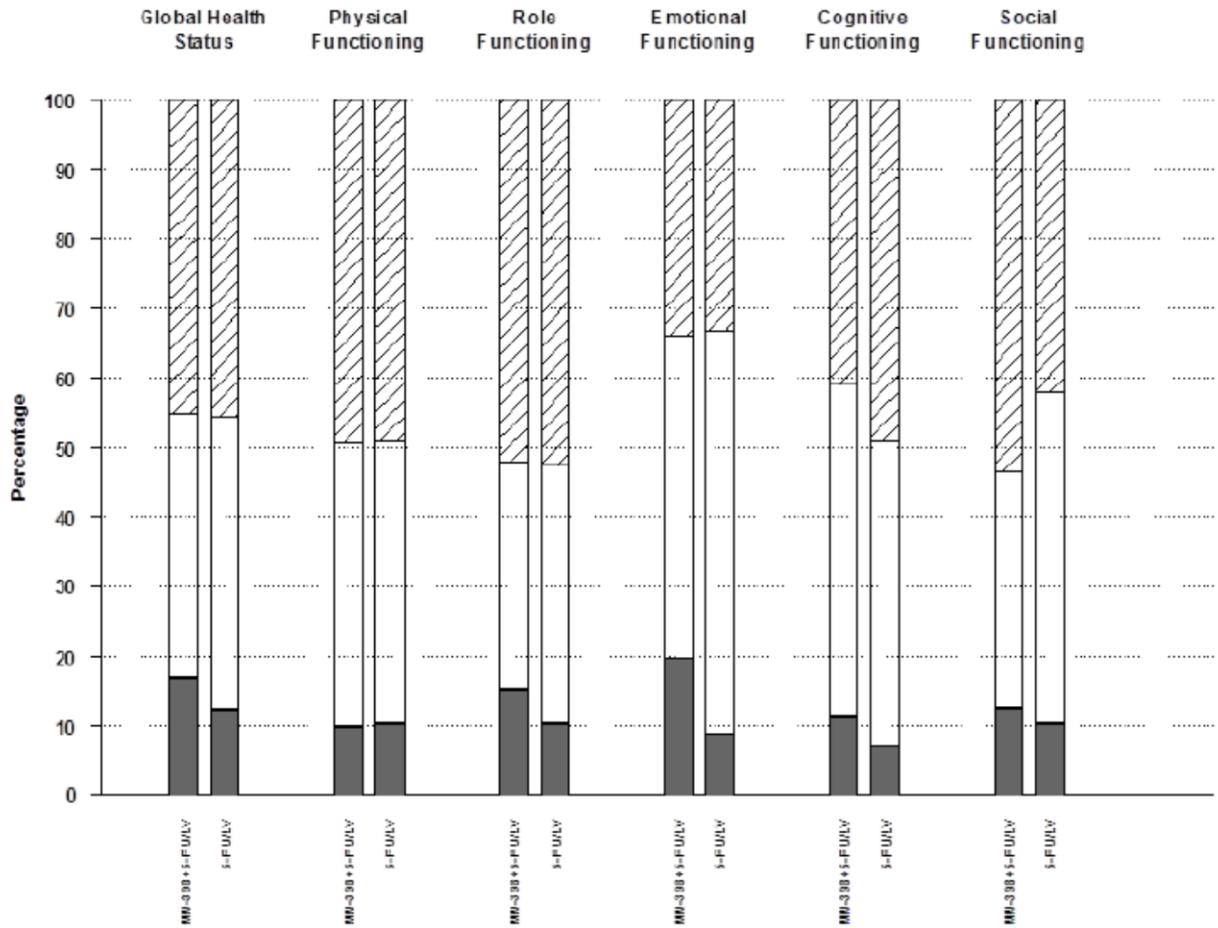
3.2.5.4 Secondary Endpoint – Patient Reported Outcomes

Figure 4 and Figure 5 show the Applicant's analyses for the PROs for the comparison of MM-398 + 5-FU/LV vs. 5-FU/LV.

Reviewer's comments:

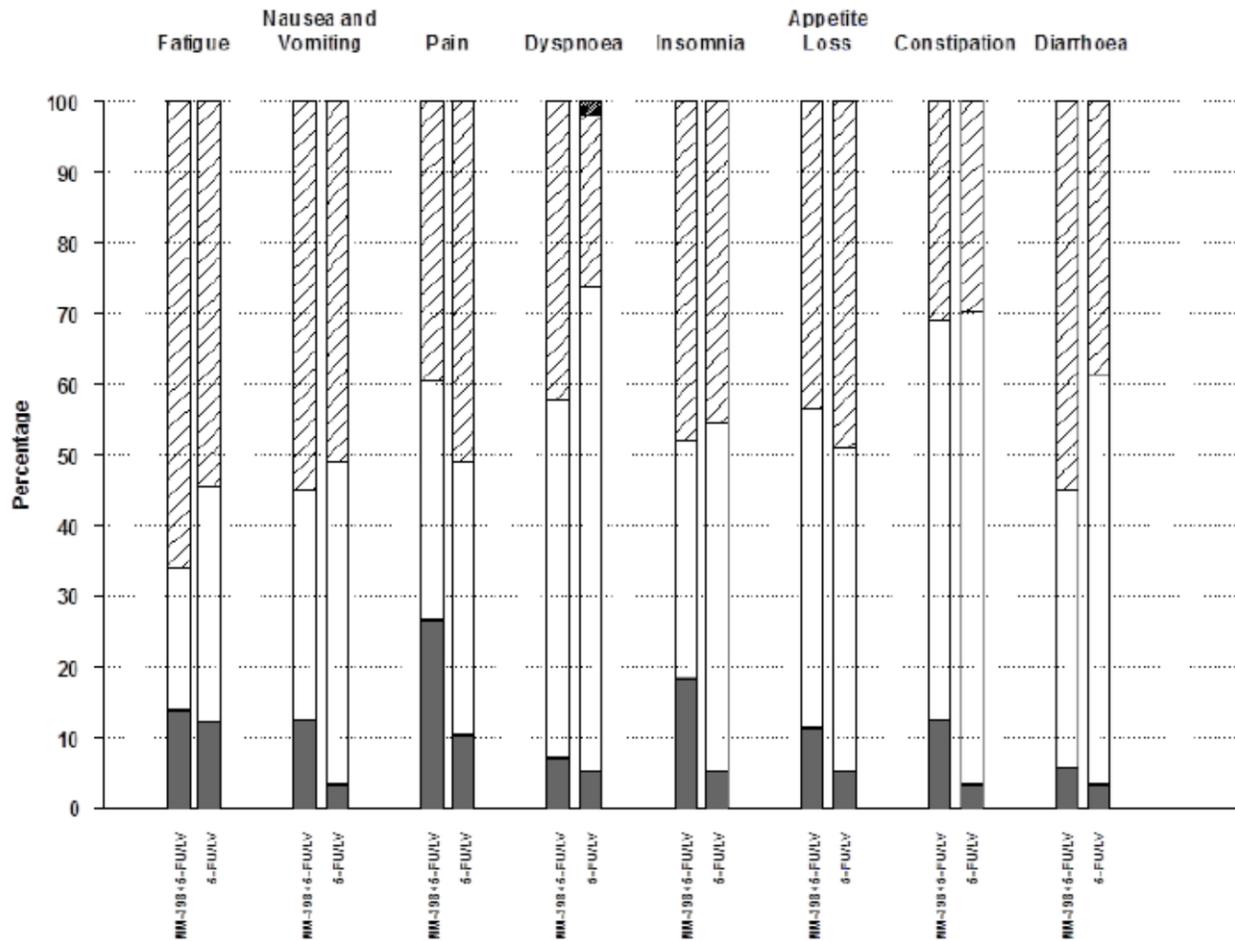
1. *Patient-reported outcome endpoints are subject to bias in an open-label study. Therefore, this reviewer considers these endpoints as exploratory.*
2. *The PRO population was used for the analysis of PRO endpoints. The PRO population is a subset of the ITT population with patients who had provided baseline and at least one subsequent assessment on the EORTC-QLQ-C30 instrument. The randomization as executed in the ITT population does not hold in this subset. These results are considered exploratory and should be interpreted with caution.*
3. *Multiplicity adjustment for the PRO endpoints was specified in the SAP but not in the protocol. However, since a Bonferroni-Holm adjustment was used to control the family-wise type I error rate at the two-sided 0.05 level for the two pair-wise comparisons of the primary endpoint OS, and the trial failed to demonstrate a statistically significant difference in the OS between the MM-398 arm and the 5-FU/LV arm, no type I error rate can be transferred to the PRO endpoints for either comparison.*
4. *Figure 4 shows that the 5-FU/LV arm appears to have a higher proportion of patients with improvement in the cognitive function but a lower proportion of patients with improvement in the social function compared with the MM-398 + 5-FU/LV arm. In addition, Figure 5 shows that the 5-FU/LV arm appears to have a lower proportion of patients with improvement in the fatigue scale score but a higher proportion of patients with improvement in the pain scale score compared with the MM-398 + 5-FU/LV arm.*

Figure 4: Applicant's Analysis of Percent of Patients with Improvement (Diagonal Shading), Stability (No Shading), or Decrease (Black Shading) in QOL Functional Scale Scores (ITT Population, MM-398 + 5-FU/LV vs. 5-FU/LV)



[Source: Clinical Study Report Figure 7-5]

Figure 5: Applicant’s Analysis of Percent of Patients with Improvement (Diagonal Shading), Stability (No Shading), or Decrease (Black Shading) in QOL Symptom Scale Scores (ITT Population, MM-398 + 5-FU/LV vs. 5-FU/LV)



[Source: Clinical Study Report Figure 7-6]

3.3 Evaluation of Safety

Please refer to the clinical review of this application for details of the safety evaluation.

3.4 Benefit-Risk Assessment

The MM-398 + 5-FU/LV arm demonstrated a statistically significant improvement in the primary endpoint OS compared with the 5-FU/LV arm. Whether the submission demonstrated an overall favorable benefit vs. risk profile for MM-398 + 5-FU/LV is deferred to the clinical team reviewing this submission.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race, Age, and Geographic Region

Table 14 summarizes OS subgroup analysis results by age, gender, race, and geographic region.

Table 14: Overall Survival Subgroup Analyses by Demographics (ITT Population, MM-398 + 5-FU/LV vs. 5-FU/LV)

	Event/Total (TRT: CTL)	HR (95% CI)^a
Age		
≤ 65	41/65 : 53/81	0.61 (0.40, 0.92)
> 65	36/52 : 33/38	0.78 (0.49, 1.26)
Sex		
Male	46/69 : 49/67	0.64 (0.43, 0.96)
Female	31/48 : 37/52	0.72 (0.44, 1.17)
Race		
White	45/72 : 58/76	0.66 (0.45, 0.97)
Black or African American	3/4 : 1/3	— ^b
Asian	23/34 : 24/36	0.54 (0.29, 0.98)
Other	6/7 : 3/4	— ^b
Region		
North America	14/19 : 14/19	0.75 (0.35, 1.57)
Europe	30/47 : 37/49	0.74 (0.46, 1.20)
Asia	23/34 : 24/35	0.51 (0.28, 0.93)
Other	10/17 : 11/16	0.58 (0.25, 1.38)

^a HRs were estimated using unstratified Cox regression model.

^b Analysis was not performed due to the small number of patients.

TRT: MM-398 + 5-FU/LV

CTL: 5-FU/LV

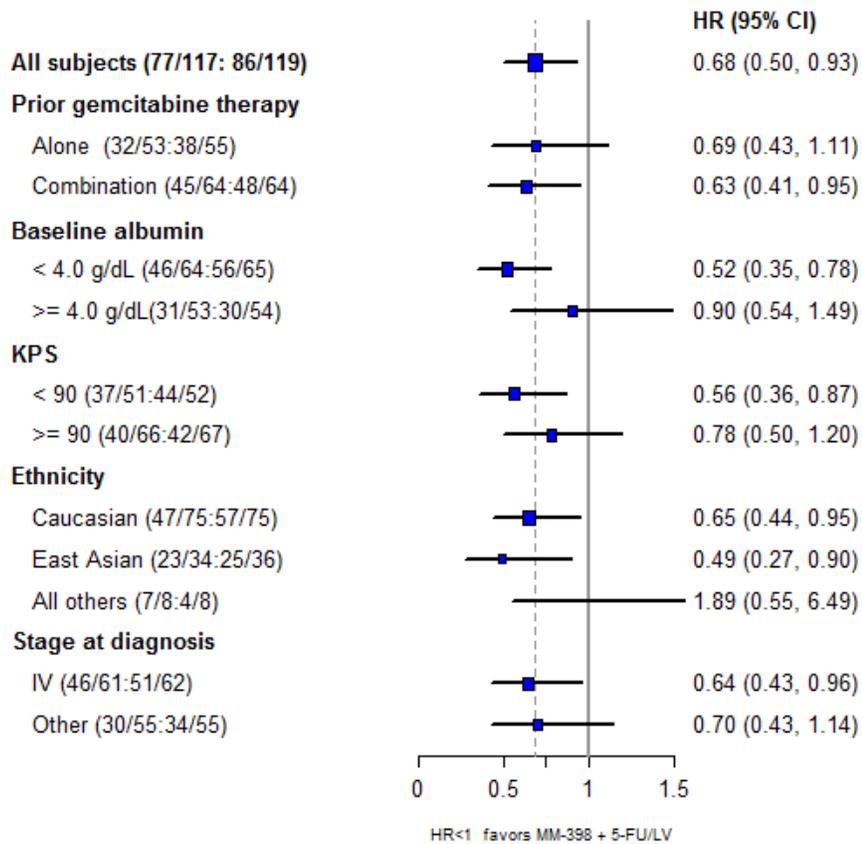
Reviewer's comment:

1. All the subgroup analyses presented in this section are considered exploratory or hypothesis generating and no formal inference may be drawn.
2. MM-398 + 5-FU/LV showed improvement over 5-FU/LV across all age groups, gender, race categories and geographic region with respect to OS, but its improvement in Asians appears to be more than that in Whites and its improvement in Asia and other regions appears to be more than that in North America and Europe.

4.2 Other Special/Subgroup Populations

Figure 6 summarizes additional OS subgroup analysis results.

Figure 6: Forest Plot of Subgroup Analyses of OS (ITT Population, MM-398 + 5-FU/LV vs. 5-FU/LV)



Reviewer's comment:

1. All the subgroup analyses presented in this section are considered exploratory or hypothesis generating and no formal inference may be drawn.
2. The OS improvement in the MM-398 + 5-FU/LV arm is consistent across various subgroups.

5 SUMMARY AND CONCLUSIONS

In this original New Drug Application (NDA), the applicant is seeking an approval of MM-398 in combination with 5-fluorouracil (5-FU) and leucovorin (LV) in patients with metastatic pancreatic cancer who had failed prior gemcitabine-based therapy based on the randomized, open-label phase 3 trial NAPOLI-1.

5.1 Statistical Issues and Collective Evidence

A brief summary of major statistical issues are presented below:

1. MM-398 monotherapy did not demonstrate a difference in OS compared with 5-FU/LV.
2. For the planned two pair-wise comparisons of OS, a Bonferroni-Holm adjustment was used to control the family-wise Type I error rate at the two-sided 0.05 level. For Bonferroni-Holm procedure, unless both hypotheses of the planned two pair-wise comparisons for the primary endpoints OS were rejected, no type I error rate can be transferred from the primary endpoints to the secondary endpoints for either comparison. Since the trial NAPOLI-1 failed to demonstrate a statistically significant difference in OS between the MM-398 arm and the 5-FU/LV arm, p-values for the secondary endpoints PFS and ORR are not interpretable for either comparison.
3. Patient-reported outcome endpoints are subject to bias in an open-label study. Therefore, this review considers these endpoints in this open-label trial exploratory.
4. No adjustment was made in the Type I error rate for multiple subgroup analyses. Therefore, all subgroup analyses are considered exploratory by the reviewer.
5. There was an imbalance in the number of patients who were randomized but not treated among the three treatment arms. This imbalance could have influenced the assessment of OS. However, since the analyses and results based on the original datasets and the amended dataset with additional information are consistent for all efficacy endpoints analyzed, this reviewer considers that the influence is small if any.

The trial NAPOLI-1 demonstrated a statistically significant efficacy of MM-398 + 5-FU/LV compared to 5-FU/LV in the primary endpoint OS. The main efficacy results based on the data cut-off date of February 14, 2014 using the amended dataset with additional information are summarized below:

1. MM-398 + 5-FU/LV demonstrated a statistically significant improvement in the OS compared to 5-FU/LV. The hazard ratio for death was 0.68 (95% CI: 0.50, 0.93; unstratified log-rank test p-value 0.014), indicating a 32% decrease in the hazard of death

in patients assigned to MM-398 + 5-FU/LV compared with patients assigned to 5-FU/LV. The KM estimates of median OS was 6.1 months (95% CI: 4.8, 8.5) for MM-398 + 5-FU/LV and 4.2 months (95% CI: 3.3, 5.3) for 5-FU/LV.

2. MM-398 + 5-FU/LV demonstrated an improvement in the PFS compared to 5-FU/LV. The hazard ratio for progression or death was 0.55 (95% CI: 0.41, 0.75; nominal p-value <0.0001), representing a 45% decrease in the hazard of progression or death in the MM-398 + 5-FU/LV arm compared to the 5-FU/LV arm. The KM estimates of median PFS was 3.1 months (95% CI: 2.7, 4.2) for MM-398 + 5-FU/LV and 1.5 (95% CI: 1.4, 1.8) for 5-FU/LV.
3. MM-398 + 5-FU/LV demonstrated an improvement in the ORR when compared with 5-FU/LV (MM-398 + 5-FU/LV: 7.7%; 5-FU/LV: 0.8%). The nominal p-value was 0.010 based on the Fisher's exact test.
4. Consistent efficacy of MM-398 + 5-FU/LV on the primary endpoint OS was observed across examined subgroups defined by gender, age, race, geographic region, prior gemcitabine therapy, baseline albumin, KPS, ethnicity and stage at diagnosis.

5.2 Conclusions and Recommendations

The trial NAPOLI-1 shows that MM-398 + 5-FU/LV demonstrated a statistically significant improvement in the primary endpoint of OS compared with 5-FU/LV in studied patients. However, MM-398 monotherapy did not show a statistically significant improvement with respect to OS compared with 5-FU/LV. Whether the results based on this trial demonstrated an overall favorable benefit vs. risk profile for MM-398 + 5-FU/LV is deferred to the clinical team reviewing this submission.

5.3 Labeling Recommendations

- The results of the primary OS analysis for the comparison of MM-398 + 5-FU/LV to 5-FU/LV will be included in the label.
- The results of the analyses for PFS and ORR for the comparison of MM-398 + 5-FU/LV to 5-FU/LV will be included in the label. (b) (4)

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/s/

HUI ZHANG
09/29/2015

KUN HE
09/29/2015

RAJESHWARI SRIDHARA
09/29/2015

NDA/BLA Number: NDA 207793

Applicant: Merrimack

Stamp Date: 4/24/2015

Drug Name: Irinotecan liposome injection

NDA/BLA Type: 505(b)(2) Priority

On **initial** overview of the NDA/BLA application for RTF:

	Content Parameter	Yes	No	NA	Comments
1	Index is sufficient to locate necessary reports, tables, data, etc.	X			
2	ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.)	X			
3	Safety and efficacy were investigated for gender, racial, and geriatric subgroups investigated (if applicable).	X			
4	Data sets in EDR are accessible and do they conform to applicable guidances (e.g., existence of define.pdf file for data sets).	X			

IS THE STATISTICAL SECTION OF THE APPLICATION FILEABLE? Yes

If the NDA/BLA is not fileable from the statistical perspective, state the reasons and provide comments to be sent to the Applicant.

NA

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Content Parameter (possible review concerns for 74-day letter)	Yes	No	NA	Comment
Designs utilized are appropriate for the indications requested.	X			
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.	X			
Interim analyses (if present) were pre-specified in the protocol and appropriate adjustments in significance level made. DSMB meeting minutes and data are available.			X	
Appropriate references for novel statistical methodology (if present) are included.			X	
Safety data organized to permit analyses across clinical trials in the NDA/BLA.	X			
Investigation of effect of dropouts on statistical analyses as described by applicant appears adequate.	X			

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/s/

HUI ZHANG
05/21/2015

KUN HE
05/21/2015