PD-023

Safety Across Subgroups in NAPOLI-1: a Phase 3 Study of nal-IRI (MM-398) ± 5-Fluorouracil and Leucovorin Versus 5-Fluorouracil and Leucovorin in Metastatic Pancreatic Cancer Previously Treated With Gemcitabine-Based Therapy

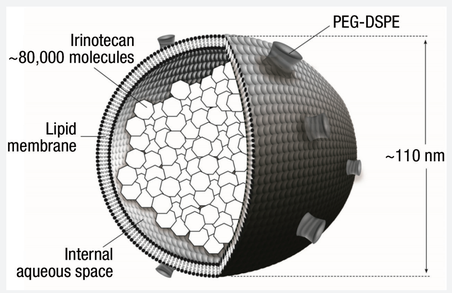
Li-Tzong Chen,[1] Jens T Siveke,[2] Andrea Wang-Gillam,[3] Richard Hubner,[4] Shubham Pant,[5] Tomislav Dragovich,[6] Vincent M Chung,[7] David Z Chang,[8] Paul J Ross,[9] Prasad Cooray,[10] Niall C Tebbutt,[11] Fabio A Franke,[12] Bruce Belanger,[13] Navreet Dhindsa,[13] Floris de Jong,[14] Khalid Mamlouk,[13] Daniel D Von Hoff[15]

[1]National Health Research Institutes – National Institute of Cancer Research, Tainan, Taiwan; [2]West German Cancer Center, University Hospital Essen, Essen, Germany; [3]Washington University in St. Louis, St. Louis, MO, USA; [4]Christie Hospital NHS Foundation Trust, Manchester, UK; [5]OU Medical Center, Oklahoma City, OK, USA; [6]Banner MD Anderson Cancer Center, Gilbert, AZ, USA; [7]City of Hope, Duarte, CA, USA; [8]Virginia Oncology Associates, Newport News, VA, USA; [9]Guy's Hospital, London, UK; [10]Box Hill Hospital, Box Hill, VIC, Australia; [11]Olivia Newton John Cancer & Wellness Centre, Austin Health, Heidelberg, VIC, Australia; [12]Hospital de Caridade de Ijuí, Ijuí, RS, Brazil; [13]Merrimack Pharmaceuticals, Inc., Cambridge, MA, USA; [14]Shire, Glattpark (Opfikon), Switzerland; [15]TGen and HonorHealth, Phoenix/Scottsdale, AZ, USA

BACKGROUND

- Pancreatic cancer is the fourth leading cause of cancer-related deaths in Europe and the seventh leading cause worldwide[1,2]
- Metastatic pancreatic ductal adenocarcinoma (mPDAC) represents a significant unmet need, with approximately 80% of patients dying within 12 months[3]
- nal-IRI (MM-398) is a novel liposomal formulation of irinotecan that exhibits extended circulation and facilitates intratumoral drug deposition when compared with nonliposomal (ie, conventional) irinotecan (**Figure 1**)[4,5]
- nal-IRI is approved by the US Food and Drug Administration, in combination with 5-fluorouracil (5-FU) and leucovorin (LV), for use following disease progression in patients with mPDAC previously treated with gemcitabine-based therapy[6]

Figure 1. nal-IRI design.



nal-IRI, liposomal irinotecan; PEG-DSPE, poly(ethylene glycol)–distearoylphosphatidylethanolamine.

- NAPOLI-1 was a phase 3 trial evaluating the efficacy and safety of nal-IRI, as monotherapy and in combination with 5-FU/LV, compared with 5-FU/LV alone, in patients with mPDAC previously treated with gemcitabine-based therapy[7]
- As of the data cutoff of February 14, 2014, median overall survival (OS) increased significantly with nal-IRI + 5-FU/LV relative to 5-FU/LV (6.1 vs 4.2 months; unstratified hazard ratio [HR], 0.67 [95% confidence interval (CI), 0.49-0.92]; $P = 0.012$), but did not differ significantly between nal-IRI monotherapy and 5-FU/LV (4.9 vs 4.2 months; unstratified HR, 0.99 [95% CI, 0.77-1.28]; $P = 0.94$)[7]
- The most common treatment-emergent adverse events (TEAEs) of all grades in patients whose treatment included nal-IRI were diarrhea, nausea, and vomiting (**Table 1**)[7]
  - Adverse events that resulted in a dose reduction occurred in 39 (33%) patients in the nal-IRI + 5-FU/LV arm, 46 (31%) patients in the nal-IRI monotherapy arm, and 5 (4%) patients in the 5-FU/LV arm
  - Adverse events leading to treatment discontinuation occurred in 13 (11%) patients in the nal-IRI + 5-FU/LV arm, 17 (12%) patients in the nal-IRI monotherapy arm, and 10 (7%) patients in the 5-FU/LV arm

Table 1. Treatment-Emergent Adverse Events From the Primary Analysis of the NAPOLI-1 Trial[7]

	nal-IRI + 5-FU/LV n = 117		5-FU/LV n = 134	
	Any Grade	Grades 3/4	Any Grade	Grades 3/4
Diarrhea	69 (59)	15 (13)	35 (26)	6 (4)
Vomiting	61 (52)	13 (11)	35 (26)	4 (3)
Nausea	60 (51)	9 (8)	46 (34)	4 (3)
Decreased appetite	52 (44)	5 (4)	43 (32)	3 (2)
Fatigue	47 (40)	16 (14)	37 (28)	5 (4)
Neutropenia[a]	46 (39)	32 (27)	7 (5)	2 (1)
Anemia	44 (38)	11 (9)	31 (23)	9 (7)

5-FU, 5-fluorouracil; LV, leucovorin; nal-IRI, liposomal irinotecan.
Data are number of patients (%). The table shows grade 3 and 4 adverse events reported in ≥5% of patients with ≥2% incidence versus 5-FU/LV.
[a]Includes agranulocytosis, febrile neutropenia, granulocytopenia, neutropenia, neutropenic sepsis, decreased neutrophil count, and pancytopenia.

OBJECTIVES

- To evaluate the safety of nal-IRI + 5-FU/LV and 5-FU/LV in the following subgroups:
  - Age (≥65 years vs <65 years)
  - Ethnicity (white vs east Asian)
  - *UGT1A1*28* allele (TA7/TA7 genotype; yes vs no)
  - Albumin level (≥4.0 g/dL vs <4.0 g/dL)
  - Karnofsky performance status (KPS) score (≥90 vs <90)

METHODS

Study Design

- NAPOLI-1 was an international, open-label, randomized, phase 3 trial
  - Patients were initially randomized to nal-IRI monotherapy (120 mg/m^2 irinotecan hydrochloride trihydrate salt equivalent to 100 mg/m^2 irinotecan free base every 3 weeks) or 5-FU/LV (200 mg/m^2 LV and 2000 mg/m^2 5-FU, every week for the first 4 weeks of each 6-week cycle)
  - Once safety data for the combination regimen became available from a concurrent study in metastatic colorectal cancer, the protocol was amended to include a third arm, nal-IRI + 5-FU/LV (80 mg/m^2 irinotecan hydrochloride trihydrate salt [equivalent to 70 mg/m^2 irinotecan free base], 400 mg/m^2 LV, and 2400 mg/m^2 5-FU over 46 hours, every 2 weeks)
    - The initial nal-IRI dose in the nal-IRI + 5-FU/LV arm was 60 mg/m^2 for patients homozygous for the *UGT1A1*28* allele (TA7/TA7 genotype) and could be increased to the standard dose (80 mg/m^2) in the absence of drug-related toxic effects
  - Randomization was stratified by baseline albumin levels (≥4.0 g/dL vs <4.0 g/dL), KPS (70 and 80 vs ≥90), and ethnicity (white vs east Asian vs all others)
- TEAEs were graded by National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0, and coded by Medical Dictionary for Regulatory Activities, version 14.1
- All TEAEs were followed until resolution or patient discontinuation
- The safety analysis population included all patients who received ≥1 dose of study drug
- The presence of the *UGT1A1*28* allele was determined by genotype testing, and homozygous patients were identified (TA7/TA7 genotype)
  - The *UGT1A1* gene codes an enzyme responsible for glucuronidation of the active metabolite of irinotecan, SN-38
  - Patients homozygous for the *UGT1A1*28* allele may be at increased risk for neutropenia, diarrhea, and other SN-38 exposure related side-effects during irinotecan treatment because of reduced glucuronidation of SN-38
- Data from the nal-IRI + 5-FU/LV arm (nal-IRI combination arm) and the 5-FU/LV arm (control arm) are presented herein (data cutoff of February 14, 2014)

Eligibility Criteria

Key Inclusion Criteria

- Adults ≥18 years of age
- Histologically or cytologically confirmed PDAC
- Documented measurable or nonmeasurable distant metastatic disease (as defined by Response Evaluation Criteria in Solid Tumors, version 1.1)
- Disease progression after prior gemcitabine or gemcitabine-containing therapy in a neoadjuvant, adjuvant (only if distant metastases occurred within 6 months of completing adjuvant therapy), locally advanced, or metastatic setting
- KPS score ≥70
- Adequate hematologic (including absolute neutrophil count >1.5 × 10^9 cells/L), hepatic (including normal serum total bilirubin and albumin levels ≥30 g/L), and renal function

Key Exclusion Criteria

- Active central nervous system metastasis
- Clinically significant gastrointestinal disorders
- Severe arterial thromboembolic events <6 months before inclusion
- New York Heart Association class III or IV congestive heart failure, ventricular arrhythmias, or uncontrolled blood pressure
- Active infection or uncontrolled fever

RESULTS

Patient Characteristics

- Of the 417 patients included in the intention-to-treat population, 398 (95%) received ≥1 dose of any study drug (safety analysis population)
- Patient demographics and baseline characteristics were well balanced between the nal-IRI combination and control arms (**Table 2**)

Table 2. Demographics and Baseline Characteristics (Safety Population)

Parameter	nal-IRI + 5-FU/LV n = 117	5-FU/LV n = 134
Sex, n (%)		
Male	67 (57.3)	73 (54.5)
Female	50 (42.7)	61 (45.5)
Age, median (range), years	63 (41-81)	63 (39-83)
Ethnicity, n (%)		
White	73 (62.4)	85 (63.4)
East Asian	33 (28.2)	44 (32.8)
Other	11 (9.4)	5 (3.7)
KPS score, n (%)		
100	19 (16.2)	16 (11.9)
90	50 (42.7)	50 (37.3)
80	39 (33.3)	57 (42.5)
70	7 (6.0)	11 (8.2)
60	2 (1.7)	0
Previous lines of metastatic therapy, n (%)		
0[a]	15 (12.8)	18 (13.4)
1	63 (53.8)	79 (59.0)
≥2	39 (33.3)	37 (27.6)
Previous anticancer therapy,[b] n (%)		
Gemcitabine alone	54 (46.2)	61 (45.5)
Gemcitabine combination	63 (53.8)	73 (54.5)
Fluorouracil	50 (42.7)	53 (39.6)
Irinotecan	12 (10.3)	14 (10.4)
Platinum	37 (31.6)	38 (28.4)

5-FU, 5-fluorouracil; KPS, Karnofsky performance status; LV, leucovorin; nal-IRI, liposomal irinotecan.
[a]Patients received neoadjuvant, adjuvant, or locally advanced treatment, but no previous therapy for metastatic disease.
[b]Columns add to >100% because some patients received more than 1 line of therapy, and regimens may include multiple drug classes.

Treatment Exposure

- Median duration of exposure to nal-IRI in the nal-IRI combination arm was 8.7 weeks (interquartile range [IQR], 5.4-22.0 weeks); mean dose intensity of nal-IRI over 6 weeks was 167.5 mg/m^2 (standard deviation [SD], 52.05 mg/m^2)
- Median duration of exposure to 5-FU was 8.7 weeks (IQR, 5.4-22.0 weeks) in the nal-IRI combination arm and 6.0 weeks (IQR, 5.9-12.1 weeks) in the control arm; mean dose intensities of 5-FU over 6 weeks were 5065.0 mg/m^2 (SD, 1539.1 mg/m^2) and 6718.0 mg/m^2 (SD, 1770.18 mg/m^2), respectively

Safety Subgroup Analysis

Age

- Incidence of any-grade and grade ≥3 TEAEs was similar between patients aged <65 years and those aged ≥65 years in each treatment arm (**Table 3**)
- Grade ≥3 TEAEs of note (difference of ≥5% between subgroups):
  - In the nal-IRI combination arm, incidence of vomiting (14.3% vs 7.4%) was higher in patients <65 years; incidence of nausea (11.1% vs 4.8%) was higher in patients ≥65 years

Table 3. TEAEs by Age

	nal-IRI + 5-FU/LV				5-FU/LV			
	<65 Years n = 63		≥65 Years n = 54		<65 Years n = 78		≥65 Years n = 56	
Any TEAE	63 (100)		53 (98.1)		77 (98.7)		55 (98.2)	
Any TEAE, grade ≥3	53 (84.1)		37 (68.5)		44 (56.4)		31 (55.4)	
Any TEAE resulting in dose modification[a]	46 (73.0)		37 (68.5)		25 (32.1)		23 (41.1)	
TEAEs (reported in ≥30% of patients in any arm)	Any Grade	Grade ≥3	Any Grade	Grade ≥3	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Vomiting	41 (65.1)	9 (14.3)	20 (37.0)	4 (7.4)	22 (28.2)	2 (2.6)	13 (23.2)	2 (3.6)
Diarrhea	39 (61.9)	9 (14.3)	30 (55.6)	6 (11.1)	22 (28.2)	5 (6.4)	13 (23.2)	1 (1.8)
Nausea	38 (60.3)	3 (4.8)	22 (40.7)	6 (11.1)	29 (37.2)	1 (1.3)	17 (30.4)	3 (5.4)
Decreased appetite	30 (47.6)	2 (3.2)	22 (40.7)	3 (5.6)	22 (28.2)	3 (3.8)	21 (37.5)	0
Neutropenia[b]	24 (38.1)	17 (27.0)	22 (40.7)	15 (27.8)	4 (5.1)	2 (2.6)	3 (5.4)	0
Fatigue	23 (36.5)	8 (12.7)	24 (44.4)	8 (14.8)	21 (26.9)	3 (3.8)	16 (28.6)	2 (3.6)
Anemia	19 (30.2)	5 (7.9)	25 (46.3)	6 (11.1)	13 (16.7)	5 (6.4)	18 (32.1)	4 (7.1)
Abdominal pain	17 (27.0)	5 (7.9)	10 (18.5)	3 (5.6)	23 (29.5)	6 (7.7)	19 (33.9)	2 (3.6)

5-FU, 5-fluorouracil; LV, leucovorin; nal-IRI, liposomal irinotecan; TEAE, treatment-emergent adverse event.
[a]Dose modification included dose reduction, dose delay, and dose discontinuation.
[b]Includes agranulocytosis, febrile neutropenia, granulocytopenia, neutropenia, neutrophil sepsis, neutrophil count decreased, and pancytopenia.

Ethnicity

- Incidence of any-grade TEAEs was similar between white and east Asian patients in each treatment arm, with the exception of diarrhea, which occurred less frequently in east Asians (**Table 4**)
- Incidence of grade ≥3 TEAEs in the control arm was similar between white and east Asian patients (56.5% vs 54.5%), whereas the incidence of grade ≥3 TEAEs in the nal-IRI combination arm was higher for east Asians compared with whites (87.9% vs 69.9%)
- Grade ≥3 TEAEs of note (difference of ≥5% between subgroups):
  - In the nal-IRI combination arm, incidence of diarrhea (19.2% vs 3.0%), fatigue (19.2% vs 0%), and vomiting (13.7% vs 6.1%) was higher in white patients; incidence of anemia (21.2% vs 5.5%), neutropenia (54.5% vs 17.8%), and white blood cell decrease (21.2% vs 2.7%) was higher in east Asian patients
  - In the control arm, incidence of abdominal pain (8.2% vs 2.3%) was higher in white patients; incidence of anemia (13.6% vs 3.5%) was higher in east Asian patients

Table 4. TEAEs by Ethnicity

	nal-IRI + 5-FU/LV				5-FU/LV			
	White n = 73		East Asian n = 33		White n = 85		East Asian n = 44	
Any TEAE	72 (98.6)		33 (100)		84 (98.8)		43 (97.7)	
Any TEAE, grade ≥3	51 (69.9)		29 (87.9)		48 (56.5)		24 (54.5)	
Any TEAE resulting in dose modification[a]	48 (65.8)		28 (84.8)		33 (38.8)		13 (29.5)	
TEAEs (reported in ≥30% of patients in any arm)	Any Grade	Grade ≥3	Any Grade	Grade ≥3	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Diarrhea	45 (61.6)	14 (19.2)	16 (48.5)	1 (3.0)	24 (28.2)	4 (4.7)	11 (25.0)	2 (4.5)
Nausea	37 (50.7)	6 (8.2)	18 (54.5)	2 (6.1)	28 (32.9)	3 (3.5)	16 (36.4)	1 (2.3)
Fatigue	35 (47.9)	14 (19.2)	8 (24.2)	0	25 (29.4)	3 (3.5)	10 (22.7)	2 (4.5)
Vomiting	34 (46.6)	10 (13.7)	22 (66.7)	2 (6.1)	23 (27.1)	4 (4.7)	12 (27.3)	0
Anemia	29 (39.7)	4 (5.5)	13 (39.4)	7 (21.2)	16 (18.8)	3 (3.5)	15 (34.1)	6 (13.6)
Decreased appetite	24 (32.9)	2 (2.7)	22 (66.7)	2 (6.1)	24 (28.2)	1 (1.2)	18 (40.9)	2 (4.5)
Neutropenia[b]	21 (28.8)	13 (17.8)	22 (66.7)	18 (54.5)	4 (4.7)	0	2 (4.5)	1 (2.3)
Abdominal pain	20 (27.4)	6 (8.2)	6 (18.2)	2 (6.1)	30 (35.3)	7 (8.2)	11 (25.0)	1 (2.3)
White blood cell count decreased	4 (5.5)	2 (2.7)	12 (36.4)	7 (21.2)	1 (1.2)	0	0	0

5-FU, 5-fluorouracil; LV, leucovorin; nal-IRI, liposomal irinotecan; TEAE, treatment-emergent adverse event.
[a]Dose modification included dose reduction, dose delay, and dose discontinuation.
[b]Includes agranulocytosis, febrile neutropenia, granulocytopenia, neutropenia, neutrophil sepsis, neutrophil count decreased, and pancytopenia.

*UGT1A1*28* Allele (TA7/TA7 Genotype)

- Although the low number of patients with the TA7/TA7 genotype makes comparison difficult, the incidence of any-grade and grade ≥3 TEAEs appeared to be similar between patients with or without the TA7/TA7 genotype (**Table 5**)
- In the nal-IRI combination arm, 3 of the 7 patients with the TA7/TA7 genotype were able to escalate the nal-IRI dose to 80 mg/m^2 without needing dose reduction
  - 1 patient escalated but required dose reduction back to 60 mg/m^2
  - 2 patients maintained the initial dose
  - 1 patient required dose reduction to 40 mg/m^2
- 1 additional patient in the nal-IRI combination arm with the TA7/TA7 genotype discontinued treatment (without dose reduction) because of grade 3 vomiting

Table 5. TEAEs by *UGT1A1*28* Allele (TA7/TA7 Genotype)

	nal-IRI + 5-FU/LV				5-FU/LV			
	TA7/TA7 Genotype n = 7		No TA7/TA7 Genotype n = 110		TA7/TA7 Genotype n = 13		No TA7/TA7 Genotype n = 121	
Any TEAE	7 (100)		109 (99.1)		13 (100)		119 (98.3)	
Any TEAE, grade ≥3	5 (71.4)		85 (77.3)		8 (61.5)		67 (55.4)	
Any TEAE resulting in dose modification[a]	4 (57.1)		79 (71.8)		5 (38.5)		43 (35.5)	
TEAEs (reported in ≥30% of patients in any arm)	Any Grade	Grade ≥3	Any Grade	Grade ≥3	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Anemia	5 (71.4)	0	39 (35.5)	11 (10.0)	1 (7.7)	0	30 (24.8)	9 (7.4)
Nausea	3 (42.9)	0	57 (51.8)	9 (8.2)	8 (61.5)	1 (7.7)	38 (31.4)	3 (2.5)
Vomiting	3 (42.9)	1 (14.3)	58 (52.7)	12 (10.9)	7 (53.8)	1 (7.7)	28 (23.1)	3 (2.5)
Abdominal pain	2 (28.6)	0	25 (22.7)	8 (7.3)	6 (46.2)	1 (7.7)	36 (29.8)	7 (5.8)
Decreased appetite	2 (28.6)	0	50 (45.5)	5 (4.5)	7 (53.8)	0	36 (29.8)	3 (2.5)
Diarrhea	2 (28.6)	1 (14.3)	67 (60.9)	14 (12.7)	4 (30.8)	1 (7.7)	31 (25.6)	5 (4.1)
Neutropenia[b]	2 (28.6)	2 (28.6)	44 (40.0)	30 (27.3)	0	0	7 (5.8)	2 (1.7)
Constipation	1 (14.3)	0	25 (22.7)	0	4 (30.8)	1 (7.7)	28 (23.1)	1 (0.8)
Fatigue	1 (14.3)	0	46 (41.8)	16 (14.5)	4 (30.8)	1 (7.7)	33 (27.3)	4 (3.3)

5-FU, 5-fluorouracil; LV, leucovorin; nal-IRI, liposomal irinotecan; TEAE, treatment-emergent adverse event.
[a]Dose modification included dose reduction, dose delay, and dose discontinuation.
[b]Includes agranulocytosis, febrile neutropenia, granulocytopenia, neutropenia, neutrophil sepsis, neutrophil count decreased, and pancytopenia.

Albumin

- Incidence of any-grade and grade ≥3 TEAEs was similar between patients with albumin levels ≥4.0 g/dL or <4.0 g/dL (**Table 6**)
- Grade ≥3 TEAEs of note (difference of ≥5% between subgroups):
  - In the nal-IRI combination arm, incidence of diarrhea (17.6% vs 6.4%) and fatigue (16.2% vs 10.6%) was higher in patients with albumin levels ≥4.0 g/dL
  - In the control arm, incidence of diarrhea (8.1% vs 1.4%) was higher in patients with albumin levels <4.0 g/dL

Table 6. TEAEs by Albumin Level

	nal-IRI + 5-FU/LV				5-FU/LV			
	Albumin ≥4.0 g/dL n = 68		Albumin <4.0 g/dL n = 47		Albumin ≥4.0 g/dL n = 70		Albumin <4.0 g/dL n = 62	
Any TEAE	68 (100)		46 (97.9)		70 (100)		60 (96.8)	
Any TEAE, grade ≥3	55 (80.9)		33 (70.2)		32 (45.7)		42 (67.7)	
Any TEAE resulting in dose modification[a]	48 (70.6)		33 (70.2)		21 (30.0)		26 (41.9)	
TEAEs (reported in ≥30% of patients in any arm)	Any Grade	Grade ≥3	Any Grade	Grade ≥3	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Diarrhea	41 (60.3)	12 (17.6)	27 (57.4)	3 (6.4)	12 (17.1)	1 (1.4)	23 (37.1)	5 (8.1)
Nausea	38 (55.9)	4 (5.9)	20 (42.6)	4 (8.5)	24 (34.3)	3 (4.3)	21 (33.9)	1 (1.6)
Vomiting	38 (55.9)	8 (11.8)	23 (48.9)	5 (10.6)	17 (24.3)	2 (2.9)	17 (27.4)	2 (3.2)
Decreased appetite	33 (48.5)	2 (2.9)	19 (40.4)	3 (6.4)	22 (31.4)	1 (1.4)	20 (32.3)	2 (3.2)
Fatigue	31 (45.6)	11 (16.2)	16 (34.0)	5 (10.6)	21 (30.0)	3 (4.3)	15 (24.2)	2 (3.2)
Neutropenia[b]	29 (42.6)	20 (29.4)	17 (36.2)	12 (25.5)	4 (5.7)	1 (1.4)	3 (4.8)	1 (1.6)
Anemia	24 (35.3)	6 (8.8)	20 (42.6)	5 (10.6)	14 (20.0)	4 (5.7)	16 (25.8)	5 (8.1)
Abdominal pain	19 (27.9)	6 (8.8)	7 (14.9)	2 (4.3)	24 (34.3)	4 (5.7)	17 (27.4)	4 (6.5)
Constipation	16 (23.5)	0	9 (19.1)	0	22 (31.4)	2 (2.9)	10 (16.1)	0

5-FU, 5-fluorouracil; LV, leucovorin; nal-IRI, liposomal irinotecan; TEAE, treatment-emergent adverse event.
[a]Dose modification included dose reduction, dose delay, and dose discontinuation.
[b]Includes agranulocytosis, febrile neutropenia, granulocytopenia, neutropenia, neutrophil sepsis, neutrophil count decreased, and pancytopenia.

Karnofsky Performance Status

- Incidence of any-grade TEAEs was similar between patients with KPS score of ≥90 or <90 (**Table 7**)
- Incidence of grade ≥3 TEAEs was similar between patients with KPS score of ≥90 or <90 in the nal-IRI combination arm; incidence of grade ≥3 TEAEs was lower in patients with KPS score of ≥90 vs patients with KPS score of <90 in the control arm (40.9% vs 70.6%)
- Grade ≥3 TEAEs of note (difference of ≥5% between subgroups):
  - In the nal-IRI combination arm, incidence of decreased appetite (8.3% vs 1.4%) and abdominal pain (10.4% vs 4.3%) was higher in patients with KPS score <90
  - In the control arm, incidence of abdominal pain (8.8% vs 3.0%) was higher in patients with KPS score <90

Table 7. TEAEs by KPS Score

	nal-IRI + 5-FU/LV				5-FU/LV			
	KPS Score ≥90 n = 69		KPS Score <90 n = 48		KPS Score ≥90 n = 66		KPS Score <90 n = 68	
Any TEAE	69 (100)		47 (97.9)		65 (98.5)		67 (98.5)	
Any TEAE, grade ≥3	52 (75.4)		38 (79.2)		27 (40.9)		48 (70.6)	
Any TEAE resulting in dose modification[a]	48 (69.6)		35 (72.9)		19 (28.8)		29 (42.6)	
TEAEs (reported in ≥30% of patients in any arm)	Any Grade	Grade ≥3	Any Grade	Grade ≥3	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Diarrhea	40 (58.0)	8 (11.6)	29 (60.4)	7 (14.6)	22 (33.3)	3 (4.5)	13 (19.1)	3 (4.4)
Nausea	37 (53.6)	4 (5.8)	23 (47.9)	5 (10.4)	19 (28.8)	1 (1.5)	27 (39.7)	3 (4.4)
Vomiting	36 (52.2)	8 (11.6)	25 (52.1)	5 (10.4)	16 (24.2)	2 (3.0)	19 (27.9)	2 (2.9)
Fatigue	29 (42.0)	8 (11.6)	18 (37.5)	8 (16.7)	18 (27.3)	1 (1.5)	19 (27.9)	4 (5.9)
Neutropenia[b]	29 (42.0)	20 (29.0)	17 (35.4)	12 (25.0)	4 (6.1)	1 (1.5)	3 (4.4)	1 (1.5)
Decreased appetite	28 (40.6)	1 (1.4)	24 (50.0)	4 (8.3)	21 (31.8)	0	22 (32.4)	3 (4.4)
Anemia	25 (36.2)	6 (8.7)	19 (39.6)	5 (10.4)	18 (27.3)	4 (6.1)	13 (19.1)	5 (7.4)
Abdominal pain	16 (23.2)	3 (4.3)	11 (22.9)	5 (10.4)	18 (27.3)	2 (3.0)	24 (35.3)	6 (8.8)
Constipation	11 (15.9)	0	15 (31.3)	0	12 (18.2)	0	20 (29.4)	2 (2.9)

5-FU, 5-fluorouracil; KPS, Karnofsky performance status; LV, leucovorin; nal-IRI, liposomal irinotecan; TEAE, treatment-emergent adverse event.
[a]Dose modification included dose reduction, dose delay, and dose discontinuation.
[b]Includes agranulocytosis, febrile neutropenia, granulocytopenia, neutropenia, neutrophil sepsis, neutrophil count decreased, and pancytopenia.

CONCLUSIONS

- **The safety profiles for nal-IRI + 5-FU/LV and 5-FU/LV were generally similar across patient subgroups; diarrhea, vomiting, and nausea were the most commonly occurring TEAEs**
- **The incidence of grade ≥3 TEAEs within the subgroups was in line with the safety profile of the overall population**
- **Study limitations included small patient numbers in some of the subgroups and lack of statistical analysis, which preclude definitive conclusions from being drawn**
- **The results of this subgroup analysis further support that nal-IRI + 5-FU/LV has a manageable safety profile in patients with mPDAC previously treated with gemcitabine-based therapy**

REFERENCES

1. Malvezzi M, et al. *Ann Oncol.* 2016;27:725-731.
2. Ferlay J, et al. *Int J Cancer.* 2015;136:E359-E386.
3. Kundranda M, Kachaamy T. *Future Oncol.* 2014;10(16):2629-2641.
4. Roy AC, et al. *Ann Oncol.* 2013;24(6):1567-1573.
5. Kalra AV, et al. *Cancer Res.* 2014;74(23):7003-7013.
6. Onivyde [package insert]. Cambridge, MA: Merrimack Pharmaceuticals, Inc.; 2015.
7. Wang-Gillam A, et al. *Lancet.* 2016;387:545-557.

ACKNOWLEDGMENTS

This study (ClinicalTrials.gov Identifier: NCT01494506) is supported by Merrimack Pharmaceuticals, Inc., Cambridge, MA, USA. Medical writing and editorial assistance were provided by Jemimah Walker, PhD, and Payal Gandhi, PhD, of ApotheCom (Yardley, Pennsylvania, USA) and were supported by Merrimack Pharmaceuticals, Inc.

POSTER PRESENTED AT THE 18TH ESMO WORLD CONGRESS ON GASTROINTESTINAL CANCER; 29 JUNE-2 JULY, 2016; BARCELONA, SPAIN